

Chronic migraine caused a higher rate of tendency to cannabinoid agonist compared to morphine

Mojdeh Mansoori^{1*}, Mohammad Reza Zarei^{1*}, Goli Chamani¹, Masoud Nazeri¹, Fatemeh Mohammadi², Samane Sadat Alavi³, Mohammad Shabani²

¹Department of Oral Medicine and Orofacial Pain, Kerman School of Dentistry, Kerman Oral and Dental Diseases Research Center, Kerman, Iran; ²Intracellular Recording Lab, Kerman Neuroscience Research Center, Neuropharmacology Institute, Kerman University of Medical Sciences, Kerman, Iran; ³Afzalipour Faculty of mMedicine, Kerman University of Medical Science, Kerman, Iran

Summary. Opioid and cannabinoid systems have considerable roles in the modulation of chronic pain as well as regulation reward circuit and addiction responses. This study investigated the effect of nitroglycerin (NTG)-induced migraine attack on the acquisition of morphine and cannabinoid-induced conditioned place preference (CPP) in male rats. Adult male rats (230-250 gr) were used. Experimental groups were included (n=10): control, opioid receptor agonist morphine (10 mg/kg), WIN55,212-2 (1 mg/kg) as a cannabinoid receptor agonist, NTG + morphine (10 mg/kg) and NTG + WIN55,212-2 (1 mg/kg). Nitroglycerin (10 mg/kg) was used to induce migraine attacks every other day for 9 days. After migraine induction, conditioning performance was assessed by CPP test. During conditioning days, morphine and WIN55,212-2 were injected subcutaneously and intraperitoneally, respectively. Anxiety and locomotor activity were evaluated using open field test (OFT). According to data, conditioning score for morphine-treated rats was significantly decreased following NTG-induced migraine ($p < 0.01$). However, NTG-induced migraine was able to increase the conditioning score in WIN55,212-2 as compared to the control group ($p < 0.05$). In OFT, there were no significant differences in locomotor activity and grooming behaviors between experimental groups. However, time spent in the center of the OFT box was significantly decreased in NTG plus morphine-treated rats as compared to control ($p < 0.05$). Moreover, rearing response in NTG - treated groups which received either morphine or WIN55,212-2 decreased as compared to the control group ($p < 0.01$). NTG induced migraine prompts a decrease in morphine and an increase in cannabinoid performances. So, these compounds' effects on drug dependency during migraine attacks may occur at different mechanisms. (www.actabiomedica.it)

Key words: migraine, nitroglycerin, morphine, WIN 55,212-2, conditioned place preference

Introduction

Migraine is an abnormal brain function, mainly due to the sensitization and activation of trigemino-vascular pathway. It is associated with recurrent severe unilateral or bilateral, pulsating headaches, and in some cases accompanied by a series of symptoms such

as nausea, vomiting, increased photosensitivity, and also cognitive, motor and emotional disturbances (1, 2). Migraines account for 64% of the cost of the community for a variety of headaches, and 93% of this cost is due to the loss of efficiency in migraine patients. If migraine is present for at least 3 months, more than 15 days a month, it calls chronic migraine (3). The impact

* Both authors contributed equally to this manuscript

of chronic migraine on quality of life and its cost is 3–4 times higher than episodic migraine (3). Chronic pain such as migraine can also cause mental disorders and affect cognitive, emotional and behavioral characteristics (4).

The opioids and cannabinoid systems are important in the processing and modulation of pain (5). Sometimes opioids and cannabinoids are used in the treatment of migraine. It has been shown that mu opioid receptor agonists such as morphine have little effect on the reduction of migraine pain and can contribute to the development of migraine to chronic type, as well as a headache caused by substance abuse (6). The synthetic cannabinoid called WIN 55,212-2 can prevent the activity of the trigeminal nerve branches (7). Use of the drug over time is potentially addictive (8). It has been reported that 0.2%–20% of patients that receive treatment of chronic pain with opioids, became dependent and addicted to it (9, 10). Addiction is a physiological response that is caused by various factors such as stress and depression, and the genetic context (family history of addiction) (4). With repeated administration of drugs, compromised mechanisms have been developed that cause short- and long-term changes in the functioning of the neurons, glial cells, neural system, and ultimately lead to behavioral changes such as tolerance and dependence (11).

