Brain Research Bulletin 125 (2016) 53–78

Contents lists available at ScienceDirect

Brain Research Bulletin

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

Review

Behavioral sensitization to ethanol: Neural basis and factors that influence its acquisition and expression

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ARTICLE INFO

Article history:
Received 28 July 2015
Received in revised form 7 April 2016
Accepted 8 April 2016
Available online 16 April 2016

Keywords:
Ethanol
Behavioral sensitization
Motor stimulant effect

ABSTRACT

Ethanol-induced behavioral sensitization (EBS) was first described in 1980, approximately 10 years after the phenomenon was described for psychostimulants. Ethanol acts on γ-aminobutyric acid (GABA) and glutamate receptors as an allosteric agonist and antagonist, respectively, but it also affects many other molecular targets. The multiplicity of factors involved in the behavioral and neurochemical effects of ethanol and the ensuing complexity may explain much of the apparent disparate results, found across different labs, regarding ethanol-induced behavioral sensitization. Although the mesocorticolimbic dopamine system plays an important role in EBS, we provide evidence of the involvement of other neurotransmitter systems, mainly the glutamatergic, GABAergic, and opioidergic systems. This review also analyses the neural underpinnings (*e.g.*, induction of cellular transcription factors such as cyclic adenosine monophosphate response element binding protein and growth factors, such as the brain-derived neurotrophic factor) and other factors that influence the phenomenon, including age, sex, dose, and protocols of drug administration. One of the reasons that make EBS an attractive phenomenon is the assumption, firmly based on empirical evidence, that EBS and addiction-related processes have common molecular and neural basis. Therefore, EBS has been used as a model of addiction processes. We discuss the association between different measures of ethanol-induced reward and EBS. Parallels between the pharmacological basis of EBS and acute motor effects of ethanol are also discussed.

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http://dx.doi.org/10.1016/j.brainresbull.2016.04.006
0361-9230/

1. Introduction

Subjects diagnosed with drug dependence exhibit a compulsive pattern of drug-taking behavior. They spend most of their time seeking the drug, using it, and recovering from its effects (Feltenstein and See, 2008). Not everyone who initiates drug consumption, however, progresses to drug abuse or dependence (Schramm-Sapyta et al., 2009). With regard to ethanol, approximately 11.5% of drinkers worldwide drink heavily weekly (World Health Organization, 2011). Therefore, it is important to assess the factors, alone and combined, that can discriminate subjects who are at risk from subjects who can maintain controlled drinking behavior despite regular contact with the drug. An important and still unanswered question is what are the processes that are involved in the transition from voluntary use to addiction. This review will focus on one of these putative processes: ethanol-induced behavioral sensitization (EBS), a phenomenon primarily expressed at the behavioral level after exposure to chronic, often intermittent, exposure to ethanol. A significant part of the review, however, will be devoted to the neural underpinnings of EBS. The Review is guided by the hypothesis that one of the reasons that make EBS an attractive phenomenon is the assumption that EBS and addiction-related processes have common molecular and neural basis. Empirical evidence supporting this phenomenon will critically discussed throughout the present work.

Before discussing the intricacies of EBS, it is noteworthy tracing back seminal studies that cemented the relevance of studying biological changes that accompany the development of addiction. Studies by Schulteis et al. (1995) and Rossetti et al. (1992) indicated that ethanol withdrawal was associated with an increase in intracranial self-stimulation (ICSS) reward thresholds and a 30% decrease in dopamine output in the ventral striatum. ICSS is a behavioral assay in which animals learn to electrically self-stimulate areas of the brain associated with reward. An increase in the intensity of the stimulation that is required to support the animal's response is taken as an index of depression or, more specifically, anhedonia (Fish et al., 2014). The administration of *N*-methyl-D-aspartate (NMDA) receptor antagonists reversed the dopaminergic deficit in the study by Rossetti et al. (1992), a result that was consistent with later work that suggested that persistent impairment in NMDA receptor-dependent long-term depression could mediate the transition to addiction (Kasanetz et al., 2010).

