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# Failure to Establish a Conditioned Place Preference with Ethanol in Rats[1]

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ASIN, K. E., D. WIRTSHAFTER AND B. TABAKOFF. *Failure to establish a conditioned place preference with ethanol in rats*. PHARMACOL BIOCHEM BEHAV 22(2) 169–173, 1985.—Previous studies have demonstrated that many drugs of abuse are able to produce a conditioned place preference in rats. We sought to determine if ethanol, injected in a wide range of doses, could also produce a conditioned place preference. Statistical analysis of our results indicated that the IP administration of the drug (50, 100, 150, 300, 600, 800, or 1000 mg/kg) failed to produce either a conditioned place preference or aversion compared to vehicle injected control rats. Under similar testing conditions a conditioned place preference was obtained with amphetamine (2 mg/kg) and this preference was not secondary to conditioned hyperactivity. In another experiment, rats were injected with ethanol through indwelling jugular cannulae at doses similar to those reported [24,26] to support (1, 2 mg/kg) or not to support (8 mg/kg) self-administration by rats. We also failed to obtain a conditoned place preference using these doses. Blood and brain ethanol levels, determined 1, 2 or 5 minutes after the administration of 2 mg/kg (IV) indicated very low ethanol levels. These results may suggest that rats do not self-administer ethanol for its intoxicating properties, and that the affective state produced by ethanol administration *per se* is not readily conditionable to environmental cues.

Ethanol Ethanol reinforcement Conditioned place preference Amphetamine reinforcement

ALTHOUGH ethanol is a major drug of abuse by man, attempts to demonstrate its reinforcing properties in naive animals have not, in many instances, met with great success. Intravenous and intragastric self-administration techniques have been used for investigating the reinforcing properties of ethanol, but the results of these studies may be frought with interpretive difficulties (for detailed discussion see Altshuler and Tally [2] and Altshuler [1]). The primary drawback with using these techniques is that response rate is typically used as the measure of the drug's reinforcing properties. However, the rate of self-administration may not accurately reflect the degree of drug-induced reinforcement and other, "non-specific" drug effects may be of primary importance in modulating response rate. Thus, drug dosage and self-administration rate may not be linearly related, but rather may follow an inverted-U shaped function (c.f. [18, 19, 24, 31, 32, 34]). Thus, the sedative effects of a drug may mask its increasing reinforcement properties. The self-administration technique also requires the animal to perform an operant (typically to press a lever) in order to obtain reinforcement; response rate must, therefore, at least to some extent, reflect the animal's capability for performing such a task. There are additional interpretive difficulties associated with the self-administration technique, particularly with regard to the development of drug tolerance and dependence, and the reader is referred to more detailed discussions of these problems [5,22].

Another popular method used to study ethanol reinforcement is the 2-bottle preference test. However, there are even more interpretive difficulties with this method than with the one discussed above, including the question of whether genetically heterogenous, non-dependent rats will drink enough to attain sufficient circulating levels of ethanol to produce significant pharmacological effects. A most forceful argument against the use of the 2-bottle preference technique is made by Cicero [6].

One experimental method which would appear to circumvent many of the problems experienced with the aforementioned techniques is the conditioned place preference (CPP) paradigm for investigating the reinforcing properties of a substance. Using this paradigm, the primary reinforcing properties of a drug are conditioned to certain environmental stimuli which, by association, acquire secondary reinforcing properties. Saline injections are paired with different stimuli and on the test day the animal, in the undrugged state, is allowed to "choose" between the stimuli. This technique only requires that the animals perform a simple operant to obtain the (condtioned) reinforcement and testing for the drug's reinforcing properties occurs in the undrugged organism; therefore, the drug cannot interact with the testing proce-

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dure. This paradigm has been successfully used to investigate the rewarding properties of a number of pharmacological agents, including heroin, morphine, cocaine, amphetamine, and enkephalin analogues (c.f. [3, 13, 14, 15, 17, 20, 21, 23]). The CPP paradigm has also been used to investigate ethanol reinforcement [4, 8, 9, 27] and during the preparation of this manuscript Van der Kooy *et al.* [29] reported a failure to establish a conditioned place preference in rats using the IV and IG routes of administration. We report here the results of a series of studies which we conducted using a wide range of ethanol dosages, including those reported to be self-administered IV by rats.

