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# Effects of Venlafaxine and Escitalopram Treatments on NMDA Receptors in the Rat Depression Model

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**Abstract** Depression may relate to neurocognitive impairment that results from alteration of N-methyl-D-aspartate receptor (NMDAR) levels. Venlafaxine and escitalopram are two drugs commonly used to treat depression. The drugs may affect expression of NMDARs, which mediate learning and memory formation. The aim of the study was to examine whether the effects of venlafaxine and escitalopram treatments are associated with NMDARs in a rat model of depression. Forty male Wistar albino rats were randomly divided into four groups ($n = 10$) as follows: control group, chronic mild stress group (CMS), venlafaxine (20 mg/kg body weight per day) + CMS, and escitalopram (10 mg/kg body weight per day) + CMS. After induction of depression, a decrease in the concentration of NR2B was observed; venlafaxine treatment prevented the reduction of NR2B expression. Escitalopram treatment did not effect the reduced levels of NR2B resulting from depression. There was no significant difference in NR2A concentration among groups. The present data support the notion that venlafaxine plays a role in maintaining NR2B receptor in experimental depression. It may be possible that treatment with escitalopram has no effect on NMDARs in experimental depression.

**Keywords** Depression · Escitalopram · Memory · NMDA receptors · Venlafaxine

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Depression is a common medical condition associated with neurochemical changes in the hippocampus (Fairhall et al. 2010). The hippocampus joins cognitive and emotional behaviors and functions in the physiology of the stress response. Depression contributes to neurocognitive deficits by impairing the hippocampal synaptic plasticity and cognitive abilities such as learning and memory (Zarate et al. 2010). It is unknown whether venlafaxine and escitalopram have effects on the processes including activities of hippocampal N-methyl-D-aspartate (NMDA) receptors (NMDARs) in depression.

NMDARs are ionotropic glutamate receptors with an important role in signaling proteins in the central nervous system (CNS). NMDARs are a heteromeric protein made of three subunits, NR1, NR2, and NR3. NR2 subunits are carried over four gene encodes, NR2A to NR2D (Monyer et al. 1992). NMDARs are involved in a variety of processes in the CNS, including synaptogenesis and synaptic plasticity. NMDARs play an important role in learning and in the long-term changes of synaptic efficacy (Gladding and Raymond 2011). It has been indicated that hippocampal NR2A and NR2B are essential for neuronal development and synaptic plasticity, and reflect the learning and memory ability (Rauner and Köhr 2011).

Although several studies suggest an important involvement of NMDARs in the pathophysiology of depression, the mechanism of antidepressive agents effects on NMDARs has not yet been elucidated. Novel approaches for depression have also focused on NMDARs, which are potential targets for treatment in depression (Zarate et al. 2010). Venlafaxine is one of the new-generation antidepression drugs that is becoming increasingly important in treating depression. Venlafaxine is used as a nontricyclic antidepressant agent that is an inhibitor of both serotonin and norepinephrine transporters; it has also a high recovery rate in patients with major depression (Wrzosek et al. 2009). Escitalopram is a commonly prescribed selective serotonin reuptake inhibitor (SSRI) and is the most widely used medication for the treatment of depression (Klein et al. 2006). It has long been established by clinical studies that escitalopram has higher treatment rates in major depression. The efficacies of both drugs for affecting memory and learning remain unknown as a result of conflicting evidence. Current studies on different classes of antidepressants in their chronic form of implementation show an increase in the number of new neurons in the hippocampus (Malberg et al. 2000).

The aim of the present study was to elucidate the effects of venlafaxine and escitalopram administration toward modulating the synaptic plasticity via hippocampal NR2A and NR2B in the hippocampi of rats with experimentally induced depression.

## Materials and Methods

### Animals

Forty male Wistar albino rats weighing 200 ± 15 g and approximately 2 months old were used in this study. They were permitted 1 week to acclimate to their surroundings before experiments were begun. They were housed on sawdust and maintained in a heated (25°C) cage on a 12 h/12 h light/dark cycle (light on at 06:00 h). The animals were placed in individual plastic cages. Standard rat food and tap water were available ad libitum for the duration of the experiments unless otherwise noted. The experimental protocol of the study was approved by the ethical committee of the medical faculty of Suleyman Demirel University. The 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 Suleyman Demirel University. The experiments reported here complied with the current laws and regulations of the Turkish Republic on the care and handling of experimental animals. The concentrations of NR2A and NR2B in the hippocampus were measured at week 4 of the experiment.

