Nimodipine is more effective than nifedipine in attenuating morphine tolerance on chronic co-administration in the rat tail-flick test

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Opioids, when co-administered with L-type calcium channel blockers (L-CCBs) show morphine like higher antinociceptive effect. This antinociceptive effect has been further investigated using a different experimental paradigm. The effect of two different L-CCBs (nifedipine and nimodipine) on morphine-induced antinociception was studied by the tail-flick test (40 min after morphine administration) in adult Wistar rats. A fixed-dose of nimodipine or nifedipine (2 mg/kg, once daily) was combined with a fixed dose of morphine (10 mg/kg, twice daily) for 10 days. Co-administration of L-CCBs significantly increased the antinociceptive effect of morphine, even 12 hr after administration. Also, nimodipine was more effective than nifedipine. Nimodipine was further studied using a higher and escalating doses of morphine (20 – 30 mg/kg twice daily for 14 days). Nimodipine increased the antinociceptive effect of morphine in the latter part of the study (days nine to fourteen) though significant difference was observed on 11th evening and 12th morning. No obvious adverse effects were observed in the present study. The results show for the first time that nimodipine is more effective than nifedipine and that these L-CCBs continue to be effective, even 12 hr after administration in the tail-flick test.

Keywords: Ca²⁺ channel blockers, Morphine tolerance, Neuronal plasticity, Nifedipine, Nimodipine

Majority of cancer patients experience moderate to severe pain, particularly during advanced stages of the disease. The World Health Organization (WHO) has developed a three-step ladder for treatment of cancer-related pain. According to this, non-opioids (e.g. acetaminophen, NSAIDs), mild opioids (e.g. dextropropoxyphene) and strong opioids (e.g. morphine or hydromorphone) are prescribed in sequential order till pain is relieved. Unfortunately, opioid administration also produces dose-related side effects like constipation, nausea, dizziness, drowsiness, dry skin and respiratory depression. Moreover, repeated opioid administration leads to tolerance. In order to avoid the side effects with increasing doses of opioid drugs, other (opioid-sparing) drugs are often co-administered with these agents. For example, ketamine, which is an N-methyl, D-aspartate (NMDA) receptor antagonist, has an opioid-sparing effect. In this regard, the therapeutic usefulness of antagonists or blockers of L-type voltage-sensitive calcium ion channels (L-VSCCs) like nimodipine needs to be further evaluated. The rationale for this drug-combination is that morphine produces antinociception by closing N- and P/Q-types of voltage-sensitive calcium channels and additional closure of L-VSCCs could reduce the development of tolerance to its antinociceptive effect.

In a randomized double-blind clinical trial on cancer patients, oral nimodipine (120 mg/day) was noted to significantly reduce the daily requirement of oral morphine. It was emphasized that nimodipine is only effective, when administered in patients already receiving oral morphine for sometime. In fact, this could explain why in an earlier study on patients in the early phase of cancer pain treatment, nimodipine failed to decrease morphine tolerance. Identical findings have been noted in an experimental study on mice where chronic administration but not acute administration of nimodipine, could increase morphine-induced antinociception. Santillan et al. also reported that hypotension was noted in 2 out of 27 patients, who had received nimodipine along with morphine. As the L-type calcium channel blockers (L-CCBs) were developed for treating hypertension, the incidence of hypotension with nimodipine was relatively less (about 8%).

