Pharmacological Reports 70 (2018) 503–508

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Original article

Antinociception induced by rosuvastatin in murine neuropathic pain

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ARTICLE INFO

Article history:
Received 11 August 2017
Received in revised form 11 October 2017
Accepted 21 November 2017
Available online 22 November 2017

Keywords:
Neuropathy
Antinociception
Rosuvastatin
Spinal cord biomarkers

ABSTRACT

Background: Neuropathic pain, and subsequent hypernociception, can be induced in mice by paclitaxel (PTX) administration and partial sciatic nerve ligation (PSNL). Its pharmacotherapy has been a clinical challenge, due to a lack of effective treatment. In two models of mouse neuropathic pain (PTX and PSNL) the antinociception induced by rosuvastatin and the participation of proinflammatory biomarkers, interleukin (IL)- 1β, TBARS and glutathione were evaluated.
Methods: A dose–response curve for rosuvastatin *ip* was obtained on cold plate, hot plate and Von Frey assays. Changes on spinal cord levels of IL-1β, glutathione and lipid peroxidation were measured at 7 and 14 days in PTX and PSNL murine models.
Results: PTX or PSNL were able to induce in mice peripheral neuropathy with hypernociception, either to 7 and 14 days. Rosuvastatin induced a dose dependent antinociception in hot plate, cold plate and Von Frey assays. The increased levels of IL-1β or TBARS induced by pretreatment with PTX or PSNL were reduced by rosuvastatin. The reduction of spinal cord glutathione, by PTX or PSNL, expressed as the ratio GSH/GSSG, were increased significantly in animals pretreated with rosuvastatin. The anti-inflammatory properties of statins could underlie their beneficial effects on neuropathic pain by reduction of proinflammatory biomarkers and activation of glia.
Conclusion: The findings of this study suggest a potential usefulness of rosuvastatin in the treatment of neuropathic pain.

Introduction

Pain is a major public health problem and it has been classified into three major types: nociceptive pain, inflammatory pain and neuropathic pain. The neuropathic pain is defined by the International Association for the Study of Pain (IASP) as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” [1]. The etiology of neuropathic pain is associated to several conditions such as cancer, surgery, diabetes, etc. and characterized by continuous or intermittent spontaneous pain, typically characterized by patients as burning, aching, or shooting. The pain may be provoked by normally innocuous stimuli (allodynia). Neuropathic pain is also commonly associated with increased pain intensity evoked by normally painful stimuli (hyperalgesia). Neuropathic pain can be induced experimentally by different animal models, between them the partial sciatic nerve ligation (PSNL) and the use of paclitaxel (PTX) an antineoplastic agent. Both models have been largely employed to study mechanisms involved in neuropathic pain.

A number of medications (oral or topical) are available for treating neuropathic pain, including gabapentin, pregabalin, carbamazepine, topiramate, valproic acid, duloxetine, venlafaxine, amitriptyline, desipramine, lidocaine. However, the mechanism of action for various drugs varies substantially and in some cases, is not well understood. For example, antiepileptic drugs may target peripheral and/or central sensitization mechanisms involved in neuropathic pain, but the exact mechanisms of action are uncertain. Topical lidocaine, blocks sodium channels, which may stabilize nerve membranes [2].

Statins are a group of drugs used for lowering cholesterol, also have other pleiotropic properties, including neuroprotection and anti-inflammatory action [3]. These substances are either fungal-derived analogs (lovastatin, pravastatin, simvastatin) or fully

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https://doi.org/10.1016/j.pharep.2017.11.012
1734-1140/

synthetic compounds (fluvastatin, cerivastatin, atorvastatin, rosuvastatin). Statins such as rosuvastatin were originally developed for their low-density lipoprotein (LDL) cholesterol-lowering effects but now it has been reported that possesses pleiotropic effects arising from their antioxidant, antinociceptive, anti-inflammatory and antiplatelet properties [4,5].

