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Ethanol in Cardiomyopathic Hamsters: Na and Water Excretion and Righting Response

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FITTS, D A *Ethanol in cardiomyopathic hamsters Na and water excretion and righting response* PHARMACOL BIOCHEM BEHAV 24(4) 967–973, 1986.—This study examined the effects of ethanol and hereditary cardiomyopathy on sodium and water excretion by golden Syrian hamsters of both sexes. Ethanol (4 g/kg) or the isotonic saline vehicle were injected IP into 60–70-day-old hamsters of normal and cardiomyopathic (BIO 14.6) strains. Urine and blood were collected after 90 or 350 min in different groups Cardiomyopathic hamsters more quickly lost their righting responses, eliminated ethanol more slowly, and had lower urine volume and sodium excretion than normal hamsters after ethanol injections Plasma creatine kinase levels were normal in all animals tested, indicating no active skeletal or cardiac lesioning in the cardiomyopathic hamsters at the time of the experiment Some factors which could contribute to the increased CNS and renal sensitivity to ethanol in cardiomyopathic hamsters include impaired ethanol metabolism, enhanced myocardial depression, and reduced atrial content of natriuretic peptides. The results do not owe to decompensated heart failure Thus, the genetic mutation which causes skeletal and cardiac myopathy in these hamsters may also affect the metabolism and sensitivity to ethanol

Body water Cardiomyopathic hamsters Creatine kinase Ethanol elimination Hematocrit Righting responses Sex differences Sodium and water excretion

DAILY ingestion of large amounts of ethanol for many years can lead to congestive heart failure and chronic sodium and water retention [4,31]. Numerous studies have examined the effects of ethanol on the hearts of alcoholic cardiac patients, and alcoholic cardiomyopathy is now thought to result from an interaction of ethanol consumption with unknown, possibly genetic, predisposing factors [31].

By contrast, very few studies have looked for similar effects of ethanol in non-alcoholic cardiac subjects (e.g., [10,18]). Existing studies of alcoholic and non-alcoholic cardiac patients have not reported sodium excretion, on the apparent presumption that any occuring sodium retention is entirely secondary to heart failure. However, even acute intoxication with ethanol can produce prolonged changes in renal sodium reabsorption, extracellular volume expansion, and natriuretic response to increased filtered loads of sodium [29, 33–38]. Neither the mechanism of this acute effect, nor its relation to sodium retention in any cardiac patients, is currently known.

Because of this lack of data, the present study was designed to investigate ethanol-induced sodium retention in a non-alcoholic animal model of cardiomyopathy, the cardiomyopathic hamster. Animals were used prior to the age of active necrosis [1,20], so any influence of ethanol in these relatively healthy young animals would owe to characteristics inherited along with the cardiomyopathy, and not to cellular necrosis and decompensation, per se. The hearts of cardiomyopathic hamsters of this age do exhibit slightly reduced cardiac contractility in highly sensitive, *in vitro* tests, despite the absence of necrosis [28], and also are deficient in bioassayable atrial natriuretic peptide activity [9]. Thus, these hamsters could be more sensitive to the myocardial depressing effects of ethanol [8, 13, 19, 32, 42], and ought to have less of a peptide-mediated natriuretic response to saline-induced volume expansion during intoxication with ethanol. Both of these factors would predict greater sodium and water retention by cardiomyopathic hamsters after ethanol. In addition to the renal measurements, the latency to the loss of righting response was observed in order to provide concurrent data relevant to a different organ system.

METHOD

Animals

Golden Syrian hamsters (*Mesocricetus auratus*) of both sexes were used. Half were BIO 14.6 cardiomyopathic hamsters, originally obtained from the Central Laboratory Animal Resources Facility at Washington State University, Pullman, WA. A colony was maintained in this laboratory for the duration of these experiments through the breeding of siblings. Control hamsters of the Simonsen strain, Sim:(SYR), were purchased at 5–6 weeks of age, and were allowed to adapt to the laboratory for at least 2 weeks prior to use in experiments. Hamsters of both strains were 60–70 days old at the time of the experiments. Body weights aver-

