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A Connectivity between LRP-1 and Alzheimer's Disease: Modulating the Transport and Clearance of Tau and Aβ Clearance from the Brain to the Liver

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Abstract

A paucity of knowledge exists in our understanding of the axonal clearance of both beta amyloid (Aβ) and Tau proteins to the liver. Peripheral clearance by the liver can remove 40–50% of Aβ burden in the brain through the glial-lymphatic (glymphatic) system, transport across the blood brain barrier and mediated by low-density lipoprotein receptor-related peptide 1 (LRP-1). The lack of LDL receptors (LDLR) enhances amyloid deposition in the brain while LDLR overexpression increases the rate of Aβ entering the hepatic system. It's important to consider the effects of organ failure on the development of AD. There are four main factors which contribute to clearance from the body. Blood flow, transport across the blood brain barrier, uptake into the liver, and elimination from the body through bile excretion all play an important role in the clearance of bioaccumulated toxic Aβ and Tau AD inducing proteins.

Keywords: Tau; Beta Amyloid (Aβ); Low-Density Lipoprotein Receptor-Related Peptide 1 (LRP-1); Blood Brain Barrier; Liver; Alzheimer's Disease (AD)

Abbreviations: AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; UPS: Ubiquitination Proteasome Pathway; APP: Amyloid Precursor Protein; GSK3β: Glycogen Synthase Kinase 3 Beta; RAP: Receptor-Associated Protein; ER: Endoplasmic Reticulum; RAGE: Receptor for Advanced Glycation End Products; LDL: Low-Density Lipoprotein; NVU: Neurovascular Units; CBF: Cerebral Blood Flow; MAPT: Microtubule-Associated Protein Tau; APP: Amyloid Precursor Protein; AD: Alzheimer's Disease.

Introduction

Alzheimer's disease (AD) results from the presence of neurotoxic beta-amyloid (Aβ) deposits in the brain and is a progressive neurodegenerative disorder. AD is the main cause of dementia among the elderly worldwide, with a poor prognosis. Despite intense efforts to develop drugs for preventing and treating AD, no effective therapies are available yet, posing a growing burden at the personal, medical, and socioeconomic levels. AD is characterized by the production and aggregation of amyloid β (Aβ) peptides derived from amyloid precursor protein (APP), the presence of hyper phosphorylated microtubule-associated protein Tau (MAPT), and microglia-induced chronic inflammation leading to neuronal loss. It's important to understand that there are a multitude of molecular events which contribute to the progression of AD. These molecular events can exacerbate the progression of AD through indirect modulation of the

primary efflux transporter; the low-density lipoprotein receptor-related peptide 1 (LRP-1). Both beta-Amyloid (Aβ) and Tau require LRP-1 for transport across the blood brain barrier. Once across the blood brain barrier, the albumin bound proteins are absorbed into the liver via the LRP-1 receptor and excreted through the bile duct for the elimination through the digestive tract.

Blood Brain Barrier and LRP-1

The blood-brain barrier is a specialized structure which supports brain integrity by regulating permeability homeostasis related to electrolyte flux, cerebral blood flow (CBF) and efficient oxygen and metabolite delivery. These restrict entry of potentially toxic and even some therapeutic agents into the brain. Blood brain barrier function is mediated by neurovascular units (NVU) comprising neurons, glial cells, pericytes, and brain endothelial cells, which maintain homeostasis of the cerebral microenvironment. Occludin and CLN-5 are transmembrane tight junction proteins involved in signal transduction of cytokines [1,2]. The high expression of these proteins on brain endothelial cells regulates the transport of essential molecules through the blood brain barrier, allowing the free and rapid diffusion of oxygen and carbon dioxide. The Low-Density Lipoprotein (LDL)-related protein-1 (LRP-1) is a type 1 transmembrane protein belonging to the LDL receptor family, which is ubiquitous throughout the body. LRP-1 functions as a scavenger receptor to participate in the endocytosis of its numerous ligands; and as a signaling receptor to modulate various cellular signaling pathways. LRP-1 has been implemented in systemic diseases such as cardiovascular T Blood, et al. [3], kidney EJ Boder, et al. [4], and related metabolic diseases.

