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Rodent models and mechanisms of voluntary binge-like ethanol consumption: Examples, opportunities, and strategies for preclinical research

Brandon M. Fritz, Stephen L. Boehm II *

Indiana Alcohol Research Center, Department of Psychology, Indiana University–Purdue University Indianapolis, Indianapolis, IN, United States

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ABSTRACT

Binge ethanol consumption has widespread negative consequences for global public health. Rodent models offer exceptional power to explore the neurobiology underlying and affected by binge-like drinking as well as target potential prevention, intervention, and treatment strategies. An important characteristic of these models is their ability to consistently produce pharmacologically-relevant blood ethanol concentration. This review examines the current available rodent models of voluntary, pre-dependent binge-like ethanol consumption and their utility in various research strategies. Studies have demonstrated that a diverse array of neurotransmitters regulate binge-like drinking, resembling some findings from other drinking models. Furthermore, repeated binge-like drinking recruits neuroadaptive mechanisms in mesolimbocortical reward circuitry. New opportunities that these models offer in the current context of mechanistic research are also discussed.

1. Introduction

With a financial burden estimated in excess of $223 billion in the United States alone (Bouchery et al., 2011), ethanol abuse has widespread negative consequences for public health and has been implicated in 79,000 deaths annually (Stahre et al., 2004). Not all excessive ethanol consumption is the same, however, and different forms of aberrant alcohol use are associated with different drinking trajectories and negative consequences (Cleveland et al., 2013; Gueorguieva et al., 2012; King et al., 2011; Mota et al., 2013). It is therefore important to explore the major subtypes of problematic alcohol use and their associated mechanisms and consequences.

One such subtype, binge drinking, is a hazardous, yet common occurrence in the United States. The National Institute on Alcohol Abuse and Alcoholism defines binge drinking (BD) as a pattern of drinking that brings blood ethanol concentration (BEC) levels to 80 mg/dl in a short period of ~2 h which can typically be achieved after four drinks for women and five drinks for men. This level of ethanol consumption lies in between light or social consumption and the extreme levels typically seen in dependent individuals. BD is also defined by periodic, rather than continuous drinking and has been associated with increased risk of car accidents, sexual assault, personal injury, and ethanol poisoning. Moreover, heavy or frequent BD may lead to a loss of control over alcohol consumption, and the development of alcohol use disorders (Courtney and Polich, 2009). Whether or not BD is associated with a progression towards *dependence* in the clinical literature is not yet clear (Chassin et al., 2002; Courtney and Polich, 2009; Hasin and Beseler, 2009; King et al., 2011), however the new spectrum of alcohol use disorder diagnosis presented in the DSM-5 is arguably more inclusive for BD behavior than was previously seen with the DSM-IV TR. Nevertheless, one in six adults in the United States reported engaging in BD about four times per month in 2010, consuming roughly eight drinks in each binge episode (CDC, 2012). Thus, there is a critical need to better understand the neurocircuitry engaged by BD, as well as how this neurocircuitry is altered by repeated bouts of BD, for informed progress in the treatment, intervention, and prevention of alcohol use disorders.

Although clinical research has provided critical information regarding the risks and consequences of BD, human studies cannot meticulously examine the biological and chemical underpinnings of BD due to ethical limitations. Rodent models have therefore been extremely valuable in efforts to understand the neurobehavioral mechanisms

Abbreviations: BD, binge drinking; BEC, blood ethanol concentration; CNO, clozapine-n-oxide; B6, C57BL/6J inbred mice; CRF, corticotropin-releasing factor; DOR, δ-opioid receptor; DREADDS, designer receptors exclusively activated by designer drugs; DA, dopamine; DAT, dopamine transporter; DID, drinking-in-the-dark; DID-MSA, drinking-in-the-dark-multi-scheduled-access; GABA, γ-aminobutyric acid; HAP, high alcohol-preferring mice; HARF, High Alcohol Research Foundation rats; HDID, high-drinking-in-the-dark mice; KOR, κ-opioid receptor; KO, knockout; D2LR, long dopamine D2 receptor isoform; LARF, Low Alcohol Research Foundation rats; miRNAs, microRNAs; MOR, μ-opioid receptor; MOR, nicotinic acetylcholine receptorx; NMDA, *N*-methyl-D-aspartate; MOR, μ-opioid receptor; NPY, neuropeptide Y; SHAC, scheduled high alcohol consumption; D2LR, short dopamine D2 receptor isoform; VTA, ventral tegmental area.

