

Can alcohol promote aromatization of androgens to estrogens?

A review

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Abstract

Increased aromatization may be a mechanism for feminization of some male alcoholics, as well as for the reported increases in plasma estrogen levels in postmenopausal women subjected to moderate alcohol consumption. Alcohol consumption-related increases in estrogen levels may in turn be partially responsible for the associated decreased risk for coronary artery disease and osteoporosis, as well as for increased risk for breast cancer. The purpose of this review is to evaluate the literature to determine whether alcohol can promote aromatization of androgens to estrogens. In male rats, chronic heavy alcohol administration (36% of total calories = 12–18 g/kg/day) led to increased aromatization of androgen in the liver, but the results were equivocal for the hypothalamus. In female rats, chronic heavy alcohol administration did not promote aromatization in the hypothalamus exposed to alcohol in utero. In human placental tissue, although *ex vivo* alcohol administration (less or more than 72 g/day) did not affect the rate of aromatization, *in vitro* incubation of choriocarcinoma cells with 5–50 mM of alcohol increased estradiol secretion, which could be due to increased aromatization. In *in vitro* human ovarian granulosa cell studies, alcohol increased, had no effect on, or decreased estradiol secretion, and in one study, 20 mM of alcohol significantly increased aromatization of androstenedione to estrogens. These results may not be fully relevant to normal human ovary because in both studies cells were heavily luteinized by gonadotropins. A study of ovariectomized rats shows that only heavy chronic alcohol intake (4.4 g/kg/day) for 10 weeks can increase plasma estradiol levels and uterine weight, which could be due to increased aromatization or delayed clearance of estradiol. In conclusion, chronic heavy alcohol administration can result in aromatization of androgens in male rat liver. It is not clear whether moderate alcohol intake can produce a similar effect in the liver, nor whether alcohol can potentiate aromatization of androgens in other tissue or organs of male rats. In females, the available information is not adequate to evaluate the effect of alcohol on aromatization. Further studies are required in both genders to evaluate the ability of alcohol (moderate vs. heavy dose) to promote aromatization of androgens to estrogens. © 2001 Elsevier Science Inc. All rights reserved.

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1. Introduction

Alcohol consumption in moderate amount has been reported to reduce the risk of coronary artery disease (Fuchs et al., 1995; Stampfer et al., 1988) and osteoporosis (Feskanich et al., 1999; Holbrook & Barrett-Conner, 1993; Laitinen et al., 1991). On the other hand, alcohol can increase the risk of breast cancer in a dose-dependent manner in postmenopausal women (Smith-Warner et al., 1998). Both beneficial and harmful effects of alcohol have

been attributed, at least in part, to estrogen because moderate alcohol consumption has been reported by some investigators to be associated with increased plasma estrogen levels in postmenopausal women (Gavaler & Love, 1992; Nagata et al., 1997; Tivis & Gavaler, 1994). Alcohol could increase plasma estrogen levels either by promoting the induction of aromatases, which can convert androgens to estrogens, or by impairing the metabolism of estrogen in liver, resulting in estrogen accumulation in the circulation. Alcohol-induced promotion of aromatization may also be responsible for increased peripheral conversion of androgens to estrogens in men with alcoholic cirrhosis (Gordon et al., 1975) and subsequent feminization of some male alcoholics (Lloyd & Williams, 1948). The purpose of

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this review is to determine whether alcohol can promote aromatization of androgens to estrogens. This review includes reports from the literature that provide at least some indication, direct or indirect, regarding the ability of alcohol to promote aromatization of androgens in various tissue or organs of animals and human beings.

