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Involvement of opioid antagonists on COX-2 activity

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Abstract

Pain is a complex process involving complex molecular and cellular mechanisms and pharmacotherapeutic strategies including nonsteroidal anti-inflammatory drugs (NSAIDs). The main mechanism of action of them, both for their adverse and therapeutic effects, is the inhibition of cyclooxygenases (COXs), one of its isoforms is COX-2 with selective inhibitors such as celecoxib, rofecoxib, and etoricoxib. The objective of this study was to evaluate the nociceptive interaction of COX-2 NSAIDs with other drugs due to the scarce information available in this regard. Antinociception was assessed by the formalin hind paw test evaluated from dose-response curves obtained before and after the i.p. administration of 1,0 mg/kg of naltrexone (NTX), or naltrindole (NTI), or nor-binaltorphimine (nor-BNI) in the assay, using at least 6-8 animals for each of at least 4 doses. Analgesic ratio (AR) expressed as the relation between ED_{50} of phase II / phase I of FHP indicates the following order of relative potency: celecoxib > parecoxib > etoricoxib. Administration of naltrexone or naltrindole induced a significant reduction of the analgesic activity of celecoxib, etoricoxib and parecoxib, reflected by an increase in the respective ED_{50} in both phases of FHP assay. However, norbinaltorphimine lack of effect. The results of the work demonstrate that opioid receptors MOR and DOR play a key role in coxib-induced antinociception in the FHP trial and while the KOR opioid receptor seems not to be involved in this antinociception.

Keywords: Celecoxib; Naltrexone; Naltrindole; Nor-binaltorphimine; Formalin assay

1. Introduction

Pain is a complex process involving complex molecular and cellular mechanisms that respond to the activation of multiple neural pathways in both the peripheral nervous system and the central nervous system. Three types have been described: nociceptive, neuropathic, and inflammatory pain, according to symptoms, mechanisms, and syndromes. The various pharmacotherapeutic strategies include a wide variety of drugs including to non-steroidal anti-inflammatory drugs (NSAIDs) which are effective analgesics commonly used for the treatment of both acute and chronic pain [1].

It has been accepted that the main mechanism of action of NSAIDs, both for their adverse and therapeutic effects, is the inhibition of cyclooxygenases (COXs) with the corresponding inhibition of the biosynthesis of prostanoids: prostaglandins, prostacyclin and thromboxane. Three COX isoforms have been described, being COX-1 constitutively expressed, COX-2 during inflammation and stress, and COX-3, although basically derived from COX-1, is involved in fever and pain. but not in inflammation [2,3].

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NSAIDs can be classified with inhibitors of each type of COX. Thus, among the selective COX-2 inhibitors are celecoxib, rofecoxib, and etoricoxib. Celecoxib is orally administered with excellent efficacy in relief inflammation and associated pain. In addition, it has better gastrointestinal tolerability compared than NSAIDs associated with COX-1 inhibition [4].

Therefore, having determined that celecoxib, etoricoxib, and parecoxib are selective inhibitors of COX-2, with analgesic and anti-inflammatory action, the available experimental evidence of their interaction with opioid receptor antagonists (MOR, DOR, and KOR) is relatively scarce and contradictory. Therefore, the purpose of this study was to evaluate the drug interaction of the above COX-2 selective drugs with naltrexone, naltrindole, and nor-binaltorphimine, in the murine chemical pain test of hind paw formalin injection.

2. Materials 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 made in accordance with the rules 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). Mice were acclimatized to the laboratory for at least 1 h before testing, used only once during the protocol, and euthanized after the test with an intraperitoneal (i.p.) injection of 60 mg/kg of pentobarbital. The minimum number of animals required to establish consistent effects of the drug treatment was used.

2.2. Measurement of antinociceptive activity

Antinociception was assessed by the formalin hind paw (FHP) test as described previously [5]. To perform the test, 20 µl of 2% formalin solution was 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 reflects tonic acute pain. The first phase is due to direct stimulation of nociceptors such as C fibre receptors and low threshold mechanoreceptors, including upregulation of substance P. Phase II spans 10 min, starting 20 min after formalin injection and reflects inflammatory pain. The second phase is related to central sensitization, due to neuronal inflammation of the dorsal horn, with the positive regulation of serotonin, histamine, prostaglandin and bradykinin. The control values for Phases I and II were 116.3 ± 7.4 s (n = 12) and 145.6 ± 9.3 s (n = 12), respectively.

