Inadequate Amyloid Clearance in Alzheimer's Disease: The Possible Role of TTR Transporter Protein and LRP-1 Receptor

Alzheimer Hastalığında Yetersiz Amiloid Klirensi: TTR Taşıyıcı Proteininin ve LRP-1 Reseptörünün Olası Rolü

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ABSTRACT

Alzheimer's disease affects large populations worldwide. However, there is not yet a blood-based minimally invasive biomarker that can provide a definitive diagnosis. There is also no curative treatment. Extracellular senile amyloid plaques, which are formed by the accumulation of amyloid derivatives in the central nervous system, have an important role in the development of Alzheimer's disease. The reason for the accumulation of amyloid derivatives in the central nervous system is shown as excess production by faulty proteolysis of amyloid precursor protein by enzymes. However, one of the causes of amyloid deposition in the central nervous system is insufficient clearance of these derivatives. Since amyloid production cannot be balanced with amyloid clearance in Alzheimer's disease, accumulation of monomers, oligomers, insoluble fibrils and plaques is observed in the central nervous system. It is argued that the deficiency or loss of function of the transthyretin transporter protein, which is thought to be involved in this removal, and LRP-1, a blood-brain barrier receptor, also may predispose to Alzheimer's disease. In this review, possible biomarkers for Alzheimer's disease, transthyretin and LRP-1-mediated amyloid clearance were examined.

Keywords: Alzheimer's disease, amyloid clearance, TTR, LRP-1, biomarkers

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ÖZET

Alzheimer hastalığı dünya çapında geniş kitleleri etkiler. Bununla birlikte, kesin tanı konulmasını sağlayabilecek kan bazlı minimal invaziv bir biyobelirteci henüz bulunmamaktadır. Ayrıca küratif bir tedavisi yoktur. Amiloid türevlerinin merkezi sinir sisteminde birikmesiyle oluşan hücre dışı senil amiloid plaklar Alzheimer hastalığının gelişmesinde önemli bir role sahiptir. Amiloid türevlerinin merkezi sinir sisteminde birikmesinin nedeni, amiloid öncü proteininin enzimler tarafından hatalı proteoliziyle aşırı üretilmesi olarak gösterilmektedir. Ancak merkezi sinir sisteminde amiloid birikiminin nedenlerinden biri bu türevlerin yetersiz klirensidir. Alzheimer hastalığında amiloid üretimi amiloid klirensi ile dengelenemediğinden merkezi sinir sisteminde monomer, oligomer, çözünmeyen fibril ve plak birikimi görülür. Bu klirenste rolü olduğu düşünülen transtiretin taşıyıcı proteininin ve bir kan-beyin bariyeri reseptörü olan LRP-1'in eksikliğinin veya fonksiyon kaybının da Alzheimer hastalığına eğilim oluşturabileceği düşünülmektedir. Bu derlemede Alzheimer hastalığı için olası biyobelirteçler, transtiretin ve LRP-1 aracılı amiloid klirensi incelenmiştir.

Anahtar Sözcükler: Alzheimer hastalığı, amiloid klirensi, TTR, LRP-1, biyobelirteçler

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INTRODUCTION

Alzheimer's disease (AD), which is the most common type of dementia, is a neurodegenerative disease characterized by advanced loss of cognitive functions, eventually leading to death and deterioration in quality of life (1, 2). The main pathological findings in AD are intracellular accumulation of neuritic plaques and neurofibrillary tangles, extracellular amyloid beta peptide deposition and cerebral atrophy that cause cognitive impairment (3, 4, 5). Also mitochondrial dysfunction, endoplasmic reticulum stress, synaptic loss and misfolded protein accumulation are responsible for the development of Alzheimer's disease (6, 7).

However, the mechanisms under those and the other pathological changes in prognosis of AD are not clear yet, several hypothesizes are proposed to explain AD's pathogenesis. For example cholinergic hypothesis emphasize the importance of acetylcholine, which is a neurotransmitter synthesized from cholinergic neurons, and is associated with critical functions in the brain, especially memory, attention, processing of sensory information, and learning. Cholinergic hypothesis proposes that degeneration of cholinergic neurons occurs in Alzheimer's disease and cognitive function and memory disorders are experienced (3, 8). Formation of neurofibrillary tangles (NFTs) is another pathological change seen in AD pathogenesis. "Abnormal phosphorylation of Tau protein" hypothesis explains the AD progress by abnormal phosphorylation of Tau protein. Aberrant or excessive phosphorylation of intracellular Tau protein impedes microtubule stabilization and axonal operation, which leads to NFTs accumulation, neuron degeneration and apoptosis of nerve cells, resulting in the occurrence of AD (9, 10).

