

## The anti-inflammatory effects of venlafaxine in the rat model of carrageenan-induced paw edema

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### ABSTRACT

**Objective(s):** Recently anti-inflammatory effects of antidepressants have been demonstrated. Venlafaxine belongs to newer antidepressants with serotonin norepinephrine reuptake inhibition property. The pain alleviating properties of venlafaxine in different pain models such as neurogenic pain, diabetic neuropathy, and fibromyalgia have been demonstrated. Anti-inflammatory effects of venlafaxine and also its underlying mechanisms remain unclear. The present study was designed to evaluate the anti-inflammatory effects of venlafaxine and determine possible underlying mechanisms.

**Materials and Methods:** We examined the anti-inflammatory effects of intraperitoneal (IP) and intracerebroventricular (ICV) administration of venlafaxine in the rat model of carrageenan-induced paw edema.

**Results:** Our results showed that both IP (50 and 100 mg/kg) and ICV (50 and 100 µg/rat) injection of venlafaxine inhibited carrageenan-induced paw edema. Also IP and ICV administration of venlafaxine significantly decreased myeloperoxidase (MPO) activity and interleukin (IL)-1β and tumor necrosis factor (TNF)-α production. Finally, we tried to reverse the anti-inflammatory effect of venlafaxine by yohimbine (5 mg/kg, IP), an alpha2-adrenergic antagonist. Our results showed that applied antagonist failed to change the anti-inflammatory effect of venlafaxine.

**Conclusion:** These results demonstrated that venlafaxine has potent anti-inflammatory effect which is related to the peripheral and central effects of this drug. Also we have shown that anti-inflammatory effect of venlafaxine is mediated mostly through the inhibition of IL-1β and TNF-α production and decreases MPO activity in the site of inflammation.

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## Introduction

Recently the role of antidepressants, particularly conventional tricyclic antidepressants (TCAs) such as amitriptyline, nortriptyline, and doxepin for alleviating various types of pain, such as inflammatory and neuropathic pain have been shown (1-3). Moreover, it has been reported that fluoxetine, paroxetine, and sertraline can modulate the ability of microglia to produce the proinflammatory-cytokine such as tumor necrosis factor-α (TNF-α) and the free radical nitric oxide (NO) (4-6). Venlafaxine is a structurally novel phenylethylamine belongs to newer antidepressants that block the synaptosomal uptake of noradrenaline and serotonin (7). The pain alleviating properties of venlafaxine in different pain models such as neurogenic pain, diabetic neuropathy, and fibromyalgia have been demonstrated (8-10). In addition venlafaxine does not

induce the usual TCAs side effects caused by their anticholinergic, antihistaminic, and alpha1-adrenergic antagonistic properties (11). Thus this drug could be a novel and promising treatment in the different kinds of inflammatory pain. But the anti-inflammatory effects of venlafaxine and the underlying mechanisms have not been fully examined. The aims of this study were to (a) determine the effect of systemic venlafaxine injections on the carrageenan-induced paw edema, (b) examine the possible involvement of central mechanism in the anti-inflammatory activity of venlafaxine, (c) determine the effect of venlafaxine on the myeloperoxidase (MPO) activity in the site of inflammation, (d) evaluate the effect of venlafaxine on inflammatory cytokines such as IL-1β and TNF-α production, and (e) investigate the potential role of alpha 2-adrenergic receptors in this effect of venlafaxine.

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## Materials and Methods

### Animals and housing conditions

The experiments were performed on male Sprague Dawley rats (200-250 g). They were housed four per cage, in a room under controlled temperature ( $23\pm 2$  °C), humidity (50%), and lighting (12/12 hr light/dark cycle), with food and water available *ad libitum*.

### Chemicals

Venlafaxine was obtained from Darupakhsh pharmaceutical Co., Iran. Carrageenan ( $\lambda$ ) was obtained from Fluka Chemical (Switzerland) and dissolved in saline solution. IL-1 $\beta$  (ALPCO, USA), and TNF- $\alpha$  (R&D Company, USA) kits were used for measurement the cytokines level.

