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Chronic intermittent ethanol exposure during adolescence: Effects on stress-induced social alterations and social drinking in adulthood

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ABSTRACT

We previously observed lasting and sex-specific detrimental consequences of early adolescent intermittent ethanol exposure (AIE), with male, but not female, rats showing social anxiety-like alterations when tested as adults. The present study used Sprague Dawley rats to assess whether social alterations induced by AIE (3.5 g/kg, intragastrically, every other day, between postnatal days [P] 25–45) are further exacerbated by stressors later in life. Another aim was to determine whether AIE alone or in combination with stress influenced intake of a sweetened ethanol solution (Experiment 1) or a sweetened solution ("supersac") alone (Experiment 2) under social circumstances. Animals were exposed to restraint on P66–P70 (90 min/day) or left nonstressed, with corticosterone (CORT) levels assessed on day 1 and day 5 in Experiment 2. Social anxiety-like behavior emerged after AIE in non-stressed males, but not females, whereas stress-induced social anxiety was evident only in water-exposed males and females. Adult-typical habituation of the CORT response to repeated restraint was not evident in adult animals after AIE, a lack of habituation reminiscent of that normally evident in adolescents. Neither AIE nor stress affected ethanol intake under social circumstances, although AIE and restraint independently increased adolescent-typical play fighting in males during social drinking. Among males, the combination of AIE and restraint suppressed "supersac" intake; this index of depression-like behavior was not seen in females. The results provide experimental evidence associating adolescent alcohol exposure, later stress, anxiety, and depression, with young adolescent males being particularly vulnerable to long-lasting adverse effects of repeated ethanol.

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1. Introduction

Alcohol use typically begins early in adolescence (Faden, 2006). This use differs from that of adults, with adolescents drinking on average twice as much per drinking episode than adults (Substance Abuse and Mental Health Services Administration, 2008). This intake sometimes reaches high levels, with 23.7% of high school seniors in the United states reporting consumption of 5+drinks (Johnston et al., 2013), >10% reporting consumption of 10+drinks and >5% reporting 15+drink consumption (Patrick et al., 2013) per drinking episode in the past 2 weeks.

Studies in laboratory animals such as the rat have likewise revealed 2–3 fold higher ethanol consumptions during adolescence than in adulthood (Doremus et al., 2005; Hargreaves et al., 2011; Schramm-Sapyta et al., 2014; Vetter-O'Hagen et al., 2009), suggesting that the elevated ethanol intake of adolescents may have a biological component. Indeed, studies in rats have revealed a number of potential contributors to elevated adolescent intake, including notable differences between adolescents and adults in their sensitivity to the acute effects of ethanol. For instance, adolescents show social facilitation in response to low doses of ethanol that is not seen in adults (Varlinskaya and Spear, 2002) and are also more sensitive than adults to ethanol's rewarding effects (e.g., Pautassi et al., 2008); these effects may make ethanol particularly desirable for adolescents. On the other hand, adolescents are less sensitive than adults to the social impairing, motor disrupting, aversive and sedative effects of higher doses of ethanol (Anderson et al., 2010; Ramirez and Spear, 2010; Silveri and Spear, 1998; Varlinskaya and Spear, 2002) – effects of ethanol likely serving to moderate drinking. This combination of age-dependent ethanol sensitivities appears to be associated with differential rates of development of neural systems underlying these ethanol effects (see Spear, 2014, for discussion). Although comparable studies in humans are not surprisingly limited due to ethical constraints regarding administration of ethanol to youth, what findings are available provide suggestions of similar age-related ethanol sensitivities in human adolescents that may help drive the elevated consumption levels characteristic of this age period (for review, see Spear, under revision).

The early initiation and relatively high use levels of alcohol by adolescents could potentially disrupt maturational changes occurring in the brain at this time in regions such as those critical for cognitive control (Casey et al., 2008), motivational responding and the processing of rewarding, arousing, aversive, social and emotional stimuli (Blakemore, 2012; Ernst and Fudge, 2009). Indeed, early onset of drinking has been found to be predictive of alcohol-related problems later in life (Grant and Dawson, 1997; Palmer et al., 2009), with those engaging in even episodic heavy drinking at an early age being more likely to develop alcohol use disorders (Bonomo et al., 2004; Hingson et al., 2006; Grant et al., 2001) and to experience a number of long-lasting adverse psychosocial consequences (Wells et al., 2004). Although these associations are not necessarily causal (Black et al., 2015; Edwards et al., 2014), evidence is emerging that binge patterns of adolescent drinking that bring blood alcohol levels to 80 mg/dl and higher can be disruptive to the developing adolescent brain (Bava and Tapert, 2010; Silveri, 2012; Spear, 2015).

Given developmental changes in alcohol-sensitive brain circuits implicated in responsiveness to social and emotional stimuli (e.g., Blakemore, 2012; Spear, 2011), it is not surprising, therefore, that anxiety, depression, and enhanced stress reactivity have often been associated with alcohol-dependency in adolescents (Martin et al., 2000). Alcohol-related problems are often evident in anxious adolescents, with social anxiety disorder sometimes noted as a particular vulnerability factor (Black et al., 2015; Buckner et al., 2006), however, causal relationships are still not fully established (e.g., Morris et al., 2005). For instance, social anxiety has been reported to often precede alcohol use disorders (Buckner et al., 2008). Sex differences are sometimes apparent, with anxiety disorders in early adolescence associated with later adolescent alcohol use in females but not males (Zehe et al., 2013). Conversely, there is also evidence that alcohol abuse can promote later expression of anxiety disorders (e.g., Falk et al., 2008; Kushner et al., 2000), with alcohol use disorders preceding the onset of anxiety more often in males than in females (Falk et al., 2008). Bi-directional associations between anxiety disorders and alcohol use could initiate a "feed-forward cycle", with anxiety symptoms inducing alcohol use for its anxiolytic effects, whereas increasing use of alcohol may further enhance anxiety symptoms (see Kushner et al., 2000).

The relationship between adolescent anxiety and alcohol use disorders is even more complicated, given emerging evidence pointing to a substantial role of stress (negative life events) in both affective disorders and adolescent alcohol use (Fidalgo et al., 2008; Lopez et al., 2005; Low et al., 2008; Rutledge and Sher, 2001; Schmidt et al., 2007). Given that the developmental transition from immaturity/dependence to maturity/independence is often stressful, it is not surprising that adolescents have been reported to experience more stressors and negative life events than either children or adults (Buchanan et al., 1992). An increased prevalence of stressors during this ontogenetic period, when combined with enhanced stress reactivity relative to other ages (Dahl and Gunnar, 2009), may contribute to the onset of psychiatric problems during adolescence. Indeed, strong associations have been reported between adolescent stress and the emergence of anxiety disorders (Barrocas and Hankin, 2011; Grant et al., 2003; Oldehinkel and Bouma, 2011). Although the relationship between alcohol use and stressful life events has been shown to be quite complex (Uhart and Wand, 2009), it has been suggested that stress is most strongly associated with heavy drinking in adolescence, with this association becoming considerably weaker later in life (Aseltine and Gore, 2000).

Human studies of the consequences of underage alcohol use do not permit systematic manipulation of critical variables, due to ethical considerations that preclude administration of alcohol to young adolescents. Similarities found between human adolescents

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