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Alcohol Withdrawal Seizures: Implications of Kindling[1]

JOHN P. J. PINEL[2]

Department of Psychology, University of British Columbia, Vancouver, British Columbia, Canada V6T 1W5

PINEL, J. P. J. *Alcohol withdrawal seizures: Implications of kindling.* PHARMAC. BIOCHEM. BEHAV. 13: Suppl. 1, 225–231, 1980.—The periodic administration of convulsive agents, even at doses or intensities that initially have no convulsive effect, can lead to a progressive and enduring increase in the susceptibility to subsequent convulsive stimulation. This kindling effect has contributed to the understanding of the convulsive effects of alcohol withdrawal in three ways. First, rats kindled by the periodic application of electroconvulsive shock, local brain stimulation, or pentylenetetrazol were found to be hypersusceptible to the convulsive effects of subsequent alcohol withdrawal, thus raising the possibility that some forms of electrical or pharmacological therapy can potentiate the alcohol withdrawal syndrome in humans. Second, the duration of seizures elicited in kindled rats has been used as a sensitive index of convulsive withdrawal effects; increases in the duration of kindled motor seizures and afterdischarges can be detected following the metabolism of a single intoxicating injection of ethanol. Third, it was suggested that the potentiation of the convulsive effects of alcohol exposure and withdrawal by prior episodes of alcohol withdrawal may reflect a kindling-like process rather than an increase in physical dependence.

Kindling Seizure Pentylenetetrazol Rat Epilepsy Electroconvulsive shock Alcohol withdrawal Amygdala Physical dependence Convulsion Afterdischarge

A VARIETY of epileptic symptoms ranging from mild tremors to grand mal seizures has been observed in human subjects following the abrupt discontinuation of chronic alcohol intoxication [7,34]. Because comparable symptoms can be reliably induced in a variety of species commonly employed in laboratory investigations (e.g. [5]), the alcohol withdrawal seizure has been the most widely investigated behavioral and electrographic manifestation of withdrawal from chronic alcohol exposure. These studies of seizures induced by alcohol withdrawal have served as the principal basis for inferring the properties of alcohol physical dependence, the presumed neuropathological change that occurs as the result of chronic alcohol exposure and mediates the physiological reaction to its withdrawal.

Although there is a substantial experimental literature on alcohol withdrawal seizures, it is only a small portion of the more general literature on various forms of experimentally-induced seizures. Unfortunately, the literature on alcohol withdrawal seizures, for the most part, has evolved independently of developments in other areas of research in the field of experimental epilsepsy. Accordingly, the purpose of the present paper is to describe a general property of experimental epilepsy, the kindling effect, and to discuss its relevance to the investigation of the epileptic effects of alcohol withdrawal.

THE KINDLING EFFECT

The kindling effect is the progressive intensification of elicited motor seizures that occurs during a series of convulsive stimulations. Because of the precedent established by early investigators [4], most studies of kindling have involved the daily administration of low-intensity amygdaloid stimulation to rats. Typically the first few stimulations are without behavioral effect, but if the regimen of daily stimulations is continued, mild automatisms are soon elicited by each stimulation. Then, with each successive stimulation, these automatisms increase in severity until motor seizures involving forelimb clonus and loss of equilibrium are reliably evoked; and eventually fits of running and periods of tonus can also be elicited. This experimental epileptogenesis ultimately, after several hundred stimulations, culminates in a rat that is truly epileptic, i.e., one in which motor seizures recur spontaneously long after the regimen of periodic stimulations has been curtailed [18,19].

The first systematic investigation of the kindling phenomenon was published in 1969 by Goddard, McIntyre and Leech [4]. In this paper, two interesting features of kindling were identified that have become the focus for many subsequent investigations—a recent review [30] of the rapidly accumulating kindling literature cited over 200 papers. First, they found that the number of amygdaloid stimulations re-

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[2]Requests for reprints should be sent to: John Pinel, Department of Psychology, University of British Columbia, Vancouver, B.C., Canada V6T 1W5.

quired before the first generalized motor seizure could be elicited was inversely related to the duration of the interstimulation interval. Kindling did not occur at all at interstimulation intervals of less than 20 min, and intervals of 24 hr or greater were found to be asymptotically efficient. Second, they found that kindling was extremely enduring, if not altogether permanent. Previously kindled rats that were stimulated again after a 12-week, stimulation-free period displayed a savings of about 90% in the number of stimulations required to elicit another generalized motor seizure.

