Published in final edited form as:

Alcohol Clin Exp Res. 2012 February ; 36(2): 207–213. doi:10.1111/j.1530-0277.2011.01600.x.

Pharmacodynamic Effects of Intravenous Alcohol on Hepatic and Gonadal Hormones: Influence of Age and Sex

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Abstract

Background—Growth Hormone (GH) - Insulin-like Growth Factor 1 (IGF-1) axis and gonadal hormones demonstrate extensively associated regulation; however, little is known about the effects of acute alcohol exposure on these hormones. This study examined the effects of intravenous alcohol on the GH-IGF-1 axis and gonadal hormone concentrations, and the influence of age and sex on their regulation.

Methods—Forty-eight healthy volunteers (24 males and 24 females each in the 21–25 and 55–65 year age groups, underwent a two-session single-blinded study. Subjects received, in randomized counter-balanced order, alcohol infusions, individually computed based on a physiologically-based pharmacokinetic (PBPK) model, to maintain a steady-state (“clamped”) exposure of 50 mg % or saline for 3 hrs in separate sessions. Blood samples collected at baseline and post-infusion in each session were assayed for levels of GH, IGF-1, free testosterone and estradiol.

Results—Acute alcohol administration resulted in changes in gonadal hormones that differed by sex. Change in free testosterone showed a significant treatment $\times$ baseline interaction ($p < 0.001$), indicating that alcohol-induced suppression of testosterone occurred predominantly in males. On the other hand, change in estradiol showed a significant treatment $\times$ sex interaction ($p = 0.028$), indicating that alcohol-induced increases in estradiol occurred predominantly in females. There was a trend for alcohol-induced decreases in IGF-1 levels. Change in GH showed a significant main effect of baseline ($p < 0.001$) and a trend for treatment by baseline interaction, suggesting an alcohol-induced decrease in individuals with high baseline GH values. There was also a significant main effect of sex ($p = 0.046$) indicating that males had greater changes in GH across treatment compared to females.

Conclusion—Alcohol induced a complex pattern of hormonal responses that varied between younger and older males and females. Some of the observed sex-based differences may help improve our understanding of the greater susceptibility to alcohol-related hepatic damage seen in females.

Keywords

Age; Alcohol; Estradiol; Growth Hormone; IGF-1; Sex; Testosterone

Introduction

Age and sex variation demonstrate significant influence on the biological and behavioral responses to alcohol exposure in humans. However, it is unclear if these changes are a result of pharmacokinetic or pharmacodynamic factors (Kalant, 1998). Previous studies have demonstrated significant differences between males and females in the pharmacokinetics (PK) of alcohol, and epidemiological data have also suggested such variation with females being reported to be more susceptible to ethanol-related hepatic damage than males (Thomasson, 1995; Thomasson, 2000; Ramchandani et al., 2001a), however, the underlying source of these differences remains to be elucidated.

One potential influence of alcohol on liver is via its effects on hormones that regulate hepatic function such as growth hormone. Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) form a hormonal axis that is constantly influenced by the presence and interaction of various pharmacologic, physiologic, and psychological mediators. Liver is a primary source of IGF-1 and a major site of GH-regulated metabolism; and is also highly responsive to gonadal hormones. Growth hormone secretion and regulation is influenced by the inhibitory action of IGF-1 on the hypothalamus with somatostatin secretion resulting in decreased GH synthesis and by the stimulatory action of gonadal hormones on the hypothalamus leading to secretion of growth-hormone-releasing hormone (GHRH), which in turn stimulates GH synthesis in the pituitary gland (Bullock, 2001).

The regulation of GH is also influenced by the sex steroidal hormones, testosterone and estrogen. Variations due to age and sex have been reported on the secretion and regulation of gonadal and axis hormones with findings that stimulated spontaneous GH secretion is higher in young women than in postmenopausal women or in young men; and with differences strongly correlating with circulating estradiol levels (Thompson, 1972) and with loss of variations in GH and IGF-I levels between men and women in old age (Ho et al., 1987). Administration of testosterone, on the other hand, leads to significant increases in GH, IGF-I, and growth velocity among young males with prior deficiency in axis hormones and growth hormone (Keenan et al., 1993; Link et al., 1986; Ulloa-Aguirre et al., 1990).

