

# The mechanism of antidepressant-like effects of piroxicam in rats

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## ABSTRACT

**Objective:** To investigate the antidepressant-like effect of piroxicam with a focus on serotonergic neurotransmission. **Materials and Methods:** Rats were randomly distributed into the following groups: 0.9% saline control; 3 mg/kg pizotifen; 10 mg/kg sertraline; 10 mg/kg piroxicam; 10 mg/kg sertraline + 10 mg/kg piroxicam; 10 mg/kg sertraline + 3 mg/kg pizotifen; and 10 mg/kg piroxicam + 3 mg/kg pizotifen. All the drugs were dissolved in 0.9% saline. Three administrations of the drugs (piroxicam and sertraline) were performed 1, 5 and 24 h before testing the animals in the open field followed by the forced swim test (FST). Piroxicam and sertraline were administered orally by gavage and pizotifen was administered intraperitoneally 30 min before gavage. Immediately after the FST, the hippocampi were rapidly dissected for neurochemical analysis in high-performance liquid chromatography. **Results:** Acute treatment with piroxicam promoted an antidepressant-like effect in the FST, which was associated with an increase in serotonin levels in the hippocampus. This effect was potentiated in the piroxicam + sertraline group but counteracted by administration of the non-selective serotonin receptor antagonist pizotifen. **Conclusion:** These results suggest that the antidepressant-like effect of piroxicam in the FST is mediated by the serotonin system; however, by different mechanisms from those of sertraline.

**Key words:** Depression, forced swim test, piroxicam, serotonin

## INTRODUCTION

Depression is a psychiatric disorder characterized by the presence of affective, psychomotor, cognitive and neurovegetative symptoms that pervade all aspects of life and affect individual's family and personal relationships,

employment and general health.<sup>[1]</sup> The pathophysiology of this disease is far from being fully understood. However, the monoamine hypothesis explains several behavioral and neurochemical aspects of the changes in serotonin (5-hydroxytryptamine [5-HT]), dopamine and norepinephrine levels in the brains of depressed patients.<sup>[2]</sup> 5-HT is known to be directly involved in the modulation of cognition, mood, anxiety, aggression, pain and neuroendocrine function, affecting neurogenesis, apoptosis, axon branching and neuronal cell survival.<sup>[3]</sup>

The neurotransmitter 5-HT is derived from the essential amino acid tryptophan. 5-HT synthesis in the brain is highly dependent on the bioavailability of tryptophan in plasma.<sup>[4]</sup> Inflammatory cytokines promote changes in the tryptophan metabolic

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pathway. Reduction in the availability of 5-HT in neurons triggers the induction of indoleamine 2,3-dioxygenase (IDO).<sup>[5]</sup> IDO is an enzyme that degrades tryptophan in tryptophan catabolites and nicotinamide,<sup>[6]</sup> reducing the bioavailability of tryptophan for 5-HT synthesis.<sup>[7]</sup> Prostaglandin E2 (PGE2) can also induce IDO,<sup>[4,8]</sup> and, in turn, increase interleukin (IL)-6 production.<sup>[8]</sup>

In addition, the inflammatory hypothesis has gained widespread attention, suggesting that inflammation mediated by immune cell activation is a key factor in depression.<sup>[9]</sup> This hypothesis is supported by the fact that patients with depression have elevated levels of proinflammatory cytokines in plasma and cerebrospinal fluid.<sup>[10]</sup> A recent meta-analysis showed that the levels of the cytokines tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and IL-6 are increased in the serum of patients with depression.<sup>[11]</sup> Thus, some authors have contended that depression is characterized by activation of the inflammatory response through the increased production of proinflammatory cytokines, such as IL-1, IL-6 and TNF- $\alpha$ , and PGE2.<sup>[12]</sup>

Piroxicam is a strong inhibitor of cyclooxygenase-2 (COX-2). It is known as a non-steroidal anti-inflammatory drug (NSAID) that has an analgesic effect. The effectiveness of piroxicam as an anti-inflammatory agent is mainly attributable to the inhibition of PGE synthesis.<sup>[13,14]</sup> Santiago *et al.*<sup>[15]</sup> demonstrated that acute treatment with piroxicam was able to exert antidepressant-like effect in the forced swim test (FST) and that prolonged treatment was able to reverse the anhedonic state of rats induced by chronic mild stress model. However, piroxicam showed increased levels of noradrenaline and 5-HT in the hippocampus. Therefore, the aim of the present study was to investigate the antidepressant-like effect of piroxicam, focusing on the serotonergic neurotransmission.

