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Caloric vs. Pharmacologic Effects of Ethanol Consumption on Activity Anorexia in Rats

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SPIGELMAN, M. N., W. S. McLEOD AND G. E. ROCKMAN. *Caloric vs. pharmacologic effects of ethanol consumption on activity anorexia in rats.* PHARMACOL BIOCHEM BEHAV **39**(1) 85–90, 1991.—Food restriction, combined with access to a running wheel, produces "activity anorexia" (self-starvation) in rats. The relative effects of ethanol and propylene glycol on activity-maintained self-starvation were examined. Young male rats were provided with access to a running wheel while on a 22.5-h food deprivation schedule. One-third were concurrently provided with a 7% solution of ethanol, one-third with a (pharmacologically weak) 7% solution of propylene glycol, and one-third with water. Results indicated that neither survival rate nor running activity were affected significantly by ethanol consumption, relative to water-drinking controls. However, increased survival rates and decreased activity were observed for those animals which consumed propylene glycol. Antagonistic effects of ethanol on energy metabolism, stress responses, and the preservation of body weight are considered in light of these findings.

Activity Self-starvation Ethanol Rats

FOOD restriction, combined with access to a running wheel, results in activity-maintained self-starvation ("activity anorexia") in rats. When placed on a 23-h food deprivation schedule and simultaneously given access to a running wheel, animals exhibit a dramatic daily increase in running activity. Simultaneously, their body weight decreases linearly, and, if permitted to continue, they die of self-starvation. Control subjects, under the same one-hour-per-day feeding regimen, but without wheel access, survive (18,19).

A biobehavioral model (6) proposes a neural substrate for activity anorexia, along with its possible evolutionary basis, viz., the value of sustained locomotor activity under conditions of food scarcity. Endogenous opiates in particular have been implicated in the depressive effect of exercise on food intake (6,15). Following exercise, for example, rats injected with endogenous opioids eat less than saline-injected controls, as do morphine-injected inactive rats. This morphine-induced reduction of food intake occurs even when rats are food deprived (21).

Some studies suggest that rats increase ethanol consumption when stressed (14), and that the drug may in fact serve as a stress-reducing agent (7, 16, 17). Ethanol's depressive effect may be on the running response itself, thus contributing to the lower morbidity and mortality in rats exposed to activity anorexia conditions. This hypothesis is supported by the finding of a significantly lower incidence of stomach ulceration in rats consuming high levels of ethanol while in a deprivation-activity situation (17). The possibility cannot be ruled out, however, that the lower mortality rates observed in ethanol-drinking rats may be due simply to the relatively high caloric content of the ethanol (7.11 kcal/g), as opposed to its specific pharmacological effects. Thus the intake of extra caloric energy might itself act to diminish the incentive for running.

The present research examined the relative caloric and pharmacological characteristics of ethanol in its effect on activity anorexia in rats, using propylene glycol as a control substance. Ethanol and propylene glycol are both relatively high in caloric density (7.1 kcal/g and 5.6 kcal/g, respectively); the latter substance, however, is considered the pharmacologically weaker of the two. Ethanol is an hypnotic, an antipyretic, an effective anesthetic, as well as a depressant, and generally affects the CNS more markedly than any other body system (9). Propylene glycol, in contrast, is relatively innocuous pharmacologically. Although some reports suggest a risk of central nervous system toxicity in humans with medical conditions if administered in excess (4,12), others have indicated toxicity only if administered long-term in healthy nonhuman animals (2,24). Propylene glycol is generally considered nontoxic and safe for use by the United States Food and Drug Administration (FDA).

Taken together, then, the evidence indicates that ethanol is likely considerably more pharmacokinetic than propylene glycol. Further, rats have been demonstrated to increase their consumption of ethanol, but not of propylene glycol, following stress induced by foot-shock (14), suggesting that propylene glycol, unlike ethanol, does not likely possess inherent stress-reducing properties.

The present study compared the relative contributions of caloric and pharmacological characteristics of ethanol and its effects on activity anorexia in rats. Seven percent solutions of ethanol and propylene glycol were made available to two groups of animals. Thus, if calories alone (vis a vis pharmacological properties) underlie the demonstrated enhanced survival of stressed rats, then increased survival in both groups would be

expected, relative to controls. However, an enhanced survival rate in the ethanol group, relative to the propylene glycol group, would indicate that the effect is due more specifically to the psychokinetic properties of ethanol.

