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Pharmacological Properties Of Venlafaxine, Mirtazapine And Escitalopram: Anti-Inflammatory And Analgesic Effects.

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ABSTRACT

The purpose of this study was to evaluate the anti-inflammatory, anti-arthritic and analgesic effects of mirtazapine, venlafaxine and escitalopram, which are well known used antidepressants. Carrageenan-induced paw edema model in rats was used to assess the acute anti-inflammatory effects. Paw volume was measured at 1, 2, 3 and 4th hour post challenge. Anti-nociceptive effect was evaluated by hot plate method. Chronic inflammation was assessed using Complete Freund's Adjuvant (CFA) model. The animals were injected with CFA in sub-plantar tissue of the right hind paw. Paw volume, ankle flexion scores, adjuvant-induced hyperalgesia and serum cytokine levels were assessed. Results obtained demonstrate that mirtazapine, venlafaxine and escitalopram significantly and time-dependently inhibited carrageenan-induced paw oedema in rats. Mirtazapine, venlafaxine and escitalopram increased the reaction time of rats in hot plate test. We observed an increase in paw volume, ankle flexion scores, thermal hyperalgesia, serum levels of interleukin-1β, PGE_2 and TNF-α, induced by intraplantar CFA injection. Regular treatment up to 28 days of adjuvant-induced arthritic rats with mirtazapine, venlafaxine and escitalopram showed anti-inflammatory and analgesic activities by suppressing the paw volume, recovering the paw withdrawal latency, and by inhibiting the ankle flexion scores in CFA-injected rats. In addition significant reduction in serum levels of interleukin-1β, PGE_2 and TNF-α levels in arthritic rats was observed by treatment with antidepressants. These results suggest that antidepressants have significant anti-inflammatory and anti-nociceptive effects in acute and chronic murine models of inflammation, which is associated with the reduction of interleukin-1β, PGE_2 and TNF-α levels.

Keywords: Antidepressants; Carrageenan**;** Anti-nociceptive; Complete Freund's Adjuvant; Cytokines.

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INTRODUCTION

Antidepressants have been widely been used for the treatment of neuropathic and non-neuropathic chronic pain [1,2]. Several antidepressants are known to possess intrinsic antinociceptive activity. Antidepressants, by inhibiting the uptake of monoamines, lead to increased amount of noradrenaline and serotonin in the synaptic cleft at both spinal and supraspinal levels causing reinforcement of descending pain inhibitory pathways [1]. Previous studies compared antinociceptive/anti-inflammatory efficacy among the three different classes of antidepressants namely tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI) and atypical antidepressants [3]. In experimental models of inflammation, fluoxetine, imipramine and clomipramine have been shown to have some anti-inflammatory activity [4]. Moreover, it has been observed that patients of chronic pain disorder are often associated with depression affecting their day to day routine [2]. Antidepressants may benefit these patients having depression along with inflammation and/or inflammatory pain disorders. Hence, this study was designed to evaluate anti-inflammatory and analgesic activities of nowadays used antidepressants.

Depression and a feeling of hopelessness are common accompaniments of chronic pain [5]. It has also been proved in about 75% of the studies that some antidepressants are superior to placebo in alleviating pain as they have some intrinsic analgesic activity [6]. A wide range of painful conditions are responsive to antidepressants and they have been used as co-analgesics in various clinical conditions, particularly diabetic neuropathy pain, rheumatoid arthritis and migraine [7]. Antidepressants with noradrenergic reuptake inhibition properties (TCA) have been reported to produce varying degrees of pain relief in several persistent or chronic pain syndromes in humans [8,9]. Tricyclic antidepressants (TCAs) were the first choice in the treatment of these pains [10]. However, these drugs have many side effects that limit their therapeutic use. Newer antidepressants as mirtazapine, venlafaxine and escitalopram which is devoid of TCAs adverse side effects, could have a therapeutic potential [11].