Lin et al., reported that neuronal LRP-1 plays a crucial role in regulating insulin signaling and glucose metabolism in the brain through GLUT 3 and GLUT 4 remediation [5]. LRP-1 deficiency in neurons and insulin resistance synergistically contribute to impaired glucose metabolism and synaptic dysfunction, which are likely the very early abnormalities that precede or accompany the initial stages of cognitive impairment [5]. Importantly, Lin L, et al. found that hyperglycemia suppresses LRP-1 expression, which further exacerbates insulin resistance, glucose intolerance, and AD pathology. Deane et al., found that the LRP-1, P-glycoprotein, and receptor for advanced glycation end products (RAGE) are examples of blood brain barrier transporters implicated in its pathogenesis due to their role in the trafficking of amyloid-β [6]. The high binding affinity of Aβ to RAGE and LRP-1 may offer a basis for development of soluble products that can act as peripheral or central binding agents for Aβ. Drugs that down regulate RAGE and up regulate LRP-1 at the blood brain barrier may have a capability to readjust the transport equilibrium for Aβ by promoting its efflux from brain into the bloodstream. In AD, as well as transgenic models of AD, RAGE is significantly up regulated at the blood brain barrier, whereas expression of LRP-1 is down regulated [6]. This change in expression of LRP-1 can be affected by upstream events such as the promoter methylation status and other epigenetic modifications responsible for gene regulation.

Modulating LRP-1

A marked loss of endothelial LRP-1 is found in AD brains and is believed to significantly impair Aβ clearance. Shackleton B, et al. reported the therapeutic potential of impeding the proteolytic cleavage activity of enzymes responsible for LRP-1 ectodomain shredding. Proteins bind to LRP-1 at the abluminal surface of the brain endothelium. Aβ and Tau are transported across the blood brain barrier, where it is then released into the general circulation for transport to the liver for organismal elimination via biliary clearance. LRP-1 shedding in the brain and Aβ clearance across the blood brain barrier indicates that reductions in brain LRP1 shedding could promote Aβ clearance across the blood brain barrier. This would attenuate Aβ accumulation in the AD brain. The enzyme, implicated in LRP-1 ectodomain shedding, is the α-secretase, ADAM10 which is a desintegrin and metalloproteinase domain containing protein. The inhibition of ADAM10 effectively reduced LRP-1 shedding and increased Aβ transit across an in vitro model of the blood brain barrier – however, suggested that LRP-1 depletion might limit the therapeutic potential due to the low LRP-1 receptor occupancy found in patients with Alzheimer's disease [7].

Bassendine MF, et al. [1] describes hepatic therapeutics such as transthyretin, which acts as a carrier of Aβ and Tau at the blood brain barrier to the liver using LRP-1. Atorvastatin has also been shown to up regulate liver LRP-1 and this effect is mediated by the sterol response element-binding protein-2 (SREBP-2). Cilostazol enhances LRP-1 expression in liver by activating PPAR through the peroxisome proliferator response element in the LRP-1 promoter [8]. Sehgal N, et al. [9] found that *Withania somnifera* reverses Alzheimer's disease pathology by enhancing low-density lipoprotein receptor-related protein in liver [10,11]. Fiedler, et al. [12] reported the significance effects of miR-122 on the hepatic based LRP-1 and platelet activity [13-16].

