Pergamon

Pharmacology Biochemistry and Behavior, Vol. 49, No. 4, pp. 1113–1117, 1994

0091-3057/94 $6.00 + .00

0091-3057(94)00260-6

BRIEF COMMUNICATION

Dissipation of Contingent Tolerance to the Anticonvulsant Effect of Diazepam: Effect of the Criterion Response

LISA E. KALYNCHUK,[1] TOD E. KIPPIN, JOHN P. J. PINEL AND CAMERON P. McINTYRE

Department of Psychology, University of British Columbia, Vancouver, B.C. V6T 1Z4, Canada

Received 18 April 1994

KALYNCHUK, L. E., T. E. KIPPIN, J. P. J. PINEL AND C. P. McINTYRE. *Dissipation of contingent tolerance to the anticonvulsant effect of diazepam: Effect of the criterion response.* PHARMACOL BIOCHEM BEHAV **49**(4) 1113–1117, 1994.—The effect of convulsive stimulations on the dissipation of tolerance to the anticonvulsant effect of diazepam was investigated using the kindled-convulsion model. Amygdala-kindled rats were rendered tolerant to diazepam's anticonvulsant effect by 25 "bidaily" (one/48 h) diazepam injections (2.5 mg/kg), each followed 1 h later by a convulsive stimulation. They were then divided into nine groups for the tolerance-dissipation phase of the experiment. Of the nine groups, three received bidaily control handling for one trial, three trials, or seven trials; three received bidaily saline injections, each 1 h before a convulsive stimulation, for one, three, or seven trials; and three received bidaily diazepam injections, each 1 h after a convulsive stimulation, for one, three, or seven trials. Finally, each rat received a tolerance-retention test (i.e., a diazepam injection followed 1 h later by a convulsive stimulation) 48 h after its last tolerance-dissipation trial. The tolerance dissipated gradually but completely over the 4-, 8-, and 16-day test intervals in the rats that received a convulsive stimulation before each injection during the tolerance-dissipation phase, whether they were injected with saline or diazepam; in contrast, tolerance did not dissipate in the rats that received saline injections but no stimulations. Remarkably, the discontinuance of the bidaily diazepam injections, even for 16 days, was not sufficient to dissipate the tolerance that had developed to diazepam's anticonvulsant effect; nor was the continuation of the bidaily diazepam injections sufficient to keep tolerance from dissipating. The present findings support previous assertions that the performance of the criterion response while undrugged is the key factor in the dissipation of contingent drug tolerance; and they provide the first controlled demonstration of the time course of the dissipation.

Amygdala Kindling Convulsion Tolerance dissipation Diazepam Benzodiazepine Anticonvulsant Seizure Rat Continent tolerance

THE development of tolerance to many drug effects has been shown to be contingent on the repeated experience of the particular drug effect under investigation (25,28). For example, Pinel et al. have found that tolerance develops to "bidaily" (one/48 h) injections of pentobarbital, carbamazepine, diazepam, ethanol, and sodium valproate in amygdala-kindled rats only when the drug is injected before each convulsive stimulation so that the anticonvulsant effect of the drug can be experienced. No tolerance develops in kindled rats that receive bidaily injections of the drug after each convulsive stimulation (16). Such tolerance, which is not the inevitable product of drug exposure, but is contingent on the repeated experience of the criterion drug effect, has been termed "contingent tolerance" (1). Contingent tolerance has been demonstrated to numerous drug effects—for example, to the effects of ethanol on maze running (7), on the decay of posttetanic potentiation in the aplysia abdominal ganglion (26), on male sexual behavior (18), and on responding to painful stimulation (5,6); to the

[1] To whom requests for reprints should be addressed.

adipsic effect of scopolamine (21); and to the anorectic effects of amphetamine (2), cocaine (29), and quipazine (24).