### Experimental Design

The animals were randomly divided into the following four groups: group 1, control ($n = 10$); group 2, chronic mild stress rats (CMS, $n = 10$); group 3, venlafaxine administered orally with chronic mild stress (venlafaxine + CMS, $n = 10$); and group 4, escitalopram administered orally with chronic mild stress (escitalopram + CMS, $n = 10$). Venlafaxine (20 mg/kg body weight per day) and escitalopram (10 mg/kg body weight per day) supplemented to CMS-induced rats constituted groups 3 and 4, respectively. The two drugs were dissolved in 2 ml of physiologic saline (0.9% w/v) and were orally (via gastric gavage) administered to the animals in groups 3 and 4 for 4 weeks. Similarly, equal amounts of physiologic saline alone were provided to animals in groups 1 and 2 as a placebo. At the conclusion of the experiment, the animals were humanely killed. Brain was removed, and both hippocampi were dissected, washed in ice-cold phosphate-buffered saline, and frozen immediately at −70°C until analyses.

### CMS Procedure

Depression in rats as a model of CMS was used. CMS has been approved as an animal model of depression (Willner et al. 1992). Induction of CMS was applied for 4 weeks as described previously: continuous overnight illumination, 40-degree cage tilt, paired housing, damp bedding (300 ml water spilled into bedding), exposure to an empty water bottle immediately after a period of acute water deprivation, stroboscopic illumination (300 flashes/min), and white noise (~90 dB) (Grippo et al. 2003). The stressors were applied in the order shown during the first week and repeated each of the following weeks for a total of 4 weeks. Control animals were placed in their home cages, where they remained undisturbed with the exception of general handling. The CMS induction procedures are listed in Table 1.

### Sucrose Preference Tests

A sucrose preference test was used to define the concept of anhedonia, which compares sucrose consumption and preference tests with the control group and baseline reduction. Sucrose consumption was measured regularly at baseline each week. After the rats were left hungry and thirsty for a period of 20 h, water and sucrose consumption were measured for a period of 1 h. Two baseline tests were performed, separated by at least 5 days, and the results reached the middle. The preference test was also conducted after the 4-week CMS period. The sucrose preference test measures anhedonia through changes in sucrose consumption (Grippo et al. 2003).

**Table 1** Time and length of stressors used in the CMS procedure

| Stressor | Sunday (h) | Monday (h) | Wednesday (h) | Thursday (h) | Friday (h) | Saturday (h) |
|---|---|---|---|---|---|---|
| Removing 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-degree cage tilt | | 11:00–7:00 | | | | |
| Paired housing | → → → | 08:00 | 18:00 → | 14:00 | 10:00 | → → → |
| Damp bedding (300 ml water added to sawdust bedding) | | | | 17:00 → | 10:00 | |
| White noise (90 dB) | | | | | 10:00–13:00 | |
| Stroboscopic illumination (300 flashes/min) | 11:00–16:00 | | 13:00–15:00 | | | |

### Western Blot Analyses

Antibodies against NR2A and NR2B were purchased from Sigma Chemical Co. (St. Louis, MO, USA). All other reagents were of analytical grade or the highest grade available. The other hippocampi (two animals per preparation) were homogenized in an ice-cold buffer [50 mm Tris–HCl (pH 7.5), 0.15 M NaCl, 1% Triton X-100, 1 mM EDTA, 2 mM EGTA, 25 µg/ml leupeptin, 25 µg/ml aprotinin and 10 µM benzamidine] to provide 1/5 homogenate using a glass–Teflon homogenizer with 18–20 strokes, and the homogenized samples were centrifuged at 10,000×*g* at 4°C in a refrigerated centrifuge for 10 min; then an aliquot was taken for protein determination. The Laemmli method was used for sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) studies (equal amounts of protein for each sample; 20 µg of protein per lane) and were separated by SDS-PAGE on 7.5% minigels, blotted electrophoretically to immobilon membrane, and incubated in Tris-buffered saline with Tween 20 (TBST) [50 mm Tris–HCl (pH 7.5–8.0), 150 mM NaCl, and 0.1% Tween 20] containing 3% bovine serum albumin (BSA) for 30 min. Proteins were separated in a gel using the SDS-PAGE procedure, and then polyvinylidene diflouride membrane (immobilon-P) was used for transfer to the transfer tank (Laemmli 1970). After the transfer procedure in the solution containing the anti-NR2A (1/3000) and anti-NR2B (1/5000), they were kept overnight. Blots were subjected to three additional 10-min washings in TBST. Afterward, the membranes were incubated with secondary antibodies for 1 h, and three additional washings were performed with TBST for 10 min. Blots were incubated in 1% BSA that included alkaline phosphatase conjugated monoclonal anti-rabbit IgG (1.0000) for 1 h at room temperature, and then additional washings were performed with TTBS for 10 min. The membrane was incubated in 20 ml of fresh reagent solution (BCIP/NBT) until color developed. Images of immunoblots were analyzed with Kodak Image Station 2000 MM Multimodal Imaging System (USA).

