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Blockade of patch-based μ opioid receptors in the striatum attenuates methamphetamine-induced conditioned place preference and reduces activation of the patch compartment

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ABSTRACT

The behavioral effects of methamphetamine (METH) are mediated by the striatum, which is divided into the patch compartment, which mediates limbic and reward functions, and the matrix compartment, which mediates sensorimotor tasks. METH treatment results in repetitive behavior that is related to enhanced relative activation of the patch versus the matrix compartment. The patch, but not the matrix compartment contains a high density of μ opioid receptors, and localized blockade of patch-based μ opioid receptors attenuates METH-induced patch-enhanced activity and repetitive behaviors. Numerous studies have examined patch-enhanced activity and the contribution of patch-associated μ opioid receptors to METH-induced repetitive behavior, but it is not known whether patch-enhanced activity occurs during METH-mediated reward, nor is it known if patch-based μ opioid receptors contribute to METH reward. The goals of this study were to determine if blockade of patch-based μ opioid receptors alters METH-induced conditioned place preference (CPP), as well activation of the patch and matrix compartments following METH-mediated CPP. A biased conditioning paradigm was used to assess CPP, and conditioning occurred over an 8-d period. Animals were bilaterally infused in the striatum with the μ-specific antagonist CTAP or vehicle prior to conditioning. Animals were tested for preference 24 h after the last day of conditioning, sacrificed and the brains processed for immunohistochemistry. Blockade of patch-based μ opioid receptors reduced METH-induced CPP, and reduced patch-enhanced c-Fos expression in the striatum following METH-mediated CPP. These data indicate that patch-enhanced activity is associated with METH-mediated reward and patch-based μ opioid receptors contribute to this phenomenon.

1. Introduction

The striatum mediates the behavioral effects of psychostimulants, and can be divided into the patch (striosome) and matrix compartments based on differences in neurochemistry and neuroanatomy. The spiny neurons of the patch compartment express a high density of μ opioid receptors, while the spiny neurons of the matrix compartment express few μ opioid receptors, but are enriched in calbindin (Gerfen et al., 1985; Herkenham and Pert, 1981; Pert et al., 1976). The patch compartment receives input from limbic cortices, and projects almost exclusively to the substantia nigra pars compacta (SNpc), which sends dopaminergic inputs back to the striatum (Fujiyama et al., 2011; Gerfen, 1984; Tokuno et al., 2002), while the matrix compartment receives input from sensorimotor cortices and comprises the majority of the direct and indirect pathways that mediate movement (Crittenden and Graybiel, 2011; Fujiyama et al., 2011; Gerfen, 1984, 1989). Based on these differences, the activity of the patch and matrix compartments are likely regulated by diverse mechanisms, and mediate different aspects of behavior.

While the matrix compartment is related to sensorimotor processing, the limbic-based circuits of the patch compartment mediate repetitive behaviors such as psychostimulant-induced stereotypy (Canales, 2005; Canales and Graybiel, 2000; Crittenden and Graybiel, 2011). Enhanced relative activation of the patch versus matrix compartment is observed during psychostimulant-induced stereotypy, and the degree of stereotypy is positively correlated with patch-enhanced activation in dorsolateral striatum (Canales and Graybiel, 2000). Since the patch compartment has dense connectivity with regions that process emotional information, stereotypy is likely the due to the enhanced relative activation of patch-based circuits, resulting in behaviors that are driven by internal emotional states, at the expense of switching to adaptive behaviors based on the external environment (Aliane et al., 2009; Canales, 2005; Canales and Graybiel, 2000; Crittenden and Graybiel, 2011). The relative enhanced activation of

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the patch compartment could contribute to the development of habitual drug abuse, due to the interactions of the patch compartment with regions that mediate reinforcement and relapse into drug-seeking behavior (Canales, 2005). Of note, previous work has shown that animals will repeatedly electrically self-stimulate when electrodes are placed in or near the patch compartment, supporting the notion that this region plays a role in processes that guide motivation and reward learning (White and Hiroi, 1998). However, whether enhanced relative activation of the patch versus matrix compartment is associated with psychostimulant-mediated reward is unknown, and the mechanisms that contribute to patch-enhanced activity during psychostimulant-mediated reward not identified.

Striatal μ opioid receptors, since they are expressed specifically on the neurons of the patch compartment are in an optimal position to modulate the activity of this region. Our previous work indicated that blockade of striatal μ opioid receptors attenuated patch-enhanced activation and stereotypy following METH treatment (Horner et al., 2010). While it has been shown that central μ opioid receptors modulate psychostimulant-mediated reward (Schroeder et al., 2007), the specific contribution of patch-based μ opioid receptors is unknown. These data indicate that μ opioid receptors play a role in the activation of neurons of the patch compartment following psychostimulant treatment, as well as psychostimulant-induced behaviors. However, whether patch-based μ opioid receptors contribute to patch-enhanced activation in the context of METH-mediated reward has not been examined. The goals of this study were to determine if patch-enhanced activity is associated with METH-mediated reward, and whether patch-based μ opioid receptors contribute to this phenomenon.

