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Evaluation of anti-colitic effect of fluvoxamine against acetic acid-induced colitis in normal and reserpinized depressed rats

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ABSTRACT

High prevalence of psychological comorbidities such as depression and anxiety in patients with inflammatory bowel disease (IBD) supports the premise that adding an anti-depressant drug with known anti-inflammatory effect to the medical treatment have beneficial effect in the course of the underlying disease. Colitis was induced by intracolonic instillation of 2 ml of 4% v/v acetic acid solution in rats. Anti-colitic effect of fluvoxamine was evaluated in two categories: A: normal rats, B: reserpinized (6 mg/kg, i.p.) depressed rats. In group A, fluvoxamine (2.5, 5, 10 mg/kg, i.p.) was administered 2 h after induction of colitis and in group B: reserpine (6 mg/kg, i.p.) was administered 1 h prior to colitis induction and then fluvoxamine (2.5, 5, 10 mg/kg, i.p.) was administered 2 h after colitis induction. Dexamethasone (1 mg/kg) was used as reference drug. All the treatments continued daily for five days. The effect was assessed on the basis of macroscopic score, biochemical (myeloperoxidase) changes and histopathological studies. Results showed that fluvoxamine (2.5 and 5 mg/kg) and dexamethasone treatment markedly reduced disease severity in both reserpinized and non-reserpinized rats as indicated by reduction in macroscopic and microscopic colonic damages while reserpine adversely exacerbated the colitis damage. Myeloperoxidase activity which was increased following colitis induction was also decreased. The findings of this study elucidate the anti-colitic and anti-inflammatory properties of fluvoxamine and so introduced it as a good candidate to treat depressive symptoms in people comorbid to IBD.

1. Introduction

Inflammatory bowel disease (IBD), which include Crohn's disease (CD) and ulcerative colitis (UC) is characterized by episodes of exacerbations and remissions (Bernstein et al., 2009). Patients frequently suffer from abdominal pain, diarrhea along with blood and/or mucus, fever, weight loss, fatigue, inflammation, ulceration and edema (Thoreson and Cullen, 2007). The chronic course of the disease can cause a wide range of psychological and interpersonal concerns to patients. Indeed, symptoms, such as fecal incontinence or soiling and lack of bowel control, can lead to a loss of self-unworthiness or cause stigmatization in patients (Sajadinejad et al., 2012). There have been many reports over the years that prevalence of psychiatric illness in particular anxiety and depressive disorders are significantly more common in patients with IBD compared to the general population (Kurina et al., 2001) and the symptoms of these conditions are more severe during periods of active disease (Graff et al., 2009). Studies show a 30% rate of depression during remission, with 80% and 55% of patients reporting anxiety and depression, respectively, during relapse (Mikocka-Walus et al., 2012a). There is increasing evidence that depressive mood exerts negative effects on the course of several chronic diseases (Turner and Kelly, 2000). As IBD is a chronic and relapsing gastrointestinal disorder, it is not separate from this rule. A recent pilot study in patients with ulcerative colitis and a conserved colon demonstrated that depression was a risk factor of relapse (Häuser et al., 2011). So, questions of quality of life and of coping strategies with the disease are particularly important. Gastroenterologists reported that treating psychological co-morbidities with antidepressants was successful in reducing pain, gut irritability, urgency of defecation and to control disease activity and lengthen remission (Mikocka-Walus et al., 2006, 2012b). Furthermore anti-inflammatory and analgesic effects of some anti-depressant drugs such as amitriptyline (Sadeghi et al., 2011), maprotiline (Hajhashemi et al., 2010a), venlafaxine (Aricioğlu et al., 2005) and fluoxetine (Abdel-Salam et al.,

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2004) have been evaluated. Systematic reviews by Mikocka-Walus et al. (2007, 2008, 2012a) indicate that antidepressants appeared not only to help certain individual patients with IBD to cope with their emotional problems, but also improved their quality of life. The published observations also hold out the intriguing possibility that anti-depressant therapy may have specifically influenced the course of their inflammatory disease. Due to lower rate of side effect in comparison to other anti-depressant drugs, SSRIs are the most wide group which is used for treating depressive symptoms (Filipovic and Filipovic, 2014). Following administration of SSRIs (citalopram, sertraline) in patients with IBD, they felt that psychological problems responded well to this treatment however these drugs have no beneficial effect on somatic aspects of the disease (Mikocka-Walus et al., 2007). Furthermore, fluoxetine was found to protect against colitis in a randomized controlled trial (Itatsu et al., 2011). So the present study aims at evaluating the effect of fluvoxamine as a potent SSRI drug with known anti-inflammatory properties, on experimental colitis in normal and reserpine induced depressed rats.