## EXPERIMENT 1

### METHOD

*Subjects*

Adult, male Sprague-Dawley (average weight 410 g), obtained from a colony maintained by the University of Illinois, served as subjects. Animals were housed 6 to a cage, with food and water available ad lib. The colony room was on a 12:12 hr, light:dark schedule.

*Apparatus*

Place preference conditioning was conducted using wood shuttle boxes. Each box contained two large end compartments, identical in size (34×25×36 cm), which were separated from one another by a smaller chamber (11×25×36 cm). Metal guillotine doors were located between the chambers. One end compartment was painted grey, while the other was painted with 3 cm black and white stripes. The center compartment was left unpainted. Each box was supported by two wheels placed outside the center of the middle compartment which allowed the boxes to tilt slightly to either side. A microswitch mounted on the end of each apparatus triggered counters situated in another room. These counters recorded the amount of time spent in each side and the number of crossovers made between the two sides.

*Procedure*

The procedure for CPP can be divided into 3 phases. In Phase 1, the animal was placed into and was allowed to explore the apparatus, with guillotine doors removed, and the number of crossovers and amount of time spent in each side was recorded. These sessions were 15 min long, and the rat was given one session a day for three days. The animal's side preference was based on data obtained from the third day's reading. Rats were then divided into control or treatment groups, matched both for side preference and time spent in the prefered side. Since, in pilot studies, we noted that distilled water-injected rats who spent an extreme amount of time in either end chamber later showed large changes in preference when tested, we eliminated any animal in the current study which spent more than 80% of the time in its "preferred" side. Phase 2 was the conditioning phase. On days 1, 3, 5 and 7, rats received, depending on their group, either 0 (N=30), 50 (N=10), 100 (N=9), 150 (N=10), 300 (N=8), 600 (N=13), 800 (N=15) or 1000 (N=11) mg/kg ethanol. The 50 and 100 mg doses were injected as 6% solutions, while the higher doses were injected in a 12% concentration. All solutions were prepared from 95% U.S.P. ethanol and distilled water. Immediately after the injection, each animal was put into the previously nonpreferred side of the apparatus and was confined there for 30 min. During this period, the guillotine doors were in place. On days 2, 4, 6 and 8, all rats were injected with distilled water in volumes equal to the ethanol injection and were placed into the previously preferred side of the apparatus for 30 minutes. During Phase 3, animals were tested for a change in side preference. The day after the last vehicle injection, the guillotine doors were removed from the appartus and rats were gently placed into the center compartment. Animals were allowed to traverse the entire apparatus for 15 minutes. During this interval, time spent in each end compartment and the number of crossovers were measured.

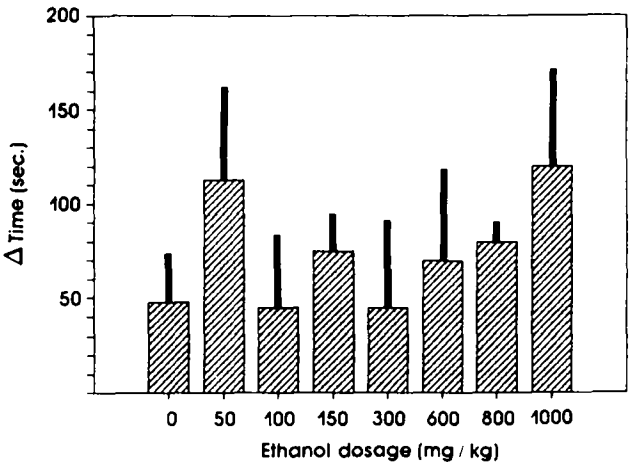


FIG. 1. Change in time spent in the previously preferred compartment on the pre-conditioning and test day for groups of animals that received various dosages of ethanol intraperitoneally.

