The Effects of Chronic Ethanol Consumption on Energy Balance in Rats

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It remains unclear how ethanol truly impacts body weight and energy balance. Dietary intake studies suggest that energy intake is greater in ethanol consumers; however, large population studies have shown that ethanol intake is in fact not associated with increased body weight. Energy expenditure (EE) has been shown to be either mildly increased or unchanged after acute ethanol intake, but the effects of chronic ethanol intake on energy balance have not been well studied. The following study was performed to prospectively examine the effects of chronic moderate ethanol consumption and its interactions with the macronutrient composition of the diet on energy balance. Male Sprague-Dawley rats (n = 16) were first randomized to either a low-fat diet (LF = 10% fat, 70% carbohydrate, 20% protein) or a high-fat diet (HF = 30% fat, 50% carbohydrate, 20% protein). Rats were then randomized to receive either a 5% ethanol solution (ethanol) or water (control) as their drinking supply (day 14) for a total of 4 groups (LF-ethanol, LF-control, HF-ethanol, HF-control; n = 4 per group). On days 7, 21, and 42, indirect calorimetry was performed. Body weight and energy intake were measured throughout the study period. The rate of weight gain was unaffected by ethanol but was increased on the HF diet. Ethanol intake averaged 14.56% ± 1.16% of total caloric intake. Both ethanol groups compensated for added ethanol calories by reducing their intake of diet, so that total energy intake was similar in all groups. As expected, respiratory quotient decreased in both ethanol groups (LF: 0.92 to 0.88; HF: 0.88 to 0.86; $P < .05$). However, EE was not affected by ethanol intake. These findings demonstrate that male Sprague-Dawley rats fully compensate for the calories associated with moderate chronic ethanol consumption and maintain energy balance regardless of the fat content of the baseline diet. This compensation suggests that ethanol calories are sensed, producing an appropriate reduction in the intake of other nutrients, and/or that ethanol impacts the regulation of dietary intake mediators.

ETHANOL IS RESPONSIBLE for more than 5% of the energy consumed in the average American diet, and for those who drink alcohol on a regular basis it accounts for approximately 10% of energy intake.[1] Ethanol is, therefore, an important macronutrient, yet its effects on energy and nutrient metabolism remain unclear. Contrary to popular belief, the evidence suggests that ethanol consumption does not lead to weight gain. This lack of an effect of ethanol on body weight, however, appears to occur despite a greater total daily caloric intake. If this is the case, then where are the extra calories going?[2]

Large population-based studies have shown that ethanol consumption does not lead to body weight gain. In fact, women drinkers appear to have reduced body weights compared to women who abstain from ethanol.[3-6] A few small prospective studies have also found that moderate ethanol consumption does not lead to significant changes in body weight or body composition in humans.[7-9] Animal studies have shown that when high doses of ethanol on the order of 30% of total caloric intake are added to the diet, body weight gain is reduced significantly.[2,10-12] Although ethanol consumption does not appear to promote weight gain, the evidence suggests that total energy intake in humans is increased with ethanol consumption, ie, ethanol calories are added to the baseline diet.[5,13-17] However, no known studies have looked at this issue prospectively by actually measuring ad libitum caloric intake in animals or humans.

If energy intake is increased with ethanol consumption yet there is no resultant weight gain then energy expenditure (EE) would be expected to be increased. A number of human studies have examined the acute effects of ethanol intake on EE by whole-room indirect calorimetry, showing either no effect or only a modest increase in EE.[18-24] There are little data on the effects of chronic ethanol consumption on total EE and no known data in animals.

The interactions between the macronutrient content of the diet and ethanol consumption may be important in energy and nutrient metabolism. Previous studies have shown that rats consuming a low-fat diet in the setting of ethanol intake have appropriate weight gain, while those on higher fat diets have a reduction in weight gain.[2,10-12,25] In diet recall studies, there is evidence that women substitute ethanol calories for carbohydrate, specifically sucrose.[3] There are no known data, however, on the interaction of macronutrient content and ethanol intake on energy balance.

