Microinjection of WIN55,212-2 as A Cannabinoid Agonist into The Basolateral Amygdala Induces Sensitization to Morphine in Rats

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ABSTRACT

Introduction: Previous studies have shown that the basolateral amygdale (BLA) is rich of CB1 cannabinoid receptors and involved in cannabinoid-induced antinociception. Also, it seems that there are functional interactions between the cannabinoid CB1 and opioid receptors in the process of sensitization to opiates. In the present study, we tried to examine the role of intra-BLA cannabinoid receptors on development of sensitization to morphine.

Methods: In this study, seventy two adult male albino Wistar rats weighting 230-280 g were included. Antinociception response of subcutaneous (sc), administration of saline (1 ml/kg), and morphine (1 and 10 mg/kg) were measured by the tail-flick test in animals that were received subcutaneous administration of morphine (5 mg/kg) or saline (1 ml/kg) once a day for three days (sensitization period), followed by five days free of drug. The dose of 1 mg/kg of morphine was selected as the appropriate (ineffective) dose in the next stages of experiment for measuring analgesia in the tail-flick test in sensitive animals which previously received bilateral intra-BLA CB1 receptor agonist, WIN55, 212-2 (0.5, 1, 2 and 4 mM/0.3 µl/side), DMSO, or saline (0.3 µl/side) during sensitization period.

Results: Bilateral intra-BLA administration of WIN55, 212-2, increased morphine-induced antinociception in ineffective dose, while this effect was not observed in the groups that received DMSO or saline. Our findings indicated that CB1 receptors within the BLA are involved in the sensitization to morphine.

Discussion: It seems that glutamatergic projections from the BLA to the nucleus accumbens are involved in the development of morphine sensitization induced by cannabinoids.

Key Words:
Sensitization,
Basolateral amygdala,
Cannabinoid receptor,
Morphine, Rat

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1. Introduction

The amygdala is a major emotional center in the limbic forebrain and involved in learning, memory, motivation, reward and punishment (Holland & Gallagher, 1999; Neugebauer, Li, Bird & Han, 2004; Kryger & Wilce, 2010). Also, it is considered as a neural substrate for the interaction between pain and emotion (Neugebauer et al., 2004). Amygdala, especially basolateral amygdala (BLA) has a high density of CB1 receptors, a cannabinoid receptor subtype that is mainly found in the CNS (Katona et al., 2001; McDonald & Mascagni, 2001). Endocannabinoids and their receptors, especially the CB1 receptors, play important roles in different physiological functions such as reward (Gardner, 2005; Solinas, Goldberg & Piomelli, 2008), addiction (Maldonado & Rodriguez de Fonseca, 2002) and nociception (Pertwee, 2001; Hohmann, 2002). It has been shown that the antinociceptive effects of WIN55, 212-2, a cannabinoid agonist, in the BLA are

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mediated by CB1 receptors. So, there is a CB1 receptor-mediated system in the BLA that can modulate pain regulatory pathways (Hasanein, Parviz, Keshavarz & Javanmardi, 2007; Ghalandari-Shamami, Hassanpour-Ezatti & Haghparast, 2011).

Recent studies demonstrate that there is functional interaction between the endogenous cannabinoid and opioid-systems in several drug reactions, including reward, tolerance, and dependence (Ledent et al., 1999; Fattore et al., 2004; Vigano, Rubino & Parolaro, 2005; Robledo, Berrendero, Ozaita & Maldonado, 2008). The cannabinoids and opioids have a crucial role in modulating each other's reward and addictive properties (Singh, Verty, McGregor & Mallet, 2004; Fattore et al., 2004). Growing evidence suggests that many of the behavioral and physiological effects of opiates are modulated by the brain's cannabinoid system (Maldonado & Rodriguez de Fonseca, 2002; Higgs, Williams & Kirkham, 2003). Acute administration of cannabinoid receptor agonists can lead to opioid peptide release and that chronic Δ9-tetrahydrocannabinol (Δ9-THC) administration increases endogenous opioid precursor gene expression (Corchero, Avila, Fuentes & Manzanares, 1997).

In addition, these two systems have been shown to interact in their effects on analgesia. It has been observed that concurrent administration of mu opioid receptor (MOR) and CB1 receptor agonists produces additive or synergistic analgesic effects (Welch and Eads, 1999).