### Surgical procedure

The rats were anesthetized with intraperitoneal (IP) injection of ketamine (50 mg/kg) and xylazine (10 mg/kg). Then an intracerebroventricular (ICV) cannula was implanted with stereotaxic coordinates: AP: -0.8 mm, L: 1.4 mm, and V: 3.3 mm, based on Paxinos and Watson atlas (12). The rats were handled daily for additional five days before the experiments to familiarize them with experimental manipulations and lessen nonspecific stress responses. At the end of the experiments rats with the ICV cannulas were sacrificed, and their brains were removed and examined to confirm the correct insertion of the cannula.

### Carrageenan-induced paw edema

100  $\mu$ l of a 1% (w/v) suspension of carrageenan  $\lambda$  was injected subplantar in the right hind paw (13). Immediately before carrageenan injection and then at 4 hr after that the volume of the paw was determined by a plethysmometer (Ugo Basile, Italy).

### Experimental design

All the applied doses in this experiment were chosen according to previous studies (14, 15).

In the first series of experiments, the effect of venlafaxine (50 and 100 mg/kg, IP; n=6) on paw edema was examined. Venlafaxine was injected 30 min before subplantar injection of carrageenan. Paw volumes (ml) were measured before carrageenan injection, and then again, at 4 hr after that. Control group was treated only with vehicle (5 ml/kg, IP; n=6). The animals were sacrificed at the end of the experiments, and the inflamed paw was collected for cytokines and MPO activity measurement.

In the second series, we used the ICV route to determine the involvement of supraspinal levels in the anti-inflammatory effects of venlafaxine. Venlafaxine was injected smoothly for 1 min through the ICV cannula (50 and 100  $\mu$ g/rat; n=6), 30 min before carrageenan injections and the paw volumes

were measured. The control group were treated by vehicle (ICV, 5  $\mu$ l; n=6). Finally, in order to evaluate the possible role of alpha 2-adrenergic receptors in the inhibitory effect of venlafaxine on carrageenan-induced inflammation, animals were pretreated with yohimbine (5 mg/kg, IP) 15 min before administration of venlafaxine. At the end of experiments animals were sacrificed and the paw tissues were collected to measure the cytokine levels and MPO activity.

### Myeloperoxidase activity assay

MPO activity, an index of polymorphonuclear leukocyte accumulation, was measured in the inflamed paw according to the modified method of Bradley (16). Paw tissue was chopped and homogenized in potassium phosphate buffer. Then, the homogenate was sonicated and centrifuged for 15 min at 4 °C. After that, potassium phosphate buffer (50 mM, pH 6.0) containing o-dianisidinedihydrochloride (0.167 mg/ml) and 0.005% hydrogen peroxide was added to the supernatant. The change in the absorbance of the reaction mixture was measured at 450 nm over a 5-min period using a UV-V in spectrophotometer. Data was expressed as the change in absorbance/min/g paw tissue.

### Measurement of the IL-1 $\beta$ and TNF- $\alpha$ level in the rat paw

TNF- $\alpha$  and IL-1 $\beta$  levels in the inflamed paws were measured using an enzyme-linked immune sorbent assay (ELISA) commercial kit according to the manufacturer's instructions. The cytokine levels were calculated after plotting the standard curves and expressed as  $\mu$ g/g tissue.

### Statistical analysis

The data are expressed as the means $\pm$ S.E.M. Data were compared by one-way analysis of variance (ANOVA) followed by Fisher's LSD post hoc test for multiple comparisons. The minimal level of significance was considered at  $P<0.05$ .

## Results

### Effect of IP injection of venlafaxine on carrageenan-induced paw edema

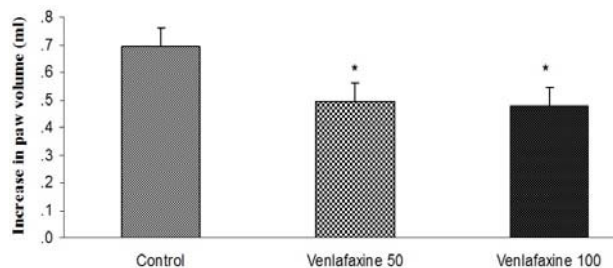
As shown in Figure 1, IP injection of venlafaxine at the doses of 50 and 100 mg/kg significantly decreased the development of paw edema as compared to the control group.

### Effect of ICV injection of venlafaxine on carrageenan-induced paw edema

As illustrated in Figure 2, ICV administration of venlafaxine (50 and 100  $\mu$ g/rat) attenuated paw edema formation as compared to the control group.

### Effect of venlafaxine on the MPO activity

The MPO activity of paw tissue was significantly



**Figure 1.** Effect of venlafaxine (50 and 100 mg/kg, IP) on carrageenan-induced paw edema in rats. Venlafaxine or the vehicle was administered 30 min prior to carrageenan (1%) injection, and the rats were evaluated for paw edema at 4 hr after carrageenan injection. The results are expressed as mean±SEM \* $P<0.05$  versus control group;  $n=6$  in all groups; venlafaxine 50 (venlafaxine 50 mg/kg, IP); venlafaxine 100 (venlafaxine 100 mg/kg, IP)

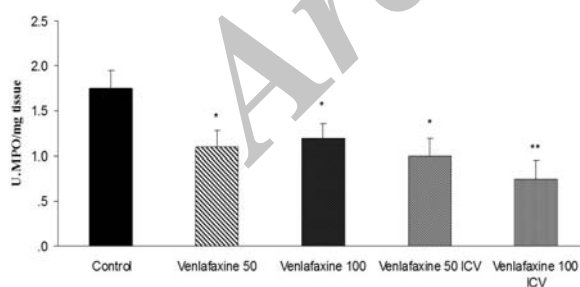
raised at 4 hr after carrageenan injections. As shown in Figure 3, venlafaxine (50 and 100 mg/kg, IP) significantly reduced MPO activity in the paw. The ICV administration of venlafaxine (50 and 100 µg/rat) also decreased the MPO activity, compared to control group.

#### Effect of venlafaxine on IL-1 $\beta$ concentration

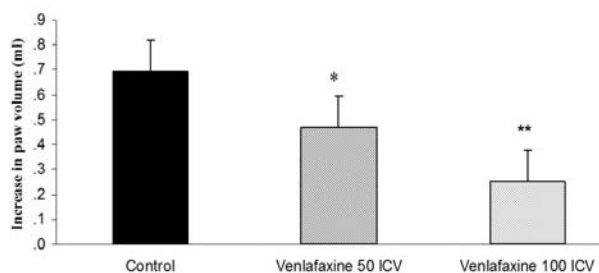
As illustrated in Figure 4, carrageenan injections significantly increased IL-1 $\beta$  concentration in the hind paw. Venlafaxine (50 and 100 mg/kg, IP) significantly reduced IL-1 $\beta$  level. The ICV administration of venlafaxine (50 and 100 µg/rat) also significantly attenuated production of IL-1 $\beta$  in the carrageenan-injected paws.

#### Effect of venlafaxine on TNF- $\alpha$ concentration

As shown in Figure 5, IP administration of venlafaxine (50 and 100 mg/kg) significantly reduced TNF- $\alpha$  production. The ICV injection of venlafaxine (50 and 100 µg/rat) also inhibited the production of TNF- $\alpha$  in the carrageenan-injected paw.



**Figure 3.** Effect of venlafaxine on MPO activity in the rat paws treated with carrageenan. The rats received IP venlafaxine (50 and 100 mg/kg, IP) or ICV venlafaxine (50 and 100 µg/rat, ICV) 30 min prior to carrageenan injection. The MPO activity was measured at 4 hr after carrageenan injection. The results are expressed as mean±SEM. \* $P<0.05$ , \*\* $P<0.01$  versus control group,  $n=6$  in all groups, venlafaxine 50 (venlafaxine 50 mg/kg, IP), venlafaxine 100 (venlafaxine 100 mg/kg, IP), venlafaxine 50 ICV (venlafaxine 50 µg/rat, ICV), venlafaxine 100 ICV (venlafaxine 100 µg/rat, ICV)



