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Retrieval-induced NMDA receptor-dependent Arc expression in two models of cocaine-cue memory

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ABSTRACT

The association of environmental cues with drugs of abuse results in persistent drug-cue memories. These memories contribute significantly to relapse among addicts. While conditioned place preference (CPP) is a well-established paradigm frequently used to examine the modulation of drug-cue memories, very few studies have used the non-preference-based model conditioned activity (CA) for this purpose. Here, we used both experimental approaches to investigate the neural substrates of cocaine-cue memories. First, we directly compared, in a consistent setting, the involvement of cortical and subcortical brain regions in cocaine-cue memory retrieval by quantifying activity-regulated cytoskeletal-associated (Arc) protein expression in both the CPP and CA models. Second, because NMDA receptor activation is required for Arc expression, we investigated the NMDA receptor dependency of memory persistence using the CA model. In both the CPP and CA models, drug-paired animals showed significant increases in Arc immunoreactivity in regions of the frontal cortex and amygdala compared to unpaired controls. Additionally, administration of a NMDA receptor antagonist (MK-801 or memantine) immediately after cocaine-CA memory reactivation impaired the subsequent conditioned locomotion associated with the cocaine-paired environment. The enhanced Arc expression evident in a subset of corticolimbic regions after retrieval of a cocaine-context memory, observed in both the CPP and CA paradigms, likely signifies that these regions: (i) are activated during retrieval of these memories irrespective of preference-based decisions, and (ii) undergo neuroplasticity in order to update information about cues previously associated with cocaine. This study also establishes the involvement of NMDA receptors in maintaining memories established using the CA model, a characteristic previously demonstrated using CPP. Overall, these results demonstrate the utility of the CA model for studies of cocaine-context memory and suggest the involvement of an NMDA receptor-dependent Arc induction pathway in drug-cue memory interference.

1. Introduction

Discrete stimuli or contexts previously associated with the rewarding properties of drugs are a major cause of relapse among addicts. When repeatedly paired with drug intake, initially neutral stimuli acquire incentive motivational value and encounters with these drug-associated cues induce intense physiological cravings in addicts (Childress, Ehrman, McLellan, & O'Brien, 1988). These conditioned responses to drug-paired cues are a major cause of relapse. Indeed, degree of craving measured during treatment for drug dependence is predictive of drug use resumption (Hartz, Frederick-Osborne, & Galloway, 2001). Because drug-paired cues evoke memories that influence drug-seeking and relapse, a better understanding of the neurobiological basis for this phenomenon will aid in the development of novel, biologically-based therapies for drug addicts.

To date, drug-cue memory interference studies have relied on measures of drug-seeking, such as instrumental responding for drug access (self-administration) or choosing a previously drug-paired environment [conditioned place preference (CPP)]. The study of drug-cue memories could be expanded to include behavioral

Abbreviations: CPP, conditioned place preference; CA, conditioned activity; *Arc/Arg3.1*, activity-regulated cytoskeletal-associated gene; IEG, immediate-early gene; NMDA, N-methyl-D-aspartate; Cg1, cingulate cortex; PrL, prelimbic cortex; IL, infralimbic cortex; OF&Cl, orbitofrontal cortex and claustrum; S1, primary somatosensory cortex; dCPu, dorsal caudate putamen; DEn, dorsal endopiriform nucleus; AcbC, nucleus accumbens core; AcbSh, nucleus accumbens shell; M1 & M2, primary and secondary motor cortices; DG, dentate gyrus; CA3 and CA1, subfields of the hippocampus; BLA, basolateral amygdala; LA, lateral amygdala; CeA, central amygdala; D-APV, D(−)-2-amino-5-phosphonopentanoic acid; vmPFC, ventromedial prefrontal cortex.

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measures distinct from drug-seeking. The conditioned activity (CA) model is a Pavlovian paradigm in which repeated, non-contingent pairings of a psychostimulant with an environment produces enhanced locomotion upon drug-free exposure to this environment (Pickens & Crowder, 1967; Beninger & Hahn, 1983; Beninger & Herz, 1986; Mazurski & Beninger, 1991). Like self-administration and CPP, CA relies on an association between environmental cues and drug. Unlike self-administration and CPP, CA is not based on preference; instead, it allows for memory strength assessment by measuring conditioned locomotion in the drug-paired context. Because the CA model employs a non-operant response, it can be used to study the neurochemical basis of drug-conditioned behaviors without the confounding influences of goal-directedness or response-reward expectancy (Olmstead, Lafond, Everitt, & Dickinson, 2001).

The activity-regulated cytoskeletal-associated gene (*Arc*/*Arg3.1*) is an effector immediate-early gene (IEG) widely implicated in experience-dependent synaptic plasticity and memory consolidation (Steward, Wallace, Lyford, & Worley, 1998; Guzowski et al., 2000; Holloway & McIntyre, 2011). Several groups have used Arc as a marker of neuronal activity to investigate corticolimbic circuits underlying drug-cue memories (Schiltz, Kelley, & Landry, 2005; Zavala, Osredkar, Joyce, & Neisewander, 2008), but direct comparisons of brain regions involved using two separate models of drug-context memories are lacking. In the present study, we examined Arc expression in brain regions activated during drug-cue memory retrieval in both the CPP and CA models, training and testing subjects in a common setting, with the behavioral task as the only variable. We sampled areas previously implicated in cue-elicited drug seeking behaviors (e.g., amygdalar, corticolimbic, hippocampal, and accumbens regions). Additionally, we measured Arc expression in regions we had no *a priori* reason to believe would be involved in drug-related memories (e.g., motor and somatosensory cortices). Because CPP and CA models both result in the formation of drug-cue associative memories, we expected substantial overlap in brain regions showing enhanced levels of Arc expression. However, because CPP consists of a choice-based component, but CA does not, task-specific regional involvement was also anticipated.