METHOD

Subjects

Eighty male Sprague-Dawley rats (Charles River), 4–6 weeks of age (175–190 g) on delivery, were used. All were individually housed in standard laboratory cages (14.5 × 24.0 cm) during the screening procedure described below. Following screening, the rats were transferred to hanging cages fitted with Wahman running wheels; a sliding door separated each cage from its wheel. Animals were maintained ad lib on Standard Purina Lab Rat Chow No. 5001 (4.25 kcal/g), in a 12-h:12-h light-dark cycle (lights on at 07:00 h).

Procedure

Screening. After 2 days of adaptation, the ethanol and propylene glycol screening procedures began. Two calibrated drinking tubes were affixed to the front of each cage. For ethanol screening, 36 rats were given one tube of water and one containing a 3% solution of ethanol every other day (ethanol discontinuous). On alternative days, two tubes of water were available. The positions of the ethanol and water tubes were reversed on alternate presentations, to avoid position preferences. Following 6 days (3 presentations of 3% solutions), the procedure was repeated, using successively increasing concentrations of 5%, 7% and 9% solutions. An identical procedure was employed in screening 36 rats with propylene glycol, with successive concentrations of 3%, 5%, 7% and 9% solutions. Those animals consuming a minimum of 2.5 g/kg body weight per day of ethanol or propylene glycol were selected for subsequent activity anorexia treatment. Few rats would drink 9% propylene glycol; therefore, the criterion concentration for both ethanol and propylene glycol was set at 7%. Of the 36 rats originally screened for ethanol consumption, 12 that drank to criterion levels were randomly selected for the activity phase of the experiment. Twelve rats from the propylene glycol group were selected in the same manner. Twelve control animals drank from two tubes of water during the screening procedure.

Habituation period (baseline). Following the screening phase, rats drinking ethanol and propylene glycol, as well as controls, were transferred to individual cages with attached running wheels. Rats in the ethanol group (ETOH) (N = 12) were given one tube of 7% ethanol, one tube of water, and food ad lib for a 4-day habituation period. Similarly, the propylene glycol (PROP) group (N = 12) received food ad lib, a tube of propylene glycol, and a tube of water for 4 days. Ethanol and propylene glycol tubes were alternated daily with their respective water tubes to preclude a position bias. The 12 control (WATER) animals received two tubes of water and food ad lib during the same 4-day period.

Activity anorexia phase. Following habituation, daily baseline measures of food intake, body weight, and ethanol, propylene glycol and water consumption were taken at 12:00 h for 4 days. On day 5, the doors to the activity wheels were opened at 09:00 h for all animals. Each of the 3 groups was further subdivided into food-ad lib and food-restricted conditions. Food-restricted rats were allowed a 90 min per day feeding period, from 12:00 to 01:30 h. The doors to the activity wheels were closed to all animals during feeding, so that wheel running could not interfere with eating. Measures of wheel running (revolutions per day) and body weight, as well as ethanol, propylene glycol and water consumption, were recorded daily, prior to the feeding period. Food intake for the deprived groups was measured by preweighing the amount of food given to each animal, and subtracting the remainder after the 90-min feeding period. Food intake for the ad lib group was measured by giving subjects a preweighed amount at 13:00 h each day, and subtracting the remainder 24 h later.

To minimize unnecessary suffering, rats were removed from the experiment when they reached a starvation criterion of 70% of their original body weight. The experiment was terminated after 20 days for all remaining rats. Survival rates were calculated in terms of the number of animals remaining in each group, i.e., those not reaching starvation criterion by the end of the study.

Statistical Analysis

Survival rates, daily wheel revolutions, food intake, body weight, and ethanol, propylene glycol and water intake were analyzed by a two-way analysis of variance [food groups (restricted vs. ad lib) × fluid groups (propylene glycol, alcohol and water)] with repeated measures [habituation period (days 1–4) and activity periods (days 5–8, 9–12 and 13–16)]. Analysis of the survival rate data included an additional activity period (days 17–20, inclusive) in the repeated measures factor.

Ethanol and propylene glycol consumptions were analyzed in terms of percent total fluid intake (%TFI) and grams per kilogram body weight (g/kg body weight). Energy intake was calculated in terms of the number of grams consumed daily of ethanol (7.11 kcal/g) and propylene glycol (5.66 kcal/g) × percentage solution × density in solution, divided by body weight, yielding a measure of kcal/kg body weight/day for each animal. Simple effects analysis and appropriate post hoc tests were applied when main effects and interactions were significant.

