E-ISSN: 2149-7222 (Online)

Journal Cellular Neuroscience and Oxidative Stress

http://dergipark.gov.tr/jcnos

Former name; Cell Membranes and Free Radical Research

HSOD
Cellular Neuroscience and Oxidative Stress Society

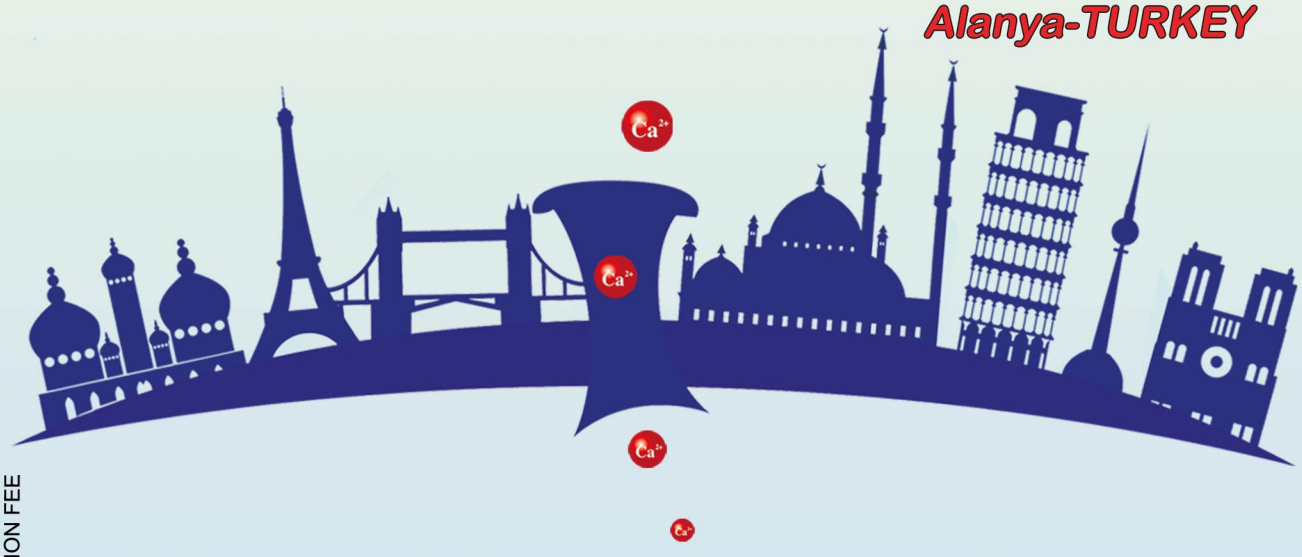
7th World Congress

Oxidative Stress, Calcium Signaling and TRP Channels

2018.cmos.org.tr

20-23 April 2018

Alanya-TURKEY



TRPWORLD

OPEN ACCESS and NO PUBLICATION FEE

Volume 10, Number 2, 2018

Journal of Cellular Neuroscience and Oxidative Stress

http://dergipark.gov.tr/jcnos

An Official Journal of the Cellular Neuroscience and Oxidative Stress Society

http://hsord.org.tr/en/

Formerly known as:

Cell Membranes and Free Radical Research (2008 - 2014)

Volume 10, Number 2, 2018

7th World Congress of Oxidative Stress, Calcium Signaling and TRP Channels

20 - 23 April 2018 Alanya / Antalya / TURKEY

2018.cmos.org.tr

Volume 10, Number 2, 2018
E-ISSN Number: 2149-7222 (Online)
Indexing: Google Scholar, Index Copernicus, Chemical Abstracts, Scopus (Elsevier),
EBSCOhost Research Database, ULAKBİM TR Dizin (Turkey)

AIM AND SCOPES
Journal of Cellular Neuroscience and Oxidative Stress is an online journal that publishes original research articles, reviews and short reviews on the molecular basis of biophysical, physiological and pharmacological processes that regulate cellular function, and the control or alteration of these processes by the action of receptors, neurotransmitters, second messengers, cation, anions, drugs or disease.

Areas of particular interest are four topics. They are;

A- Ion Channels (Na^+- K^+ Channels, Cl^- channels, Ca^{2+} channels, ADP-Ribose and metabolism of NAD^+, Patch-Clamp applications)

B- Oxidative Stress (Antioxidant vitamins, antioxidant enzymes, metabolism of nitric oxide, oxidative stress, biophysics, biochemistry and physiology of free oxygen radicals)

C- Interaction Between Oxidative Stress and Ion Channels in Neuroscience
(Effects of the oxidative stress on the activation of the voltage sensitive cation channels, effect of ADP-Ribose and NAD^+ on activation of the cation channels which are sensitive to voltage, effect of the oxidative stress on activation of the TRP channels in neurodegenerative diseases such Parkinson's and Alzheimer's diseases)

D- Gene and Oxidative Stress
(Gene abnormalities. Interaction between gene and free radicals. Gene anomalies and iron. Role of radiation and cancer on gene polymorphism)

READERSHIP

Biophysics	Biochemistry
Biology	Biomedical Engineering
Pharmacology	PhysiologyGenetics
Cardiology	Neurology
Oncology	Psychiatry
Neuroscience	Neuropharmacology

Keywords
Ion channels, cell biochemistry, biophysics, calcium signaling, cellular function, cellular physiology, metabolism, apoptosis, lipid peroxidation, nitric oxide, ageing, antioxidants, neuropathy, traumatic brain injury, pain, spinal cord injury, Alzheimer's Disease, Parkinson's Disease.

7th World Congress of Oxidative Stress, Calcium Signaling and TRP Channels

The congress organization committee wishes thanks to the sponsors below

Fullpaper Book

of

7th World Congress of Oxidative Stress,

Calcium Signaling and TRP Channels

20 - 23 April 2018

Alanya, Antalya, Turkey

with collaboration of

Cellular Neuroscience

and Oxidative Stress Society

& Neuroscience Research Center,

Süleyman Demirel University

7th World Congress of Oxidative Stress, Calcium Signaling and TRP Channels

[Organization Committee]

Congress Organization Committee

Prof. Dr. Mustafa NAZIROĞLU
Chairman
Department of Biophysics, School of Medicine
Suleyman Demirel University, Isparta, Turkey

Prof. Dr. James W. Jr. PUTNEY
1st International Vice Chairman
NIEHS Calcium Regulation Group Leader

Prof. Dr. Mohamed TREBAK
2nd International Vice Chairman
Pennstate University Medical Faculty

Assoc. Prof. Dr. Ömer ÇELİK
Congress Local Chairman
Department of Biophysics, School of Medicine
Suleyman Demirel University, Isparta, Turkey

Prof. Dr. Fatih GÜLTEKİN
Department of Biochemistry, Faculty of Medicine,
Healthy Science University, Istambul, Turkey

Prof. Dr. Süleyman KUTLUHAN
Department of Neurology, Faculty of Medicine
Suleyman Demirel University, Isparta, Turkey

Congress Secretariat
Bilal ÇİĞ & Kenan YILDIZHAN
Ramazan ÇINAR & Vahid GHAZIZADEH
Yener YAZĞAN *(Graphic Designer & Webmaster)*
Department of Biophysics, School of Medicine
Suleyman Demirel University, Isparta, Turkey

