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Contingent Tolerance to the Anticonvulsant Effects of Carbamazepine, Diazepam, and Sodium Valproate in Kindled Rats[1]

MICHAEL J. MANA,[2] C. KWON KIM, JOHN P. J. PINEL[3] AND C. H. JONES

Department of Psychology, The University of British Columbia, Vancouver, BC, Canada V6T 1Y7

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MANA, M. J., C. K. KIM, J. P. J. PINEL AND C. H. JONES. *Contingent tolerance to the anticonvulsant effects of carbamazepine, diazepam, and sodium valproate in kindled rats.* PHARMACOL BIOCHEM BEHAV **41**(1) 121–126, 1992.—The effect of convulsive stimulation during periods of drug exposure on the development of tolerance to the anticonvulsant effects of carbamazepine (CBZ), diazepam (DZP), or sodium valproate (VPA) was studied in three similar experiments. In each experiment, amygdala-kindled rats were assigned to one of three groups: one group received a drug injection (CBZ, 70 mg/kg, IP; DZP, 2 mg/kg, IP; VPA, 250 mg/kg, gavage) 1 h before each of a series of 10 bidaily (one every 48 h) convulsive stimulations, a second group received the same dose of the drug 1 h after each of the 10 stimulations, and a third group served as a vehicle control. The drug tolerance test occurred in each experiment 48 h after the 10th tolerance-development trial; every rat received the appropriate dose of CBZ, DZP, or VPA 1 h before being stimulated. In each experiment, only the rats from the drug-before-stimulation group displayed a significant amount of tolerance to the drug's anticonvulsant effect. Thus the development of tolerance to the anticonvulsant effects of CBZ, DZP, and VPA was not an inevitable consequence of drug exposure; the development of tolerance was contingent upon the occurrence of convulsive stimulation during the periods of drug exposure. These results support the idea that functional drug tolerance is an adaptation to a drug's effects on ongoing patterns of neural activity, rather than to drug exposure per se.

Carbamazepine Diazepam Sodium valproate Tolerance Contingent tolerance Anticonvulsant
Kindling Convulsion Seizure Rat Amygdala Valproic acid Behavioral tolerance

TOLERANCE has been shown to develop to the anticonvulsant effects of most antiepileptic drugs (11–13). The generality of this form of drug tolerance and its obvious clinical significance have stimulated efforts to identify the factors that influence it. It has been shown that the development of tolerance to the anticonvulsant effects of antiepileptic drugs (a) progresses at different rates for different antiepileptic drugs [e.g., (2,10)], (b) is influenced by the concurrent administration of other antiepileptic drugs [e.g., (20)], (c) is influenced by the dose [e.g., (15)] and schedule of drug administration [e.g., (12)], (d) transfers between some antiepileptic drugs but not between others [e.g., (18)], and (e) is influenced by the type of seizure that is being controlled [e.g., (19)]. The purpose of the present experiments was to determine whether the development of tolerance to the anticonvulsant effects of three commonly prescribed antiepileptic drugs, carbamazepine (CBZ), diazepam (DZP), and sodium valproate (VPA), is facilitated by the administration of convulsive stimulation during periods of drug exposure.

The idea that the development of drug tolerance might be influenced by the activity of the drug recipient during periods of drug exposure is not a new one. In 1971, Carlton and Wolgin (4) found that tolerance did not develop to the anorexigenic effects of amphetamine in rats unless the rats were allowed to eat during periods of amphetamine exposure, and they coined the term contingent tolerance to refer to drug tolerance whose development is contingent upon the subjects' activity during drug exposure. Many instances of drug tolerance have subsequently been shown to be contingent. For example, Poulos and Hinson (37) found that the development of tolerance to scopolamine's adipsic effect is contingent upon rats having the opportunity to drink during periods of scopolamine exposure. Traynor, Schlapfer, and Barondes (44) reported that the development of tolerance to ethanol's effect on the decay of posttetanic potentiation in the abdominal ganglion of the marine mollusc *Aplysia* is contingent upon tetanic stimulation being delivered during the period of ethanol exposure. Jörgenson and his colleagues [e.g., (17)] found that the development of tolerance to ethanol's analgesic effect is contingent upon rats receiving painful stimulation during periods of ethanol exposure, and a similar finding was recently reported by Advokat (1) for morphine tolerance.

