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Antinociception induced by atorvastatin in different pain models

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ABSTRACT

Atorvastatin is a statin that inhibits the 3-hydroxy-methyl-glutaryl coenzyme A (HMG-CoA) reductase. Several landmark clinical trials have demonstrated the beneficial effects of statin therapy for primary and secondary prevention of cardiovascular disease. It is assumed that the beneficial effects of statin therapy are entirely due to cholesterol reduction. Statins have an additional activity (pleiotropic effect) that has been associated to their anti-inflammatory effects. The aim of the present study was to assess the antinociceptive activity of atorvastatin in five animal pain models. The daily administration of 3–100 mg/kg of atorvastatin by oral gavage induced a significant dose-dependent antinociception in the writhing, tail-flick, orofacial formalin and formalin hind paw tests. However, this antinociceptive activity of atorvastatin was detectable only at high concentrations in the hot plate assay. The data obtained in the present study demonstrates the effect of atorvastatin to reduce nociception and inflammation in different animal pain models.

1. Introduction

Statins are a group of drugs that inhibit 3-hydroxy-methyl-glutaryl coenzyme A (HMG-CoA) reductase, the enzyme responsible for the conversion of HMG-CoA to mevalonate, the rate-limiting step in *de novo* cholesterol synthesis (Schachter, 2005) and the treatment of dyslipidemia is the most common use for this type of medications. Several landmark clinical trials have demonstrated the beneficial effects of statins therapy for primary and secondary prevention of cardiovascular disease. Because serum cholesterol level is strongly associated with coronary heart disease, it has been generally presumed that the beneficial effects underlying statins therapy are entirely due to cholesterol reduction. However, the overall benefits observed with statins appear to be greater than merely the expected changes in lipid levels, suggesting effects beyond cholesterol lowering (Greenwood et al., 2006; Liao and Laufs, 2005; Schönbeck and Libby, 2004).

Most of the effects of statins, other than their lipid lowering activity have been correlated with their anti-inflammatory activity (Van der Most et al., 2009). Statins have been recognized as anti-inflammatory drugs since the first clinical observation of pravastatin decreasing the incidence of severe acute rejections, therefore, significantly improving the 1-year survival in heart transplant recipients (Kobashigawa et al., 1995). Statins may affect the function of the immune and inflammatory cells, including natural killer cells, monocytes, macrophages, microglia and T cells (Pannu et al., 2005; Kumar et al., 2010; Wahane and Kumar, 2010). Statins were found to inhibit C-reactive protein which is a major inflammation marker (Taubes, 2002). Moreover, statins inhibit the expression of adhesion molecules, monocytes chemotaxis, and matrix metalloproteinase activity (Ferro et al., 2000). Several reviews in recent years underline the evidence of immune and inflammatory effects of statins (Schönbeck and Libby, 2004; Greenwood et al., 2006; Ghittoni et al., 2007; Dinarello, 2010). Statins are also known to attenuate the secretion of pro-inflammatory cytokine interleukins (IL-1, 2, 4, 5, 10, 12), interferon-γ, and tumor necrosis factor-α (TNF-α), decrease the activity of cyclooxygenase-2 (COX-2), thromboxanes A2, and thromboxanes B2, and enhance the synthesis of prostacyclin which may contribute to decrease platelet activation (Schönbeck and Libby, 2004). Recently, Shi et al. (2011) found that systemic daily administration of statin from days 0 to 14 could completely prevent or reverse the mechanical allodynia and thermal hyperalgesia in neuropathic pain animal. The anti-inflammatory activity of statins is due to the reduction of IL-1β. These findings are very important if they could be translated to clinical studies, since these will open a new avenue for the use of statins in neuropathic pain management (Ray, 2011).

The aim of the present study was to assess the antinociceptive activity of atorvastatin in five animal pain models. Atorvastatin was selected because it is the most prescribed statin, with one of the most favorable safety profiles of these types of drugs available (Youssef et al., 2002).

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2. Material and methods

2.1. Animals

Male CF-1 mice (30 g), housed in a 12 h light–dark cycle at 22 ± 2 °C with *ad libitum* access to food and water were used. Experiments were performed in accordance with current guidelines for the care of laboratory animals and ethical guidelines for investigation of experimental pain, approved by the Animal Care and Use Committee of the Faculty of Medicine, University of Chile. Animals were acclimatized to the laboratory for at least 2 h before testing, each animal was used only once during the protocol and sacrificed immediately after the algesiometric test. The number of animals was kept at a minimum compatible with consistent effects of the drug treatments.

