

Original Paper

Experimental Research on the Interactions between Selective COX-2 Inhibitors and Antidepressants

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REZUMAT

Cercetări experimentale privind interfezențele între inhibitori selectivi COX-2 și antidepressive

Obiective: S-a urmărit evidențierea prin testul Porsolt și testul suspendării de coadă la șoarece a unui posibil efect asupra stării timice pentru parecoxib și evaluarea interferențelor acestui medicament cu antidepressive din două clase diferite.

Material și metodă: În testul Porsolt s-au administrat doze de parecoxib în progresie geometrică cu rația 2, pentru evaluarea efectului depresiv/antidepresiv, ulterior în ambele teste s-a administrat parecoxib 40 mg/kg corp (kgc) singur sau asociat cu amitriptilina 5 mg/kgc și respectiv (doar în testul Porsolt) fluoxetina 10 mg/kgc.

Rezultate: În testul Porsolt, parecoxibul în doză de 40 mg/kgc are efect antidepresiv la parametrii scor de înot și latența imobilității. În testul Porsolt, într-un al doilea experiment, scade pentru unul din parametri (scorul de imobilitate) efectul antidepresiv al amitriptilinei însă nu influențează efectul antidepresiv al fluoxetinei. În testul suspendării de coadă nu are efect per se și nu scade efectul antidepresiv al amitriptilinei.

Concluzii: Parecoxibul are efect antidepresiv per se dar nu aduce un efect antidepresiv suplimentar atunci când este adăugat unui antidepresiv triciclic clasic sau unui inhibitor specific de recaptare a serotoninei. Este posibil ca parecoxibul să diminueze efectul antidepresiv al antidepressivelor triciclice.

Cuvinte cheie: Parecoxib, antidepressive, test Porsolt, testul suspendării de coadă

ABSTRACT

Objectives: The Porsolt test and the tail suspension test were performed on mice to investigate possible mood effects of parecoxib, and to assess the interactions between this agent and antidepressants belonging to two different classes.

Materials and methods: In the Porsolt test, parecoxib was given in geometric progression doses (ratio 2), in order to assess the depressant/antidepressant effect, then parecoxib was given in the dose of 40 mg/kg body weight (bw), either alone or in association with amitriptyline 5 mg/kg bw in both tests, and in association with

fluoxetine 10 mg/kg bw in the Porsolt test, respectively

Results: Parecoxib in dose of 40 mg/kg bw showed antidepressant effects in the Porsolt test, increasing the swimming score and decreasing the immobility latency. In the Porsolt test, in a second experiment, parecoxib decreased for one of the endpoints (immobility) the antidepressant effect of amitriptyline, and not altering in any way the antidepressant effect of fluoxetine. No effects per se were seen in the tail suspension test, and the antidepressant effect of amitriptyline was not decreased.

Conclusions: Parecoxib shows antidepressant activity per se, but does not appear to induce any additional antidepressant effect when added either to a classic tricyclic antidepressant or to a serotonin-specific reuptake inhibitor. Parecoxib may decrease the antidepressant effect of tricyclic antidepressants.

Key words: Parecoxib, antidepressants, Porsolt test, tail suspension test

INTRODUCTION

Several studies have suggested an association between depression and inflammation (reviewed in 1, 2, 3, 4). Treatment with pro-inflammatory agents (Calmette-Guerin bacillus, endotoxins) causes depressive symptoms (5, 6, 7). Non-steroidal anti-inflammatory agents, NSAIDs, particularly the COX-2 selective ones (e.g., celecoxib) showed promising results in the augmentation of the antidepressant effect in clinical studies on major depression or depressive symptomatology. The antidepressant activity of celecoxib was apparent both in the assessment of the frequency of the remissions, and in the assessment of the therapeutic response (reviewed in 8). Contrary to these studies, there is evidence that NSAIDs decrease the antidepressant effects of the antidepressant drugs. Certain NSAIDs showed depressant effects in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) clinical trial (concomitant administration of NSAIDs and antidepressants was shown to decrease the responder percentage to 45% in major depression, vs. 55% responder percentage when antidepressants were given without NSAIDs) (9). There is experimental evidence of antidepressant effects of NSAIDs in laboratory animals, particularly mice and rats, but also two studies showing that certain NSAIDs have depressant activity when given alone or in association with serotonin-specific reuptake inhibitors, SSRI (9, 10, 11, 12).

