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Free-Choice Ethanol Intake and Ethanol Metabolism in the Hamster and Rat

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KULKOSKY, P. J. AND N. W. CORNELL. *Free-choice ethanol intake and ethanol metabolism in the hamster and rat.* PHARMAC. BIOCHEM. BEHAV. 11(4) 439–444, 1979.—Hamsters, as previously reported, demonstrated greater ethanol intake and preference than rats. However, as ethanol was gradually added to a sweet solution, hamster ethanol intakes did not consistently exceed ethanol metabolic capacity for prolonged periods. In ethanol-naive hamsters and rats, alcohol dehydrogenase activities and ethanol metabolic rates of isolated hepatocytes *in vitro* and blood ethanol elimination rates *in vivo* show consistent large interspecific differences corresponding to the species' differences in ethanol intake and preference. The data suggest a limiting role of ethanol metabolism in the regulation of maximized free-selection ethanol intake by rodents, and provide an explanation for the absence of continuously elevated blood ethanol levels and alcohol withdrawal syndrome in hamsters during periods of comparatively high daily ethanol intake.

Ethanol intake Ethanol preference Alcohol dehydrogenase activity Ethanol metabolism
Hamster and rat ethanol intake and preference

THE golden hamster *(Mesocricetus auratus)* displays high ethanol intake and preference in comparison with several mammalian species [1, 15, 21, 52]. This finding led to suggestions that the hamster might be an appropriate small animal species for a free-selection model of the effects of chronic high ethanol intake observed in humans [33,49]. Although hamsters freely select quantities of ethanol within the dose range used to induce physical dependence and liver abnormalities in albino rats *(Rattus norvegicus)* [32], recent studies demonstrated no obvious signs of physical dependence or fatty liver in hamsters after prolonged, continuous selection of ethanol at these comparatively high levels [22, 26, 31, 51]. Measurements during periods of high ethanol intake [26,51] revealed that hamsters do not maintain blood ethanol at levels previously found necessary for production of physical dependence on ethanol in rats and mice [40].

The avoidance by hamsters of prolonged high blood ethanol could be due to a widely-spaced pattern of ethanol intake or to a comparatively high ethanol metabolic or excretion rate. By itself, the drinking pattern is not a sufficient explanation. The prolonged intakes that have been reported for hamsters [22, 26, 31, 51] far exceed the rat's maximum daily capacity for ethanol elimination [10, 11, 52]. Thus, if rats and hamsters had equivalent capacities for ethanol elimination per unit body weight, hamster blood ethanol levels would increase regardless of drinking pattern.

It has often been suggested that preference for and consumption of ethanol by rodents is positively related to their capacities to metabolize and eliminate ethanol [20, 21, 36, 37, 39]. Evidence includes reports of significant relations between inbred mouse strain preference for ethanol and ethanol-1-^{14}C metabolic rate [41], and a significant relation between level of consumption of ethanol and peak early blood ethanol levels after injection in rats [3,4]. Further, differences in rodent ethanol preference and consumption as functions of strain or sex [16, 17, 18, 19, 46], pregnancy and lactation [24,50], and drug treatment [42] have each been shown, in many cases, to be positively related to differences in ethanol metabolism or elimination rate. A perfect rank-order correlation of mean strain preference for 10% ethanol solution versus water with liver alcohol dehydrogenase activity has been demonstrated in 6 inbred mouse strains [38]. The activity of alcohol dehydrogenase, located almost entirely in liver, has been shown to be the most important rate determining factor in the oxidative metabolism of ethanol [10,11].

In the present study, the possibility that a species difference in ethanol intake and preference corresponds to a species difference in ethanol metabolism was examined with the golden hamster and the albino rat. Hamster and rat free-selection ethanol intakes and preferences for ethanol solutions were contrasted. The alcohol dehydrogenase activities and ethanol metabolic rates of isolated hepatocytes *in vitro* and blood ethanol elimination *in vivo* were then determined in hamsters and rats without prior access to ethanol solutions. In an attempt to maximize free-choice ethanol intake in the manner recently reported for albino rats [27], another group of hamsters was given free access to food, water and a sweet solution of gradually increasing ethanol concentration. Ethanol intake and preference of these hamsters were recorded, activities of liver alcohol dehydrogenase were determined, and total daily ethanol metabolic capacities were compared to total daily ethanol intakes.

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METHOD

Animals

Animals were 22 experimentally naive adult male golden hamsters (outbred, Lakeview Lak:LVG[SYR]), and 19 experimentally naive adult male Wistar rats (outbred, Charles River Crl:COBS[WI]BR). They were individually housed in wire-mesh stainless steel cages at an ambient temperature of 20°C and 12:12 L:D lighting cycle (8 a.m.–8 p.m. light), and had ad lib access to Purina NIH open formula rat and mouse ration and deionized water unless otherwise specified.

