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Tolerance to Alcohol's Anticonvulsant Effect is Not Under Pavlovian Control[1]

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PINEL, J. P. J. AND S. PUTTASWAMAIAH. *Tolerance to alcohol's anticonvulsant effect is not under Pavlovian control.* PHARMACOL BIOCHEM BEHAV 23(6) 959–964, 1985.—Tolerance to the anticonvulsant effect of alcohol has been shown to be contingent on the presence of convulsive stimulation during the period of intoxication. In the present experiments, manipulation of the environmental stimuli associated with alcohol administration had no effect on the development of tolerance to alcohol's anticonvulsant effect in kindled rats. Such tolerance was found not to be specific to the alcohol-predictive environment, nor was its development retarded by pre-exposing the subjects to an environment that was subsequently associated with alcohol administration. Moreover, an injection of saline to tolerant subjects in the alcohol-predictive environment did not elicit a conditioned compensatory increase in seizure duration. Thus, the Pavlovian theory of drug tolerance cannot account for the contingent tolerance that develops to alcohol's anticonvulsant effect.

Alcohol Kindling Seizures Contingent tolerance Anticonvulsant Ethanol Behavioral tolerance

IT is now well established that neither the development nor the maintenance of drug tolerance depends soley on the pattern of drug exposure. It has been frequently demonstrated that environmental stimuli, particularly those that become predictive of drug effects, can exert a substantial influence on the degree of tolerance to a variety of drugs. The most influential theoretical account of such environmental effects has been Siegel's [20] modification of Pavlov's [13] theory of conditioning. According to Siegel's Pavlovian theory of tolerance, environments in which subjects are repeatedly exposed to the central effects of a drug can become conditioned stimuli that eventually elicit conditioned compensatory responses that increase in strength with each drug exposure, and thus progressively counteract the initial unconditioned response to the drug. See Eikelboom and Stewart [6] and Poulos, Wilkinson, and Cappell [17] for modifications of, and extensions to, this theory; and see Solomon [23] and Wikler [25] for its antecedents.

Evidence of the hypothetical conditioned compensatory responses on which Siegel's Pavlovian account of drug tolerance is based has provided the strongest support for the theory. Such evidence has been furnished by experiments in which the administration of a placebo to tolerant subjects in the drug-predictive environment elicits a reaction opposite to the initial effect of the drug. For example, such placebo injections have been shown to produce hyperalgesia in rats tolerant to morphine's analgesic effect [7], hypothermia in rats tolerant to morphine's hyperthermic effect [19], hypoactivity in rats tolerant to morphine-produced hyperactivity [12], and hyperactivity in rats tolerant to alcohol-produced hypoactivity [4, 8, 11]. Additional support for this Pavlovian theory of drug tolerance has come from studies in which manipulations of the environmental stimuli associated with drug administration have been shown to influence the degree of drug tolerance in predictable ways. For example, ostensibly tolerant subjects have been found to be less tolerant to drugs when tested in environments distinct from those that had previously predicted their effects [1], and the rate at which tolerance develops has been shown to be retarded by pre-exposure to the environment in which the drug was subsequently administered [18].

The purpose of the present studies was to test the hypothesis that Pavlovian mechanisms underlie the phenomenon of *contingent* drug tolerance. Contingent drug tolerance is usually defined in terms of the difference in tolerance observed in the "drug-before" and "drug-after" conditions of the "before-and-after" design [2,3]. It has been frequently reported that tolerance develops to the effects of drugs on only those responses that occur during the periods of drug exposure, i.e., only in the drug-before condition. For example, Pinel, Colborne, Sigalet and Renfrey [15] found that tolerance developed to the anticonvulsive effects of ethanol when ethanol was administered to rats 1 hr before each of a series of convulsive stimulations but not when it was administered 1 hr after. Similarly, rats have been reported not to develop tolerance—or at least not to develop it as rapidly [9,24]—to the disruptive effects of ethanol on maze running unless they repeatedly run the maze while intoxicated, to the anorectic effects of amphetamine unless they are allowed to feed under its influence [5,17], or to the disruptive effects of delta-9-tetrahydrocannabinol on lever pressing unless they are allowed to lever press in the drugged state [10].

