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Research Article

Cysteamine Potentiates the Anti-Depressive Effects of Venlafaxine in Corticosterone-Induced Anxiety/Depression Mouse Model: Effect on Brain-Derived Neurotrophic Factor and Tropomyosin-Related Kinase B

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Abstract. The hypothalamic-pituitary-adrenal (HPA) axis abnormalities have been linked to the occurrence of severe depressive and anxiety states. Venlafaxine, a serotonin and a noradrenaline reuptake inhibitor (SNRI), is an approved antidepressant agent with evidence of non-response to treatment in a subset of patients. In this study, 48 male mice (30-38 g) were used to evaluate the possible anxiolytic and antidepressant influence of intraperitoneal (i.p.) cysteamine (150 mg/kg/day) on i.p. venlafaxine (10mg/Kg and 20mg/Kg), as well as effects on brain-derived neurotrophic factor (BDNF) level and tropomyosin-related kinase B (TrkB) gene expression in prefrontal cortex (PFC) in corticosterone-induced anxiety/depression mouse model. The present results provided evidence on insufficient venlafaxine anxiolytic and antidepressant effects in this model. However, cysteamine combined with venlafaxine caused significant antidepressant behavioral effects together with a significant increase in BDNF levels followed by TrkB receptor downregulation in mice PFC. In conclusion, we highlight the potential use of a combination therapy of venlafaxine and cysteamine as a therapeutic strategy for glucocorticoid-related symptoms of depression.

Keywords: BDNF; corticosterone; cysteamine; depression; TrkB; venlafaxine.

1. Introduction

Depression is a worldwide spread illness, with an estimated 350 million people globally affected according to the report from World Health Organization [53]. Although depression and anxiety exist as two distinctive clinical entities, a high comorbidity rate is found between both [42] predicting a chronic outcome [25] and contributes to the global burden of disease [39].

The hypothalamic-pituitary-adrenal (HPA) axis is a key neuroendocrine signaling system involved in physiological homeostasis and body response to stress. Dysregulation of this system causes development of affective disorders [13]. One of the most persistent and reproducible findings in biological psychiatry is the activation of the HPA axis in a subset of patients with

major depressive disorder [50]. Research has also indicated that corticosterone (CORT) lowers serotonin levels, resulting in depression, aggression, and other psychological conditions [34]. Moreover, chronic exposure to CORT has been shown to show anxiety like symptoms in rats and mice [10].

Currently, most effective antidepressants work through modulation of noradrenergic and serotonergic neurotransmission. However, increasing evidence shows that brain-derived neurotrophic factor (BDNF) may play a crucial role in the pathophysiology of depression and that antidepressants may partly exert their effects through regulating BDNF levels [2, 10, 34]. BDNF signaling has an important role in neuroplasticity through its receptor tropomyosin-related kinase B (TrkB) [28], in which chronic stress results in alterations in BDNF/TrkB signaling and changes in neuronal functions [31].

Venlafaxine is a selective serotonin and noradrenaline reuptake inhibitor (SNRI) and one of the most commonly prescribed medications used for treatment of mood disorders. Although it produces a rapid increase in extracellular levels of serotonin and noradrenaline, the onset of an appreciable clinical effect usually takes at least 3 to 4 weeks [55] suggesting that slow neurochemical and structural changes take place within the limbic target areas of monoaminergic projections [17].

Cysteamine is an element normally present in mammalian cells formed by degradation of coenzyme A [51]. The neuroprotective effect of cysteamine was first displayed in Huntington's disease animal models [11], and its neuroprotective effects are linked to the brain BDNF levels [4]. Currently, cysteamine is an approved medication in treatment of a rare recessive disorder, cystinosis [22]. This makes it a preferred approach for treating mood disorders because its safety is well-documented in humans.

In this study, we evaluated the influence of cysteamine on venlafaxine regarding antidepressant and anxiolytic behaviors, as well as attenuation of corticosterone-induced changes on levels of BDNF protein and TrkB gene expression in mice.

2. Materials and Methods

2.1. Experimental animal

A total of 48 male CD-1 mice (30-38 g) were used in the study, divided into six groups. Mice were maintained on a 12-h light–dark cycle. All experimental procedures were performed during the light cycle. All animal care and experimental procedures used in the study complied strictly with the European Community Council directive of 24 November 1986 (86-609/ECC) and the decree of 20 October 1987 (87-848/EEC) and were approved by the Ethical Committee on Animal Research of the Université Catholique de Louvain (LA2230419).

