Pharmacology, Biochemistry and Behavior 133 (2015) 65–82

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Review

Alcohol use across the lifespan: An analysis of adolescent and aged rodents and humans

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ARTICLE INFO

Article history:
Received 16 April 2014
Received in revised form 26 January 2015
Accepted 20 March 2015
Available online 2 April 2015

Keywords:
Alcohol
Adolescent
Aged
Cognition
Motor

ABSTRACT

Adolescence and old age are unique periods of the lifespan characterized by differential sensitivity to the effects of alcohol. Adolescents and the elderly appear to be more vulnerable to many of alcohol's physiological and behavioral effects compared to adults. The current review explores the differential effects of acute alcohol, predominantly in terms of motor function and cognition, in adolescent and aged humans and rodents. Adolescents are less sensitive to the sedative-hypnotic, anxiolytic, and motor-impairing effects of acute alcohol, but research results are less consistent as it relates to alcohol's effects on cognition. Specifically, previous research has shown adolescents to be more, less, and similarly sensitive to alcohol-induced cognitive deficits compared to adults. These equivocal findings suggest that learning acquisition may be differentially affected by ethanol compared to memory, or that ethanol-induced cognitive deficits are task-dependent. Older rodents appear to be particularly vulnerable to the motor- and cognitive-impairing effects of acute alcohol relative to younger adults. Given that alcohol consumption and abuse is prevalent throughout the lifespan, it is important to recognize age-related differences in response to acute and long-term alcohol. Unfortunately, diagnostic measures and treatment options for alcohol dependence are rarely dedicated to adolescent and aging populations. As discussed, although much scientific advancement has been made regarding the differential effects of alcohol between adolescents and adults, research with the aged is underrepresented. Future researchers should be aware that adolescents and the aged are uniquely affected by alcohol and should continue to investigate alcohol's effects at different stages of maturation.

Contents

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http://dx.doi.org/10.1016/j.pbb.2015.03.015
0091-3057/

1. Introduction

Alcohol is the most widely consumed recreational drug across the globe (Ferreira and Willoughby, 2008). The World Health Organization estimates that approximately two billion people worldwide are regular consumers of alcohol ("Global Status Report on Alcohol 2004," 2004). In the Unites States, approximately 65.44% of Americans over the age of 18 currently consume alcohol according to findings from the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Furthermore, a startling 12.92% meet the diagnostic criteria for either alcohol abuse or dependence (Chen, 2006). Since alcohol can have devastating consequences on society in terms of morbidity and mortality ("Global Status Report on Alcohol 2004," 2004), it is important to explore alcohol's influence in consumers of all ages. Although alcohol produces differential effects by age, the mechanism of action remains relatively stable throughout the lifespan. Ethyl alcohol is a small, polar molecule that is completely water soluble (Ramchandani et al., 2001). Once consumed orally, alcohol is rapidly absorbed from the stomach, duodenum, and small intestine and introduced to all fluid compartments of the body via passive diffusion (for review, see Norberg et al., 2003). Alcohol readily crosses the blood–brain-barrier and has been shown to influence neuronal proteins, ligand-gated ion channels and second-messenger systems, and neurotransmitter receptors (Crews et al., 1996; Faingold et al., 1998; Harris, 1999; Koob, 1996; Narahashi et al., 2001).

The effects of acute alcohol have been well established in adult humans and rodents. As a central nervous system depressant, alcohol acts as an anxiolytic, sedative-hypnotic, anticonvulsant, and memory disruptor (for review, see Eckardt et al., 1998). It is well recognized that acute alcohol produces marked impairments in learning and memory processes (White et al., 2000b). Adult humans show deficits in cognitive tasks such as those assessing semantic memory, verbal fluency, information-processing, working memory, and attention and planning, following consumption of alcohol (Acheson et al., 1998; Dry et al., 2012; Lister et al., 1991; Mungas et al., 1994; Peterson et al., 1990; Saults et al., 2007; Schweizer et al., 2005; Weissenborn and Duka, 2003). Notably, many of these cognitive deficits occur with quantities of alcohol near or below the legal drinking limit. For instance, impairments in working memory and processing speed are observed in adult humans at blood alcohol levels as low as 0.048% (Dry et al., 2012). Similarly, moderate alcohol doses ranging from 0.6 to 0.8 g/kg produce impairments in both male and female adults in tasks of semantic and figural memory, short- and long-term visual memory, explicit recall, and executive functions (Acheson et al., 1998; Dry et al., 2012; Lister et al., 1991; Saults et al., 2007; Schweizer et al., 2005; Weissenborn and Duka, 2003). Psychomotor performance is also negatively affected by acute ethanol (Brumback et al., 2007; Wang et al., 1992). In general, 0.4 g/kg ethanol appears to be the threshold dose for psychomotor impairments (Eckardt et al., 1998), and doses below 0.4 g/kg have little influence on human performance (Brumback et al., 2007; Hindmarch et al., 1991; Lister et al., 1991). In contrast, a significantly higher dose of alcohol may be required to produce impairments in spatial tasks. Mean blood alcohol levels of approximately 0.10 g/dl failed to impair spatial working memory or complex spatial problem solving in male and female adults when examined between 40 and 180 min after consumption (Dry et al., 2012; Weissenborn and Duka, 2003). Furthermore, cognitive processes may show differential impairment during the rising and falling limbs of the blood alcohol curve (Schweizer et al., 2005). Thus, the cognitive-impairing effects of alcohol are differentially affected by dose, time of assessment, and specific cognitive domain of interest.

