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SOCIAL CONSEQUENCES OF ETHANOL: IMPACT OF AGE, STRESS AND PRIOR HISTORY OF ETHANOL EXPOSURE

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Abstract

The adolescent period is associated with high significance of interactions with peers, high frequency of stressful situations, and high rates of alcohol use. At least two desired effects of alcohol that may contribute to heavy and problematic drinking during adolescence are its abilities to both facilitate interactions with peers and to alleviate anxiety, perhaps especially anxiety seen in social contexts. Ethanol-induced social facilitation can be seen using a simple model of adolescence in the rat, with normal adolescents, but not their more mature counterparts, demonstrating this ethanol-related social facilitation. Prior repeated stress induces expression of ethanol-induced social facilitation in adults and further enhances socially facilitating effects of ethanol among adolescent rats. In contrast, under normal circumstances, adolescent rats are less sensitive than adults to the social inhibition induced by higher ethanol doses and are insensitive to the socially anxiolytic effects of ethanol. Sensitivity to the socially anxiolytic effects of ethanol can be modified by prior stress or ethanol exposure at both ages. Shortly following repeated restraint or ethanol exposure, adolescents exhibit social anxiety-like behavior, indexed by reduced social preference, and enhanced sensitivity to the socially anxiolytic effects of ethanol, indexed through ethanol-associated reinstatement of social preference in these adolescents. Repeated restraint, but not repeated ethanol, induces similar effects in adults as well, eliciting social anxiety-like behavior and increasing their sensitivity to the socially anxiolytic effects of acute ethanol; the stressor also decreases sensitivity of adults to ethanol-induced social inhibition. The persisting consequences of early adolescent ethanol exposure differ from its immediate consequences, with males exposed early in adolescence, but not females or those exposed later in adolescence, showing social anxiety-like behavior when tested in adulthood. Adult males exposed to ethanol early in adolescence also show enhanced sensitivity to the socially facilitating effects of ethanol, whereas adult males exposed to ethanol during late adolescence demonstrate insensitivity to the socially suppressing effects of ethanol. To the extent that these results are applicable to humans, stressful live events may make alcohol more attractive for stressed adolescents and adults due to its socially facilitating and socially anxiolytic properties, therefore fostering high levels of drinking. Retention of adolescent-typical responsiveness to alcohol in adult males following

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adolescent alcohol exposure, including enhanced sensitivity to the socially facilitating effects of ethanol following early exposure and insensitivity to the socially inhibiting effects following late adolescent exposure, may put these males at risk for the development of alcohol-related disorders later in life.

Keywords

Adolescence; Ethanol; Social Consequences; Stress; Repeated Ethanol Exposure

1. Introduction

In humans, adolescence refers to a transitional period between youth and maturity that occurs predominantly during the second decade of life, although females generally show more rapid maturation than males [1]. This transformation from immaturity to maturity and dependence to independence is a gradual developmental phase than can be seen across different mammalian species [2], with adolescents often differing markedly from those younger or older in terms of responding to a number of stimuli in their environment [3, 4]. While there is no single biological event that signals its onset or offset, adolescence in humans is often considered to subsume the second decade of life, with females tending to mature earlier than males [1]. Some adolescent-typical characteristics have been found to persist into at least the mid-twenties, a period sometimes termed “emerging adulthood” [5, 6]. Likewise, in rats, a conservative age range during which both males and females appear to exhibit adolescent-typical neurobehavioral characteristics has been defined as postnatal (P) day 28–42 [4, 7, 8], although females tend to progress into adolescence slightly earlier, and animals of both sexes, especially males, continue to show signs of adolescence for some time thereafter. Given the broad developmental periods subsumed, adolescence has been subdivided into early, mid and late stages. In humans, these stages are thought to refer to approximately 10–14 years (early), 15–17 years (mid), 18–25 years (late/emerging adulthood) [5, 6], with specific physical, hormonal, and neurobehavioral changes associated with each phase [6]. In rats as well, it has recently been suggested that the period between postnatal day (P) 28 and P42 be considered early-mid adolescence, with the interval between approximately P42 and P55 (or even P65) viewed as more analogous to the late adolescence/emerging adulthood period in humans [9–11].

