RESEARCH PAPER

L-Theanine Ameliorates Chronic Unpredictable Mild Stress-Induced Depressive Behavior Through Differential Modulation of Hippocampus and Prefrontal Cortex

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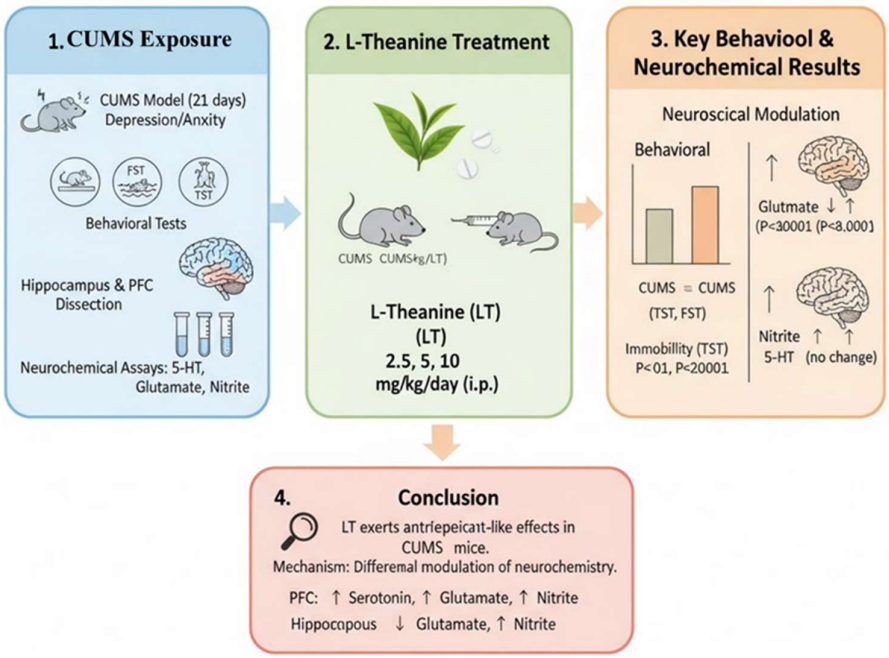
ABSTRACT

Aim: This study was designed to determine the antidepressant-like effect of L-theanine in mice exposed to chronic unpredictable mild stress (CUMS).

Methods: In the present study CUMS procedure of 3 weeks (21 days) was used for the induction of depression related behavior. On day 22nd, behavioral testing was performed using an actophotometer for locomotor activity. On day 23rd, depression-related behavior was assessed using tail suspension test (TST) and the forced swim test (FST). Following behavioral studies, mice were sacrificed, and the PFC and hippocampus were dissected for the neurochemical assays of serotonin, glutamate, and nitrite.

Results: It was observed that the daily treatment with L-Theanine (5 and 10 mg/kg/day i.p.) did not affect the activity count of the mice but ameliorated the effect of CUMS in TST ($P<0.01$, $P<0.01$) and FST. Also, the daily treatment with L-Theanine (2.5, 5, and 10 mg/kg/day i.p.) in the CUMS exposed mice significantly increased the PFC serotonin level ($P < 0.001$, $P < 0.001$, $P < 0.001$) without affecting the hippocampal serotonin level. However, the daily treatment of L-Theanine (2.5, 5, and 10 mg/kg/day i.p.) in mice exposed to CUMS significantly decreased the glutamate level ($P<0.001$) and increased the nitrite level ($P<0.001$, $P<0.001$, $P<0.001$) in hippocampal region while the the daily treatment of L-Theanine (2.5, 5, and 10 mg/kg/day i.p.) in mice exposed to CUMS significantly increased the glutamate level ($P < 0.001$, $P < 0.001$, $P < 0.001$) and nitrite level ($P<0.001$, $P<0.001$, $P<0.001$) region of the mice as compared to its respective control.

Conclusion: In conclusion, LT exerted an antidepressant-like effect in mice exposed to CUMS by increasing serotonin, glutamate, and nitrite in the PFC and decreasing glutamate in the hippocampus..



