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THE KINDLING PHENOMENON : AN INTRODUCTION AND PRELIMINARY APPLICATION

BY

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Abstract

The kindling phenomenon has attracted the attention of neuropsychiatrists in recent years. It is a direct demonstration of neural plasticity, and a model through which the process of epileptogenesis can be studied. Kindling is an experimental model of epilepsy that can be used appropriately to screen for potential anticonvulsant drugs. In this article the literature relevant to the development and technique of kindling, its basic mechanisms and potential theoretical and practical implications for psychiatry are reviewed. The technique used for amygdala kindling in the rat is described in detail, as well as methods of scoring and interpretation of seizure variables. The results of screening for the anticonvulsant properties of betaine, glutamate diethyl ester and cystine ethyl ester in kindled seizures have demonstrated no better effect than saline controls. These results are discussed in the light of methodological problems and recent findings.

Introduction

In the 1950's and 1960's numerous investigators described the seizure inducing potential of focal electrical brain stimulation. The importance of this observation was recognized by Graham Goddard in the late 1960's. Goddard (1967), coined the term kindling because

he felt that this phenomenon is analogous to lighting a fire. He was the first to make a careful description of the kindling effect and demonstrate its permanence. As well, he recognized its potential importance as an experimental model of epilepsy, and a model of learning and memory.

Kindling refers to the phenomenon where repeated administration of a subconvulsive dose of electricity leads to progressive intensification of seizure activity culminating in a generalized motor seizure.

Kindling can be elicited from many but not all brain sites (McNamara et al., 1980). In rats stimulated in the amygdala, which is the brain structure most sensitive to kindling, initial stimulations produce focal electrical activity in the form of an after discharge recorded on the EEG. Subsequent stimulations lead to progressive seizures evolving through a certain pattern:

1. Facial clonus.
2. Head nodding.
3. Forelimb clonus.
4. Rearing with bilateral convulsions.
5. Rearing and falling with bilateral convulsions (Racine, 1972).

A range of 8-30 stimulations is required to reach this stage. Once reached a stage 5 seizure is a permanent result whenever stimulation takes place. Spontaneous spikes appear on the interictal EEG especially during stages 3 and 4 of the kindling process.

For effective kindling the electrical stimulus should possess certain characteristics. Wave frequencies between 25 and 150 Hz are all effective. Intermittent stimulation is essential (15 minutes at least and one week at most between successive stimulations). Eventually the stimulus must elicit an after-discharge in order for kindling to develop. A commonly used paradigm is the periodic administration of a 1sec. Train of biphasic waves at a frequency of 60Hz (McNamara et al., 1980).

Kindling can be induced by a variety of pharmacologic agents and even electroconvulsive shock (ECS). Local brain injection (carbamylcholine or penicillin) or systemic administration (e.g. cocaine and pentylenetetrazol)

can induce kindling-like effects (Vosu and Wise, 1975; Collins, 1978; Post and Kopanda, 1976; Pinel and Van Oot, 1975; and Kilbey et al., 1979). 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 leads to progressive decline of seizure severity. No change was observed in animals given ECS at one day intervals. Such kindling effect should be considered in spacing electroconvulsive therapy in humans.

Basic Mechanisms of Kindling:

The anatomical changes underlying kindling are unclear. As evidenced by glucose uptake studies increased metabolism occurs in the kindling site as well as its synaptically related targets. Remote changes in homologous hemispheric sites have been reported but not definitely proven (Collins, 1978; Racine, 1972; and Messenheimer et al., 1979). Morphological changes underlying kindling have been suggested including collateral sprouting, new synapse formation, and enhanced communication in selected paths based upon dentritic swelling or enlargement of the presynaptic terminal. However, several groups of investigators failed to confirm these changes in experimental animals (Goddard and Douglas, 1976; Crandall et al., 1979; Racine et al., 1975).

Electrophysiologic studies indicate that a process of long-term potentiation (LTP) in selected pathways may represent the cellular mechanism underlying kindling (McNamara et al., 1980; Goddard et al., 1969). Long-term potentiation takes place at the synapse, is calcium and magnesium dependent and seems to be related to the calcium dependent phosphorylation of a synaptic membrane protein (Dunwiddie and Lynch, 1978). Like kindling, LTP is a long-term effect and is produced by electrical stimulation similar to kindling (McNamara, 1978).