2.2. Chemicals and drugs

CORT, venlafaxine, and cysteamine were purchased from Sigma, St Louis, MO, USA. Corticosterone was dissolved in 0.45% hydroxypropyl-β-cyclodextrin, while both venlafaxine and cysteamine were dissolved in saline with DMSO 5%.

2.3. Induction of the anxiety/depression mice model

The model was induced through chronic administration of CORT (140 ug/ml equivalent to 20 mg/kg/day) [35] in drinking water for 7 weeks [24]. Drinking bottles were filled twice per week and were wrapped with aluminum foil to avoid degradation of corticosterone by light.

2.4. Experimental design

Animals were divided into 6 groups, 8 mice/group. The study was carried out in 7-week period, and the antidepressant treatment has started from the beginning of the 5th week till the end of the 7th week [24].

Group one: the vehicle control group, where mice received 0.45% hydroxypropyl-β-cyclodextrin in drinking water for 7 weeks. Group two: the disease control group, where mice received CORT. Each mouse in groups 1 and 2 received a daily i.p. injection of saline with DMSO 5% starting from the 5th week till the end of the 7th week [24]. Groups three and four: the venlafaxine low dose and high dose groups, respectively, where mice received CORT, then received a daily i.p. injection of venlafaxine either 10 mg/kg/day [56] or 20mg/Kg/d [9]. Groups five and six: the cysteamine plus venlafaxine low dose and high dose groups, respectively, where mice received CORT, then received a daily i.p. injection of venlafaxine either 10 mg/kg/day or 20mg/Kg/d with i.p. cysteamine (150 mg/kg/day).

All animals were monitored for change in body weight weekly and for possible adverse effects of the treatment. At the end of the treatment, behavioral experiments were conducted, then animals were sacrificed, and immediate dissection took place for prefrontal cortex (PFC) as well as hindlimb calf muscles.

2.5. Behavioral experiments

All behavioral experiments were conducted in an equipped platform. Animals were transferred to the behavioral testing rooms approximately 30 min before the beginning of experiments for adaptation to the platform environment.

2.5.1. Functional assessment of locomotor activity

This was done by calculating ambulatory distance (cm) and velocity (cm/sec) covered by mice in arenas of the following three tests using a video tracking system (Ethovision 6.1, Noldus; Wageningen, The Netherlands). Dissection of calf muscles was done following sacrifice to asses if muscle atrophy has occurred due to chronic CORT administration.

Open field (OF)

The OF test was used to assess non-forced ambulation where mice can move freely without any influence of the examiner. Briefly, mice were placed in a square arena (60×60 cm), illuminated at 400 lux, and video-tracked for 20 min.

Light-dark box test (LDB)

The apparatus used for the LDB test consisted of a cage of Plexiglas ($21 \times 42 \times 25$ cm), divided into two sections of equal size by a partition with door [47]. The mouse was positioned in the center of an illuminated chamber and video-tracked for 10 min.

Elevated plus maze (EPM)

Mice were placed in the center of EPM that consists of two opposing open arms (exposed place) and two opposing closed arms (safer place), and the locomotor activity was recorded for 5 min.

2.5.2. Assessment of depressive behavior in mice

Tail suspension test (TST)

The test assesses the animal depressive behavior. It involves suspending mice by their tails using a metal bar. The apparatus used was made from composite wood and designed in the form of two separated compartments with the following dimensions (55 height $\times$ 60 width $\times$ 11.5 cm depth). Mice activity was video-recorded in a 6-minute period for later scoring. Normally, mice will start with escape-like behavior followed by immobility. Duration of immobility was taken for each animal. Animals climbing their tails during the test were excluded.

Forced swimming test (FST)

The FST was carried out according to Porsolt et al. (1978). Briefly, mice were individually placed in beakers instrumented with a sensor, which records vibrations due to movements, and with a camera recording the displacements in order to quantify activity levels such as swimming periods (mobility) or floating periods (immobility). Raw vibrations data from the sensors were synchronized with the video images from a camera. Automated scoring was performed using the automated FST (Bioseb, Vitrolles, France) for 6 min.

2.5.3. Assessment of anxiety behavior in mice

At the same time of locomotor activity assessment, assessment of anxiety was done using the same tests and the same video tracking system (Ethovision 6.1, Noldus; Wageningen, The Netherlands).

Open field (OF)

The frequency of travels to the center by the animals and the proportion of time spent in the center vs. periphery (sec) were measured for 20 min.

