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Editorial

Emotion is an expression difficult to define. For somepeople it means only a connotation of agitated, exited mental states. It embraces cognitive connotation, mood, affect. In the Steedeman's Medical Diccionary it is described as: "A strong feeling or an aroused mental state, directed towards a definite object and giving rise to some more or less evident physical expression".

By mean of neuropsychological studies the relationships between behavior and physical changes in the brain are stablished. In order that an emotional changes in the brain are stablished. In order that an emotional change may occur, it is necessary that the brain must be in a healthy condition concerning the sectors involved in that function.

Aiming to study the cerebral function the oldest technique employed is to analize what happens functionally in the brain, after an experimental lesion is performed in a laboratory animal, or when a pathological condition is produced in the human being.

It is necessary to consider that a limited lesion in the brain may produce a modification of behavior. Then an investigation ought to be carried out to correlate the damaged region with the neuropsychological changes. We must be aware that the evidence of a lesion on a determinated area of the brain, doesn't means that the disturbed function is originated there. Moreover, it must be considered that the absence of a brain structure may originate a functional derangement in the rest of the brain. Different sectors of the brain became excited or inhibited due to the defect of the lesioned area.

Besides other areas are trying to compensate the function of the damaged sector of the brain.

Other aspects of this problem, is that concerning experiments performed in animals, these have their limitations, but neverthless they may give important functional information.

It has been possible to obtain very valuable knowledge about the function of a normal human brain aplying different kind of techniques.

An important contribution to this kind of studies has been the use of evoked potentials. Nowaday, it is possible to determine which area of the brain is engaged in a specific function because this requires the use of a bigger amount of energy. The glucose is the fundamental metabolic element, and by means of radioisotopes it is possible to determine the increased amount of the cerebral blood flow to the involved area.

Neuropsychologists have obtained very valuable data from human beings by using selective stimuli on the brain, or by making their subjec to perform a selective response.

By these methods the investigator may infer which hemisphere may be processing a kind of stimuli or may be mediating a response.

We will refer now to the neuropsychological study. Halstead in 1947 built a test battery integrated by seven tests, which allowed him to screen patients with frontal lesions from those with nonfrontal lesions.

They are the following tests: Category. Critical Flicker Frequency, Tactual Performance, Seashore Rhythm, Speech Sounds Perception. Finger Oscilation and Time Sense Tests.

Reitan enlarged the battery to include the Wechsler Intelligence Scale, an Aphasia and Sensory Perceptual Battery, the Trail-Making Test, and Dynamometric Hand Strength.

The Hastead-Reitan Battery no longer includes Critical Flicker Frequency and Time Sanse-Reitan in 1966 said that by means of the Halsted-Reitan Battery and the Wechsler Scales it is possible to emit a very appropiate prediction with respect to the lateralization, localization and even neuropathological nature of independently verified cerebral lesions.

It is widespread knowledge that the two hemispheres have different cognitive capacities left verbal, right visuospatial. Besides they have different conditionants relative to the knowledge of the emotional stimulus. They are more clearly perceived when they accede to the right hemisphere. A face with emotional expression is better recognized when it is more evident on the left side because the mediation of the right hemisphere.

A person aflicted by a left hemiplegia, that it is to say with a right hemisphere lesion because of the impairment, the feeling of emotion has an indiferent reaction to his motor defect. In the case of a right hemiplegia, by lesion of the left hemisphere, because the normalcy of the right hemisphere is preserved, a depressive reaction to his condition has a catastrophic character.

The damage on the right hemisphere means a fault on the comprehension of an emotional prosody or to recongnise sentences with an emotional significance. Concerning their expresive manifestations, they have dificulty to evidence an emotional prosody or to show an emotional reaction on their faces.

Repeated affective stimulus may spread to the adjacent areas of the brain cortex which may determine conjugate lateral eye movements.

Experimental studies have been performed on laboratory animals and it has been observed emotional responses, mediated by the right hemisphere.

On the physiology of emotion, the frontal lobe is implicated, in the sector of the limbic frontal cortex (E. G. Cingulate gyrus, orbito frontal cortex, supplementary motor area).

The affective component of the stimulus represents of a kind of enconding of incoming information in the right hemisphere, profiting the integrative and holistic properties of the right hemisphere.

Basal Ganglia disordes besides originating motor disorders are frequently accompanied by emotional changes, probably related to specific neurotransmitters and neuromodulators disturbances.

Emotional responses and their treatment have been studied in Parkinson's disease Huntington disease, Wilson disease, progressive supranuclear palsy and Sydenham chorea.

Changes has been observed in epileptic interictal personality and emotional disorders. In these patients may be observed, sexual dysfunction, psychosis and affective symptoms that may be associated with seizures.

Concerning epilepsy it has been described as producing catastophic rage attacks interictally in children with epilepsy. An incidence of aggressive behavior has been observed in one third of patients with temporal lobe epilepsy.

Of the patients described as psychopatic there was over representation of males in lower social calsses, early life onset of seizures and left hemispheric lesions.

Studies performed with EEG in imprisoned persons accused of crimes of aggression, there is evidence that EEG abnormalities were five times as likely in the group with habitual aggression.

This contrast with a group that commited violence but was not usually aggressive.

The observed abnormalities in the EEG in the aggressive group were bilateral generally affecting frontal or temporal areas of the brain.

There is no clear evidence that aggression is an ictal manifestation. It has been accepted that there is a contribution to psychotic behavior in the epileptic from basal EEG discharges an evidence of diffuse anatomical and physiological dysfunction.

Recently the neuropsychological test has provided concrete neurological data concerning sensitive indicators of cerebral dysfunction, localizing and lateralizing it. We will mention the cases of schizophrenic patients who has been explored with neuropsycholgical test and have shown similar dysfunction to those who have left-hemisphere lesions.

It has been clearly stablished that there is a superiority of the right hemisphere for recognizing emotion by means of studies using the presentation of lateralized stimulus.

Results from these examinations has been observed employing auditory and visual stimulus, with verbal and non verbal material. It has been presented to the patients to observe two faces and to discriminate which of them has an emotional expression. The duration of the stimulus may be an important variable concerning recognition studies.

Generally the perception of an emotional stimulus seems to be more precised when the stimulus is presented in such a way that reaches first the right hemisphere.

Also the emotional expression seems to be more evident in the right side of the face.

From this be has been deduced that specialized processes exist in the right *hemisphere that act selectively with the reception and expression of emotion.*

Everything leads us to think that any emotional stimulus of thought may activate some affective composition which most probably is represented in the right hemisphere than in the left one. The repeated or strong activation of these components may have an affect which will be spread to the adjacent areas of the cortex, originating the remarkable responses observed, and promoting conjugated lateral eyes movements. The right hemisphere has integrative and holistic properties.

The thalamus is an important central structure responsable for mediating emotions.

It may be stimulated by peripheral sensoral influx or by cortical impulses.

The hypothalamus is a major effector on emotional expression, it regulates the endocrine system and the autonomic nervous system. It has been admitted that the limbic system that has connections with the hypothalamus, cortex, and thalamus has an importal rol in the emotional regulation.

If in animals are stimulated the nonspecific thalamic nuclei, and also the mesencephalic reticular formation, behavioral indexes of arousal are observed. If it is stimulated in the cerebral cortex the frontal and temporo parietal regions, and activation of the mesencephalic and reticular formation is originated, eliciting an arousal response.

The limbic system connected with the reticular formation may also produce arousal.

To feel an emotion it is necessary to have appropiate cognitive state plus certain degree of arousal. It has been already said, arousal depends on the brain stem reticular formation, non specific thalamic nuclei and certain regions of the neocortex. Emotions are accompanied by visceral changes mediated by the hypothalamus. The hypothalamus is strongly indluenced by the limbic system which receives important influxes from the neocortes, especially from the frontal lobes.

With this we can affirm that an emotion dipends of a varied anatomic structures, cortical systems to elaborate the cognitive set, limbic structures that activate the brain stem and thalamic activated centers controling the hypothalamic output.

The regulation of endocrinal and autonomical responses and of the brain stem and thalamic activating system is necessary to elicit a cortical arousal.

Studies has been carried out in order to stablish how is the arousal in patients suffering a right hemisphere lesion.

The normal hemisphere has been stimulated in patients with lesion on the right or left hemisphere, with an electrical stimulus, studying simultaneosly the galvanic skin response.

The galvanic skin responses measures the peripheral sympathic activity. which armonizes with others central measures of arousals, such as the EEG.

Patients with right hemisphere diseases show evidences of smaller arousal *responses to the galvanic skin response, than patients with lesion of the left hemisphere that suffer from aphasia. The same occurs in normal person without hemisphere lesions.*

Since neglect happens more frequently after right hemisphere lesions, it is considered that the right hemisphere may be dominant to mediate an attention arousal response.

The right hemisphere is fundamental in mediating attention and cerebral activation, in spite of the fact that patients with left hemispheric lesions are depressed, according to the localization of the lesion there may be intrahemispheric variability.

Patients has been observed with posterior perisylvian temporoparietal lesions, affected of Wernicke and transcortical sensory aphasia, they do not seem so severely depressed like those patients with anterior perisylvian lesions. Patients with thalamic aphasia also show a lower degree of depression. Concerning patients with posterior neocortical lesions, they may evidence a lesser depression, because they have a comprehension deficit and are anosognostic for their language disturbances, and don't show hemisparesis.

Patient with thalamic lesions may have difficulties in arousal, fact that may be also observed in patients with posterior neocortical lesions.

Studies about hemispheric laterality has been also performed in animal which facilitates the understanding of what happens in human being. The aboundant information thus gathered about the emotional nature of the human brain have also aid in the comprehension of findings in animal studies. It is accepted that animals also have hemispheric lateralization.

The concept of reciprocal interactions of homologous brain areas may be put to test in experiments performed in animals. In the human being this concept has been veryfied in patients affected.

Heilman, Scholes and Watson in 1975 presented the case of a pacient with a lesion in the right hemisphere in a regions homologous to Wernicke's area which determined that the patient could not comprehend the affective components of language nevertheles he maintained his aptitude to understand the propositional meaning.

Clinical cases have been found in the medical literature with similar significance.

We must keep in mind that generally our expressions embody information and affect.

Then it is logical to deduce that two areas of hemispheric homologous regions have an interaction by means of the corpus callosum communication.

Experiment in singing birds have shown hemispheric lateralization, and it is presumed that the homologous brain regions interact reciprocally.

The studies of lateralization in experimental animals will be an important contribution in our understanding of laterality of functions in the human.

Concerning the participation of the frontal lobe in the control of affect and emotion its approach was studied by Egaz Moniz when he reported the first results of prefrontal leukotomy. He observed in his patients who had either schizophrenic psychosis or severe obsessive neurosis that after the first prefrontal leucotomy a remarkable improvement of anxiety was produced.

Egaz Moniz conceived this kind of surgery when he heard about experiments performed on chimpanzees named Becky and Lucy by Jacobson in the Laboratory of John F. Fulton at Yale University.

These animal had their frontal lobes extirpated, and complete indeference observed in those instances that before elicited anguish on those animals.

Besides were source of inspiration two patients who suffered the lack of frontal lobes, one because a traumatism produce a lesion of the brain, the other because frontal lobotomy was performed in order to extirpate a frontal meningioma.

The result was indiference, lack of preocupation, no social inhibitions.

It has been stablished that an ample sector of the frontal lobe cortex, embraces structures of the limbic system, and that white matter connections serving those limbic cortex, constitute an important sector of the frontal lobe.

Besides, while the frontal lobe structures are involved in emotion, other cortical structures are also involved, the mesial an anterior temporal cortex, and differents subcortical structures, the amygdala, septum and the hypothalamus.

The cortical structures of the limbic system are very wall defined on the internal surface of the hemisphere, by the cingulate sulcus dorsally and the collateral and orbital sulci ventrally. Connecting areas such as the subcallosal gyrus, the posterior orbitofrontal, anterior insular, temporal polar and perirhinal cortices connect the cingulate and parahippocampal gyri rostrally. The retrosplenial and retrocalcarine cortice stablish a caudally connection.

As subcortical structures of the limbic system we will mention the amygdala, septum, substantia innominate, anterior thalamus, habenula, interpeduncular nucleous and some additional midbrain areas.

Interconnection pathways within the limbic lobe are cingulum, uncinate fasciculus, fimbria fornix, striaterminalis, ventral amygdalofugal pathway, mammillothalamic tract, mammillotegmental tract, stria medullaris and habenulo interpeduncular pathway, the medial forebrain bundle.

It has been stablished that some subcortical parts of the limbic system such as the central amygdaloid nucleus projects to brain stem autonomic centers.

Hypothalamus projects to the substantia innominata and amygdala which projects directly to motor related areas of the cerebral cortex. Many structures of the limbic system specially the limbic cortises have ample connections with important sectors of the motor system. The anterior part of the cyngulate gyrus has projections to the premotor and supplementary motor cortisees and this sector receive an important aflux from the rest of the limbic lobe and several subcortical parts of the limbic system. It has been also admitted projection from the lim-

bic lobe to subcortical motor structures such as the caudate nucleous, putamen and pons.

All these that we have refered to, means that the hypothalamus and the limbic system are involved in the most important functions of the brain, besides those related to the endocrine and autonomic system.

Studies performed in mammals evidences that limbic system structures receive influxes directly from the cerebral cortex and especially from areas associatives.

The records of past experiences that constitute memory is in large part sited in the cortical association areas. Probably the limbic system imputs are linked to a complex sensory events and to the way that these are registered and interected with the organism in the past.

The bilateral damage of the cingulate gyrus has generated a state of akinesia and mutism severe autonomic disturbances may be observed.

The unilateral damage of the cingulate gyrus and the supplementary motor area originate an important disturbance of behavior that perturbs the normal expression and normal experience of affect, lack of spontaneity and also nonlateralized neglect of most stimuli.

The electrical stimulation of the cingulate lead to think that this sector is associated with both the experience and expression of affect. Besides it has a primary and general function of insiting to action. Modifing affect causing either euphoria or dysphoria or affective neutrality.

If an unilateral damage occurs on the supplementary motor area, a state of mutism and akinesia is in the patient observed.

After several weeks, neither aphasia nor apraxia is appreciated. But a lack of willing to speak or move are present.

With the electrical stimulation of the supplementary motor area, the interruption of ongoing voluntary activity is observed. Vocalization and complex movement patterns are also originated. Sensory responses generally as nonpainful paresthesias may appear.

Also autonomic responses such as pupillary changes modyfications of respirato or cardiac rates, sweating.

Functionally cingulate and supplementary motor areas appear to be in a continum and constitute a structural complex related to the drive towards movement

In the majority of the patients with bilateral frontal lesions, faceiousness, euphoria, irritability, intolerance, sudden depression and impair social judjement are observed.

Most of the patients suffering from these kind of impairment are handicaped for enjoying an agreable stimulus with a gratification that may be social intellectual or anesthetic.

There is a lack of appreciation for social rules, their shallow affect and their limited response to an experience of pain.

The best way to evaluate orbitofrontal damage in the human being has been the behavior studies conducted in patients that survived herpes simplex encephalitis.

This process affect all the cortical structures of the limbic system bilaterally in these kind of ailment, the mesial and polar temporal cortices, the orbito frontal cortices and the anterior cingulate cortices, are frequently damaged and even destroyed.

The unilateral lesion of the orbitofrontal cortex is very rare. Brain tumor, specially meningiomas, may attack the orbital frontal cortex in an unilateral but not exclusive way, the lesion may also involve neighboring regions.

Ruptured anoyrisms may also damage inilaterally the orbito frontal region, but this generally cause a lesion on septal region and the anterior hypothalamus.

The symptomatology is similar to those present in bilateral frontal lesion, but more attenuated, it is accompanied with a variant of amnesci syndrome showing a profound defect of retrieval of remote as well as recent memory, in the face of remarkably preserved encoding ability.

The neurological phenomenology of basal ganglia are generally divided in four categories Postural changes range from the stooped simian posture of Parkinson disease to the hyperextended dystonic posture of progressive supranuclear palsy.

Involuntary movement of the trunk in Huntington chorea and Syndenham chorea may be observed.

Very frequently gait disturbances that vary from a shuffling, unstable bradykinetic one to a choreic or danzing gate. The involuntary movement generally are the hallmark of basal ganglia disease and tremor dystonia and a variety of dyskenesia are observed.

Perturbances of speach such as dysarthria and hypophonia to near mutism may be also present.

Very often these basal ganglia disorders may be associated with a subcortical dementia.

Forgetfulness and mild degree of cognitive impairment are present. Also emotional disorders.

The more frequent symptoms are: affective disturbance, primarely depression, and less often mania, Apathy with lack of iniciative and motivation, that may be interrupted by episodes of irritability or agression may be seen.

Psychosis and lability of emotion could be present.

These disorders are probably related with disturbed neurotransmitter biochemestry. Some drugs that affect centralamines may produce similar mood disorders and psychosis. It must be considered that alterations in catechol or indolamines metabolism may underlie the emotional changes as well the motoric features, of basal ganglia diseases.

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Modification of Emotional Expression Induced by Clinical and Experimental Epileptic Disturbances

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A relationship between specific disturbances in emotion and epilepsy, particularly temporal lobe or limbic epilepsy, has been suggested by many authors (Barraclough, 1981; Bear and Fedio, 1977; Benson et al., in press; Blumer and Benson, 1982; Flor-Henry, 1976; Gastaut et al., 1955; Gibbs, 1951; Perini and Mendius, 1984; Nielson and Kristensen, 1981; Robertson and Trimble, 1983; Standage and Fenton, 1975: Taylor, 1969; 1972), but remains a controversial issue (Stevens, 1966; Rodin and Schmaltz, 1984). One practical reason for denying such a relationship concerns the effect of such a contention on patients who suffer from epileptic disorders. Epileptics throughout history have been outcasts due to beliefs that epilepsy represents demonic possession, punishment for sins, or a contagious disease (Jelik, 1979; Temkin, 1945), and in the more recent medical past it was considered to be a form of insanity (Berrios. 1984). These misconceptions persist, to a certain extent, in all cultures and create stigmata that may be more disabling for individuals who suffer from epileptic seizures than the seizures themselves. Any inference that these patients are prone to suffer from emotional disturbances would not only add to these stigmata, but introduce further anxiety for the patient who might fear eventual emotional deterioration.

Should there be a direct relationship between emotional disturbances and epilepsy, however, its denial would be an even greater folly. Research into this issue should be encouraged since it not only represents an opportunity to elucidate pathophysiological mechanisms and anatomical substrates of emotional disturbances in non-epileptic as well epileptic individuals, but also promises the possibility of identifying means to prevent, or reverse their manifestations. That disorders of emotion are a potentially treatable cause of major disability in epilepsy should not be overlooked.

Although it is now generally agreed that patients with epilepsy often do suffer from emotional disturbances, debate centers on their cause; whether these disturbances can be ascribed entirely to psychosocial factors, antiepileptic drug effects, and neuropsychological deficits directly related to the underlying lesion, or whether they can also be induced by the epileptogenic process. Even more controversial is the contention that characteristic emotional disturbances are due specifically to temporal lobe mechanisms, perhaps facilitating limbic-hypothalamic connections, creating a reverse Kluver-Bucy Syndrome (Gastaut et al., 1955; Bear and Fedio, 1977; Blumer and Benson, 1982). This discussion will concentrate on clinical and experimental observations that address this issue.

CLINICAL OBSERVATIONS

Affective symptoms occur as ictal phenomena (Commission on Classifications and Terminology, 1981). The most common ictal affective symptom is fear, often associated with appropriate autonomic changes, and depression and anger are also seen. These negative affective ictal symptoms characteristically occur in patients with epileptogenic lesions in mesial temporal limbic structures (Wieser, 1983), and can be reproduced in some patients by electrical stimulation of hippocampus (Gloor et al., 1982; Halgren et al., 1978). Positive affective symptoms are relatively uncommon, although euphoria occurs and ictal laughter (gelastic epilepsy) is a recognized epileptic phenomenon. Gelastic seizures may be purely motor events unassociated with mirth, e.g., with infantile spasms, or may be true emotional expressions. The latter is often associated with epileptigenic lesions of the limbic system, but a single anatomical substrate for ictal laughter has not been identified (Loiseau et al., 1971). Aggressive behavior as an ictal phenomenon is extremely rare. When it occurs it has been seen in association with complex partial seizures of mesial temporal origin and consists of nondirected reactive automatisms performed at a time of impaired consciousness (Saint-Hilaire et al., 1981).

Non-directed reactive aggressive behavior is more common during the postictal period than as an ictal manifestation. This is often seen following complex partial seizures while consciousness is still impaired, but motor function is preserved, when patients overreact to threatening gestures such as attempts at restraint. Whether this is peculiar to postictal disturbances of limbic function following limbic ictal discharges is not clear. The reason it is rarely seen following generalized convulsions may be that postictal depressed consciousness in this condition occurs during a time when motor functions are also depressed.

Another postictal affective alteration is relief from depression or anxiety. Occasionally patients report that the occurrence of a complex partial or generalized convulsive seizure results in a positive alteration in mood, but this is not as common as might be supposed from the well-known therapeutic effect of electroconvulsive shock treatment for endogenous depression. Related to this phenomenon is the interesting observation that patients who experience relief from chronic recurrent complex partial seizures following anterior temporal lobectomy often develop transient depression (Horowitz and Cohen, 1968; Hill et al., 1957). This postoperative depression has, on occasion, been treated with electroconvulsive shock therapy (Hill et al., 1957). Anti-epileptic drug treatment is also occasionally associated with depression (Rivinus, 1982), and it is not clear whether this is always due to a direct pharmacological effect on the brain, as opposed to a reduction in the frequency of spontaneous epileptic seizures. The limbic system has not been specifically implicated in the mechanism of these epilepsy-related alterations in mood.

The occurrence of both ictal and postictal alterations in emotional expression cannot be challenged; however, there is considerable controversy concerning an association between epilepsy, particularly temporal lobe epilepsy, and disturbances in interictal emotional expression. Bear and Fedio (1977) identified eighteen personality traits that were commonly associated with temporal lobe epilepsy in the literature. These traits form the basis of the Bear-Fedio personality inventory. Several of these traits have been considered manifestations of deepened emotionality (Blumer and Benson, 1982); they include sobriety and interests in issues of a moral, religious or philosophical nature, as well as anger, moodiness, explosiveness, and depression. Bear and Fedio (1977) reported that patients with temporal lobe epilepsy scored higher on all eighteen personality traits than a matched nonepileptic control group; however, there were no non-temporal lobe epileptic controls. Subsequent studies by others have yielded inconsistent results. While some suggest that these disturbances reflect non-specific psychopathology related to factors such as intelligence, gender and antiepileptic drug levels (Mungas, 1982; Rodin and Schmaltz, 1984), others have found some features to be peculiar to temporal lobe epilepsy (Hermann and Reil, 1981), especially when the epileptogenic lesion is presumed to be in mesial limbic structures (Nielson and Kristensen, 1981), and when fear is a prominent ictal symptom (Hermann et al., 1982).

The two most common interictal emotional disturbances ascribed to patients with temporal lobe epilepsy are aggression and depression. Aggressive behavior has been correlated with an early onset of epileptic seizures in male patients with a low I.Q. (Taylor, 1969). No direct relationship has been demonstrated between interictal aggressive personality traits and the peri-ictal aggressive behaviors discussed previously. Depression is only recently becoming recognized as a serious interictal disturbance and may not be peculiar to temporal lobe epilepsy (Robertson and Trimble, 1983; Benson et al., in press). Studies of epileptic patients using both the Bear-Fedio inventory, and the Minnesota Multi-Phasic Personality Index (MMPI) have consistently noted elevated depression scales. The incidence of depressed mood may be as high as 75 %, and of somatic symptoms as high as 60 % (Standage and Fenton, 1975). Suicide among epileptic patients is 5 % higher than for the general population, and is 25 % higher in those with a diagnosis of temporal lobe epilepsy (Barraclough, 1981). Interictal depression may be reactive (related to despondency over restrictions on lifestyles), due to institution of a particular medication, or endogenous. Several forms of endogenous depression have been identified in patients with epilepsy, but a specific relationship between any of these forms and particular aspects of the epileptic disorder remain to be demonstrated clinically (Benson et al., in press).

There is considerable evidence for hemispheric specialization of emotional expression, with this function mediated primarily by the nonlanguage dominant hemisphere (Ross, 1981; Sackeim, et al., 1982). Although earlier literature had associated interictal depression in epileptic patients with lesions in the non-dominant temporal lobe (Flor-Henry, 1976), this has not been replicated in more recent investigations (Perini and Mendius, 1984). There are considerable procedural difficulties in attempting to use data obtained from patients with epilepsy to reach conclusions concerning hemispheric lateralization of emotional expression (Mendius and Engel, in press), and this controversy cannot be easily resolved.

EXPERIMENTAL OBSERVATIONS

Certain postictal alterations in behavior that can be experimentally induced in rats resemble postictal affective disturbances seen in patients (Caldecott-Hazard and Engel, in press). The multiple-squeak response to pain, which is believed to be an affective response involving limbic mechanisms (Carroll and Lim, 1960), is suppressed following electro-convulsive shock and kindled stage-five seizures (Caldecott-Hazard et al., 1984). The time course of this suppression corresponds to the duration of the postictal disturbance in hippocampal metabolism, as demonstrated by 2 deoxyglucose autoradiography (Caldecott-Hazard and Engel, 1985), further implicating a role for the hippocampus in mediating this affective response. Furthermore, the duration of postictal suppression of the multiple-squeak pain response is reduced by pre-treatment with naloxone (Caldecott-Hazard et al., 1983), suggesting a role for endogenous opioids.

Postictal explosive motor behavior, which can include biting, occurs rarely as a spontaneous phenomenon in kindled rats, but can be commonly elicited by touching the animal, particularly after repeated seizures (Caldecott-Hazard et al., 1984). The biting behavior has been considered a form of aggression by some authors (Pinel et al., 1977), but is probably a non-directed hyperreactivity. This postictal effect can be reduced by pretreatment with morphine, enhanced by pre-treatment with naloxone, and significantly increased by morphine withdrawal precipitated by naloxone pretreatment (Caldecott-Hazard et al., 1984). Postictal explosive motor behavior may be analogous to the postictal hyperreactivity to threat seen following temporal lobe seizures. This behavior is particularly interesting because, as in the clinical situation, it occurs following limbic seizures (induced by amygdaloid kindling) but not following generalized convulsive seizures (induced by electroconvulsive shock) (Caldecott-Hazard et al, 1984).

These studies suggest that postictal disturbances in affect are mediated, at least in part, by limbic structures and endogenous opioid mechanisms. Endogenous opioids are known to be released during epileptic seizures (Hong et al., 1979, 1980; Vindrola et al., 1981), and it has been postulated that they function as natural mood elevators (Belluzzi and Stein, 1977; Kline et al., 1977). This may be a clue to the mechanism of the beneficial effect of electroconvulsive shock therapy on clinical depression. Perhaps patients with epilepsy who experience recurrent seizures become physiologically dependent on intermittent excessively high levels of endogenous opioids, and develop clinical depression as a response to reduction of these abnormal levels between seizures, or when these seizures are abolished by successful treatment (Engel et al., 1984). Such a role for endogenous opioids in the mechanism of interictal and postoperative depression in patients with temporal lobe epilepsy remains to be demonstrated.

Studies of stimulation-induced aggression have identified anatomical substrates of predatory attack and defensive rage behaviors, which include the same limbic structures involved in temporal lobe epilepsy (Flynn et al., 1970). Defensive rage behavior can be produced by stimulation of the midbrain central gray, which receives afferent input from amygdala and is rich in opioid containing cell bodies (Bandler, 1982). Amygdaloid kindling in cats has been reported to produce an enduring reduction in predatory attack behavior, while hippocampal kindling facilitates predatory attack (Adamec and Stark-Adamec, 1975). Kindling stimulation applied to different areas of the amygdala can also produce alterations in threshold for stimulation-induced aggression (Siegel et al., in press). These observations provided the rationale for developing an animal model of epilepsy-induced enduring interictal affective disturbances.

Cats were chronically implanted with stimulating electrodes in areas of periaqueductal gray and medial hypothalamus, bilaterally, that consistently elicited defensive rage behavior. After establishing baseline thresholds for stimulation-induced defensive rage from these points, 1.0 μg of kainic acid was injected into the dorsal hippocampus unilaterally. Intermittent epileptic seizures then recurred over a period of 12 to 24 hours, initially consisting of piloerection, pupillary dilatation, hissing, mewing, and contraversive circling. After several hours, the initial ictal manifestations progressed much more rapidly, culminating in secondarily generalized convulsions. During this acute stage when spontaneous seizures occurred frequently, the cats were difficult to handle interictally, with exaggerated defensive reactions to minor threat. Thresholds for stimulation induced defensive rage were also reduced at this time.

After two to three days, a latent stage ensued when spontaneous seizures ceased and interictal behavior returned to normal. Thresholds for stimulation-induced defensive rage also returned to baseline at this time. Stimulation of amygdala or hippocampus in some cats produced first-trial generalized convulsions, or kindling developed after brief stimulation over several days. Neither procedure caused a clear alteration in interictal behavior or change in thresholds for stimulation induced defensive rage.

After several weeks, a chronic epileptic stage developed when cats again began to experience spontaneous recurrent epileptic seizures at irregular intervals. These seizures were similar behaviorally to those of the acute phase, and correlated with electrical ictal discharges in hippocampus and amygdala. Onset of the chronic stage was associated with a return of interictal hyperreactivity to threat, and a reduction in thresholds for stimulation induced defensive rage.

A peculiar aspect of the interictal hyperreactivity to threat demonstrated by these cats was a tendency for this response to be asymmetrical. Most cats demonstrated more pronounced inappropriate defensive behavior to threatening stimulation applied contralateral to the epileptic hippocampus. This strongly indicates that the interictal affective change was due to the epileptogenic process, and not a non-specific effect of chronic illness and resultant discomfort.

The interictal disturbance in affective behavior did not appear to be due to the hippocampal lesion *per se*, since it disappeared during the latent phase. This affective change also was not related to the occurrence of individual epileptic seizures since an enduring behavioral disturbance did not result when seizures were produced by hippocampal and amygdala stimulation. The interictal behavioral abnormality appeared to be dependent upon the presence of a chronic epileptogenic lesion in the hippocampus, perhaps with involvement of the amygdala as well. Threat and stimulation induced defensive rage had similar behavioral features, and neither were associated with epileptiform EEG changes. This suggests that the abnormal affective state observed during the chronic stage is an interictal, rather than ictal, phenomenon, perhaps due to pathophysiological alterations in the same limbic, diencephalic and brainstem structures responsible for stimulation induced defensive rage. Research is in progress to determine whether this interictal affective disturbance in chronic limbic epilepsy can be considered an experimental model of similar disturbances in human temporal lobe epilepsy, and if it can be utilized to elucidate the basic mechanisms of these clinical behavior disorders, as well as suggest new approaches for their prevention or treatment

SUMMARY

Disturbances in emotional expression occur in patients with epilepsy as ictal, postictal and interictal phenomena. Ictal affective symptoms such as fear, anger and depression appear to be generated from limbic structures of the mesial temporal lobe. while the anatomic substrates of euphoria and laughter are not known. Postictal aggressive behavior appears to be a nondirected hyperreactivity to perceived threat carried out during impaired consciousness, following limbic seizures. Animal studies suggest that this may be related to the release of endogenous opioids during epileptic seizures, either directly mediating affective changes, or producing explosive motor behavior as a more complicated result of opioid withdrawal. It is postulated that interictal depression, as well as the depression that occurs when epileptic seizures are abolished by successful treatment, could be explained by a physiological dependency on high levels of endogenous opioids that occur only during seizures. Interictal disturbances in emotional expression appear to be more common in patients with mesial temporal epileptogenic lesions than in patients with other forms of epilepsy or other chronic disorders. Stimulation induced predatory attack and defensive rage behaviors in cats are mediated by neurons in the medial hypothalamus and periacqueductal grey which are influenced, in turn, by afferent input from amygdala and hippocampus. Enduring alterations in affective display can be produced in cats with epileptiform discharges in hippocampus or amygdala, and this may be an appropriate model for studying the mechanisms of interictal emotional disturbances in patients with temporal lobe epilepsy.

RESUMEN

Disturbios en la expresión emocional ocurre en pacientes con epilepsia como manifestación ictal, postictal e interictal. Síntomas afectivos ictales tales como temor, ira y depresión aparecen generados desde estructuras límbicas del lóbulo temporal interno, mientras que los substratos anatómicos de eufória y la risa no son conocidos. La conducta agresiva postictal parece ser una hipereactividad no dirigida a amenaza percibida realizada durante estado de conciencia afectada, después de crisis límbicas. Estudios en animales sugieren que esto puede estar relacionado a la liberación de opioides endógenos durante crisis epilépticas, sea ocasionando directamente cambios afectivos o produciendo una conducta motriz explosiva como una consecuencia más complicada de la retirada opioide. Se ha postulado que la depresión interictal, también como la depresión que ocurre cuando las crisis epilép ticas son abolidas por un tratamiento exitoso, podría ser explicada por una dependencia fisiológica en altos niveles de opioides endógenos que ocurren sólo durante crisis. Disturbios interictales en expresión emocional se muestran más comunes en pacientes con lesiones epileptogénicas temporales internas, que en pacientes con otras formas de epilepsias u otros desórdenes crónicos.

Ataques de rapiña y conducta de rabia defensiva inducidos por estimulación en gatos son originados por neuronas en el hipotálamo interno y la gris periacueductal, las cuales son influenciadas a su vez por influjcs a ferentes de la amígdala y del hipocampo.

Alteraciones soportables en expresiones afectivas pueden ser producidas en gatos con descargas epileptiformes en hipocampo o amígdala y esto puede ser un modelo apropiado para estudiar los mecanismos de disturbios emocionales interictales en pacientes con epilepsia de lóbulo temporal.

RÉSUMÉ

Des troubles de l'expression emotionelle se produisent chez des patients épileptiques en période d'Ictus, post-Ictus ou inter-Ictus. Des symptomes d'ictus afectifs tels que la peur, la colere et la dépression aparaisent, produits dans les structures limbiques lobe temporal interne, tandis que l'euphorie et le rise son d'origine a localisation inconue. La conduite agresive post ictus parait entre une hiperactivité non dirigée a une menace perçue pendant l'état de conscience afecté an cours de la crise. L'etude chez l'animal sugére que fait peut etre dut a la libération d'opicides endogénes au cours de la crise, ce qui produirait des changements émotionels ou un comportement moteur explosif comme conséquence de la retraite de la vague d'o picides. On a pensé que la depression interictus aussi bien que celle que provoque un traitement anti-épileptique réussi, serait expliqué par une dépendance a des niveaux élevés d'opicides endogénes qui se produisent au cours des crises. Des troubles interictus de L'expression emotionelle sont plus fresquent chez des patients porteurs de lesions temporales internes que les autres épileptiques. L'agressivité et la rage défensive induites par stimulation, sur le chat, se produisent a travers les neurones de l'hypothalamus interne et la matiere grise qui entoure l'acquedouct, qui reçoivent l'influence d'influx afferents de l'amygdale et de l'hypocampe.

Des alterations "suportables" de l'expression afective peuvent etre produites, chez le chat, avec des decharges épileptiformes dans l'hypocampe ou l'amygdale ce qui peut etre un modele adequat pour etudier les mecanismes de production des troubles chez des patients épileptiques d'origine temporale.

ZUSAMMENFASSUNG

Bei epileptischen Patienten bestehen die Stoerungen des emotionellen Verhaltens als epileptis he, post-epileptische oder iner epileptische Erscheinung. Afektive Anfallssymptome wie Angst, Wut und Depression werden inden lymbischen Strukturen des mesialen Schlaefenlappens erzeugt, waehrend die anatomischen Substrate der Auphorie

und des Dachens nicht bekannt sind. Das agressive Verhalten nachhdem Anfallscheint eine Hyperaktivitaet zu sein, die nicht gegen eine apperzipierte Brohung gerichtet ist waehrend des gestoerten Bewustseinszustandes nach lymbischen Krisen.

Untersuchungen bei Tieren lassen vermuten, dass diese in Beziehung mit der Freisetzung von endogenen opioiden Substanzen waehrdn der epileptischen Krisen stehen, wodurch entweder direkt affektive Veraenderungdn hervorgerufen werden oder ein explosives motorisches Verhalten entsbelt als eine nonhkomkompliziertere Folge des Verschwindens der opioiden Substans.

Man hat behauptet, dass die interkritische De pression, ebenso wie die Depression nach als Folge erfolgreicher Behandlung sich erkrlaeren lassen als physiologische Abhaeheit von einem hohen endogenen Opioid-Ge halt, wie man dies nur waehrend der Krisen sieht. Interkritische Stoerungen des emotiven Verhaltens sind haeufiger bei Patienten mit epileptogener Laesion des mesialen Schlaefenlappens als bei Patienten mit anderen Epilepsiearten oder anderen chronischen Stoerungen. Di durch Reizung hervorgerufenen praeda torischen Anfaelle oder der defensiven Wut der Kat zen entstehen in den Neuronen des Hypothalamus internus und der Grauen Substanz um den Aquaeductus, die ihrerse its durch afferente Reizung der Amygdala und des Hyppocampus hervorgerufen sind.

Dauernde Veraenderungen des affektiven Verhaltens koennen bei Katzen durch epileptiforme Entladungen im Hyppocampus oder Amygdala hervorgerufen werden und dies koennte ein gee ignetes Modell sein, um die Pathogenie der emotionellen interkritischen Stoerungen bli Patienten mit Schlaefenlappenepilepsie zu studieren.

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Affective Symptomatology in Epilepsy

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AFFECTIVE SYMPTOMATOLOGY IN EPILEPSY

With the introduction of effective anticonvulsant medications, epileptics have been taken from the ranks of the insane and are now considered normal individuals with a treatable illness. This represents a total reversal of prior attitudes and has demanded a drastic alteration of opinion for most clinicians. The only recognized behavioral complications of epilepsy are those directly related to seizure activity. Any other psychiatric problems are considered the same as those occurring in a non-epileptic population. The program to convince physicians, epileptics and the public as a whole that epilepsy is treatable and the properly treated epileptic is behaviorally normal has been successful.

Recent studies, however, suggest that a number of interictal psychiatric problems may be directly related to the epileptic disorder. The schizophrenia-like disorder of epilepsy (1, 2, 3) and the epileptic personality (4, 5, 6) are considered interictal or chronic behavioral complications of epilepsy; several other entities such as poriomania (7), multiple personality (8, 9), and possession states (8) have been suggested to have a relationship to seizure disorder. Relatively little attention has been given to a direct relationship between affective disorder and seizures. When depression occurs in an epileptic it may be thought to represent a reaction to the presence of a chronic disease or to a chronic fear of loss of control (10). Recent studies (11, 12, 13, 14) have demonstrated that depression is frequent in seizure patients and that suicide is considerably more common in epileptics than in the general public. Three studies will be reported, each involving a quite different epileptic population investigated for the presence of depression.

EPI-HAB STUDY

In our original attempt to ascertain the frequency of depression in epileptic subjects, two populations of vocationally disabled individuals were studied, a subject group of epileptics and a control group of disabled individuals without seizures. Through the cooperation of Epi-Hab U.S.A., an organization devoted to vocational rehabilitation for epileptics, its several subsidiaries and other vocational groups, questionnaires were mailed to 503 epileptic subjects who were unemployed but were either in active vocational rehabilitation or had been interviewed for vocational rehabilitation. In each case epilepsy was considered the major cause of the vocational disability. With few exceptions, these individuals were in the lower strata of socioeconomic means.

A group of vocationally disabled non-epileptic subjects were obtained through vocational training and guidance counseling units in Los Angeles. These included individuals who were amputees, paraplegics, had severe cardiac or pulmonary disability, multiple sclerosis, or other chronic disability. All epileptic subjects and disabled controls were 18 years of age or older and other demographic characteristics such as age, male/female ratio, economic status, social isolation, criminal records, and alcohol and/or drug abuse were similar. The two groups appear adequately matched for social and vocational disability factors.

The instrument used was a 100-item inventory that covered three areas personality and behavioral characteristics, personal and psychosocial factors, and epilepsy or handicap variables. All questions requested direct yes-no responses. Of the 503 epileptic subjects contacted, 175 (34.8 percent) responded and of the 186 questionnaires mailed to control subjects, 70 (37.6 percent) were returned. The results were tabulated and analyzed using Chi-square determinations of significant values. Table 1 presents some of the relevant demographic data and includes most of the pertinent findings.

The major finding demonstrated by this study was a notable difference between the number of epileptics and the number of control subjects who responded positively to items pertaining to depression. Statistically significant differences in response were given to questions expressing feelings of hopelessness, the desire to be dead, a sense of guilt, and a history of suicide attempts. The epileptic subjects acknowledged a history of actual suicide attempts that was 4.15 times greater than that of the control subjects, a difference that easily reached statistical significance. In addition, questions concerning anger, hostility, paranoia and suspiciousness were responded to positively by the epileptics considerably more than by the nonepileptic disabled group.

Most of the abnormal behavioral traits did not show a clear relationship with epilepsy variables. While patients who claimed to have more frequent seizures tended to acknowledge more emotionality, angry outbursts and humorlessness, they did not endorse depression or suicide attempts more than did those whose epilepsy was well controlled. The only clear relationship was with medication. Many epileptics reported CNS side effects from their medications and many believed that anticonvulsants impaired their ability to think clearly and to function effectively at a job. The description of seizure symptomatology from the questionnaire response was inadequate for typing many of the seizures; thus, no correlation between seizure type and affective disorder was possible.

In summary, of a sizeable number of epileptic and control subjects who were reasonably well matched for vocational disability status, 54.7 percent of the epileptics reported significant depression compared to 30.4 percent of controls and a history of attempted suicide was given by 29.9 percent of the epileptics compared to 7.2 percent of non-epileptics. The Epi-Hab study implies that depression is a frequent and significant complicating factor in the course of epilepsy and strongly suggests that the depression that occurs in epilepsy is not to be explained solely as a reaction to the resulting disability.

BRENTWOOD VA STUDY

In an attempt to characterize the depression of epilepsy, all epileptic inpatients in the Brentwood (California) Veterans Administration Medical Center, a neuropsychiatric institution, during a 30-day period were identified and evaluated. Almost 10 percent of the total population of the psychiatric facility during that period (43/442) had a history of seizures and of these, 32 could be considered true epileptics. The additional individuals with a history of seizures included those with late state dementia, post-leucotomy, post-brain trauma or tumor surgery or other brain-damaged patients who were so cognitively impaired that they could not be assessed adequately. Even when this group of patients were excluded, the number of epileptic subjects represented 6.81 percent of psychiatric inpatients, far greater than the proportion of epileptics in the population as a whole, usually quoted at approximately 1 percent of the population (13). For purposes of this study a diagnosis of *definite* epilepsy was based on an appropriate clinical history plus reports of diagnostic EEGs. A classification of *equivocal* epilepsy was given if there was a complicating drug history, equivocal but non-diagnostic EEG results or an uncertain history of seizures. Twenty-two of the inpatients were identified as definite epileptics. Each had a longstanding history of seizures and had received anticonvulsant medications for many years but had been admitted to the neuropsychiatric hospital because of disabling psychiatric problems, not epilepsy.

Of the patients with definite epilepsy, 72.2 percent had been admitted with a diagnosis of major depression and one additional epileptic patient had an admitting diagnosis of mania; thus, almost 4 out of 5 of those epileptics with sufficient problems to warrant psychiatric hospital admission suffered some form of affective disorder. This is far above the institution's overall rate for affective disorder which averages 20 percent of admissions; in other words, depression as a cause for mental hospitalization was four times more frequent for epileptics than for non-epileptics. The findings from the Brentwood VA study demonstrate that epileptics are considerably more likely to need psychiatric hospitalization than the population as a whole (about 7 to 1) and that the reason for this hospitalization, in a vast majority of cases, is depression. ,

In an additional study at the Brentwood Medical Center, 22 of the epileptic depressed subjects and 22 non-epileptic depressed subjects were interviewed. Table 2 presents a number of the similarities and differences that were noted. The two groups were matched for severity of depression (BPRS scores) and were comparable with respect to personal, socioeconomic and other demographic factors. A striking difference was noted in the family history of depression. While almost 60 percent of the non-epileptic depressed told of one or more family members who had been treated for depression, only 13.4 percent of the epileptic depressed presented a similar history, suggesting that fewer instances of depression in the epileptics could be considered to be genetically determined.

In addition, the phenomenological characteristics of the depression were strikingly different in the two groups. In the course of the interview, many of the epileptic depressed described a spaced-out, unreal, out-of-control feeling that was present at all times. They described this detached state as a chronic depression. In addition, many in this group described episodes of psychotic behavior including hallucinations, delusions and forced actions. They described impulsive behavior, often a response to a delusional command. For many it was this latter behavior that had brought them into psychiatric hospital care. In constrast, a majority of the non-epileptic depressed complained of overwhelming sadness, worthlessness, self-deprecation etc., a dysphoric response not reported by most of the epileptic depressed. Thus, not only did the Brentwood study demonstrate that epilepsy is more common than expected in the psychiatric inpatient population but the depression that occurs in this group appears to be a psychotic depression, not the more typical dysphoric state prevalent in the non-epileptic depressed.

UCLA TELEMETRY UNIT STUDY

In a further attempt to characterize the depressive phenomena present in epileptic subjects, most individuals admitted to UCLA for telemetry study as potential candidates for temporal lobe surgery in a six month period were interviewed. The surgical candidates had been carefully screened prior to admission; most had complex partial seizures, all had ongoing seizures that were intractable to standard epilepsy therapy, and subjects with a history of significant psychiatric symptomatology tended to be excluded. All interviews were conducted by psychiatrists with particular attention given to any history of serious depression during the course of their epileptic disorder. Of the 54 subjects interviewed, 55.5 percent gave a history of one or more episodes of depression at some time during the course of their seizure disease. This figure correlates, at least roughly, with the number of epileptics in the Epi-Hab study who told of depression, confirming that depression represents a common psychiatric problem in the epileptic population. In addition, 6 of the 54 patients had made suicide attempts and another 4 admitted strong suicidal ideation. In many of these patients there was no record of depression in the clinical notes; some stated that depression had never been discussed with their physician and in only a very few had it been treated.

When asked to characterize their problems, however, the depression described by the UCLA group differed considerably from the descriptions given in the Brentwood study. A number of phenomenologically distinct types of depression were reported by the UCLA subjects. While there were many individual differences, seven relatively distinct variations of affective symptomatology were noted (see Table 3). The subjects reported a broad variety of responses that resemble, at least generally, the list of ten relationships between epilepsy and depression postulated by Betts (11). Some UCLA subjects reported major depressive episodes of appropriate duration and with sufficient neurovegetative signs to qualify for the designation in DSM-III. In some the episode was clearly drug induced, appearing when a specific medication (most often phenobarbital or primidone) was prescribed and ceasing when the medication was withdrawn. In most, however, there was no clearcut drug effect and the depressive episode(s) were independent psychiatric disorders.

Transient depressive episodes, lasting from minutes to a number of days were also reported. Some were in context to environmental situations and could be considered reactive or adjustment problems. Other transient episodes, however, occurred out of context suggesting a relationship to the seizure disorder, either as ictal or postictal events. Some patients presented pictures of chronic depressive feelings, either a chronic feeling of sadness, a consistently dysthymic state or a longstanding feeling of detachment, at times to the degree of feeling depersonalized. The latter resembled the patients interviewed in the Brentwood study. Neither of these chronic affective disorders was common in the UCLA group, probably a reflection of the psychiatric screening that preceded admission to surgical candidate status.

Episodes of elation were present in a few of the UCLA subjects, in some to a degree that could be called mania. In a few subjects episodes of both depression and elation had occurred, sufficient to suggest a bipolar pattern. True manic-depressive disease was notably uncommon in this group, however.

Finally, a number of the UCLA epileptics reported periods of irritability. The symptomatology ranged from hostility and anger to emotional lability with impulsive responses. In some the episodes appeared related to environmental stresses, in others to use of a specific medication and in still others the episodes appeared out of context and may have represented an ictal change. Most often the episodes of irritable behavior were not related to depression.

The variability of affective symptomatology was broad and may be considered to represent a cross section of affective disturbances in the public as a whole. The increased frequency of affective problems in the epileptic populations surveyed would suggest, however, that affective disorders represent a particularly troublesome problem for epileptics.

Two major findings can be inferred from the UCLA study. First, the high prevalence of depression among epileptics suggested by both of the earlier studies is further confirmed in a considerably different epileptic population, one that had been carefully screened to exclude serious psychiatric disease. Second, a great variety of depressive phenomenology was described by these epileptics. Whether the variations in symptomatology represent specific relationships to seizure type, frequency, control, duration, or to family and personal background, medication effect or other extrinsic factors is the subject of an ongoing investigation.