2. Social interactions during adolescence

The adolescent period is associated with a high significance of interactions with peers and elevated levels of social motivation (see [2] for references). Interactions with peers become particularly important during adolescence, with these interactions not only exerting a greater influence over decision-making and behavior among adolescents than they do among children and adults [12–14], but also providing a significant source of positive experiences [15]. Adolescents spend more time interacting with peers than individuals during any other developmental period [16]. Similarly, during the early adolescent age interval (P28–P35) in the rat, animals demonstrate substantial increases in social activity relative to younger or older animals, particularly the adolescent-characteristic behavior of play fighting [17–19]. Studies using rats have also shown that interactions with peers provide a significant source

of positive experiences [20] and are seemingly more rewarding for adolescents than for their more mature counterparts [3, 21]. The social interaction test has been used extensively for the assessment of anxiety-like behavior in laboratory rodents [22–24]. In the conventional social interaction test, a pair of rats is placed into a testing chamber, and overall time spent in social interactions is used as a dependent variable [22]. Yet, the discrete behavioral acts summed together for these assessments reflect behaviorally distinctive and differentially regulated forms of interactive social behaviors (e.g., social investigation and play fighting) with separable ontogenetic patterns [17, 19, 25] and differential responsiveness to seemingly anxiogenic manipulations [26]. For instance, play fighting exhibits an inverted U-shaped ontogenetic pattern that peaks around P30–35, whereas social investigation increases ontogenetically and represents a more adult-typical form of social interactions [17, 25, 27]. Play fighting, but not social investigation, is drastically increased by deprivation from social contact via isolate housing throughout the entire adolescent period [17, 19], whereas social investigation is exclusively decreased by prior history of exposure to non-social stressors [26, 28]. Taken together, these findings suggest that play fighting and social investigation may be mediated via different neural systems. Modification of the social interaction test, allowing an experimental animal to freely move toward or away from a non-manipulated social partner in a two-compartment testing apparatus, permits assessment of social motivation via a preference/avoidance coefficient in addition to measuring the frequency of play fighting and social investigation [25]. Using this modified social interaction test, we have found decreases in social preference to reflect anxiety-like alterations in social interactions [26, 28–30].

3. Ethanol-induced social facilitation

In humans, first experimentation with alcohol occurs predominantly during early adolescence [31], with underage adolescents drinking about two times more per episode than drinkers of legal age (see [32] for references and review). For instance, approximately 5.1% of 8^{th} graders, 15.6% of 10^{th} graders, and 23.7% of high school seniors in the United States reported a binge pattern of drinking (i.e., 5+ drinks in a row) during the previous two weeks [33], and even more elevated rates of binge drinking are reported among adolescents in many European countries [34]. The impact of social context on adolescent drinking is viewed as particularly important [35], with young individuals typically using alcohol in social situations [36]. Adolescent laboratory rodents also ingest more ethanol on a g/kg basis than adults under various testing conditions [37–45].

Given the importance of interactions with peers during adolescence, it is not surprising that ability of ethanol to facilitate interactions with peers may contribute to heavy drinking during adolescence. Expectancy for social facilitation from drinking is an important predictor of heavy drinking, with adolescent youth believing that alcohol will make them more confident and relaxed in a social setting [46, 47]. Ethanol-induced social facilitation is not restricted to human adolescents but is also evident in a simple model of adolescence in the rat [48]. Adolescent rats tested under familiar, non-anxiogenic circumstances demonstrate increases in social behavior following acute exposure to relatively low doses (0.5–0.75 g/kg) of ethanol, an ethanol-induced facilitation of social behavior that is predominantly characterized by an increase in play fighting and is not normally seen in

adults [18, 48–52]. The doses producing social facilitation in adolescent rats result in blood ethanol concentrations (BECs) from approximately 40 to 80 mg/dl -- within the moderate consumption range in humans [53]. Higher doses of ethanol have different social consequences, producing social inhibition, with adolescent rats being less sensitive to these adverse social effects of ethanol than their more mature counterparts [18].