### Statistical Analyses

Statistical evaluations were performed by SPSS for Windows, version 15.0, software program (SPSS, Chicago, IL, USA). In general, any significant differences between these groups were evaluated by a one-way analysis of variance (ANOVA) with subsequent group comparisons by the Bonferroni test. $P < 0.05$ was accepted as significant.

### Results

The weights were not different in groups. Comparisons of the group are listed in Table 2 for the sucrose preference

**Table 2** Sucrose (1% w/v) test results in the control and experimental groups

| Week | Control | CMS | CMS + venlafaxine | CMS + escitalopram |
|---|---|---|---|---|
| Baseline | 20.15 ± 9.48 | 18.12 ± 8.01 | 31 ± 19.21 | 14.38 ± 11.21 |
| 1 | 23.82 ± 7.50 | 19.67 ± 6.41 | 32.39 ± 13.59 | 22.35 ± 11.81 |
| 2 | 28.92 ± 11.27 | 13.98 ± 7.63 | 31.19 ± 12.70[b] | 35.29 ± 13.88[b] |
| 3 | 25.90 ± 15.12 | 9.78 ± 4.46[a] | 22.51 ± 11.81 | 35.78 ± 23.37 |
| 4 | 24.82 ± 11.37 | 9.98 ± 4.24[a] | 24.36 ± 9.61 | 31.58 ± 17.50 |

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

[b] $P < 0.05$ vs. CMS values

test. Sucrose consumption with water in the third and fourth weeks (ml/kg body weight) was significantly lower in the depression group than in baseline values. In addition, sucrose consumption with water in the second week (ml/kg body weight) was significantly higher in venlafaxine- and escitalopram-supplemented groups than in CMS groups. To evaluate protein concentrations of NMDARs, Western blot analyses were performed on hippocampal homogenates. The Western blot analyses of NR2A and NR2B are shown in Figs. 1 and 2, respectively. The density of the protein band in the control group was accepted as 100%, and data from other groups were calculated as percentages of the control value. The Western blot analysis for NR2B showed a significant ($P < 0.05$ for both) reduction of approximately 17% in CMS, compared with control, respectively. We tested the venlafaxine administration effect of NMDAR subunit concentrations on CMS rats. There was a significant increase of NR2B concentrations in the venlafaxine + CMS group (17%) according to the CMS group. We showed that NR2B concentrations in the escitalopram + CMS group decreased significantly (32%) compared with the venlafaxine + CMS group. There was no significant difference in NR2A concentration among groups.

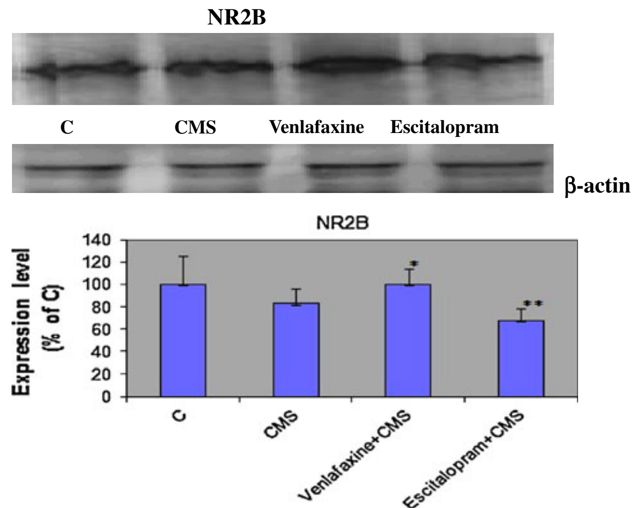


**Fig. 2** Representative Western blot of NR2B in hippocampus from four groups of rats. Experiments were performed on three independent hippocampus preparations. Size marker is indicated on the left (myosin, 205 kDa). *C* control, *CMS* chronic mild stress, *venlafaxine + CMS* venlafaxine + chronic mild stress, *Escitalopram + CMS* escitalopram + chronic mild stress. *Significant changes compared to other groups by ANOVA with subsequent group comparisons, using the Bonferroni test at the 0.05 level of significance. The protein expression levels of NR2B were normalized with the expression levels of $\beta$-actin in the same sample