In recent times, numerous open and controlled studies have shown antidepressant drugs to have an analgesic activity, especially, selective serotonin reuptake inhibitors (SSRIs), which are effective in mixed and chronic pain [12]. On the other hand, there are some studies that have altogether denied the analgesic role of SSRI [13,14]. Despite such an enormity of literature, it is not yet clear whether these can be used as analgesics, and if so, what could be the underlying mechanism. Therefore, the present study was planned with the aim of confirming the anti-inflammatory and analgesic/antinociceptive activity of SSRI (escitalopram) and atypical antidepressants (venlafaxine and mirtazapine. Mirtazapine, escitalopram and venlafaxine are extensively used antidepressants in clinical practice. Mirtazapine, a norepinephrine and specific serotonin antidepressant, enhances both serotonin (5-HT) and norepinephrine (NE) neurotransmission [15]. Escitalopram is the S-enantiomer of the racemic selective serotonin reuptake inhibitor compound citalopram with reported marked antidepressant and anxiolytic activities [16]. Venlafaxine inhibits the reuptake of 5-HT, NE and dopamine. Although its mechanism of action is similar to the tricyclic antidepressant (TCAs) drugs; it acts more specifically at those receptors and does not bind to the receptors responsible for the side effects of TCAs [17]. It has been reported that mirtazapine, escitalopram and venlafaxine have anti-ulcer effects in depressed rats receiving indomethacin [18]. These antidepressants and others appeared to exert their anti-ulcer effects by activation of antioxidant mechanisms, inhibition of toxic oxidant mechanisms in stomach tissues in addition to their anti-inflammatory effects revealed by reducing TNF-α and increasing IL-10 contents [19].

Despite the growing popularity of selective serotonin reuptake inhibitors (SSRIs) since 1980s, there are only few controlled studies of their efficacy in managing inflammation and pain while others denied SSRI-mediated analgesia [14,20,21].

Hence, the current study aimed to examine the possible anti-inflammatory effects of mirtazapine, escitalopram and venlafaxine in carrageenan-induced paw edema model and freund's adjuvant-induced arthritis model in rats as well as the analgesic effect and to compare their effects with standard drug. It seemed also important to investigate the effects of the chosen agents on certain parameters known to be involved in inflammation pathophysiology as prostaglandins (PGE_2), and pro-inflammatory cytokines.

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MATERIALS AND METHODS

Animals

Adult male albino Wistar rats weighing 130 to 160 g between 10 to 12 weeks age were obtained from the animal house colony of the National Research Centre. The animals were housed under standard light, temperature, and room humidity conditions during the study.

Ethics Statement:

This experiment was carried out in according to the recommendations in the Guide for the Care and Use of Laboratory Animals published by the US National Institute of Health (NIH Publication No. 85–23, revised 1996) and under regulations of Animal Care and Use of National Research Centre in Egypt. All surgery was performed under deep sodium pentobarbital anesthesia and all efforts were made to minimize the suffering of animals.

Materials

All chemicals for laboratory experimentation were purchased from Sigma Chemical (Germany). Indomethacin, mirtazapine, escitalopram and venlafaxine were obtained from Khahira (Egypt), Novartis (Egypt), Lundbeck (Denmark) and Wyeth (USA) companies, respectively. Drugs were prepared as suspensions in 1% tween 80 and orally administered.

Treatment protocols

The carrageenan-induced rat paw oedema

Acute inflammation was induced by injection of 0.1 ml of 1% (w/v) carrageenan in the right hind paw of rat [22]. The model was used to assess the effect on acute inflammation. Animals were assigned randomly into 5 groups; indomethacin (10 mg/kg) *group* [23,24], mirtazapine (10 mg/kg) group [18], escitalopram (20 mg/kg) group [25], venlafaxine (30 mg/kg) group [21,26], and non-treated control group. The rats received vehicle or drugs 1 h before carrageenan injection. The hind paw volume was measured immediately before carrageenan injection and at selected times thereafter by water displacement method using 7410, plethysmometer, Ugo Basile, Comerio, Italy [27]. Percent change of paw edema was calculated from zero time.

The hot plate test

For three consecutive days preceding the experiment, rats were adapted on the hot plate by placing them on a plate maintained at room temperature for 15 min each day. Each animal was then placed gently onto a 50°C hot plate to perform the test. Latency to exhibit nociceptive responses, such as licking paws or jumping off the hot plate was determined 30, 60, 120 min after administration of test substances or saline [28].