The high prevalence and adverse effects of migraine on the physiological and social functions of individuals (12) necessitate research and study in this regard. Pathophysiology of migraine is not well known. Although there are effective treatments for some patients, existing treatments are not still enough for many patients. Some clinical and pre-clinical studies indicate the effectiveness of administering opioid and cannabinoid to reduce migraine attacks (13). However, few experimental studies have been conducted on the association of migraine with tendency or avoidance of opioid or cannabinoid compounds. Human evidence just suggests there is a correlation between chronic pain and the tendency to use certain drugs, and there are few animal studies with inconsistent results. Therefore, in order to further investigate the migraine pathogenesis, the relationship between migraine and the inclination to use morphine and WIN 55,212-2 in the animal model of migraine was studied and compared.

Methods and materials

Animals

In this study, adult male Wistar rats (230–250 gr) were prepared from the Neuroscience Research Center of Kerman University of Medical Sciences. Animals were kept in special cages under 12 hours of light and 12 hours of darkness at $23\pm 2^{\circ}\text{C}$ in the animal's home and have free access to food and water. In different stages of the project, they were grouped and used according to the type of population tested. All stages of the project were carried out in accordance with the Code of Practice for Laboratory Animals of Kerman University of Medical Sciences and according to the protocol of animal behavior tests and attempts were made to minimize animal harassment. This research was conducted with the support of the Kerman Neuroscience Research Center under the Code of Ethics KNRC/95-61. After two weeks of adaptation to the laboratory environment, animals were randomly assigned into 5 groups (10 rats in each group): Control group (intact; healthy rats who did not receive any treatment), Morphine group [normal saline was injected intraperitoneally for 9 days (every other day) then morphine (10 mg/kg) was injected subcutaneously during the conditioning day], WIN group [normal saline was injected for 9 days (every other day) then WIN55,212-2 (1 mg/kg) was injected intraperitoneally during the conditioning day], NTG and morphine group [NTG was injected intraperitoneally for 9 days (every other day) then morphine (10 mg/kg) was injected during the conditioning days], NTG and WIN group [NTG was injected for 9 days (every other day) then WIN55,212-2 (1mg/kg) was injected during the conditioning days]. Figure 1 shows the algorithm, all procedures and timing diagram for tests that were used in this study.

Drugs

Nitroglycerin (NTG) (Iran, Caspian) was used to create migraine. WIN 55,212-2 (Sigma, USA) was dissolved in DMSO and morphine (Iran, Daroopaksh) in normal saline.

