

The Effects of Isoniazid on the Acquisition and Expression of Morphine-Induced Conditioned Place Preference in Mice

Amir Abbas Barzegari, Ph.D. ¹, Kamran Shahabi, B.Sc. ²

1- Assistant Professor, Department of Biology, Faculty of Basic Science, University of Maragheh, Maragheh, East Azerbaijan Province, IR Iran (Corresponding author; E-mail: Barzegaridoctora@gmail.com)

2- M.Sc. Student, Department of Biology, Faculty of Basic Science, University of Maragheh, Maragheh, East Azerbaijan Province, IR Iran

Received: 13 August, 2019

Accepted: 7 February, 2020

ARTICLE INFO

Article type:

Original Article

Keywords:

Isoniazid

Morphine

Reward

Conditioning

Abstract

Background: GABAergic drugs can modulate the rewarding properties of morphine. The objective of this study was to evaluate the effects of isoniazid, as a GABAergic agent, on the rewarding effects of morphine.

Methods: Eighteen groups of female mice (eight per group) were used in a conditioned place preference (CPP) study. On the conditioning phase of the CPP procedure, ten groups of the animals received morphine (0, 0.75, 1.5, 3, 5, and 10 mg/kg, s.c.) or isoniazid (0, 25, 50, and 75 mg/kg, i.p.) to induce CPP. Then, the effects of isoniazid on the acquisition and expression of morphine-induced CPP were evaluated. In the expression experiment, four groups of mice were conditioned with an effective dose of morphine (5mg/kg, s.c.). Then, the animals received saline or isoniazid (25, 50, and 75 mg/kg) one hour before the test, intraperitoneally. In the acquisition experiment, the other four groups received intraperitoneal saline or isoniazid (25, 50, and 75 mg/kg, i.p.) one hour before receiving the effective dose of morphine (5mg/kg, s.c.) on conditioning phase. On the test day, these animals received no treatment.

Results: Morphine but not isoniazid induced a significant CPP in mice. Morphine or isoniazid alone did not change the locomotor activity of the animals on the test day. Isoniazid pretreatment could significantly inhibit both the acquisition and expression of the morphine-induced CPP. Isoniazid also did not influence the locomotor activity of the animals in the expression and acquisition experiments.

Conclusion: Isoniazid may have a therapeutic application in morphine addiction.

Copyright: 2020 The Author(s); Published by Kerman University of Medical Sciences. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Citation: Barzegari A.A, Shahabi K. The Effects of Isoniazid on the Acquisition and Expression of Morphine-Induced Conditioned Place Preference in Mice. *Journal of Kerman University of Medical Sciences*, 2020; 27 (1): 69-81.

Introduction

Morphine, an opioid analgesic (1), has potent rewarding or euphoric effects. The relatively high prevalence of morphine abuse in the world (2, 3) and the animal experiments (4, 5) prove this issue. Scientists have shown that morphine exerts its rewarding effects by binding to μ opioid receptors on GABAergic interneurons in the ventral tegmental area (VTA)

(5). Through binding to these receptors, morphine inhibits these interneurons and removes the tonic inhibition of dopaminergic neurons in the area (i.e. VTA). The disinhibition of the projecting dopamine neurons increases their firing rate, and it elevates dopamine levels in different limbic areas of the brain, including nucleus accumbens. The elevation of dopamine levels in the nucleus accumbens is responsible for the

rewarding properties of morphine and other addictive drugs (6, 7).

There are some methods to assess the rewarding effects of addictive drugs in laboratory animals including intracranial self-stimulation, drug self-administration, and conditioned place preference (4, 8-10). Compared to the other methods for evaluating the rewarding properties of substances, CPP is a simple and low-cost procedure (9). Many studies have shown that different neurotransmitter systems of the brain modulate the rewarding effects of morphine in the CPP paradigm. These systems include but not limited to: dopaminergic, adenosinergic, cholinergic, adrenergic, nitric oxide, and GABAergic systems (4, 11-17).

Isonicotinylhydrazide, more commonly known as isoniazid, is one of the most important drugs that has been used since 1952 for the treatment of tuberculosis (18). Because of its potency, safety, inexpensiveness, and selectivity against the tuberculosis bacteria, it is widely used in the world as a first-line antibiotic against the bacteria (18). Isoniazid can affect the GABAergic system of the brain. This drug, in high doses, inhibits the activity of Glutamic acid decarboxylase (GAD). Inhibitory action of isoniazid on this enzyme is due to isoniazid-induced pyridoxine deficiency (19). Therefore, isoniazid in high doses is a GABA antagonist, and it can reduce the GABA level of the brain and thereby induces seizures (20). On the other hand, some experiments on monkeys and rats have shown that the administration of low doses of isoniazid in the animals might increase the GABA levels of the brain (21, 22). Therefore, isoniazid in low doses can act like an indirect agonist of GABA. Altogether, these results indicate that isoniazid is a modulator of the GABAergic system of the brain.

The GABAergic and the opioidergic systems of the brain have widespread interactions (4, 23). Consequently, the present research aimed to evaluate the effects of low doses of isoniazid on morphine rewarding effects using a conditioned place preference paradigm in female mice.

