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ASSOCIATION OF BDNF / TRKB AND NGF / TRKA LEVELS IN POSTMORTEM BRAIN WITH MAJOR DEPRESSION AND SUICIDE

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SUMMARY

***Background*:** *Suicide Attempts are the main complications of Major Depressive Episodes and are difficult to predict. There is still a lack of knowledge about its neurochemical aspects. There is increasing evidence that Brain-derived neurotrophic factor (BDNF) and Nerve growth factor (NGF) play a role in the pathophysiology and treatment of depression by binding and activating cognate receptors Tyrosine Kinase B (TrkB) and Tyrosie Kinase A (TrkA), respectively. This study was conducted to examine whether BDNF and / or TrkB as well as NGF and / or TrkA expression profiles were changed in the hippocampus of postmortem brain of individuals with depression who committed suicide.*

Subjects and methods: *This study was conducted with the brain tissue of 61 victims who died as a result of suicide due to depression and 25 people who died due to traffic accidents. The psychiatric history of the cases was determined by the psychological autopsy method. Samples were taken from the hippocampus region of the brain at the forensic medicine institution. After storage under appropriate conditions, protein and mRNA levels of BDNF, TrkB, NGF and TrkA were determined in the genetics laboratory.*

Results: *Average age of the suicide group was 30 and the average age of the control group was 24.5. The suicide group consisted of 70.5% male and 29.5% female cases. There was no significant difference between the groups in terms of age (p=0.062) and gender (p=0.718). BDNF, NGF, TrkA and TrkB values were found to be lower in the suicide group compared to the control group and there was a significant difference between the groups (p=<0.001; p=0.001; p=0.001; p=0.011).*

Conclusion*: Given the importance of BDNF and NGF and their cognate receptors in mediating physiological functions, including cell survival and synaptic plasticity, our findings regarding decreased expression of BDNF, TrkB, NGF and TrkA in both protein and mRNA levels of postmortem brains of suicide victims suggests that it may play an important role in the pathophysiological aspects of its behavior. Further studies in this context may be useful both in understanding the molecular basis of suicide and in designing therapeutic models targeting these molecular pathways.*

Key words: *BDNF – NGF – TrkB – TrkA – suicide - postmortem brain - depression*

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INTRODUCTION

Suicide is a major public health problem causing the death of approximately 1 million people worldwide one year (WHO 2016). Despite the devastating effects of suicide on numerous lives, there is still a lack of knowledge about its neurobiology. Some clinical and epidemiological studies suggest the stress-diathesis model in suicide (Banerjee et al. 2012). Stress diathesis model shows that suicidal risk is determined not only by the underlying psychiatric illness, but also by a continuous diathesis (van Heeringen & Mann 2014). Identifying possible biological causes for this diathesis can help develop suicide risk prediction, prevention and treatment strategies.

The role of neurotrophins in brain growth and in guiding neuronal functioning is increasingly recognized. Neurotrophins not only play an important role in cellular proliferation, migration, phenotypic differentiation and the maintenance of the developing central nervous system, but their presence in the adult central nervous system is essential for maintenance of neuronal functions and structural integrity (McAllister 2001). Many studies have shown that neurotrophic factors regulate synaptic and morphological plasticity. (Thoenen 2000, Huang & Reichardt 2001).

Nerve growth factor (NGF), the prototypical growth factor, is a protein secreted by a neuron's target cell. It is critical for the survival and maintenance of sympathetic and sensory neurons. NGF is released from target cells, binds and activates the high affinity receptor Tyrosine Kinase A (TrkA) on the neuron. It also functions as a signal molecule. (Fiore et al. 2009). The best known neurotrophic function of NGF in the nervous system is that it plays a role in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis mediated stress response.

Brain-derived neurotrophic factor (BDNF) is one of the neurotrophins that regulates neuron survival, plasticity (Tsankova et al. 2006) and synaptic function (Huang & Reichardt 2001). Specifically, tropomyosin-bound tyrosine kinase receptor binds to the receptor Tyrosine Kinase B (TrkB) and regulates many functions related to neuronal development, such as neurite development, synthesis of differentiation factors, and morphological plasticity. (Tyler et al. 2002). BDNF plays an important role in differentiation during development (Engelhardt et al. 2007), is regulated by stress (Roceri et al. 2004) and is associated with the

pathophysiology of mental disorders, especially major depression (Russo-Neustadt 2003).

