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Role of PCSK9 in Alzheimer's Disease by Modulating Brain Cholesterol Homeostasis: An Overview

Priyanka Arya[1,*], Vikram Sharma[1], Rahul Sagar[2], Surabhi Thapliyal[3]

[1]Galgotias College of Pharmacy, Greater Noida, India
[2]AnovIP, New Delhi, 110049, India
[3]Department of Pharmacology, All India Institute of Medical Sciences, Rishikesh 249203, India

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Abstract Impaired brain cholesterol homeostasis has been implicated in the development and progression of Alzheimer's disease (AD). Cholesterol is crucial for various neuronal functions, including synapse formation, neurotransmitter release, and membrane fluidity. Disruptions in cholesterol metabolism can lead to the accumulation of toxic proteins such as beta-amyloid and tau, which are hallmarks of AD pathology. Proprotein convertase subtilisin/kexin type 9 (PCSK9) was initially discovered in the brain, suggesting it may play a role in brain development and cell death. While its exact function in the nervous system and the progression of Alzheimer's disease (AD) remains unclear, PCSK9 is believed to affect neuronal and lipid receptors, such as low-density lipoprotein receptors (LDLR), LDL receptor-related protein 1 (LRP1), and apolipoprotein E (APOE). These effects can lead to decreased cholesterol uptake by neurons and glial cells, disrupting cellular functions and potentially contributing to neurodegeneration and the development of AD. Studies have shown that PCSK9 levels are elevated in the cerebrospinal fluid (CSF) of individuals with AD, suggesting a potential association between PCSK9 and AD pathogenesis. Additionally, evidence highlights that treatment with PCSK9 inhibitors like alirocumab and evolocumab reduces dendritic spine loss via reduction of microglial, astrocytic activation and amyloid β aggregation. Overall, while the exact mechanisms by which PCSK9 influences brain cholesterol homeostasis in AD are still being elucidated, accumulating evidence suggests that PCSK9 may play a role in this process and could represent a potential therapeutic target for AD. Therefore, the present review sheds light on the PCSK9 potential role in the pathogenesis of AD by modulating brain cholesterol homeostasis.

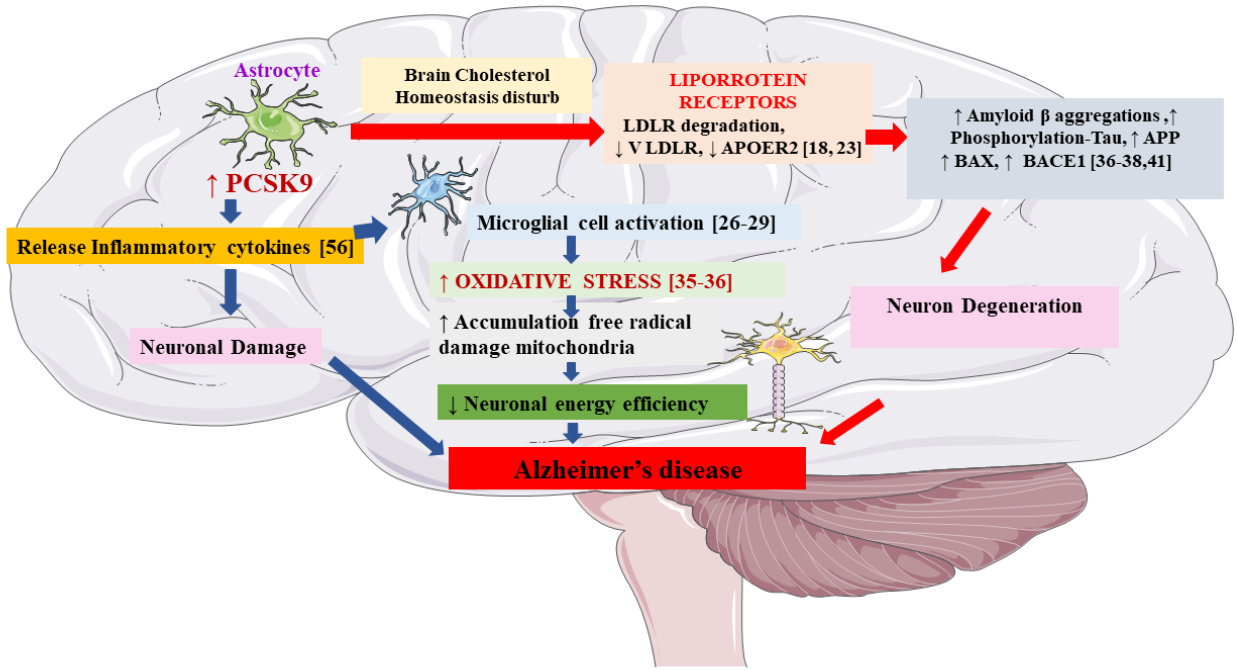
Keywords Proprotein Convertase Subtilisin/Kexin Type 9, Alzheimer's Disease, Cholesterol, Cerebrospinal Fluid, Low Density Lipoprotein Receptor, Astrocyte, Glial, Neuroinflammation

1. Introduction

Alzheimer’s disease (AD) is the most prevalent type of dementia and neurodegenerative disorder, marked by a reduction in short-term memory and cognition, significantly impairing daily functioning [1]. The disease is marked by the loss of synapses and neuronal atrophy, especially in the hippocampus and cerebral cortex. This is accompanied by the occurrence of amyloid plaques and neurofibrillary tau tangles (NFTs), which are clusters of misfolded proteins spreading throughout the brain. Researchers have identified a strong link between cholesterol levels and Alzheimer's disease [2]. Findings suggest that elevated cholesterol levels, especially during middle and later life, are connected with an increased risk of developing dementia. Notably, dyslipidemia,

characterized by high levels of LDL cholesterol, is believed to exert vascular and neurotoxic effects, contributing to the pathogenesis of AD [3]. Moreover, studies have indicated that elevated total cholesterol levels in brain membranes disrupt synaptic function, thereby contributing to cognitive decline in AD (Fig. 1) [3-5].

Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) is essential in managing cholesterol levels by promoting the destruction of hepatic low-density lipoprotein receptors (LDLR) [6]. Initially discovered in the brain, PCSK9 shows maximum production in primary embryonic telencephalon cells during the significant neurogenesis period between embryonic days 13 and 15 [7]. Knockdown experiments in zebrafish revealed that the absence of PCSK9 mRNA reflects the disruption of cerebellar neuron organization and the loss of hindbrain-midbrain boundaries, ultimately resulting in embryonic death, a phenomenon not observed in mice [8]. This review article will explore the effect of PCSK9 on brain functions, focusing on particularly its potential implications for neuronal processes and the pathogenesis of AD. Additionally, we will examine the concept of PCSK9 as a balance regulator for cholesterol and inflammation in the brain, suggesting it as a possible therapeutic target for neurocognitive disorders.



LDLR, low density lipoprotein; VLDLR, very-low-density-lipoprotein receptor; ApoER2, apolipoprotein E receptor-2; APP, Amyloid-beta precursor protein; BAX, bcl-2-like protein 4; BACE1, beta-site amyloid precursor protein cleaving enzyme 1.

Figure 1. Insights into the PCSK9 impact in Alzheimer's disease by modulating brain cholesterol homeostasis

2. Methodology

Scientific material was collected using online search engines and databases such as Science Direct, Scopus, PubMed, and Google Scholar. Keywords used for the search included “Alzheimer's disease”, “Proprotein convertase subtilisin/kexin type 9”, “cholesterol”, “cerebrospinal fluid”, “astrocyte”, “glial”, and “neuroinflammation”.

2.1. PCSK9 Biology

In 2003, PCSK9 was discovered for the first time in primary cerebellar neurons and was initially known as neural apoptosis-regulated convertase-1 (NARC-1) due to its mRNA levels increasing during apoptosis, the process of programmed cell death [9]. It is serine proteinase and the ninth member of the family named as proprotein convertases (PCs), which are responsible for converting quiescent secretory precursors into active forms of proteins and peptides. The secretory proprotein convertase family includes nine enzymes: proprotein convertase 1 (PC1), PC2, furin, PC4, PC5, paired basic amino acid cleaving enzyme 4 (PACE4), PC7, subtilisin kexin isozyme 1 (SKI-1, also known as S1P), and proprotein convertase subtilisin kexin 9 (PCSK9). Their corresponding genes are labeled PCSK1 through PCSK9 [10, 11].

2.2. Structural Features of PCSK9

The human PCSK9 gene is found on chromosome 1p32.3 and is translated within the endoplasmic reticulum (ER) into a zymogen that is around 82 kDa in size [12,13]. In the ER, mature PCSK9 is produced by autocatalytic cleavage of its pro-form at the internal VFAQ152 sequence. Once secreted, PCSK9 stays attached to its catalytic domain, functioning as a heterodimeric protein. The prodomain, which is about 17 kDa, inhibits the catalytic activity of PCSK9 [11,14,15].

Primarily secreted by hepatocytes into the bloodstream, PCSK9 is present in both active and inactive forms in the plasma. The active state of PCSK9, an entire-length heterodimer of approximately 62 kDa, mainly binds to LDL particles, protecting it from being converted into its inactive state by furin [7]. The inactive heterodimer, about 55 kDa in size, contains 15-40% of systemic PCSK9 and circulates freely. This inactive state reduces twofold affinity for the LDLR and decreases the ability to destroy it [16]. PCSK9 primarily binds with LDL, and its interaction with high-density lipoprotein (HDL) is a subject of debate and ongoing research. PCSK9's most significant role lies in its binding with the hepatic LDLR. This was discovered in 2003 when two gain-of-function mutations in the PCSK9 gene were found in a French family with autosomal dominant hypercholesterolaemia [12,17].

2.3. PCSK9 and LDLR

PCSK9 binds to LDLR, leading to its internalization and destruction. This interaction is facilitated through the epidermal growth factor-like repeat A (EGF-A) domain of LDLR. During endocytosis, in the acidic environment of the endosome, the affinity between PCSK9 and LDLR increases. Consequently, PCSK9 prevents the LDLR from adopting the open extended orientation needed for receptor recycling. Rather, the PCSK9 and LDLR complex is targeted for breakdown within the lysosome. This leads to a decrease in the number of LDLRs on the cell surface, resulting in higher plasma cholesterol levels [18].

The homeostasis of plasma PCSK9, lipid receptors, and LDL-C levels is closely intertwined. Plasma PCSK9 is primarily cleared through its binding to LDLR. Paradoxically, PCSK9's interaction with LDLR also induces LDLR degradation. This intricate relationship underscores the importance of PCSK9 in modulating LDL-C levels and highlights its potential as a therapeutic target for managing hypercholesterolemia [19]. PCSK9's interactions extend beyond just the LDL receptor (LDLR) family. While its primary interaction occurs with LDLR in the liver, it also binds to other receptors within the LDLR family, such as the LDL receptor-related protein-1 (LRP1) and the scavenger receptor B type CD36 [20].

