Evaluation of antinociceptive and anti-inflammatory effects of venlafaxine in the rat

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ÖZET

Venlafaksinin sıçanlardaki antinosiseptif ve anti-enflamatuar etkisinin değerlendirilmesi

Bu çalışmanın amacı, venlafaksinin sıçanlarda karragenan ile oluşturulan ağrı ve enflamasyon üzerindeki antinosiseptif etkilerini araştırmak idi. Ağrı, sıçanların ayaklarında, plantar yüzeye karragenan (% 1) enjekte edilerek oluşturulmuştur. Sıçanların ayak tabanlarına toksin enjeksiyonunu takip eden 2 ila 24. saatler arasında karragenan ile oluşturulan mekanik hipersensitive, mekanik uyaran yanıtı (von Frey monofilaman testi) ve ayak tabanı ödemi değerlendirilerek venlafaksinin etkinliği araştırılmıştır. Toksin enjeksiyonu öncesi venlafaksin uygulanması, periferik karragenan enjeksiyonu ile oluşturulan mekanik uyarana artmış duyarlılığı anlamlı olarak azaltmış ya da tamamen ortadan kaldırmıştır. Bu çalışma, periferik olarak uygulanan venlafaksin ön tedavisinin, enflamatuar sürecin ağrı bileşeni üzerindeki etkinliğini ortaya koymuştur.

Anahtar kelimeler: Venlafaksin, antinosiseptif, anti-enflamatuar, sıçan

SUMMARY

The aim of this study was to test antinociceptive properties of venlafaxine in rats with carrageenan-induced pain and inflammation. Pain was provoked with carrageenan (1%) injection into the plantar surface of the rat paw-pad. The effect of venlafaxine on carrageenan-induced mechanical hypersensitivity, mechanical stimulation response (the von Frey monofilament test) as well as the size of carrageenan-induced paw edema were tested at 2 to 24 hours following the toxin injection into the rat paw-pad. Pretreatment with venlafaxine significantly reduced or completely abolished the enhanced sensitivity to mechanical stimuli provoked by peripheral carrageenan injection. The study demonstrated the efficacy of peripherally applied venlafaxine pretreatment on the pain component of inflammatory process.

Key words: Venlafaxine, antinociceptive, anti-inflammatory, rat

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Introduction

Tricyclic antidepressants have been used for decades in the treatment of severe pain in non-depressed patients (McQuay et al. 1996, Tura and Tura 1990, Spiegel et al. 1983). A balanced inhibition of the uptake of both serotonin and noradrenaline is considered to be important for the analgesic effect of antidepressants. Thus, amitriptyline (Max 1987) and imipramine (Kvinesdal et al. 1984) have been shown to be effective in the treatment of neuropathic pain whereas selective serotonin reuptake inhibitors such as fluoxetine (Max 1992) seem to be less effective. Venlafaxine is a structurally novel phentylethylamine antidepressant drug. It blocks the synoptosomal uptake of noradrenaline and serotonin and, to a lesser degree, of dopamine (Lloyd 1992). Its active metabolite, O-desmethylvenlafaxine, also inhibits serotonin and norepinephrine reuptake, with potency similar to that of venlafaxine. Venlafaxine's unique pharmacological profile suggests a combined serotonin-noradrenaline mediated antinociceptive effect. It inhibits the reuptake of both serotonin and noradrenaline but not have either antihistaminergic or anticholinergic effects (Muth et al. 1986). Venlafaxine has been safe and effective in animal models, healthy human volunteers, and patients for treatment of various pain syndromes. It has been shown that it has an antinociceptive effect (Schreiber 1999), some benefit in fibromyalgia (Dwight et al. 1998), peripheral diabetic neuropathy (Kiayias et al. 2000, Lithner 2000, Davis and Smith 1999), headache (Ozyalcin et al. 2005, Adelman et al. 2000, Nascimento 1998) and post-mastectomy pain syndrome (Reuben 2002).

The present study was designed to investigate the anti-inflammatory effect of venlafaxine, an antidepressant which inhibits reuptake of both serotonin and norepinephrine, in the carrageenan model of paw inflammation.

