Protective role of BDNF in Alzheimer's disease pathophysiology and its correlation with new biomarkers: Can the role of BDNF be re-discussed?

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Abstract

Background. The pathophysiology of Alzheimer's disease (AD) is not fully understood and that new biomarkers for the condition should be presented.

Objectives. Our study aimed to determine the blood levels of some biochemical molecules and peptide proteins in AD, which is accepted as the most common cause of dementia in the world, and to elucidate the relationship between them.

Materials and methods. The study consisted of 2 groups: 40 newly diagnosed AD patients and 40 healthy individuals. Plasma levels between the 2 groups and the correlation between them were statistically analyzed.

Results. The median brain-derived neurotrophic factor (BDNF) level in the AD group was found to be higher and statistically significant compared to the control group ($p = 0.033$).

Conclusions. According to our literature review, this is the first article in which these molecules have been studied together in AD patients. In this study, we revealed the importance of these parameters and especially the instrumental role of BDNF in the form and function of the brain in AD patients. Interestingly, in the patient group, all parameters in our study showed a positive and significant positive relationship with one another ($p < 0.001$).

Key words: BDNF, Alzheimer's disease, correlation, biomarkers

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Background

Alzheimer's disease (AD) is a chronic, progressive neurodegenerative disease characterized by cognitive impairment. It is the most common form of dementia in the elderly population, and its impact is increasing worldwide. Over 47 million people are thought to be affected by AD globally.[1–3] Age is the leading risk factor and research has shown that people over 60 are more likely to develop AD.[4] The primary pathology of AD consists of amyloid-(A) deposition and neurofibrillary tangles of hyperphosphorylated tau.[5] Moreover, it is believed that neuroinflammation, microglial activation, oxidative stress, lack of metabolic energy, and neuronal death are all intimately linked to the pathogenesis of AD.[6] Synaptic dysfunction and degeneration have recently been discovered to be more significantly linked to cognitive impairments than plaques or nodes.[7] Therefore, it has become essential to investigate various novel compounds that can serve as biomarkers for the pathophysiology of AD. Enzyme structure (spermidine synthase and agmatinase), factor structure such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF) and coagulation factor V (fV), and hormone structure such as heptapeptide angiotensin 1–7 (Ang-(1–7)) and peptide proteins (neurokinin B and amyloid A) may be effective biomarkers in the early diagnosis of AD. As we look at these molecules, we can see that spermidine impacts neuronal excitability, particularly ion channels, and is included in a number of processes in the mammalian nervous system. It has also been linked to better memory function in older people at risk for AD who take spermidine supplements. Spermidine may impair memory function in older people, although the precise methods by which it does are unclear.[8,9] L-arginine generated by arginine decarboxylase is decarboxylated to yield agmatine. The mammalian brain is predicted to use agmatine as a neuromodulator, but it has been reported that its functional importance and the mechanisms of Aβ-stimulated changes in agmatine metabolism remain unclear. This is because Aβ interacts with multiple receptors to participate in a variety of neuronal functions.[10,11] The plasticity of neurons is dependent on BDNF. It is well known that the cortex, hypothalamus and hippocampus are among the brain regions where it is significantly expressed. In the hippocampus, BDNF specifically helps support the long-term potentiation of glutamatergic neurons. As a result, it aids the long-term memory storage process and is known to promote dendritic cell development and remodeling in response to altered neuronal activity.[12] Coagulation factor V, unlike most other coagulation factors, is not enzymatically active but acts as a cofactor. It is known to shed light on the molecular mechanisms responsible for its physiological and pathological properties.[13] The vascular and neurological systems are supported by the intricate signaling molecule – VEGF. The AD neuropathological symptoms have been linked to impaired hippocampus volume and cognition, and have previously been documented to have a positive relationship with VEGF in cerebrospinal fluid (CSF).[14] A recently discovered axis of the brain's renin–angiotensin system is the Ang-(1–7) axis. Angiotensin 1–7 is a heptapeptide that is created from Ang II by ACE2 and acts favorably by attaching to the MAS1 receptor. According to reports, Ang-(1–7) impacts the plasma levels of AD patients, and an Ang-(1–7) deficiency may contribute to the pathogenesis of AD.[15,16] Neurokinin B is a 10-residue neuropeptide containing histidine. It has been reported that neurokinin peptides have different potentials in many neurodegenerative diseases, especially in AD, and that the neuroprotective agent neurokinin B can shield neurons against the toxicity of Aβ peptides. The mechanisms by which neurokinin B affects the inhibition of Aβ aggregation are still unknown.[17,18] Amyloid A is actively included in the pathological processes of rheumatoid arthritis, cancer, atherosclerosis, and AD by its collection. The apolipoprotein family includes the highly conserved protein amyloid A, which is mostly produced by the liver. Its role in the pathophysiology of AD is still debated.[19] In this study, BDNF has attracted the most attention due to its potential therapeutic value and possible role in the development of neurological and psychiatric disorders, such as protein synthesis, axonal growth, dendritic cell formation, and synaptic plasticity, which are critical for learning.[20] In the definition of BDNF-related metabolic processes, the determination and comparison of some parameters were important in the evaluation of AD levels.

