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Original Article

Anti-Inflammatory Activity of a Selection of Antidepressant Drugs

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Abstract

Anti-inflammatory activity has been reported for a few of antidepressant drugs and in contrary sertraline has potentiated inflammation. In this study, anti-inflammatory effect of a collection of antidepressant drugs belonging to different classes was evaluated to help a rational selection of these drugs in disease conditions such as association of depression or anxiety with inflammatory diseases such as rheumatoid arthritis. Male Wistar rats weighing 160-200 g were used. Anti-inflammatory activity was assessed using carrageenan-induced paw edema test. Amitriptyline, nortriptyline, desipramine, trimipramine, fluvoxamine (37.5 and 75 mg/kg), fluoxetine (30 and 60 mg/kg), citalopram (10 and 40 mg/kg), doxepin and maprotiline (25 and 50 mg/kg) were administered s.c. 30 min. prior to subplantar injection of 100 µl carrageenan suspension (1% w/v). Difference of paw volume measured just before and 4 h after carrageenan injection was considered as an index of inflammation. Except nortriptyline and citalopram, all tested drugs showed anti-inflammatory activity. It seems that the anti-inflammatory effect is not correlated with inhibition of norepinephrine and/or serotonin reuptake transporters and further studies are needed to clarify the exact mechanism of their anti-inflammatory action.

Keywords: Antidepressants; Anti-inflammatory; Carrageenan.
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1. Introduction

There are several reports about the analgesic and anti-nociceptive activity of antidepressant drugs [1-4], and they are widely indicated for controlling chronic pain [5-8]. Also some investigators using carrageenan as a valid model of evaluation of anti-inflammatory drugs have reported anti-inflammatory activity for drugs such as fluoxetine, clomipramine and imipramine [9-13], and in contrary it has been reported that sertraline potentiates inflammation [9]. Since both fluoxetine and sertraline belong to the same group of antidepressants, namely selective serotonin reuptake inhibitors (SSRIs) [14], it seems that inhibition of serotonin

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reuptake by itself cannot explain the suppression of inflammation observed with fluoxetine. Another work [15] addresses the potential for bupropion to decrease inflammation by lowering tumor necrosis factor-alpha (TNF-α), and for mirtazapine to increase inflammatory process by increasing TNF-α predominantly synthesized by lymphocytes and monocytes. Since TNF-α is central in pathophysiology of several inflammatory diseases such as rheumatoid arthritis and Crohn's disease this may have obvious treatment decision implications.

Antidepressant drugs have different selectivity for increasing norepinephrine (NE) and serotonin (5-HT) in synapses, and they also differ from each other with regard to their sedativity, anticholinergic, antihistaminic and H_2-blocking potencies [14, 16], and it is not clear to what extent these pharmacological differences affect their anti-inflammatory potency. The anti-inflammatory effect of several antidepressant drugs have not been studied yet and a better understanding of the anti-inflammatory potencies of these drugs might provide guidance for the selection of these drugs in situations such as association of anxiety or depression with inflammatory disorders. Thus, in the present study citalopram, fluoxetine and fluvoxamine as SSRIs, maprotiline as a heterocyclic drug and desipramine as a tricyclic drug with selectivity for inhibition of norepinephrine reuptake, amitriptyline and nortriptyline as conventional non-selective serotonin and norepinephrine reuptake inhibitors, doxepin and trimipramine [14, 17] as antidepressants with high histamine receptor blocking activity were selected for assessment of putative correlations between the above pharmacological activities and anti-inflammatory potency.

2. Materials and methods

2.1. Animals

Male Wistar rats weighing 160-200 were used in this study. Animals were housed in groups of six per standard makrolon cage, on 12 h light/dark cycle; and air temperature was maintained at 22±2 ℃. They were offered food and water *ad libitum*. Experiments reported in this study were carried out in accordance with local guidelines for the care of laboratory animals of Isfahan University of Medical Sciences.

2.2. Drugs and chemicals

Carrageenan was purchased from Sigma-Aldrich (St. Louis, MO, USA) and dissolved in isotonic saline. Amitriptyline, nortriptyline

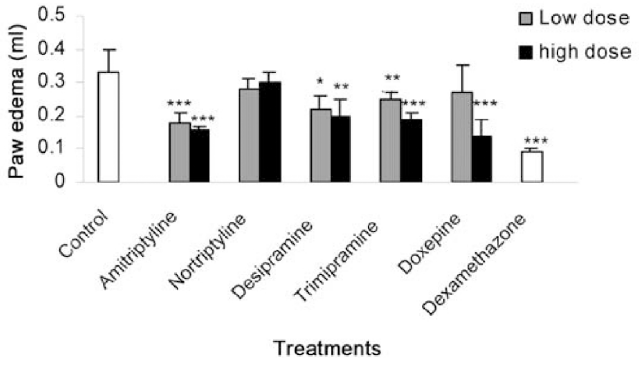

Figure 1. Anti-inflammatory Effect of five tricyclic antidepressant drugs in carrageenan rat paw edema. Amitriptyline, nortriptyline, desipramine and trimipramine (37.5 and 75.0 mg/kg) and doxepine (25.0 and 50.0 mg/kg) were injected sc 30 min. prior to carrageenan. Control group received vehicle and a group received dexamethasone (1 mg/kg) as reference drug. Data represent mean±SD of six animals in each group. *p<0.05, **p< 0.01, ***p< 0.001 represent significant difference compared with control group.

