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Original Article

Effect of venlafaxine on experimental colitis in normal and reserpinised depressed rats

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Abstract

Psychological disorders such as depression have more prevalence in inflammatory bowel disease patients and can exacerbate the clinical course of the disease, so anti-depressant therapy may have a potential to positively impact the disease course. On the other hand several antidepressant drugs have shown anti-inflammatory and immunomodulatory properties. Thus, this study aimed to explore the beneficial effects of venlafaxine on experimental colitis in normal and reserpinised depressed rats. Acetic acid colitis was induced in both reserpinised and non-reserpinised rats. Reserpinised groups received reserpine at dose of 6 mg/kg i.p.1 h prior to colitis induction and then treated with venlafaxine at doses of 10, 20, 40 mg/kg given i.p. 2 h after induction of colitis and daily for 4 consecutive days. Non-reserpinised groups treated with 10, 20, 40 mg/kg venlafaxine i.p. 2 h after the induction of colitis and daily for 4 successive days. Dexamethasone (1 mg/kg, i.p.) was used as reference drug. Colonic inflammation was evaluated using macroscopic, histological and myeloperoxidase activity measurements. Results showed that reserpine at dose of 6 mg/kg exacerbated the colitis damage. Compared to acetic acid control, venlafaxine at dose of 40 mg/kg as well as dexamethasone significantly improved colitis parameters in both reserpinised and non-reserpinised animals. Venlafaxine reduced inflammatory injury in this animal model of induced ulcerative colitis. These effects are probably mediated first through depressive behavioral changes that could be mediated through the brain-gut axis and second for the anti-inflammatory effect of the drug.

Keywords: Experimental colitis; Depression; Venlafaxine; Reserpine; Rats

INTRODUCTION

Inflammatory bowel disease (IBD) including Crohn's disease, and ulcerative colitis are considered as idiopathic diseases affecting the gastrointestinal tract (1). It is a chronic disease that has a high incidence in younger individual and lasts life-long (2). In clinical practice, disease activity is typically described as bloody diarrhea (often nocturnal and postprandial), passage of pus, mucus, or both, abdominal cramping, pain and fatigue which can present a significant challenge for daily functioning. Medical and surgical management has varying success, with up to half of IBD patients experiencing relapses every year (3). Although those with IBD have either little or no increased mortality risk relative to the general population, many patients have concerns regarding medication side effects, risk of cancer, and need for surgery. All of these aspects can contribute to psychological distress and undermine quality of life for those with IBD (4). The patients may feel frustrated, sad, and avoid social and sexual events. As a result, the illness may disrupt work, family and social life and predispose patient to anxiety and depression (5). Many review articles have now emphasized on the relationship between IBD and such psychological disorders (5-8).

Depression and anxiety are more common in people with IBD than in the general population. More than 80% of IBD patients with active disease suffered from anxiety state and approximately 60% had concomitant

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depression (9). These mental disorders have a high risk to occur during the first year after diagnosis of IBD (10). Presence of clinical depression may influence disease activity, aggravate disease symptoms, impact on the evolution of the disease (11) or the response to therapy (12).

Recent studies have provided stronger evidence for plausible mechanisms by which psychological disorder effects could be transferred into gut inflammation, including changes in intestinal permeability and mucosal pro-inflammatory cytokines (5).

Therefore, if psychological stress is indeed a pathogenic factor in IBD, then stress reduction therapy may have therapeutic benefit. Many researchers hypothesized that the course of IBD is influenced by psychological factors such as depression as it is influenced by somatic factors; so psychiatric treatment of patients improves both mental and somatic status of IBD patients (13-15).

Milne and coworkers found that a stress management course in addition to conventional treatment significantly ($P<0.05$) reduced Crohn's disease activity index over the follow up period of 1 year in a randomized trial of 80 patients with Crohn's disease (16). Although a wide variety of anti-depressants are available but there are chiefly two classes of anti-depressants that besides treatment of depression have beneficial effect in nociceptive and inflammatory condition: tricyclic anti-depressant drugs (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (17).

Recently, the anti-inflammatory effects of some anti-depressants such as fluoxetine (18), amitriptyline (19), and maprotiline (20) have been reported in a number of experimental models of inflammation.

Additionally, anti-nociceptive and anti-inflammatory effects of venlafaxine were evaluated by Aricioglu and colleagues (21) in a rat model of inflammation.

The aim of this study was therefore to evaluate the beneficial effects of venlafaxine, an antidepressant which inhibits reuptake of both serotonin and norepinephrine, in experimental colitis in normal and reserpinised depressed rats.

MATERIALS AND METHODS

Chemicals

Venlafaxine hydrochloride was a gift from Daroupakhsh Pharmaceutical Co. (Tehran, Iran). Dexamethasone was also a gift from Raha Pharmaceutical Co. (Isfahan, Iran). Reserpine, hexadecyl trimethyl-ammonium bromide (HTAB) and O-dianisidine dihydrochloride were purchased from Sigma Chemical Co. (St. Louis, Mo, USA).