The role of neurotransmitters in the kindling phenomenon is complex. Acetyl choline is an excitatory transmitter that can enhance communication at synapses and thus contribute to the development of kindling. Actual measurements of ACh and muscarinic receptors during kindling have shown a decrease. These changes

seem to be secondary to the kindling process and are explained as protective endogenous processes that guard the brain against excessive excitation (McNamara et al., 1980). Contrary to the role of ACh a block or depletion of brain noradrenalin seems to enhance the kindling process (McNamara et al., 1980).

Benzodiazepines retard the development of kindling and block kindled seizures (Racine et al., 1976; Wise and Chinerman, 1974). Benzodiazepines act through GABA release, an increased number of benzodiazepine receptors has been demonstrated after kindling (McNamara et al., 1980). Like the change in acetyl choline, this effect is secondary and is protective against the excessive excitability and seizure augmentation.

Potential Usefulness of the Kindling Model:

Kindling is an experimental model of epilepsy that can subserve the study of epilepsy in general and the study of partial seizures in particular. The slow development of kindling allows for studying the mechanisms underlying the genesis of epilepsy.

As far as psychiatry is concerned, the kindling phenomenon provides a ready instance of neural plasticity i.e. neuronal modification and consequent behavior change occurring as a result of stimulation, facilitation and reinforcement of certain pathways. It serves to illustrate that the brain is a plastic organ interacting with the environment. In this light pathological patterns of behavior can result from long term potentiation of certain pathways consequent on faulty information and communication with the environment. If a kindling effect is responsible for certain variants of pathological behavior, it may be possible to reverse such patterns through a study of the mechanisms of kindling.

There is a number of research evidence linking kindling on one hand and the mechanisms of memory and learning on the other hand. Goddard and Douglas (1976) have proposed that the engram of kindling models the engram of long term memory. Such similarity may be based upon the lasting potentiation of the excitatory postsynaptic potential in all these conditions. Like

memory mechanisms LTP is associated with an increased synthesis of synaptic proteins (Duffy et al., 1981, Shashoua and Teyler, 1982). Furthermore, repetitive electrostimulation of the hippocampus facilitates the acquisition and retention of behavioral tasks (Campbell and Milgram, 1980).

Kindling procedures can produce longlasting changes in behavior. In humans, non-epileptogenic repetitive stimulation of the amygdala yielded enduring patterns of change in affective behavior (Stevens et al., 1969). In rats kindling increases escape behavior (Pinel et al., 1977), and in cats it increases defensive behavior (Adamec, 1975). On the other hand it has been found that aggressive cats have a naturally enhanced transmission efficiency in pathways that facilitate aggression (Adamec & Stark Adamec, 1983).

Harcaz (1985), points to a number of potentially useful applications of the kindling-long term potentiation model in understanding schizophrenia. Dopaminergic hyperactivity presumed behind schizophrenic psychopathology could be the outcome of LTP-like mechanisms. Post and his associates have suggested that catecholaminergic pathways in the limbic system may become potentiated following their repeated activation by stressful events (Post & Kopanda, 1976, Post, 1977). This type of potentiation may provide the mechanism by which repeated psychological stresses in man can lead to increasing psychopathology. Subjecting animals to repeated electric foot shock leads to increased mesolimbic and mesocortical dopaminergic activity (Thierry et al., 1977). Repeated stimulation of these mesolimbic DA neurones in cats leads to a progressive onset of a behavioral syndrome characterized by fearfulness, hiding, staring and loss of social behavior (Stevens & Livermore, 1978).

Differential transmission efficiencies in certain neural pathways may explain the emergence of specific psychopathology in vulnerable individuals. According to Post (1977) various psychotic symptoms may be related to potentiation of different neuronatomical pathways. Auditory and visual hallucinations may be associated with pathologically facilitated pathways in the temporal

and occipital lobes respectively. Stereotypies, waxy flexibility, and catatonia may indicate neostriatal involvement.

The kindling model is just one example of neuronal plasticity. This brain potentiality opens the way for a more accurate understanding of brain-environment interaction and interdependence in health and disease.

The practical component of this work aims at documenting the technique of amygdala kindling in rats, reporting the methods of seizure assessment and scoring of seizure variables, and reporting on the results of screening for anticonvulsant potential of four substances in this model of epilepsy.

