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Reproductive State Modulates Ethanol Intake in Rats: Effects of Ovariectomy, Ethanol Concentration, Estrous Cycle and Pregnancy

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FORGER, N. G. AND L. P. MORIN. *Reproductive state modulates ethanol intake in rats: Effects of ovariectomy, ethanol concentration, estrous cycle and pregnancy.* PHARMAC. BIOCHEM. BEHAV. 17(2) 323–331, 1982.—Intact adult female rats had a greater preference for a 4% (v/v) ethanol solution than ovariectomized (OVX) rats in a two-tube preference situation. This preference difference was not particular to the 4% concentration, but was exhibited for solutions ranging from 1–9% ethanol. OVX animals reached peak preference at weaker ethanol concentrations than did control animals, while the volume of absolute ethanol consumed by each group was highly dependent on the concentration of ethanol offered. OVX, but not intact, rats showed a strong positive correlation between alcohol preference and preference for a saccharine solution. Pregnant and lactating rats exhibited depressed preference for 4% ethanol. Preference returned to control levels following weaning. Ethanol intake and preference varied systematically over the four-day estrous cycle, being lowest on the day of proestrus.

Rat Ethanol preference Taste Ovary Pregnancy Lactation Estrous cycle

OVARIAN hormones have been shown to play a role in the preference exhibited by rats for certain tastes. Specifically, ovariectomized rats consume much more quinine adulterated water than do intact females, while ovariectomy of naive rats markedly reduces saccharine preference [21]. Also reported is a lower preference for saccharine and lower aversion to quinine during pregnancy and lactation [20,21]. These preferences appear to be independent of the body weight differences associated with each hormonal state and are hypothesized to be the result of an interaction of estrogens and progestins.

Investigation of several mammalian species has also indicated an influence of ovarian hormones upon alcohol consumption. Earlier reports from rats provided mixed results at best. Some studies showed no effects of ovariectomy [1, 13, 17, 23], a decrease after ovariectomy [5], inhibition by a mixed gestagen-estrogen combination [5], or intake inhibition by very large (100 μg/day; [1]) doses of estradiol benzoate (EB). Prolonged EB treatment "questionably" reduced ethanol intake by deermice [4]. In normal women, estradiol had no effect on alcohol consumption [12]. However, retrospective analysis of drinking patterns by women indicates a significant reduction in alcohol consumption during pregnancy [10,11]. In these reports, loss of urge or adverse physiological effects associated with alcohol consumption, e.g., unpleasant taste or smell, were the reasons most frequently cited by subjects for the decrease. Additionally, three of four pigtailed macaques decreased ethanol selection during pregnancy and lactation [3], and lactating hamsters [2] apparently had lower preferences and absolute ethanol intake. In these species, therefore, ethanol ingestion appears to be regulated in a manner analogous to saccharine preference by pregnant rats.

The ambiguity of the rat literature, probably related to the choice and dose of hormones [1,5] and to the selection [4, 5, 17, 23] of a 10% ethanol solution from which rats usually drink little [16], led us to apply the saccharine preference model to the study of rat ethanol intake regulation. The present research was designed to extend this analogy by describing the role of ovarian hormones in the modulation of ethanol preference.

EXPERIMENT 1

Ovariectomy (OVX) in rats results in decreased preference for a 0.75% saccharine solution. The present experi-

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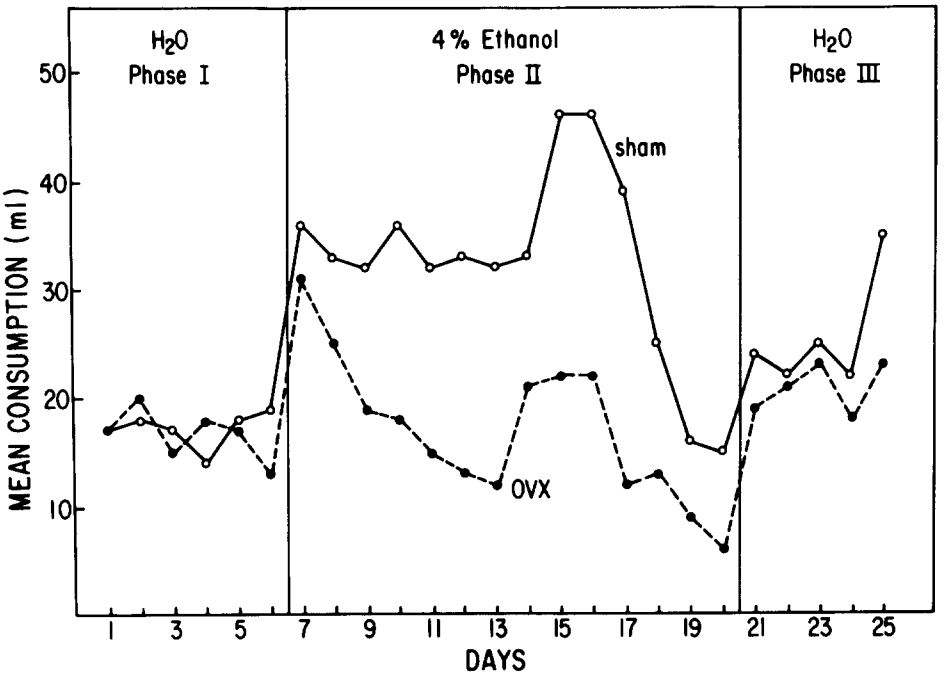

FIG. 1. Mean fluid consumption by OVX (broken line) or SH (solid line) animals. During Phase II each animal had a two tube choice of 4% ethanol or water; during Phases I and III, both tubes contained water. The figure shows fluid drunk from the Marked tube (see text).

mental design was based on that used by Wade and Zucker [20] to test saccharine preference in OVX and SH animals, with the substitution of an ethanol solution in place of saccharine.