Although there have been other reports of a CPP induced by injections of amphetamine [20,23], our apparati differed in some respects from those of others. Threfore, we sought to verify that, under our experimental conditions, a CPP could be obtained with amphetamine. Using the methods discussed above, we tested rats (N=14) for the acquisition of a CPP using 2.0 mg/kg d-amphetamine sulphate (2 mg/cc distilled water) or vehicle injections (N=15). The interval between IP injection and placement into the apparatus was 10 minutes. Control animals in both the ethanol and amphetamine studies were injected with distilled water on both sides of the chamber.

Changes in side preference were obtained by subtracting the amount of time spent by the animal on the nonpreferred side on day 3 of the pre-conditioning days from the time spent on that side on the test day. Changes in number of crossovers (i.e., activity) were determined in a similar manner. A one-way analysis of variance (ANOVA) on the difference scores was conducted to test whether changes in side preference or activity differed between vehicle and ethanol-treated groups. Differences in changes in place preference between the amphetamine and control group were tested using Student's *t*-statistic (two-tailed).

### RESULTS

Statistical analysis of side preference scores indicated that the amphetamine injected group differed significantly from the control group (mean Amph=173.7±32.7; mean

Cont=62.8±27.2, $t(27)=2.62$, $p<0.02$). These findings replicate the results of others (vide supra). However, the two groups did not differ ($p>0.20$) with regard to changes in locomotor activity. These results indicate that the change in side preference produced by amphetamine was not secondary to a conditioned increase in activity, a possibility which had not been ruled out by previous studies. In contrast, none of the ethanol treated groups showed any significant changes in side preference compared to controls ($F<1.0$). As indicated in Fig. 1, all groups tended to show an increase in the amount of time spent in the previously non-preferred compartment, but this change in preference did not differ significantly from that shown by the water control group. Changes in locomotor activity also failed to differ between the groups ($p>0.20$).

## EXPERIMENT 2

The results of the above study indicate that the IP administration of ethanol in an extensive range of dosage is unable to produce a conditioned place preference under conditions that do produce a CPP to amphetamine. These results fail to support the findings of Black *et al.* [4] who reported that 1 g/kg ethanol was able to produce a conditioned place preference in rats. However, their analysis was based on changes between the pretest and test days in the injected group rather than the difference scores compared to a control group. Although we found preference changes in some of the ethanol injected groups which differed significantly from zero, we failed to find any that also differed significantly from the preference change shown by control animals.

A number of studies have reported conditioned place aversions using dosages similar to or higher than those used here [8, 9, 27, 29]. However, only two studies [9,27] have used the same dose (1000 mg/kg) and route of administration as those used in the present study, and in one of these studies [9] a place aversion was obtained only on the second, but not the first, day of testing. It is possible that our failure to obtain a conditioned place aversion with this dose may reflect animal strain or procedural differences between the studies. Perhaps the most important procedure difference between this study and the others [9,27] is that our rats were allowed to explore the conditioning chamber prior to any ethanol injection. This exposure to the apparatus prior to drug treatment might conceivably have an effect on the subsequent aversion conditioning process.

It is possible that we were unable to demonstrate a conditioned place preference because the dosages which we administered are not those that rats find reinforcing. The self-administration literature indicates that although monkeys will self-administer ethanol in hundreds of milligrams/kg doses [11, 12, 33], rats appear to self-administer much lower dosages, typically in the mg or the hundreds of micrograms range [24, 25, 26]. These reports may indicate that rats find ethanol reinforcing only in amounts that produce low circulating blood levels of the drug, although no such measurements were made in the previous studies.

The purpose of the following experiments was two-fold: we sought to determine whether or not a CPP could be demonstrated in rats receiving IV ethanol at dosages reported to support self-administration, and we sought to investigate what blood and brain ethanol levels are attained at these dosages.