The work of Racine has revealed the electrographic factors responsible for amygdaloid kindling. Periodic stimulation below the afterdischarge threshold reduces the threshold until each stimulation elicits an afterdischarge [28]. It is the elicitation of these afterdischarges rather than the stimulation per se that is critical for amygdaloid kindling; stimulations that do not elicit afterdischarges do not kindle motor seizures or even reduce the number of supra-threshold stimulations required for subsequent kindling [29]. Initial afterdischarges remain localized to the site of stimulation and are not associated with motor activity, but with each successive stimulation, the afterdischarges spread progressively further from the site of stimulation, and motor seizures begin to accompany them. Thus, the tendency of low-intensity convulsive stimulation to produce an enduring reduction in the afterdischarge threshold and the tendency for afterdischarges once elicited to facilitate the generalization of subsequent discharges are two electrographic phenomena that can mediate the potentiation of subsequent motor seizures.

Generality of Kindling

Although most early studies of kindling were studies of rats subjected to daily amygdaloid stimulation, more recent work has established that kindling is not restricted to either rats or amygdaloid stimulation. It is more appropriately viewed as a general property of epileptic activity, thus establishing its relevance to the study of withdrawal seizures in human alcoholics.

Although the exact form of motor seizures elicited by periodic bipolar brain stimulation may vary in different species, the tendency of these seizures to increase progressively in intensity has been remarkably general. The kindling effect has been reported in an impressively long and varied list of experimental animals. In addition to rats, kindling has been observed in reptiles [32], rabbits [33], mice [10], cats [37], dogs [39], frogs [13], monkeys [4], and baboons [35]. Thus, there is little reason to doubt that such effects are relevant to human convulsive disorders.

Kindling effects have now been unambiguously demonstrated with a variety of convulsive agents. For example, pentylenetetrazol administered intraperitoneally once every 3 days to rats at doses that were initially subconvulsive elicited myoclonic responses after a few injections, and grand mal seizures were reliably elicited in some rats by the end of the experiment [11,17]. Similarly, motor seizures elicited once very 3 days by electroconvulsive shock gradually increase in severity; the latencies to both forelimb and hindlimb tonic extension decrease progressively, and the incidence and duration of tonic hindlimb extension increase [3]. Kindling effects have also been demonstrated with repeated application of audiogenic stimulation [9] or fluorothyl vapor [27]; intracerebral injections of carbachol [35] or conjugated estrogens [3]; or intraperitonal injections of cocaine [25], lidocaine [26], or chlordimeform [41].

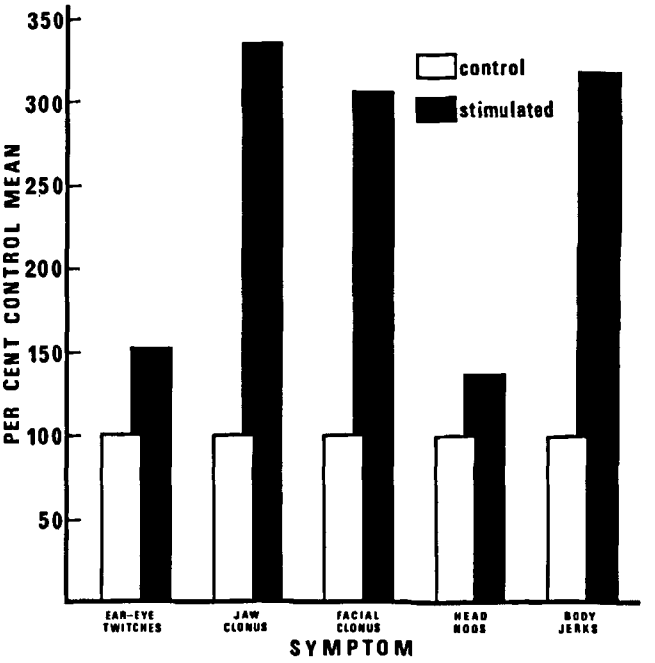

FIG. 1. The intensification of alcohol withdrawal symptoms following amygdaloid kindling. The 45 amygdaloid stimulations were administered 3 per day, 5 days per week. The controls were implanted and treated as the experimentals, except that they received no stimulation. Prior to withdrawal assessment all subjects received 45 ethanol intubations administered at 8 hr intervals. The incidence of each withdrawal symptom observed in the experimental rats is presented in comparison to its incidence in control rats arbitrarily set at 100%.