MicroRNAs (miRNAs) are small non-coding RNA molecules that regulate gene expression. Application of microRNA mimics alone sufficiently suppressed LRP-1 and microRNA inhibitors recovered LRP-1 expression, confirming microRNAs' role in silencing LRP-1. The inflammasome related cytokine IL-1β, increases NF-κB signaling and the expression of microRNAs to down regulate LRP-1 likely through the inflammasome like mechanism. Kwilas AR, et

al. [17] found three microRNAs, miR-205–5p, miR-200b-3p and miR-200c-3p, are particularly critical for LRP-1 loss [10]. MiRNA-122 is a liver-specific miRNA that is readily detectable in the circulation. Notably, circulating levels of miR-122 are strongly associated with the risk of developing metabolic syndrome [11,12]. Herr U, et al. [13] showed that p53 regulates the expression of LRP-1, inducing apoptosis through a stress intensity-dependent microRNA feedback loop. Leslie, et al. reviews the p53 related induction of LRP-1 expression through either direct pro motor binding or the conical stress pathway. A mechanism of active inhibition of de novo LRP1 translation through a p53-dependent miRNA regulatory feedback mechanism involving miR-103 and miR-107. Herr U, et al. shows that elevated LRP-1 expression causes a decrease of APP transport rate whereas reduced levels of LRP-1 cause an increase of APP transport rates. Thus, LRP-1 mediates intra neuronal trafficking of APP through sorting endocytic vesicle transport mechanisms [13]. In addition, Burke, et al. [16] demonstrated that the IκB kinase inhibitor BMS-345541 reversed IL-1β indecued-LRP-1 down regulation, implying NF-κB signaling involved in this mechanism [14].

Microglia and LRP-1

Microglial inflammation produces cytokines which disrupt the transport of both beta-Amyloids resulting in the accumulation in the brain. LRP-1 is a neuronal receptor for α-synuclein uptake, where spread also is correlated with AD. The low-density lipoprotein receptor (LDLR)-related protein 1 (LRP-1) trans membrane receptor mediates and regulates the endocytosis of apolipoprotein E (APOE) and amyloid-β (Aβ) and is key regulator for the uptake and spread of microtubule-associated protein tau (8,23,29). Interestingly, the affinity of Aβ to bind to soluble form of LRP-1 (sLRP1) in plasma has been suggested to prevent the re-uptake into the brain and serves as a potential treatment option for facilitating peripheral transport to the liver for clearance. LRP-1 controls the endocytosis of tau and its subsequent spread [15,16]. Treatment involving the resolution of the inflammatory pathway will significantly decrease the disease's progression. The severity of inflammatory mechanisms may result in lesion formation as well as and may serve as a gateway for plaque formation, which is the primary symptom for diagnosis in the clinical setting.

The role of microglia may suggest a mechanism of the phagocytosis of dying neurons and mitigate the clearance of degenerated axons and myelin debris after axonal injury in the CNS [17-34]. Yang, et al. [34] found that LRP-1 suppresses microglial activation by modulating JNK and NF-κB signaling pathways, since dysregulation of LRP-1 is associated with AD pathogenesis, Yang et al., research suggest a critical regulatory mechanism of microglial activation by LRP-1 that could be associated with other AD-related pathways, thus further nominating LRP-1 as a potential target for the treatment of AD [19]. Microglia activated by amyloid-β (Aβ) exhibit increased expression of pro-inflammatory cytokines, including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), IL-6, and IL-8, which cause neurotoxicity. Yang et al., reported toss of LRP-1 leads to increased surface expression of TNF-α receptor 1 (TNFR1) and increased phosphorylation of IκBα and NF-κB, suggesting that LRP-1 inhibition leads to NF-κB activation. LRP-1 antagonist RAP was shown to increase the production of pro-inflammatory cytokines by activating JNK and NF-κB signaling pathways. Receptor-associated protein (RAP) is a specialized endoplasmic reticulum (ER) chaperone for LDL receptor family members, including LRP-1. RAP functions in receptor folding and trafficking by blocking premature ligand binding during receptor maturation. Yang, et al. [34] concluded that NF-κB signaling pathway down-stream of LPS modulates the expression of LRP-1 in microglia [19]. Additionally, microglia act as a molecular containment to prevent the transmission of these pathogenic fragments of Tau through the induction of apoptotic proteins like p53 and caspases which promote cellular degradation that is mediated by LRP-1 activity.

