Pharmacology Biochemistry & Behavior, Vol. 38, pp. 575–580. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

The Influence of Early Postweaning Ethanol Exposure on Oral Self-Administration Behavior in the Rat

GERALD A. TOLLIVER AND HERMAN H. SAMSON

Alcohol and Drug Abuse Institute, University of Washington, Seattle, WA 98195

Received 1 October 1990

TOLLIVER, G. A. AND H. H. SAMSON. *The influence of early postweaning ethanol exposure on oral self-administration behavior in the rat.* PHARMACOL BIOCHEM BEHAV **38**(3) 575–580, 1991.—The effects of three early ethanol home cage consumption procedures on the maintenance of operant lever responding reinforced by ethanol presentation were examined in the rat. Two groups of rats, 25 and 31 days of age, were exposed to 10% (v/v) ethanol as the only fluid in the home cage for 3 or 10 days. A third group, 31 days of age, were exposed to 10% ethanol or tap water for 24 h, with the fluid alternating daily for 18 days. All animals were subsequently trained to lever press using 10% ethanol reinforcement under a decreasing water restriction schedule. All three groups were found to have substantial ethanol consumption levels during the initial exposure in the home cage, ranging from 11.2 to 11.9 g/kg/day. The animals were all successfully trained to lever press in the operant chamber with ethanol as the reinforcer when limited to 15 ml/day of water in the home cage. The average number of reinforcements per day ranged from 29 to 43.5, yielding ethanol intakes from 1.06 to 1.97 g/kg in the 30-minute operant session. However, when 50 ml/day of water was available in the home cage, ethanol reinforcements were substantially reduced, with intakes which ranged from 0.14 to 0.18 g/kg/day. The data suggest that early exposure does not enhance ethanol's reinforcing properties later in the animal's life. These results were discussed in terms the effect of early ethanol exposure on later ethanol consumption and the role of ethanol initiation procedures in oral self-administration.

Early exposure Ethanol reinforcement Ethanol initiation Rats

THE influence of early experience with alcohol on later adult consumption has been a topic of concern in the development of human alcohol abuse (3, 10, 30). It has been postulated that early exposure to alcohol could initiate the child to its reinforcing aspects, increasing the likelihood that excessive alcohol consumption would be established later in life.

Exposure to a variety of substances during the prenatal period in experimental animals can enhance preference for those substances as the animal matures [e.g., see (7)]. In addition, environmental conditions occurring in early postnatal life, such as stress, have been shown to affect subsequent ethanol intake in the rat (20–22). An interaction between these factors in the case of ethanol may lead to increased intake levels later in life. However, investigations of the influence of early ethanol experience on later ethanol intake has not received much attention in the animal literature.

Studies which examine questions relevant to these issues suggest that the type of early ethanol exposure and the measure used to assess the subsequent effects are important factors. The most frequent types of early exposure have been: prenatal exposure via the rat dam's diet (1, 4, 8, 13, 16, 19) or postnatal exposure in rat pups from birth to weaning using either intraperitoneal (IP) injection (11), inhalation (14,15), forced oral consumption with ethanol as the only fluid (18,33), or a water-ethanol choice situation (5,12). Ethanol preference, as measured in a two-bottle home cage choice situation with tap water as the other available fluid, has been used primarily as the measure of change in ethanol consumption resulting from prior ethanol exposure.

Ethanol given in the prenatal period has been the most frequently used procedure to examine the influence of early exposure on later ethanol consumption. Concentration and dose levels of ethanol consumed by the mother and the gestational period at which exposure occurred appear to be important factors in determining the effects. Two studies have reported increased ethanol preference scores following prenatal exposure. Bond (4) used a liquid diet procedure resulting in an ethanol intake of 14 g/kg/day for the exposed dams. The offspring had an increased preference for ethanol which was concentration dependent, preferring low ethanol concentration (3% to 6%) over controls, but not differing at higher ethanol concentrations (7% and 8%). In the second study, rats exposed prenatally to Chablis wine were found to have a higher wine intake level than control animals, at 170 days of age (19). However, the intake differences between these groups was small, approximately 5 ml per day. Other studies examining the effect of similar ethanol exposure doses of 12 g/kg/day and 13 g/kg/day have failed to find any ethanol preference differences

between exposed rats and control animals (13,16). In studies that have investigated the effects of low doses of ethanol exposure during gestation, 1–2 g/kg/day (1) and 2.8–3.5 g/kg/day (8), no differences in two bottle ethanol-water preference ratios were found between exposed and control offspring.