Formalin solution 35% w/w, glacial acetic acid and diethyl ether oxide were supplied by Merck (Darmstadt, Germany). All other solvents and chemicals were of analytical grade.

Animals

Male Wistar rats weighing 200–250 g were obtained from the laboratory animal house of School of Pharmacy, Isfahan University of Medical Sciences and randomly distributed into several experimental groups.

Animals were kept for a week prior to study so as to be adapted to the animal room conditions. The animal room was maintained at 22–24 °C and a lighting regimen of 12 h light/12 h dark. Rats were given standard pelleted chaw and having free access to water. All animal experiments were approved by the Ethics Committee of Isfahan University of Medical Science and performed in accordance with National Institute of Health Guide for the Care and Use of Laboratory Animals.

Determination of anti-depressant dose of venlafaxine in reserpine treated rats

In order to determine the effective anti-depressant dose of venlafaxine in colitic rats, forced swimming test, which is a common behavioral test for assessing depressant and/or anti-depressant effect, was used.

To achieve this, 44 male Wistar rats were randomly assigned to 7 groups of 6 animals each as Sham, control and test groups as follows:

Sham group: received daily i.p. injections of normal saline for 4 consecutive days.

Control group: received reserpine (6 mg/kg, i.p.) on day one and daily injections of normal saline for next four days.

Test groups: received reserpine (6 mg/kg, i.p.) on day one and daily venlafaxine (5, 10, 20, 40, 80 mg/kg, i.p.) for next four days.

All doses were freshly prepared each morning.

Forced swimming test in rats

Forced swimming test (FST) was performed on two consecutive days according to Porsolt and coworkers (22). On the first day (the third day of the experiment) the rats were individually placed in cylinders containing 25 °C water approximately 15 cm height for 15 min. On the following day (day 4) the rats were again immersed in water and total duration of immobility was measured for 5 min. The immobility time was regarded as the time spent by the rat floating in the water without struggling and making only those movements necessary to keep its head above water.

Induction of experimental colitis

All rats were fasted for 24 h before the induction of colitis but allowed free access to water. Colitis was induced according to the procedure described by the MacPherson and Pfeiffer (23). Briefly, animals were lightly anesthetized by ether, and colon was catheterized intra rectally, such that the tip advanced 8 cm proximal to the anus. Two ml of acetic acid (4% v/v in 0.9% saline) was slowly infused into the colon. Animals were then maintained in a head down position for 30 s to limit expulsion of the solution and returned.

Animal grouping

Rats were randomly divided into the following groups of six animals each: control group: received normal saline i.p. 2 h following induction of colitis; Sham group: cannulation was accomplished without induction of colitis (normal saline was administered instead of acetic acid), and rats also received normal saline i.p.; dexamethasone group: dexamethasone (1 mg/kg, i.p) as a reference drug was given 2 h following induction of colitis. Test groups included non-reserpine treated groups which received venlafaxine (10, 20, 40 mg/kg, i.p.) 2 h following induction of colitis and reserpine-treated groups which received reserpine (6 mg/kg, i.p.), 1 h prior to induction of colitis and then treated with venlafaxine (10, 20, 40 mg/kg, i.p.) 2 h following induction of colitis. Administration of medications was performed for the following four days. All drugs were administered in a volume equivalent to 1 ml /kg. All drug doses were calculated as mg/kg base, dissolved in normal saline and prepared freshly each morning.

Evaluation of colon macroscopic damage

On the day five, animals were sacrificed by means of ether inhalation. Immediately after, the abdomen was dissected open and the colon was removed and cut longitudinally, slightly cleaned in physiological saline to remove fecal residues and processed for macroscopic assessment, histological scores and biochemical marker (24).

For each specimen, distal colon wet weight (g) (8 cm from the anus) was measured. Macroscopic damage scores were determined by an independent observer according to the following criteria: 0, no macroscopic changes; 1, mucosal erythema only; 2, mild mucosal edema, slight bleeding, or slight erosion; 3, moderate edema, bleeding ulcers, or erosions, and 4, severe ulceration, erosions, edema, and tissue necrosis (25).

Then, tissue was fixed on a white plastic sheet and a photo was taken using an appropriately adjusted Nikon camera (Coolpix p100, Japan) to calculate the ulcer area. Then tissues were cut into two pieces, one piece for histopathology assessment (maintained in 5 ml formalin 10% as fixator) and the other for measuring myeloperoxidase (MPO) enzyme activity. The pieces for measuring MPO enzyme activity were frozen in liquid nitrogen and kept at -85 °C in a freezer until the day of analysis (26).

