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Scheduled access alcohol drinking by alcohol-preferring (P) and high-alcohol-drinking (HAD) rats: Modeling adolescent and adult binge-like drinking

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ABSTRACT

Binge alcohol drinking continues to be a public health concern among today's youth and young adults. Moreover, an early onset of alcohol use, which usually takes the form of binge drinking, is associated with a greater risk for developing alcohol use disorders. Given this, it is important to examine this behavior in rat models of alcohol abuse and dependence. Toward that end, the objective of this article is to review findings on binge-like drinking by selectively bred alcohol-preferring (P) and high-alcohol-drinking (HAD) lines of rats. As reviewed elsewhere in this special issue, the P line meets all, and the HAD line meets most, of the proposed criteria for an animal model of alcoholism. One model of binge drinking is scheduled ethanol access during the dark cycle, which has been used by our laboratory for over 20 years. Our laboratory has also adopted a protocol involving the concurrent presentation of multiple ethanol concentrations. When this protocol is combined with limited access, ethanol intake is maximized yielding blood ethanol levels (BELs) in excess, sometimes greatly in excess, of 80 mg%. By extending these procedures to include multiple scheduled ethanol access sessions during the dark cycle for 5 consecutive days/week, P and HAD rats consume in 3 or 4 h as much as, if not more than, the amount usually consumed in a 24 h period. Under certain conditions, using the multiple scheduled access procedure, BELs exceeding 200 mg% can be achieved on a daily basis. An overview of findings from studies with other selectively bred, inbred, and outbred rats places these findings in the context of the existing literature. Overall, the findings support the use of P and HAD rats as animal models to study binge-like alcohol drinking and reveal that scheduled access procedures will significantly increase ethanol intake by other rat lines and strains as well.

Introduction

A majority of adult Americans have a family member with an alcohol use disorder (AUD) (Research Society on Alcoholism, 2009). Moreover, close to half of adults in the US meeting life-time diagnostic criteria for alcohol dependence do so by the age of 21, and this percentage increases to approximately two-thirds by the age of 25 (Hingson, Heeren, & Winter, 2006). Today's youth are initiating alcohol use earlier and experiencing more alcohol-related problems than ever before (Bava & Tapert, 2010; Gore et al., 2011; Miller, Naimi, Brewer, & Jones, 2007; Miller, Turner, & Marlatt, 2001; Pitkänen, Lyyra, & Pulkkinen, 2005; Quine & Stephenson, 1990; Winters, 2001). Also, approximately 80% of US high school seniors have consumed alcohol, with half initiating drinking before the 8th grade (Johnston, O'Malley, & Bachman, 1999). This is alarming since an early onset of alcohol use is a predisposing factor for developing alcohol dependence (Anthony & Petronis, 1995; Chou & Pickering, 1992; Clark, Kirisci, & Tarter, 1998; Grant & Dawson, 1997; Hawkins et al., 1997).

Binge alcohol drinking (defined in general terms as consuming 4–5 drinks in ~2-h period) and achieving blood ethanol levels of 80 mg% or more (NIAAA, 2004) appears to be a behavior primarily engaged in by adolescents and young adults (<24 years old) compared with older adults (c.f., Courtney & Polich, 2009; Marczinski, Grant, & Grant, 2009; Martinic & Measham, 2008; Plant & Plant, 2006). In the US, close to 30% of high school seniors engage in binge drinking (Johnston, O'Malley, & Bachman, 1991, 1993), with 70% of college students having engaged in this behavior during high school (Wechsler, Lee, Kuo, & Lee, 2000). It has been estimated that greater than 1 out of 3 male college students in the US engage in binge drinking and that a significant proportion of these achieve blood alcohol concentrations (BACs) between 100 and 200 mg% (e.g., Wechsler et al., 2000; White, Kraus, & Swartzwelder, 2006). The seriousness of this problem is underscored by the fact that adolescents drink 11 percent of all alcohol consumed in the US, with practically all of it consumed in the form of binge drinking (NIAAA, 2012). As discussed by L.P. Spear (2010),

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Table 1
Estimated parallel ages[a] between the rat, associated developmental stage, and the human equivalent (Adapted from Bell et al., 2013).

Rat ages [post-natal days (PNDs)]								
PNDs 1–7	PNDs 8–21	PND 21	PNDs 22–27	PNDs 28–42	PNDs 43–60	PNDs 61–75	PNDs 76–90	PNDs 90–
Male 6–15 g	16–40 g	40 g	40–70 g	70–155 g	155–260 g	260–335 g	335–390 g	390–
Female 6–15 g	16–38 g	38 g	38–65 g	65–130 g	130–180 g	180–210 g	210–250 g	250–
Human ages								
Neonate	Prejuvenile	Weaning	Juvenile	Adolescent	Peri-adolescent	Early young adult	Young adult	Adult
−3 to 0 Months	0–6 Years	6 Years	7–12 Years	13–18 Years	18–21 Years	21–24 Years	25–28 Years	28 Years–

[a] Because most rat studies do not list age but many do provide body weights, estimated rat body weights (average estimates for Wistar, Long-Evans Hooded and Sprague–Dawley rats) are included here.

along with Bell, Franklin, Hauser, and Engleman (2013), parallel developmental ages between rats and humans have been estimated (estimated body weights are included for rats in Table 1, because most rat studies do not give the animal's age) using behavioral and neurobiological milestones—see Table 1.

