



PCSK9 and the nervous system: a no-brainer?

Ali Jaafar, Romuald Techer, Kévin Chemello, Gilles Lambert, Steeve Bourane

► To cite this version:

Ali Jaafar, Romuald Techer, Kévin Chemello, Gilles Lambert, Steeve Bourane. PCSK9 and the nervous system: a no-brainer?. *Journal of Lipid Research*, 2023, 64 (9), 10.1016/j.jlr.2023.100426 . hal-04465492

HAL Id: hal-04465492

<https://hal.science/hal-04465492>

Submitted on 10 Apr 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



PCSK9 and the nervous system: a no-brainer?

Ali K. Jaafar¹, Romuald Techer¹, Kévin Chemello¹, Gilles Lambert^{1,2,*} and Steeve Bourane¹

¹Laboratoire Inserm UMR 1188 DéTROI, and ²Faculté de Médecine, Université de La Réunion, Saint-Pierre, La Réunion, France

Abstract In the past 20 years, PCSK9 has been shown to play a pivotal role in LDL cholesterol metabolism and cardiovascular health by inducing the lysosomal degradation of the LDL receptor. PCSK9 was discovered by the cloning of genes up-regulated after apoptosis induced by serum deprivation in primary cerebellar neurons, but despite its initial identification in the brain, the precise role of PCSK9 in the nervous system remains to be clearly established.

The present article is a comprehensive review of studies published or in print before July 2023 that have investigated the expression pattern of PCSK9, its effects on lipid metabolism as well as its putative roles specifically in the central and peripheral nervous systems, with a special focus on cerebrovascular and neurodegenerative diseases.

Supplementary key words PCSK9 • Nervous system • Brain • Alzheimer's disease • Stroke • LDL receptor

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease primarily expressed by liver cells (1). It is synthesized as a precursor that undergoes autocatalytic intramolecular processing to form a mature protein that is secreted. In 2003, Abifadel and colleagues identified gain-of-function mutations in the *PCSK9* gene causative of familial hypercholesterolemia, an autosomal dominant trait characterized by an elevation in circulating low-density lipoprotein cholesterol (LDL-C) and premature coronary heart disease (CHD) risk (2). In 2005, a causative association was established between the presence of loss-of-function mutations in *PCSK9* and lifelong reductions in LDL-C associated with lower CHD risk (3).

Evidence for the direct role of PCSK9 in LDL metabolism came from a series of studies showing that overexpression of PCSK9 promotes the plasmatic accumulation of LDL-C in mice. Conversely, PCSK9 knockout (KO) mice are hypocholesterolemic (4). Mechanistically, the LDLR promotes the cellular uptake of LDL particles by endocytosis. In the absence of PCSK9, the acidic environment of the endosome induces the dissociation of the receptor from the particle,

and the LDLR is recycled back to the cell surface while the LDL particle is routed to the lysosome for degradation. When PCSK9 binds to the LDLR at the surface of cells, it undergoes endocytosis, and the LDLR fails to change conformation in the endosome, precluding normal recycling to the plasma membrane. The LDLR then traffics to the lysosome where it is degraded along with the LDL particle (5).

Given the mode of action of PCSK9 that acts primarily as a circulating inhibitor of the LDLR (6), as well as the healthy profile of individuals with reduced or absent PCSK9 function (7, 8) PCSK9 rapidly gained the status of a very promising drug target to lower LDL-C in humans with the ultimate goal of lowering the risk of heart disease. Several drug development strategies have been undertaken to pharmacologically inhibit PCSK9, the most advanced being two fully human monoclonal antibodies tested in large phase III outcome trials: the FOURIER program for evolocumab, and the ODYSSEY program for alirocumab (9, 10). Both have unequivocally shown that PCSK9 inhibition safely lowers LDL-C levels [56 mg/dl absolute reduction (95% confidence interval 55–57) or 59% relative reduction (95% confidence interval 58–60)] alone or on top of maximally tolerated lipid-lowering therapies (i.e. high-doses statins with or without ezetimibe) and reduces the number of cardiovascular events. In addition to monoclonal antibodies that sequester PCSK9 in the circulation and are now prescribed to patients, the small-interfering RNA inclisiran that targets PCSK9 hepatic production has recently been approved, following reports of substantial LDL lowering [50% reduction (95% confidence interval 47–53)] with this drug (11).

