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Risperidone in analgesia induced by paracetamol and meloxicam in experimental pain

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the best therapeutic options to treat pain. Their use in combination with other drugs may broaden their applicability in analgesia if their ceiling and adverse effects are reduced. The aim of this study was to evaluate the pharmacological interaction of two NSAIDs, paracetamol and meloxicam, with the antipsychotic drug risperidone in mice, in several experimental tests of nociceptive and inflammatory pain. Antinociception was assessed by dose–response curves to paracetamol and meloxicam before and after the i.p. administration of 0.5 mg/kg of risperidone. Results are presented as means ± SEM and differences were calculated by one-way ANOVA followed by Tukey's post-test. Paracetamol and meloxicam produced a dose-related antinociceptive effect with diverse potencies. Risperidone increased the analgesia mediated by paracetamol and meloxicam only in the tonic tests that detected inflammatory pain. This suggests that COX inhibition is only a partial explanation of the increased analgesic potency of paracetamol and meloxicam since the effects of NSAIDs in the CNS are mediated by multiple mechanisms. These results indicate that the combination of risperidone with paracetamol or meloxicam could be a new and effective alternative for the management of inflammatory pain.

KEYWORDS

meloxicam, paracetamol, phasic pain, risperidone, tonic pain

1 | INTRODUCTION

Pain is constantly subjected to the action of various drugs with unequal results, which may be explained by the fact that the antinociceptive activity of analgesics is directly related to their site of action and to their interaction with different chemical mediators (inflammatory soup) both in the peripheral and central nervous systems.

The best analgesic drugs for the treatment of pain are opioids and nonsteroidal anti-inflammatory drugs (NSAIDs). However, their mechanism of action in the pain pathways is not yet fully understood.

NSAIDs are primary drugs extensively used for their therapeutic role in pain, fever and inflammation. They target cyclooxygenases (COXs), which control the rate limiting step in the synthesis of prostanoids, such as prostaglandins, prostacyclin and thromboxane. There are at least three known isoforms of these enzymes: COX-1, a constitutive form found in various tissues which plays an important role in tissue integrity; COX-2, induced by inflammatory mediators and which has a role in pain and inflammation; and COX-3, found in

Abbreviations: 5-HT, serotonin; CB1, cannabinoid receptor; COX, cyclooxygenase; DA, dopamine; ED_{50}, effective dose 50; FHP, formalin hind paw; IL-1β, interleukin 1β; NFκB, nuclear factor kappa B; NO, nitric oxide; NSAIDs, non-steroidal anti-inflammatory drugs; OP, orofacial formalin; PGE2, prostaglandin E_2; TF, tail flick; TNFα, tumour necrosis factor α; TRPV1, transient receptor potential cation channel; WT, writhing test.

nerve tissues, endothelial cells and heart. NSAIDs are a group of drugs widely used in the treatment of different types of pain in spite of having adverse effects on the gastric mucosa and the renal, cardiovascular, hepatic and haematological systems. They are divided according to their chemical structure and their selectivity in relation to COXs [1, 2].

Paracetamol or acetaminophen is among the most frequently used NSAIDs. It induces analgesia not only in the brain but also in the spinal cord. The most probable mechanisms for its analgesic effects are its action on COXs and that elicited by its metabolite AM404, which activates the TRPV1 and/or CB1 receptors [3]. Nevertheless, interactions with opioidergic systems, eicosanoid systems and/or pathways involving nitric oxide may also contribute to its analgesic effects [3]. In addition, endocannabinoid signalling appears to be activated by paracetamol [3]. Another frequently used NSAID is meloxicam, which is characterized by being a powerful and selective or preferential COX-2 inhibitor, properties that allow it to be used for the treatment of inflammation and pain while having protective properties for the kidneys and gastric mucosa.

Some drugs are used as analgesic adjuvants in spite of not having been designed for the treatment of pain. This is the case of antipsychotics, including chlorpromazine, haloperidol, quetiapine, risperidone and others. Their main mechanism of action is the increase in neurotransmitters in the CNS, thus reducing pain signals. Risperidone has been described as an antagonist of dopamine (DA) and serotonin (5-HT-2). It is administered orally or intramuscularly and is used to treat schizophrenia, bipolar disorder and aggression. Side effects include movement problems, drowsiness, dizziness, visual impairment, constipation and weight gain [4]. Risperidone induces an antinociceptive effect in the tail flick test following i.p. administration (ED_{50}: 26.4 mg/kg) [4].

