Involvement of D1/D2 dopamine receptors within the nucleus accumbens and ventral tegmental area in the development of sensitization to antinociceptive effect of morphine

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1. Introduction

While the precise role for dopamine has been debated, dopamine is thought to be a key ingredient in both the development and expression of behavioral sensitization to repeated drug administration (Lodge and Grace, 2008; Pierce and Kalivas, 1997; Robinson and Berridge, 1993). It was found earlier that long-term opioid treatment leads to antinoceptive tolerance and causes a paradoxical sensitization (opioid-induced hyperalgesia) toward mildly painful (hyperalgesia) and normally innocuous (alldynia) stimuli. Prolonged morphine administration was also found to up-regulate pain neurotransmitter (such as calcitonin gene-related peptide; CGRP) levels in primary sensory neurons (Tumati et al., 2011; Zarrindast et al., 2007). Anatomical and pharmacological evidence indicates that the nucleus accumbens (NAc) is involved in opioid sensitization (Azizi et al., 2009; Kalivas and Duffy, 1995; Robinson and Kolb, 2004). The common circuitry in behavioral sensitization includes dopamine projections from the ventral tegmental area (VTA) to the NAc and glutamate projections from the medial prefrontal cortex (mPFC) to the NAc (Pierce and Kalivas, 1997). The NAc is a complex forebrain structure (Jongen-Rêlo et al., 1994), which receives massive dopaminergic input from the VTA and glutamatergic input from structures such as the hippocampus, amygdala and mPFC (Heyman et al., 1989).

In rats, dopamine-mediated antinociception has been reported in many studies (Altier and Stewart, 1998; Morgan and Franklin, 1991). The binding of dopamine to its receptors causes a change in the release of neurotransmitters which plays a key role in behavioral sensitization. For example, enhanced excitability of the VTA dopaminergic neurons that occurs with repeated cocaine is associated with a decrease in dopamine D2 autoreceptor sensitivity (White and Wang, 1984). Moreover, repeated intra-VTA injections of low doses of the D2 receptor antagonist, eticlopride, which is presumably an autoreceptor-selective, enhanced subsequent stimulant response to amphetamine (sensitization). Blockade of the dopamine D1 receptors in the VTA during the initiation phase prevents the development of amphetamine, but not cocaine sensitization (Veizina, 1996).

Morphine and amphetamine-induced analgesia are involved in increasing dopamine levels in the NAc. In a study by Altier and Stewart (1998), dopamine receptor antagonists injected into the NAc blocked the analgesic effects of intra-NAc or -VTA of substance P, morphine and amphetamine. This study suggests that tonic pain is inhibited, at
least in part, by enhanced dopamine released from terminals of mesolimbic neurons. Human and animal imaging data also suggest that the NAc is an important neural substrate of pain modulation, and intra-accumbal injection of D2 receptor agonist inhibits persistent ongoing nociception in the formalin test (Magnusson and Fisher, 2000; Taylor et al., 2003). Considering the above-mentioned findings and the interaction of opiate-mediated pain modulation and sensitization, in the present study, we tried to find out the role of dopamine D1 and D2 receptors within the NAc and VTA in the sensitization to morphine by the tail-flick test as a model of acute pain in rats.

2. Materials & methods

2.1. Animals

One hundred and thirty eight adult male albino Wistar rats (Pasteur Institute, Tehran, Iran) weighing 200–220 g were used in these experiments. Animals were housed in groups of three per cage in a 12/12 h light/dark cycle (light on between 7:00 a.m. and 7:00 p.m.) with free access to chow and tap water. The animals were randomly allocated to different experimental groups. Each animal was used only once. Rats were habituated to their new environment and handled for one week before the experimental procedure started. All experiments were executed in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 80–23, revised 1996) and were approved by the Research and Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran.

2.2. Drugs

In the present study, the following drugs were used: morphine sulfate (Temad, Tehran Iran) and SCH-23390 (Tocris Bioscience, Bristol, UK), a D1 receptor antagonist, which were dissolved in sterile saline (0.9%). Sulpiride (Tocris Bioscience, Bristol, UK), a D2 receptor antagonist, was dissolved in 10% dimethyl sulfoxide (DMSO). In separate groups, control animals received either saline or 10% DMSO as a vehicle into the NAc or VTA.