2.3. Experimental design

The antinociceptive activity of celecoxib, etoricoxib and rofecoxib was evaluated from dose response curves of drugs were administered i.p. 30 min prior to test. Dose–response curves were obtained before and after i.p. administration of 1,0 mg/kg of naltrexone (NTX), or naltrindole (NTI) or nor-binaltorphimine (nor-BNI) in the assay, using at least 6-8 animals for each of at least 4 doses. The doses used were selected according to previously published studies [6-8] and adjusted according to preliminary experiments.

2.4. Drugs

Celecoxib, etoricoxib and rofecoxib provided by local laboratories and naltrexone, naltrindole, nor-binaltorphimine from Sigma-Aldrich Chemical Co, USA.

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, McCary Group Inc., PA, USA.

3. Results

Celecoxib, etoricoxib, parecoxib, NTX, NTI and nor-BNI did not induce significant behavioural or motor dysfunction in the mice compared to controls

3.1. Antinociception induced by celecoxib, etoricoxib and parecoxib

Table 1 ED_{50} values (mean ± SEM) in mg/kg with SEM and analgesic ratio (AR) for the antinociceptive activity of celecoxib, etoricoxib and parecoxib the formalin hind paw (FHP) test of mice.

Drug	Phase I	Phase II	AR
CELECOXIB	2.2± 0.2	4.8 ± 0.7	2.1
PARECOXIB	2.2 ± 0.1	4.9 ± 0.5	2.2
ETORICOXIB	3.1 ± 0.4	9.3 ± 0.7	3.0

AR: ratio between Phase II/Phase I.