## Discussion

Depression affects millions of individuals worldwide (Nestler et al. 2002). It has been shown in patients with depression that neurochemical changes are primarily found in the hippocampus of the brain (Eriksson et al. 2011). Recently, structural abnormalities were observed in the hippocampus and other brain regions of patients with depression, and it was suggested that major depressive disorders can be associated with structural plasticity and decreased flexibility in neuronal cells (David et al. 2009). NMDARs are necessary for synapse formation and plasticity. NMDARs are involved with higher brain functions such as learning and memory (Gladding and Raymond 2011). NMDARs are implicated in certain neurological diseases (Rauner and Köhr 2011). Depression is often characterized by changes in molecules related to NMDARs (Tokita et al. 2011). NMDARs have detected depression in both clinical and preclinical studies. Improvement of learning and memory in depression is believed to be crucial for success of treatment (Fairhall et al. 2010). The NR2A and NR2B subunits of the hippocampus were well established in brain tissue. It has been reported that hippocampal NMDARs are critically involved with cognitive functioning (Karolewicz et al. 2005). NR2B was found to have a dominant role for synapses in an adult hippocampus. Dong et al. (2010) indicated that the NR2B expression was downregulated, which may cause depressive symptoms as well as learning and memory impairment. In addition, Feyissa et al. (2009) found a reduced expression of prefrontal NMDARs subunits in major depression. Similarly, in the

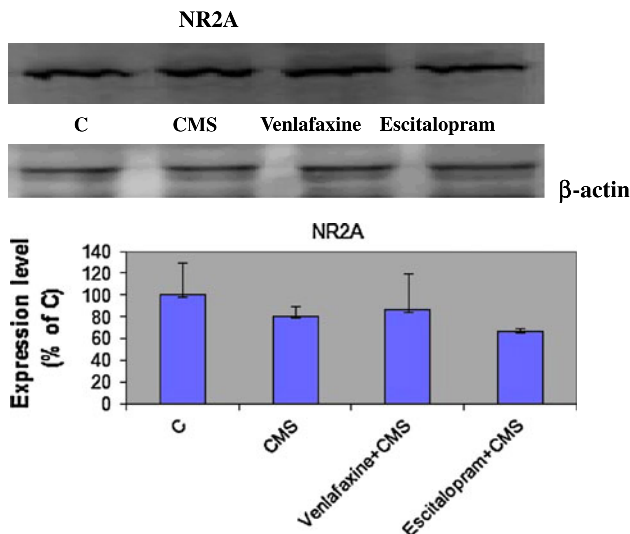


**Fig. 1** Representative Western blot of NR2A in hippocampus from four groups of rats. Experiments were performed on three independent hippocampus preparations. Size marker is indicated on the left (myosin, 205 kDa). *C* control, *CMS* chronic mild stress, *venlafaxine + CMS* venlafaxine + chronic mild stress, *Escitalopram + CMS* escitalopram + chronic mild stress. *Significant changes compared to other groups by ANOVA with subsequent group comparisons, using the Bonferroni test at the 0.05 level of significance

present study, depression resulted in a significant decreased NR2B receptors compared to the control group. The changes in NR2B concentration may have a role in cognitive dysfunctions, as shown in patients with depression. Furthermore, in a genetic rat model of depression, it was found that reduced NMDARs contributed impaired memory function.