On the other hand, interactions of cannabinoids and opioids have been observed in sensitization (Pontieri, Monnazzi, Scontrini, Buttarelli & Patacchioli, 2001a,b; Vigano et al., 2004). Sensitization is defined as an increased responsiveness to the same or lower doses of drugs after chronic repeated intermittent with drugs of abuse (Robinson & Berridge, 1993; Stewart & Badiani, 1993). It has been shown that intermittent exposure of animals to a fixed dose of morphine leads to increased behavioral response to further morphine administration, a phenomenon known as morphine sensitization (Kuribara, 1995; Vanderschuren et al., 1997). Furthermore, sensitivity to drug consumption leads to a faster response to other drugs. For example, animals that were exposed to ethanol showed sensitivity to cocaine (Itzhak & Martin, 1999). This suggests that, there is a cross-sensitization between drugs.

It has been shown previously that cannabinoid receptor agonist such as Δ9-tetrahydrocannabinol (Cadoni, Pisanu, Solinas, Acquas & Di Chiara, 2001) and CP 55940 (Norwood, Cornish, Mallet & McGregor, 2003) enhances morphine sensitization. Additionally, Haghparast et al., showed that administration of AM251, CB1 receptor antagonist, within the nucleus accumbens (NAc) produced behavioral sensitization to morphine (Haghparast, Azizi, Hassanpour-Ezatti, Khorrami & Naderi, 2009), and thus, suggested a role for these receptors in the development of morphine sensitization in the NAc –a key region involved in sensitization. Therefore, in this study, we tried to examine the effects of intra-BLA administration of WIN55, 212-2, a CB1 receptor agonist, in induction sensitivity to morphine in animal models of acute pain.

2. Methods

2.1. Animal

Seventy two adult male Wistar rats weighing 230-280 g were housed in standard plastic cages in groups of three in a room (temperature 22 ± 2 °C). They were maintained on a 12-h light/dark cycle with food and water. The experiments were carried out during the light phase of the cycle. Each animal was tested once. Six rats were used per each group. 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: WIN55, 212-2 ((R)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl) pyrrolo [1,2,3,-de]-1, 4-benzoxazin-6-yl]-1 naphthalenyl methanone mesylate) (Sigma-Aldrich, USA) that was dissolved in dimethyl sulfoxide (DMSO; Sigma-Aldrich), morphine sulfate (Temad, Iran) that was dissolved in sterile saline (0.9%). Control animals received saline and/or 10% DMSO.

2.3. Surgical Preparation

Rats were anesthetized by intraperitoneal injection of xylazine (10 mg/kg) and ketamine (100 mg/kg), and moved into stereotaxic device (Stoelting, USA). An incision was made along the midline, the scalp was retracted, and the area surrounding bregma was cleaned and dried. Stainless steel guide cannulae (23 gauge, Supa Co., Iran, 11 mm, guide cannula was 2 mm above the appropriate injection place) were bilaterally implanted in the BLA. The stereotaxic coordinates were AP=2.8 ± 0.5 mm caudal to bregma, Lat=±4.6 mm, and DV=8.7 mm ventral from the skull surface which were determined by the rat brain atlas (Paxinos & Watson, 2005: 93-97). The guide cannula was

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affixed to the skull with two stainless steel stylets. Animals were individually housed and allowed to be recovered for 4-6 days before examination.

2.4. Drug Administration

Microinjections were performed by lowering stainless steel injector cannulae (30-gauge needle) with a length of 2 mm longer than the guide cannulae into the BLA. The injector cannulae were connected to a 1-µl Hamilton syringe by polyethylene tubing (PE-20). In the present study, for drug microinjection, the animals were gently restrained by hand; then stylets were removed from the guide cannulae and replaced by 30-gauge injector cannulae. Animals received different doses of WIN55, 212-2 as a mixed CB1/CB2 agonist (0.5, 1, 2 and 4 mM/0.3µl per side) was dissolved in 10% DMSO, for three consecutive days and control animals received 10% DMSO or saline (0.3 µl/side). All drug microinjections were performed bilaterally.

2.5. Induction of Sensitization

The drug sensitization was performed with injection of drugs for three consecutive days in a room distinct from which behavioral test performed and 5 days free of the drugs.