The aim of the present work was to assess the antinociceptive activity of rosuvastatin using three models of pain: hot plate, cold plate and Von Frey assays and the associated changes of spinal cord biomarkers: IL-β, glutathione and lipid peroxidation in two murine models on induced peripheral neuropathic pain: PTX and PSNL.

Materials and methods

CF-1 male mice, weighing 28–30 g, housed in a 12-h light-dark cycle at 22 ± 1 °C with free access to food and water were used. Animals were acclimatized to the laboratory environment for at least 2 h before use. Experiments were carried out in accordance with Guide for the Care and Use of Laboratory Animals of National Institute of Health and approved by the Institutional Animal Care and Use Committee. Each animal assigned by randomization procedure was used only once, received only one dose of the drugs tested, and testing procedures were conducted on days 7 and 14 after PSNL or PTX. All drugs were freshly prepared by dissolving them in normal saline and administered intraperitoneally *(ip)* in a constant volume of 10 mg/kg, and the doses of different drugs were selected based on previous pilot study. In this study, mice were allocated at random (by chance alone) to receive one or another drug, and the investigators were blind to the drug protocol used. Control saline animals were run interspersed concurrently with the drug-treated animals (at least two mice per group), which prevented all the controls being run on a single group of mice at one time during the experiment. All experiments were performed by researcher blind to drug treatment.

The PSNL developed by Malmberg and Basbaum [6] was used. In this assay, the mice were anaesthetized with 7% of chloral hydrate, the left thigh was shaved, and the sciatic nerve was exposed. Then, the dorsal one-third to one-half of the nerve was loosely ligated with a 7.0 silk suture, and the wound closed. The control mice underwent the exact same procedure without nerve ligation. The chemotherapy induced peripheral neuropathy was induced by the administration of PTX, 6 mg/kg ip once a day for 5 days in a drug saline solution of 10 ml/kg.

Hot plate test

The hot-plate test was performed using an analgesimeter automatic (Ugo Basile, Varese, Italy) according Miranda et al., [7] calibrated at 50 ± 0.2° C and the cut-off time was set at 30 s. The control latency, in s, was 22.10 ± 0.53 (n = 12).

Cold plate test

This test was performed in the analgesimeter automatic of Ugo Basile, Varese, Italy. The temperature was kept 10 ± 0.2 °C., the behavioral responses used to estimate cold responsiveness including licking, rearing, and jumping and the cut-off time was set at 60 s [8]. The control latency, in s, was 33.82 ± 1.74 (n = 12).

Von Frey test

The animals were placed alone in 10 cm diameter cylinders equipped with a metallic mesh floor and the test was performed according to the method previously described [9] in an analgesimeter electronic Von Frey unit (Ugo Basile, Varese, Italy) and the rigid tip of a Von Frey filament (punctate stimulus) was applied to the skin of the midplantar area of the hind paw until it bends. Different filaments, ranging from 0 to 5 g were used and increasing until the animal removed its paw. The measure was repeated 5 times and the final value was obtained by averaging the measures. The control mechanical threshold, in g, was 6.72 ± 0.24 (n = 12).

IL-1β

Spinal cord IL-1β concentrations were determined to the method previously described by Miranda et al., [10]. The results were expressed as IL-1β concentration (pg/mg protein). The control value was 106.40 ± 6.54 (n = 12).

Glutathione

Reduced glutathione (GSH) and oxidized glutathione (GSSG) levels were assayed by fluorometry in spinal cord samples as described by Hissin and Hilf [11] and the GSH/GSSG ratio (control value = 29.5 ± 1.87, n = 12) was calculated as a parameter of medullar redox status.

Lipid peroxidation

Spinal cord lipid peroxidation was assessed by thiobarbituric acid reaction (TBARS) according to Ohkawa et al., [12], at pH 3.5, followed by solvent extraction with a mixture of *n*-butanol/pyridine (15:1, v/v). Tetramethoxypropane was used as the external standard, and the levels of lipid peroxides were detected spectrophotometrically at 532 nm and the results were expressed as nmol/mg protein, with a control values of 13.8 ± 0.75 (n = 12).

