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Venlafaxine Modulates Depression-Induced Oxidative Stress in Brain and Medulla of Rat

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Abstract Venlafaxine is an approved antidepressant that is an inhibitor of both serotonin and norepinephrine transporters. Medical treatment with oral venlafaxine can be beneficial to depression due to reducing free radical production in the brain and medulla of depression-induced rats because oxidative stress may a play role in some depression. We investigated the effect of venlafaxine administration and experimental depression on lipid peroxidation and antioxidant levels in cortex brain, medulla and erythrocytes of rats. Thirty male wistar rats were used and were randomly divided into three groups. Venlafaxine (20 mg/kg) was orally supplemented to depression-induced rats constituting the first group for four week. Second group was depression-induced group although third group was used as control. Depressions in the first and second groups were induced on day zero of the study by chronic mild stress. Brain, medulla and erythrocytes samples were taken from all animals on day 28. Depression resulted in significant decrease in the glutathione peroxidase (GSH-Px) activity and vitamin C concentrations of cortex brain, glutathione (GSH) value of medulla although their levels were increased by venlafaxine administration to the animals of depression group. The lipid peroxidation levels in the three tissues and nitric oxide value in cortex brain elevated although their levels were decreased by venlafaxine administration. There were no significant changes in cortex brain vitamin A, erythrocytes vitamin C, GSH-Px and GSH, medulla vitamin A, GSH and GSH-Px values. In conclusion, cortex brain within the three tissues was most affected by oxidative stress although there was the beneficial effect of venlafaxine in the brain of depression-induced rats on investigated antioxidant defenses in the rat model. The treatment of depression by venlafaxine may also play a role in preventing oxidative stress.

Keywords Venlafaxine · Depression · Antioxidant · Oxidative stress,·Chronic mild stress

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Abbreviations

GSH-Px	glutathione peroxidase
GSH	glutathione
Hb	hemoglobin
LP	lipid peroxidation
MAO	monoaminooxidase
MDA	malondialdehyde
NO	nitric oxide
PUFAs	polyunsaturated fatty acids
ROS	reactive oxygen species
SOD	superoxide dismutase
SSRIs	Selective-serotonin reuptake inhibitors

Introduction

Reactive oxygen substances (ROS) and lipid peroxides are produced by a free radical chain reaction, which can also be initiated by ROS [1]. The ROS, i.e. singlet oxygen, superoxide anion radical, perhydroxyl radical and hydroxyl radical, contribute to tissue damage [2]. ROS also cause injury by reacting with biomolecules such as lipids, proteins and nucleic acids as well as by depleting enzymatic and/or nonenzymatic antioxidants in the brain [3, 4]. There is also evidence that ROS play an important role in the pathogenesis of many diseases, particularly in neurological and psychiatric diseases due to the central nervous system vulnerability to oxidative stress [5, 6]. Glutathione peroxidase (GSH-Px) detoxifies hydrogen peroxide to water although vitamin A and beta carotene have inhibitor role on singlet oxygen radical. Therefore, ROS can be indirectly evaluated by measurement of some antioxidants such as GSH-Px, reduced glutathione (GSH), vitamins A, C and beta carotene [1]. The oxidation of catecholamines such as dopamine and serotonin by monoaminooxidase may result in increased radical burden. The inhibitory effects of serotonin on depression well documented [7]. This effect of the serotonin has been attributed to serotonin-induced decrease in dopamine central nervous system [6]. Selective-serotonin reuptake inhibitors (SSRIs) are effective in the treatment of depression. Probable mechanism of these drugs is the enhancement of net serotonergic transmission by blocking the presynaptic 5-hydroxytryptamine (5-HT) uptake site [8].

Nitric oxide (NO) known as endothelial-derived relaxing factor is a gas that transmits signals in the organism and is responsible for the cytotoxicity of activated macrophages [1, 9]. However, NO has a complex role in immune functions. Immunologic and inflammatory stimuli induce the peroxidation of NO over longer periods, and it exerts cytotoxic and cytostatic effects not only against invading cells, but also against health cells [10].