Kindling is a general phenomenon also in the sense that the increased responsiveness to convulsive agents following kindling is not specific to the agent that was administered to induce the increase. For example, kindling one brain site with electrical stimulation greatly increases the facility with which electrical stimulation can kindle other sites [4], even after the original site has been lesioned. Furthermore, periodic amygdaloid stimulation has been shown to intensify both pentylenetetrazol-induced and procaine-induced motor seizures [20], and a series of electroconvulsive shocks has been found to intensify flurothyl-induced motor seizures [27].

POTENTIATION OF ALCOHOL WITHDRAWAL BY PRIOR KINDLING

Research on the kindling phenomenon suggests that prior experience with convulsive agents could be a major determinant of an organism's susceptibility to the epileptic effects of alcohol withdrawal. Even when the antecedent agents do not themselves elicit motor seizures or electrographic discharges, they can potentiate the susceptibility to subsequent convulsive treatments, and there is no reason to expect that alcohol withdrawal would be an exception to this general effect. The remarkable generality of the kindling phenomenon raised the possibility that humans previously exposed to convulsive therapy or to any of the various routinely prescribed pharmacological agents that are convulsants at high doses [8] could be particularly susceptible to the epileptic effects of subsequent alcohol withdrawal.

In our first attempt [24] to assess the possibility of such phenomena, we demonstrated that periodic stimulation of the amygdala could change a "normal" organism into one that is particularly susceptible to the convulsive consequences of alcohol withdrawal. To do this, we compared the severity of the alcohol withdrawal syndrome in kindled and normal rats. The rats in the kindled group received a series of 45 amygdaloid stimulations over a 3-week period; whereas, the controls were subjected to the same implantation and handling procedures, but they were not stimulated. The subjects in the kindled group were stimulated at 400 μA for 1 sec, a level sufficient to produce afterdischarges in response to the first stimulation, and thus motor seizures were quickly kindled in every stimulated animal.

Three days after the last stimulation, both groups of animals were subjected to 45 intubations of a 20% volumetrically prepared alcohol solution according to a procedure that has been described elsewhere [16]. Assessment of the withdrawal effects by a researcher unaware of the experimental history of each animal commenced 9 hr after the last intubation. Each animal was observed for six 2-min periods, one every 3 hr, during which the incidence of the following five convulsive withdrawal symptoms was recorded: (1) rhythmic activity of the mouth, (2) facial tremors, (3) rhythmic eye or ear twitching, (4) myoclonic body jerks, (5) rhythmic head nodding.

It is apparent from Fig. 1 that the incidence of each of the five minor convulsive withdrawal symptoms was greater in the kindled animals than in the unkindled controls. Furthermore, three generalized clonic seizures like those elicited in the advanced stages of amygdaloid kindling were observed during the withdrawal period, and each was observed in a different kindled subject.

A second experiment in this series [24] was performed in exactly the same fashion except that the experimental subjects were stimulated below their afterdischarge threshold. Each experimental animal was stimulated below its threshold until the threshold was reduced to the point where an afterdischarge was elicited. When this occurred, the stimulation level for that animal was further reduced. Thus, the experimental animals received 45 stimulations that were almost all below their declining afterdischarge thresholds, and as a result none of the animals developed motor seizures in response to stimulation. The results of this experiment were similar to those of the first experiment; the stimulations, even though they never elicited motor seizures and rarely elicited afterdischarges, led to an exacerbation of the subsequent alcohol withdrawal reaction.

This is a particularly important observation because it establishes that repeated administration of potentially convulsive agents can change a "normal" organism to one that is particularly susceptible to the effects of alcohol withdrawal even when these agents do not themselves evoke overt responses. These results clearly illustrate the potential dangers involved in the therapeutic application of local brain stimulation and suggest that drugs such as chlorpromazine and imipramine, which have well-documented convulsive effects at high doses [8], could create hazards for alcohol abusers.

The ability of kindling with a pharmacological agent to potentiate the alcohol withdrawal syndrome has also been established [2]. Experimental rats received 41 IP injections of pentylenetetrazol at 3-day intervals; whereas, the controls were injected with an equal volume of saline. The initial injection of pentylenetetrazol produced no responses in about 70% of the experimental animals, and very mild facial tremors were noted in the remaining subjects. However, with repeated administration there was a gradual development and intensification of convulsive responses similar to that reported by other investigators [11,17]. As in our previous experiments both the experimental subjects and the placebo controls were then intubated with alcohol every 8 hr for a 2-week period, and the incidence of convulsive withdrawal reactions was then assessed. Again convulsive withdrawal symptoms were found to be more prevalent in the kindled animals.