2.6. Tail-Flick Test

The antinociceptive effect of morphine was measured by the tail-flick apparatus (Harvard, USA). Tail-flick test is an animal model of acute pain. Heat was applied in succession after the 3, 5 and 7 cm from the caudal tip of the tail. The light intensity source was manually set at about 40-50% 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 seconds. If at any time the animal failed to flick its tail within 10 seconds (cut-off point), the tail was removed from the coil to prevent damage to the skin (Haghparast, Soltani-Hekmat, Khani & Komaki, 2007). TFL (s) were expressed either as raw data or percentage of maximal possible effect (%MPE) which was calculated from the following formula:

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

To evaluate the sensitivity of animals to nociceptive stimulus, we considered the individual TFL before drug treatment as a pain threshold.

2.7. Locomotor Activity Measurement

To evaluate the effect of different doses of WIN55, 212-2 on locomotor activity in animals, total distance traveled (cm) during 10-min test period was measured by video tracking system and Ethovision software in all groups. This section was designed in order to ensure that whether the movement of the animal's tail has been affected by their real pain, or drugs affected the animal's movement (or movement of the animal's tail) in the tail-flick test.

2.8. Experimental Protocols

This study, was performed in 12 groups (n=6 each group). Animals were exposed to drug treatment for three consecutive days and after five days of treatment; tail-flick tests were performed two times after and before subcutaneous (sc) injection of morphine or saline. This test has been used for evaluating the development of morphine sensitization.

2.8.1. Dose-response Effects of Morphine on Tail-Flick Latency in Acute Model of Pain in Saline- and Morphine-Treated Rats

At first, in order to determine the ineffective dose of morphine for analgesia in sensitized rats, animals received morphine (5 mg/kg; sc) or saline (1 ml/kg; sc), for three consecutive days and then 5 days without drugs. In 9th day, tail-flick test was performed by morphine (1 or 10 mg/kg; sc) or saline (1 ml/kg; sc). The appropriate dose of morphine was chosen for evaluating its antinociceptive response as an index of sensitization.

2.8.2. Effect of Intra-BLA Injections of CB1 Receptor agonist (WIN55, 212-2) on Antinociceptive Response of Morphine in Rats

In this section, experimental groups received different doses of WIN55, 212-2 (0.5, 1, 2 and 4 mM/0.3µl) during sensitization period; and then they had a 5 days free drug injection phase. In control group, DMSO (0.3µl), as a vehicle was bilaterally injected into the BLA instead of WIN55, 212-2 during this period. Tail-flick test was performed as a model of acute pain and TFLs were recorded as antinociceptive index (%MPE) before and after administration of morphine (1mg/kg), to determine the development of sensitization.

2.9. Histology

After completion of behavioral testing, the rats were deeply anesthetized with Ketamine and Xylazine. Then, they were transcardially perfused with 0.9% saline and

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10% formalin solution. The brains were removed, blocked and cut coronally in 50-µm sections through the cannulae placements. The histological results were plotted on the representative section taken from the rat brain atlas (Paxinos & Watson, 2005: 93-97) and the neuroanatomical location of cannulae tips placements were confirmed.

2.10. Statistics

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

3. Results

3.1. Dose-Response Effect of Morphine on Tail-flick latency in Acute Model of Pain in Saline- and Morphine-Treated Rats

In this section of study, animals that were given once a day for three consecutive days effective dose (5 mg/kg; sc) of morphine (experimental groups) or saline (1 ml/kg) as control group, and in the test day, animals were treated by saline (1 ml/kg), or effective (10 mg/kg) or ineffective (1 mg/kg) dose of morphine were compared with each other. ANOVA and subsequent Newman-Keuls's tests showed that, in animals with a prior history of morphine administration, significant increase in %MPE and the induction of analgesia by ineffective dose of morphine is observed. Injection of saline instead of morphine during sensitization in the control groups was created noanalgesic response to ineffective dose of morphine. As expected, the dose of 10 mg/kg of morphine caused a significant analgesic response [$F(5,35)=49.16$, $P<0.0001$; Table 1]. Accordingly, the dose of 1 mg/kg of morphine was selected as the appropriate dose for next experiments in rats.