Accountant
Ahmi ÖZ
Department of Biophysics, School of Medicine
Suleyman Demirel University, Isparta, Turkey

7th World Congress of Oxidative Stress, Calcium Signaling and TRP Channels

[Scientific Committee]

7th World Congress of Oxidative Stress, Calcium Signaling and TRP Channels

Fullpaper Oral Presentations

Fullpaper Oral Presentations

Fulpaper Oral Presentation 1

Effect of venlafaxine on hippocampal BDNF levels in depression-induced rats

Arif DEMIRDAŞ[1], İbrahim EREN[2], Hilmi DEMIRIN[3], Onur AKTÜRK[4], Hüseyin VURAL[5]

[1]Department of Psychiatry, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey
[2]Department of Psychiatry, Beyhekim Education and Research Hospital, Konya, Turkey
[3]Biochemistry Specialist- Not affiliated
[4]Deparment of Biochemistry, Gaziantep 25 Aralık State Hospital, Gazianatep, Turkey
[5]Biochemistry Specialist- Not affiliated

Author for correspondence :
Assist. Prof. Dr. Arif DEMİRDAŞ
Department of Psychiatry, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey
Telephone: +90 2462119337;
Fax number: +90 2462112830
E-mail address: demirdasmd@yahoo.com

List of Abbreviations;
5-HT: 5-hydroxytryptamine
BDNF: Brain-Derived Neurotrophic Factor
BSA:Bovine Serum Albumin
Ca2+: Calcium
CMS: Chronic Mild Stress
ECT: Electroconvulsive therapy
IL-1 β: interleukin-1 Beta
LTP: Long-Term Potentiation
mRNA: Messenger Ribonucleic Acid
NE: Norepinephrine
SNRI:Serotonin-Norepinephrine Reuptake İnhibitor
SPSS:Statistical Package for the Social Sciences
SSRIs: Selective Serotonin Reuptake İnhibitors
TrkB: Tyrosine Kinase B

Abstract

Although antidepressant drugs have been used for approximately 60 years, very little is known about their effect mechanism. Structural abnormalities, particularly in the hippocampus, are observed in brain structures of depressed patients.

The correction of these abnormalities with treatment suggests that major depressive disorders may be associated with a decrease in cellular elasticity and structural plasticity, and antidepressant treatments may provide benefits by treating these disorders. In this study, we aimed to investigate the effect of venlafaxine treatment on the brain-derived neurotrophic factor (BDNF) and BDNF levels in the hippocampus of depression-induced rats by using the chronic mild stress (CMS) model.

In this study, 30 eight-week-old, Wistar albino male rats were divided into three groups. The first group received venlafaxine (20 mg/kg) with CMS, the second group a placebo with CMS, and the third group only a placebo (n = 10) for four weeks. At the end of the four-week period, BDNF levels in hippocampus tissues were measured.

The measurements showed that the BDNF levels of the depressed group were significantly lower than those of the control group. In our study, the hippocampal BDNF levels of the venlafaxine-administered group were similar to those of the control group and significantly higher than those of the depressed group.

In concusion, these findings show that the BDNF, which has an important function in neuroplasticity, plays a role in depression pathophysiology, and venlafaxine prevents the BDNF decrease observed in depression. This latter result supports the view that depression treatment prevents the long-term complications of the disorder.

Keywords: Depression; BDNF; Venlafaxine; Hippocampus; Neuroplasticity.

Introduction

Although antidepressant drugs have been used for approximately 60 years, very little is known to date about their effect mechanism. It is currently believed that antidepressants show their main biochemical effects

by affecting intrasynaptic concentrations of serotonin and noradrenaline. However, clinical and preclinical studies performed in recent years demonstrated that major depressive disorders might be associated with the cellular elasticity and plasticity decrease in the brain structures of affected patients, and antidepressants could be useful in treating these disorders (Manji et al., 2000; Manji et al., 2001; Manji and Duman, 2001)

The first studies about antidepressants' action mechanism in depression focused on the variations in receptor levels and neurotransmitter concentrations. However, several problems are related to this model (Duman et al., 1997). These ideas contradict the finding that therapeutic effects of antidepressants require chronic administration, but norepinephrine (NE) reuptake inhibition by serotonin occurs in a short time. In time, along with the monoamine theory, several studies pointed out an essential role related to the intracellular pathways regulating the neuroplasticity and neurodegeneration in depression etiology. Antidepressant therapy blocks the neurogenesis downregulation caused by stress (Malberg and Duman, 2003). The increase in brain-derived neurotrophic factor (BDNF) expression was shown to be a response to antidepressant therapy with different antidepressant classes, such as selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, fluvoxamine, and sertraline), selective NE reuptake inhibitors (desipramine), and dual amine reuptake inhibitors (imipramine and milnaciprane) (Popoli et al., 2002).

A member of the neutrophin family, BDNF activates the cell surface receptor with high affinity (TrkB) that matches the fosfatidilinositol-3-kinase and protein kinase B activation. Neurogenesis plays an important role in the BDNF, brain development, and plasticity by promoting synaptic plasticity and cell survival. During the development process of the cerebral cortex and hippocampus, the BDNF triggers the differentiation of neural stem cells to neurons and promotes new neuron development (Lee et al., 2002; Cheng et al., 2003). Therefore, the BDNF serves an essential function in preventing neuron deaths, and in the adult brain, it supports cell survival throughout stressful events, such as ischemia and trauma .(Larsson et al., 1999) Additionally, the BDNF stimulation in synapses develops the long-term potentiation [LTP], which is a synaptic refreshment process associated with learning and memory (Ernfors and Bramham, 2003; Leal et al., 2017). The majority of researchers focus on the hippocampus, which is known to have a role in mood disorders. The hippocampus is specifically sensitive to structural disruptions triggered by stress (Arborelius et al., 1999; Sapolsky, 2000)

Understanding the role of neurotrophic factors in depression will contribute to the knowledge about depression etiology and pathophysiology. Moreover, as antidepressant therapies cannot be limited to the release and reuptake of neurotransmitters or molecules that modulate their interaction with receptor systems, new molecules with more selective effects, including these action mechanisms, will be developed (Uzbay, 2005).

In this study, we aimed to investigate the effect of venlafaxine treatment on the BDNF and hippocampus BDNF levels of rats with the chronic mild stress (CMS) model-induced depression.

Materials and Methods

Experimental animals

This study used thirty 8-week-old, Wistar albino male rats, each weighing 200 ± 15 grams. Before the experiment, the rats were allowed to adapt to the environment for one week. The animals were kept in individual plastic cages with beds. Unless indicated otherwise, the rats had access to the standard rat food and tap water throughout the experiment. To allow the rats to get used to the sucrose, they could reach it (1% solution) freely during the week before the experimental procedure. The cage temperature was maintained at 22 ± 2 ºC; 12 hours each of light and dark cycles were maintained, with the lights turned on at 6:00 in the morning. The study was approved by the Local Experimental Animal Ethical Committee of Suleyman Demirel University (SDU).

The rats were divided into three groups. The first group received venlafaxine 20 mg/kg (n = 10) with CMS, the second group a placebo with CMS (n = 10), and the third group only a placebo (n = 10). The rats were placed into specially prepared cages with beds, with one rat staying in each cage. Homogeneous distribution was provided among the groups.