Experimental studies in rodents have also shown attenuation of opioid tolerance/increased antinociceptive effect, when these agents were combined with L-CCBs (Table 1). However,
<table>
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<tr>
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<tr>
<td>Lee and Yoburn, 2000⁷</td>
<td>Morphine (0.5-8.5 mg/kg) dose-response after acute L-CCB administration (acute antinociception)</td>
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<td>Tail-flick test</td>
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<td>Nimodipine (100 mcg/day) by osmotic minipump for 7 days followed 24 h later by morphine dose-response study</td>
<td>Tail-flick test</td>
<td>Significant increase of antinociception (Potentiation)</td>
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<td>Carta et al., 1990⁸</td>
<td>Single dose of 1.25 mg/kg morphine (acute antinociception)</td>
<td>Single dose of nifedipine (2 mg/kg) immediately before morphine administration</td>
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<td>Dierssen et al., 1990⁹</td>
<td>Sufentanil (0.01 to 3 mcg/kg) by subcutaneous route after 15 min of L-CCB (acute antinociception)</td>
<td>Nimodipine 200 mcg/kg</td>
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<td>Dose-response curve shifted to the left indicating significant antinociception</td>
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<td>Co-administration of nimodipine 1 mcg/h by osmotic minipump for 7 days</td>
<td>Tail-flick test</td>
<td>Tolerance developed to sufentanil but its expression was absent as evident by leftward shift of dose-response curve of sufentanil (0.01 to 3 mcg/kg) on 7th day; Potentiation</td>
</tr>
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<td>Antkiewicz-Michaluk et al., 1993¹⁰</td>
<td>Single dose of nifedipine followed after 15 min by morphine 5 - 12.5 mg/kg (acute antinociception)</td>
<td>Nifedipine (5 mg/kg)</td>
<td>Hot-plate test</td>
<td>Significant increase in antinociception</td>
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<td>Morphone 20 mg/kg once daily for 8 days. Each morphine injection was preceded by nifedipine 5 mg/kg (morphine tolerance)</td>
<td>Nifedipine 5 mg/kg once, 15 min before morphine</td>
<td>Hot-plate test, Tolerance evaluated by morphine 12/15 mg/kg on 9th day</td>
<td>Significant decrease in tolerance</td>
</tr>
<tr>
<td>Michaluk et al., 1998¹¹</td>
<td>Nifedipine or nimodipine or verapamil followed 20 min later by morphine 5 – 15 mg/kg once only (acute antinociception)</td>
<td>Nifedipine/nimodipine (5 mg/kg), verapamil (10 mg/kg)</td>
<td>Hot-plate test</td>
<td>Significant increase in antinociception</td>
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<td>L-CCB followed 20 min later by morphine 20 mg/kg for 5 days followed by 30 mg/kg for 3 days (all doses were once daily) (morphine tolerance)</td>
<td>Nimodipine/nifedipine at 5 mg/kg except verapamil 10 mg/kg</td>
<td>Hot-plate test</td>
<td>Tolerance was decreased by nifedipine and verapamil but not nimodipine</td>
</tr>
<tr>
<td>Contreras et al., 1988¹²</td>
<td>Single dose of 200 mg/kg of morphine in an emulsion for 30 h (Morphine tolerance)</td>
<td>Diltiazem (60 mg/kg), Flunarizine, Nifedipine and Verapamil each at 30 mg/kg in divided doses both before and after morphine administration</td>
<td>Hot-plate test (After 5 mg/kg of morphine as test dose at the end of 30 h)</td>
<td>Significant decrease in morphine tolerance by flunarizine, nifedipine verapamil but not diltiazem</td>
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conflicting results have been noted regarding the efficacy of individual L-CCBs like nimodipine. For example, in one such study, nifedipine (5 mg/kg, once daily) and verapamil (10 mg/kg, once daily) but not nimodipine (5 mg/kg, once daily) could significantly decrease morphine tolerance (20 mg/kg once daily for 5 days followed by 30 mg/kg for 3 days). On the contrary, Dierssen et al. reported that continuous nimodipine infusion (1 mcg/h for 7 days) prevented the development of tolerance to sufentanil (2 mcg/hr infusion for 7 days) as well as potentiated the antinociceptive effect of this opioid.

Thus, the objective of the present work is to compare the relative efficacy of two common clinically used L-CCBs, nimodipine and nifedipine in decreasing morphine tolerance after chronic coadministration by using the tail-flick test for analgesic activity, which is supposed to be a reliable predictor of activity of opioid as analgesics.

