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European Journal of Pharmacology 467 (2003) 145–150
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L-type Ca^{2+} channel blockers inhibit the development but not the expression of sensitization to morphine in mice

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Received 24 October 2002; received in revised form 3 March 2003; accepted 5 March 2003

Abstract

The relationship between opioid actions and L-type Ca^{2+} channel blockers has been well documented. However, there is no report relevant to L-type Ca^{2+} channel blockers and morphine sensitization, which is suggested to be an analog of behaviors that are characteristic of drug addiction. We now studied systematically the effects of three L-type Ca^{2+} channel blockers, nimodipine, nifedipine and verapamil, on morphine-induced locomotor activity, the development and the expression of sensitization to morphine. The results showed that both nimodipine and verapamil attenuated, while nifedipine had only a tendency to decrease morphine-induced locomotor activity. All three drugs inhibited the development of sensitization to morphine. However, none of them showed any effects on the expression of morphine sensitization. These results indicate that blocking L-type Ca^{2+} channel attenuates the locomotor-stimulating effects of morphine and inhibits the development but not the expression of morphine sensitization.

Keywords: Morphine; Locomotor activity; Behavioral sensitization; Nifedipine; Nimodipine; Verapamil

1. Introduction

Attention has been increasingly directed to locomotion sensitization, a phenomenon that takes place on chronic administration of psychostimulants or opioids, such as cocaine, amphetamine and morphine (Robinson and Berridge, 2000). Sensitization to morphine can be sustained for several months even after cessation of drug administration and is thought to serve as a useful animal model of plasticity and neuroadaptation associated with repeated administration of opioids that have abuse potential (Ikemoto et al., 2000). Recent studies show that sensitization has a close relationship with relapse, compulsive drug-seeking and drug-taking behavior (De-Vries et al., 1998; Kalivas et al., 1998; Robinson and Berridge, 1993, 2000). In the incentive-sensitization theory of addiction, it seems that sensitization plays an important role in compulsive drug-seeking behavior and relapse (Robinson and Berridge, 1993, 2000). Studies of drug self-administration provided evidence further supporting this theory. Prior exposure to cocaine and amphetamine, resulting in locomotion sensitization, promotes drug self-administration (Lorrain et al., 2000). Three types of stimuli: low doses of the drug itself, stress or cues previously paired with drug administration, which can produce reinstatement of self-administration, also elicit or strongly modulate the expression of locomotion sensitization (Li et al., 2000; Robinson et al., 1998). Therefore, investigation of sensitization may help us to better understand the relapse mechanisms and provide new strategies for the treatment of drug addiction.

Ca^{2+} is an important second messenger in the central nervous system (CNS) (Okita et al., 2000). Abundant evidence indicates a close relationship between opioid action and intracellular Ca^{2+} level in the CNS. Ca^{2+} chelators (i.e. EGTA and EDTA) or Ca^{2+} channel blockers such as verapamil, diltiazem and dihydropyridine-type drugs, which are suggested to decrease intracellular Ca^{2+}, potentiate opioid antinociception (Antkiewicz-Michaluk et al., 1993; Michaluk et al., 1998). In fact, electrophysiological studies have suggested that opioid receptors are functionally coupled to voltage-sensitive neuronal Ca^{2+} channels, and that the effects of opioids involve reductions in Ca^{2+} conductance (North, 1986). Chronic administration of opioids up-regu-

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0014-2999/03/$ - see front matter © 2003 Elsevier Science B.V. All rights reserved.
doi:10.1016/S0014-2999(03)01567-X

lates dihydropyridine-sensitive binding sites in the brain (Antkiewicz-Michaluk et al., 1994; Zharkovsky et al., 1993). In humans, Ca^{2+} channel blockers enhance opioid analgesia in cancer patients and surgical patients without concomitant respiratory depression or enhancement of the rewarding properties of opioids (Hoffmeister and Tettenborn, 1986; Santillan et al., 1998; Smith et al., 1999; Vaupel et al., 1993). Moreover, Ca^{2+} channel blockers have also been shown to prevent the development of opioid tolerance and to attenuate the signs of physical dependence in animals (Michaluk et al., 1998; Baeyens et al., 1987). Early reports show that L-type Ca^{2+} channel blockers attenuate morphine-induced locomotor activity (Martin et al., 1990; Pavone et al., 1992). These findings raise the possibility that blocking L-type Ca^{2+} channels may also affect the development and the expression of locomotion sensitization to morphine. However, to the best of our knowledge, little research has been done on the interaction of L-type Ca^{2+} channel blockers and morphine sensitization. Therefore, the present study was designed to investigate systematically the effects of L-type Ca^{2+} channel blockers on morphine-induced locomotor activity, the development and expression of sensitization to morphine.