The hypothesis of the study is that BDNF and NGF may be candidate molecules that can mediate the risk of major depression and suicide. Therefore, in our study, we aimed to compare the expression profiles of BDNF, TrkB, NGF and TrkA in postmortem brain tissue of patients who committed suicide due to depression with those who did not die from suicide and did not have a psychiatric history. Postmortem brain tissue from suicide victims is a useful method for studying the neurobiology of suicide. In addition, we think that sampling from a homogeneous group consisting only of cases who committed suicide due to depression will provide a better understanding of the relationship between BDNF, TrkB, NGF and TrkA-depression-suicide and contribute to the literature.

SUBJECTS AND METHODS

Subjects

Brain samples were collected from the Forensic Medicine Institute Malatya Group Presidency between January 2018 and December 2019. In the power analysis, when $\alpha = 0.05$; is taken as $1- \beta$ (power) = 0.80, it was calculated that at least 20 subjects should be taken from each group for the average change to be 26 units in BDNF, NGF, Trk A / B m RNA expression in cases of suicides related depression. Brain samples were taken from 100 cases suicide by hanging method who committed sent to the Forensic Medicine Institute Malatya Group Presidency for autopsy to form the suicide group. Diagnoses were determined by psychological autopsy method according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) V (American Psychiatric Association 2013). Exclusion criteria in the suicide group:

- suicide for reasons other than depression (impulsive suicides) and/or had comorbidities such as schizophrenia, substance addiction, and/or bipolar affective disorder;
- Causes of death such as exposure to any toxic substance, poisoning and drug consumption were excluded from the study, considering that they could affect the samples;
- cases of indeterminate death;
- major neuropathology;
- anyone over the age of 65 and under 18;
- anyone with a history of seizures or other neurological disorders that may affect brain pathology, and anyone with evidence of such conditions on a neuropathological examination.

Twenty-seven cases who committed suicide for reasons other than depression (impulsive suicides) and / or had comorbidities such as schizophrenia, substance addiction, and/or bipolar affective disorder were excluded from the study. At the same time, 12 cases who had committed suicide by methods such as drug intoxication and/or exposure to a chemical agent were excluded from the study because it may affect the brain tissue. 61 cases who had attempted suicide by hanging method and were found to have depression as a result of psychological autopsy were included in the suicide group.

The control group consisted of 25 cases who died as a result of an accident and brought to the Forensic Medicine Institute Malatya Group Presidency for autopsy. All of the brains were examined under a microscope to exclude cases with signs of pathological neurodegeneration or other lesions. Exclusion criteria for control groups included:

- cases of indeterminate death,
- major neuropathology;
- positive toxicology screenings for psychoactive and neurotoxic drugs (including antidepressants and alcohol);
- alcohol use disorder;
- a history of bipolar disorder or psychosis;
- anyone over the age of 65 and under 18;
- anyone with a history of seizures or other neurological disorders that may affect brain pathology, and anyone with evidence of such conditions on a neuropathological examination. Causes of death such as exposure to any toxic substance, poisoning and drug consumption were excluded from the study, considering that they could affect the samples.

The Psychological Autopsy Methodology

"Psychological autopsy" refers to a research method that collects comprehensive retrospective information on completed suicide victims. The purpose of the procedure is to provide a clear and accurate view of the person's life situation, personality, mental health and, if any, treatment provided by healthcare institutions before committing suicide (Isometsä 2001). The psychological autopsy procedure has two main elements: 1) extensive interviews with family members and/or other close relatives; and 2) to collect all possible medical, psychiatric and other relevant documents of the deceased. In a typical psychological autopsy, there are one or two main sources of information. In addition, relevant persons, including other close relatives, friends or staff on duty, may be interviewed (Hawton et al. 1998). This process faces some unavoidable methodological problems, but it is often accessible and offers insights into the suicidal process (Clark & Horton-Deutsch 1992).

This technique has been validated for Axis I and II diagnoses (Conner et al. 2001). In our study, the informants primarily include family members such as mother, father, siblings, friends or relatives who know the deceased person best. After obtaining written informed consent, at least one family member was interviewed by a psychiatrist using the Clinical Interview Program for

DSM-IV (SCID). Information gathered from the SCID I and II interviews and the forensic practitioner's notes and medical records were used by the interviewer to write a "case history" for each case. These case histories were later reviewed by two psychiatrists to arrive at a consensus on the DSM-IV diagnosis for each subject. Similarly, using similar diagnostic procedures, controls were confirmed to be not-mentally ill.

