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Operant alcohol self-administration in dependent rats: Focus on the vapor model

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ABSTRACT

Alcoholism (alcohol dependence) is characterized by a compulsion to seek and ingest alcohol (ethanol), loss of control over intake, and the emergence of a negative emotional state during withdrawal. Animal models are critical in promoting our knowledge of the neurobiological mechanisms underlying alcohol dependence. Here, we review the studies involving operant alcohol self-administration in rat models of alcohol dependence and withdrawal with the focus on the alcohol vapor model. In 1996, the first articles were published reporting that rats made dependent on alcohol by exposure to alcohol vapors displayed increased operant alcohol self-administration during acute withdrawal compared with nondependent rats (i.e., not exposed to alcohol vapors). Since then, it has been repeatedly demonstrated that this model reliably produces physical and motivational symptoms of alcohol dependence. The functional roles of various systems implicated in stress and reward, including opioids, dopamine, corticotropin-releasing factor (CRF), glucocorticoids, neuropeptide Y (NPY), γ-aminobutyric acid (GABA), norepinephrine, and cannabinoids, have been investigated in the context of alcohol dependence. The combination of models of alcohol withdrawal and dependence with operant self-administration constitutes an excellent tool to investigate the neurobiology of alcoholism. In fact, this work has helped lay the groundwork for several ongoing clinical trials for alcohol dependence. Advantages and limitations of this model are discussed, with an emphasis on what future directions of great importance could be.

Introduction

Increased operant alcohol (ethanol) self-administration in rats associated with alcohol dependence and withdrawal produced by alcohol vapor exposure was first demonstrated in 1996 (Roberts, Cole, & Koob, 1996). However, there was a very important body of work published prior to this that was critical in the development of this rat/ethanol-vapor/operant model. This history will be summarized in a manner that will highlight aspects of this model that engender excessive alcohol intake. We will also review what has been discovered using the vapor/operant model with respect to both environmental and biological factors. Finally, we will discuss advantages and limitations of this model with an emphasis on what future directions we believe could be of great importance. But first, what was the motivation to develop such a model? Why drinking subsequent to dependence? Why operant self-administration? Why rats?

Alcohol was involved in 3.5% of deaths in the United States in 2000, making it the third-leading cause of preventable death in this country (Mokdad, Marks, Stroup, & Gerberding, 2004). Alcohol abusers drink perhaps partly for its euphorigenic effects, but progressively more in order to avoid or reverse the negative symptoms associated with withdrawal (Cappell & LeBlanc, 1981; Edwards, 1990). Indeed, the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria for substance dependence on alcohol include a withdrawal syndrome and taking the substance (or a closely related substance) to relieve or avoid withdrawal symptoms (American Psychiatric Association, 2000), similar to the DSM-V criteria for moderate to severe substance use disorder (O'Brien, 2011; Peer et al., 2013). The affective components of withdrawal, such as anxiety, dysphoria, and depressed mood, create a motivational drive that leads to compulsive ethanol drinking behavior and relapse even after long periods of abstinence (Hershon, 1977). These affective symptoms begin as blood alcohol levels drop and can continue for weeks to months to years following withdrawal (Alling et al., 1982; Mossberg, Liljeberg, & Borg, 1985; Parsons, Sinha, & Williams, 1990). Alcohol dependence is associated with high rates of relapse, which is characterized by a return to drinking after a period of abstinence and involves the consumption of excessive amounts of alcohol (U.S. Department of Health and Human Services, 1990). Therefore, alcohol dependence is a disorder with chronic relapses, with serious consequences to the individual, family, and society. Therefore, having a model of ethanol

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self-administration in animals experiencing withdrawal and in abstinent animals is important for the advancement of better prevention and treatment approaches.

Free-choice bottle drinking models capture consummatory aspects, whereas operant self-administration is more versatile in modeling different behavioral aspects of alcohol drinking. Both the appetitive/motivational (e.g., pressing a lever [workload] to receive a dose of alcohol) and consummatory (e.g., drinking the alcohol) components of ethanol consumption can be studied in operant models (Cunningham, Fidler, & Hill, 2000; Tabakoff & Hoffman, 2000). Appetitive behaviors become compulsive as dependence progresses (Koob, 2013), in that they become persistent and repetitive without leading to actual reward or pleasure. Compulsivity is described in the DSM: continued use despite knowledge of having had a persistent or recurrent physical or psychological problem and a great deal of time spent in activities necessary to obtain the substance. Thus, assessing operant ethanol self-administration in dependent animals allows the appetitive and consummatory processes and, in particular, the compulsive nature of addiction to be studied.

Finally, there is a rich history of using rats in behavioral brain research. Issues of reliability and validity are critical in developing and utilizing animal models of complex neuropsychiatric disorders and must always be considered (Edwards & Koob, 2012; Geyer & Markou, 1995). As discussed by Bell et al. (2012), an effective animal model of alcoholism should include both positive (euphoric) and negative (eliminating negative aspects of withdrawal) reinforcement aspects. Several such models, including the one described in this review, have been developed, and are invaluable for studies of neuropharmacological mechanisms of alcoholism that would be impossible to do in humans. For example, significant understanding of the neurocircuitry involved in drug-seeking behavior in the addicted state has come from rat studies, and, indeed, rat neuropharmacological studies continue to drive the development of new medication targets (Koob, 2010).

