Original Article:
Effects of Isoniazid on the Acquisition and Expression of Morphine Dependence in Male Mice

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ABSTRACT

Background: GABAergic drugs have extensive interference with morphine's pharmacological effects, including dependence.

Objectives: The present study was conducted to evaluate the effects of isoniazid, a GABAergic agent, on the acquisition and expression of morphine-induced dependence in male mice.

Methods: Sixty-four male mice were used. The mice became dependent on morphine by administrating ten doses of morphine in four days. For the precipitation of the morphine withdrawal signs (jumping, diarrhea, and weight loss), two hours after the last dose of morphine, the mice received naloxone (4 mg/kg, IP). In the expression experiment, four groups of mice received saline or isoniazid (25, 50, and 75 mg/kg, IP) one hour before naloxone. In the acquisition experiment, the other four groups, one hour before the first six doses of morphine, received saline or isoniazid (25, 50, and 75 mg/kg, IP).

Results: In the expression experiment, all doses of isoniazid decreased the number of jumping in mice, but only the lowest dose influenced diarrhea (increased weight of diarrheal stool) significantly. The higher doses of isoniazid (50 and 75 mg/kg, IP) caused a significant reduction in the percentage of weight loss, but its lowest dose (25 mg/kg, IP) significantly increased the sign. In the acquisition experiment, isoniazid (25, 50 mg/kg IP) decreased the number of jumping and the percentage of weight loss, but not the weight of diarrheal stool.

Conclusion: Isoniazid may be a good candidate to prevent morphine withdrawal signs.

Introduction

Morphine is the main alkaloid found in opium [1, 2]. Apart from its other therapeutic applications, this drug is still one of the most important medications for treating moderate to severe pains [3, 4]. Despite the importance of morphine in medicine, its abuse has limited its medical applications. Like other exogenous and endogenous opioids, morphine exerts its pharmacologic effects through binding to the opioid receptors [5, 6]. Chronic administration of morphine (for recreational or

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medical purposes) may lead to the induction of dependence (psychological and physical) to the drug [7-9]. In the morphine dependence phenomenon, chronic exposure to opioid leads to cellular and molecular adaptations in the neurons. These adaptations are the responses of the brain to counteract the effects of morphine [10]. After the induction of dependence, abrupt cessation of morphine administration or injection of morphine antagonists, like naloxone, causes a withdrawal syndrome.

This syndrome includes typical signs like diarrhea, seizure, pain, spasm, jumping, and itching [11]. These unpleasant signs are among the most important reasons for unsuccessful attempts to stop morphine intake. Therefore, finding safe drugs that can alleviate or prevent morphine withdrawal signs may help quit the drug. Morphine dependence is a complex process, and several neurotransmitter systems of the brain may have modulatory effects on this process. Previous research has shown that drugs interacting with endocannabinoid, opioidergic, noradrenergic, serotonergic, dopaminergic, cholinergic, and GABAergic systems of the brain may alter morphine withdrawal signs and symptoms [12-20].

Isoniazid is an effective antituberculosis drug [21, 22]. Besides its antibiotic effect, it may have some modulatory effects on the GABAergic systems of the brain. Many studies have shown that by decreasing the gamma-aminobutyric acid (GABA) levels of the brain, high doses of isoniazid may induce seizures [23-25]. In this respect, isoniazid is used in animal models of drug-induced seizures [26]. However, some animal experiments have shown that isoniazid in low doses may moderately increase GABA levels of the brain [27]. Therefore, one may conclude that isoniazid has dual effects on the brain's GABA levels; it means that isoniazid in low and high doses may act as an indirect GABA agonist and antagonist, respectively. GABA is the main inhibitory neurotransmitter of the brain [28]. Drugs that elevate GABA levels in the nervous system or the agonists of this neurotransmitter produce analgesic, sedative, anesthetic, anticonvulsant, and anxiolytic effects [29-32].