Given the fundamental differences between males and females in the concentrations of the gonadal hormones, estrogen and testosterone, the sex steroidal hormones may underlie sex differences in alcohol's effect on hepatic function, possibly by influencing IGF1-GH hormonal axis regulation (Mumenthaler et al., 1999; Gruenewald and Matsumoto, 2003). The Rancho Bernardo study (Goodman-Gruen & Barrett-Connor, 1996) showed that females on Estrogen Replacement Therapy (ERT) have significantly lower IGF-1 levels than females who were not on ERT. Sex steroid differences may also contribute to sex differences in expression and function of hepatic enzymes, including alcohol dehydrogenase (ADH) (Potter et al., 1993). Conversely, alcohol may itself affect the levels and regulation of these hepatic and steroidal hormones. This may be significant as sex differences in alcohol pharmacokinetics (PK); and estrogen itself, have been postulated as determinants of the increased susceptibility of women to alcohol-related hepatic disease (Sato et al., 2001). Studies on androgen activity have also demonstrated the role of testosterone in building and maintaining muscle, fat, and bone mass, as well as its role in gonadal and Hypothalamic-Pituitary function (Gruenewald and Matsumoto, 2003). The effect of alcohol on androgen levels has been evaluated in a few studies; however, the findings have been inconsistent. Thus, the objective of this study was to evaluate the effect of acute intravenous alcohol ethanol exposure on the concentrations of GH-IGF1 axis and gonadal hormones as well as the role of age and sex on these relationships. The hypotheses guiding this study were that: (1) acute alcohol administration would result in decreases in gonadal hormones that would

differ by sex, and (2) acute alcohol administration would result in changes in IGF-1 and GH that would differ by sex and age.

Materials and Methods

Study Population

The study protocol was approved by the Combined Neuroscience Institutional Review Board at the NIH and participants were enrolled following written informed consent. The study population consisted of male and female non-smoking participants in the age groups of 21–25 and 55–65 years of age, in good health as determined by a screening evaluation consisting of medical history, physical exam, and ECG (electrocardiogram) and lab tests. Younger females with normal menstrual cycles (based on self-reports of regular frequency of menses and low variation in cycle length in the past year) and a negative urine pregnancy (human chorionic gonadotropin hormone, hCG) test prior to each study session and older females in the postmenopausal phase for at least one year prior to participation were included in the study. Participants were excluded from this study if they had a present or prior history of disease including cardiovascular, respiratory, gastrointestinal, hepatic, renal, endocrine, or reproductive disorders; current history of axis-I psychiatric illness; current or prior history of any alcohol or drug dependence or abuse; positive urine drug screen; self-reported abstinence from alcohol; pregnancy or intention to become pregnant; menstrual cycle irregularities; use of oral contraceptive pills in female subjects; or use of prescription or over-the-counter (OTC) medications known to interact with alcohol PK within two weeks of the study. The final study sample consisted of 48 participants: 12 young males (21–25 years), 12 young females (21–25 years), 12 older males (55–65 years) and 12 older females (55–65 years).

Study Design

This was a two-session, randomized, placebo-controlled, single-blind study. Participants received, in separate sessions in counter-balanced order, infusions of alcohol or saline (placebo) to achieve and maintain target breath alcohol concentrations (BrAC) of 50 mg% (or 0 mg% on placebo sessions). The typical interval between study sessions was seven days, with a range of three to thirty days to accommodate individual and clinic schedules as well as to allow all younger women to be tested in the follicular phase of their menstrual cycles (follicular phase was defined as the interval between 5 to 14 days from the start of menses). Table 1 provides demographic measures for the study participants.

