The effect of forced swim stress on morphine sensitization: Involvement of D1/D2-like dopamine receptors within the nucleus accumbens

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A B S T R A C T

Nucleus accumbens (NAc) plays an essential role in morphine sensitization and suppression of pain. Repeated exposure to stress and morphine increases dopamine release in the NAC and may lead to morphine sensitization. This study was carried out in order to investigate the effect of forced swim stress (FSS), as a predominantly physical stressor and morphine, on the development of morphine sensitization, focusing on the function of D1/D2-like dopamine receptors in the NAc in morphine sensitization. Eighty-five adult male Wistar rats were bilaterally implanted with cannulae in the NAc and various doses of SCH-23390 (0.125, 0.25, 1 and 4 μg/0.5 μl/NAc) as a D1 receptor antagonist and sulpiride (0.25, 1 and 4 μg/0.5 μl/NAc) as a D2 receptor antagonist were microinjected into the NAc, during a sensitization period of 3 days, 5 min before the induction of FSS. After 10 min, animals received subcutaneous morphine injection (1 mg/kg). The procedure was followed by 5 days free of antagonist, morphine and stress; thereafter on the 9th day, the nociceptive response was evaluated by tail-flick test. The results revealed that the microinjection of sulpiride (at 1 and 4 μg/0.5 μl/NAc) or SCH-23390 (at 0.25, 1 and 4 μg/0.5 μl/NAc) prior to FSS and morphine disrupts the antinoceptive effects of morphine and morphine sensitization. Our findings suggest that FSS can potentiate the effect of morphine and causes morphine sensitization which induces antinociception.

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1. Introduction

Mesocorticolimbic pathway has been known to be crucial for the representation of pain which nucleus accumbens (NAc) is a pivotal part in this pathway. Human imaging research revealed that, integrating signals from dopaminergic neurons of the mesencephalic, ventral hippocampus, amygdala and frontal cortices in the NAc have fundamental function in both acute and chronic pain states (Ren et al., 2015; Baliki et al., 2010; Martikainen et al., 2005). In previous studies, it was revealed that dopamine release in the NAc induces analgesia via D2 (Ansah et al., 2007) and D1 dopamine receptors (Altier and Stewart, 1998). Other studies have demonstrated that dopamine release blocks nociception in the mesolimbic/mesocortical pathway and this effect is attenuated by the dopaminergic neurons lesion in the ventral tegmental area (VTA, Saadé et al., 1997). Previous studies revealed that morphine increases extracellular dopamine concentrations in the NAc (Di Chiara and Imperato, 1988; Vander Weele et al., 2014) which induces analgesia (Morgan and Franklin, 1991). For instance, studies have shown that systemic administration of morphine induces analgesia, in part, through dopamine signaling in the striatum and this effect is reduced by either DA-depleting 6-OHDA lesions of the VTA (Morgan and Franklin, 1990) or pretreatment with dopamine receptor antagonists (Morgan and Franklin, 1991). There is also evidence that exposure to stress activates dopamine transmission in striatum as well (Altier and Stewart, 1999; Vaessen et al., 2015). One of the most sensitive stress-responsive circuits which have been implicated in pain management is known as mesolimbic dopamine circuit (Altier and Stewart, 1999; Tidey and Miczek, 1996).

It has been seen that repeated exposure to opioids and stressors augmented dopamine release in the NAc and striatum which caused sensitization (Kalivas and Stewart, 1991). Although some incongruous studies have revealed that repeated exposure to opioids and stressors reduces dopamine release in the NAc and inhibits sensitization (Karkhanis et al., 2016; Kaufling and Aston-Jones, 2015). This raises the question: which paradigms lead to sensitization? The method of morphine administration is critical for development of drug sensitization (Vetulani, 2001). Sensitization is mostly evoked with intermittent drug dosing, whereas tolerance intervenes with constant drug dosing (Hyman et al., 2006). Furthermore, behavioral sensitization occurs when a challenge injection is administered long after discontinuation of drug treatment (Robinson and Berridge, 1993). Several factors such as intensity, duration, frequency, controllability, and predictability of