2.4. PCSK9 and LRP1

LRP1 is an endocytic receptor that contributes to lipid balance, intracellular signaling, and β-amyloid peptide elimination. It may be found in a variety of cell types, including astrocytes, neurones, and vascular cells, as well as liver cells. PCSK9 promotes the destruction of LRP1 in multiple types of cells, including arterial cells and hepatocytes [21].

2.5. PCSK9 and CD36

CD36 plays a significant role in microglial activation triggered by fibrillar Aβ and in the uptake of oxidized LDL. Increased levels of PCSK9 have been found to enhance the expression of CD36 in macrophages [22]. PCSK9 binds with various receptors in the brain that are involved in the distribution of cholesterol into neurons. These include the LDLR, the very low-density lipoprotein receptor (VLDLR), and the apolipoprotein E receptor 2 (ApoER2) [23]. Overall, PCSK9's interactions with various receptors highlight its multifaceted role in lipid metabolism and suggest potential implications beyond its classical role in LDL-C regulation. PCSK9 is expressed not only in the liver but also in tissues such as the brain. small intestine, and kidney. Understanding the function of PCSK9 in the nervous system is especially crucial because the brain contains about 25% of the body's total cholesterol [24, 25]. Cholesterol regulation in the brain differs from that in peripheral tissues, and normally, neither lipoprotein nor PCSK9 penetrates into the blood-brain barrier [16].

2.6. PCSK9 and Cerebrospinal Fluid

In instances where pathological conditions compromise the blood-brain barrier, the regulation of brain cholesterol homeostasis may be affected. Research has indicated that the concentration of PCSK9 in the cerebrospinal fluid (CSF) remains relatively stable at 5 ng/ml over a 24-hour period. In contrast, serum PCSK9 levels exhibit diurnal fluctuations, ranging from 183 ng/ml in the afternoon to 552 ng/ml in the early morning [25].

This disparity between CSF and serum PCSK9 levels highlights the necessity to delve deeper into PCSK9's specific role within the nervous system. Understanding how PCSK9 operates in the brain, particularly under pathological conditions that disrupt the BBB, could offer valuable insights into neurological health and disease [26].

2.7. Brain Cholesterol Homeostasis

Cholesterol regulation in the brain undergoes dynamic changes throughout human development and aging. Initially, during brain development, cholesterol synthesis rates are elevated to facilitate the formation of a complex neuronal network [26]. This heightened synthesis involves a variety of cell types in the brain, including glial cells and neurones. However, as an individual reaches adulthood, the rate of cholesterol synthesis declines [27-29]. At this stage, astrocytes primarily take on the responsibility of producing cholesterol to maintain adequate levels for neuronal plasticity and optimal glial function. This transition highlights the adaptive nature of cholesterol homeostasis in the brain, ensuring its continuous support for cognitive processes across the lifespan [30].

The brain, shielded by the blood-brain barrier which prevents cholesterol molecules from crossing, relies on local cholesterol synthesis. However, oxidized cholesterol metabolites can traverse the barrier [31]. While nervous cells have the capacity to produce cholesterol, adult neurons gradually lose this ability and depend on astrocytes for cholesterol supply. Decreased neuronal cholesterol levels result in adverse effects like excessive tau phosphorylation, altered metabolism of β-amyloid peptides, oxidative stress reactions, and ultimately, neurodegeneration [24, 32].

The movement of cholesterol from astrocytes to neurons involves several specific molecules and receptors working together [33]. Astrocytes produce cholesterol, which is transported to neurons via particles containing Apolipoprotein E (ApoE). This process is facilitated by transporters such as ATP binding cassette transporters A1 (ABCA1), G1 (ABCG1), and G4 (ABCG4). These cholesterol-carrying particles, similar to plasma HDL, bind to neuronal receptors like the LDLR, VLDLR, LRP1 and ApoER2. The degradation of VLDLr and ApoEr2 by PCSK9 suggests its involvement in cerebral cholesterol homeostasis (Fig.1) [33-35]. Studies also indicate that PCSK9 may reduce cholesterol uptake by neurons, potentially leading to harmful effects. However, conflicting data exist; for instance, some studies suggest that PCSK9 does not affect the expression of certain receptors in the brain. Further research is needed to clarify PCSK9's role in brain cholesterol regulation [35].

