Original Research Article

THE IMPORTANCE OF INCREASED SERUM ORNITHINE LEVELS IN THE PATHOGENESIS OF ALZHEIMER AND PARKINSON'S DISEASES

Running title: Arginine catabolism effects on neuroinflammation.

ABSTRACT

Background : The aim of this study was to investigate the levels of enzymes and ornithine involved in the synthesis of polyamines in patients with Alzheimer's and Parkinson's disease and to see their positive or negative effects on the modulation of the immune system

Methods: Thirty-five healthy subjects as control group and 35 patients with Alzheimer's and Parkinson's disease were included in this study. Determination of Ornithine decarboxylase, Arginine Decarboxylase and Agmatinase levels were evaluated by using Enzyme Linked Immunosorbent Assay (Elisa kit). Ornithine levels were measured spectrophotometrically.

Results: When ornithine levels of Alzheimer and Parkinson patients were compared to the control group, differences were found as significant ($p<0.05$). On the other hand, when Ornithine decarboxylase, Arginine Decarboxylase, Agmatinase levels of Alzheimer and Parkinson patients were compared to the control group, the differences were found as insignificant ($p>0.05$).

Conclusion: Although the enzyme levels in the pathway of polyamine synthesis in Alzheimer's and Parkinson's diseases do not change, the increase in ornithine level will not contribute to the fight

mode of the immune system. On the contrary, it may change plasticity by increasing osmolality.

Key words: Alzheimer, Parkinson, Polyamine, Ornithine, Agmatine, Immunmodulation

INTRODUCTION

Alzheimer's and Parkinson's disease are two of the most common neurological diseases that cause neurodegeneration and affect many people [1]. The most valid hypothesis explaining the development of Alzheimer's disease (AD), the most common neurological disease, is the amyloid cascade hypothesis. According to this hypothesis, amyloid-β peptides (Aβ) accumulate in the cerebral blood vessels and brain parenchyma, and accumulation of hyperphosphorylated tau proteins in neurons leads to lethal disease, progressive loss of consciousness, functional impairment and memory loss [2,3]. Parkinson's disease, which is the second most common neurological disease that occurs after death of dopaminergic neurons in Substantia nigra pars compacta, causes rigidity, tremor and hypokinesia [4,5]. In addition, α-synuclein protein, which accumulates in neurons, plays a key role in Parkinson's disease. Lewy particles, which are caused by excessive accumulation of this protein in neurons, lead to pathology leading to disease progression in cholinergic and monoaminergic neurons in the brain. The diagnosis of idiopathic Parkinson's disease can be determined by applying these two major neuropathologies (neuronal loss in specific areas of the substantia nigra and widespread intracellular protein (α-synuclein) accumulation [6). In Alzheimer's disease, a different pattern of α-synuclein pathology was found to accumulate mainly in the limbic region of the brain [7]. In vitro experiments have shown that the presence of polyamines in α-synuclein accumulation and fibril formation is effective and this effective sequence has been shown

as spermin>spermidine>putrescine [8]. Although the mechanism of brain atrophy and neuronal loss is not fully known, there is a growing body of evidence recently that the lack of arginine and suppressing immunity play a critical role in the pathogenesis of AD [9]. The cells responsible primarily for the immune system in the brain are microglia cells and macrophage-like immune cells found in the brain parenchyma, which are involved in the modulation of the brain's inflammatory response [10]. The microglia are activated immediately after the ischemia. Circulating monocytes are rapidly transformed into macrophages in the brain via blood-brain barrier due to inflammation [10,11]. Microglia and macrophages are known to be essential cells in inflammation after cerebral ischemia. Polyamines have a negative regulatory effect on macrophage activation through complex associations with NO metabolism. In macrophages, NO is an intermediate product in the L-arginine oxidation process [12].

