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COMPARISON OF ACUTE AND CHRONIC EFFECTS OF NIFEDIPINE ON NALOXONE-PRECIPITATED MORPHINE WITHDRAWAL IN MICE

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ABSTRACT

Mice were rendered tolerant and dependent to morphine by subcutaneous injection of morphine over a period of 5 days. The effects of acute and chronic administration of dihydropyridine calcium channel antagonist nifedipine on the development of tolerance and naloxone-precipitated morphine withdrawal signs were investigated. A single injection of nifedipine proved to be effective in inhibiting some signs of morphine withdrawal but ineffective in blocking the development of tolerance to the ataxic action of morphine. The concurrent injections of nifedipine with morphine prevented most signs of morphine withdrawal but failed to have any effects on the development of tolerance to the ataxic action of morphine. The results suggest that alterations in dihydropyridine-sensitive calcium channels may be involved in the adaptations that occur on chronic treatment with morphine. It is also possible to conclude that separate mechanisms are involved in the development of tolerance and dependence.
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Keywords: Nifedipine; morphine withdrawal; tolerance.

INTRODUCTION

Drug addiction is one of the world's major health problems, with large direct health costs as well as massive indirect costs to society in terms of crime, loss of earnings and productivity, and social damage. Attempts to understand the mechanisms underlying drug addiction have focused on the phenomena of drug dependence, tolerance and sensitization. Drug dependence is defined as the need for continued drug exposure to avoid a withdrawal syndrome, which is characterized by physical or motivational disturbances when the drug is withdrawn. The occurrence of this syndrome in man is one of the causes of continued addiction to opiate drugs. Despite the existence of a large body of information on the subject, the mechanisms of opiate tolerance and dependence are not yet fully understood.

The molecular basis for the acute action of opiates is established as being via interaction with a family of receptors (μ, γ, κ, ε, δ) of which the μ-receptor is probably mainly responsible for the actions of morphine and the other abused opiate drugs.[1,2] The mechanisms by which μ and other opiate receptors produce their cellular effects is not yet fully known, but there is abundant evidence that neuronal calcium channels can be modulated by the action of opiates on their receptors. Opiates have been shown to have predominant inhibitory effects on

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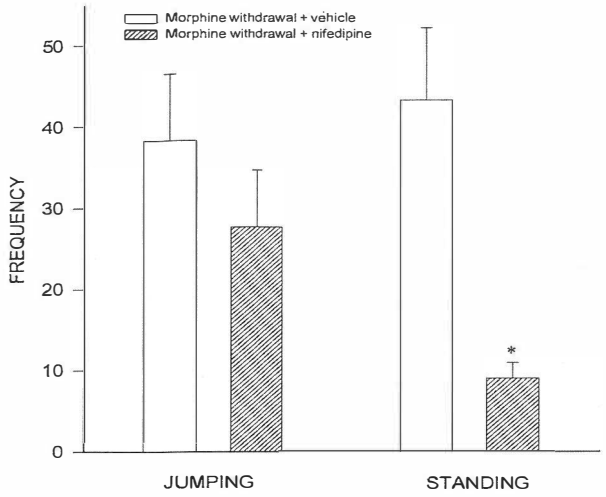

Fig. 1. Effect of acute nifedipine on naloxone-precipitated withdrawal jumps and stands in morphine-dependent mice. Chronic morphine was given in increasing doses (from 15 to 90 mg/kg) over a period of 5 days as described in *METHODS*. Nifedipine was injected in a single dose (10 mg/kg) 1 h after the last dose of morphine (1 h before naloxone injection). The withdrawal was precipitated by naloxone (5 mg/kg), withdrawal signs were observed for 30 min. Bars illustrate mean jumping frequencies (± S.E.M.) of 6 mice. * $p<0.05$, comparison between nifedipine and vehicle controls using one-way ANOVA followed Newman-Keuls post-hoc comparison.

