The kindling effect*

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Animals subjected periodically to low-intensity electrical stimulation unilaterally to the amygdala or some other brain sites gradually develop automatic behaviors which culminate eventually in convulsions. Characteristic brain wave patterns accompany these behavioral changes. A 60-Hz sine wave with a 24-h interval provides the most optimum condition of stimulation. This kindling effect shows some characteristics similar to learning events, viz, relatively permanent changes, positive and negative transfer effects, involvement of limbic system. The results suggest that two factors are involved in the kindling process: a long-term effect of positive nature (probably due to modified neural circuitry) and a short-term "aftereffect" of negative nature.

If a rat is electrically stimulated unilaterally at a low intensity, e.g., in the amygdala, he will continue to explore his environment as he would normally do. However, after a number of trials with the same intensity of stimulation, he will rear up on his hind paws and the forelimbs will begin to convulse. Apparently, the brain conditions are being modified and the animal's susceptibility to convulsing is being decreased. This procedure wherein an animal's behavior is being modified slowly over a period of trials in response to an invariant stimulus has been termed the "kindling effect" (Goddard et al, 1969; Goddard, 1972). In recent years, this paradigm has been used by a number of researchers with interesting results. The purpose of this paper is to review these efforts, mainly with the amygdala, the tissue which provides the most rapid kindling rate.

History

Electrical stimulation of the brain was initiated many years ago, e.g., in 1866 by Siminoff and in 1870 by Fritsch and Hitzig (Doty, 1970). However, it is only within recent years that such stimulation has become widespread. Brain stimulation research mainly began in the late 1940's and early 1950's with the discovery that stimulation of certain parts of the brainstem would lead to activation of large portions of the cortex. These results led to interesting theoretical formulations concerning the "reticular activation system" and its role in brain function (Delayfresnaye, 1954).

Other research which gave impetus to the brain stimulation movement was the self-stimulation experiments of Olds and Milner (1954). In these experiments, rats chose electrical brain stimulation over other reinforcers, e.g., food, even when the organism had been deprived.

The reticular formation and self-stimulation research led to a tremendous number of investigators concerning themselves with brain stimulation aspects. However, it is

only in recent research, by Goddard and his colleagues, that the changes associated with periodic brain stimulation (e.g., of the amygdala) and the development of seizure forms were the primary concern of the investigation. Previously, these changes were incidental to, and sometimes an embarrassment of, the main purpose of the research.

In 1955 Heath et al reported that stimulation parameters with human amygdala that were initially subthreshold and caused amusement later caused intense fear with an impulse to run.

A few years later, it was shown with cats by Alonso-deFlorida and Delgado (1958) that a few hours of repeated electrical stimulation of the amygdala resulted in lasting electrophysiological and behavioral changes. In one cat, the experimental session resulted in a limited motor seizure which continued independently for 27 days and ended in death. Subsequently, Fonberg and Delgado (1961) observed that amygdaloid stimulation in cats had an inhibitory effect on feeding and learned behavior. The inhibition outlasted the stimulation and became more prolonged when the amygdaloid stimulation was repeated on different days. In one animal, the seizure threshold diminished, motor and electrical manifestations increased, and generalized seizure developed. Also, Delgado and Sevillano (1961) stimulated the cat hippocampus several times a day, eventually producing convulsive behavior.

In 1963, Gunne and Reis (and Reis & Gunne, 1965) found that electrical stimulation of the amygdala in cats initially caused facial twitching, turning, chewing, and salivation. By the end of 3 h of intermittent stimulation, the same stimulus resulted in complete rage reactions including clawing, snarling, hissing, and attack. These responses continued after the termination of each train of amygdaloid stimulation.

Yoshii and Yamaguchi (1963) observed the development of a rage reaction in one cat after 40 days of repeated amygdaloid stimulation. The reaction lasted even after the animal returned to the cage, resulting in the destruction of its own electrodes. This result was

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obtained despite continuous care on the part of the authors to adjust the intensity of stimulation in an effort to avoid after discharge durations of greater than 5 sec. Other cats in their experiment developed more extensive after discharge, progressively more widespread interictal spiking, the emergence of seizure-associated head turning, or tonic-clonic convulsions.