Another perspective on the processes that are involved in the transition from voluntary use to addiction focuses on detecting individual differences at the behavioral, cellular, and genetic levels that may predispose individuals to problematic drinking. This "marker" perspective has traditionally focused on genetic factors, but the search for a single gene or even a small number of genes that are predictive of alcohol abuse liability has been difficult. Perhaps the most successful finding was the differential probability of alcoholism in subjects who exhibited genetic alterations in the functioning of aldehyde dehydrogenase (ALDH; Garver et al., 2001). This enzyme catalyzes the oxidation of acetaldehyde, the primary metabolite of ethanol. The accumulation of this metabolite in peripheral blood is associated with facial flushing, autonomic activation, and other aversive reactions that seem to protect subjects from continued alcohol use (Inoue et al., 1980). These findings fueled the development of promising preclinical genetic therapies. Ocaranza et al. (2008) observed a long-lasting reduction of ethanol drinking (from ~1.2 g/kg/day to ~0.6 g/kg/day for up to 35 days) in Wistar rats that were injected with a viral vector that carried an anti-*Aldh2* antisense gene that reduced the activity of liver aldehyde dehydrogenase by 85%. Rivera-Meza et al. (2012) utilized dual expression gene transfer to simultaneously increase the activity of liver aldehyde dehydrogenase (ADH; the enzyme that breaks down alcohol into acetaldehyde) and decrease the activity of ALDH. This treatment induced a four-fold increase in arterial acetaldehyde levels, which was associated with a 60% reduction of ethanol consumption. Interestingly, co-administration of the acetaldehyde dehydrogenase inhibitor disulfiram blocked the development of EBS (Kim and Souza-Formigoni, 2010).

An important phenomenon that has been suggested to be associated with neuroadaptations after chronic drug use is behavioral sensitization. In drug-related studies, sensitization usually refers to the enhancement of locomotor activity following chronic drug administration (Masur and Boerngen, 1980; Post, 1980). More specifically, EBS refers to the progressive and long-lasting increase in the motor-activating effect of ethanol that results from repeated, often intermittent, drug administration (Masur and Boerngen, 1980; Post, 1980; Post and Weiss, 1988).

Behavioral sensitization has been related to the transition from drug use to addiction and is postulated to reflect sensitized neural circuits that are responsible for regulating the incentive salience of stimuli, leading the individual to a pathological state of wanting the drug (Robinson and Berridge, 1993). Sensitization to morphine has been associated with greater morphine-induced conditioned place preference (CPP; Shippenberg and Rea, 1997), and repeated exposure to amphetamine facilitates amphetamine self-administration (Piazza et al., 1990). Repeated treatment with a given drug (*e.g.*, tetrahydrocannabinol and cocaine) can also enhance subsequent locomotor activity in response to another drug (*e.g.*, amphetamine; Cortright et al., 2011; Liu et al., 2007), especially in vulnerable populations. Adolescent rats that were given a very brief exposure to nicotine, but not their counterparts that were given vehicle, subsequently exhibited cocaine-induced behavioral sensitization (McQuown et al., 2009). This cross-sensitization between different drugs of abuse suggests a common mechanism that underlies the development of behavioral sensitization and a likely way by which exposure to one drug increases the vulnerability to problematic engagement with another drug. Another finding that validates behavioral sensitization as a model of the transition to addiction is that it can be observed even 12 months after the termination of repeated amphetamine administration (Paulson et al., 1991). This striking persistence suggests that neuroadaptations that are induced by repeated drug treatment can be permanent and result in relapse to drug self-administration when appropriate conditions arise (*e.g.*, re-exposure to drug-associated cues). The relationship between sensitization and relapse, however, is still under scrutiny (Lenoir and Ahmed, 2007; Steketee and Kalivas, 2011). One possibility is that both phenomena are regulated by a third mechanism, such as Pavlovian associations between drug-mediated effects and environmental stimuli.

The present review focuses on behavioral sensitization as a paradigm for analyzing the determinants and consequences of ethanol exposure, beginning with a brief historical account of the discovery of EBS (Masur and Boerngen, 1980) and the resurgence in interest following the highly influential incentive sensitization theory of addiction by Robinson and Berridge (1993, 2001, 2003, 2004, 2008). An emphasis is placed on highlighting the challenges of studying EBS and discrepancies and consistencies across the literature that may help researchers who are interested in this phenomenon design their experiments and determine the optimal experimental strategies to test their hypotheses. One of the main aims of this article is to critically review the relationship between EBS and more conventional measures of ethanol reinforcement and between behavioral sensitization and ethanol drinking. The objective it to establish whether the development of behavioral sensitization to ethanol can be considered a proxy for the increased predisposition to ingest this drug.

Other important issues are also covered, including a detailed discussion of transmitter systems that underlie EBS, the differential sensitivity to EBS that is exhibited by mice *vs.* rats, and age-related