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Research article

Nitric oxide in the medial prefrontal cortex contributes to the acquisition of cocaine place preference and synaptic plasticity in the laterodorsal tegmental nucleus

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ABSTRACT

Nitric oxide (NO), a gaseous neurotransmitter, is involved in a variety of brain functions, including drug addiction. Although previous studies have suggested that NO plays an important role in the development of cocaine addiction, the brain region(s) in which NO acts and how it contributes to cocaine addiction remain unclear. In this study, we examined these issues using a cocaine-induced conditioned place preference (CPP) paradigm and *ex vivo* electrophysiological recordings in rats. Specifically, we focused on the medial prefrontal cortex (mPFC) and laterodorsal tegmental nucleus (LDT), brain regions associated with cocaine CPP development and cocaine-induced plasticity. Intra-mPFC injection of the non-selective NO synthase (NOS) inhibitor L-NAME or the neuronal NOS (nNOS) selective inhibitor L-NPA during the conditioning phase disrupted cocaine CPP. Additionally, intra-mPFC injection of L-NPA prior to each cocaine injection prevented the induction of presynaptic plasticity, induced by repeated cocaine administration, in LDT cholinergic neurons. These findings indicate that NO generated in the mPFC contributes to the acquisition of cocaine CPP and the induction of neuroplasticity in LDT cholinergic neurons. Together with previous studies showing that NO induces membrane plasticity in mPFC neurons, that mPFC neurons project to the LDT, and that LDT activity is critical for the acquisition of cocaine CPP, the present findings suggest that NO-mediated neuroplasticity induced in the mPFC-LDT circuitry is critical for the development of cocaine addiction.

1. Introduction

Nitric oxide (NO) is a gaseous neurotransmitter associated with a variety of physiological functions and with neuroplasticity related to learning and memory [1]. Additionally, NO has been reported to play an important role in addictive behaviors induced by cocaine [2]. A previous study revealed that systemic injection of an NO synthase (NOS) inhibitor attenuates cocaine-induced conditioned place preference (CPP) and that knockout of neuronal NOS (nNOS) abolishes development of cocaine CPP [3]. Although these findings indicate a critical role for NO produced by neuronal cells in cocaine addiction, the brain regions in which NO acts and how it contributes to the development of cocaine addiction remain to be determined.

The medial prefrontal cortex (mPFC) constitutes a part of the brain's reward circuitry and is associated with learning, memory, and decision making [4–7]. Systemic cocaine administration increases the extracellular NO levels in the mPFC [8] and induces plasticity in the membrane properties of mPFC pyramidal cells in an NO-dependent manner [9,10]. Additionally, lesion of the mPFC suppresses the expression of cocaine CPP [11]. The mPFC sends excitatory projections to the laterodorsal tegmental nucleus (LDT) [12,13], which projects to the ventral tegmental area (VTA) [14,15] and is critical for reward information processing as well as cocaine CPP development [16–19]. We have previously reported that, in *ex vivo* electrophysiological recordings, repeated cocaine administration induces synaptic plasticity in LDT cholinergic neurons [16]. The plasticity in the LDT was inhibited when a NOS inhibitor was systemically administered prior to cocaine injection, suggesting an NO-dependent induction of plasticity. Moreover, inactivation of the mPFC inhibits the induction of LDT plasticity [16]. These findings suggest possible interactions among NOS activity in the mPFC, LDT plasticity, and cocaine CPP development. We hypothesize that NO released in the mPFC by cocaine administration activates mPFC neurons, leading to the induction of synaptic plasticity in the LDT and the development of cocaine CPP. Thus, in the present study, we address

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this question using a cocaine CPP paradigm with an intra-mPFC injection of NOS inhibitors and *ex vivo* whole-cell patch-clamp recordings from LDT cholinergic neurons, which were obtained from rats that had received repeated cocaine administrations with an intra-mPFC injection of a NOS inhibitor.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats weighing 180–260 g (8–10 weeks old) at the beginning of behavioral tests were maintained in a temperature-controlled (22 ± 1 °C) room under a 12-h light/dark cycle with food and water available *ad libitum*. All experiments were conducted in accordance with the National Institutes of Health guidelines and performed with the approval of the Institutional Animal Care and Use Committee at Hokkaido and Kanazawa University. All efforts were made to minimize the number and suffering of animals used in the experiments.

2.2. Drugs

Cocaine hydrochloride (Takeda Pharmaceutical, Osaka, Japan) was dissolved in saline. A NOS inhibitor Nω-Nitro-L-arginine methyl ester hydrochloride (L-NAME; Sigma-Aldrich, St. Louis, MO, USA) and nNOS inhibitor Nω-propyl-L-arginine (L-NPA; Tocris Bioscience, Bristol, UK) were dissolved in 0.1 M PBS (pH = 7.4). The doses of these drugs were determined on the basis of previous studies [20,21]: L-NAME (100 nmol) and L-NPA (2 nmol).

2.3. Surgery and microinjection

Under sodium pentobarbital anesthesia (50 mg/kg, i.p.), rats were implanted bilaterally with 25-gauge stainless-steel guide cannulae (o.d., 0.5 mm; i.d., 0.22 mm) above the mPFC (3.0 mm rostral, 0.67 mm lateral, 4.0 mm ventral to bregma) [22]. After surgery, rats were housed individually in their home cages, allowed to recover for 6–9 days, and handled each day for three consecutive days before the behavioral experiments. For microinjection, 33-gauge stainless-steel injection cannulae (o.d., 0.2 mm; i.d., 0.08 mm) were inserted bilaterally into the guide cannulae. The injection cannulae protruded 1.5 mm from the tip of the guide cannulae to reach the mPFC. Bilateral infusions were performed at a volume of 0.5 μL in each side at a rate of 0.5 μL/min and the injection cannulae were left in place for an additional 1 min after microinjection to prevent backflow.

