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ORIGINAL ARTICLE

Amitriptyline, clomipramine, and maprotiline attenuate the inflammatory response by inhibiting neutrophil migration and mast cell degranulation

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Objective: Despite the recognized anti-inflammatory potential of heterocyclic antidepressants, the mechanisms concerning their modulating effects are not completely known. Thus, we evaluated the anti-inflammatory effect of amitriptyline, clomipramine, and maprotiline and the possible modulating properties of these drugs on neutrophil migration and mast cell degranulation.
Methods: The hind paw edema and air-pouch models of inflammation were used. Male Wistar rats were treated with saline, amitriptyline, clomipramine or maprotiline (10, 30, or 90 mg/kg, per os [p.o.]) 1 h before the injection of carrageenan (300 μg/0.1 mL/paw) or dextran (500 μg/0.1 mL/paw). Then, edema formation was measured hourly. Neutrophil migration to carrageenan (500 μg/pouch) and *N*-formyl-methionyl-leucyl-phenylalanine (fMLP) (10^{-6} M/mL/pouch) was also investigated in 6-day-old air-pouch cavities. Compound 48/80-induced mast cell degranulation was assessed in the mesenteric tissues of antidepressant-treated rats.
Results: All tested antidepressants prevented both carrageenan- and dextran-induced edema. The anti-inflammatory effect of these drugs partially depends on the modulation of neutrophil migration, since they significantly counteracted the chemotactic response of both carrageenan and fMLP ($p < 0.01$). Furthermore, amitriptyline, clomipramine and maprotiline inhibited compound 48/80-induced mast cell degranulation ($p < 0.001$).
Conclusions: These results suggest an important anti-inflammatory role of heterocyclic antidepressants, which is dependent on the modulation of neutrophil migration and mast cell stabilization.

Keywords: Antidepressant agents; inflammation; neutrophil; mast cells; rats

Introduction

Heterocyclic antidepressants are widely used to treat a number of medical disorders, such as depression, social phobia, generalized anxiety, panic, obsessive-compulsive, and eating disorders. In addition to their pharmacological action on the reuptake inhibition of serotonin and norepinephrine, variable interactions with receptors, such as H1 histamine receptors, muscarinic receptors, and α-adrenergic receptors, have been reported.[1]

Several studies have suggested a potential analgesic activity of antidepressants independent of their effects on mood.[2-6] Furthermore, it has been reported that heterocyclic antidepressants are able to modulate the immune system.[7-9] In addition, a clear reciprocal effect between inflammatory mediators and development of depression is even more evident.[10-12] Since these reports, there has been growing research interest in the acute and chronic anti-inflammatory potential of these drugs.[8,13-16]

Current studies on the anti-inflammatory effects of cyclic antidepressants are mainly based on the model of carrageenan-induced paw edema,[8,13-16] and considerable progress has been achieved in this area of research. However, further investigation regarding the mechanisms involved in the anti-inflammatory activity of heterocyclic antidepressants is still needed. Therefore, we aimed to study the effect of amitriptyline, clomipramine, and maprotiline in different animal models of inflammation and to investigate the modulating properties of these drugs on neutrophil migration and mast cell degranulation.

Methods

Animals

Male Wistar rats (180-200 g) were obtained from the local animal breeding facility of the School of Medicine, Universidade Federal do Ceará (UFC), and divided into experimental groups (n=6/group). The animals

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were kept in a temperature-controlled room with free access to food and water, under 12/12h dark-light cycles, and were deprived of food 18 h previous to experiments. The local Ethics Committee for Animal Experimentation approved the study protocol, which strictly followed the NIH guidelines for care and use of laboratory animals.

Chemicals

Amitriptyline (PRODOME, São Paulo, Brazil, 25 mg tablet), clomipramine (Novartis, São Paulo, Brazil, 10 mg tablet), and maprotiline (Novartis, São Paulo, Brazil, 75 mg tablet) were used. Carrageenan, dextran 70, and *N*-formyl-methionyl-leucyl-phenylalanine (fMLP) were purchased from Sigma Chemicals (St. Louis, MO, USA). All drugs were dissolved in sterile saline solution.

