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Research Article,

The Role of Galanin, Alarin, Irisin, PGC1-A and BDNF in the Pathophysiology of Alzheimer's disease

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Abstract:
The roles of novel peptides such as peroxisome proliferator-activated receptor gamma coactivator 1- alpha (PGC1-α), irisin, brain-derived neurotrophic factor (BDNF), galanin and alarin in Alzheimer's disease (AD) are not fully known. It was aimed to plasma levels of the novel peptides that may affect the pathophysiology of AD were examined. This study was conducted as a cross-sectional. The study consisted of two groups, including 45 newly diagnosed individuals with AD and 45 healthy individuals. The peptide levels in plasma samples collected from the groups were measured by the ELISA method. The mean plasma peptide levels and age differences, between the groups, and the correlations between them were analyzed by the statistically. The means ages of both groups were over 65 years old. When plasma PGC1-α, irisin, BDNF, galanin, and alarin levels between the groups were examined, decreases were found in the group with AD (3.56±0.79ng/mL, 16.33±4.07ng/mL, 3.36±1.47ng/mL, 13.93±4.24ng/L, 31.99±11.89pg/mL, respectively) compared to the control group (4.23±1.31ng/mL, 22.19±9.61ng/mL, 4.58±2.10ng/mL, 14.4±9.01ng/L, 54.93±15.80pg/mL, respectively). In the negative correlations observed between age and plasma peptide levels. Significant positive correlations were observed between plasma PGC1-α levels and irisin, alarin, and BDNF, and the significant positive correlations were also observed between plasma BDNF levels and irisin and alarin. As far as we know, the study is the first report in which the peptides mentioned in AD were examined together. We consider that more detailed studies are needed to shed light on the roles and mechanisms of these peptides in AD.

Keywords: Alzheimer's disease; Galanin; Alarin; Irisin; PGC1-α; BDNF.

Introduction:

Alzheimer's disease (AD) is a chronic, progressive neurodegenerative disease characterized by insidious cognitive impairment. Alzheimer's disease takes place among the most common causes of dementia, and it is known that approximately 34 million people in the world suffer from this diseas [1,2]. The most significant risk factor in this disease is age, and in the studies, it was reported that AD was more common in individuals over 60 years of age [3]. The accumulation of amyloid-β (Aβ) and neurofibrillary tangles of hyperphosphorylated tau constitute the basic pathology of AD [4]. Moreover, microglial activation, neuroinflammation, oxidative stress, metabolic energy deficiency, and related neuronal apoptosis are believed to be closely related to the pathogenesis of AD [5]. The consequences of the said pathological processes involve neurodegeneration along with synaptic and neuronal loss [6].

It has been recently reported that synaptic dysfunction and degeneration are more strongly associated with cognitive impairment compared to plaques or knots. Therefore, synaptic biomarkers may serve as promising tools for detecting synaptic and mitochondrial dysfunction in the progression of AD [7]. In this sense, many new peptides that may have a biomarker value in relation to the

diagnosis and treatment of AD have been investigated [8].

The mitochondria, which are the main source of energy in the cells, are required for the excitability and survival of neurons. Mitochondrial biogenesis increases the energy production capacity of the cells and enables neurons to form and maintain functional synapses [9]. Peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC1-α) is a transcriptional coactivator defined as the main regulator of mitochondrial biogenesis and function, such as oxidative phosphorylation and detoxification of reactive oxygen species (ROS) [10]. It was initially reported to act on brown adipose tissue, and then it was also reported to play important roles in the brain [11]. PGC1-α is expressed at high levels in mitochondria-rich cells with high energy demands, such as cardiac myocytes, skeletal muscle cells, and neurons. In various studies, PGC1-α has been demonstrated to play a role in regulating the dendritic morphology and synaptic connection of neuronal circuits in the developing brain and the protection of synapses in the adult hippocampus [9]. The expression of PGC1-α, which increases under various effects such as physical activity in the body, results in the production of fibronectin type III domain-containing protein 5 (FNDC5). The proteolytic cleavage of this protein leads to the production of irisin [12]. Irisin was first described by Boström et al. in 2012 as an exercise-induced myokine that regulates peripheral energy metabolism. It was reported that irisin reprogrammed the adipose tissue metabolism, supported adipocyte browning and thermogenesis, and promoted bone strengthening [13]. Although it is mostly expressed in skeletal muscle, it is also expressed in the brain [5]. Irisin regulates hippocampal neurogenesis, changes the morphology of dendrites, and increases synapses and neural proliferation [12]. Furthermore, it largely prevents the brain infarction volume and reduces neuroinflammation and post-ischemia oxidative stres [5]. It stimulates the secretion of various factors in tissues such as muscle, brain, and adipose. Brain-derived neurotrophic factor (BDNF) represents one of the most important mediators released by irisin in the brain [12].