2.8. PCSK9 Link to Alzheimer's Disease

PCSK9, a protein involved in cholesterol metabolism, has garnered interest in relation to Alzheimer's disease (AD) pathogenesis [35]. Research suggests a potential link between PCSK9 and AD due to its role in regulating cholesterol levels in the brain. In 2023, Papotii et al. investigated PCSK9's neurotoxic effects. They assessed PCSK9's impact on astrocyte cholesterol breakdown as well as its function in delivering cholesterol to neurones for proper function [36]. They discovered that PCSK9 reduced cholesterol levels in human astrocytoma cells by 20%. This effect was amplified when beta amyloid peptide (Aβ) was present, as cholesterol was reduced by 37%. PCSK9 boosted the production of cholesterol while reducing the absorption of cholesterol from apoE-HDL particles by 36%. Additionally, it reduced by 66% and 31%, respectively, the expression of the apoE receptor 2 (ApoER2) and the LDL receptor (LDLR). However, PCSK9 did not affect ABCA1- and ABCG1-mediated cholesterol efflux or ABCA1 levels. Interestingly, exposure to Aβ reduced ABCA1 expression and activity, as well as membrane cholesterol levels. In human neuronal cells, PCSK9 decreased the uptake of cholesterol derived from apoE-HDL particles by 41% and reduced the expression of LDLR and apoER2. Neurons overexpressing PCSK9 and exposed to an astrocyte-conditioned medium also showed reduced cholesterol internalization by 39%. Overall, PCSK9 caused a 29% reduction in neuronal cholesterol levels and heightened Aβ-induced neurotoxicity (Fig. 1). The researchers concluded that PCSK9 disrupts brain cholesterol metabolism, resulting in lower neuronal cholesterol levels, which could have harmful consequences. Furthermore, PCSK9 has been shown to have neurotoxic effects, indicating that it may be a target for therapeutic intervention in Alzheimer's disease [36]. Researchers reveal that patients with AD have higher concentrations of PCSK9 (+1.4-fold increase) in their cerebrospinal fluid (CSF) as compared to individuals without AD. Moreover, the apoE4 level(+3.34-fold) was also increased [37]. From a molecular perspective, lipid rafts—specialized transmembrane microdomains function in the breakdown of the amyloid precursor protein (APP)—tend to collect cholesterol. This accumulation leads to the aggregation of insoluble particles of amyloid-beta (Aβ) in the brain tissue. Research indicates that cholesterol plays a role in promoting amyloidogenes by enhancing the structural stability of lipid rafts located near membranes. Therefore, alterations in the cholesterol content within lipid rafts can influence the deposition of Aβ [37, 38]. Picard and their

coworkers reported that increased expression of PCSK9 has been observed in the frontal cortex of patients which is the brain region primarily affected by the disease as well as also increased phospho Tau (pTau) and total Tau with AD (Fig. 1) [39]. Wu and coworkers reported that PCSK9 decreases apoEr2 while stimulating neuronal apoptosis [40]. Another preclinical study shows that feeding high-fat diets to APOE (−/−) mice causes neuronal death via upregulating the levels of PCSK9 and BACE1, as well as increases lipid buildup in the hippocampal region of the brain [41].

2.9. PCSK9 Targets Lipoprotein Receptors and their Implications in Alzheimer's Disease

LDLRs are a set of closely related cell surface receptors found abundantly in the central nervous system (CNS), known for their involvement in Alzheimer's disease (AD) pathology [42,43]. Among these receptors, LRP1 and LDLR play crucial roles in regulating levels of apoE in the brain. LRP1 interacts with apoE-antibody complexes, tissue-type plasminogen activator, myelin, and tau, influencing processes like amyloid-beta (Aβ) clearance, blood-brain barrier (BBB) disruption, myelin degradation, and tau propagation [44-46]. Meanwhile, LDLR manages cholesterol transport and apoE metabolism in neurons and astrocytes. Notably, LDLR deficiency leads to elevated apoE levels in cerebrospinal fluid (CSF), suggesting the importance of functional receptor activity in controlling apoE levels (Fig. 1) [42].

The Holtzman lab performed an experimental study where they engineered a mouse model with increased expression of LDLR in the brain using the prion promoter [47]. This model demonstrated that increased LDLR levels in the brain could lower apoE levels and mitigate Aβ-related pathology in an AD mouse model (APP/PS1). Researchers found the exacerbating effect of apoE4 on tau-mediated neurodegeneration. The question arose whether LDLR overexpression could also offer protection against tauopathy [47]. To explore this, another study done by Shi et al., in 2021 bred LDLR-overexpressing mice with the P301S mouse model of tauopathy. The resultant P301S/LDLR mice exhibited a 90% reduction in apoE levels in CSF along with reduced brain atrophy. LDLR was found expressed in various CNS cell types including microglia, astrocytes, and neurons in P301S/LDLR mice. Notably, microglial LDLR expression was correlated with apoE reduction in these cells. Furthermore, a synaptic loss in the hippocampal CA3 region was diminished, and phosphorylated tau (p-tau) levels were shifted towards an early disease phenotype, with decreased p-tau levels in the CSF of P301S/LDLR mice [48]. These findings indicate a beneficial role for brain LDLR overexpression in reducing apoE levels and mitigating neurodegenerative features in a tauopathy animal model. PCSK9 elevates cholesterol levels during brain development by lysosomal degradation of LDLR (16). Researchers reveal that in mice lacking the Pcsk9 gene, levels of the LDLR protein were notably higher in certain brain regions compared to normal mice at specific developmental stages. Additionally, the effect on the apoE level was about 25% lower in these mice (Fig. 1) [49]. Studies conducted by both in vitro and in vivo mice present conflicting findings regarding whether PCSK9 in the nervous system destroys the ApoER2, LDLR and VLDLR. When these receptors were co-transfected with PCSK9 into cultured HEK293 cells, there was a significant reduction in the levels of all three receptor proteins compared to cells without PCSK9 [50].

The precise negative influence of PCSK9 on the clearance of brain amyloid-beta (Aβ) through LRP1 receptors remains unclear [51]. PCSK9 interacts with LDLR protein family members on the cell surface, causing their lysosomal degradation and reducing the functional receptor numbers [51]. However, the specific negative effect of PCSK9 on LRP1-mediated Aβ clearance from the brain is not fully clear. Research has shown that PCSK9 enhances the destruction of LRP1 in multiple types of cells, like hepatocytes and arterial cells [52]. PCSK9 is highly abundant in nerve and vascular cells, and it may impact LRP1 levels in these specific cell types. Elevated concentrations of PCSK9 in the cerebrospinal fluid of individuals with Alzheimer's disease might increase the turnover of LRP1 in various cell types, potentially affecting the removal of Aβ across the blood-brain barrier (Fig. 1) [37].