**Figure 2.** Effect of venlafaxine (50 and 100 µg/rat, ICV) on carrageenan-induced paw edema in rats. Venlafaxine or the vehicle was administered 30 min prior to carrageenan (1%) injection, and the rats were evaluated for paw edema at 4 hr after carrageenan injection. The results are expressed as mean±SEM. \* $P<0.05$ , \*\* $P<0.01$  versus control group,  $n=6$  in all groups, venlafaxine 50 ICV (venlafaxine 50 µg/rat, ICV), venlafaxine 100 ICV (venlafaxine 100 µg/rat, ICV)

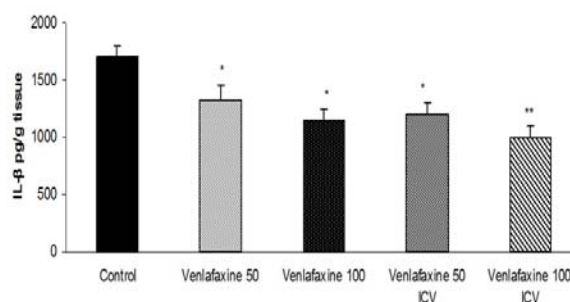
#### Effect of yohimbine on the anti-inflammatory effect of venlafaxine

Pretreatment with yohimbine (5 mg/kg, IP) 30 min prior to venlafaxine (50 mg/kg) did not alter the anti-inflammatory effect of venlafaxine (Figure 6).

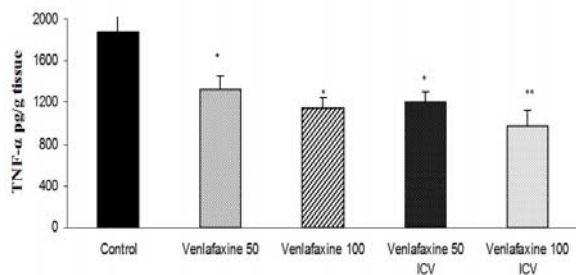
## Discussion

In the present study we showed that IP and ICV administration of venlafaxine exhibit a significant anti-inflammatory effect in rat models of carrageenan-induced paw edema. Our results showed that venlafaxine was effective in attenuating paw edema of the inflammation induced by carrageenan.

Carrageenan-induced paw edema is one of the most frequently used models for the study of inflammation, inflammatory pain, and the anti-inflammatory activity of different compounds (17, 18). Nitric oxide and inflammatory cytokines such as TNF- $\alpha$  and IL-1 are released following carrageenan



**Figure 4.** Effect of venlafaxine on IL-1 $\beta$  levels in the rat paws after carrageenan (1%) injections. Venlafaxine (50 and 100 mg/kg, IP or 50 and 100 µg/rat, ICV) was injected 30 min prior to subplantar injection of carrageenan. The results are expressed as mean±SEM. \* $P<0.05$ , \*\* $P<0.01$  versus control group,  $n=6$  in all groups, venlafaxine 50 (venlafaxine 50 mg/kg, IP), venlafaxine 100 (venlafaxine 100 mg/kg, IP), venlafaxine 50 ICV (venlafaxine 50 µg/rat, ICV), venlafaxine 100 ICV (venlafaxine 100 µg/rat, ICV)



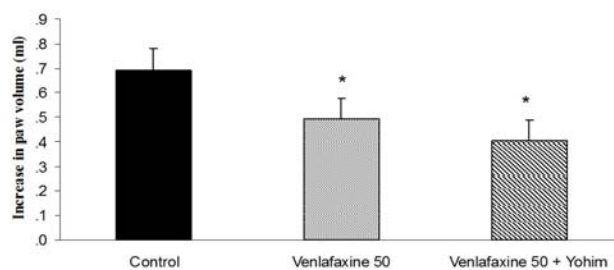
**Figure 5.** Effect of venlafaxine on TNF- $\alpha$  production in the rat paws treated with carrageenan. Venlafaxine (50 and 100 mg/kg, IP or 50 and 100  $\mu$ g/rat, ICV) was injected 30 min prior to subplantar injection of carrageenan. The results are expressed as mean $\pm$ SEM. \* $P$ <0.05, \*\* $P$ <0.01 versus control group,  $n$ =6 in all groups, venlafaxine 50 (venlafaxine 50 mg/kg, IP), venlafaxine 100 (venlafaxine 100 mg/kg, IP), venlafaxine 50 ICV (venlafaxine 50  $\mu$ g/rat, ICV), venlafaxine 100 ICV (venlafaxine 100  $\mu$ g/rat, ICV)

injections in the hind paw (19, 20). In the present study the interference of venlafaxine with PMN cells migration has been examined. Our results showed that both IP and ICV administration of venlafaxine caused a noticeable reduction in the infiltration of PMN leucocytes in the site of inflammation.