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the stressor have effect on development of drug sensitization (Holly et al., 2015). For instance, some previous studies have shown that chronic stress induces sensitization (Naef et al., 2013), or no change (Young, 2004) on dopamine release in the NAc in response to the same stimuli. Behavioral sensitization is a progressive augmentation response to a drug following repeated administration of drug or stress (del Rosario et al., 2002; Robinson et al., 1985). Conclusive evidence described NAc as a brain region which is involved in drug sensitization (Azizi et al., 2009). Glutamate inputs from the prefrontal cortex to the NAc and dopamine inputs from the VTA to the NAc are regarded as components of the well-known pathway for behavioral sensitization (Pierce and Kalivas, 1997). Opioid agonists evoke behavioral sensitization by stimulation of μ- and δ opioid receptors (Kalivas, 1985). In addition, exposure to stressful situations triggers dopamine release similar to those seen with chronic drug exposures (Kalivas et al., 1988). Chronic activation of the mesocorticolimbic dopamine system by stress (Steketee et al., 1992) or μ-opioid receptor agonists may result to a disinhibition of mesolimbic dopaminergic neurons, which would lead to an increased release of dopamine in the nucleus accumbens and thus, an improved behavioral response to drugs of abuse (Kalivas and Duffy, 1990; Vanderschuren and Kalivas, 2000). Recent investigations using selective D1 and D2 dopamine receptor antagonists have revealed that blockade of D1 receptor inhibits the development of sensitization to amphetamine and morphine (Vezina and Stewart, 1989). Also, some other studies have shown that preferential D2 receptor antagonists can block sensitization (Weiss et al., 1989). Moreover, our previous study showed that both D1/D2 dopamine receptors in the NAc play an essential role in the development of morphine sensitization (Reisi et al., 2014). This finding is consistent with the results of previous studies showing that stimulation of D1/D2 dopamine receptors is important for the development of sensitization induced by restraint stress (del Rosario et al., 2002).

In summary, administration of these factors – stress and drug – together play an essential role in the induction of behavioral sensitization; for instance, de Jong et al. (2009) revealed that cocaine-paired stress induced behavioral sensitization in rats (de Jong et al., 2009). Also, some investigations were carried out to assess the relationship between pain and morphine sensitization. For example, in our previous study, it was revealed that D1 and D2 receptors in the NAc can cause analgesia induced by morphine in sensitized rats during tail-flick test (Reisi et al., 2014). Considering the above-mentioned findings, we tried to find out the role of D1 and D2 like dopamine receptors within the NAc in the morphine sensitization induced by morphine and stress and considering the antinociceptive effect of that as well.

2. Materials & methods

2.1. Animals

Eighty-five adult male albino Wistar rats weighing 200–250 g were used in this study. Animals were housed in standard plastic cages, in a controlled room environment (22 ± 2 °C, 60% relative humidity) and maintained on a 12:12 h light-dark cycle (lights on at 7:00 am). Food and water were available ad libitum. Five to six animals were used per group. All experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 80–23, revised 1996) (Clark et al., 1996) and were approved by the Research and Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran.

2.2. Surgical preparation

Rats were anesthetized by intraperitoneal injection of xylazine 2% (10 mg/kg) and ketamine 10% (100 mg/kg), and placed into a stereotaxic device (Stoelting, USA). An incision was made along the midline, the scalp was removed and the area surrounding bregma was cleaned and dried. Additionally, lidocaine with epinephrine (0.2 ml) was injected in different locations around the incision. Stainless steel guide cannulae (23-gauge) were bilaterally implanted 1 mm above the target site (the NAc) of drug microinjections according to the rat brain atlas (Paxinos and Watson, 2007). Stereotaxic coordinates for the NAc were 1.5 ± 0.2 mm anterior to bregma, 1.4 ± 0.2 mm lateral to the midline and 7.3 mm ventral to the skull surface. The guide cannulae were secured in place using two stainless steel screws anchored to the skull and dental acrylic cement. After the cement completely dried and hardened, two stainless steel stylet were used to occlude the guide cannulae during recovery period. Rats were individually housed and allowed to recover for 5–7 days before experiments.