Protocols

A dose response curve for *ip* administration of rosuvastatin was obtained using eight animals with at least four doses expressed on the basis of the salt. A least-square linear regression analysis of the log doseresponse curve allows the calculation of the log that produced 50% antinociception (ED_{50}) for rosuvastatin, expressed as a maximum possible effect (MPE). 30 min after ED_{50} rosuvastatin administration (50 mg/kg *ip*), Von Frey, cold plate and hot plate assays and changes of spinal cord levels of IL-1β, glutathione and lipid peroxidation were measured once at 7 and 14 days in the two murine model on induced peripheral neuropathic pain: PSNL and PTX.

Drugs

All drugs were freshly dissolved in saline solution on a constant volume of 10 ml/kg administered *ip* as mg/kg. Rosuvastatin was a gift from Astra Zeneca Laboratories, Chile and Paclitaxel from Fresenius Kabi Chile Ltda.

Statistical analysis

All results are presented as means ± standard error of the means. Analysis of variance (ANOVA) followed by Tukey *post-hoc* test was used to compare the data group. All calculations were performed with the software SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp); p values less than 0.05 ($p < 0.05$) were considered significant.

Results

The pretreatment of mice with PTX (6 mg/kg, *ip*) for 5 days or with PSNL were able to induce a peripheral neuropathy accompanied with hypernociception, either to 7 and 14 days.

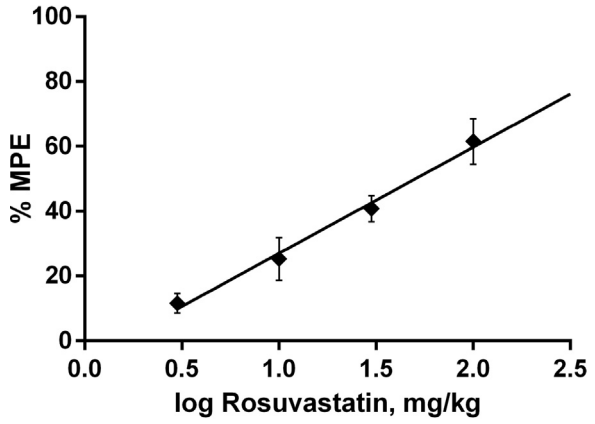

Fig. 1. Dose–response curve for the antinociceptive activity in the hot-plate test of control mice induced by rosuvastatin*via ip*. Each point is the mean ± SEM of six animals. % MPE = percentage of maximum possible effect.

Antinociception induced by rosuvastatin in the hot plate test

In the control mice, the *ip* administration of rosuvastatin at the doses of 3–100 mg/kg, induced a dose dependent antinociceptive activity the hot plate assay, reducing the latency period with an ED_{50} of 50.44 ± 5.68 mg/kg. (see Fig. 1). This ED_{50} was used in all tests.

In mice pretreated with PTX the licking time control (22.10 ± 0.53, n = 12) was reduced significantly on day 7 to 15.42 ± 1.53 (n = 6) s and on day 14 to 14.34 ± 1.71 (n = 6) s. The reduction of licking time by the pretreatment of mice with PTX was reversed by the action of rosuvastatin increasing the licking time to 18.56 ± 1.38 (n = 6) on day 7 and to 21.13 ± 0.91 (n = 6) on day 14.

In mice after PSNL the control licking time (22.10 ± 0.53, n = 12) was reduced significantly on day 7 to 12.57 ± 0.91 (n = 6) sand on day 14 to 15.38 ± 0.63 (n = 6) s. The reduction of control licking of PSNL mice was reversed by rosuvastatin increasing the licking time to 16.23 ± 0.65 (n = 6) on day 7 and to 23.83 ± 1.18 (n = 6) on day 14. All hot plate results are shown in Fig. 2A.