2.2. Writhing test

The procedure that was used has been previously described (Miranda et al., 2002). Mice were treated *per os* (p.o.) daily with saline or atorvastatin for 1 or 3 days before the assays and then injected intraperitoneally (i.p.) with 10 mL/kg of 0.6% acetic acid solution. A writhe is characterized by a wave of contraction of the abdominal musculature followed by the extension of the hind limbs. The number of writhes in a 5 min period was counted, starting 5 min after the acetic acid administration. Antinociception was expressed as an inhibition percentage of the number of writhes observed in control animals (20.4 ± 0.37, n = 22).

2.3. Tail flick test

This algesiometric test was similar to that previously described (Pinardi et al., 2002, 2003). A radiant heat, automatic tail flick algesiometer (U. Basile, Comerio, Italy) was used to measure response latencies. The light beam was focused on the animal's tail about 4 cm away from the tip and the intensity was adjusted so that baseline readings were between 2 and 3 s. An 8 s cut-off time was imposed to avoid damage to the tail. Control reaction time (latency of the response) was recorded twice, with an interval of 15 min between readings; the second reading was similar to the first. Only animals with baseline reaction times between 2 and 3 s were used for the experiments. Tail flick latencies were converted to the % of maximum possible effect (MPE) as follows:

$$\text{MPE\%} = [(\text{postdrug latency} - \text{predrug latency}) \div (\text{cut-off time} - \text{predrug latency})] \times 100.$$

Each animal was used as its own control and treated p.o. daily with saline or atorvastatin for 1 or 3 days before the assays. The dose that produced 50% of antinociception was expressed as MPE (ED_{50}) and was calculated from the linear regression analysis of the curve obtained by plotting log dose versus MPE%.

2.4. Formalin test in the hind paw

The method described by Miranda et al. (2007) was used. To perform the test, 20 μL of 2% formalin solution was injected into the dorsal surface of the mice's right hind paw with a 27-gauge needle attached to a 50 μL Hamilton syringe. Each mouse was immediately returned to the observation chamber. The degree of pain intensity was determined as the total time spent by the animal licking or biting the injected hind paw, measured by visual observation and a digital time-out stopwatch. The test shows two clear cut phases; phase I corresponds to the 5 min period starting immediately after the formalin injection and represents a tonic acute pain due to peripheral nociceptor sensitization and phase II was recorded as the 10 min period starting 20 min after the formalin injection and represents inflammatory pain. Mice were treated *per os* (p.o.) daily with saline (n = 25) or atorvastatin for 1 or 3 days before formalin injection. For each drug, analgesic effects were characterized after the administration of a minimum of four doses in logarithmic increments. The licking times observed were converted to a % of maximum possible effect (MPE) as follows:

$$\text{MPE\%} = 100 - [(100 \times \text{postdrug total licking time}) \div (\text{control total licking time})].$$

The dose that produced 50% of MPE (ED_{50}) was calculated from the linear regression analysis of the curve obtained by plotting log dose versus MPE%.

2.5. Orofacial formalin test

A modification of the method described by Luccarini et al. (2006), was used. To perform the test, 20 μL of 2% formalin solution was injected into the upper right lip of each mouse, with a 27 gauge needle. This formalin solution induced more consistent behavior and the possibility to produce less tissue damage. The mice were immediately returned to the observation chamber. The degree of pain intensity was determined as the total time period that the animal spent rubbing its lip with one of its extremities. Saline or atorvastatin was administered p.o. daily prior to the administration of formalin for 1 or 3 days before the assays. Two distinct phases were identified during the test; phase I corresponds to the 5 min period starting immediately after formalin injection and represents a tonic acute pain due to peripheral nociceptor sensitization. Phase II was recorded as the 10 min period starting 20 min after formalin injection and represents inflammatory pain. Each drug effect was characterized after the administration of at least four doses in logarithmic increments. Maximum possible effect (MPE), which represents antinociception, was calculated as follows:

$$\text{MPE\%} = 100 - [(100 \times \text{postdrug rubbing time}) / (\text{control rubbing time})].$$

The dose that produced 50% of MPE (ED_{50}) was calculated from the linear regression analysis of the curve obtained by plotting log dose vs. MPE%.