There is also evidence that response contingencies can play a role in the dissipation of drug tolerance. For example, in a study of contingent tolerance to the anticonvulsant effects of ethanol, Mana and Pinel (9) found no loss of tolerance over a 14-day retention interval in rats that received neither ethanol injections nor convulsive stimulations during the interval. In contrast, tolerance dissipated completely in rats receiving only bidaily convulsive stimulations and in those receiving bidaily convulsive stimulations and bidaily ethanol injections, as long as the stimulations were delivered to the subjects when they were drug free. Remarkably, the cessation of ethanol exposure was neither a necessary nor a sufficient condition for the dissipation of contingent tolerance: The critical factor in the dissipation of tolerance was the experience of convulsions while undrugged. This finding has been extended to the anticonvulsant effects of diazepam and carbamazepine by Mana (8) and Weiss and Post (27), respectively.

The present experiment was a further investigation of the role of the response contingency in the dissipation of contingent drug tolerance to anticonvulsant drug effects. Its purpose was to determine the course of such dissipation. The previous three studies of the effect of convulsive stimulation on the dissipation of contingent tolerance to anticonvulsant drug effects systematically evaluated the decline of tolerance after only a single retention interval: 14 days of bidaily stimulations in the study by Mana and Pinel (9), 16 days of bidaily stimulations in the study by Mana (8), and 11 days of daily stimulations in the study by Weiss and Post (27). In each case, tolerance did not decline in rats that received no drug during the retention interval, but dissipated totally in rats that received a series of convulsive stimulations while undrugged during the same period. Accordingly, little is known about the course of the decline of the tolerance to anticonvulsant drug effects except that after about 2 weeks the tolerance totally dissipates. The purpose of the present experiment was to determine whether contingent tolerance to the anticonvulsant effect of diazepam dissipates gradually or abruptly, as a step function (i.e., after one or two stimulations).

METHOD

Subjects

The subjects were 71 adult, male, Long-Evans rats purchased from Charles River Canada (Montreal, Quebec). They were individually housed in steel hanging cages in a colony room with an ambient temperature of about 21°C and a 24-h light-dark cycle (lights on at 0800 h). Purina rat chow (Richmond, IN) and water were available continuously in the home cages. All experimental manipulations were conducted in the colony room during the light phase of the light-dark cycle.

Drugs

Diazepam was purchased from Hoffman-La Roche in 10 mg/2 ml ampoule form. The vehicle was isotonic saline with 2% Tween 80 (J.T. Baker Chemical, St. Louis, MO). All drug and vehicle injections were delivered intraperitoneally in a volume of 5 ml/kg.

Surgery

A single, bipolar electrode (Plastic Products Company; MS-303-2, Roanoke, VA) was implanted in the left basolateral amygdala of each rat, under sodium pentobarbital anesthesia (65 mg/kg, intraperitoneally [IP]). The electrode tip was 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 incisor bar set at −3.3 mm (13). The electrode was secured to the skull with four stainless-steel screws and dental acrylic. Powdered tetracycline was sprinkled on the incision before suturing to reduce infection.

Kindling Phase

After a postsurgical recovery period of at least 5 days, each rat was stimulated (1 s, 60 Hz, 400 μA) three times per day, 5 days per week, for 3 weeks. There was a minimum of 2 h between consecutive stimulations. As is usual (19,23), the initial stimulations produced no behavioral response other than a momentary behavioral arrest, but by the end of the 45 kindling stimulations, almost every stimulation elicited a generalized clonic convulsion characterized by facial clonus, forelimb clonus, rearing, and loss of equilibrium. The measure of convulsion severity was the duration of forelimb clonus; this measure has been shown to be particularly reliable and sensitive to a variety of pharmacologic manipulations (15,17).