Furthermore, ulcer area was measured by Fiji-win 32 software, an image processing and analysis software inspired by NIH Image for the Macintosh (27). For each specimen ulcer index was calculated using the following equation (28).

$$\text{Ulcer Index} = \text{Ulcer area } (cm^2) + \text{Macroscopic score} \quad (1)$$

Table 1. Histological grading of colitis.

Scoring parameter	Score definition
Inflammation severity	0 (None) 1 (Mild) 2 (Moderate) 3 (Severe)
Inflammation extent	0 (None) 1 (Mucosa) 2. (Mucosa and submucosa) 3 (Transmural)
Crypt damage	0 (None) 1 (Basal 1/3 damaged) 2 (Basal 2/3 damaged) 3 (Crypts lost, surface epithelium present) 4 (Crypts lost, surface epithelium lost)

Body weight measurement

For each animal, body weight (g) was measured by a digital scale (ACCULAB V-3000, Germany) daily and during the experimental period (prior to induction of colitis and subsequently daily for 5 days) (29).

Myeloperoxidase enzyme activity measurement

According to the modified method of Bradley and coworkers (30) each tissue sample (0.1 g) was chopped and in 1 ml of 50 mM potassium phosphate (pH=6) with 0.5% HTAB and 5 mM ethylenediaminetetraacetic acid in an ice bath using Polytron homogenizer (Brinkmann/Kinematica, USA). More buffers were added to obtain a concentration equivalent to 0.1 g of colon tissue per 5 ml medium. The resultant homogenate was 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 and centrifuged at 15,000 rpm for 15 min at 4 °C. A 0.1 ml of the supernatant was mixed with 2.9 ml of 50 mM phosphate buffer (pH=6) containing 0.167 mg/ml O-dianisidine dihydrochloride and 0.0005% hydrogen peroxide. The change in the absorbance at 460 nm was measured using a UV/VIS spectrophotometer (LSI Model Alfa-1502, China).

Histological analysis

Colon tissues were individually fixed in 10% formalin, dehydrated, paraffin embedded, processed, sectioned in 4 μm thick slices, deparaffinized with xylene, hydrated and stained with hematoxylin and eosin (H&E) respectively (31).

Inflammation severity and extent as well as crypt damage were evaluated on H&E-stained and coded using a validated scoring system as shown in Table 1 (32). Total colitis index was measured by summing three sub scores of inflammation severity, inflammation extent, and crypt damage (33).

Statistical analysis

The results were reported as mean ± SEM (standard error of mean) for parametric data and median (range) for non-parametric data. One-way analysis of variance (ANOVA) followed by Tukey as post hoc test was used to compare the parametric data; non-parametric data were analyzed using Mann-Whitney test. All statistical analyses were assessed using Graph Pad Prism 5 software. Minimum level of significance was considered at $P<0.05$.

RESULTS

Effect of venlafaxine on reserpinised depressed rat using forced swimming test

Reserpine produced a significant increase in immobilization time as compared to Sham group ($P<0.01$).

Treatment with venlafaxine at doses of 10, 20, 40 and 80 mg/kg significantly ($P<0.01$, $P<0.05$, $P<0.001$ and $P<0.01$ respectively) decreased immobility time in reserpine-treated rats. However, there was no significant difference between venlafaxine at dose of 5 mg/kg and reserpinised group in immobility time (Fig. 1).

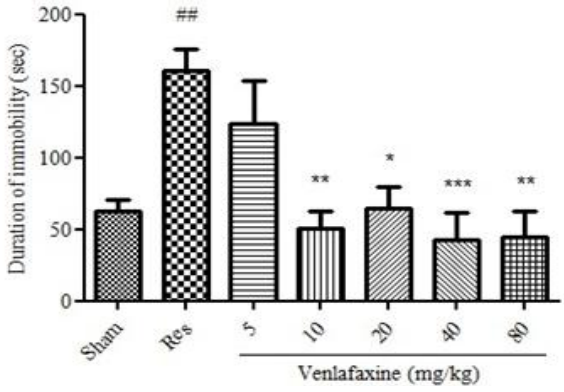

Fig. 1. Effect of venlafaxine (5, 10, 20, 40, 80 mg/kg, i.p.) on duration of immobility (s) during forced swimming test in reserpinised (6 mg/kg, i.p.) rats, Res; reserpine (6 mg/kg), i.p.; intraperitoneally. Results are expressed as mean ± S.E.M of 6 rats in each group. **P*<0.05, ***P*<0.01 and ****P*<0.001 compared to Res. $^{\#\#}P$<0.01 compared to Sham; one-way ANOVA followed by *Tukey test*.