Keywords: Chronic Unpredictable Mild Stress, Depression, Glutamate, Hippocampus, L-Theanine, Nitrite, Serotonin

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INTRODUCTION

Depression is a disorder characterized by the presence of symptoms including low mood, loss of interest, impaired concentration, sleep, cognition, and eating patterns **[1, 2]**. Depression is a considerable social and economic burden and is the leading cause of death across the world. The exact pathophysiology of depression is still not known. However, it has been reported that the depression related neurobehavioral alterations developed due to impairment of various pathways, including monoaminergic signaling, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, neuroinflammation, impaired neurogenesis, and structural and functional impairment **[4]**. It has been reported that depression is accompanied by structural and functional impairment in various structures, including the hippocampus, amygdala, and lower brainstem **[5]**. Further, the depression patients showed reduced prefrontal cortex (PFC) and hippocampus volume **[6-11]**. However, reduced hippocampal volume is not associated with the severity of depression **[12]**. Treatment includes antidepressants and psychotherapies **[13]**. Antidepressant medications are considered the first-line treatment for depression **[14]**. However, only one-third of individuals respond to the antidepressants, and the adverse effects imposed by these drugs often limit their use **[15]**. Besides this, the available antidepressants have various limitations, including adverse effects, slow onset, and high remission rate **[16]**, suggesting the importance of the development of newer, efficient, and safer antidepressants **[17]**.

Stress plays an important role in the pathogenesis of depression **[18]**. The chronic unpredictable mild stress (CUMS) model is the most commonly used stress-induced depression model **[19]**. CUMS model has the advantage that the various stressors are applied to the rodents in an unpredictable order for several times, thus preventing the occurrence of habituation, desensitization, and facilitation **[20]**. CUMS impairs homeostasis in experimental animals and induces many core symptoms, including helplessness, anhedonia, etc. **[21, 22]**. TST and FST are mainly used for the assessment of depression-like behavior in experimental animals **[23, 24]**. CUMS has been shown to decrease monoamines, including dopamine (DA), serotonin (5-HT), and noradrenaline (NA), in the hippocampus and PFC **[25, 26]**. CUMS also disrupts the activity of glutamate to contribute to depressive behavior **[27]**. Besides this, chronic stress also produces structural changes in the hippocampus and PFC region to produce the depression related changes **[28]**.

L-theanine (LT) (γ-glutamylethylamide) is a unique amino acid found in green tea and has shown potential effectiveness in patients with mental disorders **[29]**. LT modulates brain monoamine, glutamate, and glycine levels **[30]**. LT ameliorates stress-mediated behavioral and neurochemical changes in the PFC region **[31]**. LT has been shown to abolish the CUMS mediated depressive behavior and has been shown to increase the level of 5-HT, DA, and NA in the PFC and hippocampus region. LT significantly increased the levels of 5-HT, NE, and DA **[32]**. In rats exposed to CUMS of 21 days, daily treatment with LT exerts an antidepressant effect, increases neurogenesis, and decreases microglial activation **[33]**. LT (200 mg/day) for four weeks has been shown to decrease the stress-related symptoms, promote mental health, and improve cognitive impairments **[34]**. Further, it has been reported that the addition of LT (250 mg/day) to the current medication for 8 weeks reduces depressive symptoms in depression patients with MDD **[35]**. However, the exact effect of L-Theanine on the monoamines, glutamate, and nitrite levels in the hippocampal and prefrontal cortex (PFC) is still not known. Further, how the modulation of hippocampal and prefrontal cortex (PFC) monoamines, glutamate, and nitrite levels influences the depression related behavior is still not known. Therefore, in the present study, we studied the effect of L-Theanine on the depression related behavioral alterations in TST and FST and the possible modulation of hippocampal and prefrontal cortex (PFC) monoamines, glutamate, and nitrite levels.