Carrageenan- and dextran-induced paw edema

Animals were treated with saline (10 mL/kg), amitriptyline (10, 30, or 90 mg/kg, per os [p.o.]), clomipramine (10, 30, or 90 mg/kg, p.o.), or maprotiline (10, 30, or 90 mg/kg, p.o.) 1 h before the stimulus injection. Paw edema was induced by sub-plantar injection of carrageenan (300 μg/0.1 mL/paw) or dextran (500 μg/0.1 mL/paw). Control group animals received the same volume of sterile saline (0.1 mL/paw). Paw volume was measured by plethysmometry (Ugo Basile 7140 water plethysmometer) immediately before (basal volume) and at 1, 2, 3, and 4 h after carrageenan or dextran administration. Results were expressed as paw volume variation (mL), calculated by subtracting basal paw volume from the corresponding plethysmometer readings.

In vivo neutrophil migration induced by carrageenan or fMLP in air-pouch cavities

Six-day-old rat skin air pouches were produced as described by Ribeiro et al.[17] Briefly, the backs of the rats were shaved and 20 mL of sterile air injected subcutaneously. Three days later, 10 mL of sterile air were again injected to maintain pouch patency. Six days after the initial air injection, the pouches were used. Vehicle (sterile saline, 1 mL/pouch), carrageenan (500 μg/pouch), or fMLP (10^{-6} M/mL/pouch) were injected into the 6-day-old air pouches of rats previously treated with saline (10 mL/kg), amitriptyline (90 mg/kg, p.o.), clomipramine (90 mg/kg, p.o.), or maprotiline (40 mg/kg, p.o.).

Collection of exudates

Six hours after injection of the chemotactic stimulus into the air pouches, the animals were killed and the air pouches were washed by injection of 5 or 10 mL of phosphate-buffered saline (PBS) containing 5 U/mL of heparin. Cell counting was performed as described by Ribeiro et al.[17] The results were reported as the number of neutrophils x 10^6/mL exudate.

Mast cell degranulation in mesenteric tissue

Animals were given saline (10 mL/kg), amitriptyline (90 mg/kg, p.o.), clomipramine (90 mg/kg, p.o.), or maprotiline (40 mg/kg, p.o.) 1 h before euthanasia. After euthanasia, mesenteric tissues were carefully collected from the respective groups and placed into individual Petri dishes containing Ringer-Locke solution (10 mL). Mast cell degranulation was induced by tissue incubation with compound 48/80 (final concentration, 0.8 μg/mL) for 30 min. Hydrated tissue sections were immersed in a 0.1% toluidine blue solution (in 0.9% sodium chloride) for 60 s, followed by extensive rinsing in deionized water as described by Oliveira et al.[18] The percentage of degranulated mast cells per tissue section was then determined.

Statistical analysis

Data were analyzed by one-way or two-way ANOVA followed by Bonferroni's test as appropriate. Values were expressed as mean ± standard error of the mean. The level of significance was set at $p < 0.05$.

Results

Anti-inflammatory effect of different heterocyclic antidepressants in carrageenan and dextran-induced paw edema

As demonstrated in Figures 1 and 2 respectively, the intraplantar injection of carrageenan or dextran induced marked paw edema, which peaked 3 h (carrageenan) and 2 h (dextran) after the stimulus injection. Administration of amitriptyline (Figures 1A and 2A), clomipramine (Figures 1B and 2B), and maprotiline (Figures 1C and 2C) significantly prevented the development of edema ($p < 0.01$) at the highest doses tested (90 mg/kg). The most prominent effect was seen with clomipramine, which also inhibited edema formation at the dose of 30 mg/kg ($p < 0.05$). Two-way ANOVA revealed a significant main effect for treatment (amitriptyline: $F_{3,60} = 2.99$, $p < 0.05$; clomipramine: $F_{3,60} = 25.57$, $p < 0.0001$; maprotiline: $F_{3,60} = 3.47$, $p = 0.0352$) and time (amitriptyline: $F_{3,60} = 43.25$, $p < 0.0001$; clomipramine: $F_{3,60} = 25.55$, $p < 0.0001$; maprotiline: $F_{3,60} = 40.96$, $p < 0.0001$) in the carrageenan model. This was also observed for the dextran model of inflammation regarding treatment (amitriptyline: $F_{3,60} = 3.082$, $p < 0.001$; clomipramine: $F_{3,54} = 7.69$, $p = 0.0016$; maprotiline: $F_{3,60} = 1.61$, $p = 0.1603$) and time (amitriptyline: $F_{3,60} = 13.70$, $p < 0.0001$; clomipramine: $F_{3,54} = 11.98$, $p < 0.0001$; maprotiline: $F_{3,60} = 2.67$, $p < 0.05$).