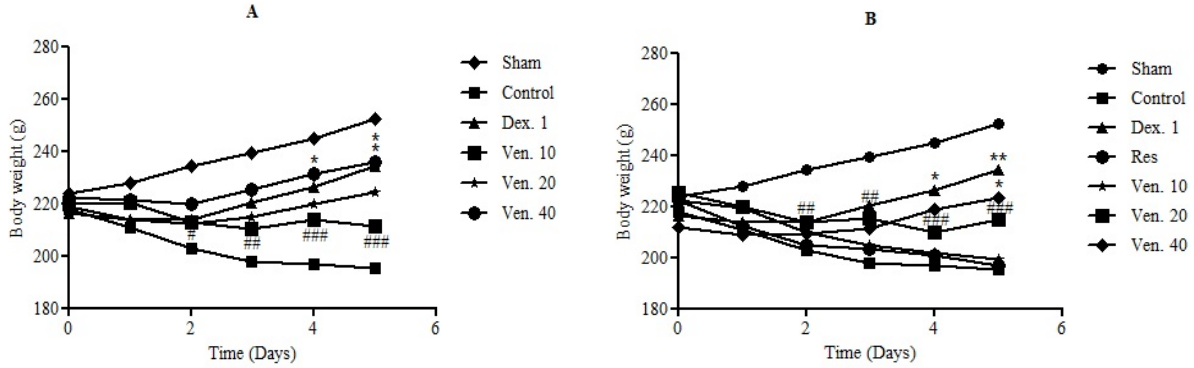

Fig. 2. Effect of venlafaxine (Ven, 10, 20, 40 mg/kg, i.p.) on body weight changes (g) in rat with acetic acid-induced colitis. Treatments were administered 2 h after acetic acid instillation and daily thereafter for 4 consecutive days. A; normal rats, B; reserpinised (6 mg/kg, i.p.) depressed rats, i.p.; intraperitoneally, Dex.1; dexamethasone (1 mg/kg), Res; reserpine (6 mg/kg), Ven; venlafaxine. Results are expressed as mean ± S.E.M of 6 rats in each group. **P*<0.05, ***P*<0.01 and ****P*<0.001 compared to control. $^{\#}P$<0.05, $^{\#\#}P$<0.01 and $^{\#\#\#}P$<0.001 compared to Sham; one-way ANOVA followed by *Tukey test*.

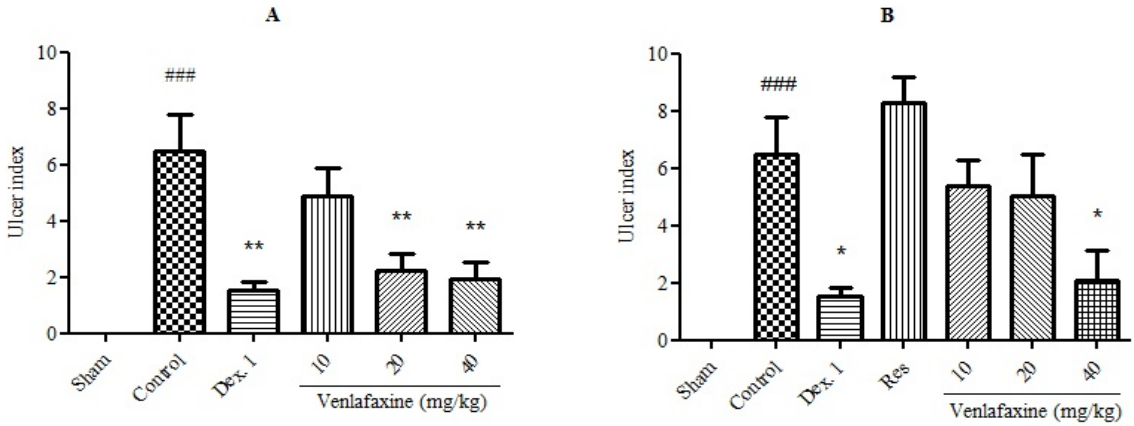

Fig. 3. Effect of venlafaxine (10, 20, 40 mg/kg, i.p.) on ulcer index. A; normal rats, B; reserpinised (6 mg/kg, i.p.) depressed rats, i.p.; intraperitoneally, Dex.1; dexamethasone (1 mg/kg), Res; reserpine (6 mg/kg). Results are expressed as mean ± S.E.M of 6 rats ineach group. **P*<0.05, ***P*<0.01 and ****P*<0.001 compared to control. $^{\#\#\#}P$<0.001 compared to Sham; one-way ANOVA followed by *Tukey test*.

Assessment of animal body weights

As it is shown in Figs. 2 and 3, acetic acid-induced colitis led to a gradual decrease in body weight as observed in control group from day two till day five. In non-reserpinised rats, treatment with venlafaxine at 40 mg/kg dose from day four till day five showed a significant improvement of the wasting disease compared to rats treated with acetic acid alone ($P<0.05$). Rats treated with dexamethasone (1 mg/kg, i.p.) also showed a decrease in body weight loss in day five ($P<0.05$). In reserpinised rats, treatment with venlafaxine (40 mg/kg, i.p.) for five days reversed the decrease trend in body weight in day five which was comparable with dexamethasone (1 mg/kg) treated rats. Significant decrease in body weight was observed in reserpine group (6 mg/kg, i.p.) as compared with Sham group.