Apparatus

Two hundred fifty and 100 ml calibrated drinking tubes fitted with valveless stainless steel spouts were used to measure fluid consumption to the nearest 1.0 ml. Spillage from drinking tubes was caught by 2 oz jars fitted with glass funnels and positioned under the cages.

Procedure

Ethanol solution and water choice test. Five hamsters and 5 rats, all without prior access to ethanol solution, received two bottles of deionized water for an initial period of 4 days. Ethanol (from U.S.P. 95%) was then added to one of the bottles at increasing concentrations from 1–14% w/v, ascending 1% on each consecutive day. Fluid intakes, ethanol intakes per kilogram of body weight, and ethanol solution preference ratios (defined as ethanol solution intake [in ml] divided by total fluid intake [ethanol solution intake (in ml) + water intake (in ml)]) were measured. Captured spillage was subtracted from apparent fluid consumption to determine intake.

Ethanol metabolism and alcohol dehydrogenase activity in vitro. Hepatocytes were isolated from ethanol-naive, 48-hr starved rats (N=9) and hamsters (N=6) using the technique of Berry and Friend [6] modified as described previously [9,25]. Incubations were conducted at 38°C in 25 ml Erlenmeyer flasks containing 4 ml of cell suspension. The incubation conditions (Table 1) were previously shown to cause isolated rat hepatocytes to metabolize ethanol at rates similar to those observed *in vivo* [10]. After 60 min, incubations were stopped by addition of 0.2 ml of 60% $HClO_4$ with vigorous mixing. After standing on ice for 20 min, the mixtures were centrifuged at 4°C, 10,000 X g for 10 min, and ethanol was measured in the acid supernatant. For the measurement of alcohol dehydrogenase activity, hepatocytes in 2 ml of each cell suspension were collected by centrifugation and resuspended in 2 ml of 0.05 M HEPES, pH 8.4, 0.33 mM dithiothreitol. Cells were disrupted by sonication, and alcohol dehydrogenase was measured in the supernatant after centrifugation at 4°C, 40,000 X g for 45 min [10,11].

Blood ethanol elimination in vivo. Five ethanol-naive hamsters and five ethanol-naive rats received a 1.5 g/kg intraperitoneal injection of ethanol administered at a concentration of 10% w/v and dissolved in 0.9% w/v NaCl. Blood samples were obtained under ether anaesthesia by cardiac puncture with a 5/8 in., 25-ga needle at 60, 90 and 120 min after injection, and assayed for ethanol content with yeast alcohol dehydrogenase [14]. Estimates of rate of elimination of ethanol were obtained by extrapolation to the time abscissa of the linear descending limb of the blood alcohol curve [52].

Gradual Addition of Ethanol to Sweetened Solution

Six ethanol-naive hamsters had ad lib access to chow and water only for an initial period of 35 days. Subjects then received an ad lib choice of chow, water, and a solution of 3.0% w/v glucose (anhydrous dextrose, Baker reagent) + 0.125% w/v sodium saccharin (Fisher purified) (N=3) + 1.0% w/v sodium chloride (Baker reagent) (N=3), for a total of 10 days. Only chow and water were available on weekends and holidays. After this period, ethanol was added to the solutions according to the following ascending concentration sequence: 0.5–10.0% (w/v) in 0.5% increments; 10.0–20.0% in 1.0% increments; 20.0–40.0% in 2.0% increments; and 40.0–70.0% in 5.0% increments, increasing one concentration per day. G/kg/day ethanol intakes and solution (+ ethanol) preference ratios were measured.

Fluid intake was determined by subtraction of measured spillage, if any, from apparent fluid consumption. All solution intakes and spillages at ethanol concentrations $\geq$20% were corrected by 20% for evaporation, as specified by Richter [34]. At the conclusion of the concentration sequence, all hamsters then received ad lib chow and water only for a final period of 40 days. After this final period, 4 of these hamsters were randomly selected, anaesthetized with an overdose of ether, and exsanguinated. The livers were removed, weighed, and homogenized with 3 volumes of 0.05 M HEPES, pH 8.4, containing 0.33 mM dithiothreitol. Homogenates were centrifuged at 40,000 X g for 45 min. The supernatants were assayed for alcohol dehydrogenase in the direction ethanol→acetaldehyde using, in a final volume of 2.0 ml: 1.0 ml of 1.0 M tris, pH 7.2 (which serves both as a buffer and as a trapping agent for acetaldehyde [14]), 0.2 ml of 28 mM NAD^+, 0.01 ml of 1.0 M ethanol, and 0.02 ml of liver extract. All assays were at 38°C. The liver capacity for ethanol oxidation was calculated assuming that the activity in the 40,000 X g supernatant represented a four-fold dilution of the activity in the intact liver.