RESULTS

Survival Rates

All rats in the food-ad lib groups survived to the end of the experiment (20 days). Rats in the food-deprived PROP group showed a better survival rate than those in the food-deprived ETOH group [mean = 6 and 1, respectively, $F(1,10) = 25.0$, $p = 0.001$], or the food-deprived WATER group [mean = 6 and 1, respectively, $F(1,10) = 25.0$, $p = 0.001$]. All food-deprived rats in the PROP group survived to the end of the experiment. In contrast, only one animal in each of the ETOH and WATER groups survived starvation criterion to the end.

Data for wheel running, food intake, body weight, ethanol, propylene glycol and water intakes, and total caloric intake for 16 experimental days (excluding days 17–20) are summarized in Table 1. Days 17–20 were excluded from the analysis because data were lacking for nonsurvivors, precluding adequate between-groups comparisons.

Wheel Running

Figure 1 demonstrates that the food-deprived rats exhibited significantly more wheel running than did the food-ad lib animals, $F(1,30) = 19.17$, $p < 0.0001$. Table 1 shows that food-deprived rats in the PROP and WATER groups ran significantly more than did their food-ad lib counterparts ($p < 0.05$). A similar pattern was evident in a comparison between the food-deprived and food-ad lib ETOH groups, though the difference only ap-

TABLE 1

OBSERVED COMPARISONS BETWEEN FOOD DEPRIVED AND FOOD AD LIB RATS FOR PROPYLENE GLYCOL, ALCOHOL AND WATER GROUPS

Dependent Measures	Propylene Glycol Groups		Alcohol Groups		Water Groups	
	Deprived	Ad Lib	Deprived	Ad Lib	Deprived	Ad Lib
Wheel run (revs/day)	1703(946)	557(73.1)*	2208(1754)	738(301)	2750(1941)	617(85.4)*
Food intake (grams/day)	9.9(2.6)	25.7(2.7)†	10.8(2.56)	24(2.5)†	11.2(3.33)	26.7(1.5)†
Body weight (kg body weight/day)	316(21.0)	391(3.22)†	313(19.3)	395(4.2)†	313(27.3)	388(6.41)†
Prop intake (g/kg body weight/day)	4.20(2.05)	1.1(0.52)†	—	—	—	—
ETOH intake (g/kg body weight/day)	—	—	3.34(0.80)	2.89(0.64)	—	—
Prop kcal (kcal/kg body wt/day)	138(84.7)	53.3(36.7)*	—	—	—	—
ETOH kcal (kcal/kg body wt./day)	—	—	211(92.6)	161(28.0	—	—
Total kcal (kcal/kg body wt./day)	1336(237)	2609(493)†	1486(410)	2591(263)†	1268(321.4)	2664(1268)*
Water intake (ml/day)	26.4(6.7)	37.0(3.02)	26.3(7.52)	28(6.4)	39.7(8.77)	43.4(4.12)

Note. Values are means for six animals. Figures in parentheses are standard deviations. *$p<0.05$; †$p<0.01$; ‡$p<0.001$.

proached statistical significance ($p=0.095$) due to the considerably greater variability in the ETOH scores. Simple effects tests revealed that for the PROP group, food-deprived rats ran significantly more than did food-ad lib subjects [means = 1,290 and 418 revs/day, respectively; $F(1,10)=4.98$, $p<0.05$]. Similarly, food-deprived rats in the WATER group ran significantly more (mean = 2,063) than did ad lib rats (mean = 464), $F(1,10)=16.15$, $p<0.03$. No significant differences in wheel running were apparent, however, between food-deprived and food-ad lib animals in the ETOH group.

Overall, the food-deprived group increased wheel running over Periods 2–4, compared to the food-ad lib groups, as indicated by a significant period × food group interaction, $F(2,60)=30.54$, $p<0.0001$.

No significant differences in wheel running were found between food-deprived groups in the PROP and ETOH groups, or between the ETOH and WATER groups in the last 2 days of Period 4, although the difference approached significance between the PROP (mean = 2,894) and WATER (mean = 5,924) food-deprived rats, $F(1,10)=4.25$, $p<0.06$, during this time.