Usefulness of selectively bred animal models to study alcohol-associated effects

Animal models have been successfully used to investigate the causes of, and develop treatments for, medical and psychiatric disorders (e.g., Griffin, 2002; McKinney, 2001; Nestler & Hyman, 2010). An animal model has the advantage of allowing the experimenter to control factors such as genetic background, environment, and prior drug exposure. Bi-directional selective breeding is a powerful genetic tool for studying many alcohol-associated phenotypes (e.g., Crabbe, 2008). Thus, this breeding strategy results in the expression of high vs. low levels of a particular phenotype, such as alcohol intake and/or preference. With this method, the expression levels of a selected phenotype tend to exceed the range of expression displayed by the foundation stock. The alcohol-preferring P and high alcohol-drinking HAD (replicate 1 and 2) rat lines were selectively bred (from a closed colony of Wistar rats and the N/NIH line, respectively) to prefer a 10% alcohol solution over water and consume greater than 5 g of alcohol/kg body weight/day (see McBride, Rodd, Bell, Lumeng, & Li, 2013). These selectively bred rats have been used to investigate the effects of continuous (24-h/day) and/or binge alcohol drinking across peri-adolescence and adulthood.

Free-choice 24-h ethanol drinking by P and HAD rats

Early work indicated that P rats, when given continuous 24-h access to ethanol (10% v/v) and water in their home cages, consumed most of their ethanol in discrete bouts (~1 g/kg in less than 1 h; resolution was limited to 1-h observations in this study) during the dark cycle (Murphy et al., 1986). These authors also reported that animals with larger bouts tended to have fewer bouts per day. In this same study, it was shown that bout number and size could be manipulated by giving P rats a single 4-h access session/day vs. 24-h continuous access or four 1-h access sessions/day, such that the largest bout size occurred under the 4-h access session, but, again with fewer bouts (Murphy et al., 1986). However, when total ethanol intake was averaged per hour, the four 1-h access sessions/day group drank the most ethanol (~1 g/kg/h) which was 4 times that of the 24-h and 2½ times that of the 4-h groups (Table 2).

In a subsequent study, Bell, Rodd, Lumeng, Murphy, and McBride (2006) and Bell, Rodd, Sable, et al. (2006) examined patterns of daily ethanol (15% v/v) intake by adolescent and adult, male and female P rats in their home cages using a lickometer setup, such that total licks on the water and ethanol bottles were recorded

Table 2
Ethanol intakes of adult and peri-adolescent P, HAD1, and HAD2 rats under 24-h free-choice access conditions.

Conditions	Ethanol intakes and blood ethanol levels (BELs)	Reference
Adult male P rats; 10% ethanol vs. water; monitored pattern of ethanol intake	~7 g ethanol/kg/day; multiple bout drinking of 1–1.5 g/h; ~70% ethanol intake in dark phase; BELs averaged 45–90 mg% during dark phase	Murphy et al., 1986
Adult male P rats; 24-h operant with escalating 2%–30%; ethanol (FR5) vs. water	Greatest intake at 15%, ~8 g/kg/day; average intake ~6 g/kg/day	Murphy, Gatto, McBride, Lumeng, & Li, 1989
Adult male P rats; male HAD1 rats; male HAD2 rats; 10% ethanol vs. water	~6 g/kg/day for P and HAD1 rats; ~5 g/kg/day for HAD2 rats	Samson et al., 1998
Adult male P rats; male HAD1 rats; male HAD2 rats; 24-h 2-lever operant; 10% ethanol (FR1) vs. water (FR1)	~3.5 g/kg/day for P rats; ~4.5 g/kg/day for HAD1 rats; ~6.5 g/kg/day for HAD2 rats; ~11 ethanol bouts/day for HAD1 rats; ~16 ethanol bouts/day for P rats; ~22 ethanol bouts/day for HAD2 rats	Files et al., 1998
Male & female peri-adolescent P rats; 15% ethanol vs. water; concurrent 10, 20, & 30% ethanol vs. water	With single ethanol concentration ~6 g/kg/day; with multiple ethanol concentrations ~10 g/kg/day	Bell et al., 2003
Male & female peri-adolescent HAD1 & HAD2 rats; 15% ethanol vs. water; concurrent 10, 20, & 30% ethanol vs. water	With single ethanol concentration ~5 g/kg/day; with multiple ethanol concentrations ~7 g/kg/day; no significant sex or line differences	Bell et al., 2004
Male & female adult & peri-adolescent P rats; 15% ethanol vs. water; monitored pattern of drinking	Adult & peri-adolescent intakes 6–8 g/kg/day; majority occurred during dark phase; BELs at end of dark phase were 40–60 mg%	Bell, Rodd, Sable, et al., 2006
Adult male P rats; 20% ethanol vs. water; intermittent access (MWF)	Peak at ~6.5 g/kg/day; ~40 mg% at 45 min into dark phase	Simms et al., 2008
Male & female adult & peri-adolescent HAD1 & HAD2 rats; 15% ethanol vs. water; monitored pattern of drinking	Adult & peri-adolescent HAD1 intakes 6–8 g/kg/day; HAD2 intakes ~6 g/kg/day except for male adolescent HAD2 intakes ~9 g/kg/day; most ethanol drinking occurred during the dark phase	Dhaher et al., 2012