2.10. PCSK9 Inhibitors Role in Alzheimer's Disease

In the United States, three pharmaceutical options are accessible for reducing PCSK9 activity: alirocumab, evolocumab, and inclisiran. Alirocumab and evolocumab are fully-human monoclonal antibodies, whereas inclisiran functions differently as a small interfering RNA (siRNA) that inhibits the intracellular production of PCSK9 [53]. PCSK9 monoclonal antibodies represent a novel approach to lipid-lowering therapy, extensively researched in hypercholesterolemia patients, either alone or alongside other lipid-lowering treatments. These antibodies have shown considerable efficacy in reducing plasma levels LDL-C, leading to improved achievement of LDL-C targets [54]. According to research, brain damage resulted from cardiac I/R injury in rats, which triggered microglial activation in the brain. Pretreatment with a PCSK9 inhibitor decreased amyloid β formation, astrocytic activation, and microglial function by preventing the loss of the dendritic spine [55]. A recent study done by Wagner and colleges in 2024, reported that long-term exposure to ethanol in rats increases the expression of PCSK9, oxidative stress, inflammatory cytokines, adhesion molecules and degrade LDLR in the brain. However, treatment with alirocumab boosts the levels of neuronal LDLR and reduces oxidative stress in neurons and brain blood vessels. Alirocumab also reduces the recruitment of microglia in key brain regions affected by ethanol exposure.

Moreover, it decreases the levels of inflammatory molecules (TNF, CCL2, CXCL3) in the brain and prevents the overexpression of molecules involved in cell adhesion such as ICAM1, VCAM1 in brain blood vessels (Fig. 1). This study highlights the potential of alirocumab to alleviate oxidative stress and modulate immune responses in the brain caused by chronic ethanol exposure [56]. Further research is necessary to understand how PCSK9 signaling affects the brain under AD.

3. Conclusions

Although the liver-related functions of PCSK9 are well-documented, its role in the brain is still undergoing intense study. Emerging evidence from both laboratory experiments and animal studies indicates that PCSK9 may play various roles in brain function. These roles encompass affecting the differentiation of neural cells into neurons, managing the degradation of LDLR family receptors in lysosomes, regulating neuronal cell death, and initiating the stimulation of astrocytes and glial cells in the brain. Research using cultured cells, preclinical models, and genetic studies has shed light on the involvement of PCSK9 in several central nervous system (CNS) disorders, including Alzheimer's disease, myocardial ischemia, atherosclerosis, hypercholesterolemia, brain stroke, and neuropsychiatric conditions. A critical question that is yet unanswered is whether PCSK9 exerts its effects on CNS disorders through direct actions in the nervous system or through systemic effects on peripheral tissues that subsequently impact the nervous system. For instance, in Alzheimer's disease, PCSK9 may directly influence the brain by reducing BACE1 expression, while indirectly affecting the brain by raising LDL-C levels, which in turn affect the development and aggregation of Aβ plaques in the brain. Furthermore, it is unclear if PCSK9 regulates inflammation locally in the brain in addition to raising plasma LDL-C levels, which may be a contributing factor to systemic inflammation. Additionally, further research is necessary to investigate whether PCSK9 monoclonal antibodies primarily exert systemic or localized effects in the brain, and whether they penetrate the blood-brain barrier during disease conditions such as Alzheimer's disease, stroke, and chronic inflammatory brain diseases.

REFERENCES

[1] Tiwari S., Atluri V., Kaushik A., Yndart A., Nair M., "Alzheimer's disease: pathogenesis, diagnostics, and therapeutics," International Journal of Nanomedicine, vol. 19, no. 4, pp. 5541-5554, 2019. DOI: 10.2147/IJN.S200490.

[2] Sheppard O., Coleman M., "Alzheimer's disease: etiology, neuropathology and pathogenesis," Exon Publications, vol. 19, no. 3, pp. 1-21, 2020. DOI: 10.36255/exonpublications.alzheimersdisease.2020.ch1

[3] Liu Y., Zhong X., Shen J., Jiao L., Tong J, Zhao W., Du K., Gong S., Liu M., Wei M., "Elevated serum TC and LDL-C levels in Alzheimer's disease and mild cognitive impairment: A meta-analysis study," Brain Research, vol. 1727, pp. 146547-146554, 2020. DOI: 10.1038/s41928-019-0233-2

[4] Feringa FM., Van der Kant R., "Cholesterol and Alzheimer's disease; from risk genes to pathological effects," Frontiers in Aging Neuroscience, vol. 24, no. 13, pp. 690367-690372, 2021. DOI: 10.3389/fnagi.2021.690372.

[5] Xu W., Tan L., Wang HF., Jiang T., Tan MS., Tan L., Zhao QF., Li JQ., Wang J., Yu JT., "Meta-analysis of modifiable risk factors for Alzheimer's disease," Journal of Neurology, Neurosurgery & Psychiatry, vol. 86, no. 12, pp. 1299-1306, 2015. DOI: 10.1136/jnnp-2015-310548.

[6] Macchi C., Banach M., Corsini A., Sirtori CR., Ferri N., Ruscica M., "Changes in circulating pro-protein convertase subtilisin/kexin type 9 levels–experimental and clinical approaches with lipid-lowering agents," European Journal of Preventive Cardiology, vol. 26, no. 9, pp. 930-949, 2019. DOI: 10.1177/2047487319831500.

