Differential patterns of neuronal activation in rostral versus caudal ventral tegmental area involved in behavioral sensitization induced by an escalating-dose morphine administration paradigm

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1. Introduction

The transition to addiction often involves a gradual process of escalated drug intake. The purpose of the present study was to characterize neuronal activation in the ventral tegmental area (VTA) and substantia nigra (SN) following chronic escalating-dose morphine exposure (days 1–7, 2 mg/kg/d; days 8–21, beginning at 10 mg/kg/d, increasing by 2 mg/kg/d, with steady-dose morphine (2 mg/kg/d, i.p., for 21 days) as the comparison. Using immunohistochemical double-staining for tyrosine hydroxylase (TH) and Fos, we found that the number of Fos-TH neurons in the rostral VTA and number of Fos-TH neurons in the lateral SN were significantly increased in escalating-dose morphine-treated rats compared with steady-dose morphine-treated rats and acute morphine-treated rats. Meanwhile, this increase was associated with robust expression of behavioral sensitization after a challenge with 10 mg/kg morphine. The number of Fos-TH neurons was significantly increased by acute morphine in the caudal VTA and SNc, but this number did not increase further with morphine pretreatment. These results demonstrate that behavioral sensitization was associated with elevated activation of dopaminergic neurons in the rostral VTA and nondopaminergic neurons in the lateral SNr, which could only be induced by chronic escalating-dose morphine rather than chronic steady-dose morphine pretreatment.

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hypersensitivity to the incentive motivational effects of drugs (Robinson and Berridge, 2008).

2. Material and methods

2.1. Animals

Male Sprague-Dawley rats (Vital River Animal Center, Beijing, China) that weighed 260–280 g at the beginning of experiment were housed five per cage (50 × 22.5 × 30 cm²) in a colony room with a controlled temperature (22–26 °C) and 12 h/12 h light/dark cycle (lights on at 7:00 a.m.). Food and water were available ad libitum. The experimental procedures were in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (publication no. 85–23, revised 1985).

2.2. Chronic morphine pretreatment

After 7 days of acclimatization to the colony room, the rats were pretreated with either a steady-dose morphine administration paradigm, escalating-dose morphine administration paradigm, or saline according to the different group assignments. Morphine hydrochloride (Qinghai Pharmaceutical Co., Ltd., Qinghai, China)/saline were administered intraperitoneally (i.p.) for 21 days. The steady-dose morphine administration paradigm consisted of a once-daily injection of 2 mg/kg morphine. The escalating-dose morphine administration paradigm consisted of a once-daily injection of 2 mg/kg (days 1–7) and an escalating-dose regimen from day 8 to day 21. A dose of 10 mg/kg was administered on day 8 and increased by 2 mg/kg/d. During the escalating-dose treatment period, three doses each day were administered (one-third the total dose of that day), separated by a 4 h interval (e.g., 10:00 a.m., 2:00 p.m., 6:00 p.m.). The rats were returned to their home cages immediately after each injection. All of the animals were weighed every other day throughout the pretreatment.

2.3. Withdrawal symptoms

Beginning the day after the last injection and continuing at daily intervals for 6 days, the rats were placed in a transparent glass cylinder (30 cm diameter, 60 cm height) and tested for signs of opiate withdrawal. Withdrawal severity was assessed according to a slightly modified rating scale described elsewhere (Cicero et al., 2002). The signs of withdrawal included body weight loss, wet-dog shakes, teeth chattering, and ptosis, which were weighted according to their prominence. These observations took place for a 60 min period on each testing day.