Materials and Methods

Subjects

One hundred and forty-four female NMRI mice weighing 20-25 g were bought from Razi Vaccine and Serum Research Institute (Karaj, Iran). In the animal house of the University of Maragheh, the animals were kept in polycarbonate rodent cages in groups of 10. Standard maintenance conditions for the animals (12/12 light-dark cycle, temperature 22 ± 2 °C) were provided. All of the rodents had free access to standard rodent chow and water. The animals spent at least a seven-day adaptation period before the beginning of the experiments. A local ethics committee of animal care and use at the University of Maragheh supervised the maintenance conditions of the animals and approved the experimental procedures that were conducted on the animals (ethical code: UM-2018-number 23). The animals were randomly allocated to 18 groups (n=8). Each animal was used only once in the experiments.

Drugs

Morphine sulfate ampoules (Darou Pakhsh Pharmaceutical Mfg. Co. Tehran, Iran) and isoniazid (Solarbio Co, China) were used in the present research. Isoniazid powder was dissolved in normal saline and administered intraperitoneally. Different doses of morphine were made by diluting the morphine solution (10 mg/ml) with normal saline and were administered subcutaneously.

Apparatus

The apparatus used in the CPP experiments was designed like that used in Sahraei et al. study with little changes (11). Each wooden apparatus was a rectangular cube (15 cm w×15 cm h×30cm L), which lacked one large side on the top. When it was needed, a partition divided the apparatus into two identical side-by-side cubic compartments (15cm w×15cm h×15cm L). The two compartments had different visual and tactile distinguishing features. One compartment was black in color with a smooth floor and the other one was white with a stainless steel mesh on its floor.

Place conditioning procedure

In a pilot study, mice showed an unconditioned preference for the black part of the apparatus. Therefore, a biased place preference paradigm was selected as a conditioning procedure in the present research. Besides, the white part of the apparatus was chosen as the drug-paired compartment in the experiments.

Each place conditioning with morphine was conducted in four steps:

1- Adaptation: in this phase, the partition between the two compartments of the apparatus was removed and each animal was individually put in the apparatus with free access to both parts of it for 10 minutes.

2- Preconditioning: this phase was conducted like the previous one. Moreover, the time in the drug-paired compartment (white compartment) was recorded with a

chronometer during the 10-minute periods of the test session. This phase was conducted 24h after the first phase.

3- Conditioning phase: this phase included the next three days of the place conditioning procedure. In this stage, first, the two parts of the apparatus were separated from each other by the partition. Each day consists of two conditioning sessions. On days 3 and 5 of the conditioning trials, each animal received morphine or isoniazid (at 9:00 a.m.) and instantly was confined to the white part of the apparatus (30 min. for morphine and 45 min. for isoniazid). In the afternoon session (at 3:00 p.m.), each mouse received saline (10ml/kg) and immediately was confined to the black side of the apparatus for the same duration as its respective drug. The methods of saline injection for morphine conditioning and isoniazid conditioning were s.c. and i.p., respectively. On the fourth day, the animals received saline in the morning and the drug in the afternoon conditioning sessions.

4- Postconditioning or test: in this phase, again the partition was removed, and each mouse was placed individually in the apparatus. The time that each animal spent in the white part of the apparatus was measured during 10 min test sessions.

In our experiments, change in preference (the difference in recorded times in drug-paired compartment in the post and preconditioning phases) was considered as the conditioning score. The percentage of change in preference was calculated with the following formula:

$$\text{change in preference percentage} = \frac{\text{difference in time spent in drug - paired compartment after and before conditioning}}{\text{time spent in drug - paired compartment before conditioning}} * 100$$

Measurement of locomotor activity

For this, two perpendicular lines divided the grand arena of each compartment of the apparatus into four equal square parts. During the 10-minute periods of postconditioning phase, in addition to time, locomotor activity was recorded for each animal. For this, each movement of the animal from one square to another one was considered as one score of locomotor activity. Placement of the animal's head and both forepaws to one part was considered as the presence of the animal in that part.

Experimental design

Experiment 1: evaluation of morphine dose-response function on the induction of conditioned place preference. For this purpose, in the conditioning days, different doses of morphine (0.75, 1.5, 3, 5 and 10 mg/kg) and saline (10 ml/kg) were injected subcutaneously to six groups of the animals and the animals were immediately placed in the drug-paired compartment of the apparatus for 30 minutes.

Experiment 2: evaluation of dose-response function of isoniazid on the induction of place preference/aversion in mice. To evaluate the ability of isoniazid to induce place preference or place aversion, in the conditioning phase, saline (10 ml/kg) and different doses of isoniazid (25, 50 and 75 mg/kg, i.p.) were administered intraperitoneally to four groups of mice, and they were confined to the white part of the apparatus for 45 minutes.

Experiment 3: evaluation of isoniazid effects on the expression of CPP with an effective dose of morphine. Four groups of animals were conditioned with an effective dose of morphine (5mg/kg, s.c.). On the postconditioning day (test day) of the experiments, one hour before the test, the animal groups

received saline (10 ml/kg), or isoniazid doses of 25, 50 and 75 mg/kg, i.p., respectively (11).

Experiment 4: evaluation of isoniazid effects on the acquisition of CPP with an effective dose of morphine. In the conditioning phase of the CPP procedure, four groups of the animals, one hour before the treatment with the effective dose of morphine, received saline (10 ml/kg) or isoniazid doses of 25, 50 and 75 mg/kg, intraperitoneally. This time, on the test day, the mice received no treatment (11).

Statistical analysis

Data analysis was performed using the IBM SPSS® software (version 18). One-way ANOVA followed by Tukey post hoc test was conducted to reveal any significant difference between the different treatment groups. Change in preference and locomotor activity were presented as mean±SEM.