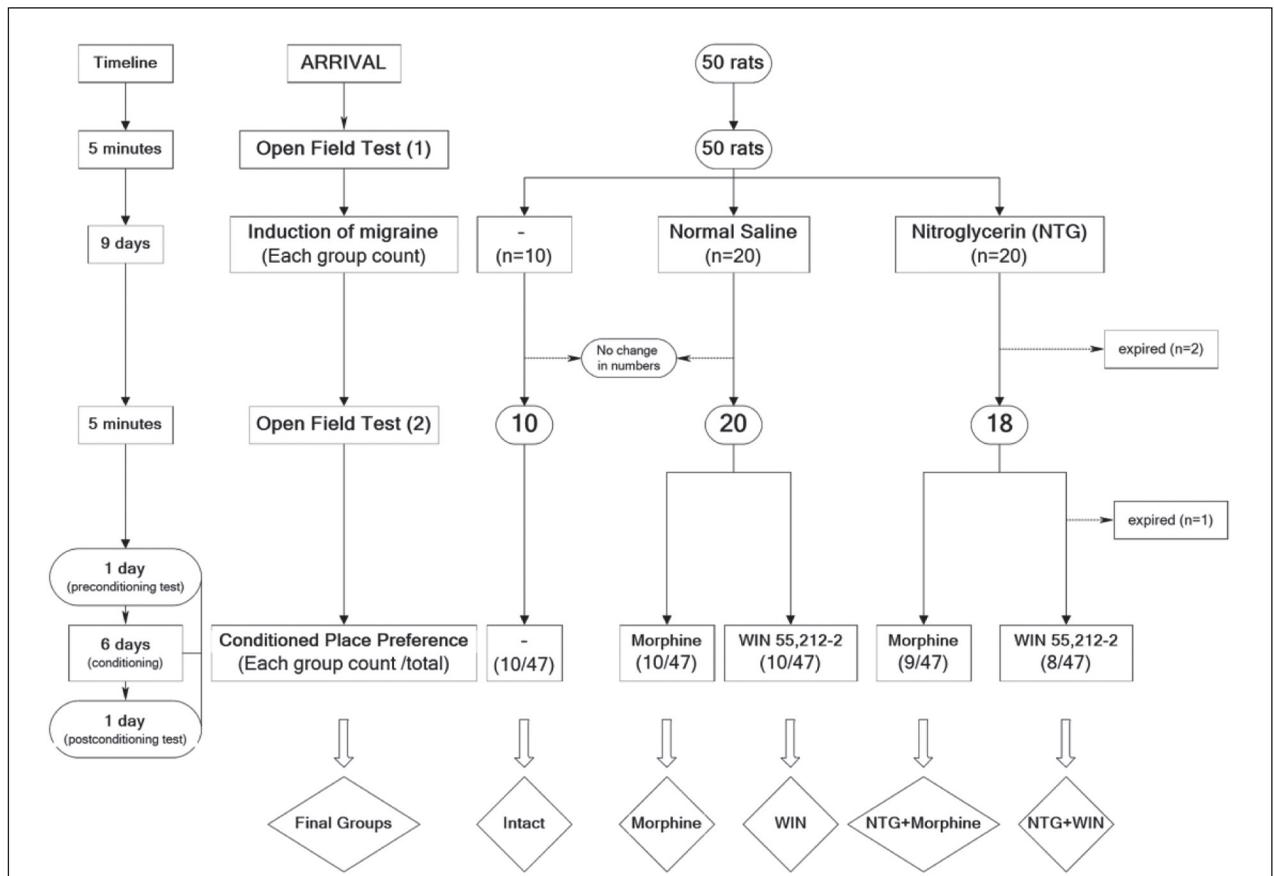


Figure 1. Arrival flow diagram: Timeline for induction of migraine, drug administration and behavioral tests

The method of inducing chronic migraine

In this study, nitroglycerin (NTG) (5 mg/ml) at a dose of 10 mg/kg was used to induce chronic migraine-like pain (14). Intraperitoneal injection of NTG is associated with the development of symptoms of migraine attacks and the sensitization of trigeminal and cortical structures involved in migraine pain. NTG infusion was performed for nine days (every other day).

Investigating the addictive behavior

To determine the addictive behavior after induction of chronic pain, conditioned place preference test (CPP) was used (15). This test is performed using a conditioned preference machine. This device has two chambers (30 by 30 cm). Their walls have horizontal and vertical lines. These rooms are connected through

a neutral chamber (25 by 15 Cm) in the middle. Each chamber has gates allowing the animal to access all three rooms freely. On conditioned days (1, 3, 5), the rat was placed in a chamber with horizontal lines after injection of the drug (morphine (10 mg/kg) or WIN-55,212-2 (1 mg/kg)) and returned to its cage after 30 minutes in this chamber. During this time the gates are closed. On non-conditioning days (2, 4, 6), the animal was injected with normal saline and the animal was placed in a chamber with vertical lines in the closed gate and returned to its cage after 30 minutes in this chamber. On the test day, all gates were opened with access to all chambers. The behavior of animal was evaluated for 20 minutes and the time spent in each chamber was recorded and the difference in time spent in the drug delivery room (morphine or WIN55,212-2) on the first day and on the day of the test was calculated as a conditioned score.