Considerable ontogenetic differences in the social consequences of acute ethanol are evident even within the adolescent period, with early adolescence being a time when adolescent-typical sensitivities to ethanol are the most pronounced. For instance, young adolescent rats tested at P28 are more sensitive to low dose ethanol-induced social facilitation and less sensitive to the social inhibition evident at higher ethanol doses than animals tested later in adolescence at P42 [50, 54].

This social facilitation is mediated, at least in part, through ethanol-induced release of endogenous ligands for the mu-opioid receptor (MOR) or an ethanol-associated enhancement of sensitivity of these receptors to their endogenous ligands, since the facilitation of play fighting by low doses of ethanol can be attenuated by the nonselective opioid antagonist naloxone, as well as by the selective MOR antagonist CTOP [55]. This finding was not surprising, given that the MOR system is implicated in modulation of play behavior, with selective MOR agonists increasing play fighting in young adolescent males and antagonists suppressing this form of social behavior (see [56] for references and review). While the endogenous MOR system plays a considerable role in facilitation of play fighting by ethanol [55], other neural systems are implicated in ethanol-associated modulation of play fighting as well. For instance, social behavior during adolescence can be facilitated by cannabinoid agonists [57, 58, 59], whereas CB1 receptor antagonists are able to diminish ethanol-induced facilitation of play behavior during early adolescence [49]. Play fighting in adolescent rats is also under inhibitory control of the NMDA system, with NMDA antagonists facilitating play fighting at low doses, but suppressing social behavior at higher doses [60] – biphasic effects on play fighting similar to those induced by ethanol [18, 50]. The NR2B subunit of the NMDA receptor may play a particularly important role, given that a selective NR2B antagonist, ifenprodil, was found to facilitate play fighting in a manner similar to that produced by low doses of less selective NMDA antagonists as well as ethanol [61].

4. Stress-related alterations

Sensitivity to the social consequences of ethanol can be modified by prior stress in adolescents and adults, although effects of stress on both social behavior and ethanol sensitivity are age-dependent. Exposure to repeated restraint (5 days, 90 min/day) during mid-late adolescence and adulthood induces anxiety-like behavioral alterations, indexed via significant decreases in social preference [26, 28, 62]. Repeated restraint stress exacerbated adolescent-typical responsiveness to the social consequences of acute ethanol in mid-adolescent animals tested after the last stressor exposure at P35, enhancing responsiveness to ethanol-induced facilitation of play fighting and further accentuating adolescent-typical insensitivities to the socially suppressing effects of ethanol [28]. Surprisingly, among late adolescents and adults (tested following the final stressor at P42 or P70, respectively),

repeated exposure to the stressor reinstated a pattern of responsiveness to the social consequences of ethanol characteristic of younger animals. Specifically, these stressed late adolescents and adults demonstrated both: (a) ethanol-induced facilitation of play fighting not evident in non-stressed controls, as well as (b) an attenuated sensitivity to the social inhibition seen at higher ethanol doses relative to their non-stressed age-mates [28, 62]. These stress effects were evident in both males and females. Ethanol-induced increases in play fighting were not associated with any increases in locomotor activity when indexed via total number of crossovers in the social test context, suggesting that these activating effects of ethanol reflect ethanol-induced facilitation of social behavior per se rather than more general activation [28, 62].

Importantly, repeated restraint in mid-late adolescent and adults also induced anxiety-like behavioral alterations under social test circumstances, as indexed by decreases in social preference [28, 62]. These decreases in social preference were effectively attenuated by acute ethanol in animals of both ages. The anxiolytic effects were not evident in non-stressed controls under social test circumstances, suggesting a stress-associated enhancement of sensitivity to the socially anxiolytic effects of ethanol. This apparent stress-associated enhancement of sensitivity to ethanol anxiolysis may be related in part to stress-induced alterations in the $GABA_A$ receptor system, a neural system shown to contribute to a number of ethanol effects [63–65], including its anxiolytic properties [53]. $GABA_A$ receptors with different subunit composition appear to differentially contribute to various ethanol effects, with α1 subunits playing a role in ethanol-induced sedation and motor impairment [66], and α2/α3 subunits implicated in anxiolytic effects of ethanol [67]. Exposure to stressors has been shown to increase expression of α2 subunits in brain regions associated with anxiety [68], and these stress-associated changes in $GABA_A$ subunit expression may play a role in the enhanced sensitivity to the anxiolytic effects of ethanol observed in adolescents and adults.

