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Rapid, transient potentiation of dendritic spines in context-induced relapse to cocaine seeking

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Abstract

Addiction to cocaine produces long-lasting, stable changes in brain synaptic physiology that might contribute to the vulnerability to relapse. In humans, exposure to environmental contexts previously paired with drug use precipitates relapse, but the neurobiological mechanisms mediating this relapse are unknown. Initiation of cocaine relapse via re-exposure to a drug-associated context elicited reinstatement of cocaine seeking as well as rapid, transient synaptic plasticity in the nucleus accumbens core (NAcore), measured as an increase in dendritic spine diameter. These results show that rapid context-evoked synaptic potentiation in the NAcore may underpin relapse to cocaine use.

Keywords

Context-induced relapse; cocaine; synaptic potentiation; dendritic spines; nucleus accumbens core

Introduction

Chronic use of cocaine produces enduring neuroadaptations in the corticostriatal brain circuitry involved in the synaptic plasticity contributing to learning behavioral tasks, including morphological changes in dendritic spines of medium spiny neurons (MSNs) of the nucleus accumbens (NA) (Dumitriu et al., 2012; Gipson et al., 2013; Shen et al., 2009). These adaptations are thought to impair the ability of the NA to process information, adaptively regulate reward-seeking behaviors, and thereby contribute to relapse to drug use in substance use disorders. Contextual stimuli associated with drug exposure can serve as occasion setters and initiate craving (Childress et al., 1993) and relapse (Crombag et al., 2008) to drug seeking that is associated with activating the glutamatergic projection from the prefrontal cortex to the nucleus accumbens (Koob and Volkow, 2010).

Contingent cue-induced reinstatement of cocaine seeking produces rapid, transient changes in spine head diameter (d_h) of MSNs in the nucleus accumbens core (NAcore) (Gipson et al., 2013). Although discrete, contingent drug-paired conditioned stimuli provoke relapse of

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drug seeking and elicit synaptic potentiation in NAc_{core}, it is unknown if non-contingent environmental contextual cues associated with the rewarding effects of cocaine also potentiate NAc_{core} MSNs. Thus, the primary objective of the present study was to test the hypothesis that re-exposure to non-contingent drug-paired contextual cues via a contextual renewal paradigm elicits simultaneous cocaine seeking behavior and rapid, transient potentiation of NAc_{core} dendritic spines. To this end, an adapted A-B-A renewal procedure (Bouton and Bolles, 1979; Crombag and Shaham, 2002) of contextual cocaine seeking was employed in which cocaine self-administration occurred in one environment (containing distinct visual, auditory, olfactory, and tactile cues). The animals then underwent extinction training in a saliently distinct environment. Contextual renewal of cocaine seeking was elicited by returning the animal to the original cocaine-paired context, and NAc_{core} synaptic strength was estimated by measuring dendritic spine diameter and density.

Materials and Methods

(See Appendix S1 for Details)

Male Sprague Dawley rats (250 g; Charles River Laboratories) were individually housed with a 12:12 hr dark/light cycle. All experimentation occurred in the dark cycle. Rats received food ad libitum until the day prior to behavioral training, after which food restriction (20 g of rat chow per day) was implemented and maintained throughout the experiment. Rats were allowed 1 week to acclimate to the vivarium before inducing anesthesia and implanting indwelling jugular catheters. All procedures were in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the Assessment and Accreditation of Laboratory Animal Care.

Cocaine self-administration and extinction training was conducted in one of two environmental contexts (Context A and Context B) which differed in visual, auditory, olfactory and tactile stimuli (see Table S1). Animals were randomly assigned to receive either A-B-A or B-A-B training conditions. Daily 2-hr cocaine self-administration or yoked saline sessions began seven days after surgery, using a Fixed Ratio 1 schedule with a 20-second time out. Active lever presses yielded a 0.2 mg infusion of cocaine as well as a light and tone stimulus. Following 10 consecutive self-administration sessions (10 infusions/day), rats began daily extinction training in the alternate context for 14 sessions where an active lever press yielded no programmed consequence. Some rats were immediately taken for spine analysis just before a renewal session (T=0). Renewal was induced by placing the animal back into its original cocaine-paired context for either 15 or 45 minutes, after which rats were anesthetized and transcardially perfused for spine analysis. Yoked saline animals were either placed back in the saline-paired context for 45 min or immediately taken for spine analysis (T=0).

Detailed procedures for dendritic spine procedures are published (Shen et al., 2009). Briefly, a confocal microscope was used to image DiI-labeled sections. Images of DiI-labeled dendrites (Fig. 1b) were acquired via optical sectioning using a 63× oil immersion objective (Plan-Apochromat, Zeiss; NA = 1.4, WD = 90 μm). Images were deconvoluted prior to analysis, and a 3-D perspective was rendered by Imaris software package (Bitplane; Saint

Paul, MN). Only spines on dendrites beginning at $>75 \mu\text{m}$ and ending at $200 \mu\text{m}$ distal to the soma and after the first branch point were quantified from cells localized to the NAc core. The length of quantified dendrites was $45\text{--}55 \mu\text{m}$. Five–12 neurons were analyzed from each animal, and the minimum end segment diameter (spine head) was set at $0.143 \mu\text{m}$. All spine density and d_h data were statistically analyzed after averaging the values for all the neurons in each animal. Behavioral data were analyzed using repeated-measures ANOVA, and a Bonferroni-corrected *post hoc t* test.