Complete Freund's Adjuvant arthritis

Adjuvant arthritis was induced by subplantar injection of 0.1 ml Freund's complete adjuvant (CFA) in the right hind paw [29]. Animals were divided into six groups; normal control group that received vehicle, CFA-arthritic group that received CFA without subsequent treatment for 30 days, indomethacin (10 mg/kg) group, mirtazapine (10 mg/kg) group, escitalopram (20 mg/kg) group, venlafaxine (30 mg/kg) group that were treated with the previously mentioned drugs orally for 30 days. Paw volume was duplicately measured just prior to adjuvant injection and at intervals of seven days for 30 days after adjuvant injection using a digital plethysmometer (UGO-BASIL Biological Research Apparatus) and the mean values were recorded [30,31]. To evaluate the arthritic progression of CFA-induced arthritis in the rat, two different parameters were measured: change in paw volume and the squeaking score in the ankle flexion test. These were considered indicators of adjuvant-induced arthritis.

Paw volumes were expressed as relative values to that of day 0 when CFA was injected. The ankle flexion test involved gentle flexion and extension of the hind limb of the arthritic rat, as described before [30].

This elicited vocalizations (squeaking) that were scored on a scale (squeaking score) as a measure of hyperalgesia. The procedure of flexion and extension were repeated 10 times in every 5 s and the rating of 0 (null) or 1 (vocalization) was given to each hind limb. This test was performed only once a day for each animal.

The paw withdrawal latency was recorded using the hot plate at day 0 of CFA injection and at day 7, 14, 21 and 28 after administration of the tested substances or vehicle.

Determination of prostaglandin-E2, interleukin-1β and tumor necrosis factor-α in the serum of arthritic rats

At the end of the experiment, rats were subjected to the following procedures: blood samples were collected from different rat groups after fasting for 12 hours; from retro-orbital venous plexus of the rats then they had been sacrificed with ether anesthesia. After centrifugation for 20 min at a speed of 3000 rounds per minute, sera were obtained for measurement of the following parameters (by using corresponding parameter rat ELISA kit according to the manufacturer's instructions): serum levels of IL-1β expressed as pg/ml and was measured following Silva et al., 2000 [32], serum levels of PGE_2, expressed as ng/ml and was determined using solid-phase extraction followed by an enzyme immunoassay determination, according to the instructions provided by the manufacturer and according to method of Nieto et al.,1998 [33], and serum TNF-α expressed as pg/ml and was determined using an enzyme-linked immunosorbent assay according to the principle of Takahashi et al., 1995 [34].

Statistical analysis

Values were expressed as means ± S.E.M. Comparisons between means were carried out using different statistical tests according to the nature of the determined parameter. Data of carrageenan-induced rat paw edema, adjuvant-induced arthritis, hot plate test, plantar test, analgesic effects which involved measuring a repeated parameter on time intervals, were analyzed using repeated measures 2-way ANOVA followed by Tukey HSD test for multiple comparisons. Results of the experiments other than those mentioned were analyzed using one way ANOVA followed by Tukey HSD test for multiple comparisons. GraphPad Prism software, version 6 (Inc., San Diego, USA) was used to carry out these statistical tests. The difference was considered significant when $p<0.05$.

RESULTS

Effect of escitalopram, mirtazapine and venlafaxine on carrageenan-induced rat paw oedema

Pretreatment with indomethacin significantly decreased the carrageenan-induced edema by 52% decrease compared to untreated control. The inhibitory effects of escitalopram, mirtazapine and venlafaxine were comparable to that of indomethacin showing non-significant change in paw oedema at the 1st, 2nd, 3rd and 4th hour of treatment. Escitalopram, mirtazapine and venlafaxine reported inhibitory effect of 57.5%, 59% and 50%, respectively, at the fourth hour of the experiment, compared to non-treated control group (**Fig.1**).