Procedures

Participants arrived at the NIH Clinical Center, having fasted since midnight (~seven hrs) prior to the study session and received a light breakfast (~300 Kcal) approximately 1 hour prior to the infusion in an attempt to standardize the effects of food on ethanol metabolism during the study (Ramchandani et al., 2001b).

A breathalyzer test was performed to ensure zero alcohol concentrations using the handheld breathalyzer Alcotest 7410 plus (Draeger Safety Inc., Co), and a urine beta-hCG test was performed on the female subjects to ensure that they were not pregnant at the start of each study session. An in-dwelling intravenous catheter was inserted into the ante-cubital vein of the non-dominant arm (preferably) using a sterile technique; this catheter was used for ethanol or placebo infusion and blood sampling.

Subjects received infusions of either 6% v/v alcohol or 0.9% normal saline administered in counter-balanced order between sessions. The infusion was administered according to an infusion-rate profile based on a physiologically-based pharmacokinetic model for ethanol

(Ramchandani et al., 1999). The profile consists of an exponentially increasing infusion rate from the start of the infusion until the target breath alcohol concentration (BrAC) of 50 mg% was reached at 15 min, followed by an exponentially decreasing infusion rate, which tapered to a constant steady-state value to maintain (or “clamp”) the BrAC at the target value for a predetermined duration of 165 min. This infusion-rate profile was computed using individualized estimates of the model parameters, which were based on the participant’s height, weight, age, gender, and simulated desired BrAC-time profile for each participant. Serial BrAC measurements were obtained using the breathalyzer to ensure that the BrACs were within 5 mg% of the target and to enable minor adjustments to the infusion rates to overcome errors in parameter estimation and experimental variability (Ramchandani et al., 1999; Ramchandani and O’Connor, 2006). During the placebo session, the same infusion rate profile was used to administer the saline infusion. At the end of 3 hours, the infusion was terminated. BrAC measurements were obtained every 15–30 min until BrAC fell below 20 mg% after which the participant was provided with a meal and discharged.

Hormone Measures

Blood samples (total volume = 10 ml at each time point) were collected at baseline and at the end of the infusion (180 minutes) during each session for measurement of hormone levels. Serum levels of IGF-1, GH, estradiol, total testosterone and sex hormone binding globulin were measured using chemiluminescence immunoassays using the Siemens Immulite Analyzer (Siemens Healthcare Diagnostics, Deerfield, IL) by the Department of Laboratory Medicine of the NIH Clinical Center, Bethesda, MD. Free testosterone levels were calculated using the equation by Vermuelen (1999).

Data Analysis

Analyses were conducted to determine if baseline levels of the hormones differed between groups and to evaluate the effect of acute alcohol exposure and the influence of age and sex on these hormone levels. Baseline values of the hormones, averaged across both sessions, were compared between groups.

For each hormone measure, the primary dependent measure was the change in hormone level from baseline to the end of the infusion, which was calculated for each session (alcohol and placebo). The change measure was compared across the age and sex groups using repeated-measures analysis of variance (RM-ANOVA) with age, sex, average baseline hormone level and treatment (alcohol or placebo) as the factors. A few hormone values (<10% of the data) were excluded from analyses due to the inability to collect samples or due to laboratory errors (such as inadequate sample volume, significant hemolysis or damaged sample vials) or values outside physiological ranges (greater than 5 times the upper limit of the normal range for each hormone). This approach was chosen because of the small number of samples involved and because of concerns about the influence of these extreme values on our analysis. Statistical analyses were conducted using SPSS version 18.0 (SPSS Inc., Chicago, IL).

Results

Table 1 lists the demographics and average baseline levels of the hormones evaluated in this study. Expected gender differences were seen for the sex hormones. GH showed a significant main effect of sex ($F(1, 31) = 4.321, p = 0.046$) and estradiol showed a significant main effect of age ($F(1, 30) = 4.748, p = 0.037$).

Effects of acute alcohol administration on hormone levels

Table 2 shows the mean change from baseline in hormone levels across study groups. Repeated measures analysis of variance showed a complex pattern of effects of treatment (alcohol vs. placebo), age and sex.

