Pharmacology Biochemistry and Behavior, Vol. 61, No. 1, pp. 143–148, 1998

0091-3057/98 $19.00 + .00

ELSEVIER

PII S0091-3057(98)00081-1

Noncontingent Drug Exposure Facilitates the Development of Contingent Tolerance to the Anticonvulsant Effects of Ethanol and Diazepam in Kindled Rats

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Received 25 April 1997; Revised 24 October 1997; Accepted 24 March 1998

KIPPIN, T. E., J. P. J. PINEL, T. J. KORNECOOK AND L. E. KALYNCHUK. *Noncontingent drug exposure facilitates the development of contingent tolerance to the anticonvulsant effects of ethanol and diazepam in kindled rats.* PHARMACOL BIOCHEM BEHAV **61**(1) 143–148, 1998—Tolerance to anticonvulsant drug effects on kindled convulsions can result from drug exposure alone, but convulsive activity during drug exposure has a substantial facilitatory effect on tolerance development. Tolerance produced by drug exposure in the absence of a criterion response (in this case convulsions) has been termed pharmacologic tolerance (10); tolerance produced by drug exposure with concomitant performance of the criterion response has been termed contigent tolerance (1). The present study examines whether noncontingent drug exposure facilitates the development of contingent tolerance to the anticonvulsant effects of ethanol and diazepam. Amygdala-kindled, Long–Evans rats were treated with either ethanol (5.0 g/kg once daily for 21 days) or diazepam (5.0 mg/kg three times daily for 10 days) in the absence of convulsive stimulation to produce pharmacologic tolerance—control rats received treatments of vehicle. Then, all of the rats were rendered contingently tolerant by a series of "bidaily" (once every 2 days) injections (ethanol 2.0 g/kg or diazepam 2.0 mg/kg), each 1 h prior to a kindled convulsion. The rats that had received noncontingent exposure to ethanol or diazepam developed contingent tolerance significantly faster than the control rats. These results suggest that the mechanisms underlying pharmacologic and contingent tolerance to anticonvulsant drug effects are additive. © 1998 Elsevier Science Inc.

Alcohol, Ethyl Diazepam Anticonvulsants Drug Tolerance Convulsions Kindling (neurology) Rats Amygdaloid body

DRUG tolerance is a reduction in the initial efficacy of a drug as a result of exposure to that drug. Himmelsbach (3) proposed that such changes represent a physiologic adaptation to the presence of the drug; however, the presence or absence of the drug is not the only factor important to the development of drug tolerance. The behavior of the drug recipient during drug exposure plays a major role in the development of tolerance. Specifically, it has been repeatedly shown that the performance of a response during drug exposure greatly facilitates the development of tolerance to the effect of the drug on that particular response—tolerance that is contingent on the performance of the criterion response during drug exposure is commonly referred to as contingent drug tolerance (1).

Contingent tolerance is typically demonstrated using the before-and-after experimental design (2). In such experiments, subjects in one group, the drug-before-test group, receive the drug before performing the criterion response and, therefore, experience the effect of the drug on the performance of the criterion response. Subjects in a second group, the drug-after-test group, receive the drug after performing the criterion response and, therefore, do not experience the effect of the drug on the performance of the criterion response. Because both

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groups receive equal drug exposure and equal experience with the criterion response, any differences in the level of tolerance between them must be due to an interaction between these two factors. It has been repeatedly reported that subjects that experience the drug effect (i.e., the drug-before-test condition) display substantially higher levels of tolerance than subjects who do not experience the drug effect (i.e., the drug-after-test condition).