DISCUSSION

One obvious observation from these studies is that epidemiologic studies of epilepsy are difficult. None of the populations that were available for study could be considered "typical"; all were strongly skewed in one or more aspects. The very low socioeconomic class of the vocational rehabilitation groups, the major psychiatric problems of the Brentwood group, and the intractible epilepsy, surgical-candidate status of the UCLA group are all relatively uncommon in general epilepsy practice. Other seizure populations, however, including seizure clinics, also serve a skewed and variable population; even the private practitioner's group of seizure patients is abnormal in that the indigent, the behaviorally abnormal and the difficultto-control epileptics are referred to academic centers. The three groups reported here were chosen on the basis of availability and these results are not presented as bona fide epidemiologic investigations; nonetheless, the findings among the three disparate epileptic populations are sufficiently consistent and commanding that a number of pertinent interpretations can be suggested.

First, the present study clearly demonstrates that depression represents a major psychiatric problem for some epileptics. This observation has been presented by other authors (10, 12, 13, 15). Betts (16) considers depression one of the more significant psychiatric problems of epilepsy and also suggests that epilepsy may cause a variety of significant affective disorders. Barraclough (12) also notes that depression is a significant problem in epilepsy and has given particular emphasis to suicide statistics. A few authors (17, 18, 19) have reported depressive phenomena in epilepsy and, conversely, some (20, 21) note that epileptic phenomenology such as *deja vu*, hallucinations, metamorphosias etc. are unexpectedly frequent in patients with serious affective disorder, raising the question of a relationship between depression and epileptic phenomena. These represent only scattered and infrequent reports, however; relatively little attention has been given to depression as a psychiatric complication of epilepsy. Most explanations of depression in epilepsy continue to emphasize reactive phenomena based on the uncertainty caused by a disorder in which the individual episodically loses full control of his or her actions. The results demonstrated by our studies suggest that, while the epileptic may suffer a reactive depression, a variety of other types of depression are also present in this population and at least some may be seizure oriented.

The UCLA study demonstrated that phenomenologically different types of depression occur in epileptic subjects. Some of these appear to be seizure related, some related to medications, and some may represent an emotional reaction to the presence of seizures but some appear to be interictal behavioral problems. While the UCLA study is not yet sufficiently advanced to confirm the phenomenological types, the importance of affective disorder in the management of epilepsy is strongly implied.

While an association between depression and socioeconomic factors has long been suggested, data from our studies suggests that this may have been overrated in the epileptic population. Similar rates of depression were found in two socially different epileptic populations. On the other hand, evidence for a relationship in some seizure patients between depression and specific epileptic phenomena, both ictal and interictal, appears convincing. Investigation of the latter relationship may provide data of value for future understanding of both affective disease and epilepsy.

If depression is present in an epileptic, the problem may demand specific therapy to achieve optimum control of the epilepsy. It would also appear that if epileptic depression is to be treated, the type of depression must be carefully outlined and the treatment modeled for the particular type of depression. Data for this approach must await clearer definition of the types of depression and experience with management of depression in the epileptic subject.

The studies reported here offer a basis for future investigations of the relationship of epilepsy and depression. Many questions can be asked. Is there an anatomical disturbance such as a limbic (or non-limbic) dysfunction that underlies some types of epileptic depresion? Is there a hemispheric factor with different manifestations of affective disorder dependent upon whether the left or right hemisphere is the site of the seizure focus? Is there an association between epileptic depression and pharmacological effects and/or neurotransmitter disorders? Is an association with social and/or environmental factors important in the production of some types of depression in the epileptic? All of these questions remain unanswered and speculative.

Future investigations of epilepsy should include not only improved seizure control through pharmacologic, surgical or other management and correlation of seizure phenomena with the electrophysiological concomitants of the ictal discharge, but an interest in both ictal and interictal behavior alterations. Optimal management of the epileptic patient demands not only seizure control but attention to and treatment of any concomitant emotional/behavioral disturbances. Depression appears to be the most frequent and one of the most dangerous behavioral disturbances associated with epilepsy.

TABLE 1

Responses of Epileptic and Non-epileptic Disabled Subjects Epi-Hab Study

	Epileptics	Non-Epileptics
Age	32.7	35.7
M/F Ratio	56/44	51/49
Social rejection	46.2	21.9 *
Job discrimination	42.7	23.9 ***
Psychiatric illness	37	14.5 ***
Medication side effects	23.8	4.6 ***
Attempted suicide	29.9	7.2 ***
Wish to be dead	29	14.5 *
Hopelessness	54.7	30.4 ***
Angry outbursts	46.4	23.2 ***
Suspect deception by others	45.9	27.5 **
Humorlessness	30.4	11.4 ***

Results are reported in percentages. Level of significance of differences between epileptic and non-epileptic disabled subjects:

* = p > 0.05
** = p > 0.01
*** = p > 0.001

TABLE 2

Characteristics of Epileptic and Non-Epileptic Depressed Subjects Brentwood VA Study

	Epileptic (n = 22)	Non-Epileptic (n = 22)
Age	40 ± 2.09	49 ± 2.58 *
M/F Ratio	17/5	21/1
Age of onset	30.7 ± 1.99	27.1 ± 2.36
History of drug or alcohol abuse	8	13
Family history of major depression	3 (13.6 %)	12 (54.4 %) *
Depression with psychotic features	16 (72.2 %)	7 (31.8 %) *
Hamilton scores	22 ± 1.08	25.5 ± 1.5
BPRS scores	26.6 ± 1.72	24.7 ± 1.35

* p = > 0.01

TABLE 3

Types of Affective Disorder in Epilepsy UCLA Study

1) Major depressive episodes
2) Transient depressive episodes
   a) out of context
   b) in context
3) Chronic sadness - (dysthymic)
4) Chronic detachment - (depersonalization)
5) Elation
6) Bipolar affective disorder
7) Irritability syndrome

SUMMARY

Questionnaire evaluation of 503 epileptics who were either in a vocational rehabilitation program or being counseled for job training and a group of 186 non-epileptic disabled in the same status revealed that 50.4 % of the epileptics reported significant depressive symptomatology compared to 30.4 % of the non-epileptic controls. Even more striking, 29,9 % of the epileptics had attempted suicide compared to 7.2 % of the non-epileptics. Serious depression is a factor of significance in epilepsy.

To probe this further, all epileptics admitted to a VA neuropsychiatric hospital in one month were evaluated. This amounted to almost 10 % of all admissions but when individuals with known brain trauma, old leukotomies, end stage dementia etc. were excluded, 6.8 % of admissions were epileptics; this is almost 7 times the prevalence of epilepsy in the community. 82.1 % of these were admitted for affective disorder, compared to 17 % of the total admissions during that period.

From the VA group 22 epileptic-depressed were matched with 22 non-epileptic depressed admitted the same month and each was interviewed. A number of distinctive features were noted: 1) psychotic features (delusions, persecutory auditory hallucinations, depersonalization) were far more prevalent among the epileptics; 2) the age of onset of depression was later in the epileptics; 3) epileptic depression was more chronic (less cyclic); 4) family history was four times greater (56 % vs. 13 %) among the non-epileptic depressed; 5) response to antidepressants was consistently poor among the epileptics.

Some of the epileptic patients related worsening of the affective disorder to flurries of spells but otherwise no clear relationship between seizure frequency, type of epilepsy or medication could be determined. However, of the 11 cases with unilateral seizure activity on EEG, 10 showed the abnormality on the left side.

RESUMEN

Evaluación cuestionaria de 503 epilépticos que estaban unos en un programa de rehabilitación vocacional, otros siendo dirigidos en educación laboral y un grupo de 186 no epilépticos de igual modo inhabilitados, revelaron que el 50.4 % de los epilépticos manifestaron una significativa sintomatología depresiva comparado a 30.4 % de los no epilépticos en control. Aun más sorprendente 29.9 % de los epilépticos habían intentado suicidio comparado a 7.2 % los no epilépticos. Una seria depresión es un factor significativo en la epilepsia.

Para registrar estos con amplitud, todos los epilépticos admitidos en un hospital neuropsiquiátrico de veteranos (VA) en un

mes, fueron evaluados. Esto alcanzaba a casi 10 % de todas las admisiones; pero cuando individuos con conocido trauma cerebral, viejas leucotomías, demencias en estado terminal, etc. fueron excluídos, 6.8 % de las admisiones eran epilépticos; esto es casi siete veces el predominio de la epilepsia en la comunidad. 82.1 % de estos fueron admitidos por desórdenes efectivos, comparados al 17 % del total de las admisiones durante este período.

Del grupo VA 22 epilépticos deprimidos fueron comparados con 22 no epilépticos deprimidos, admitidos el mismo mes y cada uno fue entrevistado. Un número de aspectos distintos fue apreciado: 1) Aspectos psicóticos (ilusiones, alucinaciones auditivas persecutivas, despersonalización) prevalecían mucho más en los epilépticos; 2) la edad de comienzo de la depresión fué posterior en los epilépticos; 3) depresión epiléptica fue más crónica (menoscíclica); 4) historia familiar fué cuatro veces mayor (56 % frente a 13 %) entre los deprimidos no epilépticos; 5) la respuesta a los antidepresivos fue notablemente pobre entre los epilépticos.

Algunos de los pacientes epilépticos relacionaron empeoramiento del desorden afectivo a repetición de crisis; pero en otros aspectos no pudo ser determinado una clara relación entre la frecuencia de la crisis, tipo de epilepsia o la medicación. No obstante, los 11 casos con actividad unilateral crítica al EEG, 10 mostraron la anormalidad en el lado izquierdo.

RÉSUMÉ

Evaluation de 503 épileptiques qui étaient ou en programe de réhabilitation vocationelle ou en education laborale et un groupe de 186 no épileptique mais egalement inaptes. L'étude a montré que le 50,5 % des épileptiques n'avaient presque pas de symptomes dépressifs comparés aux 30,4 % des non épileptiques 29,9 % des épileptiques avaient tautés le suicide, comparés a 7,2 % des non épileptiques. Une dépression sérieuse est un facteur important chez l'epileptique.

Pour enrégister cela avec amplitude, tous les epi admis dans un Hopital neuropsiquiatriqueque de Vétérants, en un mois ont éte valorés ceci refresentait el 10 % des admitions. Mais des traumas cérébraux connus, vieilles leucotomies, démences terminales, etc, furent exclues. 6,8 % des admitions était épileptiques, 7 fois le pourcentage moyen de l'epi dans la comunauté. 32,1 % furent admis pour des troubles afectifs a comparer avec le 17 % du total des admition pendant cette periode.

Du groupe des veterants, 22 épileptiques depressife furent comparés avec 22 depressifs non Epi, admis la meme mois. Tous et chaqum furent entrevus. Divers aspects fures apréciés.

1) L'aspect psichotique (ilusions, allucinations auditives, persécutoires, depersonalisation), predomine chez l'epi.

2) L'age du debut de la depression augment e chez l'épileptique.

3) La depression épileptique est plus chronique mons cyclique.

4) L'histoire familiale est plus riche (56 % contre 13 %) que chez les depressifs no épi.

5) La reponse aux anti dépressifs est pauvre chez l'epi.

Quelques patients "epi" rapportieent un agravement des desordres, avec repetition des orises; mais d'autre part on a pas put voire une relation évidente entre la frecquence de la crise, le type d'épileptic, la therapeutique.

Néamoins des 11 cas avec activité critique unilaterale a l'EEG 10 out montrés une anormalité du coté gauche.

ZUSAMMENFASSUNG

Es werden die Frageboegen von 503 Epileptikern ausgewertet, die einerseits einem vokationellen Rehabilitierungsprogram unterworfen waren, und zum anderen Teil in

der Arbeitstherapie angele itet worden waren, und einer Gruppe von 186 nicht - epileptischen Patienten, die auch behindert waren. Man fand, dass 50,4 % der Epileptiker unter bedeutender depressiver Symptomatoliegie litten, gegenueber 30,4 % der nicht-Epileptiker. Noch ueberraschender, dass 29,9 % der Epileptiker Selbstmordversuche gemacht hatten, gegenueber 7,9 % dernicht-Epileptiker. Schwere Depression ist ein bedeutender Faktor bei der Epilepsie.

Um des Studium dieses Faktors zu vertiefen, wurden alle in einem Monat in einem neuropsychiatrischen Spital der Veterans Administration (VA) internierte Epileptiker statistisch erfasst. Sie betrugen fast 10 % aller Internierten. Jedoch nachdem alle Kranken mit Gehirntaumen, alten Leukotomien und Irresein im Endstadium ausgeschlossen waren, waren die Epileptker 6,8 % aller Internierten. Das ist ungefaehr das siebenfache der Exis tenz von Epileptikern in der Gemeinschaft. 82,7 % dieser Epileptikerwurden wegen affektiver Stoerungen interniert gegenueber 17 % der gesammten Inernierungen in diesem Zeitabschnitt.

Inder Gruppe der VA wurden 22 deprimierte Epileptiker mit 22 nicht-epileptischen Deprimierten verglichen, die indemselben Monat interniert worden waren und befragt. Man stellte eine Reihe vonverschiedenen Aspekten fest:

1) psychotische Aspekte (Illusionen, auditive Persekutions-Halluzinationen, Depersonalisation) herrschten vielmehr bei den Epileptikern vor. 2) Das Alter in dem die Depression begann war bei den Epileptikern hoeher. 3) Die epileptische Depression war chronischer (veniger zyklisch). 4) Die Familienge schichtewar viermal haeufiger bei den nicht-epileptischen Deprimierten (56 % gegenueber 13 %). 5) Die Reaktion a uf Antidepressiva war bei den Epileptikerns sichtlich gering.

Einige der Epileptiker bezogen die Verschlimmerung der affektiven Stoerungen auf die haeufige Wiederholung der Krisen; aber in anderer Hinsicht konnte keine klare Beziehung zwischen der Haeufigkeit der Krisen, dem Epilepsietyp und der Behandlung ermittelt werden. Immerhin, bei 11 Faellen von einseitiger epileptischer Aktivitaet im EEG zeigten 10 die Anormalitaet auf der linken Seite.

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Midbrain Neural Mechanisms Mediating Emotional Behaviour

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INTRODUCTION

Investigations, in animals, of the basic mechanisms within the central nervous system (CNS) that mediate emotion are limited, for the most part, to the study of the behavioural manifestations of emotional states such as anger and fear. In the situation, for example, of a cat seeking to defend itself when confronted by a dog, the reaction includes: autonomic responses such as pupillary dilatation, piloerection, increased heart rate, increased blood pressure, and altered patterns of regional blood flow: and somatomotor responses, such as retraction of the ears, arching of the back, vocalization (hissing, growling, howling) and often attack or flight. The classical work of Hess and Brügger (1943), Hunsperger (1956), and Abrahams, Hilton and Zbrozyna (1964) established that co-ordinated behavioural and cardiovascular reactions, seemingly identical to those evoked naturally, could be elicited by electrical stimulation of specific brain regions (e.g. hypothalamus, midbrain) in the cat and it has been assumed from such experiments that important "centres" which integrate the cat's reaction to a real or perceived threat, hereafter referred to as the "defence reaction", are located in these parts of the CNS. Although the most detailed analysis of the neural basis of such behaviour has been carried out for the cat, and it is these data which largely provide the basis for this review, it should be noted that electrical stimulation of the hypothalamus or midbrain has elicited species-specific defence reactions in animal species as diverse as the bluegill (Demski and Knigge, 1971), green iguana (Distel, 1976), chicken (Andrews and Oades, 1973; Phillips and Yourgren, 1971), rat (Panksepp, 1971; Waldbilling, 1975; Woodworth, 1971), guinea pig (Martin. 1976), opossum (Roberts, Steinberg and Means, 1967), and several species of monkey (Jurgens and Pratt, 1979; Lipp and Hunsperger, 1978; Robinson, Alexander and Bowne, 1971). However, in none of the animals studied, including the cat, has the precise neural organization which subserves the defence reaction been adequately defined. One problem has been that it is not possible, with the technique of electrical stimulation, to determine the exact location of those hypothalamic and midbrain neurones whose excitation elicits defensive behaviour, because such stimulation excites both cell bodies and axons of passage. An alternative method of exciting central neurons is to use excitatory amino acids such as, L-glutamic acid, L-aspartic acid, D,L-homocysteic acid, (Bandler, 1984; Bandler, De Paulis and Vergnes, 1985; Goodchild, Dampney and Bandler, 1982; Neil and Loewy, 1982; Urca, Nahin and Liebeskind, 1980). As it is well established that such excitatory amino acids excite cell bodies and dendrities of neurones but not axons (Curtis and Johnston, 1974; Freis and Zeigelgansberger, 1974), the elicitation of a defence reaction by injections of excitatory amino acids within the hypothalamus or midbrain would demonstrate that this reaction is due to the specific excitation of neuronal cell bodies. In the data to be described this method has been used to delineate a part of the midbrain which contains neurones whose excitation elicits both behavioural and cardiovascular components of the defence reaction. As well, the afferents to this midbrain region have been studied by means of the retrograde transport of horseradish peroxidase.

MIDBRAIN CONTROL OF THE DEFENCE REACTION

Traditionally, the hypothalamus has been considered to be the final integrating centre for the organiaztion and control of defensive behaviour (Bard, 1928; Hess, 1957; Clemente and Chase, 1973; Smith and De-Vito, 1984) Certainly, in the cat, electrical stimulation within a large extent of the medial hypothalamus elicits a defense reaction (Hess and Brügger, 1943; Hunsperger, 1956; Nakao, 1958; Wasman and Flynn, 1962); and after either high decerebration (i.e. ablation of the telencephalon and diencephalon) (Bard, 1928; Bard and Macht, 1958) or surgical isolation of the hypothalamus (Ellison and Flynn, 1968) it has been reported that the thresholds for eliciting a defence reaction (by tactile stimulation) are significantly elevated. In contrast, if even a small portion of the posterior hypothalamus is spared the thresholds for eli-

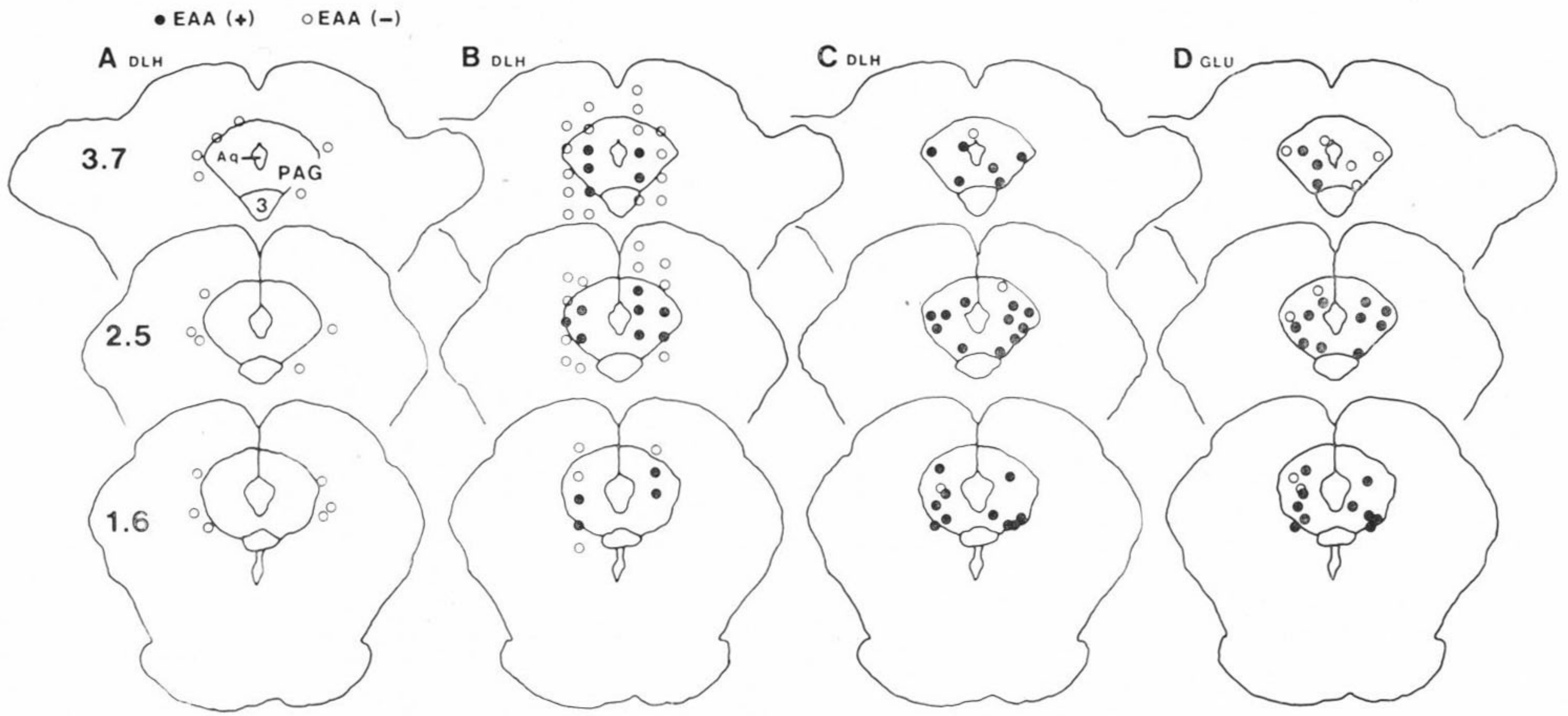

Fig. 1. — *A. Sites (open circles) in the midbrain tegmentum from which the facio-vocal signs of the defence reaction were elicited by electrical stimulation but not by DLH microinjections. B. Results of ten experiments in which DLH microinjections were made in a series of 1.0 mm, dorsal to ventral, steps through the midbrain. Sites at which the DLH microinjections elicited the facio-vocal signs of the defence reaction are indicated by filled circles. Sites at which the DLH microinjections were ineffective are indicated by open circles. C. Sites within the PAG at which both electrical stimulation and DLH microinjections elicited a defence reaction are indicated by filled circles. Sites within the PAG at which electrical stimulation elicited a defence reaction, but DLH microinjections did not are indicated by open circles. D. Sites within the PAG at which both electrical stimulation and GLU microinjections elicited a defence reaction are indicated by filled circles. Sites within the PAG at which electrical stimulation elicited a defence reaction, but GLU microinjections did not are indicated by open circles. Abbreviations: Aq, midbrain aqueduct; PAG, periaqueductal grey matter; 3, oculomotor nucleus. Coronal sections of the midbrain correspond to sections Ant. 3.7, Ant. 2.5 and Ant. 1.6 from the stereotaxic atlas of the cat brainstem of Berman (1968). For details see Bandler (1982), and Bandler, Prineas and McCulloch (1985).*

citing the defence reaction remain normal. Although these data indicate that the hypothalamus plays an important part in the initiation of emotional behaviour and perhaps a key role in the setting of levels of emotional responsiveness, a large additional body of data suggest that the midbrain contains neurones capable of mediating, independent of the hypothlamus, a fully integrated defence reaction (including attack). First, electrical stimulation of the central midbrain region (i.e. periaqueductal gray matter (PAG) and adjacent tegmentum) readily elicits an integrated defence reaction (Fernandez DeMolina and Hunsperger, 1962; Hunsperger, 1956; Skultety, 1963). Second, single neurones which dramatically increase their firing rates concomitant with the elicitation of a defence reaction have been found within this central midbrain region, but not within the medial hypothalamus (Adams, 1968). Third, lesions made in the central midbrain region eliminate or suppress the defence reactions elicited either by natural stimuli (e.g. handling, threat or attack by another animal) or by electrical stimulation of the hypothalamus (Fernandez De Molina and Hunsperger, 1962; Hunsperger, 1956; Skultety, 1963); whereas in contrast after either surgical isolation of the hypothalamus (Ellison and Flynn, 1968), or large medial hypothalamic lesions (Fernandez De Molina and Hunsperger, 1962), or high decerebration (Bard and Macht, 1958; Keller, 1932) integrated defence reactions can still be elicited either by natural stimuli (e.g. tail pinch) or by electrical stimulation of the midbrain.

IDENTIFICATION OF MIDBRAIN NEURONES MEDIATING BEHAVIOURAL COMPONENTS OF THE DEFENCE REACTION

In our initial study in the cat (Bandler, 1982) it was found that when microinjections of L-glutamaic acid were made at either midbrain or hypothalamic sites from which a defence reaction had been elicited previously by electrical stimulation, none of the hypothalamic and only some of the midbrain injections elicited the facio-vocal signs of the defence reaction. Additional experiments have made it possible to more precisely localize that portion of the mid brain which contains neurones whose excitation elicits a defence reaction (Bandler, 1984; Baadler, Prineas and McCulloch, 1985). In these experiments, injections of the excitatory amino acids, 1.0M L-glutamic acid (GLU), 1.0M L-aspartic acid (ASP) and 100mM D,L-homcysteic acid (DLH), were made at the same midbrain sites at which electrical stimulation had previously elicited a defence reaction. By making the injections in a conscious cat whose head was fixed by a restraining device, it was possible to inject small volumes (0.05μl), by directly lowering the microsyringe needle, through a guide cannula, to the same site that had been previously stimulated electrically.

Although electrical stimulation at many sites in the midbrain tegmentum adjacent to the midbrain periaqueductal grey region (PAG) readily elicits an integrated defence reaction, all excitatory amino acid injections at these sites failed to elicit the facio-vocal signs of the defence reaction (Fig. 1A). These results have been confirmed and extended in additional experiments in which a series of 100mM DLH (0.05μl) microinjections were made, in the same cats, in approximately 1.0mm, dorsal to ventral, steps through the midbrain. Consistent with the earlier results, injections of DLH in the midbrain tegmentum either dorsal or ventral to the PAG generally failed to elicit a defence reaction (Fig. 1B). In contrast to these results, injections of 1.0M GLU, 1.0M ASP, and 100mM DLH at most sites within the PAG elicited in the head-restrained cat, the facio-vocal signs of the defence reaction. These included pupillary dilatation, piloerection, retraction of the ears, hissing, growling, howling and often biting to tactile stimulation of the lips. Such reactions were usually evoked within the first 10-15 sec. following the completion of an injection. Control injections suggested that non-specific effects (e.g. osmolarity, buffering, pH) did not contribute to the elicitation of the defence reaction. Important differences were observed between the effects of 100 mM DLH and those of 1.0M GLU or 1.0 M ASP. The DLH-induced defence reactions were of longer duration (120 sec) than those following injections of either GLU (41 sec) or ASP (69 sec). Also, DLH was more effective than GLU or ASP in eliciting a defence reaction at the most rostral level of the PAG studied (Ant. 3.7). The results for PAG injections of DLH and GLU are shown in Fig. 1C and 1D respectively. Several factors which may have contributed to the longer duration of action of DLH and its greater effectiveness within the rostral PAG are its high potency (Curtis and Johnston, 1974) and the fact that, unlike L-GLU and L-ASP, the D-isomer of D,L-homocysteate is not a substrate for uptake mechanisms (Balcar and Johnston, 1972; Cox, Headley and Watkins, 1977).

It has been suggested (Hamilton, 1973; Liu and Hamilton, 1980) that the PAG should be subdivided, on the basis of differences in morphology and anatomical connections, into distinct subnuclei (e.g. dorsal, medial, lateral). The functional significance of these anatomical differences remains, however, to be established. That the facio-vocal signs of the defence reaction were evoked from injection sites located either dorsal, ventral, immediately adjacent or lateral to the aqueduct (Fig. 1C, 1D) suggest that within the limitations of our methodology, the neural substrate for the defence reaction is not restricted to any one PAG subnucleus. However, it was found, for GLU injections made within the PAG, at the most rostral level studied (Ant. 3.7), that the defence reaction was elicited by injections at only 38 % of the sites (3 of 7); whereas at more caudal levels (Ant. 2.5, 1.6) PAG injections at 79 % of the sites (19 of 25) elicited a defence reaction (Fig. 1D). A similar trend was observed for the ASP injections (Bandler, Prineas McCulloch, 1985). This suggest a possible

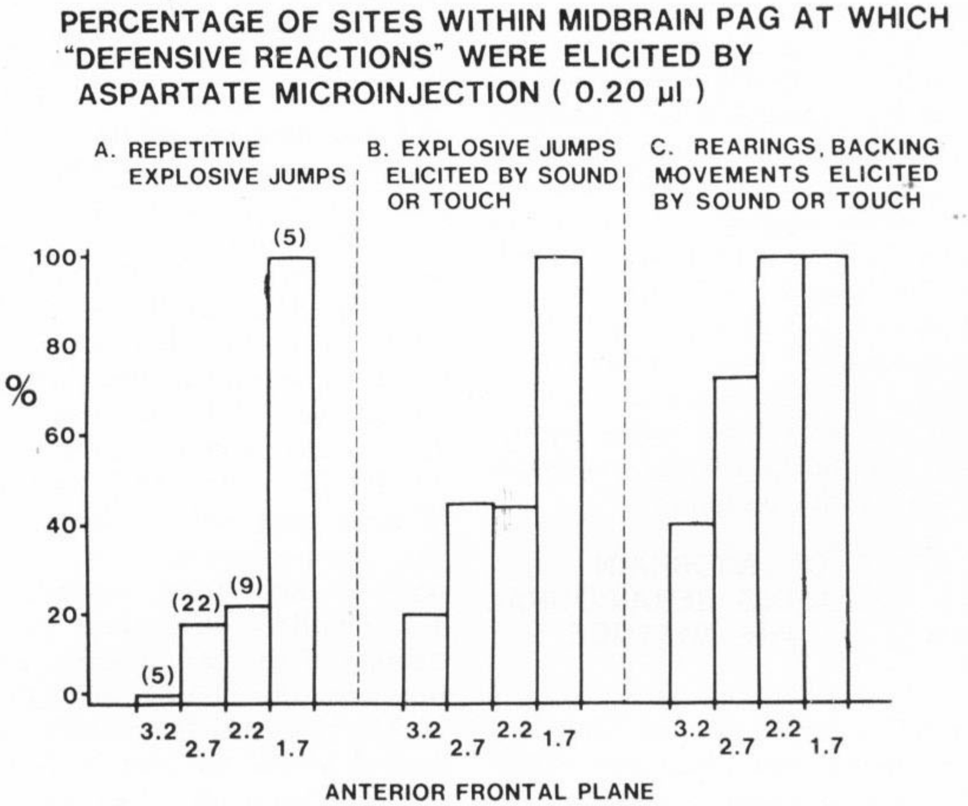

Fig. 2. — *Histogram illustrating the percentage of injection sites within the PAG of the rat, at four different frontal planes, at which three categories of defensive reactions were observed following ASP microinjections. The number of PAG sites injected at each frontal plane is indicated at the top of the first set of bars. The frontal planes, Ant. 3.2, Ant. 2.7, Ant. 2.2, Ant. 1.7 correspond to those from the stereotaxic atlas of the rat brain by Paxions and Watson (1982). For details see Bandler, Depaulis and Vergnes (1985).*

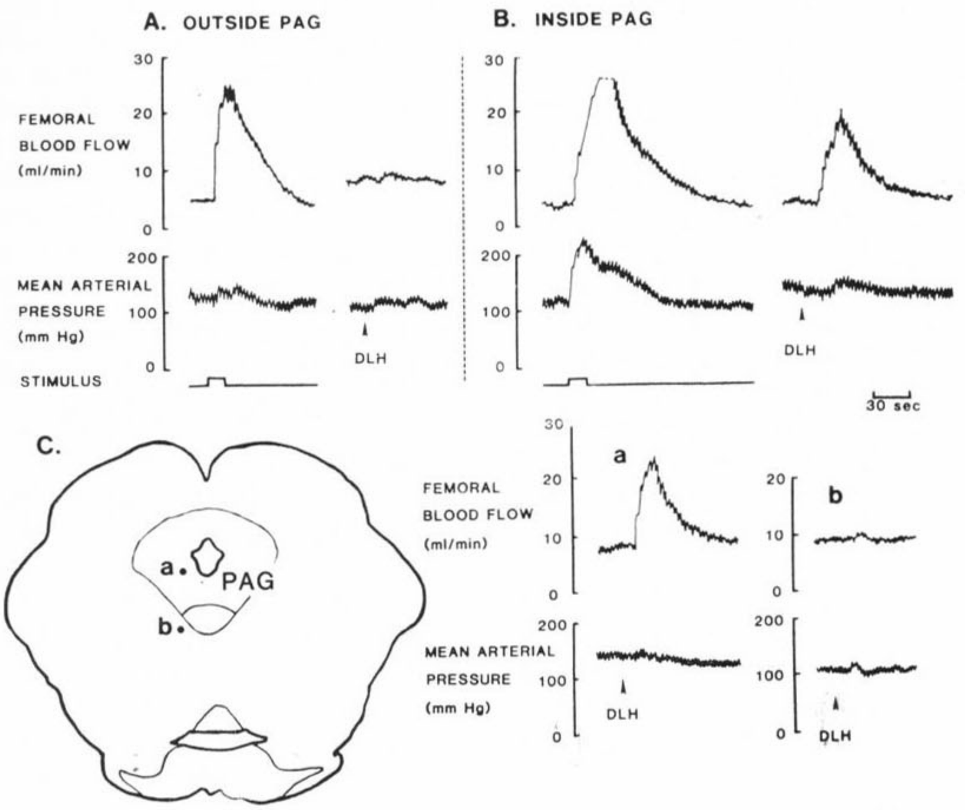

Fig. 3. — *A. Comparison of the cardiovascular responses evoked by electrical stimulation and DLH microinjection at a representative site in the midbrain tegmentum adjacent to the PAG. B. Comparison of the cardiovascular responses evoked by electrical stimulation and DLH microinjection at a representative site within the midbrain PAG. C. Comparison of the cardiovascular responses evoked by DLH microinjection at two midbrain sites ("a" and "b") separated by 2.0 mm. The arrows indicate when the DLH microinjections were made. For details see McDougall, Dampney and Bandler (1985).*

preferential localization, within the more caudal parts of the midbrain PAG, of neurones whose excitation elicits a defence reaction.

That the facio-vocal signs of the defence reaction were usually elicited within 10-15 sec of the excitatory amino acid injections suggests that the population of neurones whose excitation elicits this reaction lie close to the tip of the injection cannula. Although there is no method for precisely measureing the extent of the effective spread of the injected excitatory amino acids the fact that injections made into the tegmentum bordering the PAG never elicited a defence reaction, coupled with the finding of rostral-caudal differences in the effectiveness of injections (i.e. GLU and ASP) made within the PAG, is consistent with earlier suggestions that the effective spread of excitatory amino acids, when injected in these volumes and concentrations is probably not more than 1.0mm (see also Goodchild, Dampney and Bandler, 1982; Tan and Dampney, 1983).

It remains of course to be determined if microinjections of excitatory amino acids into the midbrain PAG of the unrestrained cat elicit a defense reaction comparable to that elicited by electrical stimulation or by a natural threat situation. Such experiments are currently being carried out in our laboratory and the preliminary results indicate that all components of either the naturally evoked or the electrically elicited defence reaction, with the possible exception of attack, can be elicited by microinjections of DLH into the PAG of the unrestrained cat. Recently we completed a study in which microinjections of excitatory amino acids were made into the midbrain of the unrestrained rat (Bandler, De Paulis and Vergnes, 1985). For the rat, defensive behaviour, characterised in its most intense form by flight (i.e. explosive jumps) rather than by submission, was readily elicited by 0.20μl injections of 1.0M ASP into the midbrain PAG. Such behaviour was significantly less frequently elicited by injections into the tegmentum adjacent to the PAG. Of particular interest was the finding that the excitatory amino acid injections were most likely to elicit defensive behaviour if made within the most caudal portions of the midbrain PAG studied. These results are shown in Fig. 2. Thus, extreme defensive behaviour (i.e. spontaneous jumps), moderate defensive behaviour (i.e. jumps elicited by sound or touch), and mild defensive behaviour (i.e. rearings, backing movements elicited by sound or touch), were each more readily elicited if the ASP injections were made at sites in the caudal part of the PAG (Ant. 1.7, 2.2) than if they were made at sites in the most rostral part of the PAG (Ant. 3.2). Taken together, the results for PAG injections of excitatory amino acids in both the rat and the cat suggest that the neurones whose excitation elicits behavioural components of the defense reaction are more prevalent in the caudal parts of the midbrain PAG.

MIDBRAIN NEURONES MEDIATING CARDIOVASCULAR COMPONENTS OF THE DEFENCE REACTION

The experiments in the cat and rat have demonstrated the existence, within the midbrain PAG, of neurones whose excitation elicits behavioural components of the defence reaction. This raises the question as to whether the excitation of the same population of PAG neurones elicits any of the Cardiovascular components of the defence reaction. As a first step towards answering this question, a series of experiments were

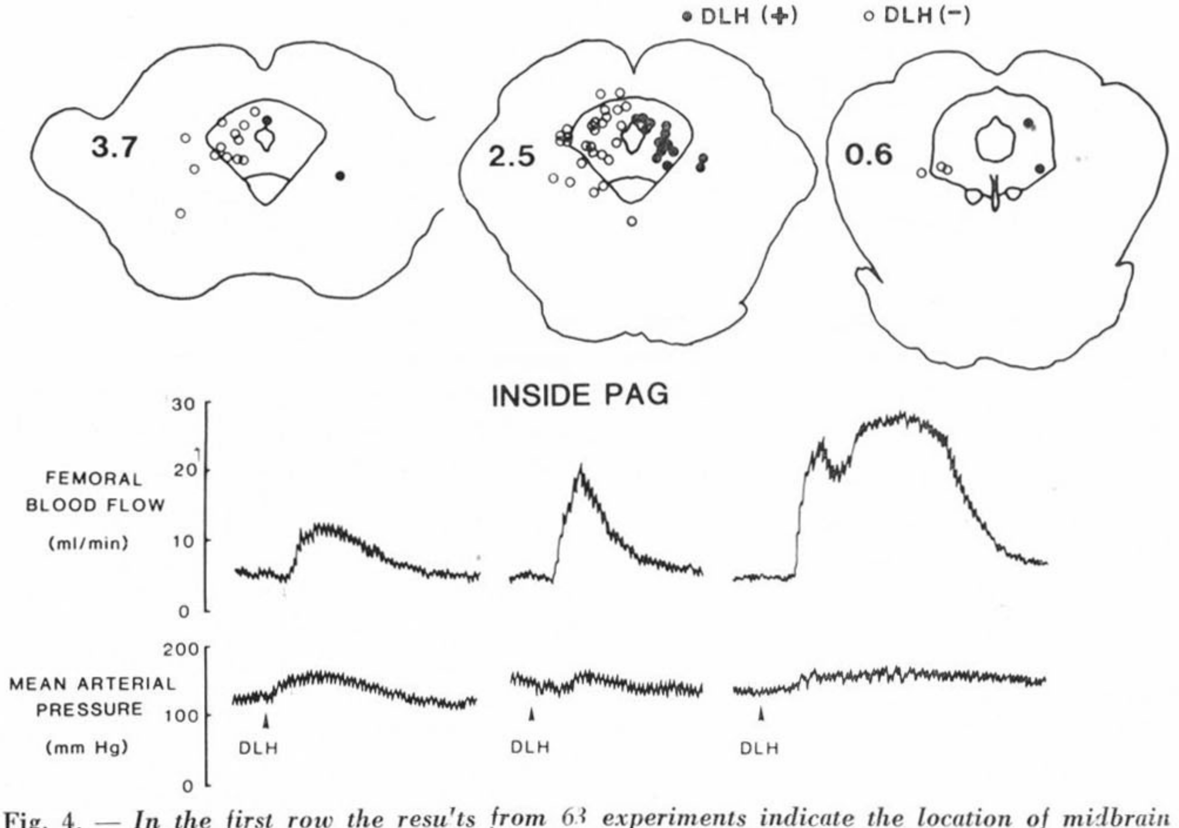

Fig. 4. — *In the first row the resu'ts from 63 experiments indicate the location of midbrain sites at which DLH was injected. The 18 sites at which a two-fold or greater increase in femoral blood flow was elicited are plotted on the right side of each section (filled circles). The 45 sites at which the DLH injection did not elicit increased femoral flow are plotted on the left side of each section (open circles). The coronal sections correspond to those from the stereotaxic atlas of the cat brainstem of Berman (1968). In the second row are shown the cardiovascular responses evoked by DLH microinjections at three representative sites located inside the PAG. For details see McDougall, Dampney and Bandler (1985).*

undertaken in the anaesthetised, paralyzed and artifically ventilated cat to determine the effect on skeletal muscle blood flow. arterial pressure and heart rate, of selective excitation of cell bodies within both the midbrain PAG and the surrounding midbrain tegmentum (McDougall, Dampney and Bandler, 1985). Emotional stress or threat, such as confrontation with a dog, has been reported previously, in conscious cats, to elicit a cardiovascular response pattern consisting of increased cardiac output, heart rate and arterial blood pressure; vasconstriction of cutaneous, renal and splanchinc beds; and vasodilatation of skeletal muscle beds (Mancia, Baccelli and Zanchetti, 1972, 1974; Martin, Sutherland and Zbrozyna, 1976). A similar pattern of cardiovascular response to threat or stress has been found also in the dog (Caraffa-Braga, Granata and Pinotti, 1973; Martin, et al 1976) and in man (Barcroft, Brod, Hejl, Hirsjarvi and Kitchin, 1960; Blair, Glover, Greenfield, and Roddie, 1959; Brod, Fencl, Hejl and Jirka, 1959).

In our initial experiments, skeletal muscle blood flow has been studied. This provides a general measure, of the extent of the induction of the cardiovascular response pattern characteristic of the defence reaction, since the overall pattern of cardiovascular change is designed to redistribute blood flow in favour of skeltal muscle (Hilton, 1982). In agreement with previous studies (Abrahams, et al 1960; Tan and Dampney, 1983) electrical stimulation readily elicited a three-fold of greater increase in femoral arterial flow from sites both in the midbrain PAG as well as within the deep layers of the superior colliculus and the tegmentum adjacent to the PAG. However, rarely were significant increases in femoral arterial flow obtained with excitatory amino acid stimulation (500mM DLH, 0.40μl) at sites outside the PAG. A comparison of the typical response pattern elicited by electrical and DLH stimulation at a site in the tegmentum adjacent to the PAG can be seen in Fig. 3A. Overall, at only 3 of 22 sites located outside the PAG, did the DLH microinjections elicit increased femoral flow and even for these three sites the increases were relatively small and not sustained.

In contrast, as can be seen in Fig. 4, at 15 of 41 sites within the PAG, DLH microinjections elicited large and prolonged increases in femoral flow. The flow increases usually began 10-20 sec after the injection, and lasted for 60-150 sec. In some cases femoral flow increased 5-7 fold. There was either no change or only a small increase in both arterial blood pressure (up to 30mm Hg) and heart rate (up to 20 beats/min). These changes are comparable to the femoral vasodilator response elicited by electrical stimulation of the midbrain or hypothalamus (Fig. 3B). Additional evidence for a strict localization of these effects to sites within the PAG was suggested by other experiments in which a series of DLH injections were made in approximately 1.5-2.0mm steps through the midbrain. The results of one such experiment are shown in Fig. 3C. Confirming the earlier results, at a site ("a") within the PAG, the DLH microinjection elicited a large increase in femoral flow accompanied by little change in blood pressure, whereas at a site ("b"), 2mm ventral to site "a" and just outside the PAG, the DLH microinjection had little effect. Another interesting result, in our experiments, was the finding of a rostral-caudal difference in the effectiveness of DLH injections made within the PAG. As can be seen in Fig. 4 (first row) for DLH injections made within the PAG, increased femoral flow was elicited by only 1 of 10 injections (10 %) at the most rostral level studied (Ant. 3.7); whereas large femoral flow increases were elicited by 14 of 31 injections (45 %) at more caudal PAG levels. This difference is significant ($p < .05, x^2$).

To summarize, the results of both the behavioural and cardiovascular experiments indicate that the midbrain PAG contains a population of neurones whose excitation elicits both behavioural and cardiovascular components of the defence reaction. Further, there is evidence of a functional heterogenity of neurones within the PAG, neurones whose excitation elicit either behavioural or cardiovascular components of the defence reaction being found within the more caudal parts of the PAG that were explored. This suggests that both the cardiovascular and behavioural components of the defence reaction are evoked by excitation of a common population of PAG neurones. However, to establish this it will be necessary to study both the cardiovascular and behavioural changes evoked by excitation of midbrain neurones, in the same animal, and under the same experimental conditions.

AFFERENTS TO MIDBRAIN NEURONES MEDIATING THE DEFENCE REACTION

Previous studies of the anatomical connections of the PAG have attempted often to relate the revealed connections to presumed roles played by the PAG in one of a number of functions (e.g. stimulation-induced analgesia (Hardy and Leichnitz, 1981; Manyth, 1982); vocalization (Jurgens and Pratt, 1979); sexual behaviour (Pfaff, 1980). However, one problem in making such functional-anatomical correlates has been the difficulty of precisely localizing, within the PAG, neurones whose excitation has particular functional consequences. Our use of microinjections of excitatory amino acids has allowed us to localize, within the midbrain PAG, a population of neurones whose excitation has a specific behavioural effect. This makes it possible to directly approach the question of specific PAG functional-anatomical relationships by studying the afferent and efferent projections of those midbrain PAG sites at which excitatory amino acid injections elicit a defence reaction. As a first step, we have studied the sources of forebrain and brainstem afferents (as revealed by the retrograde transport of horseradish peroxidase (HRP) to the same PAG sites at which GLU and DLH microinjections previously elicited the facio-vocal signs of the defence reaction (Bandler and McCulloch, 1984; Bandler, McCulloch and Dreher, 1985; Bandler and Prineas; in prep.). TELENCEPHALIC AFFERENTS TO THE PAG: Over 98 % of all HRP-labelled telencephalic neurones were found in the ipsilateral cerebral cortex. All of the cortical cells sufficently labelled to reveal their morphology were pyramidal neurones located in lamina 5. This is consistent with the general principle that cortical projections to the brainstem originate from the deep pyramidal layer of the cortex (Jones, 1981). Sixty percent of the labelled telencephalic neurones were found in frontal cortical regions: (a) the medial frontal cortex along the banks of the rostral two-thirds of the cruciate sulcus (cytoarchitectonic areas 4 and 6); (b) the medial frontal cortex ventral to this region (area 32); (c) the extension of area 6 onto the lateral cortical surface surrounding the presylvian suclus. A much smaller number of labelled neurones were found in the anterior cingulate cortex. The other major telencephalic cortices which contained a large proportion of labelled neurones were the orbito-insular cortex (INS) and the cortex surrounding the rostral one-half of the anterior ectosylvian sulcus (AES). The major cortical sources of afferent projections to the PAG are shown schematically in Fig. 5 and a histogram illustrating the percentage of the total number of HRP labelled neurones that were found in each telencephalic region is shown in Fig. 6. A different distribution and pattern of HRP labelled neurones was observed following control injections of HRP, at midbrain sites (in the tegmentum adjacent to the PAG) at which excitatory amino acid injections did not elicit a defence reaction. This suggests that the effective spread of HRP in the experimental animals was largely confined to the PAG.

