these experiments. Since 1000 to 5000 times more 25-OH-D_3 than 1,25-$(OH)_2D_3$ is required for these biological responses (*15*), it is not surprising that binding or competition were not observed with the concentration of 25-OH-D_3 used here. It is likely that displacement of 1,25-(OH)-[^{3}H]D_3 from 3.5*S* protein will be observed at concentrations of 30 to 300 n*M* 25-OH-D_3 in agreement with its relative activity in the bone system.

Both bone cytosols examined contained two high-affinity binding proteins for vitamin D_3 metabolities: a 3.5*S* protein specific for 1,25-$(OH)_2D_3$ and a 5 to 6*S* protein specific for 25-OH-D_3. Although 1,25-$(OH)_2$-[^{3}H]D_3 is distributed between 3.5*S* and 6*S* macromolecules in rat calvaria cytosol, it binds preferentially to the 3.5*S* component. A 5 to 6*S* protein which binds 25-OH-D_3 in cytosol prepared from rat bone has been demonstrated by other investigators using ion exchange chromatography (*16*). Furthermore, a similar 5 to 6*S* binding protein for 25-OH-D_3 has been demonstrated in all rat and chick tissues examined (*3, 17*). In experiments not reported here, the 5 to 6*S* 25-OH-D_3 cytosol binding protein found in rat tissues reacts with an antibody directed to the 4*S* plasma transport protein for 25-OH-D_3, suggesting that these binding proteins are similar or closely related and may not be related to receptor activity.

In chick calvaria cytosol, 1,25-$(OH)_2$-[^{3}H]D_3 bound only to the 3.5*S* protein in a manner analogous to its association with the 3.7*S* protein present in chick intestinal cytosol. Although further investigation is necessary to establish these 3.5*S* proteins as physiologic receptors for the action of 1,25-$(OH)_2D_3$ in bone, at least these proteins have high affinity and low capacity for 1,25-$(OH)_2D_3$, which are important criteria expected of a steriod hormone receptor.

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Temporal Lobe Aggression in Rats

Abstract. *Although reports of aggressive behavior in temporal lobe epileptics are common, it has proven difficult in clinical settings to gain the experimental control necessary to systematically investigate temporal lobe aggression or even to provide unequivocal evidence of its existence. Increases in aggressive behavior were observed in rats with experimentally induced epileptic foci in temporal lobe structures but not in control rats or those with foci in the caudate.*

There have been reports of aggressive behavior in temporal lobe epileptics (*1*) and of epileptic electrographic anomalies, apparently of temporal lobe origin, in subjects hospitalized or imprisoned for their violent behavior (*2*). Nevertheless, it has proven difficult in human clinical studies to gain the degree of quantification and experimental control necessary to provide unequivocal support for the view that the neural changes associated with temporal lobe epilepsy can predispose an individual to aggression (*3*). We describe here the controlled induction of temporal lobe aggression in experimental animals "kindled" with periodic electrical stimulation of the brain. Rats were periodically stimulated at low levels at one of three brain loci until motor seizures, which developed and increased in severity with each successive stimulation, were reliably elicited. Rats with an epileptic focus kindled in a temporal lobe structure (amygdala or hippocampus) were found to be more aggressive than control subjects or those with a kindled focus in the caudate nucleus.

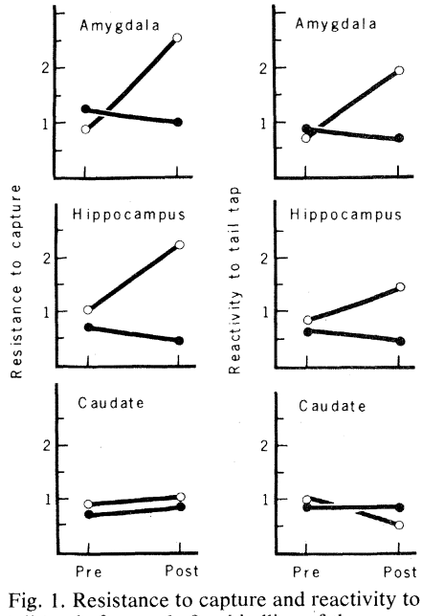

Fig. 1. Resistance to capture and reactivity to tail tap before and after kindling of the amygdala, hippocampus, or caudate. The means of the kindled and control animals are illustrated by open and closed circles, respectively.