[7] Seidah, N.G., Benjannet, S., Wickham, L., Marcinkiewicz, J., Jasmin, S. B., Stifani, S., "The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation," Proceedings of the National Academy of Sciences, vol. 100, no. 3, pp. 928–933. DOI: 10.1073/pnas.0335507100.

[8] Poirier S., Mayer G., Poupon V., McPherson PS., Desjardins R., Ly K., Asselin MC., Day R., Duclos FJ., Witmer M., Parker R., "Dissection of the endogenous cellular pathways of PCSK9-induced low density lipoprotein receptor degradation: evidence for an intracellular route," Journal of biological chemistry, vol. 284, no. 42, pp. 28856-28864, 2009. DOI: 10.1074/jbc.M109.037085.

[9] Malo J., Parajuli A., Walker SW., "PCSK9: from molecular biology to clinical applications," Annals of clinical biochemistry, vol. 57, no. 1, pp. 7-25, 2020. DOI: 10.1177/0004563219864379

[10] Barale C., Melchionda E., Morotti A., Russo I., "PCSK9 biology and its role in atherothrombosis," International journal of molecular sciences, vol. 22, no. 11, pp. 5870-5880, 2021. DOI: 10.3390/ijms22115880

[11] Seidah N. G., Mayer G., Zaid A., Rousselet E., Nassoury N., Poirier S., "The activation and physiological functions of the proprotein convertases," International Journal of Biochemistry & Cell Biology, vol. 40, no. 12, pp. 1111–1125, 2008. DOI: 10.1016/j.biocel.2008.01.030

[12] Abifadel M., Varret M., Rabès J.-P., Allard D., Ouguerram K., Devillers M., "Mutations in PCSK9 cause autosomal dominant hypercholesterolemia," Nature Genetics, vol. 34, no. 16, pp. 154–156, 2003. DOI: 10.1038/ng1161.

[13] Piper D. E., Jackson S., Liu Q., Romanow W. G., Shetterly S., Thibault S. T., "The crystal structure of PCSK9: a regulator of plasma LDL-cholesterol," Structure, vol. 15, no. 6, pp. 545–552, 2007. DOI: 10.1016/j.str.2007.04.004.

[14] Benjannet S., Rhainds D., Essalmani R., Mayne J., Wickham L., Jin W., "NARC-1/PCSK9 and its natural mutants: zymogen cleavage and effects on the low density lipoprotein (Ldl) receptor and Ldl cholesterol," Journal of Biological Chemistry, vol. 279, no. 18, pp. 48865–48875, 2004. DOI: 10.1074/jbc.M409699200.

[15] Tavori H., Fan D., Blakemore J. L., Yancey P. G., Ding L., Linton M. F., Fazio S., "Serum proprotein convertase subtilisin/kexin type 9 and cell surface low-density lipoprotein receptor: evidence for a reciprocal regulation," Circulation, vol. 127, no. 24, pp. 2403-2413, 2013. DOI: 10.1161/circulationaha.113.001592.

[16] O'Connell EM., Lohoff FW., "Proprotein convertase subtilisin/kexin type 9 (PCSK9) in the brain and relevance for neuropsychiatric disorders," Frontiers in neuroscience, vol. 14, no. 4, pp. 548880-548891, 2020. DOI: 10.3389/fnins.2020.00609.

[17] Horton JD., Cohen JC., Hobbs HH., "Molecular biology of PCSK9: its role in LDL metabolism," Trends in biochemical sciences, vol. 32, no. 2, pp. 71-80, 2007. DOI: 10.1016/j.tibs.2006.12.008.

[18] Warden BA., Fazio S., Shapiro MD., "The PCSK9 revolution: Current status, controversies, and future directions," Trends in cardiovascular medicine, vol. 30, no. 3, pp. 179-185, 2020. DOI: 10.1016/j.tcm.2019.05.007.

[19] Lagace TA., "PCSK9 and LDLR degradation: regulatory mechanisms in circulation and in cells," Current opinion in lipidology, vol. 25, no. 5, pp. 387-393, 2014. DOI: 10.1097/MOL.0000000000000114.

[20] Canuel M., Sun X., Asselin MC., Paramithiotis E., Prat A., Seidah NG., "Proprotein convertase subtilisin/kexin type 9 (PCSK9) can mediate degradation of the low density lipoprotein receptor-related protein 1 (LRP-1)," PloS one, vol. 8, no. 5, pp. e64145, 2023. DOI: 10.1371/journal.pone .0064145.

[21] Dieckmann M., Dietrich M. F., Herz J., "Lipoprotein receptors– an evolutionarily ancient multifunctional receptor family," Journal of Biological Chemistry, vol. 391, no. 20, pp. 1341–1363, 2010. DOI: 10.1515/BC.2010.129

[22] Ding Z., Liu S., Wang X., Theus S., Deng X., Fan Y., Zhou S., Mehta JL., "PCSK9 regulates expression of scavenger receptors and ox-LDL uptake in macrophages," Cardiovascular Research, vol. 114, no. 8, pp. 1145-1153, 2018. DOI: 10.1093/cvr/cvy079.

[23] Adorni MP., Ruscica M., Ferri N., Bernini F., Zimetti F., "Proprotein convertase subtilisin/kexin type 9, brain cholesterol homeostasis and potential implication for Alzheimer's disease," Frontiers in aging neuroscience, vol. 11, no. 3, pp. 111- 120, 2019. DOI: 10.3389/fnagi.2019.00 120

[24] Dietschy JM., "Central nervous system: cholesterol turnover, brain development and neurodegeneration," Biological Chemistry, vol. 390, no. 4, pp. 287-293, 2009. DOI: 10.1515/BC.2009.035.