2.3. Drugs

In the present study, the following drugs were used: morphine sulfate (Temad, Tehran Iran) and SCH-23,390 (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; Sigma-Aldrich, Germany). Both antagonists were freshly prepared with different doses and the infusion volume was 0.5 μl for each side. Saline and DMSO control groups received 0.5 μl of either saline or 10% DMSO into the NAc as controls for the rats that received SCH-23,390 or sulpiride, respectively.

2.4. Drug administration

Intra-NAc infusion was performed with a 1-μl Hamilton syringe (Hamilton Co., Reno, NV) connected to a 12-mm 30-gauge injector which was terminated 1 mm below the tip of the guide cannula. Bilateral intra-NAc infusions of SCH-23,390 (0.125, 0.25, 1 and 4 μg/0.5 μl saline), sulpiride (0.25, 1 and 4 μg/0.5 μl DMSO) or their vehicles (saline or DMSO respectively) were performed in a 0.5 μl volume per side over a 60 s duration (Reisi et al., 2014). After the infusion, the injector was removed and the stylet was replaced.

2.5. Induction of sensitization

Ten min after FSS for three consecutive days as the sensitization period, the rats were injected a single ineffective dose of morphine (1 mg/kg; sc). Five days later on the 9th day, the animals were received a single dose of morphine (1 mg/kg; sc) and then tail-flick test was applied as a model of acute pain.

One group received 5 mg/kg; sc morphine instead of 1 mg/kg during the sensitization period (Azizi et al., 2009; Reisi et al., 2014) and on the 9th day, after morphine injection (1 mg/kg; sc), tail-flick test was performed (Reisi et al., 2014).

2.6. Behavioral tests

2.6.1. Forced swim stress

Five min following the administration of either antagonist or vehicle, in order to induce stress, rats were forced to swim for 6 min in a vertical plastic cylinder (50 cm high, 30 cm in diameter) filled with clean tap water (23−27 °C) up to a level of 30 cm (Karimi et al., 2014). Trials were performed once a day for 3 consecutive days (Fatahi et al., 2014). Following each test, the rats were dried with towel and placed back into their cages for at least 10 min before other experiments (Karimi et al., 2014) which they received morphine (1 mg/kg).

2.6.2. Tail-flick test

The tail-flick test was performed as the method of D’Amour and Smith (D’Amour and Smith, 1941). Tail-flick apparatus (Harvard, USA) has been designed to precisely measure the nociceptive threshold to focused light stimulus on the rat tail. The heat was applied in succession to
A spot 3, 5 or 7 cm from the caudal tip of the tail. The light intensity source was manually set at 45% of maximal intensity, which yields baseline tail-flick latency (TFL) values in the range of 3–4 s. When the animal feels pain and flicks its tail, a sensor detects the flick, stops the timer and switches off the bulb. Therefore the reaction time of the animal is estimated and recorded automatically (Tzschentke et al., 2007; Parvishan et al., 2011). It should be noted that the small box was used during the test instead of restrainer to avoid immobilization stress. Therefore, the rat was held very gently in the corner of the box and its tail was fixed on the groove of the tail-flick set. A cut-off time of 10 s was used to avoid any tissue damage. The rats were tested before and 5, 15, 30, 45 and 60 min after morphine injection (1 mg/kg; sc). The increase in tail-flick latency was defined as antinociception and calculated as % MPE (Maximal Possible Effect) according to the following formula (Reisi et al., 2014):

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

2.7. Experimental design

Animals received treatments (morphine and/or antagonist) and physical stress for 3 consecutive days (sensitization period) and after five days of free drug and stress, on the 9th day, tail-flick test was performed and TFL was recorded before and after the morphine injection (Fig. 1).