Among early adolescents, effects of repeated restraint stress on social behavior and alterations in sensitivity to the social consequences of acute ethanol differed drastically relative to those discussed above in older adolescents and adults [62]. Unlike their older counterparts, young adolescents tested at P28 after receiving repeated restraint during the juvenile period (P24–P28) showed no attenuation in social preference. Instead, early adolescent males responded to the prior stressor exposure with a notable enhancement in baseline levels of play fighting – an effect of prior restraint not evident in early adolescent females. One of the possible explanations of these drastic age differences in the consequences of repeated restraint is that the early adolescent males tested at P28 do not respond to anxiety-provoking manipulations in a way their older counterparts do. It is unlikely, however, given that early adolescent rats, similar to their more mature counterparts, respond to a novel, anxiety-provoking test situation by transformation of social preference into social avoidance [19, 50].

An alternative possibility is that juvenile males perceived the 90-min periods of restraint as significant social deprivation. Indeed, repeated social deprivation (90 min/day for 5 days) was found to produce increases in play fighting in early-mid adolescent males, but not their female counterparts [26], with the most pronounced activating effects on play fighting

evident following social deprivation between P23 and P28 [19]. Similarly, sex differences in play fighting have been reported for socially deprived juvenile rats, with males engaging in more play fighting than females (see [17] for references and review). Taken together, these findings suggest that during the developmental period transitioning into early adolescence, males are more sensitive than females to the activating effects of social deprivation on play fighting. Interestingly, stressful events that occur even earlier in ontogeny can also enhance play fighting in young adolescents. For instance, maternal separation (3 hr/day for 14 days) during the preweanling period was observed to increase play fighting in males tested at P35 [69]. Therefore, adverse early experiences that include social deprivation are likely to enhance the adolescent-typical social behavior of play fighting in male rats.

In the rat, the developmental period between weaning and P28 corresponds to the pre-pubertal or juvenile stage of development in both males and females [10, 11]. Some researchers suggest that pre-pubertal rats differ noticeably in their responsiveness to stress relative to post-pubertal, adult rats [70–73]. Pre-pubertal stress has been shown to have long-lasting consequences: alterations in stress responsiveness in adulthood were evident following even a brief, acute stress exposure on P28 [74]. Furthermore, pre-pubertal stress enhanced anxiety-like behavior and substantially reduced exploratory behavior in adulthood [75, 76]. However, when these young animals were tested immediately after exposure to stressors, they demonstrated increases in exploratory behavior [77] and decreases in anxiety [78], findings that are reminiscent of the immediate social consequences of repeated restraint at this age.

Repeated restraint stress not only elevated baseline levels of play fighting in P28 males, but also eliminated sensitivity to the stimulatory effects of ethanol, with no ethanol-induced facilitation of play fighting evident at any dose. The lack of ethanol-induced facilitation of play fighting in stressed P28 males is likely related, at least in part, to the dramatic stress-associated increase in baseline levels of this adolescent-characteristic form of social interactions from which it might be difficult to see further stimulatory effects [62]. Indeed, among P28 females (where repeated restraint did not influence baseline levels of play fighting), ethanol-associated facilitation of play fighting was still evident, although they required a higher ethanol dose relative to their non-stressed counterparts for this effect to emerge (1.0 g/kg versus 0.5 g/kg).

As mentioned earlier, ethanol-induced social facilitation seen normally during early-mid adolescence appears to be associated, at least in part, with ethanol-related activation of the endogenous MOR system [55], with presumably more pronounced ethanol-associated activation of the endogenous MOR system in young than older adolescents and adults. The increase in sensitivity to the socially facilitating effects of ethanol induced by repeated restraint in older adolescents and adults may also be in part due to stress-induced activation of this MOR system as well [79–82]. A number of other neural systems, including endogenous cannabinoid [49, 58] and NMDA [60, 61] receptor systems may also contribute to stress-induced alterations in play fighting observed in young adolescent males and developmental alterations in sensitivity to the effects of ethanol on social behavior, given their involvement in modulation of play fighting under normal conditions as discussed earlier.