Therefore, the question arises whether a convenient coxib, namely parecoxib, may show antidepressant per se effects in albino mice, or, on the contrary, depressant effects. Another objective was the evaluation of the interactions between parecoxib and two antidepressants belonging to different classes:

amitriptyline – a classical tricyclic antidepressant, and fluoxetine – a serotonin-specific reuptake inhibitor.

Choosing parecoxib for our experiments was based on the following reasons:

- Its increased water solubility, which allows the intraperitoneal administration in mice, the most convenient way of administration in this species;
- Parecoxib had not been used in previous studies on mood changes (antidepressant/depressant);
- It is a pro-drug of valdecoxib (13), thus rendering possible the evaluation of mood changes induced by valdecoxib as well.

MATERIAL AND METHODS

Laboratory animals

Rodents were used – NMRI mice, Swiss albino strain, bred in the biological hatchery of the “Carol Davila” University of Medicine and Pharmacy, Bucharest. The animals were brought in from the hatchery 3 days before the experiments for adaptation to the new environment. They were kept in standard laboratory conditions, accommodated in acrylic plastic cages with wood shaving covered floor, 12 mice per cage, with ad libitum granulated food and water, at an environmental temperature of 21-22°C and relative humidity of 45-60%, under normal lighting conditions (between 07:00 – 19:00 hrs). The experiments were carried out in accordance with the current legislation.

Test agents

The following were used: parecoxib, amitriptyline, and fluoxetine. Pharmaceutical forms used included injectable form of the commercial prepara-

tion – parecoxib sodium (Dynastat, Pfizer), amitriptyline hydrochloride powder (Sigma Aldrich), fluoxetine hydrochloride powder (internal standard Medochemie, Cyprus), which were administered intraperitoneally.

Groups

Three experiments were performed.

Experiment I used the Porsolt test to assess the existence of any parecoxib effects on mood. Five groups of animals were used: a control group, which received normal saline intraperitoneally 2 hours before the test, a reference group which received amitriptyline intraperitoneally 30 minutes before the test, and three test groups receiving parecoxib intraperitoneally in dosages of 10, 20, and 40 mg/kg bw (in geometric progression with ratio 2), 2 hours before the test.

Experiment II used the Porsolt test to evaluate the possible influence of parecoxib on the antidepressant effects of two antidepressants with different mechanisms of action: amitriptyline, a tricyclic antidepressant, and fluoxetine, a serotonin-specific reuptake inhibitor. Six groups were used: a control group, that received intraperitoneally two injections of normal saline, one 2 hours before the test and one 30 minutes before the test, a group that received parecoxib 40 mg/kg bw and normal saline intraperitoneally, a group that received amitriptyline 5 mg/kg bw and normal saline intraperitoneally, a group that received fluoxetine 10 mg/kg bw and normal saline intraperitoneally, a group that received amitriptyline 5 mg/kg bw and parecoxib 40 mg/kg bw intraperitoneally, and a group that received fluoxetine 10 mg/kg bw and parecoxib 40 mg/kg bw intraperitoneally. Parecoxib was given 2 hours before the test, while amitriptyline and fluoxetine were given 30 minutes before the test. Normal saline was administered 2 hours before the test when given with fluoxetine and amitriptyline, and 30 minutes before the test in group that received parecoxib alone, respectively.

Experiment III used the tail suspension test to assess the interactions between the antidepressant effect of amitriptyline and the effects of parecoxib. Four groups were used: a control group that received two intraperitoneal injections with normal saline, one 2 hours before the test and one 30 minutes before the test, a group that received parecoxib 40 mg/kg bw and normal saline intraperitoneally, a group that received amitriptyline 5 mg/kg bw and normal saline

intraperitoneally, and a group that received amitriptyline 5 mg/kg bw and parecoxib 40 mg/kg bw intraperitoneally. Parecoxib was given 2 hours before the test and amitriptyline 30 minutes before the test, respectively. Normal saline was administered 2 hours before the test in the group that received amitriptyline alone, and 30 minutes before the test in group that received parecoxib alone, respectively.

The vehicles of substances/normal saline were administered in a volume of 10 ml/kg bw in experiment I, and in a volume of 5 mg/kg bw (two doses) in experiments II and III.

Test equipment

For the Porsolt test or forced swimming test in mice, the test equipment consisted of Berzelius glasses 18 cm high, 10 cm diameter, water height 12 cm, water temperature 28°C, and video recording systems.