The primary stimulus for the present experiments was our previous observation that the development of tolerance to etha-

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

[2]Present address: Department of Behavioral Neuroscience, University of Pittsburgh, 446 Crawford Hall, Pittsburgh, PA 15260.

[3]Requests for reprints should be addressed to John P. J. Pinel, Department of Psychology, University of British Columbia, 2136 West Mall, Vancouver, BC, Canada V6T 1Y7.

nol's anticonvulsant effect on kindled seizures is contingent upon convulsive stimulation being delivered during periods of ethanol exposure [e.g., (31–34)]. The specific purpose of the present experiments was to determine whether convulsive stimulation during periods of drug exposure would similarly facilitate the development of tolerance to the anticonvulsant effects of CBZ, DZP, and VPA on kindled convulsions. These three drugs were selected for study because tolerance had been shown to develop to their anticonvulsant effects on kindled convulsions in rats [(25); see also (16, 23, 40)].

METHOD

Because the three experiments reported in this paper were conducted in a similar fashion, they are described here as one.

Subjects

The subjects were 117 male Long-Evans rats (Charles River, Canada), weighing between 350 and 400 g at the time of surgery and between 550 and 650 g at the end of the experiment. The rats were individually housed in wire mesh cages with continuous access to Purina laboratory chow and water. All experimental manipulations were conducted during the light phase of the 12:12-h light:dark cycle (lights on at 8:00 a.m.).

Surgical Procedure

A single bipolar electrode (Plastic Products, MS-303-2) was implanted in each subject by conventional stereotaxic surgery under sodium pentobarbital anesthesia (65 mg/kg, IP). The target in each case was in the left basolateral amygdala [1.2 mm posterior, 5 mm lateral, and 10 mm ventral to the skull surface at bregma, with the incisor bar set at +5.0; coordinates from (29)]. The electrode was held in place with stainless steel screws and dental acrylic. Tetracycline was sprinkled on the incision before suturing, and it was added to the drinking water for 7 days after surgery.

Drugs

The DZP and CBZ were administered intraperitoneally in a 2% Tween 80 and isotonic saline vehicle at a volume of 4 ml/kg. The DZP (2 mg/kg; Hoffmann-La Roche) was injected in solution, whereas the CBZ (70 mg/kg; Geigy) was injected in suspension. Sodium valproate (250 mg/kg; Abbott) was administered in suspension by gavage in a 2% Tween 80 isotonic saline vehicle at a volume of 4 ml/kg. This route of administration was used for the VPA because we had earlier noted that it caused the rats less distress than IP injection. These doses were employed because they had been used in a previous study of tolerance to anticonvulsant drug effects in kindled rats (25).

Kindling Phase

The kindling phase began at least 7 days after surgery. During the kindling phase, each rat was stimulated (1 s, 60 Hz, 400 μA) three times per day, 5 days per week, for 3 weeks, with at least 2 h between consecutive stimulations. The rats' response to the initial stimulation was typically a brief period of behavioral arrest, but by the end of the kindling phase, each stimulation elicited a stereotypical generalized clonic convulsion characterized in sequence by facial clonus, forelimb clonus, rearing, and a loss of equilibrium [see (36,38)]. All rats progressed to the no-drug baseline phase.

No-Drug Baseline Phase

The no-drug baseline phase began 48 h after the completion of the kindling phase. During the no-drug baseline phase, each rat received four amygdala stimulations, one every 48 h (±2 h). This bidaily stimulation schedule, once initiated, was maintained for the remainder of the experiment. The duration of forelimb clonus was the dependent measure; it had been shown to be particularly reliable and to be sensitive to a variety of pharmacological manipulations [e.g., (28,31)]. Electrographic activity was not recorded. Rats that did not display at least 20 s of forelimb clonus on the last no-drug baseline trial, referred to hereafter as the no-drug baseline test, were excluded from further study (n = 8).