Previous studies indicate the extensive interference of GABAergic agents in morphine reward [33, 34], sensitization [35], tolerance [36], and dependence [19, 37]. Moreover, the administration of some GABAergic drugs has shown satisfactory results in treating various aspects of drug addiction [18, 38-40]. Therefore, the purpose of the present study was to evaluate the effects of low-dose isoniazid on the acquisition and expression of morphine dependence in male mice.

Materials and Methods

Animals

Intact, male NMRI mice with a weight range of 20-25 g were obtained from Razi Vaccine and Serum Research Institute (Alborz Province, Karaj). After transferring to the animal house at the University of Maragheh, the mice were housed in polycarbonate plastic cages. All of the mice spent 1 week acclimatization period before the initiation of the experiments. The animals were kept in a room with standard maintenance conditions, including a light-dark cycle of 12/12h (illumination at 7:00 AM) at a temperature of 22°C±2°C. In addition, all animals had free access to food and water. At the beginning of the research, the mice were randomly allocated to different groups of eight. In each part of the experiment, separate groups of mice were used, and no mice were used twice. The experimental protocols on the animals were approved by a local ethical committee for animal care and use at the University of Maragheh (Code: UM-2018-number 22).

Drugs

Drugs that were used in the experiments included isoniazid, a white powder (Solarbio Co, China), morphine sulfate ampules (10 mg/1 mL, Darou Pakhsh Pharmaceutical Mfg. Co., Tehran, Iran), and naloxone hydrochloride ampoules (0.4 mg/1 mL, Toliddaru Co., Tehran, Iran). Naloxone and isoniazid were dissolved in normal saline and were administered intraperitoneally (IP). To prepare different doses of morphine sulfate, the drug was also diluted in normal saline and was injected subcutaneously.

Induction of dependence and withdrawal syndrome in mice

The method of dependence induction in the animals was similar to Zarrindast's method [19]. This method consisted of four consecutive days and ten injection sessions in each period. On the first three days of the injection schedule, each animal received three daily doses of morphine (50, 50, and 75 mg/kg) at 9.00, 13.00, and 17.00, respectively. On these days, the dose of morphine at the last daily injection session (i.e., 17.00) was higher to prevent abstinence syndrome overnight. The last dose of morphine (50 mg/kg) was administered on the fourth day of the protocol (9:00). As one may expect, injection of high doses of morphine causes hyperactivity and Straub tail reactions in mice. For precipitation of withdrawal syndrome, two hours after the last morphine dose, each animal received naloxone (4 mg/kg, IP). Then, 2 minutes later, each animal was placed sepa-

rately in a glass cylinder (2-cm d×40-cm h), and the behavioral withdrawal signs were recorded for 30 minutes. An observer, blind to the present study, simply counted the number of jumping in each 30 min of the recorded films. To measure the weight of the stool for each animal, before placing the animal inside the cylinder, the floor of the cylinder was covered with filter paper. For each mouse, the difference between the weight of the filter paper before placing the animal into the cylinder and 30 minutes after testing time was calculated as the weight of diarrheal stool precipitated by naloxone. The weight of diarrheal stool was expressed as g of stool/100 g of the animal's body weight. The last parameter for assessing morphine withdrawal syndrome was weight loss 1 h after the naloxone injection. The difference between the weight of each animal before naloxone injection and one hour after that was considered weight loss. The percentage of weight loss was calculated as follow:

$$weigh\ loss\ percentage = \frac{weight\ loss}{weight\ before\ naloxone\ injection} \times 100$$

In a pilot study, it was shown that morphine but not saline treatment, according to the current schedule of dependence induction, could induce morphine dependence in mice (data are not shown). Therefore, this method was adopted to induce morphine dependence in the present research.