Smith and Davis [25] first reported IV ethanol self-administration by rats at a dose of 120 $\mu$/kg per injection, and they later reported ethanol self-administration by rats in dosages of 0.1, 0.3, 1 and 3 mg/kg [26]. Sinden and LeMagnen [24] have demonstrated that rats will self-administer 1 mg/kg per infusion of ethanol. These authors also indicated that their rats took multiple ethanol injections within a 5 min period when injecting this dose; the modal number of these infusions was two. Rats self-administering a 5 mg/kg per injection ethanol dosage showed rates of self-administration lower than controls receiving saline. Based on these considerations, we chose to examine the establishment of a CPP in rats treated with 0, 1, 2, or 8 mg/kg doses of ethanol. Following testing, we measured blood and brain ethanol levels in rats treated with the 2 mg dose of ethanol since this was the modal dosage self-administered in the Sinden and LeMagnen [24] study and other studies [26] also suggested that this dose would be self-administered by rats.

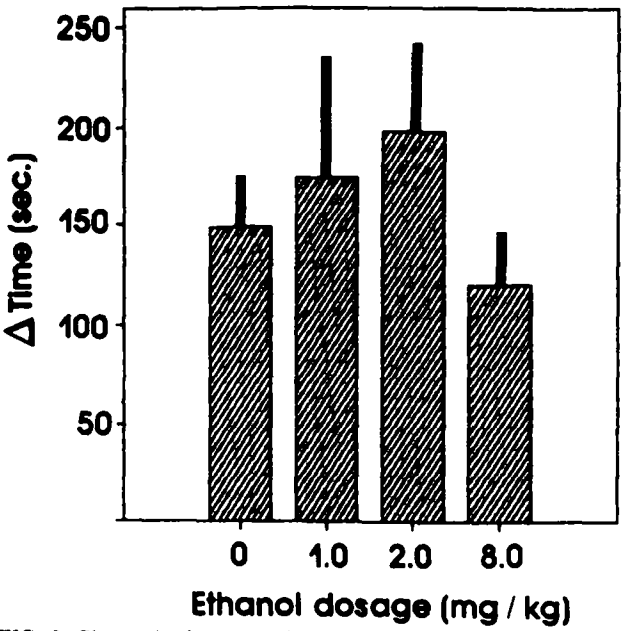


FIG. 2. Change in time spent in the previously preferred compartment on the pre-conditioning and test day for rats who received various dosages of ethanol intravenously.

### METHOD

*Subjects*

Subjects were adult, male Sprague-Dawley rats, as described above. Rats were individually housed with food and water available ad lib; they were maintained on a 12:12 light: dark schedule.

*Surgical Procedures*

Animals were anesthetized with sodium pentobarbital (50 mg/kg). The interscapular and ventral neck regions were shaved and a paramedian incision was made in the ventral neck area; a small incision was also made immediately behind the scapulae. Chronic intrajugular cannulae were implanted according to the method of Davis and Campbell [10]. Following the operation, rats were injected with 0.25 cc (IM) of an antibiotic solution (Flocillin®). Eight to 10 days later, each animal was injected with 0.10 cc of a sodium pentobar-

bital solution (50 mg/cc), followed by a 0.15 ml saline flush. This procedure was performed in order to accustom the animal to the injection procedure and to ascertain that the implanted cannula was patent by monitoring the sedation produced by the drug. The following day, animals were injected with 0.15 cc isotonic saline to further acquaint them with the infusion method.

*Behavioral Procedure*

Phase 1 of the procedure was identical to that detailed in the first experiment. During Phase 2, rats were injected on odd numbered days with either 0 (N=22), 1 (N=7), 2 (N=15) or 8 (N=6) mg/kg per infussion of ethanol (0.698%) in a volume of 0.28 cc/kg. These concentration and volume parameters were based on the method of Sinden and LeMagnen [24]. These infusions were followed by a 0.15 ml isotonic saline flush. The entire injection procedure took less than 30 sec. Rats were then immediately placed in their nonpreferred side for 20 min. On even numbered days, all rats were injected with distilled water (0.28 cc/kg) followed by the 0.15 ml saline flush. The test day (Phase 3) procedures were the same as those in the first experiment. Approximately 1 week following testing, blood and brain ethanol levels were measured in twelve rats after the injection of 2 mg/kg (0.698%) ethanol. Rats were decapitated 1, 2 or 5 min after the injection of ethanol and 50 $\mu$l trunk blood was collected in water for analysis. Brains were quickly removed and homogenized in 0.6 M perchloric acid containing 25 mM thiourea. Ethanol levels were evaluated using gas chromatography according to the method of Tabakoff *et al.* [28].

RESULTS

The mean change in side preference for each group is indicated in Fig. 2. As may be seen, all groups showed significant changes in side preference compared to zero, but there was no difference in the magnitude of this change between the control and ethanol-treated groups ($F<1.0$). Changes in locomotor activity also failed to differ between groups ($p>0.20$).

Blood and brain ethanol levels are shown in Fig. 3. As indicated, all rats showed detectable levels of both blood and brain ethanol and the decay in concentration was very rapid, although levels were still significantly above zero at 5 min.

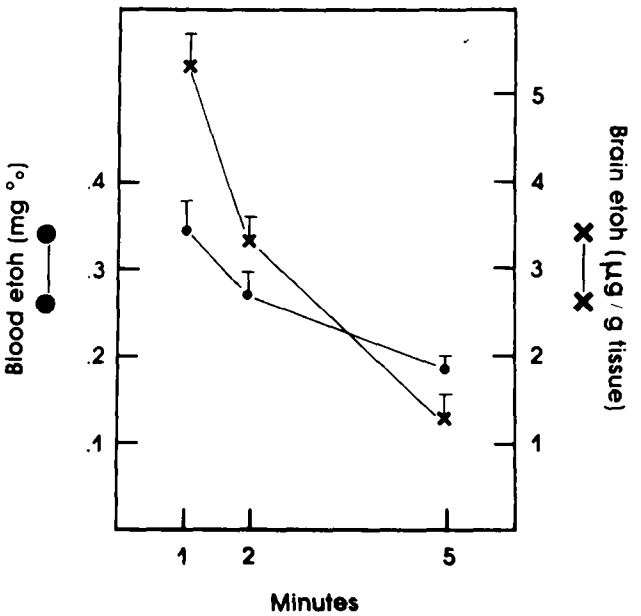


FIG. 3. Blood (●—●) and brain (×—×) ethanol levels 1, 2 or 5 minutes following the IV administration of 2.0 mg/kg ethanol.

## GENERAL DISCUSSION

The results of the present study indicate that ethanol administration is unable to produce a significant conditioned place preference under the same conditions with which an amphetamine place preference can be obtained. Thus, unlike what has been reported to occur using other drugs of abuse (vide supra), ethanol, over a wide range of doses, does not appear to be an effective unconditioned stimulus for the development of a CPP. Although it is possible that a higher ethanol dosage might induce a CPP, doses greater than 1000 mg/kg produce marked sedation in our animals, which might interfere with the conditioning process.

During the preparation of this manuscript, Van der Kooy *et al.* [29] reported the failure of both IV and IG ethanol administration to produce a CPP. The results of our study are consistent with their observations and furthermore extend their findings by failing to demonstrate a CPP using somewhat different dosages and the IP route of administration. Furthermore, our results indicate that the IV administration of low dosages of ethanol, similar to those which have been reported to support self-administration, fails to produce a CPP. These results suggest that rats may find low doses of ethanol reinforcing only if they are in control of the drug's administration. This hypothesis has also been suggested for the somewhat paradoxical finding that some drugs of abuse which are self-administered IV by rats are also capable of producing a conditioned taste aversion [30]. Alternatively, the low levels of blood and brain ethanol we report following a 2 mg/kg dose may indicate that rats may self-administer ethanol for some non-sedative, non-hypnotic action of the drug, particularly since behavioral evidence indicates that rats will self-administer ethanol at doses 20 times smaller than the one used here [26]. Two recent studies [7,16] have reported a failure to obtain low-dose IV self-administration by rats in operant chambers equipped with two levers, where the depression of only one lever resulted in an ethanol infusion. These failures to find evidence for ethanol reinforcement at doses previously reported to be self-administered by rats, along with the results reported here, strongly suggest that non-tolerant rats do not find ethanol reinforcing.

The failure to find an ethanol-induced CPP in the present study suggests that if ethanol has primary reinforcing properties, the affective state produced by its administration does not readily condition to environmental stimuli. This would make ethanol rather unique, since, as discussed previously, conditioned place preferences can be established using other primary reinforcers. One possibility, as suggested by van der Kooy *et al.* [29], is that ethanol is a secondary, rather than a primary, reinforcer. Thus, though its being paired with a primary reinforcer, ethanol will become reinforcing. However, the limited available evidence in this regard [27] suggests that ethanol may simply enhance the reinforcement properties of various primary reinforcers, such as food, sex or social contact, rather than act as a secondary reinforcer.

The contentions that ethanol may act as a secondary rein-

forcer or that it may enhance properties of a primary reinforcer form attractive hypotheses, particularly to explain the failure to obtain a CPP. However, these hypotheses may be inconsistent with observations that rats may self-administer ethanol via either the intravenous or intragastric route. It would be of interest to examine further the potency of low ethanol dosages as reinforcers using higher-order conditioning paradigms.

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## REFERENCES

1. Altshuler, H. L. Animal models for alcohol research. In: *Currents in Alcoholism VIII*, edited by M. Galanter. New York: Grune and Stratton, 1981.
2. Altshuler, H. L. and L. Talley. Intragastric self-administration of ethanol by the rhesus monkey: An animal model of alcoholism. In: *Currents in Alcoholism I*, edited by F. A. Seixas. New York: Grune and Stratton, 1977.
3. Beach, H. D. Morphine addiction in rats. *Can J Psychol* **11**: 104–112, 1957.
4. Black, R. W., T. Albiniak, M. Davis and J. Schumpert. A preference in rats for cues associated with intoxication. *Bull Psychon Sci* **2**: 423–424, 1973.
5. Cappell, H. and A. E. LeBlanc. Tolerance and physical dependence: Do they play a role in alcohol and drug self-administration? In: *Research Advances in Alcohol and Drug Problems 6*, edited by Y. Isreal, F. B. Glaser, H. Kalant, R. E. Popham, W. Schmidt and R. G. Smart. New York: Plenum Press, 1981.
6. Cicero, T. J. Alcohol self-administration, tolerance and withdrawal in humans and animals: theoretical and methodological issues. In: *Alcohol Tolerance and Dependence*, edited by H. Rigter and J. C. Crabbe, Jr. New York: Elsevier, 1980.
7. Collins, R. J., J. R. Weeks, M. M. Cooper and R. R. Russell. Prediction of abuse liability of drugs using IV self-administration by rats. *Psychopharmacology (Berlin)* **82**: 6–13, 1984.
8. Cunningham, C. L. Flavor and location aversion produced by ethanol. *Behav Neurol Biol* **27**: 362–367, 1979.
9. Cunningham, C. L. Spatial aversion conditioning with ethanol. *Pharmacol Biochem Behav* **14**: 263–264, 1981.
10. Davis, J. D. and C. S. Campbell. Chronic intrajugular, intraportal, gastric and duodenal cannulae for the rat. In: *Physiological Techniques in Behavioral Research*, edited by D. Singh and D. D. Avery. California: Brooks/Cole, 1975.
11. Deneau, G., T. Yanagita and M. H. Severs. Self-administration of psychoactive substances by the monkey. *Psychopharmacologia* **16**: 30–34, 1969.
12. Karoly, A. J., G. Winger, F. Ikomi and J. H. Woods. The reinforcing property of ethanol in the rhesus monkey. II. Some variables related to the maintenance of intravenous ethanol-reinforced responding. *Psychopharmacology (Berlin)* **58**: 19–25, 1978.
13. Katz, R. J. and G. Gomezano. A rapid and inexpensive technique for assessing the reinforcing effects of opiate drugs. *Pharmacol Biochem Behav* **11**: 231–234, 1979.
14. Kumar, R. Morphine dependence in rats: Secondary reinforcement from environmental stimuli. *Psychopharmacologia* **25**: 332–338, 1972.
15. Mucha, R. F., D. van der Kooy, M. O'Shaughnessy and P. Bucenieks. Drug reinforcement studied by the use of place conditioning in rat. *Brain Res* **243**: 91–105, 1982.
16. Numan, R., A. M. Naparzewska and C. M. Adler. Absence of reinforcement with low dose intravenous ethanol self-administration in rats. *Pharmacol Biochem Behav* **21**: 609–615, 1984.
17. Phillips, A. G. and F. G. LePiane. Reinforcing effects of morphine microinjection into the ventral tegmental area. *Pharmacol Biochem Behav* **12**: 965–968, 1980.
18. Pickens, R. and W. Harris. Self-administration of d-amphetamine by rats. *Psychopharmacology* **12**: 158–163, 1968.
19. Pickens, R. and T. Thompson. Cocaine-reinforced behavior in rats: Effects of reinforcement magnitude and fixed-ratio size. *J Pharmacol Exp Ther* **161**: 122–129, 1968.
20. Reicher, M. A. and E. W. Holman. Location preference and flavor aversion reinforced by amphetamine in rats. *Anim Learn Behav* **5**: 343–346, 1977.
21. Rossi, N. A. and L. D. Reid. Affective states associated with morphine injections. *Physiol Psychol* **4**: 269–274, 1976.
22. Schuster, C. R. and C. E. Johanson. The use of animal models for the study of drug abuse. In: *Research Advances in Alcohol and Drug Related Problems*, edited by R. J. Gibbons, Y. Israel, H. Kalant, R. E. Popham, W. Schmidt and R. G. Smart. New York: John Wiley and Sons, 1974.
23. Sherman, J. E., T. Roberts, S. E. Roskam and E. W. Holman. Temporal properties of rewarding and aversive behaviors of amphetamine in rats. *Pharmacol Biochem Behav* **13**: 597–599, 1980.
24. Sinden, J. D. and J. LeMagnen. Parameters of low-dose ethanol intravenous self-administration in the rat. *Pharmacol Biochem Behav* **16**: 181–183, 1982.
25. Smith, S. G. and W. M. Davis. Intravenous alcohol self-administration in the rat. *Pharmacol Res Commun* **6**: 397–402, 1974.
26. Smith, S. G., T. E. Werner and W. M. Davis. Comparison between intravenous and intragastric alcohol self-administration. *Physiol Psychol* **4**: 91–93, 1976.
27. Stewart, R. B. and L. A. Grupp. An investigation of the interaction between the reinforcing properties of food and ethanol using the place preference paradigm. *Prog Neuropsychopharmacol* **5**: 609–613, 1981.
28. Tabakoff, B., R. A. Anderson and R. F. Ritzmann. Brain acetaldehyde following ethanol administration. *Biochem Pharmacol* **25**: 1305–1309, 1976.
29. Van der Kooy, D., M. O'Shaughnessy, R. F. Mucha and H. Kalant. Motivational properties of ethanol in naive rats as studied by place conditioning. *Pharmacol Biochem Behav* **19**: 441–445, 1983.
30. Vogel, J. R. Conditioning of taste aversions by drugs of abuse. In: *Neurobiology of Drug Dependence I. Behavioral Analysis of Drug Dependence*. New York: Futura, 1976.
31. Weeks, J. R. and R. J. Collins. Factors affecting voluntary morphine intake in self-maintained addicted rats. *Psychopharmacologia* **6**: 267–279, 1964.
32. Wilson, M. C., M. Hitomi and C. R. Schuster. Psychomotor stimulant self administration as a function of dosage per injection in the rhesus monkey. *Psychopharmacology* **22**: 271–281, 1971.
33. Winger, G. D. and J. H. Woods. The reinforcing property of ethanol in the rhesus monkey. I. Initiation, maintenance and termination of intravenous ethanol-reinforced responding. *Ann NY Acad Sci* **215**: 162–165, 1973.
34. Woods, J. H. and C. R. Schuster. Reinforcement properties of morphine, cocaine and SPA as a function of unit dose. *Int J Addic* **3**: 231–237, 1968.