2. Materials and methods

2.1. Drugs

(±)METH-HCl was generously provided by the National Institute on Drug Abuse, and injected subcutaneously in a volume of 1 ml/kg body weight. The dose of METH (2 mg/kg; (Suzuki and Misawa, 1995)) was based on the weight of the salt. The μ opioid receptor antagonist CTAP (D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr) was obtained from Tocris Bioscience (Minneapolis, MN, USA) and dissolved in sterile buffered artificial cerebrospinal fluid (aCSF; 144 mM NaCl; 2.68 mM KCl; 1.6 mM $CaCl_2$; 2.6 mM $MgCl_2$; 0.4 mM KH_2PO_4, pH, 7.2) at 0.8 μg/μl (Schroeder et al., 2007).

2.2. Animals and surgery

Male Sprague-Dawley rats (Charles River Laboratories, Raleigh, NC, USA), weighing 250–350 g were used in all experiments. Rats were housed in plastic cages in a temperature-controlled room on a 14:10 h light/dark cycle with free access to food and water. All animal care and experimental manipulations were approved by the Institutional Animal Care and Use Committee of Mercer University School of Medicine and were in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*. The minimum possible number of animals (based on power analyses) was used for our experiments and measures were taken to minimize any suffering that might occur during our procedures.

One week after arrival at our facility, rats underwent surgery for the placement of bilateral indwelling intrastriatal cannulae. Rats were anesthetized with ketamine (90 mg/kg, i.p.) and xylazine (9 mg/kg, i.p.) and stainless steel 26-gauge guide cannulae 3.5 mm in length (Plastics One, Roanoke, VA, USA) were implanted bilaterally, based on the coordinates of Paxinos and Watson (Paxinos and Watson, 2005) in the rostral striatum, at +1.5 mm from bregma, ± 3.0 mm lateral to midline and 3.5 mm below the surface of the skull. The cannulae were secured to the skull with dental acrylic and anchored with stainless steel surgical screws inserted into the skull. The guide cannulae were kept patent with 31-gauge obturators that were the same length as the guides. Rats were allowed to recover for 2–3 days before the start of the experiment. Only rats whose cannulae were in the rostral striatum were included in subsequent analyses.

2.3. Conditioned place preference (CPP)

Conditioning chambers consisted of a 30×30×30-cm Plexiglass chamber divided into two distinct compartments separated by a removable partition. One compartment had solid gray walls, while the other compartment had vertical alternating black and white stripes that were 2.5 cm wide. Floors were stainless steel wire mesh of differing mesh size to provide differential tactile cues. One day before the start of the conditioning procedure, rats were habituated chambers for 30 min with the partition removed. Twenty-four h later, the rats were returned to the chambers for 20 min with the partition removed, and the time on each side recorded to determine each animal's initial bias. Conditioning began the next day, and consisted of 8 days of alternating saline or METH injections, with rats confined to the preferred side, as determined by the preconditioning bias test, on saline exposure days (days 1, 3, 5 and 7 of conditioning,), and the initially non-preferred side on drug exposure days (days 2, 4, 6, and 8 of conditioning; (Nygard et al., 2015)). Rats were randomly assigned to one of four groups: vehicle/saline, vehicle/METH, CTAP/saline, or CTAP/METH. Prior to each conditioning session, the dummy cannulae were removed and 31-gauge stainless steel injection cannulae that extended 1.5 mm beyond the guide were inserted into the guide cannulae. A 5-μl volume of aCSF or CTAP (4 μg/5 μl; (Schroeder et al., 2007)) was administered bilaterally at a rate of 1.0 μl/minute to the freely moving animal. After each infusion, the injection cannulae were left in place for 1 min in order to minimize fluid back flow through the cannulae. Twenty min later, each rat received an injection of saline or METH, and was immediately confined to the conditioning chamber for 30 min. On drug exposure days (i.e., days 2, 4, 6 and 8 in the initially non-preferred chamber), rats in the vehicle/METH and vehicle/saline groups were intrastriatally infused with aCSF, while animals in the CTAP/METH and CTAP/saline groups were intrastriatally infused with CTAP prior to their injections (Schroeder et al., 2007). On saline exposure days (i.e., days 1, 3, 5 and 7 in the initially preferred chamber) all groups of rats were infused with aCSF prior to injection with saline (Schroeder et al., 2007). Twenty-four h after the last conditioning session, rats underwent preference testing, with rats in the drug-free state given free access to both chambers for 20 min. The difference in seconds between the time spent in the METH-paired compartment during the preference testing and the time spent in the same initially non-preferred compartment during the bias testing prior to starting the conditioning procedure was used to calculate the degree of place conditioning (Schroeder et al., 2007). For saline-treated rats, preference was calculated as the difference in seconds between the time spent in the initially non-preferred compartment during the preference testing and the time spent in the same non-preferred compartment prior to conditioning, as previously described (Schroeder et al., 2007). A positive preference score indicates a conditioned place preference, while a negative preference score is indicative of a conditioned place aversion (Schroeder et al., 2007). Both the bias test and preference test sessions were digitally recorded and analyzed *post-hoc* using AnyMaze software. In order to determine whether differences in locomotor activity may have contributed to the animals' behavior in the CPP, *post-hoc* analysis of the distance traveled during the preference test was analyzed using AnyMaze software.

2.4. Tissue processing for immunohistochemistry

Thirty min after preference testing, rats were killed by exposure to CO_2 for 1 min followed by decapitation. The brains were rapidly harvested, flash-frozen in isopentane and stored at −80 °C until they were cut into 12-μm sections through the striatum at the level of the