Material and Method

Animals

Adult female Sprague Dawley rats (150-200 g) and Male Balb/c mice (4-5 weeks old) were used. The animals were maintained in a temperature controlled (23 ± 1°C) colony room under a 12 h day-night cycle, they were housed 4 per cage in plastic cages, and were given access to food and water ad libitum. The animals received a 1 week habituation period before the experimental procedures were initiated, during which time they were handled daily. All experimental protocols were approved by the Animal Care and Use Committee of the Marmara University, Istanbul, Turkey and were carried according to Helsinki Declaration.

Induction of the Inflammatory Response

Inflammation was induced by the intraplantar (i.pl.) injection of 100 µl 10 mg of carrageenan in 1 ml saline (%1 w/v), in the left hind paw.

Experimental Groups

The animals divided randomly into 4 groups.

1. Control group: Rats were injected 100 µl of saline (i.pl.) and served as control group.
2. Carrageenan group: Rats were injected 100 µl of carrageenan (%1 w/v, i.pl.)
3. Venlafaxine group (50 mg/kg): Rats were injected 50 mg/kg venlafaxine (i.p.) and then 30 minutes later they were injected 100 µl of carrageenan (%1 w/v, i.pl.).
4. Venlafaxine group (100 mg/kg): Rats were injected 100 mg/kg venlafaxine (i.p.) and then 30 minutes later they received 100 µl of carrageenan (%1 w/v, i.pl.).

Behavioral Tests

The following tests were used for the assessment of baseline and the variations of mechanical threshold and paw edema.

Mechanical hyperalgesia was tested, before and 2, 4, 6, 8 and 24 hours after the carrageenan injection. The von Frey filaments were used for the assessment of the baseline and the variation of mechanical hyperalgesia on the injected side compared to the opposite, non-injected paw and the other groups. For this purpose, rats were placed individually into Plexiglas cages on a wire-mesh table positioned approximately 50 cm above a standard laboratory bench. Animals were given 30 min to acclimate to the testing apparatus. A series of 10 calibrated von Frey monofilaments (1.10, 1.70, 3.30, 5.10, 8.30, 17.0, 24, 34, 50, 110 g, Somedic Sales AB) were used to assess the threshold to mechanical stimulation. Each monofilament was placed perpendicularly onto the midplantar region of the left and right hindpaws through the holes in the wire-mesh table, and pressure was applied just until the point of deflection of the monofilament, after which the monofilament was removed. The lowest amount