For the tail suspension test in mice, the equipment consisted in a 4 sqcm square wooden slat, suspended at approximately 60 cm from the floor, and video recording systems.

Experimental protocol for the forced swimming test or Porsolt test

The number of animals in each group was set at 15. The larger number of animals in the forced swimming groups was prompted by earlier research, that have set the real mean difference between the control and the reference (treated with antidepressants) groups at 50%. Using a sample size calculation software – Piface from Russel Lenth, version 1.76, with sigma 1 (for the control group) of 0.4 (40%), sigma 2 (for the test groups) of 0.5 (50%), the mean difference was found to be 0.5 (50%), which for alpha = 0.05 and test power of 0.81 (81%) results in a number of 14 animals per group in both test and control groups.

The experiments were carried out in daylight conditions, between 08:30 and 16:30 hrs. The animals were left to swim for 6 minutes. Endpoints used included immobility latency during 6 minutes, and 5-second intervals' scoring of the last 4 minutes of immobility, swimming, and climbing respectively (thus resulting in 48 scoring intervals for each animal). This method was described by Costa AP et al., 2013 (14). The scoring was performed by staff trained for this purpose, 1-2 persons per experiment. The results were read in a blinded manner (the mice were assigned in three Berzelius glasses simultane-

ously, varying the immersion order into the glasses 1, 2, and 3 of each animal group), in accordance with the test protocol.

Immobility was defined as lack of movement, with the exceptions of respiratory movements and movements required for keeping the head above the water, with no significant active movements, either horizontally or vertically. Swimming was defined as active horizontal movements at the water surface. Climbing was defined as active vertical movements at the water surface.

Immobility latency increases with the intensity of the antidepressant effect. The immobility score decreases with the intensity of the antidepressant effect, and a high score is associated with a possible depressant effect. The swimming score increases with the intensity of the antidepressant effect. The climbing score increases with the intensity of the psychomotor stimulating effect.

Experimental protocol for the tail suspension test

The number of animals in each group was set at 11. The experiments were carried out in daylight conditions, between 08:30 and 16:30 hrs. The animals were suspended by the external third of their tail, at approximately 2 cm from the tail tip. The tail was taped to the slat by an adhesive band, which made the animals unable to escape from this inconvenient position. The 4 experimental spaces were separated by cardboard screens, which made the animals unable to see each other. The animals were left suspended by their tails for 6 minutes. End-points used included 5-second intervals' scoring of immobility, swinging, and curling, respectively, thus resulting in 72 scoring periods for each animal. This method was described by Berrocoso E et al., 2013 (15). The scoring was performed by staff trained for this purpose, 1-2 persons per experiment. The results were read in a blinded manner, according to the protocol.

Immobility was defined as lack of movement, with the exceptions of respiratory movements, swinging was defined as active important horizontal movements, and curling was defined as active vertical movements.

Statistical analysis

Microsoft Excel and SPSS version 15 were used for the purposes of statistical analysis. Homogeneity dispersion tests, ANOVA, and parametric post hoc

tests – the Tukey test (based on homogenous dispersion), and the Tamhane test (not involving homogenous dispersion), were used. $P < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

The results are shown in graph form, in **Fig. 1a, b; 2a, b, c; 3a, b, c**.

Significantly increased values ($p < 0.05$, Tamhane test), consistent with antidepressant effects, were seen in the endpoint „Immobility latency” in the forced swimming test (Porsolt test) in the groups receiving amitriptyline 10 mg/kg and parecoxib 40 mg/kg bw (**Fig. 1a**).

Significantly increased values ($p < 0.05$, Tamhane test), consistent with antidepressant effects, were also seen in the endpoint „Swimming score” in the forced swimming test in the groups receiving amitriptyline 10 mg/kg bw and parecoxib 40 mg/kg bw (**Fig. 1b**).

Significantly increased values ($p < 0.05$, Tukey test) were seen in the endpoint „Immobility latency” in the forced swimming test. These values were consistent with antidepressant effects for the groups fluoxetine 10 mg/kg bw and fluoxetine 10 mg/kg bw + parecoxib 40 mg/kg bw vs. control (**Fig. 2a**).