2. Materials and Methods

2.1 Animals

Male Swiss albino mice (male, 30-40 g) were used and maintained under controlled conditions with free access to food and water. The experimental protocols were approved by the Institutional Animal Ethics Committee (SGTU/IAEC/2024/12), and the care of mice was carried out in accordance with CCSEA guidelines of the Ministry of Environment and Forest, Government of India.

2.2. Treatments

L-Theanine (LT) (Sigma Aldrich, India) and fluoxetine (FLX) (Zydus Cadilla, India) were used in the present study. Treatments were administered in a volume of 10 ml/kg, intraperitoneal (i.p.).

2.3 Chronic Unpredictable Mild Stress (CUMS)model for the induction of depression in mice

CUMS protocols include the stressors in random order with an interval of 7 days **[36, 37]**. Stressors involved in the CUMS procedure include

Stressor	Duration
Social crowding	24h
Swimming in water (at 25-30°C)	20 min
Cages tilted at 30°C	24h
Restraint stress	1.5h
Wet cage	24h
Tail pinch	2 min
Food and water deprivation	24 h

2.4 Behavioral assays

2.4.1 Locomotor Activity

The locomotor activity was determined using actophotometer. Each mice was placed in the actophotometer and activity count was determined over a period of 6 min.

2.4.2 Tail Suspension Test (TST)

Each mouse was suspended at a height of 50 cm from the tip of its tail and the immobility period was determined over a period of 6 min **[38]**.

2.4.3 Forced Swim Test (FST)

Each mouse was forced to swim in a glass vessel filled with water (25 ± 1°C), and the immobility period was determined over a period of 6 min **[39]**.

2.5. Neurochemical assay

2.5.5.1 Tissue processing

Mice were anesthetized using isoflurane, sacrificed, and then the dissection of the brain hippocampus and PFC was performed. Both the PFC and hippocampus were used for the 5-HT, glutamate, and nitrite assay.

2.5.1 Serotonin assay

Tissue samples were mixed with 5 ml HCl–butanol, followed by homogenization for 1 min, centrifuged for 10 min at 2000 rpm, and the supernatant (1 ml) was collected. To the supernatant, 2.5 ml heptane and 0.31 ml of HCl (0.1 M) were added and again subjected to centrifuging under the same conditions. Following centrifugation, the 0.2 ml lower aqueous phase was mixed with 0.25 ml O-phthaldialdehyde (OPT), heated at 100°C for 10 min, and cooled at room temperature, followed by the spectrofluorometric assay at 360-470nm. The blank solution will be HCl 0.25 ml without OPT **[40-42]**. ***(****OPT assay is a relatively simple fluorometric method, but has been reported to lack specificity and sensitivity. However, when employed in the standardized conditions, it produces reliable results)*.**

2.5.3 Nitrite assay

In brief, 100 µl of tissue sample was mixed with 100 µl of the Griess reagent and kept at room temperature for 10 min, followed by the determination of absorbance at 546 nm **[43]**.

2.5.4 Glutamate assay

In brief, 0.3 ml tissue sample was mixed with 0.1 ml phosphate solution, and the pH was adjusted to 9.0. The sample was kept undisturbed for a period of 10 min in an ice bath, followed by the determination of absorbance at 340 nm **[44]**. *Total tissue glutamate is present in the millimolar (mM) range (can be measured), while the synaptic glutamate is present in a very low micromolar range (difficult to measure*).

2.6. Experimental protocol

Male Swiss albino mice were used in the present study (n=10 in each group). The selected doses include L-Theanine (2.5, 5, and 10 mg/kg, i.p) and fluoxetine (10 mg/kg, i.p.). CUMS procedure of 3 weeks (21 days) was used for the induction of depression related behavior. On day 22nd, behavioral testing was performed using an actophotometer for locomotor activity. On day 23rd, depression-related behavior was assessed using tail suspension test (TST) and the forced swim test (FST). Following behavioral studies, mice were sacrificed, and the PFC and hippocampus were dissected for the neurochemical assays of serotonin, glutamate, and nitrite.

