



Research report

Sex-dependent consequences of pre-pubertal gonadectomy: Social behavior, stress and ethanol responsiveness

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HIGHLIGHTS

- GX decreased social preference in stressed and non-stressed males.
- GX increased baseline social preference in females.
- Acute restraint stress increased social play in males and females.
- Females developed conditioned taste aversions at a lower dose than males.

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ABSTRACT

Alcohol consumption can be enhanced or moderated by sensitivity to its aversive and appetitive properties, including positive social outcomes. These differences emerge post-pubertally, suggesting a potential role of gonadal hormones. To determine the role of gonadal hormones in sensitivity to the social impairing and social context-related attenuations in the aversive effects of ethanol, prepubertal male and female rats were gonadectomized (GX) or sham (SH) operated on postnatal day (P) 25, or left non-manipulated (NM). In adulthood (P70), rats were restrained for 90 min prior to challenge with 0.0 or 1.0 g/kg ethanol and social interaction (SI) testing. At P77, groups of 4 same-sex littermates from the same surgical condition were given access to a supersaccharin (SS) solution (3% sucrose, 0.125% saccharin), followed by an intraperitoneal injection of ethanol (0.0, 0.50, 1.0, 1.5 g/kg). Intakes of SS were examined 24 h later for expression of conditioned taste aversions. Acute stress prior to SI testing increased frequency of play fighting in both sexes, whereas there were no GX effects on this measure, social investigation nor contact. GX, however, decreased baseline social preference (a social anxiety-like effect) in males, while inducing anxiety-like increases in baseline social preference in females. The social drinking test revealed that females developed ethanol conditioned taste aversions at a lower dose relative to males, regardless of surgical condition. These findings suggest a potential role for gonadal hormones in moderating social-anxiety like behaviors but not sensitivity to the social impairing effects of ethanol or ethanol's aversive consequences in a social context.

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1. Introduction

Men drink more frequently and more per occasion than females [64] and are twice as likely as women to be diagnosed with alcohol dependence or use disorders. Women however, have shorter latencies between onset of drinking and the development of alco-

hol use disorders [18]. Interestingly, these sex differences in alcohol intake emerge post-pubertally with the development of sexually-dimorphic, adult-typical behaviors [14,39]. Age- and sex-related differences in ethanol sensitivity appear critical for understanding risk factors related to the development of alcohol use disorders, with for instance increased sensitivity to the rewarding or aversive properties of ethanol likely serving to promote or limit intake, respectively. Although, some of these sex differences may be attributable to cultural and psychosocial factors [15,60], there are also adult-typical sex differences in alcohol-related drug pharmacokinetics [16], immune responses [21] and neural sensitivity [10], suggesting that biological influences are likely as well.

Abbreviations: CTA, conditioned taste aversion; GX, gonadectomy; NM, non-manipulated; SH, sham; SS, supersaccharin solution.

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Adult-typical patterns of alcohol intake and sensitivity emerge post-pubertally during adolescence in both males and females—i.e., after the reinstatement of activity in the hypothalamic–pituitary–gonadal axis (HPG) axis that initiates puberty and ultimately leads to sexual maturation [36]. Many of the key neural, physiological and behavioral characteristics seen during the adolescent transition are conserved across mammalian species (e.g. see [65]), hence supporting the use of animal models for study of age-, sex- and hormone-related differences that are difficult to study empirically in developing humans. For instance, not only human adolescents [19], but also their rodent counterparts (see [65] for reference and review) exhibit two- to three-fold greater alcohol intakes per occasion than do adults. Studies with adolescent rats have shown them to be less sensitive than adults to many of the sedative, motor impairing, aversive, and hangover effects of ethanol that presumably serve as feedback cues to moderate drinking [2,12,44,57]. The approach of adulthood is not only associated with the dissipation of adolescent-typical ethanol sensitivities and intakes, but also the emergence of sex differences in these measures. In rats, characteristic sex differences include significantly greater ethanol intake and preference, as well as decreased sensitivity to the development of conditioned taste aversions in adult females relative to males [51], although, the latter effect varies with the number of pairings and the social context [30].

Indeed, social context is a particularly important factor in studies with ethanol. Increased social facilitation is one of the many positive expectancies associated with alcohol consumption in humans, an effect particularly pronounced in adolescents [7,23,24,31,34]. In rodent studies as well, adolescents are uniquely sensitive to the social facilitating effects of ethanol [45] while conversely being relatively insensitive to the social impairing effects of ethanol that emerge at higher doses of ethanol [45]. Both of these effects decline post-pubertally and are absent by adulthood [43].