Chronic mild stress model and sucrose preference test

In rats, CMS has been used as the depression model. The CMS procedure has been considered a suitable model to study the beginning of the antidepressant effect on animals (Willner, 1997). The CMS model was first described by Wilner (1990). Anhedonia, evaluated by the sucrose consumption test in rats, has been suggested to be a depression model with etiological reliability (Dias et al., 2003). The CMS model has been used in many studies to evaluate the effectiveness of psychotropic drugs(Sanchez et al., 2003; Orsetti et al., 2006). The depression model, developed with CMS in rats, has high validity (Van Kampen et al., 2002).

The rats were given food, water, and 1% sucrose solution as much as they wanted to make them adapt to the environment and taste sucrose. The sucrose preference test performed in the rats was the test initiation. This test was used to define the anhedonia term particularly the decrease in sucrose intake and preference compared with baseline values and the control group in the sucrose preference test (Grippo et al., 2002). In the sucrose preference test, water and sucrose consumption of the rats within one hour was observed after they were kept without food and water for 20 hours (by measuring the weight of the bottle full of water and sucrose before the test). The results were recorded as basal values. This test was performed at 12:00 every Wednesday for four weeks, and the results were recorded. Then the CMS procedure was performed. The CMS-related procedures are presented in Table 1. This test was repeated for four weeks. During CMS, the rats orally received 20 mg/kg venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI) group antidepressant. The same amount of normal saline was given orally to the control group.

Procedure

The experiment was terminated by decapitation of all the rats under 10% ketamine and 2% xylazine anesthesia. After sacrificing them, their brain tissues were removed, and hippocampus BDNF levels were measured by using the ELISA method.

Homogenization of hippocampus samples and measurement of BDNF levels

Hippocampus tissues and serum samples were weighed as soon as the removal was finished, and they were stored in a -80˚C deep freeze. One week after the dissection, 100 mM Tris/HCl (pH 7) buffer containing 2% bovine serum albumin (BSA), 1 M NaCl, 4 mM EDTA.Na2, 2% Triton X-100, 0.1% sodium azide and protease inhibitors (Sigma) 5 µg/mL aprotinin, 0.5 µg/mL antipain, 157 µg/mL benzamidine, 0.1 µg/mL pepstatin A, and 17 µg/mL phenylmethyl-sulfonyl fluoride was prepared according to the ChemiKine™ BDNF Sandwich ELISA kit procedure. After the samples were thawed, the hippocampus tissues were diluted 10 times, using the Tris/HCL buffer, and cold-homogenized at 9,500 rpm with the Ultra-Turrax T25 homogenizer. The homogenates were obtained by centrifugation for 30 minutes at 14,000 xg. The hippocampus homogenates and serum samples were studied according to the kit procedure (after twice diluting with the sample diluent), with their 20 times- and twice-diluted forms, respectively. Irrigations in this procedure were performed with the Elx50 automatic strip washer (Bio-Tek Instruments, Inc.), whereas the absorbance readings were performed automatically with the Microwell System-Reader 530 (Organon Teknika).

Statistical analysis

Statistical evaluations were performed using the SPSS 15.0 for Windows software. Generally, the significant differences between groups were evaluated by using the Kruskal–Wallis analysis of variance. Paired comparisons of the groups were performed using the Mann-Whitney U test. The Wilcoxon signed-ranks test was used to evaluate the changes in the sucrose preference tests compared to the baseline. The p value of <0.05 was considered significant.

Table 1. Chronic mild stress

	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Leaving waterless	16:00 →	08:00					
Giving empty water bottle		08:00-09:00					
Lightening the cage continuously	16:00 →	08:00			17:00 →	10:00	
Sloping the cage		11:00-17:00					
Separating the cages	→→	08:00		18:00 →	14:00	10:00	→→
Wetting the beds (300cc)					17:00 →	10:00	
90 DB noise						10:00-13:00	
Switching lights on and of continuously	11:00-16:00			13:00-15:00			

Table 2. Weekly sucrose preference test results of the three groups included in the study.

	Group 1 (Venlafaxine + CMS) Mean ± SD (ml)	Group 2 (CMS) Mean ± SD (ml)	Group 3 (Control) Mean ± SD (ml)
Basal	6.50 ± 3.50	6.78 ± 2.44	6.78 ± 2.99
Week 1	6.20 ± 2.39	5.44 ± 3.57	5.67 ± 2.73
Week 2	6.80 ± 2.49	6.56 ±2.83	6.67 ± 2.87
Week 3	6.70 ± 1.83	4.67 ± 2.40[c]	8.00 ± 2.83
Week 4	6.30 ± 1.34[a,b]	4.00 ± 1.41[d]	8.67 ± 1.41

[a]Group 1 is significantly higher than Group 2: z = -2.91, p = 0.003.
[b]Group 1 is significantly lower than Group 3: z = -2.83, p = 0.004.
[c]Group 2 is significantly lower than Group 3: z = -2.32, p = 0.02.
[d]Group 2 is significantly lower than Group 3: z = -3.56, p < 0.0001.

Table 3. Hippocampus BDNF levels of the three groups at the end of the study.

	Group 1 (Venlafaxine + CMS)	Group 2 (CMS)	Group 3 (Control)
BDNF (ng/mL)	5.84 ± 0.89[a,b]	4.88 ± 0.40[c]	5.75 ± 0.61

[a]Group 1 is significantly higher than Group 2: z = -2.368, p = 0.018.
[b]There is no significant difference between Groups 1 and 3: z = -0,163, p = 0.873.
[c]Group 2 is significantly lower than Group 3: z = -2.782, p = 0.004.

Results

Sucrose preference test results

Table 2 shows the results of the sucrose preference tests performed before and during the experiment. The comparison of the groups' test results revealed that the fourth-week results of Group 1 were significantly higher than those of Group 2 and significantly lower than those of Group 3 ($z = -2.91$, $p = 0.003$, $z = -2.83$, $p = 0.004$). Additionally, the third- and fourth-week results of Group 2 were found to be significantly lower than those of Group 3 ($z = -2.32$, $p = 0.02$, $z = -3.56$, $p < 0.0001$).

Hippocampus BDNF levels

Table 3 shows the BDNF levels in the hippocampus tissues obtained after the beginning of the experiment. The tissue levels are 5.84 ± 0.89 in Group 1, 4.88 ± 0.40 in Group 2, and 5.75 ± 0.61 in Group 3. There is a difference between the levels of Group 1 and Group 2, but the statistical significance is within the limit ($z = -2{,}368$, $p = 0.018$). No statistically significant difference is found between the BDNF levels of Group 1 and Group 3 ($z = -0{,}163$, $p = 0.873$). However, Group 2 has significantly lower levels than those of Group 3 ($z = -2{,}782$, $p = 0.004$). The hippocampus BDNF levels of the three groups at the end of the study are indicated collectively in Table 3.

Discussion

Our study's findings show that CMS is an effective method in inducing depression in rats, which had been demonstrated in previous depression studies as well (Gittos and Papp, 2001; Grippo et al., 2005). Moreover, in our study, the results of sucrose preference tests are significantly lower in the placebo plus the CMS-administered rat group compared with the venlafaxine plus CMS-administered group and the control group. This outcome suggests that the antidepressant effectiveness of venlafaxine has become evident. Similar results had been demonstrated in clinical and experimental studies (Dilbaz et al., 1999).