* Corresponding Author: Department of Psychology Indiana University–Purdue University Indianapolis, 402 N Blackford St., LD 301 Indianapolis, IN 46202, United States. Tel.: +1 317 274 6927; fax: +1 317 274 6756.
E-mail address: slboehm@iupui.edu (S.L. Boehm).

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and consequences of binge ethanol consumption. In this review, we will first describe the available binge-like drinking rodent models and discuss their application in mechanistic research, highlighting findings in key neurotransmitter systems. Finally, we will offer suggestions for future utility of these models and how they can continue to advance our understanding of the neurobehavioral and genetic mechanisms underlying binge ethanol consumption.

1.1. Rodent models of voluntary binge-like ethanol consumption

The predominant method of assessing ethanol drinking in rodents has been a two-bottle choice paradigm wherein the animal concurrently has access to an ethanol-containing solution and water. Often employed as a continuous-access model, this design allows the researcher to determine preference for the ethanol solution over water as well as total fluid intake in the animal's home cage under normal conditions (save for isolated housing). Certain mouse and rat genotypes will consume appreciable amounts of ethanol in this paradigm (Eriksson, 1970; McClearn and Rodgers, 1959; Wahlsten et al., 2006), however, the continuous nature of this drinking paradigm makes it difficult for the researcher to determine when peak drinking/BEC occurs. Indeed, a major limitation is that even animals demonstrating a significant preference for ethanol over water rarely achieve pharmacologically-relevant BECs in this paradigm (≥80 mg/dl) (Dole and Gentry, 1984; Linseman, 1987).

Limiting ethanol access to a discrete time period (typically 1–4 h each day) has been found to produce high ethanol intakes in rodents and BECs ≥ 80 mg/dl in as little as 30 min and produce measurable behavioral intoxication (Bell et al., 2006b; Crabbe et al., 2011; Cronise et al., 2005; Rhodes et al., 2005). As these observations reflect the NIAAA definition of binge drinking, a number of these models have been referred to as 'binge-like drinking models.' Studies in mouse behavioral and quantitative genetics also suggest that this binge-like drinking phenotype is not completely analogous to the continuous, two-bottle choice drinking phenotype (Crabbe et al., 2011; Fritz et al., 2014b; Iancu et al., 2013). This is an important point to consider as different genetic factors may predispose individuals for binge ethanol drinking, specifically.

A wide variety of approaches to modeling voluntary BD in rodents exist, including voluntary home cage drinking, operant paradigms, and dependence-induced drinking. In the current review, the authors have elected to focus on pre-dependent, voluntary home cage consumption paradigms in mice for a number of reasons. First, operant paradigms necessitate an appetitive response component, making interpretation of effects on binge-like ethanol *consumption*, specifically, difficult to ascertain. Second, dependence-induced models of BD require animals to be repeatedly exposed to stressful ethanol vapor inhalation for up to 12–16 h per day. The authors argue that modeling BD in this manner lacks face and construct validity as this chronic vapor exposure, not prior voluntary ethanol consumption, is likely responsible for producing the BD phenotype and therefore reflects the maintenance of already established dependence. In addition, a protracted history of binge-like ethanol consumption in a mouse model of BD did not produce well-established behavioral markers of ethanol dependence in rodents (Cox et al., 2013), although an elevation of ethanol intake was observed. With these considerations, the scope of this review is to examine BD as a pre-dependent mechanism of problematic ethanol consumption, itself. In addition, the possibility of whether prolonged BD may usher in a *transition* to dependence is discussed.