Adolescents are also especially susceptible to increased ethanol consumption for its perceived anxiolytic expectancies, especially in social situations [58]. Using a measure of social preference/avoidance in rats that compare the relative number of approaches to versus movement away from a partner as an index of social anxiety-like behavior, acute restraint stress immediately prior to social interaction testing was found to decrease social preference, with this anxiety-like effect reversed by ethanol in adolescents but not adults [46].

The emergence of sex differences in stress reactivity and ethanol sensitivity is thought to be moderated by pubertal rises in gonadal hormones. Anxiety disorders increase in frequency and severity during reproductive years and show a clear sex bias towards females [35]. These traits are affected by hormones, with females reporting greater levels of anxiety and panic states during premenstrual and postpartum-associated decreases in estrogens [37]. Given that sex differences typically emerge during adolescence and reach their full expression in adulthood, the potential role of pubertal rises in gonadal hormones has significant implications for understanding developmental periods of increased risk for the emergence of alcohol use disorders. Hence, we have used a simple animal model of adolescence in the rat to explore the role of gonadal hormones during puberty on the emergence of adult- and sex-typical ethanol responses, reasoning that gonadal hormones should play at least as important a role in these behaviors in rodents as in humans with their much greater social and environmental complexity.

In our prior work in this area, we have observed that the ethanol intake of gonadectomized (GX) males was similar to that of intact females, regardless of whether GX occurred pre-pubertally or in adulthood; GX in females, in contrast, had little impact on ethanol intake [53]. The feminization of ethanol intake in males by GX was attenuated by testosterone, suggesting an activational

role for testosterone in contributing to sex differences in ethanol intake [52]. A recent study by Torres et al. [66] reported that GX in females eliminated ethanol conditioned place preference, suggesting a potential role for estradiol in mediating the rewarding properties of ethanol, although the effects of GX on ethanol intake was not explored. In contrast, in our work to date, we have been unable to detect notable effects of GX on various alcohol sensitivities thought to influence intake and hence potentially contribute to sex-dependent differences in ethanol intake [50], although the effects of stressors and social context on GX/ethanol interactions have yet to be explored. The purpose of this study, therefore, was to investigate sex differences in the role of pre-pubertal GX on interactions between ethanol and social stimuli via examining sensitivity to: (a) the social impairing effects of ethanol following acute restraint stress; as well as (b) the aversive effects of ethanol when conditioning /testing occurs within a social context.

2. Materials and methods

2.1. Subjects

Male and female Sprague-Dawley rats bred and reared in our colony at Binghamton University were used as experimental subjects ($n = 288$) and social partners ($n = 288$). All animals were housed in a temperature-controlled (22°C) vivarium maintained on a 12:12 h light-dark cycle (lights on at 0700 h) with ad libitum access to food (Purina Rat Chow, Lowell, MA) and water. Litters were culled to 8–10, maintaining relatively equal sex ratios whenever possible. On P21, pups were weaned and pair-housed with a littermate of the same sex assigned to the same surgical condition. At all times, animals were treated in accordance with guidelines for animal care established by the National Institute of Health under protocols approved by the Binghamton University Institutional Animal Care and Use Committee.

2.2. Design

The impact of pre-pubertal gonadectomy on social impairing effects of ethanol following acute stress in adult males ($n = 144$) and females ($n = 144$) was examined using a 3 surgical condition (GX, sham-operated [SH], non-manipulated [NM]) \times 2 stress condition (acute restraint stress, no stress) \times 2 dose challenge (saline, 1.0 g/kg ethanol) factorial design, with 12 subjects from each sex placed into each experimental condition. The same animals were later used to assess ethanol's aversive effects in a social drinking context using a conditioned taste aversion (CTA) paradigm. For this phase of the experiment, 3 surgical condition (GX, SH, NM) \times 4 ethanol dose (0.0, 0.5, 1.0, 1.5 g/kg) factorial design was used, with 12 subjects from each sex placed into each experimental condition. Animals from the earlier social test conditions defined by the 2 (restraint stress vs. no stress) \times 2 (saline, 1.0 g/kg ethanol) design were re-assigned to the 4 dose conditions of the test, with prior condition counterbalanced.

2.3. Surgery

On P25, animals were anesthetized using isoflurane (3.5% initially) and maintained at surgical levels of anesthesia throughout the surgery via nose cone supplementation (3% repeated as necessary). For castration of males, each testis was removed, a suture made in each tunic and in the inguinal ring (to prevent possible herniation), and the incision closed with Vetbond tissue adhesive (3M, St. Paul, MN). For ovariectomies, an incision was made on the dorsal side of the animal, caudal to the last rib and through the skin perpendicular to the midline. On each side of this incision, an opening was made in the muscle wall via blunt dissection, with the oviduct on each side sutured proximal to the ovary, the

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