Drug Baseline Test

The anticonvulsant effect of each drug was assessed on the drug baseline test, which occurred 48 h after the no-drug baseline test. In each of the three experiments, the appropriate drug was administered to every rat 1 h before the scheduled convulsive stimulation. Rats not showing at least an 80% reduction in the duration of their forelimb clonus from the no-drug baseline test to the drug baseline test were rejected from the study: 4 rats receiving CBZ, 4 rats receiving DZP, and 10 rats receiving VPA did not meet this criterion; this suggests that the three drugs were not equipotential under the conditions of these experiments. The remaining rats in each experiment were then assigned to one of three treatment groups; either a drug-before-stimulation group, a drug-after-stimulation group, or a vehicle control group. They were assigned in such a way that the mean duration of forelimb clonus on both the no-drug baseline test and the drug baseline test were approximately equal for each group.

Tolerance-Development Phase

The tolerance-development phase of the experiments began 48 h after the drug baseline test. There were 10 bidaily tolerance-development trials in each experiment. On each tolerance-development trial, the rats from the drug-before-stimulation groups received CBZ (CBZ-Before-Stimulation, n = 11), DZP (DZP-Before-Stimulation, n = 11), or VPA (VPA-Before-Stimulation, n = 10) 1 h before each stimulation. The rats from the drug-after-stimulation groups received CBZ (CBZ-After-Stimulation, n = 10), DZP (DZP-After-Stimulation, n = 12), or VPA (VPA-After-Stimulation, n = 10) 1 h after each stimulation. The rats in the respective vehicle control groups (CBZ-Control, n = 10; DZP-Control, n = 8; or VPA-Control, n = 9) received a vehicle injection 1 h before or 1 h after each stimulation. Because the timing of the vehicle injection had no detectable effect, the before and after vehicle control groups in each experiment were combined into a single control group.

Drug Tolerance Test

In each of the three experiments, the drug tolerance test occurred 48 h after the last tolerance-development trial. The drug tolerance test in each experiment was identical to the drug baseline test; every rat in each experiment received the appropriate drug, CBZ, DZP, or VPA, 1 h before a convulsive stimulation.

Histology

Following the experiments, the subjects were sacrificed in a CO_2 chamber, and their brains were removed and sectioned to permit histological verification of the electrode sites.

Statistical Analyses

Nonparametric techniques (42) were used to assess the statistical significance of the results because the total lack of variability of the data in some conditions precluded the use of parametric statistics. Wilcoxon Signed-Ranks tests were used to assess the statistical significance of the within-subject differences ($p<0.05$, one-tailed); Kolmogorov-Smirnov tests were used to assess the statistical significance of between-group differences ($p<0.05$, two-tailed).

RESULTS

In each experiment, contingent convulsive stimulation played a key role in the development of tolerance; these results are illustrated in the three panels of Fig. 1. The test doses of CBZ (Panel A), DZP (Panel B), and VPA (Panel C) totally suppressed forelimb clonus on the drug baseline tests; the mean duration of forelimb clonus on the drug baseline test was zero or virtually zero for every rat in each of the three experiments. Then, over the course of the 10 tolerance-development trials, the rats in each of the three drug-before-stimulation groups gradually developed tolerance to the anticonvulsant effect. In contrast, there was no evidence of tolerance in any of the three drug-after-stimulation groups or in the three vehicle control groups.

Statistical analyses confirmed the significance of these differences. Wilcoxon Signed-Ranks tests confirmed that there was significantly more forelimb clonus on the drug tolerance test than on the drug baseline test for each of the three drug-before-stimulation groups ($p<0.01$). In contrast, there were no statistically significant changes in the duration of forelimb clonus between the drug baseline test and the drug tolerance test for any of the drug-after-stimulation groups ($p>0.05$) or any of the vehicle control groups ($p>0.05$). Kolmogorov-Smirnov tests provided further evidence that tolerance developed only in the three drug-before-stimulation groups. There were no statistically significant differences among the drug-before-stimulation, drug-after-stimulation, or vehicle control groups on the drug baseline test in any of the three experiments ($p>0.05$). In contrast, Kolmogorov-Smirnov tests performed on the drug tolerance test results revealed a significant difference between the drug-before-stimulation groups and the corresponding drug-after-stimulation and vehicle control groups in all three experiments (CBZ, $p<0.001$; DZP, $p<0.001$; VPA, $p<0.003$).