<table>
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<tr>
<td>Verma et al., 2000</td>
<td>Pentazocine (15 mg/kg) preceded by L-CCB (acute antinociception)</td>
<td>Nimodipine/ verapamil/ diltiazem/ flunarizine each at 20 mg/kg</td>
<td>Formalin test</td>
<td>Significant antinociception in both phases</td>
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<tr>
<td>Verma et al., 2001</td>
<td>Morphine (5 mg/kg) preceded by L-CCB (acute antinociception)</td>
<td>Nimodipine/ verapamil/ diltiazem/ flunarizine each at 20 mg/kg</td>
<td>Formalin test</td>
<td>Significant increase of antinociception at both phases.</td>
</tr>
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<td>Dogrul et al., 2002</td>
<td>Morphine dose-response curve (1, 3, 5 and 10 mg/kg). Preceded by T-type VSCC blocker (acute antinociception)</td>
<td>Miberfradil (10 mg/kg) administration along with morphine</td>
<td>Tail-flick test</td>
<td>Leftward shift of dose-response curve indicating significantly higher antinociception</td>
</tr>
<tr>
<td>Yokoyama et al., 2004</td>
<td>Morphine 3 mg/kg or 10 mg/kg by intraperitoneal injections (acute antinociception)</td>
<td>R-VSCC (CaV2.3) Knockout mice</td>
<td>Tail-flick test/ stress-induced analgesia</td>
<td>Increased antinociception</td>
</tr>
<tr>
<td>Bourinet et al., 2005</td>
<td>Morphine 10 mg/kg once daily intraperitoneal for 6 days (morphine tolerance)</td>
<td>R-type VSCC knockout</td>
<td>Tail-flick test</td>
<td>Tolerance was absent</td>
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<td>-</td>
<td>T-type VSCC (CaV3.2) knockdown in lumbar dorsal root ganglia by intrathecal injection of antisense oligodeoxynucleotide twice daily for four days</td>
<td>Paw pressure and warm-water tail immersion test</td>
<td>Significant increase in latency period of both these tests indicated antinociception in normal and mononeuropathic rats</td>
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Table 1—Summary of some relevant studies on the effect of L-type calcium channel blockers (L-CCBs) on opioid-induced antinociception; Studies on antinociception after intrathecal administration have not been included; references are indicated as superscripts—Contd.
Materials and Methods

Animals— The experiments were conducted on male adult Wistar rats weighing between 200-250 g. These were housed in groups of 2-3 rats per cage and provided food and water ad libitum. 12 hr light/dark cycle was maintained. Prior permission was obtained for the experiment from the Institutional Animal Ethics Committee.

Drugs and its administration— Morphine sulphate injection (15 mg/ml) was obtained from Government approved pharmacy. Nimodipine and nifedipine in powder form were purchased from Sigma, U.S.A and were dissolved in a vehicle containing polyethylene glycol 600, physiological saline and absolute alcohol in a ratio of 2:2:1. Also, since both nimodipine and nifedipine are light sensitive, all procedures involving these chemicals were performed under dim light. Morphine was injected subcutaneously (sc) while nimodipine/nifedipine was injected intraperitoneally (ip). Physiological saline was obtained from the local pharmacist.

Standardization of dose— Before starting the experiment, the doses of morphine and nimodipine were standardized. For this purpose, various doses of morphine (5 and 10 mg/kg, sc), nimodipine (2 and 5 mg/kg, ip) and nifedipine (2 and 5 mg/kg, ip) were injected separately in rats. The corresponding antinociceptive response was noted over a period of 2 hr (unpublished data). As expected, 10 mg/kg of morphine produced a higher antinociceptive response than 5 mg/kg. However, neither of the doses of either nifedipine or nimodipine produced an antinociceptive effect. For further studies, 10 mg/kg of morphine was administered twice daily at a fixed interval of about 12 hr. Tail-flick latency period was determined 40 min after morphine injection, both after the morning and evening injections. In those groups which received morphine + L-CCB, the latter was injected 20 min before the morning dose of morphine. Also, at this dose, neither nimodipine nor nifedipine have been reported to affect the arterial blood pressure, measured from the tail.[12]. The vehicle used to dissolve the L-CCBs were injected ip in a group of rats (n=6). However, no antinociceptive effect was observed (unpublished data).

Antinociception experiments— Antinociception was measured by the tail-flick test[19], using the tail-flick apparatus (from UGO Basile, Italy). The test was done in a temperature-controlled room (22°-25°C). Rats were gently restrained before exposing the distal part of the tail, specifically the junction area between proximal 2/3rd and distal 1/3rd of the tail to radiant heat. The time of flicking of the tail away from the heat source was noted as tail-flick latency period. Rats with a baseline latency of 2-4 sec were selected for the experiment. An upper cut-off limit of 10 sec was maintained to prevent damage to the tail. The latency period values were recorded thrice at every time point and their average was recorded. The average latency period was expressed as percentage of maximum possible effect (MPE%) by using the following formula: post-drug latency-baseline latency/cut-off latency-baseline latency × 100.

