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THE KINDLING MODEL OF EPILEPSY: A REVIEW

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Contents

1. Introduction

The kindling phenomenon represents a model of epilepsy and neuronal plasticity. This intriguing phenomenon has attracted the interest of many investigators with widely differing scientific backgrounds. The goals of this review are threefold: (1) to convey an understanding of the kindling phenomenon; (2) to critically evaluate studies seeking to elucidate the basic mechanisms of this phenomenon; and (3) to consider how the study of kindling could provide fundamental insights into human epilepsy and recovery of function after brain damage.

This review concentrates on material relevant to the themes selected; no attempt has been made to incorporate all studies of kindling. We have further restricted the review to consideration of data published in refereed journals; material published in abstracts or nonrefereed sources has not been included unless the authors have had the opportunity to personally review the data.

2. Historical perspective

The seizure-inducing potential of focal electrical stimulation of the brain was recognized by numerous investigators in the 1950s and 1960s. Delgado and Sevillano demon-

strated in 1961 that repeated administration of low levels of electrical current to the hippocampus induced progressive intensification of stimulus-induced seizure activity (Delgado and Sevillano, 1961). The potential importance of this observation was recognized by Graham Goddard in the late 1960s (Goddard, 1967).

"The progressive changes that result from repeated electrical stimulation will be referred to as the 'kindling effect'". This statement by Graham Goddard in 1969 reflected his perception of this phenomenon (Goddard *et al.*, 1969). He coined the term kindling because of the analogy to lighting a fire. He carefully characterized the kindling effect and demonstrated its permanence. Importantly, he recognized its potential as a model of human epileptogenesis, and learning and memory. His landmark paper on the subject ushered in a new era for investigation of this intriguing phenomenon (Goddard *et al.*, 1969). This growth is attested to by the hundreds of papers published on this subject in the past decade.

3. Properties of the Kindling Phenomenon

3.1. General Features

The term kindling refers to the phenomenon whereby repeated administration of an initially subconvulsive electrical stimulus results in progressive intensification of seizure activity, culminating in a generalized seizure. In rats stimulated in the amygdala, the initial stimulus often elicits focal electrical seizure activity (afterdischarge recorded on EEG) without overt clinical seizure activity. Subsequent stimulations induce the development of kindled seizures, generally evolving through the following classes: 1, facial clonus; 2, head nodding; 3, forelimb clonus; 4, rearing; and 5, rearing and falling (Racine, 1972b).

Once the enhanced sensitivity (as evidenced by a Class 5 seizure) has developed, the effect is long lasting and "kindling" has been established*. Animals left unstimulated for as long as 12 months will respond to one of the first two electrical stimuli with a Class 5 seizure (Wada *et al.*, 1974). No method of reversing the kindling effect has been reported.

Kindling can be induced by electrical stimulation of many but not all sites in the brain. The amygdala is a sensitive structure in that relatively few stimulations are required to induce kindling. The hierarchy of sensitivity (progressing from most to least sensitive) of the various sites was characterized by Goddard to be as follows: amygdala, globus pallidus, pyriform cortex, olfactory area, anterior neocortex, entorhinal cortex, olfactory bulb, septal area, preoptic area, caudate putamen, and hippocampus (Goddard *et al.*, 1969). These experiments were performed before the importance of local afterdischarge in kindling development was appreciated; sensitivities have not been systematically studied recently. However, the olfactory bulb reportedly requires fewer stimulations to kindle than the amygdala (Cain, 1977). Seizures have not been elicited with electrodes in superior colliculus, reticular formation, or cerebellum. Unpublished reports have claimed that kindled seizures can be elicited from primary visual and auditory neocortex (Cain, 1979).

The pattern of development of kindled seizures elicited by stimulation of many sites in the limbic system is similar to those from the amygdala. Kindling induced by anterior neocortical stimulation differs in that motor seizures, although mild, accompany the initial stimulation (Racine, 1975a). These seizures intensify with subsequent stimulations and assume more tonic components than limbic kindled seizures. If neocortical stimulations are continued, the seizures typical of limbic kindled seizures follow or occur simultaneously with the neocortical kindled seizure (Racine *et al.*, 1979). In contrast to the generally smooth evolution through the five classes of limbic kindled seizures, stimulation of either medial or lateral geniculate bodies elicits seizures that are sudden in onset and fully generalized from the outset (Cain, 1977). For example, after 90 stimulations

* The term kindling implies the permanent enhanced sensitivity to electrical stimulation. Animals will be referred to as "kindled" after at least one Class 5 motor seizure has been elicited.

without seizures, stimulation of the lateral geniculate may trigger a generalized motor seizure.

Kindling can be established in numerous species, including the frog (Morrell and Tsura, 1976), reptile (Rial and Gonzalez, 1978), mouse (Leech and McIntyre, 1976), rat (Goddard *et al.*, 1969), rabbit (Tanaka, 1972), dog (Wauquier *et al.*, 1979), cat (Wada *et al.*, 1974), rhesus monkey (Goddard *et al.*, 1969), and baboon (Wada *et al.*, 1975). Although some differences exist, amygdala kindling patterns are remarkably similar in many of these species. Differences exist in the sensitivity to kindling among strains within a species, as well as among species.

The nature of the electrical stimulus is an important determinant of the development of kindling. A commonly utilized paradigm consists of the periodic administration of a 1 sec train of 1 msec biphasic square-wave pulses at a frequency of 60 Hz. Stimulations with pulse frequencies of 25, 60, or 150 Hz are equally effective in inducing the development of kindling (Goddard *et al.*, 1969). By contrast, administration of 60 pulses at a frequency of 1 Hz induces neither an afterdischarge nor kindling (McNamara, 1978a). Kindling develops at comparable rates regardless of whether sine waves or rectangular pulses are utilized, and regardless of whether train durations of 1 sec or 60 sec are employed (Goddard *et al.*, 1969). Although kindling develops at comparable rates with pulse frequencies of 25, 60, or 150 Hz, 60 Hz stimuli are much more effective for triggering seizures in a fully kindled animal than are stimuli with pulse frequencies of 25 or 150 Hz (Goddard *et al.*, 1969).

The interval between stimulations represents a key variable in establishment of kindling. Stimulations (1 msec pulses at 60 Hz for 1 sec) administered at intervals ranging from 15 min to 7 days can induce kindling (Goddard *et al.*, 1969; Racine *et al.*, 1973). Greater numbers of stimulations are required when intervals of 15 or 30 min are employed (Racine *et al.*, 1973). Administration of 1 msec pulses at 60 Hz continuously for several hours does not induce kindling (Goddard *et al.*, 1969).

The electrical stimulus must induce local afterdischarge in order for kindling to develop. However, subthreshold stimulation causes a lowering of the afterdischarge threshold (Racine, 1972a). If the current intensity is set slightly below the afterdischarge threshold, repeated stimulation will lower the threshold and can lead to afterdischarge production and subsequent kindling.

3.2. SPONTANEOUS INTERICTAL SPIKING

The principal abnormality underlying partial epilepsy is the abnormally excitable behavior of neurons in an epileptic focus (Ayala *et al.*, 1973). The spontaneous interictal (between seizure) spike noted in electroencephalographic (EEG) recordings is a signal of this abnormal neuronal behavior. Spontaneous interictal spikes (SIS) have been observed in EEG recordings of humans with epilepsy and in numerous animal models of epilepsy.