History and highlights in the development of the rat operant/vapor model

Previous studies examined ethanol-drinking behavior in dependent animals. Both increases (Deutsch & Koopmans, 1973; Deutsch & Walton, 1977; Hunter, Walker, & Riley, 1974; Samson & Falk, 1974; Schulteis, Hyytiä, Heinrichs, & Koob, 1996; Veale & Myers, 1969; Wolffgramm & Heyne, 1991) and decreases (Begleiter, 1975; Myers, Stoltman, & Martin, 1972; Winger, 1988) in ethanol intake were observed. In examining these studies, it became clear that there were two general concepts that likely played a role in these differential results that would require attention prior to being able to produce a robust and reliable model. These were issues of ethanol's palatability and reinforcing properties prior to induction of dependence and concerns regarding the post-dependence withdrawal spectrum. Specifically, how should researchers produce dependence while minimizing the potential of excessive physical symptoms that would compete with appetitive and/or consummatory behaviors, thus allowing the animals to learn the association between drinking ethanol and the alleviation of withdrawal symptoms?

Deutsch and Walton (1977) used a procedure in which the rats drank a flavored solution to receive infusions of ethanol directly into the stomach and showed that dependence enhanced preference for the ethanol-paired flavor. This model bypassed the aversive taste properties of ethanol and allowed ethanol to become a reinforcer. Historically, low levels of intake hampered rat models of oral ethanol self-administration unless the animals were food- or fluid-deprived. Consumption, therefore, could be motivated by thirst or the need for the calories in the ethanol solution, and not by ethanol's pharmacological effects. This changed with the breeding of ethanol-preferring rat strains (reviewed by McBride, this issue) and, in outbred strains, the development of the sweetened solution fading procedure by Samson and colleagues (Samson, 1986). In the latter model, ethanol is initially sweetened, and ethanol concentrations are gradually increased such that non-deprived rats will maintain lever pressing for high concentrations of ethanol that result in pharmacologically relevant blood alcohol levels. The sweetener is then removed gradually so that by the end of the procedure, the rats are drinking unsweetened alcohol solutions. This development paved the way for subsequent studies by partially solving both the palatability and physiological need issues. Nonetheless, these procedures do not result in levels of alcohol intoxication to the point of dependence.

The problem of making the rats dependent was an outstanding issue. It was known that most rats would not voluntarily consume enough ethanol to induce dependence (Myers & Veale, 1972; Samson, Pfeffer, & Tolliver, 1988; Veale & Myers, 1969). Rats can be made dependent on alcohol by repeated exposure to high doses of alcohol via gastric intubation, oral gavage, mixing ethanol into a liquid diet, and systemic injections. While these techniques have been successfully used to produce dependence and subsequent increases in ethanol intake (Deutsch & Walton, 1977; Hunter et al., 1974; Schulteis et al, 1996), intubation or injections require either stressful repeated administration or surgical intragastric cannulation. Ethanol-containing liquid diet-induced dependence has been shown to produce escalated alcohol self-administration during acute withdrawal compared with control rats (Schulteis et al, 1996). However, this response pattern depends on high blood alcohol levels at the time of withdrawal, and intake during the dependence induction phase can be difficult to control in this model. In addition, the liquid diet approach can have the caveat of potential malnourishment in both the ethanol- and pair-fed groups (Rogers, Wiener, & Bloom, 1979). Several laboratories began employing vaporized ethanol exposure to induce dependence (i.e., Karanian et al., 1986; Rigter, Dortmans, & Crabbe, 1980; Rogers et al., 1979). This method has the benefit of more precise control of blood alcohol levels across varying periods of time and therefore allows for the examination of known exposure patterns on behavior, physiology, and biochemistry.

The second challenge with dependence is capitalizing on the affective symptoms without the excessive physical symptoms rendering the rats incapable of appetitive or consummatory behavior. In all three of the studies that showed decreased ethanol intake following dependence, significant physical withdrawal symptoms were observed. The majority of the rats in the Begleiter (1975) study had convulsions, and all of the monkeys in both the Myers et al. (1972) and Winger (1988) studies showed tremor during withdrawal.

Finally, a critical component of the DSM criteria for substance dependence on alcohol or moderate to severe substance use disorder must be established, namely taking the substance (or a closely related substance) to relieve or avoid withdrawal symptoms (American Psychiatric Association, 2000; O'Brien, 2011; Peer et al., 2013). This requires the animal to experience symptoms of withdrawal or abstinence with ethanol available and then to associate ethanol intake with the alleviation of these symptoms. Hunter et al. (1974) showed that rats did not voluntarily consume ethanol following a single 20-day period of forced liquid diet despite the presence of withdrawal symptoms. However, following a series of 3 liquid diet exposures followed by free choice testing, the rats transiently increased ethanol-drinking behavior, suggesting that the rats needed to learn the association between drinking ethanol and the alleviation of withdrawal symptoms.