Response contingencies have been shown to be important in the development and maintenance of tolerance to numerous drug effects. For example, the development of contingent tolerance has been demonstrated to the anticonvulsant effects of ethanol (21,24), diazepam, carbamazepine, and valproic acid (16,33); to the anorexigenic effects of amphetamine (1), cocaine (38), and quipazine (29); and to the analgesic effects of morphine (9). In each of these demonstrations, significantly more tolerance developed in those subjects that experienced the effect of the drug on the criterion response than in those subjects that received the same drug exposure without the concomitant performance of the criterion response. Performance of the criterion response also plays a critical role in the dissipation of contingent tolerance. Specifically, contingent tolerance was found to dissipate only when the criterion response was performed in the absence of the drug; mere cessation of drug administration was not sufficient to trigger the dissipation of contingent tolerance. This finding has been reported with contingent tolerance to the anticonvulsant effects of ethanol (17), diazepam (8,18), and carbamazepine (34), to the anorexic effect of amphetamine (28), and to the adipsic effect of scopolamine (27). An extensive review of contingent tolerance has been provided by Wolgin (37).

Although tolerance development is greatly facilitated by the performance of the criterion response under the influence of the drug, modest levels of tolerance can develop in response to drug exposure alone (i.e., in the absence of the performance of the criterion response); such tolerance has been termed pharmacologic drug tolerance (4). For example, Mana, Pinel, and Lê (19) and Mana and Pinel (18) found that chronic exposure to high doses of ethanol and diazepam, respectively, in the absence of convulsive activity induced modest, but significant, levels of tolerance to the anticonvulsant effect of these drugs in kindled rats. However, substantially greater amounts of drug were required to produce tolerance under these conditions than when subjects received convulsive stimulations during drug exposure.

Previous studies by LeBlanc, Gibbins, and Kalant (12,14) and Wenger and colleagues (35,36) suggested that tolerance developed under contingent and pharmacologic conditions (i.e., drug exposure with and without the concurrent performance of the criterion response, respectively) may be additive. Specifically, in these studies, greater tolerance to the ataxic effect of ethanol on the performance of a maze task or a treadmill task was produced by combinations of drug-after-test and drug-before-test conditions than combinations of vehicle-after-test with drug-before-test conditions; that is, that rats receiving drug-after-test trials and intermittent drug-before-test trials displayed more tolerance than did rats receiving equivalent vehicle after-test and intermittent drug-before-test trials (to illustrate see Table 1 and Figure 1 in ref. 14). However, the interpretation of the results of these studies is confounded by limited experimenter control over the performance of the criterion response in the model of contingent tolerance employed. Specifically, it may be possible that some components of the criterion response (e.g., walking on a treadmill) were experienced by subjects in the drug-after-test condition outside the test periods when subjects were intoxicated and spontaneously moved around their home cages. Two lines of evidence support this notion. First, Kim et al. (10) demonstrated that tolerance to the ataxic effect of ethanol develops in rats in the absence of specific behavioral testing. Further, evidence from Kalant's laboratory (13) has demonstrated that tolerance generalizes between tasks designed to assess ethanol's ataxic effect. Thus, any tolerance to the effect of ethanol on locomotion in the home cage would likely generalize to the effect of ethanol on the treadmill task. Although these findings do not explain the fact that tolerance is greater in the drug-before-test group than in the drug-after-test group, they question the extent to which the drug-after-test condition represents drug exposure without performance of the criterion response when measures of ataxia are used.

Second, LeBlanc et al. (14) found that contingent tolerance to the disruptive effect of ethanol on the moving-belt test dissipated when subjects were untested for a period of time. This finding stands in sharp contrast to those of studies examining the dissipation of contingent tolerance using other models. In studies using other models of tolerance, contingent tolerance was found to dissipate only when subjects explicitly experienced the criterion response in the absence of drug exposure (8,17,18, 27,28,34). This discrepancy may be due to the fact that subjects in the LeBlanc et al. study experienced components of the criterion response (i.e., while locomoting in the home cage) outside of testing periods, whereas in the studies that did not use measures of ataxic drug effects, the subjects would not have the same uncontrolled experience with the criterion response. Taken together, these two lines of evidence suggest that the increase in tolerance development to the ataxic effects of ethanol due to the addition of drug-after-treadmill test to drug-before-treadmill test may be an artifact of the inadequate control over the criterion response provided by this model of tolerance.