The close relationship between SIS and epilepsy prompted extensive investigation of this event in kindling. Its presence has been demonstrated in a wide variety of kindled animals including the rat (Morrell and Tsura, 1976; Rial and Gonzalez, 1978; Wada *et al.*, 1975; Lange *et al.*, 1977). SIS occurs not only in the area of the stimulating electrode but also arises independently in brain regions remote from the stimulating electrode (see Fig. 1).

A detailed quantitative assessment of SIS in rats kindled (to a single Class 5 seizure) in the amygdala demonstrated that every kindled rat manifested SIS (Fitz and McNamara, 1979). Electrode implanted unstimulated controls did not. SIS primarily involved the limbic structures, particularly the amygdala and hippocampus, with lesser involvement of the reticular formation and neocortex. The temporal pattern of development and decline of SIS was highly reproducible in all kindled rats. The maximal frequence of SIS occurred during Class 3 and 4 seizures. The frequency of SIS declined subsequent to

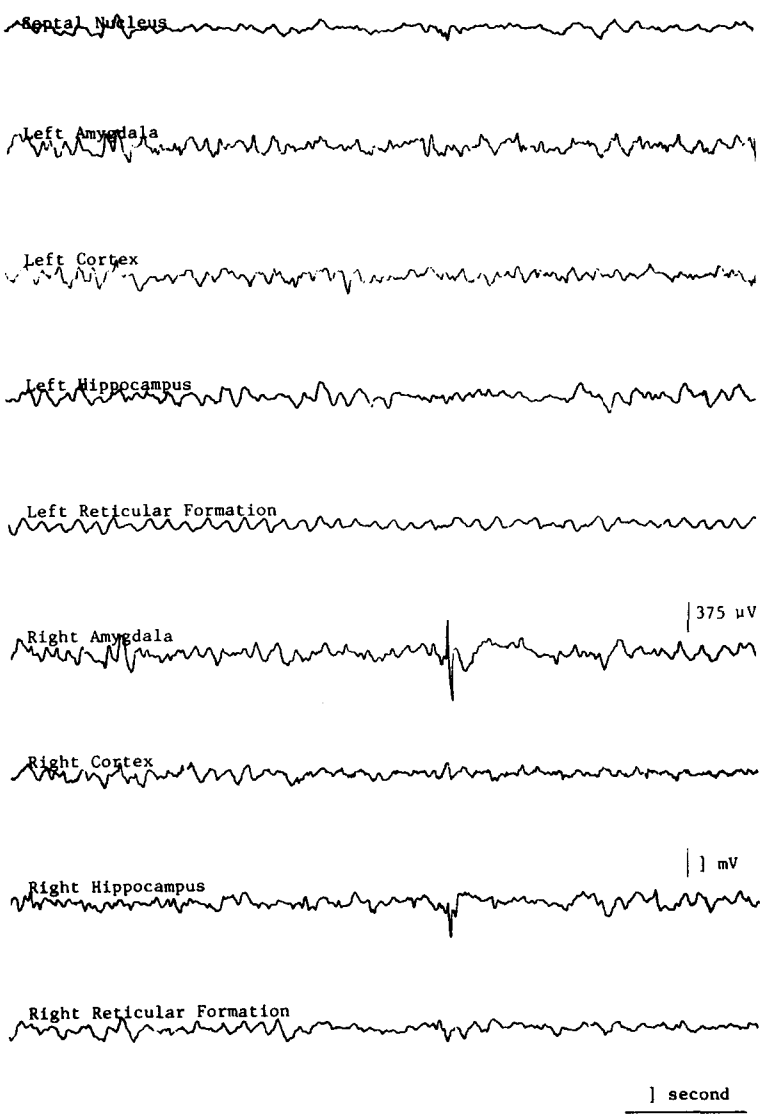

FIG. 1. This figure portrays an electroencephalographic recording from multiple depth electrodes in awake, freely moving rat following completion of kindling. The electrodes are referenced to an indifferent electrode in the skull unless otherwise specified. An interictal spike is present in the septal nucleus, the right amygdala, and the right hippocampus.

Class 4 seizures despite the continued stimulation necessary for completion of kindling. SIS disappeared entirely within 5 days after completion of kindling in these animals. Therefore the SIS was transient, whereas the enhanced sensitivity to electrical stimulation (kindling effect) was permanent.

Despite the extensive clinical and experimental evidence implicating SIS as the hallmark of a brain with epileptic potentiality, its precise functional significance in the expression of seizures is unclear. The SIS is by definition an interictal (between seizure) rather than an ictal (seizure) event. It is thus not surprising that among humans with partial epilepsy, it has been difficult to establish a direct linear relationship between the frequency of SIS and the frequency of clinical seizures.

Studies of kindling underscore the discrepancy between the frequency of SIS and the propensity to develop a seizure. For example, 7 days following completion of kindling,

SISs disappeared, yet the propensity to develop a kindled seizure persists. Likewise, SIS is greatest immediately (first few minutes) following a kindled seizure at a time when additional stimulations will not reliably produce a kindled seizure. Moreover, administration of a subthreshold stimulus does not elicit a seizure, but increases SIS and raises the threshold for elicitation of a kindled seizure (Engel and Ackermann, 1979). The subsequent decline in SIS parallels the decline in seizure threshold. These results in kindling raise the possibility that SIS represents an inhibitory mechanism which reduces the chances of seizure occurrence.

In summary, SIS marks the presence of an epileptic potentiality. SIS has been demonstrated repeatedly in kindled animals. The highly reproducible development and decline of SIS in kindling provides the opportunity to elucidate the functional significance of SIS.

3.3. SPONTANEOUS SEIZURES

A key criterion for an animal model of epilepsy is that seizures occur spontaneously, since epilepsy by definition implies the presence of spontaneous seizures (as opposed to seizures elicited by an electrical stimulus). Most kindling experiments are terminated after elicitation of a single or several Class 5 motor seizures. Spontaneous generalized motor seizures are infrequently observed in rats stimulated to this extent. However, continued periodic stimulation of amygdala, hippocampus, or entorhinal cortex of the rat leads to spontaneous motor seizures (Pinel and Rovner, 1978). In contrast to the 15–30 stimulations required to elicit a Class 5 seizure, additional stimulations (a mean of 348) results in spontaneous motor seizures in all subjects. Among subjects manifesting at least three spontaneous Class 5 seizures, spontaneous seizures persist for as long as 7 months following termination of the stimulation, suggesting that the epilepsy was permanent. Since limbic seizures with subtle or absent motor features are difficult to detect in a rat, the large numbers of seizures during the relatively brief observation sessions in this study indicate that kindling is a potent means of inducing epilepsy.

3.4. TRANSIENT INHIBITION OF KINDLING EFFECT BY KINDLED SEIZURES

The presence of endogenous inhibitory processes has been identified and characterized in kindled rats (Sainsbury *et al.*, 1978; Mucha and Pinel, 1977). Since kindling by definition implies a long-term enhancement of neuronal excitability, the presence of inhibitory processes seems paradoxical. Nonetheless, the stability of seizures in the kindling model has provided the opportunity to systematically investigate both short-term and long-term inhibitory processes in kindled animals.

Short-term inhibitory processes were defined with the following approach: (1) establishment of kindling with periodic stimulations, resulting in a stable duration of kindled seizures; (2) a subsequent rest period; (3) induction of a baseline kindled seizure; and (4) administration of a subsequent stimulus at varying intervals following the baseline seizure (Sainsbury *et al.*, 1978). The results demonstrated that stimulations could not elicit a motor seizure in any animal 10 min after the baseline kindled seizure. This inhibition gradually dissipates, so that a 70 min interval between the baseline and test stimulus resulted in complete restoration of the duration and intensity of the kindled motor seizure. (See Fig. 2.)