Objectives

This research aims to elucidate the relationship between AD patients and various molecules (spermidine synthase, agmatinase, BDNF, coagulation fV, VEGF, Ang (1–7), neurokinin B, and amyloid A). It is also aimed to reconsider the role of BDNF.

Materials and methods

Study design

This research was conducted in line with the recommendations of the Declaration of Helsinki. The Siirt University Non-Interventional Clinical Research Ethics Committee approval was obtained before the study commencement (approval No. 2022/04.06 issued on May 30, 2022). A total of 80 people participated in this study. The study's patient group comprised 40 newly diagnosed volunteer patients with AD and a control group of 40 volunteers without AD or other neurological diseases. The diagnosis was made by neurologists working in the neurology outpatient clinics of the Şırnak State Hospital (Turkey). The Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-V) was used according to the criteria established

by the National Institute of Neurological and Communication Disorders and Stroke and the AD and Related Disorders Association (NINCDS-ADRDA).[21,22] For each patient to be involved in the study, the age range of 45–90 was chosen as the inclusion criterion. Those with neurological and/or psychiatric diseases other than AD, clinical depression, brain tumors, subdural hematomas, chronic alcoholism, cognitive impairment caused by heavy exercise, use of antioxidant supplements, and those who quit voluntarily were not included in the study. Informed consent was obtained from all individuals included in this study.

Sample collection

After an overnight fast, fasting venous blood samples were taken from the participants voluntarily for the study, after an average of 10 h of fasting from the arm veins using tubes without anticoagulant (SST Vacusera, 5 mL, 235305; Disera A.Ş, İzmir, Turkey) and tubes with anticoagulant (K3 EDTA, 2 mL, 70697; sodium-citrate 3.2%, 2.7 mL; Ayset, Adana, Turkey). The tubes were gently inverted several times. Blood samples in tubes without anticoagulant and samples with sodium citrate were centrifuged at 4°C for 10 min at 4000 rpm. Complete blood count (XN 1000; Sysmex Company, Kobe, Japan), biochemical (c8000; Abbott, Abbott Park, USA) and hormonal assays (Roche Cobas 6000 c601; Roche Diagnostics, Mannheim, Germany) were carried out at Şırnak State Hospital Medical Biochemistry Laboratory. To measure the plasma levels of other molecules, the obtained plasma samples were divided into portions, placed in Eppendorf tubes and labeled. Prior to analysis, Eppendorf tubes were stored at –80°C.

Measurement of plasma levels of molecules

The BDNF, neurokinin B, agmatinase, VEGF, spermidine synthase, Ang-(1–7), serum amyloid A, and coagulation fV levels were measured in the plasma samples using human enzyme-linked immunosorbent assay (ELISA) kits (catalog No. 201-12-1303, 201-12-8627, 201-12-) 3110, 201-12-0081, 201-12-4979, 201-12-2828, 201-12-1226, 201-12-6817; SunRed Biological Technology, Shanghai, China). Absorption was measured at 450 nm with ELISA microplate reader (Thermo Scientific Multiskan GO, SN: 1510-02723; Thermo Fisher Scientific, Waltham, USA) using an antibody-coated 96-well plate. Thermo Scientific Wellwash, SN:888-3023A (Thermo Fisher Scientific) was used as the automatic washer for plate washing. Intra-test and inter-assay coefficient variables (%CV) in all kits were below 10%. All ELISA analyses for this research were done in the laboratory of the Siirt University Science and Technology Application and Research Center.