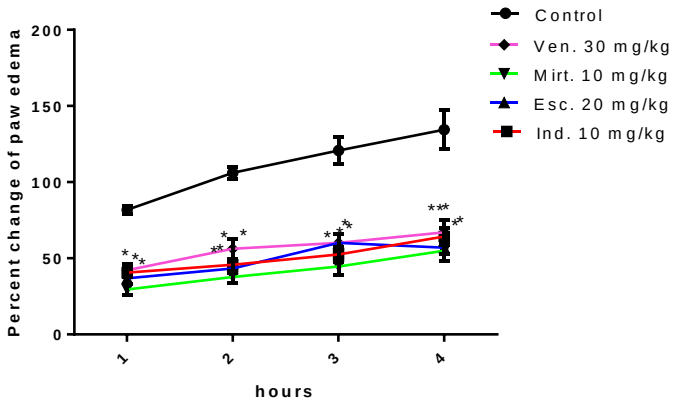

Figure 1: Effect of escitalopram, mirtazapine and venlafaxine on carrageenan-induced rat paw oedema

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Effect of escitalopram, mirtazapine and venlafaxine on rat nociception reaction time using the hot plate

Indomethacin (10 mg/kg) significantly increased the reaction time all over the experiment after 30 min of drug administration when compared to the control group. Meanwhile, the antidepressant drugs increased the reaction time at 30, 60 and 120 min following drug administration as compared with the control animals. The reaction time on the hot plate after administration of escitalopram, mirtazapine and venlafaxine was significantly elevated when compared to the control group and it was comparable to that produced by indomethacin at 30, 60 and 120 min time intervals (**fig. 2**).

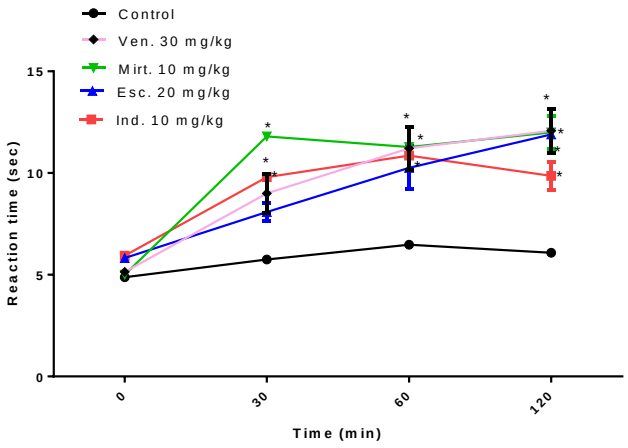

Figure 2: Effect of escitalopram, mirtazapine and venlafaxine on rat nociception reaction time

Effect of escitalopram, mirtazapine and venlafaxine on paw withdrawal latency in CFA-arthritic rats

Oral treatment with escitalopram, mirtazapine and venlafaxine increased paw withdrawal latency significantly after 14 days of drug administration compared to CFA-arthritic control. The analgesic activity of the tested antidepressants was insignificant from indomethacin analgesic activity at 14, 21 and 28 days of the experiment (**fig. 3**).

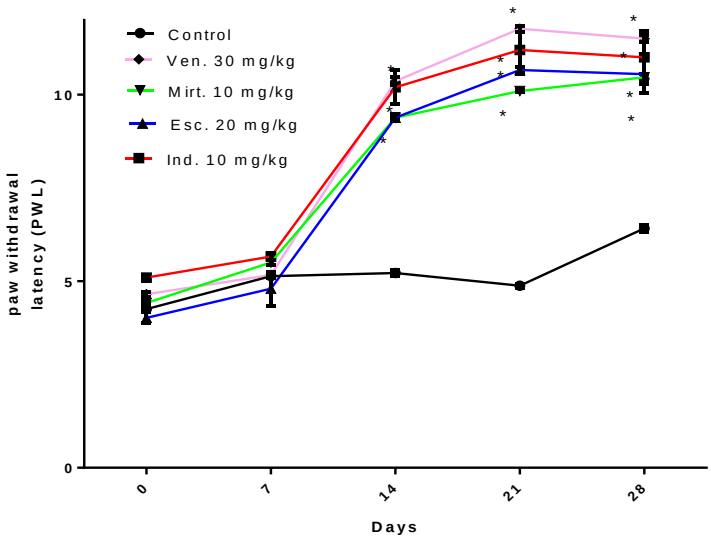

Figure 3: Effect of escitalopram, mirtazapine and venlafaxine on paw withdrawal latency in CFA-arthritic rats

