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Bidirectional Contingent Cross Tolerance Between the Anticonvulsant Effects of Pentobarbital and Ethanol[1]

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KIM, C. K., J. P. J. PINEL AND N. R. ROESE. *Bidirectional contingent cross tolerance between the anticonvulsant effects of pentobarbital and ethanol.* PHARMACOL BIOCHEM BEHAV **41**(1) 127–132, 1992.—In Experiment 1, two groups of kindled rats received a pentobarbital injection (15 mg/kg, IP) and a convulsive amygdala stimulation once every 48 h. In one group, pentobarbital was injected 1 h before each stimulation; in the other, it was injected 1 h after each stimulation. Only the rats that received pentobarbital before each stimulation became tolerant to pentobarbital's anticonvulsant effect. Cross tolerance to the anticonvulsant effect of ethanol (1.5 g/kg, IP) was also found to be greater in the pentobarbital-before-stimulation rats. Experiment 2 was designed to assess the transfer of tolerance in the opposite direction, that is, from ethanol to pentobarbital, and the results mirrored those of Experiment 1: convulsive stimulation during the periods of ethanol exposure facilitated the development of tolerance to the anticonvulsant effect of ethanol and its transfer to pentobarbital. These results support the theory that functional drug tolerance and cross tolerance are adaptations to the effects of drugs on concurrent patterns of neural activity rather than to drug exposure per se.

Ethanol Alcohol Pentobarbital Tolerance Contingent tolerance Cross tolerance Anticonvulsant Kindling Seizure Convulsion Rat Amygdala Behavioral tolerance

IN 1971, Carlton and Wolgin (3) reported that rats did not become tolerant to the anorexigenic effect of amphetamine unless they were given the opportunity to eat while drugged. This same pattern of results has been observed many times in many different contexts [see (6, 9, 34) for reviews]: (a) Running a maze or a treadmill while under the influence of ethanol has been shown to facilitate the development of tolerance to ethanol's disruptive effects on maze and treadmill running, respectively [e.g., (4, 15, 33)]. (b) Electrical stimulation during ethanol exposure has been shown to facilitate the development of tolerance to ethanol's acceleration of the decay of posttetanic potentiation in the *Aplysia* abdominal ganglion (31). (c) Eating under the influence of amphetamine [e.g., (7)], cocaine [e.g., (35)], or quipazine [e.g., (28)] has been shown to facilitate the development of tolerance to their anorexigenic effects. (d) Receiving convulsive stimulation while under the influence of carbamazepine, diazepam, sodium valproate (17), pentobarbital (21), or ethanol [e.g., (20)] has been shown to facilitate the development of tolerance to their anticonvulsant effects. These and other examples of drug tolerance whose development is enhanced by the occurrence of particular patterns of activity during the periods of drug exposure are commonly referred to as *contingent drug tolerance*, the term originally coined by Carlton and Wolgin (3).

The many and varied demonstrations of contingent drug tolerance support the view that functional tolerance is a reaction to drug effects rather than to drug exposure per se. In contingent tolerance experiments, different groups of subjects receive the same drug exposure, but only those that are given an opportunity to perform the test response under the influence of the drug become tolerant. Pinel, Mana and Kim (22) have argued that the performance of the test response while drugged is critical for the development of functional tolerance, because it is the repeated experience of the drug's effect on the test response that is critical for the development of tolerance to that effect. It is this drug-effect perspective of functional tolerance that motivated the conduct of the present experiments.

The purpose of the present experiments was to assess the role of drug effects in the transfer of tolerance between drugs. Using an extension of Chen's before-and-after experimental design [e.g., (4)] and the kindled convulsion [e.g., (8)] model of contingent tolerance to anticonvulsant drug effects [e.g., (17)], Experiment 1 assessed the degree to which experiencing the anticonvulsant effect of pentobarbital facilities the transfer of tolerance to the anticonvulsant effect of ethanol; Experiment 2 assessed the degree to which experiencing the anticonvulsant effect of ethanol facilitates the transfer of tolerance to the anticonvulsant effect of pentobarbital. Ethanol and pentobarbital were the drugs of choice because cross tolerance had been demonstrated between many of their effects (11), because previous efforts to demonstrate contingent cross tolerance had focused on

[1]All animal husbandry, surgical procedures, testing protocols, and euthanasia conformed to the guidelines of the Canadian Council for Animal Care.