In the self-stimulation studies of Wurtz and Olds (1963), more than half of the rats receiving amygdaloid stimulation developed seizures. It was not reported whether the seizures developed only after repeated stimulation. Bogacz et al (1965) clearly showed that with self-stimulation electrodes in anterior lateral hypothalamus and septal area, the seizure thresholds diminished over time. The authors were surprised to find that the seizure thresholds declined to a greater extent than the self-stimulation thresholds, and in some cases eventually fell below the self-stimulation thresholds.

Stevens et al (1969) and Ervin et al (1969) presented examples of long-latency long-lasting psychological changes in both epileptic and nonepileptic humans. In these cases, as with most studies of electrical stimulation, only one hemisphere was stimulated at a time. The lasting aftereffects may be less noticeable if confined to one hemisphere than if bilaterally represented.

Although the initial brain stimulation research used electrical methods, some research which is pertinent to the kindling event was concerned with the effects of chemicals on brain aspects. In 1961, Morrell indicated that alumina cream on cortical tissue induced an epileptic focus. When the cream stimulated the cortex of one hemisphere, the homologous tissue showed similar activity. At first this activity appeared only when the stimulated cortex was active. Later the tissue of the nonstimulated hemisphere showed spontaneous excitation even when it was isolated from the stimulated one by cutting its connections.

Using cholinergic stimulation of the cat amygdala, Grossman (1963) observed very dramatic changes. A single bilateral injection of carbachol caused seizure activity that continued to reappear two or three times daily throughout the following 5-month observation period. Pronounced changes in disposition, including viciousness and hypersensitivity, were also observed.

Baxter (1967) observed behavioral changes that lasted several hours after cholinergic stimulation of the amygdala. One cat died overnight, possibly as a result of convulsions, and one cat remained resistant to handling on the day after the injection.

Belluzzi and Grossman (1969) reported that bilateral injection of carbachol into rat amygdala was followed by major alterations in avoidance learning which persisted for several weeks after the convulsions subsided. Similarly, other studies with carbachol injected into the rat amygdala (Goddard, 1969) indicated pronounced changes in certain types of avoidance behavior which often lasted for more than 2 weeks after the injection.

Although behavioral changes following electrical and/or chemical changes were reported often, it was Goddard and his colleagues who concentrated on these aspects in a systematic research program. A brief burst of subthreshold electrical stimulation to the amygdala will eventually lead to behavioral convulsions if repeated over a number of trials, separated by at least 20 min (Goddard, 1967; Goddard et al, 1969; McIntyre, 1970; Racine, 1972; Walters, 1970). A number of parametric and anatomical studies in the rat showed that the kindling effect is a relatively permanent transsynaptic change that results from electrical activation of neurons and cannot be explained simply in terms of tissue damage, poison, edema, or gliosis (Goddard et al, 1969).

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 anatomical connections with the amygdala (Goddard et al, 1969).

A number of researchers showed that, attending behavioral changes during the kindling event, there were definite electrophysiological changes as well (Goddard et al, 1969; Racine, 1972; Tanaka, 1972). There is a unique wave form developed in the stimulated site, e.g., the amygdala, which later induces a similar wave in the homologous contralateral site.

Recently, chemical aspects of this phenomenon have been investigated. Tanaka (1972) was concerned with the effects of a number of chemicals on electrical activity and on the kindling rate with rabbits. He found that with some chemicals, e.g., phenobarbital, the usual electrical and behavioral responses during kindling were eliminated or reduced. Gaito and colleagues investigated soluble protein patterns during the kindling process and attempted to determine if kindling facilitation or retardation could be transferred from one animal to another. Negative transfer was reported with intraperitoneal administration of soluble proteins from kindled animals (Gaito & Gaito¹). However, no differences were detected in the electrophoretic patterns of soluble proteins of rats at various stages in the kindling process (Gaito et al, 1973).