The effects of ethanol experienced in the early postnatal period are also inconsistent. One study using daily ethanol IP injections in rats (0.63 to 2.50 g/kg) from day 6 to 12 after birth found substantially increased ethanol preference ratios in a two-bottle choice test when compared to the saline control animals at 120 days of age. The ethanol preference ratios for the exposed group averaged 90% and 70% for 5% and 10% ethanol respectively, while nonexposed control animals had preference ratios of 37% and 30% for the same ethanol concentrations (11).

Two studies have examined the effects of early forced ethanol consumption on later preference ratios. In Wistar rats, no increase in ethanol preference was found in animals acclimated to ethanol as the only available fluid (2% increasing to 8%) over a 4-week period beginning at 30 days of age when compared to 90-, 300- and 600-day-old animals tested with the same procedures (18). Yoshimoto (33) exposed C57BL/6M mice to 10% ethanol for 3 days as their sole fluid followed by an ethanol-water choice for the next 15 days. Mice tested at 112 days of age and exposed to ethanol at 28 and 49 days of age consumed ethanol with a higher preference ratio than did those first exposed at 70 and 91 days.

Clay (5) exposed rats to a choice between an increasing concentration of ethanol (2% to 5%) and water between 19 and 60 days of age (the early exposure group) and between 60 and 180 days (the late exposure group). While the results are difficult to interpret, the early exposure group had ethanol preferences at least 45 percentage points higher than the late exposure group. Recently, C57BL/6J mice exposed to a 10% ethanol-water choice at 3 weeks of age were found to have a small but significantly greater ethanol intake compared to control animals exposed at eight weeks of age (12).

Rats exposed to the smell of ethanol in the early postweaning period (21 days of age) were found to have ethanol preference scores above control animals 40 to 120 days later (14). Molina and his colleagues also demonstrated that ethanol odor paired with either positive or negative events led to changes in ethanol preference in early exposed animals but not in older rats (15).

Thus studies using different ethanol exposure techniques at different times in the prenatal or early postnatal periods in rats and mice have produced variable results on voluntary ethanol consumption at a later time in the animal's life. While these studies are suggestive that the early exposure can result in increased ethanol intake, they do not directly test the supposition that animals will be more susceptible to the reinforcing effects of ethanol following exposure at an early age. The relevance of ethanol preference measures to the pharmacological reinforcing properties of ethanol has been questioned (6). Other measures of ethanol consumption behavior such as an operant oral self-administration paradigm have not been used to study the effects of early exposure on ethanol's reinforcing efficacy. Therefore, the present series of studies assessed the influence of ethanol exposure in the early postweaning period in rats on the establishment of ethanol self-administration behavior in an operant paradigm.

GENERAL METHOD

Animals

Male Long Evans weanling pups, separated from their mothers at 25 to 30 days of age (60–100 g), were obtained from the breeding colony of Department of Psychology, University of Washington. Except for the animals of Experiment II, all animals were housed in individual hanging cages with free access to lab chow (Wayne F6 Rodent chow). Animals were maintained on differing fluid schedules throughout the studies as described below. The animal colony room was on a 12-h light/dark cycle (06:30–18:30).

Apparatus

The studies to be described were conducted both in the animal's home cage and in operant chambers located in a separate room. The home cages used in the studies were ($17 \times 18 \times 25$ cm) equipped with hanging food hoppers and two metal clips attached to the front wall of the cage, spaced approximately 10 cm apart. These clips allowed two 50 ml polypropylene drinking tubes to be placed on the cage, each equipped with a ball bearing drinking spout which protruded into the animal's cage.

