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ScienceDirect
Pharmacology, Biochemistry and Behavior 88 (2008) 385–392
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
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Repeated administration of nicotine attenuates the development of morphine tolerance and dependence in mice

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Received 28 May 2007; received in revised form 1 September 2007; accepted 11 September 2007
Available online 19 September 2007

Abstract

Clinical use of morphine in pain management is a controversial issue. Both nicotine and morphine are widely abused. So, investigating the interaction between nicotinic and opioid receptors is of great interest to both basic mechanistic and clinical view. We investigated the influence of repeated administration of nicotine on the development of morphine tolerance and dependence. Adult male albino mice were rendered dependent on morphine by subcutaneous (s.c.) injections three times daily for 3 days. Repeated intraperitoneal (i.p.) injection of nicotine (0.001–2 mg/kg) or saline (1 ml/kg) was performed 15 min prior to each morphine injection. Maximal possible effect (MPE%) of morphine (50 mg/kg; s.c.) was used on the fourth day as an index for the development of tolerance. Likewise, to assess the occurrence of dependence in drug-treated mice, naloxone (5 mg/kg; i.p.) was injected 2 h after the last dose of morphine. Repeated nicotine administration significantly attenuated the development of tolerance in a dose-dependent manner whereas it significantly decreased withdrawal jumping behavior in a biphasic profile (V-shape) manner. Furthermore, the central nicotinic receptor antagonist mecamylamine (0.01–0.1 mg/kg; i.p.) neither the peripheral nicotinic receptor antagonist hexamethonium (0.01 and 0.1 mg/kg; i.p.) nor the muscarinic receptor antagonist atropine (2.5–10 mg/kg; i.p.), dose-dependently antagonized both the inhibition of withdrawal jumping as well as increase in MPE% which was produced by repeated nicotine administration (0.1 mg/kg; i.p.). On the other hand, 3 days of solely nicotine treatment resulted in significant jumping behavior precipitated by naloxone after single morphine injection on the test day. The data suggests that the inhibitory effect of nicotine on the morphine tolerance and dependence is mediated by central nicotinic receptors and there is a cross-dependence between nicotine and morphine.

Keywords: Nicotine; Morphine; Tolerance; Dependence; Nicotinic receptor; Muscarinic receptor

1. Introduction

Opioid analgesics, such as morphine, are currently the most effective and frequently used pain relievers for moderate to severe pain. However, long-term administration of opioids can alter the central pain-related systems and results in opioid tolerance (decreased analgesic effect of opioids) and dependence (a behavioral state requiring continued opioids to avoid a series of aversive withdrawal syndromes). Opioid tolerance and dependence can significantly hamper the effective treatment of chronic pain with opioid analgesics (Bie and Pan, 2005; Nestler, 2004). On the other hand, Simons et al. (2005) pointed out "nicotine, a major bioactive constituent of tobacco has an antinociceptive effect that may afford opportunities for pain relief but may also contribute to the abuse liability of tobacco products". It has been suggested that most of these effects could be due to the ability of nicotine to release different neurotransmitters (Balfour, 1982; Zarrindast and Farzin, 1996). The drug has effects on many neurochemical systems; it particularly increases dopaminergic and cholinergic activity (Balfour, 1991; Clarke, 1990) and increases the release of dopamine from the limbic system (Imperato et al., 1986) and from striatal slices (Giorguieff-Chesselet et al., 1979). Also, other researches showed involvement of nicotinic cholinergic receptors in nicotine-induced antinociception (Bhargava and Saha, 2001; Simons et al., 2005). They proposed either the involvement of nicotinic receptor in morphine-induced analgesia (Bhargava and Saha, 2001) or the involvement of μ-opioid receptor in nicotine-induced antinociception (Simons et al., 2005). Previous studies

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doi:10.1016/j.pbb.2007.09.010

have shown that nicotine has a role in activating opioid system(s) (Balfour, 1982; Davenport et al., 1990). In addition, enkephalin biosynthesis and release in certain brain nuclei and adrenal chromaffin cells are activated by nicotinic receptor stimulation (Eiden et al., 1984; Houdi et al., 1991). These findings may well be related to the similar emotional behaviors that opiate addicts and cigarette smokers exhibit during abstinence from their habits (Gossop et al., 1990).