VARIOUS ASPECTS OF THE KINDLING EFFECT

Behavioral

Goddard et al (1969) reported a three-stage process during kindling. For example, electrical stimulation to the amygdala produced clonic convulsions on the average in about 15 trials. The initial stimulations have little effect on the animal's behavior (Stage 1—normal exploratory behavior); with several repetitions, overt indications of seizure activity can be observed, e.g., eye closure, chewing, salivation (Stage 2—behavioral

Fig. 1. Diagram to illustrate parallel events during kindling of amygdala unilaterally. First AD (after discharge) is a simple spike and wave form, 1 cps, with duration of from 6 to 50 sec (mean of 17 sec) and amplitude of 702 microV (mean). AD changes from a simple to a complex wave, 3-5 cps, lasting from about 10 to 100 sec, with a mean amplitude of about 986 microV. Stimulation of amygdala produces AD in ipsilateral amygdala and induces AD in contralateral amygdala after a number of ADs. ADs during this stage are complex waves, about 5 cps (with some bursts of 14-16 cps), of 50-350 sec duration (mean of 102 sec), with a mean amplitude of 986 microV. Spikes from contralateral amygdala start at low amplitude and increase until they are equal to, or nearly equal to, those of the ipsilateral site. Complete clonic convulsions occur when the amplitudes of the spikes are about the same in both amygdalae.

automatisms); with further stimulations, these automatisms culminate in a complete convulsion (Stage 3—clonic convulsion; see Fig. 1). Although certain behaviors during Stage 2 such as eye closing and chewing are relatively stereotyped and easy to identify, other behaviors can be confused with those observed during Stage 1 (e.g., arrest, head turning to ipsilateral side). However, the clonic convulsions encountered in Stage 3 are relatively the same from animal to animal. The rat stands on its hind paws and bilateral clonic convulsions ensue; these continue after the electrical stimulation is terminated. Thus Stage 3 behavior is less variable and easier to identify than that of Stage 2. This three-stage process has been reported in other laboratories also (Tanaka, 1972; Gaito et al, 1973).

Goddard et al. (1969) investigated the conditions under which kindling resulted. A 60-Hz current with a 24-h interval of stimulation provided the most optimum condition of stimulation. Kindling was induced also with intervals of 7 days and with shorter intervals (12, 8, 1, and 1/3 h). Intervals of 10 min or less resulted in adaptation—some automatic behavior could be initiated but it would not persist. Effective kindling was produced also by other frequencies (25 and 150 Hz). Three hertz was ineffective—it provided neither the characteristic behavioral nor electrophysiological changes. The changes required the electrical stimulation (i.e., no spontaneous convulsions tended to occur), but once initiated, these changes persisted for many seconds after the termination of the current.

An interesting aspect of the kindling phenomenon is

the relative permanency of the effect (Goddard et al, 1969). The convulsions occur either on the first trial or within a few trials, even after a 6-week interval of no stimulation (Goddard et al, 1969). Over a longer interval, there is usually the requirement of several trials for convulsions to occur. Thus, there is the suggestion of some loss in strength of the tendency over periods of nonstimulation. Goddard et al (1969) reported about a 10% loss in rekindling over a 3-month period.

The effect occurs in rats, cats, monkeys (Goddard et al, 1969), and rabbits (Tanaka, 1972).

Neurological

By careful analysis using sine wave electrical stimulation, Goddard et al (1969) indicated that the behavioral changes were not due to a pathological brain process but were a function of the stimulating parameters. A lesion placed at the site of the area to be stimulated eliminated the behavioral changes.

Many brain regions were not responsive, specifically the majority of the neocortex, the thalamus, and the brainstem. Those that were responsive to electrical stimulation extended from the olfactory bulbs to the entorhinal cortex, including the septal region and the hippocampus. Almost all points in this olfactory-limbic system gave positive effects. The amygdala was the most responsive; all amygdaloid nuclei appeared to be equally responsive. There was a tendency for the number of trials to the first clonic convulsion to correspond roughly with the extent of anatomical connections with the amygdaloid complex. The responsive areas with the

number of trials to first convulsion were: amygdala, 15; globus pallidus, 22; pyriform cortex, 24; olfactory area, 29; anterior limbic field, 29; entorhinal cortex, 37; olfactory bulb, 44; septal area, 55; preoptic area, 63; caudate putamen, 74; hippocampus, 77. These areas fall roughly into two systems, the anterior limbic and the olfactory limbic. Stimulation of the first system produced tonic-clonic convulsions; convulsions from the second were clonic-clonic in nature.

Both positive and negative intraanimal transfer effects are possible (Goddard et al, 1969). Kindling one amygdala reduced the number of trials required to kindle the second amygdala. However, having kindled the second amygdala, interference resulted when rekindling the first amygdala. Positive transfer resulted not only from amygdala to amygdala but from amygdala to some other brain structure, e.g., septal region (Goddard et al, 1969).