Food Intake

As expected, PROP, ETOH, and WATER groups in the

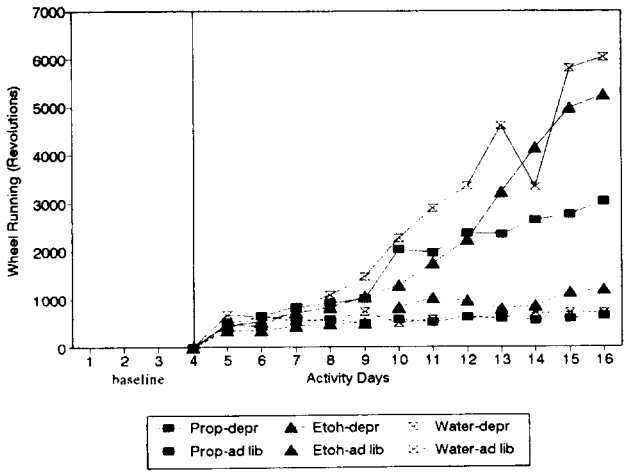

FIG. 1. Wheel running as a function of activity days (Periods 2–4) for food-deprived and food-ad lib rats in the propylene glycol, ethanol and water groups.

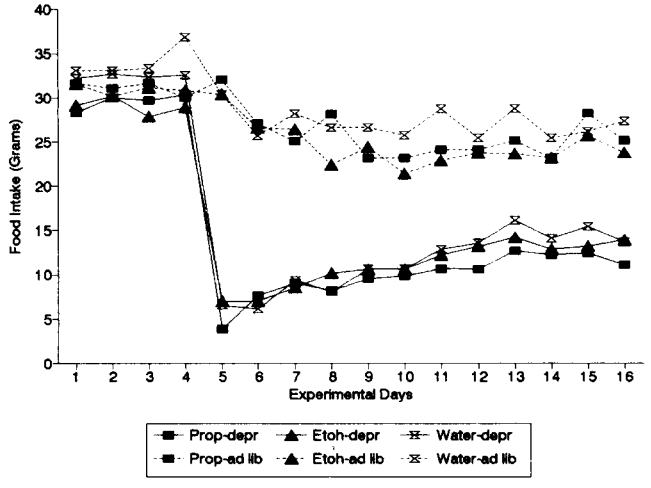

FIG. 2. Food intake as a function of experimental days (Periods 1–4) for food-deprived and food-ad lib rats in the propylene glycol, ethanol and water groups.

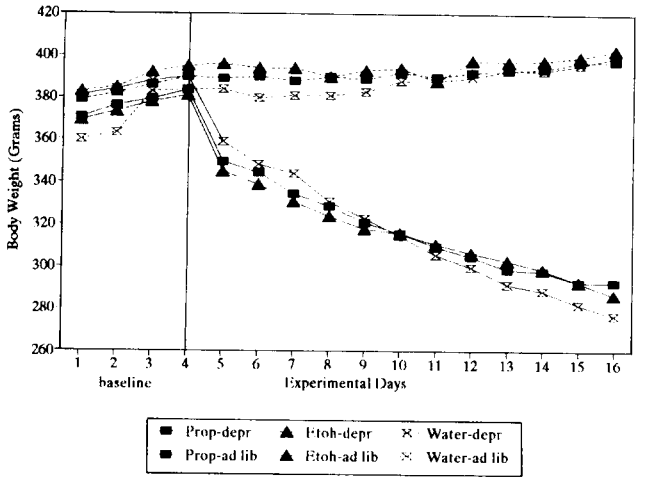

FIG. 3. Body weight as a function of experimental days (Periods 1–4) for food-deprived and food-ad lib rats in the propylene glycol, ethanol and water groups.

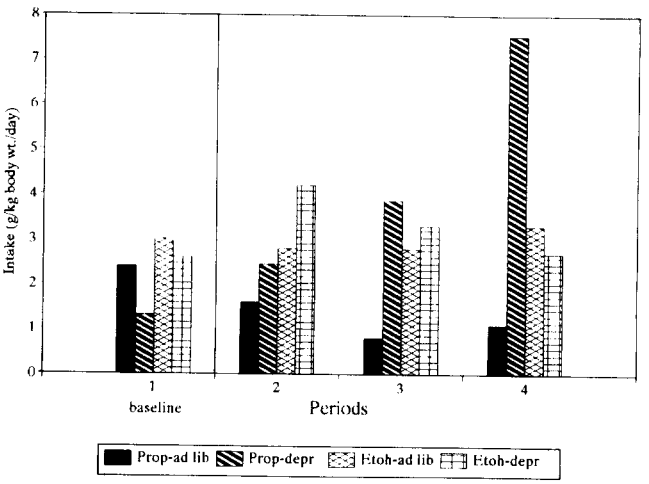

FIG. 4. Ethanol and propylene glycol consumption (g/kg body weight/day) as a function of periods, for food-deprived and food-ad lib rats in the ethanol and propylene glycol groups.