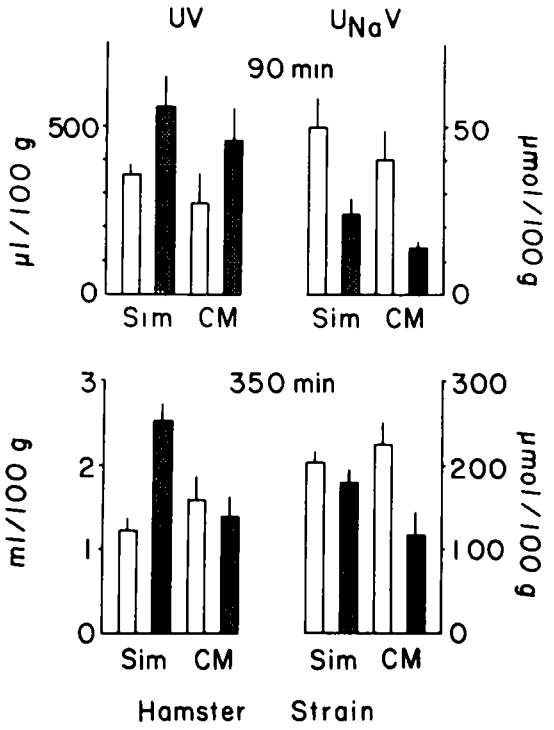

FIG 1 Urine volume (left half) and sodium excretion (right) following IP injection of saline (open bars) or ethanol (stippled) in Simonsen control (SIM) or cardiomyopathic (CM) hamsters Each group includes both sexes, N=12 ethanol or N=10 saline At 90 min (top half), all ethanol-injected hamsters excreted more urine and less sodium than saline controls At 350 min (bottom), CM hamsters displayed less diureses and sodium excretion than SIM hamsters after ethanol

aged 102±11 g for the BIO 14 6 strain and 97±6 g for the Simonsen strain prior to any treatment They were maintained on Purina No 5001 rodent chow and tap water in a ventilated room at 23°C, with a 12.12 light/dark cycle. They were kept in polycarbonate rodent cages with hardwood bedding prior to experiments

Injection Procedure

A 15% (v/v) solution of ethanol dissolved in sterile isotonic saline was injected IP into 48 male and female hamsters of the Simonsen and BIO 14.6 strains in a dose of 4 g/kg Each sex × strain group consisted of 12 hamsters Forty control hamsters received an injection of the vehicle in the same volume, 33 70 ml/kg, with 10 hamsters per group Animals were fasted 18 hr the night before the injections The hamsters' urinary bladders were voided by suprapubic massage, and body weights were taken immediately prior to injections between 0900 and 1030 hours. Ethanol-injected hamsters were then placed into a clean polycarbonate cage for observation of the postinjection loss of righting response The elapsed time was recorded from the injection to the first loss of righting response, defined as the hamster rolling onto its back with at least three paws in the air. All hamsters were then placed into urine collection cages for either 90 or 350 min, with each sex × strain × drug group divided equally between the time intervals (i.e., N=6 for ethanol injections, N=5 for saline injections, in each sex × strain × time group)

TABLE 1
BLOOD ETHANOL LEVELS

		Simonsen Strain	BIO 14 6 Strain
90 min	Male	304	325
		25	33
	Female	275	272
		12	27
350 min	Male	96	111
		17	22
	Female	76	110
		25	24

Values represent mean and S D Significant effects Strain main effect, Sex × Time interaction

Blood and Urine Collections

At the designated time after injection, hamsters were sampled for 2 0 ml of blood from the heart under ether anesthesia Samples were collected using 25-gauge heparinized needles, and 100 µl of whole blood from ethanol-injected hamsters was immediately pipetted into 0 9 ml of 3.4% (w/v) perchloric acid and frozen in airtight vials for later blood ethanol analysis Two microhematocrit capillary tubes were then drawn for hematocrit determination (Clay Adams microhematocrit centrifuge) Blood from vehicle-injected hamsters was then spun 5 min in a refrigerated centrifuge, and the decanted plasma was tightly capped and frozen for later determination of creatine kinase