Baseline Phase

The baseline phase of the experiment began 48 h after the last of the 45 kindling stimulations; it comprised five stimulations, one every 48 h. This bidaily stimulation schedule, once initiated during the baseline phase, was maintained for the duration of the experiment. A bidaily injection schedule was employed to reduce the possibility of drug accumulation (12). Each rat was injected with the saline vehicle (5 ml/kg) 1 h before the fourth baseline stimulation; here, this fourth baseline trial is referred to as the saline baseline test. On the fifth baseline stimulation 48 h later, each rat was injected with diazepam (2.5 mg/kg, IP) 1 h before a stimulation; here, this fifth baseline trial is referred to as the drug baseline test. The dose of diazepam that was used on the drug baseline test was selected because, in our experience, it is the minimum dose that will reliably block the forelimb clonus elicited by amygdala stimulation in almost all kindled rats (10). Rats that displayed < 20 s of forelimb clonus on the saline baseline test or > 10 s of forelimb clonus on the drug baseline test were not studied further: Two and five rats, respectively, failed to meet these two criteria. In addition, nine rats dislodged their electrode caps and one rat became ill during the course of the kindling and baseline phases. Thus, 54 of the initial 71 rats entered the tolerance-development phase of the experiment.

Tolerance-Development Phase

Beginning 48 h after the drug baseline test, each rat received 25 bidaily tolerance-development trials in which diazepam (2.5 mg/kg, IP) was injected 1 h before a convulsive stimulation. By the end of this tolerance-development phase, all but 10 rats met the criterion of tolerance, a mean duration of forelimb clonus on the last three tolerance-development trials that was at least 50% of the duration of that rat's forelimb clonus on the saline baseline test. Because the purpose of this experiment was to study the dissipation of tolerance, these 10 rats were not studied further, and the remaining 44 rats entered the tolerance-dissipation phase of the experiment.

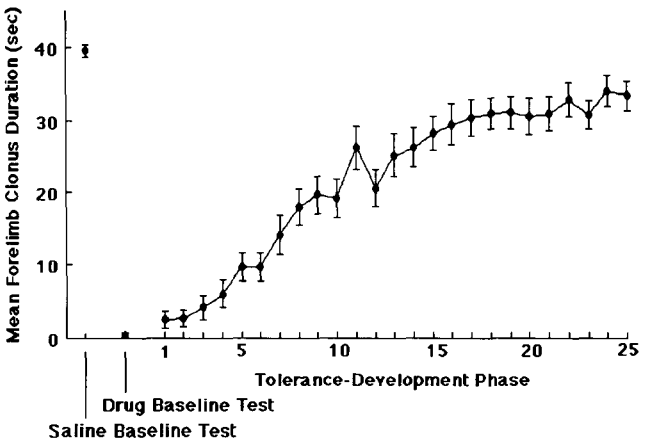

FIG. 1. The development of tolerance to the anticonvulsant effect of diazepam. On the drug baseline test, diazepam exerted a potent anticonvulsant effect, but by the end of the 25-trial tolerance-development phase, substantial tolerance to this effect had developed.

Tolerance-Dissipation Phase

The tolerance-dissipation phase began 48 h after the last trial of the tolerance-development phase. The remaining 44 rats were divided into nine groups in such a way that the mean forelimb clonus duration elicited over the last three trials of the tolerance-development phase was approximately equal for each group. Of the nine groups, three received no treatment (noDZ-noSTIM group) other than bidaily handling; they were weighed and put briefly into the plastic testing box once (n = 5), three times (n = 5) or seven times (n = 5). Three other groups received bidaily saline injections, each 1 h before a convulsive stimulation (SAL-after-STIM group) for one (n = 5), three (n = 4), or seven trials (n = 5). The final three groups received bidaily diazepam injections, each 1 h after a convulsive stimulation (DZ-after-STIM group) for one (n = 5), three (n = 5), or seven trials (n = 5). Accordingly, the design was a 3 × 3 factorial with three retention intervals and three stimulation and drug conditions.

Tolerance-Retention Test

Each rat received a tolerance-retention test 48 h after the last trial of its tolerance-dissipation phase—that is, 4, 8, or 16 days after its final tolerance-development trial. Each tolerance-retention test was identical to the drug baseline test; each rat received an injection of diazepam (2.5 mg/kg, IP) 1 h before a convulsive stimulation. The purpose of the tolerance-retention test was to assess the degree to which tolerance to the anticonvulsant effect of diazepam had dissipated.