The eight operant chambers have been described previously (23). Each chamber was equipped with two removable operant levers and two dipper style liquid delivery mechanisms (Gerbrand Corp., Model GS-5600). The levers were located on the front and back walls of the chamber with the two liquid dispenser systems mounted on a single wall spaced 17 cm apart and 4 cm above the floor. The chamber floor was made of stainless steel rods. Lever presses and liquid dipper operations were monitored and controlled by Apple microcomputers. The dippers provided access to 0.1 ml of fluid for 3 s at each operation. A 10-W house light illuminated the chamber during each session.

EXPERIMENT 1

This study employed a three-day ethanol exposure in weanling rat pups. Ethanol self-administration in an operant reinforcement paradigm was examined to determine if this exposure resulted in a increase in ethanol's reinforcing ability.

METHOD

Procedure

Eight male rat pups 31 days old (average body weight of 90.1 g) were used in this study. Upon arrival from the breeding colony, the animals were housed in individual hanging cages with a single drinking tube filled with 10% ethanol (v/v) and an unlimited supply of food. These conditions were in effect for three days followed by two days with tap water as the only fluid supply. Body weight and fluid consumption was measured daily.

Next, the water bottles were removed from the home cage 20 hours prior to the beginning of the operant training session. Each training session lasted 30 minutes and only one session occurred per day. Water restriction (20 h) was continued until each animal had learned to lever press using 10% ethanol reinforcement.

Throughout the remaining sessions ethanol reinforcements were delivered on a fixed ratio schedule where every lever response was reinforced (FR 1).

Following training, the animals were given a gradually increasing amount of water in the home cage 30 minutes after each operant session. The gradual elimination of the water restriction condition was performed as an attempt to remove fluid deprivation while maintaining ethanol reinforced responding. While fluid restriction varied slightly for each animal, the schedule can generally be described as follows: 15 ml of water in the home cage following the operant session on 2 successive days; 3 days with 20 ml; 3 days of 25 ml; 1 day of 35 ml; and finally 4 days with 50 ml supply of water on the home cage (an amount not com-

pletely consumed during the 24-hour period). The number of ethanol lever responses and ethanol reinforcements were recorded for each operant session.

RESULTS

Daily home cage ethanol consumption during the 3-day forced ethanol drinking averaged 14.0 ml/24 h and 11.3 g/kg (Table 1, Experiment 1). During this period the animals gained an average of 5 g per day (weighing 104.5 g by day three). When water only was available during the subsequent two days the animals consumed a daily average of 24.3 ml and gained an average of 5 g (weighing an average of 116.6 g on day 5).

Ethanol reinforcements during the initial phase of the 30-minute operant sessions (i.e., under 15 ml of water restriction in the home cage) was found to average 37.9 reinforcements, with a calculated ethanol intake of 1.97 g/kg. As the water restriction was gradually eliminated, ethanol reinforcements steadily declined to 6.0 with an ethanol intake of only 0.18 g/kg when 50 ml of water was available daily on the home cage (Table 1). The animals maintained a steady weight gain during the operant sessions despite the mild water restriction schedule, gaining approximately 4% of their total body weight per day.

TABLE 1

HOME-CAGE ETHANOL INTAKE UNDER THREE ETHANOL EXPOSURE PROCEDURES AND SUBSEQUENT ETHANOL REINFORCEMENTS IN THE OPERANT CHAMBER UNDER DIFFERENT LEVELS OF WATER RESTRICTION

	Home-Cage Ethanol Intake					
	ml/Day				g/kg/Day	
Exposure Groups	Mean	SD			Mean	SD
3-Day (Experiment 1)	14.0	1.3			11.3	1.1
10-Day (Experiment 2)	20.5	3.1			11.2	1.3
Alternate-Day (Experiment 3)	23.3	1.2			11.9	0.7
	Operant Session Ethanol Reinforcements/Day					
	Home-Cage Water Restriction Condition (ml/Day)					
Exposure Groups	15	20	25	30	35	50
3-Day (Experiment 1)						
Reinforcements	37.7	37.9	28.0		18.6	6.0
g/kg	1.97	1.72	1.09		0.62	0.18
10-Day (Experiment 2)						
Reinforcements	43.5	43.0	27.3	33.8	36.0	5.4
g/kg	1.85	1.54	0.83	1.03	1.08	0.14
Alternate-Day (Experiment 3)						
Reinforcements	29.0	29.6	31.8	35.4		5.7
g/kg	1.06	1.06	1.10	1.19		0.16