Additionally, behavioral studies have shown that there is a cross-tolerance between morphine- and nicotine-induced analgesia (Zarrindast et al., 1999; Biala and Weglinska, 2006) and have also suggested that similar opioid- and calcium-dependent mechanisms are involved in morphine- and nicotine-induced antinociception and in the development of cross-tolerance between these drugs (Biala and Weglinska, 2006). Despite these lines of evidence regarding a cross-tolerance between morphine- and nicotine-induced analgesia, there is no study on the influence of concurrent chronic nicotine and morphine administration on the development of tolerance to antinociceptive effect of morphine. Also, while it has been demonstrated that acute administration of nicotine attenuates naloxone-induced jumping behavior in morphine-dependent mice (Zarrindast and Farzin, 1996), the influence of chronic exposure to nicotine on the development of morphine dependence has not been studied. Therefore, this study was undertaken to test the effects of repeated administration of nicotine on the development of both morphine tolerance and morphine dependence in mice.

2. Materials and methods

2.1. Animals

A total of two hundred sixty-three adult male albino Wistar mice (Razi Institute, Tehran, Iran) weighing 18–30 g were used in these experiments. They were kept 10–12 per cage (45×30×15 cm) at a room controlled temperature (23±1 °C) and maintained on a 12-h light/dark cycle (light on 07:00 h) with free access to the standard rodent breeding diet and tap water. Each animal was used only once and was killed immediately after the experiment. All Experiments were executed in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 85-23, revised 1985) and were approved by the Research and Ethics Committee of Shaheed Beheshti Medical University.

2.2. Induction of morphine tolerance and dependence

The mice were rendered dependent on morphine using the method previously described by Marshall and Grahame-Smith (1971). Subcutaneous (s.c.) administration of morphine sulfate was three times daily at 8:30, 12:30 and 16:30 (4 h intervals between injections) on the following dosage schedule. The first three doses were 50, 50, 75 mg/kg, respectively. The higher dose at third daily injection was to avoid any overnight withdrawal as much as possible. Each of the doses was then increased by 25 mg/kg/day in subsequent days up to day three for all groups of mice, so the final dose on day three was 125 mg/kg. A dose of 50 mg/kg of morphine sulfate was also injected on the fourth day. Hyperactivity and the straub tail effect were seen after morphine injections. To assess the degree of tolerance, the antinociceptive response to drug was measured on the 4th day 30 min after injection of the drug. To test the occurrence of dependence in drug-treated mice after their tenth injection of morphine on the fourth day, naloxone was injected intraperitoneally 2 h after the last dose of morphine; the animals were immediately introduced in glass chambers and the number of jumps was recorded over a 30 min period.

2.3. Analgesia testing

The tail flick test was used for evaluating the development of tolerance to morphine. The latency to withdraw the tail from a feedback-controlled projector lamp focused on the dorsal surface of the tail was used as a measure of nociceptive responsiveness. The tail flick latency (TFL) more than 10 sec was considered as a cut-off point to avoid any tissue damage and the heat was terminated automatically upon occurrence of the tail flick or if 10 s elapsed in the absence of a flick. Tail flick response latencies (s) are expressed either as raw data or as percentage of maximal possible effect (MPE%) using the equation:

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

where post-drug latency is TFL, 30 min after the administration of last dose of morphine on the fourth day. Two tail flick tests were done on test day (fourth day) for each mouse to average them as baseline latency; then morphine sulfate (50 mg/kg, s.c.) was injected; 30 min after morphine injection two other tail flick tests were done to average them to find post-drug latency for each animal.

2.4. Jumping test

Mice were tested for the occurrence of jumping after their tenth injection of morphine (50 mg/kg, s.c.) on fourth day as described in Section 2.2. Two hours after the last dose of morphine, withdrawal syndrome (abstinence) as an index of morphine dependence, was precipitated by intraperitoneal (i.p.) injection of naloxone (5 mg/kg); then animals were placed individually on the filter paper in an open Plexiglas chamber (25×25×40 cm) and the number of jumps was recorded by an observer over a 30 min period.

2.5. Drugs

The following drugs were used: morphine sulfate (Temad Co, Iran), naloxone hydrochloride, nicotine hydrogen tartrate ([−]–Nicotine di–[+]tartrate salt), mecamylamine hydrochloride (2–[Methylamino]isocamphane; N,2,3,3–Tetramethylbicyclo[2.2.1]heptan–2–amine), hexamethonium bromide (Hexane-1,6-bis[trimethylammonium bromide]) and atropine sulfate. All drugs except morphine were purchased from Sigma-Aldrich,

Inc. All drugs were dissolved in sterile 0.9% normal saline just before the experiments.

2.6. Drug treatment

All drugs were injected intraperitoneally except morphine which was used subcutaneously using 1-ml insulin syringes. For subcutaneous (s.c.) or intraperitoneal (i.p.) injections the doses were adjusted so that each animal received a volume of at most 10 ml/kg and were prepared immediately before use. The doses of antagonists and pretreatment time were usually those used previously and shown to be pharmacologically active (Zarrindast and Farzin, 1996).