In our study, hippocampus BDNF levels are found to be significantly lower in depression-induced rats than in the control group. The brain and hippocampus BDNF levels had been investigated in several studies using different depression models. Four studies using the activity restriction model (Nibuya et al., 1995; Smith et al., 1995; Ueyama et al., 1997; Vaidya et al., 1997). and two studies using the social isolation model (Barrientos et al., 2003; Pizarro et al., 2004) reported decreased hippocampus BDNF levels. In contrast, another study reported an unchanged, rat hippocampus BDNF expression with CMS (Gronli et al., 2006). Two studies used the depression model with the restraint test; one reported decreased hippocampus BDNF levels (Xu et al., 2004), whereas the other study indicated no changes (Kuroda and Mcewen, 1998). Although the reason for these different results could not have been fully understood, it is thought to be associated with the timing of BDNF measurements.

In studies conducted on humans, low serum BDNF levels were reported in patients with major depressive disorders (Shimizu et al. 2003; Gonul et al., 2005; Gonul et al., 2005; Molendijk et al., 2011; De et al., 2014; Bus and Molendijk, 2016; Pedrotti Moreira et al., 2018).

Lower hippocampus BDNF levels in our study's CMS group and the other findings in the literature support the argument that the BDNF plays a role in depression pathophysiology. The BDNF is involved in the regulation of synaptic protein synthesis and regulates the neurotransmitter secretion via upregulation of secretory mechanisms (Tyler and Pozzo-Miller, 2001) . The BDNF provides stable and long-term development of neuron functions (Tartaglia et al., 2001).

Similar BDNF levels between the venlafaxine with the CMS-administered group and the control group support the claim that antidepressant therapy is not only symptomatic but also provides changes that will positively contribute to brain pathology causing depression or caused by depression. It has been suggested that low BDNF levels may play a role in the pathophysiology of major depressive disorders, and antidepressants may increase BDNF levels in depressive patients (even indirectly). Several studies reported that antidepressant agents of different classes increased the serum BDNF levels that were low in depressive patients (Yoshimura et al., 2007; Piccinni et al., 2008; Lee and Kim; 2008; Huang et al., 2008; Guilloux et al., 2012). The BDNF levels of depressive patients treated with venlafaxine were shown to be significantly higher than those of patients who did not receive treatment

(Matrisciano et al., 2009). In electroconvulsive therapy (ECT) -administered depressive patients, the BDNF levels were observed to increase (Marano et al., 2007; Piccinni et al., 2009; Bumb et al. 2015). Post-mortem studies showed high BDNF levels in the hippocampi of antidepressant-treated patients (Chen et al., 2001). In post-mortem depressive patients, decreased BDNF levels in their hippocampi and cerebral cortices were determined (Dwivedi et al., 2003). In another post-mortem study, decreased BDNF levels were found in major depressive patients who committed suicide (Pandey et al., 2008). In depressive patients who attempted suicide, serum BDNF levels were lower than those of the healthy control group (Deveci et al., 2008). Another study reported no significant changes in the serum BDNF levels of depressive patients receiving venlafaxine and fluoxetine therapy (Terzi et al., 2009).

Studies performed on rats also showed that antidepressant drugs and ECT increased hippocampus BDNF levels (Nibuya et al., 1995; Tyler and Pozzo-Miller, 2001; Altar et al., 2003; Xu et al., 2003). and regulated the stress-dependent BDNF decrease (Duman, 2004). On the other hand, one study reported that venlafaxine therapy did not affect the BDNF level (Solberg et al., 2001). Studies performed using venlafaxine showed that it prevented low BDNF levels in rats in which depression was induced with the chronic restraint test (Xu et al., 2004; Xu et al., 2006). In the chronic, unpredictable stress model, it was observed that chronically low doses of venlafaxine (5 mg/kg) increased the hippocampal BDNF amount, but the same effect was not observed with 10 mg/day venlafaxine administration (Li et al., 2011). An increased hippocampal BDNF level was observed with venlafaxine administration without the BDNF depression model in rats (Czubak et al. 2009). In our study, the hippocampal BDNF levels of the venlafaxine-administered group were similar to those of the control group and higher than those of the depressed group, but the statistical significance was within the limit. We used the 20 mg/kg/day venlafaxine dose in our study. Our study supports that of Xu et al. (2006). However, we used the CMS model in the rats, the closest one to depression in humans.

In our study, low BDNF levels in CMS-administered rats and nonlow levels in rats receiving venlafaxine treatment support the neuroplasticity theory in depression etiology suggested in recent years.

The downregulation of neurotrophic factor expression in some studies showed that structural changes might exist in depressed patients (Manji et al., 2003). Neuroimaging studies reported decreased hippocampus volume in depressed patients (Bremner et al., 2000; Rajkowska et al., 2000; Sapolsky, 2000). Antidepressant therapy resulted in the stimulation of neurotrophic factors and regulation of cellular morphology and/or neurogenesis. Chronic antidepressant therapy was found to increase neurogenesis in the hippocampus of adult rodents (Madsen et al., 2000; Manev et al., 2001; Sachs and Caron, 2015).

Some studies reported that antidepressant therapy reversed hippocampus atrophy in depressed patients (Watanebe et al., 1992; Sheline at al., 2003; Vermetten et al., 2003; Sachs and Caron, 2015). However, no study using venlafaxine that has been conducted on humans is available. The prominent point of these clinical studies involved cell loss and volume decrease associated with depressive disorders. It had been shown that venlafaxine prevented low BDNF levels and hippocampal cell proliferation decrease in depression . Czeh et al. (2001) reported that chronic tianeptine therapy might reverse disorders triggered by stress, such as a decrease in hippocampus volume and neurogenesis (Watanabe et al., 1992; Czeh et al., 2001).

Although it is hard to investigate the underlying mechanisms of the variations in the BDNF levels of depressed patients, some inferences could be made from the clinical data. Depression is typically associated with high adrenal glucocorticoid levels, and adrenal glucocorticoids decrease BDNF levels in rodents (Smith et al., 1995). Cytokines may have a role in the effects of depression on the BDNF. It was reported that interleukin-1 Beta (IL-1 β) levels increased in depression(You et al., 2011). The IL-1 β decreased glutamate secretion as much as it decreased Ca2+ flow (Murray et al., 1997); a decrease in Ca^{2+} flow might cause a decrease in the activity-dependent expression of BDNF in dentate gyrus (Duman, 2004).

Due to the role of the 5-hydroxytryptamine (5-HT) system in depression, the BDNF seems to have a significant effect on the branching of both intact 5-HT

neurons and neurons with neurotoxin lesions. The BDNF infusions cause hyperinnervation of 5-HT axons in the infusion site in either the cerebral cortex or hippocampus (Mamounas et al., 1995). This finding supports the claim that BDNF plays an important role in the plasticity of 5-HT neurons and can contribute to the arrangement of 5-HT nerve conduction in response to stress and antidepressant treatment.

One study reported that adult neurogenesis contributed to the antidepressant response, and it was mandatory for antidepressant drug therapy (Santarelli et al., 2003). Externally administered BDNF showed an antidepressant effect on rats (Siuciak et al., 1997; Shirayama et al., 2002; Duman, 2004; Ye et al., 2011).