Light-dark box test (LDB)

The time spent (sec) by mice in lighted chamber was measured for 10 min.

Elevated plus maze (EPM)

Time spent (sec) in the open arms and junctional "central" area was recorded for 5 min.

## 2.6. RNA extraction, real-time quantitative PCR (qPCR)

PFC samples were used for RNA extraction and purification using a commercially available kit (Qiagen RNeasy® Mini Kit). The cDNA synthesis and real-time qPCR were performed using iScript cDNA synthesis kit and IQ SYBR® Green supermix 1X (Bio-Rad) in combination with primers. TrkB gene primers utilized were as follows: forward primer: 5'CCGA-GATTGGAGCCTAACAG 3', reverse primer: 5'TGCAGGTTGCTGTTTTTCAG3'; and the housekeeping gene is beta-actin. Primer specificity was confirmed by melting curve analysis.

2.7. Brain-derived neurotrophic factor (BDNF) immunoassay

The BDNF concentrations in PFC were quantified in duplicate using mouse BDNF ELISA kit (Biorbyt Ltd.).

2.8. Statistical analysis

Data were presented as mean $\pm$ SEM, and differences between groups were compared by using a one-way analysis of variance (ANOVA), with post hoc Dunnett's multiple comparison test. Unpaired Student's t-test was used when appropriate to compare two individual groups. Significant differences were considered for $P < 0.05$. Statistical calculations were carried out with GraphPad Prism 7.03 Software (GraphPad Softwares Inc., USA).
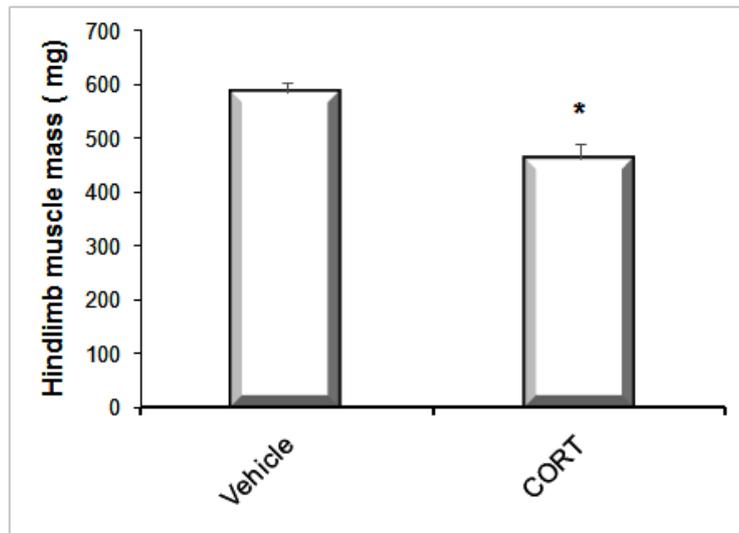
Figure 1: Effect of chronic CORT administration on hindlimb muscles mass (mg) in CORT-induced anxiety/depression mouse model. Mice were treated for 7 weeks. Values are mean ± SE (n = 8), analyzed by Student's *t*-test comparing means. *P < 0.05 versus vehicle group. CORT: corticosterone.

3. Results

3.1. Effect of chronic CORT administration on body weight and hindlimb muscles in CORT-induced anxiety/depression mouse model

Insignificant difference was found in body weight gain during the experiment among groups, data not shown. Regarding the hindlimb muscles, the current study showed a significant difference between the vehicle and CORT groups suggesting a hindlimb muscle wasting effect of CORT treatment ($P < 0.05$, Figure 1).

3.2. Effect of venlafaxine and/or cysteamine on functional assessment of locomotor activity in CORT-induced anxiety/depression mouse model

