Pharmacology, Biochemistry and Behavior 122 (2014) 37–52

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

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

Review

Stimulant and motivational effects of alcohol: Lessons from rodent and primate models

Christian Brabant [a,*], Douglas J. Guarnieri [b], Etienne Quertemont [a]

[a] Département de Psychologie, Cognition et Comportement, Université de Liège, Boulevard du Rectorat, 5/B-32, B-4000 Liège, Belgium
[b] Department of Biology, Colgate University, 13 Oak Drive, Hamilton, NY 13346, USA

ARTICLE INFO

Article history:
Received 27 June 2013
Received in revised form 17 February 2014
Accepted 6 March 2014
Available online 12 March 2014

Keywords:
Alcohol
Dopamine
Locomotion
Reward
Reinforcement
Alcoholism

ABSTRACT

In several animal species including humans, the acute administration of low doses of alcohol increases motor activity. Different theories have postulated that alcohol-induced hyperactivity is causally related to alcoholism. Moreover, a common biological mechanism in the mesolimbic dopamine system has been proposed to mediate the stimulant and motivational effects of alcohol. Numerous studies have examined whether alcohol-induced hyperactivity is related to alcoholism using a great variety of animal models and several animal species. However, there is no review that has summarized this extensive literature. In this article, we present the various experimental models that have been used to study the relationship between the stimulant and motivational effects of alcohol in rodents and primates. Furthermore, we discuss whether the theories hypothesizing a causal link between alcohol-induced hyperactivity and alcoholism are supported by published results. The reviewed findings indicate that animal species that are stimulated by alcohol also exhibit alcohol preference. Additionally, the role of dopamine in alcohol-induced hyperactivity is well established since blocking dopaminergic activity suppresses the stimulant effects of alcohol. However, dopamine transmission plays a much more complex function in the motivational properties of alcohol and the neuronal mechanisms involved in alcohol stimulation and reward are distinct. Overall, the current review provides mixed support for theories suggesting that the stimulant effects of alcohol are related to alcoholism and highlights the importance of animal models as a way to gain insight into alcoholism.

Contents

Abbreviations: 6-OHDA, 6-hydroxydopamine; ADH, alcohol dehydrogenase; ALDH, acetaldehyde dehydrogenase; BAC, blood alcohol concentration; BAES, Biphasic Alcohol Effects Scale; B-BAES, Brief Biphasic Alcohol Effects Scale; BXD RI, recombinant inbred mice; COF, consume off the floor; CPA, conditioned place aversion; CPP, conditioned place preference; CYP2E1, cytochrome P450 2E1; D_1R, D_2R, D_3R, and D_4R; dopamine D_1, D_2, D_3 and D_4 receptors; FAST, selected mouse line sensitive to the stimulant effects of alcohol; GABA, γ-aminobutryic acid; i.p., intraperitoneal; i.v, intravenous; LS, long-sleep mice; MDMA, methylenedioxymethamphetamine; NAc, nucleus accumbens; NMDA, N-methyl-D-aspartate; NP, alcohol-non-preferring rat; P, alcohol-preferring rat; PET, positron emission tomography; SLOW, selected mouse line insensitive to the stimulant effects of alcohol; SPECT, single photon emission computed tomography; SS, short-sleep mice; VTA, ventral tegmental area.

* Corresponding author at: Université de Liège, Département de Psychologie, Cognition et Comportement, Boulevard du Rectorat, 5 (B-32), B-4000 Liège, Belgium. Tel.: +32 4 366 2028; fax: +32 4 366 2859.
E-mail address: christian.brabant@ulg.ac.be (C. Brabant).

http://dx.doi.org/10.1016/j.pbb.2014.03.006
0091-3057/

1. Introduction

Alcohol consumption induces a wide variety of pharmacological and behavioral effects in humans that are dependent on the dose of alcohol ingested. Low doses of alcohol elicit appetitive gustatory responses that improve the taste of beverages such as beer or wine (Lemon et al., 2004). In addition, small amounts of alcohol increase mood states and generally reduce anxiety. Consumption of higher doses of alcohol over short periods of time (<2 h) produces sedation, motor incoordination, confusion, hypothermia and sometimes vomiting. When alcohol concentrations keep increasing, alcohol finally leads to coma and to death by respiratory depression (Vonghia et al., 2008). In some individuals, low doses of alcohol induce psychomotor stimulation and arousal. In addition, these individuals tend to experience more alcohol-induced euphoria and to drink more alcohol than regular people (Corbin et al., 2008; de Wit et al., 1987). Several studies suggest that increased sensitivity to the stimulant effects of alcohol is a risk factor for excessive alcohol consumption that can lead to alcoholism (King et al., 2011, 2014; Newlin and Thomson, 1990).