DISCUSSION

Despite a high ethanol intake during the 3-day forced ethanol consumption period in the home cage, these animals did not maintain lever pressing behavior with 10% ethanol reinforcement once home cage water restriction was removed. This occurred even when care was taken to gradually eliminate the water deprivation schedule. These animals were well conditioned to lever press during the operant sessions, taking an average of 37.7 ethanol reinforcements in 30 minutes, when only 15 ml of water was available daily on the home cage. Thus this type of limited early exposure to substantial quantities of ethanol in the home cage did not enhance the capacity of ethanol to reinforce lever pressing in the operant test situation, unless the animals were also water restricted.

EXPERIMENT 2

One explanation for the results obtained in Experiment 1 was that the ethanol exposure period was too short. Therefore, a second group of weanling rats was tested using a more extended forced ethanol drinking procedure.

METHOD

Procedure

Eight weanling rat pups, 25 days old (average weight, 76 g), were used in this study. The animals were housed four to a cage for 3 days, two per cage for 4 days, and then individually for the remainder of the study. During their initial 10 days in the laboratory, the animals had 10% ethanol as the only fluid available with an unlimited daily food supply. Body weights were taken daily. Ethanol consumption (24 h) was recorded during the final 3 days of the forced consumption period when the animals were individually housed.

Following the tenth day, tap water was put in the drinking tubes and the animals were water deprived (20 h) before starting daily operant training sessions (30 min). No ethanol was available in the home cage. Lever training using 10% ethanol as the reinforcer was begun. It took approximately 3 days to achieve stable lever press behavior. Following each training session the animals were given 15 ml of tap water on the home cage. Over the next few days the lever response requirement per reinforcement was gradually increased to FR 4, i.e., each ethanol reinforcement required four lever presses. As in Experiment 1, the animals were then given a gradually increasing quantity of water in the home cage over days in order to eliminate water restriction. While the specific amounts of water available in the home cage varied between animals, the restriction schedule was generally as follows: 6 days with 15 ml in the home cage following the operant sessions, 3 days in which 20 ml was given in the home cage, then 2 days of 25 ml, 1 day each of 30 ml and 35 ml and finally 4 days with 50 ml water on the home cage.

RESULTS

Daily ethanol intakes during the final 3 days of the home cage ethanol exposure conditions and for the operant sessions are shown in Table 1 (Experiment 2). The animals' mean body weight at the beginning of the ethanol exposure was 76 g and over the 10 days of this procedure increased to 153 g. The animals lost an average of 10 g at the initial session of the operant training due to the fluid restriction. However, this loss was regained by the third day of training. The rats showed a steady weight gain throughout the daily operant sessions with a final weight of 269 g at the end of the water restriction condition.

As with the 3-day exposure group of Experiment 1, the high levels of ethanol consumption (11.2 g/kg) found in the home cage during the forced consumption period did not provide for the

maintenance of operant behavior reinforced with ethanol when the animals had 50 ml of water per day available in the home cage (Table 1, Experiment 2). While these animals averaged 43.5 ethanol reinforcements with an ethanol intake of 1.89 g/kg under the highest water restriction condition (15 ml), with 50 ml of water in the home cage operant responding was severely reduced (5.4 reinforcements, with 0.08 g/kg intake).

DISCUSSION

While the amount of ethanol consumed in the home cage during the forced exposure for the 10-day group was higher in terms of total ml/day than the 3-day animals (20.5 ml vs. 14 ml), intake in g/kg was the same for both groups. This difference was the result of a higher body weight for the 10-day group. As with the 3-day group there was substantial ethanol intake in the initial operant sessions under the water restriction condition, indicating the strength of the operant response was initially well established.