Beyond its central role in LDL-C regulation and cardiovascular health, distinct biological effects of PCSK9 have been reported, notably in septic shock, vascular inflammation, viral infection, and cancer (12). These novel roles have been proposed to result, at least in part, from the ability of PCSK9 to bind to and enhance the degradation of other members of the LDLR family of receptors but also of the scavenger

*For correspondence: Gilles Lambert, gilles.lambert@univ-reunion.fr.



receptor CD36, CD81, the epithelial sodium channel (ENaC), and the major histocompatibility type I receptor. Yet, the precise functions of PCSK9 in extrahepatic tissues remain a matter of considerable debate (**Fig. 1**). For instance, PCSK9 is expressed in the intestine, kidney, and pancreatic beta cells, but animal models conditionally lacking PCSK9 in these organs did not successfully highlight an essential role for PCSK9 in these tissues. This is further underlined by the overt phenotype of PCSK9 liver conditional knockout mice, an animal model characterized by a total absence of circulating PCSK9 as well as a lipoprotein profile almost similar to that of complete knockouts (**13**). Originally known as Neural Apoptosis-Regulated Convertase 1 (NARCI), PCSK9 was discovered by the cloning of genes up-regulated after apoptosis induced by serum deprivation in primary cerebellar neurons (**1**), but despite its initial identification in the brain, the precise roles of PCSK9 in the central (CNS) and peripheral (PNS) nervous systems remain largely elusive.

LIPIDS ARE KEY COMPONENTS OF THE NERVOUS SYSTEM

The nervous system is one of the most lipid-rich tissues of the human body, and the brain is the richest in cholesterol (**14, 15**). Lipids account for more than a third

of the dry weight of neuronal bodies, 57% being phospholipids and 15% cholesterol, (**16**). As key determinants of membranes, lipids largely contribute to the structural integrity and physical properties of nerve cells (**17–19**). Most lipids of the nervous system are localized in myelin, a specialized membrane that forms a multilayered sheath around axons exclusively in the central and peripheral nervous system. Myelin is characterized by a very high lipid/protein ratio (**20–22**) and is particularly enriched in cholesterol (**23**), with a relative proportion of 40% cholesterol, 40% phospholipids, and 20% glycolipids. The ratio is closer to 25%:65%:10% in most other biological membranes (**24**). **Table 1** comparatively displays the lipid contents of myelin (in both the central and peripheral nervous systems) and hepatocyte membranes (**25–27**). Myelin's unique lipid composition supports its critical role in the nervous system as it allows rapid saltatory conduction of nerve impulses and provides trophic support along the axon. Slight changes in the lipid composition of myelin sheath can alter adhesive properties and lead to structural disruptions (**28**) and serious neurological disorders (**29**).

In addition, lipids are involved in various signaling processes that regulate neuronal survival and differentiation (**30, 31**) and can also be used as energy substrates (**32**) or during cellular stress in the CNS