Anti-inflammatory effect of heterocyclic antidepressants partially depends on the modulation of neutrophil migration

As shown in Figure 3, carrageenan (Figure 3A) and fMLP (Figure 3B) induced a conspicuous neutrophil migration when compared with the groups of rats that received only saline into the air pouch ($p < 0.001$). In addition,

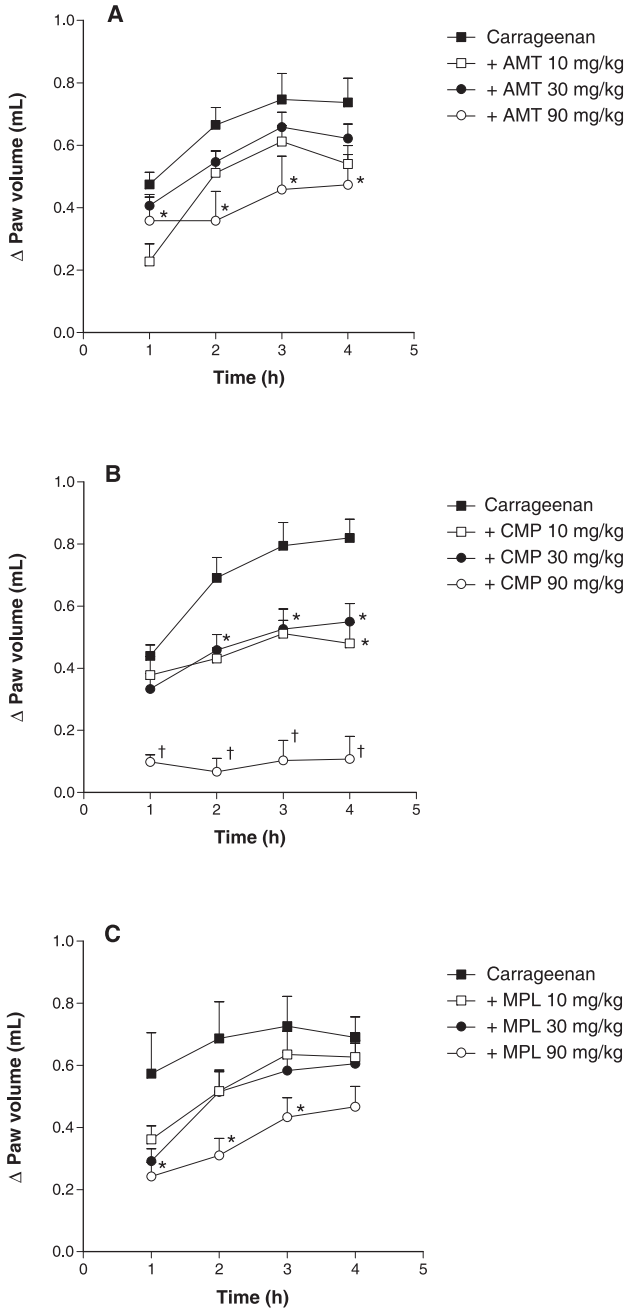

Figure 1 Effect of heterocyclic antidepressants on carrageenan-induced paw edema in rats. Amitriptyline (A), clomipramine (B), and maprotiline (C) (10, 30, and 90 mg/kg, per os [p.o.]) and saline (10 mL/kg, p.o.) were administered 1 h before carrageenan (300 μg/0.1 mL/paw) injection. Edema formation (mL) was then measured hourly up to 4 h post-carrageenan injection and subtracted from basal paw volume. Data expressed as mean ± standard error of the mean (n=6, * $p < 0.05$ and † $p < 0.01$ vs. carrageenan group). AMT = amitriptyline; CMP = clomipramine; MPL = maprotiline.

amitriptyline (90 mg/kg), clomipramine (90 mg/kg), and maprotiline (40 mg/kg) significantly counteracted the chemotactic response of both carrageenan and fMLP ($p < 0.01$) (Figures 3A and B).