Effect of venlafaxine on macroscopic features

Two parameters including ulcer index and weight of distal colon were used to evaluate the effect of venlafaxine on macroscopic features. Five days after induction of colitis, acetic-acid control and reserpine (6 mg/kg) groups experienced severe inflammation, hemorrhage, ulcer, necrosis, and thickened colon wall, while the normal macroscopic features were evident in colons of Sham group (Fig. 4). Administration of reserpine (6 mg/kg, i.p.) intensified epithelial necrosis and edema so that ulcer index and weight of colon significantly increased (Fig. 3B, 5B and 4c). Administration of acetic acid in the colon caused a significant increase in the colon weight suggesting marked inflammation and edema as compared to Sham (Fig. 5).

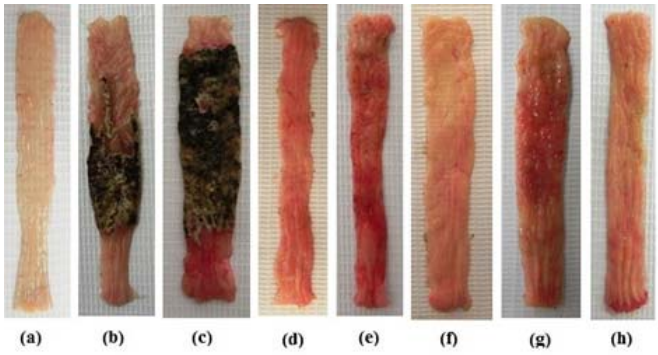

Fig. 4. Macroscopic presentation of colonic tissue 5 days after colitis induction in rats. a; normal colon, b; acetic acid-control rat, c; reserpinised (6 mg/kg, i.p.) colitic rat, d; treatment with dexamethasone (1 mg/kg, i.p.) in colitic rat, e and f; treatment with venlafaxine (20, 40 mg/kg, i.p.) in colitic rats, g and h; treatment with venlafaxine (20, 40 mg/kg, i.p.) in reserpinised (6 mg/kg, i.p.) colitic rats.

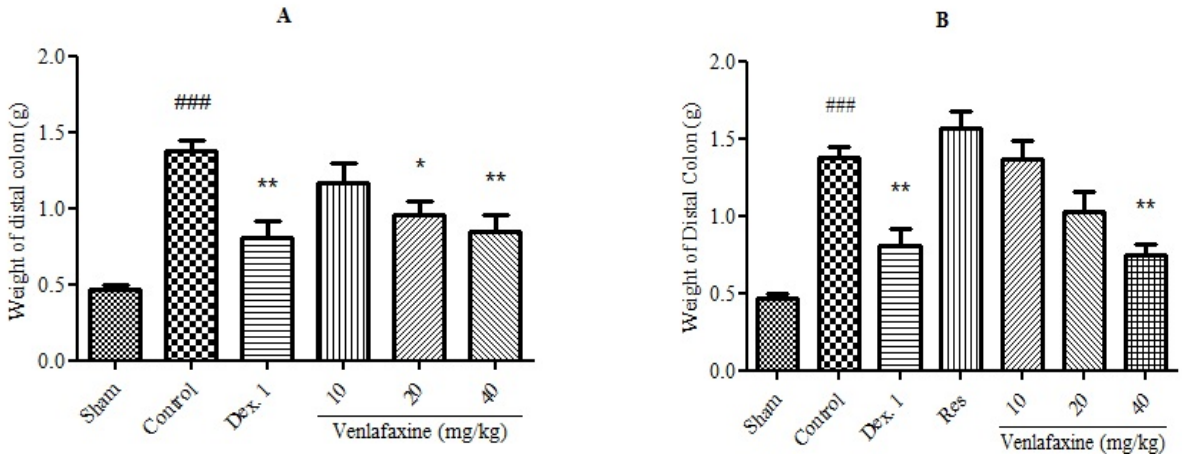

Fig. 5. Effect of venlafaxine (10, 20, 40 mg/kg, i.p.) on the weight of distal colon. A; normal rats, B; reserpinised (6 mg/kg, i.p.) depressed rats, i.p; intraperitoneally, Dex.1; dexamethasone (1 mg/kg), Res; reserpine (6 mg/kg). Results are expressed as mean ± S.E.M of 6 rats in each group.*$P<0.05$, **$P<0.01$ and ***$P<0.001$ compared to control. ###$P<0.001$ compared to Sham; one-way ANOVA followed by *Tukey test*.

As illustrated in Figs. 3, 4 and 5, dexamethasone (1 mg/kg, i.p.) as the reference drug improved macroscopic scores and thus both ulcer index and weight of distal colon was attenuated. In non-reserpinised rats, treatment with venlafaxine at doses of 20 and 40 mg/kg significantly attenuated both ulcer index and weight of distal colon (Fig. 3A, 4a). Besides in reserpinised depressed rats, venlafaxine at dose of 40 mg/kg significantly (P<0.01) attenuated weight of distal colon (Figs. 5B, 4h).