2.4. Behavioral sensitization testing

After 7 days of drug withdrawal, the animals were challenged with morphine in black Plexiglas chambers (35 × 35 × 50 cm³ height). On the day before the challenge, the rats were habituated for 1 h in the chambers. On the challenge day, after habituation for 1 h in the chambers, the rats were injected with saline or morphine (2 or 10 mg/kg) and immediately returned to the chambers where behavior was continuously monitored for 4 h. A video camera was suspended from the ceiling to record the movement tracks of each animal. An image subtraction technology was used to record the displacement of the animal. These image data were transformed into computerized digital number (in pixels) and then further computed into actual distance traveled (in centimeters). Meanwhile, the behavior of each rat was videotaped and later rated for stereotypy occurring in 1 min of every 10 min using a graded scale slightly adapted from previous studies (Miller et al., 2002; Mickiewicz et al., 2009). A stereotypy intensity scale of 0–11 was based on the following criteria: 0 (Asleep-like; resting in a head-down curled position or lying down with eyes closed), 1 (Inactive, resting quietly; lying down but eyes open, with little or no movement), 2 (Slow active; intermittent grooming, with infrequent locomotion or rearing/wall climbing), 3 (Normal active; exploratory-like behaviors, including periodic sniffing, occasional locomotion, or rearing/wall climbing), 4 (Hyperactive; frequent locomotion, with intermittent sniffing, rearing/wall climbing, or grooming the limbs, typically without a repetitive pattern), 5 (Continuous non-oral grooming over a wide area; rearing/wall climbing, sniffing, or grooming the limbs, in which the total time engaged in these behaviors exceeded 30 s in 1 min, with locomotion), 6 (Continuous non-oral grooming within a restricted area; category 5 behaviors, with little or no locomotion), 7 (Continuous oral stereotypy over a wide area; licking or biting self, in which the time spent engaged in this behavior exceeded 30 s in 1 min, with locomotion), 8 (Continuous oral stereotypy within a restricted area; category 7 behaviors, with little or no locomotion), 9 (Intermittent stereotypy licking or biting directed at walls/floor over a wide area; licking or biting directed at walls/floor, in which the time spent engaged in this behavior was less than 30 s in 1 min, with locomotion), 10 (Intermittent stereotypy licking or biting directed at walls/floor within a restricted area; category 9 behaviors, with little or no locomotion), and 11 (Continuous stereotypy licking or biting directed at walls/floor; licking or biting directed at walls/floor, in which the time spent engaged in this behavior exceeded 30 s in 1 min).

2.5. Immunohistochemistry

Two hours after the challenge with saline or 10 mg/kg morphine, the rats were deeply anaesthetized with 10% chloral hydrate (400 mg/kg, i.p.) and transcardially perfused with 150 ml of 0.9% NaCl, followed by 400 ml of 4% paraformaldehyde in 0.1 M phosphate buffer (PB), pH 7.4. The brains were postfixed for 6 h in the same fixative at 4 °C and then placed in 20% sucrose solution for 2–3 days. The brains were then snap-frozen in carbon dioxide ice at −70 °C and then immediately transferred to a freezing microtome (Leica CM1900), and 30 μm coronal sections were cut beginning at −5.00 mm to bregma (Paxinos and Watson, 1997). One of five adjacent sections was collected, and nine sections per rat were obtained. Double-labeled, two-color immunohistochemical procedures were used to visualize the presence of Fos-positive nuclei and tyrosine hydroxylase (TH)-positive cell bodies. Briefly, free-floating sections were washed in 0.01 M phosphate-buffered saline (PBS) that contained 3% H₂O₂ for 10 min. After rinsing, the sections were incubated in rabbit polyclonal antiserum (1:10000) against Fos (sc-52; Santa Cruz Biotechnology, Santa Cruz, CA, USA) overnight at 4 °C. After rinsing with PBS, the sections were incubated for 30 min at room temperature in horseradish peroxidase-linked goat anti-rabbit IgG (Zymed Laboratories, Santiago, USA). After washing, black immunoreactive nuclei labeled for Fos were revealed by a nickel-intensified (0.6% nickel sulfate) diaminobenzidine (DAB) reaction (90 s). For TH staining, the same sections were then incubated in mouse monoclonal anti-TH antibody (MAB318, 1:5000; Chemicon international, Inc., CA, USA) overnight at 4 °C. After rinsing, horseradish peroxidase-linked goat anti-mouse IgG (Zymed) was added to the sections for 30 min incubation at room temperature. Following the washes, brown TH-immunoreactive neurons were detected by a DAB reaction (120 s). The sections were mounted on gelatin-coated slides, dehydrated in alcohol, cleared with dimethylbenzene, and coverslipped with Ultramount.