Brain-derived neurotrophic factor is essential for neuronal plasticity. It is known to be expressed at high levels in brain regions such as the hippocampus, hypothalamus, and cortex. Specifically, BDNF facilitates long-term potentiation (LTP - synaptic analog of learning and memory) by supporting glutamatergic neurons in the hippocampus. Thus, it supports long-term memory storage and increases the growth and reorganization of dendritic cells in response to altered neuronal activity [14]. Galanin (GAL), a neuropeptide, was discovered in the porcine intestine in 1983. Galanin and galanin-like peptide (alarin/GALP) are the members of the galanin family. Galanin represents a 29-amino-acid-long peptide widely distributed in the brains of mammals, including rodents and humans (it contains 30 amino acid residues in humans). It regulates a large number of physiological events in the mammalian nervous system, including cognition, mood, neuroendocrine regulation, nociception, energy, and osmotic homeostasis. Moreover, a lot of pathological conditions are related to the upregulation of galanin [15]. Alarin, which is another member of the galanin family, was first discovered in the porcine hypothalamus in 1999 [16]. Although the cells expressing alarin are limited, they are primarily found in the arcuate nucleus of the hypothalamus and the posterior pituitary [17]. There is evidence that associates alarin with food intake, energy metabolism, the regulation of reproduction, and fluid intake. Moreover, recent reports have suggested that it may also play a role in conditions such as epilepsy, AD, and diabetes [18].

The current research aimed to determine the blood levels of various peptide molecules (PGC1-α, irisin, BDNF, GAL, alarin) that may be related to AD, to reveal the correlation of these molecules with each other and to shed light on the underlying molecular pathogenesis of the disease.

Subject and Methods:

Population and Study Design

This research was carried out following the Declaration of Helsinki. Prior to the study, necessary permissions were obtained from the Local Ethics Committee of Kafkas University, Faculty of Medicine (Date: 27.02.2019 No: 2019-02-77). The study was designed by a neurologist at Kafkas University, Health Research and Application Hospital, Neurology Department in a way that 45 newly diagnosed voluntary individuals with AD would constitute the patient group of the study and 45 voluntary individuals without Alzheimer's or any neurodegenerative disease would constitute the control group of the study according to the "Diagnostic and statistical manual of mental disorders (DSM-V), National Institute of

Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA)" [19,20] criteria, and the study was conducted cross-sectionally. Concerning the inclusion criteria of all patients to be included in the study, the age range was determined to be 45-90 years.

For the patient group, patients with neurological diseases and/or psychiatric disorders other than Alzheimer's disease, patients with the clinical level of depression, patients with a brain tumor, subdural hematoma and cognitive dysfunction due to chronic alcoholism, heavy exercise and fasting exceeding 24 hours, the use of antioxidant preparations, and individuals who willingly wanted to leave the study constituted the exclusion criteria of the study. The exclusion criteria for the control group were determined as the presence of dementia or another neurodegenerative disease, heavy exercise and fasting exceeding 24 hours, alcohol and substance abuse, the use of antioxidant preparations, and individuals' willingness to leave the study.

Subject Recruitment and Sample Collection

In the study, for biochemical examinations on a voluntary basis (accepting the Informed Consent Form), 5 ml blood samples were collected from individuals with vascular access from the brachial vein into biochemistry tubes (BD Vacutainer® tubes, BD-Plymouth. PL6 7L6, UK) with ethylene-diamine-tetra-acetic acid (EDTA). Tubes were gently shaken several times. To eliminate the activity of proteinases, the collected blood samples were transferred to centrifuge tubes pre-added with aprotinin (0.6 TIU/ml of blood) (Phoenix Pharmaceuticals, Belmont, CA, USA) and gently shaken again. The collected blood samples were centrifuged for 1,600 x g for 15 minutes at 4°C without wasting time in the Biochemistry Laboratory of Kafkas University Health Research and Application Hospital to obtain plasma. This process continued until the plasma samples became clear. The plasma samples obtained were portioned in Eppendorf tubes and kept at -80 °C until the analysis was conducted.