Induction of colitis caused a significant increase in the colon weight (P<0.001). A significant reduction in the colon weight was observed in the rats treated with venlafaxine at doses of 20 mg/kg (P<0.05), 40 mg/kg (P<0.01) in non-reserpinised animals and 40 mg/kg (P<0.01) in reserpinised depressed animals. Treatment with dexamethasone (1 mg/kg, i.p.) also attenuated the weight of distal colon significantly (P<0.01) in both reserpinised and non-reserpinised groups.

Effect of venlafaxine on myeloperoxidase activity

As it is shown in Fig. 6 colonic MPO activity increased in control acetic acid and reserpine group and it shows that following induction of colitis, polymorphonuclear neutrophils accumulation in the colon tissue markedly increased. Treatment of rats with venlafaxine at doses of 40 mg/kg attenuated MPO activity level in both reserpinised and non-reserpinised colitic rats (Fig. 6). Administration of dexamethasone (1 mg/kg, i.p.) also produced a significant reduction in MPO levels.

Effect of venlafaxine on histopathological features

Intracolonic administration of acetic acid resulted in edema, loss of mucosal architecture with ulceration, necrosis and acute inflammatory cell infiltration to mucus and sub-mucosal layers (Fig. 7b). Administration of reserpine (6 mg/kg, i.p.) caused exacerbation of colonic damage so that median total colitis index increased as compared to control group (Table 2). As shown in Fig. 7a, Sham group exhibited a normal architecture with intact epithelium in colonic mucosa. Treatment with dexamethasone (1 mg/kg, i.p.) attenuated the inflammation severity and extent as well as crypt damage and total colitis index in injurious colons (Table 2). Venlafaxine at dose of 40 mg/kg significantly decreased the inflammatory parameters in both reserpinised (6 mg/kg, i.p.) and non-reserpinised rats (Fig. 2).

In non-reserpinised rats, i.p. administration of venlafaxine at 20 mg/kg reduced crypt damage as compared to control acetic acid group (Table 2).

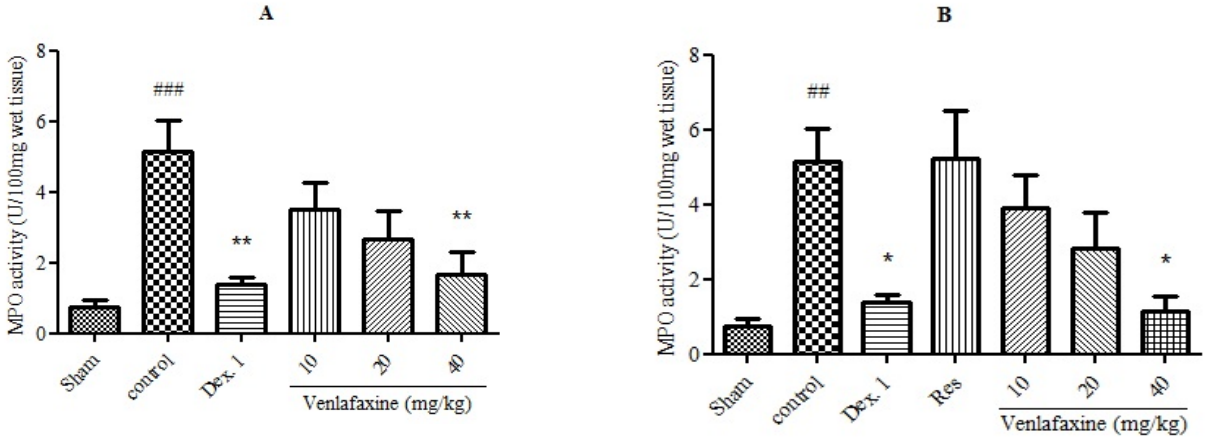

Fig. 6. Effect of venlafaxine (10, 20, 40 mg/kg, i.p.) on myeloperoxidase enzyme activity in the colonic tissue. A; normal rats, B; reserpinised (6 mg/kg, i.p.) depressed rats, i.p. intraperitoneally, Dex.1; dexamethasone (1 mg/kg), Res; reserpine (6 mg/kg). Results are expressed as mean ± S.E.M of 6 rats in each group. *P<0.05, **P<0.01 and ***P<0.001 compared to control. $^{\#\#}P$<0.01 and $^{\#\#\#}P$<0.001 compared to Sham; one-way ANOVA followed by *Tukey test*.