To our knowledge, there is no report on the effects of venlafaxine and escitalopram on NR2A and NR2B concentrations on the hippocampus in the depression rat model. It was reported that venlafaxine is not a typical tricyclic antidepressant, so it lacks some mechanisms such as blocking NMDAR, blocking ion conduction in calcium, sodium, and potassium channels, and blocking $\alpha$1-adrenergic and nicotinic receptors (Wrzosek et al. 2009). The NR2B concentration was found to be significantly increased by venlafaxine administration to the animals in the CMS-induced depression group compared to the depression group. The increase in NR2B concentration may positively affect learning and memory through venlafaxine administrations. The lack of the block NMDAR in cases of venlafaxine administration may affect memory. Consistent with our study, Bremner et al. (2007) found an increase in hippocampal function with antidepressant treatment that included venlafaxine (75 mg/day to 300 mg/day doses) in a period of $6 \pm 3$ months in people with depression. Nowakowska et al. (2002) concluded that venlafaxine improved working memory. They determined this using both spatial memory in the Morris test and working memory in the maze test for cognitive function during an administration of 20 mg/kg doses for a period of 2 weeks. They indicated that venlafaxine effects on depression and memory function may be related to the interactions between noradrenergic and serotoninergic systems. It is commonly found that antidepressant drugs exhibit their biochemical effects thorough some atypic intrasynaptic mediators like serotonin and noradrenaline (Zhong et al. 2008). It may be one possible mechanism to allow action of the serotonergic system on NMDARs channels. Previous studies have also reported extensive serotonergic deficits in the hippocampus of patients with Alzheimer disease (Kepe et al. 2006). In another study, it was reported that activation of 5-HT1A receptors indeed decreased microtubule stability, which could lead to the reduction of the delivery of NMDAR (Yuen et al. 2005). In another experimental study, milnacipram, which is a serotonin (5HT) and noradrenaline reuptake inhibitor, was applied in a single dose (10–30 mg/kg) in rats and induced suppression of long-term potentiation (LTP). The authors proposed that endogenous 5HT predominantly contributed to the suppression of LTP (Tachibana et al. 2004). It is possible that serotonin–NMDA interactions modulate neuronal excitability in the prefrontal cortex. In depressed patients, the reduction of noradrenaline release may be another possible mechanism that affects venlafaxine in hippocampi in which noradrenaline release is evoked by the activation of an excitatory receptor system (Leonard 2000). It was concluded that NMDA selectively stimulates noradrenaline release in rat brain cortex via NMDAR (Fink et al. 1989). On the other hand, it was indicated that an overdose of venlafaxine seem to have special toxicity on cognitive function. It may be possible that venlafaxine is more serotoninergic at lower doses and more noradrenergic at higher doses (García-Cabeza et al. 2011).

We speculate that another possible mechanism underlying the NMDAR subunits concentration change is through the lipid peroxidation and antioxidant system. Eren et al. (2007a, b) indicated that treatment with venlafaxine in the rat depression model may play a role in preventing oxidative stress. The possibility that reactive oxygen species can influence the expression and/or degradation of NMDAR subunits is probable. It has been reported that venlafaxine accumulates in high concentrations in hippocampal cells after entering the brain for 14 days. Venlafaxine is most able to protect the hippocampal NR2B against lipid peroxidation by depression-induced oxidative toxicity (Wikell et al. 2002). The increase in the NR2B receptor in the venlafaxine-administered group was higher according to the escitalopram-supplemented group and depression-induced rats. The NR2A receptor in the hippocampus was not different in any group. This might lead to the conclusion that the increased NR2B concentration may be related to the stimulated antioxidative system in depression-induced rats. In contrast, there was no significant change in the NR2B level through escitalopram administrations to the animals in the CMS-induced depression group compared to the control group. SSRI antidepressants were found to be associated with memory disorders, although this was poorly described in the literature. In contrast, treatment with escitalopram ameliorated emotional memory performance in the genetic rat model of depression. It was indicated that escitalopram upregulated expression of brain-derived neurotropic factor mRNA in the dentate gyrus, but not in the CA1 of the hippocampus (Hansson et al. 2011). Multiple brain areas are able to exhibit altering functions, such as emotional memory and cognition in depression (Eriksson et al. 2011).

It was shown that escitalopram (10 mg/kg) concentration reached high values in the brain (Klein et al. 2006). Escitalopram 10 or 20 mg/day produced significantly greater improvements in standard measurements of antidepressant effect (Wade et al. 2002). Ibrahim et al. found a weak effect with the administration of escitalopram on oxidative stress (Eren et al. 2007a, b). Other studies showed that citalopram, which is a SSRI, reduced NMDAR subunits by changing the level of mRNA encoding in rat

cortexes (Boyer et al. 1998). SSRIs release 5HT, which inhibits LTP induction (Kojima et al. 2003). The serotonin system is one of the main ways antidepressants play an important role in cognitive function (Davidson et al. 2000). It activated different complex manners in the CNS (Benedetta Goretti et al. 2010). It is therefore likely that escitalopram induced suppression of LTP occurred through endogenous 5HT in the synaptic cleft resulting from the blockade of reuptake processes. It was reported that endogenous norepinephrine induced a small amount of long-term depression in the hippocampus (Katsuki et al. 1997). Fluoxetine, which is an SSRI, enhanced the brain 5HT level, which indicated weakened associative memory in the rats (Nelson et al. 1997).

In conclusion, the results of our study show that experimental depression is associated with reduced NR2B, and venlafaxine repairs the reduced NR2B, so it has a protective effect on the NMDAR subunit NR2B. There were no ameliorating effects of escitalopram via the NMDAR pathway for treatment of depression. The expression of NMDARs seems to be a new target for a more effective antidepressant therapy. The effects of venlafaxine and escitalopram on the NMDAR-mediated transmission may help the clinical management of depression.

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