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Review article

Puberty, hormones, and sex differences in alcohol abuse and dependence

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Abstract

Sex differences in patterns of drinking and rates of alcohol abuse and dependence begin to emerge during the transition from late puberty to young adulthood. Increases in pubertal hormones, including gonadal and stress hormones, are a prominent developmental feature of adolescence and could contribute to the progression of sex differences in alcohol drinking patterns during puberty. This paper reviews experimental and correlational studies of gonadal and stress-related hormone changes and their effects on alcohol drinking and other associated actions of alcohol. Mechanisms are suggested by which reproductive hormones and stress-related hormones may modulate neural circuits within the brain reward system to produce sex differences in alcohol drinking patterns and vulnerability to alcohol abuse and dependence which become apparent during the late pubertal period.

Keywords: Sex differences; Alcohol drinking; Pubertal hormones

Contents

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1. Introduction

Males and females between the ages of 12 and 17 have similar patterns of alcohol use (frequency and quantity) as well as prevalence of DSM-IV alcohol abuse and dependence [101,194]. By about age 17, however, the sex-specific patterns and prevalence begin to diverge and remain disparate across the ages surveyed (12–65+), with females exhibiting fewer drinking days in the past month, fewer days of drinking 5 or more drinks in the past month, and lower prevalence of alcohol abuse and dependence. In 10- and 15 year old boys and girls, pubertal stage is associated with higher rates of substance use and abuse (including alcohol) independent of age and school grade [157]. Earlier puberty in adolescent girls is associated with younger age of onset of drinking and smoking [32,214]. The relationship between pubertal maturation and the onset of alcohol/substance use is often attributed to mediating social factors and environmental stressors. However, biological mechanisms could also contribute to the progression of sex differences in alcohol drinking patterns during puberty. These variables might include changes in reproductive hormones and stress hormone responses and their effects on adolescent brain development. The purpose of this paper is to review research on gonadal steroids, neuroactive steroids, and stress hormones and their effects on the development of sex differences in alcohol drinking and associated behaviors that emerge during puberty. Gonadal and neuroactive steroid actions on the neurotransmitter systems and neural circuits underlying alcohol seeking and reinforcement are discussed. Examples are given to illustrate potential neuropharmacological, cellular, and molecular mechanisms by which these hormone-neurotransmitter interactions may contribute to sex differences in alcohol's actions. The role of gonadal steroids in modulating the ontogeny of sex differences in the stress responsiveness to alcohol is also discussed. Finally, suggestions are proposed as to how gonadal and stress hormones might interact within structures in the brain reward circuit to promote sex-specific changes in alcohol use and misuse that occur during puberty.

2. Hormonal events associated with the onset of puberty

Puberty is a gradual physiological process that typically occurs between the ages of 6–12 years and results in the attainment of sexual maturation. This process of reproductive maturation occurs within the developmental stage of adolescence, a period when the brain is undergoing substantial structural and functional changes. For many years, the conventional belief was that puberty and adolescent brain development were two independent processes. However, the current thinking is that pubertal elevation in the secretion of gonadal steroids significantly influences the refinement of certain brain neural circuits that occurs during adolescence [190], and that these permanent steroid-dependent brain structural changes determine adult behavioral responses to hormones and other stimuli. A brief description of the major hormonal changes associated with the two main stages of pubertal development, adrenarche and gonadarche, are described in the next section.

2.1. Adrenarche

The first sign of the onset of puberty is an increase in androgen secretion from the adrenal glands. Adrenarche occurs well before pubertal activation of the reproduction axis, between the ages of 6 and 9 years of age, and results in a rise in levels of a variety of androgens, including androstenedione, dehydroepiandrosterone (DHEA), and its sulfate (DHEAS). Adrenal androgens in humans are associated with the growth of axillary and pubic hair, and increase in bone and skeletal growth.

2.2. Gonadarche

At puberty, the primary role of gonadal steroids is to support the development of sex differences in reproductive physiology and behavior. In both males and females, puberty is a period of reawakening of the hypothalamic-pituitary-gonadal (HPG) axis, which is dormant during early to mid-childhood. Re-activation of pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which was evident prenatally, stimulates pituitary secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) pulses, followed by marked increases in gonadal sex steroid output (estrogen, progesterone, and testosterone). The increase in gonadal hormones promotes maturation of the gonads, development of secondary sexual characteristics, and the initiation of menstrual cycles in females. Traditionally, pubertal hormones were thought to have a strictly activational role in reproductive behavior. However, recent evidence supports an organizational function of gonadal steroid hormones during puberty on maturation of reproductive and other social behaviors [190].

Gonadal steroids have both organizational and activational roles in the central nervous system. Activational effects are the acute actions of gonadal steroids on brain targets that facilitate expression of sex-typical behaviors in certain social contexts. Activational effects are temporary, depend upon the presence of the hormone, and are usually associated with hormonal actions in adulthood. Organizational effects refer to the ability of hormones during pre- and post-natal developmental periods to permanently establish sex differences in brain structure and function. This structural organization continues beyond the initial period of hormonal exposure, and programs the activational effects of steroids in adulthood.

3. Sex differences in alcohol drinking: laboratory studies

Sex differences in alcohol intake and responses to alcohol have been well characterized in human and animal laboratory studies. In humans, sex differences have been found in dose-related cognitive impairments [51,141], behavioral, subjective, and brain metabolic responses to alcohol intoxication [51,181,209], and patterns of alcohol intake and lifetime prevalence for alcohol dependence [67,213,212].

Sex differences in alcohol self-administration have also been observed in adult nonhuman primates [206], with males consuming approximately 1.5 fold more than females. In contrast to

humans and nonhuman primates, female rodents tend to drink more alcohol than males [109], although these differences may be influenced by environmental variables [134] and strain [39]. Of greater interest is that increased voluntary ethanol intake in female rats relative to males occurs around the time of puberty, suggesting a hormonal basis for this difference [110]. Other rodent studies have shown sex differences in behavioral responses to intoxication, such as locomotor activation [36,94,133] and loss of the righting reflex [94], which may also be affected by species or age [133,140,210]. Finally, one study examined a potential neural mechanism for sex differences in alcohol consumption and found that female rats show greater extracellular release of dopamine in the nucleus accumbens than males as well as greater consumption of alcohol [14].