Data were analyzed with 2-way analysis of variance, regression correlation analysis, and two-sample *t*-tests (2-tailed), with $p<0.05$ as significant.

RESULTS

Ethanol Solution and Water Choice Test

Mean fluid consumption by hamsters and rats as a function of ethanol concentration is shown in Fig. 1. During the initial period of 2-bottle water availability, water intakes of hamsters and rats averaged 7.7 and 28.1 ml, respectively, and differed significantly, $F(1,32)=438.0$, $p<0.05$; the effect of days was significant, $F(3,32)=4.06$, $p<0.05$, but the interaction was not. During the period of choice between ethanol solutions and water, water intakes of hamsters and rats averaged 2.7 and 28.6 ml, respectively, and again differed significantly, $F(1,112)=671.8$, $p<0.05$; the effect of concentration, $F(13,112)=5.47$, $p<0.05$, and the interaction, $F(13,112)=9.61$, $p<0.05$, were also significant. Water intake of hamsters steadily declined with increasing ethanol concentration, while water intake of rats rapidly increased to asymptote. Ethanol solution intakes of hamsters and rats averaged 10.3 and 6.5 ml, respectively, across concentrations, and differed significantly, $F(1,112)=18.4$, $p<0.05$; the effect of concentration, $F(13,112)=2.2$, $p<0.05$, and the interaction, $F(13,112)=9.86$, $p<0.05$, were also significant. Ethanol solution intakes of hamsters gradually increased to asymptote with increasing ethanol concentration, but

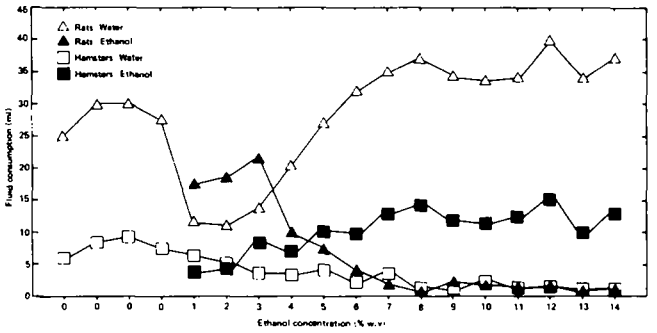

FIG. 1. Mean consumption (in ml) of water (open symbols) and ethanol solution (filled symbols) by rats (triangles) and hamsters (squares) as a function of ethanol concentration (in % w/v). Two bottles of water were available ad lib for the first four days; thereafter an ad lib choice of water and ethanol/water solution was available, with ethanol concentration increasing 1% per day.

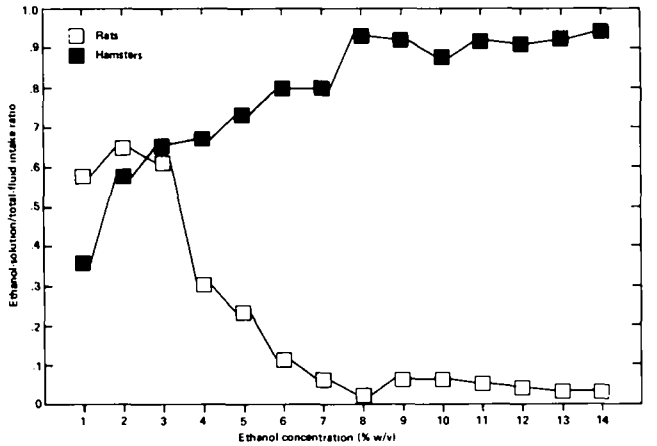

FIG. 2. Mean ethanol-solution/total-fluid intake ratio of rats (open squares) and hamsters (filled squares) as a function of ethanol concentration (in % w/v). Fluid choice conditions as in Fig. 1.

ethanol solution intakes of rats sharply declined at concentrations >3%.

Mean ethanol-solution/total-fluid ratio (E/T ratio), a measure of ethanol preference, as a function of ethanol concentration is shown in Fig. 2. E/T ratio of hamsters and rats averaged 0.79 and 0.20, respectively, and differed significantly, $F(1,112)=287.6$, $p<0.05$; the interaction was significant, $F(13,112)=9.46$, $p<0.05$, although the effect of concentration was not. Arc sine transformation of the data did not alter these conclusions.