Results

The effects of morphine on the induction of CPP and locomotor activity

One-way ANOVA showed that treatment of animals with different doses of morphine (0.75-10 mg/kg, s.c.) could induce a significant increase in conditioning score compared to the saline-treated group [$F(5,42) = 13.6, p < 0.001$] (figure 1A). Post hoc test showed that morphine dose of 5 mg/kg had the highest effect on the induction of CPP. Therefore, this dose of morphine was selected as the effective dose of morphine in the following experiments. Moreover, analysis of locomotor activity on the test day showed no significant difference between morphine- and saline-treated groups [$F(5, 42) = 1.35, p = 0.262$] (figure 1B).

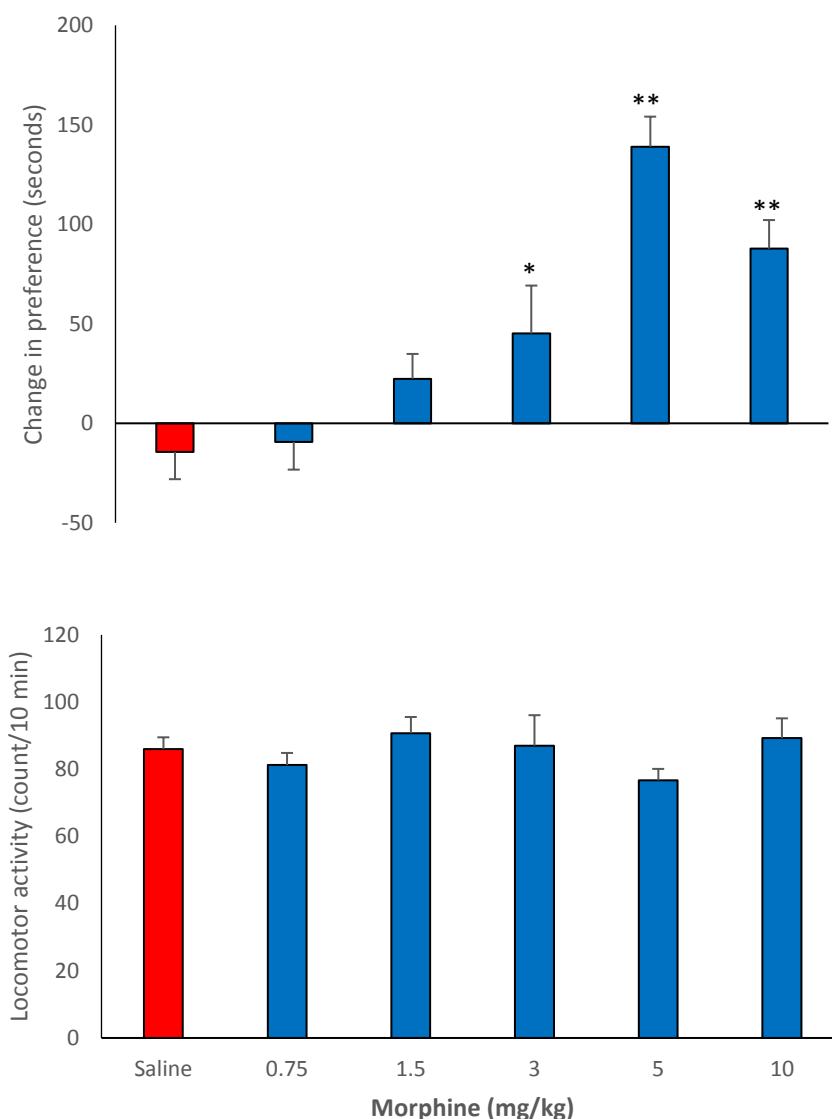


Figure1. The effects of morphine on the induction of conditioned place preference (A) and changes in locomotor activity on the test day (B)

On the conditioning days, different doses of morphine (0.75-10 mg/kg, s.c.) and saline were administered subcutaneously to six groups of mice. On the ten minute test sessions, the time in drug-paired compartment and locomotor activity were measured for each animal. Change in preference was calculated as time in drug-paired compartment on test day minus the time in preconditioning session in the same compartment. Locomotor activity in the test sessions was recorded by measuring the number of crossing from one square to another in the drug-paired compartment during the 10 min test sessions. Values are shown as mean \pm SEM. * and *** indicates $p < 0.05$ and $p < 0.001$, compared with the saline-received group, respectively.

The effects of isoniazid on the induction of CPP and locomotor activity

According to one-way ANOVA, the animal groups that received isoniazid (25-75 mg/kg, i.p.) on the conditioning days

showed no significant change in the conditioning score [$F(3, 22) = 1.21$, $p = 0.32$] or locomotor activity [$F(3, 22) = 1.44$, $p = 0.25$], compared to the saline-treated group (figure 2 A and B).