2.7.1. Effect of morphine and/or forced swim stress on increase of antinociceptive response of ineffective dose of morphine

In this experiment, three groups were determined: (1) MOR groups in which two sub-groups of animals were treated with different doses of morphine (1and 5 mg/kg; sc) for 3 consecutive days (sensitization period) and after five days of free drug and stress, on the 9th day, tail-flick test was performed and TFL was recorded before and after the injection of morphine (1 mg/kg; sc). 2.7.2. Effects of intra-accumbal administration of SCH-23390 prior to stress and morphine on antinociceptive response of morphine

In this set of experiment, to elucidate the role of D1-like dopamine receptors on development of morphine sensitization, during 3 days of sensitization different doses of SCH-23,390 (0.125, 0.25, 1 and 4 μg/0.5 μl/NAc) were microinjected just 5 min before administering the FSS and 15 min prior to morphine (1 mg/kg; sc) injection. Then for last 5 days rats did not receive any drugs or stress (no FSS, SCH-23,390 or morphine), and on the ninth day tail-flick test was performed pre- and post-injection of the ineffective dose of morphine (1 mg/kg; sc). In saline-control group, animals received saline (0.5 μl/NAc) instead of SCH-23,390 during the sensitization period. Additionally, a group just received maximum dose of SCH-2339 (4 μg/0.5 μl/NAc) (no FSS or morphine) during the first three days of protocol.

2.7.3. Effects of intra-accumbal administration of sulpiride prior to stress and morphine on antinociceptive response of morphine

To find out the role of D2-like receptors in the NAc on development of morphine sensitization, different doses of sulpiride (0.25, 1 and 4 μg/0.5 μl DMSO/NAc) were microinjected 5 min before administering the FSS and 15 min prior to morphine (1 mg/kg; sc) injection during 3 days of sensitization. After a 5-day period (no FSS, SCH-23,390 or morphine), on the ninth day, tail-flick test was applied before and after injection of the ineffective dose of morphine (1 mg/kg; sc). DMSO-control group received DMSO (0.5 μl/NAc) instead of sulpiride during the sensitization period. Additionally, a group just received maximum dose of sulpiride (4 μg/0.5 μl DMSO/NAc) during the first three days.

2.8. Histology

After performing the test, animals were deeply anesthetized with ketamine and xylazine and were transcardially perfused with 0.9% saline and 10% formalin solution. The brains were removed and cut coronally in 50 μm sections through the cannulae placements in the NAc. 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 (Electronic Supplementary Fig. 1) were included in the data analysis.

![Fig 1](image-url). Schematic time-line at different stages of the experiment with different groups used during this study. During the whole investigation, effects of different doses of morphine (1 or 5 mg/kg; sc), forced swim stress (FSS) or morphine and FSS together have been studied on antinociceptive response of morphine in 3 different groups (A, B, C), and in 2 super-groups (D and E) microinjection of different doses of antagonists into the NAc before administration of FSS and morphine, and a super group (F) microinjection of maximum dose of antagonists have been applied. Animals in all groups received above treatments during 3 days of sensitization. After 5 days free of drug and stress (rest), at the 9th day (test day) tail-flick test was applied before and after morphine injection (1 mg/kg; sc) to evaluate noiception effect.
Data were presented as mean ± SEM (standard error of mean). P-values less than 0.05 were considered to be statistically significant. The %MPEs at time set intervals in all groups were analyzed by two-way analysis of variance (ANOVA) followed by Bonferroni’s multiple comparisons test. The mean %MPEs in all groups was subjected to one-way ANOVA followed by protected Newman–Keuls test. Unpaired Student’s t-test was used to compare mean %MPEs in DMSO/saline control group with FSS + MOR group.