Anxiety and motor activity evaluation

An open field test was used to measure anxiety and motor activity before and after the induction of migraine (16). This test was performed using an open field machine. This device consists of a box with dimensions $90 \times 90 \times 30$ cm with black floor and white walls. The floor of the device is hypothetically divided by software through square and lattice lines into 25 equal central and peripheral areas. A camera is mounted on top of the device at 1.5 meters on the ceiling. The device is in the darkroom, but the environment of the device is illuminated with a small fluorescent lamp to identify the animal. Animals were transferred to the laboratory in test days for half an hour before the test then transferred to the machine and the animal's behavior was recorded in a 5-minute interval and analyzed using the software Ethovision (version 7.1). The factors involved in this test include; total distance traveled, the time spent in the center, and frequency of obsessive-compulsive behavior of the grooming and Rearing (rising on the two feet). Total distance traveled represents motor activity, reducing the time spent at the center indicates further anxiety, increasing the number of grooming and rearing, indicating more anxiety.

Statistical calculations

The results of CPP and OFT tests were analyzed by one-way ANOVA and Tukey's post-test. Also, $p < 0.05$ was considered as a significant level and the data in all graphs were presented as mean plus minus standard error (mean \pm SEM).

Results

Conditioned Place Preference Test (CPP)

The effect of NTG-induced chronic pain on the acquisition of addictive search behavior for morphine in the CPP test:

As shown in Figure 2, the conditioning score in the morphine recipient group was significantly higher than the control group ($p < 0.05$). However, after induction of chronic migraine pain with NTG, the morphine condition was inhibited ($p < 0.01$, Fig. 2).

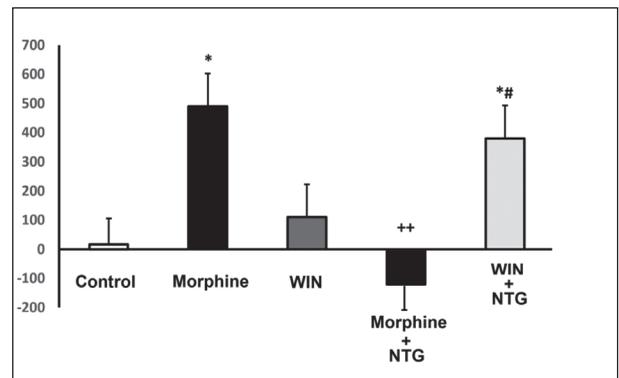


Figure 2. Effect of systemic injection of morphine and WIN55,212-2 (WIN) on the acquisition of conditioned preference in male rats with chronic migraine. Charts are plotted based on the mean \pm standard error. *: Significant difference with $p < 0.05$ compared to control group, **: significant difference with $p < 0.01$ compared to morphine group. #: Significant difference with $p < 0.05$ compared to WIN group

The effect of NTG-induced chronic pain on the acquisition of addictive search behavior for WIN55,212-2 in the CPP test:

Conditioning score in the recipient group WIN55,212-2 did not show a significant difference in comparison with the control group. However, after induction of chronic NTG-induced migraine, the rate of conditioning was increased after treatment with WIN55,212-2 compared to control and WIN groups without migraine ($p < 0.05$, Fig. 2).

Open field test (OFT)

As shown in Fig. 3, no significant difference was found in the mean of total distance traveled among test groups [$F(4,34) = 2.07$, $p = 0.110$]. Time spent in the center in the rats with chronic migraine headache that were conditioned with morphine (2.481 ± 0.396) was reduced compared to the control group (11.07 ± 3.096) ($p < 0.05$, Fig. 4). There was no significant difference (Fig. 5) in the behavior of grooming between the tested groups [$F(4,34) = .891$, $p = 0.425$]. As shown in Fig. 6, the frequency of rearing in NTG treated groups with morphine and WIN55,212-2, as well as morphine and WIN55,212-2 groups increased without NTG compared to control.