The data obtained in this study supports the finding that BDNF levels that play an important role in neural plasticity are low in patients with depression. These studies are important to test the validity of the neurotrophic hypothesis associated with depression. The upregulation of the neurotrophic factors can stop the cell loss and atrophy caused by depression and even reverse them. This can both contribute to the effects of antidepressant treatment and prevent the complications associated with depression over the long term.

Acknowledgment

Full paper of the oral presentation was summarized from Dr. Arif Demirdaş's thesis project. Abstract of the study was presented as a poster in 11th Annual meeting – Spring Symposium and European Psychiatry Symposium, 25-28 April 2007 Sheraton-Çeşme, İzmir, Turkey. The study was supported by the Scientific Research Project Unit of Suleyman Demirel University (BAP-1232-TU-06)

Authors contributions:

AD and İE formulated the present hypothesis and were responsible for writing the report. AD was responsible for inducing experimental depression and conducting tests of depression intensity. HM and OA were responsible for BDNF analyses. HV made critical revision for the manuscript.

Declaration of conflicting interests:

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

Altar, C.A., Whitehead, R.E., Chen, R., Wörtwein, G., and Madsen, T.M. 2003. Effects of electroconvulsive seizures and antidepressant drugs on brain-derived neurotrophic factor protein in rat brain. Biol. Psychiatry 54, 703–709

Arborelius, L., Owens, M.J., Plotsky, P.M., and Nemeroff, C.B. 1999. The role of corticotropin-releasing factor in depression and anxiety disorders. J. Endocrinol. 160, 1–12.

Aydemir, O., Deveci, A., and Taneli, F. 2005. The effect of chronic antidepressant treatment on serum brain-derived neurotrophic factor levels in depressed patients: A preliminary study. Prog. Neuro-Psychopharmacology Biol. Psychiatry 29, 261–265.

Barrientos, R.M., Sprunger, D.B., Campeau, S., Higgins, E.A., Rudy, J.W., Maier, S.F. 2003. "Brain-Derived Neurotrophic Factor mRNA Downregulation Produced by Social Isolation Is Blocked by Intrahippocampal Interleukin-1 Receptor Antagonist. Neuroscience. 121, 847-853.

Bremner, J.D., Narayan, M., Anderson, E.R., Staib, L.H., Miller, H.L., and Charney, D.S. 2000. Hippocampal volume reduction in major depression. Am. J. Psychiatry 157, 115–8.

Bumb, J.M., Aksay, S.S., Janke, C., Kranaster, L., Geisel, O., Gass, P., Hellweg, R., and Sartorius, A. 2015. Focus on ECT seizure quality: serum BDNF as a peripheral biomarker in depressed patients. Eur. Arch. Psychiatry Clin. Neurosci. 265, 227–232.

Bus, B.A.A., and Molendijk, M.L. 2016. The neurotrophic hypothesis of depression. Tijdschr. Psychiatr. 58, 215–22.

Chen, B., Dowlatshahi, D., MacQueen, G.M., Wang, J.F., and Young, L.T. 2001. Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. Biol. Psychiatry 50, 260–265.

Cheng, A., Wang, S., Cai, J., Rao, M.S., and Mattson, M.P. 2003. Nitric oxide acts in a positive feedback loop with BDNF to regulate neural progenitor cell proliferation and differentiation in the mammalian brain. Dev. Biol. 258, 319–333.

Czeh, B., Michaelis, T., Watanabe, T., Frahm, J., de Biurrun, G., van Kampen, M., Bartolomucci, A., and Fuchs, E. 2001. Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. Proc. Natl. Acad. Sci. 98, 12796–12801.

Czubak, A., Nowakowska, E., Kus, K., Burda, K., Metelska, J., Baer-Dubowska, W., and Cichocki, M. 2009. Influences of chronic venlafaxine, olanzapine and nicotine on the hippocampal and cortical concentrations of brain-derived neurotrophic factor (BDNF). Pharmacol. Reports 61, 1017–1023.

de Azevedo Cardoso, T., Mondin, T.C., Wiener, C.D., Marques, M.B., Fucolo, B. de Á., Pinheiro, R.T., de Souza, L.D.M., da Silva, R.A., Jansen, K., and Oses, J.P. 2014. Neurotrophic Factors, Clinical Features and Gender Differences in Depression. Neurochem. Res. 39, 1571–1578.

Deveci, A., Aydemir, O., Taskin, O., Taneli, F., and Esen-Danaci, A. 2008. Serum BDNF levels in suicide attempters related to psychosocial stressors: A comparative study with depression. Neuropsychobiology 56, 93–97.

Dias, B.G., Banerjee, S.B., Duman, R.S., and Vaidya, V.A. 2003. Differential regulation of Brain Derived Neurotrophic Factor

transcripts by antidepressant treatments in the adult rat brain. Neuropharmacology 45, 553–563.

Dilbaz, N., Özen A.R., Ay M., Güz H.,Karademir S. 1999. Venlafaksin'in major depresyonda etkinlik ve emniyeti; ümitsizlik, intihar düşüncesi ve anksiyete üzerine etkisi: Bir açık çalışma.Bull Clin Psycopharmacol.9,197-202

Duman, R.S. 1997. A Molecular and Cellular Theory of Depression. Arch. Gen. Psychiatry 54, 597.

Duman, R.S. 2004. Role of Neurotrophic Factors in the Etiology and Treatment of Mood Disorders. NeuroMolecular Med. 5, 011–026.

Dwivedi, Y., Rizavi, H.S., Conley, R.R., Roberts, R.C., Tamminga, C.A., and Pandey, G.N. 2003. Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. Arch. Gen. Psychiatry 60, 804–815.

Ernfors, P., and Bramham, C.R. 2003. The coupling of a trkB tyrosine residue to LTP. Trends Neurosci. 26, 171–173.

Gittos, M.W., and Papp, M. 2001. Antidepressant-like action of AGN 2979, a tryptophan hydroxylase activation inhibitor, in a chronic mild stress model of depression in rats. Eur. Neuropsychopharmacol. 11, 351–357.

Gonul, A.S., Akdeniz, F., Taneli, F., Donat, O., Eker, Ç., and Vahip, S. 2005. Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients. Eur. Arch. Psychiatry Clin. Neurosci. 255, 381–386.

Gould, E., Tanapat, P., McEwen, B.S., Flügge, G., and Fuchs, E. 1998. Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. Proc. Natl. Acad. Sci. U. S. A. 95, 3168–3171.

Grippo, A.J., Francis, J., Beltz, T.G., Felder, R.B., and Johnson, A.K. 2005. Neuroendocrine and cytokine profile of chronic mild stress-induced anhedonia. Physiol. Behav. 84, 697–706.

Grippo, A.J., Moffitt, J.A., and Johnson, A.K. (2002). Cardiovascular alterations and autonomic imbalance in an experimental model of depression. Am. J. Physiol. - Regul. Integr. Comp. Physiol. 282, R1333–R1341.

Grønli, J., Bramham, C., Murison, R., Kanhema, T., Fiske, E., Bjorvatn, B., Ursin, R., and Portas, C.M. 2006. Chronic mild stress inhibits BDNF protein expression and CREB activation in the dentate gyrus but not in the hippocampus proper. Pharmacol. Biochem. Behav. 85, 842–849.