Significantly decreased values ($p < 0.05$, Tamhane test), consistent with antidepressant effects, were seen in the endpoint „Immobility score” for the groups parecoxib 40 mg/kg bw, amitriptyline 5 mg/kg bw, fluoxetine 10 mg/kg bw, amitriptyline 5 mg/kg bw + parecoxib 40 mg/kg bw, and fluoxetine 10 mg/kg bw + parecoxib 40 mg/kg bw vs. control. Additionally, the antidepressant effect of amitriptyline 5 mg/kg bw was antagonized by parecoxib 40 mg/kg bw (significant increase of the immobility score after amitriptyline 5 mg/kg bw + parecoxib 40 mg/kg bw vs. amitriptyline 5 mg/kg bw) (**Fig. 2b**).

Significantly increased values ($p < 0.05$, Tukey test), consistent with antidepressant effects, were seen in the endpoint „Swimming score” for the groups parecoxib 40 mg/kg bw, amitriptyline 5 mg/kg bw, fluoxetine 10 mg/kg bw, amitriptyline 5 mg/kg bw + parecoxib 40 mg/kg bw, and fluoxetine 10 mg/kg bw + parecoxib 40 mg/kg bw vs. control (**Fig. 2c**).

No significantly altered values were seen in the endpoint „Climbing score” vs. control (data not shown).

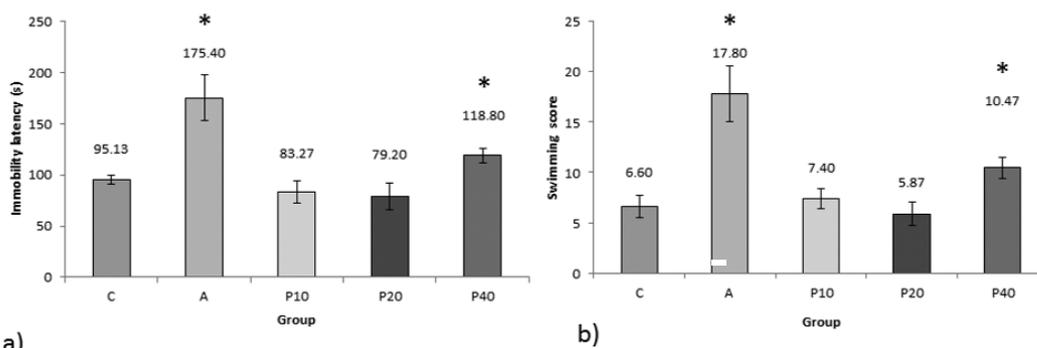


Figure 1. (a) Experiment I. Immobility latency (s) after the administration of 3 doses of parecoxib and amitriptyline 10 mg/kg. Each column shows the time elapsed from the beginning of the test to the occurrence of immobility, for each agent administered. n=15. Control (normal saline, C) 95.13±3.97. Group amitriptyline 10 mg/kg bw (A) 175.4±21.89. Group parecoxib 10 mg/kg bw (P10) 83.27±10.09. Group parecoxib 20 mg/kg bw (P20) 79.2±12.93. Group parecoxib 40 mg/kg bw (P40) 118.8±6.47 (* p<0.05 vs. the control group, Tamhane test). (b) Experiment I. Swimming score after the administration of 3 doses of parecoxib and amitriptyline 10 mg/kg. Each column shows the score recorded in the final 4 minutes of the test, for each agent administered. n=15. Control (normal saline, C) 6.60±1.09. Group amitriptyline 10 mg/kg bw (A) 17.80±2.68. Group parecoxib 10 mg/kg bw (P10). 7.40±0.98 Group parecoxib 20 mg/kg bw (P20) 5.87±1.15. Group parecoxib 40 mg/kg bw (P40) 10.47±1.00 (* p<0.05 vs. the control group, Tamhane test)