2.6.1. Experiment 1

This experiment examined the effect of repeated administration of nicotine on morphine tolerance and dependence. In this experiment, the animals received either saline or nicotine (0.001, 0.01, 0.1, 1 and 2 mg/kg, i.p.), three times daily for 3 days, 15 min before each morphine injection as described in Marshall and Grahame-Smith protocol (Section 2.2). In the fourth day, the tail flick test was used for evaluating the development of tolerance to morphine and then mice were tested for the occurrence of dependence as described in Sections 2.3 and 2.4, respectively. We also tested one group of animals as an intact (saline + saline) group, without any drug (nicotine and/or morphine) application during period of the protocol, but received morphine and naloxone on the test day (Fig. 1).

2.6.2. Experiment 2

This experiment examined the involvement of central nicotinic receptor in response to the repeated administration of nicotine on the development of morphine tolerance and dependence in mice. In this experiment, the animals received either saline or central nicotinic receptor antagonist, mecamylamine HCl (0.01, 0.05 and 0.1 mg/kg, i.p.), three times daily for 3 days, 5 min before each nicotine (0.1 mg/kg, i.p.) and morphine injections as described in experiment 1. In the fourth day, the tail flick test was used for evaluating the development of tolerance to morphine and then mice were tested for the occurrence of dependence (Fig. 2).

2.6.3. Experiment 3

This experiment examined the involvement of peripheral nicotinic receptor in effects of repeated administration of nicotine on the development of morphine tolerance and dependence in mice. In this experiment, the animals received either saline or peripheral nicotinic receptor antagonist, hexamethonium bromide (0.01 and 0.1 mg/kg, i.p.), three times daily for 3 days, 15 min before each nicotine (0.1 mg/kg, i.p.) and morphine injections as described in experiment 1. In the fourth day, the tail flick test was used for evaluating the development of tolerance to morphine and then mice were tested for the occurrence of dependence (Fig. 3).

2.6.4. Experiment 4

This experiment examined the involvement of muscarinic receptor in effects of repeated administration of nicotine on the development of morphine tolerance and dependence. In this experiment, the animals received either saline or muscarinic receptor antagonist, atropine sulfate (2.5, 5 and 10 mg/kg, i.p.), three times daily for 3 days, 15 min before each nicotine (0.1 mg/kg, i.p.) and morphine injections as described in experiment 1. On the fourth day, the tail flick test was used for evaluating the development of tolerance to morphine and then mice were tested for the occurrence of dependence (Fig. 4).

2.6.5. Experiment 5

This experiment examined the effect of repeated administration of nicotine on acute morphine tolerance and dependence. In this experiment, the animals received solely either saline or nicotine (0.001, 0.01, 0.1, 1 and 2 mg/kg, i.p.), three times daily for 3 days. The animals received only one injection of morphine (50 mg/kg; s.c.) on test day (day 4). In the fourth day, the tail flick test was used for evaluating the development of tolerance to morphine and then mice were tested for the occurrence of dependence (Fig. 5).

2.7. Data analysis

The obtained results are expressed as mean ± SEM (standard error of mean). The TFLs before and after drug administration were compared by student's paired *t*-test and repeated measures analysis of variance (ANOVA) followed by protected Tukey's test for multiple comparison. The Dunnett test was employed post-hoc to determine the basis of the significant difference compared with control groups. On the other hand, both TFLs and number of jumpings in all groups (Intact, Saline and Experimental groups) were subjected to the one-way ANOVA and Randomized blocks model followed by post-hoc analysis, as needed. *P*-values less than 0.05 were considered to be statistically significant.

3. Results

3.1. Effects of chronic exposure to nicotine on the development of morphine tolerance and dependence

Maximal possible effect (MPE%) of morphine was lower in morphine-treated group following Marshall and Grahame-Smith method ($n=22$) in comparison with intact (control) group which did not receive morphine in previous days ($n=18$; Fig. 1A). Repeated administration of different doses of nicotine 15 min prior to each morphine injection during the protocol significantly [$F(6,91)=7.711$, $P<0.0001$] attenuated the development of tolerance to morphine in a dose-dependent manner (Fig. 1A). Dunnett's post-hoc test revealed that the inhibitory effect of nicotine was significant at doses of 0.1 mg/kg ($P<0.01$), 1 mg/kg ($P<0.001$) and 2 mg/kg ($P<0.01$) as shown in Fig. 1A. On the other hand, one-way ANOVA revealed no significant difference among the pre-morphine TFLs on day 4 of intact, saline + morphine and nicotine (0.001, 0.01, 0.1, 1, 2)+morphine groups [$F(6,92)=2.011$, ns].