The present study was designed to reevaluate these earlier findings using another model of contingent drug tolerance. The kindling model of contingent drug tolerance was chosen because it allows complete experimental control over the criterion response; the subjects experience convulsions only following stimulation by the experimenter (25). The additivity of pharmacologic and contingent tolerance was assessed for ethanol and diazepam. These drugs were chosen because both drugs had been shown to have potent anticonvulsant effects on kindled convulsions and because the development of pharmacologic [diazepam: (15,18); ethanol: (19)] and contingent [diazepam: (16); ethanol: (21,24)] tolerance to the anticonvulsant effects of these two drugs had been demonstrated.

Following amygdala kindling, rats were treated with either noncontingent drug exposure to ethanol or diazepam while at the same time control rats were treated with the vehicle—none of the rats received convulsive stimulation during this period. Then, all rats received a series of drug-before-stimulation trials so that the development of contingent tolerance could be assessed. We reasoned that if the changes that underlie pharmacologic and contingent tolerance were additive, then noncontingent drug exposure would facilitate the subsequent development of contingent tolerance.

METHOD

Subjects and Surgery

The subjects were 97 male Long–Evans rats (Charles River, Canada), weighing between 250 and 350 g at the time of surgery. A single bipolar electrode (Plastic Products company, MS 303-2) was implanted in the left basolateral amygdala of each rat, under

sodium pentobarbital anaesthesia (65 mg/kg). The electrode tip was stereotaxically aimed at a site 2.8 mm posterior, 5.0 mm left, and 8.5 mm ventral to the skull surface at bregma, with the incisior bar set at −3.3 mm [coordinates from (20)]. Dental acrylic was used to secure the electrode to four stainless steel screws embedded in the skull, and powdered tetracycline was sprinkled over the incision prior to suturing to prevent infection. Following surgery, the rats were individually housed in steel hanging cages in a colony room with an ambient temperature of about 21°C and a 12L:12D cycle (lights on at 0800 h). Purina rat chow and water were continuously available.

Kindling

Following a postsurgical recovery period of at least 5 days, an electrical stimulation (1 s, 60 Hz, 400 μA) was applied through the electrode of each rat three times per day, 5 days per week, for 3 weeks, with a minimum of 2 h between successive stimulations. Prior to each stimulation, each rat was placed in a plastic box (58 × 58 × 25 cm) containing a thin layer of commercial bedding, and the stimulation lead was attached. The stimulation was delivered within a few seconds, and the rat was returned to its home cage once all convulsive activity had ceased. As is usual [see (25)], the initial stimulations produced no behavioral response other than a momentary behavioral arrest, but by the end of this regimen of 45 kindling stimulations, almost every stimulation elicited a clonic convulsion characterized by facial clonus, forelimb clonus, rearing, and loss of equilibrium.

Drugs

Ethanol was administered in an isotonic saline vehicle via gavage (intubation) in a 15% w/v solution on the noncontingent drug exposure phase trials, and it was administered in the same vehicle via IP injection in a volume of 5.0 ml/kg on the baseline tests and the contingent tolerance-development phase trials. Gavage was selected as the route of administration for ethanol during the noncontingent drug exposure phase because frequent IP injections of ethanol can lead to peritoneal irritation. Diazepam (Hoffmann–LaRoche) was administered in a 2% Tween 80 (J. T. Baker) isotonic saline vehicle via intraperitoneal (IP) injection in a volume of 5.0 ml/kg during both the noncontingent drug exposure and contingent tolerance-development phases of the experiment.