Brain Extraction

Brain and blood samples were taken from the subjects who were autopsied and included in the study at the Forensic Medicine Institute Malatya Group Presidency. 10 cc of blood was taken from the femoral vein as sterile. After the skull was opened, rain tissue samples were taken out of the skull in a sterile manner into a sterile environment, a hippocampus region was opened in the brain which was determined to take samples from. 4 samples for DNA study and 4 samples for RNA study were taken from the hippocampus and placed in separate tubes. This procedure was applied to the suicide case (n: 61) and the control group (n: 25). In taking sample; A separate scalpel was used for each procedure in brain tissue samples taken in a sterile environment. Brain tissue samples taken in a sterile environment were stored in tissue storage cabinets at -80 degrees, which can only be opened by authorized personnel, until examination.

RT-qPCR for mRNA expression of BDNF, TrkB, NGF, TrkA and ACTB

mRNA was extracted with GeneAllRiboex (Catalog no: 301-001) and Hybrid-R (Catalog no: 305-101).cDNA synthesis was done by GeneAllTranscriptorHyperScriptTM First StrandSynthesisKit (Catalog no:601-005). Real-time PCR was performed in a Light Cycler Instrument (AppliedBiosystems ™ 7500) using GeneAllRealAmpTM SYBR qPCR Master MixKit (Catalog no: 801-51) and with the primer pairs (Sentebiolab) listed in Table 1. Briefly, a reaction volume of 20 µl containing 10 µl master mix with Sybr-green, 1 µlROX dye, 1 µl forward primer, 1 µl reverse primer, 3 µl PCR grade water and 4 µl cDNA was set for each sample. The cycling protocol was as follow; initial denaturation at 95°C for 5 min, followed by 40 cycles of denaturation at 95°C for 15 sec, annealing at 60°C for 60 sec. Each sample was run triplicate. Relative mRNA expressions were calculated using β-Actin gene as the housekeeping gene using the $2^{-\Delta\Delta Ct}$ method [18] (Table 1).

Statistical Analysis

The conformity of numerical data to normal distribution was examined using Shapiro-Wilk or Kolmogorov-Smirnov tests, depending on the number of observations. Since the data did not conform to the normal distribution, median, minimum and maximum values were used as descriptors and comparisons were made with the Mann-Whitney U test. Categorical variables were shown with numbers and percentages, and comparisons were made with Pearson chi-square or continuity-corrected chi-square tests depending on the number of observations. Two-sided significance level was accepted as 0.05 in all tests. Statistical analysis was performed using IBM SPSS for Windows version 22.0 (New York, USA).

Compliance with ethical standards

This study protocol was approved by the Ethics Committee of Inonu University Faculty of Medicine (study number 2018/115) and was conducted in accordance with the ethical principles of the 2013 Declaration of Helsinki and Good Clinical Practices. Permission to use the brain material was provided by the closest relatives. The authors declare that there is no conflict of interests.

RESULTS

Demographic characteristics of suicide victims and control cases without psychiatric diagnosis

Demographic characteristics of suicide victims (n=61) and control cases without psychiatric diagnosis (n=25) were defined. The mean is 10.5 (1-24) hours for

Table 1. Primer sequences and the product size for primers

Genes	Primer Sequences	Gene Ref. Seq. Number	PCR product size (bp)
BDNF-F	5'-CTACGAGACCAAGTGCAATCC-3'	NM_001143811	147 bp
BDNF-R	5'-AATCGCCAGCCAATTCTCTTT-3'		
NGF-F	5'-GGCAGACCCGCAACATTACT-3'	NM_002506	135 bp
NGF-R	5'-CACCACCGACCTCGAAGTC-3'		
TrkA-F	5'-AACCTCACCATCGTGAAGAGT-3'	NM_001007792	91 bp
TrkA-R	5'-TGAAGGAGAGATTCAGGCGAC-3'		
TrkB-F	5'-GCAATCCATTTACATGCTCCTGT-3'	NM_006180	245 bp
TrkB-R	5'-CATATTAGGAACCGGATCACCTG-3'		
ACTB-F	5'-CATGTACGTTGCTATCCAGGC-3'	NM_001101	250 bp
ACTB-R	5'-CTCCTTAATGTCACGCACGAT-3'		