On the other hand, naloxone produced remarkable withdrawal jumping in morphine-dependent mice in comparison with the intact group ($n=21$; Fig. 1B). Chronic nicotine

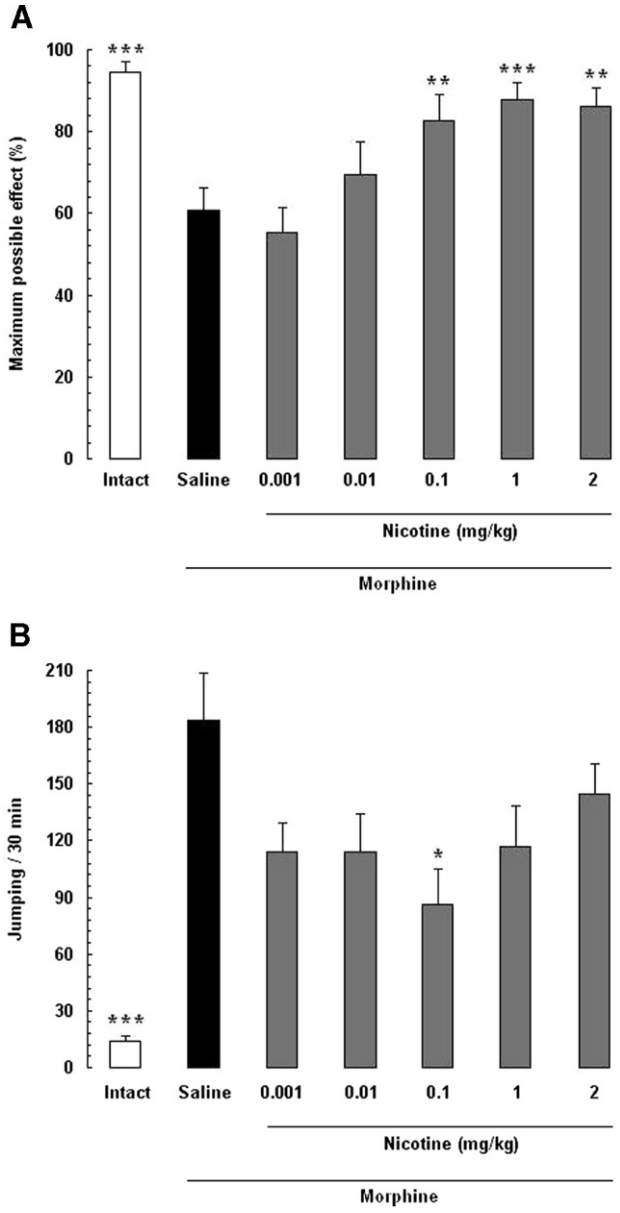

Fig. 1. Effects of different doses of repeated administration of nicotine or saline on (A) the average of maximal possible effect (MPE%) after administration of morphine (50 mg/kg; s.c.) on the test day for evaluating the development of morphine tolerance and (B) number of jumping induced by naloxone on the test day for assessing the occurrence of dependence. Each group had at least 9 mice. Results were expressed as mean ±SEM. *$P<0.05$, **$P<0.01$, ***$P<0.001$ compared with saline group.

administration, 15 min before each morphine injection during the induction of dependence, considerably decreased the number of jumping induced by naloxone on the test day [$F(6,93)=7.405$, $P<0.0001$]. Nevertheless, Dunnett's multiple comparison test showed that the inhibitory effect of nicotine was significant only at dose of 0.1 mg/kg as compared to saline+morphine-treated animals ($P<0.05$; Fig. 1B).

3.2. Effects of mecamylamine on the inhibitory action of nicotine

Pretreatment of the mice with different doses of mecamylamine (0.01, 0.05 and 0.1 mg/kg, i.p.), three times daily for 3 days, 5 min before each nicotine (0.1 mg/kg, i.p.) and morphine injections produced significant decrease in the inhibitory effect of nicotine on the development of morphine tolerance [$F(3,44)=3.206$, $P=0.0329$] and morphine dependence [$F(3,43)=4.284$, $P=0.0103$] in a dose dependent manner as compared to the nicotine+morphine-treated group that received saline instead of the drug. Tukey's multiple comparison test showed that mecamylamine only at the dose of 0.1 mg/kg could significantly reverse the inhibitory effect of nicotine on morphine tolerance (Fig. 2A)