According to the Pavlovian interpretation of contingent tolerance [24], tolerance does not develop as readily in the drug-after condition of the before-and-after design because the test becomes part of the CS predictive of the drug in subjects repeatedly exposed to the drug after the test, and these cues are absent during the tolerance test when the drug

[1]Thanks is extended to Michael Mana, George Renfrey, and Donald Bethune for their assistance in the conduct of these experiments.

is administered to all subjects before the test. If this interpretation is correct, then drug effects to which contingent tolerance readily develops should be amenable to control by manipulations of the injection environment. Accordingly, the purpose of the present experiments was to determine if tolerance to the anticonvulsant effects of ethanol, a form of tolerance that has been shown to be contingent on the administration of convulsive stimulation during each period of intoxication [15,16], is subject to Pavlovian control.

GENERAL METHOD

In both experiments, the effect of ethanol on seizure activity elicited by amygdaloid stimulation in kindled rats was assessed. The utility of the kindling procedure in the assessment of alcohol's anticonvulsive effect has been described previously [14].

Subjects

The subjects in both experiments were male, 300 to 400 g hooded rats supplied by Charles River Canada and housed individually with ad lib access to standard laboratory chow and water.

Surgery

In both experiments, a single bipolar stimulation electrode was aimed at the left amygdala of each rat, 1.2 mm posterior to bregma, 5.0 mm left of the sagittal suture, and 9.0 mm ventral to the dura. Tetracycline was sprinkled on the incision following surgery and added to the drinking water during the first 5 days of convalescence.

Kindling

Each rat was stimulated (1 sec, 60 Hz, 400 μA r.m.s.) three times per day, 5 days a week with at least 2 hr between consecutive stimulations during the 3-week kindling phase of the experiments. Each animal was removed from its cage, stimulated immediately, and returned to its home cage after the seizure. As is usual [14], the rats at first did not respond to each stimulation, but by the last of the 45 kindling stimulations, most responded to each stimulation with a clonic seizure characterized in sequence by facial clonus, forelimb clonus, rearing, and a loss of equilibrium. The dependent variable in both experiments was the duration of the period of forelimb clonus. This measure has been shown to be sensitive to experimental manipulations designed to increase or decrease seizure susceptibility [14].

Baseline

Following kindling, the rats in both experiments were subjected to a series of baseline stimulations to assess the stability of their responses to convulsive stimulation. During the baseline phase of the experiments, each subject was stimulated six times, once every 48 hr.

Treatment

Although the treatment phases of the two experiments differed, they had several features in common. The 48-hr stimulation schedule initiated during the baseline phase was maintained until the end of both experiments. On each treatment day, each subject received an intraperitoneal injection of either 1.5 g/kg ethanol in a 25% v/v solution or an equivalent volume of the saline vehicle 60 min before each stimulation. Each animal was removed from its home cage, weighed and then placed in the appropriate treatment chamber 5 min prior to receiving the injection. After receiving the injection, each rat was returned to the same chamber for 1 hr before receiving an amygdaloid stimulation and being returned to its home cage 5 min later.

Alcohol Test

In both experiments, anticonvulsive effects of ethanol were assessed in all subjects 48 hr after the last treatment trial. The alcohol test was identical to the previous alcohol treatment trials in all respects except for the environment in which it was conducted and the experimenter who conducted it.

Blood Alcohol and Histology

A sample of tail blood was taken from each subject 5 min after the alcohol-test stimulation. Ethanol levels were subsequently determined by gas chromatography [26]. Following the experiments, all animals were killed in a CO_2 chamber according to Canada Council on Animal Care guidelines, and their brains were removed and stained using the blue-dot staining technique [21] in order to determine the site of stimulation.

Statistical Analysis

Lack of homogeneity of variance necessitated the use of nonparametric procedures in the analysis of the results of both experiments. The Wilcoxon Matched-Pairs Signed-Ranks Test and the Mann-Whitney *U* Test were used to make individual a priori comparisons between and within groups, respectively.

