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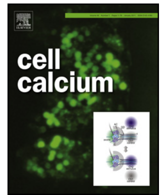

# A single dose of cocaine potentiates glutamatergic synaptic transmission onto locus coeruleus neurons

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ABSTRACT

The brainstem locus coeruleus (LC), the primary norepinephrinergic (NE) nucleus in the brain, has been implicated in the abuse of drugs such as opioids. However, whether and how the LC-NE system is involved in cocaine addiction remains elusive. Here, we demonstrated cocaine-evoked synaptic plasticity of glutamatergic transmission onto LC neurons as one of the earliest traces occurring after a single injection of cocaine. Twenty-four hours after mice were injected intraperitoneally with cocaine, the evoked α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) mediated synaptic transmission onto LC neurons were strongly potentiated without major effect on N-methyl-D-aspartate receptor (NMDAR) mediated synaptic transmission. Compared with saline-pretreated mice, AMPAR-mediated excitatory postsynaptic currents (EPSCs) of cocaine-pretreated mice showed a marked inward rectification, demonstrating the insertion of GluR2-lacking AMPARs to plasma membrane. In addition, the single injection of cocaine did not affect presynaptic glutamate release probability measured by paired pulse ratio. Furthermore, we found that the cocaine-induced potentiation of AMPAR EPSCs could be blocked by prazosin, an inhibitor of α1-adrenoreceptor (AR), indicating that cocaine increases AMPAR transmission *via* α1-ARs. These results reveal that LC-NE serves as an initial target of drug intake.

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## 1. Introduction

Cocaine addiction is considered to be an abnormal form of learning, resulting from changes in the neural circuitry that regulates reward learning and memory [1]. It is well established that cocaine exerts acute effects such as sensitization through increasing the extracellular monoamine concentrations *via* blocking the reuptake of monoamines. Although the drug is metabolized quickly, persistent traces left by the addictive drug exist in the brain [2,3]. Several studies have characterized the long-term synaptic plasticity evoked by cocaine in dopaminergic neurons and target structures of the mesocorticolimbic projections [4–7]. Single cocaine injection or chronic abuse enhances the excitatory afferents onto dopaminergic neurons in the ventral tegmental area by insertion of GluR2-lacking α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) [7–9]. Cocaine seems to drive a form of plasticity that shares some features (an increase in the AMPAR:NMDAR (*N*-methyl-D-aspartate receptor) ratio) with long-term potentiation (LTP) *via* regulating the function and expression of glutamate receptors. This cocaine-evoked long-lasting neuroplasticity is thought to play a critical role in the development of compulsive drug-seeking and cue-induced relapse [10–12].

Studies of the neural circuits underlying addictive behaviors have focused on the mesolimbic dopaminergic system, as it has been shown that almost all abused drugs, including cocaine, increase extracellular dopamine (DA) levels in the nucleus accumbens of rodents. However, growing evidence indicated that norepinephrine (NE) might also play an important role in cocaine

*Abbreviations:* α1-AR, alpha 1 adrenoreceptor; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Coca, cocaine; DA, dopamine; EPSC, excitatory postsynaptic current; GABAR, γ-aminobutyric acid receptor; LC, locus coeruleus; LTP, long-term potentiation; NE, norepinephrine; NMDAR, *N*-methyl-D-aspartate receptor; RI, rectification; PPR, paired pulse ratio; Pz, prazosin.

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addiction, since cocaine is known to have high affinity for the NE transporter [13,14]. In addition, cocaine failed to induce locomotion and sensitization in α1b-adrenoceptor (AR)-knockout mice or blockade of α1-ARs by the antagonist prazosin [15–17], implying that NE and α1-ARs are involved in addictive behaviors. The locus coeruleus (LC), the principal source of NE in the brain, projects widely to multiple brain areas and is an initial target of cocaine [18,19]. The LC neurons receive glutamatergic afferents originating mainly from the orbitofrontal cortex, anterior cingulate cortex, and amygdala [20]. And direct stimulation of LC neurons with glutamate elicits NE release from the somatodendritic region of LC neurons [21]. Therefore, modulation of glutamatergic transmission onto LC neurons could alter their activity and further affect downstream neural circuits. However, whether cocaine affects the synaptic transmission onto LC neurons has not been investigated.

Here, we set out to characterize the excitatory transmission onto NE neurons and to explore the effects of systemic cocaine in LC brain slices. Our findings demonstrated that single injection of cocaine evoked a potentiation of AMPAR-mediated synaptic transmission onto LC neurons through redistribution of AMPAR subunits, which is one of the earliest traces after first dose of cocaine administration.

## 2. Materials and methods

### 2.1. Animals

C57BL/6 mice (18–22 days old) were purchased from the Laboratory Animal Centre of Peking University. Mice were injected with 15 mg/kg cocaine (intraperitoneal, i.p.) or same volume of 0.9% saline 24 h before sacrifice. For the effect of prazosin, mice were injected with prazosin (1 mg/kg) or same volume of 0.9% saline 30 min before the single dose (15 mg/kg) of cocaine injection. All experiment procedures were approved by the Peking University Animal Use and Care Committee and performed according to the guidelines of the Association for Assessment and Accreditation of Laboratory Animals (IACUC approval no. IMM-ZhouZ-11).