Microtubule-Associated Protein Tau (MAPT) and LRP-1

Tau hyper phosphorylation is primarily mediated by Glycogen Synthase Kinase 3 Beta (GSK3β), affects microtubule dynamics and NFT accumulation, which is considered hallmark cytopathology in AD and other tauopathies [20]. It has been validated that both kinase GSK3β and acetylase EP300 are direct targets of miR-132, along with CDK5 which is indirectly repressed by miR-132 via NOS1 signaling. Thus, miR-132 emerges as the primary epigenetic regulator of the post-translational modifications of Tau [21]. The intermolecular forces between tau and LRP-1 are mediated by lysine residues in the microtubule-binding repeat region of tau. Furthermore, down regulation by degradation of LRP-1 was found to effectively reduce the propagation of tau between neurons [22]. LRP-1-expressing cells, but not LRP-1-deficient cells, promote cytosolic tau seeding in a process enhanced by APOE and identifies LRP-1 as an endocytic receptor that binds and processes monomeric forms of tau leading to its degradation. This promotes seeding by pathological forms of LRP-1 that directly binds Aβ and in turn, mediates its clearance from the brain at the blood brain barrier [23]. Phosphorylated forms of tau bind weakly to LRP-1 where the R2 domain of tau contributes to the interaction of tau with LRP-1. The N3R isoform of tau that lacks the second microtubule-binding repeat (R2) is encoded by the alternatively spliced exon 10, and bound to LRP-1 with considerably weaker affinity [24].

Boder EJ, et al. [4] also describes the binding and uptake properties of tau with post-translational modifications corresponding to those seen accumulating in AD, such as multiple phosphorylation's, and acetylation's, which diminish LRP-1-assocaited binding and uptake. Phosphorylated forms of tau bind weakly to LRP-1. The impairment of LRP-1 functionality has been implicated in the development of AD. Yamazaki et al., showed that this effects the regulation of amyloid precursor protein (APP) processing into Aβ but also mediate Aβ export across the blood brain barrier as the expression of LRP-1 is up-regulated in AD patients A Seitkazina, et al. [25,26] LRP-1 receptor pharmacological dynamics remains elusive as there are several factors which influence receptor occupancy and binding affinity and is not mutually exclusive to changes in gene expression – but rather impeded by epigenetic changes related to regulatory proteins responsible for maintaining brain function. The rate of Aβ and Tau clearance from the brain is dependent on the number of LRP-1 receptors available on the cell surface. The greater the occupancy of LRP-1 receptors available for Tau translocation across the plasma membrane has recently been highlighted as a key mechanism of non-conventional tau secretion. Tau translocation is a two-step process:

- Recruitment of tau to the plasma membrane and
- Translocation mediated by heparan sulfate proteoglycans (HSPGs) [4,7,8,27].

LRP-1, MIR-122, and the Liver

The contribution of liver dysfunction to the pathogenesis of AD is due to LRP-1 - endocytosis and the signaling receptor as expressed in multiple tissues. LRP-1, the receptor required for the cerebral and systemic clearance of Aβ. In the brain, Aβ is combined with APOE and transported to peripheral blood through LRP-1 (1). The predominant miRNA in the liver, microRNA-122 (miR-122), has been proposed to play a central role in the regulation of lipid and glucose metabolism. Inhibition of miR-122 induces fatty acid oxidation and reduces lipid synthesis; a clinical application has been suggested and thereby leads to lower levels of total cholesterol [28]. MiR-122 has been found to be associated with metabolic disease and insulin-resistivity and shows promising potential as a therapeutic measure for treating cognitive impairment related to LRP-1 dysfunction [18,20,29]. Willeit P, et al. [32] found that the inhibition of HMG-CoA reductase by atorvastatin reduces miR-122 release. However, no current studies have been able to elucidate on the effects of atorvastatin for Aβ and Tau clearance in AD patients.