Polyamines are molecules having 2, 3 or 4 amino groups. They are widely found in living organisms because they have a key role in the survival of life [13]. The major polyamines synthesized by several enzymes from the amino acid of L-Arginine are putrescine, spermidine, spermine and agmatine (Fig 1]. Polyamines play an important role in biological processes because of their interaction with many different receptors, protein kinases, nucleotide cyclases. It has been reported that the increase in the levels of polyamines may be associated with diseases such as cancer, as they have a key role in growing and dividing the cell [14,15,16]. However, due to their interaction with systems such as polyamines, catecholamines, GABA, nitric oxide (NO), glutamate, they are also associated with many psychiatric disorders, especially schizophrenia [16,17,18]. The survival of the cells that make up the organism depends on the presence of polyamines. It is known that neurodegenerative diseases

caused by cell death develop due to the differentiation of polyamine metabolism [19,20,21]. Many researchers have shown that agmatine has neuroprotective potential and develops a cognitive function in various animal models of central nervous system damage such as neurotrauma and neonatal ischemia [22,23,24,25,26]. The degraded polyamine metabolism indirectly causes the degradation of nitric oxide synthase. Increased agmatine synthesis causes suppression of NO synthesis in immunocytes and leads to defense deficiency, while decreased levels result in increased NO synthesis resulting in neurodegeneration and death of neurons (Figure 1) [27,28,29] .

Our aim in this study was to reveal the possible roles of polyamines in the pathogenesis of Alzheimer and Parkinson diseases. For this purpose, the levels and effects of arginine decarboxylase, ornitine decarboxylase, agmatinase and ornitine involved in the pathway of polyamine synthesis on the immune system were examined.

MATERIALS AND METHODS:

Patient and Control Group

The 35 patients, who applied to the Cumhuriyet University Medicine Faculty Neurology Policlinic and took diagnosis with alzheimer and parkinson, were included in the study as experimental group. Patients of all ages and both gender were included in the study. Our control group was chosen from the 35 healthy individuals who have not any systemic diseases (diabetes, hypertension and neurodegenerative disease).

Blood Samples Collection

Blood samples were taken from the controls and patients who were made the diagnosis of alzheimer and parkinson and not receive any therapy. The serums were obtained by centrifugation at 1610 x g for 10 minutes of the blood samples were preserved in 80 0C for to study.

Detection of enzyme levels

Ornithine, arginine decarboxylase, ornithine decarboxylase and agmatinase levels have been measured in serum of alzheimer and parkinson patients. Ornithine level were calculated spectrophotometrically at 515 nm using the method defined by Chinard and the value was given as µmol/ml [30]. Arginine decarboxylase, ornithine decarboxylase and agmatinase levels were determined by ELISA kit according to the manufacturer's protocol (SunRed, China).

Statistical Analysis

Mann Whitney U test was used for statistical analysis of the data. The data were stated in the tables as the arithmetical average ± Standard deviation and the level of significance was taken as 0,05

RESULTS

There wasn't any significant difference between patient groups and control group in terms of gender and age ranges (P>0.05) (Table 1). When ADC, ODC and Agmatinase enzymes, which were determined at serum levels, were compared according to the control group, no statistically significant difference was found between the two disease groups (Alzheimer and Parkinson) (P>0.05) (Table 2).

On the other hand, serum ornithine levels increased in both groups when compared with the control group, and they were statistically significant. $P<0.05$ (Table 2).

DISCUSSION:

In this study, enzymes (ADC, ODC and Agmatinase) and ornithine levels in polyamine synthesis pathway were measured in serums of Alzheimer and Parkinson's patients. When the levels of the enzymes were compared with the control as a result of analysis, no significant difference was found between the two groups of patients and control ($p>0.05$). Ornithine was higher and statistically significant in both groups when compared to the control group ($p<0.05$). Enzyme and ornithine levels in the polyamine synthesis pathway have been investigated in this study for the first time in serums of Alzheimer and Parkinson's patients. Most of the studies carried out to date regarding polyamines and their relation to these diseases were in the form of experimental animals and postmortem studies. In one postmortem study, the amount of spermidine increased in the temporal cortex (70%) and reduction in levels of putrescine (28%) were found in patients with AD [19]. In another postmortem study, there was no difference in spermidine and spermine concentrations in the basal ganglia of Parkinson, Huntington's disease (HD) and progressive supranuclear palsy (PSP) patients and it was found to decrease with age [31]. Changes in the homeostasis of polyamines play an important role in the emergence of many diseases such as cell growth, senility, memory performance, neurodegenerative diseases, metabolic diseases and cancer [32,33].