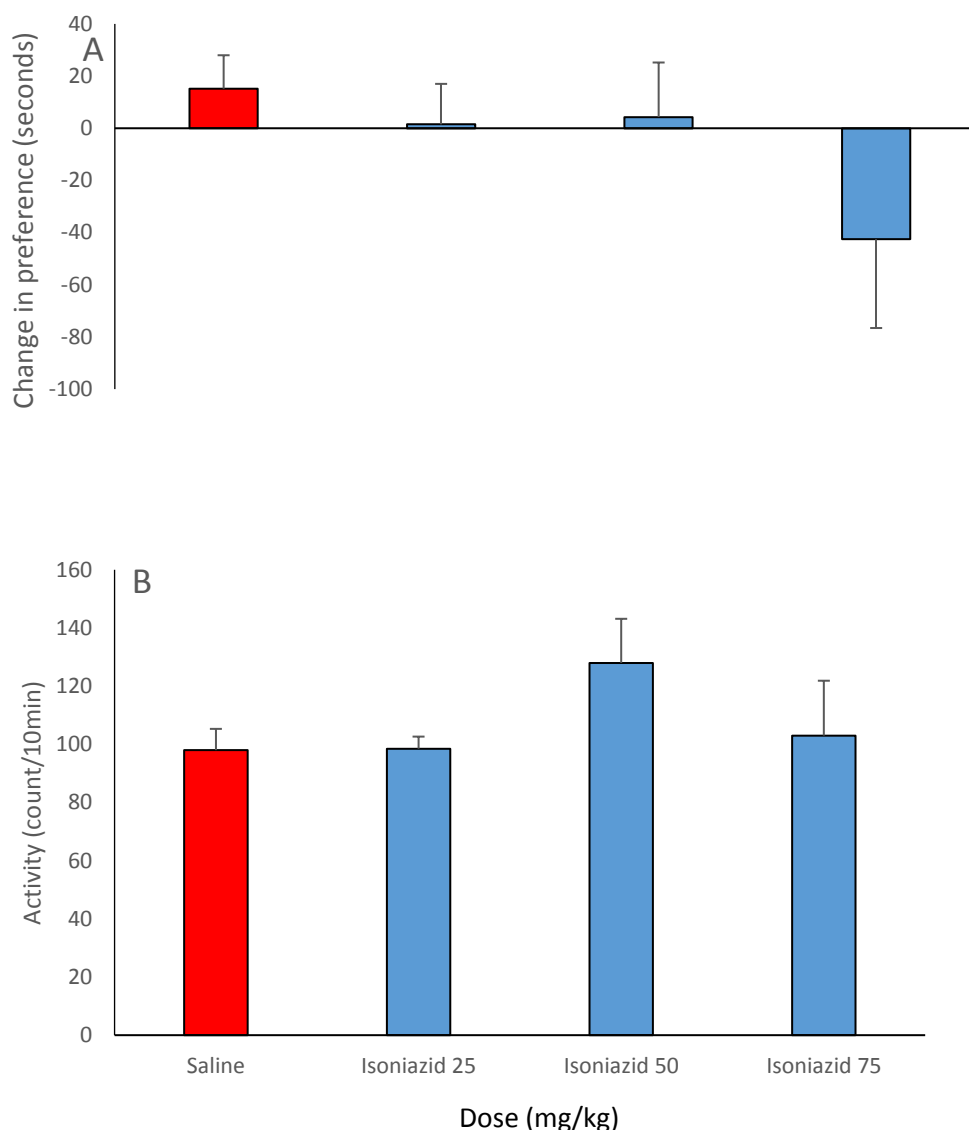


Figure2. The effects of isoniazid on the induction of conditioned place preference (A) and changes in locomotor activity on the test day (B)

On the conditioning phase, different doses of isoniazid (25, 50, and 75 mg/kg, i.p.) and saline were administered intraperitoneally to four groups of mice. On the ten minute test sessions, the time in drug-paired compartment and locomotor activity were measured for each animal. Change in preference was calculated as time in drug-paired compartment on the test day minus the time in preconditioning session in the same compartment. Locomotor activity in the test sessions was recorded by measuring the number of crossing from one square to another in the drug-paired compartment during the 10 min test sessions. Values are shown as mean \pm SEM.

The effects of isoniazid on the expression of morphine-induced CPP and locomotor activity with the effective dose of morphine

One-way ANOVA revealed that administration of isoniazid on the test day (one hour before test) could

significantly inhibit the expression of morphine-induced CPP [F (3, 25) = 13.64, $p < 0.001$] (figure 3A). Conduction of locomotor activity analysis using one-way ANOVA showed no significant effect of isoniazid on locomotor activity [F (3, 25) = 2.11, $p = 0.12$] (figure 3 B).