These are important issues in the field of nutrition and metabolism because ethanol is a calorically dense substance (7.11 kcal/g), which when consumed should therefore play a role in energy balance. In light of the major problem of obesity and overweight, and the significant intake of ethanol in this country, understanding the effects of ethanol on body weight and body composition is relevant. Before further work can be done or conclusions drawn, it is first necessary to determine the true impact of chronic ethanol consumption on energy intake and energy balance.

The present studies were undertaken to examine these questions. It was hypothesized that chronic, moderate ethanol intake would lead to a decrease in diet consumption to calorically compensate for ethanol calories, a decrease in expected weight gain, and an increase in EE. These hypotheses were tested by exposing adult male Sprague-Dawley rats to a chronic, moderate amount of ethanol for 4 weeks while on either a high- or a low-fat diet, following body weight, energy intake, EE, and

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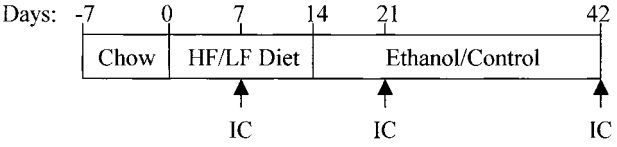

Fig 1. Study timeline. Rats were randomized to HF or LF diet on day 0. Each diet group was then randomized to ethanol or control on day 14. Indirect calorimetry (IC) was performed on days 7, 21, and 42.

respiratory quotient in comparison to controls (no ethanol exposure).

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats were obtained from Harlan (Indianapolis, IN) and housed in a temperature-controlled 12-hour light, 12-hour dark (8 PM to 8 AM) room at the Center for Laboratory Animal Care at the University of Colorado Health Sciences Center. The protocol was approved by the Animal Care and Use Committee of the University of Colorado Health Sciences Center.

Diets

Rats were allowed to acclimate to the animal care facility for 1 week. On day 0 of the study period (see Fig 1 for timeline) rats were randomized to receive an ad libitum diet either low in fat (LF: 10% fat, 70% carbohydrate, 20% protein; Research Diets Inc [RDI], New Brunswick, NJ, #D11724) or high in fat (HF: 30% fat, 50% carbohydrate, 20% protein; RDI #97120201). Body weight and energy intake were recorded on a daily basis. One week after initiation of the assigned diets (day 7), baseline indirect calorimetry was performed. Rats were then allowed to recover for 1 week.

Ethanol Intake

Within each diet group (LF, HF) rats were then randomized to ethanol consumption versus control on day 14 for a total of four groups (LF-ethanol, LF-control, HF-ethanol, HF-control, n = 4 in each group). The ethanol groups were offered a 5% ethanol solution as their sole water supply in addition to their preassigned diet. Body weight and diet/fluid consumption were then measured daily. After 1 week (day 21), repeat indirect calorimetry was performed (ethanol solution was offered to rats that were randomized to chronic ethanol consumption while in the metabolic chamber). The study period was then continued for 3 more weeks (for a total of 4 weeks of ethanol exposure) at which time a third indirect calorimetry study was performed (day 42). Control groups underwent the same procedures except no ethanol solution was offered.

Indirect Calorimetry

Rats were first acclimated to the calorimetry chambers for 18 hours. Indirect calorimetry measurements were then started the next day at 8 AM. A 4-chamber automated indirect calorimeter system developed by the Energy Balance Core Laboratory of the University of Colorado Clinical Nutrition Research Unit was used as described previously.[26] The 4-chamber system is in a room devoted exclusively to the system, allowing control of temperature, humidity, and light/dark cycle. The system is designed for continuous monitoring of up to 4 rats simultaneously. Sampling lines from each chamber have separate condensation tubes, flow controllers, and pumps so that each line has separate but identical air flow pathways from the chamber to the analyzers (Siemens OXYMAT and ULTRAMAT 5E, Germany). A multiple-channel flow meter provides separate flow rate control for each chamber. Data from each chamber are sent to a computer, which collects and processes the data continuously and calculates respiratory quotient and metabolic rate. Oxygen consumption and carbon dioxide production were measured every 6 minutes for 24 hours. This was repeated for a second 24-hour period. EE and respiratory quotient data represent the mean values over these two 24-hour periods. Rats were then returned to the animal care facility.