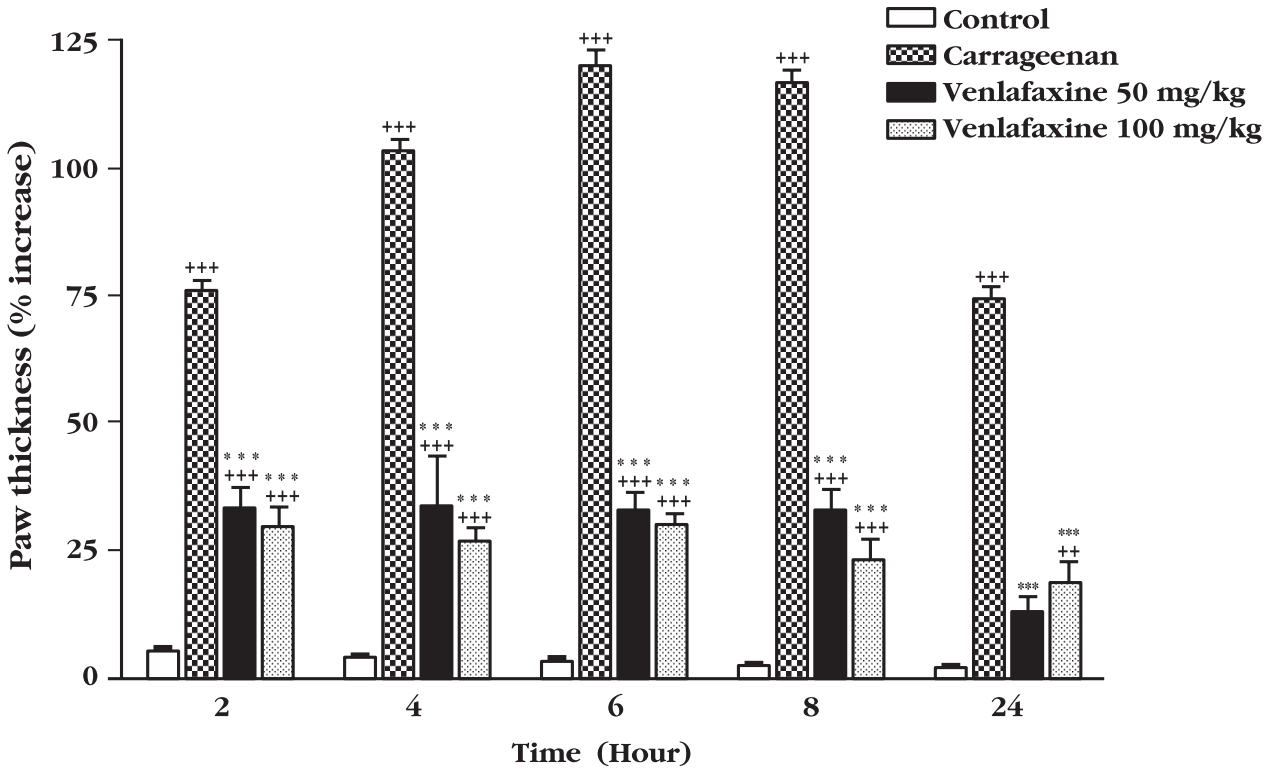

Figure 1: The effect of venlafaxine on paw thickness following the paw inflammation induced by intraplantar carrageenan injection.

Each bar corresponds to the % increase from basal value ± SEM.
*** $p<0.001$ compared to carrageenan group, ++ $p<0.01$, +++ $p<0.001$ compared to control group.

of force required to elicit a response was recorded as the mechanical withdrawal threshold in grams.

In order to quantify the paw edema induced by carrageenan, before and 2, 4, 6, 8 and 24 hours after carrageenan injection, a caliper was used to take the paw diameter, which was defined as the distance from the plantar to the dorsal surface of the center of the hind paw.

Statistical Analysis

All statistical analyses were carried out using GraphPad Prism version 4. Paw edema and paw withdrawal threshold data were expressed as the % increase ± S.E.M, and mean ± S.E.M, respectively. One way Analysis of Variance (ANOVA) followed by Tukey's post hoc test was used for experiments and $p<0.05$ was set as the level of statistical significance.

Results

The paw thickness of each animal was recorded before the experiment (Control group: 0.39 ± 0.01, Carrageenan group: 0.36 ± 0.00, Venlafaxine (50 mg/kg) group: 0.38 ± 0.01, Venlafaxine (100 mg/kg) group: 0.36 ± 0.02). These measurements served as baseline values to calculate the % increase of the paw thickness. The paw thickness of the control group did not differ during the experiment (2nd h: 5.36 ± 0.69, 4th h: 3.50 ± 0.58, 6th h: 3.31 ± 0.71, 8th h: 2.55 ± 0.43, 24th h: 1.73 ± 0.72). In the carrageenan group the significant increase was started at the 2nd hour, and then reached the maximum at 6th hour and lasted more than 24 hours (2nd h: %75.76 ± 2.48, 4th h: %103.50 ± 2.10, 6th h: %120.20 ± 2.83, 8th h: %116.90 ± 2.45, 24th h: %74.22 ±2.18). Treatment with 50 mg/kg and 100 mg/kg venlafaxine (i.p.) significantly attenuated the carrageenan induced paw edema during the observation period (50 mg/kg; 2nd h: 33.11 ± 4.00, 4th h: 33.97 ± 9.40, 6th h: 32.76 ± 3.53, 8th h: 32.69 ± 4.11, 24th h: 12.63 ± 3.24; 100 mg/kg ; 2nd h: 29.28 ± 4.21, 4th h: 27.01 ± 2.32, 6th h: 29.84 ± 2.41, 8th h: 23.23 ± 3.85, 24th h: 18.47 ± 4.24). The reduction was most remarkable at 6 h after carrageenan injection (Fig 1). Post- hoc comparisons showed significant inhibition of edema formation at all time points. The paw thickness of contralateral hind paw did