There are numerous studies indicating that ROS induced neuronal damage has an important role in the pathophysiology of depression, probably via membrane omega 3 polyunsaturated fatty acids (PUFAs) pathology [11], decreasing activity of glutathione reductase, GSH-Px, catalase and superoxide dismutase (SOD) [5] and vitamin E [12], suggesting oxidative damage. Although most of the oxygen used in brain tissue is converted to CO_2 and water, small amounts of oxygen forms ROS. The existences of PUFAs which are targets of the ROS in the brain make this organ more sensitive to oxidative damage [1, 3, 4, 13]. There are various antioxidant mechanisms in the brain that neutralize the harmful effects of ROS; however, with depression, the loss of efficiency of antioxidants mechanisms and the alterations in the proinflammatory cytokine system result in increases in the free radical formation due to the activation of phagocytic cells. Depression is characterized by activation of the inflammatory response system with increased production of procytokines [14, 15]. Proinflammatory cytokines and cytokine-induced ROS may increase lipid peroxidation (LP) [5, 16]. Psychological stress, which accompanies severe depression, may increase LP [5].

Venlafaxine is an antidepressant drug claimed to have superior clinical efficacy to comparable drugs due to a faster onset of action. It is a dual serotonin and noradrenaline reuptake inhibitor with a weak effect on dopamine reuptake. Venlafaxine has higher affinity for serotonin reuptake than for noradrenaline [17, 18]. However, whether venlafaxine reduces lipid peroxide in the cortex brain, medulla and erythrocytes in rats is currently unknown and warranted further study.

If depression increases LP, amounts of enzymatic and non-enzymatic antioxidants should be oxidized and their levels in cortex brain, medulla and RBC should be diminished. Thus, the aim of the study is to assess selected parameters of oxidative stress in rat brain in the course of depression-induced chronic stress as well as the effect of treatment with venlafaxine on pro- and antioxidative processes in the brain, medulla and blood of the investigated animals in vivo.

Materials and methods

Animals

Thirty male, Wistar albino rats weighing 200 ± 20 g were used for the experimental procedures. Rats were allowed 1 week to acclimate to the surroundings before beginning any experimentation. Animals were housed in individual plastic cages with bedding. Standard rat food and tap water were available ad libitum for the duration of the experiments unless otherwise noted. Sucrose (1%) was available ad libitum for 1 week preceding the experimental procedures to allow for adaptation to its taste. The temperature was maintained at $22 \pm 2°C$. A 12/12 h light/dark cycle was maintained, with lights on at 06.00, unless otherwise noted. Animals were maintained and used in accordance with the Animal Welfare Act and the Guide for the Care and Use of Laboratory animals prepared by the Suleyman Demirel University.

Experimental design

The animals were randomly divided into three groups: group I: venlafaxine administrated orally to depression induced-rats ($n = 10$); group II: depression induced rats ($n = 10$); group III: control animals ($n = 10$). Venlafaxine (20 mg/kg body weight, per day) was dissolved in 2 ml physiologic saline (0.9%, w/v) and it was orally (via gastric gavage) administrated to first group animals for 4 weeks although same amount of physiologic saline as placebo was supplemented to second and third groups.

Induction of depression

Chronic mild stress

Procedures of inducing chronic mild stress were summarized in Table 1. The using CMS procedure has been described previously [19, 20] and it was designed to maximize the unpredictable nature of the stressors. The CMS group was exposed to the following stressors in random order: continuous overnight illumination, 40° cage tilt, paired housing, damp bedding (300 ml water spilled into bedding), exposure to an empty water bottle immediately following a period of acute water deprivation, stroboscopic illumination (300 flashes/min), and white noise (approx. 90 dB). The stressors were presented in the order shown during the first week and repeated each of the following weeks for a total of 4 weeks. Control animals were left undisturbed in the home cages with the exception of general handling (i.e., regular cage cleaning and measuring body weight), which was comparable to the activities of the CMS group.