Gaito and Gaito¹ reported negative transfer when portions of the soluble protein fraction of kindled rats were injected intraperitoneally into naive recipients.

Electrophysiological

A number of investigators have reported electrical changes during the kindling process (Goddard, 1972; Goddard et al, 1969; Racine, 1972). Figure 1 shows these changes in the amygdala of the rat (Racine, 1972). First there is the normal electrical pattern. With repeated stimulation, the threshold for an after discharge (AD) is decreased. Soon the AD appears; it is a simple spike and wave form, 1 cps, with a duration of about 6-50 sec and a mean amplitude of 702 microV. The first AD appears before behavioral automatisms are observed. Upon further stimulation, the wave form becomes more complex and increases occur in frequency, duration, and amplitude. Then an AD is induced in the contralateral amygdala. At first the amplitude of this wave is lower than the AD in the ipsilateral amygdala. When the two are approximately equal in amplitude, clonic convulsions ensue.

Tanaka (1972) found somewhat similar electrical events with rabbits and indicated that the amygdaloid AD spread not only to the contralateral amygdala but to other parts of the brain as well, usually in an orderly sequence, viz, to the hippocampus first, then to the occipital cortex, and finally to the frontal cortex. (Tanaka recorded only from the amygdala, hippocampus, and frontal and occipital cortices.) The propagated AD usually disappeared concomitantly with or earlier than that of the original AD in the amygdala, although the hippocampus AD continued longer in some cases. Convulsive behavior coincided with the brain wave changes in the frontal cortex.

Chemical

With the changes in behavior and electrophysiology, obviously one would assume that chemical changes were occurring also (Fig. 1). Tanaka (1972) investigated the

effects of a number of chemicals on electrophysiology and behavior after the "kindling effect" was complete. When the seizures were inhibited by a drug, amygdaloid stimulations were repeated with the same or stronger intensities every 20 to 60 min until the full seizure reappeared. Diazepam selectively abolished the behavioral responses and the frontal waves, but the amygdaloid AD remained almost unaffected. Acetazolamide modified the amygdaloid AD to an abortive form of short duration; although the convulsive behavior was suppressed, some behavioral automatisms were preserved. Phenobarbital, lidocaine, and methamphetamine eliminated the AD and behavioral responses. Pentetrazol facilitated the full effect, whereas diphenylhydantoin and chlorpromazine had little or no effect on electrographic and behavioral responses.

Gaito et al (1973) found the same electrophoretic pattern of prealbumin region acidic proteins for amygdaloid kindled rats as for nonstimulated controls and for rats subjected to stimulation for varying periods prior to convulsions. An intraperitoneal injection of soluble proteins from convulsed rats resulted in a retardation in the kindling process with naive recipients if the injection contained the equivalent of two brain amounts. When one brain amount was used, no effect was noted on the kindling rate (Gaito & Gaito¹).

Effects on Learning

With some modification of neural tissue occurring during the kindling process, it might seem that other events which depend on this tissue would be affected. Such is the case. Goddard (1964) demonstrated that unilateral electrical stimulation of rat amygdala over a number of trials impaired acquisition of a conditioned suppression when delivered after each CS-US pairing. Pelegrino (1965) found that electrical stimulation of the amygdala in thirsty rats impaired the acquisition of a passive avoidance response to an electrified water spout. The intensity used in both of these studies was probably at a level so as to produce ADs, although this aspect was not indicated.

When the learning task was a one-trial passive avoidance event, Kesner and Doty (1968) obtained amnesic results when retention was tested 24 h later if the electrical stimulation immediately after the learning event was at sufficient intensity to produce after discharges. Later research (McDonough & Kesner, 1971) showed that similar results occur without the appearance of ADs if bilateral stimulation of the amygdala is used. McDonough and Kesner also reported that unilateral stimulation produced amnesia if a lesion was made in the other amygdala.

McIntyre (1970) reported that convulsions elicited by unilateral amygdaloid stimulation of the amygdala produced two kinds of interference effects on conditioned emotional response learning (CER): retrograde amnesia, for events immediately preceding the convulsion; and prograde effect, an interference in

the retention of events occurring at some time after the convulsions. Convulsions produced by stimulation of the anterior limbic field and stimulation of the amygdala not producing convulsions did not have these effects. In later work, McIntyre and Molino (1972) found that bilateral lesions of the amygdala produced the same impairment of CER learning as did the lesioning of one and kindling of the other. They reasoned that the kindled focus acts as a functional lesion interfering with the development of normal processes apparently required for learning to occur.

