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Dissociation of Tolerance to the Hypothermic and Tachycardic Effects of Ethanol

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PERIS, J. AND C. L. CUNNINGHAM. *Dissociation of tolerance to the hypothermic and tachycardic effects of ethanol.* PHARMACOL BIOCHEM BEHAV 22(6) 973–978, 1985.—Tolerance to the cardioacceleratory and hypothermic effects of ethanol was studied in unanesthetized, freely-moving rats surgically implanted with EKG electrodes and biotelemetric temperature sensors. Different groups received 0.0, 1,0 or 2.0 g ethanol/kg body weight in injections given every other day for a total of nine injections. Heart rate and body temperature were recorded for 1 hr before and 2 hr after each injection. Ethanol initially induced a monophasic dose-related cardioacceleration (80 bpm) and hypothermia (1.0°C) that persisted throughout the 2-hr sample period. Tolerance developed to the hypothermic, but not to the tachycardic effect of ethanol. Assuming that tolerance depends on level of impairment in specific neuronal pathways, this outcome suggests that these two effects of ethanol are not mediated through a common autonomic mechanism (e.g., vasomotor depression) and /or that tolerance to the hypothermic effect is due to alterations in pathways unique to the thermoregulatory system. Overall, the finding is consistent with those of studies showing development of tolerance to depressant, but not to excitatory drug effects.

Ethanol Heart rate Body temperature Tolerance Rats

THERE are relatively few studies of tolerance to ethanol-induced responses mediated by the autonomic nervous system. The one exception to this is found in the literature on ethanol's thermal effect, an effect mediated in part by autonomic mechanisms. It is well known, for example, that rodents receiving ethanol in room-temperature environments show a monophasic, dose-related hypothermia (e.g., [11,18]) that becomes smaller as a result of repeated exposure to ethanol [6,17]. However, much less is known about effects on other response systems with strong autonomic components.

The present study is concerned with the development of tolerance to a cardiovascular effect of ethanol and asks how it compares to the development of tolerance to ethanol's hypothermic effect. Specifically, the experiment focused on ethanol-induced tachycardia, which is found both in unanesthetized rats [4, 10, 33] and man [22]. Although there is one recent report of tolerance to ethanol-induced tachycardia in human subjects [8], there appear to be no systematic studies of tolerance to this effect in animals.

It has been suggested that the thermic and cardiovascular effects of moderate doses of ethanol are mediated in part by a common mechanism—central vasomotor depression [25]. The resulting increase in cutaneous blood flow presumably increases rate of heat loss, thereby reducing internal temperature. Impairment of central thermoregulatory mechanisms probably contributes to an even greater fall in body temperature [12,17]. The cardiovascular effects of ethanol may also be linked to decreased vasomotor tone. Increased heart rate is predicted as a reflexive reaction to the decrease in peripheral vascular resistance [15,25]. If ethanol affects the thermoregulatory and cardiovascular systems by a common mechanism, it is not unreasonable to suggest that tolerance might develop to effects in both systems, although perhaps at a different rate.

The study reported here evaluated this suggestion by examining the effects of repeated exposure to ethanol on the heart rate and body temperature of unanesthetized, freely-moving rats. Different groups were exposed to saline or one of two doses of ethanol (1 or 2 g/kg) at 48-hr intervals until a total of nine injections had been given. The experiment concluded with a test for tolerance during which all rats received the higher dose of ethanol.

METHOD

Subjects

The subjects were 23 adult male Holtzman albino rats weighing an average of 404 g. They were individually housed in a temperature-controlled colony room with a normal 12 hr

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light/dark cycle and were maintained on a mild food-deprivation schedule (20–25 g of food per day, which maintained animals at about 90% of their initial free-feeding weight) to reduce the chance of injection injury to the gastrointestinal system. Water was available ad lib except during test sessions.

Surgical Preparation

Two days before the start of the experiment, animals were fully anesthetized with halothane gas for surgical implantation of heart-rate monitoring electrodes and a radiotelemetric temperature monitoring device.