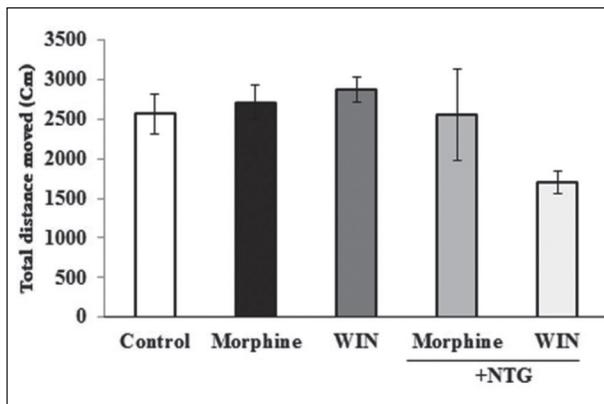


Figure 3. Comparison of total distance traveled during 5 minutes of experiment between the tested groups. Charts are plotted based on the mean \pm standard error

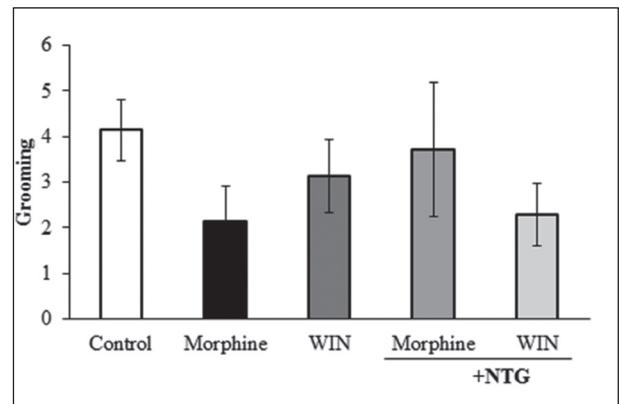


Figure 5. Comparison of the number of grooming behaviors during the 5-minute experiment between the tested groups. Charts are plotted based on the mean \pm standard error

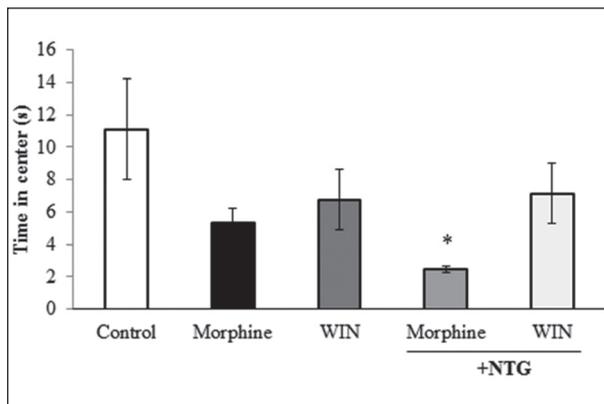


Figure 4. Comparison of the time spent in the center during the 5 minutes test between the tested groups. Charts are plotted based on the mean \pm standard error. * $p < 0.05$ vs. control

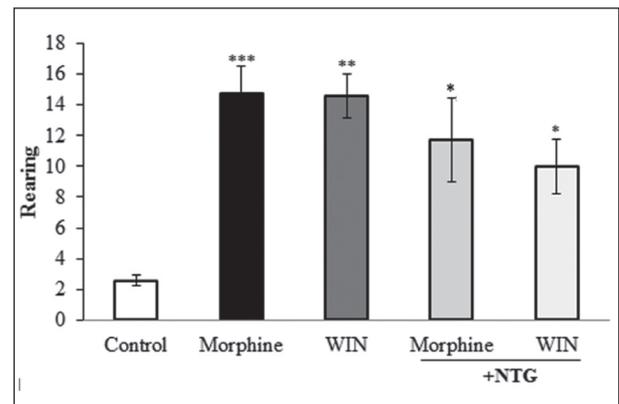


Figure 6. Comparison of the number of rearing behaviors during the 5-minute experiment between the tested groups. Charts are plotted based on the mean \pm standard error. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. control

Discussion

In the present study, the effect of chronic migraine on addictive behaviors caused by systemic injection of opioid and cannabinoid receptor agonists was evaluated. The results showed that chronic migraine increased the tendency to use cannabinoid and decreased the tendency to use morphine. Also, anxiety and motor activity evaluation of animals showed that migraine-like pain that induced with nitroglycerin does not significantly affect animal anxiety and motor behaviors.