Calculations and Statistical Analysis

The data are presented in graphical form as the mean ± SEM. Data for caloric intake were calculated as the mean intake per day corrected for body weight over the 28 days of randomization to ethanol or control. EE data were corrected for total body weight. Statistical analysis was performed with SigmaStat statistical software (Jandel Scientific, San Rafael, CA). Figures were visually inspected for potential differences between groups and over time where appropriate. Two-way analysis of variance (ANOVA) was performed to compare overall results between groups (ethanol/control, LF/HF). Two-way repeated-measures ANOVAs were used to compare groups over time.

RESULTS

Rats were of similar weights at baseline (263 ± 8.5 g). Fig 2 shows the body weights over time of the 4 different groups from initiation of ethanol (day 14) to the end of the study (day 42). Body weights and rates of weight gain were unaffected by ethanol consumption (ethanol: 1.87 ± 0.09 g/d; control: 1.93 ± 0.09 g/d). At the initiation of ethanol, after 2 weeks on the HF or LF diet, the HF diet groups had significantly greater weights than the LF diet groups (HF: 364.2 ± 13.4 g; LF: 349.6 ± 6.3 g; $P = .015$), and there continued to be a diet effect throughout the study period ($P = .009$).

Total caloric intake corrected for body weight is depicted in Fig 3. Ethanol intake averaged 25.28 ± 2.02 kcal/kg/d or 14.53% ± 1.16% of total caloric intake. There was no effect of ethanol on total caloric intake (ethanol: 174.04 ± 3.07 kcal/kg/d; control: 168.76 ± 3.07 kcal/kg/d; $P = .25$). In other words, there was complete caloric compensation for the ethanol calories consumed. HF diet intake led to a small but significant

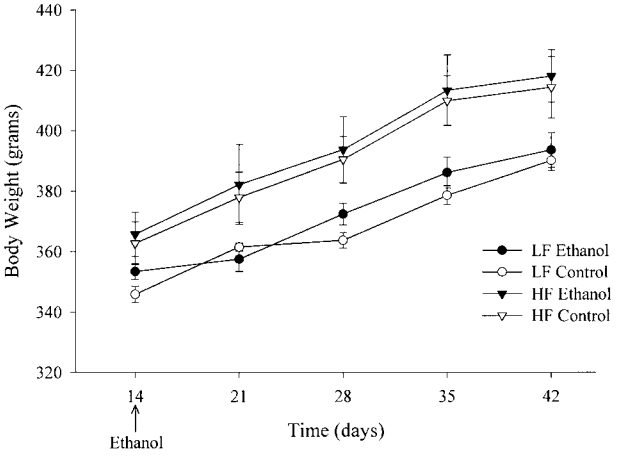

Fig 2. Body weights over time in the 4 different groups from initiation of ethanol (day 14) to the end of the study (day 42). There was no significant effect of ethanol on body weight or rate of weight gain. The data and are expressed as mean body weight in grams ± SEM (n = 4 per group).

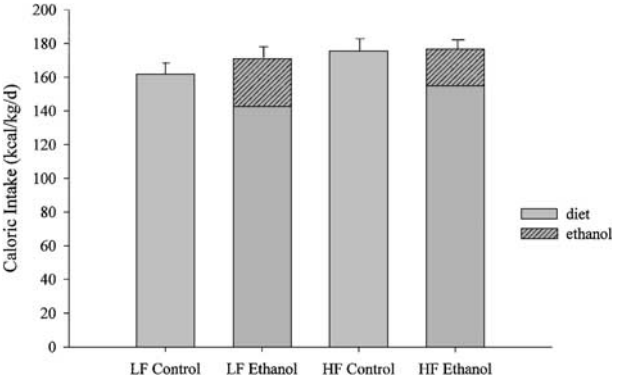

Fig 3. Total caloric intake per day corrected for body weight. Daily total caloric intake was not significantly affected by ethanol consumption (ethanol: 174.04 ± 3.07 kcal/kg/d; control: 168.76 ± 3.07 kcal/kg/d; $P = .25$). The data are mean kcal/kg/d ± SEM (n = 4 per group).

increase in total caloric intake compared to LF diet (HF: 176.27 ± 3.07 kcal/kg/d; LF: 166.52 ± 3.07 kcal/kg/d; $P = .04$).