Histological analysis revealed that all of the electrode tips were in or near the amygdala, with the majority lying within the basolateral nucleus.

DISCUSSION

The results of the present experiments establish that the administration of convulsive stimulation during periods of drug exposure can play an important role in the development of tolerance to the anticonvulsant effects of CBZ, DZP, and VPA. In each of the three experiments, considerable tolerance developed to the anticonvulsant effects in subjects that received convulsive stimulation during each bidaily period of drug exposure, but no tolerance whatsoever developed in subjects receiving the same series of bidaily injections if they were stimulated before, rather than after, each injection.

The magnitude of the tolerance effect, the periodic schedule of drug exposure, and the fact that the development of tolerance to the anticonvulsant effects of CBZ, DZP, and VPA was contingent upon the delivery of convulsive stimulation during the periods of drug exposure all argue that a functional change in the nervous system, and not a dispositional change was responsible for the development of tolerance. Moreover, these results support the view that functional drug tolerance is a response to

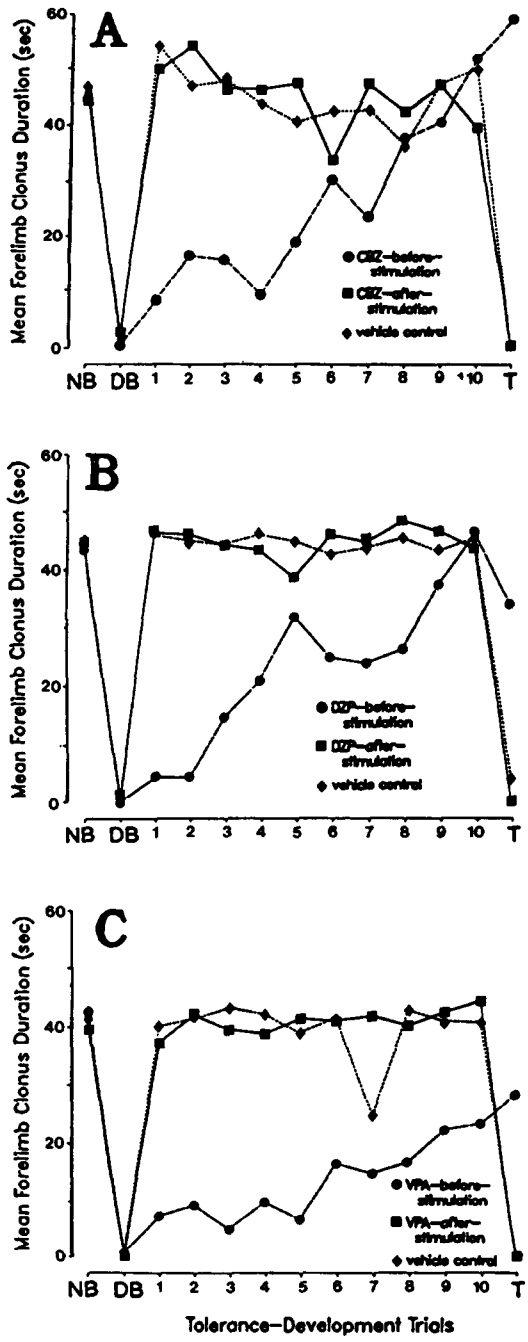

FIG. 1. Contingent tolerance to the anticonvulsant effects of carbamazepine (Panel A), diazepam (Panel B), and sodium valproate (Panel C) on kindled convulsions elicited in rats by amygdala stimulation. On the no-drug baseline test (NB), the stimulation elicited about 45 s of forelimb clonus; on the drug baseline test (DB), each of the drugs exerted a potent anticonvulsant effect; and on the drug tolerance test (T), the rats in the drug-before-stimulation groups displayed tolerance, but those in the drug-after-stimulation and vehicle control groups did not.