EXPERIMENT 1

One purpose of Experiment 1 was to determine whether or not tolerance to the anticonvulsive effect of alcohol is subject to environmental control, that is, to determine whether or not subjects display more tolerance to the anticonvulsive effect of alcohol if alcohol is administered in an alcohol-predictive environment than when it is administered in a saline-predictive environment. The second purpose was to determine whether or not a conditioned compensatory response would be elicited in subjects tolerant to alcohol's anticonvulsant effect, that is, to determine whether or not an injection of saline administered in an alcohol-predictive environment would increase the duration of forelimb clonus elicited by subsequent convulsive stimulation.

METHOD

Subjects

Of the 60 rats that began the experiment, 4 died of postsurgical complications, 2 rejected their electrode assemblies, 2 did not reliably display seizures during the baseline phase, and 9 died during the treatment phase. Thus 43 subjects completed the treatment phase of the experiment.

Treatment

Following kindling and baseline testing, all subjects meeting the criterion of stability, i.e., forelimb clonus of 10 sec or

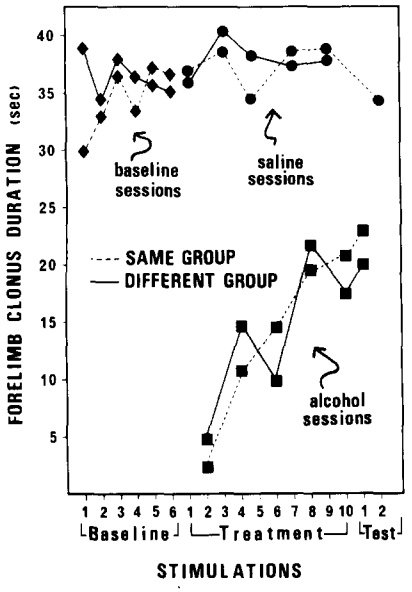

FIG. 1. The effect of saline or alcohol injections on the duration of forelimb clonus elicited in kindled rats by amygdaloid stimulation. Following 6 baseline days, the subjects in two groups received alcohol injections prior to even numbered stimulations and saline in a distinctive environment prior to odd numbered stimulations. During the alcohol test, the subjects in the Same Group received the alcohol and test stimulation in the same environment in which they had previously received it, whereas those in the Different Group received the alcohol and test stimulation in the environment in which they had previously received saline. On the saline test, the subjects in the Same Group received a saline injection in the environment in which they had always received alcohol.

more on each of the last 4 baseline days, were injected and stimulated on alternate days in one of two distinctive environments, A or B. Environment A was a 58×58×25 cm, plastic chamber lined with almond-scented shredded paper. This chamber, situated in a room upstairs from the colony room, was illuminated by both natural and artificial light. The colony room housed chamber B, which although similar to the one described above, was lined with an unscented corn cob bedding material and was illuminated entirely by artificial light. Different experimenters, A and B, were responsible for the testing in the respective environments.

On the first treatment day, all subjects were removed from their home cages by experimenter A, placed in groups of five or six in a carrying cage, and transported upstairs to test chamber A, where each subject remained in the carrying cage for 5 to 20 min. After 5 min in the test chamber, each subject was injected with either saline (n=22) or ethanol (n=21). Immediately after injection, each subject was returned to the test chamber and remained there for 1 hr before being stimulated. Each subject was removed from the test chamber 5 min after stimulation, placed in the carrying cage with five or six other subjects, and returned to its home cage.

The second day was the same as the first except that those subjects that had received alcohol on the first day received saline on the second and vice versa, and all testing was done in environment B by experimenter B. Each subject received a total of 10 treatment injections, 5 alcohol injections in the alcohol-predictive environment and 5 saline injections in the saline-predictive environment administered on alternate days.

Alcohol Test

On the alcohol test day, each subject received alcohol in one of the two test environments. Those subjects receiving alcohol in the alcohol-predictive environment comprised the Same Group, whereas those receiving alcohol in their saline-predictive environment comprised the Different Group. Subjects were divided into the two groups prior to testing in such a way that the mean forelimb clonus durations of the two groups on the fifth alcohol treatment session were approximately the same and half of the subjects in each group received their alcohol test injection in each of the two test environments.