These sex differences in alcohol consumption and behavioral response to alcohol could be due to hormonal changes that modulate neural sensitivity to alcohol. However, sex [37,141,198] and ontogenetic [17,88,96] differences in the pharmacokinetics of ethanol, which affects the amount of alcohol that reaches the brain, could also explain the sex differences in these behaviors. Therefore, to determine whether sex differences in alcohol consumption and other acute behavioral effects of alcohol are due to hormonal modulation of response to ethanol at specific brain targets and not to differences in availability of alcohol at these targets, it is essential to control for sex differences in brain ethanol concentrations. Since it has been demonstrated that systemic blood ethanol concentrations (BECs) are equivalent to brain ethanol concentrations [95,173], the most direct way to control for these pharmacokinetic differences is to measure all dependent variables (e.g., behavioral, neurochemical) in each subject at equivalent BECs. Studies using discrete behavioral outcomes, such as loss of the righting reflex in animals [94,210] or performance impairments in humans [51], can more easily measure BECs at similar time points, whereas other behaviors, such as voluntary alcohol consumption or neurochemical measures, are much more difficult to evaluate at comparable BECs. However, despite these methodological issues, it is important that research on sex differences in alcohol consumption continues, particularly from a developmental perspective.

Despite the consistent finding from epidemiological studies that sex differences in human alcohol intake emerge with the onset of puberty, most experimental research on sex differences in alcohol drinking and response both in humans and in animal models has been conducted in adult subjects. Only one study in rats [110] focused on the emergence of differential drinking patterns during the early postpubertal period. Other rodent studies indicate that age, rather than puberty *per se*, is an important variable in the expression of sex differences in the actions of alcohol [22,133], which still suggests that developmental factors including hormonal changes may be involved. Examining sex differences in alcohol consumption and response in controlled settings during the pubertal period in humans is fraught with ethical problems. The similar pattern of sex differences observed in nonhuman primates, as well as the protracted adolescent period in this species suggest that this model would be ideal for examining relationships between hormonal changes during puberty [20] and sex differences in alcohol drinking and actions in settings that control for social and environmental variables. These studies could be guided by complementary studies in rodents where it is possible to assess changes associated with puberty rapidly and inexpensively.

4. Sex differences in alcohol drinking: influence of gonadal hormones

Despite the small number of laboratory studies on sex-specific changes in alcohol drinking and other responses associated with the onset of puberty, researchers have used a number of approaches to examine the effects of gonadal hormones on these behaviors. One method, which is strictly correlational, assessed alcohol consumption throughout the menstrual cycle to determine how patterns of drinking may vary as a result of changes in levels of sex steroid hormones. Using this approach, increased alcohol intake was associated with menses [155,197] as well as the luteal and premenstrual phase of the menstrual cycle [72,130] in young adult females. However, the small number of subjects and lack of hormonal verification of menstrual cycle phase limited the findings of these studies. In adult nonhuman primates, decreased alcohol self-administration was found during menses, compared to mid-cycle or luteal phase of the menstrual cycle [129]. Female rats showed decreased absolute alcohol intake during estrus and proestrus [56,172] or no change in absolute alcohol intake across the cycle [55]. In this latter study, however, microanalysis of consumption patterns showed elevated frequency, but attenuated size of discrete drinking episodes during proestrus compared to other cycle phases. The inconsistent findings within and between species, as well as the lack of controls in human studies, make it difficult to establish a clear association between changes in endogenous hormone levels during the menstrual cycle of females and alterations in drinking patterns.

In contrast to the mixed results from studies of reproductive cycle-related patterns in alcohol drinking, a consistently positive relationship was found between alcohol consumption and levels of the male sex steroid, testosterone, in young adult college students and adolescents. Using self-report methods, a positive correlation of testosterone with alcohol consumption was found in male and female college students, but the correlation was stronger in males [107]. In female adolescents, current alcohol use (within the past month) was associated with higher levels of testosterone and estradiol, (suggesting involvement of gonadal steroids with alcohol use in these women) [120]. A very recent study in male adolescent twin pairs found significant relationships between higher levels of testosterone, increased alcohol symptoms, and DSM-IIIR diagnoses of alcohol dependence, even after adjusting for pubertal development [41]. Higher basal serum testosterone levels were also found in adult male rats selectively bred for high alcohol preference (AA) compared to the alcohol nonpreferring (ANA) selected rats, suggesting a direct or indirect association between elevated testosterone levels and high alcohol intake [5]. Of interest is that these authors suggest testosterone elevations may

be related to increased alcohol consumption through a hypothalamic opiate mechanism.

A small number of correlational studies have shown that testosterone and estradiol have opposite effects on ethanol-induced male aggression. A positive association was found between alcohol intake, testosterone levels, and certain types of aggressive responding in adult male humans [40,208] and monkeys [216,215]. Reductions in estradiol levels (presumably derived from aromatization of testosterone) were observed in adult male mice prone to ethanol-induced aggression [83,85] and men with a history alcohol-related physical or violent aggression [40]. Of particular relevance is a single study in male hamsters on the relationship between puberty, drinking, and testosterone [49]. Adolescent animals that voluntarily drank large quantities of ethanol had twice the blood concentration of testosterone than controls. However, this difference disappeared by adulthood. Nevertheless, the authors suggest that elevated exposure to testosterone during puberty may have permanently altered the hypothalamic-pituitary-gonadal axis/and or agonistic brain circuits, since these same animals showed augmented aggression in adulthood. These latter results underscore the need for research on developmental differences in alcohol's effects on hormonal levels and their relationship to subsequent brain maturation, drinking, and other alcohol-related behaviors.