a drug's effect on a particular pattern of activity in the nervous system, and not an inevitable consequence of drug exposure. According to the drug-effect theory of tolerance [e.g., (32,35)], functional drug tolerance develops to only those drug effects that are repeatedly manifested. In some instances, tolerance will develop to a drug's effect upon the basal activity of the nervous system; consequently, tolerance will develop to these effects without the nervous system becoming involved in any particular pattern of activity. In other instances, however, the expression of a drug effect may be contingent upon a particular pattern of activity in the nervous system during the periods of drug exposure [see (43), p. 290 for a similar idea expressed at the level of the GABA/benzodiazepine receptor complex]. The development of tolerance to the anticonvulsant effect of CBZ, DZP, and VPA administered on a bidaily basis appears to be such an instance: tolerance developed only when the anticonvulsant effects were repeatedly expressed, that is, only when convulsive stimulation was administered during the periods of drug exposure.

The present demonstration that convulsive stimulation can play a key role in the development of tolerance to the anticonvulsant effects of CBZ, DZP, and VPA does not imply that convulsive stimulation is a critical factor in all instances of tolerance to the anticonvulsant effects of these drugs. In fact, tolerance has been demonstrated to the anticonvulsant effects of many drugs, including both CBZ (14) and DZP (39), in the absence of contingent convulsive stimulation [see (13)]. We believe that the induction of tolerance to anticonvulsant drug effects in the absence of contingent convulsive stimulation requires a lengthy period of continuous or near continuous drug exposure. It has been emphasized by several authors [e.g., (13)] that a schedule of regular, frequent injections (e.g., one every 8 h) is more likely to produce tolerance to anticonvulsant drug effects than is a schedule of regular, infrequent injections (e.g., one every 48 h). Although tolerance to bidaily injections did not develop in the present experiment in the absence of contingent convulsive stimulation, we have demonstrated that tolerance to the anticonvulsant effects of both ethanol and DZP can develop in the absence of contingent convulsive stimulation when these drugs are administered more frequently (26,27).

The present experiments constitute the first demonstrations of contingent tolerance to commonly prescribed antiepilepic drugs. The consistency and magnitude of the effect of contingent convulsive stimulation on the development of tolerance to the anticonvulsant effects of CBZ, DZP, and VPA suggest that the occurrence of seizure activity in epileptic patients undergoing drug therapy might facilitate the development of tolerance. However, caution must be used in drawing inferences about tolerance to the effects of chronic drug exposure on spontaneously recurring seizures in human patients from studies of tolerance to the effects of bidaily injections on elicited convulsions in rats. There is no direct evidence that the development of tolerance to the anticonvulsant effects of antiepileptic drugs in human patients is influenced by either the type or the severity of concurrent seizures (45). Moreover, it has been shown that elicited-kindled convulsions and spontaneous convulsions in kindled rats can respond differently to antiepileptic drugs (30).

Tolerance appeared to develop more slowly and to a lesser degree in the VPA-before-stimulation group than in the CBZ-before-stimulation and DZP-before-stimulation groups. However, this difference must be interpreted with caution: the drugs were studied in different experiments, no effort was made to insure that their doses were equipotential, and different routes of drug administration were employed; the purpose of these experiments was not to compare the rates of tolerance development. However, the observation of weak tolerance effects to VPA is consistent with several previous observations [e.g., (25,47)], and it thus may reflect some fundamental property of VPA.

There have been several attempts to provide a theoretical account of contingent tolerance. The most widely recognized is the reinforcement-density model of contingent tolerance [e.g., (7–9)]. This model is based upon the observation that tolerance to a drug's behavioral effects often develops when the initial effect of the drug causes a loss of reinforcement. The key assertion of this model is that tolerance to a drug's effects emerges as the drug recipient develops behavioral strategies to compensate for the drug effects that are responsible for the loss of reinforcement. Although the reinforcement-density model of contingent tolerance has provided a useful framework for understanding instances of contingent tolerance that involve an obvious decrease in positive reinforcement [e.g., (4–6, 8)] or an increase in negative reinforcement [e.g., (22)], it is not useful as an explanation of instances of contingent tolerance that do not involve an obvious reinforcement mechanism. This would include instances of contingent tolerance to the analgesic effects of ethanol [e.g., (17)] or morphine [e.g., (1)] in spinally transected rats; contingent tolerance to ethanol's effects on the decay of posttetanic potentiation in the abdominal ganglia of the marine mollusc *Aplysia* (44); and contingent tolerance to anticonvulsant drug effects as described in the present paper [see also (28,31)].