A single bipolar electrode was implanted in the amygdala (N = 25), the hippocampus (N = 25), or the caudate nucleus (N = 25) of adult male hooded rats (*4*). After at least 2 weeks of recovery from surgery during which all 75 subjects were handled each day, 15 subjects from each of the three groups were randomly selected to be kindled; the remaining 10 served as handled but unstimulated controls. Each subject in the kindling groups was stimulated (1 second, 60 hertz, 400 μa root mean square) 6 days per week for the 8 weeks of the experiment. No more than three stimulations were administered on any one day, and the interval between consecutive stimulations was always greater than 2 hours (*5*). Initial stimulations rarely produced behavioral responses, but after a few stimulations, mild facial clonus was typically elicited. Then, with each successive stimulation, the convulsive reaction gradually increased in severity. In the last 6 weeks of the experiment, bilateral seizures characterized by clonus of the jaw, head, and forelimbs were reliably elicited in all three groups of kindled subjects (*6*). Behavioral tests of aggression were conducted according to the procedure described by Seggie (*7*). The aggressiveness of each subject was

assessed on six different occasions—once on each of the 3 days before the kindling subjects were first stimulated and once after 24-hour stimulation-free periods at the end of weeks 4, 6, and 8. On each occasion both reactivity to a pencil tap on the base of the tail and resistance to capture were scored on five-point scales from 0 to 4 (*8*) by an experimenter unaware of each animal's experimental history.

To simplify analysis, the means of the three prekindling scores and the three postkindling scores for both measures were determined for each subject (Fig. 1). Kindling of the amygdala or hippocampus produced significant increases in both measures of aggression, whereas implantation and handling (with or without kindling of the caudate) did not (*9*).

In view of the fact that temporal lobe structures have been repeatedly implicated in the control of aggression (*10*), it is not surprising that changes in these structures associated with the development of an epileptic focus should have some effect on aggressive behavior. However, the repeated observation of aggressive behavior in temporal lobe epileptics does not necessarily mean that temporal lobe epilepsy is associated with a change in the neural substrate for aggression. It is difficult in clinical situations to rule out the possibility that these changes in aggressive behavior are a general result of suffering repeated seizures rather than a direct consequence of the underlying neural changes. In our study, however, seizures experienced by the caudate animals were similar in number, form, and duration to those experienced by animals with amygdaloid or hippocampal foci (*6*), yet only the latter two groups of animals displayed increases in aggression.

If the kindling procedure is continued for several months, the subjects eventually develop spontaneous epileptic discharges, which can be recorded from the electrode site; these discharges become associated with spontaneous motor seizures similar to those previously elicited by the stimulations (*11*). Our experiment, however, was concluded before this stage of kindling-produced epileptogenesis was reached; spontaneous electrographic or behavioral seizures were not observed (*12*). Thus, the spontaneous seizure state does not appear to be a necessary condition for the predisposition toward violent behavior observed after hippocampal or amygdaloid kindling.

Many problems complicate the investigation of temporal lobe aggression in clinical populations. For example, it is frequently difficult to determine the exact location of epileptic foci, to quantify the complex and diverse forms of aggression seen in human subjects, and to eliminate the confounding effects of anticonvulsant medication. Thus, although the results of this study can not be applied indiscriminately to human epileptic populations, they confirm and extend clinical observations that by themselves have been unconvincing. Moreover, procedures for producing temporal lobe aggression in laboratory animals should facilitate the experimental investigation of this important clinical syndrome and in so doing provide valuable information concerning the neural substrate of aggressive behavior.