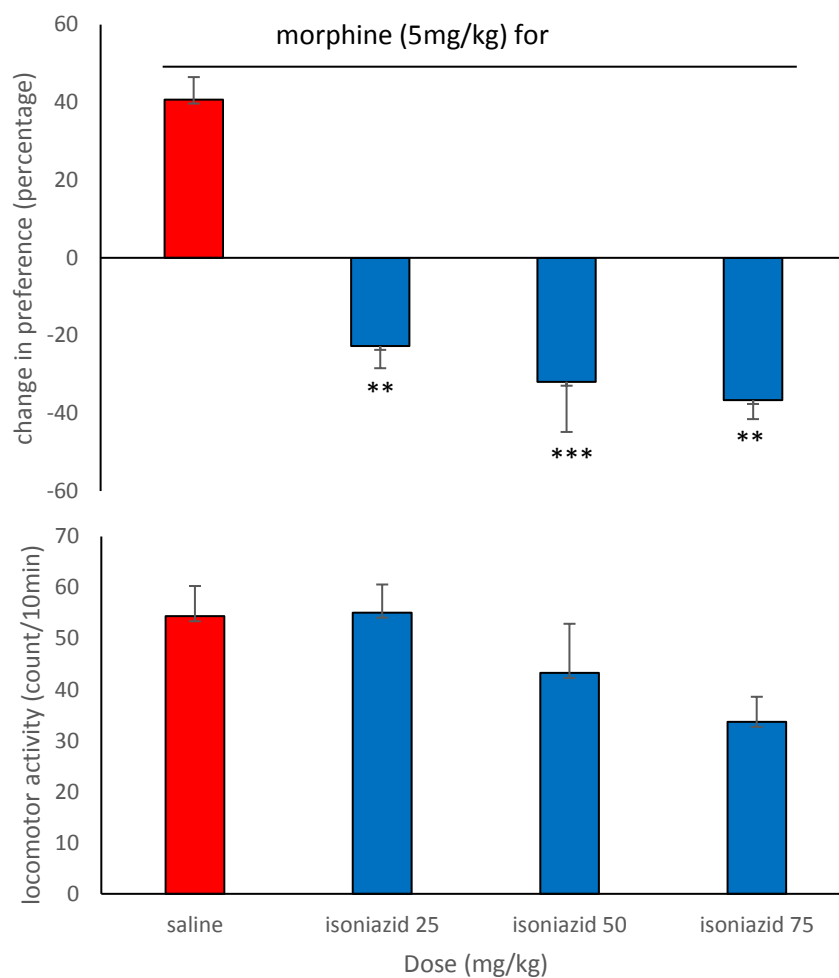


Figure 3. The effects of isoniazid on the expression of morphine-induced CPP (A) and locomotor activity on the test day (B)

Four groups of animals received the effective dose of morphine (5mg/kg, s.c.) in the conditioning phase of CPP. On the test day, the animals received isoniazid (25, 50, and 75 mg/kg, i.p.) and saline, i.p. one hour before test sessions. Change in preference was calculated as the difference between the time spent in the drug-paired compartment in the test phase and the time spent in the same compartment in the preconditioning phase. Locomotor activity in the test sessions was recorded by measuring the number of crossing from one square to another in the drug-paired compartment during the 10 min test sessions. Values are shown as mean± SEM. *** indicates $P < 0.001$ compared with the saline-treated group.

The effects of isoniazid on the acquisition of morphine-induced CPP and locomotor activity with the effective dose of morphine

One-way ANOVA analysis showed that pretreatment with isoniazid before morphine effective dose (5 mg/kg, s.c.) on the conditioning phase could induce a significant reduction in the

conditioning score on the test day [$F(3,22) = 20.47, p < 0.001$] (figure 4A). These doses of isoniazid had also no significant effect on the locomotor activities of the animals that received this drug, compared with saline-treated animals [$F(3, 22) = 0.3, p = 0.824$] (figure 4B).