Correlational studies can provide initial evidence that gonadal hormones are associated with drinking behavior and other responses to alcohol, such as aggression. However, to determine whether a specific hormone is modulating a targeted behavior, a better strategy is the use of castration or ovariectomy studies (in animals) and replacement of steroid hormones. A handful of studies have used this method to investigate the role of gonadal steroids on ethanol-induced aggression, alcohol consumption or both. Estradiol stimulated alcohol consumption and aggressive behavior, as well as restored alcohol-heightened aggression to baseline levels in adult castrated male mice [83,84]. Elevated levels of estradiol decreased alcohol consumption and had no effect on aggression in adult ovariectomized female mice [83]. Similarly, sex differences were observed with testosterone replacement, in that high doses of testosterone (7.5 mm) in male castrated mice, but not in female ovariectomized mice, increased the aggression-enhancing effects of low dose alcohol [29]. In a study using only castrated adult male rats, animals administered exogenous testosterone developed preference for alcohol at a faster rate than animals given estradiol or progesterone [108]. Finally, a study in ovariectomized female rats found that estradiol and progesterone interact with alcohol to modulate the binding kinetics of μ-opioid receptors of the hypothalamus, hippocampus, midbrain and cortex in a region-specific manner [21].

Hormone replacement studies, though limited in number and scope, suggest that gonadal hormones may influence the sex differences observed in alcohol consumption, other alcohol-related responses such as aggression, and brain receptor systems. As actions of gonadal steroid hormones on alcohol intake are confirmed, more extensive studies are needed exploring the contribution of these hormones at puberty to sex differences in alcohol consumption, response to alcohol, and the development of alcohol use disorders. This line of research is especially important since recent evidence in human adolescents suggests that activation of gonadal steroids during puberty may trigger sex differences in onset of other psychiatric disorders, including depression, antisocial behavior, and substance abuse [2,20,27,174,175].

5. Effects of reproductive hormone changes on neural circuits associated with alcohol seeking behavior

Gonadal steroids play an organizational role during brief periods of early pre- and post-natal brain development, and during adolescence to permanently establish sex differences brain structures and functions. Although puberty is primarily linked with hormonal organization and/or activation of sexual reproductive behaviors, gonadal steroids (androgens and estrogens) are also responsible for sex differences in brain structure and function unrelated to reproduction via effects on their respective receptors distributed throughout the brain [19,20,175]. In humans and/or animals, gonadal steroid actions contribute to sex-related differences in nonreproductive behaviors, such as aggression, motor activity, learning, memory, affect regulation, and drug-related responses [12,20,124,190]. These functions are subserved by brain regions outside the hypothalamus, including the hippocampus, amygdala, striatum, locus coeruleus, dorsal raphe, ventral tegmental area, cerebellum, and cerebral cortex.

Androgen receptors and two major subtypes of estrogen receptors, ER-α and ER-β, are localized in these brain regions, but their expression shows prominent sex and species differences [184,185,186,222]. Gonadal steroid hormones appear to regulate a wide variety of neurotransmitters and neuropeptides through genomic and nongenomic receptor-mediated mechanisms. In the last several years, there has been considerable interest and research on estrogen's nongenomic cellular activity in the central nervous system. This activity includes rapid actions on neuronal excitability, regulation of second messenger systems (cyclic AMP and mitogen-activated protein (MAP) kinase, effects on calcium channels and calcium release, and neuroprotection from damage by free radicals and excitotoxins [19,123,124]. Although the exact cellular and molecular mechanisms by which gonadal steroid hormones exert their influence on nonreproductive behaviors is unknown, it is clear that estrogen interacts with multiple neurotransmitter systems including serotonergic, cholinergic, and dopaminergic neurons in the neural circuits underlying alcohol reinforcement and consumption.

For example, both ER-α and ER-β are found in 5-HT neurons of the dorsal raphe nucleus [13,184], a structure that is part of the alcohol reward circuitry. Estrogen has effects on serotonergic markers within this structure and in other components of the alcohol reward system. In ovariectomized female macaques, estrogen treatment (28 days) increases expression of tryptophan hydroxylase, the rate limiting enzyme for serotonin synthesis, but decreases serotonin transporter expression and 5-HT1A receptor function in the dorsal raphe [13]. In gonadectomized male and/or female rats, estrogen (within hours or after

two weeks of treatment) stimulates 5-HT2A mRNA in the dorsal raphe and 5-HT2A receptors in several forebrain regions [53,195], but reduces 5-HT1A mRNA and receptors in limbic structures [150,149].

These studies suggest that estrogen mediates serotonergic function through classical genomic pathways and that concurrent behavioral changes would occur slowly. Very recently, however, it has been shown that estrogen produces relatively rapid changes in 5-HT function through its effects on G-protein coupling or regulation of intracellular Ca^{2+} levels [103,123,135], and that estradiol and other gonadal steroids act as noncompetitive antagonists of the 5-HT3 receptor in vitro [152,211]. Thus, some of the same midbrain and limbic serotonergic systems that are involved in alcohol reinforcement, e.g., 5-HT1A, 5-HT2, and 5-HT3 receptor systems [121,122] are also affected by estrogen treatment. Yet, we do not know whether sex differences in alcohol seeking behavior are mediated by interactions between estrogen and the serotonergic system.

Estrogens and androgens also modulate the mesocorticolimbic dopamine system, which is a central neurotransmitter in the alcohol reward system. Estrogen in particular has been shown to regulate gene expression in midbrain dopamine neurons [163] and to affect stimulated dopamine release, synthesis, innervation density, and receptor binding at their afferent targets [10,11,26,199,218]. Intracellular ER-β and androgen receptors (AR) are found in dopaminergic midbrain neurons of adult male and female rats, suggesting that these receptors may be important in gonadal hormone stimulation of midbrain DA neurons and their afferents [25]. These receptor bearing midbrain DA neurons project differentially to mesostriatal and mesolimbic structures. The ERβ-containing midbrain DA neurons project to the caudate–putamen and amygdala, but not to the accumbens, whereas the AR-containing neurons project to either the amygdala or the accumbens, but not the caudate–putamen [26]. Within the amygdala, ERβ labeled midbrain DA neurons project to the basolateral complex, while the AR labeled DA neurons project to centromedial amygdala. Thus, the selective projections of ERβ and AR-containing DA neurons to mesostriatal and mesolimbic structures involved in alcohol reinforcement could provide a mechanism for gonadal steroid influences on sex differences in alcohol consumption patterns.