By calculating the velocity and ambulatory distance traveled by the animals in OF (Figure 2a, b), LDB (Figure 2c, d) and EPM (Figure 2e, f), it was obvious that the differences between all groups were insignificant (P > 0.05). This signifies that decreased hindlimb muscle mass had no effect on the behavioral parameters assessed.
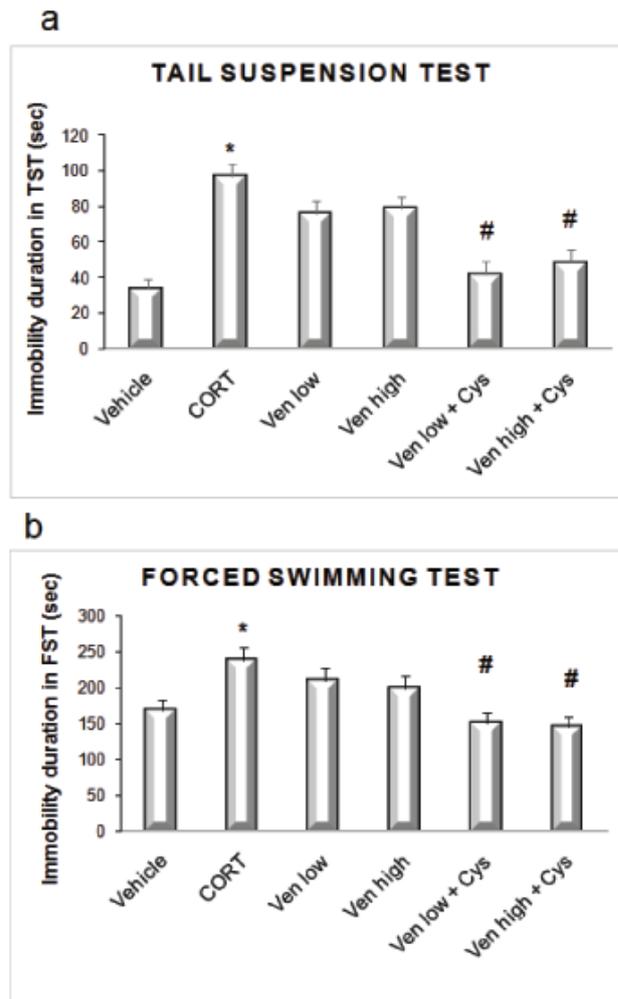
3.3. Effect of venlafaxine and /or cysteamine on depressive behavior in CORT-induced anxiety/depression mouse model

It was obvious that, CORT administration was associated with depressive behavior as revealed by the increased ($P < 0.05$) immobility time when mice hanged passively in TST (Figure 3a) and the helpless behavior and passively floating in the FST (Figure 3b) compared to the vehicle
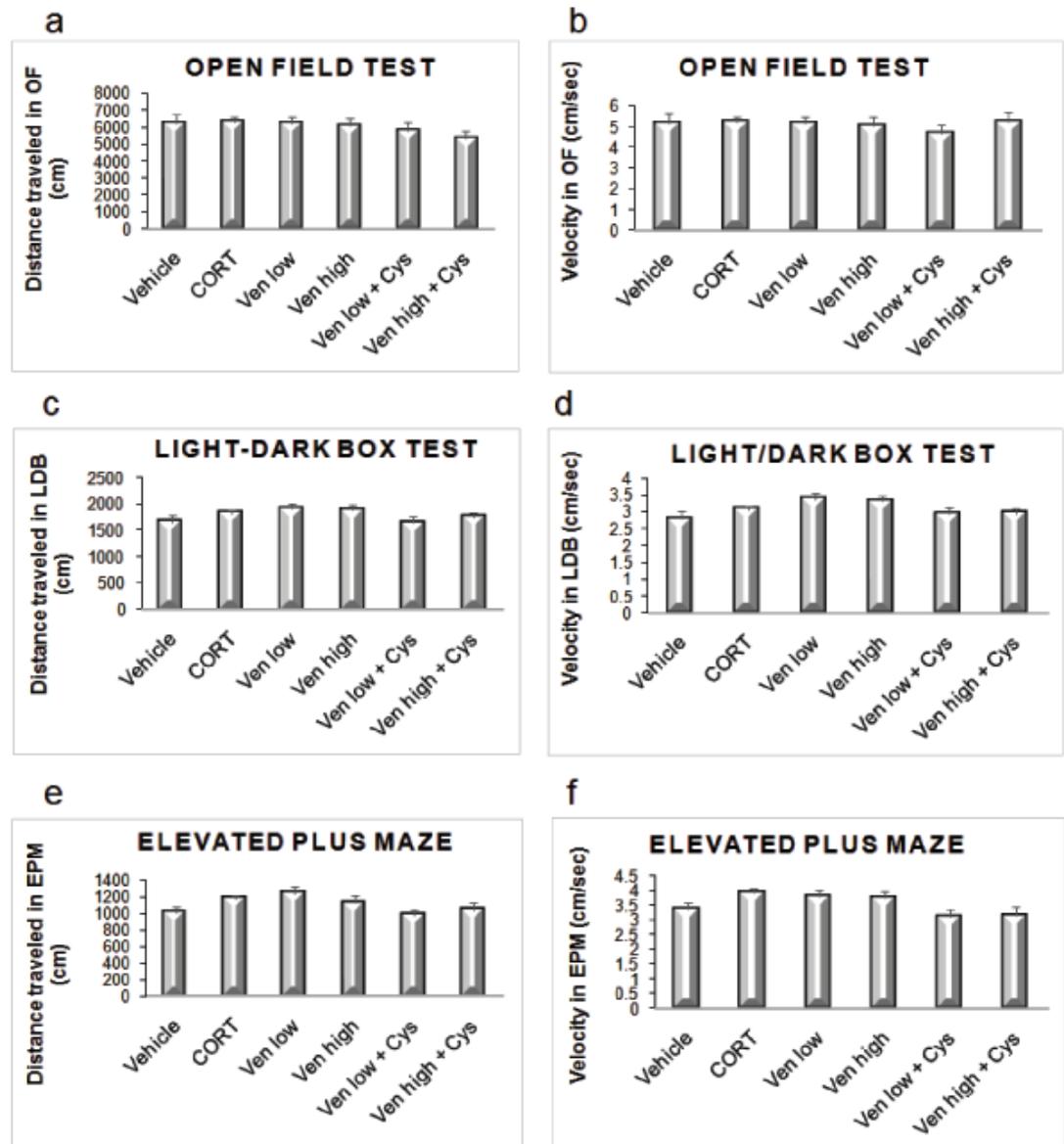
Figure 2: Effect of venlafaxine and/or cysteamine on functional assessment of locomotor activity in CORT-induced anxiety/depression mouse model. Open field during the 20-min test: distance traveled (cm) (a) and velocity of locomotion (cm/sec) (b). Light-Dark Box during 10-min test: distance traveled (cm) (c) and velocity of locomotion (cm/sec) (d). Elevated plus maze during the 5-min test: distance traveled (cm) (e) and velocity of locomotion (cm/sec) (f). Values are mean $\pm$ SE (n = 8), analyzed by one-way ANOVA followed by Dunnett's multiple comparisons post hoc test. [*]$P < 0.05$ versus vehicle group, [#]$P < 0.05$ versus CORT group. OF: Open field, LDB: Light-Dark Box, EPM: Elevated plus maze, CORT: corticosterone, Ven low: Venlafaxine 10 mg/kg/day, Ven high: Venlafaxine 20 mg/kg/day, Cys: Cysteamine 150 mg/kg/day.