The experimental evidence of interactions between NSAIDs and psychotic agents is scarce, particularly for risperidone. Thus, the purpose of this study was to evaluate the pharmacological interaction of two NSAIDs commonly used in pain therapy (paracetamol and meloxicam) with an antipsychotic drug (risperidone) in different murine antinociceptive tests.

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 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 (CBA 0852/FMUCH/2018). Research involving animals complied with all relevant national regulations and institutional policies for the care and use of animals. Mice were acclimatized to the laboratory for at least 1 h before testing, used only once during the protocol, and euthanized after the algesimeter 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 following murine tests:

1. The tail-flick test (TF) as described previously [5]. A radiant heat, automatic tail flick (Ugo Basile, Comerio, Italy) was used to measure response latencies. Baselines were obtained before the protocol and after the administration of drugs. A cut-off time of 8 sec was set to avoid tissue damage. TF latencies were converted to percentages of the maximum possible effect (% MPE) observed in control animals, 2.5 ± 0.08 s ($n = 12$).
2. The acetic acid writhing test (WT) as described previously [6]. Mice were injected i.p. with 10 ml/kg of 0.6% acetic acid solution, and the number of writhes were counted for the next 5 min. The drugs were administered 30 min prior to the acetic acid injection. Antinociception was expressed as % MPE, the number of writhes observed in control mice injected with saline (20.5 ± 0.9, $n = 12$).
3. The formalin hind paw (FHP) test as described previously [7]. 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. Phase II spans 10 min, starting 20 min after formalin injection and reflects inflammatory pain. 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.
4. The orofacial formalin (OP) test as described by Miranda et al [5]. To perform the assay, 20 μl of 2% formalin solution was injected into the right side of the upper lip next to the nose. The chemical stimulus produces tissue injury with the two distinct Phases I and II. Phase I is related to the direct stimulation of nociceptors such as C fibre receptors and

lowthreshold mechanoreceptors including the upregulation of substance P. Phase II is related to central sensitization by an inflammatory phenomenon of the dorsal horn neurons with upregulation of serotonin, histamine, prostaglandin and bradykinin. Control values for Phases I and II were 94.4 ± 3.8 s ($n = 12$) and 113.8 ± 4.8 s ($n = 12$), respectively.

Hot plate (HP). Test described previously was used [6]. In a commercial device (Ugo Basile, Italy), each mouse was placed on the heated surface and the time, in sec, between placement and licking or shaking the hind paw or jumping was recorded as response latency and is a sign of thermal nociception. Each animal was tested twice before (control latency = 15.50 ± 0.40 s, $n = 12$) and after the drug administration and the antinociceptive activity was expressed as percentage of the maximum possible effect (% MPE).

2.3 | Experimental design

The antinociceptive activity of paracetamol and meloxicam was evaluated from doseresponse curves; the drugs were administered i.p. 30 min prior to each test. Dose–response curves were obtained before and after the i.p. administration of 0.5 mg/kg of risperidone in the TF, WT, HP, FHP and OP assays 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 doseresponse curve.

2.4 | Drugs

Drugs were freshly dissolved in sterile physiological saline solution of 10 ml/kg, for i.p. administration. Paracetamol was kindly provided by Bristol-Myers-Squibb, meloxicam by *Laboratorios Saval Chile* and risperidone by Royal Pharma S.A.

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

The drugs used in this study did not induce significant behavioural or motor dysfunction in the mice at any of the doses used.

3.1 | Antinociception induced by paracetamol and meloxicam

The i.p. administration of paracetamol or meloxicam produced dose related antinociceptive effects with different potencies in the various tests. Treatment with paracetamol had the highest relative potency, expressed as ED_{50}, in the FHP II test and the lowest in the TF assay, in the following order: FHP II > OP II > FHP I > OP I > WT > HP > TF. As for the administration of meloxicam, the calculated relative potency was in the following order: WT > FHP I > OP II > FHP II > OP I > TF > HP. These results are shown in Tables 1 and 2 and depicted graphically in Figures 1 and 2.