Statistical analyses

IBM SPSS v. 21.0 (IBM Corp., Armonk, USA) was utilized for statistical analysis. Shapiro–Wilk and Kolmogorov–Smirnov tests and graphs were used to evaluate whether the data in all groups, including age, were normally distributed. According to Shapiro–Wilk and Kolmogorov–Smirnov tests, the data were not distributed normally. The normality results of the tables and graphs have been presented in the Supplementary material. The Mann–Whitney U test was employed to compare plasma median values between groups using non-normally distributed data. The scatterplots were inspected visually to check for monotonicity between the variables. Since there were monotonic relationships between the variables, Spearman's correlation analysis was employed to measure the strength of these relationships. Descriptive statistics were used for numerical variables, group median values, minimum and maximum values, and interquartile range (IQR) data. In addition, z-values and Mann–Whitney U and effect size values are presented in Table 1 and Table 2. A value of $p < 0.05$ was considered significant.

Results

A total of 80 people, 40 healthy controls (male/female ratio: 14/26) and 40 AD patients (male/female ratio: 15/25), participated in this study. The mean age of the patient group (79.88 ±7.57 years) was found to be higher than of the control group (76.43 ±10.75 years), but the difference between the groups was not statistically significant ($p = 0.225$; Table 1). When the levels of BDNF, VEGF, spermidine synthase, Ang-(1–7), serum amyloid A, and coagulation fV were examined between the groups, increases were seen in the group with AD (1.67 ±0.50 ng/mL, 1290.38 ±472.51 ng/L, 22.59 ±8.38 ng/mL, 216.50 ±83.69 ng/L, 5.71 ±2.06 µg/mL, and 39.11 ±19.21 ng/mL) compared to the control group (1.29 ±0.49 ng/mL, 1198.60 ±357.81 ng/L, 18.99 ± 6, 37 ng/mL, 176.19 ±47.31 ng/L, 5.32 ±1.89 µg/mL, and 31.94 ±7.26 ng/mL), $p = 0.033$ for BDNF, $p = 0.613$ for VEGF, $p = 0.073$ for spermidine synthase, $p = 0.056$ for Ang-(1–7), $p = 0.371$ for amyloid A, and $p = 0.485$ for coagulation fV, neurokinin B and agmatinase decreased in the group with

Table 1. Age compared between groups

Variable	Control (n = 40)				AD patients (n = 40)				Z-value	p-value
	IQR	min	max	median	IQR	min	max	median		
Age [years]	15.25	49	89	79	15	65	90	79	–1.214	0.225

The comparison was made using the Mann–Whitney U test; IQR – interquartile range; Min – minimum; Max – maximum; AD – Alzheimer's disease.

Table 2. Plasma levels of molecules compared between groups

Variables	Control (n = 40)				AD patients (n = 40)				Z-value	Effect size	p-value
	IQR	min	max	median	IQR	min	max	median			
BDNF [ng/mL]	0.71	0.01	2.30	1.24	1.17	0.69	3.48	1.49	–2.132	0.058	0.033*
Neurokinin B [ng/L]	102	93.08	398.66	257.46	142	121.21	445.67	238.85	–0.427	0.002	0.669
Agmatinase [ng/mL]	4.86	6.19	22.11	11.83	6.42	4.58	23.26	10.76	–0.846	0.009	0.397
VEGF [ng/L]	593.19	245.11	1870.67	1158.39	692.79	475.72	2565.56	1126.30	–0.505	0.003	0.613
Spermidine synthase [ng/mL]	9.52	3.94	34.51	17.63	13.72	10.24	45.92	20.02	–1.791	0.041	0.073
Angiotensin 1–7 [ng/L]	62.29	75.85	282.89	173.77	126.18	97.48	443.16	191.84	–1.911	0.046	0.056
Serum amyloid A [µg/mL]	2.74	0.60	9.71	5.11	3.36	2.34	11.30	5.78	–0.894	0.010	0.371
Coagulation factor V [ng/mL]	11.23	20.00	52.18	31.30	29.32	11.01	77.62	31.51	–0.698	0.006	0.485

The comparison was made using the Mann–Whitney U test; IQR – interquartile range; Min – minimum; Max – maximum; BDNF – brain-derived neurotrophic factor; VEGF – vascular endothelial growth factor; * statistically significant group; AD – Alzheimer's disease.