METHOD

Methods were identical for Experiments 1 and 2. Adult female rats of the Charles River Sprague-Dawley strain were randomly assigned to two groups and either ovariectomized or SH operated. The rats were anesthesized with 40 mg/kg intraperitoneal sodium pentobarbital (Nembutal; Abbott) and administered 25 mg/kg atropine sulfate. Surgery was performed 5–7 days before the experiments.

Rats were individually housed in an LD 14:10 photoperiod (lights on at 0700 hr) and at a temperature of 21±1°C. Charles River RMH 3000 dry lab chow was available ad lib. Each rat had continuous access to solutions contained in two 100 ml Richter tubes mounted on the front of the cage. A piece of white tape on the end of one tube ("Marked" tube) permitted experimenter identification of the tubes. Right-left location of the tubes was varied randomly each day. At 1900 hr daily, fluid intake was measured to the nearest ml. Tubes were cleaned and completely refilled every fourth day; on intervening days tubes were refilled only as needed.

Where appropriate, analyses of variance with repeated measures or *t*-tests for dependent or independent groups were used. Probabilities given are two tailed unless otherwise noted.

Procedure

There were twelve subjects in each group. The animals were approximately 42 weeks old and there was no significant difference in preoperative body weight between the two groups (mean OVX=345±9 g vs SH=336±8 g).

The experiment consisted of three phases. During Phase I (Days 1–6), both tubes contained tapwater. Ethanol preference testing took place during Phase II (Days 7–20), throughout which the Marked tube contained a 4% (v/v) ethanol-tapwater solution while the other contained tapwater. Each tube again contained tapwater during Phase III (Days 21–25). Body weight was recorded daily for each animal during all phases.

RESULTS

Phase I. The groups did not differ in total amount of water consumed from both tubes. SH animals drank 41±2 ml/day while OVX rats consumed 45±3 ml/day ($F(1)=1.27$, $p<0.30$).

Phase II. During Phase II, SH operated animals were found to consume a greater volume of the 4% ethanol solution (available in the Marked tube) than did OVX animals (mean=33±4 ml/day vs 17±3 ml/day for OVX animals; $F(1)=11.8$, $p<0.003$; Fig. 1). SH animals exhibited a true preference for the alcohol solution, reducing water intake (from 23 ml/day from the unmarked tube in Phase I to 15 ml/day in Phase II, $t(11)=3.12$, $p<0.01$) while increasing the volume consumed from the Marked tube from 17 ml/day in Phase I (water) to 33 ml/day in Phase II (ethanol solution; $t(11)=4.95$, $p<0.001$). In contrast, OVX animals treated the ethanol solution introduced in Phase II much like water: they decreased drinking from the Marked tube by only 2 ml (from 19 ml/day in Phase I to 17 ml/day in Phase II) and decreased volume consumed from the unmarked tube also by 2 ml (25 ml/day in Phase I to 23 ml/day in Phase II). Figure 2 depicts

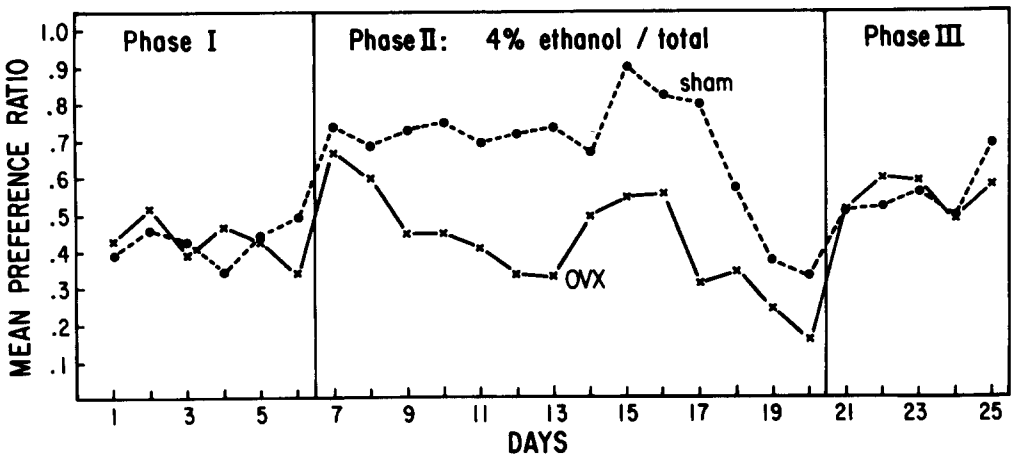

FIG. 2. Mean APR of OVX (solid line) or SH (broken line) animals. The tube which contained 4% ethanol during Phase II was the Marked tube. Preference ratios were calculated according to the formula Marked volume consumed/Total volume consumed.