3.2 | Effect of risperidone on the antinociception of paracetamol and meloxicam

Mice treated with risperidone at 0.5 mg/kg i.p. did not exhibit significant differences in pain and locomotor activity compared to controls. To determine if the effect

TABLE 1 ED_{50} values (mean ± SEM) in mg/kg and analgesic ratio (AR) for the antinociceptive activity of paracetamol in mice in the algesimeter tests, before and after treatment with i.p. risperidone (RISPER) 0.5 mg/kg

Test	ED_{50} pre-risperidone	ED_{50} post-risperidone	AR	*P*
TF	81 ± 1.18	79 ± 0.91	1.02	0.033
HP	61 ± 1.24	59 ± 1.03	1.03	0.033
WT	56 ± 0.98	40 ± 0.78	1.40	0.005
FHP I	36 ± 1.20	35 ± 0.90	1.02	0.033
FHP II	29 ± 1.08	15 ± 0.43	1.93	0.005
OP I	40 ± 1.14	40 ± 0.87	1.00	0.033
OP II	34 ± 1.30	11 ± 0.45	3.09	0.005

Note: AR: ratio between ED_{50} pre-/post-risperidone treatment. *P* values between pre- and post-risperidone treatment; $P < 0.005$, statistically significant.
Abbreviations: FHP I, formalin hind paw, Phase I; FHP I, formalin hind paw, Phase II; HP, hot plate; OP I, orofacial formalin, Phase I; OP II, orofacial formalin, Phase IITF, tail flick; WT, writhing test.

TABLE 2 ED_{50} values (mean ± SEM) in mg/kg and analgesic ratio (AR) for the antinociceptive activity of paracetamol in mice in the algesimeter tests, before and after treatment with i.p. risperidone (RISPER) 0.5 mg/kg

Test	ED_{50} pre-risperidone	ED_{50} post-risperidone	AR	*P*
TF	46 ± 2.99	45 ± 1.91	1.00	0.033
HP	38 ± 1.40	39 ± 1.35	0.97	0.033
WT	10 ± 0.80	6 ± 0.74	1.80	0.005
FHP I	11 ± 1.10	10 ± 0.86	1.00	0.033
FHP II	15 ± 1.08	10 ± 0.36	1.50	0.005
OP I	16 ± 2.27	15 ± 1.75	1.06	0.033
OP II	13 ± 1.60	6 ± 0.25	2.20	0.005

Note: AR: ratio between ED_{50} pre-/post-risperidone treatment. *P* values between pre- and post-risperidone treatment; $P < 0.005$, statistically significant.
Abbreviations: FHP I, formalin hind paw, Phase I; FHP I, formalin hind paw, Phase II; HP, hot plate; OP I, orofacial formalin, Phase I; OP II, orofacial formalin, Phase IITF, tail flick; WT, writhing test.