EE was corrected for total body weight and is shown in Fig 4. There was no effect of ethanol on EE (ethanol: 161.47 ± 3.52.1 kcal/kg/d; control: 164.73 ± 4.52 kcal/kg/d; $P = .62$). The same effects are seen with total uncorrected EE (data not shown). HF diet resulted in a significantly greater EE across all time points and treatments compared to the LF diet (HF: 175.29 ± 2.14 kcal/kg/d; LF: 150.92 ± 2.14 kcal/kg/d; $P < .001$).

Figure 5 shows the respiratory quotient values over time for the 4 groups. As expected, respiratory quotient while on the HF diet was significantly lower than on the LF diet (HF: 0.873 ± 0.005; LF: 0.904 ± 0.005; $P < .001$). Ethanol intake also resulted in a significant reduction in respiratory quotient (ethanol: 0.882 ± 0.001; control: 0.895 ± 0.001; $P < .001$). This effect was seen regardless of the diet, ie, there were no diet/ethanol interactions found on respiratory quotient. Duration of ethanol intake did not have a significant effect on respiratory quotient.

DISCUSSION

The present studies were done to examine the effects of chronic, moderate ethanol consumption on energy balance. The effects of diet composition were also explored. A number of conclusions can be drawn from these studies. First, caloric compensation was achieved by the ethanol-fed rats. Second, body weight gain was unaffected by this moderate level of ethanol consumption. Third, EE was also unaffected by ethanol consumption. Fourth, composition of the diet did not alter the ethanol effects. In summary, moderate ethanol consumption does not alter energy balance in male Sprague-Dawley rats.

The present data demonstrate that in this population of rats energy intake from the diet was reduced in the presence of ethanol consumption. The ethanol-fed rats therefore had the same total energy intake as the control animals. This compensation occurred regardless of the baseline composition of the diet. Prior studies in rats have kept the ratio of calories from diet to ethanol constant using liquid diets not allowing for ad libitum diet intake while consuming ethanol. The present findings contrast with work done in humans. These studies, using diet recall, diet diary, and preload techniques, have all shown that ethanol consumption results in greater total caloric intake, ie, ethanol calories are added to the baseline diet.[5,13-17] These methods, however, may not accurately measure or reflect true caloric intake. No other studies in rats or humans have looked at this issue prospectively by actually measuring caloric intake.

The data from the current study also show that body weight gain was not affected by ethanol consumption. In light of the dietary compensation in the ethanol-fed groups this suggests that ethanol calories were not only sensed but were used as a fuel to ensure adequate weight gain. Prior studies have shown significant reductions in the body weight gain of rats when ethanol was introduced into their diets.[2,10-12] These studies, however, have been done with high levels of ethanol intake on the order of 30% of total calories which were substituted for other macronutrients. The present findings are, however, in agreement with human studies which suggest that ethanol consumption does not lead to body weight gain.[3-6] Two prospective studies in men and women have shown that moderate red wine consumption over 6 to 10 weeks does not lead to changes in body weight or body composition.[7,8] Rumpler et al, showed no changes in body weight or body composition in lean men and women following 8 weeks of daily moderate ethanol intake, although in this study ethanol-related calories were "substituted" for carbohydrate intake.[9]

Indirect calorimetry data from the present study demonstrate that EE was also unaffected by ethanol consumption. Again this correlates with the lack of differences found in energy intake and body weight and the maintenance of energy balance. The situation has been quite different in the human literature, which suggests that body weight is unaffected by ethanol consump-