Long-term inhibitory processes have been characterized by a similar approach (Sainsbury *et al.*, 1978). In these experiments, 19 baseline stimulations were administered at 90 min intervals to previously kindled animals. (See Fig. 3.) Despite this intensive regimen, no appreciable suppression of seizures occurred during this baseline series. However, stimulation of the animal 24 hr following the 19th baseline stimulation resulted in dramatic suppression of seizure intensity and duration. These inhibitory effects gradually dissipated over a 5 day period.

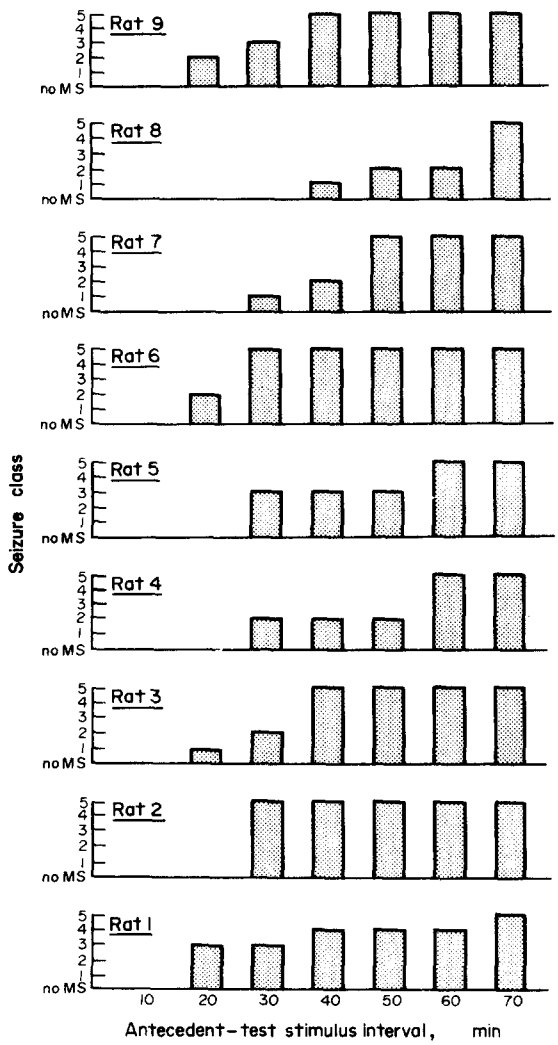

FIG. 2. Short-term inhibition of kindled seizures. Classification of motor seizures elicited by a test stimulation (400 μA) as a function of the interval (min) between the antecedent stimulation (400 μA) and the test stimulation. The degree of postseizure inhibition produced at the intervening intervals was variable between rats, the inhibition completely dissipating in some rats by the 30 min interval. Although the patterns of postseizure inhibition differed between rats, the pattern was reproducible for a given rat (*Behav. Biol.* **22**, 479–488 (1978)).

These studies demonstrate that kindled seizures can result in transient suppression of the kindling effect. The mechanisms underlying this postseizure inhibition are unclear. The long-term inhibition in particular does not likely represent neuronal exhaustion (i.e. depletion of energy stores required for neuronal firing), since long stimulation-free intervals were necessary to induce this effect.

3.5. "KINDLING" BY MEANS OTHER THAN FOCAL ELECTRICAL STIMULATION OF BRAIN

If the term kindling is expanded to imply the evolution of progressively more severe seizures in response to the periodic administration of a constant stimulus, then kindling can be induced by a variety of pharmacologic agents and even electroconvulsive shock. Drugs administered by local brain injection (e.g. carbamylcholine or penicillin) or systemically (e.g. cocaine, pentylenetetrazol) can induce kindling-like effects (Vosu and Wise,

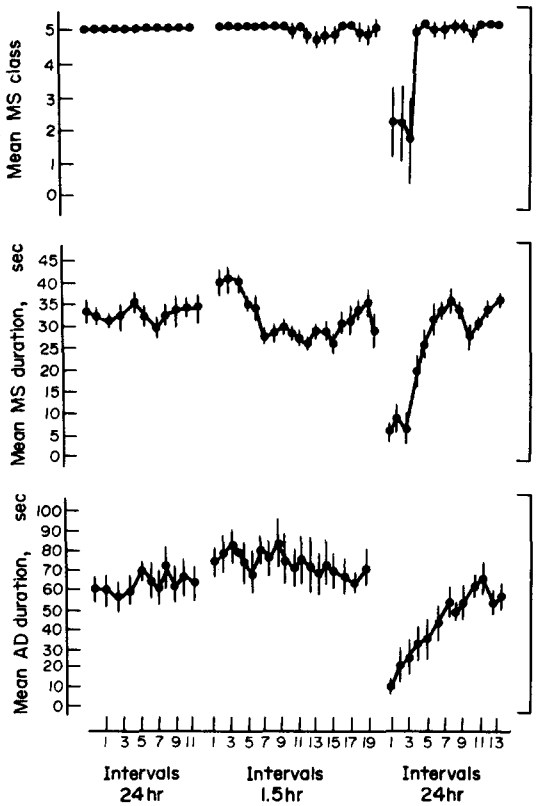

FIG. 3. Long-term inhibition of kindled seizures. Mean afterdischarge (AD) duration (bottom panel), mean motor seizure (MS) duration (middle panel), and mean motor seizure class (top panel), elicited in the kindled rats by the 11 daily baseline stimulations, the 19, 1.5-hr interval stimulations, and the 13 subsequent daily test stimulations (± standard error of the mean) (*Exp. Neurol.* **54**, 266–282 (1977)).

1975; Collins, 1978; Post and Kopanda, 1976; Pinel and Van Oot, 1975; and Kilbey *et al.*, 1979).

Local injection of carbamylcholine, a cholinergic agonist, through cannulas implanted in the amygdala initially results in little or no clinical seizure activity (Vosu and Wise, 1975). Repeated injections at 48 hr intervals result in progressively more intense seizures in a pattern similar to those of electrically kindled seizures. Injections into the caudate and hippocampus are also effective. Preliminary reports claim that this effect is long lasting and bears pharmacologic properties consistent with muscarinic receptor activation (Wasterlain *et al.*, 1980). Kindling-like effects have been established in neocortex by periodic injections of small amounts of penicillin (25 units) (Collins, 1978).

Periodic systemic administration of initially subconvulsive doses of cocaine (and other local anesthetics) ultimately leads to development of generalized seizures (Post and Kopanda, 1976; Kilbey *et al.*, 1979). Initially, cocaine induces behavioral stereotypes. Repeated administration of the constant dose eventually induces generalized convulsions (after approximately 7–14 injections) (Kilbey *et al.*, 1979). This enhanced sensitivity to cocaine persists for at least 1 month after cessation of injections.

Electroconvulsive shock can induce generalized tonic clonic seizures. Administration of ECS seizures at 3-day intervals leads to progressively more intense seizures (Ramer and Pinel, 1976). By contrast, administration of ECS at 1 hr intervals results in a progressive decline of seizure severity. No systematic changes in seizure severity occurs in animals treated at 1 day intervals. Thus, a kindling-like effect can occur following repeated ECS seizures in that progressively more intense motor seizures do occur. The

permanence of this effect has not been reported. Whether this would result in facilitated development of kindling induced by focal stimulation of the amygdala is unknown.