5. Alterations associated with repeated ethanol: Immediate and delayed consequences

Baseline levels of anxiety in adolescents of both sexes were increased not only by repeated restraint stress during adolescence, but also by repeated exposure to ethanol at this time. This elevation in anxiety-like behavior (reflected by significant decreases in social preference) was seen in adolescent but not adult animals in the social interaction test following chronic ethanol exposure (1 g/kg, i.p. for 7 days; P27–P33 for adolescents and P62–P68 for adults) [51]. This suppression in social preference was reversed by acute ethanol challenge in adolescent animals. Such social anxiety seen among adolescent animals with a history of ethanol exposure may be related at least in part to ethanol-induced disruptions in neural substrates underlying social behavior. Although experimental studies that specify neural substrates critical for peer-directed social interactions and motivation for social contacts remain limited, recent findings have revealed that frontal cortical regions, the amygdala, and ventral hippocampus, are involved in the modulation of peer-directed social behavior [83, 84], as well as in generating and regulating anxiety-like responses (see [85] for review). These brain regions undergo considerable remodeling during adolescence [2, 3, 86, 87] and likely contribute to elevations in anxiety-like behavior following not only chronic adolescent alcohol exposure but repeated restraint as well.

In the Varlinskaya and Spear [51] study, however, animals were injected intraperitoneally, exposed to ethanol daily and tested 48 hours following the last ethanol exposure, and hence it was not clear whether the social anxiety-like behavior and changes in ethanol sensitivity induced by repeated ethanol in adolescents are short-lasting and associated merely with ethanol withdrawal or whether they persist and can be detected later in life. In subsequent work, we examined delayed social consequences after an adolescent intermittent ethanol exposure (AIE) regimen (3.5 g/kg intragastrically, every other day for a total of 11 exposures), given that intermittent exposures have been shown to produce more pronounced consequences than continuous (daily) exposures [88, 89]. Animals were assessed in the social interaction test 25 days after early-mid adolescent exposure (early AIE): P25–P45; or late adolescent exposure (late AIE): P45–65, Significant anxiety-like social alterations were evident in adult male rats tested at P70, but not their female counterparts following early AIE, whereas neither males nor females demonstrated these alterations 25 days following late AIE, suggesting that early, but not late adolescence is the critical period for induction of long-lasting social consequences by repeated ethanol [90]. To the extent that our experimental findings are applicable to humans, the results of this study [90] suggest that young adolescent males are more vulnerable to the harmful effects of ethanol exposure than their female counterparts, in that social anxiety-like behavioral alterations were evident only in males following early AIE.

To a large extent, the studies that have assessed long-lasting anxiety-like alterations induced by AIE have included only male subjects. However, the inclusion of female subjects in such studies is important, given human data regarding gender differences in prevalence of alcohol use disorders and in negative consequences of excessive alcohol use [91, 92]. Indeed, adult women consume less alcohol and have fewer alcohol-related problems than men, with

18.6% of men and 8.4% of women demonstrating a lifetime prevalence for alcohol dependence [93]. However, the rate of alcohol use disorders is not different between boys and girls aged 12 to 17 [92]. Taken together, these observations suggest that adolescent males are at higher risk to become alcohol-dependent later in life than adolescent females.

One of the possible explanations of the sex differences in the social anxiogenic consequences of early AIE is that adolescent females may be less sensitive to ethanol-associated alterations within the brain systems implicated in modulation of anxiety-like behavior. Indeed, prior work examining the effects of intraperitoneal exposure to ethanol in adolescence on gene expression of two critical regulators of stress and anxiety in the paroventricular nucleus likewise reported increased corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) gene expression in males, but not females [94]. Neuroactive steroids may play a role in the greater protection of the female than the male brain from the detrimental effects of ethanol during adolescence. Progesterone-derived neurosteroids are present at higher levels in females than males [95, 96] and have been shown to have anxiolytic effects in a number of behavioral paradigms [97–100]. Therefore, higher levels of endogenous neurosteroid anxiolytics in adolescent females, relative to their male counterparts, may play a substantial role in protecting these females from ethanol-induced social anxiety-like behavioral alterations during AIE.