Table 3. Correlation analysis results of the control group

Variables	Neurokinin B [ng/L]	Agmatinase [ng/mL]	VEGF [ng/L]	Spermidine synthase [ng/mL]	Angiotensin 1–7 [ng/L]	Serum amyloid A [µg/mL]	Coagulation factor V [ng/mL]
BDNF (ng/mL)	r = 0.651** p < 0.001	r = 0.528** p < 0.001	r = 0.692** p < 0.001	r = 0.719** p < 0.001	r = 0.536** p < 0.001	r = 0.794** p < 0.001	r = 0.493** p = 0.001
Neurokinin B [ng/L]	–	r = 0.555** p < 0.001	r = 0.682** p < 0.001	r = 0.760** p < 0.001	r = 0.567** p < 0.001	r = 0.740** p < 0.001	r = 0.665** p < 0.001
Agmatinase [ng/mL]	–	–	r = 0.454** p = 0.003	r = 0.525** p < 0.001	r = 0.307 p = 0.054	r = 0.484** p = 0.002	r = 0.601** p < 0.001
VEGF [ng/L]	–	–	–	r = 0.746** p < 0.001	r = 0.611** p < 0.001	r = 0.809** p < 0.001	r = 0.567** p < 0.001
Spermidine synthase [ng/mL]	–	–	–	–	r = 0.617** p < 0.001	r = 0.742** p < 0.001	r = 0.683** p < 0.001
Angiotensin 1–7 [ng/L]	–	–	–	–	–	r = 0.587** p < 0.001	r = 0.435** p = 0.005
Serum amyloid A [µg/mL]	–	–	–	–	–	–	r = 0.548** p < 0.001

**Correlation is significant at the 0.001 level (two-tailed); r – correlation coefficient; BDNF – brain-derived neurotrophic factor; VEGF – vascular endothelial growth factor.

AD compared with the control group (267.85 ±82.45 ng/L, 11.86 ±4.24 ng/mL), respectively (270.03 ±77.89 ng/L, 12.57 ±3.59) (neurokinin B, p = 0.669, for agmatinase p = 0.397). The increase in BDNF levels in the patient group was statistically significant (p = 0.033 for BDNF; Table 2). The control evaluation of the correlation is given in Table 3 and the patient evaluation is presented in Table 4. Interestingly, the parameters in the patient group showed a positive and significant relationship with each other (p < 0.001).

Discussion

Health expenditures in the world and new medical treatments prolong life expectancy in old age and increase the share of the elderly population in the total population. The world's demographic is changing to include a larger elderly population. Alzheimer's disease is a chronic disease seen in advanced age, affecting millions of people worldwide, and is the most prevalent reason for primary neurodegenerative dementia. It progresses in stages in many people who have not yet developed advanced dementia, and can reach a level that affects the daily life of the patient, with memory difficulties during the middle stage.[23,24] There is a need for strategies to combat this devastating disease, whose prevalence rises with age. Perhaps the most significant of these strategies is to detect AD as early as possible. The depicted pathological properties of AD are amyloid-β (Aβ) and tau pathology.[25] It is a neurodegenerative, pathogenic and chronic disease of enzymes (spermidine synthase and agmatinase), factor structures (BDNF, coagulation fV, VEGF), peptide structures (neurokinin B, amyloid A), and hormone structure heptapeptide (Ang-(1–7)) proteins. We examined whether they could be effective biomarkers for the early diagnosis of AD. Interestingly, the parameters in the patient group in our study showed a positive and significant relationship with each other (p < 0.001, Table 4). The AD patient's brain tissue develops Aβ oligomers, which have a direct effect on the disease's development. One of the primary causes of neurotoxicity, Aβ oligomers, are known to produce intracellular Ca^{2+} excess and neuronal death, both of which can be avoided

Table 4. Correlation analysis results of the patient group

Variables	Neurokinin B [ng/L]	Agmatinase [ng/mL]	VEGF [ng/L]	Spermidine synthase [ng/mL]	Angiotensin 1–7 [ng/L]	Serum amyloid A [µg/mL]	Coagulation factor V [ng/mL]
BDNF [ng/mL]	r = 0.749** p < 0.001	r = 0.800** p < 0.001	r = 0.717** p < 0.001	r = 0.771** p < 0.001	r = 0.720** p < 0.001	r = 0.683** p < 0.001	r = 0.622** p < 0.001
Neurokinin B [ng/L]	–	r = 0.788** p < 0.001	r = 0.840** p < 0.001	r = 0.778** p < 0.001	r = 0.645** p < 0.001	r = 0.678** p < 0.001	r = 0.589** p < 0.001
Agmatinase [ng/mL]	–	–	r = 0.830** p < 0.001	r = 0.838** p < 0.001	r = 0.643** p < 0.001	r = 0.746** p < 0.001	r = 0.610** p < 0.001
VEGF [ng/L]	–	–	–	r = 0.793** p < 0.001	r = 0.714** p < 0.001	r = 0.732** p < 0.001	r = 0.630** p < 0.001
Spermidine synthase [ng/mL]	–	–	–	–	r = 0.721** p < 0.001	r = 0.812** p < 0.001	r = 0.665** p < 0.001
Angiotensin 1–7 [ng/L]	–	–	–	–	–	r = 0.622** p < 0.001	r = 0.539** p < 0.001
Serum amyloid A [µg/mL]	–	–	–	–	–	–	r = 0.769** p < 0.001