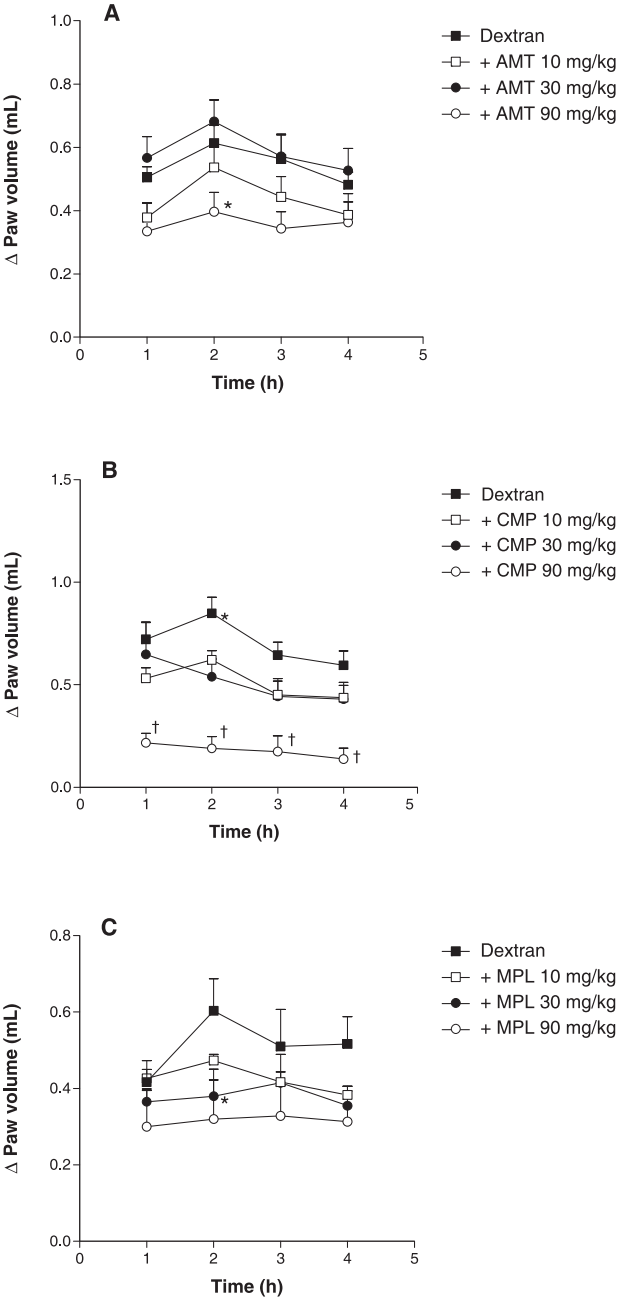

Figure 2 Effect of heterocyclic antidepressants on dextran-induced paw edema in rats. Amitriptyline (A), clomipramine (B), and maprotiline (C) (10, 30 and 90 mg/kg, per os [p.o.]) and saline (10 mL/kg, p.o.) were administered 1 h before dextran (500 μg/0.1 mL/paw) injection. Edema formation (mL) was then measured hourly up to 4 h post-dextran injection and subtracted from basal paw volume. Data expressed as mean ± standard error of the mean (n=6, * $p < 0.05$ and † $p < 0.01$ vs. dextran group). AMT = amitriptyline; CMP = clomipramine; MPL = maprotiline.