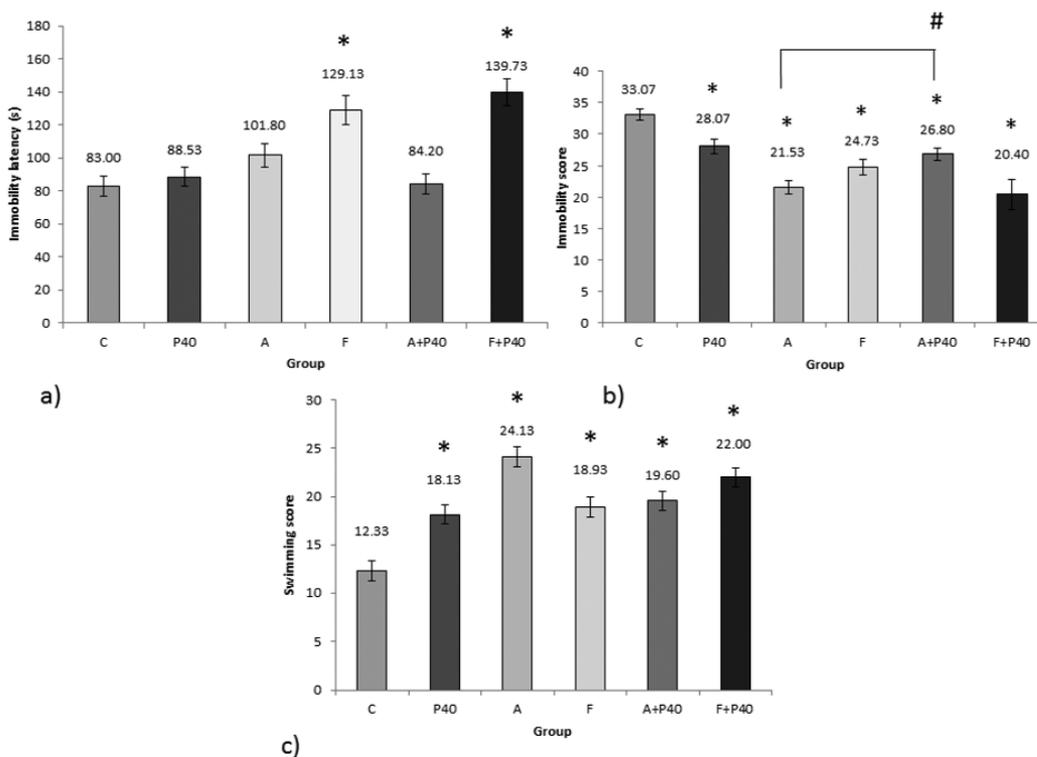


Figure 2. (a) Experiment II. Immobility latency (sec) after the administration of normal saline, parecoxib 40 mg/kg bw, amitriptyline 5 mg/kg bw, fluoxetine 10 mg/kg bw, amitriptyline 5 mg/kg bw + parecoxib 40 mg/kg bw, and fluoxetine 10 mg/kg bw + parecoxib 40 mg/kg bw. Each column shows the time elapsed from the beginning of the test to the occurrence of immobility, for each agent administered. n=15. Control (normal saline, C) 83.00±6.20; group parecoxib 40 mg/kg bw (P40) 88.53±5.56; group amitriptyline 5 mg/kg bw (A) 101.80±7.11; group fluoxetine 10 mg/kg bw (F) 129.13± 8.96; group amitriptyline 5 mg/kg bw + parecoxib 40 mg/kg bw (A+P40) 84.20±6.31; group fluoxetine 10 mg/kg bw + parecoxib 40 mg/kg bw (F+P40) 139.73±8.25 (* p<0.05 vs. control group, Tukey test). (b) Experiment II. Immobility score after the administration of normal saline, parecoxib 40 mg/kg bw, amitriptyline 5 mg/kg bw, fluoxetine 10 mg/kg bw, amitriptyline 5 mg/kg bw + parecoxib 40 mg/kg bw, and fluoxetine 10 mg/kg bw + parecoxib 40 mg/kg bw. Each column shows the score recorded in the final 4 minutes of the test, for each agent administered. n=15. Control (normal saline, C) 33.07±0.91; group parecoxib 40 mg/kg bw (P40) 28.07±1.21; group amitriptyline 5 mg/kg bw (A) 21.53±1.06; group fluoxetine 10 mg/kg bw (F) 24.73±1.29; group amitriptyline 5 mg/kg bw + parecoxib 40 mg/kg bw (A+P40) 26.80±0.92; group fluoxetine 10 mg/kg bw + parecoxib 40 mg/kg bw (F+P40) 20.40±2.36 (*p<0.05 vs. control group, Tamhane test; # p<0.05 vs. the amitriptyline 5 mg/kg bw group, Tamhane test). (c) Experiment II. Swimming score after the administration of normal saline, parecoxib 40 mg/kg bw, amitriptyline 5 mg/kg bw, fluoxetine 10 mg/kg bw, amitriptyline 5 mg/kg bw + parecoxib 40 mg/kg bw, and fluoxetine 10 mg/kg bw + parecoxib 40 mg/kg bw. Each column shows the score recorded in the final 4 minutes of the test, for each agent administered. n=15. Control (normal saline, C) 12.33±1.04; group parecoxib 40 mg/kg bw (P40) 18.13±1.08; group amitriptyline 5 mg/kg bw (A) 24.13±0.91; group fluoxetine 10 mg/kg bw (F) 18.93±1.11; group amitriptyline 5 mg/kg bw + parecoxib 40 mg/kg bw (A+P40) 19.60±0.91; group fluoxetine 10 mg/kg bw + parecoxib (F+P40) 40 mg/kg bw 22.00±2.06 (* p<0.05 vs. control group, Tukey test)