Effects of AIE on later sensitivity to the social consequences of acute ethanol challenge also were sex-specific. That is, AIE females showed little, if any, change in sensitivity to the social consequences of acute ethanol challenge, whereas both early and late AIE influenced ethanol sensitivity of males tested 25 days after AIE, although these effects differed as a function of AIE timing [90]. On the one hand, male rats exposed to ethanol during early adolescence and tested as adults showed ethanol-induced social facilitation, whereas controls demonstrated only the adult-typical inhibition of social behavior following acute ethanol challenge. This social facilitation is reminiscent of that seen normally during adolescence [18, 50], and hence is consistent with the prior suggestion that repeated exposure to ethanol during early adolescence may in some cases “preserve” an adolescent-like phenotype, including adolescent-typical ethanol sensitivities in adulthood (e.g., [101] see [102] for review). Surprisingly, anxiety-like social alterations (indexed via decreases in social preference) were not reversed by ethanol in the early AIE males. Taken together with the previous findings, these data suggest that social consequences of adolescent ethanol exposure evident in adulthood appear to differ from those observed in adolescents shortly after ethanol withdrawal. In adult males, prior early AIE resulted in the enhancement of sensitivity to the socially facilitating, rather than an enhancement of socially anxiolytic effects of ethanol that are seen during the withdrawal phase. Socially facilitating effects of ethanol have been found to be related to ethanol-induced activation of the endogenous MOR system [55] as well as NMDA receptor antagonism [61], whereas ethanol anxiolysis is generally thought to reflect interactions with the $GABA_A$ receptor system [53, 67].

In contrast to the preservation of adolescent-typical ethanol sensitivities in adult males after early adolescent ethanol exposure, adult males exposed to ethanol later in adolescence varied from their control counterparts in being notably insensitive to the socially suppressing effects of acute ethanol challenge [90]. This insensitivity to ethanol-induced social inhibition

suggests that these males may have developed chronic tolerance to the social consequences of ethanol, with this tolerance still evident 25 days after repeated exposure to ethanol. This tolerance appears functional rather than metabolic in nature, given that post-test BECs were comparable among previously ethanol-exposed and non-exposed animals. These findings are reminiscent of those reported by Sherill et al. [103], who found adolescent ethanol exposure to attenuate later sensitivity to aversive effects of ethanol in males but not females tested approximately nine weeks following adolescent exposure.

Summary

Taken together, these results demonstrate that repeated restraint stress or ethanol exposure has immediate consequences during adolescence that are evident in terms of increases in social anxiety-like behavior (indexed by notably reduced baseline levels of social preference), with acute ethanol effectively restoring social preference in these adolescents. Therefore, stressful life events as well as a history of early exposure to ethanol may foster high ethanol intake levels during adolescence in part via inducing anxiety in a social context that can be efficiently counteracted by socially anxiolytic consequences of ethanol. In adults, repeated exposure to different stressors may attenuate their sensitivity to socially adverse effects of ethanol, while making alcohol more attractive for stressed adults due to its socially facilitating and socially anxiolytic properties.

The long-lasting effects of adolescent ethanol exposure, however, differ from its immediate consequences. Young adolescent males, but not their female counterparts, are particularly vulnerable to long-lasting detrimental effects of repeated ethanol. Retention of adolescent-typical sensitivity to socially facilitating properties of ethanol could make ethanol especially appealing to these males, therefore promoting drinking later in life. Late adolescent males may be at high risk for the development of alcohol-related disorders later in life as well, given their enhanced ability to develop long-lasting chronic tolerance to the socially inhibiting effects of ethanol – tolerance that could permit ingestion of relatively large amounts of ethanol with limited negative consequences.

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Highlights

- Socially facilitating and anxiolytic effects of ethanol contribute to drinking.
- Adolescents and adults are differentially sensitive to these ethanol properties.
- Prior exposure to stress or ethanol can modify sensitivity to these social effects.
- Early and late adolescents respond differently to repeated ethanol.
- Persisting effects of repeated adolescent ethanol exposure are seen in males only.