In the polyamine synthesis pathway, two major molecules play an important role in the modulation of the immune system. These are ornithine and agmine molecules. Ornithine is the

precursor molecule of the synthesis of major polyamines (putresin, spermidine and spermine), the precursor of both L-glutamate and GABA molecules as well as the precursor of L-proline required for the synthesis of connective tissue for wound healing (Figure 1). In this study, ornithine levels were increased in both groups of patients compared to the control and statistically significant ($p<0.05$). The major metabolic ways in which the increased ornithine can go, are L-proline, L-glutamate, GABA, polyamine synthesis and urea cycle. Since the ODC levels, the rate limiting enzyme in polyamine synthesis, did not change in both patient groups, the polyamine synthase pathway would not be active (Table 2).

The entry of the increased ornithine into the urea cycle will contribute to the formation of excessive urea and thus the increase of osmolarity in many regions of the brain such as the cerebellum, cerebral cortex and brain stem [34]. Chronic osmotic pressure caused by ornithine also modifies plasticity in the hippocampal region by mediating tonic inhibition of the GABA receptor family [18,35,36]. On the other hand, the increase of L-proline synthesis for collagen production, which is necessary for connective tissue, means that immune system cells pass into the fix mode (wound healing). Thus, increased L-proline synthesis will only contribute to the synthesis of collagen [37]. The main problems of both Parkinson and Alzheimer's patients are mainly a cluster of α-synuclein and amyloid beta. Extra collagen accumulation will also increase the negative effect. This approach could not be verified for the time being because L-prolin levels could not be measured due to the limitations of the study. Another molecule that is effective in the modulation of immune cells is agmatine. The active immunocytes (microglia, macrophage) increase NO production in the M1 (fight-killing program) mode. They do this via inducible nitric oxide synthase (iNOS). Nitric oxide is a

141 twisted sharp knife; The first is the main events caused by their decreasing concentration. These are
142 reduced vascular perfusion, blockage of granulocytes in the blood vessels in the inflamed area,
143 inhibition of pro-inflammatory reactions, and thickening of the capillary membranes [38,39,40]. All
144 these adverse events lead to neurodegeneration and neuronal cell death due to inadequate oxygen
145 and glucose transport to the resulting neuronal and glial cells [41]. In the second, high
146 concentrations of NO inhibit many complexes in the respiratory chain and lead to an increase in the
147 synthesis of highly toxic compound peroxynitrite ($ONOO^-$). This highly toxic compound causes
148 mitochondrial damage and leads to mitochondrial dysfunction leading to neurodegeneration and
149 neuronal cell death [42]. When the level of arginine is reduced to an undetectable level in regions
150 with inflammation, It can be understood that Arginine metabolism is a central pathway for
151 macrophages in the immune system [43]. When inflammation occurs, the macrophages must be
152 directed to one of the "fight" or "fix" modes. Fight is a killing program (eg pathogen) and fix is a
153 wound healing program. The Fight pathway activated by macrophages results in the formation of
154 nitric oxide (NO) and cell proliferation is inhibited [44]. When the fix pathway is activated,
155 proliferation and healing process is initiated by ornithine formation (via polyamine and collagen)
156 [45,46,47,48]. Both the M1 (fight) and M2 (fix) pathways use arginine, but the NO and Ornithine
157 pathways can not be active at the same time because the metabolites of a pathway inhibit the
158 enzymes of the other pathway (Şekil 1). The fact that ADC enzyme levels which are effective in the
159 synthesis of agmatine in both groups of patients do not change and that there is no difference in
160 agmatinase enzyme in the destruction pathway will not change the amount of agmatine (Tablo 2).
161 Solubulous amyloid-Beta oligomers are responsible for synapse loss and neurodegenerative

development in Alzheimer's disease [49]. B-Amyloid 1-40 peptide regulates glutamate release by acting on glutamergic terminals [50], while B-amyloid plaques lead to increased intracellular calcium concentration and death of neurons by directly affecting NMDA receptors [51].

The absence of an increase in the amount of agmatine, the natural antagonist of the receptors, naturallyi nhibits blockage of these receptors.