2.6. Hot plate

The hot plate test was performed using a modification of the method described by Melendez et al. (2002). In this case, the animals were free to move and the assay temperature was 45 ± 1 °C. The animal behavior considered as a sign of pain was the act of licking the forelegs or jumping off the hot plate. The base line latency for this behavior was recorded with a stop-watch. The cut-off time (T_{off}) was fixed at 30 s to avoid skin damage. Several measurements were performed with a 3 min interval: two at baseline (without any drug) and two after p.o. administration of the test drug.

Hot-plate latencies were converted to a maximum possible effect % (MPE) with the same equation used in the tail-flick assays.

2.7. Protocol

Dose–response curves for atorvastatin were obtained using at least six animals for each of at least four doses. A least squares linear regression analysis of the log dose response curve allowed the calculation of the doses that produced 50% of antinociception for each drug alone.

2.8. Drugs

Atorvastatin was freshly dissolved in saline and administered *per os* (p.o.) in doses of 3, 10, 30 and 100 mg/kg and was donated by Pfizer, New York, USA. Doses were expressed on the basis of the salts.

2.9. Statistical analysis

Results are presented as ED_{50} values ± SEM or with 95% confidence limits (95% CL). The program used to perform statistical procedures was Pharm Tools Pro (version 1.27, The McCary Group Inc., PA, USA). Results were analyzed by Student's test or ANOVA followed by a Student–Newman–Keuls test. P values lower than 0.05 ($P<0.05$) were considered significant.

3. Results

Animals tested with the different doses of atorvastatin did not exhibit significant behavioral or motor dysfunctions.

3.1. Antinociception in the writhing test

The daily p.o. administration for 1 and 3 days of atorvastatin showed dose-dependent antinociceptive effects with different potencies in the writhing test of mice. Fig. 1 contains data showing dose–response curves obtained for 1 and 3 days of treatment with atorvastatin in the test. The ED_{50} values and SEM for the antinociceptive effects of orally administered atorvastatin were not significant after 1 or 3 days of administration and are shown in Table 1.

3.2. Antinociception in the tail flick test

The p.o. daily administration of atorvastatin prior to the tail flick test induced dose-dependent antinociceptive activity as can be seen in Fig. 2. ED_{50}'s for MPE are shown in Table 1. In this assay, there was no significant difference between the antinociceptive activity of atorvastatin after 1 or 3 daily treatments with atorvastatin.

3.3. Antinociception in the orofacial formalin test

The daily p.o. administration of atorvastatin for 1 or 3 days induced a dose-dependent antinociceptive activity during phase I and II of the formalin orofacial assay, see Fig. 3A and B. The corresponding ED_{50}'s for both phases are shown in Table 1. The ED_{50} values of atorvastatin-induced analgesia at 1 or 3 days are significantly different. All these results are displayed in Table 1.

3.4. Antinociception in the formalin hind paw test

The daily p.o. administration for 1 and 3 days of atorvastatin showed dose-dependent antinociceptive effects with different potencies in the formalin hind paw test, both in phase I and phase II. The dose–response curves obtained for 1 and 3 days of treatment with atorvastatin in the test can be seen in Fig. 4A and B. The ED_{50} values and SEM for the antinociceptive effects of orally administered atorvastatin were significant after 1 or 3 days of atorvastatin administration and during phase I and phase II (see Table 1).

Table 1
ED_{50} values (mg/kg ± SEM) for the atorvastatin administration *per os* in the different assays of the mice.

Assay	ED_{50}	
	1 day	3 days
Writhing	11.52 ± 1.96	13.88 ± 3.04
Tail flick	109.31 ± 30.90	106.26 ± 31.34
Orofacial formalin, phase I	25.59 ± 2.74	17.17 ± 2.89*
Orofacial formalin, phase II	28.47 ± 2.25	18.28 ± 2.10*
Formalin hind paw, phase I	69.55 ± 12.77	23.04 ± 6.16*
Formalin hind paw, phase II	25.30 ± 1.46+	8.60 ± 1.57*,+

* $P<0.05$ compared with 1 day.
\+ $P<0.05$ compared with phase I.

3.5. Antinociception in the hot plate assay

The daily p.o. administration for 1 and 3 days of atorvastatin did not show dose-dependent antinociceptive effects in the hot plate test of mice. The results show that at 100 mg/kg dose an MPE of 25.00 ± 2.03% was obtained when the mice were treated for 1 day. During the 3 day treatment the MPE was 13.40 ± 8.28%.

4. Discussion

The daily administration of atorvastatin by oral gavage induced a significant dose-dependent antinociception in the writhing, tail-flick, orofacial formalin and formalin hind paw tests. However, this antinociceptive activity induced by atorvastatin in the hot plate assay was detectable only with high concentrations.