3.2. Effect of intra-BLA Injections of CB1 Receptor agonist (WIN55,212-2) on Antinociceptive Response of Morphine in Rats

In this set of experiment, to determine the sensitization effects of CB1 receptor agonist, animals received in separate groups different doses of WIN55, 212-2 (0.5, 1, 2 and 4 mM/0.3µl per side) once a day for 3 consecutive days through bilaterally microinjected into the BLA. After 5 days, tail-flick test was performed with an ineffective dose of morphine (1mg/kg; sc). The control groups received DMSO or saline (0.3 µl/side) into the BLA, bilaterally. One-way ANOVA followed by Newman-Keuls's test [$F(5,35)=29.11$, $P<0.0001$; Figure 1] showed that microinjection of different doses of WIN55, 212-2(1, 2 and 4 mM) significantly increased in %MPEs and the induction

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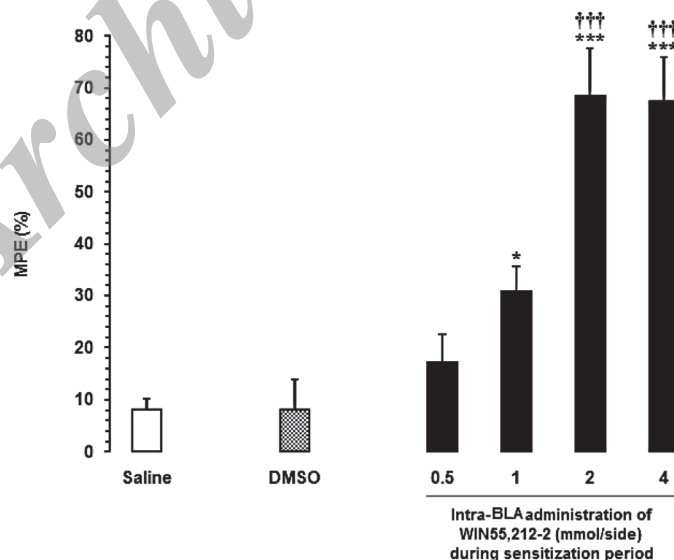

Figure 1. Effects of intra-BLA administration of different doses of WIN55, 212-2, cannabinoid receptor agonist, on MPEs as antinociceptive index of ineffective morphine (1 mg/kg; sc) in the test day. Animals received four different doses of WIN55,212-2 (0.5, 1, 2 and 4mM/side) within the BLA, once daily for three days during sensitization period, and after five days free-drug period, behavioral tests were performed before and after injection of morphine (1 mg/kg; sc). Control groups received DMSO or saline (0.3 µl/side) instead WIN55, 212-2 or morphine, respectively. Data are represented the Mean ± SEM for 6 rats.

* $P<0.05$; *** $P<0.001$ compared to saline control group.

†††$P<0.001$ compared to DMSO control group.

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of analgesia by ineffective dose of morphine as compared to control groups on the test day. The increase in the response reached its highest value in 2 mM/0.3µl per side and was not observed in 0.5 mM. In fact, the distribution of WIN55, 212-2 in sensitization period in high doses, led to sensitivity to low-dose of morphine for analgesic response.

On the other hand, Figure 2 revealed that the different doses of WIN55, 212-2 (0.5-4 mM/0.3 µl), saline and 10% DMSO (control groups), did not alter in locomotor activity in sensitized rats [$F(5,35)=0.1218$, $P=0.9963$]. Thus, the movement of the animal's tail, affected by its real pain and the drugs had no effect on the motor activity.

4. Discussion

The purpose of this study was to investigate the role of the CB1 receptors within BLA on morphine sensitization. This study showed that repeated administration of morphine (5mg/kg; sc), once a day for 3 days (sensitization period) followed by 5 days free of morphine, increased antinociceptive response by ineffective dose of morphine. This finding is consistent with previous studies showing that pretreatment with morphine causes sensitization to morphine (Vanderschuren et al., 1997; Azizi, Haghparast, & Hassanpour-Ezatt, 2009). It was previously shown that administration of different doses of morphine (0.5, 1, 2.5, 5, 7.5 and 10 mg/kg) induced conditioned place preference (CPP) at the dose of ≥5 mg/kg (Haghparast et al., 2009). Accordingly, we used dose of 1 mg/kg of morphine as an ineffective dose and 10 mg/kg as an effective dose for our experiment (Table 1).