Urine that appeared while the hamsters were in the collection cages was measured in calibrated centrifuge tubes beneath the funnels Residual urine was then washed from the sides of the funnels into separate centrifuge tubes with distilled water Hamsters were placed into the ether chamber inside a small, clean jar, so that urine which occasionally appeared during anesthesia could be aspirated and measured During blood sampling, the urethra was clamped with a hemostat to prevent urination. Animals were killed by cervical fracture under anesthesia, and any urine retained in the bladder was then collected by dissection Thus, all urine that formed after the injections was collected and measured, either in the cage, in the ether chamber, or directly from the bladder Any urine collected beneath the cages was corrected for the volume trapped on the sides of the funnels as follows The sodium concentration (see below) was determined for both the undiluted urine and the wash The volume of sodium (µmol) was then calculated for both samples Ordinarily, about 10% of the sodium excreted remained in the funnels by this analysis The volume of urine trapped in the funnels was then calculated by assuming that the concentration of the urine trapped in the funnels was the same as that in the undiluted sample. That is, (urine volume in funnel)=(sodium volume in funnel)/(sodium concentration of collected urine) Total urine volume was then calculated by addition of the trapped and collected volumes.

Blood and Urine Analyses

Sodium and potassium concentrations of the urine were determined by flame photometry (IL model 143). Blood ethanol concentrations were determined by the enzymatic method [6]. Plasma creatine kinase was determined colorimetrically (Sigma Chemical, kit No. 520). Creatine kinase determinations were made for all vehicle-injected cardiomyopathic hamsters, and for 3 of each group of 5 vehicle-injected Simonsen hamsters. No ethanol-injected hamsters were included, because ethanol artifactually elevates the plasma levels of the enzyme by producing leakage through skeletal muscle membranes [40]. Creatine kinase controls (Sigma reagent CPK-1) were interspersed with the unknowns during the analysis, and these were within the nominal range All samples either fell within the linear range of a standard curve, or were diluted to fall within that range.

Body Water Analyses

After the blood and urine samples were collected and treated as indicated above, all ethanol-injected hamsters were dissected for determination of water content in the gut and eviscerated carcass. The gut was ligated at the esophagus and anus and removed from the carcass. The gut and carcass were then weighed separately in tared jars, and the jars were placed in an oven at 95°C. After 3 days, the dried residue was crushed to release any trapped moisture, returned to the oven, and dried to a constant weight The water contents of the tissues were then calculated as the difference between the wet and dry weights, and corrected to a percentage of the body weight. Total body water was obtained as the sum of these values

Statistical Analyses

The experiment was constructed as a completely randomized design with 2 levels on each factor Thus, there were 2 sexes, 2 strains, 2 postinjection time intervals, and 2 drug conditions (ethanol vs. saline) The design was balanced for the number of subjects within each of the ethanol-injected (N=6) and saline-injected (N=5) groups An ANOVA was performed for each variable using the highest appropriate order of analysis. Post-hoc tests (multiple-t) were employed when a significance level of less than 0 05 was obtained for a given main or interaction effect

RESULTS

Ethanol-injected animals were observed for a loss of righting response prior to collection of urine. All hamsters lost the righting response, defined as rolling onto the back with at least three paws in the air, within 10 min of the 4 g/kg ethanol injection. Cardiomyopathic hamsters lost the righting response significantly faster than Simonsen hamsters, $F(1,40)=4.29$, $p<0.05$. No other effects approached significance. The means and standard deviations of the latencies for the combined sex and time groups (each N=24) were, for Simonsen hamsters, 3.23±2 57 min, and for cardiomyopathic hamsters, 2.08±0.49 min

The data for urine volume and sodium excretion are shown in Fig. 1. Analysis of variance was performed using a 3-factor design at each time point, rather than with time as a fourth factor, because of greatly differing variances at the two times. Significant sex differences (see below) were suppressed in the figure in order to clarify the presentation of strain differences.