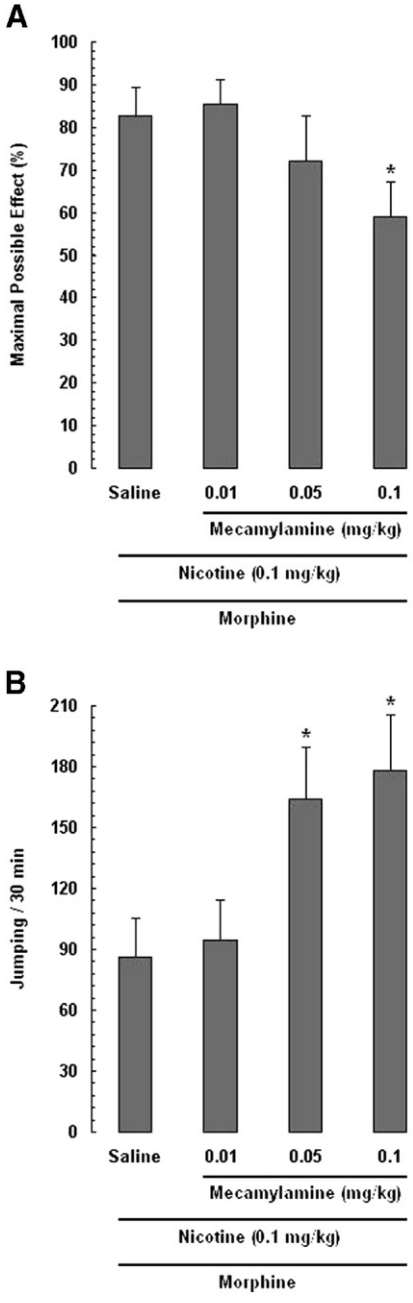

Fig. 2. Effects of different doses of mecamylamine or saline before repeated administration of nicotine on (A) the average of maximal possible effect (MPE%) after administration of morphine (50 mg/kg; s.c.) on the test day for evaluating the development of morphine tolerance and (B) number of jumping induced by naloxone on the test day for assessing the occurrence of dependence in morphine-treated mice. Results were expressed as mean ±SEM for 9–12 mice. *$P<0.05$ compared with control group.

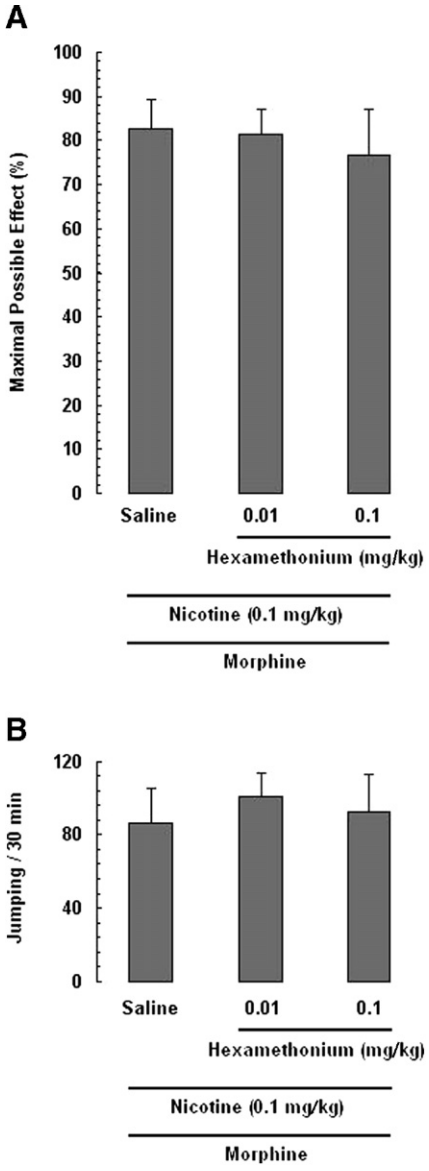

Fig. 3. Effects of different doses of hexamethonium or saline before repeated administration of nicotine on (A) the average of maximal possible effect (MPE%) after administration of morphine (50 mg/kg; s.c.) on the test day for evaluating the development of morphine tolerance and (B) number of jumping induced by naloxone on the test day for assessing the occurrence of dependence in morphine-treated mice. Results were expressed as mean ±SEM for 8–12 mice.

whereas it was able to suppress the effect of nicotine on morphine dependence significantly at doses of 0.05 and 0.1 mg/kg (Fig. 2B).

3.3. Effects of hexamethonium and atropine on the inhibitory action of nicotine

Pretreatment of animals with hexamethonium (0.01 and 0.1 mg/kg, i.p.), three times daily for 3 days, 15 min before each nicotine (0.1 mg/kg, i.p.) and morphine injections produced no significant alteration in the inhibitory effect of nicotine on the development of morphine tolerance ([$F(2,41)=0.1553$, $P=0.8567$]; Fig. 3A) and morphine dependence ([$F(2,40)=0.205$, $P=0.8156$]; Fig. 3B). Likewise, atropine (2.5, 5 and 10 mg/kg, i.p.) pretreatment produced no significant alteration in the inhibitory effect of nicotine on the development of morphine tolerance ([$F(3,40)=0.1124$, $P=0.9523$]; Fig. 4A) and morphine dependence ([$F(3,38)=0.1842$, $P=0.9064$]; Fig. 4B) in comparison with the nicotine+morphine-treated group that received saline instead of the drug.