Guilloux, J.P., Douillard-Guilloux, G., Kota, R., Wang, X., Gardier, A.M., Martinowich, K., Tseng, G.C., Lewis, D.A., and Sibille, E. 2012. Molecular evidence for BDNF-and GABA-related dysfunctions in the amygdala of female subjects with major depression. Mol. Psychiatry 17, 1130–1142.

Huang, T.L., Lee, C. Te, and Liu, Y.L. 2008. Serum brain-derived neurotrophic factor levels in patients with major depression: Effects of antidepressants. J. Psychiatr. Res. 42, 521–525.

Hughes, I., Blasiole, B., Huss, D., Warchol, M.E., Rath, N.P., Hurle, B., Ignatova, E., David Dickman, J., Thalmann, R., Levenson, R., et al. 2004. Otopetrin 1 is required for otolith formation in the zebrafish Danio rerio. Dev. Biol. 276, 391–402.

Kuroda, Y., and Mcewen, B.S. 1998. Effect of chronic restraint stress and tianeptine on growth factors , mRNA expression in the rat hippocampus. Mol. Brain Res. 59, 35–39.

Larsson, E., Nanobashvili, A., Kokaia, Z., and Lindvall, O. 1999. Evidence for neuroprotective effects of endogenous brain-derived neurotrophic factor after global forebrain ischemia in rats. J Cereb Blood Flow Metab 19, 1220–1228

Leal, G., Bramham, C.R., and Duarte, C.B. 2017. BDNF and Hippocampal Synaptic Plasticity. In Vitamins and hormones, pp. 153–195.

Lee, H.Y., and Kim, Y.K. 2008. Plasma brain-derived neurotrophic factor as a peripheral marker for the action mechanism of antidepressants. Neuropsychobiology 57, 194–199.

Lee, J., Duan, W., and Mattson, M.P. 2002. Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. J. Neurochem. 82, 1367–1375.

Li, J.J., Yuan, Y.G., Hou, G., and Zhang, X.R. 2011. Dose-related effects of venlafaxine on pCREB and brain-derived neurotrophic factor (BDNF) in the hippocampus of the rat by chronic unpredictable stress. Acta Neuropsychiatr. 23, 20–30.

Madsen TM, Treschow A, Bengzon J, Bolwig TG, Lindvall O, Tingström A. 2000. Increased neurogenesis in a model of electroconvulsive therapy. Biol Psychiatry Jun 1;47:1043–9.

Malberg, J.E., and Duman, R.S. 2003. Cell proliferation in adult hippocampus is decreased by inescapable stress. Neuropsychopharmacology 28, 1562–1571.

Mamounas, L. a, Blue, M.E., Siuciak, J. a, and Altar, C. a 1995. Brain-derived neurotrophic factor promotes the survival and sprouting of serotonergic axons in rat brain. J. Neurosci. 15, 7929–39.

Manev, H., Uz, T., Smalheiser, N.R., and Manev, R. 2001. Antidepressants alter cell proliferation in the adult brain in vivo and in neural cultures in vitro. Eur. J. Pharmacol. 411, 67–70.

Manji, H.K., and Duman, R.S. 2001. Impairments of neuroplasticity and cellular resilience in severe mood disorders: implications for the development of novel therapeutics. Psychopharmacol. Bull. 35, 5–49.

Manji, H.K., Drevets, W.C., and Charney, D.S. 2001. The cellular neurobiology of depression. Nat. Med. 7, 541–547.

Manji, H.K., Moore, G.J., Rajkowska, G., and Chen, G. 2000. Neuroplasticity and cellular resilience in mood disorders. Mol. Psychiatry 5, 578–593.

Manji, H.K., Quiroz, J.A., Sporn, J., Payne, J.L., Denicoff, K., Gray, N.A., Zarate, C.A., and Charney, D.S. 2003. Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. Biol. Psychiatry 53, 707–742

Marano, C.M., Phatak, P., Vemulapalli, U.R., Sasan, A., Nalbandyan, M.R., Ramanujam, S., Soekadar, S., Demosthenous, M., and Regenold, W.T. 2007. Increased plasma concentration of brain-derived neurotrophic factor with electroconvulsive therapy: A pilot study in patients with major depression. J. Clin. Psychiatry 68, 512–517.

Matrisciano, F., Bonaccorso, S., Ricciardi, A., Scaccianoce, S., Panaccione, I., Wang, L., Ruberto, A., Tatarelli, R., Nicoletti, F., Girardi, P., et al. 2009. Changes in BDNF serum levels in patients with major depression disorder (MDD) after 6 months treatment with sertraline, escitalopram, or venlafaxine. J. Psychiatr. Res. 43, 247–254.

Molendijk, M.L., Bus, B.A.A., Spinhoven, P., Penninx, B.W.J.H.,

Kenis, G., Prickaerts, J., Voshaar, R.O., and Elzinga, B.M. 2011. Serum levels of brain-derived neurotrophic factor in major depressive disorder: state–trait issues, clinical features and pharmacological treatment. Mol. Psychiatry 16, 1088–1095.

Murray, C.A., McGahon, B., McBennett, S., and Lynch, M.A. 1997. Interleukin-1β inhibits glutamate release in hippocampus of young, but not aged, rats. Neurobiol. Aging 18, 343–348.

Nibuya, M., Morinobu, S., and Duman, R.S. 1995. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J. Neurosci. 15, 7539–7547.

Orsetti, M., Colella, L., Dellarole, A., Canonico, P.L., Ferri, S., and Ghi, P. 2006. Effects of chronic administration of olanzapine, amitriptyline, haloperidol or sodium valproate in naive and anhedonic rats. Int. J. Neuropsychopharmacol. 9, 427–436.

Pandey, G.N., Ren, X., Rizavi, H.S., Conley, R.R., Roberts, R.C., and Dwivedi, Y. 2008. Brain-derived neurotrophic factor and tyrosine kinase B receptor signalling in post-mortem brain of teenage suicide victims. Int. J. Neuropsychopharmacol. 11, 1047–1061.

Pedrotti Moreira, F., Borges, C.J., Wiener, C.D., da Silva, P.M., Portela, L.V., Lara, D.R., da Silva, R.A., de Mattos Souza, L.D., Jansen, K., and Oses, J.P. 2018. Serum brain-derived neurotrophic factor levels in subjects with major depressive disorder with previous suicide attempt: A population-based study. Psychiatry Res. 262, 500–504.

Piccinni, A., Del Debbio, A., Medda, P., Bianchi, C., Roncaglia, I., Veltri, A., Zanello, S., Massimetti, E., Origlia, N., Domenici, L., et al. 2009. Plasma Brain-Derived Neurotrophic Factor in treatment-resistant depressed patients receiving electroconvulsive therapy. Eur. Neuropsychopharmacol. 19, 349–355.

Piccinni, A., Marazziti, D., Catena, M., Domenici, L., Del Debbio, A., Bianchi, C., Mannari, C., Martini, C., Da Pozzo, E., Schiavi, E., et al. 2008. Plasma and serum brain-derived neurotrophic factor (BDNF) in depressed patients during 1 year of antidepressant treatments. J. Affect. Disord. 105, 279–283.