Mean grams of absolute ethanol per kilogram of body weight per day intake of hamsters and rats as a function of ethanol concentration are shown in Fig. 3. Ethanol intakes of hamsters and rats averaged 7.6 and 0.92 g/kg/day, respectively, and differed significantly, $F(1,112)=449.0$, $p<0.05$; the effect of concentration, $F(13,112)=15.7$, $p<0.05$, and the interaction, $F(13,112)=22.0$, $p<0.05$, were also significant. Ethanol intake of hamsters rose with increasing ethanol concentration, but ethanol intake of rats peaked at 3%, and thereafter declined.

Ethanol metabolism and alcohol dehydrogenase activity in vitro. Mean (± standard error, SEM) ethanol metabolism

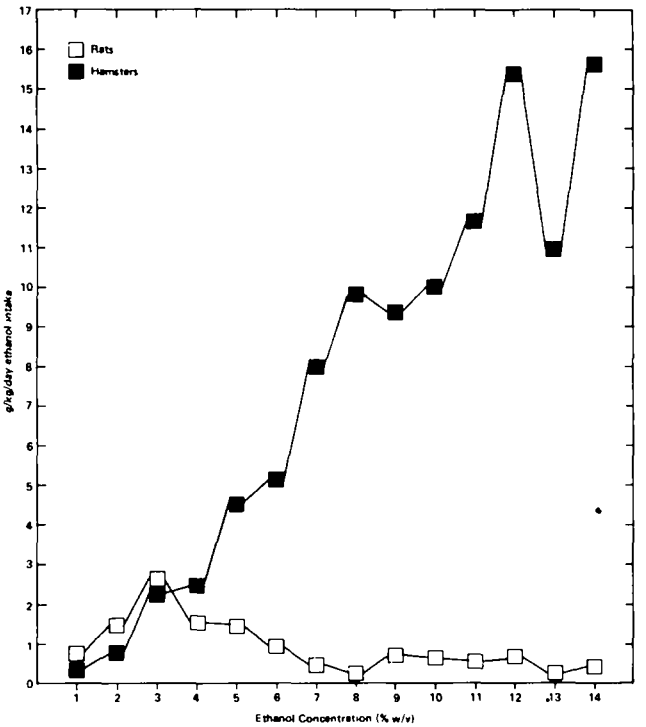

FIG. 3. Mean grams per kilogram of body weight per day intakes of absolute ethanol of rats (open squares) and hamsters (filled squares) as a function of ethanol concentration (in % w/v). Fluid choice conditions as in Fig. 1.

TABLE 1

MEAN (± SEM) ETHANOL METABOLISM AND ALCOHOL DEHYDROGENASE ACTIVITY IN HEPATOCYTES FROM HAMSTERS AND RATS

	μmol/min/g ethanol metabolism	μmol/min/g alcohol dehydrogenase activity
Hamster (N=6)	5.7 ± 0.5	9.3 ± 0.9
Rat (N=9)	2.9 ± 0.1	5.6 ± 0.2

Mean (± SEM) ethanol metabolism and alcohol dehydrogenase activity (in μmol/min/g wet weight of cells) in hepatocytes from ethanol-naive hamsters and rats. Hepatocytes were isolated and incubated as described in the Method section. For ethanol metabolism, each incubation contained about 100 mg wet weight cells, 5 mM pyruvate and 10 mM ethanol. Alcohol dehydrogenase activity was measured with ethanol as substrate as described in Method and elsewhere [10, 11].

and alcohol dehydrogenase activity (both in μmol alcohol oxidized/minute/g wet weight cells) of the hamsters and rats are summarized in Table 1. Hamsters and rats differed significantly in both ethanol metabolic rate and alcohol dehydrogenase activity of isolated hepatocytes (respective $ts=7.1$ and 4.7, $dfs=13$, $ps<0.05$). Ethanol metabolic rate was significantly correlated ($r=0.85$, $df=13$, $p<0.05$) with alcohol dehydrogenase activity.