[25] Chen YQ., Troutt JS., Konrad RJ., "PCSK9 is present in human cerebrospinal fluid and is maintained at remarkably constant concentrations throughout the course of the day," Lipids, vol. 49, no. 5, pp. 445-455, 2014. DOI: 10.1007/s11745-014-3895-6.

[26] Waelsoh H., Sperry WM., Stoyan Off VA., "Lipid metabolism in brain during myelination," Journal of Biological Chemistry, vol. 135, pp. 297-302, 1940.

[27] Quan G., Xie C., Dietschy JM., Turley SD., "Ontogenesis and regulation of cholesterol metabolism in the central nervous system of the mouse," Developmental brain research, vol. 46, no. 2, pp. 87-98, 2003. DOI: 10.1016/j.devbrainres.2003.09.015

[28] Pfrieger FW., "Role of cholesterol in synapse formation and function," Biochimica et Biophysica Acta (BBA)-Biomembranes, vol. 1610, no. 2, pp. 271-280, 2003. DOI: 10.1016/s0005-2736(03)00024-5.

[29] Lütjohann D., Breuer O., Ahlborg G, Nennesmo I., Siden A., Diczfalusy U., Björkhem I., "Cholesterol homeostasis in human brain: evidence for an age-dependent flux of 24S-hydroxycholesterol from the brain into the circulation," Proceedings of the National Academy of Sciences, vol. 93, no. 18, pp. 9799-9804, 1996. DOI: 10.1073/pnas.93.18.97 99.

[30] Zhang Y., Chen K, Sloan SA., Bennett ML., Scholze AR., O'Keeffe S., Phatnani HP., Guarnieri P., Caneda C., Ruderisch N., Deng S., "An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex," Journal of Neuroscience, vol. 34, no. 3, pp. 11929-11947, 2014. DOI: 10.1523/JNEUROSCI.1860-14.2014

[31] Björkhem I., Meaney S., "Brain cholesterol: long secret life behind a barrier," Arteriosclerosis, thrombosis, and vascular biology, vol. 24, no. 5, pp. 806-815, 2004. DOI: 10.1161/01.ATV.0000120374.59826.1b.

[32] Saito K., Dubreuil V., Arai Y., Wilsch-Bräuninger M., Schwudke D., Saher G., Miyata T., Breier G., Thiele C., Shevchenko A., Nave KA, "Ablation of cholesterol biosynthesis in neural stem cells increases their VEGF expression and angiogenesis but causes neuron apoptosis," Proceedings of the National Academy of Sciences, vol. 106, no. 20, pp. 8350-8359, 2009. DOI: 10.1073/pnas.0903541 106.

[33] Koudinov AR., Koudinova NV, "Cholesterol homeostasis failure as a unifying cause of synaptic degeneration," Journal of the neurological sciences, vol. 229, no. 10, pp. 233-240, 2005. DOI: 10.1016/j.jns.2004.11.036.

[34] Chen J., Zhang X., Kusumo H., Costa L. G., Guizzetti M., "Cholesterol efflux is differentially regulated in neurons and astrocytes: implications for brain cholesterol homeostasis," Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids, vol. 1831, no. 2, pp. 263-275, 2013. DOI: 10.1016/j.bbalip.2012.09.007

[35] Liu CC., Kanekiyo T.., Xu H, Bu G., "Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy," Nature Reviews Neurology, vol. 9, no. 2, pp. 106-118. DOI: 10.1038/nrneurol.2012.263

[36] Papotti B., Adorni MP., Marchi C., Zimetti F., Ronda N., Panighel G., Lupo MG., Vilella A., Giuliani D., Ferri N., Bernini F., "PCSK9 Affects Astrocyte Cholesterol Metabolism and Reduces Neuron Cholesterol Supplying In Vitro: Potential Implications in Alzheimer's Disease," International Journal of Molecular Sciences, vol. 23, pp. 21911-21921, 2022. DOI: 10.3390/ijms232012192.

[37] Zimetti F., Caffarra P., Ronda N., Favari E., Adorni MP., Zanotti I., Bernini F., Barocco F., Spallazzi M., Galimberti D., Ricci C., "Increased PCSK9 cerebrospinal fluid concentrations in Alzheimer's disease," Journal of Alzheimer's Disease, vol. 55, no. 1, pp. 315-320, 2017. DOI: 10.3233/JAD-160411.

[38] Vetrivel KS., Thinakaran G., "Membrane rafts in Alzheimer's disease beta-amyloid production," Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids," vol. 1801, no. 8, pp. 860-867, 2010. DOI: 10.1016/j.bbalip.2010.03.007

[39] Picard C., Poirier A., Belanger S., Labonte A., Auld D., Poirier J., "Proprotein convertase subtilisin/kexin type 9 (PCSK9) in Alzheimer's disease: A genetic and proteomic multi-cohort study," PLoS One, vol. 14, no. 8, pp. e0220254, 2019. DOI: 10.1371/journal.pone.0220254.

[40] Wu Q., Tang ZH., Peng J., Liao L., Pan LH., Wu CY., Jiang ZS., Wang GX., Liu LS., "The dual behavior of PCSK9 in the regulation of apoptosis is crucial in Alzheimer's disease progression," Biomedical Reports. vol. 2, no. 2, pp. 167-171, 2014. DOI: 10.3892/br.2013.213.