The results obtained in the writhing test are in agreement with previous works (Ghaisas et al., 2010), however the potency of atorvastatin was significantly higher than previously reported. These differences could be explained by the protocol used, either the mice strains, the doses administered, the writhe recording times and prior treatment of the mice. The pain induced by the administration of acetic acid seems to depend on the enhanced levels of prostaglandins in the peritoneal cavity receptors (Bentley et al., 1983). The antinociception induced by atorvastatin suggests the involvement of peripheral mechanism of analgesia.

This study demonstrated that atorvastatin gavage induced dose related antinociception in phase I and phase II of the hind paw formalin test, results differ compared with those of Ghaisas et al. (2010), who found dose-dependent antinociception only in phase II. A

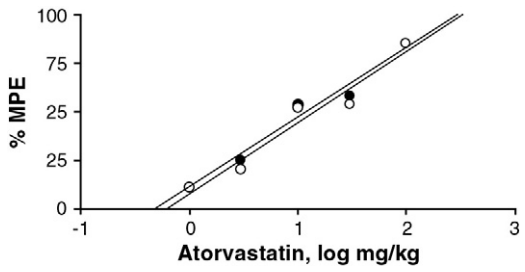

Fig. 1. Dose–effect curves for the antinociceptive activity induced by p.o. administration of atorvastatin, 1 day (●) and 3 days (○), in the writhing test in mice. Each point represents the mean of 6–8 mice. MPE: maximum possible effect %. For clarity of graph the SEM was omitted.

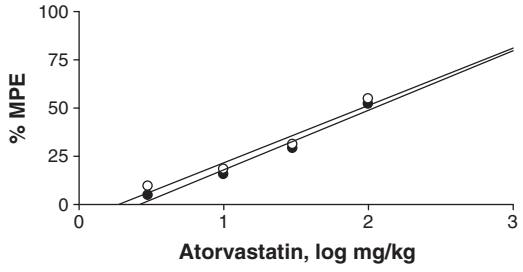

Fig. 2. Dose–effect curves for the antinociceptive activity induced by p.o. administration of atorvastatin, 1 day (●) and 3 days (○), in the tail flick assay in mice. Each point represents the mean of 6–8 mice. MPE: maximum possible effect %. For clarity of graph the SEM was omitted.

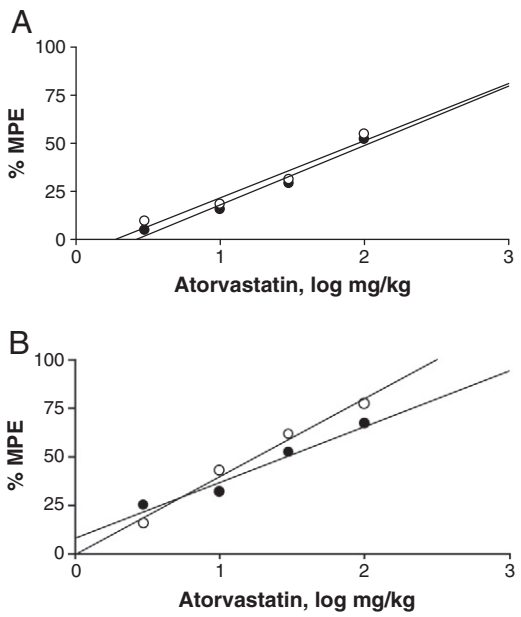

Fig. 3. Dose–effect curves for the antinociceptive activity induced by p.o. administration of atorvastatin, 1 day (●) and 3 days (○), in phase I (panel A) and phase II (panel B) of the formalin orofacial test in mice. Each point represents the mean of 6–8 mice. MPE: maximum possible effect %. For clarity of graph the SEM was omitted.

