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Nitridergic Modulation of COX-2 Efficacy

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Abstract

Pain is a common unpleasant sensory and emotional experience, in which are frequently used in their treatment the nonsteroidal anti-inflammatory drugs (NSAIDs). A group of agents with antipyretic, analgesic, and anti-inflammatory properties due to the inhibition of cyclooxygenase enzymes (COXs). Among these drugs there are a group of selective inhibitors of COX-2 named coxib that include to parecoxib, celecoxib, rofecoxib and etoricoxib. Pharmacological information on the mechanism of action of coxibs is insufficient to determine the analgesic and anti-inflammatory efficacy of these agents. There are contradictory reports regarding the antinociceptive effects of the various coxibs at the preclinical level as well as the nitridergic modulation of such actions. The objective of the present study was to evaluate the antinociceptive efficacy of parecoxib, rofecoxib, celecoxib, and etoricoxib using the formalin hind paw assay in mice and the possible contribution of the nitridergic system in the efficacy of COX-2 agents. Antinociception was assessed in a murine formalin assay using dose-response curves to coxibs before and after i.p. administration of 5 mg/kg of L-NAME. Coxibs produced dose-dependent analgesia and anti-inflammation. L-NAME administration reduced the analgesic and anti-inflammatory effectiveness of parecoxib, rofecoxib, celecoxib, and etoricoxib. These findings suggest that the effect of these agents, in addition to COX-2 inhibition, would be mediated by other mechanisms, among which nitridergic modulation would be compromised.

Keywords: Coxib; COX-2; L-NAME; Formalin test; Antinociception

1. Introduction

Pain, either nociceptive or inflammatory, of low to moderate intensity, is frequently treated with nonsteroidal anti-inflammatory drugs (NSAIDs). These drugs constitute a family of chemical compounds that share a main mechanism of action, the inhibition of cyclooxygenase enzymes (COXs) and, consecutively, the inhibition of the synthesis of prostanoids [1]. The prostanoids are involved in the generation of pain, fever, and inflammation, nevertheless, they are also involved in many other physiological processes, such as cardiovascular, reproduction, respiration, gastrointestinal, and renal systems, whose inhibition by NSAIDs leads to known number of side effects. 3 isoforms of COXs have been identified: COX-1, COX-2, and COX-3, activated by different and selective drugs [2]. COX is one of the enzymes that produce inflammatory mediators upon the activation of microglia through the biosynthesis of prostaglandins from

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arachidonic acid. The Inflammatory processes induce the activation of NOS, COXs, NADPH oxidase, caspases, MMPs, prostaglandins, IL-1β, IL-6, TNF-α, and others inflammatory mediators [3-4].

The COX-2 isoform is an inducible isoform of cyclooxygenase and the rate-limiting enzyme in synthesis of prostanoids involved in acute and chronic inflammatory states, without causing gastrointestinal side effects. COX-2 expression is normally restricted to only a few tissues (brain, testis, tracheal epithelia, macula densa of the kidney), but can be rapidly induced during inflammation. Drugs as, meloxicam and nimesulide have been classified as COX-2 preferential, due to their low COX-2/COX-1 ratios. However, coxib agents, with higher ratios, allow them to be classified as COX-2 selective. This group includes rofecoxib and celecoxib, as first-generation specimens, while parecoxib, valdecoxib, and etoricoxib are the second generation. These coxib are up to 800 to 1000 times more selective for COX-2 than for COX-1 [5]. Coxibs are NSAIDs acting as COX-2-specific inhibitor, rapidly expressed in neurons and glial cells of the brain in response to proinflammatory agents. Besides, has been implicated in brain aging and neurodegenerative diseases. Also, in antioxidative ability, mitochondrial properties, in addition to the increase anti-inflammatory and analgesic activity, protect gastric mucosa, maintain renal blood flow, and lack of antiplatelet effects. [6-7].