In contrast to the dearth of research on gonadal steroids and sex differences in alcohol-related behaviors, there is a growing body of evidence which demonstrates that gonadal hormones differentially modulate cocaine responses in males and females [12,50]. Neuropharmacological evidence indicates that alcohol and cocaine addiction result from changes mediated by similar neurotransmitter systems, such as dopamine, serotonin, and glucocorticoids distributed throughout the mesolimbic reward system and extended amygdala [105]. Thus, studies from the cocaine literature may have relevance for understanding hormonal mechanisms of sex differences in alcohol-related behaviors. For example, hormone replacement studies in rats found that the enhanced behavioral sensitization to cocaine, faster acquisition of cocaine-induced conditioned place preference, and increased cocaine self-administration in females, compared to males, are dependent on levels of estrogen [12,116,178]. In vivo microdialysis, in vitro perfusion measures, and other neurochemical assays indicate that ovarian hormones mediate sex differences in cocaine-related behaviors by altering release, levels, or turnover of monoamines in the striatum, n. accumbens, and ventral tegmental area [12,178]. Furthermore, estrogen modulates the effect of cocaine on $GABA_B$-mediated G-protein activation in the ventral tegmental area and entorhinal cortex of ovariectomized female rats [48]. Whole clamp electrophysiological experiments have shown that estrogen has rapid effects on female striatal neurons that depend on a G-protein coupled receptor [12]. It has been suggested that attenuation of K^+ stimulated increase in extracellular GABA is the mechanism by which estrogen enhances stimulated dopamine release in the striatum [90,131]. Both preclinical [221] and clinical studies [142] have found greater amphetamine-induced striatal dopamine release in males than females. This difference in dopamine depletion between males and females following amphetamine administration appears to be modulated by the effects of estrogen, but not testosterone responsiveness to amphetamine administration [142].

Taken together, these studies indicate that gonadal steroids may modulate sex differences in the behavioral and subjective effects of drugs of abuse, and possibly alcohol (see previous section), by influencing neurotransmitter systems in regions that are directly involved in brain reward circuitry.

6. Neuroactive steroids, stress hormones, and the onset of sex differences in alcohol drinking and related behaviors at puberty

6.1. Allopregnanolone

The term “neuroactive steroids” refers to steroids synthesized in the brain, adrenals and gonads that affect neuronal excitability by acting in a rapid nongenomic manner at the membrane surface of certain neurotransmitter receptors [7,158,177]. One neuroactive steroid that has received considerable attention with respect to its interaction with ethanol is the 5α-reduced, 3α-hydroxylated, progesterone metabolite allopregnanolone (3α-hydroxy-5α-pregnan-20-one) [30,138,139]. Allopregnanolone, which requires the onset of adrenarche and maturation of specific adrenal biosynthetic enzymes for its synthesis, interacts with ethanol to positively modulate the gamma-aminobutyric acid typeA (GABAA) neurotransmitter receptor complex. Therefore, these compounds share similar pharmacological properties, the most prominent being their anxiolytic and anticonvulsant effects. Of particular interest, however, is the degree to which allopregnanolone influences the positive motivating effects of ethanol and contributes to alcohol addiction. Recent findings in male rats and/or nonhuman primates indicate that acute administration of allopregnanolone selectively increases operant ethanol self-administration [91,92], substitutes for the discriminative stimulus effects of ethanol [6,16,65,87], and restores ethanol-induced elevations of allopregnanolone and duration of the loss of the righting reflex following adrenalectomy [97]. These findings suggest that acute

administration of GABAergic neuroactive steroids enhances alcohol drinking, produces similar subjective effect as alcohol, and contributes to the sedative/hypnotic effects of ethanol, although the exact mechanisms underlying these interactions remain unknown [68,139].

Few studies have investigated the role of allopregnanolone in modulating sex differences in susceptibility to alcohol abuse. Pretreatment with allopregnanolone increased voluntary ethanol intake during the first hour of exposure in male mice, whereas in females, allopregnanolone injections did not alter ethanol consumption [189]. Furthermore, consumption of ethanol, but not acute injection of ethanol increased brain allopregnanolone levels in male, but not female mice [54]. Increased sensitivity to the discriminative stimulus effects of ethanol and the ethanol-like effects of allopregnanolone was found during the luteal phase of the menstrual cycle in female monkeys [66]. Sex differences have also been found in sensitization to the anti-convulsant effects of allopregnanolone in ethanol-dependent rats, with female rats in estrous exhibiting lower seizure susceptibility and greater protective effects than male rats during ethanol withdrawal [137]. Since basal concentrations of allopregnanolone in plasma and brain are greater in female than male rats, even at puberty, and fluctuate during the estrus and menstrual cycle [24,154,158], it has been suggested that sex differences in basal levels of allopregnanolone or changes in circulating levels of allopregnanolone across the menstrual cycle could account for differences in sensitivity to exogenously administered ethanol [54,66] and/or development of physical dependence [137]. However, the ability of allopregnanolone to differentially modulate the effects of ethanol in males and females has not been examined from a developmental perspective, particularly at the onset of puberty.