At 90 min, there was a main effect of the drug treatments both for urine volume, $F(1,36)=5.18$, $p<0.05$ and for sodium excretion, $F(1,36)=20\ 86$, $p<0.001$, with ethanol-injected animals excreting more urine and less sodium. Concentration of sodium was accordingly dilute, mean value 49 mmol/l, 90 min after the ethanol injections, $F(1,36)=51\ 67$, $p<0\ 001$, compared with 166 mmol/l in saline-injected hamsters. Female hamsters of both strains excreted a greater volume of urine than males after both saline and ethanol injections at 90 min, $F(1,36)=6.40$, $p<0.05$; average sex difference 218 μl/100 g. However, females excreted significantly more sodium in the first 90 min only after saline injections (sex × drug interaction, $F(1,36)=11.42$, $p<0.01$; mean difference, 31 μmol/100 g). The mean sodium excretion for females at 90 min following ethanol injections was slightly lower than that for males, and did not differ significantly. There was not a significant sex × strain × drug interaction for any variable.

At 350 min, the strain × drug interactions were significant both for urine volume, $F(1,36)=21.23$, $p<0.001$, and for sodium excretion, $F(1,36)=4.49$, $p<0.05$. A significant ethanol-induced diuresis was still apparent in the control strain, but not in the BIO 14.6 strain, at this time (see Fig. 1). Furthermore, the ethanol-injected BIO 14.6 hamsters excreted far less sodium during the entire 350 min than any other group. Urinary sodium concentrations remained near the 150 mmol/l concentration of the injectate in saline treated animals at 350 min, 167 mmol/l, but were still lower in all ethanol-injected animals, 77 mmol/l, $F(1,36)=47.10$, $p<0\ 001$ No other variable significantly affected sodium concentration.

Sodium excretion was significantly affected by sex at 350 min, with female hamsters of both strains excreting more sodium than males, $F(1,36)=14.12$, $p<0\ 01$. A sex × strain interaction was significant at 350 min for urine volume, indicating that the mean sex difference was greater between the sexes of cardiomyopathic hamsters, 1161 μl/100 g, than between normal hamsters, 365 μl/100 g, after both ethanol and saline drug treatments, $F(1,36)=5.87$, $p<0\ 05$ No sex × strain × drug interaction was significant for any variable.

Blood ethanol levels for all groups of ethanol-injected hamsters (each n=6) are shown in Table 1. The cardiomyopathic hamsters maintained significantly higher concentrations of ethanol, $F(1,40)=6\ 12$, $p<0\ 05$, at both 90 and 350 min The sex × time interaction was significant, $F(1,40)=4\ 72$, $p<0\ 05$, and resulted from lower blood ethanol levels in female hamsters at 90, but not 350 min

Ethanol elimination rates, initial blood ethanol concentrations, and volumes of distribution could not be determined individually, because only a single blood sample was taken from each animal Therefore, these values were determined from pairs of hamsters, matched on the basis of body weight, from the 90- and 350-min time groups for each of the sex × strain factors. Linear kinetics were assumed. This analysis revealed a significant effect of sex, $F(1,20)=12\ 46$, $p<0.05$, but not strain, on the estimated *time 0* blood ethanol concentrations (C_0), as extrapolated by linear regression The means and standard deviations of these C_0 values were, for female and male Simonsen hamsters, 344±22 and 376±33 mg/dl, and for cardiomyopathic hamsters, 328±32 and 398±48 mg/dl The estimated volumes of distribution calculated from these C_0 values were, for female and male Simonsen hamsters, 117±7 and 107±9 ml/100 g, and for cardiomyopathic hamsters, 123±12 and 102±15 ml/100 g, indicating greater body water in female hamsters Elimination of ethanol did not differ according to

TABLE 2
BODY WATER DATA

		Simonsen Strain	BIO 14 6 Strain
Gut Water			
ml/100 g	Male	7 0	5 9
		0 9	0 5
	Female	8 8	7 7
		1 1	0 5
Carcass Water			
ml/100 g	Male	59 4	57 8
		1 9	3 3
	Female	58 5	62 4
		2 3	2 1
Total Water			
ml/100 g	Male	66 4	63 7
		2 1	3 4
	Female	67 3	70 1
		2 0	1 7

Values represent mean and S D for the combined 90- and 350-min, ethanol-treated groups, each n=12 Significant effects Gut Sex and Strain main effects, Carcass and Total Sex main effect, Sex × Strain interaction

sex, but was significantly slower in cardiomyopathic hamsters, $F(1,20)=5.62$, $p<0.05$. The means and standard deviations of the rates of ethanol elimination were, for female and male Simonsen hamsters, 532±58 and 510±35 mg/kg/hr, and for cardiomyopathic hamsters, 455±49 and 489±58 mg/kg/hr