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Fos immunostaining was assessed by light microscopy (Leica DM500) at 40× magnification. Bilateral, manual, and blind counts of neurons immunoreactive for Fos or Fos+TH were conducted throughout the VTA and SN (pars compacta [SNc] and pars reticulata [SNr]).

### 2.6. Data analysis

The body weight and withdrawal factor were analyzed by two-way repeated-measures analysis of variance (ANOVA), with day as the within-subjects factor and pretreatment as the between-subjects factor. In cases of significant interactions, analyses of simple effects were performed. Locomotor activity, stereotyped movements, and the number of neurons were analyzed using t-tests or one-way ANOVAs followed by the Least Significant Difference (LSD) post-hoc test. A two-tailed significance level of 0.05 was used.

### 3. Results

#### 3.1. Withdrawal symptoms

The body weights of all of the rats gradually increased throughout the pretreatment (Fig. 1A). However, a significant interaction between pretreatment and day was found ($F_{20,260} = 6.738, P < 0.001$). The simple-effects analysis revealed significant differences between groups on day 17 ($F_{2,26} = 4.10, P < 0.05$), day 19 ($F_{2,26} = 4.31, P < 0.05$), and day 21 ($F_{2,26} = 4.75, P < 0.05$). A further analysis showed that the body weights of escalating-dose morphine-pretreated rats were less than the body weights of saline-pretreated rats on day 17 ($P < 0.01$), day 19 ($P < 0.05$), and day 21 ($P < 0.01$) and less than the body weights of steady-dose morphine-pretreated rats on day 19 ($P < 0.05$) and day 21 ($P < 0.05$). No difference was found between the steady-dose morphine-pretreated group and drug-naive group on any day. For the body weights of the animals during withdrawal (Fig. 1B), a significant pretreatment × day interaction was found ($F_{12,156} = 30.23, P < 0.0001$). A further analyses revealed that the body weights of escalating-dose morphine-pretreated rats sharply declined on day 2 ($P < 0.001$), day 3 ($P < 0.001$), and day 4 ($P < 0.001$) after withdrawal compared with the last day of pretreatment (day 0). The body weights of saline-pretreated and steady-dose morphine-pretreated rats steadily increased. The weighted withdrawal factor is presented in Fig. 1C. A significant interaction was found between pretreatment and day ($F_{10,130} = 3.39, P < 0.001$), with significant differences between groups on day 1 ($F_{2,26} = 7.77, P < 0.01$), day 2 ($F_{2,26} = 7.06, P < 0.01$), and day 3 ($F_{2,26} = 3.45, P < 0.05$) after withdrawal. A further analysis showed that the withdrawal factor in escalating-dose morphine-pretreated rats was much higher than in saline-pretreated rats on day 1 ($P < 0.01$), day 2 ($P < 0.01$), and day 3 ($P < 0.05$) after withdrawal and steady-dose morphine-pretreated rats on day 1 ($P < 0.01$), day 2 ($P < 0.01$), and day 3 ($P < 0.05$) after withdrawal. No significant difference was found between the latter two groups. Accordingly, escalating-dose morphine-pretreated rats had severe withdrawal syndromes for at least 3 days postwithdrawal.

#### 3.2. Behavioral sensitization testing

As illustrated in Fig. 2A and B, a challenge with 2 mg/kg morphine did not increase locomotor activity or stereotyped behaviors either in steady-dose morphine-pretreated rats or escalating-dose morphine-pretreated rats compared with saline-pretreated rats (one-way ANOVA; locomotor activity: $F_{2,22} = 0.38, P > 0.05$; stereotyped behavior: $F_{2,22} = 0.43, P > 0.05$), although an acute morphine injection enhanced locomotion and stereotypy compared with saline injection in drug-naive rats (t-test; locomotor activity: $t_{14} = 4.84, P < 0.001$; stereotyped behavior: $t_{14} = 6.07, P < 0.001$). In contrast, when challenged with 10 mg/kg morphine, escalating-dose morphine-pretreated animals expressed robust behavioral sensitization. For locomotor activity (Fig. 2C), a significant difference was found between groups challenged with morphine ($F_{2,24} = 8.95, P < 0.01$), and escalating-dose morphine-pretreated rats had higher locomotor activity than saline-pretreated and steady-dose morphine-pretreated rats ($P < 0.01$). A further analysis showed that the locomotor activity of escalating-dose morphine-pretreated rats was much higher than in saline-pretreated rats on day 1 ($P < 0.01$), day 2 ($P < 0.01$), and day 3 ($P < 0.05$) after withdrawal and steady-dose morphine-pretreated rats on day 1 ($P < 0.01$), day 2 ($P < 0.01$), and day 3 ($P < 0.05$) after withdrawal. No significant difference was found between the latter two groups. Accordingly, escalating-dose morphine-pretreated rats had severe withdrawal syndromes for at least 3 days postwithdrawal.