6.2. Pregnenolone and dehydroepiandrosterone

Other neuroactive steroids that influence alcohol's pharmacological and behavioral effects are the Δ5-3β hydroxy steroids pregnenolone (PREG), dehydroepiandrosterone (DHEA), and their sulfate esters (PREGS and DHEAS). The conversion of cholesterol to PREG by the enzyme P450 cc is the first step necessary for the biosynthesis of all hormonal steroids [182]. PREG is then converted to DHEA by the enzyme P450c17. In the brain and periphery, DHEA and DHEAS then undergo a series of metabolic conversions that lead to the formation of testosterone and estrogen [9]. Depending on the dose, PREG, DHEA and their sulfate esters act as positive or negative modulators of GABAA and/or *N*-methyl-D-aspartate (NMDA) receptor activity [9,35,118,158,165]. For example, PREGS, DHEA, and DHEAS have positive allosteric effects on GABAA receptors in brain slices at low nanomolar concentrations and negative effects at higher micromolar concentrations [118,119]. These biphasic effects are reflected at the behavioral level by the interaction of ethanol with PREGS and DHEAS on the anxiogenic plus maze test. At low doses of PREGS (0.1 μg/kg) and DHEAS (0.5 μg/kg to 1.0 mg/kg), male mice display lower levels of anxiety on the plus maze than controls, an effect which is enhanced by ethanol [127,128]. At higher doses, PREGS (>1 μg/kg) and DHEAS (>1 mg/kg) block the anxiolytic effect of alcohol in the plus maze [86,127,128]. However, whether these biphasic dose-response interactions with ethanol in the plus maze are due to mixed agonist/antagonist effects of PREGS and DHEAS at the GABAA receptor complex or to positive modulation of the NMDA receptor are unclear. Melchior and Ritzman [126,127] found that DHEA does not show the same biphasic interactions with alcohol as DHEAS and PREGS, but enhances the anxiolytic effects of alcohol on plus maze and sleep time at all doses tested. These authors suggest that the anxiolytic effect of DHEA is due to its ability to reduce brain levels of PREGS, which has GABA antagonistic properties. Finally, the anxiolytic properties of DHEA and DHEAS may result from their being metabolized to androsterone and androstanediol which, at low doses, behave as positive GABAA receptor modulators [60].

Very little research exists with respect to the relationship between these pregnene steroids and sex differences in alcohol consumption, although it has been suggested that interactions with DHEAS and PREGS at GABAA or NMDA receptors play some role in the sex differences in the actions of alcohol due to differences in levels of these hormones between males and females [30]. A few studies on breast cancer risk found increased serum levels of DHEAS in pre- and post-menopausal women following 8 weeks of moderate alcohol consumption [34,117]. In contrast, acute administration of a moderate dose of alcohol over a 135 min period decreased salivary DHEAS in adult human males [102]. One study in human adolescents (age 13–17) of both sexes found increased serum levels of DHEAS in females and no change in males with symptoms of acute alcohol intoxication [59].

6.3. Neuroactive steroids, pubertal development and sex differences in alcohol consumption

The studies described above suggest that there are sex differences in the acute and chronic consequences of alcohol consumption on neuroactive steroid levels. However, there is little, if any, research on the etiological relationship between these steroids and sex differences in patterns of alcohol consumption during late puberty. In humans, blood and cerebrospinal fluid levels of DHEA and DHEAS increase rapidly from 6–8 years (adrenarche) through puberty in males and females to reach their highest levels during young adulthood [69,217]. Furthermore, increases in salivary levels of DHEA correlate with pubertal stage [143]. Recent data have shown increases in serum levels of allopregnanolone and DHEA in boys and girls throughout puberty that correlate with Tanner stage [42,63]. One interesting study in rats found that in both male and female rats, levels of allopregnanolone in the hippocampus varied according to pubertal development, with concentrations decreasing in both sexes from 15 days to adulthood. Interestingly, at 15 days and 60 days of age, levels of allopregnanolone were higher in females, while at 25 days levels were higher in males [154]. These results suggest that sex differences in allopregnanolone are age and possibly region-specific. Furthermore, these changes in levels may correspond to changes in the functional

role of allopregnanolone during prepuberty and in transition from prepuberty to adulthood. Therefore, it is possible that fluctuations in these neuroactive steroids during pubertal development could influence sex differences in drinking behavior.

6.4. Neuroactive steroids, stress hormones, and sex differences in alcohol consumption

As described above, acute alcohol and chronic alcohol administration alters the concentrations of neuroactive steroids in brain and/or blood of animals and humans. Furthermore, these changes in neuroactive steroid concentrations after alcohol consumption may be sex and age dependent. Acute and chronic alcohol consumption also activates the hypothalamic–pituitary–adrenal (HPA) axis, resulting in age and sex-specific changes in corticotrophin releasing factor (CRF), adrenocorticotropin (ACTH), and cortisol/corticosterone (see next section for detailed discussion of alcohol and stress hormones). However, to date, the interconnections among alcohol consumption, neuroactive steroids, and the HPA stress axis are mainly indirect.

For example, although a thorough analysis is beyond the scope of this paper, research suggests that the effects of a variety of stressors on the HPA axis are mediated by the interaction of the neuroactive steroid allopregnanolone with GABAA receptors in the hypothalamus. Specifically, since GABA acting at GABAA receptors, inhibits the release of CRF from the hypothalamus, it has been suggested that downregulation of GABAA receptor function, which occurs following an acute stressor, may contribute to activation of the HPA axis in response to such stressor. The observed elevations during stress of allopregnanolone, which is a positive modulator of GABAA receptor function, may counteract the stress-induced impairment in GABAergic transmission and limit the duration of the HPA stress response [8,137]. However, alcohol's effects on allopregnanolone–GABAA interactions, particularly with respect to the HPA stress response, have not been well studied nor has the degree to which sex and pubertal stage might alter these responses.

