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Review

Role of corticostriatal circuits in context-induced reinstatement of drug seeking

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ABSTRACT

Drug addiction is characterized by persistent relapse vulnerability during abstinence. In abstinent drug users, relapse is often precipitated by re-exposure to environmental contexts that were previously associated with drug use. This clinical scenario is modeled in preclinical studies using the context-induced reinstatement procedure, which is based on the ABA renewal procedure. In these studies, context-induced reinstatement of drug seeking is reliably observed in laboratory animals that were trained to self-administer drugs abused by humans. In this review, we summarize neurobiological findings from preclinical studies that have focused on the role of corticostriatal circuits in context-induced reinstatement of heroin, cocaine, and alcohol seeking. We also discuss neurobiological similarities and differences in the corticostriatal mechanisms of context-induced reinstatement across these drug classes. We conclude by briefly discussing future directions in the study of context-induced relapse to drug seeking in rat models. Our main conclusion from the studies reviewed is that there are both similarities (accumbens shell, ventral hippocampus, and basolateral amygdala) and differences (medial prefrontal cortex and its projections to accumbens) in the neural mechanisms of context-induced reinstatement of cocaine, heroin, and alcohol seeking.

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Abbreviations: BLA, basolateral amygdale; mOFC, medial orbitofrontal cortex; CA1, field CA1 of the hippocampus; NAc Core, nucleus accumbens core; CA3, field CA3 of the hippocampus; NAc Shell, nucleus accumbens shell; DHipp, dorsal hippocampus; OFC, orbitofrontal cortex; dlStr, dorsolateral striatium; pDHipp, posterior dorsal hippocampus; dmPFC, dorsomedial prefrontal cortex; vCPu, ventral caudate putamen; dmStr, dorsomedial striatum; VHipp, ventral hippocampus; dStriatum, dorsal striatum; vmPFC, ventromedial prefrontal cortex; dSub, dorsal subiculum; vSub, ventral subiculum; lOFC, lateral orbitofrontal cortex; VTA, ventral tegmental area; lShell, lateral nucleus accumbens shell; AP5, NMDA receptor antagonist; M+B, Muscimol+Baclofen ($GABA_A$ and $GABA_B$ receptor agonists, respectively); CART, Cocaine and Amphetamine Regulated Transcript; Naloxone-methiodide, a charged analog of naloxone (a preferential mu opioid receptor antagonist); CNQX, AMPA/kainate receptor antagonist; PP2, Src-family kinase inhibitor; CTAP, μ-opioid receptor antagonist; Ro25-6981, NR2B subunit-containing NMDAR antagonist; JNJ16259685, mGluR1-selective antagonist; SCH 23390, Dopamine D1-like receptor antagonist; LY379268, $mGluR_{2/3}$ agonist; TTX, tetrodotoxin (tetrodotoxin-sensitive voltage-gated sodium channel blocker)

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Contents

1. Introduction

Drug addiction is characterized by persistent relapse vulnerability during abstinence (Hunt et al., 1971; O'Brien, 2005). This *relapse* is a defining feature of drug addiction and a major impediment to successful treatment (Sinha et al., 2011) (Box 1). In abstinent drug users, relapse is often precipitated by re-exposure to environmental *contexts* that are associated with drug use (O'Brien et al., 1992) (Box 1). This clinical scenario is modeled in preclinical studies using a *context-induced reinstatement* procedure (Crombag and Shaham, 2002; Crombag et al., 2008), which is based on the ABA *renewal* procedure (Bouton and Bolles, 1979; Nakajima et al., 2000) (Box 1). In this procedure, laboratory animals are initially trained to self-administer a drug in a specific environmental context (context A). Following self-administration training, drug seeking is extinguished through non-reinforcement in an alternative, distinct, environmental context (context B). The contexts typically differ in their auditory, visual, tactile, olfactory, and circadian properties. After repeated extinction sessions, drug seeking is extinguished and the laboratory animal is then tested, in extinction conditions, for context-induced reinstatement in the original training context. The operational definition of *reinstatement* in this procedure is significantly higher non-reinforced operant responding in the original training context A as compared to the extinction context B (Box 1). Since the initial demonstration with speedball (a heroin–cocaine combination) (Crombag and Shaham, 2002), context-induced reinstatement of extinguished drug seeking has been observed with several major drugs of abuse (Crombag et al., 2008), including heroin (Bossert et al., 2004), cocaine (Crombag et al., 2002), alcohol (Burattini et al., 2006), and nicotine (Diergaarde et al., 2008).

In line with the aims of this special edition of *Brain Research*, in this review we summarize neurobiological findings from preclinical studies that have focused on the role of cortical and corticostriatal circuits in context-induced reinstatement of drug seeking. During the last twelve years, many studies indicate a role of several corticostriatal projections in context-induced reinstatement of drug seeking (Bossert et al., 2013). Below, we discuss these neurobiological findings separately for heroin, cocaine, and alcohol (see Table 1 for summary of findings). In addition to corticostriatal pathways, we also discuss the role of ventral tegmental area (VTA) in context-induced reinstatement of drug seeking, because dopamine (Fallon and Moore, 1978) and glutamate (Yamaguchi et al., 2007, 2011) neurons in this brain region project to the different corticostriatal areas that are covered in our review.

Note that although there are published studies on context-induced reinstatement of nicotine or methamphetamine seeking (Diergaarde et al., 2008; Widholm et al., 2011; Wing and Shoaib, 2008), we do not include these studies in our review because these studies only assessed the effect of systemic drug injections on context-induced reinstatement. We also do not review studies on relapse to drug seeking after periods of abstinence (e.g., incubation of cocaine craving) in which a single extinction session in the presence of contextual drug cues (the self-administration chamber) and discrete drug infusion cues (tone, light) is used to assess relapse to drug seeking (Fuchs et al., 2006; Marchant et al., 2013b; Pickens et al., 2011). We exclude these studies, because we and others have shown that responding in the extinction tests used to study relapse after abstinence is context-independent (Crombag et al., 2008).

2. Role of corticostriatal inputs in context-induced reinstatement of drug seeking

2.1. Heroin

The first preclinical reinstatement study on heroin-priming-induced reinstatement of heroin seeking was published in 1983 (de Wit and Stewart, 1983). Since then, several labs have investigated mechanisms of reinstatement of heroin seeking induced by heroin priming, stress, and discrete cues (Bossert et al., 2013; Shaham et al., 2000; Shalev et al., 2002). It has been known for many years that environmental contexts associated with use of heroin, and other opiates, plays a critical role in relapse during abstinence (Robins et al., 1974; Wikler, 1973). Therefore, a decade ago we began a series of studies on the neurobiological substrates of context-induced reinstatement of heroin seeking. Based on Bouton's research and theoretical writing (Bouton and Swartzentruber, 1991; Bouton, 2002), and our initial study with speedball (a heroin–cocaine combination) (Crombag and Shaham, 2002), our original intention was to study mechanisms underlying the *occasion setter's* properties of the drug-associated context, or the ability of the context to 'renew' the conditioned response to the discrete cue (compound tone-light) previously paired with heroin injections after extinction of the response to these cues in a non-drug context (Box 1).