Statistics

Only the data of the 44 rats that completed the experiment were subjected to statistical analysis. The statistical significance of the development of tolerance was assessed using a one-tailed t-test of the differences in forelimb clonus duration displayed by each rat on the drug baseline trial and the mean of its last three tolerance-development trials. The statistical significance of the dissipation of tolerance after each interval was assessed using a two-way repeated-measures analysis of variance—one at each of the three retention intervals—of the differences in the mean duration of forelimb clonus displayed by each rat on the last three trials of the tolerance-development phase and on its tolerance-retention test. In addition, posthoc analyses of simple effects were performed to assess the significance of differences between pairs of groups. The significance level for all comparisons was $p < 0.05$.

RESULTS

Figure 1 illustrates the mean forelimb clonus durations for all the rats on the saline baseline and drug baseline tests, and the acquisition of tolerance to the anticonvulsant effect of diazepam over the 25-trial tolerance-development phase. It is readily apparent that diazepam initially blocked forelimb clonus in all subjects and that substantial tolerance developed to this effect over the ensuing 25 tolerance-development trials.

Figure 2 illustrates the time course of the dissipation of this tolerance in the three conditions of the experiment. Tolerance had dissipated in the SAL-after-STIM rats and the DZ-after-STIM rats slightly after the 4-day interval, partially after the 8-day interval, and completely after the 16-day interval. In contrast, there was no decline of tolerance whatsoever in the noDZ-noSTIM rats.

Statistical analyses confirmed the significance of these effects. Analysis of the tolerance-development data (Fig. 1) indicated that the rats displayed significantly more forelimb clonus on the last three tolerance-development trials than they did on the drug baseline trial ($t(43) = 32.55$, $p < 0.0001$). Analysis of the differences between the mean of the last three tolerance-development trials and the tolerance-retention test at the 4-day interval revealed no statistically significant effects. However, analysis of the differences at 8 days revealed a significant group main effect ($F(2, 12) = 8.435$, $p < 0.006$) and a significant interaction effect ($F(2, 12) = 11.05$, $p < 0.002$). Subsequent posthoc analysis of simple effects at the 8-day interval revealed that both the SAL-after-STIM ($F(1, 12) = 5.52$, $p < 0.03$) and the DZ-after-STIM ($F(1, 12) = 8.06$, $p < 0.01$) rats displayed significantly less forelimb clonus on the tolerance-retention test than on the final three

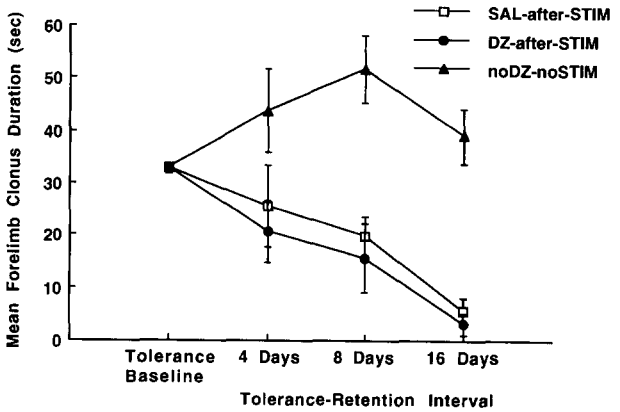

FIG. 2. The dissipation of tolerance to the anticonvulsant effect of diazepam. The mean forelimb clonus duration is shown for the last 3 days of the tolerance-development phase (Tolerance Baseline), and for the 4-, 8-, and 16-day tolerance-retention intervals. Tolerance dissipated gradually in the saline after stimulation (SAL-after-STIM) and the diazepam after stimulation (DZ-after-STIM) rats, but not in the noDZ-noSTIM rats, which displayed a slight increase in convulsion duration after the discontinuation of treatment.

tolerance-development trials, and that the noDZ-noSTIM ($F(1, 12) = 9.82, p < 0.01$) rats displayed significantly more forelimb clonus on the tolerance-retention test than on the final three tolerance-development trials. Analysis of the differences at 16 days revealed a significant group main effect ($F(2, 12) = 16.501, p < 0.0004$), a significant repeated-measures main effect ($F(1, 12) = 31.062, p < 0.0001$), and a significant interaction effect ($F(2, 12) = 15.02), p < 0.0005$). Posthoc analysis of simple effects at the 16-day interval revealed that both the SAL-after-STIM ($F(1, 12) = 26.92, p < 0.001$) and the DZ-after-STIM ($F(1, 12) = 34.06, p < 0.001$) rats, but not the noDZ-noSTIM ($F(1, 12) = 1.55, p > 0.10$) rats displayed significantly less forelimb clonus on the tolerance-retention test than on the tolerance-development trials.