3.4. Effects of repeated administration of nicotine on morphine-induced antinociception and naloxone-precipitated abstinence

As shown in Fig. 5A, 3 days of nicotine treatment (0.001, 0.01, 0.1, 1 and 2 mg/kg, i.p.) three times daily did not affect morphine-induced antinociception elicited by single morphine injection on 4th day. One-way ANOVA revealed that there is no significant difference in MPE% of morphine among nicotine-

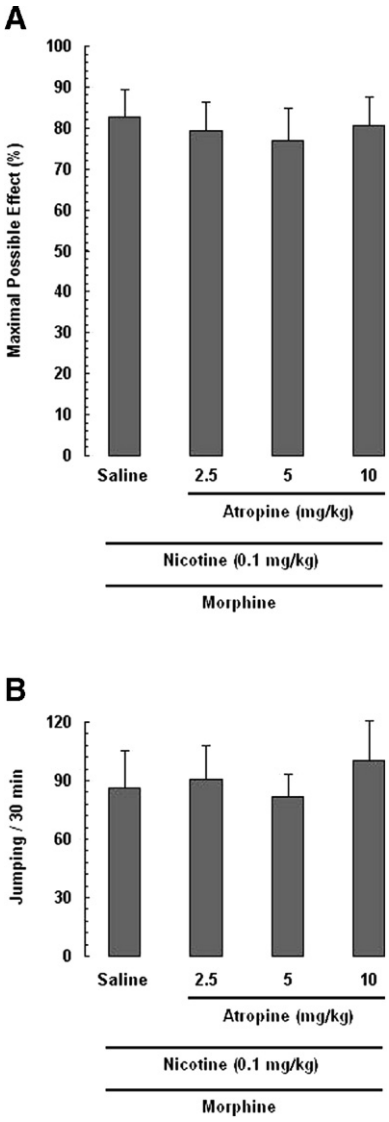

Fig. 4. Effects of different doses of atropine or saline before repeated administration of nicotine on (A) the average of maximal possible effect (MPE%) after administration of morphine (50 mg/kg; s.c.) on the test day for evaluating the development of morphine tolerance and (B) number of jumping induced by naloxone on the test day for assessing the occurrence of dependence in morphine-treated mice. Results were expressed as mean ±SEM for 8–12 mice.

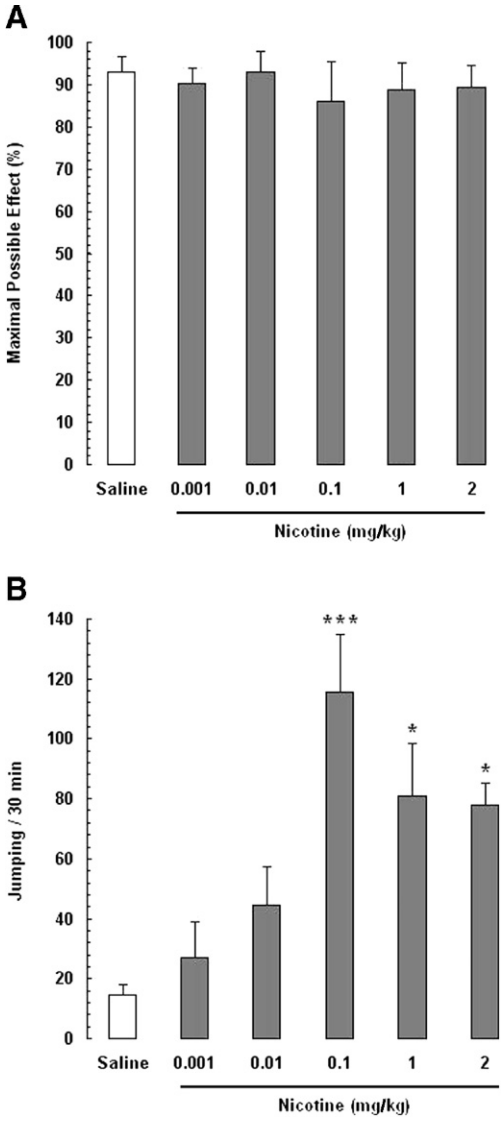

Fig. 5. (A) the average of maximal possible effect (MPE%) after administration of morphine (50 mg/kg; s.c.) on the test day for evaluating the development of morphine tolerance and (B) number of jumping induced by naloxone on the test day for assessing the occurrence of dependence following administration of different doses of nicotine or saline three times daily for 3 days. Each group had 9–12 mice. Results were expressed as mean ±SEM. *$P<0.05$, ***$P<0.001$ compared with saline group.