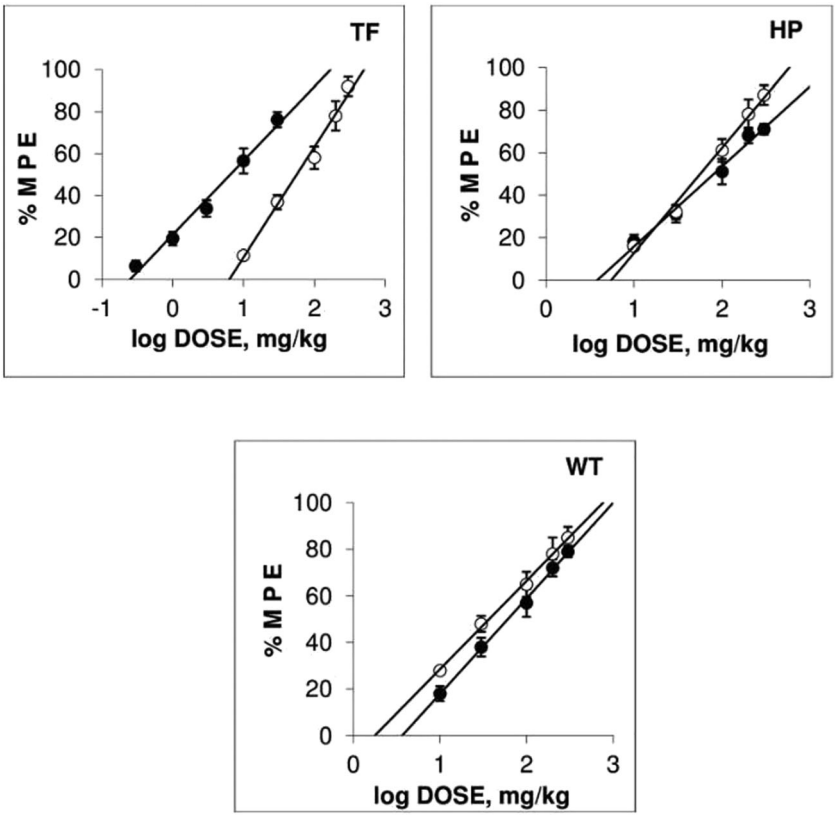

FIGURE 1 Dose–response curves for the antinociceptive activity induced in mice by the i.p. administration of meloxicam (●) and paracetamol (○) in the writhing test (WT), tail flick (TF) and hot plate (HP) assays. Each point is the mean ± SEM of 6–8 mice. % MPE: antinociception as percentage of the maximum possible effect

of risperidone was similar in potency for paracetamol and meloxicam in all the tests, complete dose–response curves were obtained for either drug in mice pretreated with risperidone. The data revealed a significant increase in the analgesic effect of paracetamol in the WT, FHP II and OP II tests. However, no significant differences were detected in the TF, HP, FHP I and OP I tests (see Table 1 and Figure 3). In addition, the changes in the ED_{50}, expressed as the ratio between the ED_{50} values, varied between 3.09 and 1.00, in the following order: OP II > FHP II > WT > HP = TF = FHP I = OP I, as shown in Table 1.

As for meloxicam, in all the algesimeter tests using mice pretreated with risperidone (0.5 mg/kg), complete dose–response curves showed a significant increase in the analgesic effect in the WT, FHPII and OP II tests, but not reaching significant differences in the TF, HP, FHP I, and OP I tests, as shown in Table 2 and Figure 4. However, the changes in the ED_{50}, expressed as the ratio between the ED_{50} values, varied between 2.20 and 0.97 in the following order: OP II > FHP II > WT > OP I = FHPI = TF = HP, as shown in Table 2.

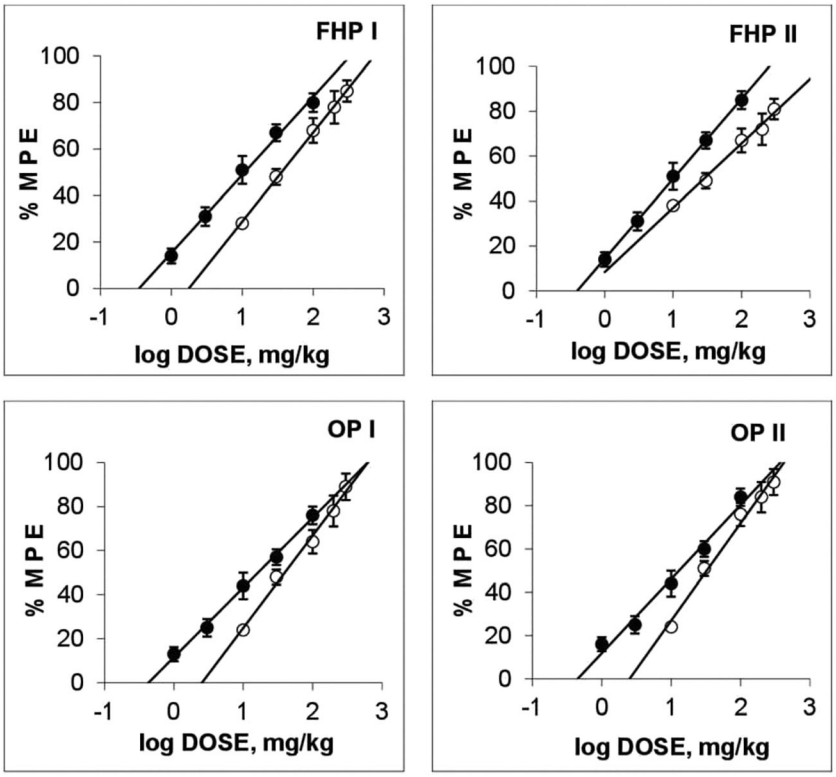

FIGURE 2 Dose–response curves for the antinociceptive activity induced in mice by the i.p. administration of meloxicam (●) and paracetamol (○) in the formalin hind paw, phase I (FHP I) and phase II (FHP II) and orofacial formalin, Phase I (OF I) and Phase II (OF II) assays. Each point is the mean ± SEM of 6–8 mice. % MPE: antinociception as percentage of the maximum possible effect