Study design

Assessment of isoniazid effects on the acquisition and expression of naloxone-precipitated withdrawal syndrome

First, 64 mice were randomly assigned to eight groups of eight. For evaluation of isoniazid effects on the expression of withdrawal signs, on the fourth day of dependence induction protocol, one hour after the last injection of morphine (50 mg/kg, SC), one group, as control, received saline, IP, and the other three groups, as the experimental groups, received isoniazid (25, 50, and 75 mg/kg, IP). Then, one hour later, naloxone was administered to all animals. For assessing the effects of isoniazid on the acquisition of morphine dependency, on the first three days of the schedule of dependence induction, one hour before each dose of morphine, one group of mice received saline, IP and the other three groups received isoniazid (25, 50, and 75 mg/kg, IP). On the fourth day, two hours after the last morphine dose (50 mg/kg, SC), naloxone (4 mg/kg, IP) was administered to all mice of each group. In the expression experiment, chronic administration of morphine caused 6 deaths in mice of the experimental groups (2 mice of each group). In the acquisition experiment, chronic administration of morphine and isoniazid resulted in the death of all mice, which received the highest dose of isoniazid (75 mg/kg). Moreover, two deaths occurred in each experimental group that received lower doses of isoniazid (25 or 50 mg/kg, IP).

Statistical analysis

In the present study, SPSS, version 18, was used for data analysis. The obtained data were expressed as Mean±SEM. One-way ANOVA followed by LSD post hoc test was used to assess significant differences between the analyzed data in animal groups.

Results

Effects of isoniazid administration before naloxone on the expression of morphine dependence behavioral sign (jumping) in the dependent mice

Injection of isoniazid (25, 50, and 75 mg/kg, IP) one hour before naloxone (4 mg/kg, IP) administration on the test day could decrease the jumping ($F_{3, 22}$=7.38, P= 0.001) significantly (Figure 1).

Effects of isoniazid administration before naloxone on the expression of morphine dependence physical signs (diarrhea and weight loss) in the dependent mice

Isoniazid injection (25, 50, and 75 mg/kg, IP), one hour before naloxone administration (4 mg/kg, IP) had a significant effect on the weight of diarrheal stool ($F_{3, 22}$= 10.36, P<0.001) and the percentage of weight loss ($F_{3, 22}$= 10.07, P<0.001). In this regard, the group that received the low dose of isoniazid (25 mg/kg, IP) showed a significant increase in the weight of diarrheal stool compared to its saline-treated counterpart. This group also showed a significant increase in the percentage of weight loss. On the contrary, the higher doses of isoniazid (50 and 75 mg/kg, IP) could reduce the percentage of weight loss of mice after the naloxone treatment significantly. These doses of isoniazid had no significant effects on the weight of diarrheal stool (Figure 2).

Effects of isoniazid treatment before morphine doses on the acquisition of morphine dependence behavioral signs (jumping)

Compared to that of the saline group, the animal groups that before each dose of morphine received isoniazid (25 and 50mg/kg, IP) showed a significant decrease in jump-

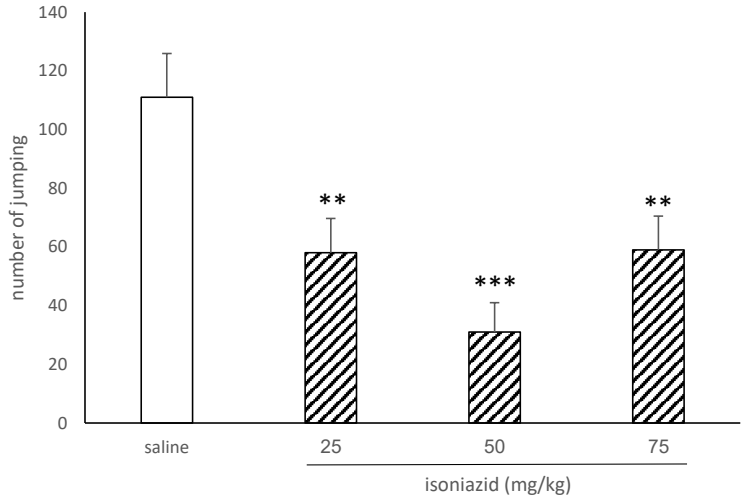

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Figure 1. Effects of saline (10 mL/kg, IP) or isoniazid (25, 50, and 75 mg/kg, IP)

Administration one hour before naloxone (4 mg/kg, IP) injection on mice jumping on the test day. Values are presented as Mean±SEM for 6-8 mice. ** and *** indicate P<0.01 and P<0.001 compared with the saline group, respectively.

ing ($F_{2, 17}$=9.87, P=0.001) that induced by naloxone (4 mg/kg, IP) injection on the test day (Figure 3).