The relationship among alcohol consumption, DHEA, DHEAS, and the HPA stress axis is even less clear. Melchior and Ritzman [128] suggest that, in their study, the anxiolytic effect of DHEA and DHEAS on the plus maze performance of mice may be due to the ability of DHEA to diminish stress-induced increases in corticosterone. However, they failed to find an effect of DHEA (0.5 mg/kg) on corticosterone levels in mice following handling, although this negative finding may be dose-related. Reddy [165] suggests that stress-induced seizure susceptibility could depend on "the balance between anticonvulsant (e.g., allopregnanolone and THDOC) and proconvulsant steroids (PREGS and DHEAS) or other factors (e.g., CRF)." Although this hypothesis has implications for alcohol-induced withdrawal seizures, research to date has not focused on the interplay of neuroactive steroids and the HPA axis in relation to alcohol withdrawal seizure susceptibility. There is also a body of literature supporting the antiglucocorticoid actions of DHEA and DHEAS, e.g., counteracting the detrimental effects of corticosterone on LTP or the neurotoxic effects of glucocorticoids [35,75,217]. Because of its antiglucocorticoid properties, alterations in DHEA, particularly changes in the plasma cortisol/DHEA ratio, have been implicated in adolescent and adult depression [75]. Finally in an attempt to link the stressors of pubertal development with adrenal and gonadal hormones, several groups studied and found correlations between the relative serum levels of testosterone, estrogen, androstenedione, cortisol, DHEA, and DHEAS and problem behaviors in adolescent boys and girls [18,146,196]. Furthermore, different patterns of hormone-behavior relations were found depending on the sex being considered and pubertal stage, and interestingly, elevated levels of the androgen androstenedione correlated with aggressive behavior in both boys and girls. Thus, there are independent threads of evidence from which one can infer a connection between pubertal changes in neuroactive steroids, stress hormones, and sex differences in drinking and other alcohol-related behaviors. One mechanism that may link these hormones to sex differences in adolescent drinking behaviors is alcohol's effects on neurosteroid metabolism. By decreasing the NAD/NADH ratio, alcohol may limit the capacity of dehydrogenases in the metabolism of neurosteroids [1]. Whether there are sex differences in these metabolic pathways may be a line of research worth pursuing.

7. Interaction of stress and gonadal hormones at puberty on sex differences in alcohol drinking

Alcohol is often consumed in response to stress in humans and animals, although the conditions under which this occurs are extremely variable and depend on many factors such as genetic predisposition, a history of experiencing stress early in life, an individual's drinking patterns, the intensity and type of stressor, controllability over the stressor, one's coping ability and the availability of social support [46,81,114,160,179,207]. In addition, even though alcohol is usually consumed to diminish stress and anxiety, acute alcohol actually stimulates a stress response by activating the HPA axis [64,168]. Furthermore, there are sex and age differences both in the types of psychological and social stressors that precipitate drinking [52,98,192] and the physiological stress response to alcohol [93,147,187]. Thus, the interrelationship between the stress response of the HPA axis and activation of the HPG axis during puberty could influence the development of sex differences in alcohol consumption that begins to emerge during late puberty.

7.1. Overview of the stress system

The central hormone system that maintains the body's equilibrium or prepares the body to cope with multiple stressors is the HPA axis. Activation of the HPA axis releases corticotropin-releasing factor (CRF), and to a lesser extent, arginine vasopression (AVP) from cells in the paraventricular nucleus (PVN) of the hypothalamus, which in turn act synergistically to release adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH stimulates the synthesis and release of glucocorticoids (cortisol in primates and corticosterone in rats) from the adrenal

gland. Increased glucocorticoids trigger a decrease in CRH and ACTH release through negative feedback action at glucocorticoid receptors in the pituitary, hypothalamus, and hippocampus [20,180,220]. The other brain system that acts in concert with the HPA axis is the sympathetic nervous system, which releases the neurotransmitter, norepinephrine both centrally and peripherally in response to stress [20,193]. In addition to the classical HPA stress axis, extrahypothalamic systems involving CRF and urocortin peptides in the central nervous system play a role in the activation and amelioration of behavioral responses to stressors [28,73,104]. Furthermore, recent research indicates that there are stressor-specific responses within central neuroendrocine systems [153], which are mediated by different functional and anatomical circuits. For example, Herman, and colleagues [76,77] have proposed that in addition to the classical reflexive circuit (spinal cord, brainstem), which mediates 'systemic' stressors, there is a hierarchical polysynaptic 'anticipatory' circuit, which processes psychological stressors and involves forebrain structures such as the hippocampus, prefrontal cortex, amygdala, and septum. The anticipatory stressors are produced by memory-dependent conditioned emotional responses to contextual stimuli or innate anxieties or predispositions, such as recognition of the dangers associated with heights or social conflicts. These anticipatory circuits can inhibit or augment responsiveness to environmental stimuli and are important determinants of HPA response. Within these complex circuits, multiple neurotransmitter systems modulate the stress response [64,77,104,193]. Sex differences in response to different stressors begin to emerge late in adolescence [111,183,192], although this research has focused mainly on changes within the HPA axis and appear to be mediated by both organizational and activational effects of gonadal steroids [147,156]. The interaction of gonadal steroids within hypothalamic and/or extrahypothalamic circuits during the period of adolescent brain remodeling may help to explain the development of sex differences in alcohol drinking.

7.2. Ontogeny of stress response to acute alcohol administration

Sex and age differences have been found in the HPA response to acute challenge doses of ethanol. Most of the basic work on the ontogeny of sex differences in the stress response following alcohol administration has been conducted in rodents. In general, female rats release more ACTH and/or corticosterone in response to acute administration of alcohol than males [148,167,166,187], with the sex differences emerging prepubertally (post-natal days 21 to 26), but not reaching adult levels until 56–60 days [147,187]. In female rats, corticosterone levels increased monotonically between preadolescence to adulthood, whereas in males, levels either peaked or reached a plateau during adolescence [187]. However, this sex difference in corticosterone response to alcohol was not consistently evident in periadolescent animals, possibly due to individual differences in levels of circulating sex steroids [147]. Based on human and animal studies, the greater HPA stress response in females compared to males has been found using a variety of stressors, and is thought to be modulated by gonadal hormones [156,201,219,220]. In female rats, estrogen stimulates pituitary–adrenal secretions, as demonstrated by gonadectomy and hormone replacement studies [100], and stress responsiveness in ACTH and corticosterone levels varies across the ovarian cycle [202]. It has been hypothesized that gonadal steroids enhance stress responsiveness in females by decreasing sensitivity to glucocorticoid negative feedback [219]. However, because glucocorticoids operate at multiple sites on the HPA axis to inhibit their release, the locus of action of female sex steroids, that is on glucocorticoid receptors, on brain CRF systems, or on responsiveness to CRF at the level of the pituitary, is still unresolved [220]. In contrast to the stimulatory effects of estrogen in females, androgens inhibit stress-related HPA activity in males. While the mechanisms by which androgens modulate HPA axis function are not fully understood, recent research using restraint stress suggests that testosterone influences the ACTH response to stress via its effects on AVP synthesis in the PVN under basal conditions, and through enhanced glucocorticoid feedback regulation [201,203].