Because electroconvulsive shock is the most widely used form of convulsive therapy, it was particularly important to determine whether electroconvulsive shocks could poentiate the alcohol withdrawal syndrome. All experimental rats in our initial attempt to answer this question [22] received a 0.5-sec, 15-mA electroconvulsive shock through implanted skull screws, and the same electroconvulsive shock was again administered to all the experimental subjects 30 days later. In the intervening period, all the experimental animals received 8 electroconvulsive shocks administered at 3-day intervals. For half of these animals, the intensity of the intervening electroconvulsive shocks was 15 mA; whereas the other half were stimulated at 75 mA. Control subjects were handled but remained unstimulated.

The two panels of Fig. 2 summarize the changes in the intensity of the electroshock convulsions observed following the two test stimulations and the eight intervening treatment stimulations. Because a major feature of electroshock seizures is a wave of tonic extension that spreads caudally along the body, the degree of its spread is a frequently used measure of seizure severity [40]. The duration of tonic forelimb extension and the incidence of tonic hindlimb extension were the two measures selected for summary in Fig. 2. The repeated administration of electroconvulsive shock at both intensities produced a gradual intensification of the convulsive response that was clearly reflected by both measures.

In the second stage of this study, both experimental and control subjects were subjected to the usual 15-day series of ethanol intubations followed by withdrawal assessments as in our previous experiments. Because the intensity of the electroconvulsive shock had no appreciable effect on the incidence of the withdrawal symptoms, the data of these two groups were combined for presentation in Fig. 3. Again the facilitatory effect of repeated convulsive stimulation is clearly illustrated; all five convulsive symptoms were more prevalent in the stimulated subjects.

In a recent series of studies [23], we subjected this potentiation of alcohol withdrawal effects by antecedent electroconvulsive shocks to parametric analysis. Because a kindling effect is not produced by electroconvulsive shocks when they are administered at intervals of a day or less [31], we wondered whether such a regimen of electroconvulsive shocks would potentiate subsequent alcohol withdrawal effects. The answer was no. Ten electroconvulsive shocks administered at 3-day intervals significantly potentiated the convulsive effects of subsequent alcohol withdrawal; whereas, those administered at 1-hr intervals did not [23].

The electroshock-produced potentiation of alcohol withdrawal effects was also shown to be a function of the number of antecedent electroconvulsive shocks and the duration of the interval between the electroconvulsive shocks and the withdrawal of alcohol [23]. Three or six electroconvulsive shocks administered at 3-day intervals did not significantly