Experimental groups (n=10 mice per group):

Group-1: Vehicle-treated mice (Control)

Group-2: CUMS mice

Group-3: CUMS + FLX (10 mg/kg, i.p.)

Group-4-6: CUMS + LT (2.5-10 mg/kg, i.p.)

2.7. Statistical analysis

Statistical analysis was performed using GraphPad Prism software (version 9.4.0) (GraphPad Software Incorporated, La Jolla, CA). Data were analyzed using One-way analysis of variance (ANOVA), followed by Dunnett *post hoc* test when found appropriate. P<0.05 was considered statistically significant.

3. RESULTS

3.1 Effect of various treatments on the locomotor activity of mice

One-way ANOVA suggested no significant effect on the activity count of mice by ($F_{5,54}$ = 2.205, P = 0.0670) (*refer to Figure 1a*).

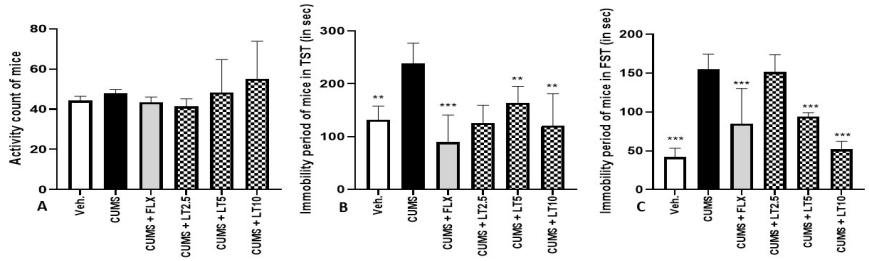

Figure-1: Effect of L-theanine on the locomotor activity and depression like behavior in mice
Values were expressed as Mean ± SEM. N=10 in each group. *P <0.05, **P <0.01, ***P <0.001 significant difference from the mice exposed to CUMS

3.2 Effect of various treatments on the immobility period of mice in TST and FST

Depression related behavior: One-way ANOVA suggested a significant effect of various treatments on the immobility period of mice in TST ($F_{5,54}$ = 15.34, P < 0.001) and FST ($F_{5,54}$ = 43.75, P < 0.001).

Tukey's *post hoc* test suggested that CUMS exposure significantly increased the immobility period of mice in TST (P<0.01) and FST (P<0.001) as compared to the control. Daily treatment with fluoxetine significantly ameliorated the CUMS mediated increase in the immobility period of mice in TST (P<0.001) and FST (P<0.001). Daily treatment with L-theanine (5 and 10 mg/kg/day i.p) significantly ameliorated the CUMS. significantly ameliorated the CUMS mediated increase in the immobility period of mice in TST (P<0.01, P<0.01) and FST (P<0.001, P<0.001). (*shown in Figure-1b and 1c*).

3.3 Effect of various treatments on neurochemical levels of mice in the hippocampus and PFC

Serotonin level*:* One-way ANOVA suggested the significant effect of various treatments on hippocampal ($F_{5,54}$ = 2.798, P = 0.0595) and PFC region ($F_{5,54}$ = 37.99, P < 0.001) serotonin levels. Tukey's *post hoc* test suggested that the CUMS exposure did not affect the serotonin level in the hippocampus but decreased the serotonin level in the PFC region (P < 0.001) of the mice exposed to CUMS. Daily treatment of fluoxetine to the CUMS mice significantly increased the PFC serotonin level (P < 0.001) without affecting the hippocampal serotonin level. Daily treatment with L-theanine (2.5, 5, and 10 mg/kg/day i.p.) to the mice exposed to CUMS significantly increased the PFC serotonin level (P < 0.001, P < 0.001, P < 0.001) without affecting hippocampal serotonin level (*shown in Figure-2a*).

