Alcohol 48 (2014) 295–299

Contents lists available at ScienceDirect

Alcohol

journal homepage: http://www.alcoholjournal.org/

Operant ethanol self-administration in ethanol dependent mice

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ARTICLE INFO

Article history:
Received 21 June 2013
Received in revised form
17 February 2014
Accepted 19 February 2014

Keywords:
Operant conditioning
Ethanol self-administration
Ethanol dependence
Mice

ABSTRACT

While rats have been predominantly used to study operant ethanol self-administration behavior in the context of dependence, several studies have employed operant conditioning procedures to examine changes in ethanol self-administration behavior as a function of chronic ethanol exposure and withdrawal experience in mice. This review highlights some of the advantages of using operant conditioning procedures for examining the motivational effects of ethanol in animals with a history of dependence. As reported in rats, studies using various operant conditioning procedures in mice have demonstrated significant escalation of ethanol self-administration behavior in mice rendered dependent via forced chronic ethanol exposure in comparison to nondependent mice. This paper also presents a summary of these findings, as well as suggestions for future studies.

Introduction

Ethanol self-administration using operant conditioning procedures has been firmly established in a number of species, including monkeys, rats, and mice (Meisch & Stewart, 1994; Samson, 1986). In these studies, animals are typically trained to make a response (e.g., press a lever) under a particular schedule of reinforcement, such that responding after either a specified number of responses (ratio schedules) or a specified period of time has elapsed (interval schedules) will result in delivery of ethanol as a reinforcer. In most studies involving oral ethanol self-administration, once the specified schedule of reinforcement was satisfied, the reinforcer (specific amount of an ethanol solution) was presented to the animals for consumption. In contrast to this procedure (termed the 'dipper' model), in other studies, once the response requirement was met, animals were provided free access to a bottle containing ethanol for a specified period of time (termed the 'sipper' model) (Samson, 2000).

It is well established that ethanol can serve as an effective positive reinforcer in these self-administration models. More recently, studies in animals with a history of dependence (chronic but 'forced' ethanol exposure and withdrawal) have demonstrated that ethanol can serve as a potent negative reinforcer as well. For example, increased ethanol self-administration was shown in studies where dependence was induced by chronic administration of ethanol in a nutritionally fortified liquid diet (that served as the animals' sole source of calories and fluid) (Brown, Jackson, & Stephens, 1998; Chu, Koob, Cole, Zorilla, & Roberts, 2007; Gilpin et al., 2009; Schulteis, Hyytiä, Heinrichs, & Koob, 1996), via intragastric infusions (Cunningham, Fidler, Murphy, Mulgrew, & Smitasin, 2013; Fidler et al., 2011, 2012), and via inhalation of alcohol vapors (e.g., Becker & Lopez, 2004; Rimondini, Arlinde, Sommer, & Heilig, 2002; Roberts, Heyser, Cole, Griffin, & Koob, 2000). In such studies, the altered physiological state associated with dependence along with the capacity for ethanol to alleviate withdrawal symptoms is posited to not only sustain ethanol self-administration, but also promote escalation of intake (Becker, 2008, 2013; Heilig, Egli, Crabbe, & Becker, 2010).

The use of operant conditioning procedures to study ethanol self-administration behavior has several important advantages over free-choice drinking models. First, this approach enables separate analysis of the appetitive (seeking) and consummatory (drinking) components of self-administration behavior. While the amount of ethanol consumed is a dependent variable common to all models of self-administration, studying the appetitive component provides an opportunity to examine the motivational effects of ethanol (i.e., how hard subjects will work to obtain access to ethanol). In addition, systematic manipulation of dose (e.g.,

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0741-8329/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.alcohol.2014.02.002

ethanol concentration) as well as the schedule of reinforcement (i.e., increasing the response requirement using progressive ratio procedures) enables a more detailed analysis of the reinforcing efficacy of ethanol. Tracking the distribution and pattern of responding also provides a more refined analysis of factors that influence self-administration behavior. Additionally, measuring the behavioral response when 'expected' ethanol delivery is terminated (extinction responding) provides a means to operationally define 'ethanol-seeking' behavior. This procedure has been extensively used in relapse models to study how presentation of discrete conditioned cues (stimuli previously associated with ethanol reinforcement) and discriminative cues (context stimuli previously associated with occasions to self-administer ethanol) reinvigorate or reinstate ethanol responding that was experimentally extinguished. While all of these operant conditioning procedures have been predominantly used to study ethanol self-administration in rats, many of these procedures also have been adopted in studies with mice.