3. Results

At first we evaluate the effect of the sensitization protocol on the baseline thresholds in the tail-flick test. Because changes in baseline responses would impact %MPE results independent of any changes in test responses. One-way ANOVA followed by Newman–Keuls multiple comparison test showed no marked differences in baseline thresholds of different experimental and control groups of SCH-23,390-treated animals (Mor, FSS, Mor + FSS, SCH-23,390/vehicle + FSS + Mor) [F(7, 39) = 1.423, P = 0.2305]. Similarly, the results revealed that there was no significant difference in baseline thresholds of experimental and control groups of sulpiride-treated animals (Mor, FSS, Mor + FSS, sulpiride/vehicle + FSS + Mor) [F(6, 40) = 1.84, P = 0.1205]. Whereas baseline thresholds had no significant differences between sensitized and nonsensitized animals, we used %MPE as an antinociceptive index during our analysis.

3.1. Effect of morphine and/or forced swim stress on antinociceptive response of morphine

In this experiment, the effect of morphine (1 or 5 mg/kg) and/or FSS was evaluated on acute models of pain during a 60-min period. In tail-flick test two-way repeated measures ANOVA followed by Bonferroni’s test for %MPEs indicated a significant difference in antinociceptive responses of animals that received morphine (5 mg/kg; MOR group) alone or FSS before morphine injection (1 mg/kg; MOR + FSS group) compared to the groups that just received morphine (1 mg/kg; MOR group) or FSS alone (FSS group) [treatment effect: F(3, 115) = 205.5, P < 0.0001; time effect: F(4, 115) = 5.005, P = 0.7354; treatment and time interaction: F(12, 115) = 0.8795, P = 0.5696; Fig. 2A].

On the other hand, as shown in Fig. 2B, one-way ANOVA followed by Newman–Keuls multiple comparison test showed that the mean of %MPEs for animals that received morphine (5 mg/kg; MOR group) alone or FSS before morphine injection (1 mg/kg; MOR + FSS group) compared to the groups that just received morphine (1 mg/kg; MOR group) are noticeably different [F(3, 26) = 72.83, P < 0.0001]. However, there was no significant difference in antinociceptive responses of MOR + FSS group compared to MOR group (5 mg/kg, Fig. 2B). Therefore, it seems that morphine (1 mg/kg) or FSS solely do not cause analgesia but when they are applied simultaneously – similar to use of morphine (5 mg/kg) – they can increase analgesia. Hereinafter, morphine (1 mg/kg) and FSS were concurrently used in the experiments.

3.2. Effects of intra-accumbal administration of SCH-23,390 prior to stress and morphine on antinociceptive response of morphine

Two-way repeated measures ANOVA followed by Bonferroni’s test for %MPEs showed a significant difference in antinociceptive response to morphine (1 mg/kg) after administration of different doses of SCH-23,390 in the presence of FSS and morphine (1 mg/kg) [treatment effect: F(7, 155) = 234.4, P < 0.0001; treatment effect: F(4, 155) = 0.921, P < 0.4137; treatment and time interaction: F(28, 155) = 0.2703, P = 0.9199; Fig. 3A].

One-way ANOVA followed by Newman–Keuls test showed that the mean of %MPEs for animals that received morphine (MOR group) or FSS (FSS group) compared to the group that received FSS before morphine injection (1 mg/kg; MOR + FSS group) are noticeably different [F(4, 22) = 42.87, P < 0.0001]. However, administration of SCH-23,390 at the lowest dose (0.125 μg/0.5 μl/lNAc) could not affect analgesia and did not have significant effect on mean of %MPEs. Unpaired Student’s t-test showed that there is no significant difference between the...
antinociceptive responses of MOR + FSS group and saline control group \[t (9) = 0.595, P = 0.5665\] (Fig. 3B). Also, there was no significant difference between the antinociceptive responses of MOR group and the group that received just the maximal dose of SCH-23,390 (4 μg/0.5 μl/NAc) \[t (9) = 0.7539, P = 0.47\] (Fig. 3).

### 3.3. Effects of intra-accumbal administration of sulpiride prior to stress and morphine on antinociceptive response of morphine

Two-way repeated measures ANOVA followed by Bonferroni’s test for %MPEs indicated significant difference in antinociceptive responses to morphine (1 mg/kg) after administration of different doses of sulpiride in the presence of FSS and morphine (1 mg/kg) \[treatment effect: F(6, 165) = 92.29, P < 0.0001; time effect: F(4, 165) = 0.5123, P = 0.7268\]; treatment and time interaction: \[F(24, 165) = 0.3926, P = 0.9155\] (Fig. 3).