2. Findings

2.1. Male rat liver

Aromatase activity was determined in the liver of male rats exposed to alcohol in a liquid diet (36% of calories) for 34–54 days (Gordon et al., 1979). The activity was determined by incubating hepatic microsomes with tritium-labeled androstenedione or testosterone for 15 to 120 min, followed by measuring the rate of formation of tritium-labeled estrone or estradiol, respectively. The hepatic aromatase activity was significantly increased with the use of androstenedione or testosterone as a substrate in alcohol-treated rats, compared with findings in pair-fed controls. In addition, in alcohol-fed rats, plasma estradiol levels increased by 60% and concomitantly plasma testosterone levels decreased by 55%, an indicator of aromatization. However, plasma levels of androstenedione and estrone were not affected by alcohol consumption. Other investigators also observed increased hepatic aromatization of testosterone to estradiol in male rats exposed to alcohol in a liquid diet (36% of calories) for 5 months (Chung, 1990). Consistent with the increased aromatization, serum estradiol levels were increased and testosterone levels were decreased significantly in this study.

2.2. Rat hypothalamus

Perinatal aromatase activity was determined in the hypothalamic preoptic area of rats exposed to ethanol (35% of calories in a liquid diet) in utero from day 14 of gestation until birth (McGivern et al., 1988). The activity was estimated by quantification of tritium-labeled water released into the incubation medium from tritium-labeled androstenedione. In male pups, fetal alcohol exposure significantly increased aromatase activity on days 18 and 19 of gestation and on postnatal day 1. However, the aromatase activity was not influenced in female pups. In a subsequent study, with the use of similar methods, other investigators were unable to show any significant effect of fetal alcohol exposure on the aromatase activity in the hypothalamic preoptic area of newborn male rats (Kelce et al., 1990). Newborn female rats were not included in the study.

2.3. Human placenta

The ability of ethanol to stimulate estrogen secretion was determined in vitro by using human placental chor-

iocarcinoma cells (Wimalasena, 1994). The cells were incubated with varying concentrations of ethanol (5–100 mM) for 2, 4, and 6 days. Ethanol significantly increased basal estradiol secretion in a dose- (5–50 mM) and time-dependent manner. In another study, human placental microsomes obtained from women exposed to alcohol during pregnancy were used to evaluate aromatization of androstenedione to estrone (Sheean, 1983). The dose of alcohol was either less than or more than the equivalent of 72 g of absolute ethanol per drinking day. The placental microsomal protein was incubated with androstenedione at 37°C for 5–20 min. The alcohol exposure did not significantly affect the rate of aromatization.

2.4. Human ovary

The ability of alcohol to promote aromatization was evaluated in vitro in human granulosa cells obtained from women injected with human menopausal gonadotropin and human chorionic gonadotropin for in vitro fertilization treatment (Saxena et al., 1990). The cells were incubated with 20 mM of ethanol for 5, 7, and 9 days. Ethanol significantly decreased estradiol secretion after 5 days of incubation, but had no significant effect after 7 or 9 days of incubation. On the other hand, when cells were incubated with ethanol (20 mM) and androstenedione, estradiol secretion was significantly greater (2.5-fold) than with androstenedione alone, suggesting a stimulating effect of ethanol on aromatization. In another in vitro study on human granulosa cells by the same group of investigators, ethanol (10 and 20 mM) significantly increased basal estradiol secretion by human granulosa cells in a dose-related manner after 7 days of incubation (Wimalasena et al., 1993).

2.5. Ovariectomized rats

The effect of chronic alcohol exposure on serum estradiol and uterus weight was determined in sexually mature ovariectomized rats (Gavaler & Rosenblum, 1987). Ethanol was administered to rats in drinking water (0%, 1.8%, 3.7%, or 5.5% ethanol, vol./vol.) for 4 or 10 weeks. Alcohol administration at any dose for 4 weeks had no significant effect on estradiol levels or uterine weight. However, alcohol administration for 10 weeks significantly increased serum estradiol levels and uterine weight only at the highest dose (5.5%).

