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Social consequences of ethanol: Impact of age, stress, and prior history of ethanol exposure

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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.

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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 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.

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

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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) days 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), and 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–P35, 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 8th graders, 15.6% of 10th 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 2 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 gram-per-kilogram 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 [57–59], 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