2. Materials and methods

2.1. Methods of handling mice

Kunming mice, initially weighing 18–22 g, were purchased from the experimental animal center of Peking University. The animals were fed ad libitum and were group-housed in a room with a controlled ambient temperature (22 ± 2 °C), humidity ($50 \pm 10\%$), and a 12-h light/dark cycle (light on 08:00 to 20:00). Animals were acclimated to the housing conditions and handled for 3–4 days before experiments. All experiments were performed during daytime. The experimental procedures were approved by the local Committee on Animal Care and Use.

2.2. Drugs and chemicals

Morphine hydrochloride was purchased from Qinghai Pharmaceutical Manufactory (China). Nifedipine and verapamil were purchased from Sigma (St. Louis, MO, USA). Nimodipine was kindly provided by Tianjin Central Pharmaceutical Manufactory (China). Nifedipine and nimodipine were suspended, using ultrasound, in 1% Tween 80. Verapamil and morphine were dissolved in saline. All drugs were administered intraperitoneally (i.p.), in a volume of 0.1 ml/10 g.

2.3. Locomotor activity

Locomotor activity was counted automatically with a Small Animal Locomotion Recording Apparatus (Shandong Academy of Medical Sciences, China), which consisted of four boxes and in each box there was one pyroelectric infrared sensor 4 cm above the floor. The sensor could detect the movements of the mice through infrared radiation. The apparatus recorded only the gross movements of the mice, whereas small movements such as gnawing or grooming could not be counted.

2.4. Experimental protocols

2.4.1. Experiment 1. The acute effects of morphine on locomotion in mice

In this experiment, mice were put into the test boxes immediately after receiving (i.p.) morphine. Locomotor counts were recorded every 10 min for 130 min.

2.4.2. Experiment 2. Effects of acute and chronic administration of nimodipine, nifedipine and verapamil on locomotor activity in mice

Mice were given nimodipine, nifedipine or verapamil 30 min before saline for five consecutive days. On day 1 and day 5, 20 min after the injection of saline, the mice were put into the test boxes and locomotor activity was monitored for 60 min. After 3 days' withdrawal from drugs, all animals were challenged with saline on day 8 and 20 min after the injection, locomotor activity was monitored for 60 min.

2.4.3. Experiment 3. Effects of nifedipine, nimodipine and verapamil on morphine-induced locomotor activity

Mice were given nifedipine, nimodipine, verapamil or vehicle (1% Tween 80 or saline) 30 min before morphine. The animals were put into the test boxes 20 min after the last injection and locomotor counts were recorded for 60 min.

2.4.4. Experiment 4. Effects of nimodipine, nifedipine and verapamil on the development of morphine sensitization

Mice were given nimodipine, nifedipine or verapamil 30 min before 10 mg/kg morphine or saline for five continuous days. After 3 days' withdrawal from drugs, all animals were challenged with 10 mg/kg morphine on day 8. Then, 20 min after the injection, the mice were put into the test boxes and locomotor counts were recorded for 60 min.

2.4.5. Experiment 5. Effects of nimodipine, nifedipine and verapamil on the expression of morphine sensitization

Mice were injected with 10 mg/kg morphine for five continuous days to induce morphine sensitization. After 3 days free from morphine, all animals were treated with one of the drug pairs as follows: vehicle + morphine, nimodipine (5, 10, 20 mg/kg) + morphine, nifedipine (7.5, 15, 30 mg/kg) + morphine or verapamil (7.5, 15, 30 mg/kg) + morphine (the interval between the two injections was 30 min). The challenge dose of morphine was 10 mg/kg. Then, 20 min after the morphine injection, animals were put into the test boxes to record locomotor activity for 60 min.

2.5. Statistics

The data are expressed as means ± S.E.M. In experiment 1, locomotor activity was analyzed using two-factor repeated measure analysis of variance (ANOVA) for time block and treatment. Post hoc comparisons were performed using Turkey's test. For the other experiments, one-way ANOVA and post hoc Turkey's test for multiple comparisons at a minimum significance level of $P<0.05$ were applied.