Following standardization, rats were divided randomly into 6 groups (Gr I-VI). These groups received physiological saline, morphine (10 mg/kg), morphine (10 mg/kg) + nimodipine (2 mg/kg), morphine (10 mg/kg) + nifedipine (2 mg/kg), nimodipine (2 mg/kg) and nifedipine (2 mg/kg), respectively for 10 days (Table 2). The volume of physiological saline injected in control group was equal to the volume of morphine solution injected in other groups. Groups receiving morphine were administered the drug twice daily at a fixed interval of about 12 hr. Tail-flick latency period was determined 40 min after morphine injection, both after the morning and evening injections. In those groups which received morphine + L-CCB, the latter was injected 20 min before the morning dose of morphine. Those groups receiving only L-CCB were injected in the morning at 0840 hr and tail-flick latency was recorded both in the morning (0940 hr) and evening (2140 hr).

In the next-part of the experiment, morphine was injected at a higher dose: 20 mg/kg for 7 days.

<table>
<thead>
<tr>
<th>Groups</th>
<th>0840 hrs</th>
<th>0900 hrs</th>
<th>2100 hrs</th>
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<tr>
<td>1</td>
<td>Physiological saline</td>
<td>Physiological saline</td>
<td>Physiological saline</td>
</tr>
<tr>
<td>2</td>
<td>Physiological saline</td>
<td>Morphine</td>
<td>Morphine</td>
</tr>
<tr>
<td>3</td>
<td>Nimodipine</td>
<td>Morphine</td>
<td>Morphine</td>
</tr>
<tr>
<td>4</td>
<td>Nifedipine</td>
<td>Morphine</td>
<td>Morphine</td>
</tr>
<tr>
<td>5</td>
<td>Nimodipine</td>
<td>Physiological saline</td>
<td>Physiological saline</td>
</tr>
<tr>
<td>6</td>
<td>Nifedipine</td>
<td>Physiological saline</td>
<td>Physiological saline</td>
</tr>
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followed by 30 mg/kg for the next 7 days, twice a day in a different group of animals. It was combined with nimodipine (2 mg/kg) once daily. All other conditions remained the same as mentioned earlier. Nimodipine was selected because it was more effective in decreasing the tolerance than nifedipine.

Naloxone reversibility—Finally, naloxone (5 mg/kg, ip), which is an antagonist of the mu-opioid receptor, was injected in a separate group of rats, which had earlier received a single dose of morphine + nimodipine. These rats had received 2 mg/kg nimodipine, 20 min before morphine (10 mg/kg) administration. Naloxone was injected after 45 min of morphine administration and tail-flick test was conducted 5 min before and 5 min after naloxone administration. The test was again repeated 15 min after naloxone injection. The purpose of this part of the experiment was to assess whether nimodipine possessed any antinociceptive effect.

Data analysis—Statistical evaluation of data was done by Kruskal-Wallis test followed by Mann-Whitney U-test, using the SPSS software. Significance was set as $P < 0.05$. Values of the tail-flick latency period are expressed as mean ±SE.

Results

Effect of nimodipine and nifedipine on morphine-induced antinociception—The physiological saline treated group did not show any change in pain sensitivity either in the morning or evening. Similarly, both nimodipine and nifedipine, when administered alone in the morning, did not show antinociception (Figs 1 and 2). Morphine alone produced maximum antinociceptive response till morning of day 2. Afterwards, values of latency period gradually decreased to reach baseline values by morning of day 8 ($P<0.05$ between days 1-7 with reference to saline). Tolerance developed more rapidly in the evening (days 1-4 and 6; $P<0.05$). However, on addition of L-CCBs to morphine once per day with morning dose, considerable antinociception was noted. With nimodipine, these values were significantly higher than morphine alone between days 4-10, both in the morning and evening. With nifedipine, the values were higher than morphine alone between days 6-8 in the morning and days 5-6 and 8-9 in the evening. When comparing morphine + nimodipine with morphine + nifedipine, the former showed significantly higher value than the latter on the

Fig. 1—Antinociception expressed as MPE% (maximum possible effect) after the morning dose of saline, morphine, morphine + nimodipine, morphine + nifedipine, nimodipine and nifedipine on different days (1-10) as compared to baseline on day 0. Morphine + nimodipine showed significantly higher antinociception than morphine alone on days 4-10 (indicated by *). Morphine + nifedipine showed significantly higher antinociception on days 6-8 (*). Morphine + nimodipine showed significantly higher antinociception than morphine + nifedipine on day 5 only (**). The number of animals in each group is indicated within brackets. Values of MPE% are expressed as mean ± SE.
morning of day 5 only; otherwise MPE% values were not significantly different from each other. Since the response of morphine + nimodipine was higher than morphine + nifedipine, the former group was taken up for further study.

Naloxone reversibility—Naloxone administration significantly reversed the antinociceptive effect of morphine at 50 and 60 min (Fig. 3). Naloxone also reversed the antinociception due to morphine + nimodipine at both the time periods to a significant extent.

Effect of nimodipine on higher-escalating dose of morphine—Morphine-induced antinociception (20-30 mg/kg) in the morning was significantly higher than saline-treated control between days 1-12 (Figs 4 and 5). However, there was a gradual decline between days 9-14 indicating development of tolerance to morphine. Also, on increasing the dose of morphine to 30 mg/kg from day 8, antinociception did not increase proportionately. This was noted both in the morning and evening. Addition of nimodipine (2 mg/kg) increased the MPE% values between days 9 to 14 in the morning though significantly higher

Fig. 2—Antinociception expressed as MPE% (maximum possible effect) at evening after administration of morphine, morphine + nimodipine, morphine + nifedipine, nimodipine and nifedipine on different days (1-10) as compared to baseline on day 0. L-CCBs were only administered in the morning. Morphine + nimodipine showed significantly higher antinociception than morphine alone on days 4-10 (indicated by *). Morphine + nifedipine showed significantly higher antinociception on days 5-6 and 8-9 (#). Morphine + nimodipine did not show significant difference from morphine + nifedipine at any time point. The number of animals in each group is indicated within brackets. Values of MPE% are expressed as mean ± SE.

Fig. 3—Antinociceptive effect of both morphine and morphine (10 mg/kg) + nimodipine (2 mg/kg) was reversed by naloxone. At 40 min after morphine administration, MPE was 100%. Naloxone (5 mg/kg) was administered at 45 min (depicted by arrow). Tail-flick latency expressed as MPE% was significantly reduced in both morphine and morphine + nimodipine treated groups (indicated by *), both at 50 min and at 1 h. The number of animals in each group is indicated within brackets. The values are expressed as mean ± SE. Baseline values refer to the MPE values before administration of any drug.
Fig. 4—Antinociception expressed as MPE% (maximum possible effect) after the morning dose of saline, morphine (20 mg/kg for 7 days followed by 30 mg/kg for the next 7 days, twice a day), morphine (20 mg/kg for 7 days followed by 30 mg/kg for the next 7 days, twice a day) + nimodipine (2 mg/kg once daily in the morning) on different days (1-14) as compared to baseline on day 0. Values of morphine-treated group was significantly higher than saline between days 1-12 (*). Morphine + nimodipine showed significantly higher antinociception than saline between days 1-12 and 14 (#). Morphine + nimodipine antinociception was significantly higher than morphine on day 12th day (**). The number of animals in each group is indicated within brackets. Values of MPE% are expressed as mean ± SE.

Fig. 5—Antinociception expressed as MPE% (maximum possible effect) in the evening after administration of morphine (20 mg/kg for 7 days followed by 30 mg/kg for the next 7 days, twice a day), morphine (20 mg/kg for 7 days followed by 30 mg/kg for the next 7 days, twice a day) + nimodipine (2 mg/kg once daily in the morning) on different days (1-14) as compared to baseline on day 0. L-CCBs were only administered in the morning. Values for morphine-treated group was significantly higher than saline between days 1-13 (*). Morphine + nimodipine treated group showed significantly higher antinociception than saline between days 1-12 and 14th day (*). Values for morphine + nimodipine were significantly higher than morphine on day 11 (*). Though values of morphine + nimodipine group were lower than morphine group on days 3-8, it was not significantly different ($P > 0.05$). The number of animals in each group is indicated within brackets. Values of MPE% are expressed as mean ± SE. Baseline values refer to the MPE% values on day 0).
antinociception to morphine was noted on the morning of day 12 only. Also, it was significantly higher than saline treated control between days 1-10, 12 and 14.

In the evening, morphine-induced antinociception was significantly higher than control on days 1-13. Morphine + nimodipine-induced antinociception was higher than control between days 1-12 and 14. However, values of morphine + nimodipine was significantly higher than morphine only on day 11. Though morphine + nimodipine group showed lower antinociception than morphine treated group between days 3-8, this difference was not statistically significant.