2.6. Postmenopausal women

Studies with postmenopausal women were designed to determine the effects of acute and chronic ethanol administration on estrogen levels in healthy postmenopausal women. In an acute study, administration of a single dose of ethanol (0.7 g/kg) had no significant effect on plasma estrone and estradiol levels in healthy postmenopausal women who were not receiving estrogen replacement

therapy (ERT) (Ginsburg et al., 1996). However, in those women who were receiving oral ERT, ethanol significantly ($P < .01$) increased estradiol levels by 300% from baseline values after 50 min of alcohol ingestion. In another acute study with postmenopausal women who were exposed to estrogen transdermal patch, serum estradiol levels increased significantly by 22% from mean baseline values after 35 min of administration of a single dose (0.75 g/kg) of ethanol (Ginsburg et al., 1995a). In these women, estrone levels were not affected significantly. In a recent review that analyzed results of seven chronic studies designed to determine an association between moderate alcohol consumption and estrogen levels in healthy postmenopausal women who were not receiving ERT, a significant positive association was observed in three studies. In the remaining four, however, no significant association was noted (Purohit, 1998).

3. Discussion

Results of two ex vivo male rat liver studies included in the review showed that alcohol can promote the aromatization of androgens to estrogens in hepatic microsomes, as well as that alcohol ingestion was associated with increased plasma estradiol levels and decreased testosterone levels, a marker of aromatization (Chung, 1990; Gordon et al., 1979). This is not unexpected because the activity of aromatase, a member of P450 enzyme system, has been demonstrated in normal human liver tissue (Smuk & Schwes, 1977). In addition, alcohol is known to induce a number of hepatic microsomal enzyme systems, including those that metabolize steroid hormones, such as the A-ring reductases (Gordon et al., 1976), the microsomal mixed function oxidases (Ishii et al., 1973), and the microsomal ethanol-oxidizing system (Lieber & DeCarli, 1970). This probably explains the underlying mechanism for feminization of some male alcoholics, especially those affected with liver disease.

The dose of alcohol used in these male rat studies was 36% of total calories in a liquid diet, which can be considered equivalent to heavy drinking in men. This dose is equivalent to daily ethanol consumption of 12–18 g/kg of body weight, and chronic alcohol administration at this dose has been shown to induce fatty liver in rats, which can attain a blood alcohol level above 20 mM or about 100 mg/dl (Lieber & DeCarli, 1989). On the basis of results obtained by Chung (1990) and Gordon et al. (1979) (discussed earlier), it is not possible to predict whether or not alcohol doses of less than 36% calories or a dose equivalent to moderate drinking in men can promote aromatization of androgens in rat liver. Moderate alcohol consumption has been defined by the US Department of Agriculture/US Department of Health and Human Services (USDA/DHHS, 1990) as no more than one drink for most women and no more than two drinks a day for most men.

Because one drink is about 12 g of absolute alcohol, moderate drinking in men (two drinks) will be equivalent to 24 g of absolute alcohol per day, and for a 60-kg man it is equivalent to 0.4 g/kg/day.

Of the two reports on hypothalamus, results of one showed significant alcohol-associated increases in aromatase activity in male rats, but not in female rats (McGivern et al., 1988). Findings in the other report showed no significant effect of alcohol in male rats, and the study did not include female rats (Kelce et al., 1990). Thus the data are equivocal as to the effect of alcohol on aromatization. The gender difference observed in one study could be ascribed to the difference in the availability of substrate androgens in the hypothalamus for aromatization.

In placental tissue, although in vitro study results showed a significant alcohol-induced increase in the secretion of estradiol from choriocarcinoma cells (Wimalasena, 1994), findings in the ex vivo study showed no significant aromatization of androstenedione by placental microsomes obtained from women exposed to alcohol during pregnancy (Sheean, 1983). Thus, results are inconclusive. Both ovarian studies were based on cultured granulosa cells obtained from women treated with gonadotropins (Saxena et al., 1990; Wimalasena et al., 1993). In these studies, depending on dose and duration, ethanol decreased, had no effect on, or increased estradiol secretion. In addition, in one study, ethanol significantly aromatized androstenedione to estrogens (Saxena et al., 1990). These results may not be fully relevant to normal human ovary because in both studies cells were heavily luteinized by gonadotropins.