Pizarro, J.M., Lumley, L.A., Medina, W., Robison, C.L., Chang, W.E., Alagappan, A., Bah, M.J., Dawood, M.Y., Shah, J.D., Mark, B., et al. 2004. Acute social defeat reduces neurotrophin expression in brain cortical and subcortical areas in mice. Brain Res. 1025, 10–20.

Popoli, M., Gennarelli, M., and Racagni, G. 2002. Modulation of synaptic plasticity by stress and antidepressants. Bipolar Disord. 4, 166–182.

Rajkowska, G., Miguel-hidalgo, J.J., Wei, J., and al, et 2000. Morphometric Evidence for Neuronal and Glial Prefrontal Cell Pathology in Major Depression. Year B. Psychiatry Appl. Ment. Heal. 2000, 328–329.

Sachs, B.D., and Caron, M.G. 2015. Chronic fluoxetine increases extra-hippocampal neurogenesis in adult mice. Int. J. Neuropsychopharmacol. 18, pyu029-pyu029.

Sanchez, C., Gruca, P., and Papp, M. 2003. R-citalopram counteracts the antidepressant-like effect of escitalopram in a rat chronic mild stress model. Behav Pharmacol 14, 465–470.

Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., Weisstaub, N., Lee, J., Duman, R., Arancio, O., et al. 2003. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science (80-.). 301, 805–809.

Sapolsky, R.M. 2000. Glucocorticoids and Hippocampal Atrophy in Neuropsychiatric Disorders. Arch. Gen. Psychiatry 57, 925.

Sen, S., Duman, R., and Sanacora, G. 2008. Serum Brain-Derived Neurotrophic Factor, Depression, and Antidepressant Medications: Meta-Analyses and Implications. Biol. Psychiatry 64, 527–532

Sheline, Y.I., Gado, M.H., and Kraemer, H.C. 2003. Untreated depression and hippocampal volume loss. Am. J. Psychiatry 160, 1516–1518

Shimizu, E., Hashimoto, K., Okamura, N., Koike, K., Komatsu, N., Kumakiri, C., Nakazato, M., Watanabe, H., Shinoda, N., Okada, S.I., et al. 2003. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biol. Psychiatry 54, 70–75.

Shirayama, Y., Chen, A.C.-H., Nakagawa, S., Russell, D.S., and Duman, R.S. 2002. Brain-Derived Neurotrophic Factor Produces Antidepressant Effects in Behavioral Models of Depression. J. Neurosci. 22, 3251–3261

Siuciak, J.A., Lewis, D.R., Wiegand, S.J., Lindsay, R.M., Lewis, D.R., Wiegand, S.J., and Lindsay, R.M. 1997. Antidepressant-Like Effect of Brain-derived Neurotrophic Factor (BDNF). Pharmacol. Biochem. Behav. 56, 131–137.

Smith, M.A., Makino, S., Kvetnansky, R., and Post, R.M. 1995. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. J. Neurosci. 15, 1768–1777.

Solberg, L.C., Olson, S.L., Turek, F.W., and Redei, E. 2001. Altered hormone levels and circadian rhythm of activity in the WKY rat, a putative animal model of depression. Am. J. Physiol. Regul. Integr. Comp. Physiol. 281, R786–R794.

Tartaglia, N., Du, J., Tyler, W. J., Neale, E., Pozzo-Miller, L., & Lu, B. 2001. Protein synthesis-dependent and -independent regulation of hippocampal synapses by brain-derived neurotrophic factor. The Journal of Biological Chemistry, 276;37585–93.

Terzi, A.D., Yazici, K., Aslan, E., lu, N., delen, B., Tot, A.S., and Yazici, A. 2009. Effects of fluoxetine and venlafaxine on serum brain derived neurotrophic factor levels in depressed patients. Prog. neuro Psychopharmacol. Biol. psychiatry 33, 281–285.

Tyler, W.J., and Pozzo-Miller, L.D. 2001. BDNF enhances quantal neurotransmitter release and increases the number of docked vesicles at the active zones of hippocampal excitatory synapses. J. Neurosci. 21, 4249–58.

Ueyama, T., Kawai, Y., Nemoto, K., and Sekimoto, M. 1997. Immobilization stress reduced the expression of neurotrophins and their receptors in the rat brain. Elsevier 28, 103–110.

Uzbay T. 2005. Nöroplastiste ve Depresyon., Çizgi Tıp Yayınevi: Ankara, Turkey.

Vaidya, V. a, Marek, G.J., Aghajanian, G.K., and Duman, R.S. 1997. 5-HT2A receptor-mediated regulation of brain-derived neurotrophic factor mRNA in the hippocampus and the neocortex. J. Neurosci. 17, 2785–2795.

Van Kampen, M., Kramer, M., Hiemke, C., Flügge, G., and Fuchs, E. 2002. The chronic psychosocial stress paradigm in male tree shrews: Evaluation of a novel animal model for depressive

disorders. Stress 5, 37–46.

Vermetten, E., Vythilingam, M., Southwick, S.M., Charney, D.S., and Bremner, J.D. 2003. Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. Biol. Psychiatry 54, 693–702.

Watanabe, Y., Gould, E., Daniels, D.C., Cameron, H., and McEwen, B.S. 1992. Tianeptine attenuates stress-induced morphological-changes in the hippocampus. Eur. J. Pharmacol. 222, 157–162.

Willner, P. 1990. Animal models of depression: An overview. Pharmacol. Ther. 45, 425–455.

Willner, P. 1997. Validity, reliability and utility of the chronic mild stress model of depression: A 10-year review and evaluation. Psychopharmacology (Berl). 134, 319–329.

Xu, H., Chen, Z., He, J., Haimanot, S., Li, X., Dyck, L., and Li, X.M. 2006. Synergetic effects of quetiapine and venlafaxine in preventing the chronic restraint stress-induced decrease in cell proliferation and BDNF expression in rat hippocampus. Hippocampus 16, 551–559.

Xu, H., Richardson, J.S., and Li, X.M. 2003. Dose-related effects of chronic antidepressants on neuroprotective proteins BDNF, Bcl-2 and Cu/Zn-SOD inrat hippocampus. Neuropsychopharmacology 28, 53–62.

Xu, Y.L., Reinscheid, R.K., Huitron-Resendiz, S., Clark, S.D., Wang, Z., Lin, S.H., Brucher, F.A., Zeng, J., Ly, N.K., Henriksen, S.J., et al. 2004. Neuropeptide S: A neuropeptide promoting arousal and anxiolytic-like effects. Neuron 43, 487–497.

Ye, Y., Wang, G., Wang, H., and Wang, X. 2011. Brain-derived neurotrophic factor (BDNF) infusion restored astrocytic plasticity in the hippocampus of a rat model of depression. Neurosci. Lett. 503, 15–19.

Yoshimura, R., Mitoma, M., Sugita, A., Hori, H., Okamoto, T., Umene, W., Ueda, N., and Nakamura, J. 2007. Effects of paroxetine or milnacipran on serum brain-derived neurotrophic factor in depressed patients. Prog. Neuro-Psychopharmacology Biol. Psychiatry 31, 1034–1037.