1.1.1. Drinking-in-the-dark

Drinking-in-the-dark (DID) was developed using the highest ethanol-drinking inbred mouse strain, C57BL/6J (B6). This drinking paradigm takes advantage of the most active circadian period in mice (3 h into the dark cycle) by replacing the animal's water bottle with an unsweetened, 20% (v/v) ethanol solution for a short period of 2–4 h each day. B6 mice will typically consume ~4–6 g/kg of ethanol by the second DID session (i.e. 2 successive days), with a significant proportion reaching BECs in excess of 100 mg/dl with repeated exposures (Fritz et al., 2014a; Lyons et al., 2008; Rhodes et al., 2005). DID has been validated as a binge-like drinking model as mice reach these intoxicating BECs in a short period of time (2–4 h) and display behavioral markers of intoxication (Fritz et al., 2014a; Linsenbardt et al., 2011; Rhodes et al., 2007). Furthermore, B6 mice have been demonstrated to develop functional and metabolic tolerance (Fritz et al., 2014a; Linsenbardt et al., 2011) as well as a greater propensity for locomotor sensitization to ethanol (Linsenbardt et al., 2011; Tarragón et al., 2012) following repeated cycles of DID, perhaps modeling valid markers of protracted ethanol abuse. Concerning whether DID produces ethanol dependence, a previous study demonstrated that although repeated DID cycles increased later ethanol intake (Cox et al., 2013), this prolonged consumption did not produce other dependence-like phenotypes typically demonstrated by rodents following ethanol vapor withdrawal (i.e. anxiety-like behavior, convulsions, ataxia). The authors concluded that DID is therefore a pre-dependent assessment of binge-like ethanol consumption although the elevation of intake with prolonged exposure may suggest a transition towards dependence. Future studies are encouraged to address this question by further extending the ethanol exposure period. Finally, genotype is an important mediator of propensity to engage in DID (Rhodes et al., 2007), and consistent with anecdotal evidence from the human literature, adolescent B6 mice consume greater amounts of binge-like ethanol than adults using DID procedures (Moore et al., 2010).

There are numerous variations of DID, particularly relating to the schedule of presentation. The original version (Rhodes et al., 2005) offers 2-h ethanol access for 3 days, and a 4-h access period on day 4. This longer access period effectively allows for greater overall ethanol intake as mice will roughly double their consumption to doses of ~8 g/kg. Others have adapted the schedule to draw out to ~14 days or longer, however only 2-h access is used. The interested reader is referred to Thiele et al. (2014) for details on setting up and using DID.

1.1.2. DID-multi-scheduled access

DID multi-scheduled-access (DID-MSA) offers 3–4 daily periods of 1-h limited access to two concentrations of ethanol concurrently (15% and 30% v/v; tap water is also freely available), spaced 2–3 h apart. Daily ethanol intake equivalent to what is reached if the ethanol access is continuous has been observed in selectively-bred high alcohol drinking P rats (Bell et al., 2006a; 2011) with mean BECs as high as 120 mg/dl after the first hour of access (Bell et al., 2006b). It should be noted that continuous two-bottle choice access to 10% ethanol and water was given before the initiation the DID-MSA protocol. Findings from gene expression studies suggest that binge-like drinking in this paradigm produces significant alterations in protein expression related to cellular structure and function in the nucleus accumbens and amygdala (Bell et al., 2006a; McBride et al., 2010). Moreover, P rats drinking ethanol in a continuous access paradigm exhibited substantially more protein alterations in the amygdala whereas DID-MSA produced more pronounced alterations in the nucleus accumbens (Bell et al., 2006a). These findings suggest that this binge-like drinking phenotype produced unique, regionally-specific changes in protein expression.

Our lab has also explored the utility of DID-MSA in B6 mice. Using a variation of the paradigm, mice were given three daily 1-h access periods, separated by 2 h, to a single bottle of 20% (v/v) ethanol for 14 days. Towards the end of the experiment, daily ethanol intakes were ≥8 g/kg and BECs were ≥80 mg/dl following the final hour of access (Melón et al., 2013). Mice that consumed ethanol in this experiment also exhibited significant ataxia on the balance beam apparatus. We have also observed similar binge-like ethanol intake in adolescent male and female selectively bred high alcohol-preferring (HAP) mice

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