2.3. Stereotaxic surgery

Rats were anesthetized by intraperitoneal injection of xylazine (10 mg/kg) and ketamine (100 mg/kg), and placed into a stereotaxic device (Stoelting, USA). An incision was made along the midline, the scalp was retracted, and the area surrounding the bregma was cleaned and dried. In addition, lidocaine with epinephrine (0.2 ml) was injected in several locations around the incision. In separate groups of animals, a stainless steel 23-gauge guide cannula was unilaterally implanted 1 mm above the intended site (NAc or VTA) of drug injections according to the rat brain atlas (Paxinos and Watson, 2007). Stereotaxic coordinates for the NAc were 1–1.2 mm anterior to the bregma, ±0.8–1 mm lateral to the sagittal suture and 6.8–7.8 mm ventral to the skull surface; and those for the VTA were 4.7–5 mm posterior to the bregma, ±0.8–0.9 mm lateral to sagittal suture and 8.2–8.4 mm from the skull surface. The guide cannula was secured in place using two stainless steel screws anchored to the skull and dental acrylic cement. After the cement completely dried and hardened, one stainless steel stylet was used to occlude the guide cannula during recovery period. Penicillin-G200000 IU/ml (0.2–0.3 ml/rat, single dose, intramuscular) was administered immediately after surgery. Animals were individually housed and allowed to recover for 5–7 days before experiments.

2.4. Drug administration

Microinjections were performed by lowering a stainless steel injector cannula (30-gauge needle) with a length of 1 mm longer than the guide cannula into the NAc or VTA. The injector cannula was connected to a 1-μl Hamilton syringe by polyethylene tubing (PE-10). Drug solution or vehicle was infused over 60 s and left in place for 60 s to facilitate drug diffusion, which was followed by replacement of the obturator. Different doses of SCH-23390 and sulpiride were slowly administered in a total volume of 0.5 or 0.3 μl into the NAc or VTA, respectively. The microinjection time for 0.1 μl volume of drugs was 10 s to prevent lesions in these areas. All drug solutions were freshly prepared on the test day, and all microinjections were unilaterally administered into the NAc or VTA.

2.5. Tail-flick test

The nociceptive threshold was measured with a tail-flick apparatus (Harvard, USA). Tail-flick test is an animal model of acute pain. Heat was applied in succession 3, 5, and 7 cm from the caudal tip of the tail. The light intensity source was manually set at about 40% of maximal intensity that yields baseline tail-flick latency (TFL) values in the range of 3–4 s. The equipment was calibrated in order to obtain two consecutive baseline TFLs between 3 and 4 s. If at any time the animal failed to flick its tail within 10 s (cut-off point), the tail was removed from the coil to prevent damage to the skin (Haghparast et al., 2007). The TFLs were measured at 5, 15, 30, 45 and 60 min after drug (SCH-23390 or sulpiride) or vehicle (Saline or 10% DMSO) microinjection into the NAc or VTA. TFLs (s) were expressed as percentage of maximal possible effect (%MPE) which was calculated from the following formula:

\[
\%\text{MPE} = \left\{ \frac{\text{Post-drug latency(s)} - \text{Baseline latency(s)}}{\text{Cut-off value(s)} - \text{Baseline latency(s)}} \right\} \times 100.
\]

To evaluate the sensitivity of animals to nociceptive stimulus, we measured the individual TFL before drug treatment as a pain threshold. We represented all data as %MPE because in this condition, we used normalized data in each group as percentage of drug effect and so, we compared these percentages in all control and experimental groups precisely. The MPE is an index of antinociception, and it can be used as a drug sensitization criterion.

2.6. Induction of sensitization

Animals received a single subcutaneous (SC) injection of morphine (5 mg/kg) for three consecutive days as the sensitization period. Five days later, animals received an ineffective dose of morphine (1 mg/kg; SC) and then the tail-flick test was performed as a model of acute pain. Our control group received saline (1 ml/kg) for three consecutive days during the sensitization period, and 5 days later the tail-flick test was performed before and after the administration of morphine (1 mg/kg; SC). This dose of morphine produced no antinociceptive response on its own in the tail-flick assay.