treated groups and saline-treated mice [$F(5,68)=0.2212$, $P=0.9521$]. On the other hand, naloxone (5 mg/kg; i.p.) injection 2 h after morphine (50 mg/kg; s.c.) administration on the fourth day following 3 days of solely nicotine treatment produced significant increase in the number of jumps per mouse during the abstinence syndrome in comparison with that of the saline group [$F(5,57)=8.285$, $P<0.0001$]. Subsequent Tukey's multiple comparison showed that naloxone could precipitate significant withdrawal jumping behaviour in groups received nicotine treatment at the doses of 0.1 mg/kg ($P<0.001$), 1 mg/kg ($P<0.05$) and 2 mg/kg ($P<0.05$). Fig. 5B shows that 0.1 mg/kg nicotine was the most effective dose regarding the number of jumping following naloxone administration splitting the graph to a biphasic profile.

4. Discussion

The present study demonstrated that concurrent administration of nicotine and morphine attenuates the process of the development of tolerance to morphine in a dose dependent manner while there was apparently no report regarding the influence of nicotine on the development of morphine tolerance. We also showed that nicotine, when administered 15 min before each morphine injection during the induction of dependence attenuates the development of morphine dependence in a biphasic profile (V-shape manner). In the present study, nicotine at the dose of 0.1 mg/kg was remarkably effective in reducing the incidence of withdrawal jumping in morphine-dependent mice. The results show that nicotinic receptor mechanism(s) may be involved in the suppressive action of nicotine. Interactions between nicotinic receptors and activation of endogenous opioid peptides, including enkephalins (Eiden et al., 1984; Houdi et al., 1991) and β-endorphin (Rosecrans et al., 1985) were observed in previous studies. Nicotine may stimulate the release of these peptides, with overactivation of opioid receptors as a result (Malin et al., 1993, 1994). It could be deduced that nicotine suppresses withdrawal jumping by such a mechanism (Zarrindast and Farzin, 1996).

Our present study also showed that the central nicotinic receptor antagonist mecamylamine, but not the peripheral nicotinic receptor antagonist hexamethonium, nor muscarinic receptor antagonist atropine, dose-dependently antagonized both the inhibition of withdrawal jumping as well as increase of TFL produced by repeated nicotine administration. This indicates the involvement of central nicotinic receptor but excludes the involvement of peripheral nicotinic receptor and muscarinic receptor in the attenuation of both morphine dependence and tolerance induced by repeated nicotine administration. Several studies demonstrated that nicotine increases release of acetylcholine in the brain (Balfour, 1982; Nordberg et al., 1989), suggesting that nicotine can directly and indirectly stimulate nicotinic receptors (Zarrindast and Farzin, 1996). Other studies also revealed that acetylcholine receptor agonists inhibit but antagonists potentiate withdrawal jumping in morphine-dependent mice (Jhamandas and Dickinson, 1973; Jhamandas et al., 1973; Brase et al., 1974).

Zarrindast and Farzin (1996) previously investigated the effect of single nicotine injection on naloxone-induced jumping behavior in morphine-dependent mice. They showed that single nicotine administration 15 min before naloxone injection remarkably reduced the incidence of withdrawal jumping in morphine-dependent mice in a dose-dependent manner. Nevertheless, our results showed that concurrent administration of nicotine with morphine attenuates the process of the development of morphine dependence in a biphasic (V-shape) profile. On the other hand, as shown in Fig. 5B, demonstrating cross-dependence, repeated administration of solely nicotine for 3 days resulted in naloxone-precipitated withdrawal jumping behavior in an inverse V-shape profile manner with the highest number of jumping at the dose of 0.1 mg/kg. This biphasic profile resulted from nicotine treatment can be explained by the involvement of dopaminergic system in nicotine effects. It has been shown that the activation of nicotinic receptors to be