Heart rate electrodes. Two 1-cm incisions were made through the skin, one dorsally, approximately 3 cm below and to the right of the base of the skull and the other, ventrally, approximately 1 cm rostral to the left foreleg. Each electrode consisted of 36-cm of 32-ga stainless-steel suture wire that was loosely looped six times through the superficial muscle beneath each incision. The wire tails were covered with polyethylene tubing (Intramedic, No. PE100) and both electrode leads were run subcutaneously to the dorsal incision. The wire ends were soldered to a plug attached to a saddle that fit around the animal's chest and back [32].

Biotelemetry device. Body temperature was detected by an implanted Mini-Mitter (Mini-Mitter Co., Sunriver, OR), a small AM-band transmitter that sends out a signal pulse at a rate proportional to the surrounding temperature. This device allows detection of temperature changes as small as 0.1°C. Two models were used: Model X-M (9 × 16 mm) and Model M (12 × 16 mm). Each unit was protected from fluid corrosion with waterproof Parafin/Elvax (R) and individually calibrated in a temperature-controlled water bath. The Mini-Mitter was inserted through a 1.5-cm ventral midsagital incision through both the skin and peritoneum wall about 5 cm below the diaphragm.

Apparatus

The animals were tested inside a clear plastic cage (23 × 20.5 × 21 cm) with wood shavings on the floor. This cage was placed inside a larger sound- and light-attenuating chamber (50 × 52 × 45 cm). A spring-covered wire "leash" connected the EKG electrodes on the animal's saddle to a swivel [5] incorporated into the ceiling of the plastic cage. After amplification, the heart rate signal was fed into a peak detector [29] that converted the R-wave into a digital signal.

A modified transistor radio was used to receive the signal broadcast from each Mini-Mitter. A PDP8/F computer timed and recorded interpulse intervals (IPIs) from the Mini-Mitters and heart rate electrodes (accurate to 20 msec). A complete description of the hardware and software used for biotelemetry can be found elsewhere [7].

Procedure

In order to habituate the animals to the injection procedure, each rat received a 0.5 ml injection of saline (IP) in the home cage three times daily for 5 consecutive days, starting 24 hr after surgery. Over the same period of time each rat was placed into the experimental chamber on two different occasions to permit habituation to the apparatus and recording procedure. The first habituation session began 48 hr after surgery and the second session was 48 hr later. During these sessions animals were weighed and then placed in the test chambers where temperature and heart rate were recorded for 180 min while the animal was undisturbed.

After the habituation phase, rats were randomly distributed to three groups. These groups differed only in the dose of alcohol administered during each tolerance acquisition session: 0, 1 or 2 g/kg (ns = 7, 8, 8). For these sessions, each rat was removed 60 min after placement in the chamber, injected (IP) and replaced in the chamber for 120 min. Ethanol was diluted with saline (17.8%, v/v) and dosage was manipulated by varying injection volume [18]. Half of Group 0 received a saline injection equivalent in volume to that of Group 2; the other half of Group 0 received the same volume as Group 1. All solutions were maintained at room temperature (25°C). Tolerance acquisition sessions occurred at 48-hr intervals; rats were left undisturbed in their home cages on days between sessions.

After 9 injection and 9 rest days, a test for tolerance was administered. During this test, all animals received a 2.0 g/kg ethanol injection 60 min after placement in the chamber.

Data Analysis

Each IPI from both the heart rate electrodes and the Mini-Mitters was timed during each min of each 3-hr session. As a way of eliminating the contribution of electrical noise to these data, all IPIs that were different by more than 20 msec from the previous IPI were ignored. In addition, all heart rate IPIs greater than 300 msec or less than 80 msec were ignored as were temperature IPIs greater than 440 msec or less than 300 msec. Using these criteria, an average of 5–15% of the heart rate IPIs and 15–25% of the temperature IPIs were discarded as errors.

The mean cardiac IPI for each minute was converted to heart rate and the mean IPI from the Mini-Mitter was converted to body temperature using the calibration values obtained previously. Scores were averaged over 10-min periods for statistical analysis. If signal errors required the data for a whole 10-min period to be discarded, an average score computed from adjacent periods was inserted in place of the discarded data. Inserted means represented less than 1% of the data reported here.

RESULTS

Two rats died during the study (one after the first ethanol injection in Group 2 and one during the tolerance test in Group 0) leaving 7, 8 and 7 subjects in Groups 0, 1 and 2, respectively. Heart rate data were obtained from all of these subjects, but due to a complete loss of the Mini-Mitter signal from five rats, the number of subjects contributing temperature data in these groups were 5, 5 and 7, respectively.

The data of primary interest were the changes in heart rate and body temperature recorded after injection. Change scores for each measure were computed by subtracting each rat's average response during the last 10 min of the pre-injection (baseline) interval from its average response during successive 10-min periods after injection. Temperature change scores from the first sample period were excluded from analysis because they primarily reflected an artifactual drop in temperature produced by the sudden introduction of room temperature fluid around the Mini-Mitter.

Baseline responses and change scores from tolerance acquisition and testing were subjected to separate analyses of variance using treatment dose as a between-groups factor and 10-min sample periods and days (when appropriate) as within-group factors. All p values less than 0.05 were considered significant.

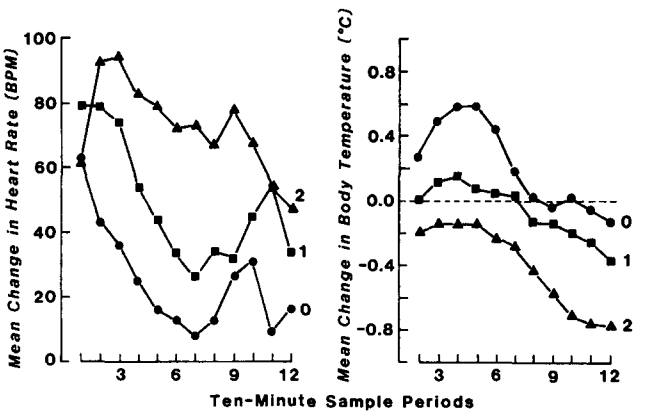

FIG. 1. Mean changes in heart rate (left panel) and body temperature (right panel) during the 2-hr period immediately after the first IP injection of saline (0) or ethanol (1 or 2 g/kg).

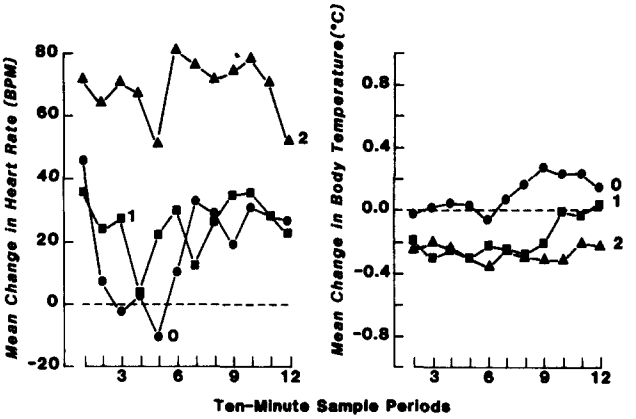

FIG. 2. Mean changes in heart rate (left panel) and body temperature (right panel) during the 2-hr period immediately after the ninth IP injection of saline (0) or ethanol (1 or 2 g/kg).

Acquisition

Heart rate. Heart rate changes after the first injection are plotted over 10-min sample periods in the left-hand panel of Fig. 1. There was a general cardioacceleration (60–80 bpm) immediately after injection in all groups, presumably induced by the handling/injection procedure. Heart rate tended to remain elevated, with the rate of return to baseline inversely related to ethanol dose. Heart rate change in the ethanol groups was still well above control levels at the end of the 2-hr test period.

The left-hand panel of Fig. 2 shows heart rate changes on the last tolerance acquisition day. Repeated exposure to injection over days did not affect the overall average heart rate reactions of the three groups, but there were changes over days in the temporal pattern of the heart rate responses after injection. In general, the magnitude of the initial accelerative reaction declined over days in all groups. At the same time, however, there was an increase in the magnitude of acceleration during later sample periods. The latter effect is illustrated in the left-hand panel of Fig. 3 which depicts heart rate change averaged over the final 30 min of each session in successive blocks of three sessions.

Statistical analysis confirmed these general observations, yielding significant effects of Dose, $F(2,19)=4.9$, Sample Periods, $F(11,209)=9.6$, Dose × Sample Periods, $F(22,209)=3.4$, and Days × Sample Periods, $F(88,1672)=2.1$. The interaction of Dose and Sample Periods primarily reflected the dose-related divergence in the reactions of the groups over time following the initial cardioaccelerative response to handling/injection. The Days × Sample Periods interaction was due to the change noted earlier in the temporal pattern of the cardiac response over successive days. The changes in heart rate over successive acquisition days did not vary as a function of treatment dose.

Temperature. The right-hand panel of Fig. 1 shows mean temperature changes after the first injection. As can be seen, handling and injection elevated body temperature in Group 0 during the first hour after injection. However, ethanol blocked that hyperthermic reaction in Groups 1 and 2, producing a dose-related hypothermia that gradually increased in magnitude over the 2-hr recording session.

Figure 2 (right panel) depicts responding on the final tolerance acquisition day. Generally speaking, repeated injections resulted in an overall increase in body temperature. That is, the magnitude of ethanol-induced hypothermia decreased, whereas handling-induced hyperthermia (in Group 0) increased slightly. This pattern of change can best be seen in the right-hand panel of Fig. 3 which plots the average temperature change over the last 30 min of the session in successive blocks of three sessions.

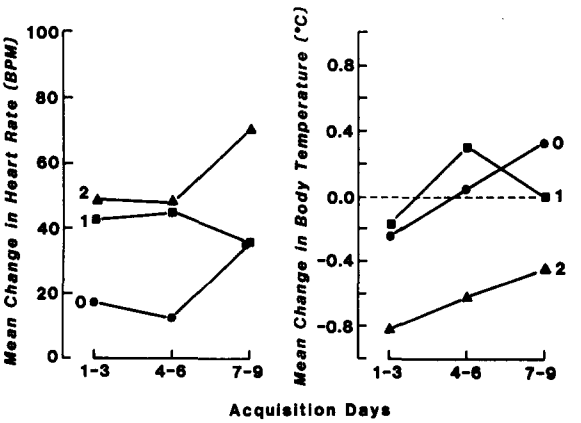

FIG. 3. Mean changes in heart rate (left panel) and body temperature (right panel) during the last 30 min of tolerance acquisition sessions (90–120 min after injection) averaged over blocks of three sessions. Different groups received injections of 0, 1 or 2 g/kg ethanol at 48-hr intervals.

Analysis of variance indicated significant effects due to Dose, $F(2,15)=9.6$, Sample Periods, $F(10,150)=2.4$, Dose × Sample Periods, $F(20,150)=4.1$, and Days × Sample Periods, $F(80,1200)=5.6$. The Dose × Sample Periods interaction was due to the fact that the hyperthermic response in Group 0 was greater during the first hour after injection whereas the hypothermic response in Group 2 was greater during the second hour. Consequently, the magnitude of differences among groups varied as a function of time after injection. The Days × Sample Periods interaction was due to greater changes over days in the temperature response during the second hour after injection (see Fig. 3). The changes in body temperature over days of acquisition did not vary as a function of treatment dose.