Agmatin activates eNOS while inhibiting iNOS from NOS enzymes. Studies on experimental animal models showed that application of agmatine in brain cells damaged by lipopolysaccharide reduced and corrected the damage with these properties [52,53,54,55].

As a conclusion, polyamin synthesis enzymes whose levels are not altered in Alzheimer and Parkinson's disease can not contribute to the prevention of neurodegeneration. Increased ornithine levels will not contribute to the fight mode of the immune system but may contribute to fix mode which increased proline's levels. But, it may contribute to the synthesis and increase of urea and impair plasticity. Also, it may assist to glutamate, GABA and urea synthesis and increase osmolarity and impair plasticity. Exposing these grey areas with more extensive studies may allow new approaches to be introduced in the treatment of such diseases.

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309 agmatine on lipopolysaccharide-injured microglia and inducible nitric oxide synthase activity. Life
310 sciences 91(25), 1345-1350.

311 Table 1. The gender and age ranges of patients and control

	Alzheimer		Parkinson	
313 Gender	Control	Patient	Control	Patient
314 Male	25	25	19	19
315 Women	10	10	16	16
316 Age (X ± S)	77 ± 11	74 ± 14	67 ± 12	68 ± 11

317 Data expressed as mean ± standard deviation

318

319 Table 2. The serum Ornithine, Arginine Decarboxylase, Ornithine Decarboxylase and Agmatinase
320 levels in patients and controls

		Alzheimer			Parkinson		
322		Control	Patient	P	Control	Patient	P
323	**ADC**	3.07±0.22	3.08±0.13	>0.05	3.11± 0.21	3.07±0.22	>0.05
324	(pg/ml) (n=35)						
325	**Agmatinase**	3.06±0.21	3.02±0.21	>0.05	3.09±0.21	3.06±0.13	>0.05

(pg/ml) (n=35)							
ODC	3.13±0.15	3.11±0.23	>0.05		3.11±0.21	3.07±0.2	>0.05
(pg/ml) (n=35)							
Ornithine	0.12±0.02	0.16±0.02	<0.05		0.14±0.03	0.16±0.02	**<0.05**
(µmol/ml)							
(n=35)							

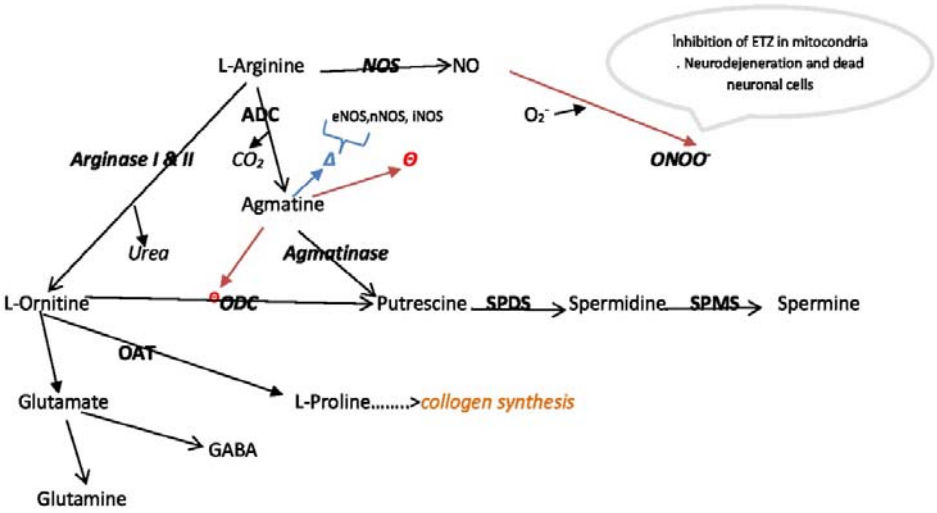

Figure 1: Regulation of NO synthesis and polyamines synthesis by agmatine. Nitric oxide synthase (NOS); endotelialNOS(eNOS); neural NOS(nNOS); inducible NOS (iNOS); Arginine decarboxylase (ADC); Ornithine decarboxylase (ODC); Spermidine synthase SPDS: Spermine synthase SPMS; γ-aminobutyric acid (GABA); Ornithine amino tranferase (OAT); Ornithine decarboxylase (ODC); inhibition; Θ; Activation Δ: