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COCAINE SELF-ADMINISTRATION AND EXTINCTION ALTER MEDULLARY NORADRENERGIC AND LIMBIC FOREBRAIN cFOS RESPONSES TO ACUTE, NONCONTINGENT COCAINE INJECTIONS IN ADULT RATS

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Abstract—Central noradrenergic (NA) signaling contributes critically to multiple behavioral effects of cocaine administration, particularly stress- and anxiety-related effects. The present study examined the ability of acute cocaine to induce the immediate early gene product, cFos, in NA neurons and stress-related neural circuits in rats that were cocaine-naïve, or had a history of cocaine self-administration with or without extinction. Rats implanted with jugular catheters were trained to self-administer cocaine (0.5-mg/kg/infusion), with a subset subsequently trained on extinction. Cocaine-naïve controls were handled daily. After a final day of self-administration, extinction, or handling, rats received an i.p. injection of either cocaine (20-mg/kg) or saline, and 90 min later were anesthetized and perfused. Tissue sections were processed for immunoperoxidase labeling of nuclear cFos with either immunoperoxidase or immunofluorescent cytoplasmic labeling of dopamine beta hydroxylase or tyrosine hydroxylase. Acute cocaine increased the number of activated NA neurons within the caudal nucleus of the solitary tract (NTS; A2 cell group) in cocaine-naïve and extinguished rats, but not in rats that only self-administered. Extinction attenuated cocaine-induced cFos activation in NA neurons of the caudal ventrolateral medulla (A1/C1 cell groups), and attenuated cFos within the paraventricular nucleus of the hypothalamus, the apex of the central neuroendocrine stress axis. Cocaine consistently increased cFos in the bed nucleus of the stria terminalis, regardless of history. NA neurons of the locus coeruleus (A6 cell group) were not activated after cocaine administration in any experimental group. Thus, the ability of cocaine to activate central stress circuitry is altered after cocaine self-administration. Our results suggest a unique role for the NTS in cocaine-induced reinstatement, as extinction training enhanced the ability of cocaine to activate NA neurons within this region. These findings suggest central NA systems originating in the caudal brainstem as potential targets for the treatment of cocaine addiction. **© 2014 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: bed nucleus of the stria terminalis, paraventricular nucleus of the hypothalamus, locus coeruleus, nucleus of the solitary tract, ventrolateral medulla, cocaine.

INTRODUCTION

Cocaine addiction is a major health and social problem that affects millions of individuals. Cocaine blocks monoaminergic reuptake transporters (Pifl et al., 1995) which leads to increased monoaminergic synaptic transmission (Bardo, 1998; White and Kalivas, 1998). Although cocaine increases transmission of all monoamines, investigations into the effects of cocaine on brain activity have classically focused on mesolimbic and mesocortical dopaminergic systems. More recent studies have revealed an important role for noradrenergic (NA) systems in mediating the behavioral effects of cocaine exposure [cf. (Weinshenker and Schroeder, 2007; Sofuoglu and Sewell, 2009). For example, NA enzymes, transporters, and receptors are critical for cocaine-induced locomotion and sensitization (Drouin et al., 2002), and manipulations of the NA system alter the ability of cocaine to support conditioned place preference (Schank et al., 2006) or aversion (Freeman et al., 2008). Increased NA transmission has been identified as a significant contributor to aversive and stressful effects of acute cocaine administration (McCance-Katz et al., 1998), and to anxiety produced by cocaine withdrawal (Buffalari et al., 2012). Further, decreased NA transmission can interfere with cocaine self-administration (Schroeder et al., 2013), while increases can enhance such behavior (Rocha, 2003). A role for NA transmission in reinstatement of cocaine-seeking behavior after extinction has been particularly well documented. Central injections of norepinephrine elicit reinstatement of cocaine-seeking behavior (Brown et al., 2011), and decreased NA signaling via adrenergic receptor blockade attenuates stress-induced (Leri et al., 2002) or cocaine-primed reinstatement (Zhang and Kosten, 2005). Inhibition of dopamine-beta hydroxylase (DbH, the rate-limiting enzyme for NA synthesis) decreases multiple forms of reinstatement (Schroeder et al., 2013), while selective inhibition of NA reuptake

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Abbreviations: ANOVA, analysis of variance; AP, area postrema; DAB, diaminobenzidine; DbH, dopamine-beta hydroxylase; LC, locus coeruleus; NA, noradrenergic; NTS, nucleus of the solitary tract; PVN, paraventricular nucleus of the hypothalamus; TH, tyrosine hydroxylase; vlBNST, ventral lateral subdivision of the bed nucleus of the stria terminalis; VLM, ventrolateral medulla.

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decreases cocaine-seeking behavior triggered by exposure to cocaine-paired cues (Economidou et al., 2011).

Despite strong evidence that NA participates in the effects of acute cocaine, cocaine self-administration, and reinstatement of cocaine-seeking, little is known regarding how cocaine affects NA neurons in either cocaine-naïve animals, or animals with a history of cocaine self-administration and extinction. Previous reports indicate that acutely administered cocaine increases cFos, a marker of neuronal activation, within the nucleus of the solitary tract (NTS) and locus coeruleus (LC) (Grabus et al., 2004; Zahm et al., 2010). However, the phenotypic identity of activated neurons has not been reported. The present study sought to elucidate the effect of acute cocaine on medullary and pontine NA cell groups, and in two primary projection targets of medullary NA neurons (McKellar and Loewy, 1982; Sawchenko and Swanson, 1982; Woulfe et al., 1990; Terenzi and Ingram, 1995), i.e., the paraventricular nucleus of the hypothalamus (PVN), and the anterior ventral lateral subdivision of the bed nucleus of the stria terminalis (vlBNST). We also examined how a history of cocaine self-administration and extinction might alter the ability of acute cocaine to activate neurons in these regions.

EXPERIMENTAL PROCEDURES

Subjects

Male Sprague–Dawley rats (Harlan, Indianapolis, IN, USA) weighing 225–250 g upon arrival were individually housed in a humidity- and temperature-controlled (21–22 °C) vivarium on a reversed light–dark cycle (lights off 07:00 h, on 19:00 h) with unlimited access to water. Rats received 20 g of food daily between the hours of 14:00 and 16:00. Training and experimental sessions were conducted during the dark phase at the same time each day (09:00–15:00) and perfusions were performed between 11:00 and 14:00. All experimental procedures were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and under local IACUC approval.

Surgery

A control group of rats ($n = 14$) was handled daily for 5 days before acute cocaine or vehicle injection. A second group ($n = 29$) was anesthetized with isoflurane and implanted with jugular catheters as described previously (Donny et al., 1998). These rats were allowed at least 7 days to recover from surgery. For the first 2 weeks after surgery, catheters were flushed daily with 0.1 ml of sterile saline containing heparin (30 units/ml), timentin (66.67 mg/ml), and streptokinase (9333 U/ml) to maintain catheter patency and prevent infection. Thereafter, catheters were flushed with heparinized saline before and after each experimental session throughout the cocaine self-administration experiments.

Self-administration training

Self-administration and extinction training was conducted in operant conditioning chambers within sound-attenuating, ventilated cubicles (Med Associates, St. Albans, VT, USA). The chambers were equipped with two retractable response levers on one side panel, with a 28-V white light above each lever, and a red house light near the chamber ceiling. Intravenous cocaine infusions were delivered via syringe pump controlled by a drug delivery system (Med Associates). Experimental events and data collection were automatically controlled by interfaced computer software (Med Associates).

After recovery from surgery, rats were trained to intravenously self-administer cocaine on a fixed-ratio 1 (FR1) schedule in operant chambers. Daily self-administration sessions were initiated by the extension of two levers into the chamber and illumination of the red house light. During each 2-h session, each active lever press resulted in an infusion of cocaine (0.2 mg/kg/50 μl infusion) along with presentation of a 5-s light-tone stimulus complex, followed by a 20-s timeout period during which active lever responses were recorded but resulted in no programed consequences. Inactive lever presses were always recorded but had no programed consequences. Rats received 12-h/2-h cocaine self-administration sessions (one session per day), during which all rats achieved a criterion of receiving least 10 infusions of cocaine.

Extinction training

After completing the self-administration phase, a subset of rats ($n = 13$) was subjected to daily extinction sessions. Extinction sessions were initiated by extension of the two levers into the chamber and illumination of the red house light. Sessions lasted 2 h, during which active and inactive lever presses were recorded but resulted in no programed consequences. All rats received 8 days of extinction training, during which responding decreased to $< 20\%$ of responding recorded during the final 3 days of cocaine self-administration.

Treatment-induced cFos induction

After 5 days of daily handling (controls, $n = 14$), 12 days of cocaine self-administration without extinction ($n = 16$), or 12 days of self-administration followed by 8 days of extinction ($n = 13$), rats were injected with either cocaine (20 mg/kg, i.p.) or saline, then returned to their home cage for 90–120 min before perfusion. This post-treatment survival time is similar to that used in previous studies examining the effects of acute cocaine on cFos induction (Nestler, 2004; Zahm et al., 2010). Perfusion and tissue collection have been previously described (Banihashemi and Rinaman, 2006). Briefly, rats were deeply anesthetized with sodium pentobarbital (Nembutal, 10 mg/kg BW i.p.) and transcardially perfused using aqueous 0.15 M NaCl for 1 min followed by 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4) for 10 min. Fixed brains were removed from the skull, blocked, frozen, and sectioned coronally (35 μm) on a freezing-stage microtome. Sections from the upper cervical spinal cord through the rostral corpus callosum were collected in six adjacent sets and stored in cryopreservant

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