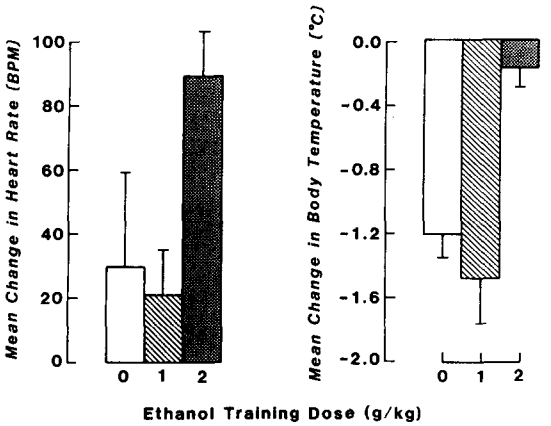

FIG. 4. Mean changes in heart rate (left panel) and body temperature (right panel) 90–120 min after a 2 g/kg challenge injection of ethanol for groups previously injected nine times with 0, 1 or 2 g/kg ethanol. Vertical lines represent standard error of the mean.

Tolerance Test

Heart rate. The challenge injection of ethanol (2 g/kg) produced an immediate increase in heart rate in all groups (35–65 bpm). The magnitude of heart rate change decreased in Groups 0 and 1 over the 2-hr test period, but remained high in Group 2. The left-hand panel of Fig. 4 shows the average change recorded during the final 30 min of testing for each group. An overall analysis of the test data yielded a significant Dose × Sample Periods interaction, $F(22,209)=1.7$, due to the divergence in heart rate change over time between Group 2 and the two other groups. A followup between-groups analysis (Newman-Keul's) of the data shown in the left panel of Fig. 4 indicated a significant difference between Group 2 and each of the other groups, but no difference between Groups 0 and 1.

Temperature. The challenge injection of ethanol produced a drop in body temperature that increased in magnitude over the session in Groups 0 and 1, but not in Group 2. Temperature changes recorded during the final 30 min of the session are shown in the right-hand panel of Fig. 4. As can be seen, the temperature change in Group 2 was substantially smaller than that in Groups 0 and 1. An overall analysis of variance indicated significant effects of Dose, $F(2,14)=10.2$, Sample Periods, $F(10,140)=18.1$, and Dose × Sample Periods, $F(20,140)=6.0$. The interaction reflected the increasing difference over time between Group 2 and the other two groups. Followup comparisons (Newman-Keul's) on responses averaged over the final 30 min showed significant differences between Group 2 and each of the other groups; Groups 0 and 1 did not differ.

Baseline Data

Heart rate was initially elevated in all groups after placement in the chamber (~420 bpm) and gradually declined over the 60-min pre-injection period. Body temperature, which was also elevated initially (~39.1°C) increased slightly during the first 30 min and then returned to lower levels. Examination of data from the habituation days indicated that these measures remained relatively constant after 60 min. In fact, this finding guided our choice of a 60-min pre-injection interval.

As indicated earlier, the individual scores recorded over the last 10 min of the pre-injection interval were used as baselines for computing the change scores described in previous sections. During tolerance acquisition the average baseline heart rates were 317, 308 and 308 bpm for Groups 0, 1 and 2, respectively. The average baseline temperatures for these groups were 38.6, 38.3 and 38.4°C, respectively. Overall Groups × Days analyses of the baseline scores during acquisition yielded no significant main effects or interactions.

Analyses of baselines for the tolerance test, however, indicated some group differences. Mean baseline heart rates for the test session were 318, 329 and 287 bpm for Groups 0, 1 and 2, respectively, $F(2,19)=4.2$. Followup analyses (Newman-Keul's) showed that only the difference between Groups 1 and 2 was significant. Because differences in baseline may alter interpretation of analyses based on change scores, the raw heart rate data from the tolerance test were also analyzed. This analysis indicated that although Group 2 showed a final heart rate that was higher than that in the other groups, differences during the last 30 min of the test were not statistically significant. The average heart rates during that time period were 348, 350 and 376 bpm for Groups 0, 1 and 2, respectively. Thus, the earlier conclusion of greater cardioacceleration in Group 2 must be tempered by the fact that their baseline was lower during the test session.