Mast cell degranulation is inhibited by heterocyclic antidepressants

As observed in Figures 4 and 5, *in vitro* incubation of mesenteric tissues with compound 48/80 significantly

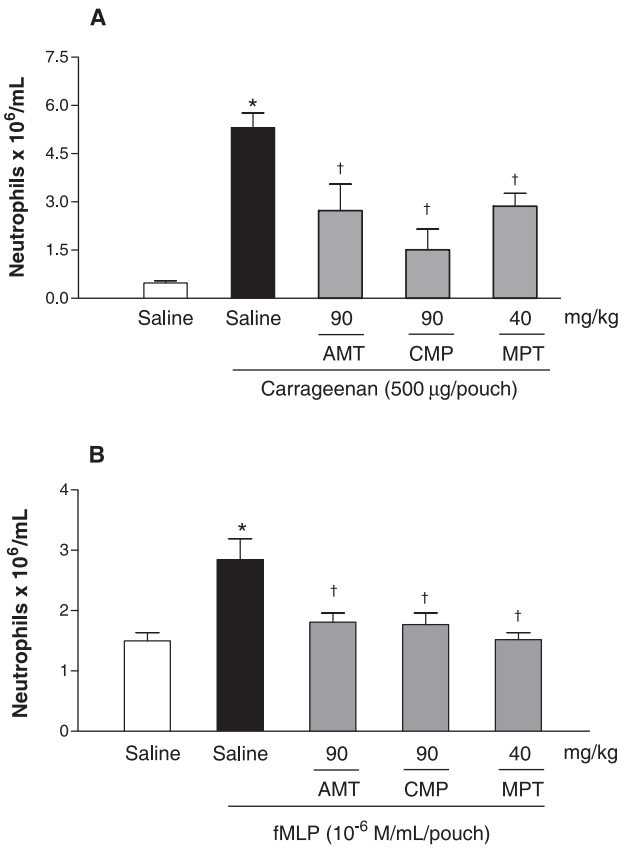

Figure 3 Effect of heterocyclic antidepressants on neutrophil migration into 6-day-old air pouches. Amitriptyline (90 mg/kg), clomipramine (90 mg/kg), maprotiline (40 mg/kg), and saline (10 mL/kg, per os [p.o.]) were administered 1 h before carrageenan (500 μg/pouch [A]) or *N*-formyl-methionyl-leucyl-phenylalanine (fMLP) (10^{-6} M/mL/pouch [B]) injection. Neutrophil count in the exudates was determined 6 h after the stimulus injection. Data expressed as mean ± standard error of the mean (n=6, * $p < 0.001$ vs. saline, † $p < 0.01$ vs. carrageenan or fMLP). AMT = amitriptyline; CMP = clomipramine; MPL = maprotiline.

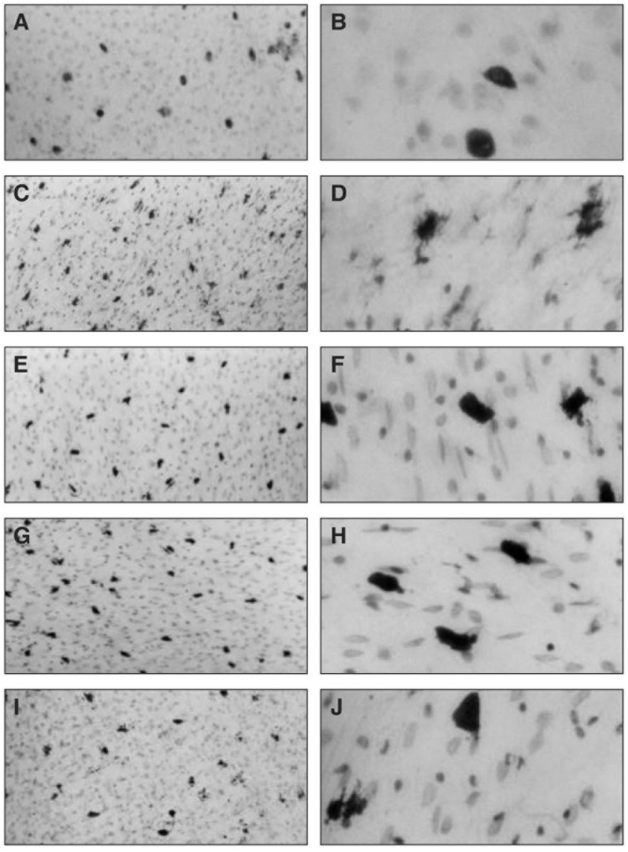

Figure 4 Effect of heterocyclic antidepressants on mast cell degranulation. Animals were killed 1 h per os (p.o.) after treatment with amitriptyline (90 mg/kg), clomipramine (90 mg/kg), maprotiline (40 mg/kg), or saline (10 mL/kg, p.o.) and the mesenteric tissue was harvested. The tissue collected was incubated with compound 48/80 (0.8 μg/mL) and stained with 0.1% toluidine blue solution. A, C, E, G and I represent 100x magnification; B, D, F, H and J represent 400x magnification. Saline (A and B), compound 48/80 (C and D), amitriptyline + compound 48/80 (E and F), clomipramine + compound 48/80 (G and H), maprotiline + compound 48/80 (I and J).