3. Results

3.1. Locomotor activity induced by morphine in mice

Mice were given saline, 5 or 10 mg/kg morphine and then locomotor activity was monitored for 130 min. During the first and second 10 min, all mice displayed high levels of locomotor activity and there was no difference between the saline-treated and morphine-treated group. This was due to the exploring behavior of the mice, and the psychomotor effects of morphine were not obvious. However, 30 min later, the locomotion of saline-treated mice kept decreasing while that of the 10 mg/kg morphine group kept increasing and this increase was significant (F(treatment)(2, 28) = 14.125, $P<0.001$, F(treatment × time)(24, 336) = 4.333, $P<0.001$). The climax of morphine-induced hyperactivity appeared about 1 h after the morphine injection and began to decay thereafter. The psychomotor effects of 10 mg/kg morphine lasted more than 2 h, and 5 mg/kg morphine increased locomotor activity only at some time points (Fig. 1). Therefore, 10 mg/kg morphine was used to induce hyperactivity in subsequent experiments.

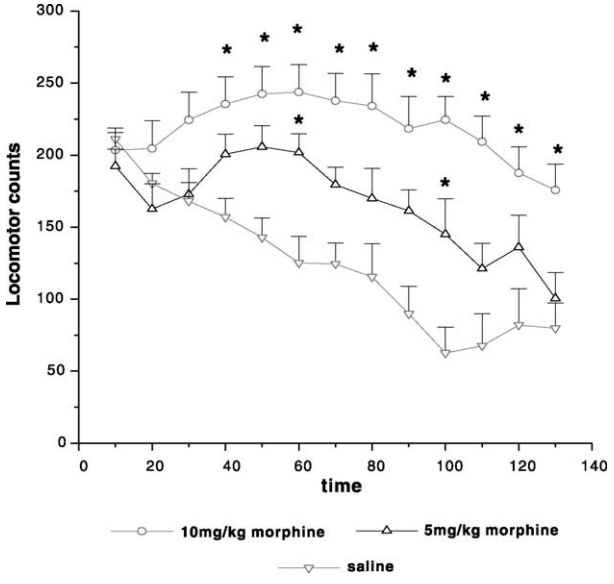

Fig. 1. Locomotor activity induced by morphine in mice. Mice were put into the test boxes immediately after an injection of either saline (0.1 ml/10 g, i.p.) or morphine (5 or 10 mg/kg, i.p.), and activity was monitored for 130 min. Data are expressed as means ± S.E.M. per 10-min interval ($n=10-11$ per group). *$P<0.05$, compared with the corresponding saline-treated group.

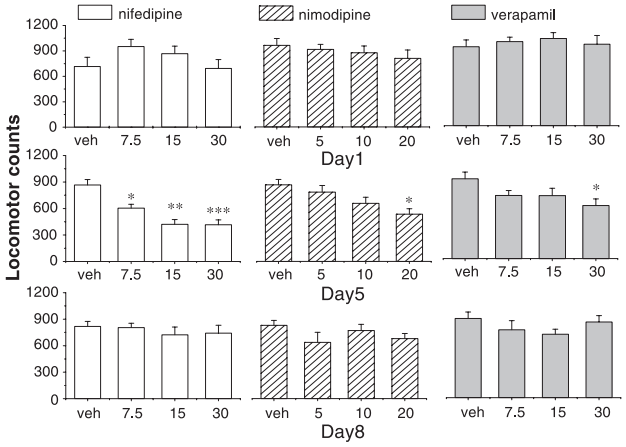

Fig. 2. Effects of acute and repeated treatment with nifedipine, nimodipine or verapamil on locomotor activity in mice. Mice were given nimodipine, nifedipine or verapamil 30 min before saline for five consecutive days. On day 1 and day 5, 20 min after the injection of saline, the mice were put into the test boxes and activity was recorded for 60 min. After 3 days' withdrawal from drugs, all animals were challenged with saline on day 8 and 20 min after the injection, locomotor activity was monitored for 60 min. Data are expressed as the means ± S.E.M. ($n=10-12$ per group). *$P<0.05$, compared with the vehicle group.