2.7. Motor activity measurement

To evaluate the effect of drugs on locomotor activity, animals were examined by open field test. Animal displacement was recorded using a 3CCD camera (Panasonic Inc., Japan) placed two meters above the open field box, and locomotion activity was measured as a total distance traveled (cm) during 10 min by Ethovision software (Version 3.1), a video tracking system for automation of behavioral experiments (Noldus Information Technology, the Netherlands).

2.8. Experimental design

2.8.1. Effects of intra-accumbal administration of D1/D2 receptor antagonists on antinociceptive responses of morphine in sensitized rats

In this set of experiments, to find out the role of D1 and D2 dopamine receptors located in the NAc on development of sensitization to...
morphine, different doses of SCH-23390 (0.25, 1 and 4 μg/0.5 μl saline) or sulpiride (0.25, 1 and 4 μg/0.5 μl DMSO) were injected into the NAc, 5 min prior to the administration of morphine (5 mg/kg; SC) during the sensitization period in separate groups of animals. After 5 days free of drug/morphine injection, the tail-flick test was performed before and after the injection of the ineffective dose of morphine (1 mg/kg; SC) in order to evaluate its nociceptive responses in sensitized animals. In vehicle groups, animals received saline (0.5 μl/rat) instead of SCH-23390 or 10% DMSO (0.5 μl/rat) instead of sulpiride in the NAc. In the saline-treated group, rats received saline (1 ml/kg; SC) instead of morphine during the sensitization period. Additionally, we had two other control groups with animals that received only the maximum dose of SCH-23390 (4 μg/0.5 μl saline) or sulpiride (4 μg/0.5 μl DMSO) in the NAc separately, during the sensitization period (Azhdari-Zarmehri et al., 2013; Sadeghi et al., 2013).

2.8.2. Effects of intra-VTA administration of D1/D2 receptor antagonists, SCH-23390 and sulpiride, on antinociceptive responses of morphine in sensitized rats

To test the role of D1 and D2 dopamine receptors located in the VTA on the development of sensitization to morphine, in separate groups of animals, different doses of SCH-23390 (0.25, 1 and 4 μg/0.3 μl saline) or sulpiride (0.25, 1 and 4 μg/0.3 μl DMSO) were injected into the VTA, 5 min prior to administration of morphine (5 mg/kg; SC) during the sensitization period. After 5 days free of drug/morphine injection, the tail-flick test was performed before and after injection of the ineffective dose of morphine (1 mg/kg; SC) to evaluate its nociceptive responses in the sensitized animals. In vehicle groups, animals received saline (0.3 μl/rat) instead of SCH-23390 or 10% DMSO (0.3 μl/rat) instead of sulpiride in the VTA. In the saline-treated group, rats received saline (1 ml/kg; SC) instead of morphine during the sensitization period. Additionally, we had two other control groups that received only the maximum dose of SCH-23390 (4 μg/0.3 μl saline) or sulpiride (4 μg/0.3 μl DMSO) in the VTA separately, during the sensitization period.

2.9. Histology

After performing the test, the animals were deeply anesthetized with ketamine and xylazine. Then, they were transcardially perfused with 0.9% saline and 10% formalin solution. The brains were removed, blocked and cut coronally in 50 μm sections through the cannulae placements. The neuroanatomical locations of cannulae tips were confirmed using the rat brain atlas (Paxinos and Watson, 2007). Only the animals with correct cannulae placements in the NAc (Fig. 1A) or VTA (Fig. 1B) were included in the data analysis.

2.10. Statistics

The results obtained were expressed as mean ± SEM (standard error of mean). The average %MPEs at time set intervals in all groups were subjected to one-way analysis of variance (ANOVA) followed by protected Newman–Keuls test for multiple comparison. P-values less than 0.05 were considered to be statistically significant.