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Effect of escitalopram, mirtazapine and venlafaxine on paw volume and the squeaking score in the ankle flexion test in CFA-arthritic rats

Regarding change in paw volume after CFA at 7 day-intervals for 30 days, control untreated rats displayed continuous increase in paw volume for 28 days as shown in fig.2. Pre- and continuous treatment with indomethacin for 30 days inhibited the increase in paw edema significantly by 50% when compared to control group. Meanwhile, escitalopram exerted an inhibitory effect that was insignificant from that of indomethacin at all measuring intervals throughout the 30 days of the experiment. On the other hand, mirtazapine and venlafaxine exhibited significant inhibitory effect on rat paw edema compared to indomethacin and escitalopram (**fig.4**).

Similarly, the vocalization test (squeaking score), a measure of hyperalgesia, revealed comparable analgesic activity of escitalopram, mirtazapine and venlafaxine to that of indomethacin when performed once daily for 30 days. The analgesic activity of the tested antidepressants exerted normal squeaking score that was insignificant from normal control (**fig.5**).

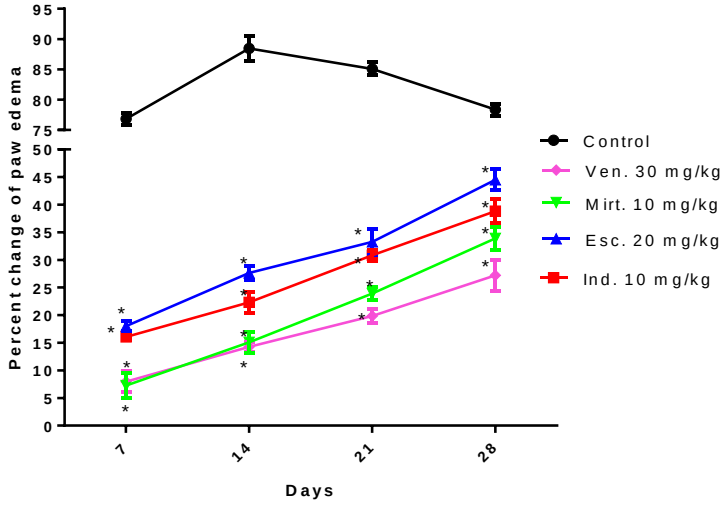

Figure 4: Effect of escitalopram, mirtazapine and venlafaxine on paw volume in CFA-arthritic rats

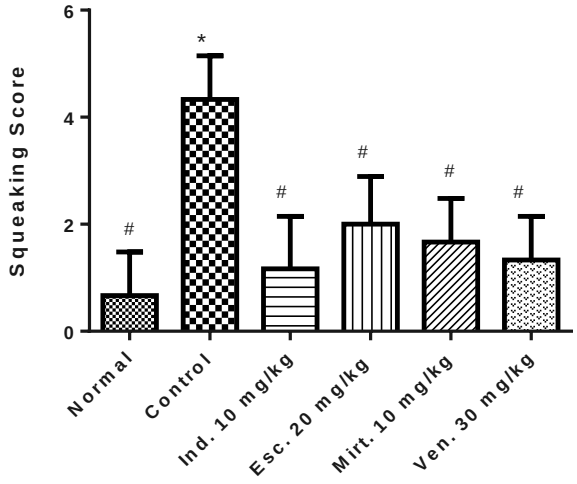

Figure 5: Effect of escitalopram, mirtazapine and venlafaxine on the squeaking score in CFA-arthritic rats

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Effect of escitalopram, mirtazapine and venlafaxine on serum levels of interleukin-1β, PGE2 and TNF-α level in arthritic rats

Oral treatment with the antidepressants, escitalopram, mirtazapine and venlafaxine, for 28 days exerted significant reduction in serum levels of IL-1β, PGE_2 and TNF-α compared to non-treated arthritic rats. Venlafaxine effect was comparable to that of the reference analgesic-anti-inflammatory drug, indomethacin, with regard to reduction of IL-1β and preservation of PGE_2 to normal level, while the three tested antidepressants failed to decrease serum TNF-α significantly compared to indomethacin (**Table1**).