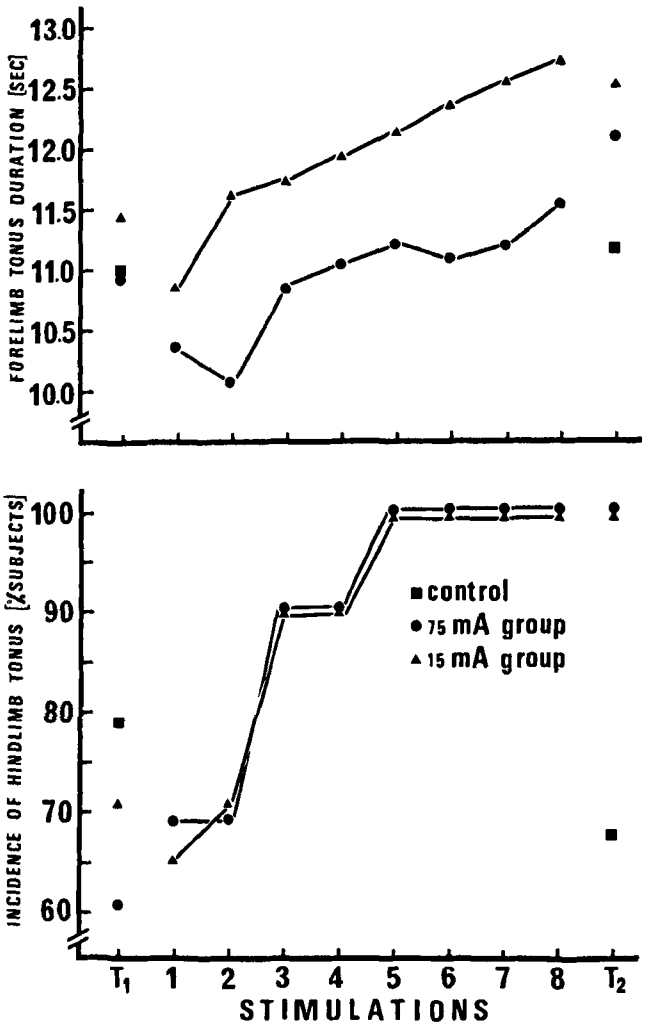

FIG. 2. Progressive increase in seizure severity produced by two intensities of repeated electroconvulsive shock (ECS). Subjects in both repeated ECS groups received two 15-mA test stimulations (T_1 and T_2), with eight intervening stimulations at either 15 or 75 mA. Also illustrated are the responses of the stimulated control subjects that received only the two test stimulations.

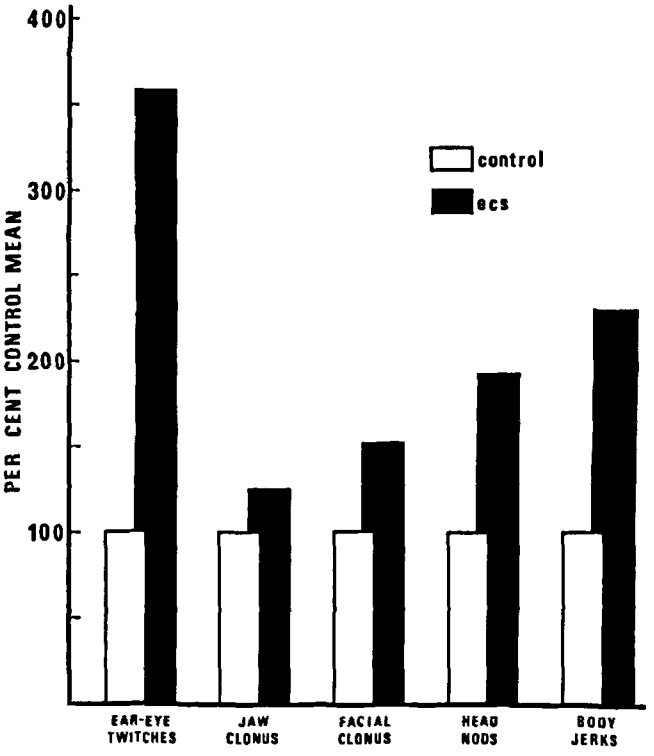

FIG. 3. The intensification of alcohol withdrawal symptoms following repeated electroconvulsive shocks (ECSs). The controls were implanted and handled, but they did not receive the series of eight ECSs. Prior to withdrawal assessment all subjects received 45 ethanol intubations administered at 8-hr intervals. The incidence of each symptom is presented in comparison to the control mean that was arbitrarily set at 100%.

increased the incidence of convulsive withdrawal symptoms, whereas 10 or 20 did. Furthermore, the potentiating effects of 10 electroconvulsive shocks on the withdrawal effects observed following 2 weeks of exposure to ethanol declined as the interval between the electroconvulsive shocks and withdrawal was increased; no significant potentiation was observed at intervals of 6 weeks or longer.

In the final experiment of this series [23], the effect of pretreatments commonly administered to patients undergoing electroconvulsive therapy was evaluated. Prior to each of 10 electroconvulsive shocks, administered at 3-day intervals, each rat received an injection of atropine sulphate, sodium pentobarbital, and succinyl choline before being placed in a low-pressure oxygen chamber. Although this combination of pretreatments blocked the usual motor response to electroconvulsive shock, it did not significantly diminish the subsequent potentiation of convulsive alcohol withdrawal symptoms observed 2 weeks after the last stimulation.

The preceding experiments clearly establish that the incidence of convulsive alcohol withdrawal symptoms can be influenced to a substantial degree by an organism's prior experience with convulsive agents. The periodic administration of local brain stimulation, pentylenetetrazol, or electroconvulsive shock increased the severity of convulsive symptoms observed in rats following 2 weeks of exposure to ethanol. Although these results should not be applied indiscriminately to human patient populations, they certainly raise the possibility that various forms of convulsive therapy can create long-range hazards for heavy consumers of alcohol.