During the tolerance test, there was an unexplained elevation in the baseline temperature recorded in Group 1. The average baselines were 38.4, 39.0 and 38.3°C for Groups 0, 1 and 2, respectively, $F(2,14)=4.5$. Followup comparisons (Newman-Keul's) showed a significant difference between Group 1 and each of the other groups. Because of the possible implications of this difference for interpretation of change scores, the raw temperature data from the tolerance test were analyzed. This analysis supported the earlier conclusion that thermic tolerance had developed only in Group 2. During the final 30 min of the test, Group 2 had an average temperature of 38.2°C, whereas Groups 0 and 1 showed temperatures of 37.2 and 37.6°C, respectively. Newman-Keul's tests indicated a significant difference between Groups 0 and 2.

DISCUSSION

This experiment showed a dissociation in the development of tolerance to two autonomic drug effects. In a dose range that yielded monophasic dose-related responses, repeated exposure to ethanol produced tolerance to the hypothermic, but not to the cardioacceleratory effect of ethanol (2 g/kg). In fact, ethanol caused a slightly greater acceleratory effect in Group 2 after tolerance acquisition, suggesting the possibility of sensitization to this effect. These results do not support the prediction that tolerance would develop to both measures because of an hypothesized common mechanism for the acute effects of ethanol (i.e., depressed vasomotor tone).

The absence of tolerance to ethanol's tachycardic effect stands in contrast to the finding of a previous report involving human subjects [8]. This discrepancy could be due to differences in any of several procedural variables (e.g., mode of administration, deprivation state) or to species differences in the mechanism of ethanol-induced tachycardia. That previous report also showed that tolerance to ethanol tachycardia in humans is environment-specific, suggesting an important role of learning in tolerance. Although the present study was not designed to assess the contribution of learning to the development of tolerance to either the cardiovascular or

thermic effects of ethanol, the treatment regimen used here was probably sufficient to induce Pavlovian conditioning (see [6]).

The data from the tolerance acquisition sessions (e.g., Fig. 3) strongly suggest that nonpharmacological processes related to handling and injection influence the organism's changing response to ethanol. Both in the case of heart rate and body temperature, control animals receiving repeated injections of saline showed changes that paralleled those of the high-dose ethanol group. These changes might reflect some kind of habituation to stress and/or a very general kind of learning (e.g., anticipation of the end of the test session based on the passage of time). Nevertheless, the difference between groups during the final tolerance test makes it clear that the presence of ethanol during acquisition sessions was critical to the development of tolerance to its hypothermic effect.

While the data clearly provide no evidence of tolerance to ethanol's tachycardic effect, the stronger conclusion that sensitization occurred appears to depend on the fact that group differences in baseline scores were observed during testing. Because these differences were not present during the earlier tolerance acquisition sessions in this study and have not been observed in a subsequent study of tolerance to these autonomic effects in our lab [23], we must conclude that they were a chance occurrence and that sensitization probably did not occur. It should be noted that the latter study, which involve 14 exposures to a 2 g/kg dose of ethanol, confirmed the main findings reported here—namely, development of tolerance to the hypothermic, but not to the cardioacceleratory effect of ethanol.

If tachycardia and hypothermia are broadly characterized as "excitatory" and "depressant" effects of ethanol, respectively, then the present outcome is generally consistent with those of studies suggesting that tolerance develops to the depressant, but not to the excitatory effects of certain drugs [27]. The latter suggestion has been supported largely by studies of locomotor behavior which show development of tolerance to the activity-reducing effects of ethanol and morphine, but no tolerance to their activity-increasing effects [1, 2, 20, 26, 30]. Although one might argue that the increase in heart rate observed here was secondary to an ethanol-induced increase in locomotor activity, this seems unlikely in light of other studies indicating that nonshocked albino rats show no increase (or even show a decrease) in activity at these dose levels [13,24].

It is possible that despite a common vasomotor mechanism for the acute effects on heart rate and body temperature, tolerance to the thermic effect of ethanol is not mediated through recovery of vasomotor tone, but is due instead to increased activity in other heat-conserving or heat-producing response systems. If repeated exposure to ethanol does not lead to centrally-mediated increases in vasomotor responsiveness [3], reflexive increases in heart rate might be expected to remain relatively constant.