Antinociception induced by rosuvastatin in the cold plate test

In mice pretreated with PTX the control licking time (33.82 ± 1.74, n = 12) was reduced significantly on day 7–19.16 ± 3.07 (n = 6) s and on day 14 to 16.27 ± 1.61 (n = 6) s. The reduction of licking time by the pretreatment of mice with PTX was reversed by the action of rosuvastatin enhancing the licking time to 24.90 ± 1.80 (n = 6) on day 7 and to 33.63 ± 2.72 (n = 6) on day 14.

In mice after PSNL the control licking time (33.82 ± 1.74, n = 12) was reduced significantly on day 7–18.58 ± 2.00 (n = 6) s and on day 14–19.95 1.90 (n = 6) s. The reduction of licking time of PSNL mice was reversed by rosuvastatin increasing the licking time to 24.97 ± 1.80 (n = 6) on day 7 and to 29.93 ± 1.78 (n = 6) on day 14. All the results obtained in the cold plate test are shown in Fig. 2B.

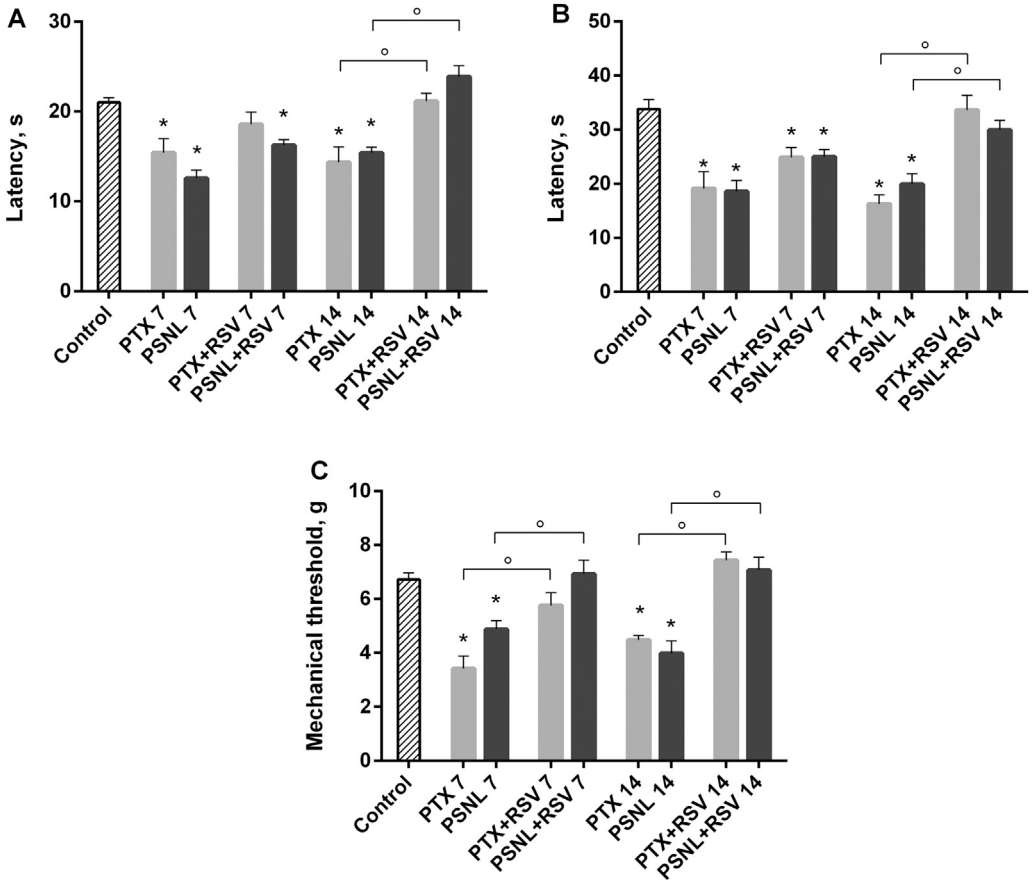

Fig. 2. (A) Dose–response curve for the antinociceptive activity in the hot-plate test in control, PTX and PSNL mice induced by rosuvastatin *via ip* at 7 and 14 days. Each point is the mean ± SEM of six animals. % MPE = percentage of maximum possible effect. (B) Effect of rosuvastatin *ip* in the cold-plate assay in control, PTX and PSNL mice at 7 and 14 days. Data are mean ± SEM of six mice. $^{*}p < 0.05$ *vs.* control; $^{\circ}p < 0.05$ between bars under the same bracket. (C) Effect of rosuvastatin *ip* in the Von Frey test in control, PTX and PSNL mice at 7 and 14 days. Data are mean ± SEM. $^{*}p < 0.05$ *vs.* control; $^{\circ}p < 0.05$ between bars under the same bracket.