ASSESSMENT OF CONVULSIVE WITHDRAWAL EFFECTS WITH KINDLED SEIZURES

Epileptic effects are additive; a convulsive agent administered at a dose too low to elicit convulsions will potentiate the convulsive effects of other agents. This general principle has been applied by a number of investigators to the study of alcohol withdrawal effects in both humans and laboratory animals. For example, photic stimulation that did not elicit epileptic responses in human control subjects did so in patients undergoing withdrawal [34], and increases in the susceptibility to seizures induced by handling, audiogenic stimulation, or electroconvulsive stimulation have been observed in rodents following withdrawal from alcohol (e.g. [5]).

Seizures kindled by amygdaloid stimulation have several features that suggest that they may be particularly useful in assessing the convulsive effects of alcohol withdrawal: (1)

The locus, frequency, and intensity of the test stimulations can be maintained under strict experimental control. (2) Seizures can be repeatedly elicited with little risk of subject attrition. (3) If suprathreshold stimulation is applied to a responsive area (e.g., amygdala), one can reasonably expect that every subject will be successfully kindled. (4) In the advanced stages of kindling, there is little variation in the duration of seizures elicited by successive stimulations, thus providing an extremely stable baseline against which even subtle changes in seizure susceptibility can be detected. (5) It is a simple matter to assess the effects of alcohol withdrawal on both the electrographic and motor aspects of the convulsive response by recording through the stimulation electrode during the motor seizure. (6) And finally, it has already been well-established that the duration of kindled seizures is a reliable index of the convulsive and anticonvulsive effects of a variety of agents (cf. [30]).

The utility of the kindling paradigm in assessing alcohol withdrawal effects is illustrated by a recent series of experiments conducted with R. F. Mucha [15]. The results of these experiments established that the kindling paradigm was sensitive enough to detect the withdrawal effects that exist after the exposure of a naive rat to a single, intoxicating dose of ethanol. Ten mature, male, hooded rats were stimulated through a bipolar electrode implanted in the amygdala three times each day at intervals never less than 30 min. After 3 weeks (5 days each week) of this regimen, each subject was stimulated once per day for 25 days. Although initial stimulations elicited no motor response whatsoever, by the end of this phase of the experiment each animal responded to each stimulation with a generalized clonic convulsion characterized in sequence by facial movements, head nodding, forelimb clonus, rearing, and loss of equilibrium.

Each of these 10 kindled rats was then stimulated 12 times, once every 3 hr. Six rats received an IP injection of 2.5 g/kg of ethanol and the other four received an equivalent volume of saline (15.7 ml of fluid per kg) 30 min before the fifth stimulation. After this sequence of test stimulations, each rat was returned to the daily stimulation regimen for 12 days before being tested as before over another 33-hr session. In this second session, those rats that had received saline during the first test received alcohol and vice versa. During each of the two test sessions, two samples of blood were taken from every animal 5 min following the cessation of the responses evoked by each of the seven post-alcohol test stimulations. Each of the pairs of samples was analyzed twice by gas chromatography, and the mean of the resulting four scores served as the measure of alcohol concentration.

The major results are summarized in Fig. 4. The durations of afterdischarges and motor seizures elicited by stimulations administered shortly after the alcohol injection were reduced appreciably, but following this suppression there was a transient, but statistically significant, increase in their duration. The results of the blood alcohol analyses confirmed the relation of the anticonvulsive and convulsive effects to the presence and absence of high blood alcohol levels, respectively.

The finding that the responsiveness of kindled rats to a series of amygdaloid stimulations is intensified following the metabolism of their first dose of alcohol is consistent with the previous reports of McQuarrie and Fingl [12] and Goldstein [5]. In the McQuarrie and Fingl study, the threshold to seizures elicited in naive mice by injections of pentylenetetrazol was reduced between 8 and 12 hr after intragastric administration of alcohol (5 g/kg); whereas, in Goldstein's