3.2. Effects of acute and repeated treatment with Ca^{2+} channel blockers on locomotor activity in mice

As shown in Fig. 2, on day 1, acute treatment with nifedipine (7.5, 15, 30 mg/kg), nimodipine (5, 10, 20 mg/kg) or verapamil (7.5, 15, 30 mg/kg) had no effects on locomotor activity in mice ($F(3,38)=1.641$, $P>0.05$, $F(3,38)=1.485$, $P>0.05$ and $F(3,44)=0.291$, $P>0.05$, respectively). However, repeated treatment with all of them decreased locomotor activity significantly when tested on day 5 ($F(3,40)=4.695$, $P<0.01$, $F(3,40)=15.550$, $P<0.001$ and $F(3,38)=3.637$, $P<0.05$, respectively). After three drug-free days and when challenged with saline on day 8, the groups pretreated with Ca^{2+} channel blockers showed the same locomotor activity as the groups pretreated with the vehicles ($F(3,40)=0.420$, $P>0.05$, $F(3,40)=1.299$, $P>0.05$ and $F(3,38)=1.127$, $P>0.05$, respectively).

3.3. Effects of nimodipine and nifedipine and verapamil on morphine-induced locomotor activity

Pretreatment with nimodipine (5, 10, 20 mg/kg) and verapamil (7.5, 15, 30 mg/kg) dose dependently attenuated the hyperactivity induced by 10 mg/kg morphine ($F(3,36)=2.999$, $P<0.05$, $F(3,42)=3.116$, $P<0.05$, respectively), while nifedipine (7.5, 15, 30 mg/kg) tended to decrease the hyperactivity induced by morphine but significance was not attained in comparison with the vehicle group ($F(3,36)=0.846$, $P=0.478$) (Fig. 3A,B,C).

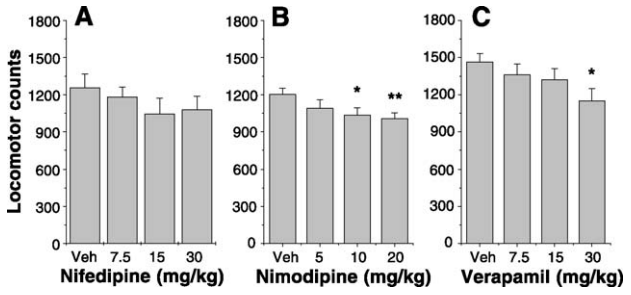

Fig. 3. Effects of nifedipine (A), nimodipine (B) and verapamil (C) on morphine-induced locomotor activity. Nifedipine, nimodipine or verapamil was injected 30 min before morphine administration. The animals were put into the test boxes 20 min later and locomotor activity was recorded for 60 min. Veh: vehicle group, treated with vehicle before morphine administration. Data are expressed as means ± S.E.M. ($n = 10–12$ per group). *$P < 0.05$, and **$P < 0.01$, compared with the vehicle group.

3.4. Effects of nimodipine, nifedipine and verapamil on the development of morphine sensitization

The psychomotor effect of morphine was significantly enhanced in mice pretreated with morphine (5 × 10 mg/kg, i.p.), 3 days after cessation of treatment (Fig. 4A,B,C). Co-administration of nifedipine (15, 30 mg/kg), nimodipine (20 mg/kg) or verapamil (30 mg/kg) inhibited the development of morphine sensitization significantly ($F(4,45) = 3.862$, $P < 0.01$, $F(4,92) = 5.742$, $P < 0.001$, $F(4,55) = 4.108$, $P < 0.01$, respectively).

3.5. Effects of nimodipine, nifedipine and verapamil on the expression of morphine sensitization

To induce sensitization to morphine, the mice were given morphine as above (5 × 10 mg/kg, i.p.). Three days after cessation of treatment, the mice were challenged with 10 mg/kg morphine. Our protocol can induce morphine sensitization in mice compared with the vehicle group ($P < 0.05$) (Fig. 5A,B,C). Treatment with nimodipine (5, 10, 20 mg/kg), nifedipine (7.5, 15, 30 mg/kg) or verapamil (7.5, 15, 30 mg/kg) before the challenge dose of morphine had no effect on the expression of morphine sensitization ($F(4,45) = 5.686$, $P < 0.01$, $F(4,45) = 8.018$, $P < 0.001$, $F(4,53) = 2.798$, $P < 0.05$, respectively) (Fig. 5A,B,C).