Change in free testosterone levels showed a significant treatment $\times$ baseline interaction ($F(1, 33) = 13.611, p < 0.001$) indicating that the effect of alcohol on free testosterone levels was dependent on the baseline level. These results indicate that alcohol induced a decrease in testosterone levels compared to placebo and that this effect was seen primarily in males, given the higher baseline values in males.

Change in estradiol levels showed a main effect of treatment with alcohol ($F(1, 30) = 4.160, p = 0.050$) and a significant treatment $\times$ baseline interaction ($F(1, 30) = 6.806, p = 0.014$) as well as a significant treatment $\times$ sex interaction ($F(1, 30) = 5.3, p = 0.028$). There was also a significant main effect of sex on change in estradiol levels ($F(1, 30) = 4.748, p = 0.037$). Thus, alcohol resulted in an increase in estradiol levels in females and a decrease in estradiol levels in males compared to placebo.

Change in IGF1 levels did not show a main effect of treatment, however it demonstrated a main effect of baseline ($F(1, 40) = 4.211, p = 0.047$) and a trend for treatment $\times$ age interaction ($F(1, 40) = 3.074, p = 0.087$). These results suggest a pattern of decrease in IGF level across both sessions, with apparently greater changes in younger compared to older subjects.

Change in GH showed a main effect of baseline ($F(1, 31) = 25.566, p < 0.001$) and main effect of sex ($F(1, 31) = 4.321, p = 0.046$), and a trend for treatment $\times$ baseline interaction ($F(1, 31) = 2.931, p = 0.097$). These results suggest that males showed greater decreases in GH levels across treatment compared to females.

Inter-relationship between alcohol-induced changes in hormone levels by age and sex groups

Given the complex pattern of effects of alcohol, age and sex on the hormone measures and the influence of baseline values, further analysis was performed after computing the percent change from baseline for each hormone measure for each treatment. Figure 1 shows the percent change from baseline in hormone levels across study groups.

In younger females, there was small percent increase in IGF-1 following alcohol compared to placebo; and a substantial (36-fold) percent increase in estradiol along with a small increase in testosterone following alcohol compared to placebo. There was an associated 4-fold decrease in GH levels following alcohol compared to placebo in this group.

In young males, there was a 2.8-fold greater decrease in IGF-1 following alcohol compared to placebo as well as a 4-fold decrease in estradiol; and 2-fold greater decrease in testosterone following alcohol compared to placebo. There was almost no change in GH levels following alcohol compared to placebo in this group.

In older females, there was a 4.7-fold greater decrease in IGF1 following alcohol compared to placebo along with a 3.2 fold greater increase in estradiol and 2-fold greater increase in testosterone levels following alcohol compared to placebo. There was an associated 24-fold increase in GH following alcohol compared to placebo in this group.

In older males, there was a small percent decrease in IGF1 following alcohol compared to placebo; along with a 2.3 -fold greater decrease in estradiol and a 2-fold greater decrease in

testosterone following alcohol compared with placebo. There was a corresponding 3.5-fold greater decrease in GH following alcohol compared to placebo in this group.

Discussion

The objective of this study was to examine the effects of acute alcohol on gonadal and GH-IGF1 axis hormones and their physiological interrelationship among various age and gender groups of healthy social drinkers. The study found effects of alcohol on hormone levels that varied with baseline levels and showed a complex pattern that differed between groups but were fairly informative about the influence of age and sex on the relationship between these hormonal effects.