On the other hand amyloid cascade hypothesis points out the accumulation of Aβ molecules. In normal circumstances, there should be a balance between the production, transport and degradation of amyloid derivatives. The disruption of this balance between the production and clearance of amyloid derivatives is thought to cause Alzheimer's disease (11, 12). The formation of amyloid derivatives increases as a result of β-secretase-mediated degradation of amyloid precursor protein. It is known that activity of beta secretases and amyloid formation increases in Alzheimer's disease (12, 13). The increase in the production of amyloid derivatives is accepted as a step in the development of Alzheimer's disease. In addition, inadequate transport of Aβ derivatives from the central nervous system to the periphery, and insufficient degradation in the liver and kidney may also lead to the accumulation of amyloid derivatives and cause Alzheimer's disease. With the deterioration of the production-clearance balance of amyloid derivatives, a tendency to Alzheimer's disease occurs and amyloid derivatives accumulated in the central nervous system trigger the formation of neurofibrillary tangles, another hallmark of the disease. This paves the way for the development of Alzheimer's disease (12, 14).

The aim of this review is to examine some steps that may cause insufficient removal of amyloid derivatives from the central nervous system, which is one of the possible developmental mechanisms of Alzheimer's disease.

Alzheimer's disease: Disruption of the balance of amyloid production, transport and degradation

Two predominant forms of Aβ are produced in humans. These are Aβ 1-40 and Aβ 1-42. The longer form, Aβ 1-42, is more prone to aggregation and is more toxic to Alzheimer's disease. Aβ molecules accumulate to form oligomers and fibrils. Thus, it prepares the ground for the development of Alzheimer's disease (15). Amyloid precursor protein is metabolized by proteolytic enzymes. These proteolytic cleavages are mediated by enzymes called α-secretase, β-secretase (BACE1) and γ-secretase. Proteolytic cleavage by α-secretase inhibits Aβ formation, thus eliminating the possibility of formation of aggregates and plaques. Therefore, α-secretase activity is considered as non-amyloidogenic amyloid precursor protein cleavage. In addition, sAPPα formed during cleavage is thought to have some neuroprotective properties. When the amyloid precursor protein is cleaved by β-secretase and γ-secretase, toxic Aβ forms are formed (15, 16).

Impairment of amyloid precursor protein degradation in favor of β-secretase and increased production of amyloid derivatives in Alzheimer's disease is an accepted approach. In fact, some of the new treatment methods planned to be developed for Alzheimer's disease include this mechanism. α-secretase enzyme activators are being tested for this purpose. Selengiline, which is a selective monoamine oxidase inhibitor, also increases the activity of the α-secretase enzyme (17, 18).

Again, statin group drugs used in the treatment of hypercholesterolemia are tried in the treatment of Alzheimer's disease, especially since they increase the activity of atorvastatin α-secretase enzyme (19). Similarly, β-secretase and γ-secretase enzyme inhibitors are also being tested for the treatment of Alzheimer's disease. One of the drugs that inhibit β-secretase enzyme is thiazolidinediones, which is an oral antidiabetic group and activates PPAR-γ (20). Today, the relationship between type 2 diabetes mellitus (DM) and Alzheimer's disease and the common mechanisms are a subject of interest and studied by researchers. By affecting the processing of amyloid-β and tau, DM may increase the rate of formation of senile plaques and neurofibrillary tangles, which are the main neuropathological features of Alzheimer's disease. Increased oxidative stress in diabetes activates inflammatory pathways and may therefore exacerbate Alzheimer's disease neuropathology. Mitochondrial dysfunction is associated with both type 2 DM and Alzheimer's disease and may lead to intracellular calcium derangement and abnormal processing of amyloid precursor protein (21, 22). The inhibition of β-secretase enzyme by thiazolidinedione group drugs suggests that there are common pathways in type 2 DM and Alzheimer's disease. It is thought that reducing peripheral insulin resistance will also be beneficial for Alzheimer's disease (23). Similarly, γ-secretase enzyme inhibitors are also tried in the treatment of Alzheimer's disease (24).

It is stated that decreased amyloid clearance contributes to the accumulation of monomers, oligomers, insoluble fibrils and plaques in the central nervous system in late-onset Alzheimer's disease. In one study, the ratio of Aβ production to Aβ clearance was found to be impaired in Alzheimer's patients compared to healthy controls (25). This study also demonstrates the importance of insufficient clearance of amyloid to balance amyloid production in the development of Alzheimer's disease.