control group. Treatment using cysteamine combined with venlafaxine either in low or high dose reversed this depressed behavior in TST and reduced ($P < 0.05$) the immobility time of mice in FST versus CORT group (Figure 3).

Figure 3: Effect of venlafaxine and/or cysteamine on depressive behavior in CORT-induced anxiety/depression mouse model. Immobility duration (sec) in Tail Suspension Test (a) and Forced Swimming Test (b). Values are mean ± SE (n = 8), analyzed by one-way ANOVA followed by Dunnett's multiple comparisons post hoc test. *P < 0.05 versus vehicle group, #P < 0.05 versus CORT group. TST: Tail Suspension Test, FST: Forced Swimming Test, CORT: corticosterone, Ven low: Venlafaxine 10 mg/kg/day, Ven high: Venlafaxine 20 mg/kg/day, Cys: Cysteamine 150 mg/kg/day.

3.4. Effect of venlafaxine and/or cysteamine on anxiety behavior in CORT-induced anxiety/depression mouse model

In the OF test, it was obvious that chronic CORT administration increased the anxiety behavior in mice in the form of a decrease in the frequency of travels to the center zone and the duration spent in it compared to vehicle ($P < 0.05$, Figure 4a, b). Additionally, CORT administration was associated with reduction ($P < 0.05$) in the time spent in light box (Figure 4c) or open arms and junctional "central" area of the maze when compared to the vehicle (Figure 4d). Treatment with venlafaxine in the two different doses, with or without cysteamine, has failed to produce any significant anxiolytic behavior in mice in either the OF, LDB, or EPM tests ($P < 0.05$, Figure 4).
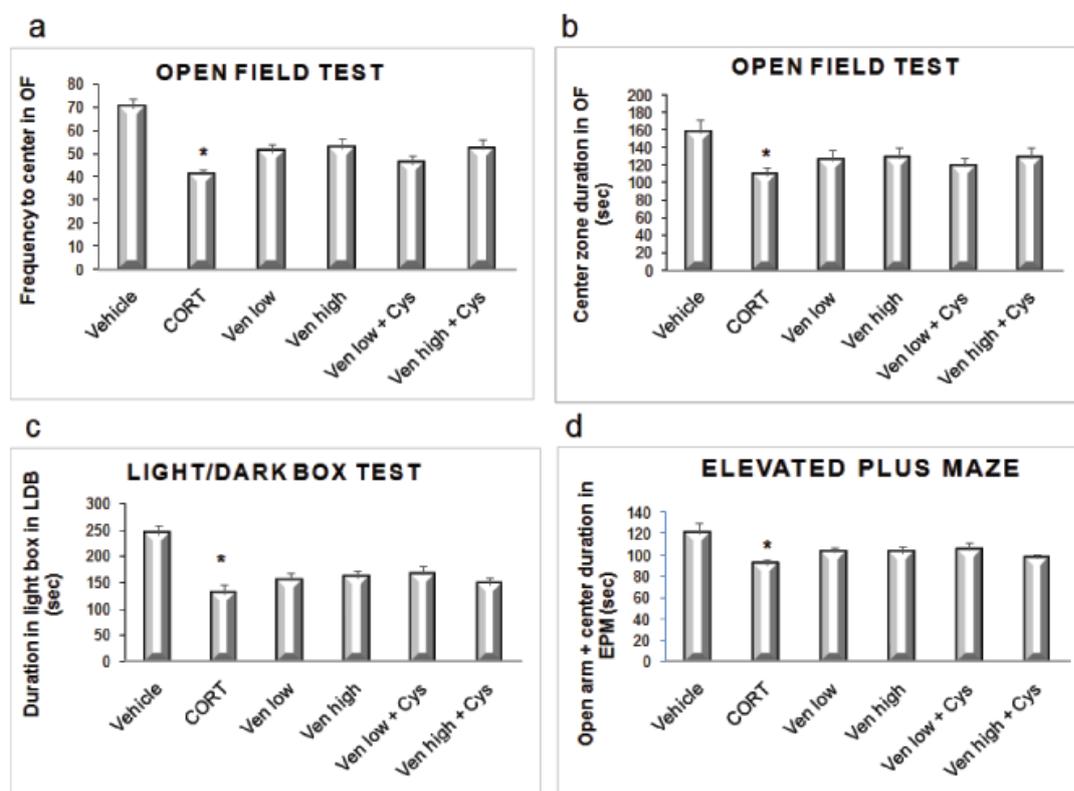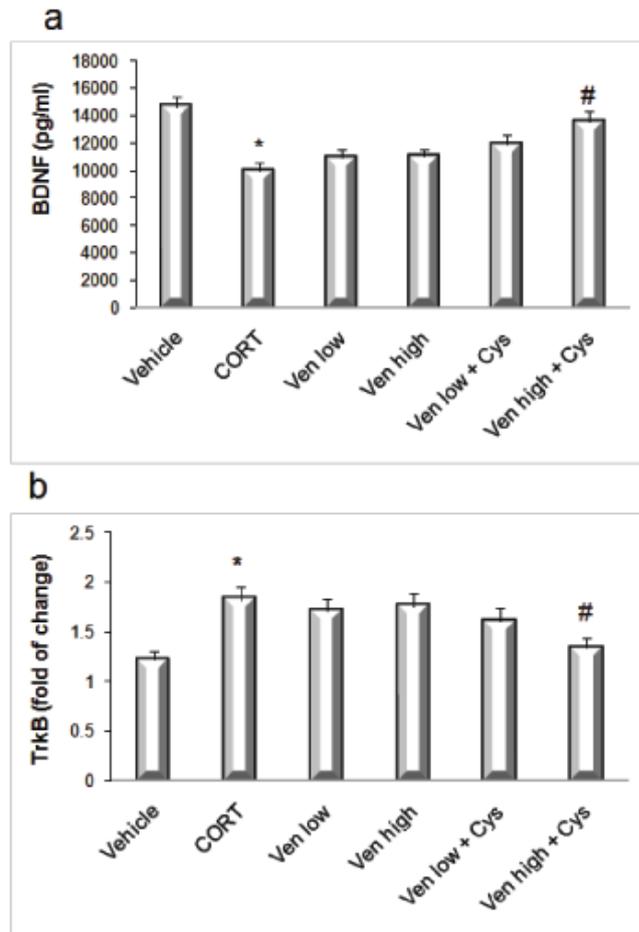
Figure 4: Effect of venlafaxine and/or cysteamine on anxiety behavior in CORT-induced anxiety/depression mouse model. Open Field test: Frequency of travels to center (a) and duration (sec) spent by the mice in the center zone (b). Light-Dark Box test: Duration (sec) spent in light box (c). Elevated Plus Maze test: duration (sec) spent in open arms and center (d). Values are mean $\pm$ SE (n = 8), analyzed by one-way ANOVA followed by Dunnett's multiple comparisons post hoc test. *$P < 0.05$ versus vehicle group, #$P < 0.05$ versus CORT group. OF: Open field, LDB: Light-Dark Box, EPM: Elevated plus maze, CORT: corticosterone, Ven low: Venlafaxine 10 mg/kg/day, Ven high: Venlafaxine 20 mg/kg/day, Cys: Cysteamine 150 mg/kg/day.