Proteins are typically refolded by chaperones, but once aggregated together become nonfunctional and can promote pathological diseases. Proteins which become non-biologically functional undergo protein degradation through the ubiquitination proteasome pathway (UPS) as well as the autophagy-lysosome system. During the development of tau pathologies, mis-localized and mis-folded tau proteins start to accumulate in the cytosol. The ubiquitination proteasome pathway mediates the clearance of soluble tau monomers and aggregates. In the ubiquitination proteasome pathway, tau proteins are tagged with ubiquitin and the ubiquitinylated tau proteins are digested by the 26S proteasome [31]. As tau pathology progresses, tau proteins assemble into large, insoluble fibrils, which exceed the capacity of the ubiquitination proteasome pathway and lead to proteasome dysfunction. The Tau aggregated filaments obturate the 26S proteasome causing accumulation in the neurons and synaptic space forming paired helical filaments [32].

Tau Clearance

Targeted protein degradation using small molecules relies on using endogenous cellular processes for protein regulation. Every cell within all living organisms has evolved mechanisms to regulate protein concentrations in response to external stimuli to maintain homeostasis. Proteolysis targeting chimeric (PROTAC) molecules have been used to target Tau for protein degradation through the proteosome pathway [5,14,15,25,31]. There are over 600 different E3 ligases and a finite amount of available 26S proteosomes for cellular protein recycling, but little is known about the mechanistic transport of these brain wastes to the liver [33]. In the liver, Aβ can be absorbed by hepatocytes via surface LRP-1 and then is excreted through the digestive tract. Both LRP-1 expressions in the liver and hepatic Aβ uptake can be significantly reduced in aging and AD animals, which suggest that there is impaired Aβ peripheral transport and clearance. Studies revealed a strong association between both peripheral liver function biomarkers, as an aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio is typically present in AD patients. Lower levels of ALT were correlated with increased Aβ deposition and exacerbated brain atrophy, while higher AST to ALT ratios was significantly correlated with reduced glucose metabolism in some brain regions, including the bilateral frontal, parietal, and temporal lobes. This observation is supported by studies where insulin promotes LRP-1 translocation to the cell membrane in hepatocytes, favoring Aβ clearance [9]. The stimulation of LRP-1-mediated liver uptake improves cognitive impairment and decreases Aβ aggregation in the brain as seen in the AD transgenic mouse model [27]. Liver dysfunction is accompanied by low LRP-1 hepatic expression and high levels of circulating Aβ. This correlation suggests that Aβ elimination decreases due to low hepatic LRP-1 activity. More research is needed to relationships between microRNA, LRP-1, and the UPS pathway with respect to Aβ and Tau clearance through hepatic activity in patients with insulin-resistivity and fatty liver in AD patients with clinical

dementia.

Conclusion

The extracellular amyloid plaques formed by the deposition of amyloid-beta (Aβ) peptides are the specific hallmark of AD. The elevated levels of Aβ as initiating factor in AD pathogenesis as well as its neurotoxic aggregates in the brain are associated with the perturbation of synaptic function. This neural network activity affects lead to cognitive deficits and neurodegeneration. Clinical symptoms of Alzheimer's Disease (AD) appear after significant brain deterioration has occurred and is correlated with the accumulation of both beta amyloid 40 and 42 (Aβ-42) and Tau proteins. The nature of hepatic toxicology on systemic systems has been suggested to be related to the inability of the liver to clear metabolic waste from the body. A metabolic protein become toxic as the peptide waste buildups in the blood and interferes with metabolic homeostasis. This suggests the critical role of the liver in promoting the clearance of metabolic brain protein wastes through the hepatic digestive system [34]. Liver diseases including cirrhosis and hepatitis can result in an increase of brain waste products in the blood. An increase in both beta amyloid and Tau proteins in the brain can impact liver function and further exacerbate molecular stress throughout the body. Since, the liver is the primary detoxification site for both amyloid beta and Tau protein waste, impairment of hepatic function can further impact neuronal degradation. LRP-1 activity can influence the rate at which bioaccumulation occurs and thus, offers a connective relationship between the known causality factors related to cognitive impairment.

Conflicts of Interest

None

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