4. Approaches to Understanding Basic Mechanisms of Kindling

4.1. ANATOMY OF KINDLING

A critical issue in kindling research centers on the following question: namely, what is the precise spatial extent of the modified neural circuitry underlying kindling? One hypothesis states that the neural reorganization responsible for kindling involves neurons restricted to the area of the kindling electrode. An alternate hypothesis claims that alterations residing in targets (i.e. neurons remote from the kindled area and related to the kindled area by monosynaptic or polysynaptic connections) of the kindled structure contribute to the kindling effect.

Evidence supporting the first hypothesis has been obtained from 2-deoxyglucose autoradiographic study of "penicillin kindling" of the neocortex (Collins, 1978). Injection of large amounts (100 units) of penicillin caused an intense motor convulsion on the first injection; subsequent injections caused *milder* convulsions. By contrast, injection of smaller amounts (25 units) of penicillin caused a relatively minor focal motor seizure initially; repeated injections at 4-day intervals caused a progressive intensification of the focal motor seizure and frequently bilateral clonic jerks of the upper extremities. 2-deoxyglucose autoradiography was used to measure neuronal metabolic activity in this paradigm. The animals "kindled" with 25 units of penicillin disclosed an increase in the size and metabolic activity of the seizure focus, together with an increase in size and intensity of most transsynaptic sites. Comparison of these findings with the autoradiographic results of animals receiving 100 units of penicillin for the first time suggested the major change during kindling takes place in the focus itself. Although alterations inherent in the transsynaptic targets of the kindled focus could not be excluded, the magnitude of the increase in the targets could be accounted for by enhanced intensity of the primary focus itself. Therefore it seems likely that the principal alteration in "penicillin kindling" involves alterations mainly at the primary seizure focus.

The second hypothesis is supported by two experimental results. Establishment of kindling by electrical stimulation in one brain region (e.g. amygdala) results in fewer stimulations required to establish kindling in a second region (e.g. opposite amygdala) (Goddard *et al.*, 1969). This phenomenon has been termed transfer. The transfer phenomenon suggests that key alterations occur in brain regions anatomically remote from the kindled structure. This suggestion was strengthened when transfer persisted despite destruction of the primary kindled structure (Racine, 1972b).

Additional support for the second hypothesis was obtained in a series of experiments utilizing kindling of the entorhinal cortex (EC) (Messenheimer *et al.*, 1979). Each EC projects heavily to the ipsilateral dentate gyrus of the hippocampal formation, but only sparsely to the contralateral dentate gyrus (DG). Unilateral entorhinal lesions massively deafferent the ipsilateral DG; this is followed within 2 weeks by a partial reinnervation of the DG due to sprouting of surviving afferent systems. Among these sprouting afferent fibers is a sparse projection from contralateral EC, which reinnervates some of the dendritic territory in the DG which was previously occupied by the ipsilateral EC projection system. These authors reasoned that if kindling via EC stimulation induced transsynaptic alterations either in the DG or further "downstream", then the neural reorganization underlying kindling should survive destruction of the primary site of kindling. The presynaptic structures which were directly activated by the kindling stimulations (the projection from the "kindled" EC) would be replaced by a system (the sprouted connections from the contralateral side) naive to the direct application of the kindling stimulus. If the sprouting projections from the contralateral EC gain access to circuitry which had been transsynaptically modified during primary kindling, then activation of the lesion

induced crossed entorhinal projections might precipitate a kindled convulsion. The experimental results were consistent with this possibility.

In normal rats, a mean of 23 daily stimulations were required to establish kindling (five Class 5 motor seizures). When the primary kindled EC site was destroyed and 2 weeks permitted for the contralateral EC to sprout in response to the lesion, kindling stimulation of the surviving EC evoked Class 5 seizures on the first or second stimulation. If the primary site was not destroyed, kindling via a contralateral EC required an average of more than five stimulations (transfer phenomenon). If sprouting were induced by unilateral EC lesion prior to any kindling stimulations, kindling via the surviving "sprouted" EC contralateral to the lesion occurred at a rate similar to normal. If kindling via the secondary site were initiated 1 day after a primary site lesion, at a time prior to completion of sprouting, the relatively immediate expression of generalized seizures via secondary site stimulation was not observed. These results were consistent with the hypothesis that EC kindling results in transsynaptic alterations either in the immediate targets of the EC (e.g. DG) or further "downstream" synaptically.

None of these three experimental approaches provides an unequivocal answer to the question. First, the relevance of penicillin kindling to electrical kindling is unclear; likewise different circuits may be operative in limbic and neocortical kindling. Secondly, although the transfer phenomenon implies the presence of alterations in anatomically remote brain regions, whether these alterations are essential to primary site kindling is unclear. Finally, EC kindling of the primary site may induce direct alterations in the contralateral unstimulated EC, either transsynaptically or by backfiring EC–EC projections; increase of the synaptic targets of the contralateral EC through lesion induced sprouting could account for the more rapid "transfer" observed. This interpretation of the results would not require alterations inherent in targets of the kindled structures.

These various limitations notwithstanding, it appears likely that the neural reorganization underlying electrically induced kindling in the limbic system involves both the kindled structure and its synaptically related targets. Defining the precise spatial extent of these circuits is essential to understanding the cellular and molecular mechanisms of the kindling phemomenon.

4.2. MORPHOLOGIC STUDIES

Kindling represents a permanent and dramatic alteration of neuronal function. This is likely accompanied by morphologic alterations at some cellular or subcellular sites. At least two major possibilities could underlie this change. Kindling could involve a morphologic rearrangement of neuronal circuits, in a pattern similar to collateral sprouting and new synapse formation occuring following lesions of the entorhinal cortex. Alternatively, kindling may involve a modification of preexisting synapses—e.g. selected connections could undergo dendritic swelling or presynaptic terminal enlargement, which might support enhanced communication in these paths.

The possibility of morphologic rearrangements seems unlikely because of the time course. Kindling has been established in times as brief as 2–4 hr (Racine *et al.*, 1973). Neuronal rearrangements described to date take much more time to develop.

The possibility that kindling is associated with structural modification of preexisting synapses seems more likely for two reasons. Application of potentiating electrical stimulations to perforant path axons appears to result in long-lasting increases in the area of dendritic spines of the target neurons (these animals were not kindled) (Fifkova and Van Harreveld, 1977). Moreover, these dendritic alterations can develop within minutes following electrical stimulation and thus would be compatible with a potentially rapid development of kindling.

Searches for morphologic alterations of this sort in kindled animals have been unsuccessful to date. Golgi studies of neurons in neocortical layers 3 and 5 of neocortically kindled rats disclosed no differences in spine branching or size in either the stimulated or

contralateral sites between kindled and control rats (Racine and Zaide, 1975c). Likewise, kindling of the hippocampus resulted in no evidence of altered dendritic morphology of granule neurons or CA3 or CA1 pyramidal neurons as assessed by Golgi methods (Crandall *et al.*, 1979).