3.5. Effect of venlafaxine and/or cysteamine on BDNF level and TrkB receptor gene expression in CORT-induced anxiety/depression mouse model

Figure 5 highlighted that CORT administration was associated with reduction in BDNF level and upregulation in TrkB receptor gene expression ($P < 0.05$) in comparison with the vehicle group. Treatment with high dose venlafaxine + cysteamine elevated the BDNF level and downregulated the TrkB receptor gene expression when compared with CORT group ($P < 0.05$, Figure 5).

4. Discussion

Several studies documented that the therapeutic effects of antidepressants are not directly due to the enhancement of monoamine neuronal signaling, but rather due to neuronal plasticity changes that take place over time [14]. Thus, the potential use of therapeutic avenues based on downstream changes common to current antidepressants may help find new antidepressants with a faster onset of action and a higher clinical efficacy. The present study evaluated the potential effect of cysteamine when combined with venlafaxine in attenuating CORT-induced anxiety

Figure 5: Effect of venlafaxine and/or cysteamine on brain-derived neurotrophic factor protein levels (pg/ml) (a). TrkB gene expression (fold of change) (b) in CORT-induced anxiety/depression mouse model. Values are mean $\pm$ SE (n = 8), analyzed by one-way ANOVA followed by Dunnett's multiple comparisons post hoc test. $^*P < 0.05$ versus vehicle group, $^#P < 0.05$ versus CORT group. BDNF: brain-derived neurotrophic factor, CORT: corticosterone, Ven low: Venlafaxine 10 mg/kg/day, Ven high: Venlafaxine 20 mg/kg/day, Cys: Cysteamine 150 mg/kg/day.

and depression-related behaviors in mice as well as changes in the levels of BDNF and TrkB receptor gene expression.

No differences in weight gain were found during the experiment among groups. This result is consistent with a study carried out previously [24], where animals were exposed to CORT in the drinking water for 7 weeks as well, and no differences in relative body weight gain between the vehicle and CORT treated mice groups during the experiment were detected. However, other studies [12, 45, 52] have shown evidence of weight loss after exogenous CORT treatment in rodents. On the other hand, and compatible with previous studies [7], CORT administration was accompanied with considerable reduction of hindlimbs muscle mass. It has been reported that CORT induces specific molecular changes followed by increased breakdown of skeletal muscle protein [21]. To conclude that the anxiogenic and depressogenic effects of CORT occur independently of the effects on muscles, we calculated the velocity and distance traveled in behavioral arenas, which, and in line with Marks et al. (2009), confirm the absence of any effect of the decreased hindlimb muscle mass on behavioral parameters assessed.

Chronic CORT delivery to rodents through drinking water mimics the circadian rhythmicity of endogenous CORT secretion in stressor-exposed rodents, disrupts glucocorticoid receptor-mediated feedback systems, and results in depressive-like behaviors that persist for a significant period of time [18, 26]. In line with Zhao et al. (2008), CORT administration was associated with the development of immobility in both TST and FST. Another study that used 7-week regimen of chronic CORT administration using a lower dose of 5 mg/kg/day in mice does not result in any significant change in immobility score in TST [24]. This suggests the presence of dose-related as well as time-dependent effects of CORT on depressive behavior. It also signifies that the dose factor and time factor are necessary for complete achievement of the model.