In addition, we showed that bilateral intra-BLA CB1 receptor agonist (WIN55, 212-2), induced analgesia with an ineffective dose of morphine in sensitive rats. The results also showed that administration of different doses of drugs and solvents could not affect the locomotor activity. So, we can say that, in effective dose of morphine-induced analgesia caused by sensitization to morphine. Therefore, CB1cannabinoidreceptorsin the BLA are involved in the morphine sensitization. This result confirmed cross-sensitization between drugs. Also, this finding is consistent with previous reports that there is an interaction between opioid and cannabinoid systems.

Previous studies have shown that there are reciprocal interactions and cross-regulate between endogenous opioid and cannabinoid systems in the brain (Vigano et al., 2005; Lopez-Moreno, Lopez-Jimenez, Gorriti & de Fonseca, 2010). Cannabinoid and opioid receptors are co-localized in the key brain regions involved in addiction and reward (Manzanares et al., 1999) and modulated similar intracellular signal transduction pathways (Shapira, Gafni & Sarne, 2002). In these regions, two systems interact with each other. Endogenous opioids have an essential role in the modulation of addictive properties of cannabinoids (Fattore et al., 2004) and endocannabinoids play an important role in modulating the rewarding effects of

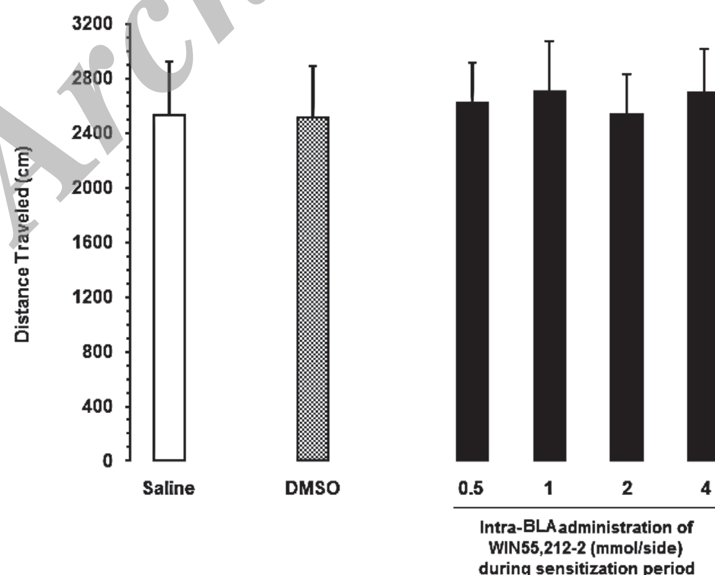

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Figure 2. Effects of intra-BLA administration of different doses of WIN55, 212-2, cannabinoid receptor agonist, on locomotor activity (distance traveled) in rats. There were no significant differences in the distance traveled between experimental and control groups. Data are represented as Mean ± SEM for 6 rats.

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Table 1. Percentage of maximal possible effects (%MPEs) of different doses of morphine and saline in animals that received morphine or saline during 3-day sensitization period.

Treatment in test day	Drug injection during sensitization period: Saline (1 ml/kg)	Drug injection during sensitization period: Morphine (5 mg/kg)
Saline (1 ml/kg)	8.2 ± 1.9	5.9 ± 3.5
Morphine (1 mg/kg)	9.1 ± 2.7	69.5 ± 9.7*** ††
Morphine (10 mg/kg)	84.5 ± 6.3*** +++	90.1 ± 4.8***

*** $P< 0.001$ different from respective saline control group

+++ $P< 0.001$ different from respective 1 mg/kg morphine group

†† $P< 0.01$ different from 1 mg/kg morphine group in saline-treated group

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morphine (Singh et al., 2004). Karimi et al., showed that cannabinoid agonist within NAc could induce place preference to morphine in a dose-dependent manner (Karimi, Azizi, Shamsizadeh & Haghparast, 2013). Also, Martin et al.,showed that morphine-induced conditioned place preference has been reduced in CB1 knock out mice (Martin, Ledent, Parmentier, Maldonado & Valverde, 2000). These results suggest that endocannabinoid may be essential for opioid activity.