Table 1: Effect of escitalopram, mirtazapine and venlafaxine on serum levels of interleukin-1β, PGE2 and TNF-α level in arthritic rats

Groups \ Parameters	IL- 1β (pg/ml)	PGE2 (ng/ml)	TNF- α (pg/ml)
Normal control	37.5 ^{b} ±2.28	16.5 ^{b} ±0.72	43.9 ^{b} ±3.12
CFA control	169.6 ^{a} ± 8.34	72.3 ^{a} ±2.65	172.3 ^{a} ±7.98
Indomethacin (10 mg/kg)	61.3 ^{ab} ± 5.71	28.6 ^{b} ±2.25	80.2 ^{ab} ±5.15
Escitalopram (20 mg/kg)	118.1 ^{abc} ±7.66	46.4 ^{abc} ±4.36	119.0 ^{abc} ±10.39
Mirtazapine (10 mg/kg)	124.5 ^{abc} ± 2.69	44.9 ^{abc} ±3.96	124.1 ^{abc} ±9.69
Venlafaxine (30 mg/kg)	66.9 ^{ab} ±3.07	29.6 ^{b} ±3.76	113.9 ^{abc} ±6.21

Data are expressed as mean ± SEM of six experiments. ^{a} significantly different from normal control, ^{b} significantly different from CFA control, ^{c} significantly different from indomethacin at $p< 0.05$.

DISCUSSION

Chronic pain management has been a challenge not only for patients to tolerate but also to clinicians to be treated effectively [9]. Being used for long term, antidepressants were observed to have antinociceptive and analgesic activities in several preclinical and clinical studies [7,9,21,35,36]. Moreover,s patients suffering from chronic inflammatory disorders show high prevalence of depression [37,38]. Therefore, in the present study SSRIs (escitalopram) and atypical antidepressants (mirtazapine and venlafaxine) were used to evaluate their analgesic/antinociceptive and anti-inflammatory effects compared to the analgesic anti-inflammatory drug, indomethacin, using the heat hyperalgesia, ankle flexion test and paw oedema in acute and chronic rat model of inflammation.

Mirtazapine displayed strong analgesic activity only after 30 min of administration similar to indomethacin-induced analgesia using hot plate analgesiometer. Moreover, mirtazapine has a dose-dependent antinociceptive efficacy in rats with diabetic neuropathy [39]. A mice study demonstrated an antinociceptive effect of mirtazapine at a dose of 10 mg/kg using a hot-plate test owing this mechanism to serotonergic, noradrenergic and opioid receptors activity of mirtazapine [40]**.**

Venlafaxine showed an antinociceptive effect at 30 mg/kg that was in accordance with various studies that proved the antinociceptive effect of venlafaxine in alleviating thermal hyperalgesia in animals [41] as well as in depression associated-radicular back pain [42,43]. Venalfaxine showed also antinociceptive effect in migraine, chronic back pain, , chronic regional pain syndrome (CRPS) [13],and in fibromyalgia with axis I psychiatric disorders [44].

Unlike other studies that reported escitalopram didn't show any nociceptive/analgesic effect using the tail-flick analgesiometer [14,20,21]. In our study, escitalopram exhibited analgesic effect that increased with time giving a reaction time similar to atypical antidepressants (mirtazapine and venlafaxine) and indomethacin using the hot plate analgesiometer. Previous literature suggested that antidepressants have a direct effect on opioid receptors and that these receptors partially mediate the analgesic effects of these antidepressants [45,46].

The SSRI (escitalopram) and the tested atypical antidepressants (mirtazapine and venlafaxine) displayed remarkable anti-inflammatory activity through reduction of carrageenan-induced paw oedema in rats comparable to indomethacin during the four hours of assessment starting from the 1st hour after carrageenan injection. Some SSRIs such as fluoxetine and doxepine exhibit the inhibitory effect on the carrageenan-induced paw edema [4]. In this regard, fluoxetine, clomipramine and desipramine have been reported to produce anti-inflammatory effects [47-49]. Moreover, venlafaxine reported significant anti-inflammatory effect in rat models of carrageenan-induced paw edema [50].