Material and Methods

Male Sprague-Dawley rats weighing 180-450 gms were used in all experiments. Fourty four rats were used but only 11 could be successfully used for drug trials. The different fates of the 44 experimental animals were as follows:

N = 4 Training rats used for perfecting the operation of electrode implantation.

N = 15 Lost the electrodes after implantation due to:

a. Loosening of cement by post operative bleeding from the skull.

b. Infection around the implantation site.

c. Rat died postoperatively from debility or infection.

N = 5 Sacrificed to confirm the site of implantation by histological sections. Stereotaxic coordinates were modified accordingly to ensure accurate implantation in the amygdala.

N = 9 Failed to start the sequence of kindling after 12-15 stimulations.

N = 11 Successfully kindled and used in drug screening.

Electrode Implantation:

Intraperitoneal aquathesin (chloral hydrate, 0.25-0.3 ml for every 100 gm body weight) was used to anaesthetize the rats. The head was shaved, and the rat fixed appropriately within a stereotaxic instrument. The scalp, fascia and periosteum were generously incised

and bleeding secured maximally. The site of drilling in the skull was located and marked according to the following coordinates on the stereotaxic instrument: one mm posterior and 4.75 mm lateral to the center of the bregma. Four small screws were attached to the skull at each corner to serve as anchors for the dental cement. A bur hole was made in the skull at the implanation site, nomeostasis again secured, and an insulated copper electrode (made in the form of a double coil) was driven into the brain 7.5 mm deep form the surface of the brain (known by passing the resistance of the meninges). Homeostasis was secured for the third time and dental cement used to make a hard layer fixing the electrode were cut to appropriate length and fixed into small pins. The latter were fixed by another layer of cement creating a double plug through which electrical stimulation could be effected. Antibiotic powder was sprayed into the wound and the ends clipped leaving the electrodes exposed to the outside.

Rats were kept isolated for a week in order to recover before starting electrical stimulation.

Electrical Stimulation (Kindling):

This was carried out each morning at approximately the same time 5 days a week. A current strength of 400 A was used through an apparatus that delivers a 0.5 second stimulus (60 Hz). The stimulating wire was designed so that the rat can move around freely with the terminals attached to the electrode in his head. A single channel EEG recording was made to trace the development of after discharge and measure accurately the onset and termination of seizure activity.

When placed in the cage the rat was left to acclimatize and explore for 3 minutes after which the stimulus was delivered, and the rat observed for seizure related variables.

Assessment and Scoring of Seizures Variables:

With daily stimulation, a kindled rat would usually progress through the following sequence of responses:
(a) No response to stimulation, or behavioral arrest,

unilateral eye closure and deviation of the angle of the mouth (3-7 stimulations).

(b) The appearance of wet shakes*. These are paroxysmal momentary shakes of the whole body involving large groups of muscles (identical with a cat or dog shaking off moisture from its body). They may be single or repeated. Behavior arrest which consists of cessation of exploratory activity and grooming after stimulation of post-ictal was rated according to the following scheme:

0 No change in movement.

+ Minimal decrease in exploration or grooming.

++++ Prolonged behavior arrest. Rat stopped all movement continuously for 3 minutes after the seizure or stimulus.

(c) The appearance of seizure activity which progressed and was rated on a severity continuum as follows (Racine, 1972).

0 = No seizure
1 = Whisker contraction.
2 = Jaw clonus.
3 = Unilateral clonus of forelimb or unilateral tonic placement.
4 = Bilateral forelimb clonus.
5 = Bilateral clonus plus rearing* and falling.

Rats were considered fully kindled when a seizure score of 5 was achieved on 3 consecutive stimulations. This usually occurred within 8-20 stimulations.

Drug Testing:

Fully kindled rats were tested twice weekly for the anticonvulsant effects of the following drugs;

Betaine monohydrate: 676 mg/10 ml saline.
1352 mg/10 ml saline.

Glutamate diethyl ester: 480 mg/10 ml water.
960 mg/10 ml water.

Cystine ethyl ester 744 mg/10 ml water

Saline injections were used for control seizures.

Drugs were prepared fresh before use and injected intraperitoneally at a dose of 1ml/100gm body weight.