Goddard found no differences between kindled and electrode implanted unstimulated control rats in the stimulated amygdala with electron microscopic techniques (Goddard and Douglas, 1975). In this study, a small electrolytic lesion was placed at the tip of the stimulating electrode upon completion of kindling in order to destroy the neurons in this area and thereby "label" their axon terminals with degeneration. The animals were sacrificed 1, 2, or 4 days after the lesion, and both presynaptic indices (e.g. length and breadth of degenerating terminals) and postsynaptic indices (e.g. length and breadth of dendritic spines) were analyzed in blinded fashion. No differences clearly attributable to kindling were detected.

The anatomic complexity of the amygdala and its connections likely hindered detection of differences between kindled and control animals in this latter study. Similar experiments in more simplified and better defined anatomic regions (e.g. entorhinal cortex and hippocampal formation) may well disclose altered synaptic morphology.

In summary, the morphologic features underlying the kindling phenomenon are presently unclear. Modification of preexisting neural circuits seems a likely possibility, but definitive evidence has not yet been obtained. Knowledge of the distribution of the altered neural circuitry underlying kindling would facilitate detection of these morphologic alterations.

4.3. Electrophysiologic Studies

The permanently enhanced response to a constant electrical stimulus in kindling suggests some type of long-term potentiation (LTP) of the neural circuitry. Thus, it seems reasonable to hypothesize that LTP observed in simpler neural circuits (e.g. hippocampal slice) represents the cellular mechanism underlying kindling. If correct, insights derived from study of LTP in simpler model systems may shed light on the basic mechanisms responsible for kindling.

4.3.1. *Long-term potentiation*

Long-term potentiation (LTP) refers to the prolonged increase in synaptically evoked neuronal response (evoked by a constant electrical stimulus) which occurs following repetitive electrical stimulation. LTP has been described in a number of hippocampal pathways (Alger and Teyler, 1976). It differs from posttetanic potentiation observed in invertebrates or at the mammalian neuromuscular junction in that once developed, its duration is prolonged.

Recent studies of LTP using the *in vitro* hippocampal slice preparation have characterized this phenomenon in greater detail (Dunwiddie and Lynch, 1978). The increase in synaptically evoked neuronal response is highly specific in that it is confined to the potentiated input. Indeed, other synaptic inputs to the same neurons are transiently depressed. Such specificity bestows on this mechanism a means of both increasing the synaptic "signal" generated by the potentiated set of synapses and decreasing the "noise" generated by other inputs.

These studies have also begun to provide some insights into the mechanisms underlying the development of LTP (Dunwiddie and Lynch, 1978). By systematically manipulating extracellular calcium and magnesium concentration, Dunwiddie and Lynch were able to selectively antagonize the development of LTP while maintaining synaptic transmission, paired pulse and frequency facilitation, and posttetanic potentiation. Thus LTP appears to be independent of these briefer forms of placticity. Moreover, the ionic conditions which antagonize LTP were similar to those which lower the depolarization-induced influx of calcium into neuronal elements. Whether calcium entry triggers a chain

of events (e.g. neurotransmitter release) which in turn elicits LTP, or whether LTP is a calcium regulated process *per se* is presently unclear.

The precise cellular site at which the alteration underlying LTP exists is also unclear. However, two lines of evidence implicate the synapse: (1) the enhanced population spike associated with LTP is parallelled by enhancement of the excitatory postsynaptic potential; and (2) the lack of alteration of antidromically induced responses in the presence of LTP mitigate against changes in electrotonic properties of postsynaptic neurons. Whether the site of alteration in the synapse lies in the presynaptic terminal, the synaptic cleft, or the dendritic spine remains to be elucidated.

In summary, current insights into the cellular and molecular mechanisms underlying LTP are limited. It does appear that synaptic transmission is necessary, but not sufficient for LTP to develop. The site of the alteration which accounts for LTP appears to be the synapse, but it is unclear precisely where within the synapse the alteration resides.

4.3.2. *Relationship of kindling to long-term potentiation*

Several lines of evidence link the LTP observed by cellular electrophysiologists to the kindling phenomenon:

(1) The intratrain frequencies of the electrical stimuli which elicit LTP are similar to those which are most efficacious in eliciting kindling. Pulses of current applied at a frequency of 1/sec induced neither LTP nor kindling, whereas comparable pulses applied at frequencies ranging from 25 to 100/sec successfully elicit both (Goddard *et al.*, 1969; McNamara, 1978a; Dunwiddie and Lynch, 1978).

(2) Induction of potentiation by electrical stimulation *without* triggering an afterdischarge results in facilitation of development of kindling, suggesting the presence of a common mechanism (Racine *et al.*, 1975b).

(3) Kindling results in a long-term enhancement of evoked potentials in multiple brain regions (hippocampus, preoptic area, and others) in response to a constant test stimulus in the kindled amygdala (Racine *et al.*, 1972c). While the precise neural circuits involved are unknown, such observations indicate the presence of a long-term enhancement of a neuronal response independent of seizure *per se*.

(4) Partial kindling induced in the perforant path is associated with long-term potentiation of the monosynaptic EPSP in the dentate gyrus elicited by perforant path stimulatffion (Douglas and Goddard, 1975).

Taken together, these observations suggest that LTP observed in simpler neural circuits may represent the cellular mechanism responsible for kindling.

Despite the circumstantial evidence, we lack definitive proof that LTP is the responsible mechanism. Such proof would require demonstration of LTP in well defined monosynaptic circuit(s) which parallels the time course of the kindling phenomenon. Moreover, reversal (by electrical or pharmacologic means) of the LTP should reverse kindling and likewise reversal of kindling should abolish the LTP.

4.4. BIOCHEMICAL AND RELATED PHARMACOLOGIC STUDIES

4.4.1. *Acetylcholine*

Acetylcholine is a putative neurotransmitter of mammalian brain with mainly excitatory effects. Much of the cholinergic input to the cortex, hippocampus, and amygdala appears to arise from neurons with cell bodies situated in the magnocellular nuclei of the ventral forebrain (Emson *et al.*, 1979). Following release from presynaptic terminals, ACh interacts with either muscarinic or nicotinic receptors and presumably initiates a chain of subsequent events by triggering a synaptic potential.

Pharmacologic evidence indicates that increased amounts of ACh exposed to brain muscarinic receptors can cause seizures. Direct application of ACh to mammalian cortex can cause epileptiform discharges; this effect is reversible with muscarinic antagonists (Daniels and Spehlmann, 1973). Likewise toxic doses of cholinesterase inhibitors lead to accumulation of ACh and cause epileptiform discharges and seizures in animals and man; these effects are reversible with muscarinic antagonists (Baker and Benedict, 1968; Grob *et al.*, 1950).

Independent pharmacologic and electrophysiologic evidence suggests that increased muscarinic cholinergic neuronal communication can contribute to the development of kindling. Systemic administration of atropine (a muscarinic antagonist) markedly retarded the development of kindling in male Sprague-Dawley rats (Arnold *et al.*, 1973; Albright *et al.*, 1979). This appears to be a strain-specific effect (Corcoran *et al.*, 1976). An additional approach demonstrated that application of kindling stimulations to the fornix resulted in a persistent and prolonged increased firing rate of single units in the hippocampus to iontophoretically applied ACh (but not to GABA or glutamate) (Burchfiel *et al.*, 1979). Finally, repeated injections of carbamylcholine (a cholinergic agonist) via cannulas implanted in the amygdala produces a kindling-like effect (Vosu and Wise, 1975; Wasterlain *et al.*, 1978). This action can be blocked by local injection of muscarinic antagonists. Together this evidence suggests that communication at synapses involving ACh and muscarinic receptors may contribute to the development of kindling.