Note: F, Forward primer; R, Reverse primer

Table 2. Comparison of suicide victims and control cases without psychiatric diagnosis in terms of postmortem interval, age and BDNF, TrkA, TrkB, NGF

	Suicide victims (n=61) Median (min.-max.)	Control subjects (n=25) Median (min.-max.)	p
Age	30 (18-80)	24.5 (18-80)	0.062
Postmorteminterval	10 (1-24)	10.5 (1-24)	0.589
BDNF	0.33 (0.02-2.42)	0.72 (0.01-33.98)	<0.001
NGF	0.09 (0.02-24.93)	0.49 (0.07-51.61)	<0.001
TrkA	0.25 (0.07-11.73)	0.84 (0.41-18.09)	<0.001
TrkB	0.6 (0-3.2)	1.11 (0.01-6.33)	0.011

Table 3. Demographic characteristics of suicide victims and control cases without psychiatric diagnosis

	Suicide victims n (%)	Control subjects n (%)	P value
Gender			0.718
Male	43 (70.5)	18 (72)	
Female	18 (29.5)	7 (28)	
Marital Status			0.965
Married	26 (42.6)	10-40	
Single	29 (47.6)	12 (48)	0
Divorced/widowed	6 (9.8)	(3-12)	
Number of Children			0.986
No	30 (49.2)	13 (52)	
1 child	6 (9.8)	(3-12)	
2 and more children	25 (41)	9 (36)	
Job			0.939
Unemployed	38 (62.3)	16 (64)	
Self employed	13 (21.3)	5 (20)	
Officer	5 (8.2)	2 (8)	
Student	5 (8.2)	2 (8)	
Education			1.000
Primary school	37 (60.7)	15 (60)	
High School	20 (32.8)	8 (32)	
College/ University	4 (6.5)	2 (8)	

postmortem interval control subjects and 10 (1-24) hours for suicide victims. Average age of the suicide group was 30 (18-80) and the average age of the control group was 24.5 (18-80). There was no significant difference between the groups in terms of age (p=0.062) and postmortem interval (p=0.589) (Table 2). The suicide group consisted of 70.5% male (n=43) and 29.5% female (n=18) cases. There was no significant difference in gender between the groups (p=0.718). The marital status, education and employment status of the groups are given in Table 3.

BDNF (Figure 1), NGF (Figure 2), TrkA (Figure 3) and TrkB (Figure 4) values were found to be lower in the suicide group compared to the control group. There was a significant difference between the groups in terms of BDNF, NGF, TrkA and TrkB values (p=<0.001; p=0.001; p=0.001; p=0.011) (Table 2).

The number of previous suicide attempts of the suicide group, whether they had contact before the suicide, the history of suicide in the family and the treatment status are given in Table 4.

Table 4. Some clinical and demographic features of the suicide group

	Case n (%)
The person he/she contacted before committing suicide	
No	47 (77)
Family	10 (16.4)
Wife / lover	4 (6.6)
Previous suicide attempt	
No	47 (77)
1 time	13 (21.3)
2 and more	1 (1.7)
Family history of suicide	
No	53 (86.9)
Yes	8 (13.1)
Treatment status	
Had no treatment	39 (63.9)
Had treatment before (not now)	15 (24.6)
Receiving treatment	7 (11.5)