One of the mechanisms thought to be effective in the development of Alzheimer's disease is the accumulation of amyloid derivatives in the brain due to insufficient removal from the central nervous system. During this removal, there may be a transporter protein thought to be involved in the transport of Aβ derivatives. This protein is transthyretin, which is known for its roles in the transport of the hormone thyroxine and retinol (26). Transthyretin may plays a role in the removal of amyloid from the brain, since it carries out this transport in one direction. When the details of this unidirectional transport were investigated, it was shown that transthyretin uses a blood brain barrier receptor to transport amyloid derivatives to the periphery. This receptor is thought to be low-density lipoprotein-related protein-1 (LRP-1), which is located only on the central side of the blood-brain barrier (26).

Transthyretin transporter protein and its possible role in Alzheimer's disease

Transthyretin (TTR), known for its roles in the transport of thyroxine and retinol, is also thought to play a role in the transport of amyloid derivatives (26). It was described in 1942 by precipitating albumin during electrophoresis of human plasma and cerebrospinal fluid samples. It was called prealbumin with this feature. It was later named thyroxine-binding prealbumin. Today it is known as transthyretin. It has been also shown that TTR only transports Aβ 1-42 from the brain to the periphery (26, 27).

TTR transporter protein is synthesized especially in the choroid plexus, liver and brain. The main source of plasma TTR is the liver, while the main source of TTR in the cerebrospinal fluid is the choroid plexus. TTR sources other than liver and choroid plexus are retinal pigment epithelium, pancreatic islet cells, and low-producing heart, skeletal muscle, spleen, and placental trophoblasts. TTR is metabolized in the liver, muscle and skin. In addition, degradation of TTR occurs in kidneys, adipose tissue and testicles. The biological half-life of TTR is approximately 2-3 days in humans, 23 hours in monkeys, and 29 hours in Buffalo rats (27).

TTR does not transport Aβ 1-42 from the periphery back to the central nervous system. Therefore this unidirectional transport suggests that TTR may reduce Aβ 1-42 load in the brain according to the amyloid cascade hypothesis (26).

There are monomeric and tetrameric forms of TTR. While the monomeric form of it is toxic, the tetrameric form of it transports only Aβ 1-42 unidirectionally from brain to the periphery, and helps the clearance of amyloid derivatives. The tetramer form is the first produced stable form (28). Destabilization of TTR in the tetramer form is thought to play a critical role in the development of cardiac amyloidosis. While tetrameric TTR alone is considered to be nonamyloidogenic, it is thought that the monomer form formed by its destabilization and dissociation has lower conformational stability, leading to the formation of amyloid fibril formation (29).

Tetrameric TTR is presumed to have a major role in inhibiting Aβ aggregation (30). Li et al. showed that all TTR forms bind better to the oligomer form of Aβ. With this feature, TTR gains importance because it may inactivate the Aβ oligomer form, which is the main cause of Alzheimer's disease (30).

In addition to its carrier properties, it is thought that TTR may play a role in neurogenesis, nerve regeneration and axonal growth in the brain (27, 31). In vitro studies have shown that TTR protein with metalloprotease activity mediates amyloid beta cleavage (32, 33). In addition to mediating Aβ clearance, it is thought that TTR may also play a role in the degradation of fibrils with its proteolytic activity (27, 34). In a study conducted with transgenic mice, it was shown that cognitive performance decreased in mice lacking the TTR gene compared to the control group (35). In addition, worsening cognitive performance in mice with normal TTR gene with aging was found to be correlated with low cerebrospinal fluid (CSF) TTR levels (36).

In humans, plasma TTR levels begin to decline after the age of 50 (37). As it is known, the incidence of Alzheimer's disease increases with advancing age. It is thought that the increase in the incidence of Alzheimer's disease in advanced age may be related to the decrease in TTR levels (27).

The search for a biomarker for Alzheimer's disease

There is no curative treatment for Alzheimer's disease and also there is no biomarker that can provide a definitive diagnosis. Definitive diagnosis of Alzheimer's disease can only be made by postmortem pathological studies (38, 39, 40). A blood-based biomarker that can diagnose Alzheimer's disease should have high sensitivity and specificity and be strong enough to make a accurate diagnosis. Biomarkers recommended for use today can be used in various combinations or in combination with clinical findings such as cognitive tests. However, there is still no blood-based biomarker that can make a definitive diagnosis for Alzheimer's disease (40). There are several biomarker suggestions that can confirm the diagnosis of Alzheimer's disease. However, with these suggested biomarkers, a definitive and easy diagnosis cannot be made yet (41). Biomarkers recommended for the diagnosis of Alzheimer's disease can be classified as genomic-based markers, plasma markers, and cerebrospinal fluid markers (42).