We (24) have proposed an alternative to the reinforcement-density model of contingent drug tolerance that is based upon widespread evidence of activity-dependent change throughout the nervous system. "Coincidence of activity may be the basic algorithm of activity-dependent changes in excitatory circuitry" [(3); p. 290]. Coincidence of activity amongst neural elements has been shown to be involved in the plasticity of neural systems as diverse as the hippocampus [e.g., (46)], the visual cortex [e.g., (41)], and the neuromuscular junction [e.g., (21)]. Given the importance of activity-dependent change throughout the nervous system, we propose that coincidence between neural activity and drug exposure may play a similar role in the development of pharmacologic tolerance. For example, it is possible that pharmacologic tolerance to the anticonvulsant effects of a drug like diazepam may develop when both GABA and diazepam concurrently bind to their respective sites on the GABA/benzodiazepine complex while neurons possessing these receptor complexes are active. When the cooccupation of the GABA-A and benzodiazepine receptors occurs while the neurons are engaged in seizure activity, a relatively more permanent change may occur (perhaps as the result of repeated depolarization of the neural membrane while the GABA-A and benzodiazepine receptors are occupied) and contingent tolerance may develop to diazepam's anticonvulsant effect.

At this point, such an activity-dependent model of drug tolerance is nothing more than conjecture. However, it does offer an alternative to the reinforcement-density model of contingent tolerance that may be more likely to explain instances of contingent tolerance that do not involve reinforcement processes. In addition, the literature on activity-dependent change in other forms of neural plasticity offers a rich physiological framework from which to begin the task of studying the relation between contingent tolerance and pharmacologic tolerance, something that is lacking in the reinforcement-density model.