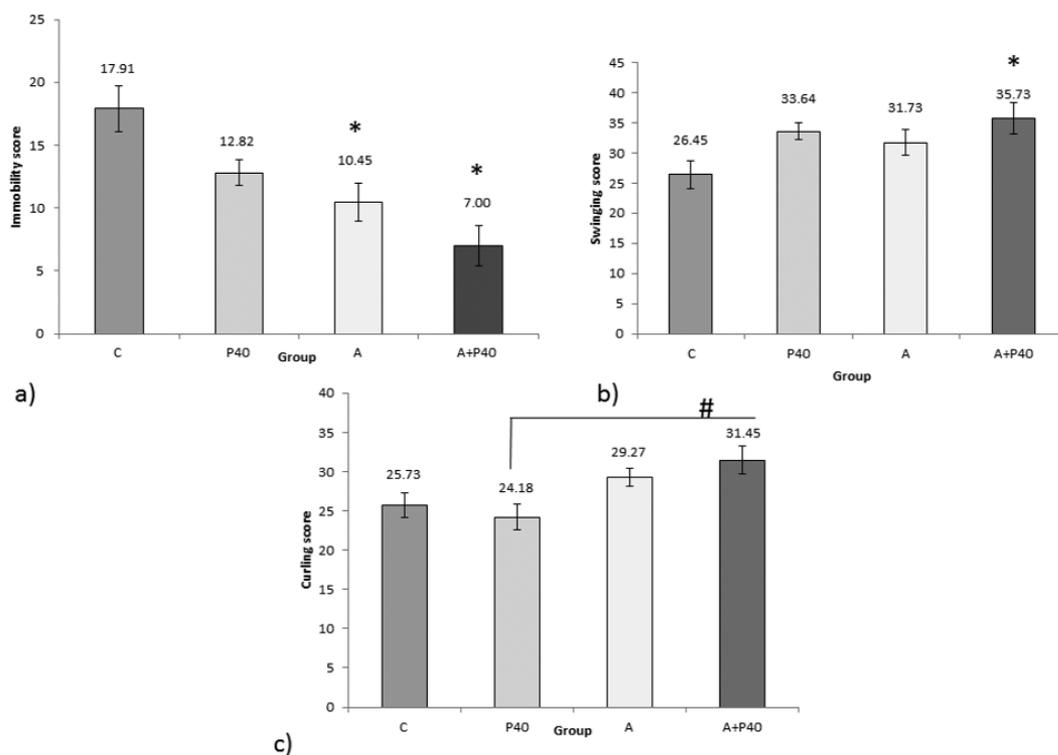


Figure 3. (a) Experiment III. Immobility score after the administration of normal saline, parecoxib 40 mg/kg bw, amitriptyline 5 mg/kg bw, amitriptyline 5 mg/kg bw + parecoxib 40 mg/kg bw. Each column shows the score recorded during the 6 minutes of the test, for each agent administered. $n=11$. Control (normal saline, C) 17.91 ± 1.81 ; group parecoxib 40 mg/kg bw (P40) 12.82 ± 1.00 ; group amitriptyline 5 mg/kg bw (A) 10.45 ± 1.49 ; group amitriptyline 5 mg/kg bw + parecoxib 40 mg/kg bw (A+P40) 7.00 ± 1.57 (* $p < 0.05$ vs. control group, Tukey test). (b) Experiment III. Swinging score after the administration of normal saline, parecoxib 40 mg/kg bw, amitriptyline 5 mg/kg bw, amitriptyline 5 mg/kg bw + parecoxib 40 mg/kg bw. Each column shows the score recorded during the 6 minutes of the test, for each agent administered. $n=11$. Control (normal saline, C) 26.45 ± 2.34 ; group parecoxib 40 mg/kg bw (P40) 33.64 ± 1.44 ; group amitriptyline 5 mg/kg bw (A) 31.73 ± 2.13 ; group amitriptyline 5 mg/kg bw + parecoxib 40 mg/kg bw (A+P40) 35.73 ± 2.60 (* $p < 0.05$ vs. control group, Tukey test). (c) Experiment III. Curling score after the administration of normal saline, parecoxib 40 mg/kg bw, amitriptyline 5 mg/kg bw, amitriptyline 5 mg/kg bw + parecoxib 40 mg/kg bw. $n=11$. Each column shows the score recorded during the 6 minutes of the test, for each agent administered. Control (normal saline, C) 25.73 ± 1.61 ; group parecoxib 40 mg/kg bw (P40) 24.18 ± 1.64 ; group amitriptyline 5 mg/kg bw (A) 29.27 ± 1.08 ; group amitriptyline 5 mg/kg bw + parecoxib 40 mg/kg bw (A+P40) 31.45 ± 1.83 (# $p < 0.05$ vs. the parecoxib 40 mg/kg bw group, Tukey test)

In the tail suspension test, the endpoint „Immobility score” showed significantly decreased values ($p < 0.05$, Tukey test) in the groups amitriptyline 5 mg/kg bw and amitriptyline 5 mg/kg bw + parecoxib 40 mg/kg bw (consistent with antidepressant effects) vs. control (Fig. 3a).

In the endpoint „Swinging score”, significantly increased values ($p < 0.05$, Tukey test) were seen in the group amitriptyline 5 mg/kg bw + parecoxib 40 mg/kg bw (consistent with antidepressant effects) vs. Control (Fig. 3b).

In the endpoint „Curling score”, significantly increased values ($p < 0.05$, Tukey test) were seen in the group amitriptyline 5 mg/kg bw + parecoxib 40 mg/kg bw vs. the group parecoxib 40 mg/kg bw (Fig. 3c).

DISCUSSION