Operant ethanol self-administration in mice

Standard operant conditioning procedures have been employed to study ethanol self-administration behavior in mice under a variety of conditions. As in the case for rats, studies have shown mice to respond for ethanol as a positive reinforcer when it is delivered orally (Meisch, 2001), intravenously (Grahame & Cunningham, 1997), and directly into the stomach via intragastric infusion (Fidler et al., 2011). While early studies showed that ethanol responding and intake is enhanced in food-deprived mice (Middaugh & Kelley, 1999), ethanol was demonstrated to be an effective positive reinforcer in non-food deprived mice as well (Ford, Fretwell, Mark, & Finn, 2007; Middaugh, Lee, & Bandy, 2000). Studies also have shown mice responding for ethanol when ethanol reinforcement is continuously available (Risinger, Brown, Doan, & Oakes, 1998), when it is made available for extended periods (~16 h) (Besheer, Lepoutre, & Hodge, 2004; Hodge et al., 2006), and when access is limited for short periods of time (~30–60 min) (Chu et al., 2007; Lopez, Anderson, & Becker, 2008; Lopez & Becker, 2014; Ramaker, Strong, Ford, & Finn, 2012; Sparta et al., 2009; Tsiang & Janak, 2006). Using the 'sipper' model described above, mice were shown to reliably respond to gain access to drink ethanol from a bottle made available for 30 min once the response requirement was satisfied (Finn et al., 2008; Ford et al., 2007). In this latter case, manipulating the reinforcement schedule to further separate the appetitive and consummatory components of the procedure enhanced both the appetitive drive to gain access to ethanol (as indicated by reduced latency to fulfill the response requirement) and the consummatory component (increased amount of ethanol consumed). Finally, a valuable feature of using mice in these studies is that it more readily facilitates examination of genetic contributions to operant ethanol self-administration behavior. Indeed, several studies have examined ethanol self-administration involving operant conditioning procedures in various genetic mouse models, including different inbred strains (Fidler et al., 2011; Grahame & Cunningham, 1997; Risinger et al., 1998), mice selectively bred for other ethanol-related phenotypes (Ford et al., 2011), and several genetically manipulated models engineered to be deficient in various target proteins (knockout models) (Grahame, Low, & Cunningham, 1998; Olive, Mehmert, Messing, & Hodge, 2000; Risinger, Doan, & Vickrey, 1999; Roberts et al., 2001; Roberts, McDonald, et al., 2000). Thus, while rats have been the predominant choice of species for operant ethanol self-administration studies, a growing body of literature indicates that operant conditioning procedures can be effectively employed in studying ethanol self-administration behavior in mice.

Operant ethanol self-administration in dependent mice

As reviewed elsewhere (Becker, 2013), numerous studies utilizing operant conditioning procedures have demonstrated increased ethanol self-administration in rats following a history of chronic ethanol exposure and withdrawal experience (Funk & Koob, 2007; Funk, O'Dell, Crawford, & Koob, 2006; Funk, Zorilla, Lee, Rice, & Koob, 2007; Gilpin et al., 2009; O'Dell, Roberts, Smith, & Koob, 2004; Rimondini, Thorsell, & Heilig, 2005; Roberts, Cole, & Koob, 1996; Roberts, Heyser, et al., 2000). In contrast, only a handful of studies have been devoted to evaluate the effect of ethanol dependence on operant ethanol self-administration using mice. The following is a more detailed description of results generated from these studies.

In one study, male C57BL/6J mice were trained to respond for ethanol for several weeks (FR4, 10% ethanol; 60-min daily sessions). Once stable responding for ethanol was attained, half the mice received chronic intermittent exposure to ethanol vapors in inhalation chambers (14 h/day for 21 days) and were given the opportunity to self-administer ethanol 8 h after being removed from the inhalation chambers each day. The self-administration sessions were extended for an additional 2 weeks after the chronic intermittent ethanol (CIE) vapor exposure was terminated. This study design resulted in elevated responding and a higher number of ethanol reinforcers earned for mice that experienced CIE exposure, but the effect was observed only during the 2 weeks after CIE exposure was terminated (Chu et al., 2007). During the 3 weeks of CIE exposure, ethanol self-administration was very similar to baseline levels and similar to control mice that did not receive ethanol vapor exposure (Chu et al., 2007). This profile of results differs from that reported in rats where ethanol self-administration was shown to progressively increase when the opportunity to respond for ethanol was provided during repeated acute withdrawal periods (Roberts et al., 1996; Roberts, Heyser, et al., 2000). This may reflect an important species difference in that mice may require a longer 'recovery' period following CIE exposure before being offered the opportunity to consume ethanol. It has been suggested that mice may require at least 48 h before ethanol is reintroduced to avoid potential conditioned taste aversion related to the CIE vapor exposure (Lopez & Becker, unpublished data).

In this study, mice were given the option to respond on one lever to obtain ethanol and on another lever to obtain water. Because of this feature, it was possible to observe that although the number of responses for ethanol reinforcement did not increase during the 3 weeks of CIE vapor exposure, preference for responding on the ethanol-related lever significantly increased in dependent mice during the course of CIE exposure, an effect that persisted after the chronic ethanol vapor exposure stopped (Chu et al., 2007). Another goal of this study was to examine whether genetic deletion of CRF1 receptors alters operant ethanol self-administration in dependent versus nondependent mice. In this case, baseline ethanol responding was first established and then wild-type controls (C57BL/6J × 129SvJ background) and CRF1 receptor knockout mice were exposed to ethanol delivered in a nutritionally fortified liquid diet for a 2-week period before operant testing resumed. Results indicated that while ethanol responding and preference were similar for both genotypes during the baseline phase, ethanol self-administration significantly increased in the wild-type controls but not CRF1 receptor knockout mice following the chronic ethanol treatment regimen (Chu et al., 2007). Thus, it was suggested that CRF1 receptors might play a significant role in mediating dependence-related escalation of ethanol self-administration.

Overall, these results are generally congruent with findings from a series of similar experiments conducted in our laboratory. Briefly, adult male C57BL/6J mice were trained to self-administer ethanol