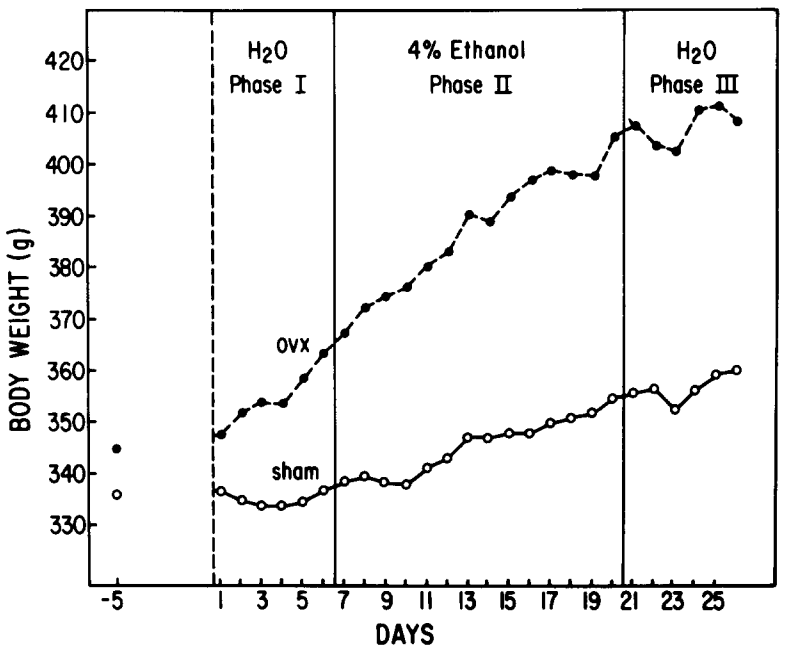

FIG. 3. Mean body weights of OVX (filled circles) or SH (open circles) animals in Experiment 1. Conditions were as in Fig. 1.

the mean alcohol preference ratios (APR=volume from Marked tube/total volume) for all phases. The two groups were marginally different with respect to the total volume of water consumed during this phase. OVX animals drank a total of 39±2 ml/day while SH consumed 46±3 ml/day, $F(1)=3.95$, $p<0.06$.

Phase III. During Phase III, both tubes again contained tapwater, and SH animals continued to drink marginally more than the OVX group (mean SH=46±3 vs OVX=38±2; $F(1)=3.99$, $p<0.06$), as total consumption for both groups fell by 2 ml/rat/day from their Phase II levels. In Phase III, however, 44% of the SH drinking was from the unmarked tube, whereas only 29% had been from this tube (water) in Phase II. There was no difference between consumption by SH or by OVX animals from Marked vs unmarked tubes in this phase.

The effect of ovariectomy on body weight is depicted in Fig. 3. Percent weight gain over the 25 days of testing was much greater for the OVX group (an 18% increase) than for the SH controls (a 7% increase). Average daily weight gain for individual OVX subjects was 2.6 g/day while SH operated animals exhibited a 1 g/day increase. This observed increase is in accordance with studies on castration and body weight in females [19]. When Phase II calculations of mean

ethanol consumption are made relative to mean body weight, SH and OVX groups also show very large differences analogous to the absolute figures: 93±11 ml/kg by SH versus 44±7 ml/kg by OVX animals ($t(22)=4.46$, $p<0.001$). Neither average body weight nor average rate of weight gain was significantly correlated with average volume of ethanol consumed per day during Phase II for either the SH or OVX animals.

EXPERIMENT 2

Ovariectomy was associated with decreased 4% ethanol consumption in Experiment 1. However, 4% ethanol was chosen as a concentration most palatable to intact rats [16]. Since ovariectomy may result in decreased metabolism rates, it is not clear whether ovariectomized rats are regulating absolute ethanol intake, or are responding to a change in taste perception. The present experiment was designed to clarify this point by comparing intake patterns of SH and OVX animals across a range of ethanol concentrations.

METHOD

Methods were as given in Experiment 1.

Procedure

Part A. Thirty females weighing about 245 g at surgery served as subjects (OVX N=15; SH N=15). Ethanol and tapwater consumption were measured over 21 days as the ethanol offered varied in concentration from 0 to 9 percent v/v. On Days 1–3, tapwater was available in both tubes (0%). From Day 4 on, the concentration of the ethanol solution offered was incremented by 1% v/v every 48 hr. Thus each ethanol concentration from 1 to 9 percent was available for two consecutive days.

Part B. Upon completing Part A, all animals received only water for 4 consecutive days. At that time, the SH and OVX groups were split, one half of each being provided with a water or 4% ethanol choice and the other half given a water or 0.75% saccharine solution choice. Animals received each choice condition for 3 days at which point the conditions were reversed for 3 days.

RESULTS

Part A

OVX animals exhibited lower mean daily ethanol solution consumption for all concentrations greater than 1% (Fig. 4C). The difference, between groups, was highly significant for all days of ethanol availability, $F(1)=10.1$, $p<0.004$. Mean APR was also lower for OVX animals (Fig. 4B; $F(1)=10.2$, $p<0.004$).

Peak ethanol solution consumption (27 ml/day) and peak APR (0.71) were exhibited by OVX animals at 3% ethanol concentration. Both preference and mean ethanol solution consumption dropped steeply, and in a linear fashion, as concentrations rose above 3%. By 7% ethanol concentration, for example, OVX animals ingested about 13% of their total fluid intake in 7% ethanol, or 4.6 ml solution/day. At the same time, SH animals exhibited greatest preference and greatest intake for 3–5% ethanol concentrations. During the six day period these solutions were offered to SH animals, approximately 34 ml/day (or about 80% of total fluid intake) was consumed as 3–5% ethanol. Although SH animals' mean preference for the ethanol solutions did not begin to decrease until 6% ethanol was offered (vs 4% for OVX group) the rate of preference decline for the two groups was very similar (Fig. 4B). In addition, at respective peak preference concentrations (OVX, 3%; SH 4%), mean APRs were not different for the two groups.