**Correlation is significant at the 0.001 level (two-tailed); r – correlation coefficient; BDNF – brain-derived neurotrophic factor; VEGF – vascular endothelial growth factor.

because of the action of N-methyl-D-aspartate (NMDA) receptor antagonists.[26] According to reports, Aβ oligomers rapidly activate NMDA receptors, and medications that inhibit the action of these receptors can stop Aβ from damaging neurons in AD.[27] Nitric oxide synthase (NOS), which helps to produce NO, is inhibited by polyamines such as agmatine and spermidine.[26] It has inhibitory effects on glutamatergic NMDA receptors in rat hippocampal neurons.[27] Nevertheless, it is uncertain where exactly NMDA receptor antagonist drugs interact.[28] From this perspective, it can be deduced that polyamines such as agmatine and spermidine, which are NMDA receptor antagonists, contribute to the pathogenesis of AD. According to our knowledge, the effect of polyamines such as agmatine and spermidine on NMDA receptor blockade in AD, which accumulates Aβ, has not yet been clarified in this mechanism in which agmatine synthase and spermidine synthase enzymes are directly involved. In our study, agmatinase enzyme levels were discovered to decrease in AD patients compared to controls. In AD, patients' spermidine synthase enzyme levels were higher than in the control group. A statistically significant decrease in agmatinase enzyme levels (p = 0.397) and a rise in spermidine synthase enzyme levels (p = 0.073) was observed; considering the short half-life in the metabolic pathway of agmatine degraded from L-arginine, the relationship between agmatine over-release or high agmatine concentrations and AD is related to the brain, CSF or AD. Agmatine levels in blood can be interpreted as affecting NMDA receptor blockade. The increase in spermidine synthase enzyme due to the spermidine step released from agmatine and ornithine may also be the source of NMDA receptor blockade. All these interpretations may explain the source of NMDA receptor blockade in the pathogenesis of AD by accumulated Aβ oligomers. Agmatine reduction, which was also observed in our AD study, can have negative consequences, including depression-like symptoms, reduced cognitive abilities and memory loss. Agmatine's multi-receptor affinity and various physiological functions and its antagonism of NMDA receptors are significant in elucidating the pathogenesis of AD. Polyamine pathway and imidazoline receptor agents restoring BDNF in β-amyloid-induced AD provide insufficient information on how they affect BDNF levels in the hippocampus. The BDNF expression, which plays a significant role in neuronal development besides the pathogenesis of AD, is a matter of considerable interest in the brains of patients with AD. In our study, BDNF levels in AD patients were detected to be higher than in controls (Table 2). The BDNF, which exhibits a statistically significant rise in blood levels (p = 0.033), is crucial to understand the pathophysiology of AD. According to one study, agmatine's antidepressant-like effects in AD are linked to decreased levels of pro-inflammatory cytokines (interleukin(IL)-6 and tumor necrosis factor alpha (TNF-α))) and elevated levels of BDNF in the hippocampus.[29] Studying the pathogenicity suggests that the VEGF system controls synapse function mechanisms which toxic soluble Aβ oligomers disrupt in the early stages of AD. Growing evidence suggests that Aβ targets excitatory synapses through a particular dendritic area and binds to a subset of neurons.[30] Because of the putative neuroprotective function of VEGF in AD, higher VEGF levels have been linked to reduced cognitive loss in studies employing AD biomarkers.[31] Compared to the control group, a drop was seen in our AD group, though this decrease was not statistically significant (p = 0.613). Abnormal levels of VEGF have been associated with Aβ deposition in AD. One of the most studied receptors among neurokinin receptors is the neurokinin 1 receptor. We also included the neurokinin B parameter from the neuropeptide family, which we think provides protection against the neurotoxic processes of AD in multiple ways. In our study, a decrease

was observed in neurokinin B levels in the AD group compared to the control group, but this decrease was not statistically significant (p = 0.669). We observed a slight, but not significant, decrease in the activity of neuropeptides and thus an increase in the metabolic half-life of the neurokinin 1 receptor substance. Neurokinin 1 receptor antagonists reduce the level of neurokinin 1 receptor substance in the cortex, hippocampus and striatum in AD and animal models where neuroinflammation-mediated changes in neural circuits were significant.[32,33]