2. Materials and methods

2.1. Animals

Male Wistar rats (200–250 g) obtained from the laboratory animal house of the School of Pharmacy, Isfahan University of Medical Sciences, Iran, were used in this experiment. Animals were kept at controlled environmental conditions where the temperature of the experimental room was maintained at 20–23 °C, relative humidity at 50–60% with a 12:12 h light/dark cycle. All animals were given access to a standard pellet diet and water. Animals were housed individually in standard cages and were acclimatized for 7 days before initiation of the treatment. The animal study was approved by the guideline of the ethical committee of Isfahan University of Medical Sciences.

2.2. Chemicals

Fluvoxamine maleate was a gift from Abidi Pharmaceutical Company (Tehran, Iran). Dexamethasone was also a gift from Raha Pharmaceutical Company (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 purchased form Merck (Darmstadt, Germany). All other solvents and chemicals were of analytical grade.

2.3. Behavioral tests

2.3.1. Determination of anti-depressant dose of fluvoxamine in reserpinized depressed rats

This part of experiment was designed to determine the optimum dose of fluvoxamine which has anti-depressant effect in reserpinized depressed animals to be used in colitis part of the experiment. So rats were randomly assigned to six groups of rats comprising six rats per group as follows: Sham group received normal saline (2 ml/kg, i.p.) daily for four days. Control group received a single dose of reserpine (6 mg/kg, i.p.) and was treated with normal saline 3 h after reserpine injection and then daily for four days. Test groups received a single dose of reserpine (6 mg/kg, i.p.) and then were treated with fluvoxamine (1.25, 2.5, 5, and 10 mg/kg, i.p.) 3 h after reserpine injection and daily for four days. Then animals were subjected to forced swimming test. So at the third day, the rats were individually placed in a cylinder containing water 15 cm in height at 25 °C for 15 min (pre-test). On the following day (fourth day) 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 that the rat spent floating in the water without struggling and making only those movements necessary to keep its head above water (Porsolt et al., 1978).

2.4. Body weight measurement

Every morning at the start of the experiment and daily thereafter, animals were individually weighed by a digital scale (ACCU-LAB V-3000) and the body weight was recorded subsequently in order to measure body weight change and also to calculate all drug doses as mg/kg base (Niu et al., 2013).

2.5. Induction of experimental colitis

Acute colitis was induced by acetic acid using a technique introduced by MacPherson and Pfeiffer (1978). Briefly, rats were fasted for 24 h before induction of colitis in stainless steel cages with free access to water. The rats were lightly anesthetized with ether and a flexible plastic catheter with an outside diameter of 2 mm was inserted 8 cm into the colon via the anus. Two milliliter 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.

2.6. Animal grouping

The rats were randomly divided into the following groups of six rats in each: Sham group: received normal saline (2 ml/kg, i.p.) without induction of colitis; control group: received normal saline (2 ml/kg, i.p.) following induction of colitis; dexamethasone group: dexamethasone (1 mg/kg, i.p.) was given 2 h following induction of colitis. Test groups include non-reserpine treated groups which received fluvoxamine (2.5, 5, 10 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 fluvoxamine (2.5, 5, 10 mg/kg, i.p.) 2 h following induction of colitis. Administration of medications was performed for the following four days. All the drug doses were prepared freshly each morning.

2.7. Assessment of colon macroscopic damage

The rats were killed 24 h after the last treatment (Day 5) by an overdose of ether inhalation. The colons were dissected, slightly rinsed with normal saline and the length and weight were measured (Minaiyan et al., 2011). Then segments of colon were used for the assessment of macroscopic and histopathology damage and measurement of tissue myeloperoxidase activity.

Macroscopic damage scores were assigned 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 (Deshmukh et al., 2010). Then, tissue was fixed on a white plastic sheet and a photo was taken using an appropriately adjusted Nikon camera (Coolpix p100) to calculate the ulcer area. Pieces were cut into two pieces, one piece for histopathology assessment (maintained in 5 ml formalin 10% as fixator) and one piece for measuring myeloperoxidase (MPO) enzyme activity. The pieces for measuring the myeloperoxidase (MPO) enzyme activity were frozen in liquid nitrogen and kept at freezer (−85 °C) (Minaiyan et al., 2013).

Furthermore, ulcer area was measured by Fiji-win 32 software, an image processing and analysis software inspired by NIH Image for the Macintosh (Ghosh et al., 2004). For each specimen ulcer