The absolute ethanol consumption difference between groups, across all days of ethanol availability was highly significant, $F(1)=12.7$, $p<0.002$. Mean daily absolute ethanol intake for OVX animals ranged from 0.22 ml/day (8% ethanol) to a peak of 0.85 ml/day (4% ethanol). This 286% difference in absolute ethanol consumption from one ethanol concentration to another indicates that OVX animals were not regulating absolute ethanol intake. The same was true for SH animals, which drank a minimum of 0.24 ml absolute ethanol/day at 1% ethanol and a peak of 1.64 ml absolute ethanol/day at 5% ethanol (a 583% increase). For both OVX and SH animals, volume of absolute ethanol consumed was highly dependent on the concentration of ethanol solution offered.

Part B

Mean APRs for OVX and SH animals were 0.19±.04 and 0.31±0.08, respectively (not significantly different). Similarly computed saccharine preference ratios also did not differ between the groups (mean OVX=0.77±0.06; SH=0.75±0.06). When individual preferences were assessed, a significant positive correlation between the APR and saccharine preference ratios was found for OVX animals, $r(13)=.703$, $p<0.01$, but not for SH animals. Similarly, OVX, but not SH, animals showed a positive correlation between the volumes of saccharine and ethanol solutions consumed, $r(.13)=.73$, $p<0.01$. These results support the view that ovarian modulation of ethanol consumption is similar to that for saccharine ingestion and that individuals treat the substances similarly.

EXPERIMENT 3

Experiments 1 and 2 demonstrated that ethanol preference is significantly reduced in the absence of ovarian hormones. Pregnancy and lactation are characterized by relatively low levels of estrogen, and high levels of progesterone. Wade and Zucker [20] found that these reproductive states are analogous to ovariectomy in that saccharine preference is effectively suppressed in pregnant or lactating, as well as in OVX, rats. Their results led to the prediction of a lowered ethanol preference for the rat during pregnancy and lactation.

METHOD

Subjects were forty female Sprague-Dawley rats (Charles River), approximately 75 days old and weighing about 176 g at the start of the experiment. All were housed in one light and temperature (21±1°C) controlled room with an LD 14:10 photoperiod (lights on at 2200 hr). Animals lived in individual wire mesh cages with Charles River RMH 3000 formula available ad lib.

Two 100 ml Richter tubes allowed for daily volumetric readings. One contained tapwater, and the other contained either a 4% v/v ethanol solution or tapwater. Right-left position of tubes varied randomly, and they were cleaned and refilled regularly.

In the first phase of the experiment (Pre-Mating), volumes were recorded every twenty-four hours and vaginal smears