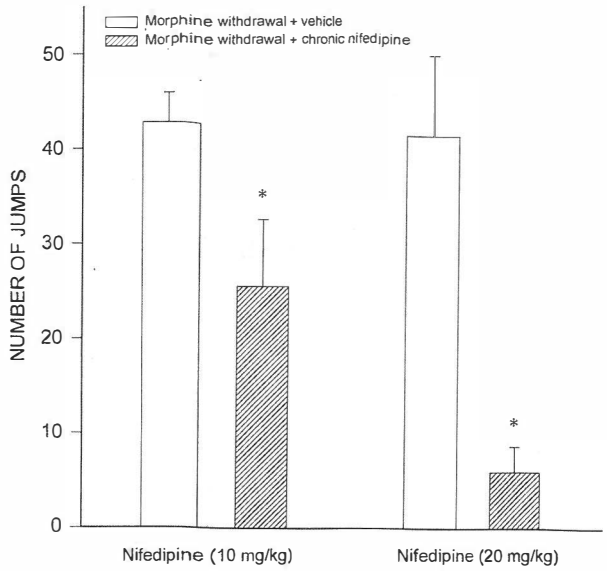

Fig. 2. Effects of chronic nifedipine treatment on naloxone-precipitated withdrawal jump in morphine-dependent mice. Morphine was given in increasing doses (from 15 to 90 mg/kg) over a period of 5 days as described in *METHODS*. Nifedipine (10 and 20 mg/kg) or vehicle injections were given once a day during the morphine treatment, the last injection of nifedipine was given 24 h before the last morphine injection. Separate groups of mice received nifedipine or vehicle injections, but no morphine. The withdrawal was precipitated by naloxone (5 mg/kg), withdrawal signs were observed for 30 min. Bars illustrate mean number of jumps (± S.E.M.) of 6 mice. * $p<0.05$, comparison between nifedipine and vehicle controls using one-way ANOVA followed by Newman-Keuls post-hoc comparison.

calcium entry through voltage-operated calcium channels in various cell lines and tissue preparations.[2,10] All these inhibitory actions underlie the decrease in neurotransmitter release and reduction of cellular excitability produced by opioid through Gi or Go subunit.

There are possibly several adaptive mechanisms that could underlie opiate tolerance and dependence, including changes in cyclic adenosine monophosphate (cAMP) and down-regulation of opiate receptors.[11] However, there is growing evidence indicating that neuronal calcium channels may be important in opiate tolerance and dependence.[12,13] The chronic administration of opiates to laboratory animals has been shown to produce an increase in calcium uptake into various brain preparations.[5,14,15] Consistent with these results, calcium channel blockers have been shown to decrease the magnitude of tolerance and reduce *in vivo* opioid agonist-induced down-regulation of μ-opioid receptors.[16-19] The number of dihydropyridine-sensitive binding sites in the CNS, thought to represent voltage-sensitive calcium channels, was increased in rats showing signs of morphine withdrawal.[20,21] The increase in dihydropyridine-sensitive sites with long-term morphine treatment is likely to be an adaptive response to its acute effects in decreasing calcium influx.

While many changes in neuronal function have been demonstrated to occur after chronic morphine treatment, it has been difficult to show whether or not they are causally related to tolerance and dependence. In the case of changes in neuronal calcium channels, additional evidence has been found, in that prevention of the increase in dihydropyridine-sensitive binding sites also prevented the development of morphine tolerance and withdrawal. Chronic administration of calcium channel antagonists, during morphine injection, prevented the appearance of tolerance to the analgesic effect of morphine and also the increase in the number of dihydropyridine-sensitive binding sites.[19] In addition, acute administration of some calcium channel antagonists before naloxone precipitation completely blocked the abstinence syndrome in morphine-dependent animals.[22-24] Calcium channel blockers have also been shown to increase the acute

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Table I. The effects of acute nifedipine (10 mg/kg) on naloxone-precipitated withdrawal signs in morphine dependent mice.

Treatments	Median behavioural scores				
	Teeth chattering	Hair raising	Sniffing	Fast breathing	Diarrhea
Morphine + Saline	3 (0-3)	3 (3-3)	3 (2-3)	3 (1-3)	2.5 (2-3)
Nifedipine + Morphine	0.5* (0-1)	2* (0-3)	1.5* (1-2)	2 (0-3)	1* (0-2)

Morphine was given in increasing dose (from 15 to 90 mg/kg) over a period of 5 days as described in "*METHODS*". Nifedipine (10 mg/kg) was injected 1 h after the last dose of morphine (1 h before naloxone injection). The withdrawal was precipitated by naloxone (5 mg/kg), withdrawal signs were observed for 30 min. *P<0.05 vs. saline control using one-way ANOVA followed by Dunn's post-hoc comparison. The results are the median scores for withdrawal signs (± interquartile ranges in parenthesis).

antinociceptive potency of morphine.[22,25-28] These results show a critical role of the L-type voltage-sensitive calcium channels in the development of tolerance and dependence to morphine.

In the current study we compared the acute and chronic effects of nifedipine on naloxone-precipitated withdrawal signs in mice.