The apolipoprotein E4 allele associated with late-onset Alzheimer's disease is considered as a genomic-based biomarker. However, genetic testing is not easily applicable for routine use. Blood lipid panels, micro RNA analysis, plasma Aβ 1-42 / Aβ 1-40 ratio are recommended as plasma biomarkers. The development of a blood-based biomarker is very important for ease of diagnosis. CSF tau level, CSF Aβ peptide levels, CSF Aβ 1-42 / total tau ratio are recommended as cerebrospinal fluid biomarkers. Although CSF markers seem to be more advantageous in terms of diagnostic accuracy, it is desired to develop a blood-based biomarker since it is more difficult and invasive to obtain CSF samples from patients than blood samples (42). A clinically useful biomarker should show high specificity and sensitivity (43). To meet these conditions, it is necessary to use several of these suggested markers together (42).

In addition, the issue of diagnosing Alzheimer's disease with neuroimaging systems is quite remarkable today. It is thought that computed tomography, positron emission tomography and magnetic resonance imaging techniques can be used for the diagnosis of Alzheimer's disease and other types of dementia. Necessary criterias for diagnosing dementia are tried to be determined by using these neuroimaging methods (44, 45). However, it is seen that it is much easier and less costly to diagnose Alzheimer's disease with a blood-based test. For this reason, studies for the development of a blood-based biomarker for Alzheimer's disease continue.

Serot et al. found that TTR levels in Alzheimer's patients were lower in CSF than in comparative controls (46). In their study, TTR concentrations were measured in CSF samples from 149 patients and were found to be quite low in those with Alzheimer's disease (46). These data suggested that the lack of adequate TTR concentrations may promote amyloid fibril formation in late-onset Alzheimer's disease (46).

After CSF TTR levels were found to be low in Alzheimer's patients, plasma levels were evaluated in order to use it as a blood-based biomarker. In a study conducted with 111 Alzheimer's patients and their controls without dementia, plasma TTR levels were found to be lower in Alzheimer's patients (47). Studies in the literature have shown that plasma TTR levels in Alzheimer's patients with cognitive impairment are significantly lower than in controls (48). In a study conducted with 90 patients with late-onset Alzheimer's disease and 50 age-matched controls without dementia, plasma protein levels of TTR were examined and found to be low in Alzheimer's patients.

Moreover, in the same study, even lower TTR levels were found in Alzheimer's patients with rapid and severe cognitive impairment (48). These data suggest that plasma TTR level can be used as a prognostic indicator for Alzheimer's disease.

In addition to considering TTR as a biomarker for Alzheimer's disease, it is emphasized that it can distinguish between rapidly progressing and slowly progressing Alzheimer's disease. It is also stated that TTR levels are important in the transition from mild cognitive impairment to Alzheimer's disease. It is thought that the TTR transporter protein may also give an idea about the prognosis of the patients and can be used in the detection of patients who may show rapid cognitive decline in a short time. It is stated that Alzheimer's patients with lower CSF and plasma TTR levels will have a more aggressive course of the disease (49, 50).

In a study in which 135 patients with mild cognitive impairment and their gender and age-matched controls were followed for 5 years, plasma TTR levels were found to be effective in the transformation of mild cognitive impairment into Alzheimer's disease. It is stated that at the time of Alzheimer's disease in patients with mild cognitive impairment, a significant decrease in plasma TTR levels is detected compared to initial measurements (49).

As a result, CSF and plasma TTR are considered as a biomarker that may be used for Alzheimer's disease and studies on this subject continue.

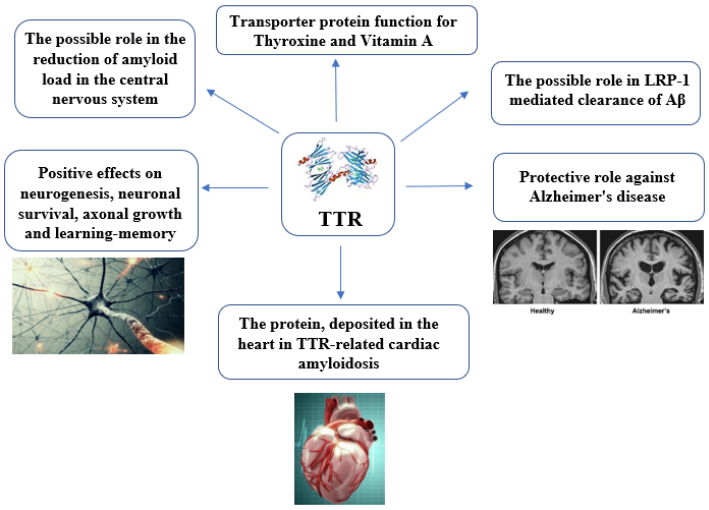

Figure 1: TTR protein

A receptor protein involved in amyloid transport: LRP-1

LRP-1 receptor protein is a member of the low molecular density lipoprotein (LDL) receptor family. LRP-1 is a versatile receptor protein and can bind many ligands. As a result of these bindings, it activates many signaling pathways (51, 52).