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REFERENCES

1. Advokat, C. Tolerance to the antinociceptive effect of morphine in spinally transected rats. Behav. Neurosci. 103:1091–1098; 1989.
2. Baltzer, V.; Baud, J.; Degen, P.; Koella, W. P. A procedure to detect development of tolerance "escape" to antiepileptic drugs; first results. In: Frey, H. H.; Fröscher, W.; Koella, W. P.; Meinardi, H., eds. Tolerance to beneficial and adverse effects of antiepileptic drugs. New York: Raven Press; 1986:63–70.
3. Bear, M. F. Activity-dependent modification of functional circuitry as a possible basis for learning. In: Changeux, J. P.; Konishi, M., eds. The neural and molecular basis of learning. New York: Wiley and Sons; 1987:281–300.
4. Carlton, P. L.; Wolgin, D. L. Contingent tolerance to the anorexigenic effects of amphetamine. Physiol. Behav. 7:221–223; 1971.
5. Chen, C. S. A study of the alcohol tolerance effect and an introduction of a new behavioral technique. Psychopharmacologia 12: 433–440; 1968.
6. Chen, C. S. A further note on studies of acquired behavioural tolerance to ethanol. Psychopharmacologia 27:269–274; 1972.
7. Corfield-Sumner, P. K.; Stolerman, I. P. Behavioral tolerance. In: Blackman, D. E.; Sanger, D. J., eds. Contemporary research in behavioral pharmacology. New York: Plenum Press; 1978:391–448.
8. Demellweek, C.; Goudie, A. J. Behavioral tolerance to amphetamine and other psychostimulants: The case for considering behavioral mechanisms. Psychopharmacology (Berlin) 80:287–307; 1983.
9. Demellweek, C.; Goudie, A. J. An analysis of behavioral mechanisms involved in the acquisition of amphetamine anorectic tolerance. Psychopharmacology (Berlin) 79:58–66; 1983.
10. File, S. E.; Wilks, L. The development of tolerance to the pro- and anticonvulsant actions of drugs acting at the GABA-benzodiazepine receptor complex. In: Frey, H.-H.; Fröscher, W.; Koella, W. P.; Meinardi, H., eds. Tolerance to beneficial and adverse effects of antiepileptic drugs. New York: Raven Press; 1986:63–70.
11. Frey, H.-H. Tolerance and dependence. In: Frey, H.-H.; Janz, D., eds. Handbook of experimental pharmacology: Antiepileptic drugs. New York: Raven Press; 1985:266–282.
12. Frey, H.-H. Experimental evidence for the development of tolerance to anticonvulsant drug effects. In: Frey, H.-H.; Fröscher, W.; Koella, W. P.; Meinardi, H., eds. Tolerance to beneficial and adverse effects of antiepileptic drugs. New York: Raven Press; 1986:7–14.
13. Frey, H.-H. Tolerance to antiepileptic drugs effects: Experimental evidence and clinical significance. Pol. J. Pharmacol. Pharm. 39: 495–504; 1987.
14. Frey, H.-H.; Löscher, W. Pharmacokinetics of carbamazepine in the dog. Arch. Int. Pharmacodyn. Ther. 243:180–190; 1980.
15. Greenblatt, D. J.; Shader, R. I. Dependence, tolerance, and addiction to benzodiazepines: Clinical and pharmacokinetic considerations. Drug Metab. Rev. 8:13–28; 1978.
16. Hönack, D.; Löscher, W. Amygdala-kindling as a model for chronic efficacy studies on antiepileptic drugs: Experiments with carbamazepine. Neuropharmacology 28:599–610; 1989.
17. Jørgenson, H. A.; Berge, O. B.; Hole, K. Learned tolerance to ethanol in a spinal reflex separated from supraspinal control. Pharmacol. Biochem. Behav. 22:293–295; 1985.
18. Kim, C. K.; Pinel, J. P. J.; Hudda, M. M.; Wong, D. J.; Yung, A. Tolerance to the anticonvulsant effects of phenobarbital, trimethadione, and clonazepam in kindled rats: Cross tolerance to carbamazepine. Pharmacol. Biochem. Behav. 41:115–120; 1992.
19. Koella, W. P.; Meinardi, H. On the methodology for the detection and detailed study of tolerance in man. In: Frey, H.-H.; Fröscher, W.; Koella, W. P.; Meinardi, H., eds. Tolerance to beneficial and adverse effects of antiepileptic drugs. New York: Raven Press; 1986:163–169.
20. Lai, A. A.; Levy, R. H.; Cutler, R. E. Time-course of interaction between carbamazepine and clonazepam in normal man. Clin. Pharmacol. Ther. 24:316–323; 1978.
21. Landmesser, L. T. The development of specific motor pathways in the chick embryo. Trends Neurosci. 7:336–339; 1980.
22. LeBlanc, A. E.; Kalant, H.; Gibbons, R. J. Acquisition and loss of behaviorally augmented tolerance to ethanol in the rat. Psychopharmacology (Berlin) 48:153–158; 1976.
