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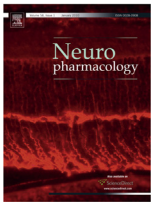

Invited review

Extinction of drug seeking: Neural circuits and approaches to augmentation

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ABSTRACT

Extinction training can reduce drug seeking behavior. This article reviews the neural circuits that contribute to extinction and approaches to enhancing the efficacy of extinction. Extinction of drug seeking depends on cortical-striatal-hypothalamic and cortical-hypothalamic-thalamic pathways. These pathways interface, in the hypothalamus and thalamus respectively, with the neural circuits controlling reinstatement of drug seeking. The actions of these pathways at lateral hypothalamic orexin neurons, and of perifornical/dorsomedial hypothalamic derived opioid peptides at kappa opioid receptors in the paraventricular thalamus, are important for inhibiting drug seeking. Despite effectively reducing or inhibiting drug seeking in the short term, extinguished drug seeking is prone to relapse. Three different strategies to augment extinction learning or retrieval are reviewed: pharmacological augmentation, retrieval – extinction training, and provision of extinction memory retrieval cues. These strategies have been used in animal models and with human drug users to enhance extinction or cue exposure treatments. They hold promise as novel strategies to promote abstinence from drug seeking.

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1. Introduction

Just as animals, including humans, readily learn to self-administer a variety of drugs, so too can they learn to reduce this drug seeking. Drug seeking behavior is extinguished when the contingency between drug seeking and delivery of the drug reward is broken. This reduction in drug seeking is robust but it is not completely permanent. Drug seeking can be reinstated under a number of conditions including following presentations of a drug prime (De Wit and Stewart, 1982), a stressor (Shaham and Stewart, 1995), a drug associated stimulus (De Wit and Stewart, 1982), or by a return to the training context when extinction training occurs in a different context (Crombag and Shaham, 2002). The conditions under which drug seeking can be reinstated in animal models are similar to the circumstances promoting relapse to drug use in humans, such as stress/negative affect (Shiffman and Waters, 2004) and exposure to drug-associated people and places (Drummond et al., 1995). Animal studies of reinstatement of drug seeking are therefore powerful tools to understand the neurobiology of relapse (Shaham et al., 2003).

Studies of the behavioral and neural mechanisms of extinction of drug seeking have the potential to be equally powerful in understanding how drug seeking can be reduced. The finding that responding that has been lost via extinction training can be recovered or reinstated under these conditions has been interpreted to mean that extinction training results in new learning and memory formation. The most popular view of this learning is that retrieval of extinction memories is bound to the context and time of extinction training (Bouton, 2004, 2002). This occurs because extinction learning involves learning about the same stimuli and actions as initial drug self-administration learning. At the end of extinction training, animals hold conflicting memories about the status of drug-associated stimuli and actions. These have been associated with both the presence and absence of drug rewards. To resolve this conflict or ambiguity, animals are hypothesized to rely on contextual information for retrieval of the extinction memory (Bouton, 1994a, 1994b, 1993). This view of extinction as involving new context-dependent learning and memory formation, competing with the original learning for control over motivation and behavior, is strongly supported by a wealth behavioral data. It suggests that the reduction in drug self-administration behaviors during extinction training is not a passive process. Instead, this reduction is an active process that may have a defined neural circuitry. In this paper I review work from our laboratory, and that of others, that has begun to map this circuitry.

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In extinction training, animals engage in the full repertoire of drug seeking behavior but do not receive the drug reward. In human drug users, explicit extinction training during treatment, if used at all, is limited to exposures to drug-associated stimuli and abstinence does not appear to involve explicit extinction at all. However, cue exposure treatments can involve explicit extinction of proximal actions involved in drug use (Dawe et al., 1993; Raw and Russell, 1980) and abstinence invariably involves extinction of distal actions associated with drug seeking. The relationship between extinction of instrumental and Pavlovian associations in animal models of drug seeking and clinical treatments for drug use is clearly an important one. However, the aim of our studies of extinction of drug seeking in animals has not been to model extant treatments or approaches to abstinence, but rather to understand the neural circuits that reduce drug seeking.

2. Neural circuits for extinction of drug seeking

2.1. Corticostriatal-hypothalamic pathway

The nucleus accumbens shell (AcbSh) is an important locus for inhibiting drug seeking after extinction training. Peters, LaLumiere and Kalivas (Peters et al., 2008) trained rats to respond for i.v. cocaine and then extinguished this responding. Peters et al. (2008) reported that reversible inactivation of the AcbSh prior to test via infusions of the GABA agonists baclofen and muscimol reinstated extinguished responding. This suggests that activity in AcbSh is important for inhibiting drug seeking after extinction training. We were able to show that this role extends to the extinction of alcohol seeking. We (Millan et al., 2010) trained rats to respond for alcoholic beer and then extinguished this responding. On test, rats received infusions of baclofen and muscimol and these infusions reinstated responding. Glutamate actions at AcbSh AMPA receptors appear especially important for the expression of extinction. Extinction of cocaine-seeking up regulates expression of the GluR1 and GluR2/3 AMPA receptors subunits in AcbSh and viral-mediated over-expression of these subunits in AcbSh inhibits cocaine seeking and reduces stress-induced reinstatement of cocaine seeking (Sutton et al., 2003). Moreover, AcbSh microinjections of an AMPA receptor antagonist dose-dependently reinstate extinguished responding for an alcoholic beer reinforcer (Millan and McNally, 2011). However this role of AcbSh AMPA is complex. Just as extinction of cocaine seeking regulates expression of the GluR1 and GluR2/3 AMPA receptors subunits, so too is incubation of cocaine craving associated with an increase in expression of GluR1-containing (Anderson et al., 2008) and an increase in GluR2-lacking AMPA receptors (Conrad et al., 2008).