Contrary to the suggestion of the pharmacologic and physiologic studies, direct biochemical studies are consistent with a *decrease* of muscarinic cholinergic neuronal communication in amygdaloid kindled rats. Muscarinic cholinergic receptors have been repeatedly demonstrated to be decreased in the limbic system of rats sacrificed 1 day following completion of kindling (i.e. elicitation of a single Class 5 kindled seizure) induced by hourly stimulations (McNamara, 1978a; Byrne *et al.*, in press; Dasheiff and McNamara, in press). Decreased numbers of receptors are present in membranes in the stimulated amygdala and both hippocampal formations. Microdissection studies demonstrated that the hippocampal formation declines resides mainly in the dentate gyrus (Byrne *et al.*, in press). Declines of muscarinic receptors are often but not invariably present in the contralateral unstimulated amygdala. Neocortical muscarinic receptors are not altered. Neither electroshock seizures, pentylenetetrazol seizures nor administration of electrical current without kindling caused muscarinic receptor alterations. Thus amygdala kindling is associated with declines of muscarinic receptors in a highly specific distribution within the limbic system. Moreover, the receptor declines appear to be related to the kindling process itself or to some property of kindled seizures distinct from other seizure types.

Analysis of the time course of the receptor alterations disclosed that the receptor declines were first detectable late during the development of kindling (Dasheiff *et al.*, 1980). Maximal declines of the receptors occurred on the day following completion of kindling. The declines were transient in that significant alterations were no longer detectable 7 days following completion of kindling. At no time were significant increases of muscarinic receptors detected. (See Fig. 4.)

Measurement of presynaptic cholinergic indices and of the degradative enzyme acetylcholinesterase provided a more complete biochemical profile of cholinergic communication in kindled rats (Dasheiff *et al.*, 1980). Acetylcholinesterase activity was unchanged in the limbic system (amygdalas, dentate, and hippocampal gyri) of kindled rats (sacrificed 1 day following kindling) in comparison to electrode implanted unstimulated controls. Choline acetyltransferase, the enzyme responsible for the synthesis of ACh, was not increased in the limbic system of kindled rats, again sacrificed 1 day following kindling. Finally, sodium-dependent high-affinity choline uptake, a biochemical index of cholinergic presynaptic neuronal activitity, did not increase during kindled seizures, nor during the development or following completion of kindling. Together with the muscarinic receptor declines, these biochemical indices imply that muscarinic cholinergic neuronal communication is decreased in the limbic system of animals sacrificed 1 day following

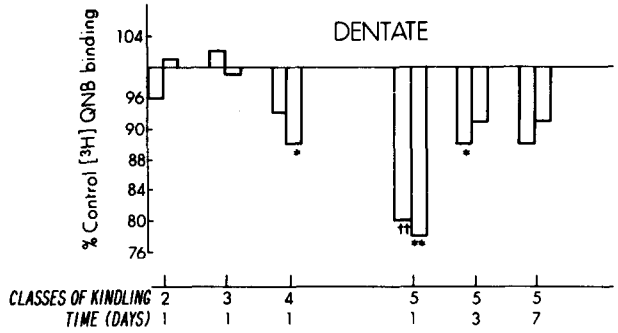

FIG. 4. Time course of muscarinic cholinergic receptor declines in the dentate gyri (obtained from hippocampal formation) during development and following completion of kindling in right amygdala. Muscarinic receptors were measured with [^{3}H] quinuclidinyl benzilate (QNB) binding under equilibrium conditions. The data are expressed as the percent of kindled divided by control times 100 in the left and right sides. The class of kindling established by amygdaloid stimulations is listed at the bottom; immediately below is the interval (in days) between establishment of kindling and sacrifice. The levels of significance (p values paired *t*-test, one tailed) reflected by the symbols are: *$p < 0.01$; **$p < 0.005$; ** signs < 0.0005.

completion of amygdala kindling. There was no indication from any of these indices at any time that cholinergic neuronal communication was increased.

Several lines of evidence imply that these biochemical alterations represent a consequence of limbic seizures rather than contributing to the development or maintenance of the kindling process. First, the time course of the receptor declines is most consistent with this interpretation. The fact that the receptor declines were maximal following completion of kindling argues against a role in the development of kindling. The transient nature of the receptor alterations argues against a role in maintaining the permanence of the kindling process. Rather, the occurrence of the maximal declines following the repeated stimulation induced seizures required to establish kindling suggests that the receptor declines represent a consequence of kindled seizures. Secondly, amygdala kindling can be accomplished with equal efficiency in the presence or absence of the cholinergic neuronal input to the hippocampal formation, suggesting that this path is not essential to kindling established in the amygdala (Dasheiff and McNamara, in press). Third, the direction of the altered cholinergic neuronal communication in kindling—namely a decrease—seems consistent with a consequence of seizures. Since enhanced communication at these synapses can cause seizures, it seems reasonable that an endogenous protective response to repeated limbic seizures would reduce the efficacy of interneuronal communication at these synapses.

In summary, biochemical evidence indicates that muscarinic cholinergic neuronal communication is decreased at least transiently in the limbic system of amygdala kindled rats. This most likely represents a consequence of the repeated limbic seizures induced during establishment of the kindling process.

4.4.2. *Noradrenalin*

Noradrenalin is a putative neurotransmitter in mammalian brain with mainly inhibitory effects. The cell bodies of noradrenergic neurons are situated in the locus ceruleus and lateral ventral tegmental regions of the brain stem; these neurons project in a widespread and diffuse pattern to the forebrain. Following release from presynaptic terminals, noradrenalin interacts with either α- or β-adrenergic receptors and presumably mediates a synaptic potential and perhaps a chain of subsequent events (e.g. activation of adenylate cyclase).

Pharmacologic approaches have been employed to gain some insight into the role of noradrenalin in the development of kindling. Reserpine depletes catecholamines in the brain, presumably by blocking reuptake of catecholamines by synaptic vesicles in catecholaminergic nerve terminals. Reserpine markedly accelerated the development of amygdala kindling in comparison to saline treated controls (Arnold *et al.*, 1973). Although this finding supported the notion that noradrenalin depletion caused the increased rate of kindling, the presence of reserpine induced alterations in dopamine and serotonin precluded any definitive conclusions.

More direct evidence for the role of noradrenalin was obtained by selective use of the neurotoxin 6-hydroxydopamine. Properly used, this agent mediates selective, extensive, and permanent damage to catecholamine neurons. Since the projection patterns of noradrenalin and dopamine to the forebrain take different courses, circumscribed injections into one of these paths can selectively destroy either noradrenergic or dopaminergic neurons. Utilizing such an approach, it has been recently demonstrated that depletion (90%) of forebrain noradrenalin markedly accelerates the development of amygdala kindling (Mason and Corcoran, 1980).

These data suggest two roles of noradrenergic neuronal communication that may be potentially important in kindling. A decrease in noradrenergic neuronal communication could directly contribute to the development of kindling. Alternatively, the kindling process could develop by an independent mechanism; in this case an increase in noradrenergic neuronal communication could develop in an effort by the brain to limit the expression of the abnormal neuronal excitability. In this instance, noradrenalin could be functioning as an endogenous anticonvulsant. Direct biochemical investigations of kindling are essential to assess these possibilities.