Several observations are suggested by the data. First, the most heavily labelled regions were the primary motor cortex (area 4) and that portion of the medial prefrontal cortex (areas 6 and 32) which appears to correspond to the "frontal oculomotor area" (Guitton and Mandl, 1978a,b). Functionally, it has been suggested that this later region is involved in the selection of visual targets to be brought onto the retinal area of high acuity (i.e. the area centralis). Thus, while earlier speculations about projections from medial prefrontal cortex to the PAG have emphasized a role in the modulation of emotional behaviour, including particularly the affective component of nociception (e.g. Hardy and Leichnitz, 1981, Manyth, 1982), these data suggest that frontal cortex-PAG connections may play,

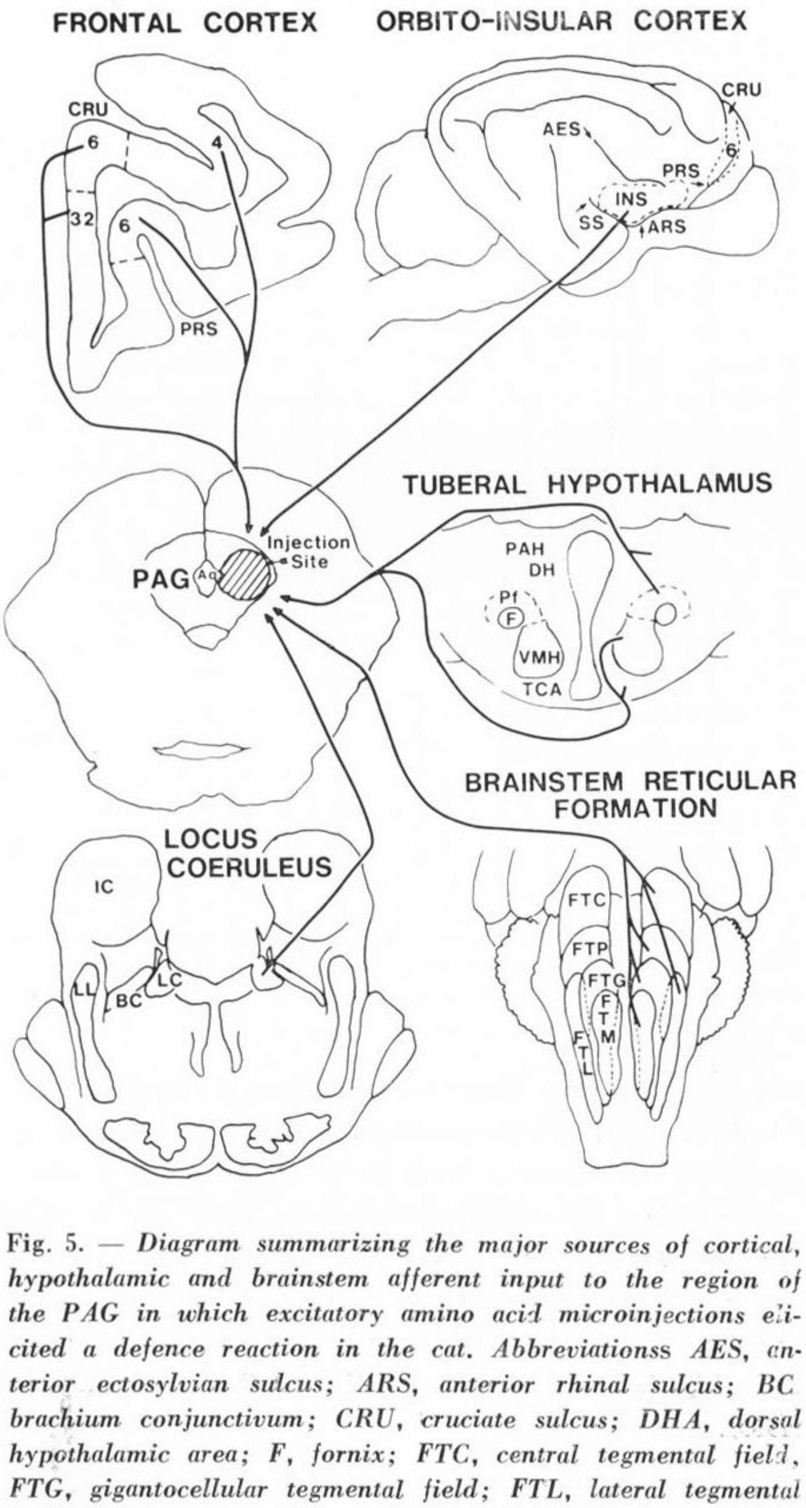

Fig. 5. — *Diagram summarizing the major sources of cortical, hypothalamic and brainstem afferent input to the region of the PAG in which excitatory amino acid microinjections elicited a defence reaction in the cat. Abbreviationss AES, anterior ectosylvian sulcus; ARS, anterior rhinal sulcus; BC brachium conjunctivum; CRU, cruciate sulcus; DHA, dorsal hypothalamic area; F, fornix; FTC, central tegmental field, FTG, gigantocellular tegmental field; FTL, lateral tegmental field; FTM, magnocellular tegmental field; FTP, paralemniscal tegmental field; IC, inferior colliculus; INS, orbito-insular cortex; LC, locus coeruleus; LL, lateral lemniscus; PAG, periaqueductal grey matter; PAH, caudal paraventricular hypothalamic nucleus; PF, perifornical hypothalamic area; PRS, presylvian sulcus; SS, sylvian sulcus; TCA, region of the tuber cinereum; VMH, ventromedial hypothalamic nucleus; 4, 6, 32, cortical area 4, 6 and 32 respectively. For details see Bandler and McCulloch (1984) and Bandler, McCulloch and Dreher (1985).*

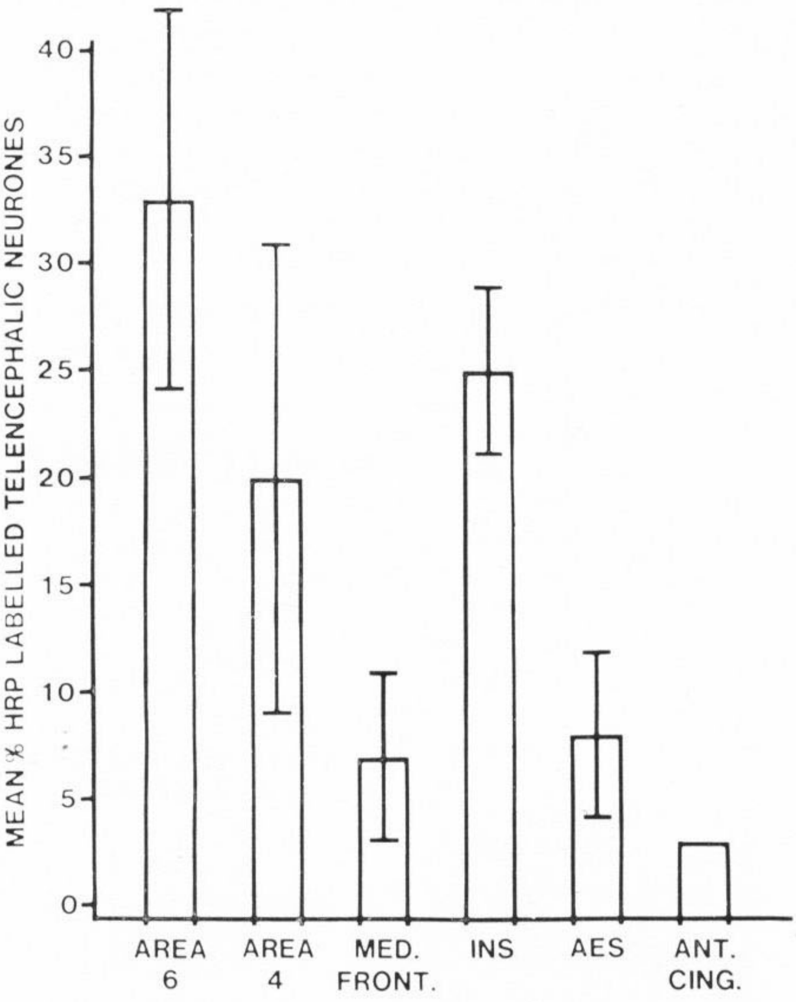

Fig. 6. — *Histogram illustrating the regional distribution of labelled neurones within the telencephalon following HRP injection in the region of the PAG in which excitatory amino acid injections elicited a defence reaction in the cat. The data are from 4 cats. The standard deviation for each histogram bar is indicated. Abbreviationss ANT CING, anterior cingulate cortex; MED FRONT, medial frontal cortex (area 32); rest as in Fig. 5. For details see Bandler, McCulloch and Dreher (1985).*

as well, a significant role in integrating the activity of PAG neurones involved in defence with cortical mechanisms for visually-directed attention and visually-guided motor behaviour. Second, the region of the orbito-insular cortex (which contained 25 % of the labelled telencephalic neurones) contains many polysensory neurones (i.e. auditory, somatosensory and visual) and it has been proposed that an important function of the orbito-insular cortex may be the temporal pattern discrimination of such stimuli (Colavita and Weisberg, 1979; Fallon and Benevento, 1977; Loe and Benevento, 1969). Thus, this cortical region may be an important source of such "higher" sensory input to the PAG. Third, there was a relative paucity of labelled neurones within the basal telencephalon, suggesting that there is little direct, monosynaptic input to these PAG neurones from many structures (i.e. amygdala, septum, preoptic region) known to play an important role in the modulatory control of the defence reaction (Flynn, 1976; Seigel and Edinger, 1981). Such input could perhaps alternatively be relayed to the PAG via the diencephalon.

DIENCEPHALIC AFFERENTS TO THE PAG: Approximately the same number of diencephalic (mean, 391 neurones) and telencephalic (mean 395 neurones) neurones were labelled with HRP in the experimental cats. Nearly all (99 %) of the diencephalic labelled neurones were found in the ipsilateral hypothalamus or subthalamus, with an occasional labelled neurone in the ipsilateral thalamus, usually in the reticular nucleus. The major finding was that 78 % of the labelled diencephalic neurones were found in the tuberal hypothalamic region, specifically: (a) the ventromedial hypothalamic nucleus (VMH) and adjacent perifornical region (Pf); (b) the region of the tuber cinereum (TCA); (c) the region comprising the caudal part of the paraventricular hypothalamic nucleus (PAH), and the dorsal hypothalamic area (DHA). These sources of hypothalamic afferents to the PAG are shown schematically in Fig. 5. The parts of the hypothalamus heavily labelled include the region (i.e. VMH, Pf, PAH, DHA) in which electrical stimulation elicits a defence reaction. It was surprising therefore to find, in a preliminary study, that microinjections of L-GLU within this part of the hypothalamus (at sites at which electrical stimulation previously elicited a defence reaction) did not elicit any signs of a defence reaction (Bandler, 1982). These negative results with GLU urgently require clarification as the tuberal hypothalamic region: (1) represents, in terms of absolute numbers of labelled cells, the largest source of forebrain afferent input to the PAG; (2) corresponds to that hypothalamic region which receives substantial afferent input from those basal telencephalic areas known to modulate defensive behaviour, but which do not themselves have a direct, monosynaptic input to the PAG.

BRAINSTEM AFFERENTS TO THE PAG; The same experimental brains used for the analysis of forebrain afferents to the PAG have been used for the study of the brainstem afferents. In contrast to the almost totally ipsilateral origin of forebrain projections to the PAG, labelled neurones in the brainstem were found both ipsilateral and contralateral to the PAG injection site. However, ipsilaterally labelled cells predominated in the midbrain and pons, whereas both ipsilaterally and contrataterally labelled cells were found in the medulla. The number of labelled neurones in the brainstem (mean, 702 neurones) was approximately the same as the total number of labelled neurones in the forebrain (mean, 786 neurones). The largest number of labelled brainstem neurones (36 % of the total) were found within the tegmental fields of the braistem reticular formation. Overall 25 % of the labelled neurones were found in the ipsilateral reticular formation and 11 % in the contralateral reticular formation. The percentages of total labelled neurones within individual tegmental fields were as follows: (a) the central tegmental field of the midbrain (FTC), 10 % of the total (7 % in the ipsilateral FTC); (b) the paralemniscal tegmental field of the caudal midbrain and rostral pons (FTP), 5 % of the total (4 % in the ipsilateral FTP); (c) the gigantocellular tegmental fields of the pons and medulla (FTG), 9 % of the total (7 % in the ipsilateral FTG); (d) the magnocellular tegmental field of the pons and medulla (FTM), 4 % of the total (3 % in the ipsilateral FTM); (e) the lateral tegmental field of the pons and medulla (FTL), 8 % of the total (4 % each, in the ipsilateral and contralateral FTL). The other brainstem region which contained a large percentage of the total number of labelled neurones was the locus coeruleus (LC), 12 % of the total (10 % in the ipsilateral LC). These sources of brainstem afferents to the PAG are shown schematically in Fig. 5. Smaller percentages of the total number of labelled brainstem neurones were found in the ipsilateral substantia nigra, pars reticulata (4 % of the total), the midbrain dorsal raphe nucleus (4 % of the total), the contralateral paramedian pontine reticular formation (4 % of the total), and the contralateral and ipsilateral solitary nuclei (2 % of the total).

Although the largest number of labelled brainstem neurones were found in the reticular formation, the diversity and scatter of these neurones, both between and within the various tegmental fields belies any functional-anatomical interpretations. The other major brainstem projection to the PAG originated from the region of the locus coeruleus. Studies in the cat (Chu and Bloom, 1974) and the kitten (Jones and Friedman, 1983), employing histofluorescence techniques for catecholamine neurones, and in the rat, using anterograde radioautographic methods (Jones and Moore, 1977), had previously reported the existence of efferent projections from the locus coeruleus to the PAG. Although, it remains to be established that the LC neurones labelled in this study are noradrenergic, that at least some are, is suggested by the histofluorescence data and the fact that the LC complex contains the largest and densest aggregation of noradrenergic neurones in the mammalian CNS (Jones and Friedman, 1983; Wiklund, Leger and Persson, 1981). It should be noted that in the freely moving cat, identified noradrenergic LC neurones manifest their most significant increase in single unit activity when the cat is subjected to noxious, threatening or stressful stimuli (Jacobs, personal communication). Such findings are consistent with earlier suggestions that LC neurones play an important integrative role in an organism's response to stress (e.g. Amaral and Sinnamon, 1977). Assuming that the LC neurones labelled with HRP in our study are noradrenergic, a possible function could be to "modulate" or "enhance" the synaptic effects of other PAG inputs, such that PAG neurones are better able to integrate a defence reaction when the organism is threatened. This kind of synaptic "modulatory" or "enhancing" influence of noradrenergic neurones at their target sites has been suggested previously (e.g. Bloom, 1980).

SUMMARY

Emotional behaviour is readily induced by stimuli which represent a real or perceived threat to the organism's survival. Such behaviour, in mammals, consists of a complex, but species-stereotyped pattern of somatomotor and autonomic responses, often referred to as the defence reaction. Although experiments have demonstrated that the patterns of somatomotor and autonomic responses characteristic of such a reaction can be readily elicited by electrical stimulation of the hypothalamus or the midbrain, the neural organization within these regions which subserves the defence reaction has not been adequately defined. In the work described microinjections of excitatory amino acids (L-glutamate, L-aspartate and DL-homocysteate) were made into the midbrain of cats and rats The advantage in using excitatory amino acids is that they excite cell bodies and dendrites of neurones but not axons of passage, which is the major drawback of electrical stimulation studies.

Injections of these excitatory amino acid into the midbrain periaqueductal grey region (PAG) of either the cat or the rat elicited the behavioural signs of a defence reaction. As well, in the anaesthetised and paralyzed cat, the cardiovascular pattern characteristic of the defence reaction (i.e skeletal muscle vasodilatation, tachycardia, increased arterial pressure) was elicited by excitatory amino acid microinjections within the midbrain PAG. In contrast, injections of excitatory amino acids into the midbrain tegmentum failed to elicit either the behavioural or the cardiovascular components of the defence reaction. These results indicate: (a) that the effective midbrain region for the elicitation of the defence reaction, as defined by excitatory amino acid injections, is significantly smaller that had been suggested previously by electrical stimulation and lesion studies; (b) that the midbrain PAG contains a population of neurones whose excitation can generate both behavioural and cardiovascu-

lar components of the defence reaction. The sources of forebrain and brainstem afferents to these PAG neurones also were studied by the method of the retrograde transport of horseradish peroxidase. Although the functional significance of the projections remains to be established, the major sources of afferents to the PAG region, containing neurones whose excitation elicits a defence reaction, arise from frontal "oculomotor" and motor cortices, a polysensory insular cortical region, the tuberal region of the hypothalamus, brainstem reticular formation tegmental fields and the locus coeruleus.

This research has been supported by grants from the Australian National Health and Medical Research Council. We wish to thank J. Marlowe and M. McCall for their excellent technical assistance.

RESUMEN

Conducta emocional es inducida espontaneamente por estímulos que representan una amenaza real o percibida a la supervivencia del organismo. Tal conducta en mamíferos, consiste de un complejo pero estereotipado por especies modelo de respuestas somatomotoras y autonómicas, a menudo referidas a la reacción de defensa.

Aunque los experimentos han demostrado que las respuestas somatomotoras y autonómicas características de tal reacción pueden ser prontamente promovidas por estimulación eléctrica del hipotálamo o el mesencéfalo, la organización neural dentro de estas regiones las cuales soportan la reacción de defensa no han sido adecuadamente definidas.

En el trabajo descrito microinyecciones de aminoácidos excitatorios (L-glutamato, L aspartato, y DL-homocisteato) fueron hechas en el mesencéfalo de gatos y ratas. La ventaja de usar aminoácidos excitatorios es que ellos excitan cuerpos celulares y dendritas de neuronas pero no axones de paso, lo cual es el mayor inconveniente de estudios de estimulación eléctrica.

Las inyecciones de estos aminoácidos excitantes en la región gris periacueductal del mesencéfalo (PAG), del gato o la rata, provocaron signos de conducta de una reacción de defensa. También en el gato anestesiado y paralizado, el modelo cardiovascular característico de la reacción de defensa (vasodilatación en la musculatura esquelética, taquicardia, aumento de la presión arterial) fue promovido por microinyecciones de aminoácidos excitantes dentro del mesencéfalo PAG. En contraste inyecciones de aminoácidos excitantes en el tegmentum del mesencéfalo fallaron en promover sea los componentes de conducta o cardiovasculares de la reacción de defensa. Estos resultados indican: (a) que la región mesencefálica efectiva para la promoción de la reacción de defensa, como la provocada por las inyecciones excitantes de aminoácidos, es significativamente más pequeña que había sido sugerida previamente por estudios la estimulación eléctrica y lesión; (b) que el mesencéfalo PAG contiene una población de neuronas cuya excitación puede generar componentes de conducta y cardiovascular de la reacción de defensa. Las fuentes de cerebroanterio y tronco cerebral aferentes a estas neuronas PAG también fueron estudiadas por el método del transporte retrógrado de peroxidasa ábano. Aunque la significación funcional de las proyecciones queda por ser establecida, la fuente mayor de aferentes a la región PAG que contienen neuronas cuyo estímulo promueve una reacción de defensa, salen de la corteza frontal oculomotora y motora, una región cortical insular polisensitiva, la región tuberal del hipotálamo, formación reticular del tronco cerebral campos tegmentales y el locus ceruleus.

Esta investigación ha sido sostenida por subvención del Consejo Australiano Nacional de Salud y de Investigación Médica. Deseamos agradecer a J. Marlowe y M. McCall por su excelente colaboración técnica.

RÈSUMÉ

Le comportement émotional est induit spontanément por des stimulus que perçoivent une menace réelle ou perçue a la survivence de l'organisme celle conduite est un complex stereotypé a chaque espece de mamifère a un modele somatomotrice et automatiques, souvant en relation avec des reflexes de défense.

Malgis les experiences qui ont montré que les modeles de réponses somatomatrices et autonomes specifiques a ce type de réactions peuvent êtres provoquées rapidement por des éxitations électriques de l'hypotalamus ou du mésencéphale, le'organisation neurale de ses régions lesquelles souffrent la réaction de défense n'ont pas encore eté clairement definies. Les expériences montrent que des micro injections d'amino-acides (L glutamate, L aspartate, et DL homocisteate) furent instelées dans le mésencephale de chats et de rats. Les aminoacides exitent les corps celulaires et les dendrites des neurones mais non les axones de pasage qui présentent des inconvenients pour l'étude des éxitations électriques.

Les injections d'amino-acides dans la matière grise periacqueduct du meséncephale (PAG) sur le chat ou le rat, produit une réaction de défense.

Au contraire le injection d'amino-acides dans le tegmentum du meséncephale ne produisent mem pas les composants de conduite ou cardiovasculaires des réactions de défense.

Chez le chat anesthesié et paralisé le modele de la réaction de défense a été provoqué por les microinjection d'amino-acides dans le meséncephale PAG. au contraire les injections dans le tegmentum mésencephalique ne provoquent ni les composants de conduite on cardio vasculaires de la reation de défense. Ces resultats indiquent (a) que la region mésencephalique efective pour la production des reactions de défense, comme celles provoqués par les injection d'amino-acides est bien plus petite que ce qu'avait superé par les études de stimulation électrique et les lésions. (b) que le mésencephale PAG contient un conglomerat celulaire dont l'exitation peut provoquer, des comportement de conduite et cardio vasculaire des reactions de défense. Les sources cerebro anterieur y tronccerebral afferentes vers ces neurones PAG ont été etudiées au moyen de la méthode du transport rétrograde de la peroxidase.

La signification fenctionelle des proyections doivent encore être etahlies, mais la source afférente principale de la région PAG qui contient les neurones dont les stimulation provoquent une reaction de défense sort des cortex frontal oculo mateur et moteur, une region corticale insulai polisensitive, la region tubaire de l'hypotalamus, la formation reticulaire du tronc cerebral, les champs tegmenteux et le locus ceruleus.

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Nous desirons remercier Marlowe y M. McCall pour leur exelent colaboration technique.

ZUSAMMENFASSUNG

Die emotionelle Verhaltungs weise ist spontan durch Reize hervorgerufen, die eine wirkliche oder empfunde ne d/Drohung gegen das Ueberleben des Organismus darstellen. Solch eine Verhaltungsweise bei den Saeugetieren besteht aus einem komplaxen. aber je nach Spezie, stereotypen Modell von somatomotori schen und autonomen Reaktionen, die oft Abwehrreaktion ge nannt werden. Obwohl Experimente gezeigt haben dass die Modelle soma tomotorischer und autonomer Reaktionen, die charakteristisch fuer eine solche Verhaltungsweise sind, leicht durch elektrische Reizung des Hypo-

thalamus im Mes encephalon hervorgerufen werden koennen, die neurale Organisation in dieser Region, die Abwehrreaktion vermitteñt, ist noch nicht richtig definiert worden. In der beschriebenen Arbeit wurden Mikroinye ktionen von exzitatorischen Aminosaeuren (L-Glutamat, L-Asparagat und DL-H omozysteatat) in das Mesencephalon von Katzen und Ratten ausgefuehrt. Der Vorteil der exzitatorischen Aminosaeuren ist, dass diese die Zellkoerper und Dendriten der Nervenzellen reizen aber nicht die Axonen, was das groeste Hindernis bei der Untersuchung durch elektrische Reizung darstellt.

Die Inektion dieser stimulierenden Aminosaeuren in die graue periaquaeductale Region des Mesencephalon (PAG) der Katze oder Ratte rufen die Symptome des Verhaltens der Abwehrreaktion hervor. Auch bei der anaesthesierteen oder paralysierten Katze wurde das fuer die Abwehrreaktion charakteristische cardiovasculaere Modell (Gefaesserweiterung der Skeletmuskulatur, Tachycardie, Erhoehung des Blutdrucks) durch Injektionen von stimulierenden Aminosaeuren in das Mesencephalon PAG hervorgerufen. Dagegen gelang es nicht, mit Injektionen von stimulierenden Aminosaeuren ins Tegmentum des Mesencephalon die Symptome der Verhaltungsweise noch der cardiovasculaeren Reaktion der Abwehrreaktion hervorzurufen.

Diese Ergebnisse zeigen an; a) dass die effektive mesencephale Region fuer die Provokation der Abwehrreaktion, wie die durch die Injektion stimulierender Aminosaeuren provozierte, bedeutend kleiner ist als man vorher gedacht hatte, als man sie mittels elektrischerund traumatischer Reizung studierte; b) dass das Mesence phalon (PAG) eine Ansammlung von Neuronen hat, deren Reizung die Verhaltungsweise und die cardiovasculaeren Symptome der Abwehrreaktion hervorrufen koennen. Der Ursprung der afferenten Wege des Vorderhirns und des Hirnstamnes zu den PAG-neuronen wurden auch untersucht durch diese Methode des retrograden Transports der Meerrettich - Peroxidase. Obwohl die funktionelle Bedeutung der Projektionen noch festgestellt werden muss, gehtder wichigste Ursprung der afferenten Wege zur PAG Region, die Neuronen enthalten, deren Reizung eine Abwehrreaktion hervorruft, von der frontalen, oculo-motorischen und motorischen Rinde einer polysensitiven insulaeren Rindenregion, der tuberalen Regiondes Hypotha lamus, der reticulaeren Formation des Hirnstammes, des Tegmentum und des Locus Coeruleus aus.

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Effects of Temporal Lobe Epileptiform Activity Upon Aggressive Behavior in the Cat[1]

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Introduction

During the past two decades, it was established that the amygdala can powerfully regulate aggressive behavior in the cat. Studies by Egger and Flynn[7] and later by Siegel et al.[16],[17] and Block et al.[3] indicated that the amygdala can differentially modulate hypothalamically elicited quiet biting attack behavior. Specifically, it was noted that subconvulsive levels of electrical stimulation applied to the medial two-thirds of amygdala and pyriform cortex suppressed the quiet attack response while facilitation of the occurrence to attack resulted from stimulation of the lateral and central nuclei. Stoddard-Apter and MacDonnell[18] also observed that subseizure electrical stimulation of the medial amygdala could facilitate the occurrence of affective defense behavior elicited from the cat's medial hypothalamus.

From these studies, a number of questions may be raised which are fundamental to our understanding of the manner in which the temporal lobe regulates emotional behavior during such disease states as temporal lobe epilepsy. Of primary interest is whether, in fact, seizures induced into the amygdala can modify the attack response. Secondly, it would be important to determine whether seizure foci induced at all sites throughout the amygdala and adjoining pyriform cortex have uniform or differential effects upon the attack response. Finally, it would be of interest to determine whether the effects upon attack behavior resulting from seizures induced acutely (by electrical stimulation) differ from those induced chronically (by cobalt powder). The present report has attempted to address these issues.

Methods

Eighteen adult cats of either sex which weighed between 2.5 and 4.0 kg. were employed in this study. Electrodes for stimulation and recording were placed into the amygdala and hypothalamus. Details concerning the implantation of electrodes, stimulation and recording procedures and experimental test chamber are described elsewhere[3,16].

Acute Induction of Seizures

One week post surgery, sites in the hypothalamus of seven cats were identified from which affective defense behavior could be obtained. In two additional cats, quiet biting attack sites were obtained that could be used as a basis for comparison of the effects of temporal lobe seizures upon hypothalamically elicited responses. The affective defense response latency was defined as the duration of time required to elicit hissing behavior within 20 sec. and the quiet biting attack response latency was defined as the duration of time required for the cat's teeth to make contact with the back of an anesthetized rat's neck. Hypothalamic current intensities ranged from 0.10 to 0.80 mA. Then, stable baseline attack response thresholds, utilizing the Method of Limits, were determined on alternate days for a period of 1-3 weeks. Following establishment of stable baseline responses, an electrode was implanted into a region of the amygdala or pyriform cortex which was capable of modulating the latency response for affective defense (or quiet attack), utilizing the dual stimulation procedures described by Block et al.[3] In brief, paired trials of single stimulation of the hypothalamus alone were compared with dual stimulation of the hypothalamus and amygdala/pyriform cortex. Under each condition, stimulation of the hypothalamus and

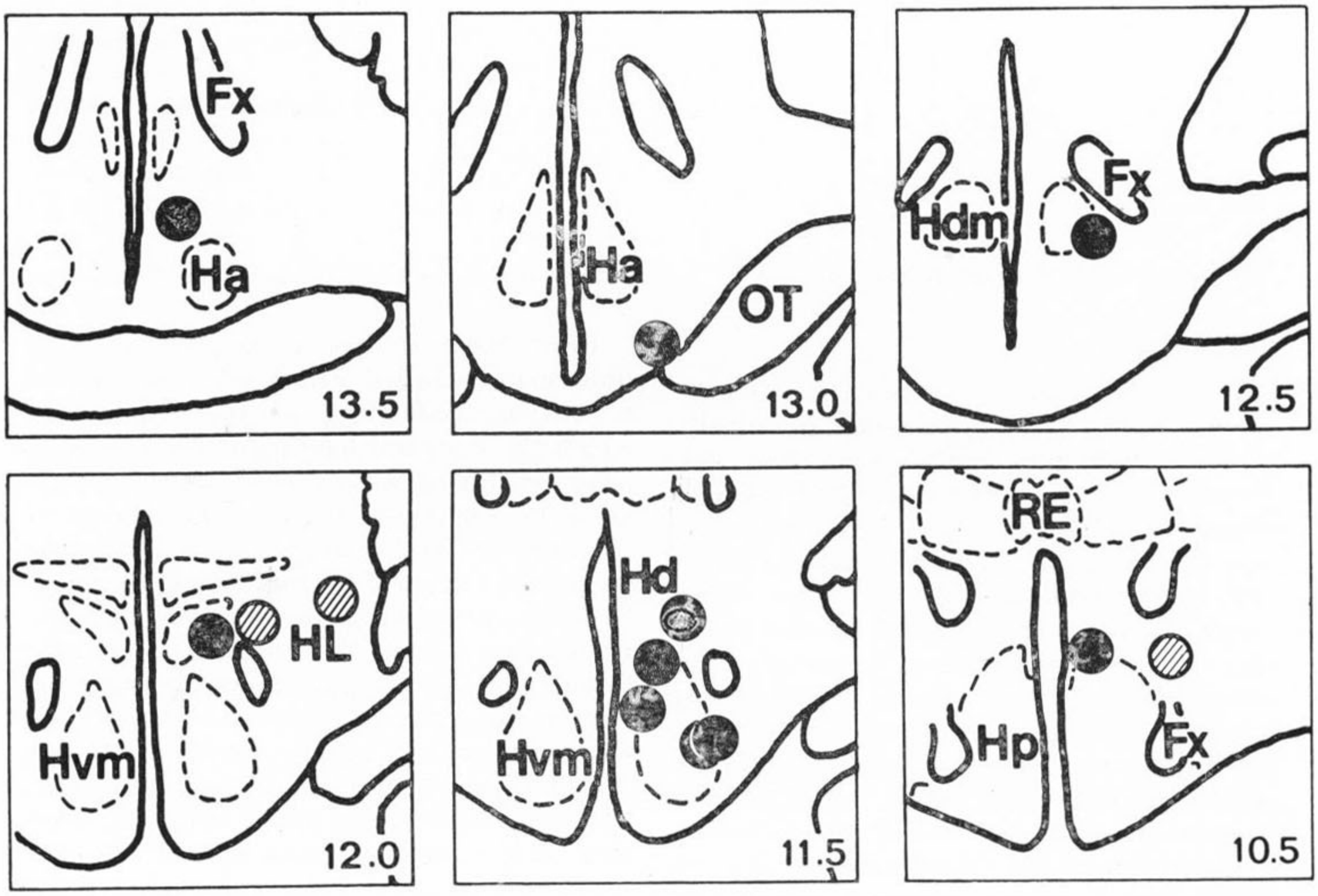

Fig. 1. — *Sites within the hypothalamus from which affective defense (closed circles) and quiet biting attack (hatched circles) were respectively elicited. Numbers in lower right hand corner of each panel for this figure and for Fig. c indicate frontal plane of section.*

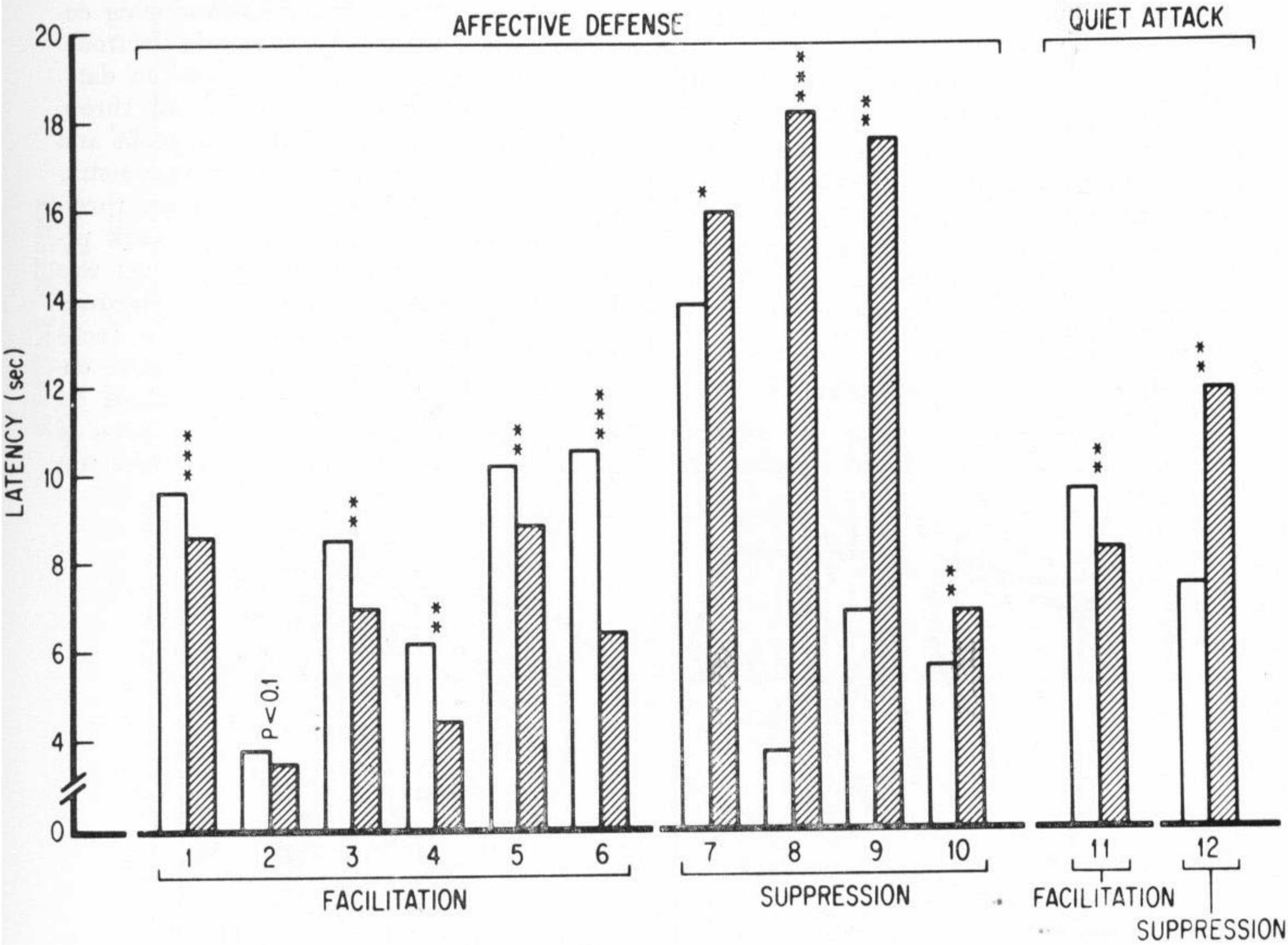

Fig. 2. — *Bar graphs indicate that concurrent subconvulsive stimulation of the amygdala or adjoining cortex and hypothalamus alters latencies for hypothalamically elicited attack behavior. For each pair of histograms, the first (open) bar corresponds to the mean attack latency for stimulation of the hypothalamus alone; the second (hatched) bar represents the mean attack latency for dual stimulation of the hypothalamus and temporal lobe structure. (*$p<0.05$; **$p<0.01$; ***$p<0.001$).*

amygdala/pyriform cortex was applied continuosly until a response occurred or until 20 sec. had elapsed. Current levels delivered to the amygdala/pyriform cortex were below seizure threshold. An A-B B-A paradigm was employed to sequence the order of trials of single and dual stimulation. A t-test for paired observations was used to analyze differences in affective defense latencies between trials of single and dual stimulation.

At the completion of modulation testing, seizures were elicited from those temporal lobe sites from which significant modulation of affective or quiet attack had been obtained. Seizures were induced on alternate days over a 1-4 week period. On a given day, 3-5 seizures were induced at half hour intervals by electrical stimulation of the amygdala/pyriform cortex. Stimulation was terminated when seizures were elicited or at 20 sec. Current intensities used to induce seizures ranged between 0.15-0.80 mA. Seizures were characterized by EEG spikes of high amplitude and high frequency and by concomittant myofacial twitching or other types of related motor responses typical of generalized convulsions. Thresholds for both attack reactions were determined by the Method of Limits both before and after the administration of seizures within test days but were never tested during ictal periods. The statistical analysis was derived from behavioral data obtained in the time period prior to seizure induction on each of the last three days when seizures were administered.

Following the last day of seizure induction, affective defense thresholds were again determined over a 1-5 week 'post-seizure' recovery period. A t-test for independent observations was employed to compare the mean attack thresholds during seizure test sessions with those recorded both before seizure induction and after cessation of seizures.

Chronic induction of seizures

In this aspect of the study, an attempt was made to create a 'chronic' seizure focus in the temporal lobe by introducing cobalt powder through a cannula-electrode. Nine animals have been examined to date. Cannula electrodes were implanted throughout different levels of the amygdala and pyriform cortex. Prior to cobalt administration, affective defense baseline level thresholds were determined over a 1-3 week period. Then, cobalt powder (25-50 mg) was introduced through the cannula electrode in order to produce a chronic seizure focus at a given temporal lobe site. Affective defense thresholds were again determined on alternate days following the introduction of cobalt. At the completion of a two-week test

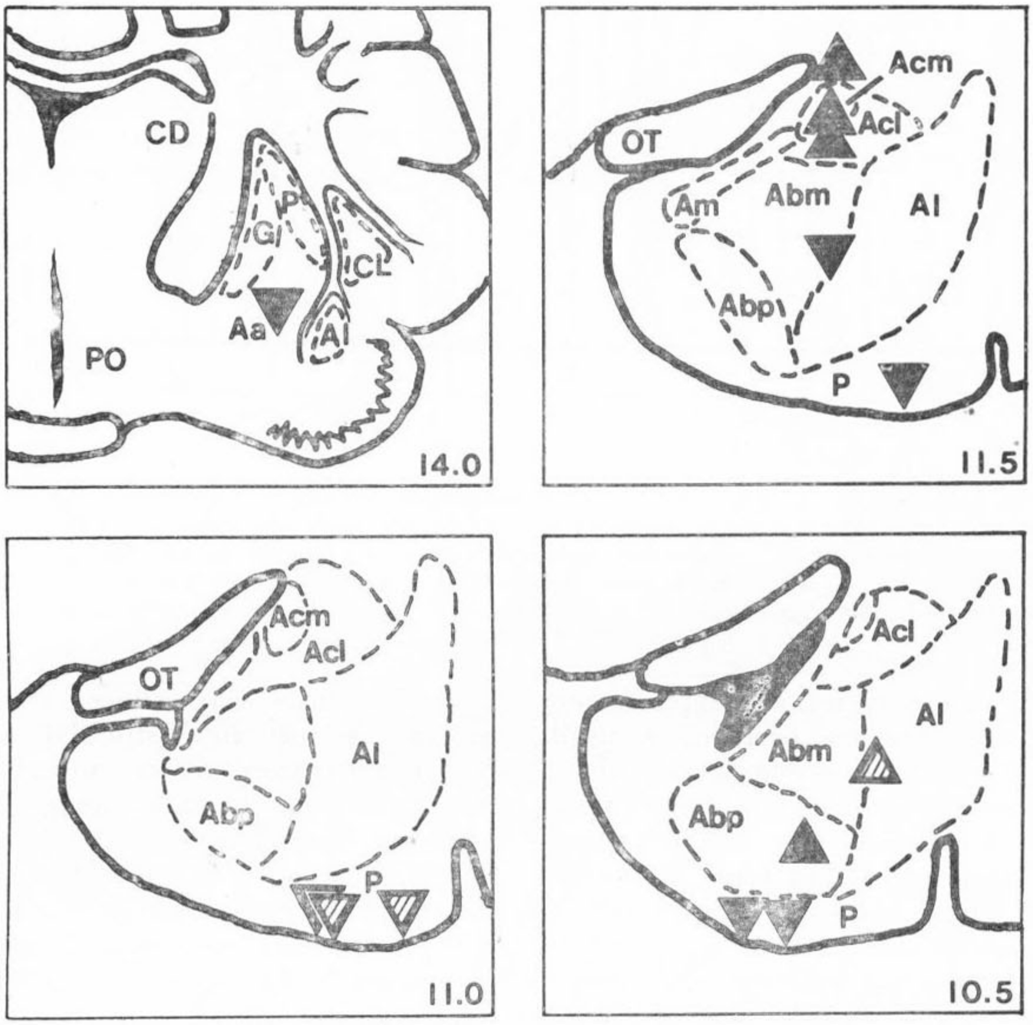

Fig. 3. — *Seizure foci within the temporal lobe which altered hypothalamically elicited affective defense (closed triangles) and quiet attack (hatched triangles) thresholds. Each stimulation site had also previously been shown to modulate attack behavior at subconvulsive current intensities (see Fig. 2). Triangles facing up, response threshold increase following induction of seizures; triangles facing down, response threshold decrease following induction of seizures. Overlapping triangles (lower left panel) indicate an individual site from which electrically induced seizures resulted in significant alterations in thresholds for both affective defense and quiet biting attack behavior.*

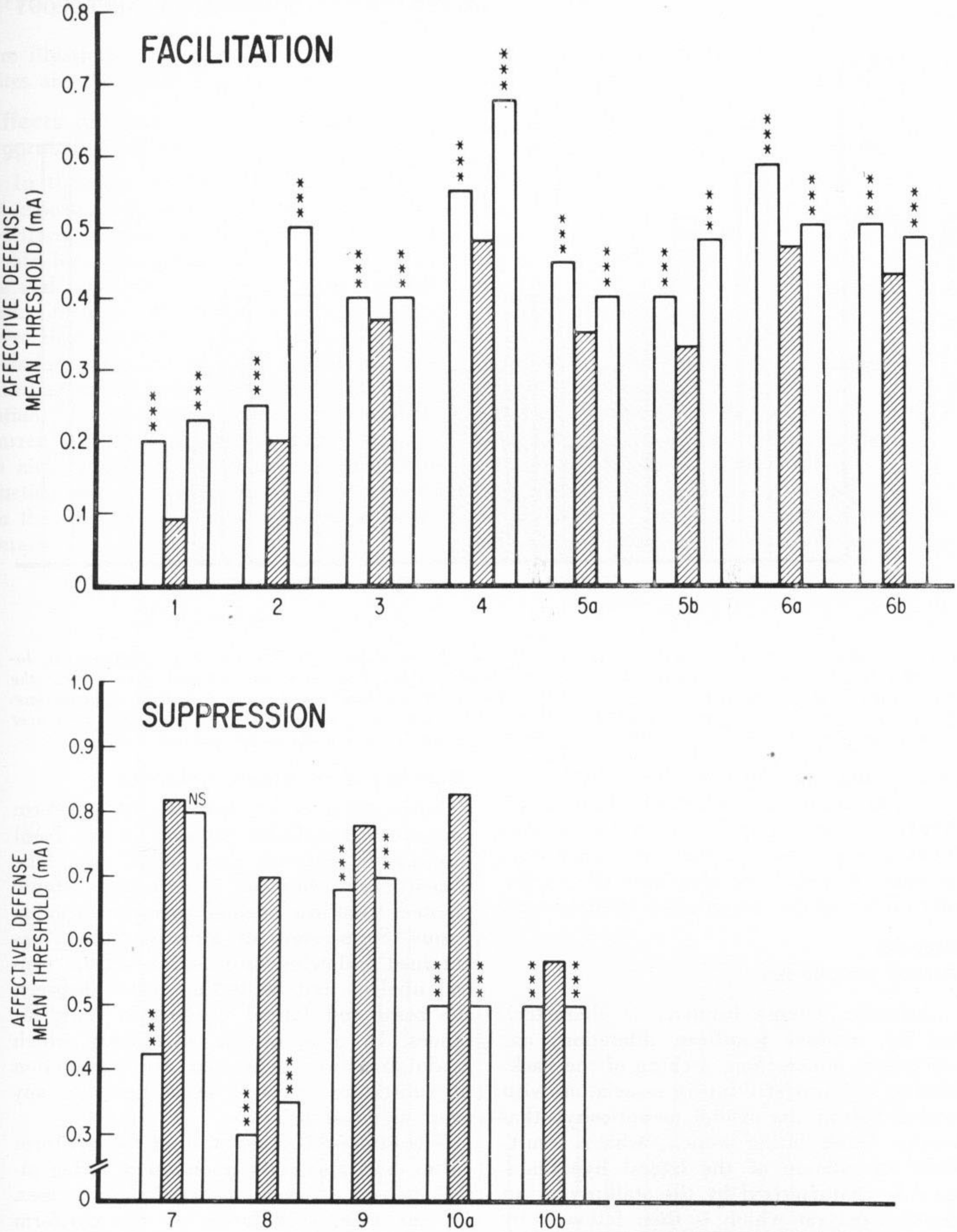

*Fig. 4. — Bar graphs indicate that affective defense thresholds are lowered when seizures are induced at sites from which response facilitation had previously been demonstrated. Affective defense thresholds are also elevated following the induction of seizures at sites from which suppression of this response had been shown. Note recovery of postseizure threshold values toward preseizure baseline levels. First open bar, mean baseline response threshold determined prior to induction of seizures; hatched bar, mean response threshold obtained during the last three days in which seizures were induced; last open bar, mean response threshold obtained during baseline recovery in the postseizure period. Astericks above the first open bar indicate t-test probabilities which compare mean affective defense threshold response values between preseizure baseline and seizure sessions while those above the third bar indicate comparisons between seizure and postseizure sessions. (***$p<0.001$; NS, non-significant).*

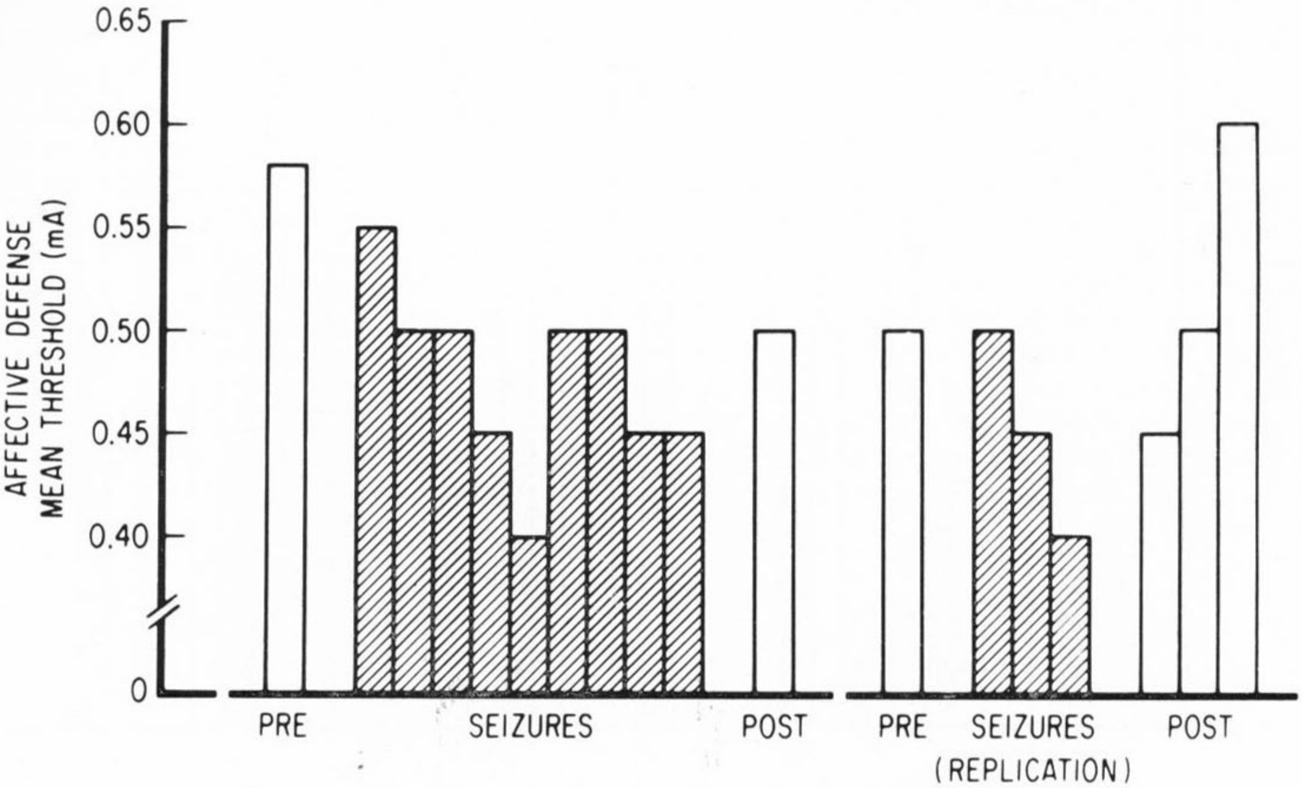

Fig. 5. — *Bar graphs indicate that response threshold levels for affective defense behavior are lowered following seizures initiated from the pyriform cortex. Pre- and post-seizure bars reflect the mean threshold values determined from trials run over one-week periods and include approximately 250 stimulation trials for each of these periods. Seizures were initially run on alternate days over a nine-day period and the procedure was replicated again over a three-day period.*

period, lidocaine hydrochloride (xylocaine hydrochloride) was delivered through an Alzet osmotic minipump into the seizure focus at a rate of 1 ul/hr. over seven days in order to reduce or eliminate the excitatory effects of the amygdaloid seizure focus.

Results

Attack responses

Affective defense behavior is characterized by marked pupillary dilatation, ear retraction, piloerection, arching of the back, hissing and paw striking in association with stimulation of the medial preopticohypothalamus. Quiet biting attack, which results from stimulation of the lateral hypothalamus, is characterized by the stalking of an anesthetized rat which is then followed by a vigorous bite to the back of its neck. Aside from pupillary dilatation, other overt signs of sympathetic activity are not apparent during this response. Maps indicating the loci of both affective and quiet biting attack sites for Part I (acute induction of seizures) of this study are shown in Fig. 1.

Modulation of attack behavior

Stimulation of six sites in the pyriform cortex, magnocellular division of the basal nucleus, or anterior amygdaloid area facilitated the occurrence of affective defense elicited from the medial preopticohypothalamus. Suppression of affective attack was obtained following stimulation of the central nucleus and borderline region between the basal and lateral nucleus in four instances. In none of the sites from which modulation was generated did stimulation at subseizure current levels generate any overt signs of behavior.