Migraine is associated with sensitization of trigeminal pathways, which can lead to increased sen-

sitivity to pain, allodynia (response to non-painful stimuli), and disturbance in emotional functioning during or between attacks (17, 18). In this study, NTG was used to induce migraine. This compound is a nitric oxide producer that, after systemic injection, activates the nuclei involved in pain processing and is used as a well-known and commonly used animal model for laboratory migratory induction (19).

Chronic pain associated with anatomical and neurochemical changes in brain structures involved in perception and controlling pain. These conditions can cause long-term molecular changes in the brain reward cycle and pain perception that are the basis of addictive

behaviors to analgesics and pain modulating disorders (20, 21). On the other hand, disruption of the brain reward pathways is one of the main mechanisms of drug abuse (22). It is shown that substance and drug abuse lead to changes like chronic pain in the brain. Therefore, pathways between chronic pain and addiction are common and changes in each one can affect another (20).

In the present study, the induction of migraine with NTG increased the tendency to WIN55,212-2 as an agonist of both CB1 and CB2 receptors that has analgesic and anti-inflammatory effects (23, 24). It has been shown that the activation of CB1 receptors in the substantia nigra in the basal ganglia increases the amount of stimulation of dopaminergic neurons and the release of dopamine, the main neurotransmitter involved in rewarding behavior (25, 26). Also, the activation of presynaptic CB1 receptors in cortical glutaminergic assays reduces the release of glutamate and reduces the stimulus flow transmission (27, 28). The induction of migraine with NTG is associated with increased sensitivity to pain and increased density of cannabinoid attachment sites in mesencephalon (14).

The endocannabinoid system can also affect the performance of the reward system and addictive behavior by modulating the release of neurotransmitters involved in this pathway, such as glutamate, GABA, serotonin and dopamine (29). Systemic injection of CB1 agonist has been shown to activate the mesolimbic pathway and dopamine release (30). Also, at the nucleus accumbens, other major centers involved in the rewarding behavior of cannabinoid receptor activation, modulate the release of GABA and glutamate at the base of the skull (28, 31). Thus, the ability of cannabinoids to activate dopaminergic flow and modulate inhibitory and stimulating pathway can partly explain the tendency for these compounds to be used in NTG-induced migraine. In fact, interference in the molecular pathway and the target points of the cannabinoid and dopaminergic system can be involved in making cannabinoids dependent.

Chronic headaches are associated with significant changes in synaptic plasticity, which can lead to increased intracellular calcium and nitric oxide formation (32). Increased calcium ion in the post-synaptic neuron has been shown to produce endocannabinoids

(32, 33). However, determining the mechanism of addictive behavior to cannabinoids in migraine induction conditions requires supplementary studies. In this regard, the use of cannabinoid receptor agonists and antagonists in pathways involved in the rewards and addiction cycles in migraine induction conditions can be helpful.

Another aim of the present study was to investigate the effect of induction of migraine with NTG on the tendency to use morphine. Our results show that chronic migraine decreased the tendency to use morphine. Information on the chronic use of opioid combinations for the treatment of pain is disproportionate. While many studies have shown the potent effects of opioid drugs, including morphine, on chronic pain, there is little evidence of a positive effect of the opioid on improving quality of life (34, 35).