Baseline Phase

Following kindling, all of the rats received at least five baseline stimulations, which were administered "bidaily" (one every 48 h). A vehicle injection was administered 1 h prior to the second-to-last baseline stimulation; this trial is henceforth referred to as the vehicle baseline test. On the final baseline trial, all rats received a drug injection 1 h before the convulsive stimulation; this trial is henceforth referred to as the drug baseline test. Of the 97 rats, 40 rats received the ethanol vehicle on the vehicle test and ethanol (2.0 g/kg) on the drug baseline test, and 57 rats received the diazepam vehicle on the vehicle baseline test and diazepam (2.0 mg/kg) on the drug baseline test. For these and all subsequent tests, the dependent measure of convulsion severity was the duration of forelimb clonus. The four rats that displayed less than 20 s of forelimb clonus on the vehicle baseline test and the four rats that displayed more than 10 s of forelimb clonus on the drug baseline test were eliminated from the study. These rejection criteria were adopted because the development of tolerance to anticonvulsant drug effects can be obscured by the inclusion of subjects that do not display both reliable convulsions following stimulation and a large initial response to anticonvulsant drug effects. Also eliminated from the experiment were two rats that rejected their electrode assemblies and five rats that developed running fits.

Noncontingent Drug Exposure Phase

The rats that met the criteria for inclusion in the experiment were divided into four groups: ethanol-transfer ($n = 14$), ethanol-control ($n = 14$), diazepam-transfer ($n = 32$), and diazepam-control ($n = 16$). Assignment was such that each transfer group and its respective control group had approximately the same mean forelimb clonus scores on the two baseline tests as well as the same mean body weight.

The noncontingent drug exposure phase began 48 h after the drug baseline test. All the rats received either drug or vehicle administration without convulsive stimulations during this phase. For the ethanol-transfer and ethanol-control groups, this phase consisted of 21 daily gavage treatments, which resulted in the loss of six rats due to complications; the ethanol-transfer group received ethanol (5.0 g/kg in vehicle) and the ethanol-control group received vehicle on each gavage treatment. For the diazepam-transfer and diazepam-control groups, this phase consisted of three injections per day for 10 days; the diazepam-transfer group received injections of diazepam (5.0 mg/kg in vehicle) and the diazepam-control group received injections of vehicle. Similar protocols have been used by Mana, Pinel, and Lê (19) and Loscher and Schwark (15) to produce pharmacologic tolerance to the anticonvulsant effect of ethanol and diazepam, respectively.

Contingent Tolerance–Development Phase

Following the noncontingent drug exposure phase, the development of contingent tolerance to the anticonvulsant drug effects was assessed in all rats by a series of bidaily drug-before-stimulation trials, each of which was identical to the drug baseline test; 1 h before each convulsive stimulation, rats in the ethanol-transfer and ethanol-control groups received injections of ethanol (2.0 g/kg) and the rats in the diazepam-transfer and diazepam-control groups received injections of diazepam (2.0 mg/kg). These protocols had been shown to be effective methods in producing contingent tolerance to the anticonvulsant effects of both ethanol (21) and diazepam (16).

Transfer from noncontingent drug exposure to contingent tolerance conditions was assessed in two ways: the amount of decline in the ability of ethanol and diazepam to block forelimb clonus during this phase, and the number of trials required to attain a criterion of contingent tolerance. A rat was considered to have achieved the criterion of contingent tolerance when the duration of its forelimb clonus elicited on two consecutive contingent tolerance-development trials was at least 50% as long as the forelimb clonus elicited in the same rat on the vehicle baseline test [this criterion has been shown previously to be useful in assessing the development of contingent tolerance to anticonvulsant drug effects: (8,11,17)].

Histology

At the conclusion of the experiment, all subjects were sacrificed with CO_2. Their brains were removed, fixed in formalin, sliced along the coronal plane, mounted on slides, and then stained with cresyl violet to confirm the location of the electrode placements. Inspection of the stained sections revealed that all the electrode tips were located in the amygdala, with the majority lying within the basolateral nucleus.

Statistics

Differences between the transfer groups and their respective control groups were assessed using between within mixed-design ANOVAs for forelimb clonus duration data on contingent tolerance-development phase trials with follow-up comparisons using the Tukey method. *t*-Tests were used for the comparisons of the level of pharmacologic tolerance apparent on the first trial of the contingent-tolerance development phase and the number of trials required to attain the criterion of contingent tolerance.