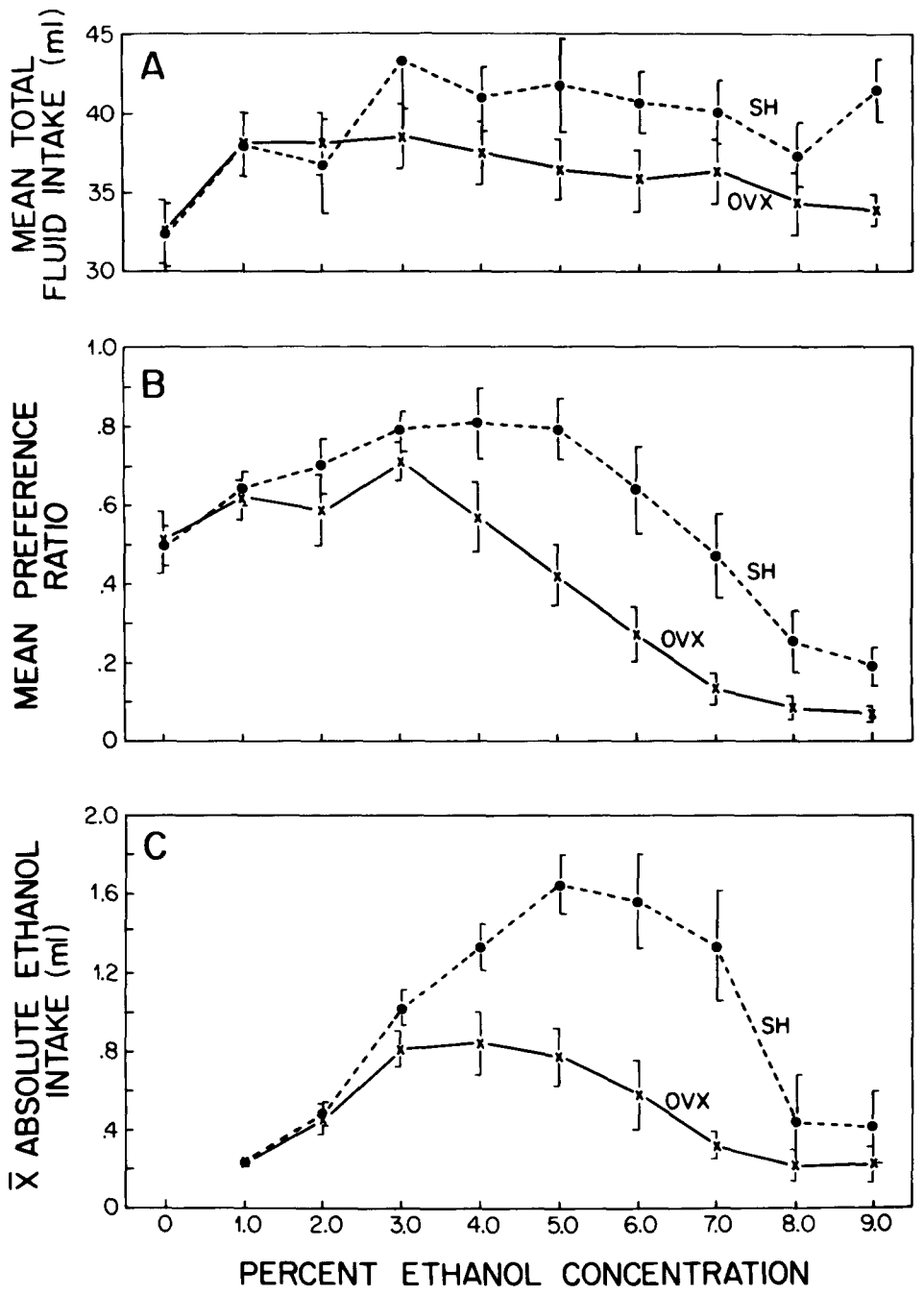

FIG. 4. (A) Mean daily fluid consumption by OVX or SH animals according to the concentration of ethanol. (B) Mean Apr for OVX or SH animals according to the concentration of ethanol. (C) Mean absolute ethanol intake by OVX or SH animals according to concentration of ethanol. OVX=solid line; SH=broken line. Vertical brackets indicate±1 SE.

were analyzed daily to determine the stage of the estrous cycle. After ≥2 estrous cycles, the animals were divided into three groups. Sixteen rats were assigned to a "Pregnant" group, and sixteen to a water-ethanol control group (W-E Controls). Both water and 4% ethanol were available to these rats throughout. The remaining eight animals had water available in both drinking tubes and served as a second control group (W-W Controls).

Individuals from the Pregnant group were placed overnight with a stud male on the evening of proestrus, as determined by vaginal smears, and were returned to home cages the following morning. Day one of pregnancy was identified as the day following mating if a vaginal plus was found, or if sperm were present in the daily smear. When neither plug nor sperm were found, the female was again mated on her next estrous. In this way, all animals assigned

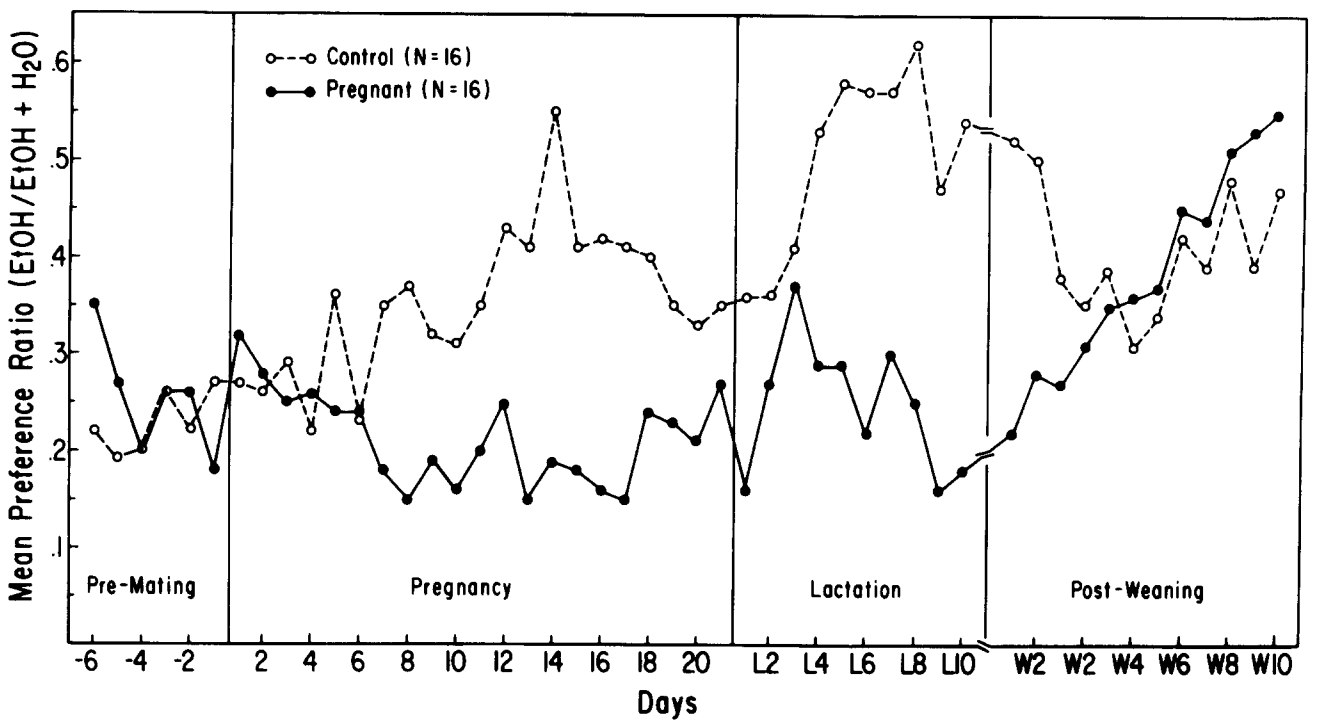

FIG. 5. APR of Pregnant (solid line) or intact Control (broken line) animals across four phases of the reproductive process.

to the Pregnant group were fertilized within eight days. For control animals, the third (N=8) or sixth (N=8) day of this mating period was designated as Day 1 of the pregnancy phase.