Sucrose preference tests

Sucrose preference tests, as employed previously [19, 21] were used to operationally define anhedonia.

Specifically, anhedonia was defined as a reduction in sucrose intake and sucrose preference relative to the intake and preference of the control group. A sucrose preference test consisted of first removing the food and water from each rat's cage (both CMS and control groups) for a period of 20 h. Water and 1% sucrose were then placed on the cages in preweighed glass bottles, and animals were allowed to consume the fluids freely for a period of 1 h. Two baseline preference tests were performed, separated by at least 5 days, and the results were averaged. A preference test was also conducted following the 4-week CMS period.

Anesthesia and tissue and blood sampling

Animals were rested and fasted for 12 h after the last venlafaxine supplementation before sacrificing. Rats were anesthetized with a cocktail of ketamine hydrochloride (50 mg/kg) and xylazine (5 mg/kg) administered intraperitoneally (i.p.) before sacrifice of each rats and removal of the cortex brain, medulla and blood samples. Five milliliter blood samples were obtained by cardiac puncture into tubes containing sodium EDTA. The brain areas were also taken as follows, the cortex was dissected out after the brain was split in the mid-sagittal plane. Following removal of the cortex, the medulla was dissected from total brain as described in our previous study [13].

Cortex brain and medulla tissues were washed twice with cold saline solution, placed into glass bottles, labeled and stored in a deep freeze (–30°C) until processing (maximum 10 h). After weighing, the cortex and medulla were placed on ice, cut into small pieces, using scissors, and homogenized (2 min at 5,000 rpm) in a five volumes (1:5, w/v) of ice-cold Tris–HCl buffer (50 mM, pH 7.4), by using a glass Teflon homogenizer (Caliskan Cam Teknik, Ankara, Turkey). All preparation procedures were performed at 4°C.

Table 1 Procedures of inducing chronic mild stress

	Sunday (h)	Monday (h)	Tuesday	Wednesday (h)	Thursday (h)	Friday (h)	Saturday (h)
Taking water bottles	16:00 →	08:00					
Adding empty water bottles		08:00–09:00					
Continuous illumination	16:00 →	08:00			17:00 →	10:00	
40° cage tilt		11:00–17:00					
Paired housing	→ → →	08:00		18:00 →	14:00	10:00	→ → →
Damp bedding (300 cc)					17:00 →	10:00	
White noise (90 dB)						10:00– 13:00	
Stroboscopic illumination (300 flashes/min)	11:00–16:00 h			13:00–15:00			

The blood samples were separated into plasma and erythrocytes by centrifugation at 1,500 g for 10 min at +4°C. The erythrocyte samples were washed three times in cold isotonic saline (0.9%, v/w), then hemolyzed with a nine-fold volume of phosphate buffer (50 mM, pH 7.4). After addition of butylhydroxytoluol (4 μl per ml), Half of hemolyzed erythrocytes sample was stored at –30°C for <3 months pending measurement of enzymatic activity. The remaining hemolyzed erythrocytes samples were used for immediate LP levels.

Lipid peroxidation (LP) and nitric oxide (NO) determinations

LP levels in cortex brain and medulla homogenate and hemolyzed erythrocytes were measured with the thiobarbituric-acid reaction by the method of ref. [22] as described in previous studies [2]. The quantification of thiobarbituric acid reactive substances was determined by comparing the absorption to the standard curve of malondialdehyde equivalents generated by acid catalyzed hydrolysis of 1,1,3,3 tetramethoxypropane. The values of LP were expressed as μmol/g Hb or μmol/g protein. In the current study we used the thiobarbituric-acid reaction method for determination of LP. Although the method is not specific for LP, measurement of thiobarbituric-acid reaction is an easy and reliable method, which is used as an indicator of LP and ROS activity in biological samples.