Histologic analysis revealed that all of the electrode tips had been positioned in or on the boundary of the basolateral nucleus of the amygdala.

DISCUSSION

These results confirm the previous findings of Mana and Pinel (9), Mana (8), and Weiss and Post (27) that the administration of convulsive stimulations in the absence of drug is critical for the dissipation of contingent tolerance to anticonvulsant drug effects. Tolerance to the anticonvulsant effects of diazepam did not dissipate in rats that did not receive diazepam during the 16-day retention interval when they were not stimulated during this interval. In contrast, tolerance dissipated gradually, but completely, over the 16-day retention interval in rats that were stimulated before each bidaily injection, even when they continued to receive diazepam. Thus, the withdrawal of diazepam alone was neither necessary nor sufficient for the dissipation of tolerance, and the continuation of diazepam administration was neither necessary nor sufficient for the retention of tolerance once it had developed. Instead, the critical factor in the dissipation of tolerance appeared to be the repeated elicitation of the criterion response (convulsive activity) in the absence of diazepam; rats exposed to the same regimen of bidaily diazepam injections that made them tolerant lost their tolerance when a convulsive stimulation was administered before each injection.

Similar support for the importance of a response contingency in the dissipation of tolerance has been provided by other studies. For example, it has been shown that rats will not lose their tolerance as rapidly to the effects of tetrahydrocannabinol on lever pressing unless they can lever press in the absence of drug (11), to amphetamine's anorectic effect unless they can eat in the absence of the drug (22), or to scopolamine's adipsic effect unless they can drink in the absence of the drug (21). However, in each of these experiments, the dissipation of tolerance was assessed after a single retention interval. Thus, they provided no information about the time course of the dissipation of contingent tolerance.

The primary purpose of the present experiment was to assess the time course of the dissipation of contingent tolerance to the anticonvulsant effect of diazepam. In particular, our goal was to determine whether the dissipation of tolerance to anticonvulsant drug effects would be a step function (i.e., whether it would dissipate entirely after the experience of a single convulsion in the absence of the drug), or whether it would dissipate gradually over a series of convulsions. The results clearly support the latter view: The dissipation of tolerance to the anticonvulsant effect of diazepam was apparent after two drug-free convulsions, but it did not approach baseline until the eighth drug-free stimulation. Although this is the first experiment systematically to assess the time course of the dissipation of contingent tolerance to anticonvulsant drug effects, a study by Weiss and Post (27) did provide relevant, but uncontrolled data. Weiss and Post did not include a no-stimulation control group in their study because its primary purpose was not to describe the time course of the dissipation of contingent tolerance. However, their data suggest that contingent tolerance to the anticonvulsant effect of carbamazepine dissipates gradually; they reported a progressive dissipation of contingent tolerance after three, five, and 11 daily trials of carbamazepine-after-stimulation treatment, which is a time course of dissipation similar to the one observed in the present experiment.

At all three retention intervals, the rats in the noDZ-noSTIM control group displayed convulsions that were longer than those observed on the tolerance test, although this difference achieved statistical significance on only the 8-day test. This unanticipated increase could reflect the action of convulsive withdrawal effects conditioned to the stimulation environment, or it could reflect a shift in the convulsion baseline caused by an increase in the duration of the antecedent interstimulation interval. On the basis of the present findings, it is impossible to chose between these alternatives, or indeed, to be confident that the increase is a reliable one.