For the study of pain, different animal models have been implemented that have been essential to evaluate the efficacy of analgesic and anti-inflammatory drugs. Among these tests, used mainly in rodents, are the writhing test, the hot plate, the tail-flick, the formalin test, and others. Formalin administration is a model of inflammatory pain in experimental animals. This method elicits a biphasic pattern of pain behavior, with a phase of acute pain (phase I) followed by a phase of inflammatory pain (phase II) [8].

An important mediator of nociception is nitric oxide (NO), for which there is various experimental and clinical evidence showing that NO has a complex role in the modulation of nociceptive processing both centrally and peripherally. As a non-selective antagonist of the enzyme nitric oxide synthase (NOS), which synthesizes NO, is the L-NG-Nitro arginine methyl ester (L-NAME) has been widely used both preclinically and clinically. In addition to its antagonistic effect, the compound exerts other actions, of which the production of reactive oxygen species (ROS), sympathetic activation and, paradoxically, the increase in NO have been reported [9].

There is limited information on the analgesic and anti-inflammatory efficacy of COX-2 agents in the formalin test, one of the most widely used assays to assess such activity in murine. Therefore, the purpose of this work was to evaluate the antinociceptive efficacy of parecoxib, rofecoxib, celecoxib, and etoricoxib using the formalin hind paw assay in mice and the possible contribution of the nitridergic system in the efficacy of COX-2 agents.

2. Material and methods

2.1. Animals

Male CF-1 mice (25-30 g) from the Central Animal Facility of the Universidad de Chile, Faculty of Medicine were used. Animals were kept under a 12 h light-dark cycle at 22±1 °C with free access to food and water (*ad libitum)*. All animal procedures were performed in accordance to the Ethical Guidelines of the International Association for the Study of Pain and approved by the Animal Care and Use Committee of the Faculty of Medicine. (CBA 0852/FMUCH/2018). The mice were acclimatized to the laboratory for at least 1 h before the test, used only once during the protocol and sacrificed after the algesimeter test with an intraperitoneal injection (i.p.) of 60 mg/kg of pentobarbital. The minimum number of animals needed to establish consistent effects of pharmacological treatment was used.

2.2. Measurement of antinociceptive activity

Antinociception was assessed by the formalin hind paw (FHP) test as described previously [10]. To perform the test 20 µL of 2 % formalin solution were injected into the dorsal surface of the right hind paw. The pain was assessed as the time spent licking or biting the injected paw, expressed in seconds and converted to % MPE. The test shows two phases, each associated to a different type of pain. Phase I spans the first 5 min following the formalin injection and is due to the direct stimulation of nociceptors such as C-fibre and low-threshold mechanoreceptors including the up-regulation of substance P. This phase reflects tonic acute pain. Phase II spans 10 min, starting 20 min after formalin injection and reflects inflammatory pain is related to central sensitization due to the inflammatory phenomena within the dorsal horn neurons including the up-regulation of serotonin, histamine, prostaglandin and bradykinin [8]. The control values for phase I and phase II were 126.40 ± 8.48 sec (n =12) and 155.71 ±10.20 sec (n=12), respectively.

2.3. Experimental design

The antinociceptive activity of COX-2 drugs were evaluated from dose–response curves, the drugs were administered i.p. 30 minutes prior to FHP test. Dose response curves were obtained before and after the i.p. administration of 5 mg/kg of L-NAME using at least 6 animals for each of at least 4 doses. The ED_{50}, dose that induces 50% of the MPE, was calculated from a linear regression of the corresponding dose–response curve.

2.4. Drugs

Drugs were freshly dissolved in sterile physiological saline solution of 10 mL/kg, for i.p. administration. Parecoxib and celecoxib were kindly provided by Pfizer Chile, etoricoxib and rofecoxib by Merck Sharp & Dome, Chile.

2.5. Statistical analyses

Results are presented as means ± standard error of the mean (SEM). The statistical differences between the results were assessed by one-way analyses of variance (ANOVA) followed by Tukey's post-test; p values less than 0.05 ($p<0.05$) were considered to reflect statistically significant differences. Statistical analyses were carried out using the program Pharm Tools Pro, version 1.27, Mc Cary Group Inc., PA, USA.