The effects of stimulation of the pyriform cortex and amygdala upon quiet biting attack behavior were considered in two cases. In one case, stimulation of the pyriform cortex differentially modulated attack behavior by suppressing quiet attack while facilitating the occurrence of affective defense. A second point located in the lateral nucleus facilitated quiet attack behavior. Bar graphs indicating the effects of amygdaloid stimulation upon attack behavior are illustrated in Fig. 2. The loci of these sites are shown in Fig. 3.

Effects of acute seizure induction upon aggressive behavior

In the data described below, the effects of repeated application of amygdaloid and pyriform cortical seizures upon the thresholds for hypothalamically elicited affective and quiet attack behavior were considered. The sites chosen for seizure induction were those described above from which modulation of attack behavior could be identified at subseizure current levels of stimulation. In each instance, the mean threshold current for eliciting attack behavior prior to and following the course of seizure induction was compared to that determined on the specific days when seizures were generated.

Seizures induced in the amygdala or pyriform cortex resulted in myofacial twitching, salivation, miturition, and bilateral myoclonic jerks which often evolved into convulsions characterized by generalized afterdischarges. The patterns of seizure discharges were regular and were of high frequency and high amplitude. The duration of seizures varied from those which were stimulus bound to 140 sec. post stimulation.

Concerning affective defense reactions, seizures induced in amygdaloid and pyriform cortical sites associated with facilitation of this response resulted in a highly significant lowering of the behavioral threshold. Changes in mean threshold values as a function of seizure administration ranged from 25 to 125 uA and were most frequently observed by the second week of seizure induction. During the post-seizure recovery

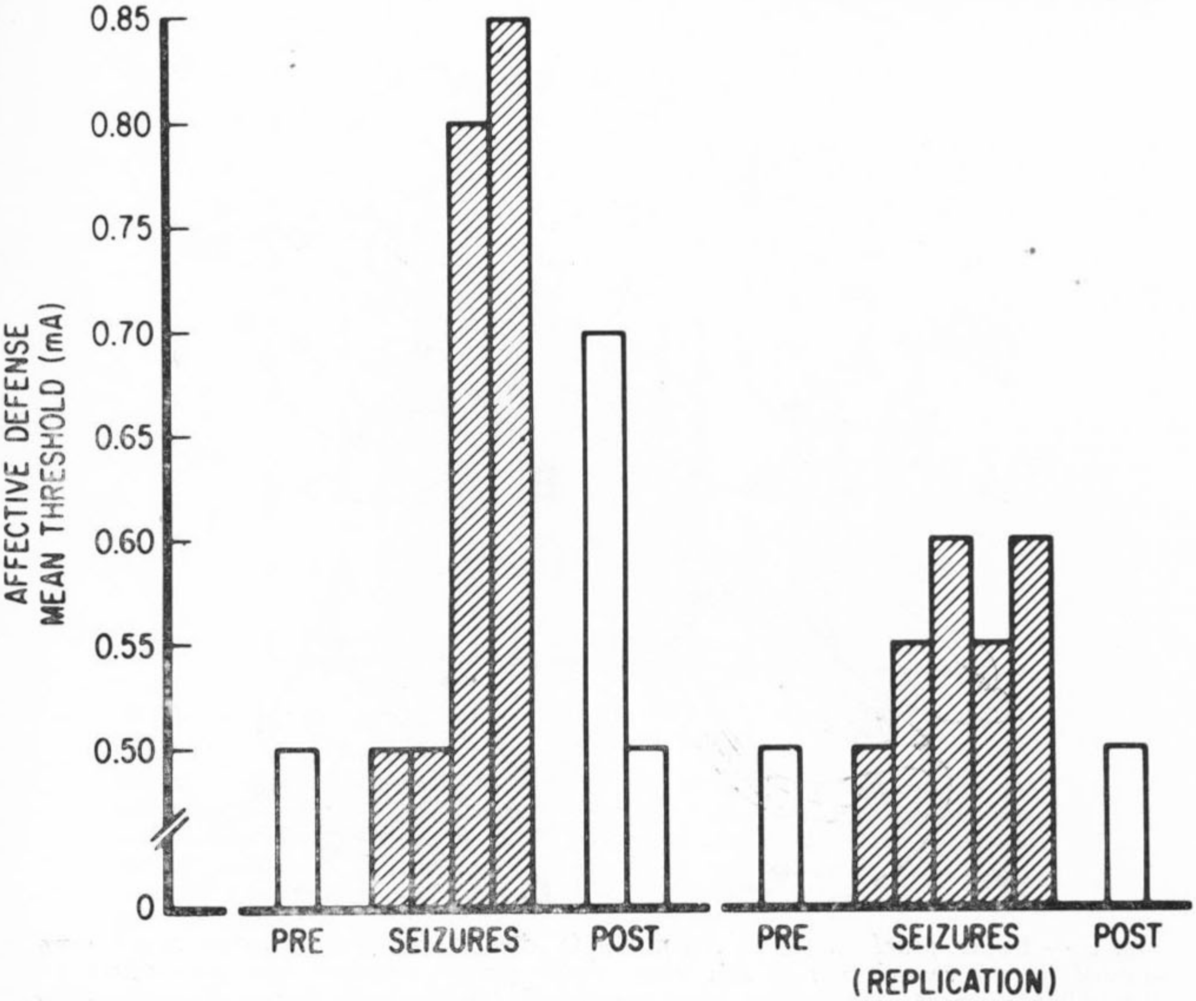

Fig. 6. — *Bar graphs indicate that threshold values for affective defense behavior are markedly elevated following the induction of seizures from the central nucleus. Note the recovery of response threshold toward the level indicated during the preseizure baseline period and the replication of this effect. Test session were comparable to those shown in Fig. 5.*

period, there was also a tendency for attack thresholds to return to pre-seizure baseline levels.

Regarding the effects of seizures induced at sites associated with suppression of affective attack, it was revealed that the application of this procedure resulted in marked increases in affective defense thresholds for each of the sites tested. Mean increases in threshold between pre-seizure and seizure days varied from 50 to 400 uA. Post-seizure testing also revealed decreases in affective defense thresholds in four of the five sites examined. Mean decreases ranged from 25 to 350 uA, thus suggesting that the effects of seizures upon thresholds for hypo-

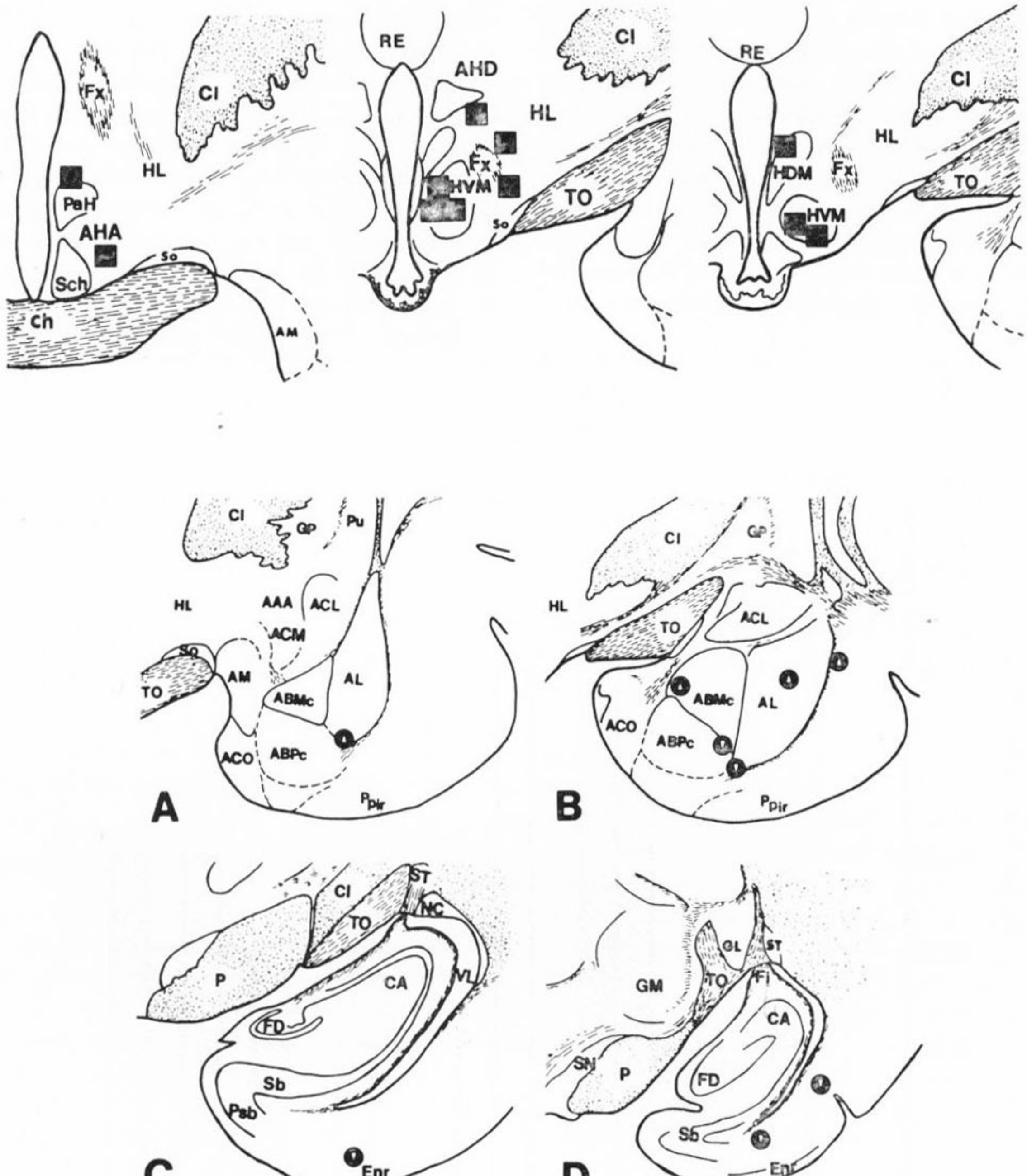

Fig. 7. — Upper panel: maps of hypothalamic sites from which affective attack were elicited for the second part of this study; lower panel: temporal lobe sites where cobalt-chloride chronic seizure foci were established. White arrows facing down, lowering of affective defense response threshold following injection of cobalt; white arrows facing up, elevation of affective defense response threshold following cobalt injection. Note that reductions in attack thresholds resulted mainly from injections placed into the pyriform-entorhinal area while elevations in response threshold resulted from chronic seizures induced primarily in the region of the lateral nucleus.

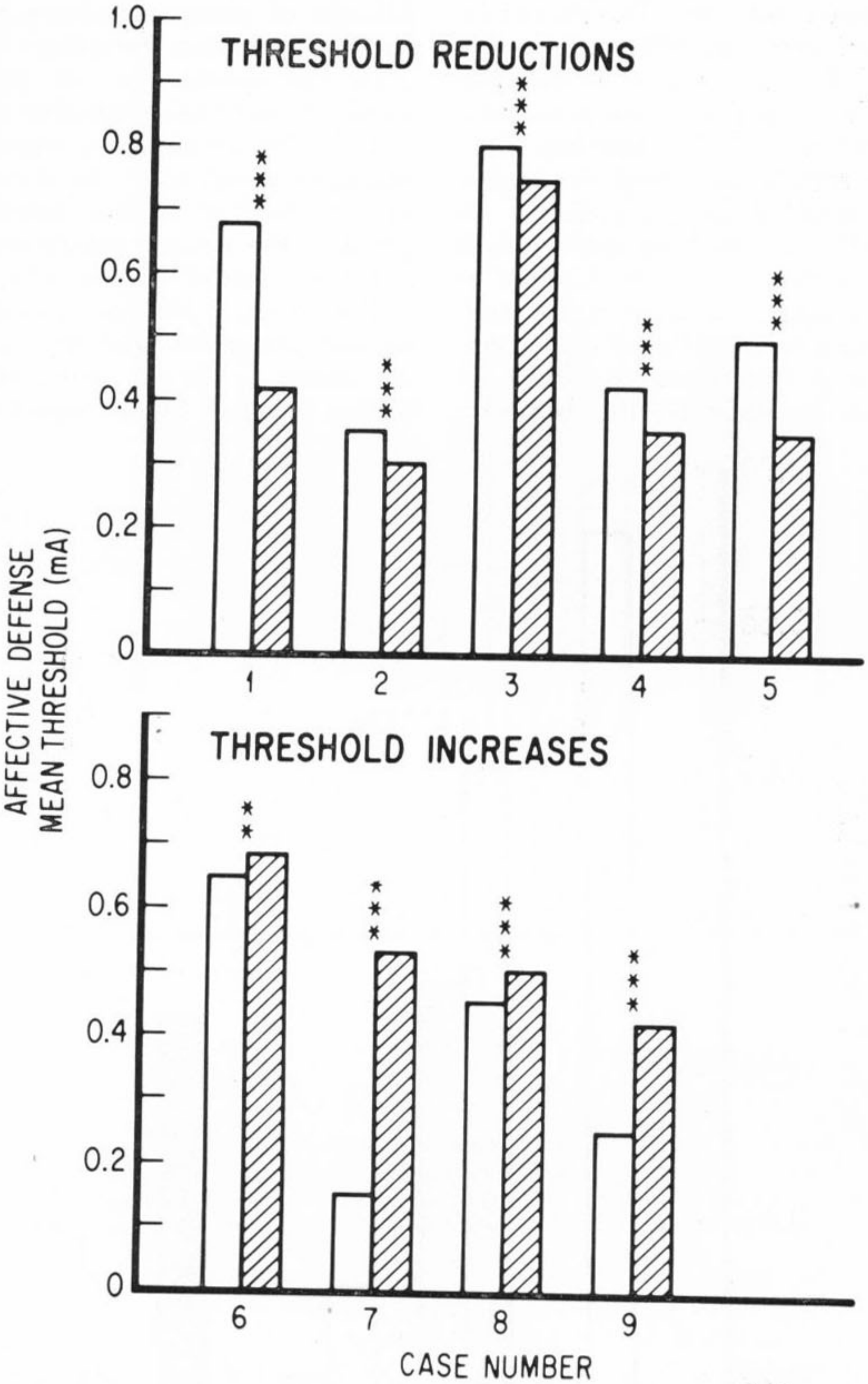

Fig. 8. — *Bar graphs indicate that chronic induction of seizures by cobalt chloride administration can significantly alter the hypothalamic response threshold for affective attack. Open bar, threshold values obtained during preseizure baseline testing period of approximately one week; hatched bar, threshold values obtained during post cobalt injection period of approximately two weeks.* (***$p<0.001$; **$p<0.01$).

thalamically elicited affective aggression appear to be reversible. The results of these findings are indicated in Fig. 4. Profiles of two individual cases - one associated with decreases in attack threshold and the other associated with increases in attack threshold are illustrated in Figs. 5 and 6.

In the present study, we were also able to compare the effects of seizures in two cases upon a second form of aggression quiet biting attack behavior. The results indicated that seizures can differentially modify the thresholds for affective defense and quiet attack. In particular, it was noted that at one pyriform site which suppressed quiet attack during subseizure stimulation, seizure induction resulted in a significant decrease ($p<.001$) of 50uA in mean attack threshold. In addition, seizures induced at a lateral amygdaloid site from which facilitation of quiet attack had been demonstrated resulted in a significant ($p<.001$) increase in mean threshold for this behavior.

Effects of chronic seizure induction upon aggressive behavior

In the second part of this study, we sought to determine whether chronic seizure induction (with the application of cobalt chloride) could alter the threshold response for affective defense reactions. In this phase of the study, consideration was given to the analysis of seizure induction upon affective defense behavior elicited from the medial preopticohypothalamus whose loci are shown in the top panel of Fig. 7. The bottom panel of Fig. 7 depicts the locations

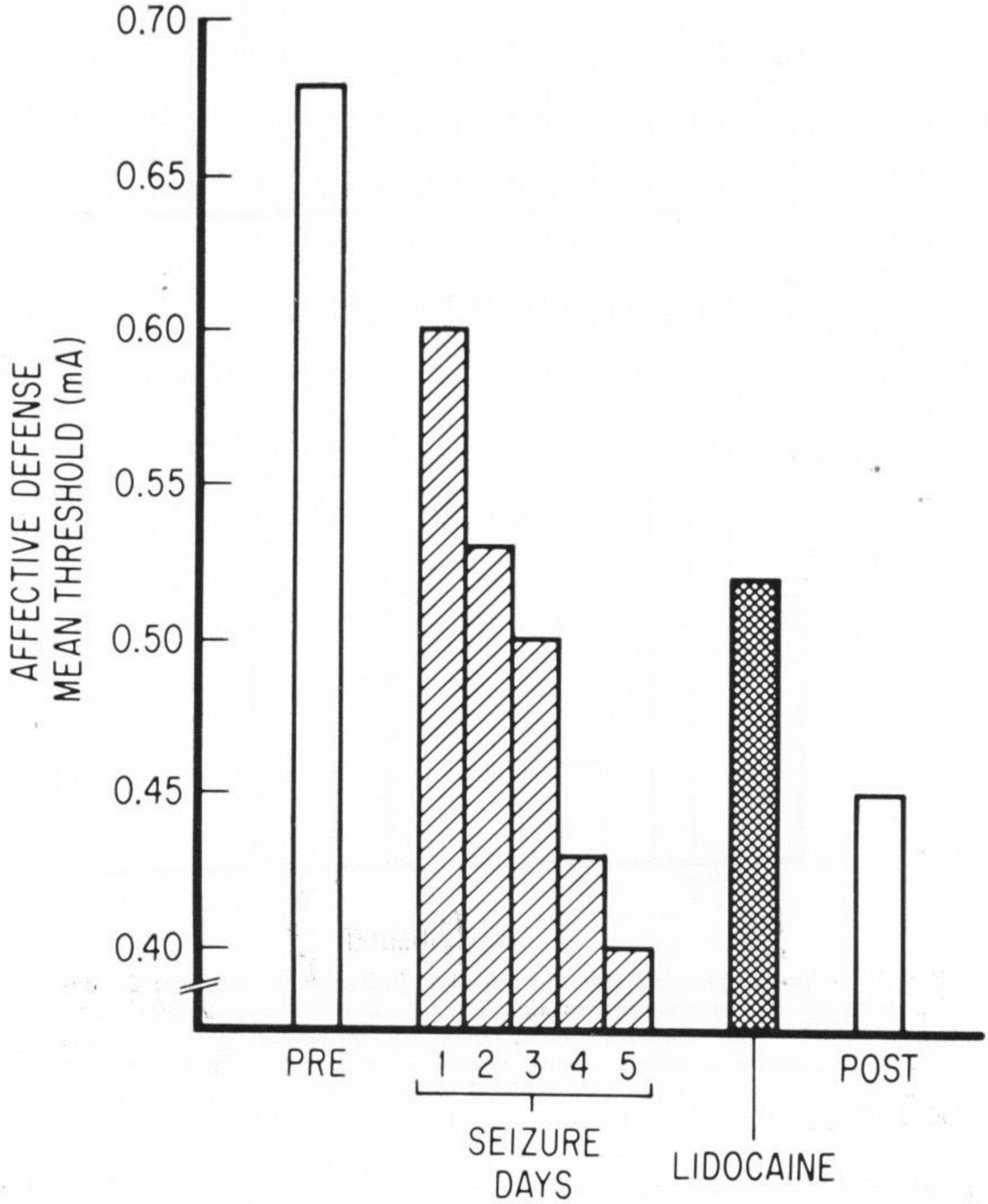

Fig. 9. — Bar graphs indicate a reduction in affective defense threshold following establishment of an amygdaloid chronic cobalt seizure focus. Note that lidocaine administration reversed the effect of cobalt seizures but that the response threshold was again lowered in the absence of lidocaine.

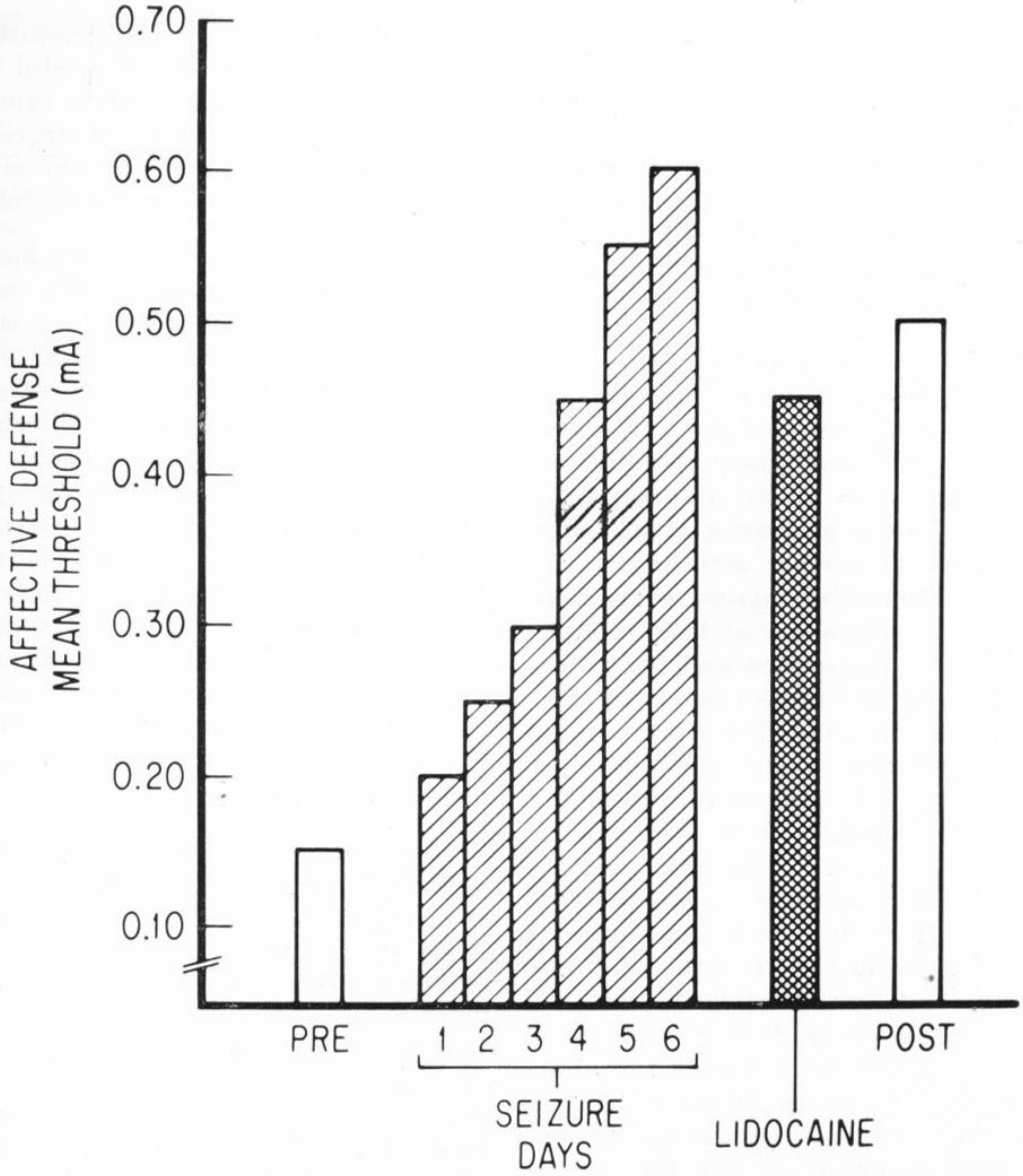

Fig. 10. — *Bar graphs indicate an elevation in affective defense threshold following establishment of an amygdaloid chronic cobalt seizure focus. Note that lidocaine administration reversed the effect of cobalt seizures, but that the response threshold tended to become elevated in the absence of lidocaine.*

of cannula-electrode tips where cobalt-induced seizures were generated as well as the directionality of the effects of such seizures upon affective defense behavior.

As illustrated in the bottom panel of Fig. 7 and in Fig. 8, the administration of cobalt-chloride resulted in a significant modification of the attack thresholds in nine cases ($p < .001$). Significant reductions in attack thresholds followed cobalt administration in five of the cases, while elevations in thresholds were noted in four other animals. Of particular interest is the relationship of the anatomical loci of the injections to their effects upon attack behavior. It appears that seizures generated from sites located in either the pyrifrom-entorhinal region or in that portion of the basal nuclear complex proximal to the pyriform cortex were associated with reductions in attack thresholds, while elevations in thresholds were linked to chronic seizures induced primarily in the lateral amygdaloid nucleus. Further illustrations of these effects are shown in Figures 9 and 10 for two individual cases. Note both the progressive modification of attack thresholds over time after cobalt injections as well as the temporary partial reversal of these effects following lidocaine administration (at the rate of iul/hr. over seven days via an Alzet minipump) which presumably reduced or eliminated the excitatory effects of the amygdaloid seizure focus. A replication study of these findings currently in progress in our laboratory has provided additional support for the findings described above.

Discussion

The results of the present study indicate that seizures induced either acutely or chronically at sites throughout the temporal lobe can significantly modify the thresholds for affective defense and quiet attack behavior. The findings further indicate that the direction in which the aggressive reactions are modified is a function of both the anatomical focus of the seizure and the nature of the behavioral responses considered. Specifically, it was observed that seizures induced in the pyriform or entorhinal cortices, anterior amygdaloid area, or magnocellular division of the basal nucleus generally resulted in a reduction of the threshold for affective defense behavior, while seizures associated with central and lateral nuclei were linked to an elevation in threshold for this response. It should be noted that seizures induced at these foci resulted in a modification of threshold values for affective attack in the same direction as previously shown during modulation testing with subseizure levels of stimulation. In contrast, in those cases where quiet biting attack behavior was examined, threshold changes due to seizures were opposite to the latency changes observed during modulation testing. In particular, increases in quiet attack thresholds followed repeated seizure induction at a site where subseizure stimulation facilitated attack, while a decrease in attack thresholds followed repeated seizures induced at a site from which subseizure stimulation suppressed quiet attack.

It is significant to note that if the variables of brain locus and type of behavioral response examined are crucial ones in the determination of the directionality of aggressive reactivity following seizures, then they may possibly account, in part, for the divergent findings observed in both the animal[1], [11],[15] and human[2],[5],[8],[9],[12],[13] literature. At the very least, it would be most useful if future studies could attempt to more carefully relate clearly defined forms of aggressive behavior to focal seizures situated in specific nuclear regions of the temporal lobe.

Little is known of the possible mechanisms subserving temporal lobe regulation of aggressive behavior. From the studies in our laboratory[4],[20] and elsewhere[6],[10], it may be suggested that epileptiform activity associated with a reduction in thresholds for affective defense behavior would follow a monosynaptic pathway from the pyriform cortex and the adjoining medial amygdala to the ventromedial nucleus via the stria terminalis or a disynaptic route involving the bed nucleus of the stria terminalis. In a related study, Stoddard-Apter and MacDonnell[18] demonstrated that strial fibers comprise the principal efferent pathway of the amygdala for facilitation of affective defense behavior.

Less is known about the amygdaloid pathways which may subserve threshold elevations in affective defense behavior. Since the primary structures that seem to be associated with elevations in affective defense thresholds include the central and lateral amygdaloid nuclei, it is reasonable to suggest that their efferent pathways may provide the anatomical substrate over which these threshold elevations are mediated. The primary route would include the ventral amygdalofugal pathway and its principal target nucleus - the substantia innominata[20], whose axons, in turn, supply the lateral hypothalamus[19],[20]. Here, an additional assumption is required - namely, that of a connection between the lateral and medial hypothalamus from which affective defense reactions are elicited. The anatomical basis for this pathway has previously been established[14].

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS USED IN FIGURES

Aa (or AAA), anterior amygdaloid area
Abm, magnocellular division of basal amygdaloid nucleus
Abp, parvocellular division of basal amygdaloid nucleus
Acl, lateral division of central amygdaloid nucleus
Acm, medial division of central amygdaloid nucleus
AHA (or HA), anterior hypothalamic area
AHD, anterior dorsal hypothalamus
Am, medial amygdaloid nucleus
CA, cornu Ammonis
CH, optic chiasm
CI, internal capsule
Cl, claustrum
ENT, entorhinal area
FD, fascia dentata
Fi, fimbria
Fx, fornix
GL, lateral geniculate nucleus
GM, medial geniculate nucleus
GP, globus pallidus
Hd (or Hdm), dorsal hypothalamic area
HL, lateral hypothalamus
HP, posterior hypothalamus
Hvm, ventromedial hypothalamic nucleus
OT (or TO), optic tract
P (Ppyr), prepyriform area (Fig. 7, P used to denote cerebral peduncle).
Pa, paraventricular nucleus
Psb, presubiculum
Pu, putamen
RE, nucleus reuniens
Sb, subiculum
Sch, suprachiasmatic nucleus
SN, substantia nigra
So, supraoptic nucleus
ST, stria terminalis

SUMMARY

Experiments were performed to determine the effects of temporal lobe seizures upon hypothalamically elicited aggressive behavior in the cat. Seizures were induced either acutely by electrical stimulation or chronically by cobalt chloride injection involving the pyriform or entorhinal cortices, or those subnuclei of the amygdala which had previously been shown to modulate aggressive responses at subseizure current levels. The results demonstrate that in both the acute as well as the chronic seizure model, a significant modification of affective defense thresholds followed induced seizures. The directionality of effects was dependent upon the anatomical location of the induced seizure. Seizures generated from sites in the pyriform or entorhinal cortices or basal amygdaloid complex generally resulted in a lowering of the affective defense threshold. In contrast, seizures generated from the lateral or central nuclei resulted in an elevation of the affective defense threshold. The directionality of the effects of seizures upon quiet attack thresholds was opposite to those described for affective defense. Here, seizures induced from the pyriform cortex were followed by an elevation in the quiet attack response threshold, while a decrease in threshold for this response followed seizures induced in the lateral nucleus.

RESUMEN

Se realizaron experimentos con el propósito de determinar los efectos de crisis del lóbulo temporal sobre la conducta agresiva provocada hipotalamicamente en el gato.

Las crisis fueron inducidas sea en forma aguda por estimulación eléctrica o crónica por inyección de cloruro de cobalto involucrando cortezas piriforme o entorinal, o aquellos subnúcleos de la amígdala que habían mostrado previamente modular respuestas agresivas en niveles comunes subcríticos. Los resultados demuestran que tanto en el modelo agudo de crisis como en el crónico, una modificación significativa de umbrales de defensa afectiva, siguieron a las crisis inducidas. Los efectos eran dirigidos de acuerdo a la localización anatómica de la crisis inducida. Crisis generadas desde áreas en las cortezas piriforme o entorinal o complejo basal amigdaloide, en general ocasionaba una disminución del umbral de defensa afectiva. En oposición crisis generadas desde los núcleos lateral o central ocasionaron una elevación del umbral de defensa afectiva. La orientación de los efectos de las crisis sobre umbrales de ataques leves resultó opuesta a aquellas descritas para la defensa afectiva. Las crisis inducidas desde la corteza piriforme fueron seguidas por una elevación en el umbral de respuesta de ataque leve, mientras un decrecimiento en el umbral para esta respuesta siguió a las crisis inducidas en el núcleo lateral.

RÉSUMÉ

Des experiences sont faites pour determiner les effetes de crises du lobe temporal sur la conduite agresive à partir de l'hypotalamus chez le chat.

Les crisis sont induites en forme aigu par stimulation électrique, ou chronique par injection de chlorure de cobalt et qui interesse le cortex piriforme ou les noyaux de l'amygdales qui avait eté préalablement capables de moduler des réponses agressives à des niveaux sous critiques. Les résultats montrent, aussi bien dans le modèle aigu que dans le modèle chronique, une modification sensible des sevils de défense affective suivirent les crises induites. Les effets étaint dirigés d'apres les localisation de la crise induite. Les crises provoquées depuis des crises du cortex piriforme ou entorinal ou complexe basal amygdaloide, en général, provoquaient une diminution du sel de la défense affective. D'autre part les crises provoquées depuis les noyaux latéraux où centraux provoquaient une élévation du sevil de défense. L'orientation des effets de la crise sur les sevils de crises légères furent oposés a ceux qui furent décrits pour la défense affective.

Les crises induites depuis le cortex piriforme furent suivies d'une élévation du sevil de réponse de crise légere, tandiqui un abaissement du senil pour cette réponse suivit les crises induites dans le noyau latéral.

ZUSAMMENFASSUNG

Es wurden Versuche unternommen mit dem Zweck die Auswirkungen von Krisen des Schläfenlappen auf das hypothalamisch verursachte agressive Verhalten der Katze zu bestimmen.

Die Krisen wurden hervorgerufen sei es in akuter Form durch elektrische Reizung, sei es chronisch durch Injektion von Kobaltchlorid mit Einschluss piriformer oder entorinaler Hirnrinde oder derjenigen Kerne unter der Mandel, die vorher eine klare agressive Reaktion auf üblichem subkritischen Niveau gezeigt hatten. Die Ergebnisse zeigen, dass sowohl in der akuten Art der Krise wie in der chronischen eine deutliche Änderung der Schwellenwerte afektiver Verteidigung auf die eingeleiteten Krisen folgte. Die Folgen waren in Übereinstimmung mit dem anatomischen Ort gerichtet der eingeleiteten Krise. Krisen, die aus dem Gebiet piriformer oder entorinaler Hirnrinde oder aus dem basalen Komplex der Mandel entstanden waren, verursachen im Allgemeinen eine Verringerung des Schwellenwertes afektiver Verteidigung. Im Gegensatz dazu verursachten Krisen aus dem seitlichen und zentralen Kernen eine Erhöhung des Schwellenwertes afektiver Verteidigung. Die Richtung von Auswirkungen von Krisen auf Schwellenwerten leichter Angriffe zeigte sich entgegengesetzt zu den beschriebenen für afektive Verteidigung. Krisen, die von der piriformen Hirnrinde eingeleitet sind, waren von einer Erhöhung des Schwellenwertes einer Reaktion mit leichtem Angriff gefolgt, während eine Erniedrigung des Schwellenwertes für diese Antwort auf die Krisen folgte, die vom seitlichen Kern eingeleitet sind.

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Emotional Disturbances in Limbic System Dysfunction

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INTRODUCTION

Analysis of the neuronal organization of the limbic system reveals the very intimate relationship of the amygdala with highly integrative subcortical structures. Fibres from the amygdala converge mainly upon the septum and hypothalamic regions; in addition, impulses from the amygdala reach the hippocampus via the piriform cortex. In turn, the hippocampus discharges into the same septohypothalamic zone by way of the fornix. This anatomical arrangement creates favourable conditions for a very close function coordination between the amygdala and the hippocampus. The important role of this anatomical and functional relationship becomes more and more apparent, for it seems evident that the reinforcing effect of such motivational forces as emotion, as well as the laying down of memory traces, are equally essential for the selection of behavioural patterns (see Gloor, 1960 and Olds, 1958).

The central position of the hypothalamus in emotions depends upon its function as the chief outlet of the neural messages chiefly from primitive parts of the brain to effector organs, striated muscles, smooth muscles and glands. One of the oldest parts of the brain involved in behaviour is the reticular formation of the brain stem. This poly-synaptic structure is situated centrally in the midbrain and extends rostrally to the hypothalamus, sub-thalamus and thalamus to affect behaviour in a complex fashion. Some reticular impulses are transmitted directly to the neocortex.

Stimulation of the amygdala can produce arousal reactions of many different kinds. These arousal effects are widespread and involve many neuronal systems, both autonomic and somatic. In some ways they are reminiscent of the effects found from stimulation of the midbrain reticular formation. There is ample evidence of differentiation within the amygdala for this behavioural dimension, too. The arousal system of the amygdala seems to be independent of the midbrain reticular formation since the arousal effects produced by amygdala stimulation can be found after lesions of the medbrain reticular formation. The cortical arousal effects initiated from the dorsal amygdala stimulation can suppress epileptiform discharges produced by the application of penicillin to the neocortex.

Clinical observations suggest that the limbic system, unlike the neocortex, derives subjective information in the form of emotional feelings which influence behavior required for self-preservation and the preservation of the species (MacLean, 1962). The most important evidence for this is provided by clinical cases with epileptogenic foci in or near the limbic cortex. As Penfold and Jasper (1954) have demonstrated during surgical intervation in such cases, either with the epileptic charge itself or with electrical stimulation of the involved cortex, patients may experience a wide variety of vivid emotional and visceral feelings.

NEURAL SUBSTRATES OF LIMBIC EPILEPSY

The amygdaloid connections as a substrate for limbic epilepsy.

It has been shown that of all subcortical areas tested, the amygdala has one of the lowest thresholds for EEG seizures and overt convulsions following electrical stimulation (Alonso-de Florida and Delgado, 1958; Delgado et al., 1971; Goddard et al., 1969). The ictal symptoms of temporal lobe epilepsy are well known since the days of Hughlings Jackson (1899) who described them in detail under the heading "Uncinate Group of Seizures". Jackson described aural automatism occurring in uncinate fits as licking, chewing, tasting, and smacking movements. In the opinion of Magnus et al., (1952), masticatory seizures involve a distrubance of consciousness and constitute a type of automatism. Salivation, taste, and smell may be ictal accompaniments, suggesting that the area from which masticatory seizures originate is a sensorimotor region for oral functions. These authors concluded that, to obtain mastication from the temporal region, a subcortical mechanism must be activated, and the most likely subcortical structure is the amygdala.

As mentioned above, some clinical features of certain temporal lobe epilepsy probably reflect amygdaloid functions; the lower range threshold and outbursts of aggression suggest an upset in the function of the amygdala. Following such seizures, aggressive behaviour may occur in individual cases as part of a confusion state. The inter ictal features of temporal lobe epilepsy such as sudden or violent outbursts of rage and irritability can possible be understood in terms of the amygdala. The limbic system appears to play an important part in the experience of fear and anger and in initiating the associated patterns of behaviour. Egger and Flynn (1963; 1967) stress the fact that one of its important functions, and of the amygdala in particular, is to modulate the activity of other areas, especially the hypothalamus. The limbic system receives signals from cortical and other centres concerned with the external environment and other signals indicating the state of the viscera or the internal environment. It is suitably placed to compute requirements and to initiate appropriate actions which will be subject to modification by previous learning experiences and, particularly in man, through the intervention of the frontal cortex and the dorsomedial nucleus of the thalamus (MacLean, 1958) which permit predictions of the possible outcome of the proposed course of action. Kluver and Bucy (1937) described the effects of bilateral temporal lobectomy on rhesus monkeys. Of the various components of the Kluver-Bucy syndrome the most obvious is tameness and placidity - which can be regarded as an unresponsiveness to fear and anger-provoking stimuli. Lesions restricted to the amygdala have a similar effect and have been demonstrated in a wide range of animals (Goddard, 1964). Amygdalectomized animals can still show normal aggression and fighting if the stimulus is strong enough.

Chatrian and Capmann (1960) could, by stimulation of the amygdala, provoke all the EEG characteristics of psychomotor fit, but this would not occur upon isolated stimulation of the hippocampus. They never found any seizure activity on the cortical electrodes without activity in the amygdala, but amygdala activity was frequently found in paroxysms without any reflection of this on the cortical electrodes. Stimulation of the amygdala can produce arousal reactions of many different kinds. These arousal effects are widespread and involve many neuronal systems, both autonomic and somatic. In some ways they are reminiscent of the effects found from stimulation of the midbrain reticular formation.

Synergy of Mesolimbic Cholinergic. Monoaminergic Mechanisms.

The cell bodies of monoaminergic (MA) neurons occupy different situations in the brain from those of cholinergic neurons, but the course and distribution of their fibres are to some extent similar. Both are largely a heavy cholinergic and DA innervation. The two systems operate in close synergy. Dopamine in particular has been implicated as an inhibitory transmitter in the amygdala (Ben-Ari et al., 1977). The apparent presence of *cholinergic* and *monoaminergic* neurons in the limbic system suggest a certain parallel with the peripheral autonomic nervous system. In the hippocampus, for example, histochemical stains have indicated that its main afferent pathways are cholinergic in type. On the other hand, radioautographic and fluorescent studies have detected a notable concentration of NA in the hippocampus. Serotonin studies have indicated a relatively high concentration in the grey matter of the hippocampus.

These findings are of special interest in view of the evidence that tranquilizing and psychotropic drugs known to affect the metabolism of serotonin and noradrenaline appear to have some predilection of action on hippocampal function as revealed by changes in the EEG (MacLean, 1970). MacLean also points out that the limbic system seems not only to exert powerful influences on the autonomic and neuroendocrine centres, but may also be the reacting organ to double antagonistic (and probably synergestic) innervation of the peripheral organs. Finally, there is a difference between the central cholinergic and MA systems that recalls a distinction between the parasympathetic and sympathetic innervation of the periphery, and which may well have functional implications: the cell bodies of MA neurons tend to be further removed from their target areas. In some regions of the brain e.g. the superior colliculus and the olfactory tubercle, and also the neostratum, the cholinergic innervation appears to be largely an intrinsic one. This suggests that the MA systems are more divergent than the cholinergic systems and may be expected to produce more generalized effects.

LIMBIC EPILEPSY AND THE DYSCONTROL SYNDROME

Descriptive associations between limbic epilepsy and mental disorders are very old

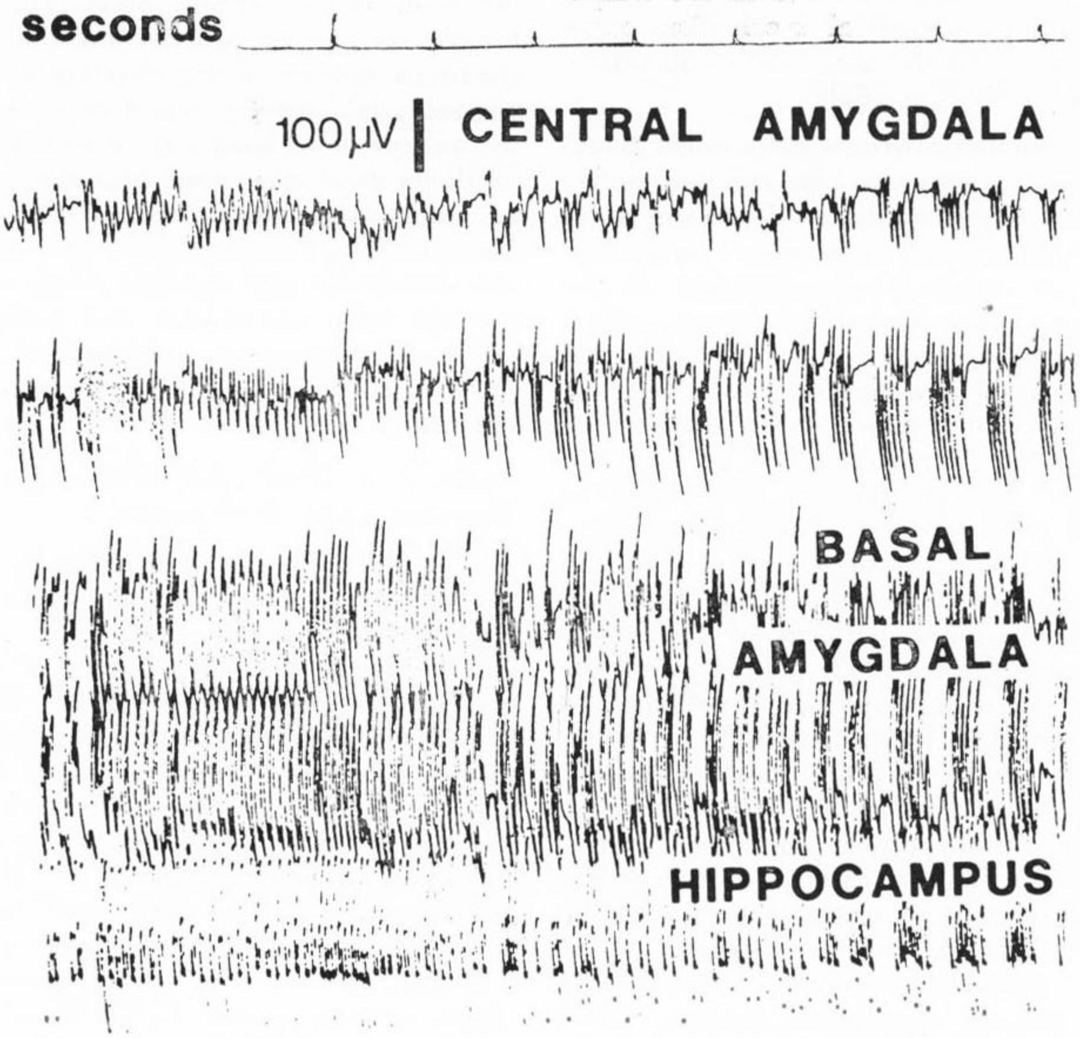

Fig. 1. — *EEG record showing after discharge in limbic structures following kindling stimuli. The top tracing is: central amygdala-globus pallidus; the second is: central amygdala-basal; the third and fourth: within the basal amygdala; the fifth tracing is: within hippocampus.*

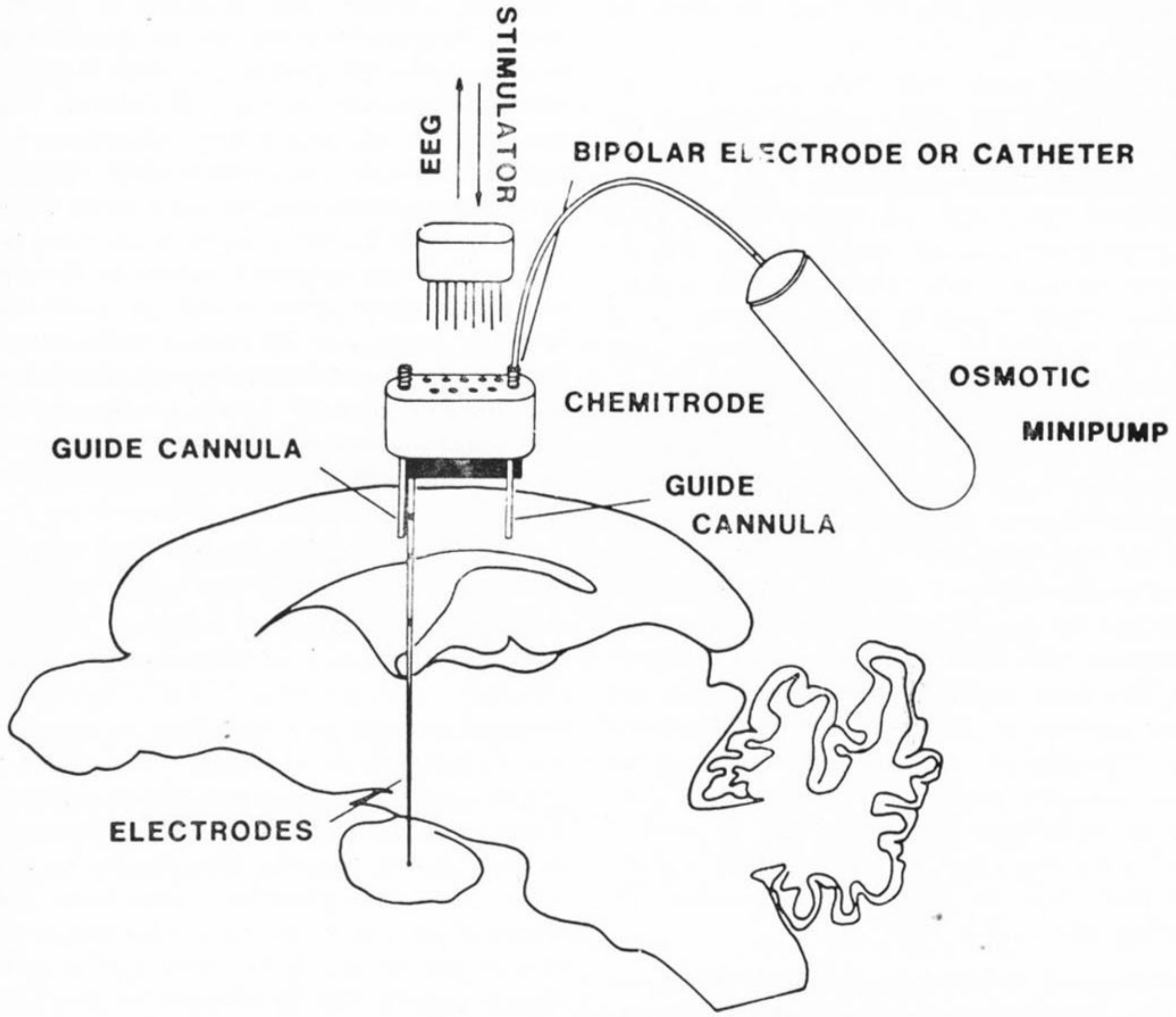

Fig. 2. — *Illustration showing the chemitrode-minipump assembley.*

and are found throughout the literature. Recent investigations have shown that dysfunction of the limbic system of the brain underlies many disturbances of emotion and may result in some psychotic manifestations. The interseizure symptomatology of some patients with psychomotor (limbic) epilepsy may be indistinguishable from that of paranoid schizophrenia. Irritative lesions in or near the limbic cortex give rise to epileptic discharges accompanied by emotional feelings of terror, fear, strangeness, unreality, sadness, wanting to be alone, and feelings of paranoid nature (MacLean, 1970). There may also distortions of perception, again reminding one of the endogenous toxic psychosis. MacLean believes that of all the clinical entities there is perhaps none that has a greater potentiality for shedding light on mechanisms underlying psychic functions in man than psychomotor or limbic epilepsy.