induced a notable mast cell degranulation (Figures 4B and C) when compared with tissues incubated with saline (Figures 4A and B, $p < 0.001$). Furthermore, this effect was prevented ($p < 0.001$) when animals were previously treated with amitriptyline (90 mg/kg, Figures 4E and F), clomipramine (90 mg/kg, Figures 4G and H), and maprotiline (40 mg/kg, Figures 4I and J). The percentage of degranulated cells is expressed in Figure 5.

Discussion

In the present study, we demonstrated that the heterocyclic antidepressants amitriptyline, clomipramine, and maprotiline exert anti-inflammatory effects by a mast cell-dependent mechanism and by inhibition of neutrophil migration. These observations were achieved by the classic protocols of carrageenan and dextran-induced paw edema, neutrophil migration in the 6-day-old rat air pouch, and mast cell degranulation in the rat mesentery.

In previous studies, the doses of amitriptyline, maprotiline, and clomipramine used to test their potential anti-inflammatory effects ranged from 5 to 80 mg/kg.[4,8,13-16] In all cases, these agents were given intraperitoneally, which partially explains the lower doses injected. In general, long-term treatment of patients with antidepressants involves oral administration. Therefore, in order to better mimic the clinical settings, gavage was used in our study as the preferential route of administration for the antidepressants tested. In addition, the oral route commonly requires higher doses of drugs due to several reasons, including lower bioavailability and erratic absorption.

Several published articles report the inhibitory effect of antidepressants on edema formation due to intraplantar injection of carrageenan.[8,13-16] Despite progress regarding the mechanisms involved in the anti-inflammatory effect of these drugs, some questions remain to be

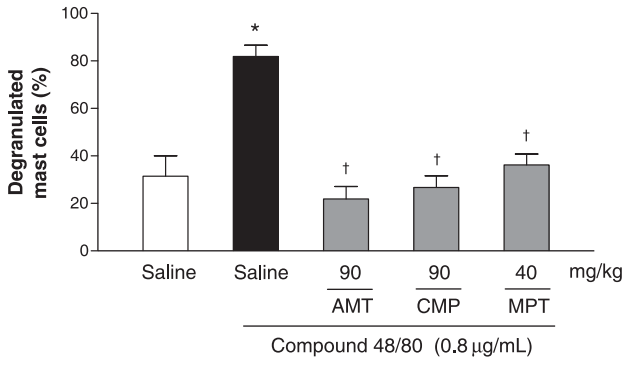

Figure 5 Effect of heterocyclic antidepressants on mast cell degranulation. Animals were killed 1 h per os (p.o.) after treatment with amitriptyline (90 mg/kg), clomipramine (90 mg/kg), maprotiline (40 mg/kg), or saline (10 mL/kg, p.o.) and the mesenteric tissue was harvested. The tissue collected was incubated with compound 48/80 (0.8 μg/mL) and stained with 0.1% toluidine blue solution. Data represent the percentage of degranulated cells and were expressed as mean ± standard error of the mean (n=6, * $p < 0.001$ vs. saline, † $p < 0.01$ vs. compound 48/80). AMT = amitriptyline; CMP = clomipramine; MPL = maprotiline.

answered. For instance, which inflammatory cells would be involved in the anti-edematogenic effect of antidepressants? Do all antidepressant drugs share the same anti-inflammatory mechanism?