Effects of isoniazid treatment before morphine doses on the acquisition of morphine dependence physical signs (diarrhea and weight loss)

In groups that on the days of dependence induction, received isoniazid (25 and 50 mg/kg IP) before morphine, no significant effect on the weight of diarrheal stool ($F_{2,17}$=0.43, P= 0.65) was observed. However, the low dose of isoniazid decreased the percentage of weight loss ($F_{2,17}$=3.4, P=0.05) after naloxone treatment (4 mg/kg, IP), compared to that of the saline-treated group (Figure 4).

Discussion

The main findings of the present research were as follows. The administration of isoniazid before naloxone on the test day had modulatory effects on the withdrawal syndrome; all doses of isoniazid significantly decreased the number of jumping, but only its low dose increased the volume of diarrhea. The low amount of isoniazid also increased the percentage of weight loss, while its higher doses (50 and 75 mg/kg, IP) decreased the sign significantly. Furthermore, administering isoniazid before morphine (on days of dependence induction) could reduce the number of jumping and weight loss percentage but not the weight of diarrheal stool. Therefore, one may

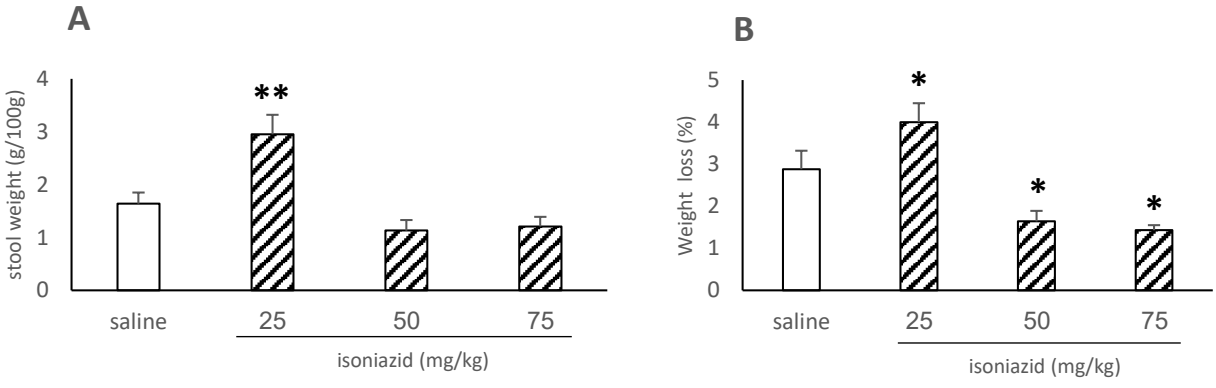

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Figure 2. Effects of saline (10 mL/kg, IP) or isoniazid (25, 50, and 75 mg/kg, IP)

Administration one hour before naloxone (4 mg/kg, IP) injection, on the test day, on stool weight (A) and percentage of weight loss (B) in male mice. Values are presented as Mean±SEM for 6-8 mice. * and ** indicates P<0.05 and P<0.01 compared to the respective saline-treated group.

Figure 3. Effects of saline (10 ml/kg, IP) or isoniazid (25, 50 mg/kg, IP)
Administration one hour before morphine administration during the first three days of dependence induction on mice jumping, on the test day. Values are presented as Mean±SEM for 6-8 mice. *** indicates P<0.001 compared with the saline group.

conclude that isoniazid may interfere with the acquisition and expression of morphine dependence processes.

In the present experiments, administration of morphine according to Zarrindast's protocol [41] could induce dependence in the male mice. This result is in line with previous research by other groups that used a similar protocol for inducing morphine dependence in mice [42-44].