NO measurement is very difficult in biological specimens, because it is easily oxidized to nitrite (NO^-) and subsequently to nitrate (NO^{-3}) which serve as index parameters of NO production. The method for spinal cord nitrite and nitrate levels was based on the Griess reaction [23]. Total nitrite ($NO^{-2} + NO^{-3}$) was measured by spectrophotometry (Shimadzu, UV-Pharmaspec 1700, Japan) at 545 nm after conversion of NO^{-2} to NO^{-3} by copperized cadmium (Cd) granules. A standard curve was established by a set of serial dilutions (10^{-2}–10^{-3} mol/l) of sodium nitrite. Results were expressed as micromol per gram protein (μmol/g prot.).

Reduced glutathione (GSH), glutathione peroxidase (GSH-Px) and protein assay

The GSH content of hemolyzed erythrocyte, cortex brain and medulla homogenates was measured at 412 nm using the method of ref. [24] as described own studies [3, 4]. GSH-Px activities of the cortex brain, medulla and erythrocytes were measured spectrophotometrically at 37°C and 412 nm according to

the ref. [25]. The protein content in the brain and medulla was measured by method of [26] with bovine serum albumin as the standard. The hemoglobin (Hb) content in the erythrocyte was measured by method of ref. [27].

Determination of vitamin A and C concentrations

Vitamins A (retinol) were determined in the brain homogenates by a modification of the method described by ref. [28]. Around 5 mg of cortex brain samples were saponified by the addition of 0.3 ml 60% (w/v in water) KOH and 2 ml of 1% (w/v in ethanol) ascorbic acid, followed by heating at 70°C for 30 min. After cooling the samples on ice, 1 ml of water and 3 ml of n-hexane were added and mixed with the samples and then rested for 10 min to allow phase separation. Five hundred microliter portions of the hexane extracts were measured spectrophotometrically at 37°C and 325 nm. Calibration was performed using standard solutions of all-trans retinol in hexane.

Quantification of ascorbic acid was performed to ref. [29]. Initially 200 μl of tissue homogenate, erythrocyte hemolyzate or standard preparations of ascorbic acid was precipitated with 800 μl of trichloroacetic acid on ice for 5 min and centrifuged at 3,000 rev/min. Thereafter, 500 ml of the supernatant was diluted to 2 ml with double distilled water, and 200 ml of folinciocalteous. After 10 min the absorbance the samples were measured 760 nm with the spectrophotometer.

Statistical analyses

All results are expressed as means ± SD. To determine the effect of treatment, data were analyzed using one-way ANOVA repeated measures. P-values of less than 0.05 were regarded as significant. Significant values were assessed with LSD test. Data was analyzed using the SPSS statistical program (version 9.05 software, SPSS Inc. Chicago, Illinois, USA).

Results

Sucrose (1%, w/v) test results in the depression plus venlafaxine, depression and control groups were shown in Table 2 and consumption of water with sucrose at 3rd and 4th weeks as ml/kg body weight was significantly ($P < 0.05$) lower in depression group than in control and venlafaxine administered group.

The mean LP values in the three groups of cortex brain, medulla and erythrocytes were shown in Figs. 1 and 2. The mean values in depression plus venlafaxine

administered group, depression and control groups were found 206.20, 272.46 and 221.85 for cortex brain, 423.60, 637.77 and 476.86 for medulla as µmol/g protein, 1.80, 2.33 and 1.75 for erythrocytes as nmol/g Hb, respectively. The results showed that the levels of LP levels of cortex brain, medulla and erythrocytes in depression group were significantly ($P < 0.05$) higher than in the control group. Administration of venlafaxine to depression induced rats caused to decrease in LP levels of three tissues and the levels of LP levels of cortex brain, medulla ($P < 0.05$) and erythrocytes ($P < 0.05$) in venlafaxine administered group were significantly lower than in the depression group.