## MATERIALS AND METHODS

### Animals

Fifty-six male Wistar rats from our breeding colony, 3 months of age and weighing 280–320 g at the beginning of the experiments, were used. The animals were randomly housed in groups of five in polypropylene cages with wood shavings as bedding and maintained in a temperature-controlled room ( $22 \pm 2^\circ\text{C}$ ) on a 12 h/12 h light/dark cycle (lights on at 7:00 AM). The animals had free access to water and food throughout the experiment. The studies were performed in accordance with the guidelines of the Committee on the Care and Use of Laboratory Animals, United States National Institutes of Health. The experimental protocol complied with the recommendations of the Federal University of Paraná and was approved by the University Ethics Committee (protocol no. 470).

### Experimental design

The rats were randomly distributed into seven groups ( $n =$  eight per group): 0.9% saline control group; 3 mg/kg pizotifen (non-selective 5-HT receptor antagonist; Novartis, São Paulo, Brazil); 10 mg/kg sertraline as the positive control group (selective 5-HT reuptake inhibitor; EMS, São Paulo, Brazil); 10 mg/kg piroxicam (NSAID; EMS, Brazil); 10 mg/kg sertraline + 10 mg/kg piroxicam (to evaluate whether the mechanism of action of piroxicam, regarding its antidepressant-like effect, would be the same as a selective 5-HT reuptake inhibitor); 10 mg/kg sertraline + 3 mg/kg pizotifen; and 10 mg/kg piroxicam + 3 mg/kg pizotifen (to evaluate the involvement of the serotonergic system in the antidepressant-like effect of piroxicam as a non-selective 5-HT receptor antagonist). All the drugs were dissolved in 0.9% saline. Three administrations of the drugs (piroxicam and sertraline) were performed 1, 5 and 24 h before testing the animals in the open field, followed by the FST.<sup>[16]</sup> Piroxicam and sertraline were administered orally by gavage and pizotifen was administered intraperitoneally 30 min before gavage. All the drugs were administered in a constant volume of 1.0 mL/kg. Immediately after the FST, the brain of animals was dissected for neurochemical analysis.

### Open field test

The apparatus consisted of a round arena (100 cm diameter, 45 cm height), with the floor divided into 19 units.<sup>[17]</sup> The animals were gently placed on the right side of the open field and allowed to freely explore the arena for 5 min. Two motor parameters were recorded: Locomotion frequency (i.e. the number of crossings from one unit to another) and rearing frequency (i.e. the number of times the animals stood on their hind legs). The open field was washed with 5% ethanol solution before the behavioral test to eliminate possible bias caused by odors left by previous rats.

### Modified FST

The procedure was described by Slattery and Cryan *et al.*<sup>[16]</sup> The test was conducted in two sessions. In the training session, the rats were placed in a tank (25 cm diameter, 60 cm height) that contained water at a temperature of  $24 \pm 1^\circ\text{C}$  and depth of 25 cm for 15 min. Twenty-four hours after the training session, the rats were subjected to the FST for 5 min, which was videotaped for subsequent quantification of the following parameters: Immobility (i.e. the lack of motion of the whole body, consisting of only small movements necessary to keep the animal's head above the water), climbing (i.e. vigorous movements with the forepaws in and out of the water, usually directed against the wall of the tank) and swimming (i.e. large forepaw movements that displaced water to move the body around the cylinder, more than necessary to merely keep the head above the water). The water was changed after each animal to avoid the influence of water temperature and substances left from the previous session.