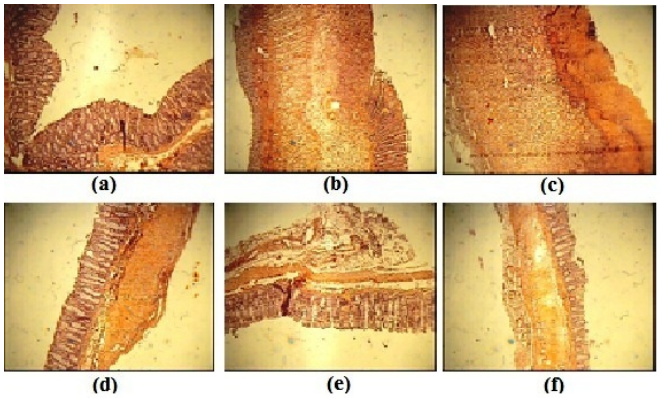

Fig. 7. pathologic presentation of rat colonic tissue following five days treatment. a; Sham group showing intact epithelial surface, b; acetic acid control group showing gross damage to mucosal layer with crypt damage, c; treatment with reserpine (6 mg/kg, i.p.) in reserpine group showing severe damage to mucosal and submucosal layers with crypt damage, d; treatment with dexamethasone (1 mg/kg, i.p.) in dex. 1 group showing improved colonic damage with moderate inflammation, e and f; treatment with venlafaxine (40 mg/kg) in non-reserpinised and reserpinised (6 mg/kg, i.p.) groups respectively showing moderate destruction of mucosal layer however healing effect and repairing in mucosal layer is also evident; H&E staining with magnification of 10x, i.p.; intraperitoneally.

Table 2. Effect of venlafaxine (Ven, 10, 20, 40 mg/kg, i.p.) on pathologic parameters of colitis induced by acetic acid in normal and reserpinised (6 mg/kg, i.p.) depressed rats.

Groups	Inflammation severity (0-3)	Inflammation extent (0-3)	Crypt damage (0-4)	Total colitis index (0-10)
Sham	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Control	3 (2-3)	2 (2-3)	4 (1-4)	9.5 (6-10)
Dex. 1	0.5 (0-1)**	0 (0-2)**	0 (0-2)**	1 (0-5)**
Ven. 10	2 (1-3)	3 (1-3)	3 (2-4)	7.5 (6-10)
Ven. 20	1.5 (0-3)	2.5 (0-3)	1.5 (0-3)*	7.5 (0-9)
Ven. 40	1 (0-3)*	1.5 (0-3)*	0 (0-3)**	3.5 (0-8)**
Res	3 (1-3)	3 (1-3)	4 (1-4)	10 (4-10)
Res + Ven. 10	2.5 (2-3)	3 (1-3)	3 (2-4)	8 (6-10)
Res + Ven. 20	2 (1-3)	3 (1-3)	2 (1-4)	6.5 (4-9)
Res + Ven. 40	1 (0-2)**	1 (0-2)**	0.5 (0-2)*	2 (0-7)**

Dex.1; dexamethasone (1 mg/kg), Res; reserpine (6 mg/kg), i.p.; intraperitoneally. Values are presented as median (range) of six rats in each group. *P<0.05, **P<0.01 compared to control, *Mann-Whitney test*.

DISCUSSION

Some researchers have proposed that prevalence of psychological disorders especially depression and anxiety is higher in patients with IBD particularly within the first year of diagnosis (10). These psychological disorders may impact on the clinical course of disease, have the potential to exacerbate disease activity and may disturb the mainstream treatment of IBD disease (33).

There is a bidirectional interaction between the gut and the brain through the autonomic nervous system and the circumventricular organs in physiological and pathological conditions called brain-gut axis (34). Environmental signals, such as stress or depressive symptoms, are perceived initially by the central nervous system (CNS). Signals are transmitted through this innervated plexus to the gut, and become involved in the initiation and relapse of experimental colitis (35). Despite the absence of any firm evidence to support this belief, Kurina and colleagues reported that in patients with IBD, depression and anxiety, should be thoroughly screened and would benefit from psychological treatment (10). For the first time, in the current study, we used a set of animal models to evaluate the role of venlafaxine on the experimental colitis in normal and reserpinised depressed rats. In this regard, before starting the experimental model of colitis, we conducted behavioral tests to discover the

appropriate antidepressant dose of venlafaxine to figure out if the beneficial effect of venlafaxine is mediated either through change in behavioral mood through the brain-gut axis or through its inherent anti-inflammatory effect.