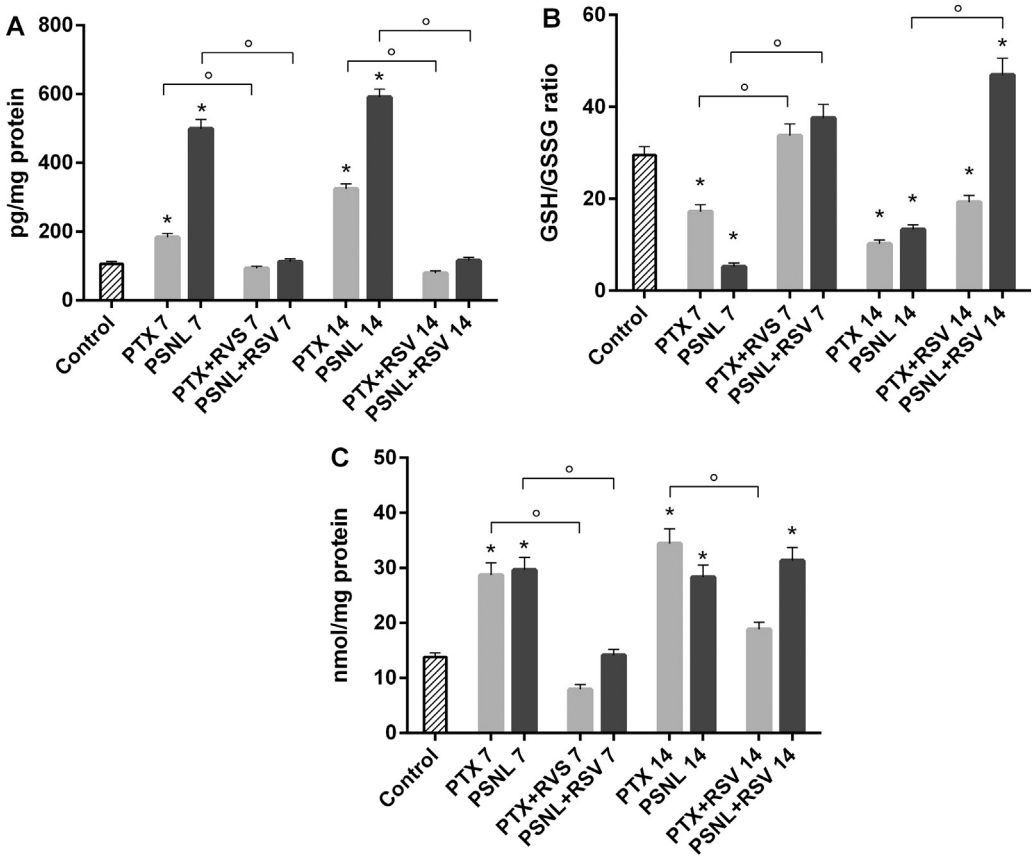

Fig. 3. (A) Effect of rosuvastatin *ip* on the mice spinal cord levels of IL-1β, in control, PTX and PSNL mice, at 7 and 14 days; $^{*}p < 0.05$ *vs.* control; $^{\circ}p < 0.05$ between bars under the same bracket. (B) Effect of rosuvastatin *ip* on the mice spinal cord levels of GSH/GSSG ratio, in control mice, PTX and PSNL mice, at 7 and 14 days; $^{*}p < 0.05$ *vs.* control, $^{\circ}p < 0.05$ between bars under the same bracket. (C) Effect of rosuvastatin *ip* on the mice spinal cord levels of TBARS, in control mice, PTX and PSNL mice, at 7 and 14 days; $^{*}p < 0.05$ *vs.* control, $^{\circ}p < 0.05$ between bars under the same bracket.

Antinociception induced by rosuvastatin in the Von Frey test

In mice pretreated with PTX the control mechanical threshold (6.72 ± 0.24, n = 12) was reduced significantly on day 7 to 3.41 ± 0.46 (n = 6) s and on day 14 to 4.48 ± 0.16 (n = 6) s. The reduction of the mechanical threshold by the pretreatment of mice with PTX was reversed by the action of rosuvastatin enhancing the withdrawal time to 5.76 ± 0.47 (n = 6) on day 7 and to 7.43 ± 0.30 (n = 6) on day 14.

In mice after PSNL the control mechanical threshold (6.72 ± 0.24, n = 12) was reduced significantly on day 7 to 4.87 ± 0.32 (n = 6) s and on day 14 to 3.38 ± 0.46 (n = 6) s. The reduction of the mechanical threshold of PSNL mice was reversed by rosuvastatin increasing the withdrawal time to 6.92 ± 0.57 (n = 6) on day 7 and to 7.06 ± 0.48 (n = 6) on day 14. All these results of Von Frey assay are shown in Fig. 2C.

Rosuvastatin and changes of spinal cord levels of IL-1β