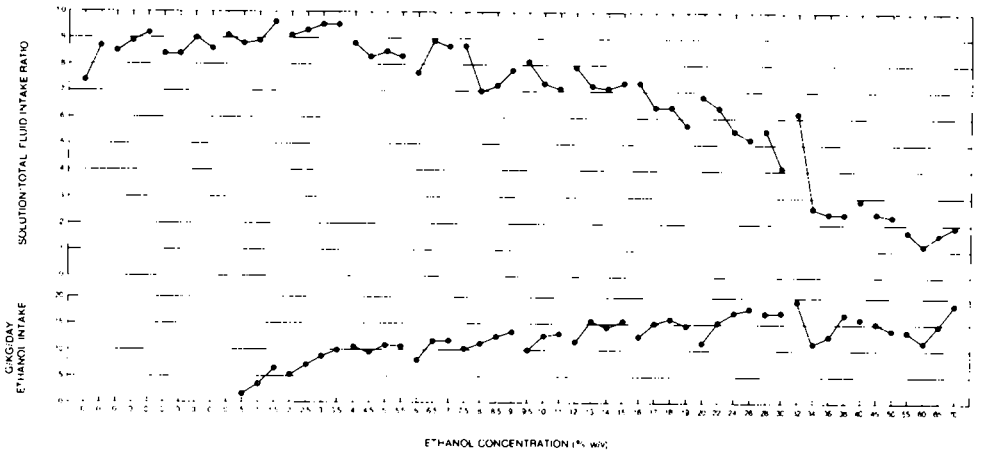

FIG. 4. Mean grams per kilogram of body weight per day intakes of absolute ethanol and solution/total-fluid intake ratio as a function of ethanol concentration of solution (in % w/v) for hamsters with an ad lib choice of water and sweetened solution (+ ethanol).

Blood ethanol elimination in vivo. Mean ± SEM estimated blood ethanol elimination rates of hamsters and rats after intraperitoneal injection of 1.5 g/kg ethanol were 595.8 ± 26.1 and 264.8 ± 44.6 mg/kg/hr, respectively, and differed significantly ($t=6.4$, $df=8$, $p<0.05$).

Gradual addition of ethanol to sweetened solution. Mean g/kg/day ethanol intake and solution/total-fluid intake ratio (S/T ratio) of hamsters as a function of added ethanol concentration (in percent w/v) are shown in Fig. 4. Ethanol intake initially increased with ethanol concentration, but then became relatively constant at 15–20 g/kg/day at ethanol concentrations ≥13%. Mean ethanol intake and concentration were significantly correlated ($r=0.85$, $df=44$, $p<0.05$); the least-squares fit equation is: y(in g/kg/day)=x(in percent w/v)/(0.25+(0.05x)). Mean S/T ratio for the sweetened solutions without added ethanol was 0.86; S/T ratio was not consistently below this mean until the ethanol concentration was ≥8%, and did not decline consistently below 0.50 until all concentrations ≥34%. However, the S/T ratio declined proportionally with ethanol concentration, and mean S/T ratio and concentration were significantly correlated ($r=-0.95$, $df=54$, $p<0.05$); the least-squares fit equation is: y (in S/T ratio)=0.89–0.013 x(in percent w/v).

Mean (± SEM) activity of liver alcohol dehydrogenase of these hamsters was 11.1 ± 1.2 μmol of ethanol oxidized/minute/g of wet weight cells. Mean (± SEM) body and liver weights were 132.5 ± 7.0 and 6.3 ± 0.7 g, respectively. Mean activity of liver alcohol dehydrogenase of these hamsters did not differ significantly from that of the ethanol-naive hamsters, but was significantly higher than that of the ethanol-naive rats ($t=6.59$, $df=11$, $p<0.05$).

DISCUSSION

Alcohol intakes and preferences reported in the present experiment are in agreement with values previously reported for the golden hamster [1, 2, 8, 15, 22, 26, 31, 33, 48, 49, 51, 52] and this strain of albino rat [27]. Hamsters displayed levels of ethanol intake and preference much higher than those of rats, in agreement with previous reports of higher preference for 10% ethanol solutions by hamsters in comparison with albino rats [1, 15, 26]. The peak ethanol intake by hamsters under conditions of gradual addition of ethanol to a sweet solution (19.3 g/kg/day) is approximately double that recently reported for albino rats (9.3 g/kg/day) under similar conditions [27].

Observed activities of liver alcohol dehydrogenase, ethanol metabolism in isolated hepatocytes, and blood ethanol elimination rates in ethanol-naive hamsters and rats show large species differences that correspond to the observed large species differences in ethanol intake and preference. Values reported for ethanol metabolism in the hamster and rat are consistent with previous determinations [10, 11, 51, 52]. Determinations of ethanol metabolism show that hamsters receiving access to sweetened ethanol solutions typically do not consume ethanol for prolonged periods at levels beyond their estimated maximal capacity for ethanol oxidation, as also observed in the rat [27]. Thus the absence of both continuously elevated hamster blood ethanol levels and consequent alcohol withdrawal syndrome during periods of comparatively high ethanol intake [22, 26, 31, 51] might be attributed to a comparatively high rate of ethanol metabolism. Relatively higher excretion rate in the hamster is an unlikely explanation of the observed differences in ethanol elimination since 4-methyl-pyrazole administration (an inhibitor of alcohol dehydrogenase [11]) results in maintenance of high blood ethanol levels in hamsters [51]. This finding [51], the correlation of ethanol metabolism and alcohol dehydrogenase activity *in vitro* observed in the present experiment, and the recent demonstration of close agreement between liver alcohol dehydrogenase activities and ethanol elimination rates *in vivo* in rats with varied nutritional states [29] indicate that the species difference in liver alcohol dehydrogenase activity may explain the observed species difference in ethanol elimination.