Main effects of acute alcohol administration on hormone levels

Acute alcohol administration resulted in a significant decrease in testosterone levels; this finding was primarily driven by the effect in younger males and reflected in the significant influence of baseline values on the alcohol effect. These effects are somewhat consistent with previous studies showing decreases in testosterone levels following acute alcohol intake, an effect thought to be mediated by an inhibition of gonadal testosterone synthesis (Gordon et al., 1976; Mendelson et al., 1977; Ellingboe, 1987; Valimaki et al., 1990, Orpana, 1990). However, there have been recent reports of acute increases in testosterone following acute alcohol intake in healthy males as well as in premenopausal females, an effect thought to be related to an alcohol-induced change in redox state in the liver (Sarkola et al., 2000; Sarkola and Eriksson, 2003). As suggested by Sarkola and Eriksson (2003), alcohol may be acting at multiple points in the testosterone pathway – inhibition of gonadal synthesis resulting in lower levels, and inhibition of hepatic redox state resulting in higher levels. In our study, the longer duration of exposure may favor the gonadal effects, resulting in the observed decrease in testosterone levels.

The effect of acute alcohol administration on estradiol was more complex: females showed an increase in estradiol levels, while males, particularly in the older group, showed a decrease in estradiol levels following acute alcohol administration, as illustrated in figure 2. The findings in females is consistent with Sarkola et al., (1999) who showed increased estradiol levels following acute oral doses of alcohol in premenopausal women; an effect attributed to changes in the redox state in the liver by alcohol. There do not appear to be many studies looking at the effect of acute alcohol administration on estradiol levels in men; one study (Valimaki et al. 1984) reported no change in estradiol levels following a large oral dose of alcohol (resulting in peak BrAC of 0.15 g%) in healthy men.

The effects of alcohol on IGF-1 and GH levels are less clear. There was a trend for alcohol-related decreases in IGF-1, particularly in the younger subjects who had higher baseline levels compared to the older subjects. Since the liver is the primary source of IGF-1, this may reflect a direct inhibitory effect of alcohol on IGF-1 synthesis. Indeed, animal studies have demonstrated a decrease in IGF-1 levels following ethanol exposure, although in these studies these decreases were seen following chronic exposure (Sonntag and Boyd, 1988; Sonntag and Boyd, 1989; Soszynski and Frohman, 1992). These studies have also demonstrated that the suppression of IGF-1 by ethanol does not appear to be mediated by changes in GH secretory dynamics (Sonntag and Boyd, 1989), but may be related to reduction in IGF binding protein (IGF-BP3) (Breese and Sonntag, 1995). In these studies, animals exposed to alcohol also demonstrated altered feeding behavior, including food deprivation, which can also result in suppression of IGF-1 as well as IGF-binding protein and IGF-1 mRNA levels (Breese et al., 1991)

Growth hormone also showed a trend for treatment by baseline interaction suggesting an alcohol-induced decrease in individuals with high baseline GH values. Given the pulsatile nature of GH release, some high baseline GH levels could be due to the baseline sample being obtained during the peak of a pulsatile release of GH. As a result, the change in GH level following infusion could be partly due to the difference between these high baseline levels and lower (trough) levels obtained following the infusion. There was also a significant effect of sex indicating that males had greater changes in GH across treatment compared to females.

Inter-relationship between alcohol-induced changes in hormone levels: age- and sex-related differences

Examination of the relative hormonal changes following ethanol allowed for a better understanding of the pathways underlying hormonal regulation in the various age and sex groups. As illustrated in figure 2, growth hormone is regulated by IGF1 secreted by the hepatic pathway as well as by sex hormones that act to induce GH release by the pituitary (Hypothalamo-hypophysial (HH) pathway) (Chernausek, 1983). In younger females, it appears that alcohol induced GH decrease may be related to the small increase in IGF1, i.e., the hepatic pathway, and is seen despite the increases in estradiol following alcohol in this group. In older females, alcohol-induced a decrease in IGF1 and an increase in estradiol and testosterone resulting in a corresponding increase in GH, suggesting that both HH and hepatic pathways may have been involved in alcohol's effect on higher GH levels.

Younger males showed decreases in IGF-1 as well as in the sex hormones but no change in GH following alcohol. Older males also showed decrease in IGF-1 and sex hormones, as well as decrease in GH following alcohol. This suggests that acute alcohol administration inhibits hormonal regulation at the hepatic and hypothalamic levels in men as described in figure 2b and 2d, and this may be related to some of the clinical manifestations of GH deficiency and low testosterone seen in alcoholics (Jorgenson et. al, 1989).