2.4. CPP test

CPP tests were conducted as described previously [17,18]. The CPP chambers consisted of two equally-sized compartments (30 × 30 × 30 cm) with distinct tactile and visual cues (one compartment had a black floor and walls with an equally spaced stainless-steel vertical grid on the floor, and the other had a white floor and walls with stainless-steel grid on the floor), which were separated by a removable partition. The CPP chambers were set in sound-attenuating boxes equipped with a ventilating fan. On days 1 (habituation) and 2 (pretest), rats freely explored the two compartments for 900 s, and the time spent in each compartment during the exploratory period and locomotor activity were measured using infrared sensors (Supermex, Muromachi Kikai, Tokyo, Japan), which were positioned on the top cover of each compartment. Rats that spent > 80% (> 720 s) of the total time (900 s) in one side on day 2 or showed a difference of > 200 s in the time spent in one side between days 1 and 2 were eliminated from subsequent procedures. We used a bias-like protocol [23], in which the compartment where each rat spent less time on day 2 (pretest) was designated as their cocaine-paired compartment. On days 4–9 (conditioning), rats were given alternating injections of cocaine (20 mg/kg, i.p.) or saline (1 mL/kg, i.p.) and confined to one compartment for 30 min on six consecutive days. On cocaine-conditioning days, rats were given a bilateral intra-mPFC microinjection of L-NAME, L-NPA or vehicle 5 min before their cocaine injection. On day 11 (posttest), rats were allowed to explore the two compartments freely for 900 s, and the time spent in each compartment during the exploratory period and locomotor activity were measured. The CPP scores were calculated by subtracting the time spent in the cocaine-paired compartment during the pretest from that during the posttest.

2.5. Histology

After the CPP tests, the brains were rapidly removed and frozen in powdered dry ice. Coronal sections (50 μm) of the mPFC were prepared using a cryostat, thaw-mounted onto slides, stained with thionin, and examined under a microscope.

2.6. Electrophysiology

2.6.1. Animal preparation

Sprague-Dawley rats weighing 80–140 g (3–6 weeks old) were randomly distributed to two groups that received alternating injections of saline (1.0 mL/kg, i.p.) or cocaine (20 mg/kg in saline, i.p.) once a day for six consecutive days in their home cage. Electrophysiological experiments were conducted on the next day.

2.6.2. Drug injection into the mPFC

Under sodium pentobarbital anesthesia (50 mg/kg, i.p.), rats were implanted bilaterally with 25-gauge stainless-steel guide cannulae (o.d., 0.5 mm; i.d., 0.22 mm) 1.0 mm above the mPFC (2.8 mm rostral, 0.65 mm lateral, 3.0 mm ventral to bregma). We previously found that this coordinate was appropriate to target the mPFC in juvenile rats [16]. After surgery, rats were housed individually in their home cage, allowed to recover for 2–8 days before injecting drugs. For microinjection, 33-gauge stainless steel injection cannulae (o.d., 0.2 mm, i.d., 0.08 mm) were inserted bilaterally into the guide cannulae. The injection cannulae protruded 1.0 mm from the tip of the guide cannulae to reach the mPFC. Five min before each cocaine injection, L-NPA (2 nmol/side) or vehicle was administrated bilaterally in a volume of 0.5 μL/side at a rate of 0.5 μL/min, and the injection cannulae were left in place for an additional 1 min after microinjection to prevent backflow. To confirm the placements of drug injection histologically, 1% Cresyl Violet solution dissolved in saline (0.5 μL/side) was injected into the mPFC just before the rats were decapitated. After removing the rostral part of the brain during the slice preparation as described below, coronal sections (50 μm thick) including the mPFC were prepared with a cryostat, thaw-mounted onto slides, stained with thionine, and examined under a microscope.

2.6.3. Slice preparation and electrophysiology

The drug-treated rats were anesthetized with sodium pentobarbital and decapitated. The brains were submerged in ice-cold modified Ringer's solution containing (in mM) choline chloride, 125; KCl, 4.0; NaH_2PO_4, 1.25; $MgCl_2$, 7.0; $CaCl_2$, 0.5; $NaHCO_3$, 26; glucose, 20; ascorbate, 1.0; and pyruvate, 3.0; and bubbled with 95% O_2–5% CO_2 (pH 7.4). Parasagittal slices (250 μm thick) of the LDT were cut with a Microslicer (VT1200S, Leica Microsystems, Wetzlar, Germany) and incubated at 32–34 °C for 15–30 min in standard Ringer's solution containing (in mM) NaCl, 125; KCl, 2.5; NaH_2PO_4, 1.25; $MgCl_2$ 1.0; $CaCl_2$, 2.0; $NaHCO_3$, 26; and glucose, 25; and bubbled with 95% O_2–5% CO_2 (pH 7.4) and then transferred to standard Ringer's solution at room temperature. Slices were mounted in a recording chamber on an upright microscope (BX-51WI, Olympus, Tokyo, Japan) and continuously superfused with the standard Ringer's solution at a flow rate of 2–2.5 mL/min. Whole-cell voltage-clamp recordings were obtained from LDT

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