MATERIAL AND METHODS

Animals

Male TO mice (Pasteur, Tehran) weighing 25-30 g were housed in a cage with controlled room temperature of 22-25 degrees. Food and water were available *ad libitum*. Tests were performed only after the mice had acclimated to the above environment for at least 7 days. All experiments were carried out between 09:00 and 13:00 h., except for the injections of morphine, which was carried out between 08:00 and 18:00. Each animal was used for only one experimental condition.

Drugs

Morphine sulfate (TEMAD, Iran), naloxone hydrochloride (TEMAD, Iran) and nifedipine (Norton Health Care, Germany) were dissolved in Tween 20 (0.5% in distilled water). Morphine was administered subcutaneously (s.c.) while naloxone and nifedipine were given intraperitoneally (i.p.) in a constant volume of 10 mL/kg body weight. The control animals received the equivalent volume of vehicle.

Chronic treatment with morphine

Morphine was injected s.c. daily at 08:00 and 18:00. According to the schedule described by Kamei and Ohsawa,[29] the morphine dose was increased progressively from 15 to 90 mg/kg over a period of 5 days, i.e. 1st day (15 and 15 mg/kg at 08:00 and 18:00, respectively), 2nd day (30 and 30), 3rd day (45 and 45), 4th day (60 and 90) and 5th day (90 mg/kg at 18:00 only). The control mice received s.c. vehicle injections. For the induction of tolerance to morphine, mice received a similar chronic treatment with morphine.

Chronic treatment with nifedipine

Nifedipine, (10 mg/kg, i.p.) or vehicle injections were given once a day during the morphine treatment, the last injection of nifedipine was given 24 h before morphine withdrawal so that the effects of the chronic treatment, rather than any acute actions, would be studied. Separate groups of mice received nifedipine or vehicle injections, but no morphine. For acute studies, nifedipine was given 1 h after the last dose of morphine (1 h before naloxone).

Morphine withdrawal

Withdrawal signs were precipitated by injecting naloxone (5 mg/kg, i.p.) 2 h after the final injection of morphine. Immediately after a naloxone injection, the mice were individually placed in an observation box and were observed for 30 min for the occurrence of withdrawal-related behaviors. The signs of withdrawal were evaluated either by scoring the intensity of the signs from 0 to 3 points (teeth chattering, hair raising, sniffing, fast breathing and diarrhea) or by counting the number of events (jumping and standing).

Tolerance to morphine was assessed at 24 h after the cessation of chronic morphine treatment (see above). The ataxic effects were measured using a rotating rod with a rotation speed of 4.5 rpm. Injections of morphine were given, and the mice were placed on the rotating rod at 15

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min intervals and the time spent on the rod measured. The doses of morphine used in the rotorod test were chosen on the basis of prior experiments to almost, but not completely, prevent the ability of the naive mice to stay on the rotating rod. Tolerance to this action would therefore be seen easily. A maximum time of 180 s was allowed.

Statistics

Data from counted signs were assessed by one-way analysis of variance (ANOVA), and if significance was detected, post-hoc comparison test (Newman-Keuls) was performed. Qualitative scores were analyzed with Kruskal-Wallis one-way ANOVA followed by the Dunn's test for post-hoc comparisons. In all comparisons, $p< 0.05$ was considered significant.

RESULTS

Morphine-dependence and naloxone challenge

In chronically treated mice, naloxone administration precipitated the standard behavioral signs of withdrawal (jumping, standing, teeth chattering, hair raising, sniffing, fast breathing and diarrhea) in morphine-treated animals and did not trigger behavioral changes in saline-injected control groups.

Effects of acute nifedipine in morphine withdrawal

The effects of acute nifedipine (10 mg/kg) on various signs of withdrawal are illustrated in Fig. 1 and Table I. Nifedipine significantly decreased the number of standings, hair raising and diarrhea in morphine-dependent mice ($p<0.01$, compared with morphine alone) but had no effects on other signs of withdrawal. In saline-injected control groups, the injection of nifedipine did not trigger any behavioural changes (data not shown).

Effects of chronic nifedipine in morphine withdrawal

When nifedipine (20 mg/kg) was given concurrently with morphine it significantly reduced the following sings of withdrawal: jumping, standing, teeth chattering, sniffing, and fast breathing (Fig. 3 and Table II; $p<0.05$ compared with vehicle-treated animals). Nifedipine at lower dose of 10 mg/kg was also effective in reducing most of the signs of withdrawal (Fig. 2).