Despite clear evidence implicating AcbSh in the inhibition of drug seeking after extinction, many questions remain about this role. First, the AcbSh is also important for promoting reinstatement of drug seeking, especially context-induced reinstatement (Bossert et al., 2006, 2007; Chaudhri et al., 2009; Fuchs et al., 2008). For example, reversible inactivation of AcbSh (Fuchs et al., 2008), infusions of dopamine D1R antagonists (Bossert et al., 2007; Chaudhri et al., 2009), or infusions of group II metabotropic glutamate receptor agonists (Bossert et al., 2006), each prevent context-induced reinstatement of drug seeking. In general, pauses or reductions in the activity of AcbSh medium spiny neurons are associated with initiation of reward seeking or consumption (Krause et al., 2010). Thus, there is a dual role for AcbSh in promoting (i.e. reinstatement) and preventing (i.e. extinction) drug seeking. Second, the AcbSh afferents critical for inhibiting drug seeking after extinction remain poorly understood. There is some evidence from functional disconnection studies that a projection from infralimbic prefrontal cortex (IL) to AcbSh may be important. Peters et al. (2008) reported that inactivation of IL, or pharmacological disconnection of the IL from AcbSh reinstated extinguished cocaine seeking. Yet retrograde tracing studies from the AcbSh have not identified a specific IL – AcbSh pathway recruited during extinction expression (Bossert et al., 2012; Hamlin et al., 2009), and in other studies reversible inactivation of IL had no effect on extinction expression (Willcocks and McNally, 2013). Moreover, ventromedial PFC (vmPFC) (including dorsal IL and ventral PL) has been implicated in the incubation of cocaine craving (Koya et al., 2009). Finally, under some conditions, selective silencing of vmPFC neurons (Bossert et al., 2011) or disconnecting a vmPFC – AcbSh pathway (Bossert et al., 2012) can prevent reinstatement which is the opposite to that expected if IL were solely responsible for inhibiting drug seeking. Basolateral amygdala (BLA) afferents to AcbSh have also been implicated in extinction expression. Specifically, we showed that a glutamatergic projection from BLA to AcbSh mediates inhibition of alcoholic beer seeking after extinction. Pharmacological disconnection of BLA and AcbSh, via BLA reversible inactivation and AcbSh infusions of an AMPA receptor antagonist, prevented expression of extinction of alcoholic beer seeking (Millan and McNally, 2011). Conversely, a glutamatergic pathway from BLA to Acb, including AcbSh, is also implicated in drug seeking (Stuber et al., 2011). These findings that multiple cortical and subcortical inputs to AcbSh may be involved in the extinction and reinstatement of drug seeking are unsurprising (Mogenson et al., 1980). It is possible that these differences are related to differences between drug reinforcers as well as to differences in anatomical specificity of the various manipulations across the different studies. Regardless, they emphasize the need to understand why and when these different inputs are recruited as well as to understand the potential differences in function supported by them.

The answers to these questions may come from a deeper understanding of the functional consequences of AcbSh neuronal organization. AcbSh medium spiny neurons exist as neuronal ensembles with distinct afferents and efferents (Wright et al., 1996; Wright and Groenewegen, 1996, 1995), and hence are embedded in distinct compartments. It is likely that different compartments of AcbSh neuronal ensembles contribute to the distinct functions of reinstatement and extinction as well as selecting between different inputs to control behavior (Goto and Grace, 2008). In fact, there is some evidence that this is the case for extinction and reinstatement of drug seeking. We (Marchant et al., 2009) labeled AcbSh neurons that project to the lateral hypothalamus (LH) and studied their activity during tests for the context-induced reinstatement and extinction of alcoholic beer seeking. Neurons in the ventral regions of the medial AcbSh (AcbShV) and projecting to LH were recruited during expression of reinstatement, whereas neurons in the dorsomedial region of the medial AcbSh (AcbShDm) and projecting to LH were recruited during expression of extinction. This suggests a dorsal–ventral functional compartmentalization within the medial AcbSh that promotes (ventral) or prevents (dorsal) drug seeking, with these different compartments sharing similar efferents but with distinct functions. Interestingly, these dorsal and ventral AcbSh compartments receive different afferents from the medial prefrontal cortex (PFC), including from different neurons within the same vmPFC subregions (Thompson and Swanson, 2010). A dorsal–ventral distinction is one possible compartmentalization within AcbSh relevant to understanding extinction of drug seeking. It could help resolve some of the contradictory findings in the literature regarding the role of PFC–AcbSh interactions in regulating reinstatement and extinction of drug seeking.

The AcbSh projects extensively to LH (Marchant et al., 2009; Yoshida et al., 2006). These projections are important for inhibiting drug seeking after extinction training. As noted above, a specific projection from AcbShDm to LH is recruited during extinction expression (Marchant et al., 2009). Moreover, reinstatement of drug