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them (5, 13, 21), and because tolerance had been demonstrated to their anticonvulsant effects (21,22).

GENERAL METHOD

Subjects

The subjects in the two experiments were adult male, 350 to 500 g, hooded Long-Evans rats obtained from Charles River, Canada. Each rat was individually housed in a standard stainless steel hanging cage, with continuous access to Purina rat chow and water. All experimental manipulations occurred during the light phase of the 12:12-h light:dark cycle at approximately the same time of the day (lights on at 8:00 a.m.).

Surgery

Following the administration of sodium pentobarbital (65 mg/kg, IP) and atropine sulphate (0.04 mg, IP), a single bipolar electrode (Plastic Products Company, MS-303-2) was stereotaxically directed at the left basolateral amygdala of each rat: 1.2 mm posterior, 5.0 mm to the left, and 10 mm ventral to the skull surface at bregma, with the incisor bar set at +5.0 mm [coordinates from (19)]. The electrode assembly was secured to the skull with stainless steel screws and dental acrylic, and tetracycline was sprinkled over the incision before suturing.

Kindling Phase

After at least 5 days of postsurgical recovery, each of the rats was stimulated (400 μA, 60 Hz, 1 s) three times per day, 5 days a week for 3 weeks, with at least 2 h separating consecutive stimulations. At first, the stimulations produced no behavioral response other than a momentary cessation of ongoing activity, but by the end of this regimen of 45 kindling stimulations, each stimulation produced a stereotypical generalized-clonic convulsion [see (25,27)]. The measure of convulsion severity was the duration of the forelimb clonus elicited by each stimulation. This measure is positively correlated with other measures of kindled convulsion severity (e.g., convulsion class), and it has been shown to respond systematically and reliably to a variety of pharmacological manipulations [e.g., (12, 16, 20)]. Electrographic activity was not monitored.

No-Drug Baseline Phase

The no-drug baseline phase of both experiments began 48 h after the last stimulation of the kindling phase; it comprised four stimulations, which were delivered one every 48 h (±2 h). This schedule of bidaily stimulations, once initiated, was maintained for the duration of each experiment. The isotonic saline vehicle (7.5 ml/kg volume, IP) was injected 1 h prior to the fourth and last no-drug baseline stimulation; this was the no-drug baseline test. Any rats that did not display at least 20 s of forelimb clonus on the no-drug baseline test were not studied further.

Drug Baseline Test

Forty-eight h after the no-drug baseline test, each rat received the drug baseline test. In Experiment 1, each rat received an IP injection of pentobarbital (15 mg/kg in isotonic saline; in a sodium salt form; BDH Chemicals), and in Experiment 2, each rat received an IP injection of ethanol (1.5 g/kg in a 25% v/v solution in isotonic saline); all injections were delivered in a volume of 7.5 ml/kg. Then, 1 h later, each rat received a convulsive stimulation so that the initial ability of pentobarbital and ethanol to block kindled convulsions could be assessed; rats that displayed more than 20 s of forelimb clonus on the drug baseline test were not studied further. The particular doses of pentobarbital and ethanol that were employed in the present experiments were chosen because the results of previous studies [e.g., (1, 2, 21)] suggested that in most rats they were initially just sufficient to produce a complete suppression of forelimb clonus.

Tolerance-Development Phase

Prior to the tolerance-development phase, the subjects in each experiment were divided into two similar groups in such a way that the mean duration of their forelimb clonus on the no-drug and drug baseline tests and their mean body weights were approximately equal. The tolerance-development phase of both experiments began 48 h following the drug baseline test; it comprised 10 bidaily stimulations and 10 bidaily injections of the drug that was delivered on the drug baseline test (pentobarbital in Experiment 1; ethanol in Experiment 2). On each tolerance-development trial, the rats in one group (drug-before-stimulation group) received the drug 1 h before the convulsive stimulation, and the rats in the other group (drug-after-stimulation group) received the drug 1 h after the stimulation.