Furthermore, the presence of these receptors in several brain regions known analgesic activity and also, produce a synergistic analgesic effect when the µ and CB1 receptor agonist are used simultaneously (Welch & Eads, 1999), supports the possibility of interaction between these two systems to produce analgesic effects in neuronal circuits. Cannabinoid receptor antagonist, AM251, reversed morphine-induced analgesia in inflammatory model of pain (Fonseca Pacheco et al., 2008). The combination of low-doses of Δ9-THC, a cannabinoid agonist, and morphine created a high antinociceptive effect (Cichewicz, Martin, Smith & Welch, 1999). In addition, Trang et al., showed that co-administration of AM-251 and morphine reduced the development of tolerance and dependence in mice (Trang, Sutak & Jhamandas, 2007).

On the other hand, studies indicate that there is a cross-talk between the opioid and cannabinoid systems in the process of sensitization to opiates (Vigano et al., 2004; Pontieri et al., 2001a,b). It was previously shown that pretreatment with cocaine and ethanol, show sensitization to cocainein rats (Itzhak & Martin, 1999). Also, chronic treatment with methyl phenidate, was induced cross-sensitization with amphetamine (Yang, Swann & Dafny, 2003). These results suggest that, there is a cross-sensitization between drugs. A study showed that Pre-exposure to the cannabinoid receptor agonist CP 55940 enhances morphine behavioral sensitization (Norwood et al., 2003). Additionally, Haghparast et al., showed that administration of AM251 within the NAc produced behavioral sensitization to morphine and induced CPP in an ineffective dose of morphine; they suggested that sensitization may be due to up-regulation of synaptic connection of opioid receptors in the absence of CB1 cannabinoid receptors (Haghparast et al., 2009; Azizi et al., 2009). We showed that, intra-BLA administration of cannabinoid agonist can increase antinociceptive response of ineffective dose of morphine, and therefore, induce the morphine sensitization. Our findings confirm previous reports that cannabinoids are involved in the development of morphine sensitization and supports previous findings that there is an interaction between opioids and cannabinoids.

On the other hand, Cadoni et al., showed that Δ9-THC-induced behavioral sensitization is associated with alteration in dopamine transmission in the NAc subdivisions (Cadoni, Valentini & Di Chiara, 2008). Behavioral evidence suggests that changes in glutamatergic or dopaminergic neurotransmission may be involved in morphine sensitization. Some evidence suggests that sensitivity to opiates can alter levels of dopamine and glutamate in different brain regions (Cadoni & Di Chiara, 1999; Sepehrizadeh et al., 2008). It seems that glutamate receptors which play an important role in mediating the rewarding

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properties of morphine, they may be involved in functional interactions between CB1 cannabinoid receptors and opioidergic systems in the NAc and central amygdala (Watanabe et al., 2002; Rezayof, Golhasani-Keshtan, Haeri-Rohani & Zarrindast, 2007). Moreover, glutamatergic transmission is involved in behavioral sensitization to morphine in the hippocampus (Farahmandfar et al., 2011). Previously, it has been shown that NMDA receptors located in the NAc, mediate the antinociceptive responses of cannabinoid within the BLA; it seems that the glutamatergic projection from the BLA to the NAC is necessary to enhance the analgesic effects of cannabinoid (Ghalandari-Shamami et al., 2011). Hence, it looks that the glutamatergic efferent from BLA to the NAc may be involved in morphine sensitization which mediated with cannabinoids.

In conclusion, it was shown that the CB1 cannabinoid receptor in BLA, are involved in sensitization to morphine in controlling pain pathways. Our study also confirmed the cross-talk between cannabinoid and opioid systems. However, our study did not reveal the mechanism of sensitization, exactly. It requires a detailed review at the molecular levels in the regions involved in the sensitization which linked with BLA. The nucleus accumbens is a candidate for this. NAc is one of the regions involved in sensitization that receive glutamatergic input from the BLA. It looks that glutamatergic connection from BLA to the NAc be important in induction of sensitization mediated whit cannabinoids. Detailed molecular analysis of the NAc in the recent our study will be helpful for better understanding of what occurred during sensitization.

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