Saline Test

Only those subjects that had received their alcohol test injections in the alcohol-predictive environment participated in a saline test administered 48 hr later. These subjects were injected with saline in the alcohol-predictive environment (environment A for half the rats and B for the others) 1 hr prior to stimulation.

RESULTS

The results of Experiment 1 confirm previous reports that tolerance develops rapidly to alcohol's anticonvulsive effect on kindled seizures. The mean duration of forelimb clonus elicited in the 43 subjects completing the treatment phase of the experiment increased markedly from 3.09 sec on the first alcohol trial to 14.40 sec by the fifth, $t(43)=5$, $p<0.002$.

Because the purpose of the present study was to identify factors that influenced the development of this tolerance, only those subjects that displayed some evidence of tolerance were included in the test phases of the experiment—the 10 subjects whose mean clonus durations on the last three alcohol trials of the treatment phase were not greater than on the first were not tested. Thus, participating in the testing were 33 subjects, 17 in the Different Group and 16 in the Same Group. The data of these subjects are presented in Fig. 1, which illustrates the major findings of this study.

Baseline

It is clear from Fig. 1 that stable baselines were achieved by the end of the baseline period and that the groups did not differ significantly over this period (all Mann-Whitney p's>0.10).

Treatment

During the treatment phase of the experiment, all subjects received 10 stimulations, five following saline injections and five following alcohol injections on alternate days. A comparison of the duration of the forelimb clonus elicited on the five saline trials with the clonus durations of the baseline phase (see Fig. 1) established that the addition of a saline injection 60 min before the convulsive treatment had no significant effect on its duration. The duration of the clonus elicited on the last baseline day did not differ significantly (all Wilcoxon p's>0.10) from the duration of the clonus elicited on any of the 5 saline treatment days in either the Different Group or the Same Group. Moreover, there was no significant shift in the baselines of either group over the 5 saline trials, and the two groups did not differ significantly on any of these 5 days (all Mann-Whitney p's>0.10).

The performance of the subjects on the five alcohol treatment trials is noteworthy in two respects. The first is that there was a substantial decrease in the anticonvulsive effect of alcohol over the five trials in both the Same, $t(16)=0$, $p<0.002$, and Different, $t(16)=0$, $p<0.002$, groups. The second is that the groups did not differ significantly on any of the five trials (all Mann-Whitney p's>0.10).

Alcohol Test

It is clear in Fig. 1 that the subjects in both groups were tolerant to alcohol on the alcohol test day; the alcohol test injection produced substantially more forelimb clonus in both the Different Group, $t(17)=5$, $p<0.004$. and the Same Group, $t(16)=0$, $p<0.002$, subjects than did the first alcohol injection. However, it is equally clear in Fig. 1 that the injection environment had no effect whatsoever on the duration of forelimb clonus, $U(16,17)=133$, $p>0.10$.

Saline Test

Injection of saline in the alcohol-predictive environment on the saline test day did not elicit the increase in forelimb clonus duration predicted by Siegel's theory; the seizures elicited in the subjects of the Same Group on the saline test were not longer than those elicited following saline injections in the saline-predictive environment during the treatment phase of the experiment. In fact, there was a small but insignificant decline in duration on the saline test day.

Histology and Blood Alcohol

With the exception of two placements in the claustrum, one in the Same group and one in the Different group, all electrode tips were situated in the amygdaloid complex. The mean levels of alcohol found in the blood of the Same Group (2.9 g/l) and Different Groups (2.4 g/l) 5 min after the alcohol-test stimulation subjects did not differ significantly, $U(16,17)=135$, $p>0.10$.

EXPERIMENT 2

The purpose of Experiment 2 was to determine whether CS pre-exposure, a treatment that has a major effect on Pavlovian conditioning, would influence the development of tolerance to alcohol's anticonvulsant effects. Would repeated exposure to the alcohol-predictive cues without the alcohol retard subsequent development of tolerance to alcohol's anticonvulsant effects?