Measurement of Peptide Levels in Plasma

PGC1-α, irisin, BDNF, GAL, and alarin levels were studied in plasma samples using human ELISA kits (catalog no; YLA1036HU, YLA1361HU, YLA0580HU, YLA1774HU and YLA4151HU; lot no; YLAZXV0475, YLA64WDV0, YL018SWEJV, YLXBNYRR41 and YLV748RF3S1, respectively, Biotech Co. Ltd., Shanghai, China) as specified in the kit procedures. The absorbances were read spectrophotometrically at a wavelength of 450 nm in the ELX800 ELISA Reader. Bio-Tek ELX50 (BioTek Instruments, USA) was utilized as an automatic washer in plate washing. The results were reported as ng/mL for PGC1-α, ng/mL for irisin, ng/mL for BDNF, ng/L for GAL, and pg/mL for alarin. The measuring ranges of the kits were 0.05 - 30 ng/mL, 0.2 - 60 ng/mL, 0.05 - 10 ng/mL, 0.5 - 100 ng/L, 3 - 380 pg/mL, respectively. The minimum measurable levels of the kits were 0.021 ng/mL, 0.095 ng/mL, 0.01 ng/mL, 0.26 ng/L, and 1.03 pg/mL.

The intra-assay and inter-assay coefficient variables (CV%) of all kits were < 10%. All ELISA analyses in this study were performed in Kafkas University, Faculty of Medicine, Medical Biochemistry R&D laboratory.

Statistical Analysis:

All data acquired from the study were analyzed by the Statistical Package for Social Science (SPSS®) Version 22.0 (SPSS Inc, Chicago, USA) for Windows® to reveal the differences in the disease and control groups. Kolmogorov-Smirnov and Shapiro-Wilk tests were conducted for the purpose of determining the distribution of continuous data in terms of normality. The Mann-Whitney U test was applied to nonparametric data to compare the mean plasma peptide levels between the groups. Student's t-test was applied to parametric data to reveal the mean differences of ages between the groups. Spearman's correlation analysis was carried out for the purpose of investigating the correlations between data. For numerical variables, the descriptive statistics were presented as group mean ± standard deviation (Mean±S.D). $p<0.05$ was used to express the lowest level of significance between the group means.

Results:

This study was conducted with a total of 90 individuals consisting of 45 healthy individuals (male/female 15/30) and 45 individuals with AD (male/female 19/26). In our research, the mean age of the patient group (70.97±6.05 years) was found to be higher in comparison with the mean age of the control group (68.91±6.82 years), but the difference between groups was found to be statistically insignificant (p=0.065) (Table 1).

When plasma PGC1-α, irisin, BDNF, GAL, and alarin levels between the groups were examined, decreases were found in the group with AD (3.56±0.79 ng/mL, 16.33±4.07 ng/mL, 3.36±1.47

ng/mL, 13.93±4.24 ng/L, 31.99±11.89 pg/mL, respectively) compared to the control group (4.23±1.31 ng/mL, 22.19±9.61 ng/mL, 4.58±2.10 ng/mL, 14.4±9.01 ng/L, 54.93±15.80 pg/mL, respectively) (p=0.023 for PGC1-α, p=0.000 for irisin, p=0.000 for BDNF, p=0.000 for alarin). The decreases in plasma GAL levels in the patient group were found to be statistically insignificant (p=0.260 for GAL) (Table 1).

