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Further studies on anti-inflammatory activity of maprotiline in carrageenan-induced paw edema in rat

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ABSTRACT

Antidepressant drugs are commonly used for treatment of different medical disorders besides of psychiatric diseases. Accumulating evidence suggests that antidepressants exhibit anti-inflammatory activity *in vivo* and *in vitro* conditions, but the mechanisms of this property are not clear very well. In our earlier work, we demonstrated that i.c.v. and i.p. injection of maprotiline, as an antidepressant, decreased paw edema at the fourth hour after subplantar injection of carrageenan. Therefore, this work was undertaken to investigate anti-inflammatory effects of maprotiline in more details. Our results verified that i.p. (25 and 50 mg/kg) and i.c.v. (100 μg/rat) application of maprotiline significantly reduced paw edema at 1, 2, 3 and 4 h intervals after carrageenan challenge. Pathological examinations and MPO activity also showed that both i.p. and i.c.v. maprotiline considerably inhibited infiltration of PMN leucocytes into the inflamed paws. Additionally, i.p. and i.c.v. maprotiline at all applied doses noticeably declined levels of IL-1β into the site of inflammation, while only i.p. maprotiline at a dose of 50 mg/kg significantly decreased TNF-α levels in the carrageenan-injected paws.

These results confirmed anti-edematogenic activity of i.p. and i.c.v. maprotiline in the carrageenan induced paw edema model and showed that these properties of maprotiline might be mediated through inhibition of PMN infiltration and release of IL-1β and TNF-α.

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1. Introduction

Although antidepressant drugs are broadly prescribed for several medical purposes besides the management of psychiatric disorders, pharmacological properties of these drugs are not clear very well [1–3]. Increasing evidence suggests that antidepressants produce anti-inflammatory activity both *in vitro* and *in vivo* conditions [4–7]. Abdel-salam et al. reported that fluoxetine, amitriptyline and trazodone exhibit anti-inflammatory effect on carrageenan-induced paw edema while sertraline exacerbated paw edema [8]. Our previous findings also demonstrated the anti-inflammatory activities of amitriptyline and fluvoxamine [9,10].

Anti-inflammatory activity of antidepressant agents could be important from several aspects. First, amine theory is the common hypothesis regarding effectiveness of antidepressants in the management of depression, but this theory does not completely describe the beneficial effects of antidepressant compounds in the treatment of psychiatric diseases [11]. Moreover, etiology of depression remains as an open question [12]. Therefore, inflammatory properties of antidepressants would provide a new avenue to portray these obscure problems concerning etiology and treatment of depression. In line of these statements, some studies have reported the role of immune system and pro-inflammatory cytokines in the expression of depression [13]. Second, it has been suggested that production of pro-inflammatory mediators are involved in the producing of pain [14]. Since, antidepressants are prescribed in the control of various types of inflammatory pain such as irritable bowel syndrome and osteoarthritis [15,16], it is possible that the anti-inflammatory effects of antidepressants have an important function in the analgesic activities of them.

Maprotiline, as an atypical antidepressant, well tolerated owing to its favorable side effect profile and less interfering with autonomic system than first-generation of antidepressants [17,18]. Maprotiline is a SNRI

Abbreviations: AP, anterior–posterior; ANOVA, one-way analysis of variance; CNS, central nervous system; EDTA, ethylenediaminetetraacetic acid; ELISA, enzyme-linked immunosorbent assay; HTAB, hexadecyl trimethyl-ammonium bromide; i.c.v., intracerebroventricular; IL-1β, interleukin-1β; i.p., intraperitoneal; μl, microliter; mg/kg, milligram per kilogram; ml, milliliter; MPO, myeloperoxidase; PBS, phosphate buffered saline; PMN, polymorphonuclear; rpm, rotations per minute; SNS, sympathetic nervous system; SNRI, selective norepinephrine reuptake inhibitor; SSRIs, serotonin-specific reuptake inhibitor; TCAs, tricyclic antidepressants; TNF-α, tumor necrosis factor-α; V, ventral; w/v, weight per volume.

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that interacts with some receptors such as histaminergic, adrenergic and cholinergic [19–22]. In our previous works; we reported that central and peripheral injection of maprotiline exerts anti-inflammatory effect in the carrageenan induced paw edema model [23]. Therefore, in this study, we wanted to further examine the possible mechanisms involved in the anti-inflammatory activity of maprotiline.

2. Materials and methods

2.1. Animals

Male Wistar rats (200–250 g) were purchased from the animal house of the Faculty of Pharmacy, Isfahan University of Medical Sciences. All rats were housed in groups of four per cage, under a 12:12 h light/dark cycle with free access to food and water. After surgical implantation of an i.c.v. cannula, animals were maintained one per cage to avoid possible dislocation of the cannula. The experiments were carried out in accordance with local guidelines for the care of laboratory animals of the Isfahan University of Medical Sciences.

2.2. Chemicals

Maprotiline hydrochloride was donated by Razak Pharmaceutical Co. (Tehran, Iran) and dissolved in a hydroalcoholic solution (70% isotonic saline; 30% ethanol). Carrageenan (lambda) was purchased from Fluka Chemical (Switzerland) and dissolved in isotonic saline. Indomethacin (Sigma, USA) was suspended in a 2% (w/v) of aqueous carboxy methylcellulose. HTAB, aprotinin A, bovine serum albumin, phenylmethylsulfonyl fluoride, benzethonium chloride, EDTA, tween 20 all purchased from Sigma Chemical Company (St. Louis, MO, USA). TNF-α (R&D Company, USA), and IL-1β (ALPCO, USA) kits were used for evaluation of biochemical parameters.