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**Fig. 1.** (A) Body weights of the rats throughout the pretreatment. (B) Body weights and (C) withdrawal scores in rats following the cessation of daily morphine or saline injections. The data are expressed as mean ± SEM. *$P < 0.05$, **$P < 0.01$, compared with saline-pretreated group; †$P < 0.05$, ††$P < 0.01$, compared with steady-dose morphine-pretreated group; ‡‡‡$P < 0.001$, different from body weight on last day of pretreatment (day 0).**

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activity than saline-pretreated rats (LSD post-hoc test; *P* < 0.001) and steady-dose morphine-pretreated rats (*P* < 0.01). For stereotyped behaviors (Fig. 2D), a significant difference was found between the three groups (*F*$_{2,13}$ = 4.74, *P* < 0.05), and escalating-dose morphine-pretreated rats had stronger stereotyped behavior than saline-pretreated rats (*P* < 0.01). An acute morphine (10 mg/kg) injection increased locomotion and stereotypy compared with saline injection in saline-pretreated rats (locomotor activity: *t*$_{13}$ = 4.48, *P* < 0.001; stereotyped behavior: *t*$_{13}$ = 6.15, *P* < 0.001).

### 3.3. Fos and TH immunohistochemistry

Fig. 3 presents examples of neurons double-labeled for Fos and TH in the VTA, and the schematics show specific subregions of the VTA and SNr. When the numbers of Fos+TH-positive (Fos+/TH+) neurons throughout the VTA were analyzed, no significant differences were found between the three groups challenged with morphine (*F*$_{2,13}$ = 1.49, *P* > 0.05; data not shown). Fos+/TH+ cell counts at all of the selected coordinates are shown in Fig. 4A. We found that Fos+/TH+ neurons were not uniformly distributed throughout the VTA, and the numbers of these double-labeled cells were not similar among groups at most of the coordinates, with the exception of −5.6 mm from bregma. Therefore, the sections that ranged from −5.15 to −5.45 mm from bregma were considered the rostral VTA, whereas all of the sections that ranged from −5.75 to −6.35 mm from bregma were considered the caudal VTA (Bolanos et al., 2005). The double-labeled cells within these two subregions were separately counted. In the rostral VTA (Fig. 4B), a morphine injection had no effect on the Fos+/TH+ cell count in saline-pretreated rats compared with saline injection (*t*$_{8}$ = 0.81, *P* > 0.05), but it induced a marked increase in the number of double-labeled neurons in escalating-dose morphine-pretreated rats compared with saline-pretreated rats and steady-dose morphine-pretreated rats (*F*$_{2,13}$ = 5.43, *P* < 0.05; LSD post-hoc test, *P* < 0.05 and *P* < 0.01, respectively). In contrast, in the caudal VTA (Fig. 4C), a significant difference in the number of Fos+/TH+ neurons was found between the morphine injection and saline injection in drug-naive animals (*t*$_{8}$ = 2.99, *P* < 0.05), but no significant difference was found between the three groups challenged with morphine (*F*$_{2,13}$ = 0.36, *P* > 0.05).