food-ad lib condition ate significantly more than their food-deprived counterparts, $F(1,30) = 103.62$, $p<0.0001$. Table 1 shows that the difference was significant for all three groups. Figure 2 demonstrates a significant period × food interaction, $F(2,60) = 48.2$, $p<0.0001$, the result of an initially low food intake by the food-deprived groups, which steadily increased over Periods 2–4. The ad lib groups showed no such changes in food intake over time.

Body Weight

Body weight data showed that all food-deprived groups weighed significantly less than the ad lib groups, $F(1,30) = 76.12$, $p<0.0001$. This was not observed during baseline period (days 1–4), when all groups were fed ad lib and were denied wheel access. Table 1 shows that body weight difference was significant between all three food-deprived groups and the food-ad lib controls. Figure 3 demonstrates a steady linear decline in body weight for the food-deprived groups only, as indicated by a significant period × food groups interaction, $F(2,60) = 100.22$, $p<0.0001$.

There was a significant weight loss main effect for periods 2 to 4, $F(2,60) = 48.22$, $p<0.0001$, as illustrated by Fig. 3. That is, weight loss occurred only during the activity phases. There was also a significant period × food group interaction, $F(2,60) = 100.29$, $p<0.0001$, indicating that the decline in body weight was evident only in the food-deprived groups. In contrast, the body weight of food ad lib groups did not change over periods and did not differ from baseline (period 1) levels.

Propylene Glycol and Ethanol Intake

Figure 4 illustrates propylene glycol and ethanol consumption for food-deprived and food-ad lib animals. In the nondeprived condition, rats clearly preferred ethanol, and consumed significantly more of it (mean = 20.88 %TFI) than of propylene glycol (mean = 6.05 %TFI), $F(1,10) = 26.92$, $p<0.0004$. Table 1 shows that overall, ethanol consumption is not significantly affected by whether the animals eat ad lib or are deprived. The only change in ethanol intake was reflected in a small linear decrease by the food-deprived group over Periods 2–4; the ethanol × food groups interaction approached significance, however, $F(3,30) = 2.43$, $p<0.085$. Propylene glycol intake, on the other hand, was significantly greater in deprived than in nondeprived animals (means = 18.4 and 33.0 g/kg body weight, respectively; $p<0.002$). A significant main effect for Period, $F(3,30) = 6.59$, $p<0.002$, and a significant Period × Food Group interaction, $F(3,30) = 12.99$, $p<0.001$, indicate that the deprived rats increased their propylene glycol intake over Periods 2–4, relative to ad lib animals.

Energy Intake

Food-deprived rats ingested significantly more calories from ethanol (mean = 30.00 kcal) during Period 2 than from propylene glycol (mean = 13.4 kcal), $F(1,10) = 9.23$, $p<0.02$. Otherwise, there were no significant differences between PROP, ETOH, and WATER groups for food-deprived rats. When the total number of kcal/kg body weight/day was calculated (i.e., food kcal + ethanol kcal for ETOH rats, and food kcal + propylene glycol kcal for PROP rats) no significant differences were observed between the food-deprived groups.

DISCUSSION

The results of this investigation have revealed several interactions between ethanol, stress, and activity in the rat. The consumption of ethanol in moderate concentrations (approximately 2.5 g/kg body weight/day) by food-deprived animals did not enhance their survival rates, relative to food-deprived rats given only water. This finding is consistent with that of another investigation (17), which reported lower morbidity and mortality associated with high ethanol consumption (4.5 to 6.0 g/kg body weight/day), but not with moderate or low ethanol intake. It appears that the relation between ethanol intake and survival may well be dose-dependent.

The poor survival rate of the ethanol group suggests that neither the pharmacokinetics nor the caloric energy in ethanol enhanced survival likelihood. Indeed, had the rats consumed ethanol for energy, the food-deprived group ought to have consumed more than the food-ad lib group. However, since both groups drank moderate amounts, it would appear that pharmacokinetics or other properties of ethanol motivated them.