The 10-day exposed animals maintained a higher amount of ethanol reinforced responding in the operant sessions during which water was restricted to 30 ml and 35 ml than the animals from the 3-day exposure condition. This effect appeared to be the result of a fluid imbalance, for the 10-day animals also consumed all of the 50 ml of water in the home cage, which was not observed in Experiment 1. When larger drinking tubes were placed on the home cage it was discovered that the animals of this group drank between 50 and 70 ml of water per day. Normally, in our experience, animals in this weight range drink between 25 and 30 ml of water/day. It is unclear why this excessive water consumption occurred, but it appeared to have influenced ethanol responding.

EXPERIMENT 3

Results from the first two experiments suggest that early exposure to ethanol via a forced drinking procedure does not enhance the reinforcing aspects of ethanol for properties other than its fluid characteristics. Operant behavior could not be maintained in nonwater-restricted animals under the conditions tested. This is in marked contrast to the results in adult animals who can be initiated to ethanol reinforcement by a variety of procedures which do not require water restriction for the maintenance of responding (9,24).

There is evidence suggesting that animals exposed to ethanol on a periodic schedule (i.e., every other day) show substantial increases in ethanol consumption (31). It was postulated that early exposure using an alternate-day procedure might enhance later ethanol reinforced responding in the operant paradigm.

METHOD

Procedure

Male, Long Evans rats (N = 8), 31 days old when obtained (average weight 90 g), were housed in individual hanging cages. The animals were given tap water for the first two days, followed by a single day with 5% ethanol. Then over the next eighteen days, 10% ethanol and tap water were alternatively available. Body weight and fluid consumption were measured daily.

Following the home cage ethanol exposure, the animals were water restricted for 20 hours prior to the operant training sessions. The same procedure used in Experiment 1 for the operant training was followed. The animals learned the lever response reinforced with 10% ethanol usually within 3 days. An FR 1 schedule was used throughout the operant sessions. As in the previous two experiments, the animals were given an increasing amount of water in the home cage following the daily (30 min) operant session. The schedule of water restriction was 1 day at 15 ml, 3 days of 20 ml, followed by 1 day each at 25 ml and 30 ml, and finally 4 days of 50 ml water in the home cage.

RESULTS

Ethanol consumption in ml and g/kg for the home cage and operant sessions are presented in Table 1 (Experiment 3). Ethanol intake matched water intake during the home cage alternate-day condition (i.e., 23.3 ml/day ethanol vs. 22.0 ml/day water). The average body weight at the beginning of ethanol exposure was 90 g. The animals showed a steady weight gain during the 20 days of this condition, ending with an average weight of 216 g. There was a 12 g weight loss at the start of the operant training due to the water restriction in the home cage. However, this loss was regained by the end of the 3 days of training. The average body weight gain over the daily operant sessions matched the weight gain during the alternate-day period, i.e., approximately 6 g per day.

The results of the water restriction conditions on operant responding found that the number of ethanol reinforcements/session ranged from 29.0 to 35.4 when 15 to 30 ml of water was available in the home cage. However, reinforcement levels and ethanol intake declined markedly as the home cage water supply was further increased (5.7 reinforcements and 0.16 g/kg ethanol intake under the 50 ml condition).

DISCUSSION

Despite the high levels of ethanol intake in the home cage (11.9 g/kg per day) during the forced alternate day exposure, lever press behavior was not maintained with 10% ethanol reinforcement. This result is identical to those observed in Experiments 1 and 2.

GENERAL DISCUSSION

The purpose of these experiments was to determine if forced ethanol consumption in the home cage during the early postweaning period would influence oral ethanol self-administration associated with lever response behavior. In each experiment, animals consumed substantial quantities of ethanol in the forced condition and were successfully trained to respond in the operant situation using 10% ethanol reinforcement under mild water restriction. Despite this experience, the early exposed animals failed to maintain the ethanol-reinforced operant behavior when the fluid restrictions were removed.

The effects of early ethanol exposure can be interpreted in terms of an increased sensitivity to stress, seen as an increased ethanol preference when the animals are subjected to stressful conditions. The positive effects on ethanol preference of prenatal exposure were found in animals which had also had intervening behavioral tests, an open field test (4) and a series of learning set tests (19). Increased preference could be the result of a combination of prenatal exposure and the stress of the intervening test procedures, for it has been shown that prenatal exposure to ethanol leads to an increased sensitivity to particular forms of stress in rats (2, 17, 27, 28, 32).

This interpretation receives support when it was found that female rats exposed to ethanol from day 8 to parturition (12 g/kg/day), and who were not different from control animals in terms of the ethanol preference scores, were found to significantly increase their ethanol intake levels when given daily shock sessions (16). The ethanol intake by the pair-fed control animals was only slightly increased in this chronic stress condition. The prenatal animals consumed 4.94 g/kg/day in the two-bottle preference situation, which was roughly double the intake of the control animals.

Hayashi and Tadokoro (11) gave rats IP ethanol injections day 6 through 12 after birth and tested them in a discriminated avoidance task at 60 days of age. The early exposure animals were found to require a greater number of trials to learn this task compared to the saline controls, presumably, therefore, receiving more shocks, which might explain the substantial differences found in the ethanol preference ratios between these groups at 120 days of age. The early exposure animals averaged preference ratios 40 percentage points higher than the control animals for 10% ethanol (70% versus 30% respectively).

Early ethanol exposure via inhalation has been found to increase later ethanol preference ratios (14,15). The enhanced ethanol preference found in this study could be interpreted as the result of a stressful fluid restriction test condition used to determine the subsequent ethanol consumption levels.

Finally, the results of the present experiments can also be interpreted as being related to the stressful conditions of the water restriction schedule. Under these conditions, all of the animals which had consumed large quantities of ethanol in the early postweaning period demonstrated high levels of ethanol intake in the operant situation. When the water restriction condition was removed ethanol intake declined dramatically.

The main issue underlying the present experiments was to determine if ethanol, experienced in the early postweaning period, would then function as a reinforcing stimulus associated with lever press behavior in an oral self-administration paradigm without the need for any additional initiation procedures. The results of most other early ethanol exposure studies have used ethanol preference ratios exclusively as the dependent variable. Since a preference change was not the measure of interest in the present studies, it is not known whether the forced exposure procedures used in Experiments 1–3 had any influence on ethanol preference. Preference measures have been criticized as not being an accurate measure of ethanol's pharmacological effects or its reinforcing properties (6,29). Unfortunately, under most applications, the two-bottle choice technique lacks any qualification of the pattern of ethanol intake. Animals may have a marked 24-h ethanol intake when measured once a day, but they could distribute drinking in small bouts over the entire 24-hour period resulting in no measurable pharmacological effects. Thus, the two-bottle home cage preference method may be too insensitive to detect subtle effects on the pattern and size of intake bouts that result from the effects of early ethanol exposure. For example, in two studies which failed to find detectable differences in preference ratios following early exposure, when a second condition was added, i.e., an injection of zimeldine or shock stress, clear effects of the early exposure were found (8,16). Thus, early exposure may alter various aspects of ethanol's actions while not affecting total daily intake.

We have argued that in order to establish lever press behavior associated with oral ethanol self-administration in nonfood- and nonwater-restricted rats, it is necessary to use some type of an initiation procedure (9,24). We have postulated that initiation produces drinking patterns which result in high ethanol intakes in a short time, overcoming the initial negative taste and olfactory cues and allow ethanol's pharmacological actions to occur. It was hypothesized that forced ethanol drinking at the time of weaning might function as an initiation procedure. In addition, the use of a mild water restriction during training of ethanol reinforced lever pressing has been partially successful in initiating ethanol-reinforced behavior in adult rats (26). Why these procedures failed to initiate ethanol reinforced responding in the present experiments is unknown. Clearly, during the initial exposure periods, all three procedures used resulted in substantial 24-hour ethanol intakes. When operant training was completed prior to the removal of water restriction, the animals were demonstrating substantial ethanol intakes during the operant sessions. These two findings taken together would suggest that initiation should have resulted, but that was clearly not the case.

We have repeatedly found in adult animals that simply producing high ethanol intakes in the home cage using either forced or food and/or water restriction conditions without an operant component generally fail to result in the maintenance of ethanol reinforced behavior when the limiting conditions are no longer in effect (25). It appears that many processes can interact to maintain ethanol reinforced behavior (water restriction being one), but only certain procedures can result in maintenance without limiting food or water. How these factors are interrelated to ethanol seeking behavior remain central to understanding the controlling factors in human ethanol use and abuse.