People who use opioid due to chronic pain usually do not experience opiate-induced euphoria in addicts. What is happening in these patients is restlessness and the risk of addiction is low in the administration of opioid for chronic non-cancerous pain (36). Therefore, the negative effects of chronic pain on euphoria can reduce the tendency to take medication. Of course, in chronic pain situations, the use of appropriate opioids does not cause addiction, but administration of opioid without dose adjustment in susceptible individuals can lead to addiction (37).

Chronic pain can also affect the physiological function of μ -opioid receptors. Research has shown that the long-term administration of opioid increases the substance-P in sensory neurons and increases stimulatory neurotransmitters from primary afferent neural fibers after stimulation (38). Neuropathic pain has been shown to reduce the function of μ -opioid receptors in the ventral tegmental area of the brain (39). On the other hand, the absence of μ -opioid receptors reduces the effect of analgesia, place preference and physical dependence on morphine (40). Also, the expression of μ -opioid receptors in the primary afferent neural fibers, which receiving the pain, initiates resistance to the analgesic effect and induces hyperalgesia caused by the opioid. This complication was prevented by co-administered an agonist and antagonist of the μ -opioid receptor (41). Therefore, in the present study, it is possible that chronic migraine with changes in the

function of opioid receptors is effective in reducing the tendency to use morphine.

Another finding of the present study was that the induction of chronic migraine pain in the treatment group with morphine resulted in a reduction in the time spent in the center compared with the control group. However, there were no significant effects on motor activity and grooming behaviors in the treated groups with morphine or WIN55,212-2.

Chronic pain can affect physiological responses to emotional and anxiety situations (42). Studies show that many of the painful conditions are associated with increased anxiety behaviors (43). Recently it is reported that dental pulp stimulation with capsaicin can increase anxiety behavior in anxiety tests in rats (44, 45). In migraine patients, the function and structure of important brain regions are interrupted with emotional responses to the pain. The association between anxiety and migraine abnormalities is bilateral. Patients with anxiety disorder have a higher risk of migraine and migraine patients (especially chronic migraine) are more likely to develop anxiety disorders (46). It has been shown that acute stress reduces NTG-induced hyperalgesia and chronic stress increases the effect of NTG-induced hyperalgesia (47). Studies show that morphine can have diverse and sometimes contradictory effects on anxiety responses (48, 49). Anxiety can activate and modify the internal opioid system. The activation of a stress response is a possible target for mechanisms in which pain can modulate the effect of opiates (50, 51).

The endocannabinoid system is also closely related to stress responses and plays an important role in counteracting the effects of stress. Following chronic stress, CB1 receptor function disrupts and exacerbates the effects of stress such as anxiety and illness (52). On the other hand, the risk of dependence on cannabis is five times higher in people with anxiety disorder (53). In the present study, chronic injection of nitroglycerin as an animal model of migraine did not have a significant effect on animal anxiety and motor behaviors. However, NTG-induced pain due to changes in receptor function may be partly related to the anxiety behavior observed in the morphine group. In any case, the determination of the relationship between migraine pain, anxiety and function of opioid and endocannabinoid systems requires additional studies.

Conclusion

The results of this study showed that the chronic migraine without significant effects on motor activity and anxiety behavior reduced tendency to morphine and increased the tendency to use cannabinoid in rats. Therefore, opioids and cannabinoid systems may be involved with different mechanisms for modulating chronic pain of migraine and drug dependence.

As a suggestion, this will be certainly an introduction to future advanced research to evaluate and compare the effect of different doses of morphine and cannabinoid on migraine treatment or dependence.

Highlights:

- CPP score for morphine-treated rats decreased following NTG-induced migraine
- NTG induced migraine prompts an increase in cannabinoid performances.
- Tendency to use cannabinoid was higher than morphine in chronic Migraine

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Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Correspondence:

Dr. Mohammad Shabani

Intracellular Recording Lab,

Kerman Neuroscience Research Center,

Neuropharmacology Institute,

Kerman University of Medical Sciences, Kerman

Tel. 09133978116

Fax +98-343-226-4198

E-mail: shabanimoh@yahoo.com; and shabani@kmu.ac.ir