The data of these experiments show that relatively high alcohol dehydrogenase activity, ethanol metabolism, and blood ethanol elimination are correlates of the comparatively high ethanol intake and preference of the golden hamster. This finding of corresponding differences in two rodent species' free-selection ethanol intake and ethanol metabolism is in accord with previous demonstrations of positive relations between rodent ethanol intake and ethanol metabolism or blood elimination [16, 17, 18, 19, 24, 30, 38, 41, 42, 46, 50]. Correlations have also been shown between level of alcohol consumption and peak early blood ethanol

levels after injection [3,4]. However, many studies have failed to demonstrate a significant correlation of ethanol intake or preference with ethanol eliminative capacity or metabolism [36, 37, 44, 45]. Also, in many experiments showing corresponding differences in ethanol intake and metabolism, the magnitude of observed metabolic differences appeared too small to account for the very large differences in intake [36, 37, 43].

A relationship between ethanol consumption and metabolism might be most apparent when intakes approach the limits of eliminative capacity. When intakes are maximized, the consequences of cumulative ethanol ingestion might have more obvious and immediate aversive impact and place ethanol eliminative capacity in a limiting relation to ethanol intake. When free-selection ethanol intakes were maximized by gradual addition of ethanol to a highly-preferred vehicle (present study, [27]), solution intakes decrease proportionally with ethanol concentration, and ethanol intakes do not consistently exceed ethanol metabolic capacity for prolonged periods. Thus, under the conditions of intake maximization, a limiting function of ethanol metabolism in the control of ethanol intake is observed (see also [39]). This limiting relation may not be functional when intakes are low, and no clear relation between intake and metabolism need be observed.

A physiological basis for the comparatively high ethanol metabolism of hamsters might be the reported fermentation of food that takes place in the pregastric pouch of the hamster's bi-compartmented stomach [23,47]. Relatively high levels of liver alcohol dehydrogenase activity might be present as a genetic or developmental adaptation to ethanol production in the pregastric pouch. A suggested ecological interpretation of the high consumption of ethanol by hamsters is that the typical diet of their desert forebears comprises many bitter tasting substances, and precludes innate sensory aversion to the strong taste of alcohol [52]. This speculation is consistent with the reported relatively high concentration threshold for avoidance of quinine hydrochloride by hamsters [7], but a high bitter avoidance threshold alone does not explain the apparent avidity of the hamster for ethanol solutions.

In summary, the data of these experiments show that the hamster's comparatively high free-selection ethanol intake and preference is accompanied by a comparatively high liver alcohol dehydrogenase activity, ethanol metabolism, and blood ethanol elimination rate. The hamster's relatively high metabolic capacity is independent of prior ethanol intake, and may represent an inborn or developmental adaptation to a fermentative pregastric digestive system. These findings may be interpreted as evidence for a limiting function of maximal ethanol metabolic capacity in the regulation of maximized free-choice ethanol intake, and may reflect the avoidance by rats and hamsters of oronasal discriminative stimuli previously paired with high blood ethanol levels [5, 12, 13, 28, 35].