(Amin Co. Iran), desipramine (Exir Co., Iran), fluoxetine (Arya Co., Iran) doxepine and citalopram (Sigma, USA) were dissolved in 0.9% NaCl. Other drugs including trimipramine, fluvoxamine (Alborz Darou Co., Iran) and maprotiline (Razak Co. Iran) were dissolved in ethanol.

2.3. Anti-inflammatory activity

The anti-inflammatory activity was evaluated by the carrageenan-induced paw edema test in the rat [18]. Male Wistar rats (160-200g) were briefly anaesthetized with ether and injected subplantarly into right hind paw with 0.1 ml of 1% (w/v) suspension of carrageenan in isotonic saline. The left hind paw was injected with 0.1 ml saline and used as a control. Paw volume was measured prior and 4 h after carrageenan administration using a mercury plethysmograph (Ugo Basil, Italy).

Drugs were administered 30 min. prior to carrageenan injection. The doses of drugs employed were based on previous studies describing anti-nociceptive or anti-inflammatory effects for these agents [11, 12, 19] or justifying according to relative antidepressant potencies of drugs.

Control groups received equivalent volume (1 ml/kg) of the vehicle. Dexamethasone (1 mg/kg) was used as positive control.

2.4. Data analysis

Data obtained were expressed as mean (±SD). Differences between groups were statistically analyzed by one-way analysis of variance (ANOVA) followed by Duncan as the post hoc test using the software package SPSS version 10. Differences were considered statistically Significant at p values less than 0.05.

3. Results

As seen in figures dexamethasone, a corticosteroid drug significantly (p<0.001) reduced carrageenan-induced paw edema. Among tricyclic antidepressant drugs, nortriptyline (Figure 1) and from selective serotonine reuptake inhibitors citalopram did not exert any significant anti-inflammatory activity (Figure 2). Doxepin and fluoxetine exerted effective anti-inflammatory effects only at the high dose (50 mg/kg for doxepin and 60 mg/kg for fluoxetine) (Figures 1 and 2). Other antidepressant drugs showed considerable anti-inflammatory effect at both applied doses. Maprotiline as a heterocyclic antidepressant could exert significant (p<0.001) anti-inflammatory activity at both applied doses (Figure 3).

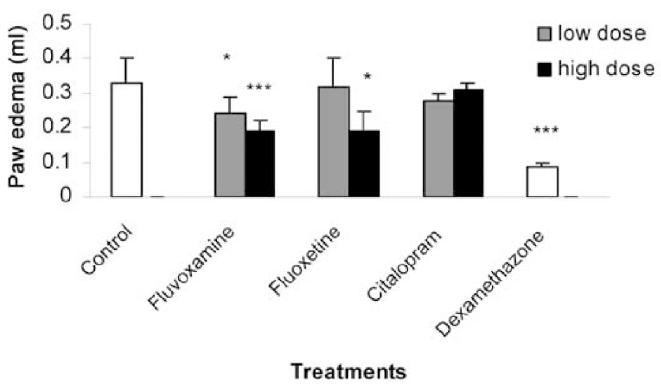

Figure 2. Anti-inflammatory Effect of three SSRI antidepressant drugs in carrageenan rat paw edema. Fluvoxamine (37.5 and 75.0 mg/kg), fluoxetine (30.0 and 60.0 mg/kg) and citalopram (10 and 40 mg/kg) were injected sc 30 min. prior to carrageenan. Control group received vehicle and a group received dexamethasone (1 mg/kg) as reference drug. Data represent mean±SD of six animals in each group. *p<0.05, ***p< 0.001 represent significant difference compared with control group.

4. Discussion

Results of the present study clearly demonstrated that some antidepressant drugs have considerable anti-inflammatory effect. In this study, only nortriptyline and citalopram were ineffective. In cases of maprotiline, desipramine, fluvoxamine, trimipramine and doxepine this is the first report of their anti-inflammatory effect.