The mean vitamin A concentrations in the three groups were shown in Fig. 2. The mean values in the venlafaxine administered group, depression and control groups were 6.59, 5.58 and 6.03 nmol/g tissue, respectively. There were no significant differences in the vitamin A concentrations among the groups.

The mean NO levels in the three groups of cortex brain, medulla and erythrocytes were shown in Fig. 3. The mean values in depression plus venlafaxine administered group, depression and control groups were found 5.73, 7.03 and 5.38 for cortex brain, 14.90, 15.56 and 12.98 for medulla as µmol/ g protein, 29.67, 25.40 and 29.89 for erythrocytes as µmol/g Hb, respectively. The results showed that the levels of NO in

cortex brain in depression group were significantly ($P < 0.01$) higher than in the control group. The NO levels in cortex brain in venlafaxine administered group were significantly ($P < 0.01$) lower than in the depression group. There were no significant differences in the NO levels in medulla and erythrocytes between control and depression groups.

The mean GSH-Px activities in the three groups of cortex brain, medulla and erythrocytes were shown in Fig. 4. The mean values in depression plus venlafaxine administered group, depression and control groups were found 27.58, 16.81 and 25.66 for cortex brain, 13.41, 14.33 and 14.61 for medulla as IU/g protein, 29.67, 25.40 and 29.89 for erythrocytes as IU/g Hb, respectively. The results showed that the levels of GSH-Px in cortex brain in depression group were significantly ($P < 0.05$) lower than in the control group. The GSH-Px activities in cortex brain in venlafaxine administered group were significantly ($P < 0.01$) higher than in the depression group. There were no significant differences in the GSH-Px activities of medulla and erythrocytes between control and depression groups.

The mean GSH values in the three groups are shown in Fig. 5. The mean values in the venlafaxine administered group, depression and control groups were 29.92, 24.62 and 29.76 for cortex brain, 27.41, 24.62 and 32.17 for medulla as µmol/ g protein, 3.27, 3.29 and 3.48 for erythrocytes as µmol/ g Hb, respectively. Although GSH level was decreased in the depression group of medulla ($P < 0.05$) according to control group, a significant increase in GSH levels in cortex brain was observed in the venlafaxine administered group ($P < 0.05$) compared to control group.

The mean vitamin C concentrations in the three groups were shown in Fig. 6. The mean values in the venlafaxine administered group, depression and control groups were 70.42, 50.73 and 62.48 µmol/ g protein

Table 2 Sucrose (1%, w/v) test results in the depression plus venlafaxine, depression and control groups ($n = 10$, mean ± SD)

Weeks	Depression + venlafaxine (ml/kg)	Depression (ml/kg)	Control (ml/kg)
Basal	30.00 ± 21.02	34.23 ± 13.14	32.31 ± 12.64
1	33.44 ± 14.64	27.56 ± 16.45	26.07 ± 10.79
2	32.20 ± 12.60	30.46 ± 11.63	29.68 ± 13.51
3	23.61 ± 11.09	22.93 ± 11.21[*]	27.42 ± 12.79
4	25.37 ± 9.95	21.87 ± 12.80[*]	33.70 ± 11.79