In the expression experiment, the death of two mice from each experimental group was observed before the test day. The animals in the expression experiment died because in our protocol for induction of dependence, high doses of morphine were used. Therefore, the toxic effects of morphine were expressed in some mice that were more susceptible to the drug effects. Other protocols for the induction of morphine dependence use lower doses of morphine [45], but we used this method because of the rapid induction of morphine dependence in this protocol.

The present study results showed that isoniazid pretreatment could significantly reduce the expression of jumping behavior induced by naloxone in mice. One explanation for these results is that isoniazid in low doses may behave like an indirect agonist of GABA receptors and increase the GABA level, as described later. The elevation of GABA in the brain leads to some anxiolytic, sedative, and analgesic effects [29, 30, 32]. Therefore, administration of isoniazid on the test day may reduce the pain and anxiety induced by naloxone injection, decreasing the number of jumping on the test day. Previous research by Zarrindast et al. showed that administration of both GABAA and GABAB agonists reduces the jumping of morphine-dependent mice after naloxone administration [19]. Moreover, one research has been

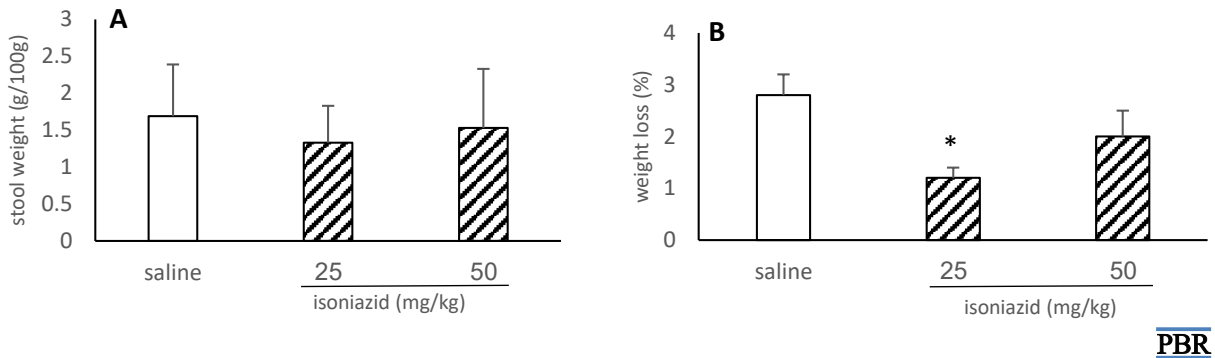

Figure 4. Effects of saline (10 mL/kg, IP) or isoniazid (25, 50, mg/kg, IP)
Administration one hour before receiving of morphine during the first three days of dependence induction, on diarrhea (A) and the percentage of weight loss (B) on the test day. Values are presented as Mean±SEM for 6-8 mice. * indicates P<0.05.

demonstrated that valproate (an indirect GABA agonist) had good effects on decreasing both the acquisition and expression of morphine withdrawal signs [46]. Finally, in one pilot study in human subjects, valproate administration was helpful in the treatment of benzodiazepine withdrawal in opioid-dependent patients [47].

In our study, administration of the low dose of isoniazid (25 mg/kg, IP) on the test day exacerbated diarrhea induced by naloxone significantly; the higher amounts of isoniazid had no significant effect on diarrhea. In a study by Mahfouzi et al., the frequency of diarrhea was decreased in the morphine-dependent mice that received baclofen (a GABAB receptor agonist), bicuculline (competitive antagonist of GABAA receptor), and picrotoxine (a noncompetitive antagonist at GABAA receptors) before naloxone [37]. While GABAB receptor activation has inhibitory effects on intestinal motility, activation of GABAA receptors may have stimulatory effects on the propulsive activity of the colon. Previous studies on mice have also shown that elevation of GABA levels in the colon had a biphasic impact on colon motility. At the beginning of GABA elevation in the colon, this neurotransmitter mainly binds to the GABAA receptors; this binding increases the acetylcholine release and propulsive activity of the colon. As the GABA level increases, it activates the GABAB receptors that have opposite effects on intestinal motility (decreases the colon motility) [48]. Therefore, it is likely that the low dose of isoniazid (25 mg/kg, IP) that elevates the GABA level slightly activates the GABAA receptors that increases the colon motility. This effect of isoniazid is added to the effects of naloxone in inducing diarrhea. The volume of diarrhea was increased on the test day compared to the saline-treated group.