3. Results

3.1. Antinociception induced by celecoxib and ketorolac

The i.p. administration of parecoxib, rofecoxib, celecoxib and etoricoxib produced a dose related antinociceptive activity in phase I and II of the FHP assays of mice (see Fig.1).

Tested drugs turned out to be more potent in phase I than in phase II of the FHP. Thus, etoricoxib was 3.16-fold, celecoxib was 2.04-fold, rofecoxib was 1.78-fold, and parecoxib was 1.52-fold. This relative potency, expressed as ED_{50}, can be seen in Table 1.

Figure 1. Dose response of parecoxib, rofecoxib, celecoxib and etoricoxib.

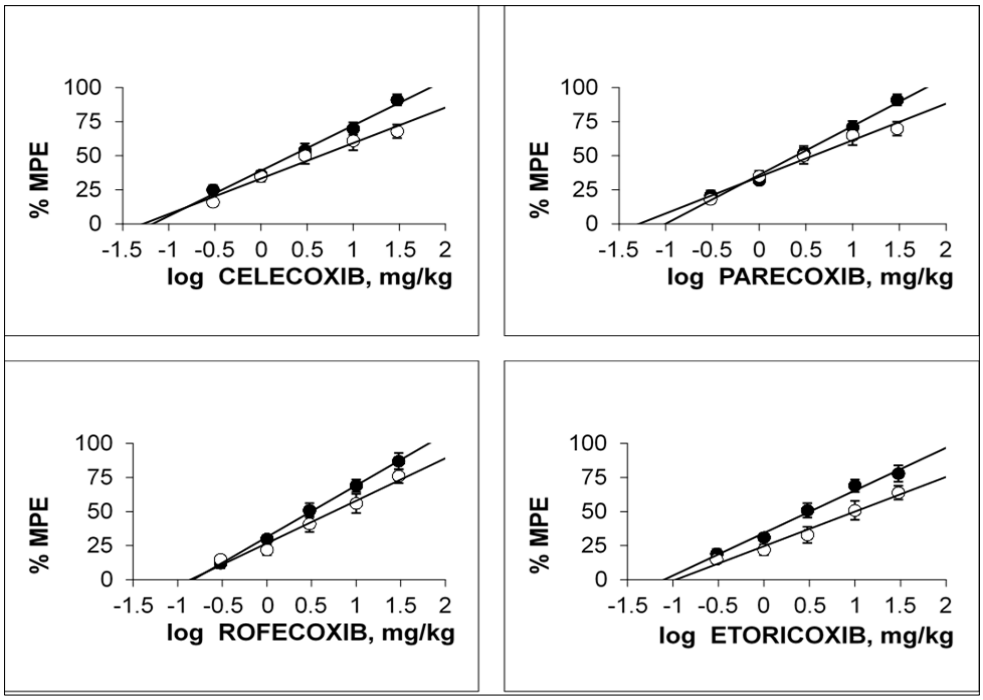

Figure 1 Dose response curves for the antinociceptive activity in mice by i.p. administration of celecoxib, parecoxib, rofecoxib and etoricoxib in the formalin hind paw, phase I (●) and phase II (○) assay. Each point is the mean ± SEM of 6-8 mice. % MPE: antinociception as percent of the maximum possible effect

Table 1 ED_{50} values (mean ± SEM) in mg/kg and analgesic ratio (AR) for the antinociceptive activity of parecoxib, celecoxib, rofecoxib and etoricoxib on mice formalin hind paw test (FHP) before and after pretreatment with 5 mg/kg i.p. of L-NAME