3. Results

Data indicated that repeated administration of morphine (5 mg/kg; SC), once daily for three days (sensitization period) followed by 5 days with no morphine injection, increased the antinociceptive response in the tail-flick test induced by the ineffective dose of morphine. This dose of morphine does not show any antinociceptive effect in normal conditions. Results showed that injection of morphine (5 mg/kg; SC) during the sensitization period increases %MPE of the ineffective dose of morphine (1 mg/kg; SC) from 2.43 ± 1.4% in naive to 47.75 ± 4.01% in the sensitized animals (P < 0.001). Therefore, to evaluate the role of D1/D2 dopaminergic receptors in sensitization to morphine, the ineffective dose of morphine (1 mg/kg; SC) was used. The tail-flick test as an acute model of pain was carried out in all experimental groups that separately received D1 and D2 dopamine receptor antagonists in the NAc or VTA just before morphine administration during the sensitization period.

3.1. Effects of intra-accumbal administration of D1 receptor antagonist, SCH-23390, on development of morphine sensitization

In this set of experiments, we examined the dose–response effects of different doses of SCH-23390 (0.25, 1 and 4 μg/0.5 μl saline), a selective D1 receptor antagonist, and microinjected into the NAc during the sensitization period on antinociception induced by morphine (ineffective dose; 1 mg/kg) in sensitized animals. Fig. 2 shows that intra-accumbal administration of different doses of SCH-23390 during the sensitization period just before the administration of morphine (5 mg/kg; SC), after the free drug injection phase, can decrease the %MPE as an
antinociception index. One-way ANOVA followed by Newman–Keuls multiple comparison test revealed that the blockade of D1 dopamine receptor decreases the antinociceptive effect of morphine (1 mg/kg; SC) in a dose-dependent manner \([F(5, 37) = 11.92; P < 0.0001]\). Although different doses of SCH-23390 (1 and 4 μg/rat) significantly decreased the development of morphine sensitization \((P < 0.05 \text{ and } P < 0.001, \text{ respectively})\), administration of maximal dose of SCH-23390 (4 μg/rat) alone into the NAc did not affect the baseline TFLs at time set intervals in comparison with the saline control group.

### 3.2. Effects of intra-accumbal administration of D2 receptor antagonist, sulpiride, on development of morphine sensitization

To find out the role of D2 dopamine receptor within the NAc in the sensitization to morphine, we examined the dose–response effects of different doses of sulpiride (0.25, 1, and 4 μg/0.5 μl DMSO), a selective D2 receptor antagonist, microinjected into the NAc during the sensitization period on antinociception induced by the ineffective dose of morphine (1 mg/kg; SC). One-way ANOVA followed by Newman–Keuls multiple comparison test \([F(5, 39) = 26.42; P < 0.0001]\; Fig. 3] revealed that the blockade of D2 dopamine receptor dose-dependently decreases the %MPE and antinociceptive response of morphine (1 mg/kg; SC) after the free drug injection phase in sensitized rats. As shown in Fig. 3, although different doses of sulpiride (1 and 4 μg/rat) significantly decreased the development of morphine sensitization \((P < 0.01 \text{ and } P < 0.001, \text{ respectively})\), administration of maximal dose of sulpiride (4 μg/rat) alone into the NAc did not affect the baseline TFLs at time set intervals in comparison with the saline control group.

On the other hand, one-way ANOVA indicated that none of the groups that received the maximal dose of D1 or D2 dopaminergic receptor antagonist in the NAc showed significant differences in distance traveled \([F(5, 35) = 0.8445, P = 0.5291]\; Electronic Supplementary

### 3.3. Effects of intra-VTA administration of D1 receptor antagonist, SCH-23390, on development of morphine sensitization

In this set of experiments, we examined the dose–response effects of different doses of SCH-23390 (0.25, 1 and 4 μg/0.3 μl saline) micro-injected into the VTA during the sensitization period on antinociception induced by morphine (1 mg/kg; SC) in sensitized animals. Fig. 4 shows that intra-VTA administration of different doses of SCH-23390 during the sensitization period just before administration of morphine (5 mg/kg; SC), after the free drug injection phase, can decrease the %MPE and the antinociceptive response of morphine. One-way ANOVA followed by Newman–Keuls multiple comparison test \([F(5, 37) = 8.83; P < 0.0001]\) revealed that the blockade of D1 dopamine receptor during the sensitization period decreases the antinociceptive effects of morphine (1 mg/kg; SC) after free drug injection phase in rats. Although different doses of SCH-23390 (1 and 4 μg/rat) significantly decreased the development of morphine sensitization \((P < 0.05), \text{ administration of maximal dose of SCH-23390 (4 μg/rat)}\) alone into the VTA did not affect the baseline TFLs at time set intervals in comparison with the saline control group. On the other hand, the effect of D1 dopamine receptor blockade in the VTA on the development of morphine sensitization was less than that in the NAc.