The mechanism by which antidepressant drugs alleviate inflammation is not clear, though inhibition of substance P or involvement of the pituitary adrenal axis have been suggested to play a role in the anti-inflammatory effect of fluoxetine [11, 19]. Antidepressant drugs have many pharmacological actions. Whilst the majority of currently used antidepressants act as serotonin or noradrenaline reuptake inhibitors [16], the role of serotonin or noradrenaline reuptake blockade in antidepressant- induced anti-inflammatory activity has not been explored. In addition to their expression within the central nervous system, evidence indicates that serotonin and noradrenaline transporters are also expressed on peripheral blood mononuclear cells [20, 21]. Moreover, it has been reported that serotonin and noradrenaline released from lymphocytes and monocytes [21] exert some immunomodulatory properties via interacting with receptors present on immune cells [22]. In this study, citalopram, which is a selective serotonin reuptake inhibitor, did not exert a significant suppression of carrageenan-induced edema, but the observed fluoxetine effect is consistent with previous works [10, 11, 23], and fluvoxamine as another potent SSRI drug elicited an anti-inflammatory response. Abdel-Salam and his coworkers [9] showed that sertraline, another SSRI drug, instead of being anti-inflammatory, exacerbated the carrageenan- induced inflammation.

This makes it unlikely that modulation of serotonergic neurotransmission accounts for the anti-inflammatory properties described for fluoxetine and the other antidepressants.

On the other hand, while amitriptyline showed marked anti-inflammatory activity, nortriptyline was ineffective. These drugs belong to the same class (tricyclic antidepressants) and their chemical structure is very similar; nortriptyline differing from amitriptyline only by one methyl group [14]. Since both drugs are potent inhibitors of serotonin and norepinephrine reuptake transporters, it seems that inhibition of the transporters cannot provide a complete explanation for anti-inflammatory activity of amitriptyline. In addition, we also examined

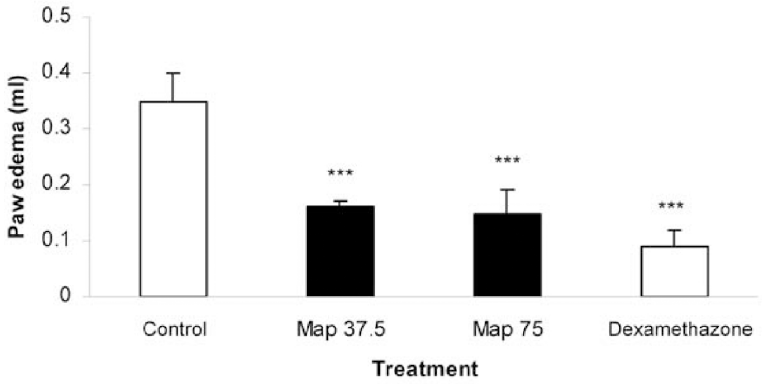

Figure 3. Anti-inflammatory Effect of maprotiline as a heterocyclic antidepressant drug in carrageenan rat paw edema. Maprotiline (37.5 and 75.0 mg/kg) was injected sc 30 min. prior to carrageenan. Control group received vehicle and a group received dexamethasone (1 mg/kg) as reference drug. Data represent mean±SD of six animals in each group. ***$p< 0.001$ represent significant difference compared with control group.

the ability of trimipramine, a tricyclic antidepressant that lacks significant monoamine reuptake inhibitory properties [17] and this drug unlike nortriptyline showed significant anti-inflammatory effect. These results again do not support a link between anti-inflammatory activity and inhibition of amine reuptake transporters. Bianchi *et al*. [23] suggested that changes in local mediator release might underlie the anti-inflammatory effects of clomipramine and fluoxetine because PGE2 immunoreactivity and substance P concentrations in the inflammatory exudate were reduced following the administration of these drugs. The carrageenan edema is characterized by distinct phases with the involvement of different mediators. Histamine, serotonin and bradykinin are responsible for the edema in the first 2 h after carrageenan injection, while prostaglandins are involved later [24-26]. Therefore, it is also possible that some of the anti-inflammatory effects observed with tricyclic antidepressants and in part with heterocyclic ones are due to interference with the release or activity of these mediators.

Antidepressant drugs interact with alpha-adrenoceptors, muscarinic, H_1 and H_2 histaminic receptors to different extents [14], and it is not clear which of these effects are (is) involved in anti-inflammatory response.

It has been reported that H_2-receptors are involved in the induction of rat paw edema, especially those induced by histamine and carrageenan [27] and since in the present work doxepin and trimipramine which have potent H_2-blocking activity [28, 29] significantly suppressed carrageenan edema. It seems that at least a part of anti-inflammatory effect of these drugs may be explained by inhibition of H_2 histamine receptors. In conclusion, results of the present study provided evidence for an anti-inflammatory effect of maprotiline, amitriptyline, trimipramine, desipramine and doxepine and to a lesser extent fluoxetine and suggest that these drugs may be useful in the management of some inflammatory syndromes and also for patients who suffer from both inflammatory and psychological disorders.

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