### Determination of hippocampal 5-HT and metabolite concentrations

Hippocampi were rapidly dissected after the FST and stored at  $-80^{\circ}\text{C}$  until the neurochemical quantification. The endogenous concentrations of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) were assayed using reverse-phase high-performance liquid chromatography (HPLC) with electrochemical detection. Briefly, the system consisted of a Synergi Fusion-RP C-18 reverse-phase column ( $150 \times 4.6$  mm i.d.,  $4\ \mu\text{m}$  particle size) fitted with a  $4\text{ mm} \times 3.0\text{ mm}$  pre-column (Security Guard Cartridges Fusion-RP), an electrochemical detector (ESA Coulochem III Electrochemical Detector) equipped with a guard cell (ESA 5020) with the electrode set at 350 mV and a dual electrode analytical cell (ESA 5011A), a LC-20AT pump (Shimadzu) equipped with a manual Rheodyne 7725 injector with a  $20\ \mu\text{L}$  loop. The column was maintained inside a temperature-controlled oven ( $25^{\circ}\text{C}$ , Shimadzu). The cell contained two chambers in series: Each chamber included a porous graphite coulometric electrode, a double counter electrode and a double reference electrode. Oxidizing potentials were set at 100 mV for the first electrode and at 450 mV for the second electrode. The tissue samples were homogenized with an ultrasonic cell disrupter (Sonics) in 0.1 M perchloric acid containing sodium metabisulfite 0.02% and internal standard. After centrifugation at 10,000 g for 20 min at  $4^{\circ}\text{C}$ ,  $20\ \mu\text{L}$  of the supernatant was injected into the chromatograph. The mobile phase, used at a flow rate of 1 mL/min, had the following composition: 20 g citric acid monohydrated (Merck), 200 mg octane-1-sulfonic acid sodium salt (Merck), 40 mg ethylene diamine tetraacetic acid (EDTA) (Sigma) and 900 mL HPLC-grade water. The pH of the buffer running solution was adjusted to 4.0 then filtered through a  $0.45\ \mu\text{m}$  filter. Methanol (Merck) was added to give a final composition of 10% methanol (v/v). The neurotransmitter and metabolite concentrations were calculated using standard curves that were generated by determining in triplicate the ratios between three different known amounts of the internal standard. The unit was expressed as ng/g of wet tissue.

### Statistical analysis

The Kolmogorov–Smirnov test was used to ensure that the data satisfied the criteria for performing analysis of variance (ANOVA). The data were analyzed using one-way ANOVA followed by the Newman–Keuls *post hoc* test. The level of significance was  $P < 0.05$ .

## RESULTS

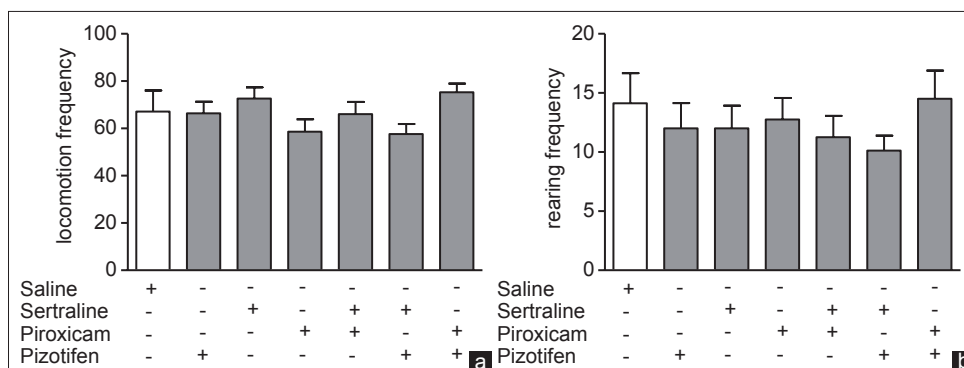
### Effects of acute treatment on behavior

In the open field test [Figure 1a], the frequencies of locomotion ( $F_{6,55} = 1.399$ ,  $P = 0.2339$ ) and rearing ( $F_{6,55} = 0.5825$ ,  $P = 0.7425$ ; Figure 1b) 1 h after acute administration revealed that none of the treated rats exhibited differences in these parameters compared with the control group.