The results of this experiment are inconsistent with the assumption that the cessation of drug exposure is the sufficient cause of the dissipation of drug tolerance—no decline in tolerance was observed, even after 16 drug-free days, in the noDZ-noSTIM rats. However, they are consistent with, and indeed were predicted on the basis of, the drug-effect theory of tolerance. According to the drug-effect theory, functional drug tolerance, like other forms of neural adaptation, is a response to the disruption of particular patterns of neural activity, not to the mere presence of the disruptive agent (16,20). Just as an adaptation to vision-displacing prisms is a specific corrective reaction to the experience of their disruptive effects on visuomotor performance, functional drug tolerance is a specific corrective reaction to the disruptive effects of drugs on concurrent patterns of neural activity (8,21). More germane to the present experiment is the drug-effect view of the dissipation of tolerance. According to this view, the dissipation of tolerance, like the development of tolerance, is an adaptation to the disruption of neural activity, specifically to patterns of neural activity that have adapted to the presence of the drug. Accordingly, the drug-effect theory predicted the major finding of the present experiment: that the experience of convulsive activity in the absence of diazepam would be the main causal factor in the dissipation of tolerance to its anticonvulsant effect.

Several clinical studies lend support to the present findings. For example, Gastaut and Low (4) reported that the anticonvulsant effect of clobazam was reinstated in tolerant patients by a period of interrupted treatment during which seizures were allowed to recur. Similarly, Doyle et al. (3) reported that epileptic patients who experienced seizures during an interruption of their antiepileptic medication had 50% fewer seizures than before the interruption once their antiepileptic treatment was resumed. This pattern of clinical findings is not limited to the treatment of epilepsy: Pazzaglia and Post (14) reported that a patient who was tolerant to the antinociceptive effect of carbamazepine responded to treatment after an interruption of medication during which he experienced several bouts of trigeminal neuralgia. These clinical results, in combination

with the present findings, suggest that discontinuing drug therapy for brief periods under close medical supervision may be an effective means of dissipating problematic levels of drug tolerance, providing that the symptoms reemerge during the drug-free period.

ACKNOWLEDGEMENTS

This research was supported by a British Columbia Health Care Research Foundation Grant to J.P.J.P., and by a Medical Research Council of Canada postgraduate scholarship to L.E.K.