2.3. Surgical procedure

The animals were anesthetized with i.p. injection of a ketamine (50 mg/kg) and xylazine (10 mg/kg) mixture. Then, the animals were placed in a stereotaxic frame (Stoelting, USA), and an i.c.v. cannula was implanted with stereotaxic coordinates: AP, −0.8 mm; L, 1.4 mm; and V, 3.3 mm, according to Paxinos and Watson [24]. The animals were handled daily for five days before the experiments to acclimatize them to manipulation and minimize nonspecific stress responses. Rats with the i.c.v. cannulas were euthanized at the end of the experiments, and their brains were examined to confirm the correct implantation of the cannula.

2.4. Carrageenan-induced rat paw edema

The rats received a subplantar injection of 100 μl of a 1% (w/v) suspension of -carrageenan in the right hind paw [25]. The paw volume was measured by a Plethysmometer (Ugo Basile, Italy) immediately before subplantar injection of carrageenan and then at 1, 2, 3 and 4 h afterwards. The data were presented as the variation in the paw volume (ml) and were compared to pre-injection values.

2.5. Experimental design

The doses of maprotiline used in this study were chosen from our previous work [23].

In the first series of tests, effect of i.p. maprotiline (25 and 50 mg/kg, $n = 6$) on carrageenan-induced paw edema was studied. Animals were treated with i.p. maprotiline 30 min prior to subplantar injection of carrageenan. The paw volumes (ml) were measured before carrageenan challenge, and then again, at 1, 2, 3 and 4 h after that to determine the variation in paw inflammation over the time course. Control group received only vehicle (i.p.; $n = 6$). A group of animals was pretreated with indomethacin (10 mg/kg; $n = 6$) and used as the positive control. Finally, animals were euthanized, and the carrageenan-injected paws were collected for the evaluation of cytokine parameters.

Results of our previous works showed that supraspinal sites are involved in the second phase (4 h after carrageenan test) of carrageenan-induced paw edema in rats. In the second group, i.c.v. injection of maprotiline was done to determine whether it produces anti-inflammatory effects in the first phase of inflammation (0–2 h after carrageenan challenge) or not [17]. Maprotiline was injected slowly for 1 min through the cannula (100 μg/rat, $n = 6$) 30 min prior to carrageenan in a volume of 10 μl and the paw volumes were recorded according to the indicated method in the before step. The control group received vehicle (i.c.v.; 10 μl; $n = 6$). At the end of experiments, animals were euthanized, and the carrageenan-injected paws were collected for the evaluation of cytokine parameters.

In the third group, we wanted to investigate the effects of i.c.v. and i.p. maprotiline on PMN migration and tissue destruction induced by carrageenan. Briefly, animals were divided into four groups (nine rats in per group) including vehicle group, i.p. maprotiline (25 and 50 mg/kg), i.c.v. maprotiline (100 μg/rat) and indomethacin (10 mg/kg, i.p.). Four hours following injection of carrageenan, animals were euthanized, and the carrageenan-treated paws were removed for pathological and MPO activity assessments.

2.6. Histopathologic examination

In the third group, three samples of the carrageenan-injected paws were taken and fixed in the 10% formaldehyde solution for one week. Then, the fixed biopsies were embedded in paraffin and cut into 3–4 μm slices. The slices were mounted on the glass slides and stained with hematoxylin and eosin for light microscopy analysis. The evaluation was done by a pathologist in a blinded way.

2.7. MPO assay

The MPO activity in paw skin was measured based on the modified method of Bradley [26]. The biopsies of carrageenan-injected paws of five samples in the third group were removed and weighted and then each sample was finely chopped in 1 ml of 50 mM potassium phosphate buffer containing 0.5% HTAB. The chopped tissue was transferred to a homogenizing tube and the container was rinsed with 2×1 ml HTAB in buffer solution. More buffers were added to obtain a concentration equivalent to 5 ml per 0.1 g of paw tissue and homogenized (15,000 rpm) for 4×45 s at 1 min intervals. Next, the homogenate was transferred to a sample tube, sonicated in an ice bath for 10 s, then subjected to a sequence of freezing and thawing 3 times, and sonicated again for 10 s. Afterward, the suspensions were centrifuged at 15,000 rpm for 15 min in 4 °C and then the supernatant decanted for examination. The activity of MPO in supernatants was measured spectrophotometrically: 0.1 ml of the supernatant was added to 2.9 ml of 50 mM K_3PO_4 buffer (pH = 6.0) containing O-dianisidine dihydrochloride (0.167 mg/ml) and 0.005% hydrogen peroxide. The absorbance of the reaction mixture was determined at 450 nm using a UV–Vis spectrophotometer. The activity of MPO was reported in units (U) per gram tissue weight of wet tissue.

2.8. Determination of the IL-1β and TNF-α levels in the rat paw

TNF-α and IL-1β levels in the paw tissues were evaluated by enzyme-linked ELISA as described previously [27]. Four hours after carrageenan challenge, the collected samples were weighed; snap frozen on liquid nitrogen and stored at −70 °C to be processed for IL-1β and TNF-α determinations. Skin tissue was homogenized in PBS (pH = 7.4) containing 0.4 M NaCl, 0.05% Tween-20, 0.5% bovine serum albumin, 0.1 mM phenylmethylsulfonyl fluoride, 0.1 mM benzethonium chloride, aprotinin A 20 KI, and 10 mM EDTA. The homogenates were

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