Findings in the younger females suggest that alcohol induces increases in sex hormone level, which targeted the liver to decrease IGF1, which in turn resulted in stimulation of the hypothalamus to initiate GH synthesis; this was not evident in older females having lowered estrogenic and GH values demonstrated in figure 2a and 2c. In males, decreases in sex hormones could not induce the hepatic pathway, and no significant effect of gonadal hormones in GH synthesis could be established.

Estrogen has been reported to suppress plasma IGF1 levels and liver IGF-1 mRNA expression (Borski et al., 1996) and hepatic physiology shows a strong relation with the sex differences in gene expression controlling the GH secretion (Potter et al., 1993). This relationship has been reported previously in older females and males (Frantz and Rabkin, 1965), and that IGF-1 does not show significance or variations with age may be attributed to similar levels as reported in both males and females (Ho et al., 1987).

In conclusion, this study demonstrated acute effects of intravenous alcohol administration on the GH-IGF-1 axis hormones and sex hormones that were complex, and varied by age and sex. While males showed suppression of testosterone, females showed increases in estradiol following alcohol. There was a general trend for decreases in IGF-1 levels following acute alcohol. The resulting effect of these hormonal changes on GH levels was less clear. While this study does not clearly identify a mechanism for some of the harmful effects of alcohol on the liver, some of the sex differences observed in this study might help in improving our understanding of the greater susceptibility to hepatic damage seen in female following chronic alcohol use.

Acknowledgments

Support: Division of Intramural Clinical and Biological Research, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health.

The authors gratefully acknowledge the NIH Clinical Center Alcohol Clinic and Day Hospital staff for clinical support, laboratory research staff (Elizabeth Edwards, Mike Hoefer, Nina Saxena, Shilpa Kumar, Seth Eappen) for data collection support, and the study volunteers for their participation in the study.

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Figure 1.

Mean ($\pm$ SE) percentage change in concentration of GH-IGF1 axis hormones and steroidal hormones across study groups, following alcohol and placebo administration. Open bars: placebo; Closed bars: alcohol.

Figure 2.

Influence of acute alcohol on hepatic and hypothalamic metabolic pathways of growth hormone regulation. Fig 2a. Increase in IGF1 rates as a result of the collective effects of alcohol exposure directly as well as due to the increase in free testosterone and estradiol. Decrease in GH concentration shows both predominant inhibitory effects of hepatic mediation and masking effects of the gonadal response on HH mediation of GH synthesis at the hypothalamus in younger females due to elevated IGF1. Fig 2b. Consistent decrease in the free testosterone, estradiol, as well as in IGF1 and GH during acute alcohol exposure in younger males suggests inhibition of both hepatic and HH mediation of hormone regulation. Fig 2c. Decrease in IGF1 rates, and increase in estradiol and free testosterone during the alcohol exposure shows sufficient gonadal concentrations influencing suggesting HH mediation resulting in GH elevation in older females. Lower IGF1 concentration may be attributed to higher susceptibility to harmful effects of alcohol on liver function; and age-associated concentration lowering of gonadal hormones, not effective enough to trigger response for IGF1-mRNA expression. Fig 2d. Older males show a significant increase in IGF1 concentrations during alcohol exposure resulting in a decrease in GH concentration supporting hepatic mediation of GH regulation. Free testosterone and estradiol decreased as well without affecting both the IGF1 and GH synthesis.

Table 1

Summary of morphometric measures and baseline hormone levels for study participants.