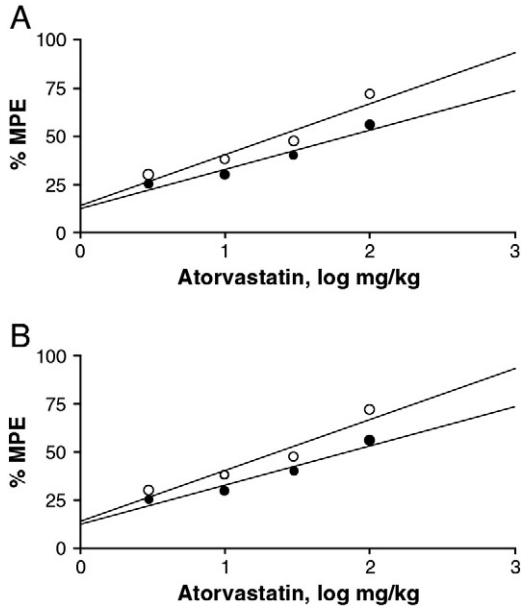

Fig. 4. Dose–effect curves for the antinociceptive activity induced by p.o. administration of atorvastatin, 1 day (●) and 3 days (○), in phase I (panel A) and phase II (panel B) of the formalin hind paw test in mice. Each point represents the mean of 6–8 mice. MPE: maximum possible effect %. For clarity of graph the SEM was omitted.

rational explanation could be the difference in the protocol mice used: strain, time of pre-treatment and dose. The injection of formalin in the hind paw induces nociception by direct stimulation of the nerve fibers representing neuropathic pain in phase I and in phase II, it involves inflammatory pain mediated by prostaglandins, histamine, serotonin, bradykinin and cytokines (Hunskaar and Hole, 1987; Chichorro et al., 2004). The antinociception produced by atorvastatin in this trial represents a reduction of neuropathic pain accompanied by a decrease in the formation of the mediators of inflammation.

In the hot plate test, atorvastatin showed antinociceptive activity only with high doses (100 mg/kg during 1 or 3 days). These results partially agree with previous reports (Ghaisas et al., 2010), which did not demonstrate any significant antinociception with the 1, 3 and 10 mg/kg doses of p.o. atorvastatin after 0, 0.5, 1 and 2 h of administering the atorvastatin. The explanation to this differential effect may be due to the doses and timing of action of atorvastatin.

This is the first study in which the administration of 2% of formalin orofacial solution in the mice's right upper lips was used as an algesiometer test. In this assay, atorvastatin induced a dose-dependent antinociceptive activity both in the phase representing tonic acute pain (phase I) as in that equivalent to inflammatory pain (phase II).

The results of the present study, obtained by oral gavage of the animal with atorvastatin, reveal consistent findings for the antinociception and anti-inflammatory activity of statins in different animal models. This agrees with the conclusion that statins have anti-inflammatory properties regardless of their ability to lower cholesterol (Dinarello, 2010). Further evidence of the anti-inflammatory effects of statins relates to the inhibition of cyclooxygenase-2 expression (Hernández-Presa et al., 2002). Statins also up-regulate the expression and the activity of nitric oxide synthase, explaining the antinociceptive effect of atorvastatin. Furthermore, the antinociceptive effect of atorvastatin may be due to the inhibition of the cytokine and prostaglandin release (Santodomingo-Garzón et al., 2006). The daily p.o. administration of atorvastatin effectively induced antinociception by decreasing local production of pro-inflammatory cytokines and chemokines (Barsante et al., 2005).

Recent studies have demonstrated the antinociceptive effect of atorvastatin in two different models of mechanical inflammatory hypernociception in mice. This antinociceptive effect involves inhibition of cytokine and prostanoid release and stimulation of NO production by constitutive NOS (Santodomingo-Garzón et al., 2006). Furthermore, in another study, atorvastatin and rosuvastatin showed significant anti-inflammatory activity in acute and chronic models of inflammation. Atorvastatin and rosuvastatin also showed antinociceptive activities in acetic acid – and formalin – induced nociception in mice (Ghaisas et al., 2010). Statins are also known to attenuate the secretion of pro-inflammatory cytokine interleukins (IL-1, 2, 4, 5, 10, 12), interferon-γ, and tumor necrosis factor-α (TNF-α), decrease the activity of cyclooxygenase-2 (COX-2), thromboxanes A2, and thromboxanes B2, and enhance the synthesis of prostacyclin which may contribute to decrease platelet activation (Schönbeck and Libby, 2004). Furthermore, the antinociception and antiinflammatory activity of statins are likely attributable to their immunomodulatory effects (Shi et al., 2011).

In conclusion, this study demonstrates the antinociceptive and antiinflammatory effects of atorvastatin in five different animal pain models. These activities could be justified in basis of previous mechanism of action of statins reported, such as inhibition of cyclooxygenase-2 expression, up-regulation of the expression and activity of nitric oxide synthase, inhibition of cytokine and prostaglandin release, their immunomodulatory effects and possible direct antinociceptive action on nociceptors.

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