[*] $P < 0.05$ vs. basal values

Fig. 1 The effects of venlafaxine on lipid peroxidation levels in cortex brain and medulla in rats, (mean ± SD). [a] $P < 0.05$ as compared with group control. [*] $P < 0.05$ as compared with depression group
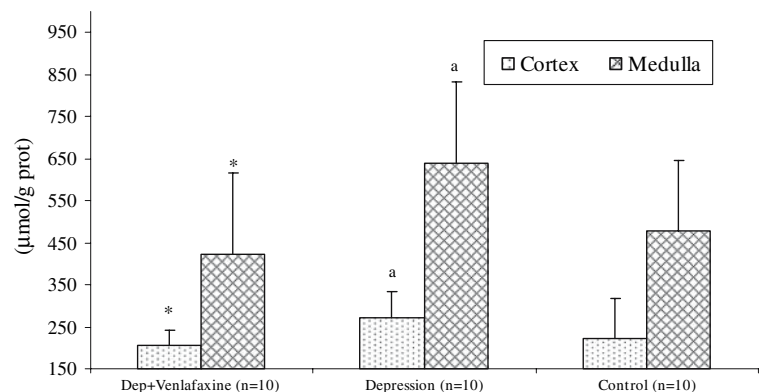
Fig. 2 The effects of venlafaxine on lipid peroxidation in erythrocytes (nmol/g Hb) and vitamin A in cortex brain (nmol/g tissue) in rats, (mean ± SD). [a] $P < 0.05$ as compared with group control. [*] $P < 0.05$ as compared with group depression
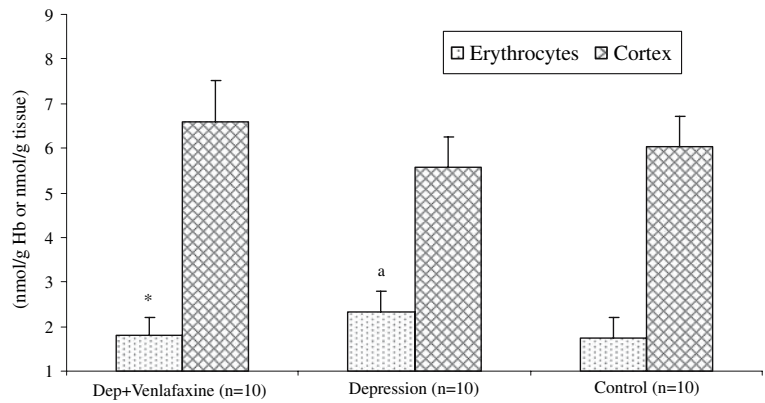

Fig. 3 The effects of venlafaxine on nitric oxide levels in cortex brain, medulla (μmol/g protein) and erythrocytes (μmol/g Hb) in rats, (mean ± SD). [a] $P < 0.05$ as compared with group control. [*] $P < 0.05$ as compared with group depression
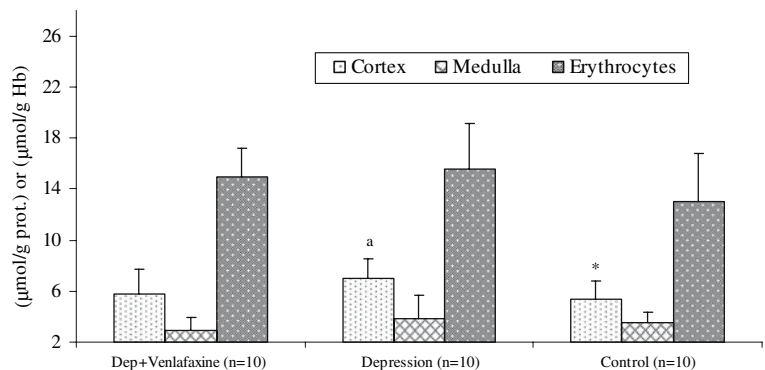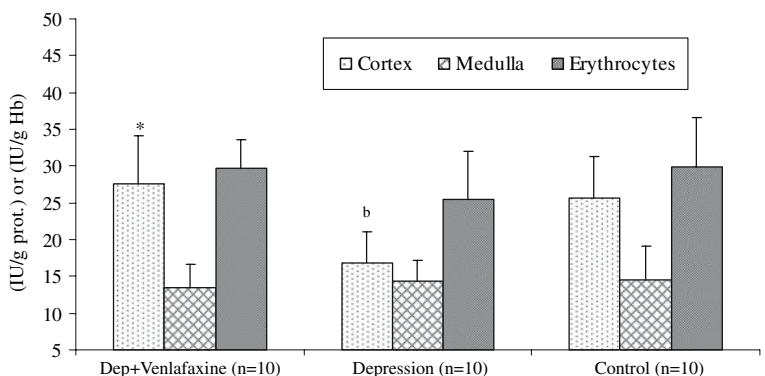

