Alcohol xxx (2015) 1–8

Contents lists available at ScienceDirect

Alcohol

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

Corticostriatal circuitry and habitual ethanol seeking

Jacqueline M. Barker [a,*], Laura H. Corbit [b], Donita L. Robinson [c], Christina M. Gremel [d], Rueben A. Gonzales [e], L. Judson Chandler [a]

[a] Department of Neuroscience, Medical University of South Carolina, Charleston, SC 29425, USA
[b] School of Psychology, University of Sydney, Sydney, Australia
[c] Bowles Center for Alcohol Studies, Department of Psychiatry, University of North Carolina, Chapel Hill, NC, USA
[d] Department of Psychology, Neuroscience Graduate Program, University of California San Diego, La Jolla, CA, USA
[e] Department of Pharmacology, The University of Texas at Austin, Austin, TX, USA

ARTICLE INFO

Article history:
Received 4 January 2015
Received in revised form
22 March 2015
Accepted 26 March 2015

Keywords:
Habit
Alcohol
Prefrontal cortex
Dorsal striatum
Nucleus accumbens
Orbitofrontal cortex

ABSTRACT

The development of alcohol-use disorders is thought to involve a transition from casual alcohol use to uncontrolled alcohol-seeking behavior. This review will highlight evidence suggesting that the shift toward inflexible alcohol seeking that occurs across the development of addiction consists, in part, of a progression from goal-directed to habitual behaviors. This shift in "response strategy" is thought to be largely regulated by corticostriatal network activity. Indeed, specific neuroanatomical substrates within the prefrontal cortex and the striatum have been identified as playing opposing roles in the expression of actions and habits. A majority of the research on the neurobiology of habitual behavior has focused on non-drug reward seeking. Here, we will highlight recent research identifying corticostriatal structures that regulate the expression of habitual alcohol seeking and a comparison will be made when possible to findings for non-drug rewards.

Introduction

Identification of the neurobiological substrates of habitual ethanol seeking may help to guide the development of novel therapeutic strategies that can enable restoration of behavioral control. While reducing ethanol-seeking habits is not expected to be a stand-alone cure for addiction, or a solution for all individuals with alcohol-use disorders, the ability to restore cognitive control over ethanol-seeking behaviors may enable traditional therapeutic strategies. Despite the applicability of this model to addictive behavior (Everitt, 2014; Kalivas, 2008), a preponderance of the research into the neuroscience of habitual behavior has been performed with models of non-drug reward seeking (e.g., Yin & Knowlton, 2006), rather than ethanol. While it can be argued that the structures mediating non-drug habits regulate the development of habitual behavior in general, recent work suggests that alcohol reinforcers may differentially engage the neurocircuits that control behavioral flexibility (Barker, Taylor, De Vries, & Peters, 2014; Corbit, Nie, & Janak, 2012; Mangieri, Cofresí, & Gonzales, 2012; Shillinglaw, Everitt, & Robinson, 2014). In this review, we will focus on the novel application and extension of these findings to the development of habitual ethanol-seeking behavior that, in part, characterizes alcohol-use disorders. We will provide a framework for the role of habitual processes in ethanol-seeking behavior and summarize findings presented at the 2014 Alcoholism and Stress Meeting in Volterra, Italy with the intention to highlight novel observations on the role for corticostriatal circuits in the regulation of ethanol-seeking behavior (for a more in-depth review of the neuroanatomy of habitual processes in ethanol seeking, see Barker & Taylor, 2014; O'Tousa & Grahame, 2014).

Modeling conditioned behavior in alcohol-use disorders

In recent years, there has been a burgeoning interest in understanding drug seeking that is not mediated by the immediate rewarding properties of drugs of abuse. Work in both animals and humans has suggested drugs of abuse, including alcohol, are sought not only for their positive rewarding properties, but also out of habit (Adams, 1982; Dickinson, Wood, & Smith, 2002; Robbins & Everitt, 1999). In other words, while drugs of abuse are initially sought for their rewarding properties, over time and with repeated performance, drug seeking transitions to habitual reward-seeking behaviors that are more independent of the drug's immediate

* Corresponding author.
E-mail address: Barkerj@musc.edu (J.M. Barker).

http://dx.doi.org/10.1016/j.alcohol.2015.03.003
0741-8329/

rewarding properties. These habitual behaviors can be either self-initiated or elicited by environmental or interoceptive stimuli. This may contribute to compulsive drug seeking which occurs despite negative consequences of drug taking. This suggests that early drug-seeking behavior may be more goal directed and performed in relation to the expected rewarding effects via an expected action-outcome relationship. In contrast, habitual behavior is thought to be less sensitive to changes in outcome value or action-outcome contingency (Adams, 1982; Adams & Dickinson, 1981; Colwill & Rescorla, 1985; Dickinson, 1985). These working definitions led to objective methods for assessing instrumental response strategy. By manipulating either the action-outcome contingency (a method called contingency degradation) or outcome value (often through outcome devaluation methods), it can be determined whether an action is being performed in a goal-directed or habitual manner.

A significant literature implicates aberrant cue sensitivity and habit learning in addiction. In human addicts, drug-paired cues have been shown to elicit drug craving and motivate drug-taking and approach behaviors (Koob & Volkow, 2010; Pickens et al., 2011; Sinha & Li, 2007; Yoder et al., 2009). In rodent models, the ability of drug-paired cues to promote drug-seeking and relapse-like behaviors has been well established using conditioned place preference (for review see Tzschentke, 1998) and cue-induced reinstatement paradigms (McFarland & Kalivas, 2001). In addition, reward-paired cues have been shown to invigorate instrumental reward seeking through the use of Pavlovian-to-instrumental transfer (PIT) paradigms.