Acute ethanol produces similar cognitive and motor impairments in adult rodents. Robust findings indicate that spatial learning and memory, in particular, is sensitive to acute ethanol. Frequently, ethanol is administered via i.p. injection and spatial performance is assessed in tasks such as the water maze and radial arm maze 30 min post-injection. Using these methods, deficits in spatial cognition have been observed at doses equal to or exceeding 1.25 g/kg ethanol in adult rodents (Acheson et al., 2001; Berry and Matthews, 2004; Chin et al., 2010; Gibson, 1985; Givens, 1995; Matthews et al., 1995, 1999, 2002; Matthews and Silvers, 2004; Wright et al., 2003). Spatial impairments are not seen following doses equal to or below 1.0 g/kg ethanol (Acheson et al., 2001; Matthews et al., 2002; Novier et al., 2012). In contrast, working memory deficits are observed at lower doses of ethanol; Givens and McMahon (1997) reported that doses as low as 0.75 g/kg acute ethanol resulted in task impairments consistent with working memory and attention deficits in adult rats. Furthermore, acute ethanol impairs rodent motor functioning on tasks including the tilting plane, accelerating rotarod, and aerial righting reflex (Gallate et al., 2003; Van Skike et al., 2010; White et al., 2002b). Typically, ataxia is observed in adult rodents at doses of 1.5 g/kg ethanol or greater when administered via i.p. injection (Van Skike et al., 2010; White et al., 2002b). Therefore, comparable to research with humans, the effects of ethanol on behavior vary according to the dose and task employed. The adverse effects of long-term alcohol consumption have also been thoroughly examined in human adults. Chronic, heavy drinking has been shown to cause decreases in overall brain mass and atrophy of underlying brain structures including the cortex, hippocampus, and cerebellum (Beresford et al., 2006; Cala et al., 1978; Harper and Kril, 1985; Kril et al., 1997; Pfefferbaum et al., 1992; Torvik and Torp, 1986). Accordingly, long-term alcohol use causes cognitive deficits in tasks of working memory (Ambrose et al., 2001), problem-solving (Beatty et al., 1993), visuospatial perception (Beatty et al., 1996; Errico et al., 1991), and executive functioning (Pitel et al., 2007). Similarly, impairments in motor skills such as coordination, balance, and gait are also observed in human alcoholics (Sullivan et al., 2000; York and Biederman, 1991). Although no absolute threshold for alcohol-induced damage to occur has been identified, it appears that dose, duration, and pattern of alcohol consumption mediate injury from chronic alcohol (Hayes et al., 2013). Human studies reporting cognitive decline from excessive drinking often assess participants who consumed alcohol for an average of twenty years, upwards of 19 standard drinks per day (Ambrose et al., 2001; Pitel et al., 2007). However, lower quantities of alcohol have been shown to result in moderate cognitive deficits. Parsons and Nixon proposed that individuals meeting a threshold quantity of five or more standard drinks per occasion for at least five days a week for one year may experience some deficits in cognitive performance. Cognitive deficits become more probable and potentially greater with increasingly higher quantities of alcohol consumption (Parsons and Nixon, 1998). Fortunately, many domains of cognition appear to be partially or fully reversible with periods of abstinence (Brandt et al., 1983; Fein et al., 2006; Mann et al., 1999). Still, some aspects of cognition, such as spatial processing, have been shown to persist for as long as six years after abstinence (Fein et al., 2006).

Consistent with findings with humans, rodents treated with chronic ethanol also show distinct changes in brain morphology and function. Chronic ethanol treatment has been shown to cause cell death and structural alterations in the olfactory bulb, cortex, and hippocampus of adult rodents (Crews et al., 2000; Franke et al., 1997; King et al., 1988; Lukoyanov et al., 1999; Obernier et al., 2002a,b; Paula-Barbosa et al., 1993; Riley and Walker, 1978; Walker et al., 1980). Commonly, chronic ethanol is administered to rodents using liquid ethanol diet (or ethanol in tap water) and dependence is initiated in 14 days or less using this method (Devaud et al., 1997; Harris et al., 1984; Lal et al., 1991; Morrow et al., 1992). However, research with rodents suggests that a binge-like pattern of ethanol exposure may enhance the likelihood of neural damage (Hunt, 1993). Indeed, neurodegeneration has been observed in the cortico-limbic regions in as few as four days when ethanol is administered multiple times a day via gavage (Crews et al., 2000; Obernier et al., 2002a). Moreover, a recent study suggests that brain damage may occur in rats following a single day of binge ethanol exposure. Hayes et al. (2013) exposed adult male Sprague–Dawley rats to 25% ethanol diet intragastrically every 8 h for either one or two days. Animals