The mice pretreated with PTX the control spinal cord levels of IL-1β (106.40 ± 6.54, n = 12) were significantly increased at 7 and 14 days to 182.80 ± 11.20 (n = 6) and 324.20 ± 14.52 (n = 6), respectively. The increased levels of IL-1β induced by pretreatment of PTX were reduced by the administration of rosuvastatin to 92.68 ± 7.20 (n = 6) on day 7 and to 79.24 ± 6.17 (n = 6) to day 14.

In mice after PSNL the control spinal cord levels of IL-1β (106.40 ± 6.54, n = 12) were significantly increased at 7 and 14 days to 499.00 ± 27.32 (n = 6) and 591.10 ± 23.09 (n = 6), respectively. The increased levels of IL-1β induced by pretreatment of PTX were reduced by the administration of rosuvastatin to 112.30 ± 8.68 (n = 6) on day 7 and to 115.90 ± 9.03 (n = 6) to day 14. The results of IL-1β are shown in Fig. 3A.

Rosuvastatin and changes of spinal cord levels of glutathione

The mice pretreated with PTX, were the control spinal cord ratio GSH/GSSG (29.5 ± 1.87, n = 12) significantly decreased at 7 and 14 days to 17.20 ± 1.51 (n = 6) and 10.20 ± 0.85 (n = 6), respectively. The administration of rosuvastatin reversed the decreased ratio induced by pretreatment of PTX to 33.70 ± 2.61 (n = 6) on day 7 and to 19.25 ± 1.51 (n = 6) to day 14.

In mice after PSNL the control spinal cord ratio GSH/GSSG (29.5 ± 1.87, n = 12) were significantly decreased at 7 and 14 days to 5.24 ± 0.81 (n = 6) and 13.30 ± 1.02 (n = 6), respectively. The administration of rosuvastatin reversed the decreased ratio induced by PSNL pretreatment to 37.60 ± 2.93 (n = 6) on day 7 and to 46.95 ± 3.63 (n = 6) to day 14. All these results of glutathione are shown in Fig. 3B.