Throughout the next two phases (Pregnancy and Lactation), daily monitoring of volume consumption continued for animals in all groups. A metal plate, attached to the bottom of the pregnant animals' cages at parturition, prevented loss of pups through the wire mesh cage floor. Following Day 10 of Lactation volume reading was suspended, as pups were becoming sufficiently mobile to reach the drinking tubes. One large bottle containing water was offered in place of the Richter tubes to animals of all groups during this suspension.

At age twenty-one days pups were weaned and, twenty-four hours later, the two-tube ethanol-water choice was reinstated for the dam, as well as for the control groups. Daily volume recording was resumed for the twelve days of this final phase (Post-Weaning).

RESULTS

Ethanol Preference

The first 20 days of pregnancy were used for analysis because pup delivery occurred on Day 21 or 22 and disrupted normal fluid consumption. Prior to mating, APR and total ethanol consumption were not different for animals of the Pregnant vs W-E Control groups, and ethanol preferences remained similar for the first six days of pregnancy. Beginning with day seven after mating and continuing throughout pregnancy, however, the APR of pregnant animals was markedly lower than that of the W-E Controls (Fig. 5). Across the entire pregnancy phase, the groups were marginally different, $F(1)=3.49, p<0.068$, but when the comparison was made for days 7 to 20 of pregnancy the difference was highly significant, $F(1)=6.42, p=0.016$.

During the ten days of Lactation observed, APRs of control and pregnant animals diverged further: W-E Controls consumed a mean of 51% of their fluids from the ethanol tube, while only 25% of the total fluid consumed by pregnant dams was 4% ethanol. This difference is also highly significant, $F(1)=13.2$, $p<0.002$. Formerly pregnant animals demonstrated a steady increase in APR during the Post-Weaning phase. Within three days, the preference of the post-lactational animals was no longer significantly below that exhibited by W-E Controls and the similarity in preference persisted through the last observation day (Fig. 5). Neither was there a difference in preference between groups when all 12 days of the Post-Weaning phase were analyzed. The days-by-group effect was highly significant for this phase, reflecting the steady preference rise of the pregnant group, to the level exhibited by control animals, $F(11)=3.20$, $p<0.001$.

Volume of Ethanol Consumed

Although pregnant and control animals demonstrated striking differences in APR throughout pregnancy and lactation, the groups did not differ on mean volume of ethanol consumed during any of the observed phases (Fig. 6). Therefore, the lower APRs of pregnant animals were not the result of a marked decrease in total ethanol consumed. Instead, lower preference was achieved during pregnancy by a dramatic increase in water consumption ($F(15)=16.8, p<0.001$; Fig. 7), while ethanol drinking only mildly increased. Mean consumption from the water tube per pregnant animal rose from about 22 ml/day Pre-Mating to about 38 ml/day (a 73%

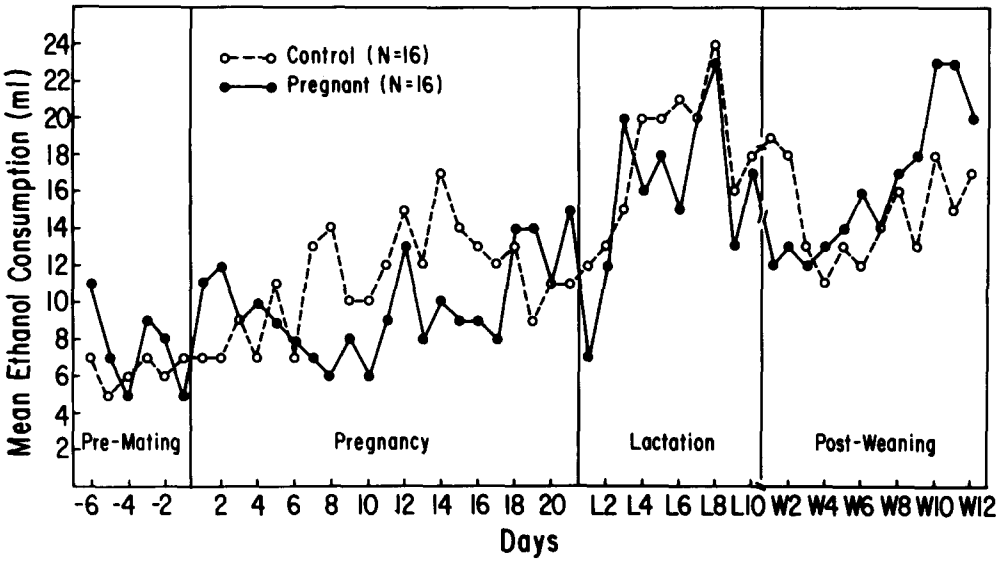

FIG. 6. Mean volume of 4% ethanol consumed by Pregnant (solid line) or intact Control (broken line) animals across four phases of the reproductive process.