Table 1. Differences in Average Age and Plasma Peptide Levels between the Groups

	Control (n=45)	Alzheimer's Patient (n=45)	*P*
	Mean±SD	**Mean±SD**	
Age (year)	68.91±6.82	70.97±6.05	0.065
PGC1-α (ng/mL)	4.23±1.31	3.56±0.79	0.023*
Irisin (ng/mL)	22.19±9.61	16.33±4.07	0.000#
BDNF (ng/mL)	4.58±2.10	3.36±1.47	0.000#
GAL (ng/L)	14.4±9.01	13.93±4.24	0.260
Alarin (GALP) (pg/mL)	54.93±15.80	31.99±11.89	0.000#

The mean age differences between the two groups were made according to Student's t-test, *p-value < 0.05 in comparison with the control group (according to the Mann-Whitney U test); #p-value < 0.001 in comparison with the control group (according to the Mann-Whitney U test).

P: indicates the significance of differences in age and peptide levels between the groups according to Student's t-test and Mann-Whitney U test, SD: refers to Standard deviation, BDNF: Brain-derived neurotrophic factor, GAL: Galanin, GALP: Galanin-like peptide (Alarin), PGC1-α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha.

According to Spearman's correlation analysis conducted to reveal the correlation between the selected peptides, significant positive correlations were observed between plasma PGC1-α levels and irisin (r:0.404, p=0.000), alarin (r:0.283, p=0.000), and BDNF (r:0.657, p=0.000). Significant positive correlations with plasma BDNF levels were observed not only in PGC1-α levels but also between irisin (r:0.502, p=0.000) and alarin (r:0.451, p=0.000) levels. Furthermore, in the negative correlations observed between age and plasma peptide levels, a significant correlations were revealed between age and plasma irisin (r:-0.222, p=0.038) and PGC1-α levels (r:-0.162, p=0.049) (Table 2).

Table 2. Correlations between the Parameters Examined

		Age	BDNF	Irisin	Alarin (GALP)	GAL	PGC1-α
Age	Spearman's Correlation	1	-.152	-.222*	-.105	-.084	-.162*
	Sig. (2-tailed)		.061	.038	.096	.118	.049
BDNF	Spearman's Correlation		1	.502#	.451#	.162	.657#
	Sig. (2-tailed)			.000	.000	.190	.000
Irisin	Spearman's Correlation			1	.190	.201	.404#
	Sig. (2-tailed)				.200	.203	.000
Alarin(GALP)	Spearman's Correlation				1	.074	.283#
	Sig. (2-tailed)					.094	.000
GAL	Spearman's Correlation					1	.199
	Sig. (2-tailed)						.147
PGC1-α	Spearman's Correlation						1
	Sig. (2-tailed)						

According to Spearman's correlation analysis: *Correlation is significant at the 0.05 level (2-tailed); #Correlation is significant at the 0.01 level(2-tailed).

BDNF: Brain-derived neurotrophic factor, GAL: Galanin, GALP: Galanin-like peptide (Alarin), PGC1-α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha.

Discussion:

Alzheimer's disease represents a neurodegenerative disease that is considered to be the most common cause of dementia worldwide [1]. While the etiology of this disease remains uncertain, age is considered to be the most significant risk factor, and it is reported that AD is more common in individuals over 60 years of age [3,21]. In our study, it was determined that the mean age of individuals diagnosed with AD was higher in comparison with the control group, but the difference between them was statistically insignificant.

This findings show that the ages of the two groups that make up our study are close to each other and homogeneously distributed. The mean age of individuals with AD was consistent with the literature [3,22]. It is known that oxidative stress increases in different pathophysiological conditions, including aging, cancer, age-related metabolic disorders, and neurodegenerative diseases. The excessive production of ROS, which leads to oxidative stress, causes mitochondrial dysfunction and reduced mitochondrial biogenesis by damaging mitochondrial proteins/enzymes, membranes and deoxyribonucleic acid [23], which is accused of being an important pathology of AD [24]. Furthermore, various studies indicate that PGC1-α plays active roles in regulating mitochondrial biogenesis [10]. For example, it was reported that the overexpression of PGC1-α stimulated dendritic cell number and molecular differentiation of synapses by stimulating mitochondrial biogenesis and that the processes of spinogenesis, synaptogenesis, and neurogenesis were inhibited as a result of the inhibition of PGC1-α activity, and thus, neuron degeneration was triggered [9]. Furthermore, it was also reported that PGC1-α levels might be downregulated as a result of neuron inflammation associated with these pathologies [10,25]. In another study, it was demonstrated that telomere dysfunction, which triggers aging and cell apoptosis, supressed PGC1-α network [26]. In the research carried out by Qin et al., it was reported that the decreased expression of PGC1-α in AD might be a consequence of Aβ neuropathology, and it was attempted to reveal the correlation between PGC1-α and various pathologies [27]. In our study, plasma PGC1-α levels were significantly lower in individuals with Alzheimer's disease compared to the control group (Table 1). Also, a significant negative correlation was found between plasma PGC1-α levels and aging (Table 2). When these results are evaluated with the mechanisms attributed above, they suggest that PGC1-α may be depleted to suppress increased ROS levels as a result of impaired biogenesis, dysfunction, and cellular damage in neuronal cells associated with aging in Alzheimer's (Figure 1).