With respect to sex differences in HPA axis response to alcohol, a small number of studies have specifically investigated the role of gonadal steroids in modulating the greater response of females than males to acute alcohol administration. In one study, the neonatal steroidal milieu was manipulated to determine the organizational effects of androgens on HPA responsiveness to alcohol [147]. Rats of both sexes were gonadectomized or treated with testosterone within 24 h after birth, and then tested for HPA response to 3 g/kg ethanol at 61 days of age (postpubertal period). Only intact males compared to the other groups (gonadectomized males and females, intact females, masculinized females) showed quantitatively smaller ACTH and corticosterone responses to ethanol, suggesting that sex differences in HPA responsiveness are due to activational rather than organizational effects of testicular androgens. In adult female rats, levels of ACTH and corticosterone secreted in response to a 1.5 g/kg dose of ethanol varied over the estrous cycle (levels of both hormones increased during proestrus and estrus), and gonadectomy of adult males and female animals eliminated sex differences in alcohol-induced secretion of ACTH, but not corticosterone [166]. Using castration and hormone replacement methods in adult male rats, it was found that, in response to ethanol (3 g/kg), circulating levels of estradiol (E2) enhance ACTH release, but not corticosterone, whereas androgens suppress release of corticosterone, and not ACTH [148]. This study also examined whether steroidal regulation of hypothalamic CRF and AVP levels might be the basis for sex differences in ACTH release following alcohol exposure. Alcohol treatment increased AVP and CRF mRNAs in the PVN of intact males, but unexpectedly decreased CRF mRNA in castrated males implanted with E2. The effect of alcohol on CRF mRNA in intact males, but not in castrated males pretreated with E2, suggests an androgen receptor-mediated rather than an estrogen receptor-mediated effect. However, in this study, the direct influence of testosterone and its metabolites on levels of CRF mRNA following acute alcohol treatment was not addressed. To some extent these results typify the amplifying effect of estrogens and inhibitory effect of androgens on the HPA response to stressors. However, the

reasons for the observed discordance between ACTH and corticosterone secretion and the failure to find E2-dependent increases in CRF and AVP levels following alcohol administration remain unclear. Furthermore, the studies discussed above were conducted in either neonatal or adult animals, but there is little if any research on the cellular or molecular mechanisms by which sex and gonadal steroids at puberty interact on the alcohol-induced HPA stress response. A recent study by Viau and colleagues [204] using restraint stress found that gonadal regulation of the HPA axis develops at puberty by very distinct mechanisms in males and females. Restraint-induced Fos protein and AVP heteronuclear RNA in the PVN were lower in 60 day old than 30 day old male rats, and dependent on circulating levels of testosterone. No age-related shifts in these synaptic and transcriptional markers occurred in females. However age-related changes in CRF synthesis occurred in females, but not males, as indicated by steady-state alterations in basal CRF mRNA expression in the PVN. These findings underscore the complexity and specificity of gonadal steroid effects on the HPA axis, and point to the need for research on the nature by which sex differences in alcohol-induced HPA activity changes as a function of puberty. Furthermore, there is little, if any research on the ontogeny of sex differences in the expression of CRF parameters in the extrahypothalamic stress system and how they might mediate sex differences in drinking patterns at puberty.

7.3. Interaction of gonadal and stress hormones in the development of sex differences in alcohol drinking

As discussed in the previous section, gonadal steroids modulate sex differences in HPA stress response to ethanol challenge, and further, these differences emerge during puberty. The questions that remain are how do these sex differences in alcohol-induced stress response contribute to sex differences in drinking patterns and development of alcohol dependence that occurs at puberty, and what are the cellular and molecular mechanisms underlying these events?

One possibility for sex differences in alcohol consumption is the interaction of gonadal steroids and glucocorticoid response to alcohol. Although the precise mechanisms are unknown, as with other stressors, there is some evidence that estrogen enhances while androgens inhibit the glucocorticoid response to alcohol [148] and that these effects may emerge at puberty as a result of the activation of gonadal hormones. Glucocorticoids have been shown in male rats to contribute to the reinforcing effects of drugs of abuse, including alcohol [44,45], possibly mediated directly by glucocorticoid stimulation of dopamine release in the nucleus accumbens [159], or indirectly through stimulation of the hypothalamic opioid system [64]. The role of the mesolimbic dopamine system is supported by the fact that corticosterone implants in the ventral striatum selectively increased alcohol consumption in males rats, but not when implanted in the septum, hippocampus, or thalamus [43]. Although purely speculative, it may be that because female rats have higher blood levels of corticosterone in response to ethanol as they mature [187] resulting from increases in circulating estrogen, they may require less ethanol than males to achieve its rewarding effects. Unfortunately, the research implicating glucocorticoids in the rewarding effects of alcohol or other drugs of abuse has only used males. Therefore, whether similar rewarding effects of glucocorticoids occur in females, are mediated by the mesolimbic dopamine system, or act in conjunction with sex steroids to contribute to the development of sex differences in drinking behavior is unknown.

Sex differences in drinking behavior may also be mediated by interactions between neurotransmitter systems in the mesocorticolimbic reward pathway and traditional CRH-HPA stress axis or the extrahypothalamic CRH (eCRH) stress circuits. For example, it has been suggested that the greater prevalence of stress-related anxiety or mood disorders in female compared to male alcoholics may be linked to abnormalities in the bidirectional relationship between serotonergic neurotransmission and the CRH-HPA-eCRH systems [4]. There are several lines of evidence to support this contention. First, neuroanatomical and pharmacological studies indicate that 5-HT regulates the CRH-HPA and eCRH stress axes at various levels, and that these hormones have reciprocal actions on 5-HT function [33,99,115,162]. Furthermore, interactions between 5-HT and the CRH-HPA and eCRH stress axes appear to mediate the response to certain stressors [71,161], although their interaction with respect to the acute alcohol stress response and alcohol's rewarding effects is unclear.

Second, both 5-HT neurotransmission [121] and CRH-HPA/eCRH stress systems [73,104] have been implicated in the pathogenesis of alcohol dependence, and more recently, investigators have begun to make connections between these two systems in the etiology of this disorder. For example, Le et al. [112] found that, in male rats, infusion of a CRF antagonist into the median raphe nucleus, which contains 5-HT neurons, prevented the resumption of stress-induced drinking. Interactions between 5-HT and the CRH-HPA axis have also been found in nonhuman primate models [82] and in human alcoholics [74].

Finally, as described in earlier sections, sex and gonadal steroids influence 5-HT and CRH-HPA function [13,156,176,220], with females showing, for example, greater resistance to cortisol negative feedback than males [220], increased sensitivity to exogenous CRH administration [15,62,167], and increased 5-HT mediated stress response in female animals [61] or women [144]. Given the colocalization of CRF receptors, 5-TH neurons, and estrogen β receptors in the raphe nuclei [13,113], a structure that is an integral part of the mesocorticolimbic reward system and CRH-HPA/eCRF stress systems, it is logical to surmise that these two systems interact in the etiology of sexual dimorphisms in alcohol dependence.

Similar cross-directional relationships between neurotransmitter-stress systems and gonadal steroids can be hypothesized to influence the development of alcohol dependence with comorbid antisocial personality disorder (ASPD). This form of alcohol dependence, also referred to as Type II alcoholism [31], has a higher prevalence in males than females and is associated with personality traits of low harm avoidance, high sensation seeking, as well as impulsive, aggressive, and antisocial behavior. Neuropharmacological evidence has linked male-

limited Type II alcoholism and aggression most prominently with serotonin [79,80,205], but other neurotransmitters including GABAA, opiates, and norepinephrine have been implicated in rodent and primate models [5,79,80,125,132]. All of these neurotransmitters mediate CRF-HPA and/or eCRF responses to multiple stressors (including alcohol) in animals [76,104,137] and humans [3,64,151,191]. Furthermore, as mentioned above, sex and gonadal steroids influence CRF-HPA/eCRF function, with males exhibiting, in general, less CRF-HPA stress responsiveness to alcohol and other stressors than females [147,148,156,204,220].

One brain structure that could be important for delineating the neurotransmitter-stress/gonadal steroid interactions underlying sex differences in alcohol dependence with ASPD is the central nucleus of the amygdale (CeA). Recent data suggest that glucocorticoid receptors in the CeA play a 'feed forward' role in stress regulation serving to potentiate HPA responses [78], and glucocorticoid deficits in the CeA have been implicated in the hypoarousal-driven aggression associated with ASPD [70]. The CeA is anatomically connected to putative structures in the alcohol reward system [106,121] and contains neurochemical and neuroendocrine elements that are linked to alcohol dependence with comorbid ASPD (see above). More specifically, the CeA is comprised of GABA and opiate neurons and receptors [200], dense neuroadrenergic and serotonergic inputs [23,47,136], and CRF neurons that are co-localized with glucocorticoid receptors [89]. These CRF neurons receive monoaminergic innervation [23,38,47], and together with opiate neurons may modulate local GABAergic transmission [200]. Furthermore, findings from neuropharmacological and electrophysiological studies in rats point to a more direct association between the CeA and alcohol-related behavior. That is, both GABA and opiate antagonists injected into the CeA selectively decrease acute ethanol self-administration [57,106]. Ethanol self-administration during acute withdrawal is reduced by pretreatment of a GABA agonist directly into the CeA [171]. The anxiogenic effects of ethanol withdrawal are reversed by administration of a CRF antagonist into the CeA [164]. Both acute and chronic ethanol increase GABA transmission and release in the CeA [169,170], the former being mediated by CRF [145]. Finally, in rat, androgen receptors are located in the lateral part of the CeA, which coincides with CRF and monoamine expressing neurons [58,89,188]. Thus, the CeA is a structure that could mediate neurotransmitter-stress/gonadal interactions, but as yet, no research has investigated its integrative role in the development of sex differences in alcohol dependence with ASPD, which is more prominent in males.

8. Summary and conclusions

This review emphasized the role of gonadal hormones, neurosteroids, and stress hormones on sex differences in drinking patterns and other actions of alcohol that emerge at the stage of late puberty. Whereas there is some evidence in adult humans and animals that these hormones influence alcohol consumption and responses in a sex-specific fashion, there are very few studies that have investigated the developmental progression of these sex differences in alcohol drinking behavior and/or the influence of pubertal hormone changes on this process. The new and exciting data on structural and functional rewiring of the brain that occurs during adolescence has sparked renewed interest in the potential organizational role of elevated hormone levels during puberty on remodeling the adolescent brain. These organizational changes result in enduring changes in males and females on a wide range of behaviors. Since adolescence is a time when both males and females are becoming initiated to alcohol and some begin drinking heavily, it is imperative that we begin to understand the mechanisms by which changes in the various hormonal systems at puberty may modify reward circuits during adolescence to promote sex differences in drinking behavior as well as the reciprocal actions of adolescent alcohol exposure on shaping hormonal, brain, and behavioral changes. Some human research on the effects of hormonal exposure of the adolescent brain on sex differences in drinking behavior could be carried out in individuals with delayed or precocious puberty or other hormonal disorders. However, to conduct more controlled studies, it is important that nonhuman primate and rodent models be used to study the effects of hormonal presence or absence during different periods of development, including adolescence, on the structural and neurochemical development of brain reward systems and the resulting sex differences in drinking and dependence liability that emerges in late puberty and persists into adulthood.

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