RESULTS

Figure 1 shows the mean forelimb clonus duration for each group of rats on the vehicle baseline test, the drug baseline test, and the contingent-tolerance development phase trials. It is readily apparent from Fig. 1 that both ethanol and diazepam had substantial anticonvulsant effects on the drug baseline test. It is also apparent that the rats in the diazepam-transfer group developed significant pharmacologic tolerance relative to the rats in the diazepam-control group, $t(46) = 3.419$, $p < 0.05$; however, pharmacologic tolerance was not apparent in the ethanol-transfer group rats, $t(26) = 0.169$, $p > 0.05$.

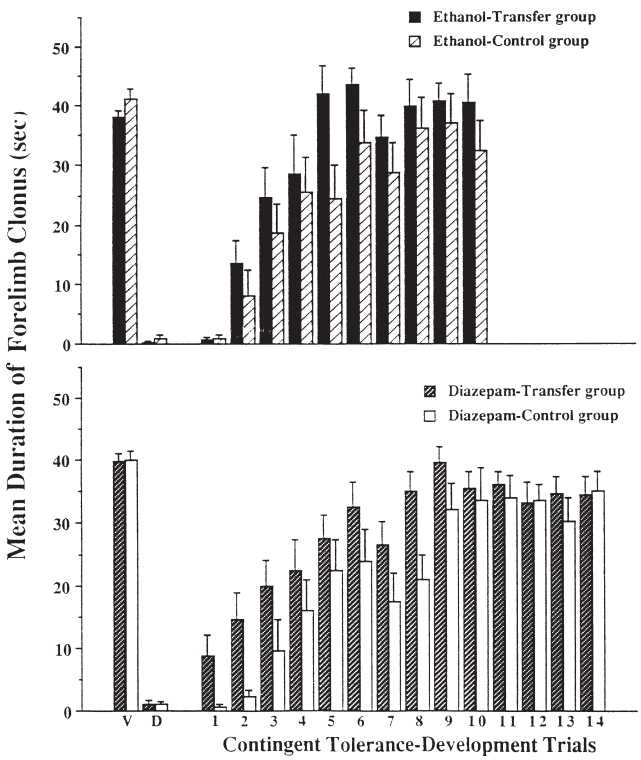

FIG. 1. The mean (±SEM) duration of forelimb clonus on the vehicle baseline test (V), drug baseline test (D), and the contingent tolerance–development phase trials; trial 1 serves as a pharmacologic tolerance test. The diazepam-transfer group displayed significant pharmacologic tolerance relative to the diazepam-control group ($p < 0.05$), whereas the ethanol-transfer and the ethanol-control groups did not differ significantly ($p > 0.05$). However, both the ethanol-transfer and the diazepam-transfer groups displayed significant transfer from noncontingent drug exposure to contingent tolerance, as reflected by a significant main effect of group during the contingent tolerance–development phase (ps < 0.05).

Moreover, as shown in Fig. 1, both of the transfer groups displayed more forelimb clonus throughout the contingent tolerance-development phase than their respective control groups. The statistical significance of these observations was confirmed with mixed-design ANOVAs. For the comparison of the ethanol-transfer and ethanol-control groups, there was a significant main effect of group, $F(1, 260) = 6.816$, $p < 0.05$, and a significant main effect of trials, $F(9, 260) = 19.248$, $p < 0.05$, with trial 1 differing significantly from trials 3 through 10, and trial 2 differing significantly from trials 5 through 10; no other trials differed significantly. The interaction between groups and trials was not significant, $F(9, 260) = 0.683$, $p > 0.05$. For the comparison of the diazepam-transfer and diazepam-control groups, there was a significant main effect of group, $F(1, 686) = 13.01$, $p < 0.05$, and a significant main effect of trials, $F(13, 686) = 13.53$, $p < 0.05$, with the following trial means differing significantly: trial 1 vs. trials 4 through 12, trial 2 vs. trials 5 through 14, trial 3 vs. trials 8 through 14, and trial 4 vs. 9 through 14. The interaction between group and trials was not significant, $F(13, 686) = 0.651$, $p > 0.05$.