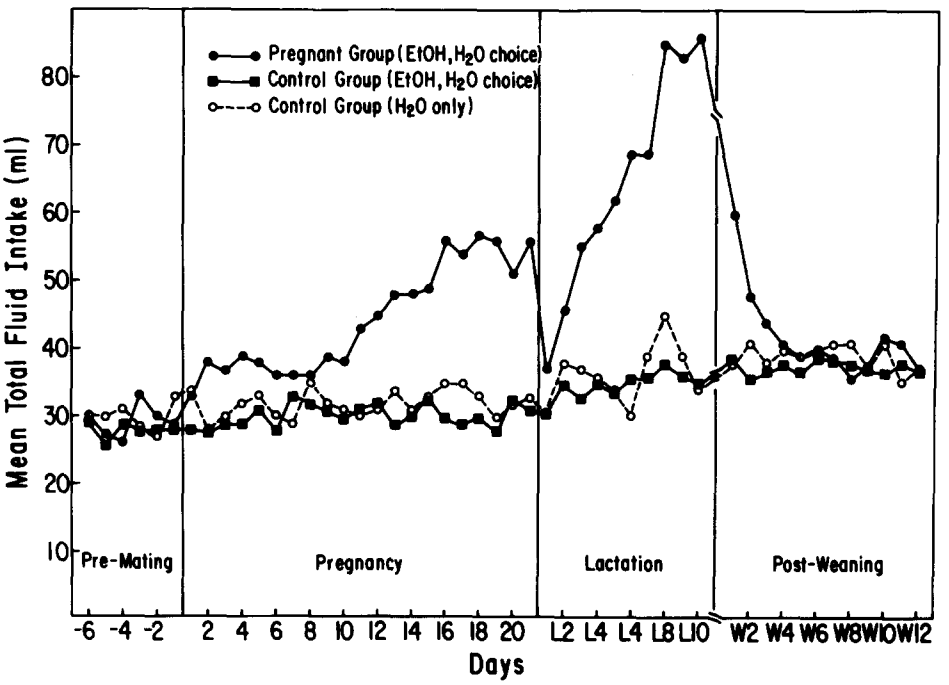

FIG. 7. Mean total fluid consumed by Pregnant (filled circles), intact Controls (filled squares) or intact Controls which always had a choice of two tubes of water (open circles) across four phases of the reproductive process.

increase) for days 7 to 20 of pregnancy, while drinking from the ethanol tube changed only from 7 to 9 ml/day (29%) over the same period.

A similar situation existed during Lactation. Ethanol consumption during lactation was greater than during pregnancy (16 vs 9 ml/day), but this change was completely offset by further large increases in water consumption, $F(15)=16.78$, $p<0.001$. By Day 10 of Lactation, the last day recorded in this phase, individual dams were drinking approximately 85 ml total fluid/day: 16 ml as 4% ethanol and 69 ml as water (78% vs 103% increase above pregnancy consumption levels). In contrast, the increase in ethanol consumed by the Pregnant group across days of the Post-Weaning phase was highly significant, $F(15)=2.94$, $p<0.002$. Thus, following

weaning, an APR level equivalent to that of control animals was not achieved by merely reducing water intake, but through a simultaneous significant increase in ethanol consumption.

Body Weight

Although pregnant and control animals did not differ in total volume of ethanol consumed during the Pregnancy phase, mean body weights of the two groups diverged during this time. Pregnant animals gained weight at a much faster rate, by late pregnancy (14 to 17 days gestation), mean body weight of pregnant dams was about 300 g, while W-E Controls weighed approximately 239 g. Thus, when ethanol consumption is expressed as ml of ethanol solution consumed per kilogram of body weight, group differences do emerge. During the four day period mentioned above (Days 14–17 Pregnancy phase), for example, control animals drank an average 61 ml/kg 4% ethanol, while ethanol consumption for pregnant animals averaged only 30 ml/kg ($t=2.28$, $p<0.03$).

Total Consumption

Figure 7 shows the total fluid consumption according to group and the magnitude of increased consumption by pregnant and lactating rats may be appreciated. At the same time, it is evident that there is no difference during any phase in the total fluid consumption of the two control groups. W-E Control animals did not drink any more, or less, fluid than did the W-W group. Availability of 4% ethanol, with moderate consumption, then, did not seem to influence total fluid intake.

Estrous Cycle

Fluid intake across the estrous cycle was analyzed for all W-E drinking rats exhibiting two consecutive four-day cycles within the first fifteen days of the experiment. Sixteen animals met these criteria. Figure 8 shows that mean ethanol solution intake, total fluid consumption and APR were lowest on Day 4 of the cycle (proestrus). In each case, there was a significant effect of estrous cycle day ($p<0.013$, $p<0.001$ and $p<0.036$, respectively). Mean water consumption did not vary with the estrous cycle. These data support the view that rats may regulate ethanol intake as a source of calories during the estrous cycle [19].