It may be that the effects of early exposure can be observed when other more effective initiation procedures than the mild water deprivation are employed. One effect of early exposure might be to alter the negative taste factors related to ethanol drinking, as shown by some preference studies. If this is the case, the initiation of ethanol seeking behavior might be facilitated by such early exposure, suggesting that early exposure alone will not necessarily result in ethanol seeking behavior, but could facilitate other initiation procedures. If this is the case, using a secondary-reinforcement (9) or a sucrose-fading procedure (24) after early forced ethanol exposure might result in observable alterations of ethanol's reinforcing efficacy. Only additional studies will be able to determine if this is correct.

ACKNOWLEDGEMENTS

This work was supported in part by grants from National Institute on Alcohol Abuse and Alcoholism (AA07404 to H.H.S.) and the Alcohol and Drug Abuse Institute, University of Washington. The authors wish to thank Miki Haraguchi for her technical assistance throughout this research.

REFERENCES

1. Abel, E. L.; York, J. L. Absence of effect of prenatal ethanol on adult emotionality and ethanol consumption in rats. J. Stud. Alcohol 40:547–553; 1979.
2. Angelogianni, P.; Gianoulakis, C. Prenatal exposure to ethanol alters the ontogeny of the β-endorphin response to stress. Alcohol.: Clin. Exp. Res. 13:564–571; 1989.
3. Blane, H. T.; Hewitt, L. E. Alcohol and youth: An analysis of the literature. Rockville: NIAAA; 1960–1975:1977.
4. Bond, N. W.; DiGiusto, E. L. Effects of prenatal alcohol consumption on open-field behaviour and alcohol preference in rats. Psychopharmacologia 46:163–165; 1976.
5. Clay, M. L. Conditions affecting voluntary alcohol consumption in rats. Q. J. Stud. Alcohol 25:35–55; 1964.
6. Cicero, T. J. A critique of animal analogues of alcoholism. In: Majchrowicz, E.; Noble, E. P., eds. Biochemistry and pharmacology of ethanol, vol. 2. New York: Plenum; 1979.
7. Galef, B. E.; Henderson, P. W. Mother's milk: A determinant of the feeding preferences of weaning rat pups. J. Comp. Physiol. Psychol. 78:213–219; 1972.
8. Grace, G. M.; Rockman, G. E.; Glavin, G. B. Effect of prenatal exposure to ethanol on adult ethanol preference and response to zimelidine in rats. Alcohol Alcohol. 21:25–31; 1986.
9. Grant, K.; Samson, H. H. Induction and maintenance of ethanol self-administration without food deprivation in the rat. Alcohol 2:317–322; 1985.
10. Haertzen, C. A.; Kocher, T.; Miyasato, K. Reinforcement from the first drug experience can predict later drug habits and/or addiction: Results with coffee, cigarettes, alcohol, barbiturates, minor and ma-