*** Counted for 3 minutes after the seizure or stimulus.**

*** Mean number of wet shakes-Kruskal Wallis Test $P<0.01$.**

Each drug testing was followed by two stimulations (30 minutes and 2 hours later) in order to control for rapid and more delayed onset of drug action.

Results and Comment

I- Seizure Variables in Kindled Rats:

Table I illustrates the characteristics of maximal seizures in the 4 most commonly stimulated rats.

Table (I)

Rat Serial Number	Stim. No.	Seizure Duration (sec)@	Wet Shakes (Mean N)* 1st Stim.	Wet Shakes (Mean N)* 2nd Stim.	Behavior arrest c 1st Stim.	Behavior arrest c 2nd Stim.
1	12	60.3±6.12	0.5	3.3	3.7	2.5
2	20	49.1±4.8	0.4	1.3	3.0	2.0
4	18	80.4±11.3	8.7	10.6	3.2	1.9
12	6	41.3±6.5	10.0	10.3	2.0	1.0

@ Seizure duration in seconds - One way ANOVA P<0.01.
*** Mean number of wet shakes - Kruskal Wallis Test P<0.01.**
c Degree of behavioral arrest - Kruskal Wallis Test N.S.
± Standard Deviation from the mean.

Seizure duration fluctuates within a moderate range in each rat (Lowest range 17 sec., and highest range 38 sec.). Standard deviation is also comparatively small. Each rat seems to have his specific seizure duration with some overlap. The differences among the 4 rats in seizure duration are highly significant ($F_{3, 52, 55} = 63.8$, $P<0.01$).

The mean number of wet shakes increases in every rat after the second stimulus (1½ hours after the first stimulus). However, these increases are not statistically significant. The number of wet shakes that follows a seizure seems to be relatively fixed and stable for

each rat. The differences in the mean number of wet shakes among the four rats is statistically significant (Kruskal Wallis Test $P<0.01$).

Contrary to the changes observed in wet shakes, behavioral arrest decreases with repeated stimulation in each rat (Table I). This effect is independent from the drug effects since it was equally observed in saline control conditions. Rats do not differ significantly from each other in the degree of behavioral arrest they exhibit.

Taken collectively the effect of repeated stimulation is to increase the number of wet shakes and decrease the degree of behavioral arrest. Seizure duration was almost unaffected by repeated stimulation. These changes may reflect an enhanced CNS excitability as a result of repeated stimulation. This finding is similar to what Sainbury et al. (1978), report on the effects of repeated stimulation. These authors report a decrease seizure severity if stimulation is repeated within 70 minutes but no suppression if repeated after a longer interval. Our finding as regards seizure severity and duration confirm this report but also suggest an enhanced excitability evident in the increased number of wet shakes and decreased behavior arrest.

Our results indicate that each rat has its uniform seizure characteristics. Such differences may be the result of minute differences in electrode location. Otherwise, it may be suggested that there are individual variations in the potentiations. There is a general pattern but the specific repertoire of each animal is constant.

Three drugs with probable anticonvulsant properties were tested in appropriate doses, viz betaine monohydrate, glutamate diethyl ester, and cystine ethyl ester. Six saline control testings were used as controls. None of the seizure components or post-seizure variables assessed in this study could demonstrate a superiority of drug over saline control. The most important variables Viz seizure severity and duration remained remarkable constant althrough table (II).

II- Anticonvulsant Drug Screening in Kindled Rats:

Table (II)

Drug Dose	Rats N=	Mean Seizure score ½ hr.	Mean Seizure score 2 hr.	Seizure duration ½ hr.	Seizure duration 2 hr.	Wet Shakes ½ hr.	Wet Shakes 2 hr.	Behavior arrest ½ hr.	Behavior arrest 2 hr.
Betaine Monohydrate									
676mg/kg	5	5	5	58.2	64.6	6	5.6	3	2.6
1352mg/kg	14	4.9	5	62.3	62.3	5.1	4.7	2.4	1.4
Glutamate Diethyl Ester									
480mg/kg	3	5	5	69.7	65	6.7	8.7	3.3	3.3
960mg/kg	7	4.9	5	58.9	60.6	4.1	4.4	3.3	2.7
Cystine Ethyl Ester									
744mg/kg	6	5	5	65.5	60.1	1	4.7	3.1	2.7
Saline Controls									
-	5	5	5	56	56.2	5.2	6	2	1.4

No significant differences between drug tested and saline tested rats on any measure.