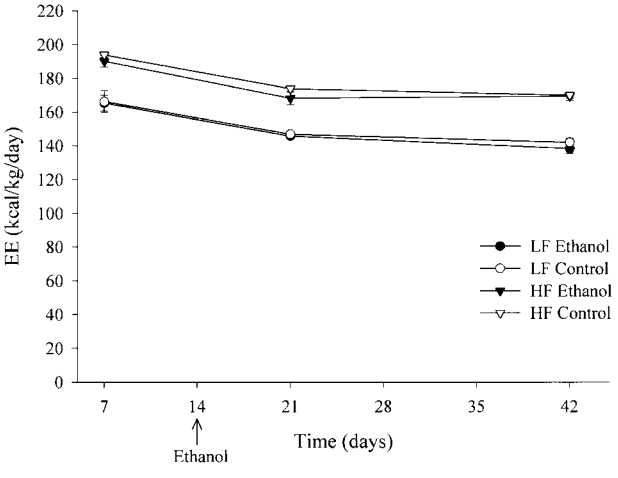

Fig 4. EE corrected for total body weight over time. Measurements were made after 1 week of assigned diet (day 7), 1 week of ethanol exposure (day 21), and 4 weeks of ethanol exposure (day 42). There was no ethanol effect on EE (ethanol: 161.47 ± 3.52.1 kcal/kg/d; control: 164.73 ± 4.52 kcal/kg/d; $P = .62$). The values are expressed as the mean kcal/kg/d ± SEM (n = 4 per group at each time point).

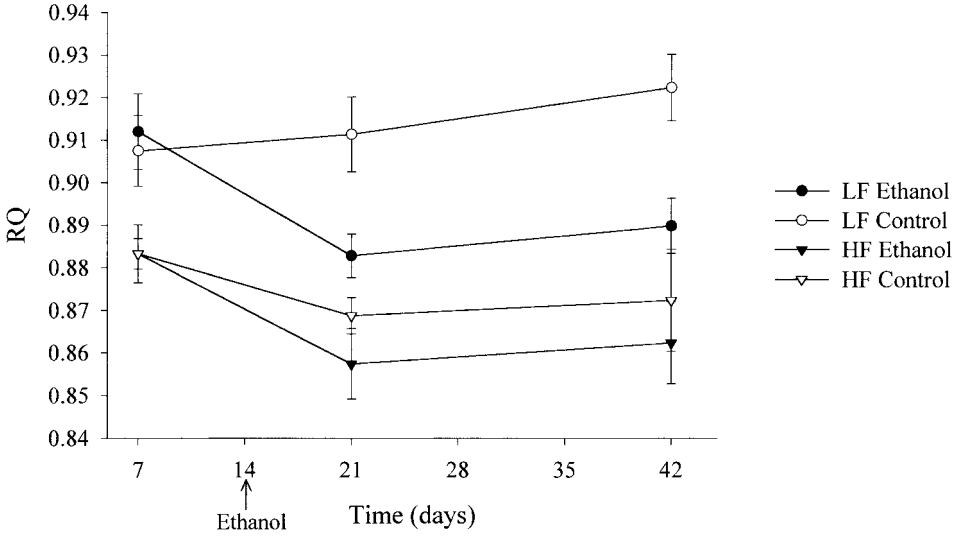

Fig 5. Respiratory quotient (RQ) values over time. Measurements were made after 1 week of assigned diet (day 7), 1 week of ethanol exposure (day 21), and 4 weeks of ethanol exposure (day 42). As expected, RQ while on HF diet was significantly lower than on the LF diet (HF: 0.873 ± 0.005; LF: 0.904 ± 0.005; *P* < .001). Ethanol intake also resulted in a significant reduction in RQ (ethanol: 0.882 ± 0.001; control: 0.895 ± 0.001; *P* < .001). Data are expressed as mean RQ ± SEM (n = 4 per group at each time point).