Drug Tolerance Test

The drug tolerance test occurred 48 h after the last tolerance-development trial. Every rat received the drug that it had received previously (pentobarbital in Experiment 1; ethanol in Experiment 2) 1 h before the scheduled convulsive stimulation, so that the development of tolerance to the anticonvulsant effect of the drug could be compared in the drug-before-stimulation and the drug-after-stimulation groups.

Cross-Tolerance Phase

The cross-tolerance phase began 48 h after the drug tolerance test. During the cross-tolerance phase, the rats received ethanol if they had received pentobarbital during the tolerance-development phase (Experiment 1) or pentobarbital if they had previously received ethanol (Experiment 2). Each injection was administered to every subject 1 h before each of 10 bidaily convulsive stimulations. Cross tolerance was assessed in two ways: (a) by the inability of the first injection of the second drug to suppress forelimb clonus, and (b) by the rate at which the subjects achieved an a priori criterion of tolerance to the second drug; this criterion of tolerance was the number of trials that it took for a rat to display forelimb clonus on two consecutive trials that was at least 50% as long as that displayed on the no-drug baseline test.

Histology

At the conclusion of each experiment, all subjects were killed with CO_2 and perfused intracardially with 4% formalin. Their brains were removed, preserved in formalin, frozen, sliced along the coronal plane, mounted on slides, and then stained with cresyl violet. Each of the electrodes terminated in the left amygdala or at its boundary.

Statistical Analysis

The statistical significance of the results was evaluated with Wilcoxon-Mann-Whitney tests (29) for between-group comparisons and Sign tests (29) for within-subject comparisons; the sig-

nificance level was $p<0.05$, one-tailed. Nonparametric analyses were employed because the total lack of variability in some conditions precluded parametric analysis. The data of only those rats that completed the experiment were included in the statistical analysis.

EXPERIMENT 1

The purpose of Experiment 1 was to demonstrate that both the development of tolerance to the anticonvulsant effect of bidaily injections of pentobarbital and the transfer of this tolerance to the anticonvulsant effect of ethanol are contingent upon the convulsive stimulation being delivered during the periods of pentobarbital exposure.

METHOD

Electrodes were implanted in 30 rats; however, three did not meet the criterion on the no-drug baseline test, one did not meet the criterion on the drug baseline test, and one became ill before the completion of the experiment. Accordingly, 25 rats completed the Experiment, 13 in the pentobarbital-before-stimulation group and 12 in the pentobarbital-after-stimulation group.

RESULTS

The results of Experiment 1 are illustrated in Fig. 1. Prior to the tolerance-development phase, the two groups did not differ in their responsiveness to the convulsive stimulation on the no-drug baseline test or to the anticonvulsant effect of pentobarbital on the drug baseline test; they were originally assigned to groups on the basis of these scores. However, after the tolerance-development phase, the pentobarbital-before-stimulation rats were substantially more tolerant to pentobarbital and more cross tolerant to ethanol than were the pentobarbital-after-stimulation rats.

The statistical significance of the results was established by both within-subject and between-group tests. The subjects in the pentobarbital-before-stimulation group ($p<0.001$), but not those in the pentobarbital-after-stimulation group ($p>0.05$), displayed a significant increase in forelimb clonus duration from the drug baseline test to the drug tolerance test. Accordingly, on the drug tolerance test, the forelimb clonus of the pentobarbital-before-stimulation rats was significantly longer than that of the pentobarbital-after-stimulation rats ($p<0.001$). During the cross-tolerance phase of the experiment, the pentobarbital-before-stimulation rats displayed significantly longer forelimb clonus after the first ethanol injection than did the pentobarbital-after-stimulation rats ($p<0.025$), and they also achieved the criterion of cross tolerance more rapidly (mean = 2.7 versus mean = 6.2 ethanol injections; $p<0.001$). Two of the rats in the pentobarbital-after-stimulation group did not reach the criterion of ethanol tolerance during the 10 cross-tolerance trials, thus they were assigned a score of 10 for the purpose of calculating the group means. The two groups did not differ significantly in their reactions to the final ethanol injection ($p>0.05$).