REFERENCES

1. Arvola, A. and O. Forsander. Comparison between water and alcohol consumption in six animal species in free-choice experiments. *Nature* **191**: 819–820, 1961.
2. Arvola, A. and O. A. Forsander. Hamsters in experiments of free choice between alcohol and water. *Q. Jl Stud. Alcohol* **24**: 591–597, 1963.
3. Belenko, S. and S. C. Woods. Physiological correlates of ethanol self-selection by rats. *Physiol. Psychol.* **1**: 155–157, 1973.
4. Belenko, S. and S. C. Woods. Blood-ethanol levels predict amount of ethanol consumption by rats. *Physiol. Psychol.* **3**: 422–424, 1975.
5. Berman, R. F. and D. S. Cannon. The effect of prior ethanol experience on ethanol-induced saccharin aversions. *Physiol. Behav.* **12**: 1041–1044, 1974.
6. Berry, M. N. and D. S. Friend. High yield preparation of isolated rat liver parenchymal cells. *J. Cell Biol.* **43**: 506–520, 1969.
7. Carpenter, J. A. Species differences in taste preferences. *J. comp. physiol. Psychol.* **49**: 139–144, 1956.
8. Carver, J. W., J. B. Nash, G. A. Emerson and W. T. Moore. Effect of pregnancy and lactation on voluntary alcohol intake of hamsters. *Fedn Proc.* **12**: 309, 1953.
9. Cornell, N. W., P. Lund, R. Hems and H. A. Krebs. Acceleration of gluconeogenesis from lactate by lysine. *Biochem. J.* **134**: 671–672, 1973.
10. Crow, K. E., N. W. Cornell and R. L. Veech. The role of alcohol dehydrogenase in governing rates of ethanol metabolism in rats. In: *Alcohol and Aldehyde Metabolizing Systems, Vol. III*, edited by R. G. Thurman, J. R. Williamson, H. Drott and B. Chance. New York: Academic Press, 1977, pp. 335–342.
11. Crow, K. E., N. W. Cornell and R. L. Veech. The rate of ethanol metabolism in isolated rat hepatocytes. *Alcoholism: Clin. exp. Res.* **1**: 43–47, 1977.
12. Davison, C., G. Corwin and T. McGowan. Alcohol-induced taste aversion in golden hamsters. *J. Stud. Alcohol.* **37**: 606–610, 1976.
13. Davison, C. S. and W. J. House. Alcohol as the aversive stimulus in conditioned taste aversion. *Bull. Psychon. Soc.* **6**: 49–50, 1975.
14. Dickinson, F. M. and K. Dalziel. The specificities and configurations of ternary complexes of yeast and liver alcohol dehydrogenases. *Biochem. J.* **104**: 165–172, 1967.
15. Emerson, G. A., R. G. Brown, J. B. Nash and W. T. Moore. Species variation in preference for alcohol and in effects of diet or drugs on this preference. *J. Pharmac. exp. Ther.* **106**: 384, 1952.
16. Eriksson, C. J. P. Ethanol and acetaldehyde metabolism in rat strains genetically selected for their ethanol preference. *Biochem. Pharmac.* **22**: 2283–2292, 1973.
17. Eriksson, K. and K. K. Malmström. Sex differences in consumption and elimination of alcohol in albino rats. *Annls Med. exp. Biol. Fenn.* **45**: 389–392, 1967.
18. Eriksson, K. and P. H. Pikkarainen. Differences between the sexes in voluntary alcohol consumption and liver ADH-activity in inbred strains of mice. *Metabolism* **17**: 1037–1042, 1968.
19. Eriksson, K. and P. H. Pikkarainen. Strain and sex differences in voluntary alcohol consumption, liver ADH activity and aldehyde-oxidizing capacity in inbred strains of mice. *Jap. J. Stud. Alcohol* **5**: 1–7, 1970.
20. Forsander, O. A. Metabolic tolerance to alcohol as a possible limiting factor in its consumption. *Q. Jl Stud. Alcohol* **23**: 480–482, 1962.
21. Forsander, O., J. Kohonen and H. Suomalainen. Physiological alcohol consumption. *Q. Jl Stud. Alcohol* **19**: 379–387, 1958.
22. Harris, R. A., W. Krause, E. Goh and J. Case. Behavioral and biochemical effects of chronic consumption of ethanol by hamsters. *Pharmac. Biochem. Behav.* **10**: 343–347, 1979.
23. Hoover, W. H., C. L. Mannings and H. E. Sheerin. Observations on digestion in the golden hamster. *J. Anim. Sci.* **28**: 349–352, 1969.