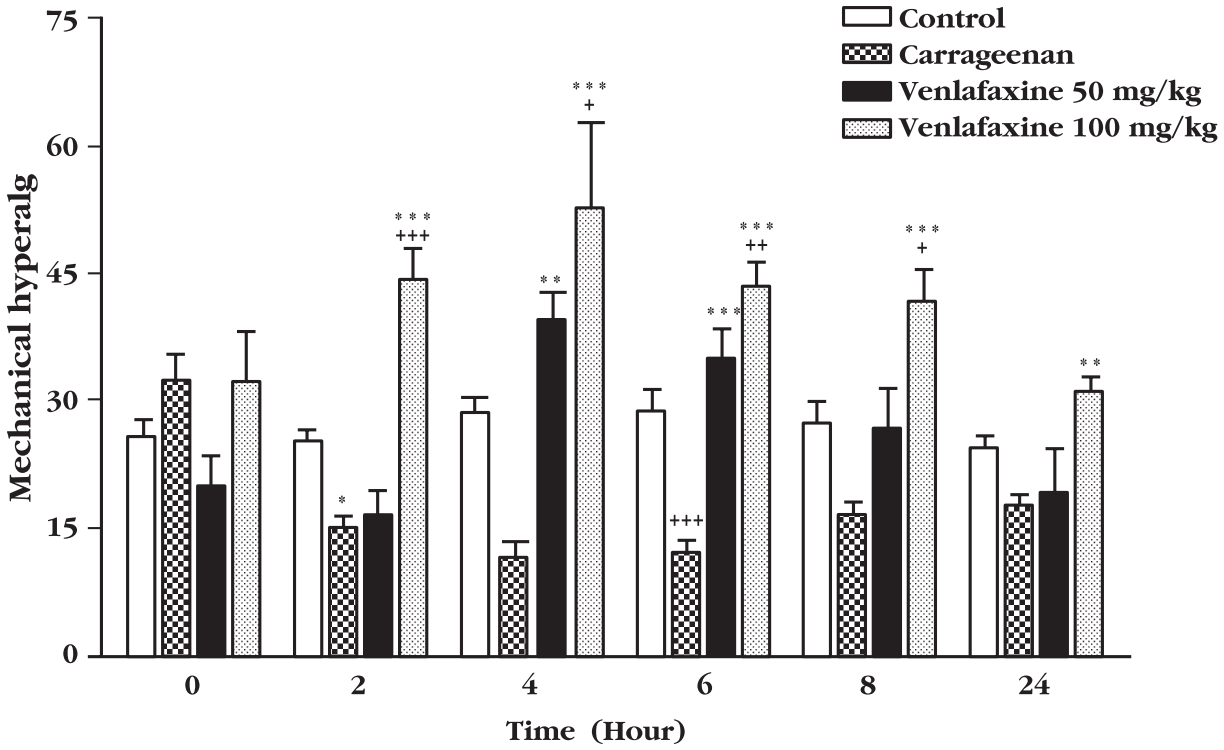

Figure 2: The effect of venlafaxine on mechanical hyperalgesia following the paw inflammation induced by intraplantar carrageenan injection. The basal bar corresponds to the average measurements made on the rats before the injections.

Each bar corresponds to the mean value ± SEM.
** $p<0.01$, *** $p<0.001$ compared to carrageenan group, + $p<0.05$, ++ $p<0.01$, +++ $p<0.001$ compared to control group.

not differ from that in the control (data not shown).

The mechanical threshold of each animal was recorded before the experiment (Control group: 25.63 ± 2.02, Carrageenan group: 32.60 ± 2.44, Venlafaxine (50 mg/kg) group: 19.27 ± 4.11, Venlafaxine (100 mg/kg) group: 32.01 ± 6.19). These measurements served as baseline values to calculate the decrease of the mechanical threshold. The mechanical threshold of control group did not differ during the experiment (2nd h: 25.25 ± 1.25, 4th h: 28.13 ± 2.36, 6th h: 28.50 ± 2.79, 8th h: 27.25 ± 2.72, 24th h: 24.38 ± 1.63). In the carrageenan group the significant decrease was started at the 2nd hour, then reached the maximum at 6th hour and lasted 24 hours (2nd h: 14.76 ± 1.54, 4th h: 11.78 ± 1.42, 6th h: 11.78 ± 1.42, 8th h: 16.83 ± 1.18, 24th h: 17.53 ± 1.38). Treatment with 100 mg/kg venlafaxine (i.p.) significantly attenuated the carrageenan induced mechanical hyperalgesia during the observation period (100 mg/kg; 2nd h: 44.00 ± 4.02, 4th h: 52.57 ± 10.33, 6th h: 43.14 ± 3.23, 8th h: 41.71 ± 4.10, 24th h: 31.14 ± 1.84). 50 mg/kg venlafaxine was effective at 4th h and 6th h (50 mg/kg; 2nd h: 16.43 ± 2.87, 4th h: 39.33 ± 3.37, 6th h: 35.00 ± 3.42, 8th h: 26.88 ± 4.64, 24th h: 19.23 ± 5.05). The mechanical threshold of contralateral hind paw did not differ from that in the control (data not shown).