Discussion

As reported earlier by several authors (Table 1), the present study shows that addition of L-CCBs to morphine significantly decreased the development of tolerance on chronic administration of morphine. The decrease of tolerance was noted even 12 hr after the administration of L-CCBs, in the present study (Figs 1 and 2). This has not been reported earlier to the best of our knowledge. Also, both nimodipine and nifedipine, when administered alone, did not show any significant antinociceptive effect during the 10 day period. The vehicle alone, in which L-CCBs were dissolved, also did not produce any antinociceptive effect. Besides closure of L-VSCCs, co-administration of L-CCBs (diltiazem, verapamil and nimodipine) with morphine have been reported to increase the level of morphine in the serum, which could be due to sharing of common biodegradative pathway (through cytochrome CYP3A) and/or decrease in hepatic blood flow due to hypotension. Hypotension was not a factor in the present study due to selection of a low dose of nimodipine, which probably did not affect mean arterial blood pressure. Peripheral mechanisms like inhibition of calcium channels in peripheral nerves could have also contributed as verapamil has been shown to potentiate morphine analgesia through peripheral mechanisms only.

Among the two L-CCBs, nimodipine appeared to be more effective than nifedipine in attenuating morphine tolerance. Though the exact reason for higher efficacy of morphine + nimodipine is unknown, certain associated findings could prove useful in explaining this discrepancy. Classic L-CCBs having the dihydropyridine structure have been observed to block T-type VSCCs channels as well. An earlier study showed that nimodipine is more effective than nifedipine in blocking these channels. Similarly, nimodipine has been reported to also block N-type VSCCs in comparison to nifedipine, which mainly blocks L-type channels. Again, nimodipine is supposed to be more lipophilic than nifedipine, which could have promoted its entry into CNS through the blood-brain barrier.

Naloxone was able to reverse the combined antinociceptive effect of morphine + nimodipine. This indicated that the higher antinociceptive action of morphine + nimodipine is µ-opioid receptor mediated and closure of L-VSCCs plays a secondary role. Naloxone was administrated at a high dose (5 mg/kg) because it was necessary to block morphine’s interaction with all the three types of opioid receptors (µ, δ and κ). Only then the antinociceptive effect of nimodipine, if any, would be known. No behavioural depressant effect or motor incoordination was noted after injecting either of the L-CCBs in the present study as well as in earlier studies.

Combination of nimodipine with a higher dose of morphine (20 mg/kg followed by 30 mg/kg for 14 days) showed decreased tolerance between days 9th to 14th (Figs 4 and 5). However, significant decrease in comparison to morphine was only seen on the evening of 11th day and the morning of 12th day. In comparison to saline-treated animals, morphine + nimodipine treated group showed significantly higher values on days 1-12th and 14th. Corresponding values for morphine were higher than control on days 1-12th. While these data support the earlier findings in the present work, it also indicates that there are other forms of alterations in intracellular signalling mechanisms, which decrease the antinociceptive effect of morphine on repeated administration. In contrast to the present result, Michaluk et al. had reported that nimodipine (5 mg/kg) was ineffective in decreasing tolerance to morphine. This difference in observation could be due to difference in morphine dosage as well as to the method of pain testing (hot-plate vs tail-flick test).

Among the various VSCCs (L-, N-, P/Q-, R- and T-types), L-type (CaV1) calcium channels are probably the most thoroughly studied. L-type calcium channels are divided into four subgroups - CaV1.1, CaV1.2, CaV1.3 and CaV1.4. Mammalian neurons predominantly express CaV1.2 (about 75%) and CaV1.3 (about 20%) channels, which are located on
the cell membrane of somata and dendrites. Influx of calcium ions through the L-VSCCs activates cytoplasmic signalling molecules that take part in processes like synaptic plasticity and gene expression. Both synaptic plasticity and gene expression are inter-related because long-term changes in the neuron require new gene expression. For example, calcium influx through L-VSCCs leads to activation of calmodulin-dependent protein kinases that phosphorylates a number of downstream targets including CRE (cyclic AMP response element-binding) protein. CREB is constitutively bound to cAMP response elements (CREs) found within many genes. This transcription factor is involved in the transcription of immediate early genes and could be important for formation of long-term memory in the brain. It has been earlier reported that increased CREB activation occurs in the spinal cord after morphine tolerance. Thus, it is possible that L-CCBs used in the present experiment could have delayed the development of morphine tolerance by reducing CREB activation. Presently, we are studying CREB expression in the spinal cord of morphine + nimodipine treated rats in comparison to saline/morphine treated rats.

In conclusion, the results of the present study indicate that co-administration of L-CCBs like nimodipine could decrease morphine tolerance and might prove useful in the treatment of chronic opioid-responsive pain.

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References