24. Komura, S., Y. Niimi and Y. Yoshitake. Alcohol preference during reproductive cycle in female C57BL mice. 1. Relationship between alcohol preference and liver alcohol dehydrogenase activity. *Jap. J. Stud. Alcohol* **5:** 91–96, 1970.
25. Krebs, H. A., N. W. Cornell, P. Lund and R. Hems. Isolated liver cells as experimental material. In: *Regulation of Hepatic Metabolism*, edited by F. Lundquist and N. Tygstrup. New York: Academic Press, 1974, pp. 726–750.
26. Kulkosky, P. J. Free-selection ethanol intake of the golden hamster *(Mesocricetus auratus). Physiol. Psychol.* **6:** 505–509, 1978.
27. Kulkosky, P. J. Effect of addition of ethanol and NaCl on saccharin + glucose polydipsia. *Pharmac. Biochem. Behav.* **10:** 277–283, 1979.
28. Lester, D., M. Nachman and J. LeMagnen. Aversive conditioning by ethanol in the rat. *Q. Jl Stud. Alcohol* **31:** 578–586, 1970.
29. Lumeng, L., W. F. Bosron and T. -K. Li. Quantitative correlation of ethanol elimination rates *in vivo* with liver alcohol dehydrogenase activities in fed, fasted and food-restricted rats. *Biochem. Pharmac.* **28:** 1547–1551, 1979.
30. McClearn, G. E., E. L. Bennett, M. Hebert, R. Kakihana and K. Schlesinger. Alcohol dehydrogenase activity and previous ethanol consumption in mice. *Nature* **203:** 793–794, 1964.
31. McMillan, D. E., F. W. Ellis, G. D. Frye and J. R. Pick. Failure of signs of physical dependence to develop in hamsters after prolonged consumption of large doses of ethanol. *Pharmac. Biochem. Behav.* **7:** 55–57, 1977.
32. Mello, N. K. A review of methods to induce alcohol addiction in animals. *Pharmac. Biochem. Behav.* **1:** 89–101, 1973.
33. Reiter, R. J., K. Blum, J. E. Wallace and J. H. Merritt. Pineal gland: Evidence for an influence on ethanol preference in male Syrian hamsters. *Comp. Biochem. Physiol.* **47:** 11–16, 1974.
34. Richter, C. P. Production and control of alcoholic cravings in rats. In: *Neuropharmacology: Transactions of the Third Conference*, edited by H. A. Abramson. New York: Josiah Macy, Jr. Foundation, 1957, pp. 39–146.
35. Riley, A. L., E. C. Lotter and P. J. Kulkosky. The effects of conditioned taste aversions on the acquisition and maintenance of schedule-induced polydipsia. *Anim. Learn. Behav.* **7:** 3–12, 1979.
36. Rodgers, D. A. Factors underlying differences in alcohol preference among inbred strains of mice. *Psychosom. Med.* **28:** 498–513, 1966.
37. Rodgers, D. A. Factors underlying differences in alcohol preference of inbred strains of mice. In: *The Biology of Alcoholism, Vol. 2: Physiology and Behavior*, edited by B. Kissin and H. Begleiter. New York: Plenum Press, 1972, pp. 107–130.
38. Rodgers, D. A., G. E. McClearn, E. L. Bennett and M. Hebert. Alcohol preference as a function of its caloric utility in mice. *J. comp. physiol. Psychol.* **56:** 666–672, 1963.
39. Rodgers, D. A. and G. E. McClearn. Sucrose versus ethanol appetite in inbred strains of mice. *Q. Jl Stud. Alcohol* **25:** 26–35, 1964.
40. Samson, H. H. and J. L. Falk. Pattern of daily blood ethanol elevation and the development of physical dependence. *Pharmac. Biochem. Behav.* **3:** 1119–1123, 1975.
41. Schlesinger, K., E. L. Bennett and M. Hebert. Effects of genotype and prior consumption of alcohol on rates of ethanol-1-^{14}C metabolism in mice. *Q. Jl Stud. Alcohol* **28:** 231–235, 1967.
42. Schlesinger, K., R. Kakihana and E. L. Bennett. Effects of tetraethylthiuramdisulfide (Antabuse) on the metabolism and consumption of ethanol in mice. *Psychosom. Med.* **28:** 514–520, 1966.
43. Schneider, C. W., S. K. Evans, M. B. Chenoweth and F. L. Beman. Ethanol preference and behavioral tolerance in mice: Biochemical and neurophysiological mechanisms. *J. comp. physiol. Psychol.* **82:** 466–474, 1973.
44. Segovia-Riquelme, N., J. J. Vitale, D. M. Hegsted and J. Mardones. Alcohol metabolism in "drinking" and "nondrinking" rats. *J. biol. Chem.* **223:** 399–403, 1956.
45. Segovia-Riquelme, N., I. Campos, W. Solodkowska, G. González, R. Alvarado and J. Mardones. Metabolism of labeled ethanol, acetate, pyruvate, and butyrate in "drinker" and "nondrinker" rats. *J. biol. Chem.* **237:** 2038–2040, 1962.
46. Sheppard, J. R., P. Albersheim and G. E. McClearn. Enzyme activities and ethanol preference in mice. *Biochem. Genet.* **2:** 205–212, 1968.
47. Silverman, H. J. and I. Zucker. Absence of post-fast food compensation in the golden hamster *(Mesocricetus auratus). Physiol. Behav.* **17:** 271–285, 1976.
48. Sinclair, J. D. and B. Sheaff. A negative alcohol-deprivation effect in hamsters. *Q. Jl Stud. Alcohol* **34:** 71–77, 1973.
49. Slighter, R. G., Jr. Alcohol selection and position selection in hamsters caged singly and in groups. *Q. Jl Stud. Alcohol* **31:** 20–27, 1970.
50. Thiessen, D. D., N. Whitworth and D. A. Rodgers. Reproductive functions and metabolic capacity as determinants of alcohol preference in C57BL female mice. *J. comp. physiol. Psychol.* **63:** 151–154, 1967.
51. Thurman, R. G., M. A. Bleyman and D. E. McMillan. Rapid blood ethanol elimination and withdrawal resistance in the Syrian golden hamster. *Pharmacologist* **20:** 160, 1978.
52. Wallgren, H. and H. Barry, III. *Actions of Alcohol*. New York: Elsevier, 1970.