Effects of chronic nifedipine on morphine tolerance

Mice receiving chronic treatment with morphine showed maximal ataxic effects on day 1. However, the animals developed tolerance to the ataxic effects of morphine on day 3 and this effect was further increased on day 5. Chronic nifedipine treatment (10 mg/kg, once daily) had no significant effects on the development of tolerance to the action of morphine in the rotarod test (Fig. 4).

DISCUSSION

Chronic administration of opiates usually results in physical dependence as measured by the appearance of withdrawal symptoms after cessation of the drug, or when an opiate antagonist is delivered. In the present study the schedule of chronic morphine treatment produced tolerance and physical dependence which was exhibited by various qualitative (teeth chattering, hair raising, sniffing, fast breathing and diarrhea) and quantitative (jumping and standing) signs, after injection of naloxone.

In the naloxone-precipitated withdrawal study, a single injection of nifedipine (20 mg/kg) 1 h after the last morphine injection (1h before naloxone) significantly reduced the withdrawal-induced standings, hair raising and diarrhea. Co-administration of nifedipine (10 or 20 mg/kg) during chronic morphine treatment, proved to be

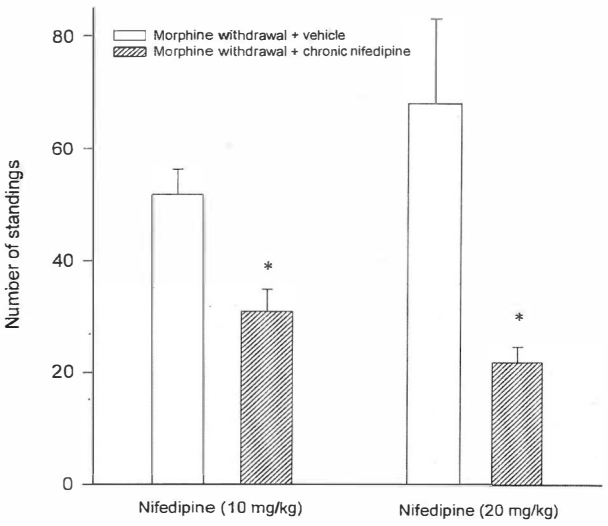

Fig. 3. Effects of chronic nifedipine (10 and 20 mg/kg) on naloxone-precipitated withdrawal stands in naive (control) and morphine-dependent mice. Morphine was given in increasing doses (from 15 to 90 mg/kg) over a period of 5 days as described in *METHODS*. Nifedipine or vehicle injections were given once a day during the morphine treatment, the last injection of nifedipine was given 24 h before the last morphine injection. Separate groups of mice received nifedipine or vehicle injections, but no morphine. The withdrawal was precipitated by naloxone (5 mg/kg), withdrawal signs were observed for 30 min. Bars illustrate mean number of stands (± S.E.M.) of 6 mice. * $p<0.05$, comparison between nifedipine and vehicle controls using one-way ANOVA followed by Newman-Keuls post-hoc comparison.

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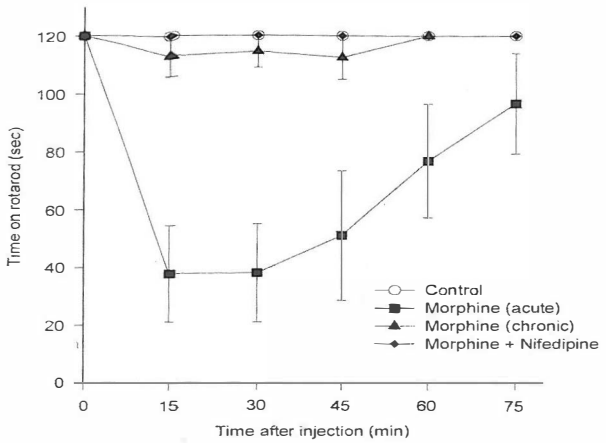

Fig. 4. Effects of chronic nifedipine treatment (10 mg/kg) on the development of tolerance in mice treated chronically with morphine. Morphine was given in increasing doses (from 15 to 90 mg/kg) over a period of 5 days as described in *METHODS*. Nifedipine or vehicle injections were given once a day during the morphine treatment, the last injection of nifedipine was given 24 h before the last morphine injection. Data are the mean and S.E.M. of 6 mice.

more effective than the single injection in preventing the morphine withdrawal syndrome in mice. The chronic effect of nifedipine on morphine withdrawal syndrome was unlikely to be due to its presence in the brain, as nifedipine treatment was stopped 24 hours before the test. The doses of nifedipine required to affect the morphine withdrawal syndrome were lower than those which were required for the cardiovascular actions of this compound.