In the study with ovariectomized rats, there was no indication of aromatization in rats exposed to 1.8%, 3.7%, or 5.5% of alcohol in drinking water for 4 weeks or in rats exposed to 1.8% or 3.7% for 10 weeks (Gavaler & Rosenblum, 1987). Only those rats exposed to the highest dose of alcohol (5.5%, equivalent to 4.4 g/kg of body weight/day) for 10 weeks exhibited significant increases in plasma estradiol levels and uterine weight. Thus, the effect was dose-dependent as well as length of exposure-dependent. Because the rate of aromatization was not measured, this effect could be attributed either to increased aromatization of androgens in the peripheral circulation or to delayed clearance of estrogen from the body. A dose of 4.4 g/kg/day should be considered heavy drinking for female rats because this is equivalent to 264 g (or 22 drinks, considering one drink = 12 g) of absolute alcohol per day for a 60-kg woman. Because administration of lower doses of alcohol (1.8%, equivalent to 1.5 g/kg/day; or 3.7%, equivalent to 3.4 g/kg/day) did not increase estradiol levels or uterine weights significantly after 4 or 10 weeks of exposure, it can be deduced that moderate drinking does not affect aromatization in ovariectomized female rats.

In the acute study with postmenopausal women who were not receiving ERT, there was no indication of alcohol-induced aromatization of androgens as a single

dose of alcohol exposure did not increase plasma estrogen levels (Ginsburg et al., 1996). However, in those postmenopausal women who were receiving ERT, acute alcohol exposure significantly increased estradiol levels (Ginsburg et al., 1995a; Ginsburg et al., 1996). This effect seems to be due to impairment of estradiol metabolism by alcohol, and not to aromatization, because in a study with postmenopausal women exposed to estradiol patch, the half-life of estradiol was significantly increased (378 min) after ethanol ingestion (0.75 g/kg of body weight), compared with findings with carbohydrate placebo (245 min) (Ginsburg et al., 1995b). Because it is not clear whether chronic moderate alcohol consumption can increase estrogen levels in postmenopausal women (Purohit, 1998), it is not possible to predict whether moderate alcohol consumption can promote aromatization of androgens in postmenopausal women.

4. Summary

In male rats, heavy chronic alcohol administration (36% of total calories = 12–18 g/kg/day) can promote aromatization of androgens to estrogens in liver, but the data are equivocal for the hypothalamus. Alcohol-induced hepatic aromatization may be responsible for the feminization of some male alcoholics. Whether moderate alcohol consumption can promote hepatic aromatization in male rat is not known. Also, it is not known whether alcohol can promote aromatization in other tissue or organs of rats, such as adrenal glands, adipose tissue, bones, and skin.

In female rats, chronic alcohol administration did not promote aromatization in the hypothalamus exposed to alcohol in utero. In human placental tissue, the results are inconclusive because although ex vivo alcohol administration (less or more than 72 g/day) did not significantly affect the rate of aromatization, in vitro incubation of choriocarcinoma cells with alcohol (5–50 mM) resulted in increased estradiol secretion. Although results of studies with human ovarian granulosa cells show that alcohol can promote aromatization, the results cannot be applied to normal tissue because granulosa cells were obtained from women treated with gonadotropins. Results of studies with ovariectomized rats show that only heavy chronic alcohol intake (4.4 g/kg/day) for 10 weeks can increase plasma estradiol levels and uterine weight, which could be due to increased aromatization or delayed clearance of estradiol. Studies measuring the rate of aromatization are required to evaluate the ability of alcohol to promote aromatization of androgens. In postmenopausal women, because it is not clear whether alcohol can increase plasma estrogen levels, it is not possible to predict whether alcohol can promote aromatization. Thus, findings from available studies in the literature do not provide adequate information to evaluate fully the ability of alcohol to promote aromatization of androgens in females.

Further studies, in vitro and in vivo, are required in both genders to determine the ability of alcohol (moderate vs. heavy doses) to stimulate aromatization of androgens to estrogens in various tissue or organs.

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