The mean (±SEM) numbers of trials that it took the rats in the four groups to achieve the criterion of contingent tolerance during the contingent tolerance-development phase were 4.571 (±0.343) for the ethanol-transfer group, 6.214 (±0.629) for the ethanol-control group, 5.429 (±0.486) for the diazepam-transfer group, and 8.00 (±0.730) for the diazepam-control group. Both the diazepam-transfer and ethanol-transfer groups displayed significant savings; that is, both groups required significantly fewer trials to attain the criterion of contingent tolerance than did their respective control groups [ethanol: $t(26) = 2.115$, $p < 0.05$; diazepam: $t(46) = 2.993$, $p < 0.05$].

DISCUSSION

The major finding of the present experiment was that noncontingent exposure to either ethanol or diazepam facilitates the subsequent development of contingent tolerance. The ethanol-transfer and diazepam-transfer groups experienced longer convulsions throughout the contingent tolerance-development phase (see Fig. 1) and achieved the criterion of contingent tolerance in significantly fewer trials than did the respective control groups. This suggests that there is transfer between the changes that underlie pharmacologic tolerance (i.e., tolerance produced by contingent drug exposure). It should be emphasized, however, that the combination of noncontingent and contingent drug treatment did not produce higher levels of tolerance; by the end of the contingent tolerance-development phase, the transfer and control groups achieved similar levels of tolerance.

Statistically significant differences in the trials-to-criterion measure of contingent tolerance occurred despite the lack of a statistically significant interaction effect (see Fig. 1). It appears that the significant difference in the trials-to-criterion measure resulted from the combination of the tendency for the transfer groups to be generally more tolerant and to have slightly steeper acquisition curves than their controls. Additionally, the finding that contingent tolerance to ethanol developed following substantially fewer trials than contingent tolerance to diazepam may reflect either differences in the effectiveness of the chosen doses or that contingent tolerance develops at different rates to these drugs. It is important to note that a limitation of the present study design is that total drug exposure was not equated between the transfer and control groups. It is also important to note the relative amount of drug necessary to produce tolerance under contingent and noncontingent conditions; many large-dose injections of drug pro-

duce no detectable or little tolerance under the noncontingent conditions, whereas a few small dose injections produce substantial tolerance under the contingent conditions. Further studies should examine the transfer between noncontingent and contingent drug exposure in the opposite direction of that demonstrated in the present experiments; that is, the transfer from contingent tolerance to noncontingent tolerance. Nevertheless, the present finding that there is transfer from noncontingent drug exposure to contingent tolerance suggests that the mechanisms underlying pharmacologic and contingent tolerance to anticonvulsant drug effects are at least partially additive.

The results of the present experiment confirm reports that contingent tolerance develops to the anticonvulsant effect of both diazepam (16) and ethanol (21,24). They also confirm reports that pharmacologic tolerance develops to the anticonvulsant effect of diazepam (15,18). However, in contrast to the report of Mana, Pinel, and Lê (19), significant pharmacologic tolerance to ethanol was not observed in the present study—a finding that was unexpected in view of the fact that the ethanol protocol employed in the present experiment was identical to that used by Mana et al., with the exception that we used Long–Evans rather than Wistar rats. This apparent lack of pharmacologic tolerance with facilitation of subsequent contingent tolerance can be interpreted in at least two ways. On the one hand, the fact that noncontingent exposure to ethanol produced savings in the subsequent development of contingent tolerance may indicate that pharmacologic tolerance to ethanol did develop but that it was masked by the test dose being too high. On the other hand, the present finding may indicate that even when noncontingent drug exposure is insufficient to produce pharmacologic tolerance, there is an acceleration of subsequent contingent tolerance. This latter interpretation is consistent with the results of Kalant et al. (7), who found that even after it had dissipated, pharmacologic tolerance to the ataxic effect of ethanol still accelerated the subsequent development of contingent tolerance, however, the difficulties in distinguishing between pharmacologic and contingent tolerance to ataxic drug effects raised earlier must still be considered.