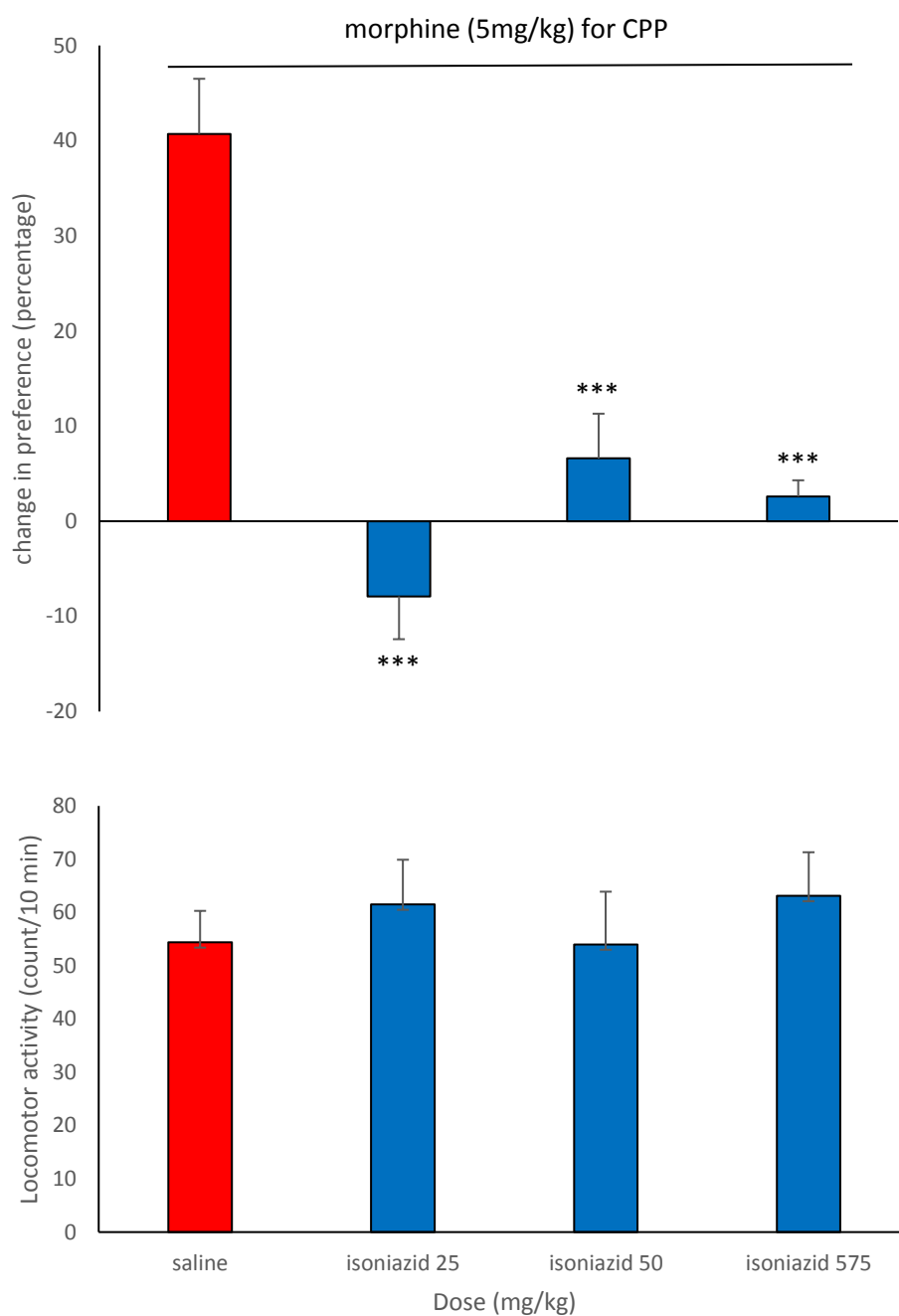


Figure 4. The effects of isoniazid on the acquisition of morphine-induced conditioned place preference (A) and locomotor activity on the test day (B)

Four groups of mice received intraperitoneal saline and isoniazid (25, 50, and 75 mg/kg) one hour before receiving the effective dose of morphine (5 mg/kg, s.c.) in the conditioning sessions. In the test phase, the animals received no treatment. Change in preference was calculated as the difference between the time spent in the drug-paired compartment in the test phase and the time spent in the same compartment in the preconditioning phase. Locomotor activity in the test session was recorded by measuring the number of crossing from one square to another in the drug-paired compartment during the 10 min test sessions. Values are shown as mean \pm SEM. *** indicates $P < 0.001$, compared with saline-treated group.

Discussion

The present study showed that morphine could significantly induce a dose-dependent CPP. It is in line with the results of several previous studies that have shown the rewarding effects of morphine using the CPP model in various species (4, 23). Evidence suggests that morphine rewarding effects are due to its binding to μ opioid receptors (5, 24). Apart from the induction of CPP to the drug-paired compartment, morphine had no significant effect on the locomotor activity of the animals on the test day. It indicates that the changes in locomotor activity of the animals did not affect the time that the animals spent in the morphine-paired compartment on the test day. Contrary to morphine, pairing isoniazid administration with the white part of the apparatus could not induce any CPP or CPA (conditioned place aversion) in the mice. As far as we know, isoniazid has not been used in previous studies in the induction of CPP/CPA. Clinical studies have shown that isoniazid might have euphoric or mood-elevating properties in some patients who received isoniazid for the treatment of tuberculosis (25-27); however, it seems that the isoniazid-induced euphoria is not sufficient to induce CPP in mice. On the other hand, the results of previous CPP studies using various GABAergic drugs, as conditioning stimuli, are different. Some of the GABAergic agents did not affect CPP, but the others induced CPP or even CPA. Isoniazid had also no significant effect on locomotor activity on the test day.

In another part of the present research, it was found that isoniazid could inhibit the expression of morphine-induced CPP, dose-dependently; administration of isoniazid on the test day reduced CPP score in mice that had received the effective dose of morphine on the conditioning days. Moreover, in the expression experiment, isoniazid had no significant effect on

the locomotor activity on the test day. Therefore, this ruled out the hypothesis that isoniazid inhibits the expression of morphine-induced CPP through affecting the locomotor activity of the animals. In other words, the observed effects of isoniazid are due to the modulation of the rewarding effects of morphine. The role of the GABAergic system in the expression of morphine-induced CPP is complex, and different GABA receptors and brain regions, including VTA, amygdala, and hippocampus, are involved in the phenomenon (15, 28, 29). This issue becomes more complex when we know that GABAergic agents (depend on their concentration) may have biphasic effects on the expression of morphine-induced CPP (15) and also with this observation that both GABA_A agonists and antagonist may have inhibitory effects on the expression of morphine-induced CPP (28).

At last, isoniazid administration before the effective dose of morphine in conditioning days could abolish the acquisition of morphine-induced CPP. Previous research by Perry and Hansen showed that administration of low doses of isoniazid to rats might induce a moderate increase in the GABA level of the rat brain (21); it is on the contrary to high doses of the drug that reduce the GABA levels of brain and thereby induce seizures (20, 30). One explanation of this effect of isoniazid in low dose may be differential effects of isoniazid on inhibition of glutamic acid decarboxylase (GAD) and GABA-transaminase (GABA-T); isoniazid is a more potent inhibitor of GABA-T than GAD. Therefore, the net result of the activation of the two enzymes by isoniazid is the indirect elevation of GABA levels (21). From these results, it can be concluded that in our experiments, administration of isoniazid also elevated the GABA content of mice brains. Previous research has shown that both GABA_A and GABA_B receptors are located on dopaminergic neurons of