	Young Females (n=12)	Young Males (n=12)	Older Females (n=12)	Older Males (n=12)
<u>Morphometrics</u>				
Age [years]	23 ± 1	23 ± 1	59 ± 4	59 ± 2
Height [cm] ¹	166 ± 7	177 ± 10	163 ± 7	177 ± 7
Weight [kg] ²	62.7 ± 11.8	78.0 ± 10.6	67.5 ± 9.2	86.4 ± 16.0
<u>Average Baseline Hormone Levels</u>				
Free Testosterone ³	3.8 (± 4.0)	125.1 (± 95.6)	0.3 (± 0.1)	24.9 (± 48.0)
Estradiol ⁴	75.4 (± 58.3)	33.0 (± 8.6)	33.0 (± 8.3)	49.1 (± 16.4)
Insulin-like Growth Factor-1 ⁵	224.1 (± 35.6)	221.0 (± 57.6)	124.5 (± 45.3)	137.0 (± 38.7)
Growth Hormone	0.97 (± 1.13)	0.19 (± 0.14)	0.60 (± 0.75)	0.84 (± 1.67)

¹ p<0.001 for difference between males and females.

² p<0.001 for difference between males and females.

³ main effect of sex (p=0.001), main effect of age (p=0.014), sex × age interaction (p=0.021).

⁴ sex × age interaction (p=0.006).

⁵ main effect of age (p<0.001).

Normal ranges:

Insulin-like Growth Factor-1 (ng/mL) - female: 182–780, male: 114–492

Growth Hormone (ng/mL) – female: 0.0–10.0, male: 0.0–5.0

Free Testosterone (pg/mL) – female: 3–19, male: 90–300

Estradiol (ng/dL) – female (Luteal [Pre-ovulatory]): 1.9[11]–16[41], (post-menopausal: ≤ 3.5), male: 1.4–5.5.

Table 2

Mean ($\pm$ SD) change from baseline in hormonal concentration across study groups.

Hormone Levels	Younger Females (n=12)		Younger Males (n=12)		Older Females (n=12)		Older Males (n=12)	
	Placebo	Ethanol	Placebo	Ethanol	Placebo	Ethanol	Placebo	Ethanol
Free Testosterone ¹ [pg/mL]	0.58 ($\pm$ 2.16)	0.80 ($\pm$ 3.42)	1.90 ($\pm$ 35.42)	-11.20 ($\pm$ 24.37)	0.02 ($\pm$ 0.08)	0.04 ($\pm$ 0.05)	6.59 ($\pm$ 22.16)	3.49 ($\pm$ 12.93)
Estradiol ² [mg/dL]	-1.51 ($\pm$ 5.39)	11.96 ($\pm$ 13.52)	5.82 ($\pm$ 15.47)	1.62 ($\pm$ 8.27)	-3.30 ($\pm$ 2.82)	3.84 ($\pm$ 7.60)	2.56 ($\pm$ 12.95)	-7.26 ($\pm$ 9.76)
Insulin-like Growth Factor-1 ³ [ng/mL]	-8.82 ($\pm$ 13.98)	-5.91 ($\pm$ 15.80)	-6.00 ($\pm$ 11.41)	-14.10 ($\pm$ 11.25)	-0.50 ($\pm$ 12.69)	-1.34 ($\pm$ 8.36)	-7.58 ($\pm$ 14.90)	-4.17 ($\pm$ 15.41)
Growth Hormone ⁴ [mg/mL]	0.53 ($\pm$ 2.89)	-0.15 ($\pm$ 1.07)	2.63 ($\pm$ 3.93)	1.38 ($\pm$ 3.40)	-0.11 ($\pm$ 0.38)	-0.11 ($\pm$ 1.94)	1.99 ($\pm$ 2.03)	-0.80 ($\pm$ 3.92)

¹ treatment $\times$ baseline interaction ($p < 0.001$).

² main effect of treatment ($p = 0.050$), main effect of sex ($p = 0.037$), treatment $\times$ sex interaction ($p = 0.028$), treatment $\times$ baseline interaction ($p = 0.014$).

³ main effect of baseline ($p = 0.047$), trend for treatment $\times$ age interaction ($p = 0.087$).

⁴ main effect of baseline ($p < 0.001$), main effect of sex ($p = 0.046$), treatment $\times$ baseline interaction ($p = 0.097$).