One-way ANOVA followed by Newman-Keuls test showed that the mean of %MPEs for animals that received morphine (MOR group) or FSS (FSS group) compared to the group that received FSS before morphine injection (MOR + FSS group) are noticeably different \[F(2, 17) = 77.03, P < 0.0001; Fig. 4B, left panel\]. As it can be seen in the right panel of Fig. 4B, microinjection of different doses of sulpiride (1 and 4 μg/0.5 μl/NAc) dose-dependently inhibits antinociception compared to DMSO- control group \[F(3, 24) = 22.65, P < 0.0001\]. These results showed that sulpiride significantly decreased the mean of %MPE as an antinociceptive index. However, administration of sulpiride at the lowest dose (0.25 μg) could not inhibit analgesia and did not affect the mean of %MPEs. Unpaired Student’s t-test showed...
that there is no significant difference between the antinociceptive response of MOR + FSS group and DMSO control group \[t (10) = 0.4756, P = 0.6446\] (Fig. 4B). Also there is no significant difference between the antinociceptive response of MOR group and the group that animals received maximal dose of sulpiride (4 μg/0.5 μl/NAc) \[t (8) = 0.613, P = 0.557\].

4. Discussion

In this study, the data showed that D1 and D2 like dopamine receptor antagonists in the NAc inhibit the development of sensitization induced by morphine and stress, thereby abolishing antinociceptive effect of morphine in acute pain test. More specifically, it was found
that pretreatment with SCH-23390 and sulpiride as the D1 and D2 dopamine receptor antagonists which were infused directly into the NAc, blocked the development of sensitization induced by the low dose of morphine (1 mg/kg) and FSS concurrently, thereby eliminating the antinociceptive effect of morphine (1 mg/kg) in tail-flick test. In this research, two different doses of morphine (1 and 5 mg/kg) were solely injected during three consecutive days to investigate the antinociceptive effect of morphine induced by sensitization. Our findings revealed that only high dose of morphine led to antinociception induced by sensitization and low dose of morphine did not have any antinociceptive effect. On the other hand, we applied FSS alone as a physical stress for three consecutive days to investigate the effect of FSS on morphine sensitization. In our result, it was revealed that FSS did not show any antinociceptive effect due to sensitization. So, animals were exposed to FSS and the low dose of morphine (1 mg/kg) concurrently to investigate the potentiation effect of simultaneous application of drug and physical stress on development of sensitization. The experiment showed that paired administration of FSS and low dose of morphine induced sensitization and displayed antinociception in the presence of the ineffective dose of morphine (1 mg/kg) in tail-flick test. This finding is consistent with the results of previous studies showing that opioids and other drugs of abuse have important role in the development of drug sensitization (van Ree et al., 1999). In previous studies, it was reported that although the lower doses (less than 5 mg/kg) of morphine did not show any significant effect, chronic injection of morphine (5 mg/kg; sc) for 3 consecutive days (sensitization period) followed by 5 days of free drug injection induced sensitization in conditioning place preference (CPP) test (Azizi et al., 2009). Repeated administration of morphine (5 mg/kg; sc) for 3 consecutive days after 5 days of free drug injection augmented analgesic effect of morphine in tail-flick test (Reisi et al., 2014). Previous research revealed that animals which were formerly exposed to stress may become sensitized to some addictive drugs such as amphetamine (Robinson, 1988; Antelman et al., 1980). Chronic exposure to stress may lead to an augmentation of the locomotor effect of morphine (Stohr et al., 1999; Deroche et al., 1995). These findings might sound to be in contrast with our findings which suggest that animals that were only exposed to stress may not be sensitized to morphine. However, this controversial result may be a consequence of differences in frequency and type of stress (del Rosario et al., 2002; Hahn et al., 1986) and the type of behavior being monitored (del Rosario et al., 2002). According to our results, another study on sensitization by cocaine demonstrated that cocaine was paired with stress induced behavioral sensitization (de Jong et al., 2009).