The acute carrageenan-induced inflammation is characterized by two distinct phases; the initial phase observed around (0-1 h) is attributed to the release of histamine, serotonin, bradykinin and substance p, while the delayed phase (after 1 h) is mainly sustained by polymorphonuclear (PMN) cells recruitment to the inflammatory site with production of several pro-inflammatory mediators involved in the inflammatory response of carrageenan [51,52]. Hence, escitalopram, mirtazapine and venlafaxine reduced the paw edema when injected during the initial or the late phases (30 or 90 min after carrageenan injection), it is possible that they would have interfered with the PMN infiltration or inhibited the release of PMN leukocyte-derived mediators during the initial phase.

As the exact anti-inflammatory mechanism mediated by the antidepressants are still not fully elucidated, our study extended to evaluate the effect of SSRI and atypical antidepressant on CFA-induced arthritis in rats in an attempt to delineate their analgesic and anti-inflammatory activity. The results revealed potent analgesic activity after seven days of treatment by escitalopram, mirtazapine and venlafaxine using hot plate analgesiometer and extended throughout the period of experiment i.e 28 days. Moreover, the joint pain score assessed by the squeaking score, a measure of hyperalgesia, was maintained at normal levels in rats treated with antidepressants that further supported the analgesic effects of escitalopram, mirtazapine and venlafaxine.

Of note, the analgesia produced by the tested antidepressant was accompanied by remarkable anti-inflammatory activity, manifested by reduction in rat paw oedema measured by plethysmometer. The progression of inflammation following CFA injection was aggravated by the release of inflammatory mediators and cytokines at the site of inflammation [53]. In this arthritic model, higher level of PGE_2 (an index of COX-2 activity), thromboxane B_2 (an index of COX-1 activity), and pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 are seen in the serum and synovial fluid along with development of joint pain [54].

Treatment with escitalopram, mirtazapine and venlafaxine mitigated the increase in inflammatory mediators, PGE_2, and pro-inflammatory cytokines, IL-1β and TNF-α, following CFA injection compared to arthritic animals. The SSRI, escitalopram, may exert its anti-inflammatory effect via mechanisms involve increased serotonin secretion and a stimulatory effect on the pituitary-adrenocortical function in experimental animals [55,56]. As manipulation of central levels of serotonin can affect the peripheral inflammation [57,58], the activation of hypothalamo-pituitary-adrenal axis (HPA) apart from biogenic amine metabolism results in the secretion of cortisol, with strong endogenous anti-inflammatory property, from the adrenal cortex [59] which is another hypothesis introduced to explain the analgesics and anti-inflammatory effects of SSRI [24]. In accordance, depressive disorders are accompanied with elevated serum levels of pro- and anti-inflammatory cytokines, TNF-α and IL-6, [60] while SSRI significantly reduces serum TNF-α levels in depressive patients [61].

Further extensive research is warranted in this area, as data is scant on the potential anti-inflammatory effects of escitalopram despite a recent finding that escitalopram lowers the level of soluble interleukin 2 (IL-2) receptor [62].

With regard to noradrenergic and specific serotonergic antidepressant (NaSSA) drug, venlafaxine, which reduced IL-1β and PGE_2 levels providing potent anti-inflammatory activity attributed to the blockade of noradrenaline and serotonin uptake with inhibition of IL-1β and TNF-α production and decreases MPO activity in the site of inflammation [50]. Further, mirtazapine, an $alpha_2$-adrenoreceptor antagonist which increases central noradrenergic and serotonergic neurotransmission [63], could have similar anti-inflammatory activity owing to increased mono-amine neurotransmission. In contrary, others stated that mirtazapine increased TNF-α levels during medical illness [64].

In conclusion, the present study revealed anti-nociceptive/analgesic effect along with potent anti-inflammatory activity of escitalopram, mirtazapine and venlafaxine. Thus, further ensures the use of antidepressants in patients with comorbid diseases that are related to systemic inflammation and physical disorders such as rheumatic arthritis that is usually accompanied by depression.

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