Glutamate level*:* One-way ANOVA suggested the significant effect of various treatments on hippocampal ($F_{5,54}$ = 18.29, P < 0.001) and PFC ($F_{5,54}$ = 185.7, P < 0.001) glutamate levels. Tukey's *post hoc* test revealed that CUMS exposure significantly increased the glutamate level in the hippocampus (P < 0.001) without altering the PFC glutamate level as compared to the control group. Daily treatment of fluoxetine to the CUMS mice significantly decreased the hippocampal glutamate level (P < 0.001) without affecting the PFC glutamate level. Daily treatment with L-theanine (2.5, 5, and 10 mg/kg/day i.p.) to the mice exposed to CUMS significantly decreased the hippocampal glutamate level (P<0.001) but significantly increased the PFC glutamate level as compared to its respective control (*shown in Figure-2b*).

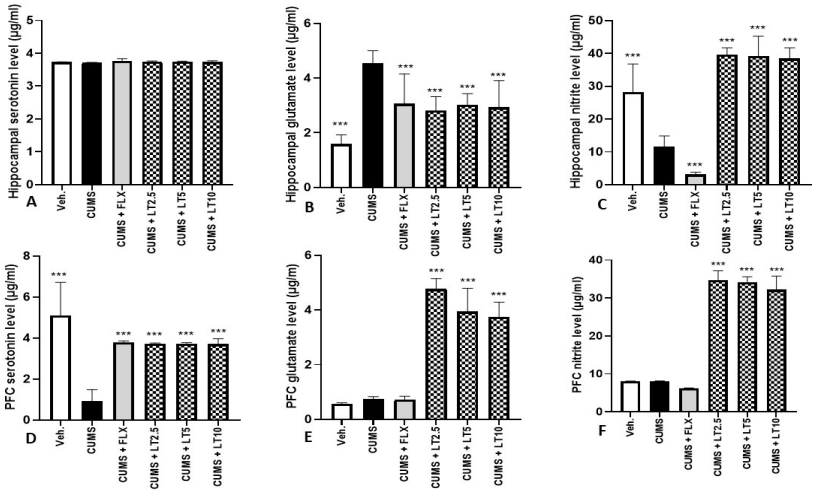

Figure-2: Effect of L-theanine on PFC and Hippocampal serotonin, glutamate, and nitrite levels
Values were expressed as Mean ± SEM. N=10 in each group. *P <0.05, **P <0.01, ***P <0.001 significant difference from the mice exposed to CUMS

Nitrite level: One-way ANOVA suggested the significant effect of various treatments on hippocampal ($F_{5,54}$ = 109.0, P < 0.001) and PFC ($F_{5,54}$ = 585.7, P < 0.001) nitrite level. Tukey's *post hoc* test suggested that exposure of mice to CUMS significantly decreased the hippocampal nitrite level (P<0.001) without affecting PFC nitrite level as compared to control. Daily administration of fluoxetine to the CUMS mice further significantly decreased the hippocampal nitrite level (P<0.001) without affecting the PFC nitrite level. Further, the daily treatment of LT (2.5, 5, and 10 mg/kg/day i.p.) to the mice exposed to CUMS significantly increased the hippocampal (P<0.001, P<0.001, P<0.001) and PFC (P<0.001, P<0.001, P<0.001) nitrite level (*shown in Figure-2c*).

4. Discussion

In the present study, CUMS exposure induced depressogenic behavior and reduced the 5-HT level in PFC without affecting the hippocampal 5-HT level in the experimental mice. CUMS exposure has been shown to increase the hippocampal glutamate level, but did not affect the PFC glutamate level. Similarly, CUMS exposure decreased the hippocampal nitrite level, but did not affect the PFC nitrite level as compared to control. LT (5 and 10 mg/kg/day for 7 days) ameliorates the CUMS induced depression in mice without affecting the hippocampal 5-HT

level, but increases the PFC 5-HT level. Further, daily administration of LT (5 and 10 mg/kg) significantly reversed the effect of CUMS on the hippocampal and PFC glutamate and nitrite levels. Thus, the present findings suggested that the LT reversed the depressogenic effect of CUMS by increasing the PFC 5-HT, glutamate, and nitrite levels. LT treatment did not affect the hippocampal 5-HT level, but decreased the hippocampal glutamate and increased the hippocampal nitrite level.