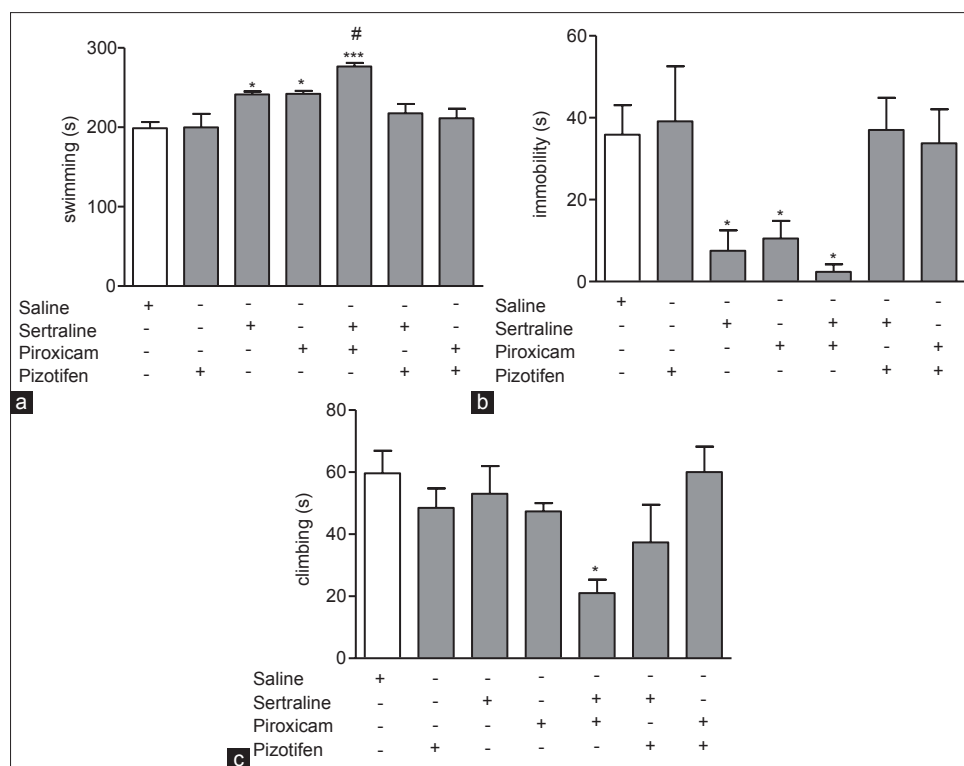
In the FST, swimming time significantly increased after acute treatment with sertraline, piroxicam and sertraline + piroxicam compared with the control group ( $P < 0.05$ ,  $P < 0.05$  and  $P < 0.001$ , respectively). The sertraline + piroxicam group also exhibited a significant increase in swimming time compared with the sertraline and piroxicam groups (both  $P < 0.05$ ;  $F_{6,55} = 8.115$ ,  $P < 0.0001$ ; Figure 2a). The sertraline, piroxicam and sertraline + piroxicam groups exhibited a significant decrease in immobility time compared with the control group after acute treatment (all  $P < 0.05$ ;  $F_{6,55} = 4.407$ ,  $P = 0.00121$ ; Figure 2b). Only the sertraline + piroxicam group exhibited a decrease in climbing compared with the control group ( $P < 0.05$ ;  $F_{6,55} = 3.189$ ,  $P = 0.0010$ ; Figure 2c).

### Determination of 5-HT and metabolite levels after acute treatment

The levels of 5-HT in the hippocampus significantly increased in the sertraline ( $P < 0.05$ ), piroxicam ( $P < 0.05$ ), piroxicam + sertraline ( $P < 0.001$ ), pizotifen ( $P < 0.05$ ), pizotifen + sertraline ( $P < 0.05$ ) and pizotifen + piroxicam ( $P < 0.05$ ) groups compared with the control group. Additionally, the sertraline + piroxicam group



**Figure 1:** Open field (a) locomotion and (b) rearing frequency. (One-way analysis of variance test followed by the Newman–Keuls *post hoc* test; mean  $\pm$  SEM)