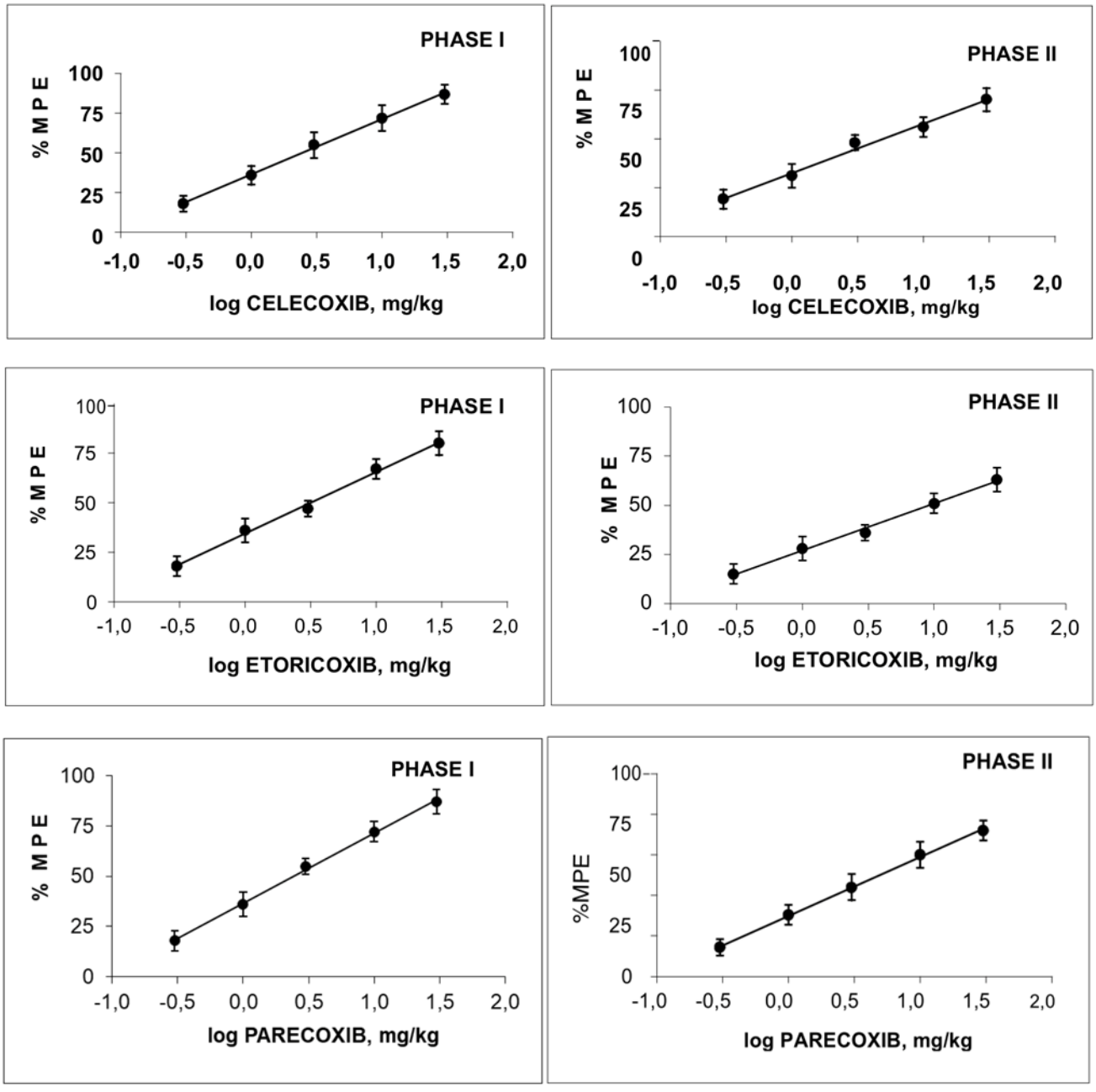

Figure 1 Dose–response curves for the antinociceptive activity induced by the i.p. administration of celecoxib, etoricoxib and parecoxib in phase I and phase II of formalin hind paw assay of mice. Each point is the mean ± SEM of 6–8 mice. % MPE: antinociception as percentage of the maximum possible effect.

The i.p. administration of celecoxib or etoricoxib or parecoxib produced dose dependent antinociception with different potencies in the mice FHP, as can be seen in Fig. 1.

The analgesic ratio (AR) expressed as the relation between ED_{50} of phase II / phase I of FHP indicates the following order of relative potency: celecoxib > parecoxib > etoricoxib (see table 1).

3.2. Effect of naltrexone on the antinociception induced by celecoxib, etoricoxib and parecoxib

To determine the effect of 1 mg/kg i.p. of naltrexone a complete dose-response curves to coxibs were constructed in mice pretreated with NTX. The data obtained demonstrates a significant decreased of the analgesic activity of celecoxib, etoricoxib and parecoxib, reflected by an increase in the respective ED_{50} in the both phases of FHP assay (see table 2).

Table 2 ED_{50} values (mean ± SEM) in mg/kg for the antinociceptive activity of celecoxib, etoricoxib, and parecoxib in the mice formalin hind paw (FHP) assay before and after pretreatment with 1 mg/kg of naltrexone (NTX), or naltrindole (NTI) or nor-binaltorphimine (nor-BNI).

CONDITION	CELECOXIB		ETORICOXIB		PARECOXIB	
	PHASE I	PHASE II	PHASE I	PHASE II	PHASE I	PHASE II
Control	2.2±0.2	4.8±0.7	3.1± 1,7	9.3±0.7	2.2±0.1	4.9±0.5
Plus NTX	4.2 ±0.4*	9.1±1.1*	8.1 ±1.1*	15.7±1.1*	4.1±0.2*	9.4±0.6*
Plus NTI	4.5 ±02*	8.3±0.9*	8.6 ± 0.6*	17.9±1.4*	4.1±0.1*	9.8±0.3*
Plus nor-BNI	2.6 ±0.1	5.1±0.8	3.2 ± 0.3	10.8±0.9	2.0±0.1	5.1±0.6

*: P>0.05 compared with control.

3.3. Effect of naltrindole on the antinociception induced by celecoxib, etoricoxib and parecoxib

To evaluate the effect of 1 mg/kg i.p. of naltrindole a complete dose-response curves to coxib were constructed in mice pretreated with NTI. The data obtained reveals a significant decreased of the analgesic activity of celecoxib, etoricoxib and parecoxib, reflected by an increase in the respective ED_{50} in the both phases of FHP assay (see table 2).