Alternatively, it may be that the dissociation of tolerance to the cardiovascular and thermic effects of ethanol reflects a more fundamental difference in the mechanisms that underlie those effects. For example, alterations in hypothalamic thermoregulatory centers may be more critical to ethanol's overall thermic effect than changes in vasomotor tone. It may also be that the cardioacceleratory effect of ethanol is due less to vasomotor depression than to stimulation of catecholaminergic activity either by ethanol's intermediate metabolite, acetaldehyde [31], or by other mechanisms [9]. To the extent that the mechanisms underlying these autonomic reactions to ethanol differ, so might the development of tolerance, assuming that tolerance depends on level of functional impairment in specific neuronal pathways [16]. When viewed in this way, the present failure to find tolerance to the tachycardic effect of ethanol might indicate that these dose levels simply did not produce sufficient impairment of the cardiovascular system.

Finally, this experiment joins a growing body of studies that fail to show generalization of tolerance across different response systems in the same animal (e.g., [14, 19, 21, 28]). Although not entirely conclusive, such outcomes encourage rejection of the notion that tolerance reflects a unitary underlying process [16,21].

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REFERENCES

1. Babbini, M. and W. M. Davis. Time-dose relationships for locomotor activity effects of morphine after acute or repeated treatment. *Br J Pharmacol* **46:** 213–224, 1972.
2. Brady, L. S. and S. G. Holtzman. Locomotor activity in morphine-dependent and post-dependent rats. *Pharmacol Biochem Behav* **14:** 361–370, 1981.
3. Chan, T. C. K. and M. C. Sutter. Ethanol comsumption and blood pressure. *Life Sci* **33:** 1965–1973, 1983.
4. Crow, L. T. Effects of alcohol on heart rate. *Physiol Behav* **3:** 71–73, 1968.
5. Cunningham, C. L. A cable-swivel device for delivering shock to tail or harness electrodes. *Behav Res Methods and Instrum* **10:** 106, 1978.
6. Cunningham, C. L., J. C. Crabbe and H. Rigter. Pavlovian conditioning of drug-induced changes in body temperature. *Pharmac Ther* **23:** 365–391, 1984.
7. Cunningham, C. L. and J. Peris. A microcomputer system for temperature biotelemetry. *Behav Res Methods and Instrum* **15:** 598–603, 1983.
8. Dafters, R. and G. Anderson. Conditioned tolerance to the tachycardia effect of ethanol in humans. *Psychopharmacology (Berlin)* **78:** 365–367, 1982.
9. Engel, J. and S. Liljequist. The involvement of different central neurotransmitters in mediating stimulatory and sedative effects of ethanol. In: *Stress and Alcohol Use*, edited by L. A. Pohorecky and J. Brick. Amsterdam: Elsevier, 1983, pp. 153–169.
10. Fitzgerald, R. D. and G. L. Stainbrook. The influence of ethanol on learned and reflexive heart rate responses of rats during classical aversive conditioning. *J Stud Alcohol* **11:** 1916–1930, 1978.
11. Freund, G. Hypothermia after acute ethanol and benzyl alcohol administration. *Life Sci* **13:** 345–349, 1973.
12. Freund, G. Ethanol-induced changes in body temperature and their neurochemical consequences. In: *Biochemistry and Pharmacology of Ethanol*, vol 2, edited by E. Majchrowicz and E. P. Noble. New York: Plenum Press, 1979, pp. 439–452.