Ervin et al. (1955) found that 81 % of 42 patients with EEG foci in the temporal lobes had a diagnosis of schizophrenia, whether or not there was an associated epilepsy. Personality disorder is the most frequent diagnosis. Depression is next, followed by the diagnosis of inadequate personality and phychosis. In both men and women who continued to have psychiatric symptoms, delusions were much less prominent than depression. Reports have also been made of patients with schizophrenia-like psychosis. Thought disorder and blunt affect, as well as primary delusions and hallucinations, were present, and occasionally, catatonic features. The criteria for defining agressive behaviour were acts of explicit physical violence. Most of the aggressive patients were young boys with an early age of onset of seizures.

In recent years there has been increased recognition of the occurrence of seizures involving behavioural automatisms. Visceral disturbances and personality and thought disorders (Baldwin and Bailey, 1958; Gastaut, 1953; Glaser and Dixon, 1957; Glaser, 1967; Lennox 1960; Penfield and Jasper, 1954). They appear in at least 25 % of all seizures states in childhood and in over 50 % of those in adult life. They may coexist with generalized and grand mal convulsions, but occur much less frequently in association with petit mal epilepsy. This complex seizure disorder has been designated as "psychomotor" because of its common association with lesions of the temporal lobe and its involvement with temporal lobe functions, the term "temporal lobe seizure" has also been applied, particularly since the investigations of Jackson (1931). However, the disturbances of functions involved in these seizures strangely implicate the integrated structures considered to be within the *limbic lobe*, and in 1953 Fulton suggested that these be regarded as "seizures involving the limbic lobe".

Pathological Substrates of Limbic Epilepsy.

The pathological changes underlying temporal lobe epilepsy and their pathogenesis have been considered by several groups of neuroscientists working in this field. Analysis of the pathological findings show that small focal lesions were encountered in about 25 % of the cases; the location of such lesions was found to be particularly marked in the anterior, inferior, and inferomedial portions of the temporal lobe. In the remaining cases diffuse and disseminated lesions comprising cortical atrophy and white matter gliosis in varying proportions were observed ranging from marked to minimal. In some of the more severely affected cases sclerosis of the hippocampus (Ammon's horn) usually extending to the uncus was also observed, and less frequently of the amygdala as well (Falconer et al., 1958).

It has been shown that in cases with diffuse lesions there is a more frequent history of epilepsy, a higher incidence of abnormal birth, a younger age of onset of epilepsy, and a frequent association of hemiatrophy of the skull, all indicating that frequently the epilepsy arose in early childhood. When the variety of personality disorders were compared with the pathological findings, certain important distinctions could be discerned. Thus in the subgroup of cases with Ammon's horn sclerosis outbursts of aggressive behaviour were noted in more than half the cases, a proportion nearly twice as great as in any other subgroup. Grahd mal was present in only a few of the tumours and haematomas, while it was present in more than half the cases with diffuse lesions.

Certain fit characteristics were analyzed for their incidence in the main subgroups without any striking correlations being noted. The incidence of abdominal, cephalic, olfactory and gustatory, fear, familiarity, strangeness, memory, and *deja vu* sensations was approximately the same throughout the various subgroups, as was the incidence of mastication during seizures. The commonest aura by far in the two groups was an abdominal (usually epigastric) sensation. These observations are in keeping with the dictum that is not so much the nature of a pathological process which determines the fit-pattern as its site.

There is also a marked similarity in the EEG findings of the various pathological subgroups. It is noteworthy that in almost half the cases with tumor or haematoma, lesions which presumably are strictly unilateral in situation, there was an apparently independent subsidiary focus of spike discharges in the opposite temporal lobe. It is also noteworthy that independent subsidiary foci in the opposite temporal lobe were also noted in a similar proportion of the cases with disseminated lesions (with or without Ammon's horn sclerosis). However, if cases showing spread of discharges from the ipsilateral temporal lobe to the opposite temporal lobe were also included, the proportion in which the opposite temporal lobe was involved was greater with Ammon's horn sclerosis than in the other subgroups.

Scrutiny of the various operative results suggest that there are certain diagnostic criteria by which one can tend to predict the underlying pathology, and so anticipate the therapeutic result. Thus in the subgroup of focal discrete lesions was usually found an onset of epilepsy in adult life, no family history of epilepsy, absence of a history of abnormal birth or infantile epilepsy, symmetry of the skull, and with air encephalograms perhaps another diagnostic or a relative smallness of the temporal horn. In spite of the tumours nature of many of the lesions, symptoms may have been present for many years (a mean of 10 years in some cases). Falconer, et al. (1958) emphasized that if there is a personality change, a history of agressiveness is often present. With this background and no other obvious etiological factor such as severe head injury or arteriosclerosis apparent in the history, the likelihood of a tiny tumor or of a haematoma must be considered.

The Kindling Model of Limbic Epilepsy.

Adamec (1980) presented evidence on lasting behavioural after-effects of repeated amygdaloid stimulation. Adamec's data show that predatory behaviour in the cat can be altered following daily repeated amygdaloid stimulation. He did not stimulate his cats to the point of behavioural convulsions, but repeated the stimulus a few times to lower the after-discharge threshold. This was done bilaterally. The rat killing behaviour of these cats was studied before and after the threshold reduction. Several other studies on the kindling effects were reported recently by Racine et al. (1976). Of central importance to the present argument (kindling model of limbic epilepsy) are the data of these investigators showing marked alteration of evoked potentials following kindling in the amygdala. Potentials evoked in secondary sites by test pulses applied to the primary (kindled) focus are increased in amplitude following kindling. All components of potentials evoked in the hippocampus, preoptic area, ventromedial nucleus of the hypothalamus and frontal pole by amygdaloid stimulation were increased in amplitude following amygdaloid kindling.

If changes in synaptic transmission underly the kindling phenomenon, and if these changes may also underly other more normal physiological processes (e.g. learning), then it is important to consider the pattern of activation required to produce these changes. Racine and colleague determined that it was necessary to trigger epileptiform discharges in order to develop most of the kindling effects. Stimulation that was below after-discharge did not appear to facilitate subsequent kindling with suprathreshold stimulation. If after-discharge were required to produce the kindling effects then it was felt it was necessary to determine the pattern of cell discharge which occurred during an after-discharge. The authors found that the afterdischarge-mimicking pattern of stimulation produced a very strong recruiting response in secondary sites when applied to the amygdala and was effective in the triggering of "first trial" generalized convulsions if run continuously for several minutes.

If one may generalize from the stimulation pattern back to the after-discharge pattern on which it was based, then one of the striking features of an epileptiform discharge is that it is ideally suited for the production of a strong potentiation effect on secondary foci. It seems a likely possibility that the potentiation characteristics of amygdaloid after-discharges might be critical to the kindling phenomenon.

Most of this work has been done on amygdaloid kindling, which probably serves as a good model for most *limbic kindling*. Although the kindling effect can be obtained from stimulation of areas outside of the amygdala, responsive areas are largely restricted to the limbic system and related structures. Within the limbic system, the amygdala has been found to be particularly responsive. There is also a suggestion that the responsiveness of particular areas is related directly to the extent of their connections with the amygdala. Limbic system epileptiform after-discharge develop as the experiment progresses.

Several experiments have shown that the changes in neural response underlying many of these developments are not restricted to the primary (stimulated focus). After completion of amygdaloid kindling, for example, fewer stimulations are required in secondary limbic sites to develop generalized seizures, even after removal of the "kindled" primary focus. These "transfer" experiments established that transnaptic changes in neural response were developing as a result of the kindling treatment. There are a number of features of the kindling effect which are consistent with the hypothesis that synaptic transmission is permanently facilitated between neural structures as a result of kindling. It has not yet been determined, however, that the kindling effect is a result of changes at the synaptic level. Nevertheless, in view of the fact that many examples of synaptic plasticity have been demonstrated, it seems reasonable at this stage to concentrate on the synapse and in neurotransmitters in our investigation of the kindling phenomenon.

Limbic Cholinergic Hypersensitivity.

It was explained above that there are some data which supports the hypothesis that synaptic transmission is permanently facilitated between neural structures as a result of the kindling effect. We will no concentrate on the possible neurotransmitter mechanisms underlying limbic epilepsy. The changes in neural response underlying the kindling processes are not restricted to the primary focus. After completion of the amygdaloid kindling, fewer stimulations are required in secondary limbic sites to develop seizures, even after removal of the kindled primary focus. These "transfer" experiments established that trans-synaptic chan-

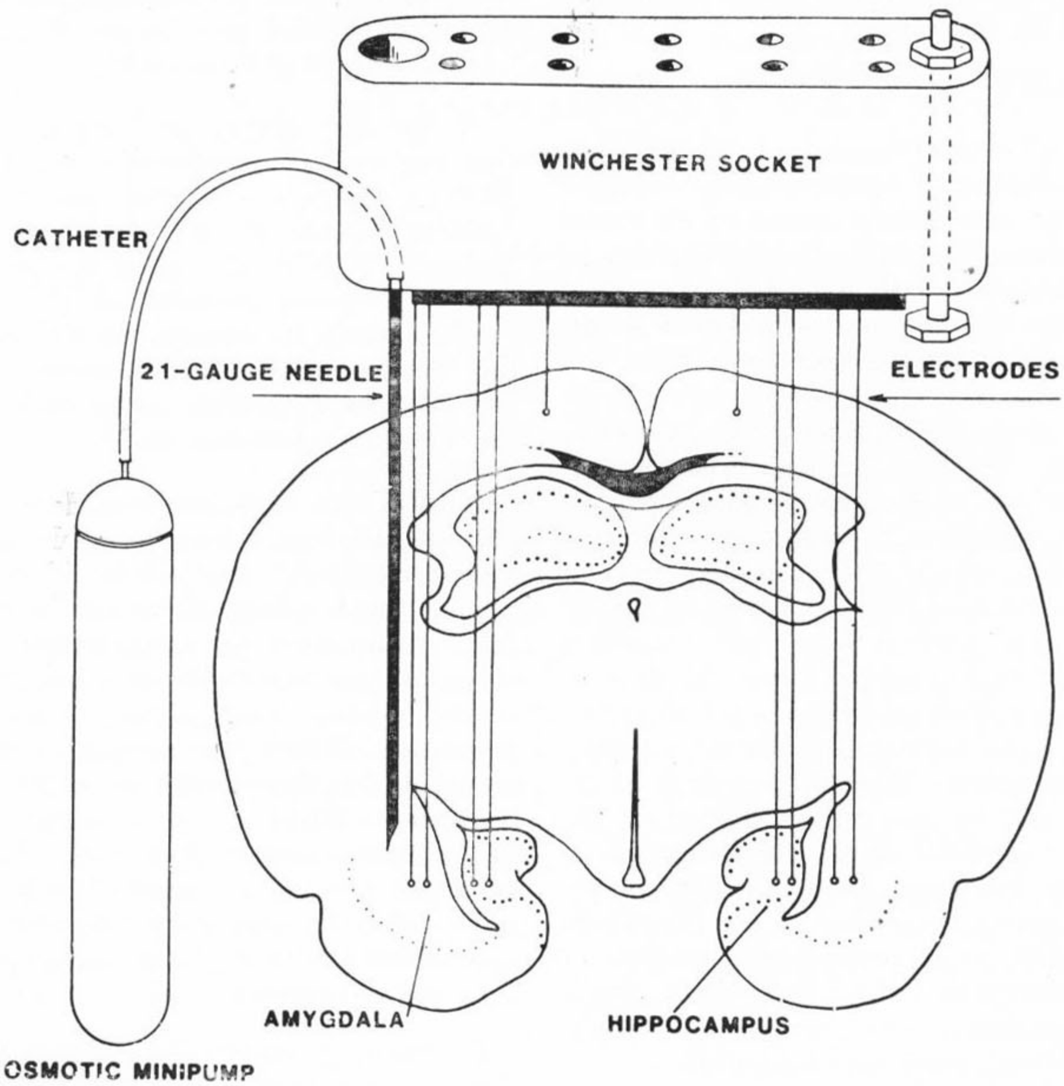

Fig. 3. — *Illustration showing the osmotic minipump and bilateral electrode implanation.*

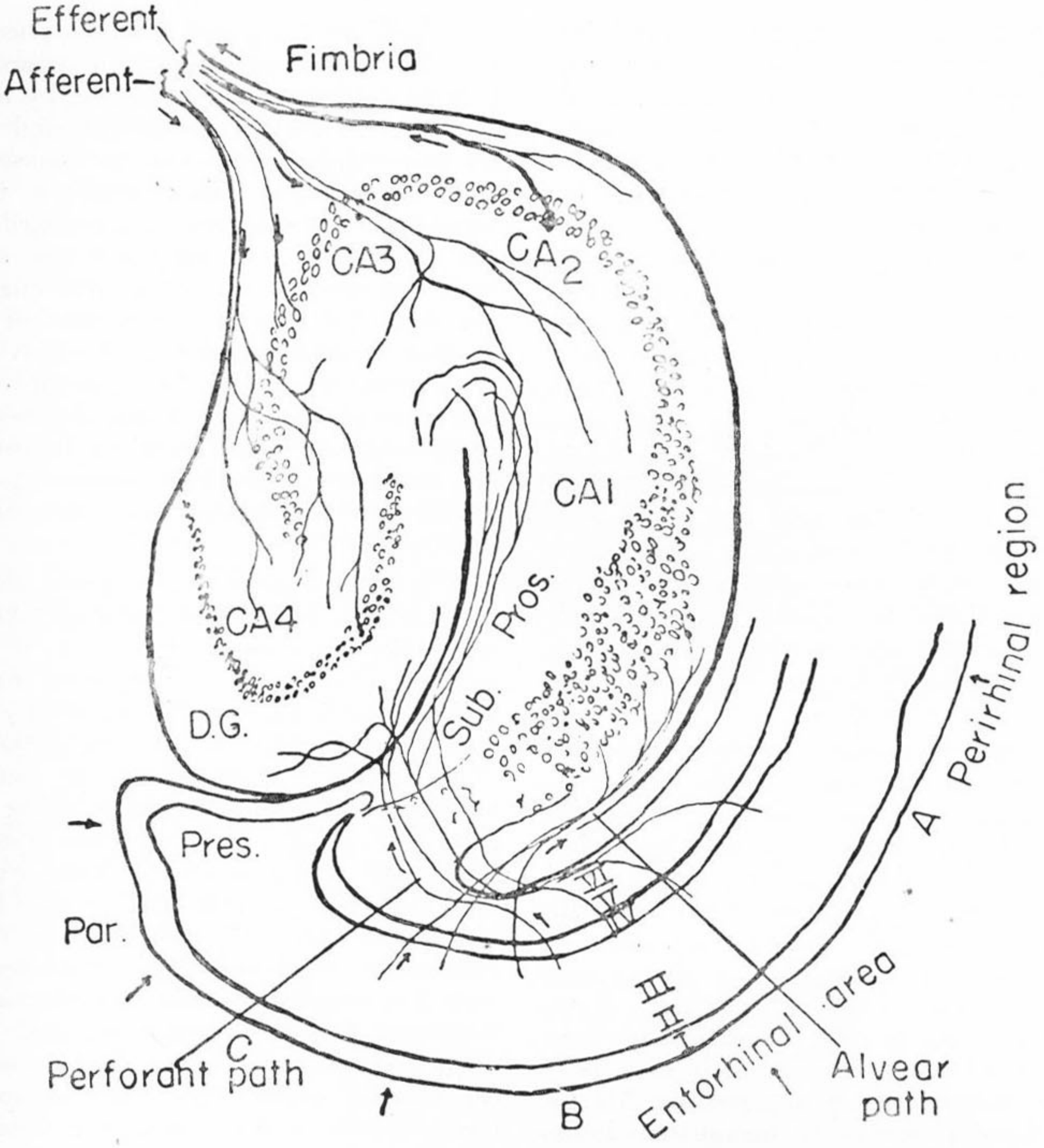

Fig. 4. — *Illustration showing different parts of the hippocampal formation. Note that CA3 of the hippocampus in most susceptible to degenerative changes following seizure activity.*

ges in neural response were developing as a result of the kindling process. Several lines of evidence demonstrate that when the amygdala is stimulated, either electrically or chemically, long-lasting changes occur somewhere in the limbic brain. These changes may be irreversible. The effect can be related to seizure activity present at the time of stimulation.

Participation of Muscarinic Dholinergic Receptors in Kindling.

During recent years there has been increasing evidence of the involvement of cholinergic mechanisms in the cortical mediation of desynchronized activation of the EEG which characterizes the "arousal" response. Celesia and Jasper (1966) have shown that the rate of liberation of acetylcholine (ACh) from the surface of the neostigmized cortex in the cat may increase two to four times during desynchronized cortical activations with arousal, as compared to that obtained during slow wave and spindle sleep. Furthermore, studies of chronically isolated cortex, which have been reported to show spontaneous epileptiform discharges, show increased sensivity to topically applied ACh (Echlin and Battista, 1963). Increased reactivity of the isolated cortex to ACh suggests that supersensitivity to endogenous ACh may be a factor in cortical epileptogenesis.

Partial or total isolation of the cerebral cortex was offered recently as a model for the study of focal epilepsy but several investagators (see Ferguson and Jasper, 1971; Chu et al., 1971; Spehlmann, et al., 1971). These authors investigated the implications of denervation (or "disuse") superdensitivity to putative transmitters. Echlin and Battista (1963) indicated that after weeks or months, the isolated cortex showed spontaneous epileptiform discharges and increased sensitivity to topically applied AcH. Isolated cortex may sustain prolonged epileptiform afterdischarges. This is one measure of supersensitivity.

A causal relationship berween supersensitivity and an alteration in the cholinergic system has been suggested (Echlin and Battista, 1962), based on the observations that there is a decrease in the AChE activity in isolated cortex (Hebb et al., 1963; Rosenberg and Echlin, 1968) and a *decrease in AChE activity parallels in the increase supersensitivity*. Increased reactivity of the isolated cortex to ACh suggests that supersensitivity to endogenous ACh may be a factor in cortical epileptogenesis. All my histochemical studies in mammalian brains (referred to above) point to the fact that some of the highest (AChE) activity in the whole brain is to be found in limbic structures, particularly the basal amygdala.

Recently, Chu et al, (1971) studied the effect of cortical undercutting and long-term electrical stimulation on synaptic AChE. These authors found that a decrease in AChE activity parallels the increase in supersensitivity. In this investigation the authors were studying partial or total isolation of the cerebral cortex as a model for focal epilepsy. They reached the conclusion that a decrease in the activity of AChE and the supersensitivity in undercut cortex are likely to be the consequences of the loss of cholinergic innervatuon and of synaptic "disuse" following denervation.

It has been suggested that the phenomenon of supersensitivity of the neuronally isolated cortex may be explained by an increased sensitivity of subsynaptic and possibly nonsynaptic membranes as a consequence of denervation. This is analogous to the supersensitivity observed in denervated muscle. Cannon (1939) suggested that abnormality of cortical cells in epilepsy might be the result of loss of innervation of cells another example of increased sensivity in denervated structures. The increase excitability has been likened to the degeneration supersensitivity which develops in peripheral structures after interruption of their neural input (Cannon and Rosenblueth, 1949).

It is not yet clear if the neural changes that underly amygdaloid kindling take place within cholinergic circuits or if these circuits simply play a supportive role in seizure development. The possibility that cholinergic circuits are involved in the kindling process is indicated by the fact that atropine retards amygdaloid kindling (Arnold et al. 1973). This and other aspects of cholinergic hypersensitivity have recently been discussed by Burchfiel et al. (1979) who found that ACh was the only neurotransmitter for which they could demonstrate a relationship to kindling phenomena. Vosu and Wise found that repeated cholinergic stimulation (carbachol) produced behavioural seizures after several applications, similar to those seen with electrical stimulation, suggesting an important role for cholinergic circuitry in subcortical propagation of epileptiform activity. Similar results were presented by Wasterlain et al. (1978) who further showed that mixing the injected carbachol with the muscarinic cholinergic antagonist atropine reduced seizure. It has recently been reported (Girgis, 1980b) that only a few electrical kindling stimuli are needed to produce prolonged supersensitivity to intracerebrally injected physostigmine. This supersensitivity is correlated with further progression of kindling. Scopolamine, givem I. M, in doses of $120 ug/kg$, suppresses this kindling induced seizures.

Our own findings and those mentioned above show that cholinergic kindling sensitivity of limbic structures parallel electrical kindling sensitivity (Girgis, 1980c). This fits best with the hypothesis that it is cholinergic circuits at the site of stimulation that mediate both *electrically* and *chemically* induced kindling (Girgis, 1981) and that are involved in the retardation of seizure development by anticholinergic drugs. McNamara (1978) found a selective, transient reduction in muscarcinic cholinergic receptor binding in both the stimulated and centra-lateral amygdaloid regions following kindling. Engel and Sharpless (1977) performed a study to examine the hypothesis that kindling itself might produce a decrease in catecholamine-mediated inhibitory influences of the stimulation site, since this could be one mechanism of kindled alterations in excitability. As indicated earlier in this paper, dopamine in particular has been implicated as an inhibitory transmitter in the amygdala. The data reported by Engel and Sharpless mentioned above are consistent with the hypothesis that the enduring focal hyperexcitability produced by kindling stimulation may, in part, be attributed to an enduring stimulus - induced focal decrement in the catechol-mediated inhibition at the site of stimulation.

A permanent alteration in neuronal excitability probably underlies the human epileptic state, particularly the post-traumatic epilepsy, which is most likely to be related to kindling. Some patients who seem to have made good recovery from head injury become epileptic at some time later. Penfield (1956) indicated, that an "incubation" period elapses between the causative brain trauma and the first epileptic attack, and the underlying process may require months or even years to reach fruition. The fact that scopolamine significantly suppressed the kindling-induced seizures in our experiments could have implications for the pharmacological therapy of epilepsy (Girgis, 1981a).

THE USE OF GLUTAMATE AND KAINIC ACID IN LIMBIC RESEARCH

During the last few years, the use of kainic acid (KA) proved to be a useful tool for investigating metabolic and pathological changes in epilepsy (Tremblay et al., 1983). These investigators described an increased glucose uptake in a number of cerebral structures following intra-amygdaloid injections of KA. Most of these structures belong to, or are closely related to, what is traditionally called the "limbic system". The structures that show an increased glucose consumption, subsequent to KA injections are, with few exceptions, identical to those that are sensitive to the toxic effect that KA exerts on structures distant to the site of injection.

Using kainic acid (either alone or combined with glutamine acid), we have studied its epileptogenic properties and also the associated degenerative changes occurring in limbic structures (Girgis, 1985). The prolonged depolarizing effect, with subsequent lowering of threshold of stimulation that would be associated with an abnormal accumulation of excessive quantities of glutamate, we have been able to successfully chemically kindle the amygdala obtaining stage 4 seizure. Intracerebral implantation of 'chemitrodes' was done in limbic structures of cat brain (as shown in Fig. 2). In some experiments, repeated injections were made by a microsyringe. In others, steady-state flow of glutamate was produced by means of an osmotic minipump (Fig.), lasting one to two weeks.

In some experiments, we used KA in minimal doses prior to the glutamate minimum, and this catalyzing the reactor, acted as a primer in the production of the original (pathological) locus as found in the human disorder. Stage 6 seizure was observed in these preparations. In these preparations, the pathological changes in the uncus and CA3 fields of the hippocampus correspond well with the metabolic changes as studied by the deoxyglucose method of Tremblay et al., (1983) mentioned above. The present study indicates that intense amygdaloid epileptiform discharge plays a role in the pathogenesis of remote lesions. It is also likely that these excitotoxins have a role in the brain damage associated with sustained limbic seizures.

In all these preparations, the EEG showed very high amplitude spike activity

(Fig.). Similar EEG results were found in earlier experiments where cholinergic agents were used for producing animal models of limbic epilepsy (Girgis, 1981b). As stimulation of acetylcholine receptors results in sustained seizure activity which damages the brain by unknown mechanisms, and as endogenous glutamate has possible excitotoxic action, it seems likely that glutamate may have a role in the brain damage associated with the sustained limbic seizures. Recent studies support the theory of glutamate as an endogenous neurotoxin (Sanberg and Johnston, 1981; Girgis, 1985). By extrapolation, glutamate is therefore capable, via its necrotizing effect, of producing the epileptic focus associated with limbic epilepsy.

SUMMARY

Malfunctioning of the limbic system may result in sumptoms that do not involve any apparent change or disease in brain structures. As will be shown in this presenation, experimentally induced chemical changes in certain limbic structures often result in behavior similar to the interseizure symptomatology of human limbic epilepsy. In man, this condition may be associated with personality disturbances or even a clinical picture indistinguishable from that of certain forms of schizophrenia. Distortions of perception may occur. Of the variety of epilepsies, which begin in, or are confined to, a particular part of the brain, the most important with regard to impulsive or episodic dyscontrol is limbic epilepsy.

In association with the suggestion that the kindling phenomenon is involved in the development of some forms of human epilepsy, and that the behavioral disturbances associated with them may also reflect dysfunction within the limbic system, recent studies have also suggested the possible relevance of limbic system kindling for the development of psychopathology in primary and secondary affective illness. In some earlier studies-using cerebrally implanted chemitrodes - we found that cholinergic kindling sensitivity of certain limbic areas, parallels electrical kindling sensitivity. This is consistent with our previous pharmacological investigations implicating muscarinic cholinergic synapses in the genesis of limbic epilepsy.

More recently, we used osmotic-minipump assembly for intracerebral injection of glutamate and kainic acid. This study indicates that intense amygdaloid epileptiform discharge pays a role in the pathogenesis of 'remote' lesions. It is also likely that these excitotoxins have a role in the brain damage associated with sustained limbic seizures.

RESUMEN

Disturbios funcionales del Sistema límbico pueden ocasionar síntomas que no involucran ningún cambio aparente o enfermedad en las estructuras cerebrales. Como será mostrado en esta presentación, cambios químicos inducidos experimentalmente en ciertas estructuras límbicas a menudo resultan en conducta similar a la sintomatología intercrítica de la epilepsia límbica humana. En el hombre, esta condición puede estar asociada con disturbios de la personalidad o mismo un cuadro clínico indistinguible del de ciertas formas de esquizofrenia. Pueden ocurrir distorsiones de percepción. De la variedad de epilepsias, las que comienzan, o están confinadas a un sector particular del cerebro, las más importantes en lo relativo a impulsivo o episódico desajuste es la epilepsia límbica.

Asociado con la sugerencia de que el fenómeno del impulso está involucrado en el desarrollo de algunas formas de epilepsia humana y que los disturbios de conducta asociados con ellos pueden también reflejar disfunción en el seno del sistema límbico, recientes estudios han también sugerido la relevancia posible de impulsar del sistema límbico para el desarrollo de psicopatología en enfermedad afectiva primaria y secundaria. En algunos estudios anteriores empleando quimitrodos implantados en el cerebro, encontramos que la sensibilidad impulsiva colinérgica de ciertas áreas límbicas, es paralela a la sensibilidad eléctrica de los im-

pulsos. Esto es consistente con nuestras previas investigaciones farmacológicas implicando sinapsis colinérgicas muscarínicas en la génesis de epilepsia límbica.

Más recientemente usamos una unión osmótica minibomba para inyección intracerebral de glutamato y ácido Kainico. Este estudio indica que descarga intensa epileptiforme, amigdaloide juega un rol en la patogénesis de lesiones "remotas". Es también probable que estas excitotoximas tienen un papel en el daño cerebral asociado con ataques límbicos sostenidos.

RÉSUMÉ

Cestains troubles fonctionels du systeme limbique paivent ne pas provoquer de changements aparents ou non dans les structures cerebrales. Comme il sera montré au cour de celle presentation, des changements chiniques induits expérimentalement dans certaines structures limbiques provoquent souvent des comportements similaires a ceux de la conduite intercrise de l'epilisie limbique humaine. Chez l'homme cette syptomatologie peut etre associée a des troubles de la personalité ou meme des tableaux similaires a certaines forme de squisophénie. Il peut y avoir des troubles de la perception. Parmi les epilepsie, celles qui commencent ou restent confinées a une seeteur particulier du cerveau, les plus importantes, en relation avec l'impulsivité, ou episodies de desorganisation, sont l'epilepsie limbique.

Associe a la possibilité que les impultions soient en relation avec quelques formes d'epilepsie humaine et que les troubles de la conduite qui en défendent et qui peuvent etre dut a un trouble au systeme limbique. de recentes études ont aussi montrés la possibilité d'impulser le complexe limbique pour le developement de la psychopathologie de la maladie afective primaire et secondaire. Dans des travaux anterieurs il était employé des "chimiotzodes" implantés dans le cerveau, et on trouve que la sensibilité impulsive colonergique de certaines zones limbiques est paralille a la sensibilité electrique des impulsions. Ceci est en accord avec nos investigations anterievres de farmacologie qui indique des synapses cholinergiques muscariniques dans la génese de l'epilepsie limbique.

Plus recement on a utilisé una minipompe osmotique pour l'inyection intracerebrale de glutamate et d'acide kainique. Cette etude met en evidence une decharge amygdalienne epileptiforme et qui jove un rele tres important dans la pathogenie des lesion eloignées.

Il est aussi probable que ces exitotoximes ont une responsabilité dans les lesions cerebrales provoqués par les crises limbiques repetées.

ZUSAMMENFASSUNG

Die funktionellen Stoerungen des limbischen Systems koennen Symptome hervorrufen, die ansch einend keine Veraenderung oder Erkrankung der zerebralen Strukturen. beinhalten. Wie indieser Arbeit gezeigt wird, erzeugen ha eufig chemische Veraenderungen, die experimentell an gewissen limbischen Strukturen hervorgerufen werden, eine Verhaltungsform, die aehnlich ist der interkritischen Symptomatologie der limbischen Epilepsie beim Menschen. Be im Menschen kann dieser Zustand in Verbindung mit Stoerungen der Persoenlichkeit stehen oder sogar mit einem kllnischen Bild, das man nicht unterscheiden kann von gewissen Formen der Schizophrenie. Es kann zu Perzeptionsstoerungen kommen. Unter den verschiede nen Formen der Epilepsie, die in einem bestimmten Sektor des Gehirns anfangen oder dort beschraenkt bleiben, ist die wichtigste der impulsiven oder episodischen Stoerungen, die limbische Epilepsie.

Ausser der Idee, dassdas Phaenomen des Impulses zur Entwicklung einiger Formen der Epilepsie be im Menschen gehoert, und dass die Stoerungen der Verhaltungsweise mit ihnen vergesellschaftet sind, auch die Dysfunktion im limbischen System widerspiegeln koennen, haben neustre Untersuchungen auch den Gedanken nahegelegt, dass die Reizung des limbischen Systems

moeglicherweise wichtig ist fuer die phychopathologische Entwicklung der primaeren und se kundaeren Erkrakung. Bei einigen Untersuchungen, vorher, hat man Chimiotroden ins Gehirn eingesetzt undman fand, dass die Chollnergische Impulsive Sensibilitaet gdwisser limbischer Zonen parallel geht mit der elektrischen Sensibilitaet der Impulse. Dies bestaetigt unsere frueheren pharmakologischen Untersuchungen ueber cholinergisch-muskarinische Synaps is bei der Entstehung der limbischen Epilepsie.

Detztdns benutzten wir einen Osmotisch-Minipumpen-Apparat fuer die intrazerebrale Injektionvon Glutamat und Kaimic Saeure. Diese Untersunchung zeigt an, das intensive amygdaline epileptiforme Entladungen eine Rolle bei der Pathogenese "remoter" Laesionen spielen. Es ist auch wahrscheinlich, das diese Excito-Toxine eine Rolle spielen bei der Hirnschaedigung mit anhaltenden limbischen Anfa ellen.

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Hypothalamic Output Controlling Reticulospinal and Vestibulospinal Systems Important for Emotional Behavior

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Relation of Reflex to Motivational Components of Behavior

Sexual behavior in man is an emotional and motivated behavior involving limbic and hypothalamic structures regulating autonomic function. Even in the female rodent, it has been known since the early work of Warner (1927) that a female rat will cross an electrified grid to get to a male rat and that the frequency with which she does this is a function of her estrous condition. Meyerson and Lindstron (1973) clearly demonstrated that sexual motivation in the female rodent is a function of estradiol and is specifically sexual rather than generally social. They showed in runway choice experiments that estradiol increases the ovariectomized female rat's preference for intact males over castrate males or females.

That at least some aspects of reproductive behavior in the female rodent are motivated should not be too surprising. Motivational signals, especially humoral signals, have major impacts upon hypothalamic neurons, and neurons controlling lordosis behavior, the copulatory posture of the female rat, reside in the ventromedial nucleus of the hypothalamus (VMN) which contains large numbers of the necessary estradiol concentrating cells (Pfaff and Keiner, 1973). It has been shown with prolonged electrical stimulation and in ablation studies that VMN facilitates lordosis performance (Pfaff and Sakuma, 1979 a,b); furthermore, Davis and co-workers (1982) showed that nanograms of estradiol implanted directly into VMN permits lordosis in response to adequate stimulation by the male within 48 hrs of implantation. About 30 % of estradiol concentrating cells project to the midbrain central gray (Morrell and Pfaff, 1982). Rapid facilitation of lordosis occurs following electrical stimulation of central gray (CG) and following local infusions of LHRH into CG (Sakuma and Pfaff, 1979; 1983). Sakuma also showed that CG projects to nucleus gigantocellular (NGC) of the medullary reticular formation by antidromic invasion, and that antidromic invasion was enhanced by VMN stimulation and by systemic estradiol (Sakuma and Pfaff, 1980 a,b). Large lesions of NGC cause severe deficits in lordosis (Modianos and Pfaff, 1979). Stimulation and ablation studies show that Deiter's nucleus is also necessary for the behavior (Modianos and Pfaff, 1976 a,b). Therefore, as would be predicted, spinal animals will not perform lordosis, but the anterolateral columns through which reticulospinal, vestibulospinal, spinoreticular and spinovestibular fibers travel, is a sufficient link between the brainstem and spinal cord to permit the behavior (Kow et al., 1977).

Medial hypothalamic neurons also project to the limbic system upon which many

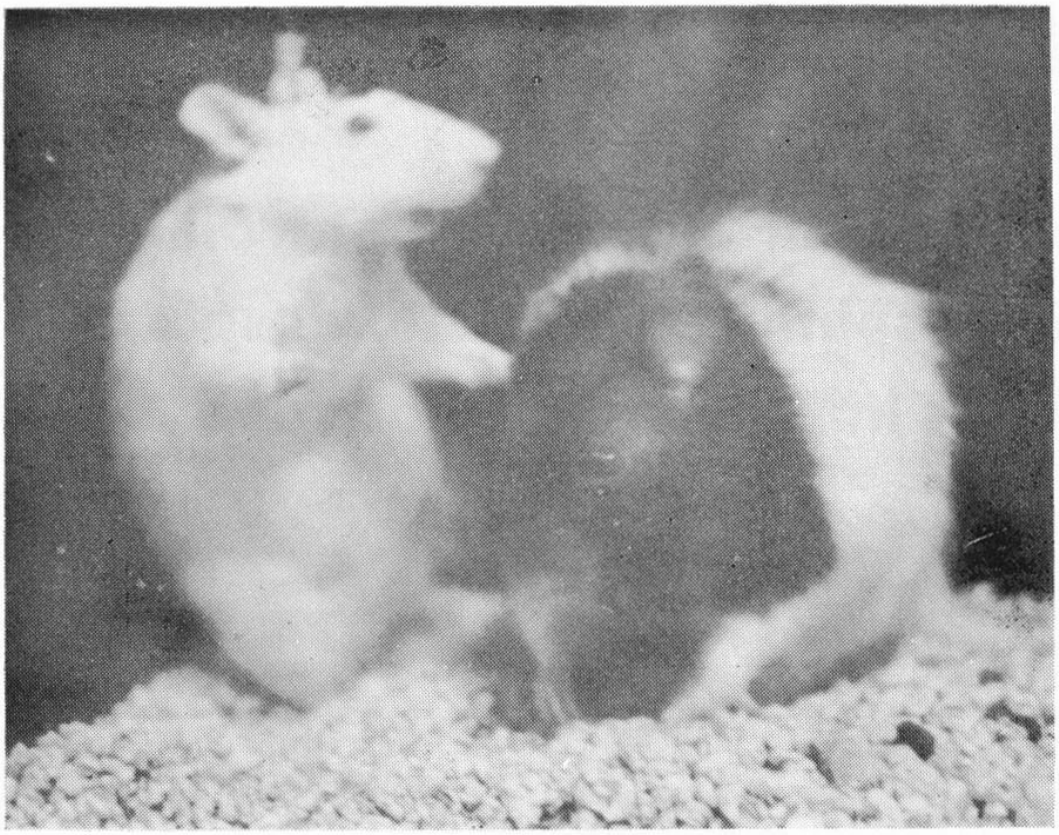


Fig. 1. — *Photograph taken during a 10 minute mating test immediately following a 10 ul intrathecal injection of 1ug bicuculline to a Sprague-Dawley ovariectomized female rat implanted for more than one week with an estrogen silastic and primed with 500 ug progesterone 4 hr preceding the test (the male is black hooded). The female, rearing with her back against the wall of the cage, is actively avoiding contact by the male. Photograph by Denis R. Giblin.*

emotional states depend, and limbic structures project heavily back to the medial hypothalamus: e.g. Sakuma and Pfaff (1982) showed that VMN neurons can be antidromically invaded from the amygdala and that the amygdala has synaptic projections to the same VMN neurons that can be antidromically invaded from CG. Anatomical evidence for a direct projection from amygdala to CG has been demonstrated in the rat, cat and monkey (Beitz, 1982; Hopkins and Holstege, 1978 and Mantyh, 1982). Electrophysiological evidence for a short latency direct excitatory projection from basolateral amygdala to central gray in the monkey has been reported by Sandrew and Polletti (1984).

We hypothesize that controls of somatosensory input, partly through GABA, can not only gate reflex responses to cutaneous stimuli, including lordosis behavior, but also impact the general disposition of the animal to contact stimuli which are important for a variety of social behaviors.

Control of Cutaneous Inputs Important for Copulatory and Other Social Behaviors

While a general sexual *motivation* in the female rat has been demonstrated, one can also view the copulatory aspect of female reproductive behavior, lordosis, as an estrogen-dependent somatosensory *reflex* under suprasegmental control. Data from current experiments in our laboratory on mating behavior show that one can discriminate between the two aspects of sex behavior (i.e., the general disposition to somatosensory input and the lordosis reflex response) with intrathecal injections of the GABA antagonist bicuculline. We chose to examine the effects on reproductive behavior of bicuculline administered into the spinal cord because the distribution of Gabaergic terminals in the spinal cord parallels that of the spinal cord estrogen concentrating cells and from this distribution one would predict that both estrogen and GABA play a role in modulating the transmission of sensory information. Both are present in higest concentration in the substantia gelatinosa and dorsal to the central canal (McLaughlin et al., 1975; Morrell et al., 1982); both are noticeably absent from motoneurons, by contrast with androgen receptors (Breedlove and Arnold, 1983).

Within 5 minutes of injections of 1-4 nM (0.5 - 2ug) of bicuculline into the lumbar subarachnoid space, female rats develop a syndrome of hyperalgesia (Schwartz-Giblin and Pfaff, 1985; manuscript in progress, 1986). This can be quantified as an aversive response to von Frey hair stimulation of the skin of the trunk which was innocuous in the control period. Furthermore, in mating tests occuring within the first 10 minutes of an intrathecal injection of bicuculline, an ovariectomized female primed with estrogen and progesterone will avoid male contact by kicking, rearing, turning over or getting into the corner of the test cage (Fig. 1). When an Avoidance Index equal to the number of kicks, turns over and rearings of the female divided by the number of mounts and attempted mounts by a stud male is calcuated, invariably (6/6 females) the Avoidace Index increases following bicuculline: (mean $\pm$ S.E.) before, 8.7 $\pm$ 3.09; after, 57.3 $\pm$ 23.41, ($p < o.1$ t test two-tails) but not following saline: before, 37.3 $\pm$ 27.34; after 9.7 $\pm$ 9.66 (n=3). Yet *despite* contact avoidance, if the male can mount well, the lordosis reflex is not significantly affected qualitatively or quantitatively. The data show that for the same 10 minute period following drug, the Lordosis Quotient (L.Q.), which is equal to the number of elicited lordoses divided by the number of mounts with thrusting, shows no change: (mean $\pm$ S.E.) before, 94.2 $\pm$ 3.74; after, 87.5 $\pm$ 6.80 (n=6).

The effect of bicuculline is undoubtedly occuring in the spinal cord; the latency of 1.5-3 min is short, and equal volumes of fast green dye at similar concentrations injected intrathecally show evidence of pene-

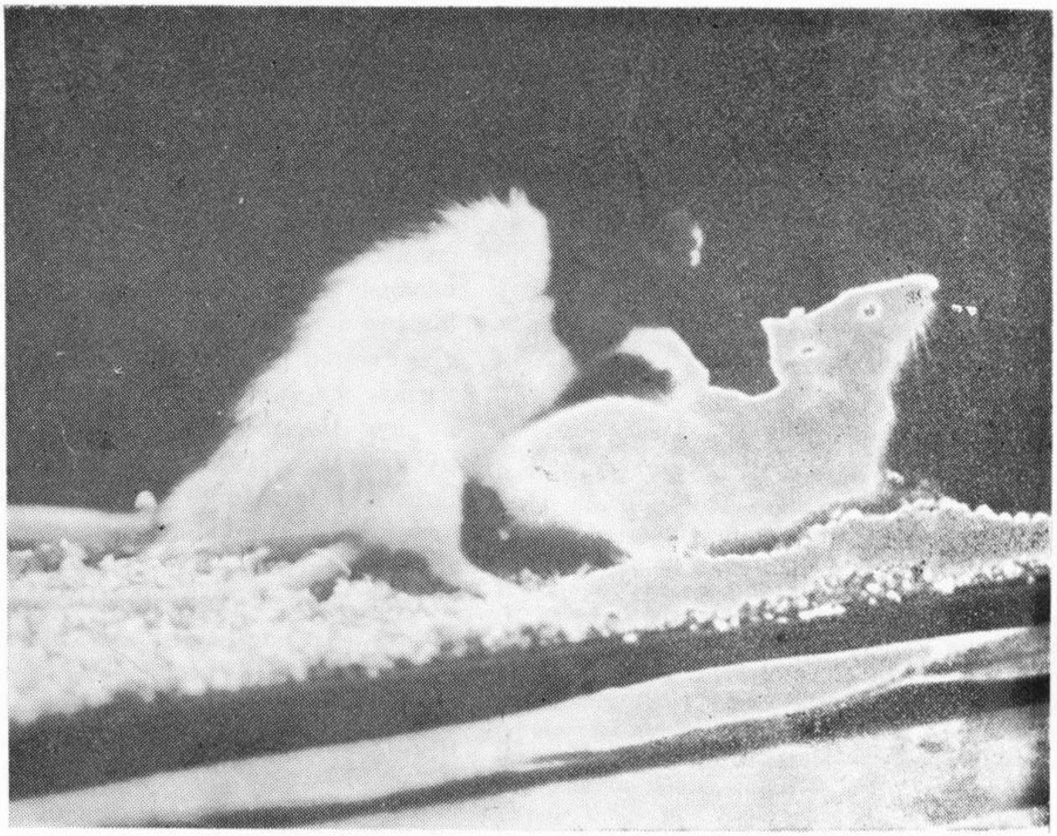


Fig. 2. — *The lordosis posture of the female rat involves extension of the spine throughout its length. Rump elevation exposes the perineum and is therefore essential for fertilization. Photograph by Denis R. Giblin.*

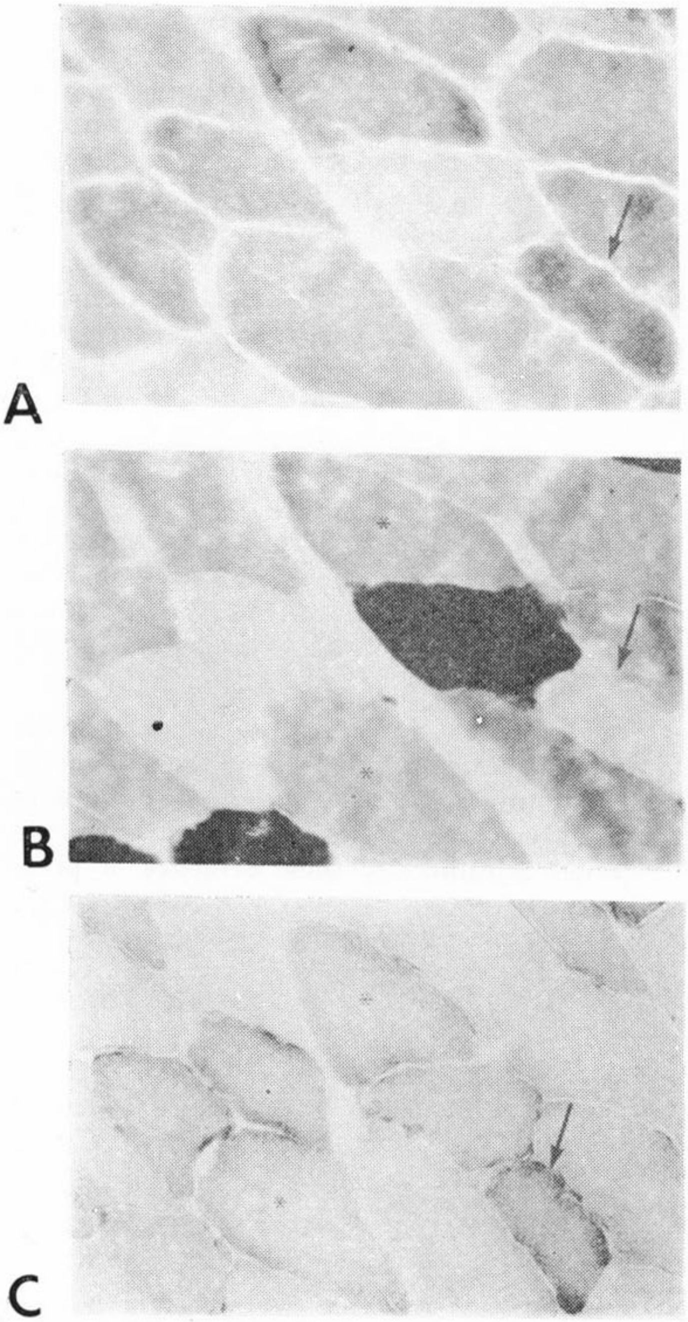


Fig. 3. — *Serial sections from the superficial part of lateral longissimus muscle in which slow-twitch oxidative (SO) fibers comprise 18 % of the total number of fibers. In A and B the tissue is stained for ATPase after pre-incubation in A at pH 9.4 and in B at pH 4.35. The darkly stained SO fiber in B is alkaline labile and therefore does not stain in A. In C the tissue is stained for NADH-tetrazolium reductase to reveal the fibers which would be predicted to be fatigue-resistant: both the fast-twitch oxidative-glycolytic (FOG) and SO fibers. The arrow indicates a typical FOG fiber which shows intense staining for ATPase after alkaline pre-incubation but no stain after acid pre-incubation; in C it shows the characteristic subsarcolemma distribution of formazan granules. A more acid-resistant fast-twitch oxidative-glycolytic fiber, FOG(a) is indicated by the asterisk; this fiber type has also been described in cat tibialis anterior (Dum and Kennedy, 1980).*

tration into the brain in only 1 out of 7 animals sacrificed within 15 minutes.

What could be the spinal mechanism of bicuculline-evoked hyperalgesia? Bicuculline is known to block presynaptic inhibition i.e. primary afferent depolarization (PAD) evoked by GABA at GABA-A receptors on primary afferents in the spinal cord (Levy, 1977; Curtis and Lodge, 1982). GABA is present in terminals presynaptic to primary afferent terminals in the substantia gelatinosa of the rat spinal cord (Barber et al., 1978). GABA acting at A receptors has been shown to depolarize lumbar A beta and A delta fibers more than C primary afferent neurons, (Desarmenien et al., 1984). The large low threshold cutaneous afferents, the A beta fibers, are responsible for the pudendal nerve-evoked response in axial muscles which we believe is part of the substrate for the lordosis reflex response (Cohen et al., 1985).