3.4. Effect of nor-binaltorphimine on the antinociception induced by celecoxib, etoricoxib and parecoxib

In mice pretreated with 1 mg/kg i.p. of nor-binaltorphimine, no significant differences in the efficacy of the analgesic activity of celecoxib, etoricoxib, and parecoxib were detected, which is reflected by no change in the respective ED_{50} values in both phases of the FHP trial (see table 2).

4. Discussion

NSAIDs represent an important class of compounds for the treatment of pain and inflammation, but the side effects associated with COX-1 inhibitors and the discovery of the second isoform of cyclooxygenase prompted the design of selective COX-2 inhibitors with increased efficacy and reduced side effects. These facts have allowed a marked expansion of pharmacology and therapeutics.

The results presented confirm the analgesic effect (phase I) and the anti-inflammatory action (phase II) of the coxibs used. At the same time, they are consistent with previous studies indicating the same effects of celecoxib, etoricoxib, and parecoxib [9-12].

The objective of this study was to evaluate in a murine chemical pain model, the FHP, the interaction between selective COX-2 inhibitors and the opioid receptor antagonists. The existing background reveals that there are varied and seems conflicting interactions, since some reports have suggested reduction of the coxib induced effect some have reporter no effect. These differences may be due to the type of pain, the dose or the animal tested. As example, NTX has been reported to reduce the efficacy of celecoxib [13-15]. Furthermore, NTI decreases the efficacy of celecoxib [16-17]. However, nor-BNI lacks effectiveness 16] or reduces the action of celecoxib [17].

The findings of this study demonstrated a reduction in the nocifensive response to the chemical noxa (formalin) induced by celecoxib, etoricoxib, and parecoxib mediated by the opioid antagonists NTX and NTI. However, nor-BNI had no effect. These results suggest that opioid receptors MOR and DOR play a key role in coxib-induced antinociception in the

FHP trial and while the KOR opioid receptor seems not to be involved in this type of antinociception. The results reveal a complexity in these interactions that could be interpreted by the several mechanisms of action attributed to the drugs in combination.

Thus, the COX-2 selective drugs possess, in addition to the selective inhibition of COX-2, other mechanisms involved in nociception, including the suppression of neuronal and astrocyte activation, accompanied by 5-HT and NA [11], activation of MOR opioid receptors primarily [15-17] and participation of cannabinoid mechanisms [17].

Additionally, it is accepted that opioids act both at the pre and postsynaptic level, which has made it possible to describe different mechanisms of action, including the blockade of Ca^{+2} channels, the inhibition of the release of substance P and glutamate, the activation of NMDA release, increased potassium channel activity [18,19]. In addition to the mechanisms described, naltrexone it has been described acting as antagonists of toll-like receptor 4 (TLR4) [19], a key receptor for initiating microglial activation and for maintaining pain, especially neuropathic pain by increasing proinflammatory cytokines, substance P, nitric oxide, and excitatory amino acids [20]. Besides, a possible role of nitric oxide in the activity of naltrindole has been reported [21]. Nevertheless, naltrexone is a potent competitive inhibitor with the highest affinity for the MOR opioid receptor; however, it is a weaker antagonist of the KOR and DOR opioid receptors.[22]

5. Conclusions

The present preclinical study demonstrated the antinociceptive and anti-inflammatory activity induced by celecoxib, etoricoxib and parecoxib, representatives' inhibitors of COX-2 isoform of enzyme cyclooxygenase, in a murine nociceptive model of a chemical nature, the formalin administration in the hind leg. This activity was dose-dependent in both phases of the model and modulated by the action of the opioid receptors MOR and DOR. Since, the effect of naltrexone and naltrindole antagonists is evident, molecular studies are needed to certify and evaluate the nature of this interaction between COX-2 and opioid receptors.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that the research was conducted without potential conflict of interest.

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Author contributions

All authors contributed directly and substantially to the study and approved the final version of the manuscript.

Statement of ethical approval

The study and procedures with animals were carried out in accordance with the standards of the International Association for the Study of Pain and approved by the Committee for the Care and Use of Animals of the Faculty of Medicine of the University of Chile: CBA 0852/FMUCH/2018.

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