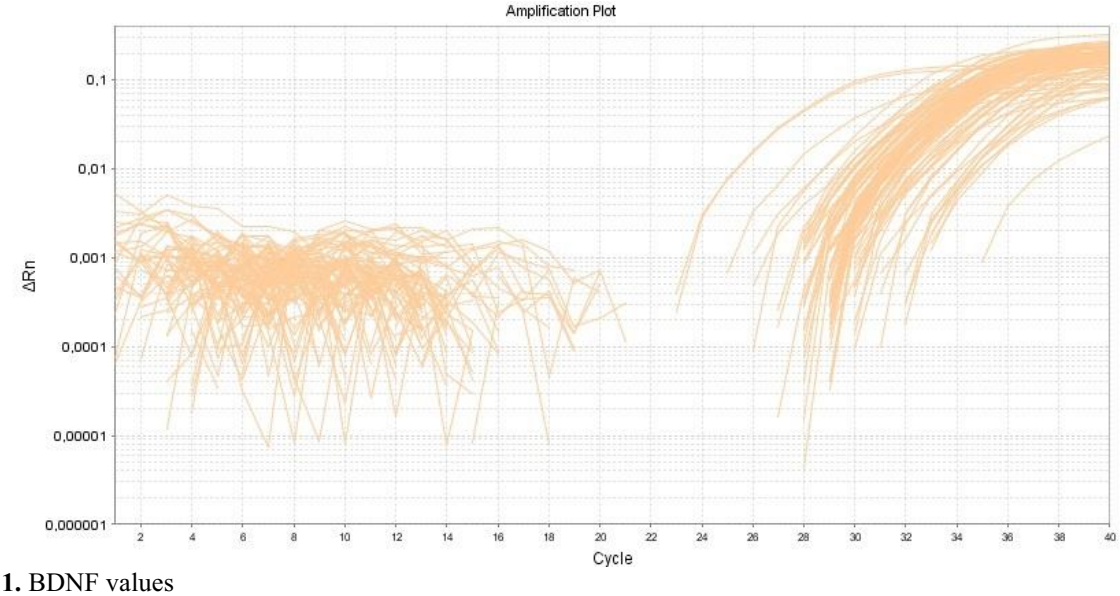

Figure 1. BDNF values

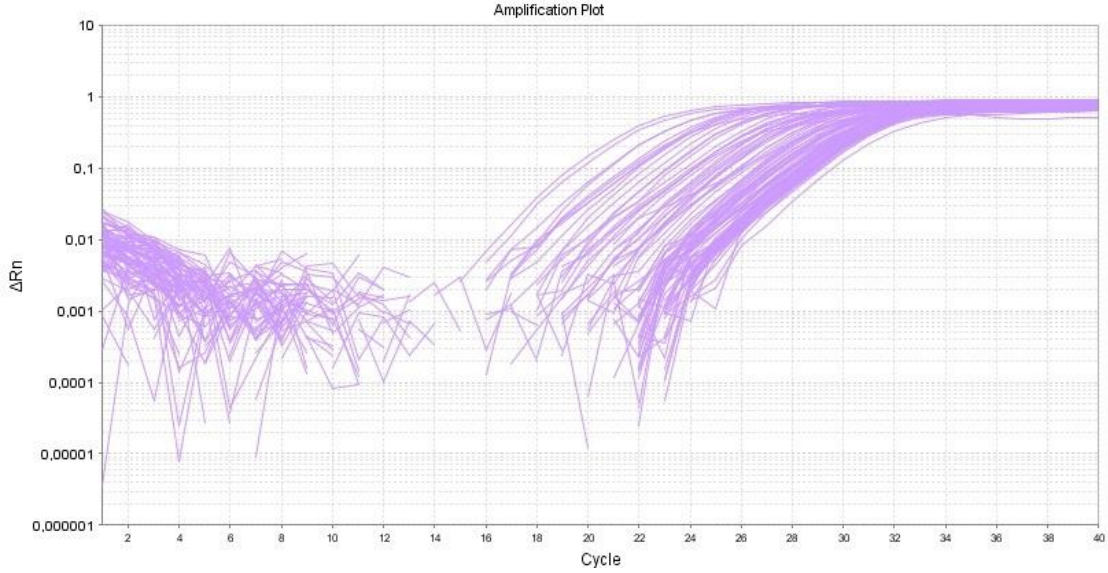

Figure 2. NGF values

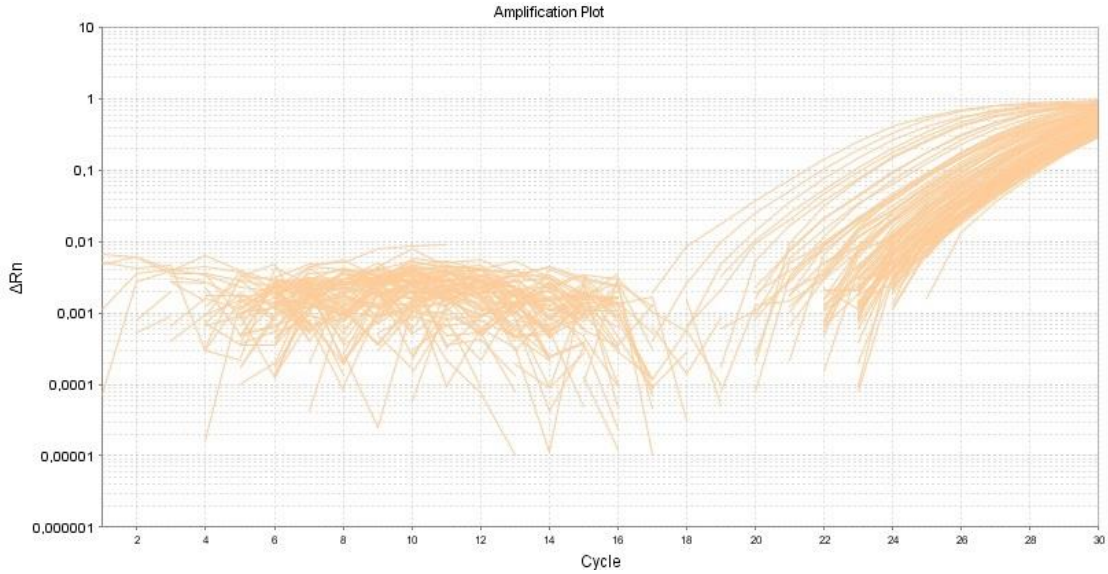

Figure 3. TrkA values

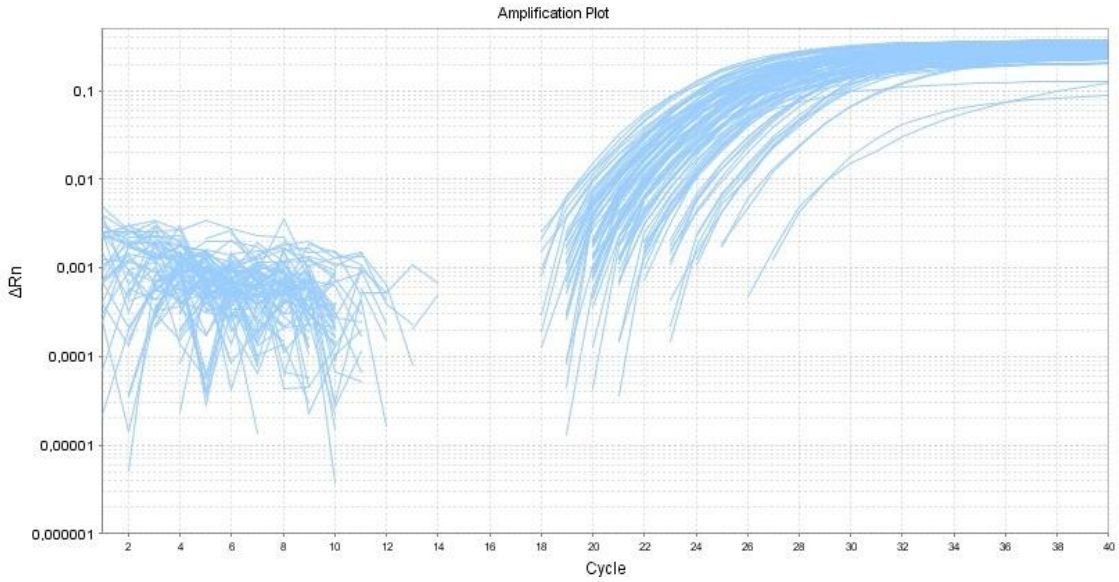

Figure 4. TrkB values

DISCUSSION

In this study, the quantitative values of BDNF, NGF and their cognate receptors TrkB and TrkA in both protein and mRNA levels in the hippocampus of 61 patients who had completed suicide attempt due to depression and 25 non-psychiatric healthy controls were researched. The main result of our study is that there was a statistically significant decrease in protein levels of BDNF, NGF and their receptors in the suicide group.

Much evidence suggests that BDNF is critically reduced in mood disorders and plays an important role in the response to most antidepressant treatments (Caviedes et al. 2017). BDNF is found in nearly all brain regions, neurons, glia, and vascular compartments, and is involved in many central activities, including development, neurogenesis, gliogenesis, synaptogenesis, neuroprotection, and memory and cognition (Kowianski et al. 2018). Neurotrophins exert their effects by binding to three types of tropomyosin-associated kinase (Trk) receptors - TrkA, TrkB and TrkC (Binder and Scharfman 2004). BDNF uses a dual receptor system – preferably binds to the TrkB receptor (Cowansage et al. 2010). The interaction of BDNF with the TrkB receptor plays a role in cell survival and contributes to synaptic potential (Lu 2003).