Rosuvastatin and changes of spinal cord levels of lipid peroxidation

The mice pretreated with PTX the control spinal cord levels of TBARS (13.8 ± 0.75, n = 12) were significantly increased at 7 and 14 days to 28.70 ± 2.24 (n = 6) and 34.40 ± 2.70 (n = 6), respectively. The increased levels of TBARS induced by pretreatment of PTX

were reduced by the administration of rosuvastatin to 7.90 ± 0.85 (n = 6) on day 7 and to 18.80 ± 1.34 (n = 6) to day 14.

In mice after PSNL the control spinal cord levels of TBARS (13.8 ± 0.75, n = 12) were significantly increased at 7 and 14 days to 29.60 ± 2.28 (n = 6) and 28.30 ± 2.20 (n = 6), respectively. The increased levels of TBARS induced by pretreatment of PTX were reduced by the administration of rosuvastatin to 14.10 ± 1.10 (n = 6) on day 7 and increased to 31.30 ± 2.44 (n = 6) to day 14. This results means that the increase of TBARS in PSNL + RSV was reverted by rosuvastatin only at 7 days, however was maintained at 14 days. TBARS results are shown in Fig. 3C.

Discussion

The results obtained in this study, in which two murine models of neuropathic pain were used, rosuvastatin was shown to induce dose-dependent antinociception associated with changes in biomarkers of inflammation.

Rosuvastatin was able to increase the latency of pain onset in PTX and PSNL treated mice, either in the hot plate and cold plate tests. Moreover, rosuvastatin also increase the mechanical threshold in the Von Frey test in this neuropathic models

Rosuvastatin administration confirms the antinociceptive and anti-inflammatory activities induced by statin in the different types of algesiometer tests. These effects could be related to the inhibition of proinflammatory factors, such as IL-1β, IL-6, IL-10, TNF-α, iNOS, PGE_2 [13–15]. However, the effect of rosuvastatin in the hot plate test differs from a previous study which reports lack of effect in this test due to statins did not act *via* central pain receptors [13]. The lack of concordance between the cited results could due to the different protocols used: temperature of device, time of the measure of reaction.

It has been demonstrated that peripheral neuropathy is a common side effect of PTX administration or PSNL mice, manifested as allodynia or hiperalgesia with direct action on the processing and secretion of proinflammatory mediators, such as IL-1β, TBARS and glutathione [16–21].

The significant increase of highly active proinflammatory cytokine IL-1β induced in PTX and in PSNL mice was reduced by pretreatment with rosuvastatin. This finding supports the antiinflammatory properties described for rosuvastatin related with an attenuated activation of proinflammatory cytokines in the glial cells [22–25].

The spinal cord biomarker glutathione, expressed as the GSH/GSSG ratio significantly decreased at 7 and 14 days, either PTX or PSNL mice, was increased significantly by pretreatment with rosuvastatin, which implies an antioxidative properties of this drug. This effect seem to be independent of HMG-CoA reductase inhibition [26–28].

The significant increase of TBARS in PTX and PSNL mice, was reverted by the administration of rosuvastatin. This finding demonstrates that rosuvastatin exerts antioxidative effects, action seem to be independent of HMG-CoA reductase inhibition, involving a reduction of oxidative stress [26–29].

The findings of the present study demonstrate the antinociceptive and anti-inflammatory properties of rosuvastatin in neuropathic pain, whether of chemical or surgical origin. The anti-inflammatory properties of statins could underlie their beneficial effects on neuropathic pain by reduction of proinflammatory factors (specifically IL-1β, TBARS and glutathione) and the inhibition of glia activation.

In conclusion, the data of this study suggest a potential usefulness of rosuvastatin in the treatment of neuropathic pain. This effect is likely attributable to their immunomodulatory action related to the inhibition of proinflammatory factors.

Conflict of interests

The authors declare no conflicts of interest in this work.

Funding

Partially supported by project UNAB DI-1349-16/R.

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