[41] Zhao XS., Wu Q., Peng J., Pan LH., Ren Z., Liu HT., Jiang ZS., Wang GX., Tang ZH., Liu LS., "Hyperlipidemia-induced apoptosis of hippocampal neurons in apoE (-/-) mice may be associated with increased PCSK9 expression," Molecular Medicine Reports, Vol. 15, no. 2, pp. 712-718, 2017. DOI: 10.3892/mmr.2016.6055

[42] Andersen OM., Willnow TE., Lipoprotein receptors in Alzheimer's disease. Trends in neurosciences, Vol. 29, no. 12, pp. 687-94, 2006. DOI: 10.1016/j.tins.2006.09.002

[43] Shinohara M., Tachibana M., Kanekiyo T., Bu G., "Role of LRP1 in the pathogenesis of Alzheimer's disease: evidence from clinical and preclinical studies: Thematic Review Series: ApoE and Lipid Homeostasis in Alzheimer's Disease," Journal of Lipid Research, vol. 58, no. 7, pp. 1267-1281. DOI: 10.1194/jlr.R075796.

[44] Mendiola AS., Tognatta R., Yan Z., Akassoglou K., "ApoE and immunity in Alzheimer's disease and related tauopathies: Low-density lipoprotein receptor to the rescue," Neuron, vol. 109, no. 15, pp. 2363-2365. DOI: 10.1016/j.neuron.2021.07.013.

[45] Herz J., "LRP: a bright beacon at the blood-brain barrier," The Journal of Clinical Investigation, vol. 112, no. 10, pp. 1483-1485, 2003. DOI: 10.1172/JCI20337.

[46] Chang CW., Shao E., Mucke L., "Tau: Enabler of diverse brain disorders and target of rapidly evolving therapeutic strategies," Science, vol. 26, no. 7, p. eabb8255, 2021. DOI: 10.1126/science.abb8255.

[47] Chen Y., Strickland MR., Soranno A., Holtzman DM., "Apolipoprotein E: structural insights and links to Alzheimer disease pathogenesis," Neuron, vol. 109, no. 2, pp. 205-221, 2021. DOI: 10.1016/j.neuron.2020.10.008.

[48] Shi Y., Andhey PS., Ising C., Wang K., Snipes LL., Boyer K., Lawson S., Yamada K., Qin W., Manis M., Serrano JR., "Overexpressing low-density lipoprotein receptor reduces tau-associated neurodegeneration in relation to apoE-linked mechanisms," Neuron, vol. 109, no. 15, pp. 2413-2426, 2021. DOI: 10.1016/j.neuron.2021.05.034.

[49] Poirier S., Mayer G., Benjannet S., Bergeron E., Marcinkiewicz J., Nassoury N., Mayer H, Nimpf J, Prat A, Seidah NG. "The proprotein convertase PCSK9 induces the degradation of low density lipoprotein receptor (LDLR) and its closest family members VLDLR and ApoER2," Journal of Biological Chemistry, vol. 25, no. 4, pp. 2363-2372, 2008. DOI: 10.1074/jbc.M708098200.

[50] Rousselet E., Marcinkiewicz J., Kriz J., Zhou A., Hatten ME., Prat A., Seidah NG., "PCSK9 reduces the protein levels of the LDL receptor in mouse brain during development and after ischemic stroke," Journal of Lipid Research, vol. 52, no. 7, pp. 1383-1391, 2011. DOI: 10.1194/jlr.M014118.

[51] Kysenius K., Muggalla P., Mätlik K., Arumäe U., Huttunen HJ., "PCSK9 regulates neuronal apoptosis by adjusting ApoER2 levels and signaling," Cellular and Molecular Life Sciences, vol. 69, no. 6, pp. 1903-1916, 2012. DOI: 10.1007/s00018-012-0977-6.

[52] Xia XD., Peng ZS., Gu HM., Wang M., Wang GQ., Zhang DW., "Regulation of PCSK9 expression and function: mechanisms and therapeutic implications," Frontiers in Cardiovascular Medicine, vol. 15, no. 8, pp. 764030-764038, 2021. DOI: 10.3389/fcvm.2021.764038

[53] Rifai MA., Ballantyne CM., "PCSK9-targeted therapies: present and future approaches," Nature Reviews Cardiology, Vol. 18, no. 12, pp. 805-806, 2021.

[54] Kaddoura R., Orabi B., Salam AM., "Pcsk9 monoclonal antibodies: an overview," Heart Views, vol. 21, no. 2, pp. 97-103, 2020. DOI: 10.4103/HEARTVIEWS.HEARTVIEWS_20_20.

[55] Apaijai N., Moisescu DM., Palee S., McSweeney CM., Saiyasit N., Maneechote C., Boonnag C., Chattipakorn N., Chattipakorn SC., Pretreatment with PCSK9 inhibitor protects the brain against cardiac ischemia/reperfusion injury through a reduction of neuronal inflammation and amyloid beta aggregation. Journal of the American Heart Association, vol. 8, no. 2, p. e010838, 2019. DOI: 10.1161/JAHA.118.010838.

[56] Wagner J., Park LM., Mukhopadhyay P., Matyas C., Trojnar E., Damadzic R., Jung J., Bell AS., Mavromatis LA., Hamandi AM., Rosoff DB., "PCSK9 inhibition attenuates alcohol-associated neuronal oxidative stress and cellular injury," Brain, Behavior, and Immunity, vol. 119, no. 22, pp. 494-506, 2024. DOI: 10.1016/j.bbi.2024.04.022.