Concomitant with this effect of the low dose of isoniazid, the percentage of weight loss in the animal group that received the low amount of isoniazid was significantly higher than the saline-treated group. On the contrary, in the groups that received higher doses of isoniazid, the weight loss percentage was significantly lower than the saline group. In these isoniazid high-dose groups, the volume of diarrhea was less than the saline-treated group, but the differences were not significant.

In the acquisition experiment, in the group of mice that received the highest dose of isoniazid (75 mg/kg, IP), the death of all the animals was observed. The animals in the acquisition protocol died in our experiment because the time interval between isoniazid injections was relatively short (as the time interval between morphine injections was short, too). Therefore, administering each dose of isoniazid might increase isoniazid concentrations in the brain. In the animals that received the highest amount of isoniazid (75 mg/kg), the accumulation of isoniazid in the brain shifted its effects from GABA elevation to GABA reduction as a convulsant drug. Moreover, morphine by itself (in high doses) may have some pro-convulsant effects [49]. The outcome of these two properties was the sensitivity of the mice to seizures, and with the slightest stress (at the time of injections), the death of mice from seizures occurred. Apart from this unexpected effect, in the animals that were pretreated with the lower doses of isoniazid (25 and 50 mg/kg, IP) on the days of dependence induction, the drug could significantly decrease the naloxone-induced jumping and weight loss percentage, but not diarrhea.

Our results are in good agreement with a previous study by Suzuki et al. In their research, co-administration of diazepam (a GABAergic agonist) with chronic morphine could prevent the development of morphine dependence in mice [50]. As mentioned before, the low dose of isoniazid possibly increases colon motility. This effect probably counteracts part of the effects of morphine on the induction of constipation. Therefore, counter adaptations against morphine effects decrease in the colon, and on the test day, naloxone-induced diarrhea was reduced compared to the control group that received saline before morphine. The insignificant effects of isoniazid on diarrhea may be the more potent effects of morphine on intestinal motility than the isoniazid.

Previous research showed that chronic morphine causes adaptations in the ventral tegmental area (VTA) area that leads to an increase in GABA release upon induction of withdrawal [51, 52]. One hypothesis that may explain the effects of isoniazid on the acquisition of morphine dependence is the opposite effects of isoniazid and morphine on GABA levels of the VTA. While acute morphine decreases the GABA level of VTA [53], the low doses of isoniazid may increase the concentration of GABA in the area. These effects may counteract each other, and therefore during chronic morphine exposure, GABA adaptations do not occur in the VTA. However, the speculation should be tested in the future (for example, by assessing GABA levels in the VTA after IP or intracerebroventricular administration of the isoniazid into the VTA by microdialysis method).

Conclusion

Our previous research showed that isoniazid could reduce morphine rewarding effects, tolerance, and sensitization [54, 55]. Besides these effects, the present study

showed that isoniazid interferes in the development and the expression of morphine dependence in mice. Altogether, these results indicate that isoniazid may be a good candidate for preventing the addictive properties of morphine. Importantly, it should be noted that to achieve the best results, the dose of isoniazid should be selected accurately.

Ethical Considerations

Compliance with ethical guidelines

In all experiments on animals, every effort was made to observe ethical measures. A local ethical committee for animal care and use at the University of Maragheh approved all the experimental protocols on the animals (Code: UM-2018-number 22).

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Authors' contributions

Conceptualization, supervision, data analysis, and writing the original draft: Amir Abbas Barzegari; Data collection: Kamran Shahabi.

Conflict of interest

The authors declared no conflict of interest.

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