DRUG	ED 50 ± SEM FHP Phase I	ED 50 ± SEM FHP Phase II	AR control	AR after L-NAME
Parecoxib control	2.46 ± 0.24	3.76 ± 0.55	1.52	-
After L-NAME	5.98 ± 1.03*	7.90 ± 3.14*	-	1.32
Rofecoxib control	3.10 ± 0.34	5.53 ± 0.85	1.78	-
After L-NAME	7.89 ± 2.67*	9.21± 2.34*	-	1.16
Celecoxib control	2.13 ± 0.23	4.36 ± 0.73	2.04	-
After L-NAME	5.23 ± 1.54*	7.82 ± 2.19*	-	1.49
Etoricoxib control	3.15 ± 0.35	9.95 ± 1.80	3.16	-
After L-NAME	8.56 ± 2.51*	19.59± 2.98*	-	2.28

FHP: formalin hind paw. AR: ratio between ED50 phase I / phase II. * $P < 0.05$, compared with respective control. The number of mice for each group was 12.

3.2. L-NAME effect in the efficacy of parecoxib, celecoxib, rofecoxib and etoricoxib

Mice treated with 5 mg / kg i.p. of L-NAME did not modify the behavior of the control mice. To determine the interaction of L-NAME a curve dose-response to parecoxib, celecoxib, rofecoxib and etoricoxib, was performed in FHP assay. Pretreatment of mice with 5 mg/kg i.p. of L-NAME, a reduced analgesic efficacy was obtained by parecoxib, celecoxib, rofecoxib and etoricoxib in both phases of FHP test through of a significant shift of the ED_{50}. All these results can be seen in Tables 1 and 2.

Table 2 Shift of the ED_{50} values for the antinociceptive activity of parecoxib, rofecoxib, celecoxib and etoricoxib in FHP test of mice

Drug	Shift in FHP-I	Shift in FHP-II
Parecoxib	1.00	1.00
Plus, L-NAME	0.41	0.47
Rofecoxib	1.00	1.00
Plus, L-NAME	0.39	0.60
Celecoxib	1.00	1.00
Plus, L-NAME	0.41	0.56
Etoricoxib	1.00	1.00
Plus, L-NAME	0.37	0.51

The shift values are the ratio of values of ED_{50} before and after the treatment with L-NAME. FHP-I: formalin hind paw, phase I, FHP-II: formalin hind paw, phase II. The number of mice for each group was 12.

Figures 2 and 3 show the changes induced by pretreatment with L-NAME on the ED_{50} of parecoxib, rofecoxib, celecoxib, and etoricoxib, both in phase I and phase II of the FHP assay of mice.