VTA and activation of these receptors leads to a decrease in dopamine release in the nucleus accumbens (31). Therefore, it seems that the elevation of GABA levels of VTA by isoniazid inhibits the dopaminergic neurons. Consequently, disinhibition of GABAergic interneurons by morphine cannot increase dopamine release in the nucleus accumbens. Therefore, the rewarding effects of morphine diminished and isoniazid inhibited the acquisition of morphine-induced CPP. However, this hypothesis should be tested by further studies. For example, it can be tested by systemic or intra-VTA administration of isoniazid and evaluation of GABA levels in the area and also through evaluating the firing rate of dopaminergic neurons in the animals pretreated with isoniazid before morphine administration. In line with this hypothesis, GVG, an irreversible GABA-transaminase inhibitor, and a reversible GABA-transaminase inhibitor (aminoxy-acetic acid and ethanolamine- O-sulfate), could prevent heroin self-administration in rats. In this experiment, the effects of GABA-T inhibitors on heroin self-administration depended on GABA_B receptors (32). Moreover, administration of GVG before methamphetamine, heroin, and ethanol could prevent the effects of these drugs in the elevation of dopamine in the nucleus accumbens (33). Further research in this area revealed that GVG had the same effect on cocaine's effects on dopamine and this effect was mediated through GABA_B receptors (34). In another study, it was demonstrated that administration of Valproic acid sodium, an antiepileptic drug, before morphine could abolish the acquisition of morphine-induced CPP in rats. This effect was partially ascribed to the inhibitory action of

Valproic acid sodium on GABA-T and increase in GABA levels of brain (35).

Another mechanism that may explain the effects of isoniazid on the acquisition of morphine-induced CPP is the possible effects of isoniazid on memory and concentration. The reason is that isoniazid may decrease NMDA receptor density in the hippocampus (36). The role of these receptors in memory processes has been established in many researches (37-39). Therefore, it can be concluded that isoniazid may abolish the acquisition of morphine CPP by impairing memory. At last, because isoniazid did not change the locomotor activity in the acquisition experiment, the effect of this drug cannot be ascribed to change in the locomotor activity.

Conclusion

Isoniazid is a low-cost drug and its low doses were effective in the reduction of the rewarding effects of morphine. Therefore, it may have other therapeutic applications in the treatment of morphine addiction or possibly other drugs of abuse.

Acknowledgements

This study was conducted in the animal house of the University of Maragheh. We sincerely thank Dr. Arash Khorrami (Vice Chancellor for food and drug at Maragheh University of Medical Sciences) who provided us with morphine ampules.

Conflict of interest

We have no conflict of interest to declare.

References

1. Wiffen PJ, Wee B, Moore RA. Oral morphine for cancer pain. *Cochrane Database Syst Rev* 2016; 4:CD003868.
2. Volkow ND, Jones EB, Einstein EB, Wargo EM. Prevention and treatment of opioid misuse and addiction: a review. *JAMA Psychiatry* 2019; 76(2):208-16.
3. Compton WM, Volkow ND. Major increases in opioid analgesic abuse in the United States: concerns and strategies. *Drug Alcohol Depend* 2006; 81(2):103-7.
4. Tzschentke TM. Measuring reward with the conditioned place preference paradigm: a comprehensive review of drug effects, recent progress and new issues. *Prog Neurobiol* 1998; 56(6):613-72.
5. Becker A, Grecksch G, Brödemann R, Kraus J, Peters B, Schroeder H, et al. Morphine self-administration in μ -opioid receptor-deficient mice. *Naunyn Schmiedebergs Arch Pharmacol* 2000; 361(6):584-9.
6. Xi ZX, Stein EA. GABAergic mechanisms of opiate reinforcement. *Alcohol Alcohol* 2002; 37(5):485-94.
7. McClung CA. The molecular mechanisms of morphine addiction. *Rev Neurosci* 2006; 17(4):393-402.
8. Negus SS, Miller LL. Intracranial self-stimulation to evaluate abuse potential of drugs. *Pharmacol Rev* 2014; 66(3):869-917.
9. Bardo M, Bevins RA. Conditioned place preference: what does it add to our preclinical understanding of drug reward? *Psychopharmacology (Berl)* 2000; 153(1):31-43.
10. Koob GF. Drugs of abuse: anatomy, pharmacology and function of reward pathways. *Trends Pharmacol Sci* 1992; 13(5):177-84.
11. Sahraei H, Barzegari AA, Shams J, Zarrindast MR, Haeri-Rohani A, Ghoshoni H, et al. Theophylline inhibits tolerance and sensitization induced by morphine: a conditioned place preference paradigm study in female mice. *Behav Pharmacol* 2006; 17(7):621-8.
12. Zarrindast MR, Fattahi Z, Rostami P, Rezayof A. Role of the cholinergic system in the rat basolateral amygdala on morphine-induced conditioned place preference. *Pharmacol Biochem Behav* 2005; 82(1):1-10.
13. Manzanedo C, Aguilar MA, Rodríguez-Arias M, Miñarro J. Effects of dopamine antagonists with different receptor blockade profiles on morphine-induced place preference in male mice. *Behav Brain Res* 2001; 121(1-2):189-97.
14. Manzanedo C, Aguilar MA, Do Couto BR, Rodríguez-Arias M, Miñarro J. Involvement of nitric oxide synthesis in sensitization to the rewarding effects of morphine. *Neurosci Lett* 2009; 464(1):67-70.
15. Sahraei H, Amiri YA, Haeri-Rohani A, Sepehri H, Salimi SH, Pourmotabbed A, et al. Different effects of GABAergic receptors located in the ventral tegmental area on the expression of morphine-induced conditioned place preference in rat. *Eur J Pharmacol* 2005; 524(1-3):95-101.
16. Sahraei H, Ghazzaghi H, Zarrindast MR, Ghoshoni H, Sepehri H, Haeri-Rohan A. The role of alpha-adrenoceptor mechanism (s) in morphine-induced conditioned place preference in female mice. *Pharmacol Biochem Behav* 2004; 78(1):135-41.