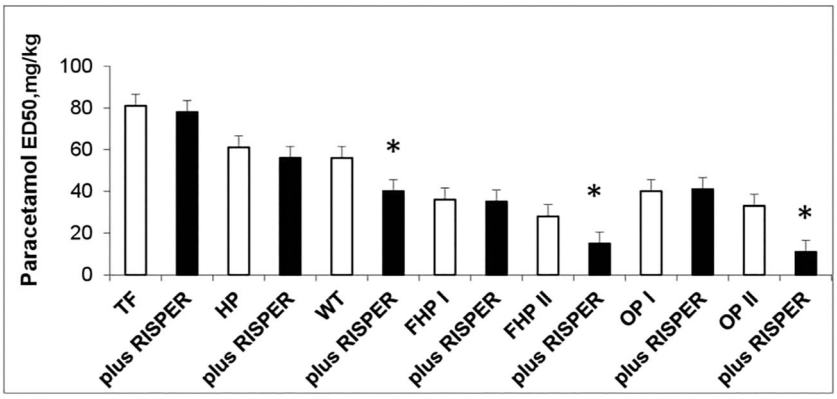

FIGURE 3 Effect of risperidone pretreatment on the ED_{50} of paracetamol in the tail flick (TF), hot plate (HP), writhing test (WT), formalin hind paw, Phase I (FHP I) and Phase II (FHP II), and orofacial formalin, Phase I (OF I) and Phase II (OF II) assays. The ED_{50} obtained before and after pretreatment with risperidone is shown in white and black columns, respectively. Columns represent the mean ± SEM of 6–8 mice.
*: $P < 0.05$, versus without risperidone pretreatment

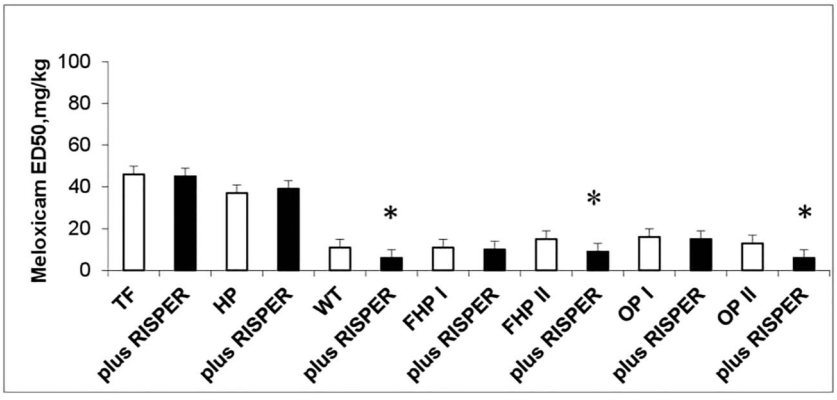

FIGURE 4 Effect of risperidone pretreatment on the ED_{50} of meloxicam in the tail flick (TF), hot plate (HP), writhing test (WT), formalin hind paw, Phase I (FHP I) and Phase II (FHP II) and orofacial formalin, Phase I (OF I) and Phase II (OF II) assays. The ED_{50} obtained before and after pretreatment with risperidone is shown in white and black columns, respectively. Columns represent the mean ± SEM of 6–8 mice.
*: $P < 0.05$, versus without risperidone pretreatment