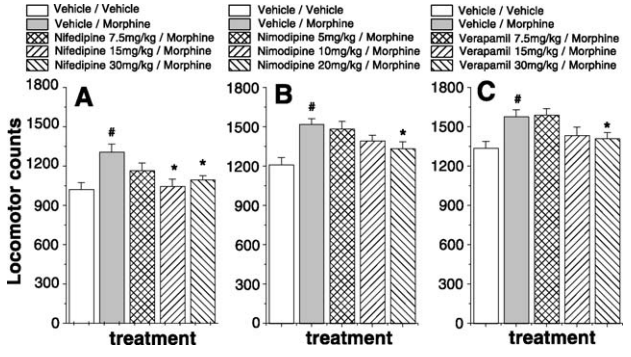

Fig. 4. Effects of nifedipine (A), nimodipine (B) and verapamil (C) on the development of morphine sensitization. From day 1 to day 5, the mice were given one of the drug pairs as follows: vehicle/vehicle, vehicle/morphine, nifedipine/morphine, nimodipine/morphine, verapamil/morphine. After cessation of drugs for 3 days, all animals were challenged with 10 mg/kg morphine on day 8 and 20 min after morphine injection, locomotor activity was monitored for 60 min. Data are expressed as the means ± S.E.M. ($n = 10–20$ per group). *$P < 0.05$, compared with vehicle/morphine group. #$P < 0.05$, compared with vehicle/vehicle group.

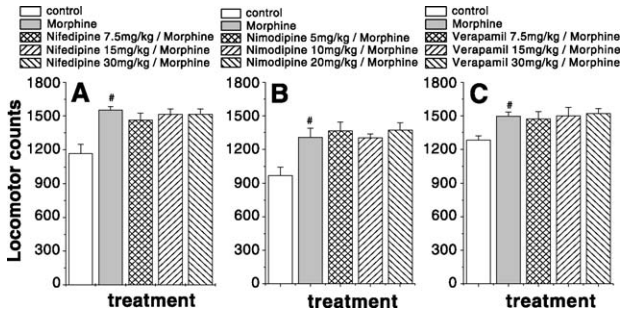

Fig. 5. Effects of nifedipine (A), nimodipine (B), and verapamil (C) on the expression of morphine sensitization. Mice in the control group were given saline and the other mice received 10 mg/kg morphine for 5 days. On day 8, the mice were given vehicle/10 mg/kg morphine or nifedipine/10 mg/kg morphine, nimodipine/10 mg/kg morphine, verapamil/10 mg/kg morphine and, 20 min after the injection, were put into the test boxes for recording of the locomotion counts for 60 min. Data are expressed as means ± S.E.M. ($n = 10–12$ per group). #$P < 0.05$, compared with the control group.

4. Discussion

The present results confirmed early reports about the interaction between L-type Ca^{2+} channel blockers and morphine-induced locomotor activity (Martin et al., 1990; Pavone et al., 1992). Treatment with nimodipine or verapamil prior to morphine resulted in attenuation of the locomotor activating effect of morphine. Pretreatment with nifedipine had a tendency to inhibit morphine-induced hyperactivity. In our experiment, a single dose of nimodipine, nifedipine or verapamil per se had no effect on locomotor activity. These results indicate that blocking the L-type Ca^{2+} channel attenuates the locomotor activating effect of morphine without affecting baseline locomotor activity.

The data shown in Fig. 3 demonstrate that nifedipine, nimodipine or verapamil, inhibited the development of morphine sensitization, suggesting that the L-type Ca^{2+} channel is critically involved in the development of morphine sensitization. In contrast, none of the drugs showed any effect on the expression of morphine sensitization. Further discussion of the possible mechanisms follows.

Morphine (10 mg/kg) (i.p.)-induced locomotor stimulation significantly in mice. This is in agreement with early research (Rethy et al., 1971; Oliverio, 1975). Recent work showed that some Ca^{2+} channel blockers have no influence on psychomotor effects of morphine (Doğrul and Yesilyurt, 1999). The different doses of morphine used may account for this discrepancy. In Doğrul's experiment, a higher dose

of morphine (20 mg/kg) was used to induce hyperactivity in mice, while in our and the other two experiments, only 10 mg/kg was used (Martin et al., 1990; Doğrul and Yesilyurt, 1999; Pavone et al., 1992). In the present study, 30 but not 7.5 mg/kg verapamil attenuated morphine-induced locomotor activity, which had been shown previously (Martin et al., 1990; Doğrul and Yesilyurt, 1999).