GABA is also known to inhibit strongly, the activity of high threshold and wide dynamic range spinothalamic projection neurons in laminae I and V of primate dorsal horn (Willcockson et al., 1984). Applications of bicuculline topically to rat spinal cord has been demonstrated to increase the C fiber-evoked activity of wide dynamic range dorsal hhorn neurons and also observed to increase A fiber-evoked activity (Dickenson et al., 1985). Such an effect of bicuculline would tend to signal nociception because under normal conditions cells in lamina I of the cat, for example, are strongly excited by nociceptive inputs but only weakly excited but very strongly inhibited by low threshold inputs (Steedman, Molony and Iggo, 1985). Many of these cells in lamina I terminate in the midbrain in and around CG and have collateral ending in the medullary reticular formation (McMahon and Wall 1983, 1985; Swett et al., 1985). In addition, by blocking GABA produced PAD, bicuculline would tend to increase the synaptic efficacy of nociceptive inputs carried in A delta fibers and in addition, increase the efficacy of low theshold cutaneous afferents in the cutaneous reflex circuit leading to lordosis. The combined effect would be to promote contact avoidance by eliciting hyperalgesia to innocuous tactile stimulation but to sustain the copu-

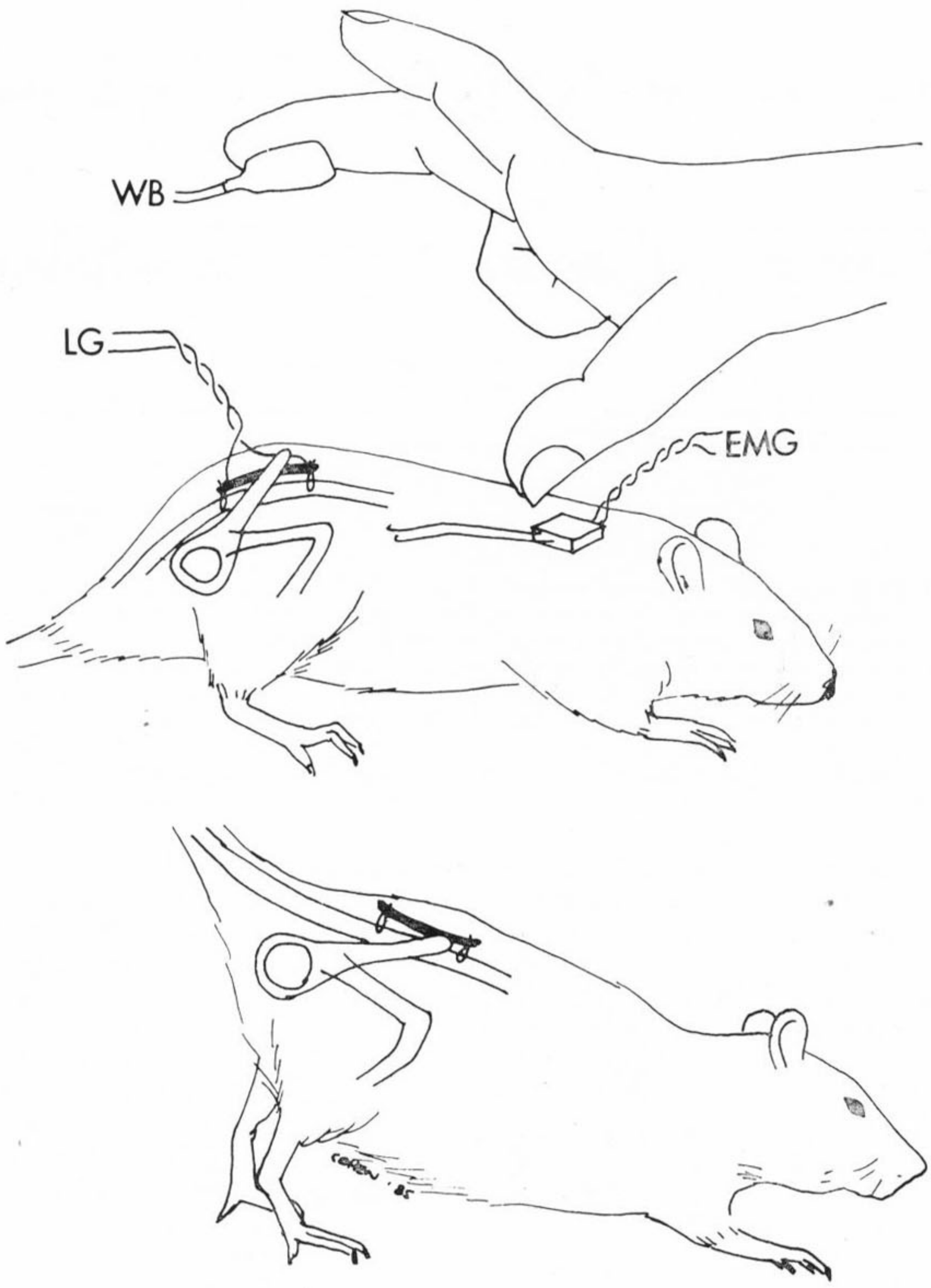


Fig. 4. — *Diagram of the method used to record EMG from awake, unrestrained female rats during the performance of manually elicited lordosis. See text for description.*

latory reflex response under adequate stimulation conditions.

During mating tests with ovariectomized females primed with estrogen, behaviors very similar to that observed with intrathecal bicuculline can be seen. Females demonstrate active and passive avoidance of the male but display an adequate lordosis response to adequate somatosensory stimulation by the male. Only after sufficient estrogen replacement or treatment with both estrogen and progesterone does the female lose her irritability and, infact show soliciting behavior. Our working hypothesis is that one of the roles of estrogen-concentrating neurons in the spinal cord is to modify sensory signalling by modulating GABA transmission. Specifically, since the irrita-

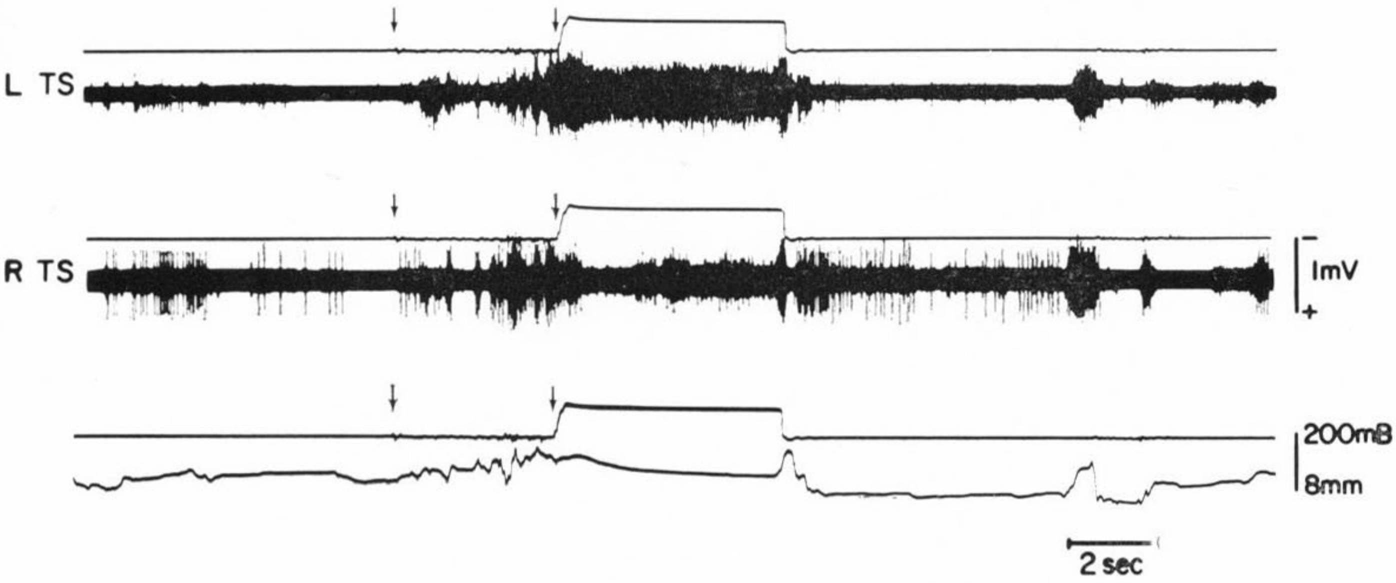


Fig. 5. — *Axial EMG and axial movement evoked by lordosis-eliciting manual stimulation. The upper trace in each record is the stimulus trace; it records the pressure output of a water bulb (WB) on the terminal phalanx of the experimenter's middle finger. Small repetitive fluctuations in the WB record beginning at the first arrow indicate bilateral palpation of the animal's flanks with the thumb and middle finger; the second arrow indicates the onset of perineal pressure applied by the index and middle finger forked around the tail base. The lower trace in the upper and middle record is the EMG of left TS and right TS, respectively. The lower trace in the bottom record indicates length gauge (LG) resistance which is linearly related to changes in gauge length. LG shortening is indicated by an upward deflection in this figure only and reflects rump elevation. The WB is calibrated in millibars (mB): 1 mB=0.75 mmHg.*

bility associated with zero or low levels of estrogen mimics that seen during blockade of GABA transmission, we suggest that decreased activity in the dorsal horn GABA pathways is associated with decreased concentrations of the ovarian steroid hormone. We further postulate that high levels of ovarian steriod hormone activate dorsal horn GABA pathways since estrogen plus progesterone protect against irritability but are incapable of doing so in the presence of the GABA receptor antagonist, bicuculline.

By viewing lordosis as a somatosensory reflex, one can hope to dissect the individual components of the complex behavior in order to elucidate how the estrogen-related hypothalamic output regulates the final common pathway, the lumbar axial motoneurons. Our ultimate goal is to decipher how estrogen, in effect, closes the reflex circuit.

Reflex Organization, Motor Control

In lordosis, the legs are extended, the back and neck are extended and the rump and tailbase are elevated (Fig. 2). Rump elevation is necessary for fertilization to take place. Brink and colleagues (1980 a,b) showed that the muscles which are appropriately connected to accomplish this movement are the axial muscles, in particular TS and LL. The receptive field of the reflex is the dorsal skin contacted by the pressure of the male during mounting and the perineum upon which he thrusts (Pfaff et al., 1977). Although mounting is anything but a subtle stimulus, Kow et al. (1979) demonstrated that the behavior is lost following cutaneous denervation proving that subdermal receptors are not sufficient to elicit the behavior in the rat; neither is brushing hairs sufficient. Lordosis-eliciting pressures activate slowly adapting low threshold mechanoreceptors which in the rat, like the primate are predominantly innervated by A beta fibers (Lynn and Carpenter, 1982; Georgopoulos, 1976).

The muscles involved in the behavior are also active in postural regulation. Are they adapted for the ballistic type movements characteristic of lordosis against forces by a male who can be double the weight of the female? Using the conventional techni-

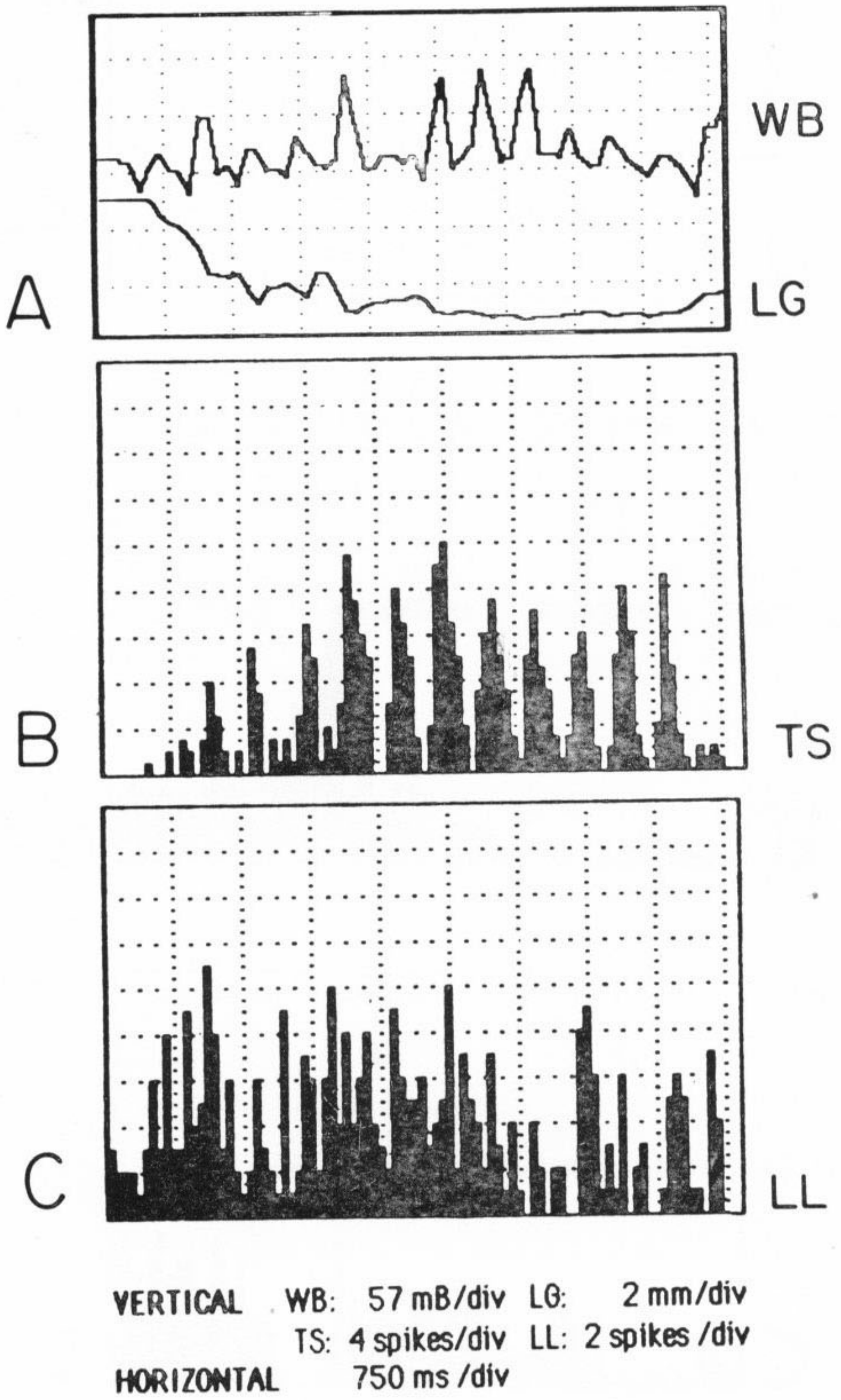


Fig. 6. — *Data comparable to that shown in Fig. 5 after digital processing. The upper channel of the digital scope display in A shows the stimulus trace (WB) during bilateral flank palpation at 2/sec. The lower channel records changes in length gauge (LG) resistance. In this figure and in Figure 7 decreased LG resistance, i.e. length gauge shortening is indicated by a downward deflection and reflects rump elevation. B and C are multi-unit firing rate histograms of EMG activity in TS and LL, respectively. The histograms are triggered from the onset of the sweep in A. From Schwartz-Giblin, Femano and Pfaff, 1984, by permission.*

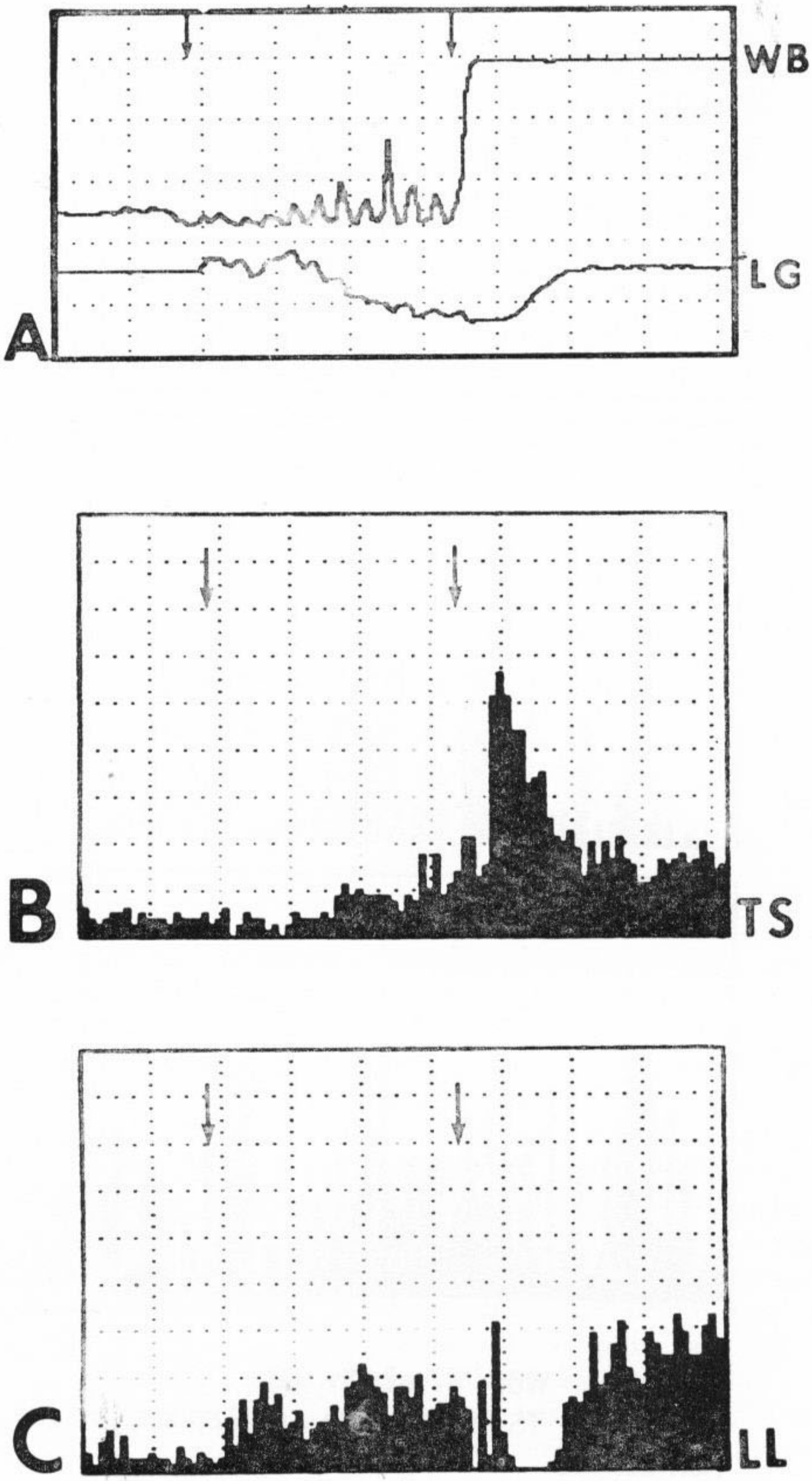


Fig. 7. — *Different patterns of multi-unit EMG activity are evoked in TS and LL during sustained perineal pressure. A Bilateral flank palpation begins at the first arrow; perineal pressure begins at the second arrow. The WB and LG traces show a progressive and cumulative effect of flank stimulation on rump elevation (as in fig. 6). Comparison of the multi-unit EMG firing rate histograms triggered from the onset of the sweep in A shows a stronger dynamic response to perineal pressure in TS than in LL. Calibrations for one vertical division of the grid and one horizontal division of the grid. Vertical: WB=127 mB/div, LG=3.2 mm/div. Vertical: B 8 spikes/div; C 8 spikes/div. Horizontal: 1.5 sec/div.*

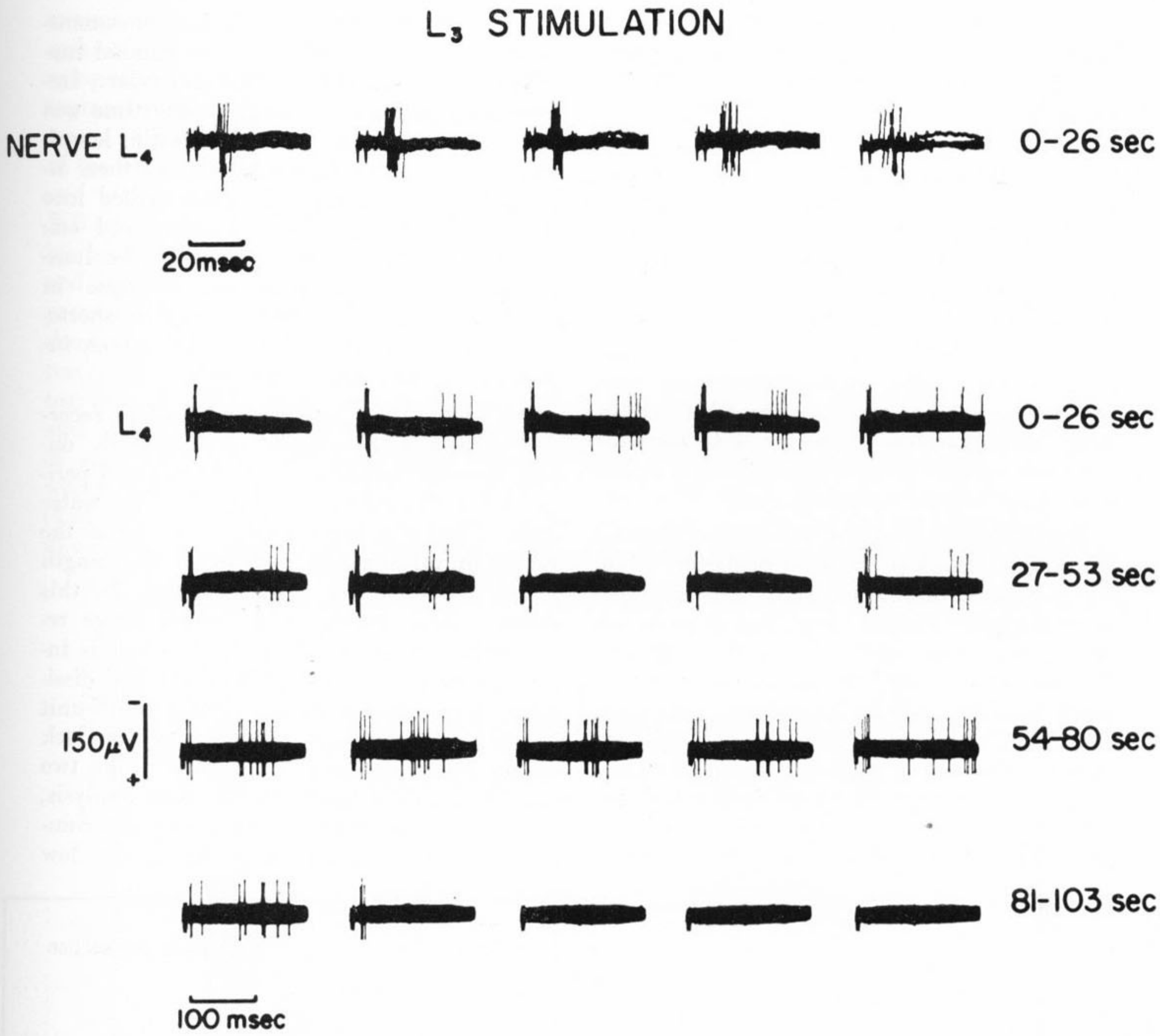


Fig. 8. — *A cutaneous-evoked polysynaptic nerve response recorded in an estrogen-treated rat. The bottom four rows are continuous records from 0-103 secs recorded from the muscle branch of the L nerve during 2/sec stimulus trains of 25 uA to the distal cutaneous branch of the L nerve. The upper row of records (0-26 sec) shows the early response at a faster sweep speed. All records contain five superimposed traces. From Schwartz-Giblin et al., 1984 by permission.*

ques of serial section muscle histochemistry to visualize myosin ATPase and mitochondrial oxidative enzymes, we found what might at first seem surprising for a postural muscle, that lateral longissimus LL is predominantly a fast muscle by histochemical criteria (Schwartz-Giblin et al., 1983). The slow-twitch oxidative fibers are segregated in the superficial region along the length of the muscle and in a medial deep region in the caudal most part of the muscle near its insertion into the ilium. Even in the superficial region, 78 % of the fibers are fast twitch fibers and therefore capable of acquiring large tensions (Fig. 3). Of these about 20 % stain for oxidative enzymes making them presumptive fast fatigue resistant fibers (FR fibers by Burke's nomenclature, see Burke et al., 1973). In the medial caudal region all the fibers stain for oxidative enzyme. Therefore, LL appears to be ideally suited for the ballistic movements required during lordosis: It has a preponderance of fast twitch muscles fibers to develop large tensions and according to the reverse recruitment theory (Kanda, Burke and Walmsley, 1977) fast-twitich fibers are preferentially recruited by cutaneous fibers which make up the afferent limb of the lordosis reflex.

Our next step was to record from the axial muscles in awake unrestrained rats during lordosis behavior (Schwartz-Giblin et al., 1984). Our immediate purpose was to describe the onset and duration of multiunit EMG activity in two axial muscles TS and LL with respect to each other, with respect to the somatosensory stimulus and with respect to the elicited movement. Our ultimate goal for axial muscle EMG recording during lordosis behavior is to describe a muscle profile of the behavior such as has been done for the stepping cycle.

For these experiments we elicited lordosis by manual flank-perineal stimulation (Fig. 4). A small water-filled bulb was attached to one of the fingers used for stimulation and it was connected to a statham gauge. The output provided a measure of the pressure applied and its onset and duration. The EMG electrodes were twisted pairs of teflon coated 50 u diameter tungsten wires which were connected to an implanted, insulated dual channel differential amplifier chip. The low impedance output lead from the animal served to minimize movement-related artifacts resulting from manual manipulation and the elcited behavior. Implanted in the animal at the same time was a 20 mm long mercury-in-silastic length gauge which was prestretched and then attached by suture through holes drilled into the dorsal spines of one lumbar and one sacral vertebra so that it spanned the lumbo-sacral vertebral junction. Changes in length gauge resistance produced by shortening during rump elevation gave us an independent measure of lordosis.

An example of our raw EMG data recorded concomitantly from TS bilaterally during manual stimulation of flanks and perineum is illustrated in Fig. 5. The water bulb (WB) pressure trace is above the EMG in all records and above the length gauge trace in the bottom record. In this figure, *only*, decreases in length gauge resistance equivalent to rump elevation is indicated by an upward deflection. The dissimilar time course of the EMG multi-unit activity bilaterally is evidence of the lack of cross-talk in our recordings from two contiguous axial muscles. For data analysis, EMG spikes were led to a window discriminator with the threshold level set low

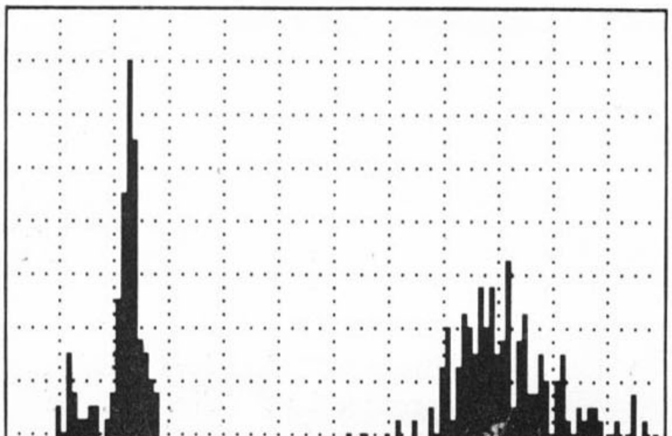
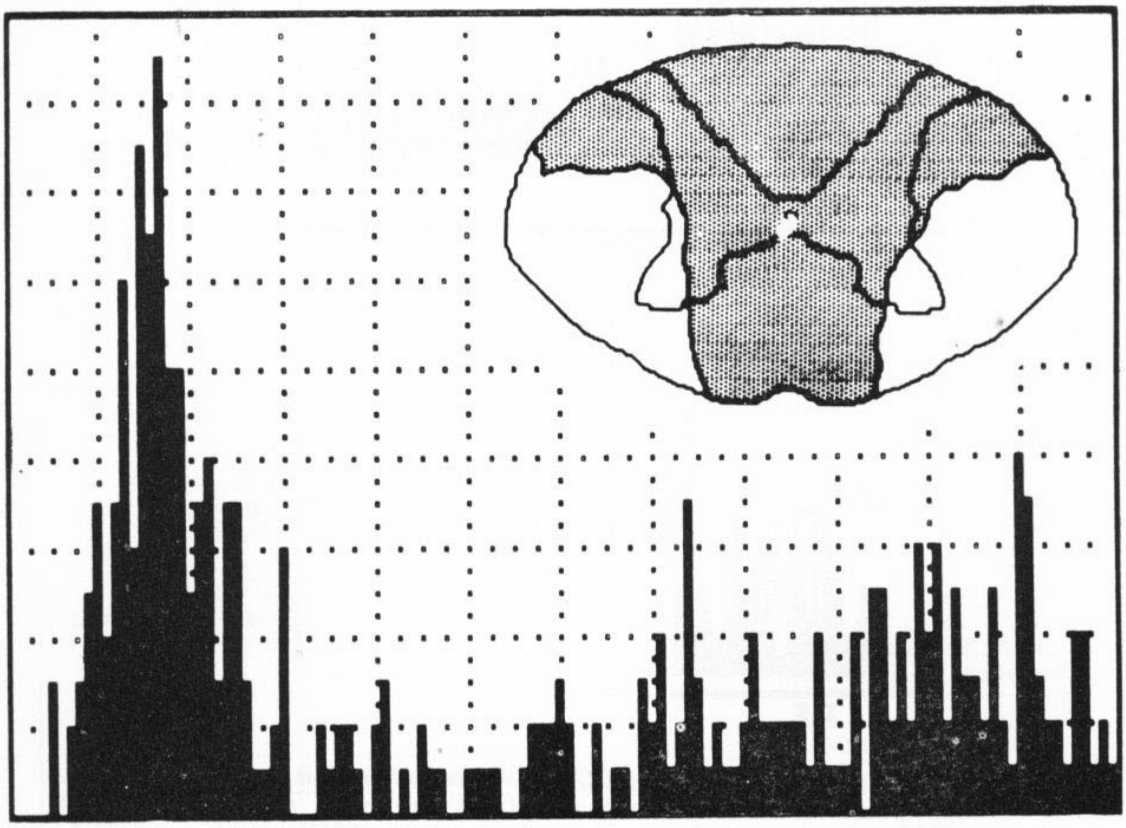


Fig. 9. — *Left: PST histogram of the response evoked in the L4 lateral longissimus muscle nerve by bilateral stimulation of the pudendal nerves with triple shock trains at 50 uA repeated 2/sec. Accumulated sweeps: n=87. Vertical scale: 4 spikes/div., horizontal scale: 10 msec/div. Right: The pudendal nerve-evoked response in an L3 lateral longissimus muscle nerve one day following complete transection of the spinal cord at the T4 level. Stimulation to the pudendal nerves was applied bilaterally and consisted of triple shock trains at 100 uA repeated 2/sec. Accumulated sweeps: n=125. Vertical scale: 2 spikes/div., horizontal scale: 10 msec/div. From Cohen, Schwartz-Giblin and Pfaff, 1986, by permission.*

enough so as not to bias against small units; spike-triggered pulses were fed to a microcomputer programmed to display PST histograms (Cohen and Pfaff, 1984). The two traces in Fig 6 A are digital scope displays of the DC records of applied pressure (WB) and length gauge resistance (LG). In the WB trace small fluctuations correspond to bilateral flank palpation whereas the sustained plateau corresponds to sustaied perinel pressure. Rump elevation is indicated by a *downward deflection* on the length gauge trace. The bottom two records are PST histograms of EMG units recorded from TS and LL. Bilateral flank palpation at rates of about 2/sec evoked axial EMG activity which was sometimes remarkably time-locked to the stimulus and in other cases more generally excitatory. The LG which reflects rump elevation, progressively shortened showing a cumulative effect of flank stimuli on the lordosis reflex. The patterns of response recorded ipsilaterally from TS and LL during bilateral perineal pressure suggest that the medial axial muscles represented by TS may be more responsive to the dynamic phase of applied pressure than LL (Fig. 7). The burst of EMG units in TS was recruited on the rising phase of pressure and markedly declined after maximum rump elevation. The LL EMG activity by contrast, was less responsive to the onset of pressure, had a longer peak latency and the response was sometimes sustained throughout the pressure plateau and throughout rump elevation. The maximum length gauge response occurred almost invariably, after the onset of perineal pressure and after the



L4 Muscle Nerve
75 µA Bilateral Stimulation at 2/sec
Vertical: 2 spikes/division Horizontal: 10 ms/division
Total Number of Sweeps: 80

Fig. 10. — *The pudendal nerve-evoked response recorded in the L4 lateral longissimus muscle nerve of a rat one day following transection of the medial and dorsal columns of the spinal cord as was shown in the inset. Stimulation applied to the pudendal nerves consisted of bilateral triple shock trains at 75 uA repeated 2/sec. Accumulated sweeps: n=80. Vertical scale: 2 spikes/div., horizontal scale: 10 msec7div. From Cohen, Schwartz-Giblin and Pfaff, 1986, by permission.*

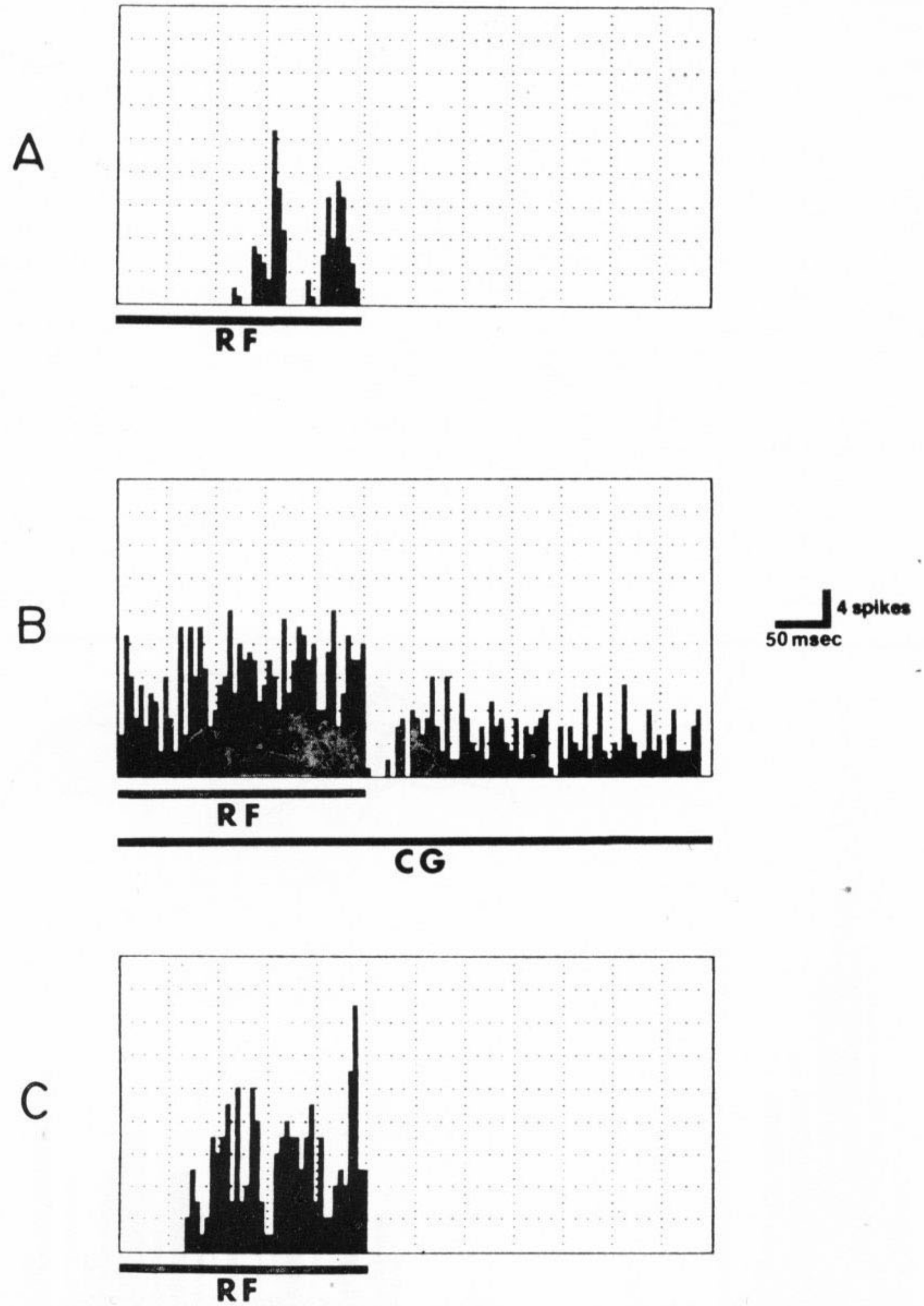


Fig. 11. — *Midbrain central gray (CG) facilitates multi-unit axial EMG activity evoked by trains of stimuli to the medullary reticular formation (RF). A shows a PST histogram of the steady state multi-unit EMG activity evoked by 20 trains (250 msec, 200Hz, 30uA) to RF. During continuous stimulation (100 Hz, 30uA) to central gray in B only, the frequency of EMG units is increased both during and after the RF train. C shows the response to RF alone following CG stimulation. Vertical scale: 4 spikes/sec in A and B; 2 spikes/sec in C. Horizontal scale: 50 msec/div.*

maximum EMG response. In some recordings the activity of both TS and LL declined rapidly after maximum rump elevation analagous to voluntary ballistic contractions in man reported by Desmedt and Godeaux (1977) and Bigland-Ritchie and co-workers (1983). During strong lordoses, 2/3 of EMG responses in TS occurred within 50 msec of the onset of perineal pressure; LL EMG responses tended to have longer latencies.

In order to get more precise information about the minimal latency of axial motoneurons in response to stimulation of lordosis-relevant receptive fields, we went to acute studies under urethane anesthesia. We electrically stimulated either the cutaneous nerves from the dorsal skin contacted by the male rat during mounting (Schwartz-Giblin et al., 1984) or the pudendal nerve which innervates the perineum (Cohen et al., 1985). An example of recordings from a lateral longissimus muscle branch of the L4 dorsal ramus during stimulation of a cutaneous branch from the L3 dorsal ramus is shown in Fig. 8. Single shocks were ineffective in evoking muscle nerve responses: brief trains of pulses at a rate of 2 trains/sec were adequate. The salient features of the response are the following. Axial motor nerves discharge at a mean latency of 9.5 msec from the last pulse in the train and again at 50 msec or later. Habituation of both early and late discharges occurred with repeated stimulation. The probability of obtaining an early response in these acute experiments was not altered by hormone treatment, but there was a tendency (significant at .05) for late discharges to occur more frequently in ovariectomized females treated with estrogen as compared to untreated controls.

Following stimulation of the pudendal nerve the evoked response in the axial muscle nerves looked quite similar (Fig. 9; Cohen et al., 1985). An early response from 5-30 msec was frequently 10 or more times background nerve activity. This was

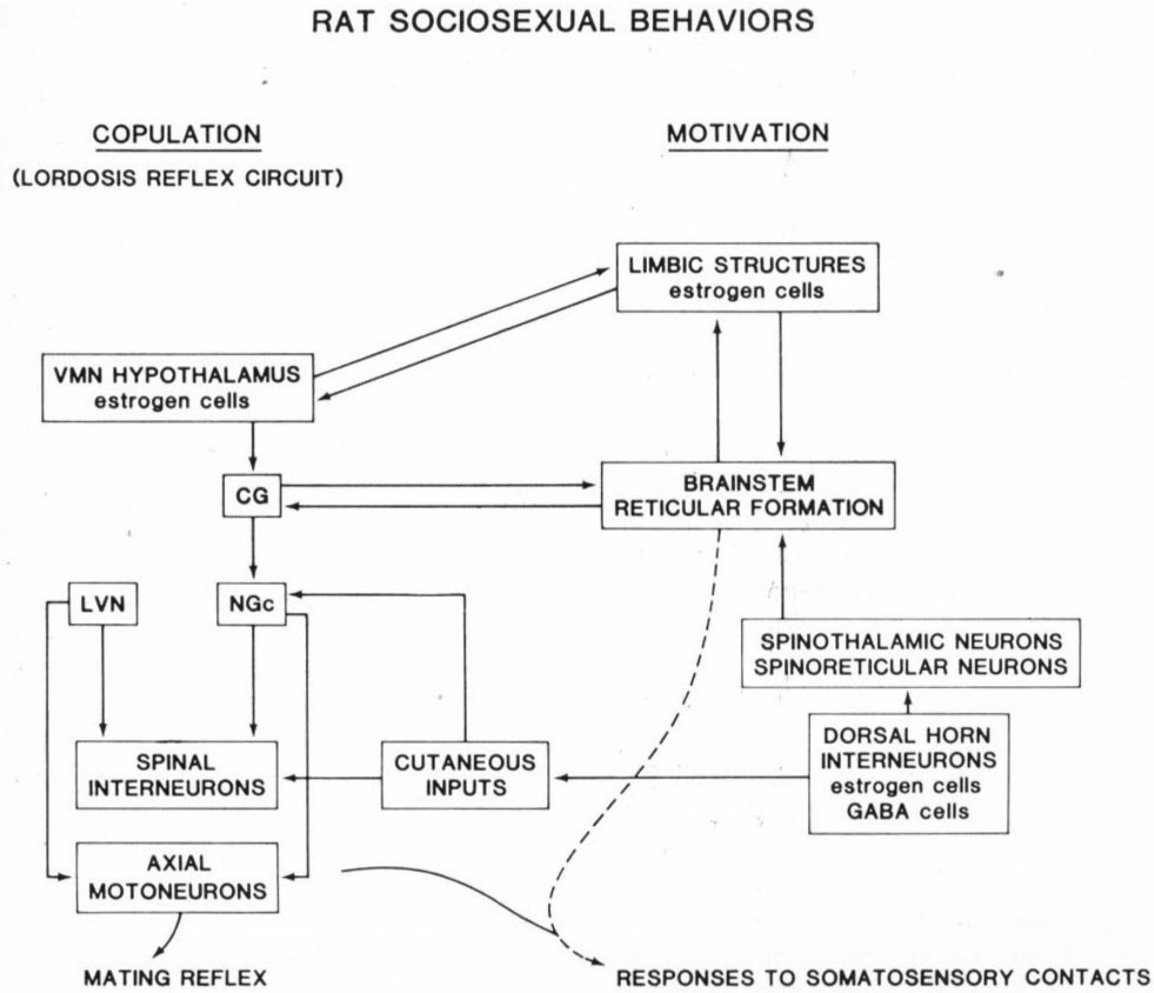


Fig. 12. — *Summary schema showing lordosis reflex pathway, pathways involved in motivated behaviors involving somatosensory signals and postulated sites for their interaction. Abbreviations: CG, midrain central gray; LVN, lateral vestibular nucleus; NGc, nucleus gigantocellularis of the medullary reticular formation.*

followed by a period of depressed firing out to 50 msec and a subsequent late peak with a mean latency of 100 msec. Stimulus intensities sufficient to excite A beta fibers but subthreshold for A delta fibers were adequate to elicit the pudendal nerve response just as A beta mechanoreceptors are adequate for lordosis.

The late activity of the pudendal nerve-evoked response in female rats was unaffected by hormone treatment. The dissimilarity between the effect of hormone on late discharges in response to the two *different afferent inputs* suggests that the hormone sensitive part of the cutaneous reflex circuit is more involved with the flank palpation and the dorsal pressure exerted by the male during mounting. In this regard, the effects of progesterone to facilitate proceptive female sexual behaviors such as ear wiggling and hopping and darting are elicited by touching the flanks and rump and are often curtailed by male thrusting against the perineum.

Cohen and co-workers (1986) found that the late activity was dependent on suprasegmental input to the axial motoneurons. Total spinal transections eliminated all late activity but an early fixed latency response persisted (Fig. 9). Total spinal transections also abolish lordosis behavior (Kow et al., 1977).

Partial transections of the spinal cord which destroyed all but the anterolateral columns show that the anterolateral columns are necessary and sufficient to elicit the typical pudendal nerve evoked response just as is the case for lordosis behavior (Fig. 10).

We knew from our earlier experiments that the reticulospinal (RS) tract which travels in the anterolateral columns has a strong excitatory effect on axial EMG. For example, trains of stimuli to NGc activate axial EMG units with a mean latency of 6 msec with respect to individual pulses in the train (Femano et al., 1984 a,b. Such latencies are consistent with a monsynaptic connection between RS fibers and axial motoneurons in the rat and have been confirmed by Cottingham and colleagues (1986a). Monosynaptic connections between RS and axial motoneurons also have been reported for cat (Wilson et al., 1970). We therefore decided to test the effects of combined threshold stimulation to nucleus gigantocellularis (NGc) of the reticular formation and pudendal nerve (Cohen et al., 1985). The results of these experiments clearly demonstrate that combined stimulation increases the number of axial motoneurons recruited and decreases the latency of the axial motoneuron response. Therefore, a common neuronal pool is shared between NGC and the pudendal nerve reflex circuit which may be interneuronal or the final common pathway itself, the axial motoneurons.

During lordosis behavior, reticulospinal fibers could be activated tonically by descending influences from central gray (CG) initiated by the hypothalamus and/or by ascending spinoreticular (SR) influence evoked by the cutaneous input. We have electrophysiological data which are consistent with both hypotheses.

Evidence for central gray facilitation of the RS response in axial muscles has been demonstrated by Cottingham and co-workers (1986a) and is illustrated in Fig. 11. The records are post-stimulus time histograms of multi-unit axial EMG activity. The reticular formation (RF) stimulus train is on for 250 msec in all records and evokes EMG units for the duration of the train. The CG stimulus is on throughout record B *only*. It can be seen from the histogram in B that concurrent stimulation to CG increases the frequency of EMG units firing both during and after RF stimulation. Since initially, CG stimulation on its own did not evoke EMG activity nor did repeated RF stimulation produce an after discharge on its own, the two inputs were mutually facilitatory. Since only a weak direct pathway from CG to lumbar spinal cord has been demonstrated in the rat (Mantyh and Peschanski, 1982) the CG effect must be via the reticular formation and act to prolong the descending excitatory drive on axial muscle. Anatomical and physiological evidence for direct connections from CG to NGC have been documented (Gallager and Pert, 1978; Hamilton and Skultety, 1970; Sakuma and Pfaff, 1980).

Cottingham and co-workers (1986b) have also shown that lateral vestibulospinal fibers excite axial motoneurons and this effect is facilitated by concurrent RF stimulation. The LVN effect is also facilitated from central gray (Cottingham et al., 1986c). Since CG does not project to the lateral vestibular nucleus (LVN) the facilitatory effect of CG on LVN must be via the reticular formation since LVN and RF are also mutually facilitatory.

We have indirect evidence for afferent activation of NGC by pudendal nerve stimulation (Sullivan et al., 1986). The evidence comes from experiments in which our strategy was the following: During pudendal nerve stimulation in urethane anesthetized rats we looked for a reflection of NGC activation in the EEG while at the same time recording axial multi-unit EMG activity. The rationale for these experiments was based on the early reports of Scheibel and Scheibel (1958) which described individual cells in rat NGC which send ascending branches to intralaminar thalamus and descending branches to the spinal cord and a more recent double labeling study in the rat by Waltzer and Martin (1984) which shows very few doubled labeled cells but shows that neighboring NGC cells project either to diencephalon or to spinal cord. The results of these experiments are summarized in Table 1. When the pudendal nerve stimulus was presented during slow wave EEG, the probability of EMG units being evoked by the stimulus was significantly greater ($p<.001$) when the stimulus also desynchorized the EEG. When the stimulus failed to desynchronize the EEG, axial muscle units were not evoked. These and related data suggest that reticular activation upon pudendal nerve stimulation could facilitate lumbar axial motoneuron responses to subsequent stimulation.

Somatosensory Controls Relevant for Social Behaviors As Well As Reproductive Behavior Reflexes

We hypothesize that under the control of hypothalamic estrogen concentrating cells, the outputs of preoptic and basomedial hypothalamic neurons, by release of peptides such as LHRH onto central gray neurons, can set into motion a cascade of descending facilitatory drives which ultimately increase the excitability of spinal neurons in cutaneous reflex pathways required for lordosis (Fig. 12). Thus, central gray neurons which receive convergent input from mediobasal hypothalamus, limbic structures and from spinoreticular cells responsive to convergent noxious and low threshold cutaneous stimulation and which make reciprocal connections with the brainstem reticular formation, may integrate the motivational and reflex properties of sexual behavior. McMahon and Wall (1983) speculate that the ascending spinal projection "is well placed to signal the functional state of the substantia gelatinosa and this information could be used to regulate brainstem influences on the spinal cord. Since these cells did not project to the thalamus, it may be that the information they carry is used other than for purely sensory processes" (McMahon and Wall., 1985). The output from midbrain central gray to the medial medullary reticular formation has been demonstrated electrophysiologically to facilitate the reticulospinal and vestibulospinal activation of axial motoneurons: the final common pathway of sexual behavior in the female rat.

One of the motivational aspects of sexual behavior is likely to be related to the general disposition of the female to somatosensory stimulation and this would be important for a variety of social behaviors. Tolerance for somatosensory input regulates the frequency of male contacts, as shown by Emery and Moss (1984) after small mediobasal hypothalamic lesions and by our data following intrathecal bicuculline. Thus, one of the roles of the regions of the CNS that contain estrogen concentrating cells such as the hypothalamus and the substantia gelatinosa of the spinal cord may be to modulate the signalling of somatosensory information, and that this effect may influence motivational processes important for estrogen-dependent sexual kreflex behaviors and for a variety of other social responses.

TABLE 1

RESPONSES TO PUDENDAL NERVE STIMULATION

		(n=68) Units evoked	Units Not Evoked
EEG State	Prestim. Slow Poststim. Fast	45	6
	Prestim. Slow Poststim. Slow	0	17
	$p < .001$ (2×2 x^2 test)		

From Sullivan et al., 1986

SUMMARY

The reproductive behavior of the female rodent, lordosis, is a hormone-dependent somatosensory reflex under suprasegmental control. Lordosis is executed by the deep lumbar back muscles in response to stimulation during a male mount; the resulting rump elevation is necessary for impregnation. The reflex will only occur if the female has been exposed to sufficient levels of estradiol and progesterone for some time previously. Insufficient hormone priming evokes irritability which suggests that the specific behavioral reflex is affected by a general disposition to somatosensory input. The hormone need be present only in specific estrogen concentrating cells in the basomedial hypothalamus for the somatosensory stimulation to be effective.

Electrophysiology has demonstrated that systemic estradiol increases the resting output of neurons in the ventromedial nucleus (VMN) of the hypothalamus. These project, among other places, to the midbrain central grey. Stimulation of VMN, and estradiol, increase the excitability of a population of central grey neurons which project to the medullary reticular formation. Reticulospinal neurons excite lumbar back muscle motoneurons at brief fixed latencies and facilitate the responses of these motoneurons to cutaneous inputs from the receptive field of the lordosis reflex. Vestibulospinal neurons, necessary for lordosis behavior, have been shown to excite lumbar axial muscles and to have facilitatory interactions with the reticulospinal input (Cottingham et al. Soc. for Neurosci. Abstract 1985).

As would be predicted from the above neural circuitry, large lesions of the VMN markedly reduce lordosis behavior, perhaps by reducing the female's motivation for copulation and tolerance for somatosensory input as measured by the frequency of coital contacts allowed in testing situations where the female controls social contacts (Emery and Moss, 1984). Smaller VMN lesions do not alter the ability of the female to perform lordosis in response to successful male mounts. We have made a parallel observation at the level of the spinal cord. In estrogen-primed ovariectomized rats, intrathecal injections of GABA antagonists evoke a syndrome of hyperalgesia to light tactile stimuli that were previously innocuous. Interference with the signalling of cutaneous information by intrathecal bicuculline (1 nM-4 nM in 5-10 ul) results in the female displaying both passive and active avoidance of contacts by males during mating encounters. But, if the male can mount well, lordosis behavior is not reliably reduced.

The general disposition to somatosensory stimulation may be one of the requisite conditions for reproductive behavior and may regulate the probability of fertilization. Under optimal conditions the female rat must be autonomically and motorically aroused but analgesic to that the somatosensory input approapriate for reproduction will not be treated as aversive. One could speculate that one of the roles of regions of the CNS that contain hormone concentrating cells such as the hypothalamus and the dorsal horn of the spinal cord is to modulate the quality of the effective somatosensory stimulus.

RESUMEN

La conducta reproductiva del roedor hembra, lordosis es un reflejo somatosensorial dependiente de hormona bajo control suprasegmental.

La lordosis es originada por musculatura lumbar profunda en respuesta a la estimulación durante el acoplamiento; la resultante elevación del trasero es necesaria para la fecundación. El reflejo sólo ocurre si la hembra ha tenido previamente niveles suficientes de estradiol y progesterona. Irritabilidad en el comportamiento de la hembra se origina por un muy bajo nivel hormonal, lo cual sugiere que el reflejo de conducta específica se afecta por una disposición general al influjo somatosensorial. La hormona debe estar presente sólo en células que concentren estrógeno en el hipotálamo basal interno para que la estimulación somatosensorial sea efectiva.

Por medio de la electrofisiología, se ha podido demostrar que administrando sistemáticamente estradiol se aumenta las acciones potenciales de las hormonas en reposo integradas en el núcleo ventromedial (VMN) del hipotálamo. Ellas se proyectan entre otras áreas en el gris central del mesencéfalo. La estimulación de VMN y el estradiol acentúan la excitabilidad de neuronas integradas en el gris central del mesencéfalo las cuales se proyectan a la formación médulo reticular.

Las neuronas retículo espinales excitan las motoneuronas de los músculos lumbares de un modo regular y breve y facilitan las respuestas de estas motoneuronas a los estímulos cutáneos desde el sector receptivo del reflejo de lordosis. Se ha también demostrado que las neuronas vestíbulo espinales necesarias para la ejecución del reflejo de lordosis; excitan los músculos lomboaxiales y facilitan las acciones de las neuronas reticuloespinales (Cottingham et al. Soc. for Neurosci. Abstract 1985).

Como puede predecirse por el circuito neuronal antes mencionado que lesiones extensas a nivel del VMN pueden reducir en forma marcada el comportamiento de la lordosis.

Esto puede ser debido a la falta de motivaciones copulatorias de la parte de la hembra y tambien por la falta de tolerancia a los estímulos somatosensoriales, medida por la frecuencia de los coitos permitidos durante el test, cuando la hembra controla sus relaciones sociales. (Emery and Moss, Hormones and Behavior, 1984). Pequeñas lesiones del VMN no alteran la habilidad de la hembra para lograr lordosis en respuesta a montar afortunadas del macho. Nosotros hemos hecho una observación semejante al nivel de la médula espinal. En ratas ovariectomizadas y tratadas con estrógenos hemos constatado que inyecciones intratecales de GABA antagonistas las convierten en hiperalgésicas al menor estímulo tactil, al que ellas eran antes indiferentes.

Después de una inyección intratecal de bicuculina (1nM-4nM en 5-10 u 1) interviniendo al nivel de las señales cutáneas, hemos también constatado que la hembra evita activa y pasivamente el contacto con el macho, en encuentro de pareja. Pero si el macho puede montar bien, la respuesta de lordosis no es sistemáticamente reducida.

En el acto sexual parece que una disposición general a la estimulación somatosensorial sea necesaria porque ella controla la probabilidad de la fertilización. Bajo condiciones óptimas la rata debe ser excitada también insensibilizada de modo que los estímulos somatosensoriales necesarios para la reproducción no sean tratados como molestos. Puede pensarse también que uno de los papeles de las regiones del CNS que contiene células hormonales tales como el hipotálamo y la gris dorsal de la médula espinal consiste en modular la calidad del estímulo efectivo somatosensorial.

RÉSUMÉ

Lordosis, le comportement réproductif du rat, est un reflex somatosensoriel contrôlés suprasegmentalement et sous effet d'hormonal. Lordosis est effectué par les muscles lombaro-dorsaux durant l'accouplement. Le resultant est une elevation de la croupe de la femelle lors de l'impregnation. Une dose suffisante d'oestradiole et progesterone est nécessaire pour que le reflex s'effectue. Une irritabilité dans le comportement de la femelle est dû-t-au niveau hormonal trop bas; cela semble indiquer qu'une disposition générale soit nécessaire pour la performance de lordosis. Pour permettre une stimulation somatosensorielle efficace, oestradiole doit être present primordiallement chez les cellules specifique sensible cette hormone; celle ci se trouve dans la partie basomediale de l'hypothalamus.

Avec l'aide de l'electrophysiologie, il a été possible de démontrer que l'administration systematique d'oestradiole augment les actions potentielles des neurones au repos, faisant partie du noyau ventromedial (VMN) de l'hypothalamus. Certain d'entre les neurones se projetent dans le gris central du mesencephal. La stimulation du VMN ainsi que l'injection d'oestradiole augmente la sensibilité des neurones occupant le gris central du mesendephal, particulièrement celles qui projetent dans la formation medulo-reticulaire. Les neurones reticulospinales stimulent les neurones moteures des muscles lombaires d'une façon régulière et brève. Les neurones reticulospinales facilitent aussi la réponse des neurones moteure du dos aux stimuli cutanés nécessaires l'enchaînement du reflex de lordosis. Il a été aussi démontré que les neurones vestibulospinales nécessaire à l'execussion du reflex de lordosis, exitent les muscles lombaro-dorsaux et facilitent les actions des neurones reticulospinales (Cottingham et al., Soc. for Neuroscience Abstract, 1985).

Il pourrait être deduit d'après le circuit neuronal note si-dessus, que des lesions larges au niveau du VMN peuvent diminuer le comportement de lordosis de façon importante. Cela peut-etre dû-t-au manque de motivations copulatoires de la part de la femelle, et aussi peut-etre au manque de tolerances aux stimuli somatosensorielles mesures d'après la fréquence de coitus permis lors du test, lorsque la femelle contrôle ses rapports sociaux (Emery and Moss, Hormones and Behavior, 1984). Parcontre, lors de l'accouplement, si la monte du mâle est complète, des lesions moins larges au niveau du VMN n'ont pratiquement pas d'effets sur le comportement de lordosis du rat. Nous avons fait une observation semblable au niveau de la moëlle epinière: Chez les rats ovariectomizés et traités a l'oestradiole, nous avons constaté que des injections intrathecal des GABA antagonistes les rendent hyperalgesic au moindre stimulus tactile, bienqu'ils y soient au paravant indifferents. Après une injection intrathecal de bicuculline (1nM-4nM in 5 ul) intervennant au niveau des signaux cutanés, nous avons aussi constaté que la femelle évite aussi bien passivement, qu'activement, le mâle lors de l'accouplement. Parcontre, si la monte du mâle est correcte, le comportement de lordosis ne diminue pas d'une façon systematique.

Lors de l'accouplement, il semble qu'une disposition générale à la stimulation somatosensorielle soit nécessiare puisqu'elle contrôle la probabilité de la fertilization. Sous les conditions optimales, le rat doit être excité de manières aussi insensibilizée afin que les décharges somatosensorielles nécessaire à la réproduction , ne soient pas interpretées comme douloureuses. Il semble aussi que l'un des rôles des regions du CNS contenant des cellules hormonales, comme l'hypothalamus et la region grise dorsal de la moëlle epinière soit de contrôler le charactère de la stimulation somatosensorielle.

ZUSAMMENFASSUNG

Das reproduktive Verhalten des weiblichens Nagers, genannt Lordosis, ist ein hormonabhängiger somatosensorischer Reflex unter suprasegmentaler Kontrolle. Lordosis wird als Antwort auf die Stimmulation während des Sexualaktes unter Vermittlung der

tiefen Lumbarmuskulatur ausgeführt die resultierende Rumpfanhebung ist wichtig für die Begattung.

Der Reflex ist nur dann auslösbar, wenn das Weibchen vorher einer entsprechend hohen Östradiol-und Progesteron Dosis ausgesetzt war. Eine ungenügende Hormonvorbehandlung provoziert Reizbarkeit als Hinweis dafür, daβ der spezifische Verhaltensreflex von einer allgemeinen Bereitschaft gegenüber somatosensorischen Einflüssen abhängt. Damit die somatosensorische Stimulation effectiv ist, muss das Hormon nur in den spezifischen Östrogen haltigen Zellen im basomedialem Anteil des Hypothalamus vorhanden sein.

In electrophysiologischen Studien wurde gezeigt daβ systemische Östradiolgabe eine Erhöhung der Neuronen Aktivität im ventromedialen Kern (VMN) des Hypothalamus auslöst. Diese projezieren unter anderem zum zentralen grau des Mittelhirns Stimulation des VMN zusammen mit Östradiol erhöhen die Erregbarkeit einer Population von Neuronen die zur medullären Formtio reticularis projezieren. Reticulospinale Neurone aktivieren die Motoneurone der lumbalen Rückenmuskulatur mit geringer Latenz und ermöglichen die Antwort dieser Motoneurone auf Hautreize aus dem rezeptiven Areal für den Lordosis Reflex. Die vestibulospinalen Neurone die für das Lordosisverhalten notwendig sind, und die lumbaraxialen Muskulatur und erleichtern die Wechselwirkung mit den reticulospinalen Input.

Wie man auf grund des nervösen Reflexes voraussagt würde, ist das Lordoseverhalten nach groβen Lesionen des VMN deutlich reduziert. Dies ist vieleicht darauf zurückzuführen, daβ die Motivation des Weibchens für die Kopulation vermindert ist, ebenso wie die Toleranz für den somatosensorischen Input wie aus Messungen der Häufigkeit des Geschlechtsverkehrs in Testsituationen hervorgeht, wo das Weibchen den sozialen Kontakt bestimmt. Kleinere Lesionen des VMN verändern die Fähigkeit des Weibchens die Lordose in Beantwortung der männlichen Begattung durchzuführen nicht.

Wir haben ähnliche Beobachtungen auf der Ebene des Rückenmarks gemacht. Die intrathekale Injektion von GABA Antagonisten in Östrogen vorbehandelte ovariektomierte Ratten ruft ein Syndrom der Überempfindlichkeit gegenüber leichte Berührungsreize hervor, die vorher ohne Effekt waren. Unterbricht man die Signale über Hautkontakte durch intrathekale Verabreichung von Bicucullin (1nM 4nM in 5ul) so zeigt das Weibchen sowohl passives als auch aktives avoidance Verhalten gegenüber Kontakten mitem Männchen während der Begattung. Wenn das Männchen gut aufreiten kann, ist das Lordoseverhalten nicht zuverläβig reduziert. Die allgemeine Bereitschaft gegenüber somatosensorischer Stimulation mag eine der Voraussetzungen für das reproduktive Verhalten sein und die Wahrscheinlichkeit der Fertilization erhöhen. Unter optimalen Bedingungen muβ die weibliche Ratte sowohl vegetativ als auch motorisch erregt werden jedoch schmerzfrei, sodaβ der somatosensorische Input der für die Reproduktion notwending ist, nicht gegenteilig beeinfluβt wird. Man könnte spekuliern, daβ eine der Funktionen derjenigen ZNS Areale, die Hormonkonzentrierende Zellen enthalten wie zum Beispiel der Hypothalamus und das dorsale Horn des Rückenmarks die in der Modulation der Qualität effektiver somatosensorischer Stimuli ist. Der Hypothalamus reguliert über reticulospinale und vestibulospinale Systeme das emotionale Verhalten.

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The Effects of Nutrition on Brain Function, Behavior and Learning: Directons for Integrative Research

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Introduction

That the putative neurotransmitters catecholamines (norepinephrine, epinephrine, dopamine) and other members of these category (i.e. octopamine, phenylethylamine, tyramine) are synthesized from two precursors, the amino acids phenylalanine and tyrosine, and that they can effect behavior, is known. That the diet is a source of these amino acids is also accepted.

The tendency persists in oversimplifying this relationship. For example, catecholamine synthesis is also under the control of pituitary hormones (i.e. ACTH), adrenocortical hormones, sex hormones, nerve growth factor, various hypothalamic releasing factors, such as the melanocyte inhibitory factor [MIF] and thyrotropin releasing hormone [TRH], and other general trophic substances. Even genetically-linked strain differences in catecholamine synthesis have been reported (i.e. phenylethanolamine-N-methyltransferase, tyrosine hydroxylase) bearing serious consideration when studying behavior. Since catecholamines treated with formaldehyde vapor result in compounds that emit fluorescence, little of what is known about dopamine today, for example, would be possible without fluorescence photomicrography, radioautography, and electron microscopy. Even environmental factors can confound studies of blood brain membrane permeability as it relates to catecholamine distribution. Recent work by several investigators in multi-species animal studies have found that non-ionizing radiation (i.e. microwaves) can significantly effect blood brain permeability.

The question must then be asked: to what degree is nutrition important in relating neurological findings when attempting to understand human behavior? This issue can not be dismissed lightly. Recent interest in aspartame and its diketopiperazine is just one example of a nutritionally-related area of major interest to neurologists. Physicians are reporting an alarming frequency, intensity and specificity of behavioral symptoms associated with aspartame intake. One recent communique reports on two adult females with severe depressive reactions with accompanying suicidal ideations along with profound fatigue, episodic confusion, an inability to concentrate, and memory dysfunction for recent events (Stanfield, 1985). In the same report are described two children, ages 10 and 14, with hyperactivity, apparent learning impairment, purportedly due to a shortness in attention span and general hyperirritability.

In all four cases the behaviors were ameliorated or resolved within not more than 10 days after the abstinence of aspartame consumption. Most of the behavioral problems were linked to the ingestion of not less than 1,200 ml. of diet soda or diet cola per day. Behavioral dysfunctions of such a temporal nature are not even described in the otherwise thorough work *Aspartame: Physiology and Biochemistry* (Stegink and Filer, 1984).

Calorie-underconsumption malnutrition's effects on human fetal development is better understood than calorie-overconsumption malnutrition, the latter phenomena being more likely throughout developed nations and among the upper classes in developing countries. However, with both developed and underdeveloped countries intrauterine growth retardation can be found increasing the incidence of small-for-date babies, occasionally referred to as small for gestational age [SGA] (not to be confused with premature babies). Frequently, in developing countries, small-for-date babies may have nutritional deficiences, be unable to suck, and suffer from metabolic disorders such as protein intolerance, neonatal hypocalcemia, impaired thermoregulation, and neonatal hypoglycemia, in addition to, small brain size and decreased activity of various important enzymes (i.e. acetylcholine esterase). In both worlds the resolution of this problem is very complex, requiring the consideration of numerous socioeconomic factors.

For example, excess intake of alcohol and/or smoking can result in intrauterine growth retardation. The only source of nutrition for the fetus is maternal blood. As a result, infants born to mothers addicted to alcohol have shown abnormal cell migration in autopsied brains (Clarren et al, 1978), weaker suckling pressure (Martin et al, 1978), etc. In fetal alcohol syndrome [FAS], central nervous system dysfunctions manifested as neurologic, behavioral, and intellectual, appear as features, in addition to, growth deficiencies, and characteristic facial patters involving the eyes (short palpebral fissures), mouth (i.e. thin upper vermillion, infant retrognathia), nose (hypoplastic philtrum), and maxilla (hypoplastic). Combining smoking with alcohol intake can increase the incidence of human stillbirths two to five times that of alcohol alone. Smoking alone can increase the likelihood of having a hyperkinetic child and /or one with impaired visual-motor integration, decreased birth weight, and smaller head circumference.

Through multi-species animal studies, alcohol's effects related to the timing of intake and period of gestation have been possible. In fetuses of dams consuming 35 percent of calories from alcohol, dopamine levels were low in fetuses, remaining low even after birth (Detering et al, 1980). Hyperactivity commonly reported in children today has been found in pups born to dams fed alcohol, but not food additives (Branchey and Friedhoff, 1976). These and other physiological, biochemical and morphological changes can be attributed to alcohol intake, rather than nutritional deficits, much more readily than in human studies since in most animal studies pair-feeding was employed.

All of the above discussions are probably known to the majority of the audience. They demonstrate the vigorous multidisciplinary activity of scientists exploring neurotransmitters, malnutrition, blood-brain barrier systems, exogenous toxins and their effects on the CNS, inborn errors of metabolism, growth characteristics of the brain, and neuropeptides. However, in reviewing the literature, relatively few studies, even in animals, have attempted as yet to carefully examine the increasing body of formative literature suggesting a much more direct link between nutrition and maladaptive behavior patterns (i.e. hyperkinesis, overactivity, sociopathy, functional neurosis, etc.).

It is the opinion of the author, that there exists a "crying" need for neurological investigations of recent controlled studies examining maladaptive behavior in children and adults. It seems imperative that a experimentally-derived set of theories is required to further those researchers not adequately familiar with neuroanatomical and neurochemical methods for investigation.

Clearly, such investigations will require a familiarity with current literature. Therefore, it will be my intent to briefly present, in the remainder of this paper, an overview and "feeling" for some of the recent substantive and even provocative findings in behavioral research. Hopefully, this will provide potential directions for further neurological ihvestigations.

Hypersensitivity and Behavioral Disturbances

Psychological and behavioral effects of food and chemical exposure in sensitive individuals have been demonstrated under double-blind random controlled conditions (King, 1981a, 1981b, 1984; Rea et al, 1984). In a double-blind, crossover, placebo-controlled trial employing an oligoantigenic diet, specific foods and food additives have been shown to cause or exascerbate behavioral disorders, seizures (Egger et al, 1985), and migraines (Egger et al, 1983). The oligoantigenic diet treatment of behavior disturbances study found that artificial food colors and preservatives most frequently provoked adverse behavioral reactions, followed by cow's milk, chocholate, grapes, wheat, oranges, cow's cheese, hen's eggs, peanuts, and corn. However, neither the artificial food colors or preservatives caused adverse behavioral reactions unless consumed with other foods. The study further found numbers of foods for which no subject reacted, namely, cabbage, lettuce, cauliflower, and celery. Interestingly, the onset of adverse behavioral reactions was frequently delayed, usually by hours or several days (Ave. = 2.2 days).

A latter study, by pediatric neurologist Dr. Joseph Egger and colleagues, is particularly provoking to current paradigms about the etiology of seizures. The randomized, crossover, placebo-controlled trial of the effects of foods on seizures was called for after it was noted that 13 of 14 children with behavioral disorders and a history of seizures, requiring anticonvulsant medication, no longer required medication, once placed on a diet totally avoiding foods suspected of provoking behavioral disturbances. A separate larger study by neurologists, immunologists and nutritionists, confirmed these findings (Egger, et al, in press).

Another double-blind study of children with behavior disturbances investigated 140 children using a modified elimination diet and challenge protocol devised for the management of recurrent urticaria. 86 of these children experienced significant improvement when salicylates were eliminated. 75 percent of these children reacted to a double-blind challenge with salicylates but not to placebos (Swain et al, 1985). Development of such a modified diet was only possible after extensive biochemical analysis of 333 foods and spices for salicylate content (Swain, Dutton, and Truswell, 1985).

These and similar well controlled studies have unfortunately revealed little as to the precise neurological mechanism inherent in the behavioral response to foods, or food additives.

Hypoferremia, Cognitive Impairment, and Behavioral Disorder

Tucker and colleagues at the U.S. Department of Agriculture's's Human Performance Laboratory have provided stronger evidence of hypoferremia influencing left hemisphere activity and cognitive performance (Tucker et al, 1984). Less activation of anterior right hemisphere was characteristic of higher iron status. Dopamine receptor function in rats is a mediating factor between iron deficiency and behavioral impairment (Youdim et al, 1978). In rats, iron deficiency decreases the behavioral effects of dopamine agonists (Ashkenazi, Ben-Schachar, and Youdim, 1982). Monoamine oxidase [MAO], a catabolic enzyme (like aldehyde dehydrogenase) might be involved in such behavioral changes, since iron, a co-factor for tyrosine hydroxylase and tryptophan hydroxylase, is essential in MAO activity through its involvement in membrane structural proteins. However, it is not clear if iron is required for the action of the enzyme in catalysis or synthesis (Oreland, 1971; Sourkes and Missala, 1976), as MAO, a flavoprotein, does not contain heme. Yet, platelets of iron-deficient humans have consistently been shown to have below normal levels of MAO (Youdim et al, 1975).

Hypoferremia has been related to conduct disorders in male school children (Webb and Oski, 1974). Cognitive impairments have been shown to be related to hypoferremia in a well designed double-blind study of children (Pollitt et al, 1982).

Given the increasing evidence of a relationship between hypoferremia and cognitive impairment, behavior disorders and possibly even antisocial behavior, further research is warranted.

Sub-clinical Thiamine Deficiency and Functional Neurosis and Impulsivity

In an uncontrolled, non-random, study of functional neurotics, ages 3 through 45, a marked feature was sub-clinical thiamine deficiency, determined through erthrocyte transketolase activity. In most cases this condition was directly linked to a diet relatively high in refined carbohydrates, without additional fortification of thiamine (Lonsdale and Shamberger, 1980). Adolescents in this study were found to display the following characteristics: implusiveness, irritability, aggressiveness, a tendency to be angered easily, and a sensitivity to criticism. (These characteristics are very common among chronic juvenile delinquents.) Saturation of these adolescents' tissues with thiamine through supplementation resulted in a reported complete improvement in mental health and behavior. Support for the association of thiamine to functional neurosis also comes from a 172 subject consecutive admissions study (Carney et al, 1982).

Rindi and co-workers (1980) have demonstrated in rat studies that low thiamine leaves the cerebellum, pons and medulla, the most vulnerable brain tissues among all brain regions. Low thiamine levels have been shown to decrease levels of glutamic acid, glutamine, aspartic acid and GABA. This is probably due to diminished activity of thiamin-dependent pyruvate dehydrogenase complex [PDHC].

Behavioral scientists and nutritionists would value the contributions of other investigators, such as Rindi and his co-workers, in further elucidating the effects of various vitamin and mineral deficiencies and excesses on brain function.

Zinc Deficiency and Anorexia Nervosa and Anorexia Bulimia

The eating disorder anorexia nervosa has received increasing attention from both medical and behavioral researchers. Formally, it was thought within the province of psychology only, but recent evidence fully places its potential successful treatment well within medical boundaries.

Anorexia Nervosa and Bulimia Nervosa have until recently not received adequate attention as a metabolic disorder. Thymulin (Zn-facteur thymique serique) activity, a well-defined thymic hormone, and triiodo thyronine (T3), have been found significantly depressed in anorexia nervosa patients (Wade et al, 1985). But recently Bryce-Smith and Simpson (1984, 1985) have described remarkably rapid improvements in intractable anorexic nervosa cases after a daily routine of a hydrated zinc sulfate solution (Zinc Talley/Zinc Challenge, Metagenics, Laguna Hills, California). Impairment of zinc tissue status can result in depression, neurosis, dysgeusia, and anorexia. Using the zinc solution, the anorexic is asked to describe the taste of the solution after swirling it in their mouth for 10 seconds. Dependent upon the intensity of the response the same solution of zinc is recommended according to specific guidelines described by Bryce-Smith. Within days both a resumption of eating occurs in addition to a steady increase in weight as long as the zinc solution is consummed.

Certainly given the fact that anorexia nervosa has the highest mortality rate among all mental illnesses, considerable research opportunities exist to study the zinc associated hormonal, enzymatic and protein synthesis processes accounting for this vastly improved method of treatment.

SUMMARY

These examples of current research on nutrition and behavior potentially of considerable interest to neurology, provides a glimpse of the potentials for further multidisciplinary research between the behavioral and medical sciences. For a further more exhaustive examination of nutritional and behavioral science research, the reader is encouraged to review two papers by this author (Schauss, 1983; Schauss, 1985).

RESUMEN

Estos ejemplos de investigación corriente sobre nutrición y conducta potencialmente de gran interés en neurología, suministra visión de los potenciales para un futuro de investigación multidisciplinaria entre ciencias médicas y de conducta.

Para un más amplio y exaustivo examen de investigación científica de nutrición y conducta se exhorta al lector a revistar dos publicaciones del autor (Schauss 1983, Schauss 1985).

RÉSUMÉ

Les exemples d'investigation, courantes en nutrition et conduite, de grand interêt en neurologie, et qui donnent un aperçu des possibilités pour des investigations futures, multidisciplinaires entre science médicale et étude des comportements.

Pour un examen plus complet et plus scientifique de la nutrition et la conduite, il est sugeré de se rapporter à deux publications de l'autteur (Schauss 1983 et Schauss 1985).

ZUSAMMENFASSUNG

Diese Beispiele geläufiger Forschung über Ernährung und Verhalten, von möglichem grossen Interesse für die Neurologie, eröffnen die Aussicht auf Zukunftsmöglichkeiten multidisziplinärer Forschung zwischen medizinischer und Verhaltenslehre.

Für eine umfänglichere und genauere Prüfung der wissenschaftlichen Forschung über Ernährung und Verhalten wird der Leser eingeladen 2 Veröffentlichungen des Verfassers kennen zu lernen (Schauss 1983, Schauss 1985).

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Limbic Traces and Interictal Behaviour: Basic Science and Clinical Approaches

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BASIC SCIENCE APPROACHES

One of the purposes of the research in our laboratory has been to develop an animal model of the impact of limbic epilepsy on interictal behaviour using the domestic cat. The essential questions asked are; can seizures change behaviour in a lasting manner; and do these changes persist interictally? A related question is what pre-ictal factors contribute to interictal outcome?

The approach taken is modelled after the neuroethological approach to understanding the neural substrates of behavioural plasticity that has proven very successful in invertebrates (Hawkins and Kandel, 1984). Five steps are involved: 1) select behaviour(s) within the natural repertoire of the animal, assuming in this case that limbic circuit function is best understood in terms of adaptive natural behaviours; 2) map the neural circuitry underlying the behaviour; 3) determine how the behaviour(s) may be changed, in this case how repeated seizures change behaviour; 4) using the map, determine the locus, or loci, within the neural circuitry which mediate(s) the behavioural change; and 5) determine the molecular mechanism of behavioural change at that locus or loci.

This approach has been important both in our choice of animal to investigate and in our choice of experimental epilepsy as a model. The cat was chosen because of the work of Flynn, Bandler and colleagues (reviewed in Adamec and Stark-Adamec, 1983d) who have been mapping the neural circuitry underlying predatory aggressive and defensive behaviour in the cat for more than 20 years. Their work suggests that a variety of networks, involving thalamic, hypothalamic and brain stem systems, control the neural and behavioural response to complex species-relevant stimuli that evoke defensive behaviour and predatory aggression. Major modulating inputs to these networks originate in a number of limbic structures. For example, the basomedial amygdala (BM) tonically inhibits predatory attack while facilitating defensive behaviour. Tonic facilitators of attack are the lateral amygdala and ventral hippocampus (VHP) (Adamec & Stark-Adamec, 1983d).

Because the VHP and BM appear to tonically modulate attack and defence, we investigated how these limbic areas contribute to naturally occuring behavioural dispositions toward attack or defence. We felt that an understanding of the normal functioning of limbic areas in behaviour was important to interpreting how limbic seizures alter that functioning.

Model of Experimental Epilepsy. The method of lastingly increasing epileptogenicity of limbic tissue we chose was "partial kindling" (Racine, 1978). Partial kindling involves daily application of short trains of high frequency electrical stimulation to a chosen neural locus. Partial kindling produces lasting, interictally maintained, changes in neuronal excitability, including: 1) reduced afterdischarge threshold (ADT, the minimal current in the train required to produce an electrographic seizure or afterdischarge); and 2) lasting potentiation of synaptic transmission (long term potentiation LTP) (Adamec, 1978; Adamec & Stark-Adamec, 1983 a,c; Douglas and Goddard, 1975; Racine, 1978). These changes are incremental, occurring in a stepwise manner. This property of partial kindling permits the investigation of the development of limbic epilepsy and the impact of that development on behaviour. In this way, short-term, immediate post-ictal effects of seizures per se may be separated from lasting interictal effects related to repeated limbic seizures and a developing epilepsy.

CAT PERSONALITY AND LIMBIC COMMUNICATION

Behavioural Disposition. Our first goal was to determine whether stable dispositions toward aggression and defence existed in the adult cat. Quantitative ethological analysis of withdrawal, approach, and attack revealed stable dispositions toward attack or defence over retest periods of six months to four years (Adamec, 1978; Adamec, Stark-Adamec & Livingston, 1980). The major factor contributing to individual differences was sensitivity to environmental threat - the more aggressive the cat, the less the sensitivity to threat. Measures of defensive response to different threats correlate highly, suggesting that a common substrate mediates defensive response to different enviromental threats. The stability and generality of sensitivity to threat has the properties of a defensive "personality trait" (Adamec, 1978: Adamec, Stark-Adamec & Livingston 1983).

Limbic Modulators and Behavioural Disposition. Differences in defensiveness are correlated with how different parts of the limbic system communicate with each other. Thus far, we have investigated three limbic circuits neurophysiologically. The first circuit is the basal amygdalo-ventromedial hypothalamic circuit (AM-VMH). This pathway is relevant because: 1) it represents a major excitatory outflow of the BM (Murphy, 1972); 2) the VMH is part of the medial hypothalamic circuitry controlling defensive response in the cat (Adamec, 1976; Stokman & Glusman, 1970); and 3) the electrophysiology of potentials evoked in the VMH by BM stimulation is well understood (Murphy, 1972). The second circuit is the amygdaloventral entorhinal cortex (AM-ENT), which transmits neural activity from the amygdala into the trisynaptic circuit of the VHP (Adamec & Stark-Adamec, 1986; Krettek & Price, 1978). This circuit is of interest because it may be one source of complex sensory input into the VHP via temporal cortical inputs through the amygdala (Adamec et al., 1986; Prelevic, Burnham & Gloor, 1976). The third circuit is the perforant path input to the dentate area of the VHP (PP-VHP). This circuit is of interest because: 1) its electrophysiology is well understood; and 2) it permits field potential analysis of local synaptic excitability, including a) strength of synaptic drive, b) cell excitability, and c) local recurrent inhibition (Adamec, McNaughton, Racine & Livingston, 1981; Barnes, 1979; Tuff, Racine & Adamec, 1983).

Electrically evoked field potential analysis of these pathways revealed stable differences between cats of different dispositions. The more defensive the cat: 1) the greater the transmission of excitatory neural activity in the AM-VMH circuit (Adamec, 1978; Adamec & Stark-Adamec, 1984); 2) the less the transmission of excitatory activity in the AM-ENT; and 3) the greater the local recurrent inhibition in the dentate (PP-VHP) (Adamec & Stark-Adamec, 1984; Adamec & Stark-Adamec, 1986).

Aggressive and defensive cats do not differ with respect to synaptic drive or cell excitability in the VHP. Enhanced recurrent inhibition in the dentate in defensive cats likely attenuates the response of VHP to high frequency input, reducing VHP output to the septum (Watson, 1983) which results in a reduction of the tonic facilitation of VHP on attack.

,Taken together, the data suggest that behavioural disposition is dependent on the pattern of distribution of flow neural information through a variety of limbic circuits. More defensive cats display a bias for information flow through the neural substrate of defence, i.e. enhanced flow through the AM-VMH circuit, with reduced flow of information through AM-ENT and PP-VHP circuits. Aggressive cats, on the other hand, display a neural bias for information flow away from the VMH. Instead, information in routed toward the VHP via the AM-ENT pathway. Information flow through the VHP is enhanced by reduced recurrent inhibition. In this way, the VHP, a tonic attack facilitator, may dominate limbic and behavioural response to input.

Partial Kindling - Effects on Behavioural Disposition and Limbic Communication. Partial kindling of BM or VHP produces a number of lasting, interictally maintained behavioural and neurophysiological changes. These include lowered local ADT and lasting behavioural changes persisting 60-120 days after the last seizure, i.e., as long as the cats are kept (Adamec, 1978; Adamec & Stark-Adamec, 1983 b,c). Behavioural changes do not depend on continued seizures or ADT decreases for their maintenance (Adamec, 1978; Adamec & Stark-Adamec, 1983 b,c). Behavioural changes do not result from a single or even several seizures, but require 7 to 19 seizures for their production. Two types of behavioural change have been observed: 1) a lasting increase in defensive response to environmental threat; or 2) a lasting decrease in defensiveness accompanied by an increase in predatory aggressiveness. These behavioural changes are accompanied by equally long-lasting changes in transmission of non-epileptic activity within the three circuits described above. When a lasting increase in defensiveness occurs post-ictally, there is a lasting increase in AM-VMH transmission which is necessary for behavioural change (Adamec, 1978; Adamec & Stark-Adamec, 1983 c, Adamec & Stark-Adamec, 1986). In addition, there is an increase in local recurrent inhibition in the VHP (Adamec et al., 1983 c), and varying degrees of change in the AM-ENT circuit.

Cats in which AM-ENT transmission increases show less of an increase in defensiveness than cats in which AM-ENT transmission does not change, despite equal increases in AM-VMH transmission and in recurrent inhibition in the VHP (Adamec & Stark-Adamec, 1986). These findings suggest that there is a behaviourally effective antagonism between AM-ENT and other circuits, a relationship consistent with the differences in transmission in the AM-ENT pathway observed between naturally defensive and aggressive cats. Since cats displaying increases in AM-ENT transmission do not differ behaviourally prior to repeated seizures, it is unclear why they show the neurobehavioural pattern that they do. There is, thus, an element of uncertainty about degree of interictal behavioural outcome. Nevertheless, there is a neural correlate suggesting that seizures may produce limbic trace patterns which are antagonistic, modulating degree of behavioural change.

Pre-ictal behavioural state, however, does influence interictal outcome. Increased defensiveness may be produced by partial kindling of AM or PP-VHP circuitry in naturally defensive cats (Adamec, 1978; Adamec & Stark-Adamec, 1983 b,c). In contrast, partial kindling of the VHP in naturally aggressive cats decreases defensiveness and increases aggressiveness (Adamec, 1978; Adamec et al., 1986). Aggressive cats may be made more defensive, however, by partial kindling of the amygdala (Adamec, 1975, 1976, 1978). Thus pre-ictal personality interacts with location of the experimental focus to determine interictal behavioural outcome.

CONCLUSIONS

The data unequivocally answer the questions originally posed. First, seizures can alter behaviours lastingly and interictally. Second, pre-seizure personality is an important factor in determining the nature of behavioural change. Moreover, the data suggest the following generalizations about the impact of experimental limbic epilepsy on interictal behaviour: 1) Repeated seizure activity in limbic circuits produces lasting interictal effects on emotional behaviour and limbic function. These effects require repeated seizures for their production but not for their maintenance. 2) Naturally occurring pre-ictal behavioural disposition and state of pre-ictal limbic communication likely interact with limbic seizures to determine interictal behavioural outcome. The interaction is complex, and involves both pre-seizure personality and locus of the experimental focus. 3) A variety of interictal changes in limbic function persist after partial kindling, but not all of them are necessary for lasting behavioural change. The critical neurophysiological parameter mediating behavioural change appears to be lasting changes in transsynaptic communication of neural activity between limbic structures. 4) Changes in transsynaptic communication appear as enhanced excitatory synaptic drive (hyperfunctional interictal traces) or as reductions in excitability due to enhanced recurrent inhibition (hypofunctional interictal traces). 5) The neuroanatomical distribution of interictal traces is important in determining the nature and degree of interictal behavioural change. For example, interictal increases in defensiveness are best understood as the result of both a seizure-induced hyperfunction (e.g., in the AM-VMH pathway) and a seizure-induced hypofunction (e.g., due to enhanced recurrent inhibition in the VHP). 6) Hypo - and hyperfunctional changes themselves do not predict behavioural change. Rather, the circuits in which they occur do. This latter conclusion indicates the value of the neuroethological approach to the study of the question of epilepsy and behaviour. Without some understanding of how circuits changed by epilepsy participate in normal behavioural functioning, little can be learned about how those neural changes participate in behavioural change.

The findings in animals provide a case in point for clinical epilepsy. They suggest that a developing epilepsy which invades the limbic system can have lasting behavioural effects. They also suggest the complexity, and potential unpredictability of the impact of seizures on behaviour.

The human case is undoubtedly much more complex than that presented for the cat. Some guidelines for research in humans, however, are suggested by the research in animals. One is that careful quantification of behaviour, paying due respect to its complexity in humans, is warranted. Secondly, involvement of limbic tissue in repeated seizure discharge may be an important factor in whether an epilepsy has behavioural effects of an emotional nature. Finally, individual differences in pre-ictal neurobehavioural characteristics of persons afflicted with epilepsy may effect the pattern of seizure spread to produce a variety of behavioural responses to the seizure disorder. Behavioural and neural function measurements should be designed to deal with this potential element of complexity.

CLINICAL APPROACHES

One of the controversies in the clinical epilepsy literature revolves around the issue of whether psychological problems are an inevitable concomitant of seizure disorders (e.g., Bear, 1977, 1979, 1983; Bear & Fedio, 1977; Hermann, 1977; Hermann & Riel, 1981; Mungas, 1982, 1983; Rodin, Schmaltz & Twitty, 1984; Stevens, 1966, 1973, 1975, 1977; Tizard, 1962). As we have described elsewhere (Stark-Adamec & Adamec, 1985), the controversy, which focuses mainly on complex partial seizure (CPS) patients, has been fueled by poor research methodology and by overstatement. The diametrically opposed results reported in the clinical literature could be interpreted to mean that some, but not all, seizure disorder patients would experience interictal personality disturbance. More particularly, our data from partially kindled cats lead to the prediction that seizure patients at risk for neurophysiologically-based psychological problems would be those with limbic involvement in the seizure discharging.

INDIVIDUAL DIFFERENCES

To address the first component of the issue, it is necessary to ask: whether problems experienced by seizure patients are distinguishable from those experienced by nonpatients; whether the problems are psychiatrically relevant; and whether these problems are distinct from those experienced by patients with other chronic illnesses. Accordingly, the responses of 70 seizure patients, 92 psychiatry patients, 28 dialysis patients and 447 nonpatients to a psychometrically improved modification of Bear and Fedio's (1977) Personal Behaviour Inventory were compared. (Details of samples, multivariate statistics and results may be found in Stark-Adamec, Adamec, Graham & Hicks, 1986).

To summarize briefly, psychiatry patients obtained significantly higher scores than nonpatients on 24 of the 26 dimensions assessed by our questionnaire - indicating that our instrument may be tapping psychiatrically relevant aspects of human behaviour. Similarities between seizure, psychiatry, and dialysis patients indicated that the compulsivity, humourlessness, and hyposexuality attributed to seizure patients as a function of their neuropathophysiology (e.g., Bear, 1977) appear to be more a function of being a chronic patient, than of being a seizure disorder patient. However, seizure patients did report a number of psychological problems independent of what might be termed a "sick person syndrome". Seizure patients presented themselves as significantly more angry, emotional, and preoccupied with religious and philosophical concerns relative to both nonpatients and dialysis patients. Moreover, their self-reported dependence, confusion, tendency to record all details and to consider the story of their life to be of educational value to others were as elevated as that reported by psychiatry patients.

It must be noted, however, that caution is advisable when attempting to characterize seizure patients psychologically, for not all seizure patients responded in this manner. In fact, of the patient groups examined, those with seizure disorders were the most heterogeneous in terms of their scores on these measures. Although approximately one third of seizure patients were indistinguishable statistically from psychiatry patients, virtually the same proportion were statistically indistinguishable from nonpatients on the dimensions tapped by the questionnaire. Furthermore, there were no significant differences between patients with CPS, those diagnosed as CPS with secondary generalization, and primary generalized seizure patients in terms of psychological problems. Thus, characterization of CPS patients as displaying a unique syndrome of sensory-limbic hyperconnection (Bear, 1979) would appear to be inaccurate.

PREDICTION OF RISK

Although not all seizure patients experience psychosocial problems, a significant proportion do report psychiatrically relevant difficulties. Prediction of which seizure patients would be at risk for psychological problems would be significant both theoretically and clinically. The fact that the limbic system is involved in the integration of emotional states with memory and cognition (Gloor, Olivier, Quesney, Andermann & Horowitz, 1982), and that epileptogenic alteration of the limbic system produces lasting changes in emotional response (Adamec & Stark-Adamec, 1983 a,b,c) led us to hypothesize that repetitive limbic discharging might play a key role in the production of psychological problems experienced by seizure patients.

Our own work, in conjunction with that of Hermann, Dikmen, Schwartz & Karnes (1982) suggested that an aura, or set of auras, might serve as a non-invasive marker of degree of limbic involvement in seizure discharges (Stark-Adamec & Adamec, 1985). Consequently, we developed a 33-item Aura Questionnaire to assess patterns of aura experiences in relation to patterns of psychological problems (Stark-Adamec et al., 1986).

Our data from the Aura Questionnaire, though based on a sample of only 34 seizure patients, are very promising. Those seizure patients who, on the basis of their pattern of scores on our Personal Behaviour Inventory, were statistically indistinguishable from psychiatry patients were also much more likely, than were those statistically indistinguishable from nonpatients, to experience a particular subset of auras. Five of the six auras in this subset, which we find associated with psychosocial problems, have been shown by others (Halgren, Walter, Cherlow & Crandall, 1978) to be evocable by direct electrical stimulation of the human limbic system, viz.: changes in brightness of light; perception of formed images; alterations in the loudness, pitch, or quality of sounds; hatred as an emotion which just comes "out of the blue"; and dizziness. Consistent with our kindling hypotheses (Adamec & Stark-Adamec, 1983a), frequency and intensity of aura experiences were highly positively correlated.

CONCLUSIONS

It is clear from these studies that investigations of psychological concomitants of seizure disorders require a multivariate approach, both in design of instruments and in the analysis of the data, in order to reflect the complexity of human behaviour. It is noteworthy that seizure diagnosis was not predictive of psychological disturbance. However, experience of particular auras may prove to be a valid predictor of risk for psychopathology in seizure disorder patients in general.

Consistent with our animal research, auras which may reflect limbic participation in the seizure discharge were associated with psychological problems. It one adopts the kindling model of epileptic modification of limbic function, one could hypothesize that repeated epileptic activation of the limbic system in patients at risk alters limbic function interictally in a manner analogous to that reported with partial kindling in cats. An interesting implication of the kindling orientation is that there need not be an epileptic focus in the limbic system: all that is required is that seizure activity repeatedly invade particular limbic circuits to put the patient at risk.

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SUMMARY

The relationship between limbic traces and stable behavioural states in experimental animals is of relevance to the question of how repeated limbic seizures alter behaviour interictally. We have found that cats differ naturally with respect to defensive response to environmental threat. Some cats are naturally more defensive than others. These behavioural differences are stable and persist into adulthood. Neurophysiological correlates of defensiveness have been found in limbic pathways implicated in the natural modulation of defensive behaviour. These naturally occurring limbic traces are of two types: enhanced transmission of nonepileptic excitatory activity across synapses which resemble long term potentiation; and enhanced neural inhibition in local circuits which may attenuate response of those circuits to input.

Repeated limbic seizures lastingly alter both limbic traces and defensive behaviour. Limbic trace patterns mediating behavioural change are best understood as interictally maintained hyper - and hypofunctions of circuits modulating attack and defence. It is not the hyper - or hypofunctional changes per se which alter behaviour, rather it is where these changes occur in particular limbic circuits which determines the nature and degree of interictal behavioural change.

The findings in animals suggest that repeated invasion of limbic tissue by seizure activity produces lasting interictal effects on emotional behaviour and limbic function in the absence of further seizures. Testable hypotheses regarding interictal behavioural disturbance in seizure patients may be derived from the results with experimental animals. One hypothesis is that seizure patients at risk for neurophysiologically based psychological problems would be those with limbic involvement in the seizure discharging. It is further hypothesized that aura experiences might serve as a non-invasive marker of the degree of this limbic involvement. Data are reviewed from studies which support both hypotheses.

RESUMEN

La relación entre los rastros límbicos y los estados estables de conducta en animales experimentales es significativo en lo concerniente al modo como las crisis límbicas repetidas modifican la conducta interictal. Nosotros hemos observado que los gatos se distinguen naturalmente en lo relativo a sus respuestas defensivas frente a una amenaza del ambiente. Algunos gatos son por naturaleza más defensivos que otros. Estas diferencias de conducta son estables y las mismas persisten hasta que los gatos llegan a ser adultos. Las correlaciones neurofisiológicas de la defensa han sido encontradas en las vías límbicas implicadas en la normal modulación de la conducta defensiva. Existen dos tipos de rastros límbicos que se originan naturalmente; la transmisión acentuada de la actividad excitatoria no epiléptica a través de sinapsis equiparables a la potenciación prolongada; y la inhibición neural acentuada en los circuitos locales que puede atenuar la respuesta de estos circuitos al impulso de entrada. Las crisis límbicas repetidas modifican en forma sostenida los trazos límbicos y la conducta defensiva. Los modelos de los trazos límbicos que se interponen en una modificación de la conducta deben ser comprendidos sobretodo como hiper o hipo funciones de circuitos mantenidos interictalmente que modulan el ataque y la defensa. No son estos cambios hiper o hipofuncionales en su condición de tales que modifican la conducta, pero más bien el lugar en los circuitos límbicos donde se producen estos cambios que determina la naturaleza y el grado de la modificación de la conducta interictal.

Los resultados de las investigaciones sobre los animales sugieren que la invasión repetida del tejido límbico por la actividad de las crisis produce efectos interictales durables sobre la conducta emocional y sobre la función límbica en ausencia de nuevas crisis. Hipótesis que pueden ser puestas a pruebas concernientes a la perturbación de la conducta interictal en pacientes que sufren de crisis pueden ser deducidas de los resultados obtenidos sobre animales experimentales. Una hipótesis en particular sugiere que pacientes con crisis y que están expuestos a problemas psicológicos con base neurofisiológica sean aquellos con implicancia límbica en la descarga de las crisis. Otra hipótesis establece que experiencias de las auras pueden ser como un indicador "no invasivo" del grado de esta implicancia límbica. Lo expuesto deriva de los estudios que apoyan ambas hipótesis.