23. Löscher, W.; Schwarck, W. S. Development of tolerance to the anticonvulsant effect of diazepam in amygdala-kindled rats. Exp. Neurol. 90:373–384; 1985.
24. Mana, M. J. Pharmacologic tolerance and contingent tolerance to anticonvulsant drug effects. Unpublished doctoral dissertation. University of British Columbia; 1990.
25. Mana, M. J.; Kim, C. K.; Pinel, J. P. J. Tolerance to the anticonvulsant effects of carbamazepine, diazepam and sodium valproate in kindled rats. Pharmacol. Biochem. Behav. 41:109–113; 1992.
26. Mana, M. J.; Pinel, J. P. J. RO 15-1788 induced reversal of pharmacologic tolerance, but not contingent tolerance, to diazepam's anticonvulsant effect. Soc. Neurosci. Abstr. 16:165.16; 1990.
27. Mana, M. J.; Pinel, J. P. J.; Lê, A. D. Tolerance to the anticonvulsant effect (ACE) of ethanol: Lack of a response contingency. Alcohol 23:A45; 1988.
28. Mana, M. J.; Pinel, J. P. J. Response contingency and the dissipation of ethanol tolerance. Alcohol Alcohol. Res. (1):413–416; 1987.
29. Pellegrino, L. J.; Pellegrino, A. S.; Cushman, A. J. A stereotaxic atlas of the rat brain. 2nd edition. New York: Plenum Press; 1979.
30. Pinel, J. P. J. Effect of diazepam and diphenylhydantoin on elicited and spontaneous seizures in kindled rats: A double dissociation. Pharmacol. Biochem. Behav. 18:61–63; 1983.
31. 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.
32. Pinel, J. P. J.; Kim, C. K.; Mana, M. J. Contingent tolerance to the anticonvulsant effects of drugs. In: Wada, J., ed. Kindling 4. New York: Raven Press; in press.
33. Pinel, J. P. J.; Mana, M. J.; Renfrey, G. Contingent tolerance to the anticonvulsant effects of ethanol. Alcohol 2:495–499; 1985.
34. Pinel, J. P. J.; Mana, M. J. Kindled seizures and drug tolerance. In: Wada J., ed. Kindling 3. New York: Raven Press; 1986:33–408.
35. 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: F. A. Davis Publishing; 1990:115–125.
36. Pinel, J. P. J.; Rovner, L. Experimental epileptogenesis: Kindling-induced epilepsy in rats. Exp. Neurol. 58:190–202; 1978.
37. Poulos, C. X.; Hinson, R. E. A homeostatic model of Pavlovian conditioning: Tolerance to scopolamine-induced adipsia. J. Exp. Psychol. [Anim. Behav.] 10:75–89; 1984.
38. Racine, R. J. Modification of seizure activity by electrical stimulation: II. Motor seizure. Electroencephalogr. Clin. Neurophysiol. 32: 281–294; 1972.
39. Rosenberg, H. C.; Chiu, T. H.; Teitz, E. I. Studies on the mechanism of tolerance to benzodiazepines. In: Frey, H.-H.; Fröscher, W.; Koella, W. P.; Meinardi, H., eds. Tolerance to beneficial and adverse effects of antiepileptic drugs. New York: Raven Press; 1986:53–62.
40. Rosenberg, H. C.; Tietz, E. I.; Chiu, T. H. Tolerance to anticonvulsant effects of diazepam, clonazepam, and clobazam in amygdala-kindled rats. Epilepsia 30:276–285; 1989.
41. Shaw, C.; Cynader, M. Disruption of cortical activity prevents ocular dominance changes in monocularly deprived kittens. Nature 308: 731–734; 1984.
42. Siegel, S.; Castellan, N. J. Nonparametric statistics for the behavioral sciences. New York: McGraw-Hill; 1988.
43. Teitz, E. I.; Rosenberg, H. C.; Chiu, T. H. Autoradiographic localization of benzodiazepine receptor downregulation. J. Pharmacol. Exp. Ther. 236:284–292; 1986.
44. Traynor, A. E.; Schlapfer, W. T.; Barondes, S. J. Stimulation is necessary for the development of tolerance to a neuronal effect of ethanol. J. Neurobiol. 11:633–637; 1980.
45. Wigström, W.; Gustafsson, B.; Huang, Y. Y.; Abramham, W. C. Hippocampal long-term potentiation is induced by pairing single afferent volleys with intracellularly injection depolarizing current pulses. Acta Physiol. Scand. 126:317–319; 1986.
46. Voskuyl, R. On the methodology for detection and characterization of tolerance in animals, In: Frey, H.-H.; Fröscher, W.; Koella,

W. P.; Meinardi, H., eds. Tolerance to beneficial and adverse effects of antiepileptic drugs. New York: Raven Press; 1986; 160–163.
47. Young, N. A.; Lewis, S. J.; Harris, Q. L. G.; Jarrott, B.; Vajda, F. J. E. The development of tolerance to the anticonvulsant effects of clonazepam, but not sodium valproate, in the amygdaloid kindled rat. Neuropharmacology 26:1611–1614; 1987.