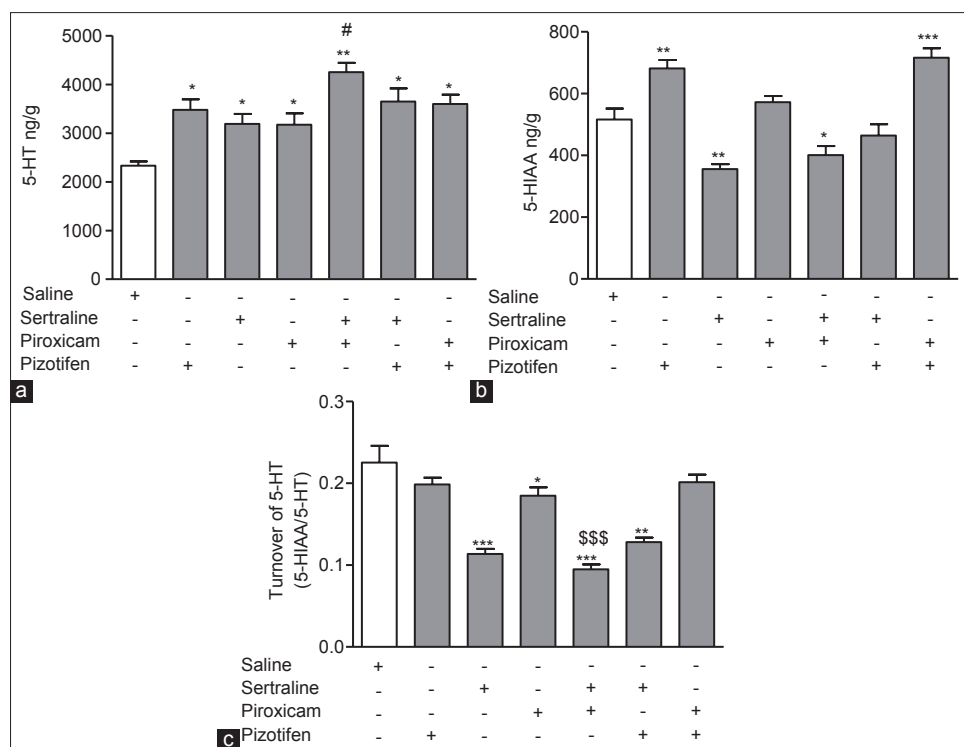
**Figure 2:** Forced swim test (a) swimming, (b) immobility and (c) climbing time. \* $P < 0.05$  and \*\*\* $P < 0.001$  compared with the saline group; # $P < 0.05$  compared with the sertraline and piroxicam groups (one-way analysis of variance followed by the Newman–Keuls *post hoc* test; mean  $\pm$  SEM)

exhibited a significant increase in the 5-HT levels compared with the sertraline and piroxicam groups (both  $P < 0.05$ ;  $F_{6,55} = 8.104$ ,  $P < 0.0001$ ; Figure 3a). The pizotifen and pizotifen + piroxicam groups exhibited significant increases in the metabolite 5-HIAA ( $P < 0.01$  and  $P < 0.001$ , respectively) compared with the control group. The sertraline ( $P < 0.01$ ) and piroxicam + sertraline ( $P < 0.05$ ) were found to have decreased 5-HT levels compared with the control group ( $F_{6,55} = 22.14$ ,  $P < 0.0001$ ; Figure 3b). The turnover of 5-HT in the hippocampus significantly decreased in the sertraline ( $P < 0.001$ ), piroxicam ( $P < 0.05$ ), piroxicam + sertraline ( $P < 0.001$ ) and pizotifen + sertraline ( $P < 0.01$ ) groups compared with the control group. Additionally, the sertraline + piroxicam group exhibited a significant decrease in the turnover of 5-HT levels compared with the piroxicam groups ( $P < 0.001$ ;  $F_{6,55} = 22.67$ ,  $P < 0.0001$ ; Figure 3c).

## DISCUSSION

In the present study, we found that acute treatment with piroxicam promoted an antidepressant-like effect in the FST, which was strongly associated with an increase in the 5-HT levels in the hippocampus. Moreover, this effect was potentiated by piroxicam + sertraline, but counteracted by administration of the non-selective 5-HT receptor antagonist pizotifen.

The involvement of the 5-HT system in the antidepressant-like effect of piroxicam was studied using non-selective 5-HT antagonists to examine behavioral responses to piroxicam in the FST. In the present study, we used the FST and assessed climbing, swimming and immobility. The main advantage of this model is that it allows correlations to be made between the analyzed behaviors and different neurotransmitter systems (e.g. swimming and the serotonergic system, climbing), and serotonin reuptake blockers increase swimming time.<sup>[16]</sup> According to the present results, the animals treated with piroxicam or sertraline exhibited an increase in swimming time compared with animals treated with saline. Additionally, the combination of piroxicam and sertraline potentiated the swimming time increase compared with either treatment alone. This suggests that the observed changes are related to the serotonergic, given that the swimming time of piroxicam + sertraline group was higher when compared with the sertraline groups or piroxicam alone. It is likely that both act in the serotonergic system but by different mechanisms. In addition, the data that showed reversal of the antidepressant-like effect of piroxicam by pizotifen pre-treatment supports the hypothesis that the 5-HT system is directly involved in the antidepressant effect of piroxicam. Furthermore, the increased 5-HT levels, inflicted by the piroxicam + sertraline treatment, contrasted with the reduced metabolite levels, possibly indicating a synergistic antidepressant effect promoted by those drugs. However, it