Postmortem genetic association studies in suicide victims with or without depression, investigating the BDNF-suicide relationship suggest that suicidal behavior may be associated with a decrease in BDNF function (Dwivedi 2010).

There are numerous data in suicide neurobiology involving BDNF and its main receptor TRKB. (Costanza et al. 2014). However, while most genetic studies on suicide attempts in depressive patients deal with BDNF, TRKB has not been adequately studied. (Mirkovic et al. 2016). Similar to our work it has been shown that TRKB and BDNF protein expression in the prefrontal cortex and hippocampus of suicide complements decreased compared to healthy non-psychiatric controls. However, in this study, patients with diagnoses such as schizoaffective disorder, schizophrenia, and bipolar affective disorder were also included in the suicide group in addition to patients with depression. (Dwivedi et al. 2003). The fact that research was conducted in a heterogeneous group may be an important limitation in interpreting the findings of the study. Similarly, in the hippocampus of those who died of suicide in heterokene groups (Banerjee et al. 2013) and in your prefrontal cortex (Karege et al. 2005) low BDNF protein has been reported.

Nerve growth factor (NGF) is a neurotrophin that regulates numerous physiological mechanisms that result in neurotrophic, metabotrophic, and / or immunotrophic effects. Alzheimer's disease, psychiatric disorders (such as depression and schizophrenia), and neurodegenerative diseases have the effect of altering brain levels of NGF (Ciafrè et al. 2020).

MDD patients exhibit reduced serum NGF; the same decrease was observed in postmortem brain examination of the hippocampus (Wiener et al. 2015). NGF may be important to counteract the neurotoxic effects of glucocorticoids, which are elevated during stress (Scully and Otten 1995). The observed reduction in NGF after a stressful experience is pathophysiologically significant. The results of our study showing a significant decrease in hippocampal NGF and TrkA expression among individuals who died of suicide due to depression compared to normal controls support the findings of Banerjee and his colleagues (Banerjee et al. 2013). The results of our study demonstrate the significantly defective brain neurotrophin environment in suicide victims. It is important in strengthening the role of neurotrophins in the pathophysiology of suicide.

Several experimental evidence clearly shows that serum analysis of neurotrophins, including NGF, can be quite useful as a biomarker to explain the early onset of various psychiatric disorders. However, as different researchers suggest, there are currently no specific and reliable biomarkers for each psychiatric disorder, but combined screening of biomarkers seems to be the only alternative to improve early diagnosis and clinical follow-up of the psychiatric individual (Ciafrè et al. 2020). The findings of our study are important in terms of strengthening the findings about the role of neurotrophins in the pathophysiology of suicide, since it had a higher number of subjects compared to the studies in the literature, and the suicide cases that were completed as a result of the hanging method were included in the study.

Major depressive disorder (MDD) is one of the most common brain disorders that includes depression, fatigue, decreased concentration, decreased interest in normal daily activities, and suicidal intentions (Iwabuchi et al. 2014). Many neurotrophins, including NGF and BDNF, play a role in the pathogenesis of MDD (Tanti & Belzung 2013). Suicide attempts are the main complications of major depressive episodes. 15% of major depressive patients attempt suicide during their lifetime (Chen & Dilsaver 1996). The prediction of SA during MDE is difficult for clinicians and is an important public health problem. Therefore, it may be useful to identify biomarkers that can improve SA estimation. Genetic and biochemical biomarkers are interesting because of high inheritance of suicidal behavior (Brent & Melhem 2008).

Limitations

Psychological Autopsy process faces some unavoidable methodological problems. It will also benefit to generalizing the larger sample group findings.

CONCLUSION

Although the current findings are particularly important for understanding the neurochemical basis of suicide, further studies are needed on the molecular mechanisms of these stress-related neurochemical changes. In this context, further studies may be useful both in understanding the molecular basis of suicide and in designing therapeutic models that target these molecular pathways.

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Contribution of individual authors:

Lale Gönenir Erbay & Rıfat Karlıdağ, conceptualized the research question and initial design of the study, which was then contributed to by Mücahit Oruç, Yılmaz Çiğremiş & Osman Celbiş.

The analysis was completed by ale Gönenir Erbay & Mücahit Oruç.

The initial manuscript draft was written by Lale Gönenir Erbay, which was then contributed to by Rıfat Karlıdağ, Mücahit Oruç, Yılmaz Çiğremiş & Osman Celbiş.

All authors provided approval for the final manuscript draft.

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