Discussion

The present study demonstrated the effectiveness of peripherally applied venlafaxine in reducing hyperalgesia induced by carrageenan injection in the rat paw. Venlafaxine inhibited both carrageenan-induced rat paw edema and paw thickness indicating that it has an anti-inflammatory potential.

Intraplantar injection of carrageenan proves long lasting hyperalgesia and edema formation (from 2 to 24 hours). Carrageenan-induced marked inflammatory edema and thermal as well as mechanical hyperalgesia are most pronounced at 2-24 hours. In the present experiment 25 mg/kg venafaxine failed to significantly affect the size of carrageenen-induced paw edema whereas 50 and 100 mg/kg venlafaxine had significant effect. In the time course of the experiment, venlafaxine 50 and 100 mg/kg significantly inhibited paw edema. In mechanical hyperalgesia experiments, high

dose of venlafaxine was effective at all time points and low doses up to 24 hours.

Tricyclic antidepressants relieve neuropathic pain and the analgesic properties of tricyclic antidepressants have been substantiated in human experimental pain models. The analgesic effect of tricyclics is probably caused by inhibition of presynaptic reuptake of serotonin and noradrenalin, perhaps in combination with blockade of sodium channels and an N-methy-D-aspartate (NMDA) antagonist-like action. Selective serotonin reuptake inhibitor antidepressants have been found to be less effective than tricyclics for neuropathic pain (Sindrup 1999). It has been speculated that drugs with a selective inhibition of presynaptic reuptake of both serotonin and noradrenaline, but without the postsynaptic receptor blocking and ion-channel-blocking effect seen with the tricyclic antidepressants, could have the analgesic effect of the tricyclics. There are a few numbers of studies on a selective serotonin reuptake inhibitor (SSRI) fluoxetine, on the carrageenan-induced paw inflammation in the rat. It has been shown that it displayed marked anti-inflammatory activity, inhibiting paw edema. The non-selective noradrenaline (NA) and serotonin (5-HT) reuptake inhibitors imipramine, amitriptyline and clomipramine displayed anti-inflammatory activity in the carrageenan model of paw inflammation. Antidepressant drugs showed antinociceptive properties in the tail-electric stimulation assay with amitriptyline and trazodone being the most effective in this respect. Duloxetine, a selective but balanced serotonergic and noradrenergic reuptake inhibitor, was evaluated in the acute nociceptive pain models of tail flick and hot plate in mice and in the persistent and/or inflammatory pain models of acetic acid-induced writhing in mice, carrageenan-induced thermal hyperalgesia and mechanical allodynia in rats, and capsaicin-induced mechanical allodynia in rats (Jones et al. 2005). Therefore previous studies confirmed anti-inflammatory and anti-nociceptive effect for some antidepressant drugs and indicate that SSRIs differently affects inflammation.

Venlafaxine has been effective in several animal models of pain (Marchand et al. 2003a, b, Schreiber et al. 1999, Lang et al. 1996). Venlafaxine relieved thermal hyperalgesia, neuropathic pain due to chronic constriction injury (CCI) of the sciatic nerve (Marchand et al. 2003a, Lang et al. 1996), paw pressure in a rat model of unilateral mononeuropathy (Uyar et al. 2003).

In conclusion, our results suggest that venlafaxine, an antidepressant which inhibits reuptake of both serotonin and norepinephrine, possesses important peripheral antinociceptive effect that may contribute to its effectiveness as an anti-inflammatory drug. Further experimental studies are required to determine the potential benefit of venlafaxine for the treatment of inflammation.

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