13. Frye, G. D. and G. R. Breese. An evaluation of the locomotor stimulating action of ethanol in rats and mice. *Psychopharmacology (Berlin)* **75:** 372–379, 1981.
14. Hogans, A. F., O. M. Moreno and D. A. Brodie. Effects of ethyl alcohol on EEG and avoidance behavior of chronic electrode monkeys. *Am J Physiol* **201:** 434–436, 1961.
15. Juchems, R. and R. Klobe. Hemodynamic effects of ethyl alcohol in man. *Am Heart J* **78:** 133–135, 1969.
16. Kalant, H. Behavioral criteria for tolerance and physical dependence. In: *The Basis of Addiction*, edited by J. Fishman. Berlin: Dahlem Konferenzen, 1978, pp. 199–220.
17. Kalant, H. and A. D. Le. Effects of alcohol on thermoregulation. *Pharmacol Ther* **23:** 313–364, 1984.
18. Linakis, J. G. and C. L. Cunningham. Effects of concentration of ethanol injected intraperitoneally on taste aversion, body temperature and activity. *Psychopharmacology (Berlin)* **64:** 61–65, 1979.
19. Mansfield, J. G., R. S. Benedict and S. C. Woods. Response specificity of behaviorally augmented tolerance to ethanol supports a learning interpretation. *Psychopharmacology (Berlin)* **79:** 94–98, 1983.
20. Masur, J. and R. Boerngen. The excitatory component of ethanol in mice: A chronic study. *Pharmacol Biochem Behav* **13:** 777–780, 1980.
21. Mucha, R. F., H. Kalant and M. A. Linseman. Quantitative relationships among measures of morphine tolerance and physical dependence in the rat. *Pharmacol Biochem Behav* **10:** 397–405, 1979.
22. Naitoh, P. The effect of alcohol on the autonomic nervous system of humans: Psychophysiological approach. In: *The Biology of Alcoholism, Vol. 2: Physiology and Behavior*, edited by B. Kissin and H. Begleiter. New York: Plenum Press, 1972, pp. 367–433.
23. Peris, J. Associative and nonassociative mechanisms in the development of tolerance to the thermic and cardiovascular effects of ethanol. Unpublished doctoral dissertation, Oregon Health Sciences University, Portland, 1984.
24. Pohorecky, L., E. Makowski, B. Newman and E. Rassi. Cholinergic mediation of motor effects of ethanol in rats. *Eur J Pharmacol* **55:** 67–72, 1979.
25. Ritchie, J. M. The aliphatic alcohols. In: *The Pharmacological Basis of Therapeutics (6th edition)*, edited by A. G. Gilman, L. S. Goodman and A. Gilman. New York: Macmillan, 1980, pp. 376–390.
26. Schnur, P., F. Bravo and M. Trujillo. Tolerance and sensitization to the biphasic effects of low doses of morphine in the hamster. *Pharmacol Biochem Behav* **19:** 435–439, 1983.
27. Seevers, M. H. and G. A. Deneau. Physiological aspects of tolerance and physical dependence. In: *Physiological Pharmacology*, vol 1, edited by W. S. Root and F. G. Hofmann. New York: Academic Press, 1963, pp. 565–640.
28. Sherman, J. E. The effects of conditioning and novelty on the rat's analgesic and pyretic responses to morphine. *Learn Motiv* **10:** 383–418, 1979.
29. Shimizu, H. Reliable and precise identification of R-waves in the EKG with a simple peak detector. *Psychophysiology* **15:** 499–501, 1978.
30. Tabakoff, B. and K. Kiianmaa. Does tolerance develop to the activating as well as the depressant effects of ethanol? *Pharmacol Biochem Behav* **17:** 1073–1076, 1982.
31. Truitt, E. B. and M. J. Walsh. The role of acetaldehyde in the actions of alcohol. In: *The Biology of Alcoholism, Vol. 1: Biochemistry*, edited by B. Kissin and H. Begleiter. New York: Plenum Press, 1971, pp. 161–195.
32. Weeks, J. R. Long-term intravenous infusion. In: *Methods in Psychobiology*, vol 2, edited by R. D. Myers. London: Academic Press, 1972, pp. 155–168.
33. Wilkin, L. D., C. L. Cunningham and R. D. Fitzgerald. Pavlovian conditioning with ethanol and lithium: Effects on heart rate and taste aversion in rats. *J Comp Physiol Psychol* **96:** 781–790, 1982.