The explanation for the effects of nifedipine may lie in the involvement of calcium channels in various actions of opiates. Opioid drugs have acute actions in blocking calcium channels, as well as activating potassium channels, and these effects are thought to contribute to their central actions.[30] Chronic administration of morphine and other opioid agonists has been shown by several groups to produce an increase in brain calcium concentration as well as increase in the number of dihydropyridine binding sites in membranes prepared with dissected brain regions.[31] Recent data has shown that concurrent calcium channel antagonist administration with morphine prevents the naloxone-induced upregulation of [^{3}H]nitrendipine binding sites.[19] In addition, acute administration of different types of calcium antagonists given before naloxone precipitation has been shown to completely block the abstinence syndrome in morphine-dependent rats.[19] The prevention of both increased Bmax and the abstinence syndrome in morphine-dependent animals suggests that the increase in calcium channel number could be an important adaptation mechanism for counteracting the decrease in intraneuronal calcium caused by morphine.

In the present study the chronic administration of nifedipine failed to inhibit the development of tolerance to the ataxic effects of morphine. Previous data concerning the effects of calcium antagonists on the development of tolerance to opiate drugs have been contradictory. For example, Contreras et al. (1993) showed that

Table II. The effects of chronic nifedipine treatment on naloxone-precipitated withdrawal signs in morphine dependent mice.

Treatments	Median behavioural scores				
	Teeth chattering	Hair Raising	Sniffing	Fast Breathing	Diarrhea
Morphine + Saline	3	3	3	3	2
	2-3	3-3	3-3	1-3	0-3
Morphine +Nifedipine	0.5*	1*	2*	1*	2
(10mg/kg)	0-1	0-3	2-3	0-3	1-2
Morphine+Nifedipine	1.5*	3	1.5*	1*	1
(25mg/kg)	1-3	1-3	1-2	0-2	0-2

Morphine was given in increasing dose (from 15 to 90 mg/kg) over a period of 5 days as described in "*METHODS*". Nifedipine, (10 or 25 mg/kg) or vehicle injections were given once a day during the morphine treatment, the last injection of nifedipine was given 24 h before the morphine withdrawal. Separate groups of mice received nifedipine or vehicle injections, but no morphine. The withdrawal was precipitated by naloxone (5 mg/kg), withdrawal signs were observed for 30 min. *$p<0.05$ vs. saline control using one-way ANOVA followed by Dunn's post-hoc comparison. The results are the median scores for withdrawal signs (± interquartile ranges in parenthesis).

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the acute tolerance to morphine, which is seen 30 h after the first dose, was decreased by co-administration of flunarizine, nifedipine or verapamil with morphine. Diltiazem was also tested in this study but did not significantly alter the tolerance. Decreased development of tolerance to other opiate drugs has been reported with calcium channel antagonists. Tolerance to the antinociceptive and the respiratory depressant effects of sufentanil was decreased when nimodipine was given concurrently.[18,32] More recently Michaluk et al (1998) demonstrated that in rats, in which morphine injection was proceeded by calcium channel antagonists nifedipine and verapamil, no tolerance appeared at the end of the experiment. In contrast, nimodipine in the study of these authors did not prevent the development of tolerance. In their previous studies, Antkiewicz-Michaluk et al. (1990) investigated the effects of concurrent chronic treatment with nifedipine on the development of morphine tolerance and withdrawal signs. Although no clear effect of the nifedipine was seen in this study on the tolerance development, no signs of abstinence were seen in rats treated with morphine plus nifedipine, while rats given morphine alone showed the characteristic withdrawal signs. Quantification of the withdrawal severity by counting head shakes indicated a significant decrease when nifedipine was given. Nifedipine has a shorter duration of action, and is removed from the body within 4h from acute injection, so it is unlikely that the decrease in withdrawal signs was due to acute action of residual dihydropyridine; this was further supported by the lack of effect of nifedipine on the action of morphine when the opiate was given 24 h after dihydropyridine. The effect of nifedipine may therefore have been on the adaptive mechanisms responsible for the withdrawal signs.

In conclusion, the present study demonstrated that both acute and chronic nifedipine injections could prevent the signs of morphine withdrawal although not to the same extent. These results provide additional evidence to support the involvement of calcium channels in the adaptive mechanisms responsible for the withdrawal signs. Nifedipine in current dose seems to be ineffective in affecting the tolerance to the ataxic effects of morphine suggesting a different mechanism of action for the development of tolerance and dependence to morphine. Further studies with various doses of nifedipine could provide further clues for the exact effects of this drug.

ACKNOWLEDGEMENT

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