The LRP-1 receptor is thought to be involved in Aβ clearance. Because LRP-1 is thought to be a receptor for TTR to transport of Aβ from the central nervous system to the periphery. In addition, studies with in vitro blood brain barrier models showed that this receptor is present only on the central side of the blood brain barrier and not on the blood side. It is thought that this is how the TTR transports Aβ unidirectionally (26). In addition, in study with transgenic mice, it was determined that LRP-1 expression was lower in mice lacking the TTR gene (TTR -/-) compared to controls. On the other hand, in transgenic mice (TTR +/+) containing the TTR gene bilaterally, both brain LRP-1 expression was higher and plasma amyloid load was lower. These findings suggest that TTR may also regulates the expression of LRP receptor protein (26).

Various studies have shown that LRP-1 receptor expression is decreased in Alzheimer's disease and there is a loss of function in this receptor (53, 54, 55). The blood-brain barrier plays a very important role in brain homeostasis by controlling the transport of substances. It is planned to develop new treatments for diseases by modulating the expressions of proteins found in the blood brain barrier. LRP-1, an endocytic receptor, is abundantly expressed in blood brain barrier endothelial cells.

LRP-1 is thought to be the receptor involved in Aβ transport from the brain to the periphery. It can also activate many signaling pathways.
It has been shown in human and animal studies that LRP-1 levels in brain tissue decrease in Alzheimer's disease (56, 57). Studies emphasize that increasing brain LRP-1 expression may have a positive effect on cognitive functions (58).

In particular, the liver is considered as the site of degradation of amyloid derivatives (59, 60). It has been shown that the receptor that provides the uptake of these derivatives to the liver, which is the site of destruction of amyloid derivatives that cause Alzheimer's disease, is also LRP-1. Rapid peripheral clearance of Aβ is mediated mainly by LRP-1, which is located on the surface of liver cells (61). It has been shown that decreased hepatic LRP1 levels are associated with decreased peripheral Aβ clearance in aged rats (62).

Kidneys, which are responsible for the removal of many substances from the body, also take part in the systemic clearance of amyloid derivatives together with the liver. For example, it has been reported that unilateral nephrectomy causes Aβ accumulation, neuronal loss and neuroinflammation in the brain in mice undergoing the unilateral nephrectomy model. These findings confirm that the kidney is involved in the degradation of Aβ derivatives (63). However, the receptor protein and degradation mechanism that allows amyloid derivatives to be taken into the kidney are still a matter of curiosity (61, 63).

It is known that the kidney expresses the LRP-2 (megalin) receptor, which is from the same receptor family as LRP-1 (64, 65). LRP-1 or other LDL receptor family receptors may be involved in the renal uptake mechanism of amyloid derivatives for degradation.

The pathways induced by tissue plasminogen activator (tPA) and LRP-1 signaling have been found to be associated with many organs and their diseases (66). Binding of various ligands to the LRP-1 receptor leads to the activation of many signaling pathways (61). Signaling by binding of tPA to the LRP-1 receptor has been associated with fibrosis, especially in kidney tissue (66). However, the renal uptake receptor mediating amyloid destruction, which is of great importance for Alzheimer's disease, and the mechanisms in the kidney are not clearly known. Therefore, more work is needed on this subject.

CONCLUSION

The death toll from Alzheimer's disease is increasing day by day. The quality of life of both Alzheimer's patients and their caregivers is adversely affected. Although research has made progress in the diagnosis, treatment and prevention of many diseases, the same cannot be said for Alzheimer's disease. Because we still have little idea about the pathological processes that lead to the onset and subsequent progression of Alzheimer's disease.

The role of cerebral amyloid plaques in the development of Alzheimer's disease is known. The cause of amyloid deposition may be overproduction or insufficient clearance from the central nervous system. Transthyretin transporter protein and LRP-1 blood-brain barrier receptor are thought to be involved in the removal of amyloid derivatives from the central nervous system. The LRP-1 receptor is also the hepatic uptake receptor for degradation of amyloid derivatives, but the receptor that performs this function in the kidney is not clear. More studies are needed to clarify these mechanisms and to develop ways that can be used for treatment.

Conflict of interest

No conflict of interest was declared by the authors.

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