"Alcoholism" usually refers to alcohol dependence which is defined as the compulsive and uncontrolled consumption of alcohol beverages. What essentially characterizes alcohol dependence is the inability to control the use of alcohol despite the occurrence of psychological and physical problems (American Psychiatric Association, 2000). In other words, the main feature of alcohol dependence is the inability to stop using the substance even though the person is aware of its harmful effects. This feature of alcohol dependence makes it a human disease since animals lack the ability to understand a causal relationship between alcohol and its consequences on physical and mental health. Despite this limitation, animal studies have improved our understanding of alcohol dependence because many pharmacological and behavioral effects produced by alcohol in humans are also present in animals (Bell et al., 2006; Grant and Bennett, 2003; Guarnieri and Heberlein, 2003). For example, in several animal species including humans, alcohol has a biphasic effect on motor activity with low doses causing hyperactivity and high doses producing sedation, ataxia and motor incoordination (Frye and Breese, 1981; Gerlai et al., 2000; Graham et al., 2009; Singh and Heberlein, 2000; Hendler et al., 2013; Schwandt et al., 2007; Vonghia et al., 2008). It is noteworthy that the biphasic nature of the effects of alcohol can be found under two conditions: when low and high doses of alcohol are compared and as a time-related change with large doses of alcohol (Pohorecky, 1977). Fig. 1 illustrates the first condition and shows that low/moderate doses of alcohol increase locomotion of mice whereas high alcohol doses attenuate their activity (Quoilin et al., 2012). As for the second condition, a specific alcohol dose can under certain circumstances cause a reduction in locomotor activity shortly after drug administration followed by an increase in locomotion or vice versa. For example, the intraperitoneal (i.p.) injection of a high dose of alcohol (4 g/kg) can cause a decrease in motor activity in mice followed by an elevation in activity (Frye and Breese, 1981). Thus, the absorption of a specific amount of alcohol can sometimes produce consecutively both stimulant and sedative effects.

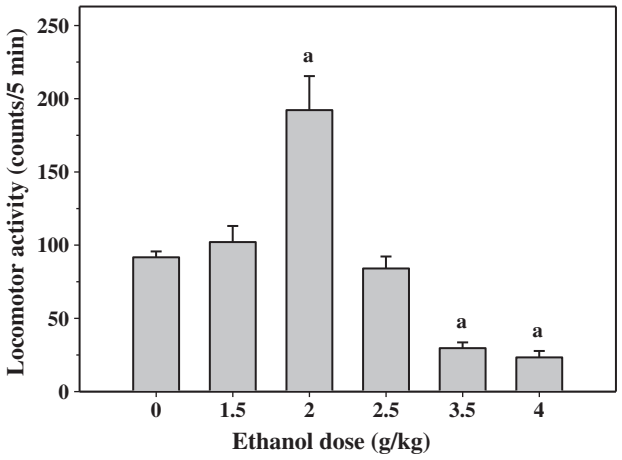

Fig. 1. Locomotor effects of alcohol in Swiss Webster mice. Data are expressed as mean ± SEM locomotor activity scores recorded during the first 5 min following an intraperitoneal injection of alcohol (0, 1.5, 2, 2.5, 3.5, 4 g/kg). (a): significantly different from mice treated with saline.
Adapted from Quoilin et al. (2012).

Different theories have suggested that there exist a causal link between the acute stimulant effects of drugs and addiction. These theories are based on the fact that virtually all addictive drugs, at least at some doses, cause psychomotor activation. This is particularly obvious for psychostimulant drugs such as cocaine, amphetamine, MDMA (methylenedioxymethamphetamine) or methylphenidate (Fletcher et al., 2006). In addition to alcohol, other drugs typically considered as sedative-hypnotics can increase psychomotor activity like benzodiazepines (Christmas and Maxwell, 1970; Zhang et al., 2011) and barbiturates (Jacobs and Farel, 1971; Zhang et al., 2011). Increases in motor activity can also be induced by opiates (Iwamoto, 1984; Mori et al., 2000; Murphy et al., 2002), phencyclidine (Iwamoto, 1984; Mori et al., 2000; Simmons et al., 2010), THC (Δ^9-tetrahydrocannabinol) (Sañudo-Peña et al., 2000), nicotine (Benwell and Balfour, 1992; Simmons et al., 2010) and caffeine (El Yacoubi et al., 2000; Zhang et al., 2011).

The observation that all addictive drugs share stimulant properties is the basis of the *psychomotor stimulant theory of addiction* proposed by Wise and Bozarth in 1987. This theory suggests that addictive drugs activate a common neurobiological mechanism in the mesolimbic dopamine system that mediates both their reinforcing and psychomotor stimulant effects. The mesolimbic dopamine system includes dopaminergic neurons in the ventral tegmental area (VTA) of the midbrain and their projections in the limbic forebrain, especially in the nucleus accumbens (NAc) (Pierce and Kumaresan, 2006). According to the *psychomotor stimulant theory of addiction*, psychomotor activation induced by drugs is assumed to lead to approach behaviors facilitating the compulsive taking of drugs.

The *differentiator model* proposed by Newlin and Thomson (1990) suggests that initial sensitivity to both the stimulant and sedative effects of alcohol predicts future alcohol use and alcoholism. This model assumes that individuals that are likely to develop alcohol-related problems are more sensitive to the stimulant effects of alcohol and less sensitive to its sedative effects. The *differentiator model* is based on the fact that people frequently like stimulant effects and do not like sedative effects. Therefore, it suggests that individuals who experience stimulation rather than sedation after alcohol consumption will usually find alcohol more rewarding than regular people.

The stimulant effects of alcohol when studied in humans are rarely measured objectively and usually refer to the subjective state of stimulation individuals report after alcohol absorption (Hendler et al., 2013). Research on the stimulant effects of alcohol has essentially been conducted in animals in which behavioral stimulation can easily be evaluated