Percentage water was measured directly by desiccation of the gut and carcass components of all ethanol-injected hamsters, and the data are presented in Table 2. There were no significant effects involving the time factor, so the 90- and 350-min groups have been combined in the table, with each group thus consisting of 12 hamsters. Water content of the gut was significantly affected by strain, $F(1,40)=25.17$, $p<0.001$, and by sex, $F(1,40)=66.44$, $p<0.001$ Females sequestered more water in the gut than males, and Simonsen hamsters had higher gut water content than cardiomyopathic hamsters. Sexes and strains did not interact for the gut water measure

Percentage carcass water showed an interaction of sexes and strains, $F(1,40)=14.94$, with the cardiomyopathic female hamsters having greater carcass water than any of the Simonsen hamsters or the male cardiomyopathic hamsters (see Table 2). The latter groups did not differ among themselves Sexes and strains also interacted on the total body water measure, $F(1,40)=16.26$, $p<0.001$, with the cardiomyopathic females having significantly more, and the cardiomyopathic males less, body water than either sex of the Simonsen strain.

In summary of the body water data, the Simonsen male and female hamsters had equal body water, although it tended to be distributed more in the gut for females than males. Cardiomyopathic males had the least gut water, apparently the result of being both male and BIO 14 6, had marginally lower carcass water; and had significantly less total body water than any other group Female cardiomyopathic hamsters had the highest total body water values. The ranking of the sex × strains groups in terms of total body water is the same as the ranking in terms of estimated volume of distribution of ethanol (see above), $r(2)=0.96$, $p<0.05$ This correlation supports the assumption of linear ethanol elimination kinetics for the present purposes

Creatine kinase levels of these 60–70 day old hamsters were not significantly affected by strain, sex, or time after injection The values averaged between 20 and 41 Sigma Units/ml, which indicates a borderline elevation of the enzyme in all groups tested [39] Such an elevation might be expected after IP injections, or in blood sampled via heart puncture, which could release a small amount of the enzyme by direct myocardial damage By contrast, creatine kinase levels of cardiomyopathic hamsters from the same colony, reared under similar conditions to an age of 100 days, yielded greatly elevated concentrations in 3 males (620±181 Sigma Units/ml) and 3 females (1258±125 Sigma Units/ml) The timing of the onset of lesion activity in these cardiomyopathic hamsters, as indicated by creatine kinase levels, was thus between 70–100 days Creatine kinase levels are a known indicator of myocardial lesion activity in cardiomyopathic hamsters [20,21], and an earlier, more severe onset of the lesions in females, as found here, is common [1]

Hematocrits were lower in female than male hamsters of both strains, $F(1,72)=11.34$, $p<0.01$, and were lower in cardiomyopathic hamsters of both sexes, $F(1,72)=15.16$, $p<0.001$, regardless of the drug treatment In addition, there was a dramatic interaction of the drug treatments with time, $F(1,72)=84.31$, $p<0.001$ The average hematocrit for both strains and sexes increased somewhat following saline injections, from 51 4% at 90 min to 52 9% at 350 min This indicated ongoing recovery from hemodilution and volume expansion after the saline load However, the hematocrit of ethanol-injected hamsters at first increased to 54 5% at 90 min, and then fell to 48 1% at 350 min

In summary, cardiomyopathic hamsters of strain BIO 14 6 maintained higher blood ethanol levels, lost the righting response earlier, increased urine flow less, and reduced sodium exretion more than Simonsen hamsters after 4 g/kg ethanol Plasma creatine kinase levels were not elevated in the cardiomyopathic hamsters of the injection study Female hamsters of both strains showed lower blood ethanol levels at 90 min, but not 350 min, excreted water faster after loads of saline or ethanol, and excreted sodium faster after saline but not ethanol, than did males of the same strain