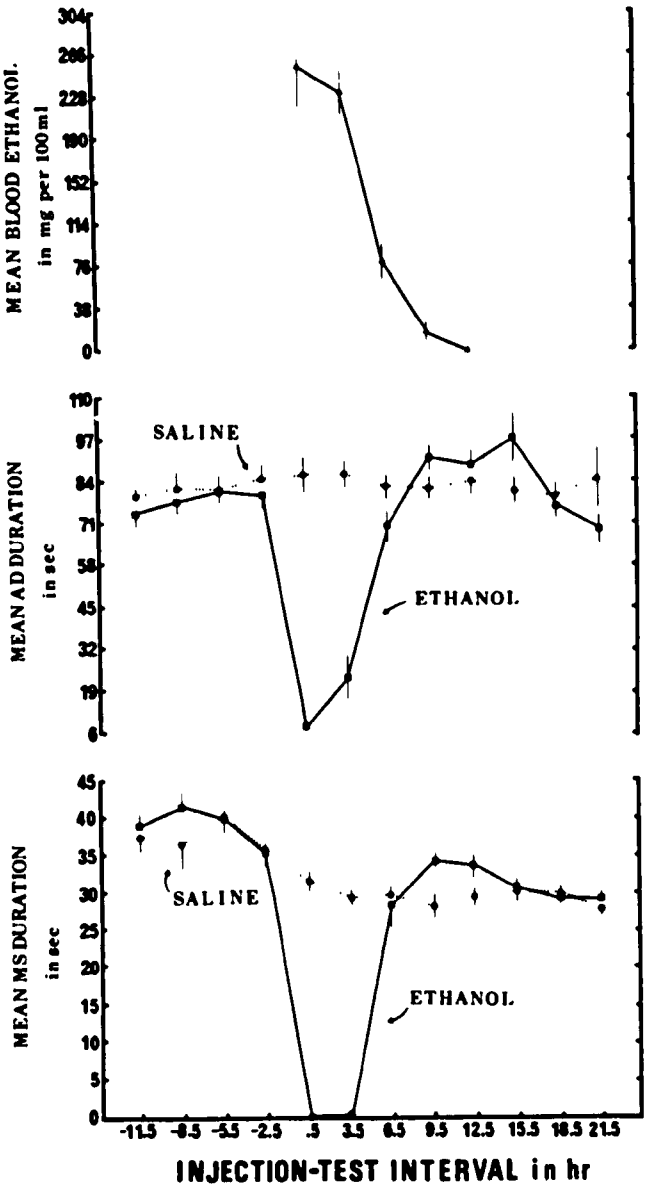

FIG. 4. Mean duration of afterdischarges (ADs) and motor seizures (MSs) elicited by amygdaloid stimulation in kindled rats before and after a single, intoxicating injection of ethanol. Seizure susceptibility was reduced substantially by the presence of ethanol but was increased significantly following its metabolism. From Mucha and Pinel [15].

experiments, 5 g/kg alcohol produced an increased susceptibility to a series of handling-elicited seizures 7 hr after injection into naive mice.

Unfortunately, neither the results of Experiment 1 nor those of McQuarrie and Fingl or Goldstein provide unambiguous evidence of convulsive withdrawal effects following a single injection of alcohol; in each case there is a more parsimonious explanation. In view of the fact that susceptibility to further seizures is temporarily reduced following a seizure [15], the heightened responsiveness of the subjects to convulsive stimulation during the withdrawal period could have resulted from a decline in inhibition from seizures, themselves suppressed by the initial anticonvulsant effects of the alcohol. Thus, the intensification of seizures during

the withdrawal period could have been an artifact of the multiple-seizure assessment schedule rather than being a symptom of withdrawal. Accordingly, in a subsequent control experiment, each subject received only one convulsive stimulation following alcohol exposure.

In this experiment, 12 previously kindled rats were stimulated at the same time each day for 48 consecutive days. On Days 15, 17, 19, and 21, six animals received an IP injection of 2.5 g/kg of ethanol, and the other six received an equivalent volume of saline (15.7 ml per kg). These injections were administered either 0.5, 7, 14, or 21 hr before the daily stimulation. A second series of four injections was administered on Days 36, 38, 40, and 42, but during this second series the animals that had previously received the alcohol injections received the saline and vice versa.

The results of this experiment confirmed those of the previous one; the ethanol reduced the duration of seizures elicited 5 hr after the injection but increased the duration of those elicited at 14 hr after injection. Because each test stimulation was administered to each subject exactly 24 hr after its last seizure, the facilitation of seizure activity in the withdrawal period could not be attributed to a diminution of post-seizure inhibition. Therefore, this experiment comprised the first unambiguous evidence for the existence of convulsive withdrawal effects following brief exposure to ethanol.