jor tranquilizers, stimulants, marijuana, hallucinogens, heroin, opiates and cocaine. Drug Alcohol Depend. 11:147–165; 1983.
11. Hayashi, T.; Tadokoro, S. Learning retardation and enhanced ethanol preference produced by postnatal pretreatments with ethanol in adult rats. Jpn. J. Pharmacol. 37:269–276; 1985.
12. Ho, A.; Chin, A. J.; Dole, V. P. Early experience and the consumption of alcohol by adult C57BL/6J mice. Alcohol 6:511–515; 1989.
13. McGivern, R. F.; Clancy, A. N.; Mousa, S.; Couri, D.; Noble, E. P. Prenatal alcohol exposure alters enkephalin levels, without affecting ethanol preference. Life Sci. 34:585–589; 1984.
14. Molina, J. C.; Serwatka, J.; Spear, N. E. Changes in alcohol intake resulting from prior experiences with alcohol odor in young rats. Pharmacol. Biochem. Behav. 21:387–391; 1984.
15. Molina, J. C.; Serwatka, J.; Spear, L. P.; Spear, N. E. Differential ethanol olfactory experiences affect ethanol ingestion in preweanlings but not in older rats. Behav. Neural Biol. 44:90–100; 1985.
16. Nelson, L. R.; Lewis, J. W.; Liebeskind, J. C.; Branch, B. J.; Taylor, A. N. Stress induced changes in ethanol consumption in adult rats exposed to ethanol *in utero*. Proc. West. Pharmacol. Soc. 26: 205–209; 1983.
17. Nelson, L. R.; Taylor, A. N.; Lewis, J. W.; Poland, R. E.; Redei, E.; Branch, B. J. Pituitary-adrenal responses to morphine and footshock stress are enhanced following prenatal alcohol exposure. Alcohol.: Clin. Exp. Res. 10:397–402; 1986.
18. Parisella, R. M.; Pritham, G. H. Effect of age on alcohol preference by rats. Q. J. Stud. Alcohol 25:248–252; 1964.
19. Phillips, D. S.; Stainbrook, G. L. Effects of early alcohol exposure upon adult learning ability and taste preferences. Physiol. Psychol. 4:473–475; 1976.
20. Pohorecky, L. A. Interaction of ethanol and stress: Research with experimental animals—An update. Alcohol Alcohol. 25:263–276; 1990.
21. Rockman, G. E.; Hall, A.; Markert, L. Early weaning effects on voluntary ethanol consumption and stress responsivity in rats. Physiol. Behav. 40:673–676; 1987.
22. Rockman, G. E.; Borowski, T. B. The effects of environmental enrichment on voluntary ethanol consumption and stress ulcer formation in rats. Alcohol 3:299–302; 1986.
23. Roehrs, T. A.; Samson, H. H. Relative responding on concurrent schedules: Indexing ethanol's reinforcing efficacy. Pharmacol. Biochem. Behav. 16:393–396; 1982.
24. Samson, H. H. Initiation of ethanol reinforcement using a sucrose-substitution procedure in food- and water-sated rats. Alcohol.: Clin. Exp. Res. 10:436–442; 1986.
25. Samson, H. H. Initiation of ethanol-maintanied behavior: A comparison of animal models and their implication to human drinking. In: Thompson, T.; Dews, P. B.; Barrett, J., eds. Advances in behavioral pharmacology: Neurobehavioral pharmacology, vol.6. Hillsdale: Lawrence Erlbaum; 1987:221–248.
26. Samson, H. H.; Pfeffer, A.; Tolliver, G. A. Oral ethanol self-administration in rats: Models of ethanol seeking behavior. Alcohol.: Clin. Exp. Res. 12:591–598; 1988.
27. Taylor, A. N.; Branch, B. J.; Liu, S. H.; Kokka, N. Long-term effects of fetal ethanol exposure on pituitary-adrenal response to stress. Pharmacol. Biochem. Behav. 16:585–589; 1982.
28. Taylor, A. N.; Branch, B. J.; Liu, S. H.; Wiechmann, A. F.; Hill, M. A.; Kokka, N. Fetal exposure to ethanol enhances pituitary-adrenal and temperature responses to ethanol in adult rats. Alcohol.: Clin. Exp. Res. 5:237–246; 1981.
29. Tolliver, G. A.; Sadeghi, K. G.; Samson, H. H. Ethanol preference following the sucrose-fading initiation procedure. Alcohol 5:9–13; 1988.
30. Ulman, A. D. First drinking experience as related to age and sex. In: Pittman, D. J.; Snyder, C. R., eds. Society, culture and drinking patterns. New York: John Wiley; 1962:259–266.
31. Wayner, M. J.; Greenberg, I.; Tartaglione, R.; Nolley, D.; Fraley, S.; Cott, A. A new factor affecting the consumption of ethyl alcohol and other sapid fluids. Physiol. Behav. 8:345–362; 1972.
32. Weinberg, J.; Gallo, P. V. Prenatal ethanol exposure: Pituitary-adrenal activity in pregnant dams and offspring. Neurobehav. Toxicol. Teratol. 4:515–520; 1982.
33. Yoshimoto, K. The influence of age upon alcohol drinking behavior. Med. Sci. Res. 16:755–756; 1988.