You, Z., Luo, C., Zhang, W., Chen, Y., He, J., Zhao, Q., Zuo, R., and Wu, Y. 2011. Pro- and anti-inflammatory cytokines expression in rat's brain and spleen exposed to chronic mild stress: Involvement in depression. Behav. Brain Res. 225, 135–141.

3rd International Brain Research School

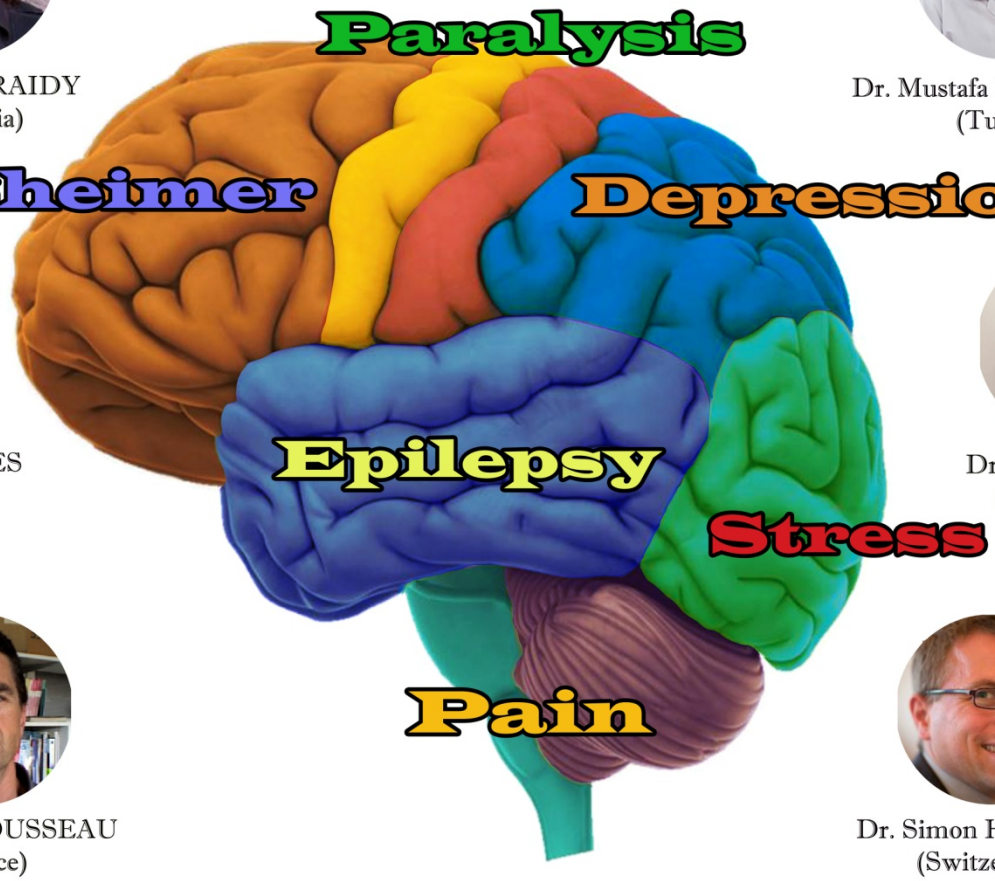
Cellular Neuroscience and Oxidative Stress Society

25 June - 1 July 2018 - Isparta / TURKEY

2018.brs.org.tr

Dr. Nady BRAIDY
(Australia)

Dr. Mustafa NAZIROĞLU
(Turkey)



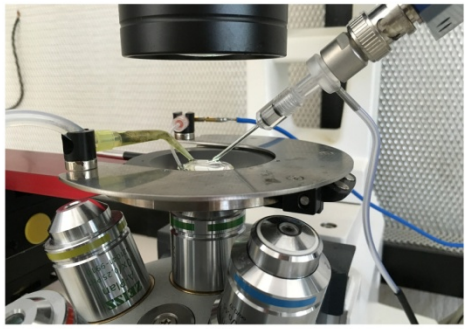
Dr. Sergio PAREDES
(Spain)

Dr. László PECZE
(Switzerland)

Dr. Denis ROUSSEAU
(France)

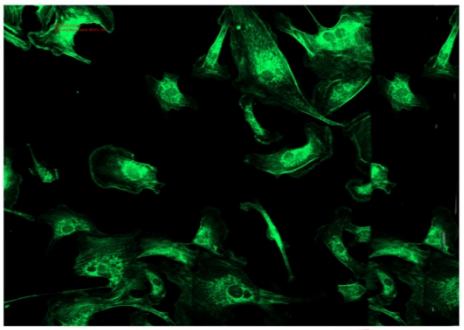
Dr. Simon HEBEISEN
(Switzerland)

Patch Clamp & Calcium Signaling



Cell Culture

Western Blot & Confocal Microscope



Design: Yasin Yaşgan

Contact:
Neuroscience Research Center,
Suleyman Demirel University,
Faculty of Medicine, Isparta / TURKEY
Tel: +90 246 211 36 41
e-mail; norobam@sdu.edu.tr

Date:…… Contributor Name: ……..

Contributor Address:…….

Manuscript Number (if Know):

Re: Manuscript entitled…..……

For publication in Journal of Cellular Neuroscience and Oxidative Stress (JCNOS) published by Cellular Neuroscience and Oxidative Stress Society (http://hsord.org.tr/), Isparta, Turkey.

Submission of a manuscript implies:
- that the work described has not been published before (except in the form of an abstract or as part of a published lecture, review or thesis);
- that it is not under consideration for publication elsewhere;
- that its publication has been approved by all co-authors, if any, as well as by the responsible authorities at the institute where the work has been carried out;
- that, if and when the manuscript is accepted for publication, the authors agree to automatic transfer of the copyright to this publisher;
- that the manuscript and figures will not be published elsewhere in any language without the consent of the copyright holders;
- that written permission of the copyright holder is obtained by the authors for material used from other copyrighted sources, and that any costs associated with obtaining this permission are the authors' responsibility.

Copyright notice: The contributor and the company/employer agree that all copies the final published version of the contribution or any part thereof distributed or posted by them in print or electronic format as permitted herein will include the notice of copyright as stipulated in the journal and a full citation to the journal as published by Cell Membranes and Free radical Society, Isparta, Turkey.

CHECK ONE BOX

( ) Contributor owned work:

Contributor's Print name and title……

Contributor's signature…….Date:……

Co- Contributor's Print name and title……

Contributor's signature…….Date:……

Co- Contributor's Print name and title……..

Contributor's signature…….Date:……

Co- Contributor's Print name and title…….

Contributor's signature…….Date:……..

Co- Contributor's Print name and title……..

Contributor's signature……Date:…….…...

( ) Company-Institution owned work:

Company-Institution (Employer for here)…..……..…..Date:……...

Authorized signature……...…….……Date:…….....

( ) U.S. Government work ( ) U.K. Government work ( ) Other Government work

Journal of Cellular Neuroscience and Oxidative Stress

Principal Contact

Prof. Dr. Mustafa NAZIROGLU / Editor in Chief
Suleyman Demirel University, Faculty of Medicine, Department of Biophysics
32260 Cunur - Isparta / TURKEY
Phone: +90 246 2113641 Fax: +90 246 2371165
mustafanaziroglu@sdu.edu.tr
biophysics@sdu.edu.tr