It was also found that pretreatment with SCH-23390 and sulpiride that were infused directly into the NAc, blocks sensitization development induced by low dose of morphine (1 mg/kg) and FSS concurrently and then eliminates antinociceptive effect of the ineffective dose of morphine (1 mg/kg) in tail-flick test. These findings are in line with the results of previous studies implicating dopamine system in pain suppression (McMahon et al., 2013) and morphine sensitization which was induced by stress (Kalivas and Stewart, 1991; Deroche et al., 1992) and opioids (Robinson and Berridge, 1993) and more specifically, implicating elevated dopamine activity in the NAc in this effect (Kalivas and Stewart, 1991). These findings are consistent with the results of previous studies demonstrating that analgesia induced by morphine is mediated by D1 and D2-like dopamine receptors in the NAc (Altier and Stewart, 1998). Previous studies revealed that exposure to stress also causes dopamine release in mesocorticolumbic dopamine neurons (Altier and Stewart, 1999). Exposure to stress, pain or both triggers the pain inhibitory system via activation of mesolimbic dopamine neurons (Altier and Stewart, 1998; Altier and Stewart, 1999). According to some studies, administration of D1/D2 selective receptor antagonists decreases analgesia induced by swim stress in rat (Fazli-Tabaei et al., 2006). Thus, stress can induce antinociception through actuation of the opioid and non-opioid system (Madden et al., 1977). It seems that D1/D2 dopamine receptors are involved in analgesia induced by stress (Fazli-Tabaei et al., 2006) and morphine (Altier and Stewart, 1998).

It was also revealed in previous studies that intra-accumbal administration of SCH-23390 and sulpiride into the NAc inhibits the development of sensitization, and then eliminates antinociceptive effect of morphine during acute pain test (tail-flick test, Reisi et al., 2014). It was also found that administration of selective D1and D2 receptor antagonists inhibits behavioral sensitization to amphetamine and morphine (Vezina and Stewart, 1989). In line with this, some previous studies have demonstrated that preferential D2 receptor antagonists inhibits sensitization (Weiss et al., 1989). Moreover, postmortem studies demonstrated that exposure to acute and chronic stress increases dopamine release produced by a subsequent stress or drug (Kalivas and Dufy, 1989). Exposure to some experimental stressors stimulates mesocorticolumbic dopamine transmission; for instance exposure to restraint, foot shock, conditioned fear, injection (Kalivas and Abhold, 1987). Moreover, stress causes corticosterone secretion via HPA axis activation (Attarzadeh-Yazdi et al., 2013) and corticosterone secretion causes dopamine release into some brain regions such as the NAc (Rouge-Pont et al., 1998).

This study revealed that D1 and D2 like dopamine receptor antagonists in the NAc inhibit the development of sensitization induced by morphine (1 mg/kg) and FSS. On the other hand, de Jong et al. (2009) demonstrated that administration of cocaine and stress induced behavioral sensitization by activating the HPA axis. Nevertheless, during this investigation, adrenalectomy was carried out in order to show whether corticosterone had a role in sensitization and it revealed that, development of sensitization was inhibited in the absence of corticosterone (de Jong et al., 2009). Recent study revealed that administration of FSS and morphine (5 mg/kg) simultaneously reduces the acquisition but not the expression of morphine-induced CPP (Attarzadeh-Yazdi et al., 2013). It is possible that different doses of morphine led to this discrepancy.

5. Conclusion

In conclusion, the results of the present study indicate that a mechanism underlying the inhibition of pain in sensitized rats may stimulate dopamine receptors in the NAc by dopamine release from terminals of mesolimbic neurons. The evidence that stress and morphine alone play a role in dopamine release in the NAc suggests that these two could potentiate the effect of each other, leading to morphine sensitization.

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