It is well known that the edematogenic effects of carrageenan and dextran occur through different pathways.[19] A biphasic inflammatory response due to carrageenan injection has been suggested,[20] with the participation of several inflammatory mediators, including prostaglandins, bradykinin, and serotonin,[21] cytokine production by resident macrophages, and neutrophil migration to the lesion site.[21,22] On the other hand, dextran-induced edema is chiefly a result of mast cell degranulation. Therefore, the use of various experimental approaches is essential to better determine the mechanism through which anti-inflammatory substances produce their effects.

In our study, we demonstrated the protective effect of different antidepressants on both the carrageenan and dextran models of rat paw edema, suggesting that the function of both neutrophils and mast cells might be modulated by these drugs. Regarding carrageenan, our findings are in accordance with other studies.[8,13-16] However, to the best of our knowledge, this is the first report of a protective effect of the tested drugs against dextran-induced edema.

It has been well established that polymorphonuclear (PMN) leukocyte infiltration plays an important role in the inflammation induced by carrageenan in the hind paw model. Additionally, taking into consideration that antidepressants are potent inhibitors of edema formation in that animal model, we decided to test the hypothesis of an effect of these drugs on neutrophil recruitment. For that purpose, we used the air-pouch model. The rat air pouch is a cavity that differs from others, such as the peritoneum, by its absence of mast cells.[23] We intended to investigate whether the tested antidepressant drugs would still produce an anti-inflammatory response in the absence of these cells.

We demonstrated that the effects of both carrageenan and the direct chemotactic factor fMLP were markedly inhibited by amitriptyline, clomipramine, and maprotiline. Several other studies have already stated the anti-inflammatory effect of antidepressants. Sacerdote et al.[9] showed that clomipramine was able to block human neutrophil chemotaxis *in vitro*. The same authors also demonstrated a similar modulating effect on macrophages *in vivo*.[24] These authors attributed that activity over inflammatory cells to the cyclic chemical structure of clomipramine, noting that other non-cyclic antidepressant drugs, such as fluoxetine and fluvoxamine, do not modify cell migration. Sadeghi et al.[16] further showed that both local and intracerebroventricular administration of amitriptyline elicits a marked reduction in the infiltration of PMN leukocytes into the carrageenan-treated paws, according to pathological examination and the activity of myeloperoxidase in the inflamed paw tissues. These findings were corroborated by Vismari et al.[8] by intravital microscopy, further showing the involvement of α1-adrenoceptors in the anti-inflammatory effects of amitriptyline. In addition, Hajhashemi et al.[25] revealed that systemic administration of maprotiline reduces the development of carrageenan-induced paw edema in the rat. Maprotiline is also effective in decreasing edema when it is injected at the time of or after inducing inflammation.[15]

The participation of preformed mast cell products, such as serotonin and histamine, is the main mechanism involved in the short-lived edematogenic response elicited by dextran injection.[19] In our study, all of the tested antidepressants had a protective effect against dextran-induced edema. Lo et al.[19] demonstrated that the accumulation of protein-free filtrates induced by dextran is not affected by treatment with indomethacin, whereas the infiltration of plasma protein and neutrophils in response to carrageenan is inhibited, suggesting the involvement of different mediators. Taking into consideration the participation of mast cells in dextran-induced edema, we assessed the possible effect of cyclic antidepressants on these cells. We observed a prominent effect of all drugs tested on preventing mast cell degranulation in the rat mesentery.

The mechanism through which tricyclic antidepressants can inhibit mast cell secretion was investigated by Clemons et al.[26] These authors suggested a reduction of intracellular calcium ion levels due to amitriptyline and prochlorperazine treatment. However, the modulating effect of antidepressants on mast cells seems to vary depending on the drug.[27] As we showed in the present paper, an effect on mast cells might be a characteristic of most heterocyclic antidepressants.

In our opinion, some mechanistic aspects concerning the anti-inflammatory activity of antidepressants at the molecular level have yet to be elucidated. These aspects include their effects on cytokine release, the modulation of inflammatory pathways regulated by these mediators,

and, further, how leukocyte trafficking is affected both in acute and in chronic inflammation.

In summary, the results of the present study provide evidence of the modulating effect of heterocyclic antidepressants on neutrophil migration and on mast cell stabilization. These findings might have an implication for the treatment of several inflammatory conditions, including allergic diseases.

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Disclosure

The authors report no conflicts of interest.

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