These findings indicate clearly that none of the drugs tested has a demonstrable anticonvulsant action in kindling seizures. Betaine was formerly demonstrated to have anticonvulsant properties in pentylenetetrazol (PTZ) induced seizures in mice (Freed et al., 1979) and rats (Hamdi & Freed, 1985). The betaine effect was much more prominent with intracerebroventricular administration than with intraperitoneal injection (Hamdi & Freed, 1985). Betaine's failure to control kindled seizures may be attributed to the route of administration reflecting blood-brain barrier problems rather than actual failure. The convulsant properties of certain amino acids has been established (Freed et al., 1985; Segal, 1976). The role of amino acid antagonists in reversing some forms of experimental epilepsy has been documented (Freed & Michaelis, 1978; Freed, 1985). We have tried without success two presumably amino acid antagonists selected on the basis of structural similarity and esterification.

Lastly, we should give a few words of caution that might have caused a type II error in our work:

(1) Drug doses used were based upon previous experience and research as well as known toxicity. A different dosage schedule may be more effective.

(2) Utilizing the intraperitoneal route may have hampered efficient access of the drug to critical brain regions on account of the presence of the blood-brain barrier.

(3) Kindling seizures are electrically induced. They might be an unusually resistant form of seizures not akin to epilepsy, but more akin to electroshock. Actually, Freed et al., (1979) have demonstrated that betaine could not control electroshock induced seizures in mice.

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موجز

ظاهرة التوقد : تقديم وتطبيق مبدئى

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اجتذبت ظاهرة التوقد انتباه أطباء النفس والأعصاب فى السنوات الأخيرة، فهى تعد دليلا مباشرا على المرونة العصبية ونموذجا يمكن من خلاله دراسة عملية تكوين البؤرات الصرعية.. وبالاضافة إلى ذلك يمكن اعتبار هذه الظاهرة نموذجا تجريبيا للصرع يمكن استخدامه فى البحث عن العقاقير ذات الخصائص المضادة للصرع.

يستعرض هذا المقال التراث المرجعى المرتبط بوصف ظاهرة التوقد وكيفية إحداثها بالاضافة إلى الميكانزمات الأساسية المحدثة لها والتطبيقات العملية والنظرية لهذه الظاهرة فى مجال الطب النفسى. ثم يصف المقال تفصيليا الطريقة المستخدمة لإحداث التوقد فى النواة اللوزية (الاميجدالا) فى فئران التجارب، كما يصف وسائل تسجيل وتقييم متغيرات النوبات الحادثة.. وأخيرا يعرض البحث نتائج اختبار الخصائص المضادة للصرع للمواد الآتية: البتين، استر الجلوتامات ثنائى الأيثيل، واستر السيستين الأيثيل.. وقد تبين عدم تفوق أى من هذه المواد على محلول الملح الفسيولوجى فى السيطرة على النوبات الصرعية الناتجة من التوقد.. ونوقشت هذه النتائج فى ضوء مشكلات التطبيق والاكتشافات الجديدة فى هذا المجال.

التوقد : بمعنى اتقد أى استمر نشيطاً متوهجاً (أو الاستثارة الدائمة).

ABSTRAIT

Le Phenomene de "Kindling"
Introduction et Application Preliminaire

Le phenomenon de 'Kindling' a attiré l'attention des neuropsychiatres durant ces recentes années. Ce phenomene est une demonstration directe de la plasticité nerveuse et un modèle par lequel le processus de l'epileptogenese peut être étudie. Le 'Kindling' est un modele experimental de l'epilepsie qui pourrait être utilisé pour mettre à l'épreuve des medicaments a effet anticonvulsif potentiel.

Dans cet article la literature ayant rapport au developement et à la techinque du 'Kindling', ses mechanismes de base et ses implications theoriques et pratiques dans le domaire psychiatrique sont étudiés. La technique utilisée pour le 'Kindling' de l'amygdale chez le rat est decrite en detail, ainsi que les methodes d'evaluation et d'interpretation des variables convulsives.

Les resultats de l'essai des proprietés anticonvulsives du betaine, glutamate diethyl ester, et cystine ethyl ester dans ces convulsions experimentales a demontré un effet superieur au control placebo. Ces resultats sont discutés prenant en consideration les problèmes methodologiques ainsi que les données recentes.