One potential mechanism underpinning the pathogenesis of AD is potassium channel malfunction. The neuroprotective effects brought about by the neurokinin 1 receptor are mediated by a few voltage-gated potassium channels. Administration of neurokinin 1 receptors inhibits Aβ-induced disturbance of cognitive functions by inhibiting Aβ-induced upregulation of potassium channel subunits and Aβ-type K^+ currents.[34,35] Serum amyloid A, the precursor protein synthesized in the liver, whose physiological role has not been fully elucidated, is an acute phase reactant whose blood level increases in response to various diseases. Inflammation in the brain in AD is demonstrated by the proteins involved in the complement cascade and the presence of α-1-antichymotrypsin (ACT). However, although local inflammation is strongly involved in the pathogenesis of AD, studies that mention the presence of amyloid-A in the AD brain have not been found. In our study, there was an increase in serum amyloid-A levels in the AD group; however, it was not statistically significant (p = 0.371). Large-scale studies are needed to explain this mechanism. A potential biomarker of AD is the Ang-(1–7) heptapeptide. Angiotensin 1–7 is said to be beneficial for facilitating neuronal functioning and reducing apoptosis in memory-related brain structures in AD patients.[36] In our study, Ang-(1–7) levels increased in the AD group compared to the control group, but this increase was not statistically significant (p = 0.056). Therefore, evaluating these effects may be a promising strategy for the discovery of therapeutics or biomarkers for AD, as upregulation of these pathways is expected to have a significant effect on AD pathogenesis.[37]

In AD, BDNF levels tend to decrease in regions where memory and cognitive functions are regulated, especially in the hippocampus and cortex of nerve cells. This can lead to less exposure of nerve cells to BDNF, and thus a decrease in supporting factors important for cell survival, growth and communication. Decreased BDNF levels can contribute to nerve cell damage and death. Therefore, increasing or maintaining BDNF levels may be an important target for the treatment and prevention of AD. Research on this topic shows that strategies such as BDNF-boosting drugs or lifestyle changes can help reduce the effects of AD by increasing the survival and function of nerve cells. However, research in this area is still ongoing, and the exact mechanism of the BDNF effect on AD and its therapeutic potential need to be better understood. In our study, we found a significant increase in BDNF profile. However, AD, which is a neurological disease, has been associated with low levels of BDNF. A systematic review and meta-analysis concluded that in 15 analyzed studies, 2067 AD patients had significantly lower serum BDNF levels than healthy controls.[38] While discussing the effects of all parameters that could be biomarkers in the AD pathophysiology, we noticed the increased levels of BDNF. The role of BDNF in relation to AD, which has not yet been fully elucidated, is important because of its effects on the pathophysiology of the disease and neuroplasticity. Due to the small number of study patients we cannot draw any definitive conclusions, but a larger-scale study may support our hypothesis in the future.

Limitations

The limitation of this study is the small number of patients. Different results could be obtained if the study was conducted with a larger number of patients.

Conclusions

We concluded that BDNF may be increased as a result of the effect of agmatine reduction on β-amyloid-induced AD in neuroinflammation by activating imidazoline receptors. Exactly how BDNF is effective in AD is not yet clear and research is ongoing. It is observed that the studies conducted in this area show promising results – the regulation of BDNF levels or drugs that interact with BDNF may have the potential to slow the progress of the disease. However, it is important to remember that AD is a complex condition, and a single molecule is not sufficient to cure the disease. Further studies and clinical trials can help develop potential new methods and drugs for the treatment of AD. Large-scale studies are needed to elucidate the mechanisms of this disease. While BDNF levels are observed to decrease in AD patients, we saw an interesting BDNF increase in our study. We think that the reason for this may be the high level of protein-containing nutrition in the region and the use of plant-based appetizers with meals that may have affected BDNF levels. Finally, we believe that experiments using AD models should use these parameters to clarify their function in disease identification and management.

Supplementary data

The Supplementary materials are available at https://doi.org/10.5281/zenodo.8406302. The package comprises of the following files:

Supplementary Table 1. Normality test results for age.
Supplementary Table 2. Parameters normality test results.
Supplementary Table 3. Control grubuna ait scatterplots.
Supplementary Table 4. patient grubuna ait scatterplots.

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