RÉSUMÉ

Le rapport entre les traces limbiques et des états de comportement stable chez les animaux expérimentaux est significatif en ce qui concerne la manière dont les crises limbiques répétées modifient le comportement de façon interictale. Nous avons trouvé que les chats se distinquent naturellement quant à leur réponse défensive à une ménace environnementale. Certains chats sont de nature plus défensifs que d'autres. Ces différences de comportement sont stables et elles persistent jusqu'à ce que les chats deviennent adultes. Les corrélatifs neurophysiologiques de la défense ont été retrouvés dans les voies limbiques impliquées dans la modulation normale du comportement défensif. Il y a deux types de traces limbiques qui se produisent naturellement: La transmission accrue de l'activité excitatoire non-épileptique à travers les synapses qui ressemblent à la potentiation à longue terme; et l'inhibition neurale accrue dans las circuits locaux qui peut attenuer la réponse de ces circuits à la consommation.

Les crises limbiques répétées modifient

de façon durable les traces limbiques et le comportement défensif. Les modèles des traces limbiques qui s'interposent dans une modification de comportement doivent être comprises surtout comme des hyper - et des hypo-fonctions de circuits maintenus interictalement qui modulent l'attaque et la défense. Ce ne sont pas ces changements hyper - ou hypo-fonctionel en tant que tels qui modifient le comportement mais plutôt le lieu dans les circuits limbiques où se produisent ces changements qui détermine la nature et le degré de la modification du comportement interictal.

Les résultats de la recherche sur les animaux suggèrent que l'envahissement répété du tissu limbique par l'activité des crises produit des effects interictaux durables sur le comportement émotionnel et sur la fonction limbique en l'absence de nouvelles crises. Des hypothèses testables concernant la perturbation du comportement interictal chez les patients qui souffrent de crises peuvent être tirées des résultats des expériences sur des animaux expérimentaux. Une hypothèse en particulier veut que les patients qui souffrent de crises et qui sont sujets à des problèmes psychologiques à base neurophsiologique soient ceux ayant des complications limbiques dans la décharge des crises. Une autre hypothèse propose que des expériences des auras peuvent servir comme marque non-envahisseur du degré de ce rôle limbique. Les données examinées viennent des études qui appuient en faveur des deux hypothèses.

ZUSAMMENFASSUNG

Das Verhältnis zwischen Randspuren und stabilen Verhaltenszuständen in Versuchstieren ist von Bedeutung für die Untersuchung von der Wirkung wiederholter Randanfälle auf das zwischenkrampfzeitliche Verhalten. Unsere Ergebnisse zeigen, daß Katzen natürlich unterschiedlich auf Drohungen von der Umwelt reagieren. Einige Katzen sind von Natur aus defensiver als andere. Diese unterschiedlichen Verhaltensweisen sind stabil und dauern lebenlänglich. Nervenphysiologische Korrelate der Selbstverteidigung sind in den Randbahnen gefunden worden, die mit der natürlichen Abstimmung defensives Verhaltens in Zusammenhang stehen. Diese natürlich vorkommenden Randspuren sind zweierlei: gesteigerte Übermittlung nicht-epileptischer aufreizender Tätigkeit über Synapsen, die langfristiger Potentiation ähneln; und gesteigerte Nervenhemmung in lokalen Bahnen, wodurch die Reaktionen dieser Bahnen auf Eingangsenergie vermindert sein mag.

Wiederholte Randanfälle bewirken nachhaltige Änderungen sowohl in den Randspuren als auch im Selbstverteidigungsverhalten. Randspurenmuster, die Verhaltensänderungen vermitteln, lassen sich am besten als zwischenkrampfzeitlich aufrechterhaltene Hyper - und Hypofunktionen von den Bahnen beschreiben, die Angriff und Verteidigung regulieren. Es sind weder die hyper - noch die hypofunktionellen Änderungen an sich, die das Verhalten ändern, sondern es ist der Ort, wo diese Änderungen in besonderen Randbahnen stattfinden, der die Art und den Grad der zwischenkrampfzeitlichen Änderung im Verhalten bestimmt.

Die Befunde von Tierversuchen deuten darauf hin, daß die wiederholte Invasion des Randgewebes durch Anfälle zu nachhaltigen zwischenkrampfzeitlichen Wirkungen auf das emotionelle Verhalten und die Randfunktion führt, auch ohne weitere Anfälle. Prüfbare Hypothesen bezüglich zwischenkrampfzeitlicher Verhaltensstörung in Patienten mit Anfällen lassen sich von Ergebnissen mit Versuchstieren herleiten. Eine solche Hypothese lautet wie folgt: Patienten mit Anfällen, die Gefahr laufen, nervenphysiologisch verursachte psychologische Probleme zu haben, wären diejenigen, bei denen Randmitwirkung bei der Auslösung der Anfälle vorkommt. Die weitere Hypothese bietet sich an, daß Vorgefühlerfahrungen vor Anfällen vielleicht als Hinweis auf den Grad dieser Randmitwirkung dienen könnten. Meßwerte von Untersuchungen, beide Hypothesen unterstützen, werden besprochen.

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Complex Behavioral Chains of Temporo-Limbic Epilepsy and their Relationship to Emotional Phylogenesis: Ictal Laughter

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Clinical observation indicates there is an order or specific sequence of propagated events (the "epileptic march") in the seizures of given individuals. Further, there may be a similar sequence across individual boundaries in those with the same seizure type. The latter finding suggests preferential species-specific pathways in epileptic propagation. Such chains of stereotyped sequential behavioral fragments may elucidate phylogenesis particularly of basic motor patterns and emotional states.

A pioneer study in the propagation pathways of temporo-limbic seizures is that of Stevens (1957) who made a sequential content analysis of 40 patients. The most common emotional experiences in temporo-limbic epilepsy contain painful feeling tone, generally related to fear; Stevens notes the "near-ubiquitous succession of the epigastric or gastric sensation by that of fear".

The method of Stevens' sequential content analysis may be illustrated by her Case 2: gastric--- fear--- bad odor; visions--- threatening vision, death fear--- running, fight or smoking--- generalized (grand-mal) seizure.

If we assume a set of loci, that is a series of successive points of neural propagation, this seizure may be shown as follows, with the loci(L) numbered consecutively:

L1 gastric
L2 fear
L3 bad odor; visions
L4 threatening vision, death fear
L5 running; fight or smoking
Grand-Mal

The method of sequential content analysis is herein applied to gelastic epilepsy in an attempt to throw light on laughter's accompaniments and possible phylogenesis. 25 cases were selected from the literature. Therefore, these cases are not exhaustive and are not based on personal observation. Epileptic unfolding, occurring quickly and often with an over-lapping sequence of events, may bewilder the most careful observer of the "march". Nevertheless, cases are available in which the sequence is adequately noted. The more valuable cases are those without gross lesional disease of the brain since these might disrupt a natural propagation pattern. Despite their frequent association with such disease, cases occurring in infancy and childhood are included for their developmental value and for establishing the very early ontogenetic appearance of the laughter mechanism.

Adult and childhood cases are temporo-limbic in seizure type and in almost all instances, a temporal lobe focus is demonstrated electroencephalographically.

PROPAGATION ALONG LOCI OF SEIZURE CHAIN

Druckman and Chao (1957) reported 11 children with epileptic laughter, of whom 5 were one year of age or younger.

1. Epileptic laughter at age 4 years. The seizure progression may be schematized as follows:
   L1 "drew" up right leg or all limbs
   L2 laughter
   End of seizure
2. Epileptic laughter at age 16 months:
   L1 arms and legs stiffen
   L2 laughter
   End of seizure
3. Epileptic laughter at age 14 weeks:
   L1 extension of left arm; flexion of legs and head
   L2 stare; laugh
   End of seizure
4. Epileptic laughter at age 17 months:
   L1 eyes roll back; mouth pulls to right; arms abduct; lower limbs flex on trunk and quiver
   L2 laughter
   End of seizure
5. Epileptic laughter at age 8 months:
   L1 extensor spasm of arms and legs; sudden extension of arms and legs into spread-eagle position
   L2 laughter
   End of seizure

   In this individual, the laughter might also precede the extensor limb movements.
6. Epileptic laughter at age 12 months:
   L1 head and eyes turn to left; flexion of head and all four limbs
   L2 laughter
   End of seizure
7. Epileptic laughter at age 12 months:
   L1 massive flexor spasms
   L2 laughter
   End of seizure
8. Epileptic laughter probably beginning at age 6 years. Seizure schematized, observed at age 10 years, 7 months, apparently *in* sleep.
   L1 laughter
   L2 clammy; cold; swallows; eyes roll up; hands wave; body stiffens
   End of seizure; returns to sleep
9. Epileptic laughter at age one year:
   L1 falls to floor
   L2 gets off floor
   L3 head drops to chest; appears dazed, laughter
   End of seizure
10. Age of onset of epileptic laughter in this child is not clear.
    L1 epigastric pain
    L2 bi-frontal headache; vomiting
    L3 laughter
    End of seizure
11. Epileptic laughter at age 2 years, 9 months, during sleep; later in childhood, epileptic laughter observed while awake.
    L1 Aroused from sleep laughing; dazed; face flushed
    End of seizure
    During waking state:
    L1 sits down
    L2 laughter with "eyes set"; fingers playing about lips.
    End of seizure
12. In the case, 13 years of age, of Ames and Enderstein (1975), the seizure progression may be schematized as follows:
    L1 stare
    L2 laughter
    L3 verbalization
    L4 repetitive abduction-adduction movements of upper limbs; head turns to left; face pale
    End of seizure
13. In the case studied and observed at 20 years of age by Gumpert, Hansotia and Upton (1970), the seizure progression may be schematized as follows:
    L1 vacant expression
    L2 eyes deviate to right
    L3 arms raise in front of chest
    L4 head turns to right with high pitched laughter; muscle tone increased particularly on right side
    End of seizure
14. In the case, 11 years of age, of Jacome and Risko (1984), the seizures resembled cataplexy, but their epileptic nature was established by EEG.
    L1 giggling
    L2 loss of muscle tone, "becoming limp" and falling
    End of seizure

15. In the case 26 years of age, of Jacome, McLain and FitzGerald (1980), the seizures were induced by the volitional rapid hyperextension of the trunk and neck to an extreme position with arms extended and fingers flexed.

L1 extension posture
L2 subjective sensation of sexual pleasure
L3 loss of consciousness
L4 stands upright, appears dazed
L5 generalized loss of tone with falling
L6 loud laughing and extremity movements such as flailing of arms and kicking
L7 occasional lip-smacking, perioral cyanosis, pupillary dilation and piloerection
L8 immobile
End of seizure

16. First case, 12 years of age, of Lehtinen and Kivalo (1965):

L1 sensation of tension
L2 laughter, red in face, verbal automatism
L3 laughter might change into crying
End of seizure

17. In the second case, 19 years of age. of Lehtinen and Kivalo (1965), there are several descriptions of the seizure progression. Two of these may be schematized as follows:

L1 "everything gets muddled"
L2 stare
L3 repetitive motor automatisms related to on-going activity; everything happening very rapidly
L4 laughing; illusion of talking to some person
End of seizure
The second description:
L1 suddenly stops walking; drops object
L2 head turns to left; laughter; hands bend slightly; legs stiffen
L3 face bluish-red
End of seizure

18. In the first case, 29 years of age, of Roubicek (1946), the seizure progression may be schematized as follows:

L1 eyes fixed
L2 laughter
L3 face turns red; facial grimace
L4 redness of face turns cyanotic
L5 cough; expirations
End of seizure

19. The second case, 15 years of age, of Roubicek (1946):

L1 up from bed to wash
L2 laughter
L3 running
L4 hopping
End of seizure

20. The seizure progression in a pre-adolescent female reported by Chen and Forster (1973) may be schematized as follows:

L1 laughing
L2 running; laughing
L3 tapping hands; laughing
End of seizure

21. In the first case, 11 years of age, of Daly and Mulder (1957), an infiltrating left temporo-occipital tumor was present, but the "march" of the seizure is well—recorded.

L1 stare
L2 flushing of face, dilation of pupils
L3 Marked turning of head to left; conjugate deviation of eyes to left; might turn around in counterclockwise direction
L4 laughter; adversion of head and eyes sustained
End of seizure; post-ictal aphasia

22. The second case, 36 years of age, of Daly and Mulder (1957):

L1 stare
L2 incoherent verbalizations
L3 walk; laugh
End of seizure

In the same case, pentylenetetrazol (metrazol) activation yielded the following progression:

L1 smile
L2 laughter
L3 eyes opened; laughter; verbalizations
End of seizure

23. Gascon and Lombroso (1971) encountered 10 cases of epileptic laughter. Five are described in some detail. Of those not so described, 3 had a pleasurable subjectivity with automatisms. None of the 5, described in detail, experienced pleasure or dysphoria.

Noteworthy is their case 5 whose laughter seizures, beginning at 29 years of age, occurred in sleep.

L1 noise like a laugh, sometimes like a cry; smile but sometimes "hurt" expression
L2 body turns to right
L3 wakes up; incoherent verbalizations
End of seizure

24. In Case 3 of the four reported by Weil, Nosik and Demmy (1958), ictal laughter appeared at the age of 7 months. Later in boyhood, a seizure was observed during EEG recording.

L1 laughter
L2 chewing; swallowing
L3 flexion right arm
End of seizure

25. Money and Hosta (1967) reported two cases of laughing seizures with sexual precocity, apparently secondary to hypothalamic involvement. In both cases, flushing of the face occurred during the seizure. Laughter was observed by the authors in the first case whose laughing seizures began in adolescence.

L1 tingling feeling
L2 laughter; eversion of eyes to right; vascular flushing of face and neck; shoulders held back; tremor of upper torso, head and arms
End of seizure

DISCUSSION

Although only 25 cases are analyzed from a large literature, some trends seem discernible. No characteristic sequential pattern seems present in laughter seizures. However, associated phenomena occur. Motor accompaniments are almost invariable. These are not of fine type but tend toward massive movements of head, trunk and extremities, those of the upper extremities often being unique. There are adversive movements of the head and eyes, occasionally of the trunk. There may be coordinated action movements, for example running and hopping. Alterations in truncal posture or tone occur. Incoherent verbalizations may appear. Vasomotor facial alterations, particularly reddening or blushing, sometimes pallor are relatively frequent.

Unlike the Stevens' series, epigastric phenomena are rare, occurring in only one case. Not only the epigastric but the other two sensations of Jackson's classical uncinate triad, namely olfactory and gustatory, are not encountered. Lip smacking and swallowing movements are each encountered in only one case. Also unlike the complex psychical and hallucinatory states of the Stevens' series is the paucity of inner emotional or mental states, often considered to be a feature of an uncinate locus. Pleasurable feeling tone may occur but in no instance is a true dysphoria (fear or depression) reported.

Although there may be less predictability in the chain of propagation, the motor phenomena may represent a chain of loci related to laughter. Laughter is considered an ancient mechanism because of its appearance early in ontogeny and because of its limbic - hypothalamic - mesencephalic - rhombencephalic substrata, as shown not only in the epileptic cases but in various clinical-pathological studies. Any ancient behavioral mechanism may become through time, the final pathway of more than one function.

In primates and other high mammals, facial and body displays convey information about motivational states and serve as social signals. Bekoff (1977) in his study of a mammalian social signal, the canid play bow, finds marked stereotypy of this display, implying a programmed neural basis for its initiation and sequencing.

Laughter is a human display, a social signal. One of its early functions may be to express and signal triumph. Observe, as in a newspaper photograph, the jubilant triumphant victor of an athletic contest. The posture is erect, perhaps even hopping or jumping upward the arms are outstretched abducted from the body and abducted vertically, reaching upward often with fingers flexed to form fists; the mouth is open with some lateral retraction of its corners.

This motor attitude is reminiscent of the case cited of Jacome, McLain and FitzGerald in which the seizure trigger, and it would seem the first seizure event, is hyperextension of trunk and neck with arms extended and fingers flexed; later in the seizure, the arms flail coincident with the laughter. The abduction-adduction movements of the upper limbs in the case cited of Ames and Enderstein may also be related to this motor attitude in that the abduction movements follow a vertical path.

Triumph is the highly pleasurable emotion of the foe vanquished, the prey killed, the river forded--- in short, the emotion of obstacles overcome, of fear and uncertainty transcended, of survival not only insured but enhanced. The triumph display expresses this inner state and also signals the achievement to others of the group.

Perhaps later in human history, in duos or group assemblages, laughter became associated with humor. Yet, a major component of humor is its sense of triumph. The laughter is a victor---that is, superior to the other being ridiculed, mocked, artfully attacked. Such modulated aggression is a bedrock of humor but is not all-inclusive. There are other components, for example the surprise, the novelty of incongruity.

In social laughter, there is often facial flushing and, should the humorous situation intensify, vigorous extremity and trunk movements. There may also be reduction or loss of muscle tone as demonstrated by Paskind (1932) and in the cases cited of Jacome and Risko; and Jacome, McLain and FitzGerald. The loss of muscle tone, also seen in the laughter engendered cataplectic reaction of narcolepsy, may be viewed as an adaptation which eliminates the possibility of motor action and converts a fundamentally aggressive mental state into a pleasurable social sharing.

Although this phylogenetic exploration is necessarily speculative, the study of behavioral chains, particularly those across individual boundaries, as in the temporo-limbic epilepsies, should throw light on the origins of human species-specific behavior. Complex behavioral chains are also available for study in certain "imperative" ideas of the waking state and in certain dream types. Recurrent stereotyped dysphoric dreams are in some instances identical or equivalent to temporo-limbic seizures (Epstein 1964, 1966, 1979) and, as such, seem to follow a specific path of propagation, sometimes with a connection to an unicinate locus (Epstein 1981). The more common "normal" dream, on the other hand, may well be the product of a larger and less clearly defined cerebral field, although some of its loci may also have phylogenetic import.

SUMMARY

There may be a specific sequence of propagated events in temporo-limbic epilepsy. The discharge may therefore traverse a phylogenetically determined arrangement of brain loci. In a survey of ictal laughter, no specific sequence is apparent, but certain motor and autonomic accompaniments occur. The motor accompaniments may throw light on phylogenetic components of human laughter.

RESUMEN

Puede ocurrir una secuencia específica de eventos propagados en epilepsia témporo límbica. La descarga puede por lo tanto atravesar un dispositivo filogeneticamente determinado de localización cerebral. En una observación de risa ictal no es aparente una secuencia específica, pero ocurren ciertas asociaciones motoras y autonómicas. Las asociaciones motoras pueden arrojar luz sobre componentes filogenéticos del reír humano.

RÉSUMÉ

Il peut se produire une séquence d'évemements propagés en épilepsie temporo limbique. La décharge peu par consequent traverser un dispositif disposé filogénétiquement déterminé de localisation cerebrale.

Une observation d'un rictus (rire ictial) n'est pas aparament une séquence spécifique, mais il existe certaines associacions motrices et autonomes. Les associacions motrices penveut donner des éclair cicements sur les composants filogénétiques du rire humaine.

ZUSAMMENFASSUNG

Eine spezifische Aufeinanderfolge verschiedener Geschehen können im Falle temporo-lymbischer Epilepsien auftreten. Die Entladung kann daher eine bestimmte phylogenetische Zerebralstruktur durchbrechen. Während eines iktalen Lachens ist eine spezifische Aufeinanderfolge nicht erkennbar, doch treten gewisse motore bzw. autonome Assotiationen auf. Die motorischen Assotiationen können wahrscheinlich phylogenetische Komponente des menschlichen Lachens erklären.

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Sexually Dimorphic Pattern in the Hypothalamic and Limbic Brain

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I. Introduction

Male-female differences in adult neuroendocrine and behavioral responses largely depend on differences in the organization of the brain. These sex differences in brain organization are brought about by the exposure of undifferentiated brain to the organizational action of sex steroids (Goy and McEwen, 1980; Arai et al., 1983). On the morphological basis, sex difference in nuclear volume, dendritic branching and synaptic pattern has been demonstrated in certain brain areas. Evidence is accumulating that sex steroid plays a significant role in modulating postnatal neuronal maturation and neural circuit formation (Goy and McEwen, 1980; Arai, 1981). Sex steroids given perinatally affect the cell number in certain neuronal groups (Döhler et al., 1982; Breedlove and Arnold, 1983). Aromatizable androgen or estrogen has been found to stimulate markedly the formation of very complex networks of neurite branches in preoptic or hypothalamic explants (Toran-Allerand, 1981). Furthermore, synaptogenesis can be facilitated by neonatal treatment with estrogen in the hypothalamic and limbic structures (Arai, 1981). These findings provide evidence for a possible mechanism underlying sexual differentiation of the brain, especially the hypothalamic and limbic structures which are abundant in receptors for sex steroids. These structures are involved in the control of neuroendocrine and behavioral responses, possibly in emotional responses, too.

In this article, morphological correlates of sexually dimorphic brain are discussed in relation to reproductive and behavioral functions, because sexually dimorphic brain functions are thought to be reflected by differences in brain structures.

II. Structural sex difference in the brain at light microscopic level.

Gorski and his coworkers (1978) have found a striking sex difference in the preoptic area of the rat. Here, the volume of an intensely staining component of the preoptic area is markedly larger in the male than in the female. They called it the sexually dimorphic nucleus of the preoptic area (SDN-POA). Since the neuronal densities in the two sexes are comparable but the neural cluster of the SDN-POA in the male is much larger, they concluded that the male SDN-POA contains many more neurons. Moreover, the volume of the SDN-POA in female rats can be modified by perinatal treatment with testosterone (Döhler et al., 1982). Although the mechanisms of hormone action are still not clear, sex steroid may play an important role in modifying neurogenesis or neuronal survival du ring the development of the SDN-POA. Analogues of the rat SDN-POA have been identified in the gerbil (Yahr and Commins, 1983), ferret (Tobet et al., 1983) and guinea pig (Hines et al., 1985). More recently, the presence of an analogue of the SDN-POA in human brain has been demonstrated (Swaab and Fliers, 1985). Morphometric analysis showed that the human SDN-POA is 2.5 times as large in male as in women and contains 2.2 times as many neurons.

Sex difference in nuclear volume was also found in the ventromedial nucleus (Matsumoto and Arai, 1983), the bed nucleus of the stria terminalis (Hines et al., 1985) and the medial amygdaloid nucleus (Mizumaki et al., 1983). In the ventromedial nucleus (VMN), for example, the nuclear volume was significantly greater in males than in females. Neonatal castration of male rats which produces functionally 'feminine males' decreased the nuclear volume to a level comparable to that of the females. The situation was almost the same with the medial amygdaloid nucleus (MAN). These results suggest that sexual dimorphism in these nuclei is not determined genetically at birth, but rather dependent on the neonatal hormone environment.

Sex difference in dendritic branching has been studied in the preoptic neurons using Golgi impregnation method. In the male hamsters, the dendritic field was significantly larger than that of the females (Greenough et al., 1977). A similar sex difference has also been found in the preoptic area of the monkey brain (Ayoub et al., 1983). Neurons of males showed more dendritic branching and a higher frequency of spines. Recently, we examined the density of the dendritic spines in the neurons of the rat medial amygdaloid nucleus. A sex difference in number of spines was found in one type of neurons which had 2-3 principal dendrites arranged in a cylindrical pattern. This type of neurons was most common in the medial amygdaloid nucleus. The number of spines of this type of neurons was significantly greater in male rats than in females. Since spines are thought to be a postsynaptic element and the width of dendritic field correlates with the neuronal receptivity, the presence of a sex difference in these parameters may suggest that the capacity for processing neural informations is different between the two sexes in these brain areas.

III. Synaptic sexual differentiation in the brain.

Raisman and Field (1973) provided the first electron microscopic evidence for sexual dimorphism in synaptic organization of the rat dorsomedial POA. The number of synapses on the dendritic spines (spine synapses) of non-amygdaloid origin in females was larger than in males. Neonatal castration of males caused an increase in the number of spine synapses to almost the same level as in the females, whereas the reduction of the spine synapses to the male level was induced by neonatal injection of androgen into females. Thus, the neonatal presence of testicular androgen is responsible for the development of sexual dimorphism in synaptic organization in this area.

Sexually dimorphic synaptic pattern has also been demonstrated in four other regions; the arcuate (Matsumoto and Arai, 1980), ventromedial (Matsumoto and Arai, 1985a), suprachiasmatic (Güldner, 1982; Le Blond et al., 1982) and medial amygdaloid nucleus (Nishizuka and Arai, 1981a). In the arcuate nucleus (ARCN), the situation in regard to axodendritic synapses was almost the same as in the dorsomedial POA; reduction of spine synapses following neonatal androgen treatment of females, and restoration of spine synapses by neonatal castration of males. For axosomatic synapses, the incidence in males was greater than in females. This was reversed by manipulation of neonatal hormone environment (Matsumoto and Arai, 1980). Since spine synapses are probably excitatory, it could be assumed that the neural information converging onto the neurons of the POA and ARCN is quantitatively and/or qualitatively different between the two sexes.

In the VMN, there is a regional difference in distribution of sex steroid receptors

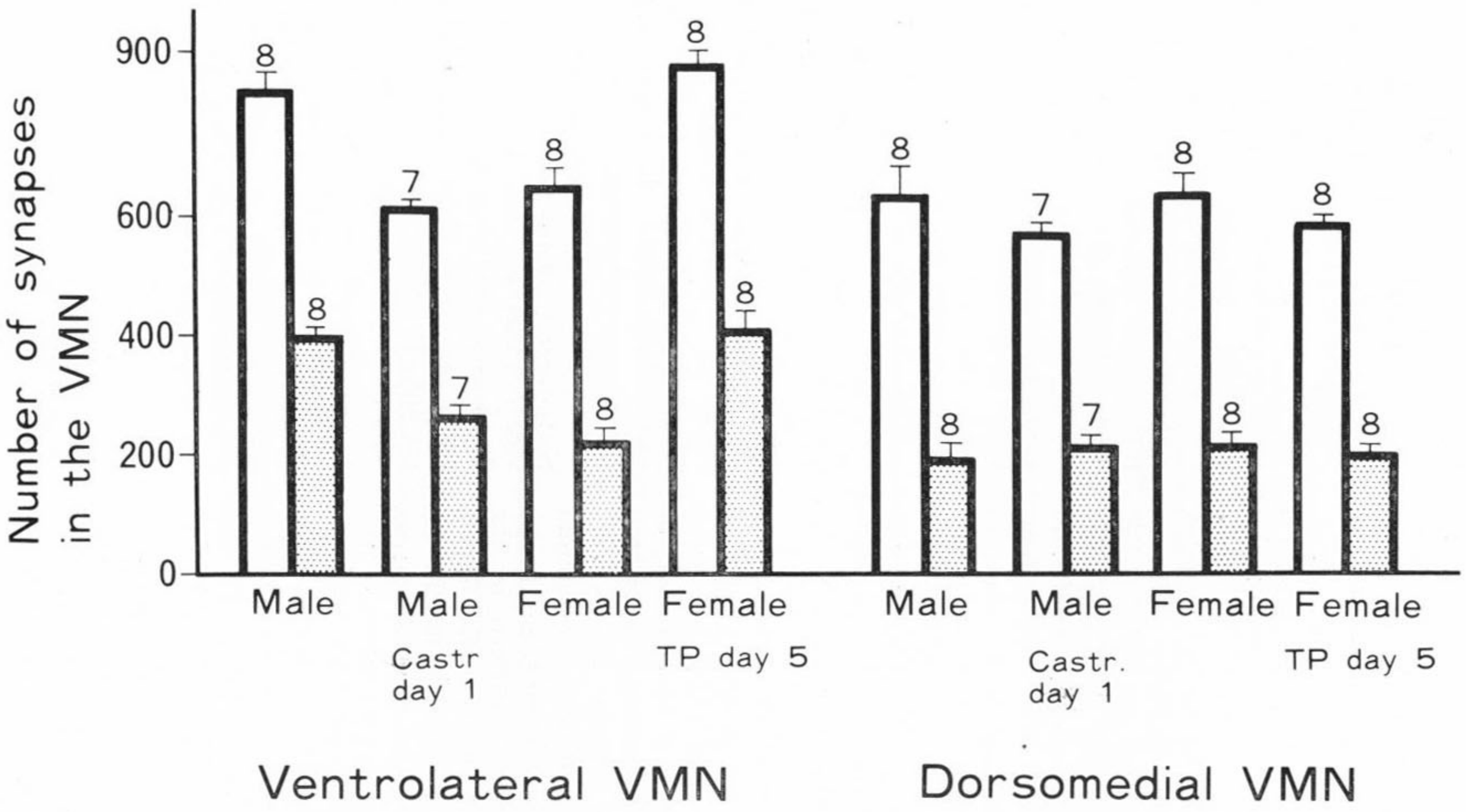

Fig. 1. — *The numbers of axodendritic shaft and spine synapses in the VL-VMN and DM-VMN of normal, and neonatally androgenized or castrated rats. Open bars indicate the number of shaft synapses and dotted ones, the number of spine synapses. Male= normal male rats; Male Castr. day 1 = male rats castrated on day 1; Female= normal female rats; Female TP day 5= female rats treated with testesterone propionate (TP) on day 5. Vertical bars indicate SEM. Numbers above the vertical bars refer to the number of rats examined.*

(Pfaff and Keiner, 1973). The ventrolateral subdivision of the VMN contains much more sex steroid receptors than other parts of the nucleus. Sexually dimorphic synaptic pattern was found in the ventrolateral part of the VMN (VL-VMN), whereas no sex difference in synaptic pattern was seen in the dorsomedial part of the VMN (DM-VMN), which contains only a few sex steroid receptors (Matsumoto and Arai, 1985a). As shown in Fig. 1, the numbers of shaft and spine synapses in normal males were significantly greater in the VL-VMN than in the DM-VMN. In normal females, however, there was no significant difference in the numbers of shaft and spine synapses between the DM-VMN and the VL-VMN. Moreover, the numbers of shaft and spine synapses in the VL-VMN were significantly greater in normal males than in normal females. Castration of males on day 1 significantly reduced the numbers of shaft and spine synapses in the VL-VMN to the level comparable to those of normal females. In contrast, neonatal treatment of females with androgen on day 5 significantly increased the numbers of shaft and spine synapses to the level comparable to that of normal males. In the DM-VMN, there was no significant difference in the numbers of shaft and spine synapses among normal and experimental animals. These results confirm the importance of neonatal sex steroid environment for the development of the sexually dimorphic synaptic pattern in the VMN. The facts that the sexually dimorphic synaptic pattern was not found in the DM-VMN and that in the absence of neonatal androgen the synaptic pattern of the VL-VMN was not different from that in the DM-VMN indicate that neurons containing sex steroid receptors in the sexually undifferentiated VMN respond differently from other non-responsive neurons to the organizational action of androgen. The regional difference in distribution of the neurons with sex steroid receptors may well correspond to a regional difference in the sexually dimorphic synaptic organization in the VMN. This may provide evidence indicating that synaptic sexual differentiation occurs specifically in the sex steroid-concentrating neuronal system.

IV. Possible mechanisms of the sexual differentiation of brain structure.

According to autoradiographic studies, most of the POA neurons become postmitotic by about day 16 of gestation. However, mitotic activity of the neurons of the SDN-POA continues to occur on day 18 of gestation (Jacobson and Gorski, 1981). When thymidine is administered on day 14 of gestation, the labeling index in female SDN-POA is significantly higher than in males, but upon thymidine exposure on day 17 the sex difference is reversed. The latter sex difference might be related to testosterone surge reported to occur on day 18. Thus, the sex difference after exposure to thymidine on day 14 or day 17 of gestation could be due to a difference in neurogenesisor neuronal death during the development (Gorski, 1984).

The final cell divisions of the neuroblasts which give rise to preoptic, arcuate, ventromedial or amygdaloid neurons also occur from days 13 to 18 of gestation in the rat (Ifft, 1972; Altman and Bayer, 1978). In the neonatal brain, the neuropil matrix of these areas is still in an immature state which is characterized by the presence of extracellular space, the presence of growth cones, and a paucity of synapses (Arai, 1981). The major neural circuits driving postpubertal neuroendocrine and/or behavioral functions are not yet established. Thus, the environment of these areas is easily accessible to organizational action of sex steroids. Using *in vitro* culture methods, stimulation of neuritic and dendritic growth in the preoptic and hypothalamic explants in response to sex steroid treatment has been reported (Toran-Allerand, 1976; Toran-Allerand et al., 1983). In the brain transplantation experiments, the volume of the transplant from newborn rat POA was found to be increased by treatment with estrogen *via* the host animals (Matsumoto et al., 1985b). Sex steroid may actually be neurotropic in such growth.

Maturation of the neural substrates may vary among the neuronal groups. In the MAN, although the synaptic number is quite small at neonatal ages, the synaptic

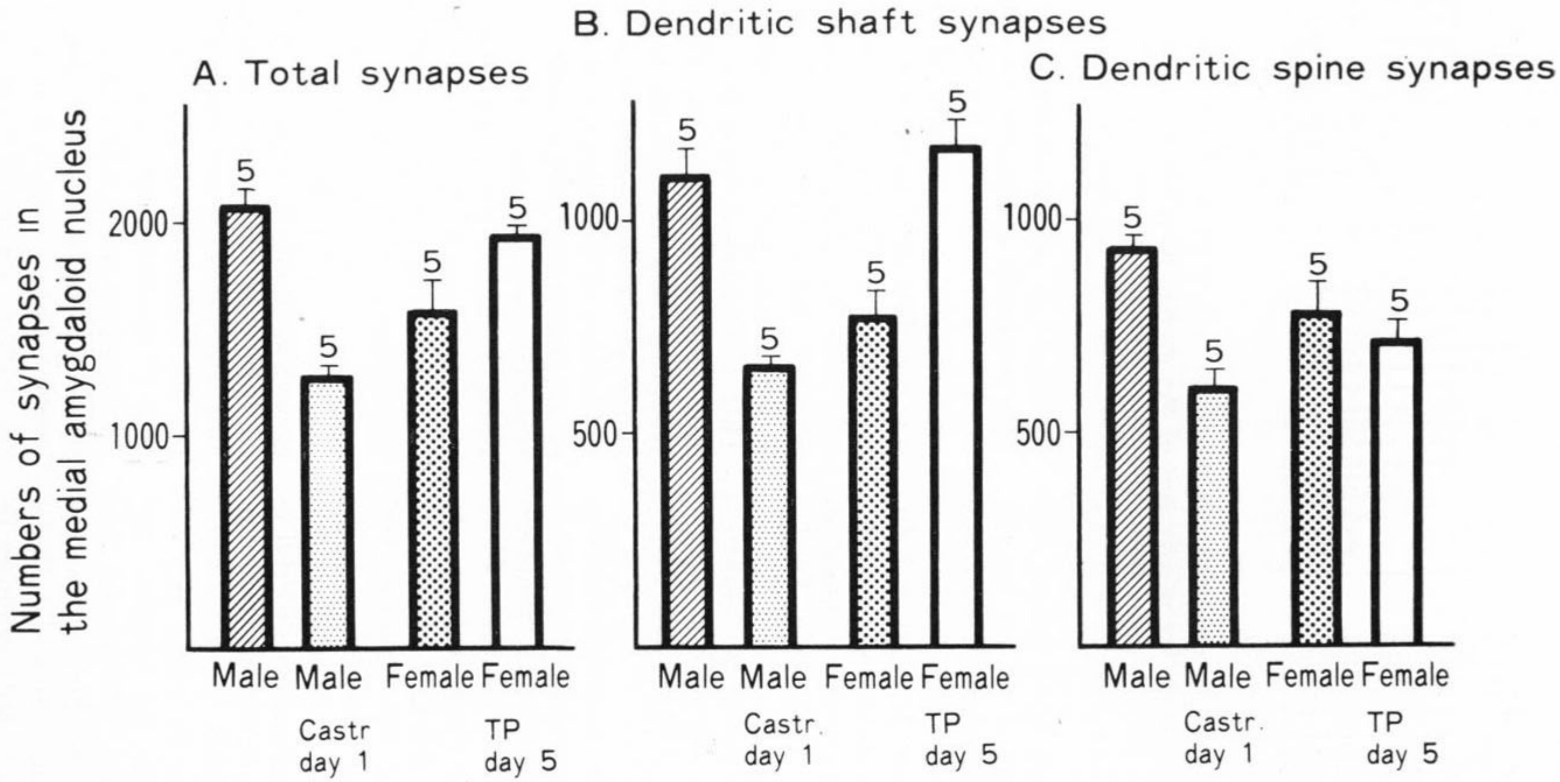

Fig. 2. — *Number of total (A), dendritic shaft (B) and dendritic spine synapses (C) per a field of 10,000 sq. μm in the medial amygdaloid nucleus of normal, oil-treated and neonatally-estrogenized female rats at 1, 11, 21, 31 or 90-100 (=adult) days of age. The total synapses (A) include the numbers of dendritic shaft synapses, dendritic spine synapses, somatic synapses and a few synapses of which postsynaptic elements could no be discriminated in an 10,000 sq. μm area.*

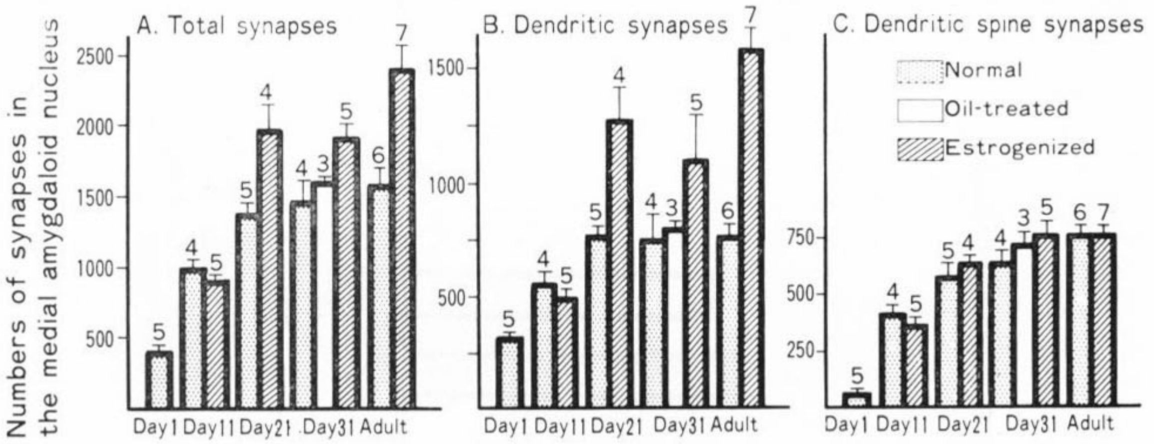

Fig. 3. — *Numbers of total (A), dendritic shaft (B) and dendritic spine synapses (C) per field of 10,000 sq. μm in the middle part of the medial amygdaloid nucleus of adult rats.*

density reaches the adult level before day 21 (Nishizuka and Arai, 1981b). In the POA (Lawrence and Raisman, 1980) and VMN (Matsumoto and Arai, 1985c), it reaches a plateau between days 20 and 30. In the ARCN, the completion of synaptogenesis is delayed to around the onset of puberty (Matsumoto and Arai, 1976; 1981)

Sex steroid has been found to markedly facilitate synaptogenesis during the postnatal development of the ARCN and MAN. Fig. 2 illustrates the effect of estrogen on synaptogenesis during the postnatal development of the MAN. Here estrogen given in early postnatal days specifically promotes the formation of shaft synaptogenesis. Since intraneuronal conversion from androgen to estrogen is currently believed to be prerequisite for the exertion of the organizational effect on the developing brain (MacLuski and Naftolin; 1981), this provide clear evidence for a possible mechanism underlying synaptic sexual differentiation of this nucleus. Actually in the MAN, the total number of synapses is larger in males and androgenized females than in females and reonatally castrated males (Nishizuka and Arai, 1981a). As shown in Fig. 3, this sex difference can be attributed to a significant increase in the number of shaft synapses in response to organizational action of testicular androgen in males. Moreover, shaft synaptogenesis in the newborn medial amygdaloid tissue grafted into the anterior eye chamber of adult ovariectomized rats is also markedly facilitated by estrogen given *via* the host animals (Nishizuka and Arai, 1982). The mean number of shaft synapses was significantly larger in the graft exposed to estrogen *via* the host than in those treated with oil alone, the number of spine synapses being not significantly different between estrogen - and oil-treated grafts. This is consistent with the results *in situ*, suggesting that the predominance of shaft synaptogenesis in response to organizational action of estrogen seems to be a characteristic feature of the neurons of the MAN. Since the extrinsic factors could be eliminated from the amygdaloid tissues by intraocular transplantation, the postsynaptic element is a possible candidate which plays an active rôle in estrogen-induced facilitation of synaptogenesis.

Recently it has been reported that α-bungarotoxin binding capacity in the medial amygdala of the mouse is sexually dimorphic and permanently modified by neonatal sex steroid manipulation (Arimatsu et al., 1981). Furthermore, addition of estrogen in the aggregating cell culture stimulates a significant increase in the toxin binding capacity within 7 days *in vitro* (Arimatsu et al., 1985). These findings suggest the possible correlation between sexual differentiation of the synaptic organization and neonatal activation of postsynaptic elements by sex steroid.

V. Functional significance of structural sex difference of the brain.

Most of the sexually dimorphic neuroendocrine and behavioral functions in the adult are dependent on the availability to the brain of an organizational action of aromatizable androgen or estrogen during a critical perinatal period. This may have an anatomic basis in neuronal differentiation. In the five regions the preoptic area, the arcuate nucleus, the ventromedial nucleus, the suprachiasmatic nucleus and the medial amygdaloid nucleus, the synaptic organization has been found to be sexually dimorphic. All these except the suprachiasmatic nucleus are known to contain a large number of sex steroid receptors (Pfaff and Keiner, 1973). For the suprachiasmatic nucleus, possible factors, inducing synaptic sexually dimorphic pattern might exist in the afferent side coming from the sex steroid-concentrating neuronal system to the suprachiasmatic nucleus.

The problem is how sexual dimorphism in these morphological parameters correlates with sex differences in functions. Gorski, for example, has suggested that his SDN-POA is involved in sexual behaviors, but the studies are yet inconclusive (Gorski, 1984). The functional significance of the sexually dimorphic synaptic pattern in the ARCN is not known. However, one of the possible role of the ARCN is to serve an interface for fibers of releasing and inhibiting hormone producing neurons which terminate to the median eminence. This may have a critical influence on the regulation of pituitary hormone secretion.

The VMN is considered to play a key role in regulating various autonomic, neuroendocrine and behavioral functions, for example, the control of feeding behavior (Nance, 1976), sexual behavior (Goy and McEwen, 1980; Pfaff, 1980), aggressive behavior (Colpaert and Wiepkema, 1976; Panksepp 1971) and the release of various pituitary hormones (Bernardis and Frohman, 1970; Brownstein et al., 1974; Christensen and Groski, 1978). In particular, involvement of this nucleus in aggressive behaviors is of interest to consider the mechanisms for emotional responses. Although the origin of afferent fibers participating in the sexually dimorphic synaptic pattern in the VMN could not be determined, morphological and electrophysiological studies have revealed that the VMN has extensive connections with intra- and extrahypothalamic areas such as the preoptic-anterior hypothalamus, amygdala, hippocampus and midbrain, etc. (Morrell et al., 1981; Palkovits and Záborsky, 1979; Renauld, 1979; Swanson and Cowan, 1975). There is evidence suggesting that neural connectivity between the amygdala and the medial basal hypothalamus through the POA is sexually dimorphic (Dyer et al., 1976), a possible contribution of the amygdalo-hypothalamic circuitry to the development of the development of synaptic dimorphism could be assumed. Furthermore, the neural outputs of the VMN projecting to the midbrain central gray are sexually dimorphic in neural connectivity and sensitivity to estrogen, both of which are critically dependent on neonatal sex steroid environment (Sakuma and Pfaff, 1981; Sakuma, 1984). It is highly probable that the sex difference in both inputs and outputs of the VMN reflects the different behavioral functions its role in regulating sexual behavior, feeding behavior and aggressive behavior.

The possible significance of the MAN difference may lie in the sexually dimorphic regulation of gonadotropin secretion. Luteinizing hormone surge can be evoked by electrical or electrochemical stimulation of the medial amygdala in female and neonatally castrated male rats whereas the stimulation is ineffective in male and androgenized female rats (Arai, 1971). Amygdala is also thought to play a role in sexually dimorphic response in aggression (Meaney et al., 1981). Lesions in the amygdala had different effects on aggressive behavior between male and female rats, these lesions depressed aggressive behavior in males, but were without effect in females. Lesions in other areas had no sex-dependent effects; septal lesions increased aggression in both males and females, while lesions of the VMN reduced fighting in both sexes. Lesions of the POA did not affect aggressive behavior by males or females (Beatty, 1984). It is possible that the region which is critical for the sex difference in aggressive behavior might be the same region which is affected by organizational action of androgen. Supportive evidence is available suggesting that bilateral androgen implantation into the amygdala left in place from days 2 to 10 increased play fighting in females (Beatty, 1984). Thus, the possibility may arise that the androgen-induced sexually dimorphic changes in the neural substrates in the amygdala are responsible for the sex difference in these behavioral responses. Therefore, it is possible that altough only limited morphological evidence for sexual dimorphism is available at present, the sum of sexually dimorphic structures in the various parts of the brain. whether they have direct or indirect connections with each other, play a critical in the psychoneuroendocrinological differences between males and females.

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SUMMARY

Sexual dimorphism in morphological parameters such as nuclear volume, dendritic field and synapse organization has been found in certain brain regions hypothalamic and limbic structures where receptors for sex steroids are abundant. For the development of these sexually dimorphic features the perinatal presence of sex steroids is responsible. Evidence is accumulating that sex steroids play a significant role in modulating postnatal maturation and neural circuit formation. Furthermore, synaptogenesis can be facilitated by neonatal sex steroid treatment in the hypothalamus and amygdala. These provide a possible mechanism underlying sexual differentiation of the brain. The next problem is therefore to make it clear when sexual dimorphism in these morphological parameters correlates with sex differences in reproductive and behavioral functions.

RESUMEN

Dimorfismo sexual en parámetros morfológicos tales como volumen nuclear, campo dendrítico y organización sináptica, ha sido hallado en ciertas regiones cerebrales, estructuras hipotalámicas y límbicas donde son abundantes los receptores para esteroides sexuales. Para el desarrollo de estas formas sexualmente dimórficas es responsable la presencia perinatal de esteroides sexuales. Se acrecienta la evidencia de que los esteroides sexuales juegan un papel significativo en la modulación de la maduración postnatal y en la formación de circuito neural. Además la sinaptogénesis puede ser facilitada por tratamiento neonatal de esteroide sexual en el hipotálamo y la amígdala. Esto suministra un posible mecanismo que sostiene la diferenciación sexual del cerebro. El problema que sigue es por lo tanto clarificar cuando el dimorfismo sexual en estoa parámetroa morfológicos está condicionado con diferencias sexuales en funciones reproductivas y de conducta.

RÉSUMÉ

Le Dimorphisme sexual entre les paramètres morfologiques tels que le volume nucléaire, champs dendritique et organization sinaptique, ont été trouvés dans certaines régions cerebrales, structures hypothalamiques et lymbiques, régions dans lesquelles abondent les recepteurs de steroides sexuels. Pour que ces formes sexuellment dimorfiques puissent se developper, elles doivent necessairement se trouver en presence de steroides sexuels.

Il est chaque fois plus évident que les steroides sexuels ont un rôle important dans le modulation de la maturité post-natale et de la formation des circuit neural. En outre, la sinaptogenèse peut être facilitée par un traitement neo-natal avec des stéroides sexuels dans l'hypotalamus et l'amygdale. Ceci sugere une mecanisme possible qui explique les diferences sexuelles du cerveau. Le problème a resondre est de savoir quand le dimorfisme sexuel des paramètres morfologiques est la condition des diferences sexuelles des fonctions reproductives et de la conduite.

ZUSAMMENFASSUNG

Sexueller Dyphórmismus in morphologischen Parametern z.B. Nuklear-volumen, dendritsche Felder und synaptische Organisation wurde in verschiedenen zerebralen, hypothalamischen und lymbischen Strukturen, wo die Rezeptoren der sexuellen Steroiden sich häufen, gefunden. Zur Entwicklung dieser sexuellen dyphormischen Strukturen ist die perinatale Anwesenheit der Sexualsteroiden, die eine wichtige Rolle in der postnatalen Reifemodulierung, sowie in der Bildung des Nervenkreislaufes spielen, von zunehmender Wichtigkeit. Ausserdem kann die Synaptogenese durch neonatale Behandlungsmethoden mit sexuellem Steroid, der auf Hypothalamus und Amigdala wirkt, beeinflusst werden. Das könnte einer der Mechanismen sein, die zur sexuellen Zerebraldifferenzierung führen. Die nachfolgende Frage wäre zu klären, wann der sexuelle Dyphormismus in diesen morphologischen Parametern von den sexuellen Unterschieden der reproduzierenden und Verhaltensfunktionen bedingt ist.

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