DISCUSSION

The present results demonstrate greater apparent sensitivity to ethanol in cardiomyopathic than in normal hamsters This sensitivity was expressed both in the loss of righting response measure and in sodium and water retention Several explanations for these effects are possible, including (1) variations in absorption time, distribution of ethanol, or reduced ethanol metabolism; (2) increased myocardial depression in the hearts of cardiomyopathic hamsters, or (3) reduced ability to secrete atrial natriuretic factor during ethanol-induced volume expansion The results do no depend on a precipitation of imminent decompensated heart failure, because vehicle-injected cardiomyopathic hamsters of this age and source had no active cardiac necrosis, as indicated by normal levels of plasma creatine kinase Creatine kinase, an intracellular enzyme in muscle tissue, is released into the blood during injury, and thus is a reliable

marker of necrosis in cardiomyopathic hamsters [20,21]. This test has been verified in this laboratory with respect to cardiac lesion activity (D. A. Fitts and D. D. Reichenbach, unpublished). Cardiomyopathic hamsters from this colony, 30–40 days older than the ethanol-injected hamsters, did exhibit such elevations of creatine kinase, indicating that the onset of lesion activity occurred between 70 and 100 days of age

Ethanol Elimination and Metabolism

One explanation for the apparent increase in sensitivity could be that cardiomyopathic hamsters maintained higher blood ethanol levels. This difference could have resulted from faster absorption of ethanol, differences in distribution volume, and/or slower ethanol metabolism. The volume of distribution was a major factor in the sex difference in blood ethanol level, but could not have been the primary determinant of the strain difference, because the two sexes of cardiomyopathic hamsters were at opposite extremes both in the estimated volume of distribution of ethanol and in measured total body water.

A strain difference was observed in the volume of water present in the gut at both 90 and 350 min following ethanol injections. The lower gut water content in cardiomyopathic hamsters could have indicated that there was less volume available for immediate dilution, so that more rapid absorption of more concentrated ethanol occurred. Faster absorption could account for the earlier loss of righting response between strains, except that there was also a difference between sexes in gut water volume without a corresponding sex difference in righting response. Furthermore, the estimated C_0 blood ethanol values showed an effect of sexes, but not of strains The accuracy of these C_0 values is supported by the high correlation between the volumes of distribution calculated from them and the measured total body water. Thus, blood ethanol levels cannot account for the strain difference in the loss of righting response. Cardiomyopathic hamsters are probably more sensitive to this CNS effect of ethanol.

Strain differences in sodium retention would be more dependent on the rate of metabolism, rather than the initial absorption, of ethanol because the response occurs over several hours after injection. Ethanol elimination rates in both strains were high in comparison with other species, which is typical of hamsters [25,41]. However, the cardiomyopathic hamsters eliminated ethanol 9% slower than the Simonsen strain overall, and ended the experiment (at 350 min) with 28% higher blood ethanol levels than control hamsters, suggesting some impairment of ethanol metabolism in this strain. This undoubtedly would contribute to the reduced excretion of sodium by cardiomyopathic hamsters

Reduced elimination of ethanol does not always imply reduced ethanol metabolism. For instance, reduced myocardial performance (see below) might have reduced blood flow to the liver, which in turn could have altered elimination and sodium and water excretion without a change in metabolism.

Whether the reduced elimination of ethanol by cardiomyopathic hamsters accounts for all of the observed sodium and water retention remains an open question. At 350 min after ethanol injection, the Simonsen hamsters had excreted 10% less sodium than their saline-injected controls. For cardiomyopathic hamsters the figure was 45% less. Simonsen hamsters increased urine volume by 79% at 350 min, while cardiomyopathic hamsters decreased volume by 25% from their saline-injected controls. It seems likely that these large differences would require more than a 9% change in elimination rate if that were the only factor. Other differences exist between the strains which could plausibly influence sodium and water exretion in this way, and they should be considered.

Atrial Natriuretic Factor

Cardiomyopathic hamsters of strain BIO 14.6 are deficient in bioassayable activity of atrial natriuretic factor (ANF) [9]. This family of peptides has only recently been identified [11, 17, 23], and appears to play a role in the homeostatic response to extracellular volume expansion [43]. Intravenous injection of ANF produces a rapid and potent natriuresis, diuresis, and vasorelaxation in otherwise normally hydrated animals [11,24]. The peptide also inhibits adrenal synthesis of aldosterone [7,12], inhibits the release of aldosterone stimulated by angiotensin, potassium, or ACTH [7], and may act on the brain to facilitate diuresis [15]. All of these responses are helpful in the restoration of normal body sodium and fluid balance from the expanded state. It has been suggested that the deficiency of ANF in cardiomyopathic hamsters may thus play a part in the massive retention of sodium and water observed in this strain during congestive heart failure [9].