KINDLING AND THE STUDY OF PHYSICAL DEPENDENCE

Physical dependence is the presumed neuropathological change that develops during alcohol exposure and leads to the abstinence syndrome once the alcohol has been withdrawn. It is frequently viewed as an adaptive process (cf. [6]). According to this view, the presence of alcohol in the body produces changes in the nervous system that counteract its effects. Then when the alcohol is withdrawn the system is no longer "in balance", and a withdrawal reaction occurs that is opposite to the primary drug effect.

Because the adaptive process that constitutes physical dependence has not been identified, the only way that changes in physical dependence can be studied is by inferring them from changes in the severity of the ensuing withdrawal reaction. Thus, attempts to study physical dependence by assessing the epileptic consequences of alcohol withdrawal are based on the assumption that the intensity of withdrawal reaction is a measure of the degree of the underlying physical dependence.

The kindling phenomenon illustrates an obvious instance in which the intensity of the behavioral seizure is *not* directly related to the intensity of the eliciting stimulus. During the course of kindling the severity of the motor seizures increases dramatically although the intensity of the eliciting stimulus remains unchanged. Thus, in instances where organisms have been previously exposed to convulsive agents, their convulsive reactions to alcohol withdrawal may be disproportionately greater than the physical dependence that elicited them.

This point has a direct bearing on attempts to study the development of physical dependence following multiple periods of alcohol exposure. Several investigators (e.g. [2,38]) have reported that the withdrawal reactions of experimental animals were more severe after a second period of exposure than after the first. For example, Baker and Canon [1] recently reported that a second 21-day period of exposure to an ethanol liquid diet resulted in more withdrawal seizures than did the first, even though there was a 16-day interval between the two periods of exposure.

Although the usual interpretation of such studies is that the development of physical dependence is potentiated by prior physical dependence [1,6], the kindling phenomenon suggests another possibility. Perhaps multiple periods of physical dependence and withdrawal kindle of the organism; alcohol withdrawal in a dependent organism might increase the susceptibility to the convulsive effects of subsequent periods of alcohol exposure and withdrawal without increasing the degree of physical dependence. It has been demonstrated with numerous agents that the period administration of constant levels of a convulsive treatment leads to seizures of progressively increasing severity. Thus, it is not necessary to assume that prior periods of exposure and withdrawal facilitate the physiological changes that we call physical dependence. It is more parsimonious to assume that withdrawal of alcohol from dependent organisms increases their general susceptibility to seizures rather than increasing the magnitude of the physiological changes that elicit them. The mechanisms underlying the potentiation of alcohol withdrawal effects by previous withdrawal may be similar to those responsible for the potentiation of alcohol withdrawal effects by antecedent amygdaloid stimulations [24], injections of pentylenetetrazol [21], or administration of electroconvulsive shock [22,23].

Another facet of the literature on kindling has important implications for the study of alcohol physical dependence. Kindling occurs only at long interstimulation intervals because of a phenomenon termed post-seizure inhibition. In the period immediately following a seizure, an organism is less likely to respond to further convulsive stimulation. For example, the susceptibility to a second kindled amygdaloid seizure is reduced for about 90 min following the elicitation of the first. The inhibition is greater the more severe the first seizure, and following a series of 19 seizures elicited at 1.5-hr intervals the post-seizure inhibition lasted for several days [14].

Post-seizure inhibition is particularly obvious in the advanced stages of kindling. After several hundred consecutive seizures have been elicited, a subject may fail to respond to the stimulation [18]. Subsequent observation of that subject usually reveals that it is spontaneously epileptic. Spontaneous seizures experienced in the home cage inhibit the usual response to convulsive stimulation during formal test trials.

Such results illustrate the dangers inherent in attempts to define the severity of the epileptic effects of alcohol withdrawal in terms of a single assessment made at a single point in time. Those experimental animals most responsive to the effects of withdrawal may have spontaneous electrographic and/or behavioral symptoms that could interfere with the experimenter's attempts to observe or elicit seizures during prescribed tests, and thus these particularly responsive animals may be mistakenly judged to be the least responsive.

CONCLUSION

The preceding discussion is an attempt to illustrate the relevance of the kindling phenomenon in particular and the experimental epilepsy literature in general to the investigation of alcohol dependence and withdrawal effects. Alcohol withdrawal is only one of the many ways of eliciting seizures that have been subjected to extensive laboratory research. A knowledge of phenomena, such as the kindling effect, that seem to hold for many types of experimental epilepsy can serve as a valuable source of new approaches to the investigation of alcohol-produced epileptic effects.

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