Previous studies have shown that N-methyl-D-aspartate (NMDA) glutamate receptors are required for both the induction of *Arc* transcript (Lyford et al., 1995) and for targeting the newly synthesized transcript to active synapses (Wallace, Lyford, Worley, & Steward, 1998; Steward & Worley, 2001). Using CPP, we have previously demonstrated that NMDA receptor antagonist (MK-801 or memantine) administration immediately following memory retrieval diminishes cocaine-paired compartment preference in subsequent tests (Alaghband & Marshall, 2013). Although the CA model has been used to investigate the role of NMDA receptors in acquisition (Stewart & Druhan, 1993; Cervo & Samanin, 1996) and expression (Bespalov & Zvartau, 1996; Bespalov, Zvartau, Balster, & Beardsley, 2000) of drug-cue memories, no studies to date have used CA to interrogate drug memory maintenance and persistence. Here, we used CA to explore the role of NMDA receptors in post-retrieval modification of a cocaine-context association. Specifically, these experiments compared the effects of systemic administrations of two NMDA receptor antagonists, MK-801 and memantine, on cocaine-CA memory maintenance.

2. Materials and methods

2.1. Subjects

Male Sprague–Dawley rats (Charles River Laboratories; Hollister, CA) weighing 200–225 g upon arrival were individually housed in a temperature-controlled (21 ± 2 °C) colony room with *ad libitum* access to food and water. Lights were on from 06:00 to 18:00, and all training and testing procedures were conducted between 08:00 and 14:00 each day. All experiments were conducted in accordance with the National Institutes of Health guidelines for animal care and were approved by the Institutional Animal Care and Use Committee of the University of California, Irvine.

2.2. Drugs

Cocaine-HCl, (+)-MK-801 hydrogen maleate, and memantine-HCl were purchased from Sigma–Aldrich (St. Louis, Missouri, USA) and dissolved in saline (0.9% NaCl). For training, cocaine-HCl was dissolved to a final concentration of 12 mg/ml (of the salt) and administered in a volume of 1 ml/kg body weight. MK-801 and memantine (0.2 and 10 mg/kg, respectively; doses as free-base) and 0.9% saline were given at 2 ml/kg body weight. All drug treatments and saline were administered intraperitoneally (i.p.). The two NMDA receptor antagonists were used to ensure that any effects were due to common actions on this receptor system. Both MK-801 and memantine function as open-channel antagonists that block NMDA receptors only when these channels are activated (Chen et al., 1992). However, MK-801 and memantine interact with the NMDA receptor complex in distinct ways. Memantine is a low-affinity blocker with rapid blocking kinetics (Ribeiro Do Couto, Aguilar, Manzanedo, Rodríguez-Arias, & Miñarro, 2004; Tzschentke & Schmidt, 1999), while MK-801 is a high-affinity blocker with slower kinetics (Parsons, Danysz, & Quack, 1999). Additionally, these compounds differ in their binding site. MK-801 binds to the PCP site inside the pore of the receptor (Moring, Niego, Ganley, Trumbore, & Herbette, 1994; Sakurada, Masu, & Nakanishi, 1993), whereas memantine is believed to bind at or near the Mg2+ binding site (Chen & Lipton, 1997; Chen et al., 1992).

2.3. Apparatus

2.3.1. Place preference apparatus

Conditioning took place in a three-chamber apparatus (Med Associates, Inc.) consisting of two larger compartments (28 × 21 cm) separated by a smaller compartment (12 × 21 cm). The two larger compartments differed in visual, olfactory, and tactile cues. One compartment had white walls and a wire mesh floor above pine shavings, while the other compartment had black and white checkered walls and a metal-bar floor above cedar shavings. The middle compartment had two gray walls and a solid gray polyvinyl floor above corncob bedding. Additionally, this middle compartment had a white wall and a checkered wall leading into the correspondingly patterned adjacent compartments. Guillotine doors, patterned to match the outer compartments, separated the three compartments and were lowered on training days and raised on test days. Photobeams located in the walls were used to quantify time spent and distance traveled in each compartment.

As described below, some animals were placed in a control environment consisting of a clear plastic box (40 × 40 cm), distinct from the home cage, located in a room separate from both the CPP apparatus and holding rooms.

2.3.2. Activity chamber apparatus

Conditioning took place in activity monitors (Med Associates, Inc.) consisting of open-field boxes (43.2 × 43.2 × 30.5 cm) with transparent Plexiglas walls and an opaque plastic floor. Boxes were equipped with 16 photocell beams (2.5 cm off the floor) for measuring horizontal activity.