No studies have yet examined the role of ANF in the sodium-retentive response to ethanol intoxication. Ethanol produces expansion of the extracellular space even when electrolyte intake is restricted [29,36], apparently by redistributing cellular water into the extracellular space [22]. In the dog, renal plasma flow and glomerular filtration rate both increase during the later phases of intoxication, and the filtered load of sodium increases [5, 34, 35, 37]. Reabsorption of sodium increases, as well, and the net result is sodium retention [5, 34, 35, 37]. This enhanced reabsorption is resistant even to increased filtered loads of sodium during infusions of sodium chloride or bicarbonate, suggesting a defect in the sensory or afferent component of the natriuretic response to volume expansion [37]. A disturbance in the secretion or biological action of ANF by ethanol could account for this afferent defect That is, ethanol may reduce either the secretion or biological action of ANF in normal animals following ethanol, and this reduced ANF activity could then favor reabsorption of sodium during ethanol-induced volume expansion. Animals with deficient atrial ANF content would thus show greater deficits in response to expansion, and retain even greater quantities of sodium.

In the present study, hematocrits were greatly reduced at 350 min following ethanol, suggesting either volume expansion, red cell dehydration, or both. The lower hematocrits in cardiomyopathic hamsters in all conditions is characteristic of the strain [27], and there was no evidence that this measure was differentially affected in the BIO 14.6 strain after ethanol. The reduction in sodium excretion by cardiomyopathic hamsters, as well as the reduced urine volume, could therefore be a result of the reduced atrial ANF available for secretion in response to volume expansion in the BIO 14.6 strain. These possible effects of ethanol on ANF secretion and activity warrant further examination.

Myocardial Depression

Another potential contribution to the reduced renal excretion in cardiomyopathic hamsters is an ethanol-induced

myocardial depression [8, 13, 19, 32, 42]. Reduced myocardial contractility creates compensatory changes in sympathetic responses [8,30], and might affect renal function [26]. Highly sensitive *in vitro* tests have detected reduced contractility in the hearts of BIO 14.6 hamsters even at a very young age [28], although the functional implications of these findings are unknown. Possibly, this cardiac impairment could be exaggerated during ethanol intoxication, such that the compensatory sympathetic and renal events are also enhanced. The extent to which this may happen is unknown

Finally, other, more fundamental changes in cellular metabolism or membrane functions may be responsible for both the CNS and renal changes observed here. Cardiomyopathic hamsters have multiple metabolic defects, including defects of membrane composition, in several organ systems [2, 3, 14], and an interaction of these problems with ethanol might provide a unifying explanation of these several events. There is still much that is not known about the hamster's response to ethanol, such as the prolonged diuresis (see Fig 1) that far outlasts the rising phase of blood ethanol. This response was not seen in cardiomyopathic hamsters. An unusually prolonged reduction in the secretion of vasopressin might explain the dilute diuresis in normal hamsters after ethanol The lower urine volume in ethanol-injected cardiomyopathic hamsters at 350 min probably owes simply to an increased reabsorption of sodium (Fig 1), but a strain difference in vasopressin secretion remains a possibility These questions, combined with the hamster's peculiar controls of sodium metabolism [16], should urge caution in the interpretation of these results with respect to other species

In summary, ethanol injections produced exaggerated CNS and renal responses in a strain of cardiomyopathic hamsters, and these responses were not fully explained by differences in blood ethanol levels Plasma creatine kinase measurements indicated that the hamsters were not undergoing active lesioning of myocardial tissue at the time of injection, and so the changes could not be explained as a precipitation of decompensated heart failure in animals with severely diseased hearts. Ethanol appears to interact with processes inherited along with the cardiomyopathy to produce these effects These processes may include impaired ethanol metabolism, reduced ability to secrete atrial natriuretic peptides, and myocardial depression

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