### 3.4. Effects of intra-VTA administration of D2 receptor antagonist, sulpiride, on development of morphine sensitization

In the last set of experiments, to find out the role of D2 dopamine receptor within the VTA in the sensitization to morphine, we examined the dose–response effects of different doses of sulpiride (0.25, 1 and 4 μg/0.3 μl DMSO) microinjected into the VTA during the sensitization period. In saline control group, animals received saline instead of morphine during the sensitization period. In sulpiride control group (hatched bar), animals received the maximal dose of sulpiride (4 μg) alone in the NAc during the sensitization period. Each point shows the mean ± SEM for 5–8 rats. **P < 0.01, ***P < 0.001 different from the saline control group.

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Fig. 1. Thus, the blockade of these receptors in the NAc did not affect the TFLs in the nociceptive test due to changes in the locomotor activity.

Fig. 2. Effects of different doses of intra-accumbal SCH-23390 (0.25, 1 and 4 μg/0.5 μl saline) as a D1 receptor antagonist during the sensitization period on %MPE of ineffective dose of morphine (1 mg/kg; SC) in the tail-flick test after free drug injection phase. In saline control group, animals received saline instead of morphine during the sensitization period. In SCH-23390 control group (hatched bar), animals received the maximal dose of SCH-23390 (4 μg) alone in the NAc during the sensitization period. Each point shows the mean ± SEM for 5–8 rats. **P < 0.01, ***P < 0.001 different from the respective drug-control group.

Fig. 3. Effects of different doses of intra-accumbal sulphiride (0.25, 1 and 4 μg/0.5 μl DMSO) as a D2 receptor antagonist during the sensitization period on %MPE of ineffective dose of morphine (1 mg/kg; SC) in the tail-flick test after free drug injection phase. In saline control group, animals received saline instead of morphine during the sensitization period. In sulpiride control group (hatched bar), animals received the maximal dose of sulphiride (4 μg) alone in the NAc during the sensitization period. Each point shows the mean ± SEM for 5–8 rats. **P < 0.01, ***P < 0.001 different from the saline control group. †P < 0.01, ††P < 0.001 different from the DMSO control group.
period on antinociception induced by morphine. One-way ANOVA followed by Newman–Keuls multiple comparison test revealed that the blockade of D2 dopamine receptor in the VTA can not affect the %MPE and antinociceptive effects of morphine (1 mg/kg; SC) after free drug injection phase in sensitized rats (Fig. 5). None of the different doses of sulpiride affected the baseline TFLs at time set intervals in comparison with the DMSO control group.

On the other hand, one-way ANOVA indicated that none of the groups that received the maximal dose of D1 or D2 dopaminergic receptor antagonist in the VTA showed significant differences in traveled distance \( F(5, 35) = 0.1165, P = 0.9878 \); Electronic Supplementary Fig. 2). Thus, the blockade of these receptors in the VTA did not affect the TFLs in the nociceptive test due to changes in the locomotor activity.