Additionally, we observed Fos expression in numerous TH-negative neurons (Fos+/TH− cells) throughout the VTA. Greater variability was apparent in the number of Fos+/TH− cells in the rostral than in the caudal VTA among the groups of animals (Fig. 4D), so these cells were analyzed similarly. In the rostral VTA (Fig. 4E), no significant difference was found in Fos+/TH− cell counts between the morphine injection and saline injection in drug-naive animals (*t*$_{8}$ = 1.85, *P* > 0.05), but the morphine challenge significantly increased the number of Fos+/TH− cells in escalating-dose morphine-pretreated rats compared with saline-pretreated rats and steady-dose morphine-pretreated rats (*F*$_{2,13}$ = 4.62, *P* < 0.05; LSD post-hoc test, *P* < 0.05 and *P* < 0.05, respectively). However, in the caudal VTA (Fig. 4F), the morphine challenge did not significantly enhance the number of Fos+/TH− cells either in saline-pretreated rats (*t*$_{8}$ = 1.67, *P* > 0.05) or morphine-pretreated rats (*F*$_{2,13}$ = 0.60, *P* > 0.05).

In the SNc, a significant increase was found following acute morphine injection compared with saline injection in drug-naive rats (*t*$_{8}$ = 3.92, *P* < 0.01), but no significant difference was found between the groups challenged with morphine (*F*$_{2,13}$ = 0.18, *P* > 0.05; Fig. 5A). Abundant cells stained only for Fos (Fos+/TH−) were observed in the SNr. As one of the output stations of the basal ganglia, the SNr is topographically organized to receive functionally segregated parallel corticostral projections. Accordingly, the SNr was transected along its major axis into medial, middle, and lateral portions (Deniau et al., 1996). Fos+/TH− cell counts in the medial SNr, regarded as the medial prefrontal territory, and lateral SNr, regarded as the sensorimotor
4. Discussion

The present study showed that the escalating-dose morphine regimen produced distinct physiological and behavioral consequences compared with the steady-dose regimen, including physical dependence and robust behavioral sensitization (i.e., sensitized locomotor activity and stereotypy). However, the most significant finding in the present study was the differential patterns of dopamine neuronal activation in the rostral vs. caudal VTA. The morphine challenge notably activated dopamine neurons in the caudal VTA in rats pretreated with saline or morphine, but no additional dopamine neurons were activated in escalating-dose morphine-pretreated animals compared with drug-naive and steady-dose morphine-pretreated rats. In contrast, the numbers of activated dopamine neurons in the rostral VTA were not increased in drug-naive or steady-dose morphine-pretreated animals but were dramatically elevated in escalating-dose morphine-pretreated animals after morphine challenge. These results precisely coincide with the well-established functional differences between the rostral and caudal VTA. The presence of two distinct subregions of the VTA was first demonstrated by Arnt and Scheel-Kruger (1979) and subsequently by others (Ikemoto et al., 1997, 1998) using intracranial administration of γ-aminobutyric acid (GABA)ergic compounds. Subsequently, several studies (Ikemoto and Wise, 2002; Rodd-Henricks et al., 2000; Rodd et al., 2005; Zangen et al., 2002) showed that rats stably self-administered endomorphin–1, the cholinergic agonist carbachol, ethanol, and cocaine into the caudal VTA. Endomorphin–1 and the cholinergic agents induced conditioned place preference (CPP) only when microinjected into the caudal VTA. Additionally, intra-caudal VTA injections of endomorphin–1 were more effective at inducing locomotion. These findings suggest that drug reward sites in the VTA are concentrated in the posterior region of this dopamine cell group, at least for some types of drugs. Consistent with these studies, we found that an acute morphine injection enhanced dopamine neuronal activation in the caudal but not rostral VTA in drug-naive animals, providing direct evidence that the main site of action of acute morphine resides in the posterior rather than anterior portion of the VTA. This is supported by a higher density of µ-opioid receptors in the caudal VTA than in the rostral VTA (German et al., 1993; Mansour et al., 1995) because systemic morphine has been shown to have potent effects on dopamine neurons by acting on µ-opioid receptors in the mid-brain (Bontempi and Sharp, 1997).

Nevertheless, the expression of behavioral sensitization in escalating-dose morphine-pretreated animals in the present study was accompanied by enhanced activation of dopamine neurons in the rostral VTA where activation of the same neurons was absent in non-sensitized animals (steady-dose morphine-pretreated rats), suggesting that certain neuronal adaptations in the rostral VTA were specifically related to the escalating-dose regimen. Several studies have established a distinction between the rostral and caudal VTA using viral-mediated gene transfer to mimic some neural adaptations in the VTA observed after chronic morphine. For example, artificial elevations of glutamate receptor 1 (GluR1) levels in the rostral VTA were associated with increased sensitivity to the locomotor-stimulating and rewarding (reflected by CPP) properties of morphine, whereas the same GluR1 manipulation in the caudal VTA rendered the animals aversive to the drug-paired chamber in the CPP paradigm (Carlezon et al., 1997, 2000). Moreover, the locomotor response to morphine was increased when phospholipase C–γ was over-expressed in rostral VTA but decreased when the manipulation was performed in the caudal VTA (Bolanos et al., 2005). These findings and those of the present study suggest that neural adaptations in the rostral VTA induced by repeated morphine
exposure appear to be at least partially responsible for the increased sensitivity to morphine.

In the present study, we also found that the number of activated TH-negative neurons increased exclusively in the rostral VTA in escalating-dose morphine-pretreated rats compared with steady-dose morphine-pretreated rats and acute morphine-treated rats. Interestingly, previous studies demonstrated that a considerable number of viral-infected neurons in the rostral VTA were TH-negative neurons (approximately 50%), whereas more infected neurons were TH-positive in the caudal VTA (Carlezon et al., 2000; Olson et al., 2005). These phenomena imply that TH-negative neurons in the rostral VTA could also be involved in the expression of behavioral sensitization. Therefore, the role for the caudal VTA as a trigger-zone for acute morphine action and role

Fig. 4. Fos expression in the VTA after a challenge with 10 mg/kg morphine. The counts of neurons (A) double-labeled for Fos+TH (Fos+TH+) and (D) labeled only for Fos (Fos+) were plotted at all coordinates of the VTA. Fos+TH+ neurons and Fos+TH− neurons in the (B, E) rostral VTA and (C, F) caudal VTA were counted, respectively. The data are expressed as mean ± SEM. *P < 0.05, **P < 0.01. VTA, ventral tegmental area; TH, tyrosine hydroxylase.

Fig. 5. Fos expression in the SN after a challenge with 10 mg/kg morphine. (A) Counts of neurons double-labeled for Fos+TH (Fos+TH+) in the SNc. (B, C) Counts of neurons labeled only for Fos (Fos+TH−) in the (B) medial SNr and (C) lateral SNr. The data are expressed as mean ± SEM. *P < 0.05, **P < 0.01. SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; TH, tyrosine hydroxylase.
for the rostral VTA in the increased sensitivity to the stimulant properties of morphine suggest that the caudal VTA may be a direct target of initial drug use. After repeated drug exposure when behavioral sensitization occurs, the rostral VTA may be gradually recruited. However, how these activated dopaminergic and nondopaminergic neurons in the rostral VTA regulate the expression of behavioral sensitization requires further investigation.

The morphine challenge significantly activated dopamine neurons in the SNc in animals pretreated with morphine or saline, but no difference was found between the three groups. Therefore, we did not find a progression of neuronal dopamine levels from the mesolimbic to nigro-dorsal striatal dopamine pathway after chronic escalating-dose morphine administration. However, in the lateral SNr but not medial SNr, the number of Fos-positive cells in escalating-dose morphine-pretreated animals was much greater than in steady-dose morphine-pretreated animals or acute morphine-treated animals. This marked enhancement of Fos expression in the lateral SNr appears to be related not only to sensitized behavior but also to drug dose because another study found that Fos expression was significantly heightened in the SNr only in high-dose amphetamine-sensitized rats and not in low-dose amphetamine-sensitized rats (McPherson and Lawrence, 2006). Because the medial and lateral SNr receive segregated information from the medial prefrontal cortex (mPFC) and sensorimotor cortex, respectively (Deniau et al., 1996; Joel and Weiner, 2000), the present results may reflect an imbalance between prefrontal and sensorimotor corticostriatal transmission that could underlie the expression of behavioral sensitization specifically induced by high drug doses (Aliane et al., 2009).

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