**Figure 3:** 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) hippocampal (a) 5-HT, (b) 5-HIAA and (c) turnover 5-HT. \* $P < 0.05$ , \*\* $P < 0.01$  and \*\*\* $P < 0.001$  compared with the saline group; # $P < 0.05$  compared with the sertraline and piroxicam groups, \$\$\$ $P < 0.001$  compared with the piroxicam group (one-way analysis of variance followed by the Newman–Keuls *post hoc* test; mean  $\pm$  SEM)

appears that such outcome, most likely, is an acute effect, as the 5-HT turnover rates are decreased in that group. Hence, it is conceivably the occurrence of a strong involvement of the serotonergic neurotransmission in the antidepressant mechanism generated by piroxicam.

The 5-HT system plays an important role in mood disorders.<sup>[18]</sup> Changes in 5-HT metabolism are involved in the pathophysiology of depression.<sup>[19]</sup> Several mechanisms have been proposed to account for the depressogenic action of cytokines, including decrease in the availability of plasma tryptophan (i.e. the precursor of 5-HT) in the brain by activation of the tryptophan-degrading enzyme IDO.<sup>[5]</sup>

The role of inflammation in the pathophysiology of depression has become more recognized in the literature, being described as the inflammatory or cytokine hypothesis of depression.<sup>[20]</sup> Evidence suggests that continuous activation of the immune and/or chronic inflammation system can be one of the pathological processes of depression.<sup>[21]</sup> In addition, the neuronal COX-2 expression is related to apoptosis and it is involved in the response to stress.<sup>[22]</sup> According to Maes *et al.*,<sup>[23]</sup> dysfunction in the serotonergic system in depression is the result of cell-mediated immune activation. An initial inflammatory response in innate immunity initiates the activation of a cascade that results in the activation and recruitment of cells responsible for adaptive immunity.<sup>[24]</sup> Therefore,

proinflammatory cytokines released during the innate and adaptive immune responses can lead to the development of central nervous system disorders.<sup>[25]</sup> Studies have shown that stress conditions are associated with an increase in the hypothalamic–pituitary–adrenal (HPA) axis activity and elevated serum corticosterone.<sup>[26]</sup> Studies by Guimaraes *et al.*<sup>[27]</sup> and Joca *et al.*<sup>[28]</sup> support the idea that activation of the HPA axis in response to chronic stress induces changes in the hippocampal serotonergic system, predisposing the individual to the development of depression. Thus, animal and human studies indicate that cytokines, such as TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and interferon, interact with many pathophysiological domains that characterize depression, including neurotransmitter metabolism, neuroendocrine function, synaptic plasticity and behavior.<sup>[29]</sup> According to Maes *et al.*,<sup>[5]</sup> proinflammatory cytokines are able to reduce the level of 5-HT through the activation of IDO. IDO is an enzyme that degrades tryptophan to catabolites of tryptophan (TRYCATs) and nicotinamide, reducing the bioavailability of tryptophan for the synthesis of 5-HT,<sup>[11]</sup> still being able to reduce the availability of 5-HT through the activation of IDO.<sup>[5]</sup>

An interesting finding of the present study was the synergistic antidepressant effect of piroxicam and sertraline. The effect of FST piroxicam in rats appears to be different from the effect of sertraline. One hypothesis to explain the present results may be related to changes in the levels of cytokines and PGE2



after piroxicam treatment. Anti-inflammatory drugs, such as piroxicam, exert their actions by inhibiting inflammation and, consequently, cytokine release, thereby avoiding the activation of IDO and preventing reductions of 5-HT.

## CONCLUSION

In conclusion, the antidepressant-like effect of piroxicam is mediated, at least in part, by alterations in 5-HT systems probably induced by the enzyme IDO. This conclusion is supported by the fact that the non-selective blocker of serotonin receptors was able to inhibit the antidepressant-like effect of piroxicam on FST, despite the increase in hippocampal serotonin observed in animals treated with the same. Furthermore, the combined use of piroxicam and sertraline demonstrated a synergistic effect, suggesting that the antidepressant-like effect of piroxicam is due to different mechanisms of selective serotonin reuptake inhibitor.

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