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Role of amygdala in drug memory

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ABSTRACT

Drug addiction is a chronic brain disorder with the hallmark of a high rate of relapse to compulsive drug seeking and drug taking even after long-term abstinence. Addiction has been considered as an aberrant memory that has been termed "addiction memory." Drug-related memory plays a critical role in the maintenance of learned addictive behaviors and emergence of relapse. Disrupting these long-lasting memories by administering amnestic agents or other manipulations during specific phases of drug memory is a promising strategy for relapse prevention. Recent studies on the processes of drug addiction and relapse have demonstrated that the amygdala is involved in associative drug addiction learning processes. In this review, we focus on preclinical studies that used conditioned place preference and self-administration models to investigate the differential roles of the amygdala in each phase of drug-related memory, including acquisition, consolidation, retrieval, reconsolidation, and extinction. These studies indicate that the amygdala plays a critical role in both cue-associative learning and the expression of cue-induced relapse to drug-seeking behavior.

1. Introduction

Addiction is defined as a loss of control over drug use and obsessive drug seeking despite predictable adversity. It is characterized by compulsive drug-taking behavior and high rates of relapse to drug use even after prolonged abstinence from drug taking (Childress et al., 1999; Grant et al., 1996; Kilts et al., 2001). Although numerous studies have been conducted in the past several decades, the neural mechanisms that underlie drug addiction remain unclear, and no effective medications exist to cure drug addiction (Kalivas & Volkow, 2005). Many studies have convincingly supported the hypothesis that addiction usurps normal neural processes that underlie learning and memory. The formation of long-term drug-related associative memory contributes to persistent drug use and relapse to compulsive drug seeking when abstinent human addicts or animals are reexposed to previously drug-paired cues (Hellemans, Everitt, & Lee, 2006; Nestler, 2001; Robbins, Ersche, & Everitt, 2008).

The term "memory of addiction" was first used by Mello in 1972. It was soon recognized as a comprehensive concept within the "reinstatement" framework, with implications for the entire addiction syndrome (Edwards & Gross, 1976). Emphasis on the process of conditioned learning has deepened our understanding of the important role of learned experiences in the development and maintenance of addictive behaviors, which has been demonstrated in both preclinical and clinical research (O'Brien, Childress, McLellan, & Ehrman, 1992). In human addicts, addiction syndromes that comprise compulsive drug taking and seeking may be controlled by learned conditioned associations between the intense reinforcing effects of repeated drug use and drug-paired cues. Investigations of the neural mechanisms that underlie conditioned associations are helpful to understand their role in relapse and its prevention (O'Brien, Childress, Ehrman, & Robbins, 1998). Accumulating evidence indicates that addiction is a pathological emotional memory-related disease because of the overwhelmingly intense associations between addictive behaviors and the social context where drug use behavior occurs. This has been supported by evidence that addicts are prone to recurrent drug craving and drug use when they are exposed to previously conditioned cues that predict the reinforcing effects of abused drugs (Leshner, 1997). The formation of drug-related memory results from repeated drug intake and may control persistent addictive behavior that consists of unmanageable loss of control for drug use and compulsive craving (Heyne, May, Goll, & Wolffgramm, 2000; Wolffgramm & Heyne, 1995). Therefore, revolutionizing our understanding of the nature of addiction and addiction memory can improve treatment strategies for addicts. Behavioral therapy methods, such as "cue-exposure therapy," have been based on this progression of our understanding of drug addiction (Flor, Knost, & Birbaumer, 1997; Szegedi et al., 2000). However, drug-related memory stubbornly persists, and behavioral therapy methods cannot suppress its expression or modify the original drug-related memory (Boening et al., 2001).

The amygdala is primarily considered as a brain center that controls emotional responses, supported mainly by several studies that used fear conditioning paradigms (LeDoux, 2000; LeDoux,

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2003; Pare, Quirk, & Ledoux, 2004). From the perspective of anatomical structures, the amygdala has intricate bidirectional connections with the prefrontal cortex (PFC) that are more elaborated in human and nonhuman primates than in rodents (Ghashghaei & Barbas, 2002; Ghashghaei, Hilgetag, & Barbas, 2007; Wise, 2008). Complicated bidirectional projections also exist between higher sensory areas and single sensory areas and the amygdala (Amaral, 2003). The amygdala also projects nerve fibers to the mesolimbic system (Brog, Salyapongse, Deutch, & Zahm, 1993; Groenewegen, Berendse, Wolters, & Lohman, 1990), such as the nucleus accumbens (NAc), which has been shown by functional magnetic resonance imaging (fMRI) studies to be activated when craving occurs in cocaine addicts (Bonson et al., 2002; Breiter et al., 1997; Childress et al., 1999). The amygdala is considered as the primary region for encoding both aversive (LeDoux, 2003) and appetitive (Everitt, Cardinal, Parkinson, & Robbins, 2003) conditioned stimulus information in conditioned learning. When addicts are exposed to drug-related stimuli, including drug paraphernalia and cues, even after a prolonged period of drug abstinence, drug craving is intensely elicited, resulting in relapse to drug intake (Dackis & O'Brien, 2001; Gawin, 1991). Laboratory animal studies have demonstrated that the amygdala is crucial for conditioned drug seeking. The basolateral amygdala (BLA) plays a critical role in the formation of cocaine-induced conditioned place preference (Fuchs, Weber, Rice, & Neisewander, 2002). The indispensable role of the BLA is also revealed in another animal model, cocaine self-administration, using a second-order schedule of reinforcement (Everitt, Morris, O'Brien, & Robbins, 1991; Kantak, Black, Valencia, Green-Jordan, & Eichenbaum, 2002; Whitelaw, Markou, Robbins, & Everitt, 1996). Additionally, the central nucleus of the amygdala (CeA) has been shown to be required for the acquisition and expression of morphine-induced CPP (Rezayof, Zarrindast, Sahraei, & Haeri-Rohani, 2002; Zarrindast et al., 2004) and the incubation of drug craving (Li et al., 2008; Lu et al., 2005).