EXPERIMENT 2

Experiment 2 was the converse of Experiment 1; its purpose was to demonstrate the transfer of contingent tolerance to anticonvulsant drug effects from ethanol to pentobarbital.

METHOD

Electrodes were implanted in 30 rats, but one rat failed to meet the criterion on the no-drug baseline test and another became ill before the completion of the experiment. Accordingly, 28 rats completed the experiment, 14 in the ethanol-before-stimulation group and 14 in the ethanol-after-stimulation group.

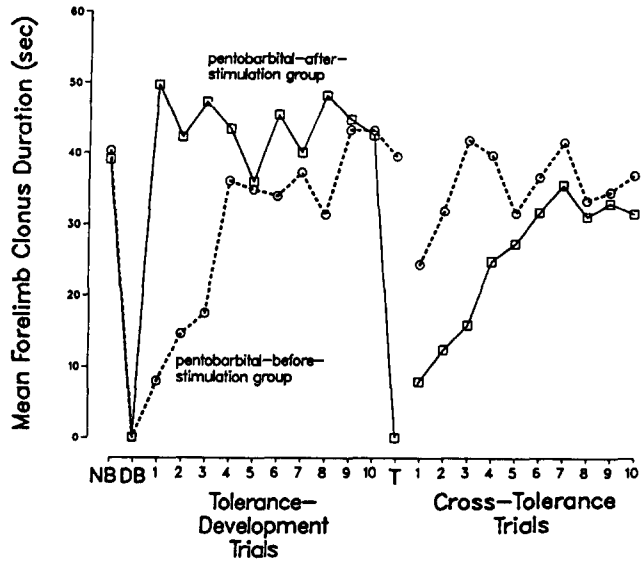

FIG. 1. Contingent tolerance to the anticonvulsant effect of pentobarbital (15 mg/kg) and its transfer to the anticonvulsant effect of ethanol (1.5 g/kg) on kindled convulsions elicited by amygdala stimulation in rats. During the tolerance-development phase, 10 bidaily (one every 48 h) pentobarbital injections were administered either 1 h before (pentobarbital-before-stimulation group) or 1 h after (pentobarbital-after-stimulation group) a convulsive stimulation; only those rats that received pentobarbital before the stimulations displayed tolerance to pentobarbital's anticonvulsant effect. During the subsequent cross-tolerance phase of the experiment, greater cross-tolerance to ethanol's anticonvulsant effect was found in the pentobarbital-before-stimulation rats. NB: no-drug baseline; DB: drug baseline test; T: drug tolerance test.

RESULTS

The results of Experiment 2 are illustrated in Fig. 2. Prior to the tolerance-development phase, the two groups did not differ in their responsiveness to the convulsive stimulation on the no-drug baseline test or to the anticonvulsant effect of the ethanol on the drug baseline test. However, after the tolerance-development phase, the ethanol-before-stimulation rats were more tolerant to ethanol and more cross tolerant to pentobarbital than were the ethanol-after-stimulation rats.

As in Experiment 1, the statistical significance of these results was confirmed by both within-subject and between-group tests. The subjects in the ethanol-before-stimulation group ($p<0.001$), but not those in the ethanol-after-stimulation group ($p>0.05$), displayed a statistically significant increase in forelimb clonus duration from the drug baseline test to the drug tolerance test. Accordingly, on the drug tolerance test, the forelimb clonus of the ethanol-before-stimulation rats was significantly longer than that of the ethanol-after-stimulation rats ($p<0.001$). During the cross-tolerance phase of the experiment, the ethanol-before-stimulation rats achieved the criterion of cross tolerance significantly more rapidly than did the ethanol-after-stimulation rats (mean = 4.6 versus mean = 7.7 pentobarbital injections; $p<0.005$). Three rats in the ethanol-after-stimulation group did not achieve the criterion of pentobarbital tolerance during the 10 cross-tolerance trials and were assigned a score of 10 for the