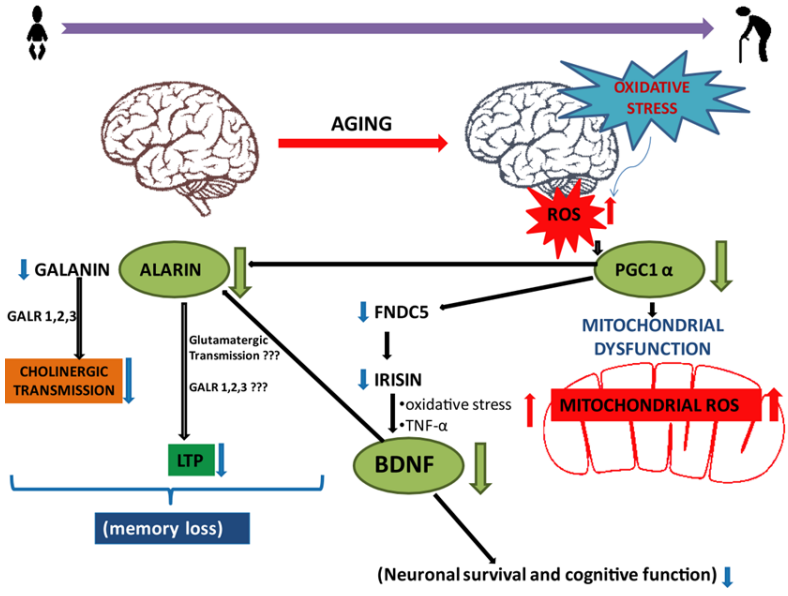

Figure1. Peptides-related potential pathways in the pathogenesis of Alzheimer's disease

Since energy is needed during neuronal development in a healthy brain, peroxisome proliferator-activated receptor gamma coactivator 1- alpha (PGC1-α) increases and this triggers the formation of irisin. It promotes the release of irisin, many neutrophic factors. The most important of these is brain-derived neurotrophic factor (BDNF). The increase in reactive oxygen species (ROS) and mitochondrial dysfunction associated with aging in Alzheimer's may be due to a decrease in PGC1-α while causing a decrease in PGC1-α. PGC1-α decreases due to these conditions and decreases the synthesis of irisin by reducing proteolytic cleavage via fibronectin type III domain containing 5 (FNDC5). Decreased irisin decreases BDNF release. Low BDNF levels cause declines in neuronal survival and cognitive functions. Associated with the reduction of PGC1-α and BDNF, alarin levels may decrease independently of galanin, or these decreases may indicate that alarin may cause memory loss without affecting the same receptors as galanin.

Irisin is described as one of the hormones that have protective effects on central nervous system (CNS) neurons obtained by the proteolytic cleavage of FNDC5 [12]. Irisin synthesis may contribute to the reduction of AD risks by increasing hippocampal proliferation through the signal transducer and activator of transcription 3 (STAT3) signal. It triggers the expression of BDNF, which is known to take a critical part in synaptic function and neuronal survival (Figure 1) [5]. It inhibits neuronal damage that is caused by oxidative stress by the activation of the protein kinase B (Akt) / extracellular signal-regulated kinases 1 and 2 (ERK1 / 2) signal and protects neurons by decreasing the secretion of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α). Furthermore, under ischemic conditions, ROS-the NOD-like receptor pyrin 3 (NLRP3) suppresses inflammatory signaling and ensures the survival of neurons [28]. In the research performed by Lourenco et al., a reduction in irisin levels in the cerebrospinal fluid (CSF) was reported in individuals with AD in comparison with controls, and it was reported that the cause of it could be the accumulation of Aβ [29]. In our study, it was determined that plasma irisin levels were significantly lower in individuals with AD in comparison with the control group (Table 1) and that there was a significant positive correlation between plasma irisin levels and PGC1-α levels (Table 2). While these data indicate that the conversion of FNDC5 to irisin decreased due to the decrease in PGC1-α, they also answer why irisin levels may have decreased in the group with AD (Figure 1).