4. Discussion

The purpose of the present study was to evaluate the effect of intra-accumbal and intra-VTA administration of D1 and D2 dopamine receptor antagonists on the development of sensitization to morphine. The major findings of this study indicated that (a) the blockade of D1 dopamine receptors in the NAc or VTA dose-dependently attenuate morphine-induced sensitization while (b) unilateral administration of D2 receptor antagonist, sulpiride, into the NAc but not VTA reduce morphine-induced antinociception in sensitized animals. A number of studies have provided convincing evidence that the brain and spinal cord dopaminergic system is involved in nociception. For example, early studies have demonstrated that subcutaneous administration of drugs increase extracellular dopamine levels at the level of the NAc and VTA (Franklin, 1989). Moreover, fMRI studies have shown that the NAc is activated during pain relieving sensations acupuncture (Wu et al., 1999). In the NAc, increasing the release of dopamine has an antinociceptive response; an effect which is mediated through D1 and D2 receptors (Altier and Stewart, 1998). In addition to its stimulus-induced antinociceptive effects, dopamine may also tonically inhibit nociception in the mesolimbic/mesocortical circuits, because lesion of the dopaminergic neurons of the VTA results in hyperalgesic responses (Saadé et al., 1997). Dopaminergic neurons of the VTA in particular are involved in both endogenous and morphine-induced antinociception. This may occur through an increase in release of dopamine in the areas receiving the VTA projecting neurons including the mPFC, NAc and medial striatum (Burkey et al., 1999).

In our study, we indicated that intra-accumbal administration of different doses of the D1 receptor antagonist (blockade of this receptor) decreases the antinociceptive effects of morphine in a morphine-sensitized rat. Furthermore, we showed the same results for the D2 receptor antagonist in the NAc. However, these results in the VTA are different from the NAc. Our findings showed that the blockade of D1 and D2 receptors in the VTA had a lesser, almost negligible effect on the development of morphine sensitization. These findings are consistent with the data that showed that the stimulant effects of morphine are known to be mediated by the mesolimbic dopaminergic system through an increase in dopamine release in the NAc and VTA (Saal et al., 2003), and it was expected that dopamine receptors would have an important role in the mechanisms underlying this phenomenon. Microdialysis studies have demonstrated that most, if not all, abused drugs increase extracellular dopamine levels at the level of the NAc (Chau et al., 2010; Taslimi et al., 2012). Moreover, behavioral evidence suggests that changes in dopaminergic and/or opioidergic neurotransmission may be involved in the behavioral sensitization to morphine. Since morphine enhances both dopamine synthesis and release in the dopaminergic system via activation of μ-opioid receptors in the VTA, it
is likely that morphine-induced sensitization might be elicited by a similar mechanism (Azizi et al., 2009). In the present study, we showed that microinjection of D1 and D2 receptor antagonists into the NAc can prevent the antinoceptive effects induced by morphine in the tail flick test. Liljequist and Engel (1984) demonstrated that prolonged ethanol administration produced an increased sensitivity of the dopamine receptors in the NAc. In another study, Camarini et al. (2011) showed that the D1 receptor antagonist attenuated the development of ethanol sensitization and blocked the expression of this phenomenon (Abrahao et al., 2011; Camarini et al., 2011). It has been indicated that augmented dopamine release, which increases the occupation of D1 and D2 subtypes in the striatum and the NAc, significantly contributes to behavioral sensitization (Burger and Martin-Iverson, 1994). Therefore, we suggest that D1 and D2 dopamine receptors in the NAc and only D1 dopamine receptors in the VTA are involved in the development of sensitization to morphine, at least in part, through increasing the level of dopamine in these areas during exposure to morphine. However, more investigations are needed to find out the exact role of these dopamine receptors in opioid sensitization.

On the other hand, down-regulation of neuronal D2 dopamine receptors after chronic ethanol exposure has been found in several other studies (Franklin et al., 2009; Thielen et al., 2004; Vollow et al., 1997). Striatal D2 receptor down-regulation has also been found in the brains of human alcoholics (Vollow et al., 2007). Recently, Franklin et al. (2009) showed that 24 h of withdrawal after 5 days of ethanol exposure altered dopaminergic regulatory mechanisms, due in part to the reduction of D2 autoreceptor function in the NAc. Considering the above-mentioned studies, it seems that exposure to morphine during the sensitization period may alter dopaminergic receptor functions in these areas; and these changes in the dopaminergic system can cause a modification in mechanisms underlying opioid sensitization. However, further pharmacological, immunohistochemical and molecular electrophysiological investigations are needed to elucidate the hypothesis of the actual role of dopamine receptors in these areas; and whether these mechanisms are involved in modulating morphine-induced antinociception and sensitization in animal models of pain.

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