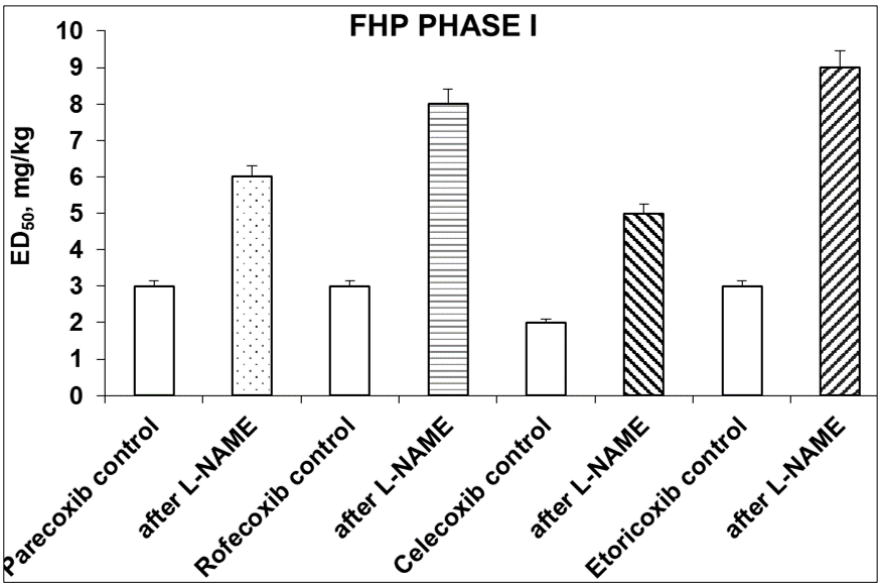

Figure 2 Effect of L-NAME on ED_{50} of COX-2 in phase I of formalin hind paw

Effect of L-NAME on the ED_{50} of parecoxib, rofecoxib, celecoxib and etoricoxib in the formalin hind paw, phase I (FHP I) assay. The ED_{50} before (white column) and after (hatched column) pretreatment with L-NAME. Columns represent the mean ± SEM of 6-8 mice. Hatched columns are significant versus to control, p=<0.05.

4. Discussion

The findings obtained in this study with the selective inhibitors of COX-2, celecoxib, parecoxib, rofecoxib and etoricoxib [11] are consistent with the previously described analgesic efficacy of these drugs. Thus, this activity in celecoxib has been reported in the tail flick, formalin and writhing tests [12-18]. However, there is a difference with the reports of Gowayed et al., and Rezende et al., since the NSAIDs (COX-2) used induced a significant.

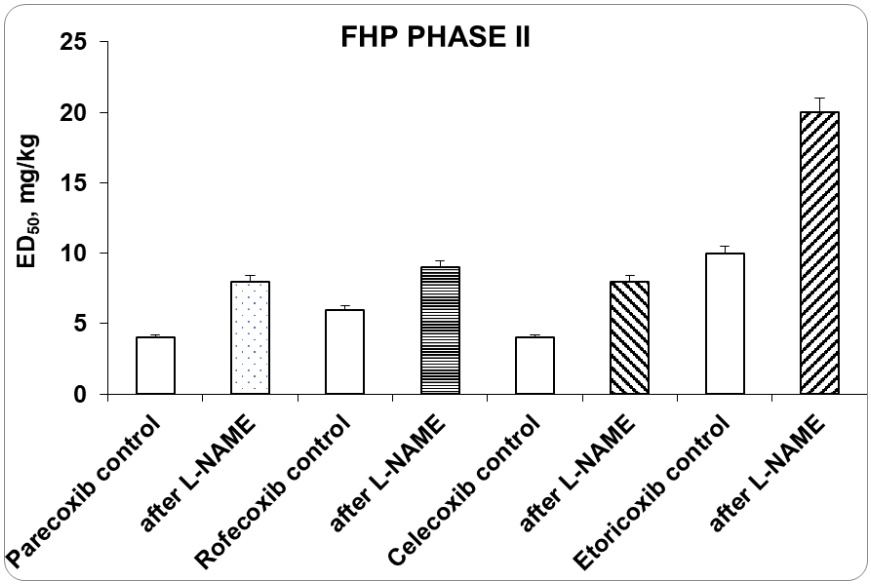

Figure 3 Effect of L-NAME on ED_{50} of COX-2 in phase II of formalin hind paw

Effect of L-NAME pretreatment on the ED_{50} of parecoxib, rofecoxib, celecoxib and etoricoxib in the formalin hind paw, phase II (FHP II) assay. The ED_{50} before (white column) and after (hatched column) pretreatment with L-NAME. Columns represent the mean ± SEM of 6-8 mice. Hatched columns are significant versus to control, p=<0.05.

Effect in the phase I formalin trial. An even greater difference is the lack of a significant effect of celecoxib in both phases of the formalin test reported by Torres-López et al. [17]. The differences indicated here may be due to the different experimental protocols, such as the doses used, the routes of administration, and the animal species, among others. Also, it has been reported celecoxib analgesia induced in inflammation and neuropathic pain [18, 19].

Furthermore, the results obtained in the present study are in agreement with the analgesic activity of parecoxib in orofacial formalin test reported by Isiordia-Espinoza et al., [20] and the formalin hind paw by Noriega et al., [21]. It is necessary to specify that parecoxib, the prodrug of valdecoxib, presented significant and dose-dependent analgesia only in the second phase of the trial with formalin [22]. In addition, the current results of parecoxib are concordant with those obtained in the acetic acid writhing test by Pinardi et al., 2005 [23]. And in the neuropathic pain assay by Becker et al., 2013 [24]. A similar effect with parecoxib was obtained by Padi et al., 2004 in the carrageenan test. Nevertheless, in the same study, the authors report that parecoxib had no effect in two models of acute pain: acetic acid and formalin hind paw test. [25]. Besides, the present results of rofecoxib are in agreement with those obtained in the formalin hind paw assay by Dudhgaonkar et al. 2002 [26]. Also, it has been described analgesic effects of rofecoxib that are in line with the present findings in writhing test [27] and in acute inflammation assay [28]. Likewise, in agreement with the current results, analgesic activity has been described for etoricoxib in a model of carrageenan-induced paw hyperalgesia and adjuvant-induced arthritis by Riendeau et al., [29]. Moreover, analgesia induced by etoricoxib was find in the carrageenan, writhing and formalin tests [30]. Etoricoxib induced analgesia in carrageenan, and writhing and formalin tests in mice]. Also, using the writhing test similar analgesia of etoricoxib was reported by Grangeiro et al., and Janovsky and Krsiak [31, 32].

Selective COX-2 inhibitors: parecoxib, rofecoxib, celecoxib, and etoricoxib have antipyretic, anti-inflammatory, and analgesic effects mainly due to inhibition of prostaglandin biosynthesis, however, other mechanisms have been proposed to mediate analgesic activity. It has been suggested that in the antinociceptive activity of rofecoxib is mediated by the serotonin system through the central 5- HT_2, 5-HT_3 and 5-HT_4 receptors [33]. Likewise, it has been suggested that the analgesia induced by celecoxib is accompanied by suppressions of neuronal and astrocytic activations [14-16]. Also, in the celecoxib analgesia it has been proposed the involvement of endogenous opioid/cannabinoid systems, inhibition protein kinase C ε and inhibition substance P synthesis [15-16]. Similarly, it has been proposed that rofecoxib act as antinociceptive through an interaction mediated by the nitric oxide (NO) stimulates the activity of COX-2 [26].

Drugs inhibitory of COX-2 are widely utilised alone to treat pain in preclinical assay, such as the formalin hind paw, but the use in combination is limited and the result sometime contradictory. The purpose of the current study was to study, in a murine preclinical test, the nitridergic interaction with selective COX-2 drugs. The findings demonstrated a significant reduction induced by nonselective nitric oxide (NO) synthase (NOS) inhibitor, L-NAME, on the efficacy analgesia of parecoxib, rofecoxib, celecoxib and etoricoxib in the first neurogenic phase as in the second inflammatory phase of the hind paw assay. The possible explanation for the results obtained, may be elucidated by the pharmacological differences described among the mechanism of action of selective COX-2. Furthermore, the combination of L-NAME with selective COX-2 can be activated in both phases of the formalin test by more common pathways, so more studies are needed to specify the mechanism of action.

5. Conclusion

The measure of analgesia and anti-inflammatory efficacy of selective COX-2, in the current study, reveal a marked decreasing induced by the nonselective nitric oxide (NO) synthase (NOS) inhibitor, L-NAME. The pharmacological differences in the mechanism of action, aggregated to COX inhibition, of parecoxib, rofecoxib, celecoxib and etoricoxib could be the explanation for the findings of the present research.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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Authors' contributions

All authors contributed equally in preparing all parts of the work and approved the version submitted for revision.

Statement of ethical approval

Hereby, Hugo F. Miranda, I assure that the manuscript: "NITRIDERGIC MODULATION OF COX-2 EFFICACY" complies with being an original research work, that has not been sent for publication elsewhere, that it has been prepared by all the authors and are responsible for their content. All animal procedures were performed in accordance with the ethical guidelines of the International Association for the study of pain and approved by the animal care and use committee of the Faculty of Medicine, University of Chile, (CBA 0852/FMUCH/2018).

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