Advanced age, which is an important risk factor in the pathology of Alzheimer's disease, leads to the shortening of telomeres that play a role in the protection of chromosomes. It was confirmed that telomere shortening played a causal role in neurodegenerative diseases due to aging [5]. In the research carried out by Rana et al., in which the length of telomeres was used as an indicator of aging, it was reported that with increasing age, the length of telomeres decreased and plasma irisin levels decreased. Furthermore, in the same study, it was emphasized that irisin could act as an anti-aging hormone [30]. In our study, significant negative correlations were found between age and plasma irisin and PGC1-α levels (Table 2). These data also suggest another mechanism that explains the low levels of irisin and PGC1-α as a result of increased DNA damage and telomerase activity that increases with aging in individuals with AD.

Brain-derived neurotrophic factor (BDNF) is known to play critical roles in the formation of neuronal circuits by promoting neuronal survival, neurite growth and synaptogenesis (Figure 1). It was reported that BDNF showed these effects by inducing anti-apoptotic Bcl-2 family members and the expression of caspase inhibitors and by inhibiting pro-apoptotic proteins, e.g. Bax and Bad [31]. Furthermore, BDNF increases the repair of damaged DNA in neurons by providing the upregulation of antioxidant enzymes and suppresses the neuron's cytotoxic response and learning deficits against Aβ toxicity in AD [28,31]. Besides these mechanisms, when various studies evaluating plasma BDNF levels in AD were examined, it was found that the results in the literature were conflicting [32]. For example, in a study performed by Hwang et al., it was reported that plasma BDNF levels were significantly lower in individuals with AD than healthy controls. The researchers argued that low plasma BDNF levels with AD might be associated with widespread brain amyloidosis [33]. In another recent study carried out by Balietti et al., BDNF levels in plasma were higher in the group with AD than controls, in contrast to the previous study. The researchers predicted that plasma BDNF levels might have increased as a trophic stimulation attempt to compensate for deficits caused by Aβ accumulation or to compensate for neuronal loss in

AD [32]. In our study, it was determined that plasma BDNF levels were significantly lower in individuals with AD than in the control group (Table 1). These data are parallel with the results of the first study attributed above. However, they are in contrast with the results of the second study. It is considered that this difference may be caused by the difference in the diagnostic criteria and stages of the disease in the formation of the Alzheimer's patient group in the studies. Furthermore, a probable explanation of the inconsistency in the literature is the lack of AD cohort overlap. Our suggestion that the changes in peripheral BDNF concentration may be related to the stage of AD could not be investigated extensively since our sample size was not very large, which is a limitation of our study. In addition to these, we predicted that BDNF might be depleted while attempting to compensate for the Aβ accumulation associated with the basic pathology of AD. Furthermore, the fact that BDNF levels may have decreased due to decreased PGC1-α and irisin levels in AD was another prediction of us. This prediction was supported by significant positive correlations we found between plasma BDNF and PGC1-α and irisin levels in the present study (Table 2) (Figure 1).