Experiment I showed the antidepressant effect of parecoxib 40 mg/kg bw in the Porsolt test, and, as expected, the antidepressant effects of amitriptyline 10 mg/kg bw.

In Experiment II, all agents, given either alone or in various combinations, showed antidepressant effects. The antidepressant effect of the combination amitriptyline-parecoxib was however significantly lower than the antidepressant effect of amitriptyline given alone, suggesting that parecoxib, however being antidepressant when given alone, partially antagonizes the antidepressant activity of amitriptyline. No statistically significant differences were seen between the antidepressant effects of fluoxetine given alone and those of the combination fluoxetine-parecoxib. Therefore parecoxib, even if an antidepressant when given alone, in combination with fluoxetine is

apparently unable to increase the effects of the latter. On the other hand, parecoxib does not antagonize the antidepressant effects of fluoxetine, as seen with amitriptyline.

In the tail suspension test (Experiment III) parecoxib showed no effects per se. The partial antagonizing by parecoxib of the antidepressant effects of amitriptyline was not confirmed in this test.

Parecoxib does not seem to induce an additional antidepressant effect when added to a classic tricyclic antidepressant or to a serotonin-specific reuptake inhibitor. Moreover, parecoxib partially antagonized the antidepressant effects of amitriptyline in one of the tests.

These results are consistent with other literature data showing that imipramine, another tricyclic antidepressant similar to amitriptyline, shows different effects in the two tests used: the Porsolt test and the tail suspension test, respectively (16).

It would be a challenge to hypothesize on the mechanism of the antidepressant effect of parecoxib. The experimental data shown here suggest that the serotonergic pathway is not involved, as the effects of fluoxetine were not influenced, while the antagonizing of the amitriptyline effects is difficult to explain. It may be induced by another mechanism, not involving the monoaminergic system.

CONCLUSIONS

- 1) Parecoxib showed an antidepressant effect per se in the experimental conditions shown above.
- 2) Parecoxib does not seem to induce an additional antidepressant effect when added to a classic tricyclic antidepressant or to a serotonin-specific reuptake inhibitor.
- 3) Parecoxib may decrease the antidepressant effects of tricyclic antidepressants.

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