Intraperitoneal administration of reserpine in an excess dose depletes monoamine levels in the brain for more than a week and induces depressive behavior (36,37). The decrease in monoamine levels induced by reserpine permits the use of animal model of depression induced by this agent as a screening tool for the study of the antidepressant effect of venlafaxine. Intraperitoneal administration of a single dose of reserpine (10 mg/kg, i.p.) successfully induced depression which persisted for more than a week and treatment of the depressed animals for nine days reduced the sign of depression behavior (38). Furthermore, in a recent study, depression was induced by the administration of a single dose of reserpine and depression behavior and anti-depressant effect was evaluated using FST (39). In accordance with above mentioned studies, reserpine at dose of 6 mg/kg was administered i.p. to induce depression during the period that anti-colitis and anti-depressant effect of venlafaxine was evaluated by forced swimming test. FST is also the most widely used technique to assess antidepressant effects in small rodents. Most of the clinically active antidepressants are active in the forced swim test (40,41). Rénéric and Lucki demonstrated that anti-depressant effect of venlafaxine at doses of 10, 20, 40 and 80 mg/kg dose-dependently reduced immobility and increased swimming behavior in the FST (42). Our results also showed that venlafaxine at doses of 10, 20, 40 and 80 mg/kg reduced the immobility time induced by i.p. injection of reserpine (Fig. 1). However, only 10, 20 and 40 mg/kg of venlafaxine were used in the ulcerative colitis experiments.

Acetic acid-induced colitis is a rapid and reproducible model of colitis for screening of drugs with anti-colitic activity. This model has similarity to pathological and clinical features of the human ulcerative colitis (43,44). The results of the current study indicated that following five days treatment, venlafaxine improved colonic macroscopic and histological damages in both normal and reserpinised depressed rats. Twenty four hours after induction of colitis animal showed colonic hemorrhage and bloody stools with malnutrition which caused weight loss during the five days of experiment. Treatment of animals with venlafaxine at dose of 40 mg/kg improved body weight loss from day four as seen with reference group received dexamethasone at 1 mg/kg. Venlafaxine also at dose of 40 mg/kg corrected the elevated amount of biochemical marker MPO. Following induction of colitis, infiltration of neutrophils and other immune cells increased in the inflamed tissues that caused an increase in MPO activity enzyme level in the tissue (45). In the preset study, MPO activity was conspicuously enhanced in control rats and did not show any significant difference with control group receiving reserpine at dose of 6 mg/kg.

It has been reported that antidepressants increase intracellular concentration of cAMP in immune cells through activation of noradrenaline and serotonin receptors (46). This may be one of the mechanisms by which venlafaxine at the mentioned dose alleviated inflammation in the experimental colitis.

However, little attention has been paid to the role of depression in predisposition to inflammatory conditions of the gastrointestinal tract. In this study, we used reserpine induced depression model to show increased susceptibility to the experimental colitis in which this vulnerability could be reduced by antidepressant therapy. Administration of the reserpine as depressing agent; at dose of 6 mg/kg conversely exacerbate the colitis condition as indicated in macroscopic, histological and MPO measurements. Induction of depression in animal models such as maternal separation in mice increases vulnerability to intestinal inflammation. It is hypothesized that increased intestinal permeability facilitate the enhanced severity of subsequent dextran sulphate sodium colitis which is reversed by treatment with tricyclic antidepressant desipramine (47). In the present study induction of depression by administration of reserpine (Fig. 1)

exacerbated the colitis damage while treatment with venlafaxine attenuated the increased susceptibility to colitis in reserpinised depressed rats.

Mast cells of the intestinal mucosa serve as end effectors of the brain-gut axis and release several pro-inflammatory mediators following stress and other psychological disorders that can profoundly affect GI physiology by inducing intestinal hyperpermeability and activation of mucosal immune function (34). Reserpinised treated rat with the anti-depressant venlafaxine showed decreased colitis severity as compared with untreated reserpine group. Thus treatment of these psychological disorders by anti-depressant venlafaxine can modulate the function of these immune cells and reduce intestinal inflammation.

Furthermore, experimental evidence is accumulating that various types of antidepressants (particularly TCAs and SNRIs) exert anti-inflammatory and analgesic effects. Anti-inflammatory and analgesic effects of venlafaxine have been also reported in some studies. Anti-nociceptive effect of venlafaxine on painful peripheral diabetic neuropathy, fibromyalgia and headache has been evaluated in clinical studies. Anti-nociceptive effect of venlafaxine at doses of 10 and 22.5 mg/kg in mice (tail flick and writhing tests) has been reported and it is realized that this effect could possibly have central as well as peripheral action (48). Anti-inflammatory effect of venlafaxine in carrageenan-induced paw edema in rats has also been reported (21). Since colitis is an inflammatory condition of intestine, it is deduced from our results that some beneficial effect of venlafaxine in experimental colitis might be, in part, due to its anti-inflammatory and anti-nociceptive effects.

CONCLUSION

The results of this investigation showed anti-inflammatory effect of the anti-depressant, venlafaxine in acetic acid-induced colitis. Our results confirmed that a coherent communication exist between depression and the course of IBD probably through the brain-gut axis. This correlation was previously approved in irritable bowel syndrome, the issue which has historical background when IBD was considered as a psychosomatic disease. Further studies are suggested to evaluate other anti-depressant drugs with similar pharmacological properties in the treatment of ulcerative colitis.

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