Direct biochemical studies of this neurotransmitter system in kindling suggest that noradrenalin is involved, but its precise role remains to be defined. Tyrosine hydroxylase is the rate-limiting enzyme in noradrenalin synthesis. The activity of this enzyme was found to be decreased in the stimulated amygdala of kindled rats (sacrificed 4 weeks following kindling) compared with sham-operated and non-operated controls (Farjo and Blackwood, 1978). The effects of electrical current and seizures were not controlled for in these studies, and the potential contribution of these variables needs to be excluded. Nonetheless, this initial observation is consistent with the first possibility noted above—namely that a decrease of noradrenergic communication may contribute to the development of kindling.

Measurement of noradrenalin levels in the stimulated amygdala of kindled animals disclosed no significant differences from electrode implanted unstimulated controls (Engel and Sharpless, 1977). Measurement of noradrenalin levels and noradrenalin turnover in whole cerebral hemispheres 1 week following completion of amygdala kindling also disclosed no differences from controls (Wilkison and Halpern, 1979).

Additional biochemical studies have focused on the β-adrenergic membrane receptor, a molecular entity that is presumably situated in the postsynaptic membrane. The interaction of noradrenalin with this receptor triggers a chain of events culminating in the biologic response. Measurement of these receptors in membranes prepared from multiple brain regions demonstrated decreased numbers of binding sites in both the stimulated and contralateral amygdaloid regions of animals sacrificed 3 days following completion of kindling in the amygdala (McNamara, 1978b). Controls for these animals underwent electrode implantation but were not stimulated. Electrical current without kindling did not modify the amounts of this receptor. Measurement of this receptor in animals sacrificed at additional times after kindling (1 hr, 1 day, and 7 days) disclosed no significant differences from controls. Thus the decline in β-adrenergic receptors developed between 1 and 3 days following kindling, and occurred only transiently.

This time course supports the notion that the β-adrenergic receptor decline represents a resonse to the kindling process rather than a cause of it. Preliminary studies from other laboratories have described reductions in cerebral cortical β-adrenergic receptors following repeated electroshock seizures (Bergstrom *et al.*, 1979). Together these observations

raise the possibility that the decline in β-adrenergic receptors following kindling is related to the kindled seizures themselves, rather than any property of kindling *per se*.

In summary, the selective depletion of forebrain noradrenalin dramatically facilitates the development of amygdala kindling. Whether altered noradrenergic neuronal communication actually plays any meaningful role in kindling is presently unknown. There is no evidence that communication at these synapses is increased. Rather, the reduced tyrosine hydroxylase activity in the stimulated amygdala 1 month following completion of kindling suggests that communication of these synapses may be decreased. The marked facilitation of amygdala kindling by depletion of forebrain noradrenalin underscores the need for a complete biochemical assessment of noradrenergic neuronal communication in discrete regions within the stimulated amygdala at multiple points in time. A number of indices need to be measured, including noradrenalin turnover, α- and β-adrenergic receptors, and biologic responses linked to these receptors.

4.4.3. *Dopamine*

Dopamine is a putative neurotransmitter with mainly inhibitory effects. Dopaminergic cell bodies are located in the substantia nigra and project to the corpus striatum and mesolimbic and cortical regions.

Selective destruction of the dopaminergic neurons by injection of 6-hydroxydopamine into the nigrostriatal path did not significantly alter the development of kindling (Mason and Corcoran, in press). Likewise, neither metrazol nor electroshock seizures were modified by destruction of dopaminergic neurons. While these data suggest that dopamine is of minor importance in kindling, these lesions destroyed only 60% of the dopamine. Moreover, the efficacy of the lesion in destroying dopamine in the *amygdala* was not assessed.

Direct measurement of dopamine content disclosed reduced amounts in the stimulated amygdala 1 month following completion of kindling (Engel and Sharpless, 1977). This finding is consistent with the independent observation of decreased tyrosine hydroxylase activity in the stimulated amygdala 1 month after kindling. Clarification of the significance of dopamine alterations in kindling will require a complete biochemical profile of dopaminergic synaptic function and elucidation of the effects of selective, extensive destruction of amygdala dopamine on the rate of kindling.

4.4.4. *GABA and benzodiazepines*

Abundant evidence implicates GABA as the principal inhibitory neurotransmitter in mammalian brain. In the hippocampal formation, GABA appears to be the neurotransmitter of the basket cells which mediate powerful recurrent inhibitory actions on pyramidal and granule neurons (Andersen, 1975).

The benzodiazepines are potent anticonvulsant agents. These drugs may act by enhancing GABA receptive neurons' responses to GABA (Choi *et al.*, 1977; MacDonald and Barker, 1978). Binding sites to radioactive benzodiazepines have recently been identified in brain membranes (Squires and Braestrup, 1977). These binding sites likely represent receptors which mediate the pharmocologic action of these drugs.

Benzodiazepines have been repeatedly demonstrated to retard the development of kindling (Racine *et al.*, 1976; Wise and Chinerman, 1974). In addition, once kindling has been established, these drugs are potent blockers of electrically induced kindled seizures (Racine *et al.*, 1976; Wise and Chinerman, 1974; Babington and Wedeking, 1973). These pharmacologic data suggested that brain benzodiazepine receptors may be altered following kindled seizures.

Direct biochemical studies demonstrated that repeated kindled seizures cause a long-lasting (at least 24 hr) increase of benzodiazepine receptors in membranes from the

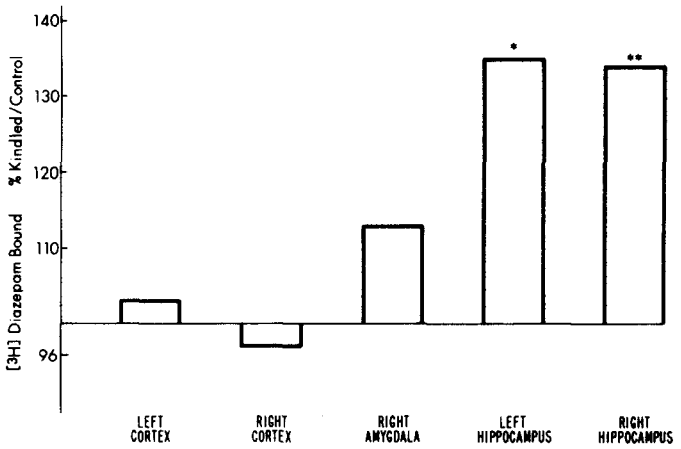

FIG. 5. Effects of kindled seizures on brain benzodiazepine receptors. Benzodiazepine receptors were measured with [^{3}H] diazepam binding under equilibrium conditions. Binding was measured in membranes prepared from animals sacrificed 1 day after a mean of 16 stimulations in the right amygdala. The data are expressed as the percent of kindled seizures divided by control times 100 in the regions designated at the bottom of the figure. *$p < 0.005$, **$p < 0.001$.

hippocampi of Sprague-Dawley rats (McNamara *et al.*, 1980). (See Fig. 5.) These receptor elevations appear to be related to seizures rather than the kindling process for two reasons: (1) repeated electroshock seizures induced increased numbers of the hippocampal benzodiazepine receptors; and (2) establishment of kindling with fewer seizures failed to induce significant increases. Neither repeated hypoxia nor repeated administration of electrical current without inducing seizures caused an increase of benzodiazepine receptors. Together these findings demonstrate that repeated seizures cause increased numbers of hippocampal benzodiazepine receptors.