REFERENCES

1. Carlton, P. L.; Wolgin, D. L. Contingent tolerance to the anorexigenic effects of amphetamine. Physiol. Behav. 7:221-223; 1971.
2. Demellweek, C.; Goudie, A. J. Behavioral tolerance to amphetamine and other psychostimulants: The case for considering behavioral mechanisms. Psychopharmacology 80:287-307; 1983.
3. Doyle, W. K.; Perrine, K.; Dogali, M. Decreased frequency of seizures after antiepileptic drug holiday in medically refractory epilepsy. Epilepsia 31:640; 1990.
4. Gastaut, H.; Low, M. D. Antiepileptic properties of clobazam, a 1,5 benzodiazepine, in man. Epilepsia 20:437-446; 1979.
5. Jorgensen, H. A.; Berge, O.; Hole, K. Learned tolerance to ethanol in a spinal reflex separated from supraspinal control. Pharmacol. Biochem. Behav. 22:293-295; 1985.
6. Jorgensen, H. A.; Hole, K. Learned tolerance to ethanol in the spinal cord. Pharmacol. Biochem. Behav. 20:789-792; 1984.
7. LeBlanc, A. E.; Gibbons, R. J.; Kalant, H. Behavioral augmentation of tolerance to ethanol in the rat. Psychopharmacologia 30:117-122; 1973.
8. Mana, M. J. Contingent and pharmacological tolerance to the anticonvulsant effects of antiepileptic drugs. Ph.D. thesis, University of British Columbia; 1990.
9. Mana, M. J.; Pinel, J. P. J. Response contingency and the dissipation of ethanol tolerance. Alcohol Alcohol Res. (Suppl 1):413-416; 1987.
10. Mana, M. J.; Kim, C. K.; Pinel, J. P. J.; Jones, C. H. Contingent tolerance to the anticonvulsant effects of carbamazepine, diazepam, and sodium valproate in kindled rats. Pharmacol. Biochem. Behav. 41:109-113; 1991.
11. Manning, F. J. Role of experience in acquisition and loss of tolerance to the effect of Δ-9-THC on spaced responding. Pharmacol. Biochem. Behav. 5:269-273; 1974.
12. Morton, D. J. Pharmacokinetics of twelve anticonvulsant drugs in the rat. Neuropharmacology 23:1125-1127; 1984.
13. Paxinos, G.; Watson, C. The rat brain in stereotaxic coordinates. Sydney: Academic Press; 1982.
14. Pazzaglia, P. J.; Post, R. M. Contingent tolerance and reresponse to carbamazepine: A case study in a patient with trigeminal neuralgia and bipolar disorder. J. Neuropsych. Clin. Neurosci. 4:76-81; 1992.
15. Pinel, J. P. J.; Colbourne, B.; Sigalet, J. P.; Renfrey, G. Learned tolerance to the anticonvulsant effects of alcohol in rats. Pharmacol. Biochem. Behav. 18:507-510; 1983.
16. Pinel, J. P. J.; Kim, C. K.; Mana, M. J. Contingent tolerance to the anticonvulsant effects of drugs on kindled convulsions. In: Wada, J. A., ed. Kindling 4. New York: Plenum Press; 1990:283-294.
17. Pinel, J. P. J.; Mana, M. J.; Kim, C. K. Effect-dependent tolerance to ethanol's anticonvulsant effect on kindled seizures. In: Porter, R. J.; Mattson, R. H.; Cramer, J. A.; Diamond, I., eds. Alcohol and seizures: Basic mechanisms and clinical implications. Philadelphia: FA Davis; 1990: 115-125.
18. Pinel, J. P. J.; Pfaus, J. G.; Christensen, B. K. Contingent tolerance to the disruptive effects of alcohol on the copulatory behavior of male rats. Pharmacol. Biochem. Behav. 41:133-137; 1991.
19. Pinel, J. P. J.; Rovner, L. Experimental epileptogenesis: Kindling-induced epilepsy in rats. Exp. Neurol. 58:190-202; 1978.
20. Poulos, C. X.; Cappell, H. Homeostatic theory of drug tolerance: A general model of physiological adaptation. Psych. Rev. 98: 390-408; 1991.
21. Poulos, C. X.; Hinson, R. E. A homeostatic model of Pavlovian conditioning: Tolerance to scopolamine-induced adipsia. J. Exp. Psych. Animal Behav. Proc. 10:75-89; 1984.
22. Poulos, C. X.; Wilkinson, D. A.; Cappell, H. Homeostatic regulation and Pavlovian conditioning in tolerance to amphetamine-induced anorexia. J. Comp. Physiol. Psych. 95:735-746; 1981.
23. Racine, R. J. Modification of seizure activity by electrical stimulation: II. Motor seizure. Electroencephalogr. Clin. Neurophysiol. 32:281-294; 1972.
24. Rowland, N.; Carlton, J. Different behavioral mechanisms underlie tolerance to the anorectic effects of fenfluramine and quizapine. Psychopharmacology 81:155-157; 1983.
25. Teitz, E. I. Repeated anticonvulsant testing: Contingent tolerance to diazepam and clobazam in kindled rats. Epilepsy Res. 11:89-101; 1992.
26. Traynor, A.; Schlapfer, W.; Barondes, S. Stimulation is necessary for the development of tolerance to a neuronal effect of ethanol. J. Neurobiol. 11:633-637; 1980.
27. Weiss, S. R. B.; Post, R. M. Development and reversal of contingent inefficacy and tolerance to the anticonvulsant effects of carbamazepine. Epilepsia 32:140-145; 1991.
28. Wolgin, D. L. The role of instrumental learning in behavioral tolerance to drugs. In: Goudie A. J.; Emmett-Oglesby, M. W., eds. Psychoactive drugs: Tolerance and sensitization. Clifton, New Jersey: Humana Press; 1990:17-114.
29. Woolverton, W. L.; Kandel, D.; Schuster, C. R. Tolerance and cross-tolerance to cocaine and d-amphetamine in rats. J Pharmacol. Exp. Ther. 205:525-535; 1978.