Fig. 4 The effects of venlafaxine on glutathione peroxidase activities in cortex brain, medulla (IU/g protein) and erythrocytes (IU/g Hb) in rats, (mean ± SD). [b] $P < 0.01$ as compared with group control. [*]$P < 0.01$ as compared with depression group

for cortex brain, 12.09, 12.79 and 15.47 nmol/g Hb for erythrocytes, respectively. The results showed that the vitamin C concentrations in cortex brain in depression group were significantly ($P < 0.05$) lower than in the control group. The vitamin C concentrations in cortex brain and erythrocytes in venlafaxine administered group were significantly ($P < 0.01$) higher than in the depression group although there were no significant differences in the vitamin C level of erythrocytes between control and depression groups.

Discussion

We observed that NO and LP levels in the brain, medulla and erythrocytes were increased by depression although investigated enzymatic and nonenzymtic antioxidant decreased. As a novel result of the current study, 28 day venlafaxine supplementation caused a decrease in LP and NO levels although values of the antioxidants were increased by the supplementation.

Fig. 5 The effects of venlafaxine on the GSH levels in cortex brain, medulla (μmol/g protein) and erythrocytes (μmol/g Hb) in rats, (mean ± SD). [a] $P<0.05$ as compared with group control. [*] $P < 0.05$ as compared with group depression
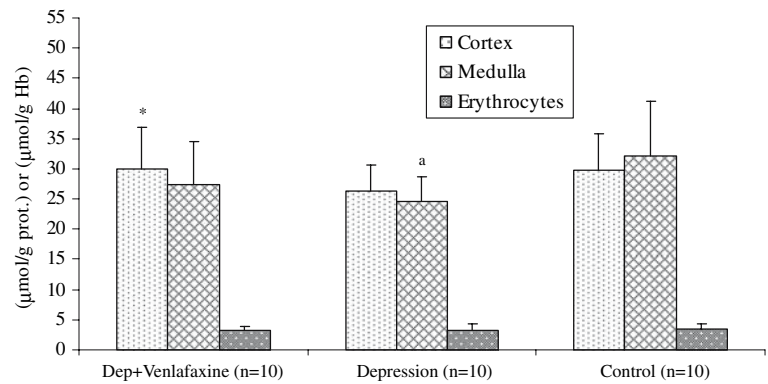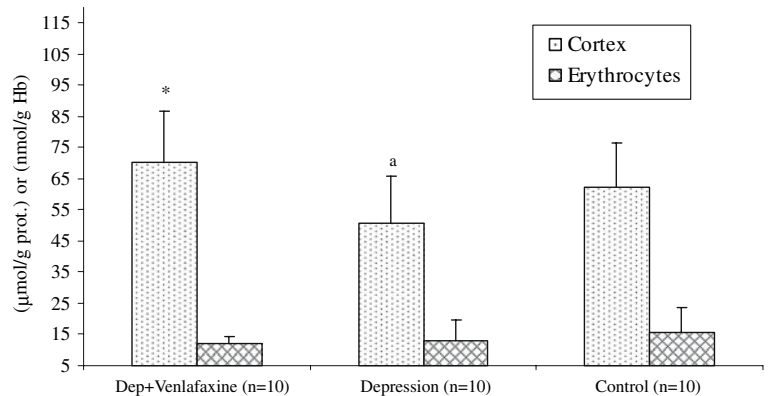

Fig. 6 The effects of venlafaxine on vitamin C concentrations in cortex brain (μmol/g protein) and erythrocytes (nmol/g Hb) in rats, (mean ± SD). [a] $P < 0.05$ as compared with group control. [*] $P < 0.01$ as compared with depression group