4 | DISCUSSION

NSAIDs are commonly used in the treatment of pain, but their ceiling effect and their adverse effects curtail their use. For these reasons, combinations of NSAIDs have been used in multimodal analgesia. In this work the interaction between an antipsychotic (risperidone) and two frequently used NSAIDs (paracetamol and meloxicam) was evaluated. The results presented herein confirm the marked dependency of the analgesic efficacy on the dose as reported in the literature, for both paracetamol and meloxicam, in different animal pain assays, independently of the animal model or the nociceptive stimulus, either for tonic pain, as in the TF or HP tests, or for phasic pain, as in the WT, FHP or OP tests [5, 8–11]. Similarly, the current study addressed two types of experimental animal pain: phasic pain (tail flick and hot plate tests) and tonic pain (acetic acid writhing, formalin hind paw and formalin orofacial assays). The phasic pain is of short duration and shows the onset of the injury, the receptors are rapidly activated by the stimulus and emit a response that may be diminished. The other model includes tonic receptors which are sensory receptors that respond slowly to stimuli and generate the corresponding action potential. Tonic or visceral pain is poorly localized and usually radiates, so chemical stimuli such as formalin or acetic acid are used to investigate it.

The current study showed a significant decrease in the ED_{50} of paracetamol and meloxicam due to the action of risperidone, but only in the tonic algesimeter tests: formalin and acetic acid. Results are concordant with a previous study with other NSAIDs: ketoprofen, piroxicam, nimesulide, parecoxib and paracetamol [8]. The first phase of the formalin test is due to direct stimulation of nociceptors such as C fibre receptors and low threshold mechanoreceptors, including upregulation of substance P, while 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. On the other hand, in the acetic acid contortion test, the activation of nociceptors occurs with a subsequent localized visceral inflammation due to the release of mediators from tissue phospholipids by the action of prostaglandins synthesized by COXs [12].

The effect of risperidone on the significant increase in the analgesic activity of paracetamol in the WT, FHP II and OP II tests could perhaps be related to an augmented COX inhibition produced by the antipsychotic drug. However, it has not been fully and irrefutably proven that the COX-1, COX-2 and COX-3 isoenzymes mediate the antinociception of paracetamol. Other mechanisms have been proposed for the analgesic effect of paracetamol in which risperidone might be involved directly or indirectly. As an example, the inhibition of the NOS enzyme has been proposed. On the other hand, paracetamol has been reported as a prodrug of the endocannabinoid system since its metabolite AM404 activates TRPV1, an agonist of CB1 [3]. There is evidence that the analgesia of paracetamol is related with the descending serotonergic pathway [13]. Another possibility to explain the analgesia induced by paracetamol could be the participation of opioid neurotransmitters [14]. As detailed, there are multiple postulates to explain the analgesic mechanism of action of paracetamol in which risperidone could participate.

The administration of risperidone induced a significant increase in the analgesic activity of meloxicam in the WT, FHP II and OP II tests. This increase could be due to changes in the pharmacodynamic properties of meloxicam, the most important of which may be the increase in COX-2 inhibition, given that meloxicam has been categorized as a preferential or selective inhibitor of this isoform. There are other mechanisms of action of meloxicam on which the antipsychotic drug could be exerting its influence. Among them, it has been postulated that it could decrease the concentration of NF-κB and the subsequent production of pro inflammatory cytokines: TNF-α, NO, IL-1β and PGE2 [15–17]. Additionally, meloxicam has also been reported to reduce the levels of COX2, EP1 and EP2 significantly [18]. There are other mechanisms of action of meloxicam in which the antipsychotic drug could be involved. A systemic reduction of IL-1β levels and the fact that meloxicam is able to decrease the levels of the proinflammatory cytokines TNF, IL-6 and IL-17 have also been reported [19, 20].

The findings of the present study indicate that the antinociceptive effect of paracetamol and meloxicam is modulated by risperidone and that, regardless of their mechanism of action, risperidone enhances the anti-inflammatory analgesic potency of paracetamol and meloxicam.

5 | CONCLUSIONS

This study demonstrates that there is a functional interaction between risperidone and the analgesic properties of paracetamol and meloxicam in murine models of acetic acid and formalin tonic pain. This interaction appears to be mediated by the multiple mechanisms of action of NSAIDs. These results allow us to suggest that the combination of risperidone with paracetamol or meloxicam may represent a new and effective alternative for the therapeutic handling of inflammatory pain.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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ETHICS STATEMENT

Not applicable.

AUTHOR CONTRIBUTIONS

H. F. M. and V. N. conceived and designed the research and wrote the manuscript. V. N. and F. S. performed the experiments. R. S. Z. and J. C. P. analysed and participated in the interpretation of data. All authors contributed directly and substantially to the study and approved the final version of the manuscript.

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