The mechanisms through which L-type Ca^{2+} channel blockers attenuate psychomotor effects of morphine have not been elucidated. One possibility may be relevant to mesolimbic dopamine, which is thought to be involved in morphine-induced hyperactivity (Vezina et al., 1987; Kalivas and Duffy, 1987). L-type Ca^{2+} channel blockers have antidopaminergic properties (Pucilowski, 1992). Nimodipine, nifedipine and verapamil, dose dependently antagonize apomorphine-induced yawning and penile erections in rats (Argiolas et al., 1989; Czyrak et al., 1990). In both naive and morphine-abstinent rats, nifedipine inhibits apomorphine-induced hyperactivity (Antkiewicz-Michaluk et al., 1994). Therefore, L-type Ca^{2+} channel blockers may attenuate morphine-induced hyperactivity through an antidopaminergic action. In addition, serotonergic and adrenergic systems may modulate morphine-induced hyperactivity. Co-administration of fluoxetine, a selective serotonin reuptake inhibitor, decreases morphine-induced locomotion (Sills and Fletcher, 1997). Prazosin, an α_1-adrenoceptor antagonist, administered 30 min before morphine, either systemically or locally and bilaterally into the prefrontal cortex, reduces the stimulatory influence of morphine on locomotion (Drouin et al., 2001). The locomotor hyperactivity induced by morphine in mice lacking the alpha1b subtype of adrenergic receptors was greatly decreased when compared with that of wild-type littermates (Drouin et al., 2002). In fact, it has been shown that some Ca^{2+} channel blockers activate serotonergic transmission and antagonize morphine-induced noradrenalin release in the hypothalamus (Gaggi et al., 1993; Martinez-pinero et al., 1993).

Our results showed that co-administration with nifedipine, nimodipine or verapamil inhibited the development of morphine sensitization. Although repeated treatment with Ca^{2+} channel blockers per se (nimodipine, nifedipine and verapamil given for 5 days 30 min prior to saline injections) decreased locomotor activity when tested on day 5, there were no differences in locomotor activity between the groups pretreated with Ca^{2+} channel blockers and the control groups after 3-day cessation of drugs and on challenge with saline on day 8. This means that chronic treatment with Ca^{2+} channel blockers may not affect the locomotor activity on the challenge day. The finding that L-type Ca^{2+} channel blockers inhibit the development of behavioral sensitization is consistent with the results indicating that repeated stimulation of L-type Ca^{2+} channels in the rat ventral tegmental area mimics the initiation of behavioral sensitization to cocaine (Licata et al., 2000). The ventral tegmental area is thought to be critically involved in the development of morphine and psychostimulant sensitization (Trujillo, 2000). Therefore, L-type Ca^{2+} channels may play an important role in the development of behavioral sensitization.

Co-administration with L-type Ca^{2+} channel blockers attenuates the development of morphine tolerance, dependence and sensitization, suggesting that the L-type Ca^{2+} channel may also play a role in morphine-induced neural and behavioral plasticity (Michaluk et al., 1998; Baeyens et al., 1987).

Chronic but not acute administration of morphine increases the density of dihydropyridine binding sites in brain (Antkiewicz-Michaluk et al., 1990), and withdrawal from morphine can further increase it (Zharkovsky et al., 1993). This may not reflect compensation for prolonged inhibition of Ca^{2+} channels by morphine since chronic administration of Ca^{2+} antagonists decreases, instead of increasing, the number of brain dihydropyridine sites (Panza et al., 1985). Co-administration of nimodipine with morphine blocks the increase of cerebral dihydropyridine binding. It is likely that these changes reflect a kind of neural plasticity and concurrent L-type Ca^{2+} channel blockers obstruct this process.

None of nifedipine, nimodipine or verapamil had any effects on the expression of morphine sensitization. This contrasts with L-type Ca^{2+} channel blockers attenuating the morphine-induced hyperactivity and inhibiting the development of morphine sensitization. One possibility is that chronic morphine may alter the density and the function of L-type Ca^{2+} channels as described above. Therefore, nimodipine, nifedipine and verapamil at the doses that formerly decreased morphine-induced locomotor activity had no effect on the expression of morphine sensitization. The other possibility may be that development and expression of morphine sensitization share different mechanisms (Vandershuren and Kalivas, 2000).

In conclusion, the present study confirmed the effects of L-type Ca^{2+} channel blockers on morphine-induced locomotor activity. Based on the evidence that L-type Ca^{2+} channel blockers attenuate the development of morphine tolerance, dependence and sensitization, we suggest that the L-type Ca^{2+} channel is involved in morphine-induced neural and behavioral plasticity. Since the L-type Ca^{2+} channel is functionally changed on chronic administration of morphine, nimodipine, nifedipine and verapamil at the doses that formerly decreased morphine-induced locomotor activity had no effect on the expression of morphine sensitization.

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