Bresnahan and Routtenberg (1972) reported that unilateral low-level stimulation did not disrupt acquisition in a repeated trials passive avoidance learning task but did impair retention. With the level of stimulation used, no ADs were present. The site responsible for the impairment was found to be the medial nucleus of the amygdala. Stimulation of the dorsal hippocampus, however, did not affect acquisition or retention.

THEORETICAL POSSIBILITIES

Goddard et al (1969) and McIntyre and Goddard (1973) indicated that stimulation of one amygdala facilitated kindling in the other amygdala (intraanimal positive transfer), although increased latency resulted. Rekindling of the first amygdala was then impaired (intraanimal negative transfer). To account for these effects, and for the development of convulsions from the initial stimulation, Goddard et al (1969) maintained that two specific but widespread neural circuits were established. One was developed during stimulation of the first amygdala. During kindling of the other amygdala, the second circuit utilizes and ties into response elements of the first circuit and triggers convulsions in fewer trials than were required with stimulation of the first amygdala. As a result of this utilization, however, the circuits are changed to correspond with the activity of the second region and lose some of their correspondence with the first one. A few trials are necessary to reestablish the original connection with the first circuit.

In the development of convulsions, the modified neural circuits could be limbic-limbic or limbic-motor in nature. Research by Racine et al (1972) suggested that this development was dependent upon the increased strength of limbic-limbic connections rather than the strengthening of limbic-motor connections.

Goddard (1972) and McIntyre and Goddard (1973) suggested a two-factor model to account for the original kindling and for the transfer effects. These are: (a) a long-term effect of positive nature, due to modified neural circuitry; (b) a short-term "aftereffect" of negative nature. The modified neural circuitry are those discussed above. The exact nature and mechanism of the "aftereffect" are not indicated. The "aftereffect" is able to suppress seizure activity in different parts of the

nervous system, is proportional to the number of convulsions, and spontaneously dissipates over time; complete dissipation occurs in 2 weeks or so (Goddard & McIntyre, 1973). It is possible that the "aftereffect" is chemical in nature. Thus, the interanimal retardation effect of Gaito and Gaito¹ may be expressing the Goddard and McIntyre intraanimal "aftereffect."

IMPLICATIONS OF THE KINDLING RESULTS

An Analogue of Learning

Goddard et al (1969) pointed out the similarity of kindling to the learning process. For example, each shows relatively permanent changes resulting from repeated experiences, the limbic system is implicated in both, both involve transsynaptic changes in function, both demonstrate positive transfer effects, and in both cases the acquisition of a new response results in retroactive interference with old responses. A number of other individuals have noted the similarity of kindling aspects to learning events (e.g., Kesner & Doty, 1968; McIntyre, 1970; Bresnahan & Routtenberg, 1972). The results discussed above (Effects on Learning) also suggest the similarity of kindling aspects to the learning process.

This paradigm was suggested by Gaito (1974) as a technique which would allow for the evaluation of chemical events underlying a behavioral change in molecular psychobiology research without some of the problems associated with the usual learning task. He emphasized the stereotypy and automaticity of the third stage and relative freedom from factors such as motivation, stress, variability, and other aspects which contaminate usual learning paradigms. Thus, this paradigm could be useful as a "learning type" design without some of the extralearning problems.

An Analogue of Epilepsy

The similarity between kindling and epilepsy is quite obvious as a number of individuals have indicated (Goddard, 1972). Kindling appears to be an experimentally produced type of epilepsy. Thus, these procedures would seem to provide an excellent paradigm with which to evaluate various chemicals and agents which affect convulsion susceptibility (Tanaka, 1972; Gaito & Gaito¹).

Possible Effect During Therapeutic Brain Stimulation

Goddard and McIntyre (1972) pointed out that the kindling results have implications for the use in humans of therapeutic brain stimulation via depth electrodes. Although some positive results may occur with the repeated stimulations that are involved, these repeated trials may induce the development of seizure activity and, eventually, clinical convulsions in response to the stimulating current. Thus, in each individual case, the possible benefits to be obtained via stimulating should be weighed against the possible development of convulsive tendencies.

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NOTE

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