It is known that the neuropeptide galanin (GAL) is widely distributed in the CNS and modulates some neurotransmitter systems, such as cholinergic, noradrenergic, serotonergic, and neuroendocrine pathways. While it is argued that galanin and GAL receptors are overexpressed in degenerated brain regions associated with cognitive reduction in AD, the functional consequences of GAL plasticity remain uncertain [34]. For example, in some animal studies, it was reported that the overexpression of galanin inhibited the secretion of acetylcholine (ACh) required for cholinergic transmission in some brain regions associated with AD [35] and restricted long-term potentiation (LTP) [36]. On the contrary, in another research conducted, it was reported that the increase in GAL in basal forebrain (CBF) nucleus basalis (NB) neurons that undergo selective cell loss in AD improved cholinergic activity by the upregulation of the choline acetyltransferase enzyme and promoted neuronal survival [35]. In our study, in contrast to various studies mentioned, plasma GAL levels were lower in the group with AD in comparison with the control group. This result suggests that galanin levels may have decreased to compensate for neuronal cell death and the impaired cholinergic system in AD (Figure 1). Furthermore, we consider that there is a need for studies with larger samples to reveal the correlation between galanin and the pathology of AD.

It is known that alarin, which is another member of the galanin family, is associated with nutritional behavior, hormone secretion, reproductive cycle, pain, learning, and memory. In a study performed by Dong et al., it was reported that alarin and GAL were involved in the modulation of synaptic transmission [37]. In the literature, there is no cross-sectional study demonstrating the correlation between alarin and the pathogenesis of AD, as far as we investigated. In our study, it was determined for the first time that plasma alarin levels were significantly lower in individuals with AD than in the control group (Table 1). Decreased plasma alarin levels observed in the Alzheimer's disease group were also supported by a positive correlation between PGC1-α and BDNF and alarin (Table 2) (Figure 1). Furthermore, no correlation was found between alarin levels and galanin levels (Table 2). Although it was reported in previous studies that these two peptides belonging to the same family might affect the same receptor group in synaptic transmission [37], our results suggested that galanin and alarin functioned with different mechanisms in the pathophysiology of AD. This result may provide useful information for more detailed studies aimed at revealing the correlation between these peptides and the pathogenesis of AD. It should not be forgotten that the better the roles of these peptides in the pathogenesis of Alzheimer's disease are clarified, the more they can benefit the advances in the diagnosis and treatment of the disease.

Conclusions:

As far as we know, this study is the first report in the literature that examined the relevant peptides that may be related to the pathogenesis of AD. In the research, plasma levels of BDNF, irisin, PGC1-α, GAL, and alarin were found to be low in AD (Table 1). In the negative correlations observed between age and plasma peptide levels. Significant positive correlations were observed between plasma PGC1-α levels and irisin, alarin, and BDNF, and the significant positive correlations were also observed between plasma BDNF levels and irisin and alarin (Table 2). When these findings are evaluated cumulatively, the increase in ROS and mitochondrial dysfunction associated with aging in Alzheimer's may be due to a decrease

in PGC1-α and decreases the synthesis of irisin by reducing proteolytic cleavage via FNDC5. Decreased irisin may be decrease BDNF release. Low BDNF levels can cause declines in neuronal survival and cognitive functions. Associated with the reduction of PGC1-α and BDNF, alarin levels may decrease independently of galanin, or these decreases may indicate that alarin may cause memory loss without affecting the same receptors as galanin. As a finally, we consider that the studies on these endogenous peptides should be supported by exogenous experimental AD models to shed light on their role in the diagnosis and treatment of the disease.

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Conflict of interest:
"The authors declare no conflict of interest."

Abbreviations:
Ach, acetylcholine; Akt, protein kinase B; Aβ, amyloid-β; BDNF, brain-derived neurotrophic factor; CBF, cholinergic basal forebrain; ERK1 / 2, extracellular signal-regulated kinases 1 and 2; FNDC5, fibronectin type III domain-containing protein 5; GAL, galanin; alarin/GALP, galanin-like peptide; LTP, long-term potentiation; NB nucleus basalis; NLRP3, NOD-like receptor pyrin 3; PGC1-α, peroxisome proliferator-activated receptor gamma coactivator 1-α; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; TNF-α, tumor necrosis factor-alpha.

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Author contributions:
HFG. CY. CEE. OG. and NK. Study Conception or Design; HFG. Data Processing, Collection, Perform Experiment; HFG. CEE. Analysis and Interpretation of Results; HFG. CY. CEE. OG. NK. Draft Manuscript Preparation, Visualization; HFG. CY. Critical Revision or Editing of the Article; HFG. CY. CEE. OG. NK. Final Approval of the Version to be Published; HFG. CY. CEE. OG. NK. Supervision; HFG.

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