tion despite increased total energy intake. It has been hypothesized that EE must therefore be increased with ethanol consumption in order to explain the "lost calories." A number of studies have examined the acute effects of ethanol intake on EE by whole-room indirect calorimetry. They have shown either no effect or only a mild increase in EE.[18-24] There are only very limited data examining the effects of chronic ethanol on EE, with no studies using doubly labeled water. Cordain et al showed no significant changes in resting metabolic rate by indirect calorimetry after 6 weeks of daily wine intake.[8] Rumpler et al also showed that 8 weeks of moderate ethanol intake had no effect on EE as measured by whole-room indirect calorimetry, although total energy intake was held constant.[9]

The current study showed that there was no significant interaction of ethanol intake and the macronutrient composition of the diet on body weight, EE, or respiratory quotient. The macronutrient content of the diet, however, did have independent effects on energy balance. As expected, the HF diet resulted in greater weight gain, especially during the first two weeks. Respiratory quotient was also reduced on the HF diet. Unexpectedly, the current study found a small but significant macronutrient effect on EE with animals randomized to the HF diet having a greater EE than those on the LF diet. It is unclear why this occurred, but these findings are in agreement with other data from our laboratory showing that a HF diet is associated with an increase in EE in some strains of rats (Jackman MP, Bessesen DH, unpublished observation, 2001). This increase in EE is seen primarily during the night cycle when the animals are eating and most active. Regardless of the baseline diet, however, ethanol intake had no effect on EE in the current study.

Interestingly, studies on lipid metabolism have suggested that acute ethanol intake results in a milieu favoring fat storage. Fat oxidation and lipolysis appear to be significantly inhibited following ethanol intake in humans.[18-23,27-31] Both human and animal studies have shown that hepatic de novo lipogenesis appears to be enhanced with acute ethanol intake in the fed state.[32-39] Dietary ethanol-derived carbons also appear to be converted to lipid in rats, with storage of these carbons in adipose tissue.[40] However, these results have not been examined in the setting of chronic ethanol intake. Perhaps there is an adaptation to chronic ethanol exposure that does not lead to fat storage as would be suggested by the current study.

The present study examined and clarified the effects of chronic ethanol consumption on energy balance. There are, however, several limitations that need to be discussed. First, these studies were performed in rats. It is unclear whether these findings in the Sprague-Dawley rat model can be generalized to other species, specifically humans. These animals were exposed to ethanol in a manner that is quite different from the ethanol consumption habits of humans. Ethanol intake in humans may also lead to changes in the macronutrient composition of the diet. Therefore, caution should be taken in extrapolating the findings of this study to humans. Second, the present studies have only examined the metabolism of a single dose of ethanol. Preliminary data from our laboratory showed that when lean, adult Sprague-Dawley rats were offered a 5% ethanol solution ad libitum, in addition to there usual food and water supply, they would consume approximately 10% to 15% of their total daily caloric intake as ethanol and would not drink from their usual water supply. This amount of ethanol intake was felt to be clinically pertinent, representing an average, moderate dose in humans. Proportionally, this is a much bigger dose for rats than for humans (when expressed in gram of ethanol per kilogram of body weight) although significantly lower than the 30% to 40% used in other published studies.[2,10-12] This is an important point as different amounts of daily ethanol intake may have profound metabolic and clinical implications. Third, the present studies have only examined the effects of ethanol in male animals. Both human and animal studies suggest that there may be significant gender effects on ethanol's metabolism.[3-6,40]

In conclusion, these findings demonstrate that male Sprague-Dawley rats fully compensate for the calories associated with moderate chronic ethanol consumption and maintain energy balance regardless of the macronutrient composition of the baseline diet. Based on these findings, future studies on the

effects of ethanol consumption on energy balance should be done in human subjects and should also be done using higher doses of ethanol. In addition, this compensation suggests that ethanol calories are sensed, producing a reduction in the intake of other nutrients and/or that ethanol impacts the regulation of dietary intake mediators. It will, therefore, be important to examine the effects of ethanol intake on the expression of chemical mediators of nutrient intake, such as, leptin, agouti-related peptide, neuropeptide Y, orexins, and their related receptors.

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