METHOD

Of the 30 subjects that started this experiment, 1 subject was eliminated after the baseline phase due to a malfunctioning electrode and 4 subjects died. Accordingly, 25 rats completed the experiment.

After the six bidaily baseline stimulations, subjects were assigned to one of two groups, which were pre-exposed to the alcohol-related environment (Pre-exposure Group, n=13) or to a control environment (Control Group, n=12) prior to each of the succeeding five stimulations. The pre-exposure subjects were injected and stimulated by Experimenter A in environment A using the saline administration and stimulation procedure described in Experiment 1. The control subjects were also injected with saline and stimulated during the pre-exposure phase but by Experimenter B in Environment B.

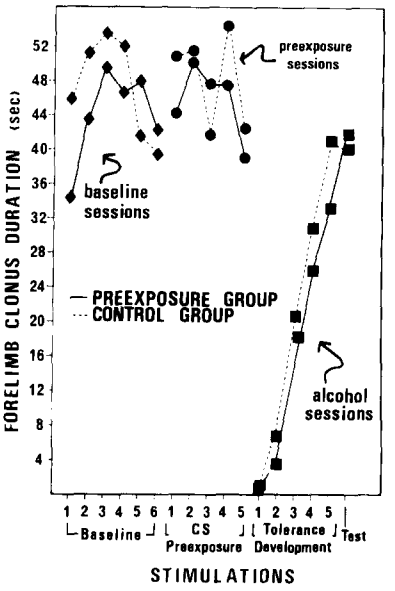

FIG. 2. The development of tolerance to the anticonvulsant effect of alcohol following pre-exposure to the alcohol-predictive environment. In the pre-exposure phase, subjects in the Pre-exposure Group received saline 1 hr prior to amygdaloid stimulation in the environment in which they would subsequently receive alcohol while Control Group subjects received saline in a distinctive environment. In the tolerance-development phase, all subjects received alcohol and stimulation in the environment to which the Pre-exposure subjects had previously been exposed.

After the five pre-exposure or control trials, all subjects were injected intraperitoneally with ethanol in Environment A, 1 hr prior to each of the six subsequent stimulations.

RESULTS

Pre-exposure to the cues that would subsequently be associated with alcohol administration did not attenuate the rate of tolerance development. The mean level of seizure activity exhibited by the Pre-exposure and Control Group subjects during the baseline, pre-exposure, tolerance development, and test phases of the experiment is shown in Fig. 2. Clearly, the two groups did not differ significantly at any stage of the experiment.

The tips of all electrodes were found to be situated in the amygdaloid complex. The mean levels of blood ethanol found in the pre-exposure (3.1 g/l) and control (2.9 g/l) subjects did not differ significantly, $U(13,12)=131$, $p>0.10$.

GENERAL DISCUSSION

Both Experiments confirmed the finding of Pinel *et al.* [15,16] that tolerance to alcohol's anticonvulsant effect develops rapidly when convulsive stimulation is administered during the periods of alcohol intoxication; however, neither experiment provided any evidence of the involvement of Pavlovian conditioning in the development of tolerance to alcohol's anticonvulsive effect. In Experiment 1, tolerant subjects tested in a saline-predictive environment were found to be just as tolerant to the anticonvulsive effect of alcohol as those tested in an alcohol-predictive environment, and saline administered to tolerant subjects in the alcohol-predictive environment did not elicit a conditioned compen-

satory increase in seizure activity. In Experiment 2, the pre-exposure of the subjects to the environment in which they subsequently received alcohol did not affect the ensuing development of tolerance to the anticonvulsive effect of alcohol.

The fact that tolerance to alcohol's anticonvulsive effect is not amenable to Pavlovian conditioning has two major implications. First, it shows quite clearly that Pavlovian conditioning cannot account for all manifestations of drug tolerance. Thus, although there is considerable evidence that Pavlovian factors play an important, if not critical, role in the development of some types of drug tolerance, it is clear that tolerance can, in some situations, develop in the absence of such influences [5,23]. Second, the present finding brings into question the Pavlovian interpretation of contingent tolerance. The fact that alcohol's anticonvulsant effects have been shown to be contingent on the administration of convulsive stimulation during the periods of alcohol exposure [15,16] even though such tolerance is not amenable to Pavlovian conditioning, suggests that contingent tolerance is not a product of Pavlovian influences.