The relationship between cortisol and BDNF plasma levels is notable [3], in which corticosteroid-induced downregulation of BDNF expression had been reported [43, 57]. It is possible that a normalization of cortisol and BDNF expressions may play a key role in treatment outcome of depression. Chronic CORT exposure in the present study has led to a reduction in the BDNF levels, inconsistent with other studies [19, 20, 24]. The TrkB, the receptor of BDNF, plays a key role in stress-induced changes in neuroplasticity [6], and TrkB alterations have been linked to a number of stress related psychiatric disorders. The present results revealed that CORT upregulates TrkB receptors expression. This finding shows a discrepancy with other studies that show a downregulation of TrkB expression in mood disorders [15, 24, 48, 60]. However, the present results can be explained by the fact that the brain PFC has responded to the decreased BDNF levels by CORT administration by increasing the expression of TrkB receptors.

Moreover, CORT induced anxiety behavior shown through its deleterious effects on mice behavior as evident in OF, LDB, and EPM tests. This was consistent with previous studies assessing effects of chronic CORT administration on anxiogenic behavior [1, 10].

In the present study, venlafaxine alone in the two doses used showed slight improvement in behavioral assessments of anxiety and depression, yet it failed to show significant values. These subtle responses to venlafaxine can be partially explained by a study conducted by Samuel group [41] who reported that the majority of animals have manifested anxiety/depression phenotype following chronic CORT treatment; however, mouse subjects tended to show a bimodal distribution in response to antidepressant treatment, suggesting a responder and non-responder groups. Later, the same group of researchers have identified the occurrence of resistance capacity of this chronic CORT treatment model [40]. In addition, a study has shown that chronic treatment with multiple classes of antidepressants can reverse the behavioral effects associated with chronic CORT in most, but not all, animals. The exact mechanisms underlying resistance to antidepressant treatment remain unknown [36]. In addition, cysteamine combined with venlafaxine has failed to produce anxiolytic effects.

Cysteamine is currently regarded as a neuroprotective agent with evidence of suppressing oxidative stress and cortical neuron apoptosis and improving neurological deficits [58]. Mice have displayed differential responses across the multiple behavior tests used in response to combination of venlafaxine and cysteamine favoring antidepressants over anxiolytic effects. Possibly, the mouse strain in the present study could be responsible for this differential response. The behavioral patterns present in various mouse strains have long assisted in the characterization of neural processes influenced by strain-dependent inheritable characters [5, 8, 27, 38].

An elevation in BDNF levels was detected in the present study when cysteamine was combined with venlafaxine. This is in agreement with previous studies that have shown the potential of cysteamine to raise BDNF levels [4, 32, 49]. A previous study has suggested that a dysregulation in BDNF expression may be a common feature of treatment-resistant depressed patients [57]. This could explain cysteamine capability to attenuate the antidepressant resistance to venlafaxine through the rise of BDNF levels in the PFC in the chronic CORT model. On the other side, cysteamine combination with venlafaxine has induced downregulation of TrkB receptor expression in PFC in response to elevated BDNF levels. This finding goes in harmony with studies that have described downregulation mechanisms as adaptive phenomena that make the systems more resilient in responding to ligand perturbations, thereby improving the stability of the system states [44]. Downregulation of TrkB signaling upon BDNF exposure has also been reported in cultures of cortical [23, 54] and hippocampal neurons [16, 54].

In contrast, a considerable number of studies have shown that antidepressant treatment leads to TrkB receptor upregulation [30] and activation [37]. Possibly, this TrkB downregulation in the treatment group could be occurring temporarily and to be followed later by upregulation of TrkB receptors in response to treatment. Similarly, a previous study has reported that following TrkB degradation and downregulation, a compensatory TrkB mRNA upregulation may also ensue [46].

In conclusion, our results provide evidence on existence of resistance to venlafaxine treatment in anxiety/depression model induced by CORT. Future studies targeting the molecular mechanisms underlying the differences between venlafaxine responders and non-responders should provide better understanding. Cysteamine could provide a benefit of reducing resistance to venlafaxine antidepressant effects in CORT model. In addition, we have confirmed the effects of cysteamine to elevate BDNF in brain PFC. However, further evaluation of this compound for antidepressant properties is needed. An important advantage is that cysteamine tolerability has been previously demonstrated in human subjects. Finally, through this study, we highlight the potential use of a combination therapy of venlafaxine and cysteamine as a novel therapeutic strategy for glucocorticoid-related symptoms of depression if enough clinical trials are available.

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Competing Interests

The authors declare no competing interests.

Acknowledgments

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