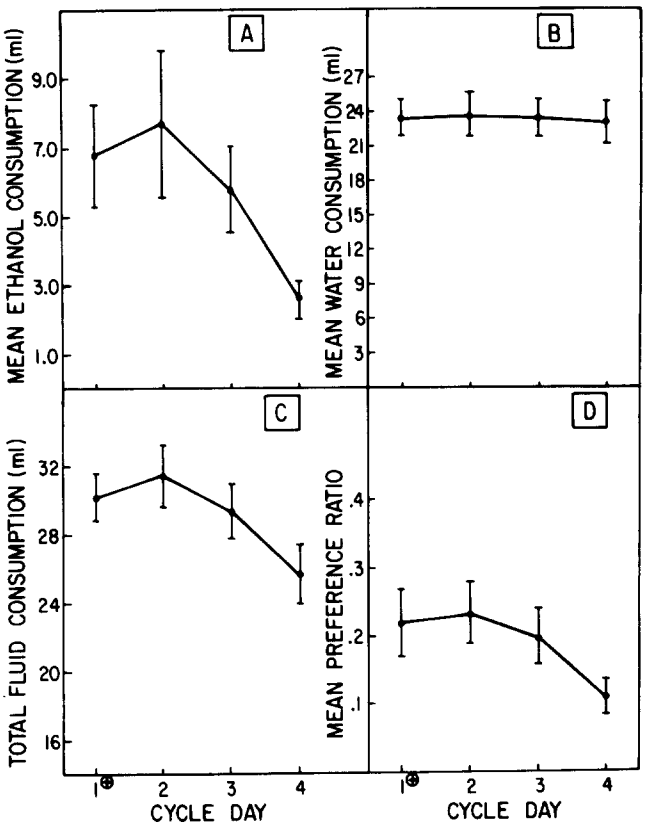

FIG. 8. Indicators of fluid consumption across the estrous cycle of intact rats: (A) Mean intake of 4% ethanol; (B) Mean intake from the water tube; (C) Total fluid intake; and (D) APR. Day 4 of the cycle is proestrous.

GENERAL DISCUSSION

The data from Experiment 1 indicate that presence of intact ovaries significantly enhanced preference for a 4% ethanol solution in adult female rats. SH operated controls drank almost two times more ethanol solution than did OVX rats in a free choice situation. At the same time, OVX animals gained approximately two and a half times more weight than did the SH animals so that when viewed as ml/kg consumed, the difference between groups is magnified.

Alcohol consumption, therefore, was not positively correlated with body weight gains between groups and, furthermore, the data demonstrate that no relationship between alcohol consumption and body weight existed within SH or OVX groups. Thus, alcohol preference by adult female rats seems to be relatively independent of body weight. These results support previous investigations of gonadal influence on response to alimentary stimuli. Wade and Zucker [21] and Zucker [24] demonstrated that OVX rats had a decreased preference for a saccharine solution which appeared to be independent of resulting body weight gains.

Experiment 2 demonstrates lower APR and intake in OVX rats at each ethanol concentration from 2–9% (v/v). For both groups, absolute ethanol intake was highly dependent on the solution concentration offered. SH animals consumed over two times more absolute ethanol when offered in a 5% concentration than when offered at 7 or 8%. Similarly, absolute ethanol intake for OVX animals ranged from less than 0.3 ml/day (8%, 9%) to more than 0.8 ml/day (4%) depending upon the ethanol concentration offered.

Therefore, it seems likely that both OVX and SH animals regulate selection of ethanol according to taste properties of the solutions rather than caloric value. The difference in intake between groups indicates a difference in response to the gustatory stimuli. At 1% concentration, both SH and OVX rats consumed ethanol in preference to water and in almost identical volumes. However, OVX animals greatly decreased consumption after maximum preference at 3% ethanol, while SH animals did not exhibit declining preference until 6% ethanol was offered. The rate of decline was essentially the same for both groups. The results support the view that OVX rats are more responsive or sensitive to the negative cues from ethanol solutions than are SH rats.

The effect of pregnancy and lactation upon preference for 4% ethanol, seen in Experiment 3, also suggests that ovarian hormones modulate taste responsiveness. Alcohol prefer-

ence was significantly reduced from nonpregnant control levels in pregnant and lactating rats, and preference returned to control levels within several days of weaning. Similar data have been obtained from mice [15]. These results further extend the analogy between ethanol and saccharine preference, as saccharine preference also decreased during pregnancy and lactation in rats and increased following weaning [21].

In both the present experiment and the saccharine studies, however, the decreased preferences observed during pregnancy and lactation were achieved through a dramatic increase in water consumption while ethanol or saccharine consumption was increased only slightly, or not at all. This feature of the rat data distinguishes it from literature dealing with alcohol consumption during pregnancy in humans. Although total fluid intake during pregnancy has not been reported, several studies [7, 8, 10, 11] found decreased alcohol intake by pregnant women as was found in mice [15]. Therefore, while rats achieved lower APRs during pregnancy by increasing water consumption, pregnant women and mice appear to directly reduce alcohol intake.

Ovariectomy dramatically reduces the level of endogenous estrogen, and is assoicated with decreased ethanol self-selection. At the same time, analysis of ethanol consumption and APR across the estrous cycle revealed decreased preference for ethanol during proestrus (present results and [1]), a time when estrogen levels are high. This result is somewhat inconsistent with the ovariectomy data and suggests that ovarian hormones may not modulate taste preferences directly, but may operate on responsivity through another system, possibly the adrenal glands or possibly by inducing metabolic changes [19] which indirectly affect calorie consumption.

Adrenal cortical insufficiency has been associated with increased sensitivity to auditory, olfactory, and gustatory stimuli (e.g. [6]). In addition, adrenalectomized rats reject saccharine solutions at concentrations that are highly palatable to normal animals [18]. Because OVX results in decreased output of corticosterone from the adrenals [9], it is possible that ovarian hormones influence taste perception through their effect on adrenal hormone levels. A subsequent report [14] examines the relationship between the ovaries and adrenals with respect to modulation of ethanol self-selection.

ACKNOWLEDGEMENTS

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