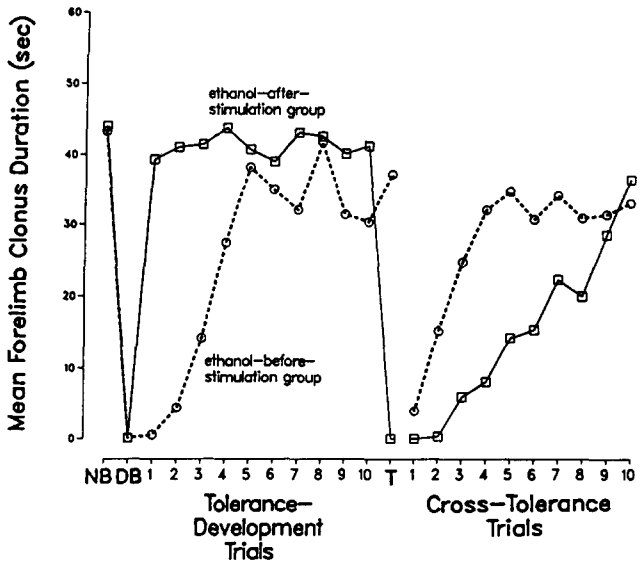

FIG. 2. Contingent tolerance to the anticonvulsant effect of ethanol (1.5 g/kg) and the contingent transfer of tolerance to the anticonvulsant effect of pentobarbital (15 mg/kg) on kindled convulsions elicited in rats by amygdala stimulations. During the tolerance-development phase, 10 bi-daily (one every 48 h) ethanol injections were administered either 1 h before (ethanol-before-stimulation group) or 1 h after (ethanol-after-stimulation group) a convulsive stimulation; only those rats that received ethanol before the stimulations displayed tolerance to ethanol's anticonvulsant effect. Similarly, during the subsequent cross-tolerance phase, greater cross-tolerance to pentobarbital's anticonvulsant effect was found in the ethanol-before-stimulation rats. NB: no-drug baseline; DB: drug baseline test; T: drug tolerance test.

purpose of calculating the mean. Unlike the results of Experiment 1, the difference between the duration of forelimb clonus displayed by the two groups was not significantly different on the first cross-tolerance trial ($p>0.05$). On the final trial of the cross-tolerance phase, the two groups did not differ significantly in their duration of forelimb clonus ($p>0.05$).

GENERAL DISCUSSION

The results of the present experiments make four points about drug tolerance. First, they confirm previous reports that tolerance develops to the anticonvulsant effects of pentobarbital (21) and ethanol [e.g., (20,23)] on kindled convulsions. Second, they confirm previous reports of cross tolerance between many of the effects of pentobarbital and ethanol (11), including their anticonvulsant effects (21). Third, they confirm previous reports that tolerance to the anticonvulsant effects of pentobarbital (21) and ethanol (20,23) are facilitated by the administration of the convulsive stimulation during the periods of drug exposure. Fourth, they provide the most systematic evidence of the facilitatory role of drug effects in the transfer of tolerance from one drug to another. The present experiments thus support the theory that functional drug tolerance and functional cross-tolerance are adaptive reactions of the nervous system to the effects of drugs on concurrent patterns of neural activity, rather than to mere drug exposure. They suggest that the development of tolerance to anticonvulsant drug effects on kindled convulsions is caused by the repeated disruption by the drug of the patterns of epileptic neural activity that are elicited by the stimulation, and they suggest that functional drug tolerance transfers beteen drugs that disrupt concomitant neural activity in similar ways.