Results

Drug-paired contextual stimuli elicited robust active lever pressing compared to inactive lever pressing during extinction at $T=15$ and $T=45$ ($F_{(5,41)} = 47.27$, $P < 0.001$; Fig 1a). Akin to the time course of reinstatement to discrete conditioned cues (Gipson et al., 2013), the increase in lever pressing was maximal during the first 10 min of the session, and progressively decreased for the remainder of the session. Cumulative distribution of d_h revealed a rightward shift at $T=0$, and a further shift at $T=15$ compared to yoked saline (two-way ANOVA, group: $F_{(5,1721)} = 7046$, $P < 0.0001$; d_h $F_{(4,1721)} = 70.57$, $P < 0.0001$; interaction: $F_{(20,1721)} = 18.63$, $P < 0.0001$; Fig 1c). At $T=0$, d_h was increased in rats extinguished from cocaine self-administration ($0.414 \pm 0.014 \mu\text{m}$) compared to yoked saline animals at both $T=0$ ($0.343 \pm 0.023 \mu\text{m}$) and $T=45$ ($0.347 \pm 0.022 \mu\text{m}$), supporting long-lasting synaptic potentiation after cocaine withdrawal (Figs 1c/d) (Wolf, 2010). Mean d_h was further increased at $T=15$ ($0.488 \pm 0.007 \mu\text{m}$), and returned to pre-reinstatement levels by $T=45$ ($0.398 \pm 0.014 \mu\text{m}$; one-way ANOVA; $F_{(4,233)} = 10.20$, $p < 0.0001$). No change in spine density was found between groups (Fig 1e).

Discussion

The present study shows that akin to discrete cue-induced reinstatement of cocaine seeking (Gipson et al., 2013), initiation of context-induced cocaine relapse elicits rapid, transient increases in NAc core d_h . In addition to the NAc core, the nucleus accumbens shell (NAshell) also plays an important role in context-induced cocaine relapse, as both accumbens subregions have been found to facilitate context-induced motivation to seek cocaine (Fuchs et al., 2008). Thus, in the future it will be of interest to examine if rapid plasticity also occurs in the NAshell in context-induced cocaine relapse. Given the importance of environmental contexts previously associated with drug use in precipitating relapse, the current findings extend the possibility that targeting the rapid LTP-like plasticity underlying initiation of relapse to drug seeking may have potential relevance to relapse prevention and pharmacotherapy development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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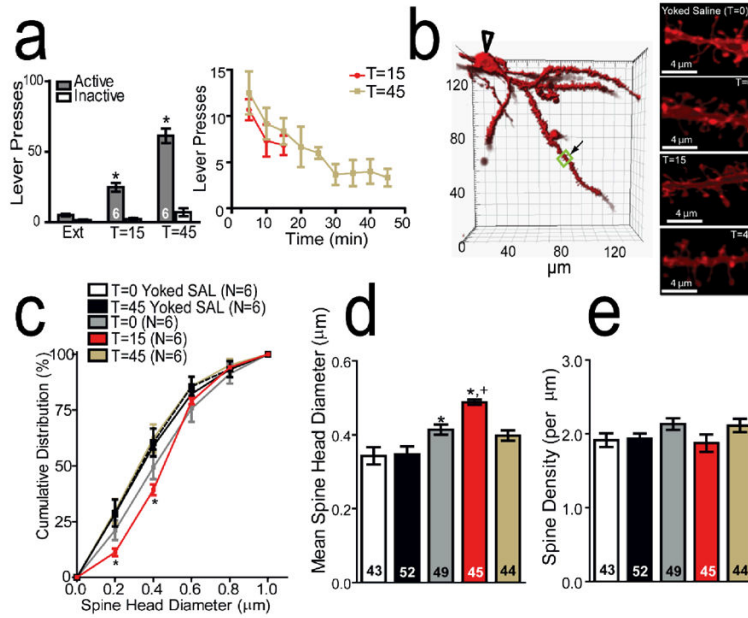


Figure 1. Contextual reinstatement of cocaine-seeking rapidly enlarges spine head diameter in NAc core MSNs
(a) Contextual reinstatement of cocaine-seeking increased active lever pressing at 15 or 45 min prior to euthanizing rats for spine measurements. Time course of active lever pressing during the cue reinstatement session. **(b)** Example of NAc core medium spiny neuron. Clear arrow - location of soma; boxed region - segment analyzed from a T=0 animal. Sample dendrites from NAc core spiny cells in yoked saline ($d_h = 0.342 \mu\text{m}$) or cocaine-trained rats at T=0 ($0.411 \mu\text{m}$), T=15 ($0.498 \mu\text{m}$), or T=45 ($0.399 \mu\text{m}$) min after contextual reinstatement. **(c)** Cumulative d_h frequency plot. **(d)** Cocaine self-administration increased d_h at T=0 compared to yoked saline. Spine d_h was further elevated at T=15, and returned to pre-reinstatement levels at T=45. **(e)** No change in spine density was found between groups. * $p < 0.05$, compared to yoked saline or extinction lever presses, + $p < 0.05$, compared to T=0 cocaine.