involved in stimulating the release of dopamine from the striatum and the limbic system (Goodman, 1974; Balfour, 1982; Imperato et al., 1986). Additionally, Zarrindast and Farzin (1996) showed that a selective D_1 receptor antagonist SCH 23390 decreased the effect of nicotine on withdrawal jumping behavior induced by naloxone. Alternatively, Gomaa et al. (1989) reported that the dopamine D_2 receptor agonist, bromocriptine potentiates morphine withdrawal signs. Also, it has been shown that the dopamine D_1 and D_2 receptors bring about opposite influences on morphine antinociception (Zarrindast and Moghaddampour, 1989). Regarding these lines of evidence, it seems that nicotine, at low doses (0.001-0.1 mg/kg; Fig. 1B), indirectly causes the inhibition of jumping through dopamine D_1 receptor stimulation in a dose-dependent manner. However, in 1 and 2 mg/kg doses of nicotine, D_1 and D_2 receptors may both account for nicotine effects but in opposing direction. Therefore, despite the increase in nicotine dose, attenuation of naloxone-induced withdrawal jumping was decreased. On the other hand, Simons et al. (2005) suggested that both nicotinic and μ-opioid receptors are involved in nicotine-induced antinociception. Furthermore, Bhargava and Saha (2001) showed that pretreatment with mecamylamine decreased the analgesic effect of morphine and concluded that nicotinic cholinergic receptors are involved in morphine-induced antinociception. With respect to aforementioned lines of evidence since (i) there is a cross-dependence between nicotine and morphine treatment in mice (ii) the profile of naloxone-induced withdrawal jumping in solely nicotine-treated mice mirrors the profile of the nicotine-induced attenuation of withdrawal jumping in morphine-dependent mice (iii) μ-opioid receptor is involved in nicotine-induced antinociception, and (iv) nicotinic cholinergic receptor is involved in morphine-induced antinociception, it can be implied that nicotine and morphine, in part, use a common mechanism of action. We propose that nicotine is likely to act as a partial agonist agent at receptor(s) involved in pain modulatory pathway where morphine exerts its effect, because it attenuates the development of morphine dependence but it causes per se significant withdrawal jumping in a mirroring profile.

However, mechanisms other than discussed may be involved. For instance, Concas et al. (2006) showed that nicotine and morphine share the ability to induce marked changes in the brain and plasma concentrations of neurosteroids either after acute administration or during withdrawal from chronic treatment. Repeated exposure to nicotine or morphine resulted in the development of tolerance to the steroidogenic effects of the respective drug. They concluded that changes in neurosteroid concentrations mediated by activation of the hypothalamic–pituitary–adrenal (HPA) axis may both contribute to the early acquisition phase of nicotine or morphine addiction and serve to counteract the anxiety-like behavior associated with nicotine or morphine withdrawal. Similar opioid-cholinergic interactions have been suggested to be involved in nicotine induced antinociception and nicotine withdrawal syndrome (Biala et al., 2005) as well.

On the other hand, we found that concurrent administration of nicotine and morphine during the method previously described by Marshall and Grahame-Smith to render mice dependent on morphine, significantly attenuates the development of tolerance to analgesic effect of morphine in a dose-dependent manner, as measured by tail flick response to noxious heat stimulus. This effect of nicotine may be mediated by a nicotine-induced upregulation of μ-opioid receptor since Wewers et al. (1999) demonstrated that chronic administration of nicotine is accompanied by an upregulation of μ-opioid receptor in the striatum of rats. In addition, Walters et al. (2005) showed that phosphorylation of CREB and upregulation of functional μ-opioid receptors are required for nicotine conditioned reward. Indeed, it has been shown that not only rewarding effect of nicotine is absent in mice lacking μ-opioid receptor (Berrendero et al., 2002) but also nicotine-mediated increases in phosphorylation of CREB is absent in these mice (Walters et al., 2005). So it is possible that nicotine attenuates morphine tolerance through increase in CREB phosphorylation as it has been suggested that lower propensity of fentanyl to produce tolerance is due to sequential activation of CREB and the binding of CREB and CREB binding protein to the promoter of μ-opioid receptor gene (Lee and Lee, 2003). Nonetheless, it is not known whether other mechanisms are involved or not. For instance, it has been shown that acute intraperitoneal administration of nicotine (0.3-2 mg /kg) or morphine (5–30 mg/kg) produced dose- and time-dependent increases in the cerebrocortical and plasma concentrations of pregnenolone, progesterone, and allopregnanolone and the effects of both drugs were abolished by adrenalectomy–orchiectomy (Concas et al., 2006). So it may be implied that nicotine attenuates the development of tolerance to morphine-induced analgesia by involving HPA axis.

At last, repeated nicotine administration attenuated morphine tolerance in a dose-dependent manner but morphine dependence in a biphasic profile (V-shape) manner. This may be other evidence supporting the hypothesis that mechanisms involved in the development of tolerance and dependence are separated. Finally, the highest effect of naloxone in attenuating the withdrawal jumping achieved by 0.1 mg/kg dose of nicotine and neither higher doses nor lower doses. Roughly, this amount of nicotine dose is representative of human smoking (Wewers et al., 1999). Therefore, it may be correlated to the fact that most smokers use fairly this range of cigarette smoking and may be related to dopaminergic D_1 and D_2 receptors.

Acknowledgements

The authors would like to thank Dr. Salar Fallahian and Mrs. Tooka Aavani for their comments and editing our manuscript. This study was supported by the Neuroscience Research Center, Shaheed Beheshti Medical University, Tehran, Iran.

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