Previous attempts to demonstrate contingent cross-tolerance have been less systematic, and thus less convincing, than the present experiments. Pinel et al. (21) demonstrated greater transfer of tolerance to anticonvulsant drug effects from pentobarbital to ethanol in rats that had received convulsive stimulations in the drugged state, but at only one of two doses and only in rats that had been exposed to pentobarbital in a prior experiment. Commissaris and Rech (5) found that tolerance to the disruptive effect of pentobarbital on rotorod performance developed only in rats that practiced the task while under the influence of pentobarbital, but such practice was not found to significantly facilitate the transfer of tolerance to the disruptive effect of ethanol on rotorod performance. However, in another condition they found the opposite; practice on the rotorod under the influence of pentobarbital did not facilitate the development of tolerance to pentobarbital's effect on the task, but it did facilitate its transfer to the disruptive effect of ethanol. Lê et al. (13) showed that practice on the moving belt test under the influence of ethanol facilitated the transfer of tolerance to the disruptive effect of pentobarbital on the task; however, it did not facilitate the development of tolerance to ethanol in the same rats. Streather and Hinson (30) demonstrated greater transfer of tolerance to anorexigenic effects from amphetamine to apomorphine in rats allowed to eat in the drugged state, but only at one of two doses; furthermore, eating under the influence of amphetamine did not facilitate the transfer of anorexigenic tolerance to fenfluramine. Woolverton et al. (35) found that eating under the influence of cocaine facilitated the transfer of tolerance to the anorexigenic effect of amphetamine in rats. Jørgenson, Fasmer and Hole (10) demonstrated greater transfer of tolerance to the inhibitory effect on the tail-flick reflex in spinally transected rats from ethanol to clonidine in rats repeatedly tested under the influence of ethanol.

The apparent lack of significant transfer of tolerance from ethanol to pentobarbital on the first cross-tolerance trial in Experiment 2 warrants comment. We believe that this result is a consequence of a floor effect, of the fact that the test dose of pentobarbital was too high to be sensitive to the difference in the sensitivity of the two groups to the anticonvulsant effect of pentobarbital that existed on the first test trial. Accordingly, a significant difference did not manifest itself until the third test trial, when the level of tolerance had increased in both groups. This interpretation makes three important methodological points: that it is critical to select a sensitive test dose in the study of tolerance, that it is difficult to compare the development of tolerance and cross-tolerance in different drugs, and that it is advantageous to employ a multiple trial savings method of assessing cross-tolerance, as opposed to a single test trial.

Five lines of evidence suggest that contingent tolerance and contingent cross-tolerance to anticonvulsant drug effects reflect functional, rather than dispositional, changes. First, contingent tolerance to the anticonvulsant effect of ethanol has been observed in the absence of significant changes in blood ethanol levels (20). Second, the periodic schedules of drug administration that have been used to induce contingent tolerance [e.g., one injection every 2 or 4 days; (24)] are not optimal for the induction of dispositional changes [see (14)]. Third, contingent tolerance to anticonvulsant effects does not dissipate over a 2-week drug free period unless the subjects receive convulsive stimulation during the interval [(18); see (32)]. Fourth, contingent tolerance to anticonvulsant drug effects dissipates in subjects that are maintained on the very same schedule of drug injections that induced the tolerance if convulsive stimulations are administered during the intervening drug free periods (18). Fifth, contingent tolerance has been demonstrated to a wide variety of anticonvulsant drugs, which differ markedly in their

metabolic properties [e.g., (12, 16, 32)]. Although it is impossible to totally rule out the possibility that contingent tolerance to anticonvulsant drug effects is dispositional, the evidence strongly supports a functional interpretation.

Most studies of drug tolerance are based on the implicit assumption that drug exposure is both the necessary and sufficient condition for the development of functional drug tolerance. In contrast, the drug-effect theory (22) views drug exposure as necessary but not sufficient; tolerance is assumed to develop only to those effects of a drug that are repeatedly experienced. In this sense, functional drug tolerance to the behavioral effects of drugs can be viewed as akin to sensorimotor adaptation. For example, consider the relation between contingent drug tolerance and the adaptation that occurs to the disruptive effects of laterally displacing prisms on visual-motor coordination [see (26)]. The adaptation to the effects of laterally displacing prisms on visual-motor coordination does not result from mere exposure to the prisms; subjects who wear the prisms but engage in no visual-motor activity while they are wearing them do not adapt to their effects. Adaptation to the effects of the prisms on visual-motor activity occurs only if the subject engages in visual-motor activity while wearing the prisms and thus experiences their disruptive effects on visual-motor activity. We believe that the recognition that functional drug tolerance is akin to sensorimotor adaptation can be a source of interesting hypotheses about the nature of functional drug tolerance, its causes, and the neural changes that underlie it. It suggests that the patterns of neural activity that occur during drug exposure play an important role in the development of functional tolerance to drug effects and in their transfer to other drugs.

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