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4. The rats weighed between 285 and 530 g (Canadian Breeding Farm and Laboratories, St. Constant, Quebec). Electrodes were constructed of insulated Nichrome wire (diameter, 0.03 inch) and were implanted according to one of the following stereotaxic coordinates: amygdala, 1.5 mm posterior to bregma, 4.2 mm lateral to the sagittal suture in the right hemisphere, and 8.8 mm ventral to the dura; hippocampus, 4.0 mm posterior to bregma, 4.9 mm to the right of the sagittal suture, and 4.1 mm ventral to the dura; caudate, 1.9 mm anterior to bregma, 3.2 mm to the right of the sagittal suture, and 4.7 mm ventral to the dura. Histological examination confirmed that all electrodes were positioned in the appropriate target structures.
5. The kindling effect does not occur unless stimulations are distributed [G. V. Goddard, D. C. McIntyre, C. K. Leech, *Exp. Neurol.* **25**, 295 (1969)].
6. There were no significant differences in the rates of kindling attributable to the site of stimulation ($P > .10$) in contrast to the observations of G. V. Goddard, D. C. McIntyre, and C. K. Leech (*5*). However, the current intensity used in the Goddard study (50 μa) may not have been high enough to reliably elicit afterdischarges from all sites. In our study, the 400-μa stimulations never failed to elicit an afterdischarge.
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8. Resistance to capture: 0, remains calm when approached and grasped; 1, shys from hand when grasped; 2, avoids hand by running, struggling when captured, or both; 3, leaps to avoid capture and struggles vigorously when captured; 4, leaps and struggles and bites when captured. Response to tail tap: 0, no response; 1, flinches or twists; 2, flinches and moves away rapidly; 3, jumps; 4, jumps at least 6 inches.
9. The mean score of each kindled group was compared to the mean score of its nonstimulated control group both before and after epileptogenesis. None of the three experimental groups was significantly different from its respective controls on either of the two measures before kindling began (all P's $> .05$). However, postkindling means of the hippocampal and amygdaloid groups were significantly greater than those of their respective controls (resistance to capture: amygdala, $t = 3.38$, $P < .003$; hippocampus, $t = 5.04$, $P < .00009$; reactivity to tail tap: amygdala, $t = 3.18$, $P < .005$; hippocampus, $t = 5.84$, $P < .00002$). In contrast, the postkindling means of the caudate group were not significantly greater than those of their controls (both P's $> .05$).
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Suprachiasmatic Nucleus: Use of ^{14}C-Labeled Deoxyglucose Uptake as a Functional Marker

Abstract. *Glucose consumption of the rat suprachiasmatic nuclei (SCN) was studied under various experimental conditions by means of the [^{14}C]deoxyglucose (DG) technique. The results show that glucose consumption of the SCN, in contrast to other brain structures, is a function of both the time of day and environmental lighting conditions. These data are consistent with the hypothesis that the SCN have an essential role in circadian rhythm regulation and indicate that the DG technique may provide a novel approach for the study of the central neural mechanisms underlying circadian rhythm regulation.*

Mammalian circadian rhythms can be entrained by environmental light and in the absence of light become free-running with a periodicity of approximately 24 hours. The presence of such stable, free-running rhythms without environmental cues has suggested the existence of a central rhythm generator (an endogenous neural clock) (*1*). Recent experiments have strongly suggested that the suprachiasmatic nuclei (SCN) may play an important role in the neural generation and regulation of circadian rhythms. For example, ablation of the SCN results in (i) elimination of the circadian rhythmicity in adrenal corticosterone content (*2*), in pineal *N*-acetyltransferase activity (*3*), drinking behavior and locomotor activity (*4*), and (ii) in alteration of sexual functions (*5*). In addition, the