The present finding that noncontingent drug administration facilitates the subsequent development of contingent drug tolerance extends the findings of previous transfer studies in three ways. First, they extend these findings to include a second effect of ethanol. In the present study this finding was demonstrated with the anticonvulsant effect of ethanol, while previous studies had only examined the ataxic effect of ethanol on the performance of various treadmill or maze tasks (12,14, 35,36). Second, the present study also extends this effect to include a second drug, diazepam. Third, the present study extends this effect to include the facilitation of contingent tolerance development by prior chronic administration of the drug. Recently, we have also shown that prior acute exposure to diazepam facilitates the development of contingent tolerance to the anticonvulsant effect of diazepam (11). It is important to point out that in all of these studies similar effects on the development of tolerance were found: noncontingent drug exposure resulted in small amounts of tolerance; drug exposure accompanied by the performance of a criterion response resulted in relatively large amounts of tolerance. Moreover, in all the aforementioned studies noncontingent drug exposure facilitated the development of contingent tolerance.

Weiss and Post (33) reported that the development of contingent tolerance to the anticonvulsant effect of carbamazepine was inhibited by concurrent, noncontingent carbamazepine administration, a finding that seems to contradict that of the present study. However, there are at least three differences between the Weiss and Post study and the present one that might account for this apparent contradiction. First, in the Weiss and Post study, noncontingent drug was delivered in food with consumption under the control of the rats, whereas in the present study, noncontingent drug was always administered under the control of the experimenter by IP injections or gavage. Second, in the Weiss and Post study, noncontingent and contingent drug was delivered concurrently, whereas in the present study noncontingent and contingent drug exposure was delivered in sequence. Thus, there may have been large differences in the magnitude of the drug effect experienced by subjects when they received convulsive stimulations. Third, the drug used by Weiss and Post was carbamazepine, and the present study used ethanol and diazepam; thus, the present finding may not generalize to all drugs. The nature of this contradiction is unclear, and its resolution will require future research. However, the majority of studies indicate that contingent tolerance development is facilitated by noncontingent drug administrations.

The findings of transfer experiments are also relevant to theories that claim the development of tolerance obeys Pavlovian conditioning principles [e.g., (30)]. On the one hand, transfer experiments do not refute the extensive body of evidence, demonstrating that the expression of tolerance is facilitated by cues predictive of drug exposure [see (31,32) for reviews]. On the other hand, the facilitation of contingent tolerance by noncontingent drug exposure demonstrates that the critical pairing between drug exposure and performance of the criterion response is not Pavlovian in nature. According to a Pavlovian framework, initial unpaired drug exposure followed by drug exposures paired with the criterion response, and concurrent paired and unpaired drug exposures would inhibit tolerance development. However, the opposite appears to be true: contingent tolerance development is facilitated by additional unpaired drug administrations.

The drug–effect theory of tolerance (5,6,22,23,26) provides a framework for the interpretation of the present findings. According to the drug–effect theory, tolerance develops to drug effects not to drug exposure per se; that is, tolerance develops only to the effects of drugs on patterns of neural activity that is disrupted by the drug. The major prediction of this theory is that tolerance to a particular effect of a drug (e.g., an anticonvulsant effect) will develop most rapidly when the criterion response (e.g., a convulsion) is disrupted during periods of drug exposure; however, it also predicts that a small amount of tolerance will develop by the same mechanism when the criterion response is not elicited during periods of drug exposure if activity in some of the neural circuits involved in the criterion response is disrupted by the drug. For example, the drug–effect theory predicts that tolerance to anticonvulsant drug effects will develop in the absence of convulsive stimulation because some of the circuits involved in convulsive activity are likely to be spontaneously active during the periods of drug exposure. Accordingly, the drug–effect theory accounts for the observations of pharmacologic tolerance that many high dose noncontingent injections of drug produce only small amounts of tolerance. It also accounts for the observations of contingent tolerance that a few low-dose, contingent injections produce substantial tolerance.

ACKNOWLEDGEMENTS

This research was supported by a grant from the British Columbia Health Care Research Foundation.

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