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Full Length Article

Possible antidepressant effects of vanillin against experimentally induced chronic mild stress in rats

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ABSTRACT

Vanillin is a flavoring agent widely used in food and beverages such as chocolates and dairy products and it is also used to mask unpleasant tastes in medicine. It has been reported to have antioxidant, anti-inflammatory and antiapoptotic properties. The current study was designed to investigate the protective effects of vanillin against experimentally induced stress in rats. Briefly rats were subdivided into four groups. Three groups were subjected to chronic mild stress and the fourth group served as normal control group. One week before induction of stress drugs or saline was administered daily and continued for another nine weeks. At the end of the experimental period behavioral tests including sucrose preference test, forced swim test and elevated plus maze test were assessed. In addition, brain biochemical parameters including MDA, GSH, NO and serotonin were determined. Vanillin succeeded to restore the behavioral and biochemical changes associated with stress. It significantly increased sucrose consumption in sucrose preference test and time spent in open arm in elevated plus maze test as compared to stress control group. It also reduced immobility time in forced swim test and time spent in closed arm in elevated plus maze test. Additionally, it significantly decreased brain MDA and NO levels and significantly increased brain GSH and Serotonin levels compared to stress control group. It could be concluded that vanillin showed beneficial protective effects against experimentally induced stress in rats.

1. Introduction

Depression is a disabling and widely distributed disorder that is associated with exposure to stressful life events. Studies of chronic stress in animal models and postmortem tissues from depressed patients demonstrated reduced size of limbic brain regions that regulate mood and cognition, and decreased neuronal synapses in these brain areas may play a major role in the pathogenesis of depression (Masi and Brovedani, 2011).

So far, the specific mechanism of depression is not well defined; yet, theories mainly focus on the involvement of the

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neurotransmitter serotonin. Compounds that suppress the elevated concentration of serotonin in the synaptic cleft have been authenticated to possess antidepressant effects (Belmaker and Agam, 2008). Recently, oxidative stress has shown important role regarding psychiatric diseases such as depression and has been suggested as an important factor in the pathogenesis of depression (Ng et al., 2008). Maes et al. (2011) demonstrated the entanglement of oxidative and nitrosative stress in the pathophysiology of depression.

Treatments for depression include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin–noradrenergic reuptake inhibitors (SNRIs), and other atypical antidepressant drugs such as monoamine oxidase inhibitors (MAOIs) (Nemeroff, 2007). However, the efficiency of these antidepressants is variable, and most of them possess serious adverse effects including sleep disturbance, sedation, agitation and tiredness, thus, there is a crucial demand for brand new, efficient, and well tolerated antidepressants (Nestler et al., 2002).

Venlafaxine is an SSNRIs mainly used in the treatment of depression and obsessive diseases (Golden and Nicholas, 2000). Pharmacokinetic data demonstrated venlafaxine as a sole treatment in many clinical trials (Mbaya, 2002). It restrains the serotonin transporter by binding the receptor at a site other than active binding site for serotonin (Murphy et al., 2004). Venlafaxine was selected in the present study as a standard drug because it is widely prescribed for treating major depression and it is well tolerated with fewer side effects (Dubovicky et al., 2014).

Vanillin (4-hydroxy-3-methoxybenzylaldehyde) is the main component of natural vanilla. Vanillin has been widely used as a flavoring agent and preservative in food and cosmetics. Vanillin has a beneficial protective role against oxidative stress such as protein oxidation and lipid peroxidation in hepatic mitochondria (Liu and Mori, 1993). Moreover, Vanillin has also demonstrated an ability to inhibit the lipopolysaccharide (LPS)-stimulated nuclear factor kappa-B activation and cyclooxygenase-2 gene expression in murine macrophages. It also reduces the expression of proinflammatory cytokines such as interleukin (IL)-1β, IL-6, interferon-γ, and tumor necrosis factor-alpha (TNF-α) (Murakami et al., 2007).

The present research was constructed to elucidate the beneficial role of vanillin in chronic mild stress induced in rats and to explicate the possible underlying mechanisms.

2. Materials and methods

2.1. Animals

Male Wistar Albino rats (230–250 g) supplied from the National Cancer Institute, Cairo, Egypt were used in all the experimental procedures. Rats were left to acclimatize in the animal facility of the Faculty of Pharmacy, Beni Suef University, for one week. All animals were kept under a 12 h light–dark cycle, with controlled humidity (60–80%) and constant temperature (22 °C ± 1 °C). Food and water were supplied ad libitum except when rats were submitted to chronic mild stress (CMS). All experimental procedures were controlled and approved by the Ethics Committee of Faculty of Pharmacy, Beni Suef University.

2.2. Drugs and chemicals

Venlafaxine and vanillin were obtained from Sigma-Aldrich, USA. All other chemicals were of the highest category available in the market. Venlafaxine and vanillin were freshly prepared just before administration to the rats by dissolving them in normal saline.

2.3. Experimental design

After an accommodation period of one week, rats were randomly distributed into four groups ($n = 8$ rats per group) as follows: Group I, normal control group. In this group rats received regular diet and water ad libitum only. Rats did not receive any treatment. Group II (untreated stress group): Animals were subjected to CMS regime and received 1 ml of saline orally for 9 weeks. Groups III and IV: Rats received venlafaxine, 40 mg/kg and vanillin 100 mg/kg respectively as a single oral daily dose one week before induction of CMS and continued for another 9 weeks.

2.4. Chronic mild stress (CMS)

For consecutive twenty eight days, rats were randomly subjected to one of the following external stimulus one each day: food restriction for 24 h, switching of day and night, unclean cages (150 ml of water per cage) for 22 h, cage inclining (45 degree) for 22 h, overcrowded housing (8 animals per cage) for 12 h, introduction of an unusual odor (air freshener) for 12 h, administration of restraint stressor for 20 min, cold stress 4–8 °C and heat stress 38–39 °C for 20 min and intermittent noise for 5 h for 3 periods (Nirmal et al., 2008).

2.5. Behavioral tests

2.5.1. Sucrose preference test (SPT)

Before starting sucrose preference test, rats were kept singly and accustomed for 48 h of forced sucrose solution (1%) drinking using two bottles on each side. Soon after, rats were subjected to 16 h water deprivation and then, two preweighted bottles were put for each rat. The first one has 1% sucrose solution and the second has water. To escape bias, the side of the two bottles was randomly allocated. After one hour, the bottles were reweighted and the alteration in weight difference was calculated. Sucrose preference was calculated as a percentage of the consumed 1% sucrose solution in relation to the total amount of liquid intake (Jiang et al., 2013).

2.5.2. Forced swim test (FST)

Each rat was forced to swim in a cylindrical box. For each rat the total time of immobility during 5 minutes was calculated. Rat was considered immobile when it stopped struggling and floated without movement in the water, doing only moves that make its head above water. The drug is said to have antidepressant like effect if there is a significant decrease in the time of immobility (Porsolt et al., 1979).