CUMS model is a classic model mainly used for establishing depression in experimental animals **[46, 47]**. CUMS model has been shown to induce depressive symptoms, including associability, hopelessness, helplessness, sex apathy, weight loss, etc. **[48, 49]**. In the present study, CUMS of 3 weeks induces depressive behavior in mice characterized by the increase in the immobility period of mice in TST and FST. It has been reported that the CUMS exposure induce depression related behavior in TST and FST **[50-52]**. The present findings revealed that the CUMS exposure did not affect hippocampal 5-HT level but decreased the 5-HT level in PFC region. Previous findings have shown that the CUMS exposure decreases 5-HT level in hippocampal and PFC region **[53]**.

5-HT dysfunction has been implicated in the pathogenesis of depression **[54]**. DRN is the main source of 5-HT for the various limbic regions, including PFC and hippocampus **[55-58]**. It has been reported that the CUMS exposure is responsible for the neuronal cell death in DRN, which is responsible for the disruption of neuronal enervation to mPFC, further resulting in the reduced postsynaptic 5-HT currents and 5-HT concentration **[59-61]**. Further, the present findings have shown that the CUMS exposure decreases the 5-HT level in the PFC, suggesting that CUMS mainly affects the PFC to induce depressogenic behavior. Stress has been shown to promote dendritic atrophy, dendritic spine, and volume loss in the hippocampus and PFC **[62, 63]**. CUMS exposure in the present study only increased the level of glutamate in the hippocampus, while the glutamate concentration in the PFC region did not increase significantly compared to the control. Glutamate is the main excitatory neurotransmitter in the brain and the dysregulation of glutamate release is the major factor involved in the pathogenesis of depression **[64-66]**. Previous studies have shown that the glutamate level decreases in the PFC of individuals exposed to CUMS **[67]**. Further, it has been reported that the PFC glutamate level decreases during the first episode of depression **[68, 69]**, and the chronic or remitted–recurrent MDD subjects showed reduced PFC glutamate level compared to the depression patients with first episode **[70]**, suggesting the reduced PFC glutamate level might represent a state marker for depression **[71]**. However, in the present study CUMS exposure only increases the hippocampal glutamate level, suggesting that the depressogenic effect of CUMS is mediated through the increase of hippocampal glutamate level. Further, the previous studies have shown that the CUMS exposure increases the hippocampal glutamate level **[72, 73]** and the latter is responsible for the excitotoxicity and neuronal cell loss in the hippocampus region **[74, 75]**. Besides this, the CUMS exposure did not affect the PFC nitrite level, but decreased the hippocampal nitrite level in the present study. NO has been implicated in the pathogenesis of depression **[76, 77]** and the reduced NO level has been observed in depression **[78]**. It has been reported that the hippocampal nNOS is regulated by the stress response mediated through the glucocorticoid receptors (GR) **[79]**. Further, chronic stress has been shown to inhibit nNOS expression and production of NO to induce depressive behavior **[80]**.

Fluoxetine is mainly used as the standard antidepressant drug in various preclinical studies **[81]**. In the present study, chronic treatment with fluoxetine has been shown to reversed the CUMS induced depression like behavior in experimental mice. The findings were in context with the previous studies suggesting that the chronic treatment with fluoxetine reversed the CUMS induced depressive related behavior in experimental animals **[82, 83]**. In the present study, daily administration of fluoxetine before CUMS exposure increased the serotonin level in PFC without affecting the PFC glutamate and nitrite levels. PFC region of are rich in the serotonergic neurons and is thus modulated by the SSRIs treatment **[84-87]**. The present findings have suggested that the chronic treatment with fluoxetine significantly decreased the hippocampal glutamate and nitrite levels in the mice exposed to CUMS stress without affecting hippocampal 5-HT level. These findings suggest that the fluoxetine mediated increase of PFC serotonin and reduction of hippocampal glutamate level are responsible for the antidepressant effect in mice exposed to CUMS. However, the antidepressant effect of fluoxetine is accompanied by a reduction in the NO level. The production of NO is dependent on the expression of nNOS, and the latter is dependent on the glutamate-mediated activation of the NMDA receptor. However, fluoxetine treatment decreased the hippocampal glutamate level and, therefore, suppressed the production of NO. Previous findings have suggested that the daily administration of fluoxetine reverses the CUMS mediated increase in the hippocampal glutamate level [**88**]. Further, it has been reported that the antidepressant treatment restores the level of glutamate to a normal level **[89]**.