Depression is characterized by activation of the inflammatory response system with increased production of procytokines [14, 15]. MDA is a major oxidative degradation product of membrane unsaturated fatty acid and has been shown to be biologically active with ROS properties (3). In the present study, exposure to depression enhanced cortex brain, medulla and erythrocytes damage and LP in the animal system. Activation of immune cells by proinflammatory cytokines leads to over production of ROS, which leads to an increase the levels of LP as MDA and over production of ROS interfere with sutructure and ratio of PUFA [1], and causes loss of fluidity the biological membrane. As a result of those alterations, the biological membranes induce cytokine production [1]. On the other hand, elevation of LP induces phospholipase A2, which changes receptor functions in the cell membranes, induces immune cells, and leads to secretion of interleukins from T cells [30] and it may increase LP [5, 16]. After administrating venlafaxine, the results demonstrate treatment of rat with venlafaxine effectively protected the rats against depression-induced brain damage, shown by increased cortex brain GSH-Px activities and GSH levels and decreased LP and XO levels.

One of the most important intracellular antioxidant systems is the glutathione redox cycle. Glutathione is one of the essential compounds for maintaining cell integrity because of its reducing properties and participation in the cell metabolism [9]. The exact mechanisms of the depression-induced changes in the brain GSH concentrations are not completely elucidated. Thus, glutathione may modulate metal reduction, and the thiol portion is very reactive with several chemical compounds, mainly with superoxide radicals agents such [4, 9]. On the other word, this may be due to the fact that depression causes a significant decrease in cysteine and cystine in the brain because cysteine is the rate-limiting precursor for glutathione synthesis [1, 31]. In this study, the decrease in the GSH concentration in cortex brain and medulla as a result of depression may account for the increased LP. We have found that LP levels in cortex brain and medulla are negatively correlated with GSH in the depression (data not shown). These findings are similar to results of other investigators studying GSH in relation to risk factors in depression illness subjects [1, 5].

GSH-Px is the main enzyme of the enzymatic antioxidant defense system responsible for protection against the increase in ROS production. Hydrogen

peroxide formed by the catalytic reaction of SOD is both a reactive form of oxygen and a normal cellular metabolite, and it is further detoxified by GSH-Px and catalase [1, 9]. GSH-Px activities in cortex brain and erythrocytes were reduced in the depression groups. The reduced activities of GSH-Px could be due to its depletion or inhibition as a result of the increased production of free radicals. Depression increases catecholamine metabolism as well as increased activity of phagocytic cells resulting in the over production of hydrogen peroxide, which detoxifies GSH-Px [8, 12]. The decrease in cortex brain vitamin C and GSH-Px values in animals during depression has been attributed to the generation of free radicals and LP [8, 12, 32].

Recent two studies suggested that patients with major depression were associated with elevated LP levels [5, 33]. Controlled studies reveal elevated MAO activity in patients with major depression [7]. On the other hand, it has been reported that increased ROS production may cause the destruction of phospholipids and altered viscosity of neuron membranes, and consequently the changes in membrane viscosity may affect serotonergic and catecholaminergic receptor functions [6, 8]. The catecholamines including dopamine and norepinephrine are associated with the oxidative stress, thus conditions causing the increased catecholamine metabolism may increase the radical burden as observed in depression. [1]. As a result, it is tempting to speculate that these relationships support a possible etiopathogenetic association between oxidative stress and depression. Venlafaxine has a protective affect on the oxidative stress by inhibiting serotonin reuptake and noradrenaline mechanisms because it is a dual serotonin and noradrenaline reuptake inhibitor with a weak effect on dopamine reuptake [17, 18].

In conclusion, oxidative stress may play a role in the pathogenesis of depression in the rat brain. Our results suggest that also responses of the brain to oxidative stress by depression are quite different from those in medulla and erythrocytes and the beneficial effect of venlafaxine on glutathione and antioxidant system by depression, up-regulation of GSH-Px, GSH and vitamins A and C levels in the cortex brain.

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