Repeated kindled seizures induced by entorhinal cortical stimulation causes increased release of [^{3}H] GABA from hippocampal slices exposed to depolarizing concentrations of extracellular potassium (Liebowitz *et al.*, 1978). Whether this [^{3}H] GABA release was calcium dependent (and presumably released from synaptic terminals) was not demonstrated. Likewise, the effects of other seizure types on [^{3}H] GABA release were not tested. Thus, it is unclear whether this biochemical alteration is a property of kindling *per se*, or rather a property of repeated seizures.

In summary, the benzodiazepines retard the development of kindling and block-kindled seizures. These effects may be mediated in part by interaction with benzodiazepine receptors, leading to enhanced GABA mediated inhibition. Biochemical studies demonstrate that repeated seizures, whether induced by kindling or electroshock, cause increased numbers of hippocampal benzodiazepine receptors. Repeated kindled seizures are also associated with increased [^{3}H] GABA release from hippocampal slices. The biochemical changes of this neurotransmitter system likely represent a response to kindled seizures rather than the biochemical mechanism underlying kindling for two reasons: (1) the benzodiazepine receptor increases are linked to seizures rather than kindling; and (2) the increased GABA release favors enhanced synaptic inhibition, rather than excitation.

5. Potential Usefulness of the Kindling Model

Kindling is being utilized as a model for study of partial seizures, epileptogenesis, and neuronal plasticity. The ultimate goal of each of these investigational lines is to understand the *biology* of the process, thereby necessitating correlative biochemical, pharmaco-

logic, morphologic, and electrophysiologic studies. Kindling offers several important advantages over other models of these processes: (1) the absence of degenerative morphologic alterations eliminates a potential confounding variable in interpretation of biochemical studies; (2) the absence of exogenous toxins (e.g. pentylenetetrazol, alumina gel) simplifies biochemical studies; (3) the possibility of administering comparable amounts of current without kindling permits control for this variable; and (4) the ability to kindle in multiple sites permits choice of the site most appropriate for the experimental goals (e.g. limbic versus neocortex; known neurotransmitter path; etc.).

5.1. MODEL OF PARTIAL SEIZURES

Kindled seizures triggered by amygdaloid stimulation are analogous to human complex partial seizures with secondary generalization. Kindled seizures triggered by anterior neocortical stimulation are analogous to elementary partial seizures. These seizures offer an excellent opportunity to screen new agents for potential use as antiepileptic drugs. The seizure pattern can be stabilized and seizures triggered at the investigator's convenience, thereby optimizing testing at the time of appropriate drug serum concentrations and simplifying seizure detection and assessment of drug effect. Further, one can ascertain the relative efficacy of the drug on elementary versus complex partial seizures. Studies of antiepileptic drugs on kindled seizures to date suggest in a general way that this model will be predictive of drug efficacy in humans (Wada, 1977). The absence of detailed information on the relative efficacy of standard antiepileptic drugs on well defined seizures types in humans presently limits more precise assessment of predictive value*.

The opportunity to study endogenous mechanisms of partial seizures may ultimately prove to be of even greater significance than the use of kindling for screening antiepileptic drugs. For example, a well defined consequence of repeated limbic seizures is a long-lasting but transient suppression of the kindling effect. Stated differently, repeated limbic seizures suppress neuronal excitability to such an extent that kindled seizures cannot be elicited by electrical stimulation. Analogous endogenous inhibitory mechanisms may play a key role in human epilepsy. In depth electrode investigations of humans undergoing evaluation for surgical treatment of medically intractable complex partial seizures, we have on occasion eliminated the patient's antiepileptic drugs in efforts to capture spontaneous seizures. These patients reveal a surprising discrepancy between clinical and electrographic seizure activity. Indeed, we have observed patients with repeated (several times/hr) electrical seizure activity with infrequent (one every couple of days) clinical seizures†. The persistent abnormal excitability with only periodic spread resulting in clinical seizures suggests the presence of potent endogenous inhibitory mechanisms.

This enhancement of inhibition in response to persistent excitability teleologically seems to be a reasonable consequence of repeated seizures. This inhibition likely has both adaptive and maladaptive consequences. The adaptive consequences would be a reduced likelihood of a clinical seizure. Maladaptive consequences would likely reflect impairment of functions normally mediated by the inhibited neurons. In accord with this thinking, recent studies of humans with intractable seizures claim that the temporal lobe triggering the seizures has impaired function (as assessed by memory testing, 2-deoxyglucose uptake with positron emission tomography, generation of β-activity on EEG following thiopental infusion, or increased afterdischarge threshold) (Engel *et al.*, submitted for publication).

* Exemplary of the paucity of detailed human information is the absence of a published double-blind prospective study comparing the relative efficacy of phenytoin, carbamazepine, phenobarbital, or primidone on human elementary or complex partial seizures.

† The term electrical seizure activity as used here does not imply spontaneous interictal spiking but rather frank electrographic seizures reminiscent of afterdischarges observed in kindling.

Study of kindled seizures provides the opportunity to investigate these endogenous inhibitory mechanisms. Repeated kindled seizures are associated with biochemical evidence of decreased muscarinic cholinergic neuronal communication. This may represent a biochemical mechanism contributing to endogenous inhibition. A detailed understanding of the cellular consequences of this molecular event could serve as a framework for extrapolating these studies to humans with epilepsy. Pharmacologic regulation of these molecular events could lead to improved seizure control.

5.2. Model of Epileptogenesis

The graded onset of the kindling effect provides an outstanding opportunity to study mechanisms underlying epileptogenesis. Although the precise relationship of kindling to human epileptogenesis remains speculative, several observations suggest that a kindling process may occur in humans: (1) repeated periodic, electrical stimulation of the thalamus through a depth electrode was temporally related to the onset of elementary partial epilepsy in a human (Sramka *et al.*, 1977); (2) the latency between brain damage and onset of seizures in human posttraumatic epilepsy is consistent with a kindling-like effect; (3) detailed studies of several humans demonstrated that extended periods of epileptic seizures arising from one temporal lobe were followed by development of epileptic seizures arising from the contralateral (and presumably originally uninvolved) temporal lobe (Morrell, 1979). Together these findings imply that kindling may share the mechanisms underlying some forms of human epileptogenesis.

5.3. Model of Neuronal Plasticity

Kindling represents a means of modifying neuronal function of preexisting neural networks by electrical stimulation. Understanding the basic mechanisms responsible for kindling in biochemical and physiological terms would provide a rational basis for attempting to modify neural networks in a desirable and controlled fashion. Such information may prove useful in promoting recovery of function after brain damage with either pharmacologic or electrical tools. Instances in which such strategies could theoretically be employed are numerous, and include stimulation of occipital cortex in acquired blindness and stimulation of the spinal cord in paraplegia following cord injury.

6. Conclusion

Although the phenomenologic aspects of kindling have been characterized in considerable detail, we currently lack any meaningful understanding of the basic mehcanisms underlying this phenomenon. For example, no reproducible morphologic differences have been identified between kindled and control animals. With respect to electrophysiologic studies, whether a process identical to long-term potentiation in model systems is the key cellular mechanism underlying kindling is unknown. Finally, the biochemical findings generally reflect the consequences of kindled seizures, and in many instances nonkindled seizure controls have not been studied.

Our fundamental understanding is limited because of the complexity of the mammalian brain, together with the likely possibility that multiple but selected neural circuits are altered. Identification of which neural circuits are altered is essential for understanding the cellular and molecular nature of the alterations. Although understanding kindling is a formidable task, the potential implications of such insights warrant vigorous efforts toward this goal.

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