L-theanine (LT) is a unique non-protein amino acid that has shown effectiveness in mental disorders **[90]**. In the present study, LT was administered to the mice before CUMS exposure, and it was observed that the daily LT (5 and 10 mg/kg) treatment significantly reversed the depressogenic effect of CUMS in experimental mice. Daily LT treatment did not affect the hippocampal 5-HT level, decreased the glutamate level, and increased the nitrite level. Daily LT treatment increased the PFC 5-HT, glutamate, and nitrite levels. Thus, our findings revealed that the antidepressant like effect of the L-theanine was accompanied by an increase in PFC 5-HT and glutamate levels and a reduction of hippocampal glutamate levels. Further, the LT treatment increases the NO level in both the PFC and the hippocampus. It has been reported that the LT treatment significantly reversed the stress-mediated alteration of behavioral and neurochemical levels in the prefrontal cortex **[91**. In CUMS model, L-theanine treatment has been shown

to increase the level of 5-HT in PFC **[92]**. Thus, our findings were consistent with the previous findings. Further, the antidepressant like effect of L-theanine might be due to the reduction of hippocampal glutamate level and restoration of PFC glutamate level and increased in the hippocampal and PFC nitrite level. Hippocampus play an important role in the regulation of hypothalamus-pituitary-adrenal (HPA) axis **[93]**. In depression, hippocampus show reduced expression of glutamate transporters, resulting in the decreased synaptic clearance of glutamate responsible for the increased extracellular glutamate level **[94, 95]**. LT treatment has been shown to decrease the hippocampal glutamate level in mice subjected to CUMS to exert an antidepressant-like effect. It has been reported that the stimulation of NMDA receptors in medial PFC exerts a positive effect on depression in rats **[96]** as the stress-induced depression is accompanied by the reduction of PFC glutamate level **[97]**. It has been reported that the enhancement of nitrite levels in the hippocampus can mediate the antidepressant effects of certain substances **[98]**. Further, LT treatment has been shown to increase the hippocampal and PFC NO levels to exert an antidepressant-like effect. Chronic stress has been shown to inhibit the expression of nNOS and production of NO **[80]**, and LT treatment ameliorates the effect of chronic stress on NO production.

In conclusion, CUMS exposure results in the region-specific alterations of neurochemicals. CUMS exposure decreases the PFC serotonin level, but increases the hippocampal glutamate level and decreases the hippocampal nitrite level, reflecting disrupted excitatory balance and compromised synaptic plasticity. Thus, fluoxetine exerts its antidepressant effect mainly by increasing the PFC serotonin levels, and thus corrects CUMS -induced deficits in the PFC serotonin level responsible for the improvement in depressive behavior. Fluoxetine treatment decreases the hippocampal glutamate levels, suppresses the stimulation of the NMDA receptor responsible for the downregulation of neuronal nitric oxide synthase (nNOS) activity, resulting in decreased production of NO. Thus, the antidepressant action of fluoxetine is relatively limited to serotonergic modulation. In contrast, LT restores the PFC serotonin level, decreases the hippocampal glutamate level, suggesting attenuation of hippocampal excitotoxicity, but increases the PFC glutamate level, reflecting the positive modulation of cortical activity. LT further increased the hippocampal and PFC nitrite level, suggesting the modulation of NMDA receptor and nNOS, suggesting its influence on the synaptic plasticity, neurovascular coupling, and stress resilience.

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