### 2.2. Brain slice preparation

Horizontal brain slices (300 μm) were prepared and processed as described previously [22]. Briefly, mice were anesthetized with urethane (1.5 g/kg, i.p.) and decapitated. The brain was quickly removed and sliced on a vibratome (Leica VT1200s, Wetzlar, Germany) in ice-cold cutting solution containing (in mM): 125 NaCl, 2.5 KCl, 25 $NaHCO_3$, 1.25 $NaH_2PO_4$, 3.7 $MgCl_2$, 0.1 $CaCl_2$, and 10 glucose (adjusted to pH 7.3–7.4, saturated with 95% $O_2$ and 5% $CO_2$). The slices were incubated for 30 min at 37 °C and then maintained at room temperature (22–25 °C) in a solution containing (in mM): 125 NaCl, 2.5 KCl, 25 $NaHCO_3$, 1.25 $NaH_2PO_4$, 1.3 $MgCl_2$, 2.5 $CaCl_2$, and 10 glucose, and bubbled with 95% $O_2$/5% $CO_2$ for 1 h before recording.

### 2.3. Electrophysiological recordings

LC neurons were identified by their distinct anatomical and electrical discharge properties [21,22]. Whole-cell recordings were performed using an EPC9/2 amplifier and Pulse software (HEKA Elektronik, Lambrecht/Pfalz, Germany). Cells were voltage-clamped at −60 mV with 2–4 MΩ patch pipettes. The internal solution contained (in mM): 130 K-gluconate, 10 KCl, 2 $MgCl_2$, 2.5 Mg-ATP, 0.25 Na-GTP, 10 HEPES, and 0.4 EGTA, pH 7.3. The access series resistance of the neurons used for analysis was <15 MΩ. Data were filtered at 2.9 kHz and digitized at 10 kHz.

Synaptic currents were evoked by stimuli (0.2 ms, 5 V) at 0.1 Hz through a bipolar electrode (S88K, Grass Instruments, Quincy, MA) positioned rostral to the LC. AMPAR-mediated excitatory postsynaptic currents (EPSCs) were recorded in the presence of bicuculline (10 μM) to block γ-aminobutyric acid receptors (GABARs) and D-AP5 (D (−)-2-amino-5-phosphonovaleric acid, 50 μM) to block NMDARs. The NMDA component was calculated as the difference between the EPSCs measured in the absence and presence of D-AP5 at a holding potential of +40 mV. Finally, the AMPAR:NMDAR ratio was calculated by dividing the average peak amplitude of AMPAR-mediated EPSCs by that of NMDAR-mediated EPSCs. All EPSCs used for analysis were averaged from 10 consecutive traces. Spontaneous EPSCs were recorded in the presence of bicuculline. For miniature EPSC recording, cells were incubated with tetrodotoxin (1 μM) and bicuculline. A micro-perfusion device (MPS-2; INBIO, Wuhan, China) with a fast exchange time (<100 ms) among eight channels was used to perfuse drugs locally onto the cells. Stopcocks and an isometric pump (Peri-Star 291, WPI, Sarasota, FL) provided perfusion at 1–2 ml/min. Cocaine was from Qinghai Pharmaceutical Co., People's Republic of China, and other chemicals were from Sigma (St. Louis, MO) unless otherwise stated.

### 2.4. Data analysis

Data were analyzed with IGOR Pro software (WaveMetrics, Lake Oswego, OR). Miniature EPSCs and spontaneous EPSCs were analyzed using the Mini Analysis Program (Synaptosoft, Decatur, GA). All values are presented as mean ± SEM. Statistical comparisons were performed with the two-tailed unpaired Student's *t*-test. A difference of $p < 0.05$ was considered significant (*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$).

## 3. Results

### 3.1. Single cocaine injection potentiates AMPAR-mediated transmission onto LC neurons

Excitatory afferents to LC neurons play important roles in regulating the activity of LC neurons. To determine whether single injection of cocaine affects glutamatergic synaptic transmission onto LC neurons, we recorded the EPSCs in brain slices. Field stimulation of excitatory afferents in LC brain slices evoked both AMPARs and NMDARs mediated currents [23]. So, we quantified the components of AMPAR-EPSCs and NMDAR-EPSCs recorded in LC cells from mice that received saline or cocaine (15 mg/kg) injection on the previous day. AMPAR-mediated EPSCs were recorded in the presence of bicuculline (10 μM) and the NMDAR antagonist D-AP5 (50 μM) at a holding potential of −70 mV, while NMDAR-mediated EPSCs were calculated as the difference between EPSCs measured in the absence and presence of D-AP5 at holding potential of +40 mV. The ratio of the amplitude of AMPAR EPSCs to NMDAR EPSCs in the cocaine-treated mice was increased by ∼100% compared with control mice (Fig. 1A and B). We then analyzed the kinetics of EPSCs recorded at −70 mV and +40 mV (Fig. 1C–F). Single cocaine exposure caused a strong potentiation of the peak amplitude of EPSCs recorded at −70 mV (Fig. 1E), but the EPSCs recorded at +40 mV were unchanged (Fig. 1C and D). The EPSCs parameters rise-time and decay time recorded at −70 mV and +40 mV remained intact in mice with cocaine administration (Fig. 1D and F), indicating that single dose of cocaine does not affect the kinetics of EPSCs. These results demonstrate that a single cocaine administration selectively increases AMPAR-mediated synaptic transmission at the holding potential of −70 mV.

To identify the component of AMPAR-mediated EPSCs, we used the specific calcium permeable AMPAR antagonist Naspm onto the LC neurons. Naspm, a synthetic analogue of Joro spider toxin, is a potent and selective $Ca^{2+}$ permeable AMPA receptor blocker

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