As mentioned above carrageenan injection also aggravates the release of pro-inflammatory cytokines such as TNF- $\alpha$  and IL-1 $\beta$ . Cytokines have a vital role in the generation and deterioration of inflammatory disease (21-24).

Our results also showed that IP and ICV injection of venlafaxine significantly reduced the IL-1 $\beta$  production in carrageenan-injected paw tissues. Systemic and central injection of venlafaxine also decreased the concentration of TNF- $\alpha$ .

Multiple lines of studies have shown central mechanisms that modulate peripheral inflammation. Previous reports have shown that noradrenaline suppresses the production of IFN- $\alpha$  and enhances the production of IL-10, so has significant negative immune regulatory effects. By administration of  $\beta$  and  $\alpha_2$ -adrenoceptor agonists and antagonists, it has been shown that the noradrenaline not only inhibits the IFN $\gamma$  production through  $\beta$  and  $\alpha_2$ -adrenoceptor activation, but also stimulates IL-10 production by  $\beta$ -adrenoceptor activation. Noradrenaline dose-dependently inhibits IL-6 secretion from murine spleen slices under bacteria-rich conditions; it also causes a dose-dependent inhibition of lipopolysaccharide (LPS)-induced IL-6 production (25-27). It is well known that venlafaxine causes alterations in central norepinephrine and serotonin neurotransmitters (7). Locus coeruleus which is one of the most important nuclei involved in depression, pain, and inflammation is inhibited by venlafaxine through  $\alpha_2$ -adrenoceptor mediated mechanism (28-30). Activation of the  $\alpha_2$ -adrenoceptors leads to a progressive reduction in locus coeruleus electrical activity (29). It could be suggested that enhancement of norepinephrine concentrations in the locus coeruleus



**Figure 6.** Effect of yohimbine on the anti-inflammatory effect of venlafaxine. The results are expressed as mean $\pm$ SEM. \* $P$ <0.05 versus control group,  $n$ =6 in all groups, Venlafaxine 50 (venlafaxine 50 mg/kg, IP), Venlafaxine 50+Yohim (venlafaxine 50 mg/kg, IP in concurrent with yohimbine 5 mg/kg, IP)

via venlafaxine can lead to over activation of  $\alpha_2$ -adrenoceptors and suppression of locus coeruleus electrical activity (28).

Our results showed that ICV administration of venlafaxine attenuates the development of paw edema.

Thus the effect of venlafaxine on central nerves system to alter neuroimmune interactions and/or sympathetic nervous system activity that affect the function of the immune system could be considered as one of the possible mechanisms of venlafaxine responsible in attenuation of inflammation.

It is also possible that venlafaxine changes the activity of descending neuronal pathways projecting from the brain to the spinal cord and leads to the inhibition of the peripheral nerve activity and dorsal root reflexes associated with the neurogenic component of inflammation (31).

Body of evidences showed the connection between the inflammation and the generation of pain. Previous studies have demonstrated that the inhibition of pro-inflammatory cytokines generation attenuates the hyperalgesia induced in different inflammatory processes (22, 23). Therefore, it seems that the effect of venlafaxine on PMN cells migration, TNF- $\alpha$ , and IL-1 $\beta$  production may participate in its analgesic effect.

## Conclusion

Results of the present study showed that venlafaxine has anti-inflammatory property and suggested that at least some of this effect is mediated through supraspinal and peripheral sites.

Moreover, we found that venlafaxine decreased PMN leucocytes infiltration and the generation of inflammatory cytokines (IL-1 $\beta$  and TNF- $\alpha$ ). Thus it is possible that analgesic effects of venlafaxine are mediated through its effects on the pro-inflammatory mediators.

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