Two types of behavioral manipulations have been shown to influence the development of drug tolerance: manipulations of the environmental stimuli that are predictive of drug effects and manipulations of the responses that occur during drug exposure. There appear to be two important reasons why the experimental investigation of the former factor has taken precedence over the study of the latter. First, in most instances it is easier to manipulate the environment in which a drug is administered than to control the responses of subjects during intoxication. Second, study of the effects of drug-associated environmental cues on tolerance has been greatly facilitated by the existence of a useful theoretical framework, i.e., the Pavlovian theory of tolerance. Be that as it may, it is quite clear that, at least in the case of tolerance to alcohol's anticonvulsant effect, the manipulation of drug-associated cues has much less effect on the development of tolerance than does the manipulation of the responses of subjects during intoxication. If, as in the present study, rats receive convulsive stimulation following each alcohol injection, they display substantial tolerance after only five trials (see Fig. 2), if they do not receive such stimulation during intoxication, no tolerance at all develops (e.g., [16]). On the other hand, in the present studies manipulation of the environmental stimuli associated with alcohol administration had no discernible effect on the development of tolerance to alcohol's anticonvulsant effect.

There has been only one other systematic attempt to compare the effects of Pavlovian manipulations and response contingency on drug tolerance, the recent series of studies of tolerance to amphetamine-induced anorexia by Poulos, Wilkinson and Cappell [17]. Surprisingly, although there is no obvious similarity between amphetamine-induced anorexia and the anticonvulsant actions of alcohol, the conclusions reached by Poulos *et al.* on the basis of these studies vary little from our own. Although Poulos *et al.* found tolerance to amphetamine-induced anorexia to be both contingent on previous experience with food in the drugged state and subject to Pavlovian control, they concluded that these were separate processes. Moreover, they argued that the effects of response contingency were pre-eminent, that is, that the interaction with food was necessary for the development of tolerance to the anorectic effects, but that once this essential condition was met, Pavlovian variables could influence the development of tolerance. The fact that tolerance to the anticonvulsant effects of alcohol, which had been shown to be contingent on the occurrence of convulsive stimulation, was uninfluenced by Pavlovian manipulations in the present studies confirms both the independence and pre-eminence of response contingency in relation to Pavlovian effects in the development of drug tolerance.

In view of the fact that manipulations of the environmental stimuli predictive of alcohol did not influence the levels of tolerance achieved by the subjects in the present experiments, it is not surprising that such manipulations did not influence the levels of ethanol found in tail blood sampled following the test trial. Because no blood samples were taken before the regimen of alcohol injections, these measures have no bearing on the question of whether changes in the metabolism of alcohol underlie the development of tolerance to its anticonvulsant effect. However, a previous report suggests that such is not the case. Pinel *et al.* [15] found that tolerance to the anticonvulsant effects developed in the absence of a significant decline in the levels of blood ethanol from the first to last tests in their series.

In many instances in which the major finding is a negative one, the sensitivity of the dependent measure warrants careful consideration; however, this is not such an instance. If Pavlovian effects were the basis for the contingent tolerance that develops to the inhibitory effects of alcohol on forelimb clonus duration, then Pavlovian manipulations should systematically influence this same measure. Clearly, they did not. There was no indication whatsoever of the *decreases* in forelimb clonus duration that should have resulted from pre-exposing subjects to the injection environment or from changing the environment once tolerance had developed, or of the *increases* that should have resulted from placebo injections administered to tolerant subjects in the alcohol-predictive environment. This is not to say that we did not record other measures of motor seizure severity; we routinely monitor motor seizure latency and class [14]. However, because these measures have proven to be less sensitive than the forelimb clonus duration measure and highly correlated to it, they did not warrant extensive discussion in the present context. Suffice it to say, that the effects of response contingency on the development of tolerance to alcohol's anticonvulsant effect has invariably been reflected in all three of these measures of motor seizure severity, whereas Pavlovian manipulations have affected none of them.

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