17. Rezayof A, Zarrindast MR, Sahraei H, Haeri-Rohani A. Involvement of dopamine receptors of the dorsal hippocampus on the acquisition and expression of morphine-induced place preference in rats. *J Psychopharmacol* 2003; 17(4):415-23.
18. Murray JF, Schraufnagel DE, Hopewell PC. Treatment of tuberculosis. A historical perspective. *Ann Am Thorac Soc* 2015; 12(12):1749-59.
19. Casey RE, Wood JD. Isonicotinic acid hydrazide-induced changes in the metabolism of γ -aminobutyric acid in the brain of four species. *Comp Biochem Physiol B* 1973; 45(4):741-8.
20. Wood JD, Peesker SJ. A correlation between changes in GABA metabolism and isonicotinic acid hydrazide-induced seizures. *Brain Res* 1972; 45(2):489-98.
21. Perry T, Hansen S. Sustained drug-induced elevation of brain GABA in the rat. *J Neurochem* 1973; 21(5):1167-75.
22. Perry TL, Urquhart N, Hansen S, Kennedy J. Gamma-aminobutyric acid: drug-induced elevation in monkey brain. *J Neurochem* 1974; 23(2):443-5.
23. Zarrindast MR, Rezayof A. Morphine-induced place preference: interactions with neurotransmitter systems. *Iranian Journal of Pharmaceutical Research* 2007; 6(1):3-15.
24. Olmstead MC, Franklin KB. The development of a conditioned place preference to morphine: effects of microinjections into various CNS sites. *Behav Neurosci* 1997; 111(6):1324-34.
25. Lorenz TH, Calden G, Ousley JL. A study of the effects of isoniazid on the emotions of tuberculous patients. *Am Rev Tuberc* 1953; 68(4):523-34.
26. Arbex MA, Varella Mde C, Siqueira HR, Mello FA. Antituberculosis drugs: drug interactions, adverse effects, and use in special situations-part 1: first-line drugs. *J Bras Pneumol* 2010; 36(5):626-40.
27. Jackson SL. Psychosis due to isoniazid. *Br Med J* 1957; 2(5047):743-6.
28. Rezayof A, Razavi S, Haeri-Rohani A, Rassouli Y, Zarrindast MR. GABAA receptors of hippocampal CA1 regions are involved in the acquisition and expression of morphine-induced place preference. *Eur Neuropsychopharmacol* 2007; 17(1):24-31.
29. Zarrindast MR, Ahmadi S, Haeri-Rohani A, Rezayof A, Jafari MR, Jafari-Sabet M. GABAA receptors in the basolateral amygdala are involved in mediating morphine reward. *Brain Res* 2004; 1006(1):49-58.
30. Asehinde S, Ajayi A, Bakre A, Omorogbe O, Adebesein A, Umukoro S. Effects of jobelyn® on isoniazid-induced seizures, biomarkers of oxidative stress and glutamate decarboxylase activity in mice. *Basic Clin Neurosci* 2018; 9(6):389-96.
31. Westerink BH, Kwint HF, deVries JB. The pharmacology of mesolimbic dopamine neurons: a dual-probe microdialysis study in the ventral tegmental area and nucleus accumbens of the rat brain. *Journal of Neuroscience* 1996; 16(8):2605-11.
32. Xi ZX, Stein EA. Increased mesolimbic GABA concentration blocks heroin self-administration in the rat. *J Pharmacol Exp Ther* 2000; 294(2):613-9.
33. Gerasimov MR, Ashby CR Jr, Gardner EL, Mills MJ, Brodie JD, Dewey SL. Gamma-vinyl GABA inhibits methamphetamine, heroin, or ethanol-induced increases in nucleus accumbens dopamine. *Synapse* 1999; 34(1):11-9.
34. Ashby CR Jr, Rohatgi R, Ngosuwan J, Borda T, Gerasimov MR, Morgan AE, et al. Implication of the GABA_B receptor in gamma vinyl-GABA's

- inhibition of cocaine-induced increases in nucleus accumbens dopamine. *Synapse* 1999; 31(2):151-3.
35. Mu P, Yu LC. Valproic acid sodium inhibits the morphine-induced conditioned place preference in the central nervous system of rats. *Neurosci Lett* 2007; 426(3):135-8.
36. Cicek E, Sutcu R, Gokalp O, Yilmaz HR, Ozer MK, Uz E, et al. The effects of isoniazid on hippocampal NMDA receptors: protective role of erdosteine. *Mol Cell Biochem* 2005; 277(1-2):131-5.
37. Tsien JZ, Huerta PT, Tonegawa S. The essential role of hippocampal CA1 NMDA receptor-dependent synaptic plasticity in spatial memory. *Cell* 1996; 87(7):1327-38.
38. Morris RG. NMDA receptors and memory encoding. *Neuropharmacology* 2013; 74:32-40.
39. Nakazawa K, McHugh TJ, Wilson MA, Tonegawa S. NMDA receptors, place cells and hippocampal spatial memory. *Nat Rev Neurosci* 2004; 5(5):361-72.