While a majority of what is known about cue-mediated reward seeking has focused on non-drug rewards (e.g., sucrose) or psychostimulants, there is growing evidence that ethanol-paired cues may impact reward-seeking behavior in ways that differ from these reinforcers. For example, in a study of PIT (conducted under extinction conditions), when rats were trained that a discrete cue predicted ethanol delivery, presentation of that same cue in the presence of a lever that previously earned ethanol resulted in enhanced responding (Corbit & Janak, 2007). These observations suggest that the motivational properties of the alcohol-paired stimulus invigorated responding. This result is expected based on previous studies with non-drug reward. What was unique, however, about the alcohol-predictive cue was that when it was presented while animals had access to a lever that previously earned sucrose, sucrose-seeking behavior was also increased by the alcohol-predictive stimulus. Under particular training conditions, stimuli that predict a reward other than that earned by an instrumental response can also enhance instrumental responding – an effect known as general PIT. However, typically a stimulus that predicts a reward earned by another trained, but currently unavailable response does not increase and may even reduce responding (Corbit & Balleine, 2005; Nadler, Delgado, & Delamater, 2011). Thus, the finding that ethanol cues invigorate reward seeking in a general – potentially habitual – way, rather than in an outcome-specific manner, as is typical for cues paired with non-drug reward, is an important distinction between the effects of stimuli paired with alcohol compared to other rewards (Corbit & Janak, 2007; Glasner, Overmier, & Balleine, 2005). Furthermore, as general and specific PIT effects rely on independent neural circuits (Corbit & Balleine, 2005, 2011; Corbit, Janak, & Balleine, 2007), the observed general effect of alcohol-predictive stimuli may indicate that alcohol-predictive stimuli recruit different neural substrates than stimuli paired with natural rewards. In addition, ethanol-paired contexts have been shown to render non-drug reward seeking insensitive to changes in outcome value (Ostlund, Maidment, & Balleine, 2010). This suggests that simply being exposed to ethanol-paired contexts promotes a shift from goal-directed to habitual behavior. While it is unclear how exposure to these cues and contexts drives the expression of habitual behavior, one attractive idea is that drug-paired cues impinge upon cognitive resources that may be necessary for the expression of goal-directed actions (e.g., Jentsch & Taylor, 1999; Tiffany, 1990).

Habitual behaviors are of particular interest in understanding persistent alcohol seeking that contributes to alcohol-use disorders. Indeed, alcoholics have been shown to have increased reliance on habit-like response strategies as well as activation of the neurocircuitry supporting habitual behavior, as compared to control subjects (Sjoerds et al., 2013). However, it is unclear whether these differences predate drug exposure and potentially represent increased risk for the development of alcohol-use disorders, or whether differences in response strategy selection in alcoholics result from chronic ethanol exposure itself. Importantly, work in animal models has demonstrated that there are both individual differences in risk for the formation of ethanol-seeking habits (Barker, Zhang, et al., 2014) as well as ethanol-induced changes in the development of habitual behaviors (Corbit et al., 2012). In particular, prior to any ethanol exposure, it has been shown that individuals with high Pavlovian approach toward a food reinforcer also show rapid development of ethanol-seeking habits. This suggests that pre-existing differences in cue reactivity may predispose certain individuals toward loss of flexible ethanol seeking. Considerable evidence also indicates that ethanol itself may drive the development of habitual behaviors. Indeed, habitual control over ethanol self-administration has been shown to develop more rapidly than for non-drug reinforcers (Corbit et al., 2012; Dickinson et al., 2002). Recent work has also revealed that this is not due to the use of an ethanol reinforcer *per se*; indeed, self-administered alcohol is not always sufficient to promote habit formation (Hay, Jennings, Zitzman, Hodge, & Robinson, 2013; Samson et al., 2004; Shillinglaw et al., 2014). Instead, ethanol exposure can produce changes in the neural circuits encoding goal-directed and habitual behaviors that ultimately facilitate the transition away from goal-directed actions to habitual behavior (Corbit et al., 2012).

Regulation of reward seeking within the striatum

A significant literature has identified striatal subregions as critical regulators of reward-seeking behavior. While the ventral striatum is thought to be largely involved with cued outcome-mediated behaviors, the more dorsal aspects of the striatum appear to have distinct contributions to goal-directed and habitual reward-seeking behavior. The nucleus accumbens (NAc) can be subdivided into two primary subregions – the NAc shell and the core – with distinct network connectivity with the prefrontal cortex (PFC). The NAc shell receives extensive input from the more ventral infralimbic PFC, a structure known to be required for the expression of habitual behavior (Barker, Taylor, & Chandler, 2014; Coutureau & Killcross, 2003). The more dorsal prelimbic PFC, which plays a role in the acquisition of goal-directed actions (Killcross & Coutureau, 2003; Tran-Tu-Yen, Marchand, Pape, Di Scala, & Coutureau, 2009), more extensively innervates the NAc core. Though their precise roles differ, both the NAc core and NAc shell have been implicated repeatedly in the integration of reward information that is critical for the performance of Pavlovian and instrumental behaviors (Hart, Leung, & Balleine, 2014; O'Doherty et al., 2004). In particular, as with other reinforcers, NAc core and NAc shell inactivation differentially impact the effect of ethanol cues on behavior. For example, inactivation of NAc core, but not NAc shell, reduces conditioned responding for ethanol cues (Gremel & Cunningham, 2008), as well as renewal of responding in non-ethanol paired contexts (e.g., LaLumiere & Kalivas, 2008; Peters,