Activity anorexia is also known as activity-stress in other experimental contexts (10, 13, 17), and provides an effective method for inducing demonstrable stress-related effects. In the present study, all three groups of food-deprived rats manifested several behavioral signs of stress, though there were large individual differences between groups. The animals were generally agitated and startled easily, they exhibited excessive general activity, and proved extremely difficult to handle, once the experimental phase of the study had begun. Despite the fact that all deprived rats were physically barred from the wheels during the daily 90-minute feeding period, their hyperactivity nevertheless often interfered with their eating. Frequently, they would grasp and then discard their food pellets several times before finally settling down to eat. At other times, they would grasp a food pellet and attempt to reenter the activity wheel, perseverating in this futile activity. There is considerable observational support, then for the possibility " . . . that the reduction in food intake is brought about, in part, by a general heightened excitability, and that when the rat finally does have the opportunity to feed it is unable to eat efficiently because it is too excited" (18).

The role of ethanol in ameliorating stress effects is complicated by studies reporting increases, decreases, or no change in ethanol intake following stress [for an excellent review, see (16)]. Our study indicated no difference in overall ethanol consumption between stressed (food-deprived) and nonstressed (food-ad lib) animals, except for a quite small decrease in intake over Periods 2 to 4 for the former group, and similar to the result of another study (17). It is unlikely, then, that the ethanol ingested by food-deprived rats in the present study was consumed as a stress palliative.

An important finding in this study was the significantly enhanced survival of the rats ingesting a propylene glycol solution, increasing their consumption particularly over Periods 2 to 4. Consumption peaked in Period 4, when body weight was lowest. Moreover, the food-deprived group consumed significantly more propylene glycol than the food-ad lib group. Taken together, the results strongly suggest that the food-deprived rats consumed propylene glycol for its caloric (energy) value. Certainly this finding is in agreement with other reports of attempts by rats to compensate for nutrient intake when normal patterns and rates of feeding is disrupted (3).

A closer inspection of the ETOH and PROP groups indicates that propylene glycol intake was quite low compared to ethanol intake by food-ad lib rats. This difference may be due to the fact that propylene glycol is a mild gastrointestinal irritant (22). If the animals consumed propylene glycol for its caloric benefit, it seems reasonable that they would endure its discomfort once body weight had fallen sufficiently below optimum level. Ethanol, on the other hand, was not likely consumed solely for its energy content. Despite these differences, statistical analysis revealed that the caloric intake from propylene glycol and ethanol did not differ significantly between the two food-deprived groups. Nevertheless, the ETOH group still exhibited a lower survival rate than did the PROP group. The food-deprived PROP rats exhibited lower rates of wheel running than either the ETOH or WATER groups. In the activity anorexia paradigm, a higher rate of change in wheel running over time predicts that weight loss and starvation will occur more quickly (5, 6, 15). This relationship accounts for the lower survival rate of the ETOH animals, whose caloric intake was comparable to the PROP group: the PROP rats simply expended less energy by virtue of their lower wheel-running scores than did the ETOH or WATER groups.

Energy loss from higher wheel running rates in the ETOH rats is further exacerbated by ethanol's deleterious effects on energy storage and utilization; ethanol metabolism produces byproducts that waste energy through heat dissipation, and damages the energy-generating efficiency of mitochondria (11). It also alters lipid profiles of many types of cells in several tissues, causing fatty acid deficiencies (20), and results in in situ carbohydrate depletion and hypoglycemia (8,20). Further, when exercising rats are given ethanol as part of their diets, their body weight is, on average, lower than that of exercising rats on an ethanol-free (but calorically identical) diet (1). Thus changes in metabolism due to ethanol may well result in a minimal net caloric gain, or even a net loss, for the animal.

Parenthetically yet ironically, small quantities of alcohol act as a stomachic, and are often given to hospitalized patients to stimulate appetite (23). Despite this claim, however, no clear-cut conclusions can be drawn from this study concerning activity anorexia and ethanol consumption in rats. Further research, designed to delineate more precisely the interactions between activity, food restriction, and alcohol consumption, is currently in progress. Activity anorexia conditions, it appears, provide a dramatic circumstance in which rats are not inclined to palliate stress by consuming alcohol.

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