The role of the amygdala in drug addiction has been well reviewed (Bernardi, Ryabinin, Berger, & Lattal, 2009; Koob, 2009). Given that drug-related memory has important implications in drug addiction and relapse and that the amygdala plays an indispensable role in encoding conditioned drug-related information, the present review focuses on studies that the amygdala plays different roles in various phases of drug-related memory using self-administration and CPP animal models. The characteristics and functions of the self-administration and CPP procedures have been discussed in detail in previous reviews (Lu, Shepard, Hall, & Shaham, 2003). The subjective reinforcing effects produced by drugs serve as unconditioned stimuli in the self-administration procedure. In the CPP procedure, reinforcement is produced by passively received drugs, and the drug-paired context or cues serve as conditioned stimuli. The association between drug reinforcement in the training procedure and the drug-paired context or cues can be established by repeated training sessions. After the conditioned response to unconditioned stimuli is established, such acquired behaviors can be extinguished by repeated exposure to the prior drug-paired context or cues without drug delivery. In both the self-administration and CPP procedures, the extinguished behaviors can be reinstated by the drugs used in the training sessions or the drug-paired cues or context (Mueller & Stewart, 2000; Parker & McDonald, 2000), which has been termed as reinstatement (Stretch, Gerber, & Wood, 1971).

2. Role of amygdala in drug memories assessed by drug-induced conditioned place preference

2.1. Cocaine and methamphetamine

Learned associations between the environmental context or discrete cues and the reinforcing effects of cocaine have been considered to play significant roles in cocaine use and relapse (O'Brien et al., 1998). Our recent study revealed that the neuronal protein kinase cyclin-dependent kinase 5 (Cdk5) in the BLA is a key molecule in the consolidation and reconsolidation of associative memories between cocaine-paired environmental cues and the reinforcing effects of cocaine in the CPP procedure (Li et al., 2010). In this study, we investigated whether the consolidation and reconsolidation of cocaine cue memories can be inhibited by microinjection of the Cdk5 antagonist β-butyrolactone into the BLA or CeA. We found that microinjection of β-butyrolactone into the BLA but not CeA immediately after cocaine training sessions disrupts the consolidation of cocaine cue memories, but this effect disappear when the antagonist was microinjected 6 h after the training sessions. The results indicate that Cdk5 activity in the BLA mediates the consolidation process of cocaine cue memories. Additionally, Cdk5 activity in the BLA is required for the reconsolidation of cocaine cue memories. These findings suggest that the BLA is a key brain area for various phases of cocaine cue memories. In addition to Cdk5, we recently demonstrated that the reconsolidation of cue memories associated with cocaine requires GSK-3β activation in the BLA (Wu et al., 2011). Several studies have indicated that different molecular mechanisms in the BLA complex are required for cocaine cue memories. Previous studies have demonstrated that phospholipase D-linked metabotropic glutamate receptor (mGluR) signaling, the protein kinase C (PKC) signaling pathway, and protein synthesis in the BLA are important for the expression of cue-conditioned responses to cocaine (Krishnan et al., 2011; Lai et al., 2008). The role of the BLA and signaling molecules in the retrieval of cocaine cue memories has been well established in the cocaine-induced CPP model (Lai et al., 2008). The expression of established cocaine-induced CPP can be blocked by systemic administration of anisomycin, a nonspecific protein synthesis inhibitor, 30 min before the retrieval test. A similar phenomenon can be mimicked by microinjection of anisomycin or cycloheximide into the BLA before the retrieval test, suggesting that the BLA is a critical region in the mediation of the retrieval of cocaine cue memories. To investigate the signaling pathways in the BLA, intra-amygdala infusion of the PKC inhibitor NPC 1543 or mitogen-activated protein/extracellular signal-regulated kinase kinase (MEK) inhibitor U0126 blocked the expression of cocaine-induced CPP in a subsequent test without co-occurring locomotor activity holdback or aversive effects induced by the manipulations. The evidence provided by this experiment indicates that the PKC signaling pathway and downstream protein synthesis in the BLA control the retrieval of cocaine cue memories (Lai et al., 2008).

The noradrenergic system is known to be required for the reconsolidation process after a stable memory has been activated, which has been well studied in both aversive and appetitive experience learning (Abrari, Rashidy-Pour, Semnanian, & Fathollahi, 2008; Bernardi, Lattal, & Berger, 2006; Debiec & Ledoux, 2004; Diergaarde, Schoffelmeer, & De Vries, 2006; Fricks-Gleason & Marshall, 2008; Przybyslawski, Roullet, & Sara, 1999; Robinson & Franklin, 2007). The involvement of the noradrenergic system in cocaine-related memory has been demonstrated in cocaine-induced CPP in animals (Bernardi et al., 2009). The impairment of reconsolidation of cocaine-induced CPP produced by post-retrieval systemic administration of propranolol suggests that β-adrenergic receptors are critical for the reconsolidation of cocaine memory. To determine the precise mechanism that mediates the impairment of reconsolidation of cocaine-induced CPP produced by post-retrieval systemic administration of propranolol, the nonspecific β-adrenergic receptor antagonist was replaced by specific β_1, β_2, and α_1 receptor antagonists, and systemic administration was replaced with intra-BLA infusion. In addition to systemic administration, post-retrieval intra-BLA infusion of β_2 and α_1 receptor antagonists

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