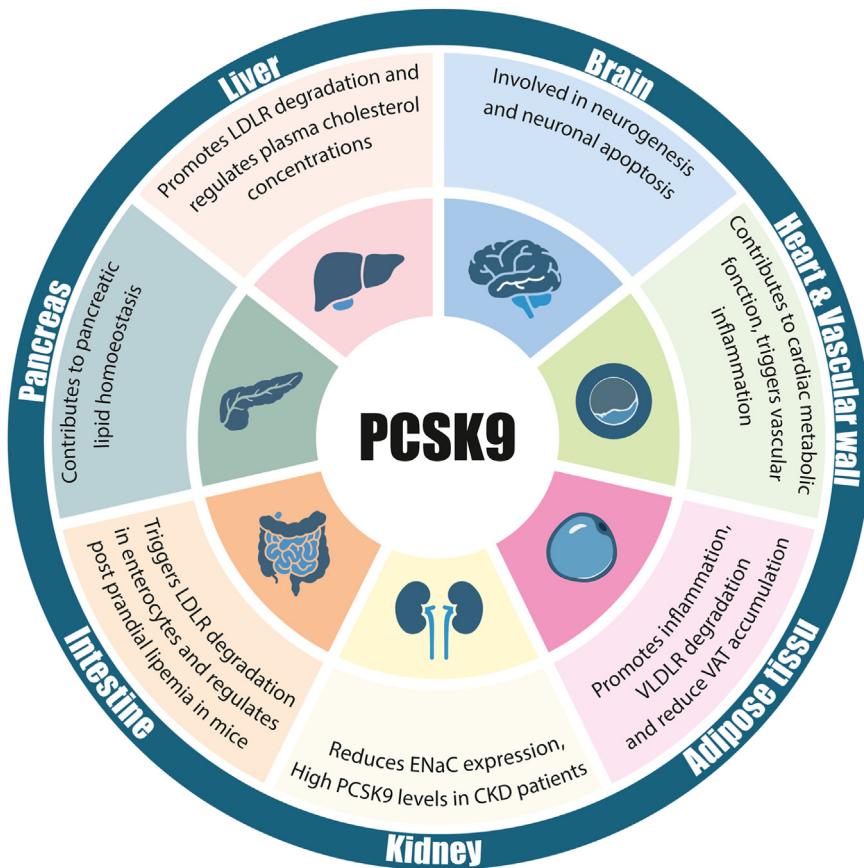


Fig. 1. The multifaceted roles of PCSK9 in extrahepatic tissues. CKD, chronic kidney disease; VAT, visceral adipose tissue.

TABLE 1. Lipid composition of myelin in the peripheral nervous system (PNS), central nervous system (CNS) and of liver cells plasma membranes

	PNS myelin	CNS myelin	Liver Plasma Membranes
Cholesterol	41%	46%	17%
Phospholipids	42%	33%	59%
Phosphatidylethanolamine (PE)	12%	13%	7%
Phosphatidylcholine (PC)	10%	7%	24%
Phosphatidylserine (PS)	7%	7%	4%
Phosphatidylinositol (PI)	<1%	<1%	4%
Sphingomyelin (SM)	13%	6%	20%
Glycolipids	11%	20%	7%
Cerebrosides	10%	17%	-
Sulfatide	1%	3%	-
Other lipids	6%	1%	17%

All values are expressed as molar percentages of total lipids.

(33). The molecular pathways governing lipid metabolism in the nervous system are tightly regulated, their central role in nerve function and CNS homeostasis being clearly underlined by the observation that disturbances of lipid homeostasis often associate with the onset of neurological disorders (34, 35). For instance, inherited disorders of cholesterol biosynthesis (e.g. the Smith-Lemli-Opitz syndrome) or metabolism (e.g. Cerebrotendinous Xanthomatosis) are causative of severe neurological symptoms and possibly myelin defects (36, 37). Given the lipid-demanding nature of the nervous system, and the central role of PCSK9 in cholesterol metabolism, several studies have explored the expression and function of PCSK9 in these tissues.

A CONVERTASE IMPLICATED IN NEURAL APOPTOSIS AND NEUROGENESIS

Apoptosis

PCSK9 was initially discovered in apoptotic primary cerebellar neurons (1, 38). PCSK9 exhibits pro-apoptotic properties in potassium-deprived cerebellar granule neurons and nerve growth factor-deprived dorsal root ganglion neurons, by reducing apolipoprotein E receptor 2 (ApoER2) abundance and thereby anti-apoptotic signaling pathways (39, 40). Likewise, PCSK9 inhibition attenuates neuronal apoptosis after middle cerebral artery occlusion (MCAO) injury in hyperlipidemic mice, an effect also associated with apoER2 upregulation (41). In contrast, PCSK9 displays anti-apoptotic properties in U251 human glioma cells. PCSK9 gene silencing leads to cell shrinkage, loss of membrane integrity, nuclear fragmentation, and chromatin compaction, whereas PCSK9 overexpression in these glioma cells restores normal morphology (42). Thus, it seems that PCSK9 could have both pro- and anti-apoptotic effects in different cell lines. In vivo, data about the role of PCSK9 in apoptosis are still very limited and need further investigation to confirm these observations.

Neurogenesis

Given the critical role of apoptosis during the development or degeneration phases of the nervous system, studies have been undertaken to unravel the role of PCSK9 in neurogenesis. PCSK9 expression is detectable during the early stages of neurogenesis (three somite stages, 10.33 h post fertilization in zebrafish) and during telencephalic and cerebellar embryonic neurogenesis (E12.5 and E17-P15, respectively, in mice). PCSK9 expression in the adult brain is low and only observed in areas where neurogenesis occurs, such as cortical, intracranial, and cerebellar granule neurons in zebrafish and the rostral extension of the olfactory peduncle (RE-OP) in mice (1, 43, 44). In humans, PCSK9 can be detected in the cerebrospinal fluid, albeit at much lower concentrations than in the plasma (on average 5 and 200 ng/ml, respectively) (45). PCSK9 overexpression in mouse embryonic neural progenitor cells leads to an increase in the number of postmitotic neurons from undifferentiated neuroepithelial cells (1). The role of PCSK9 in neuronal differentiation does not seem to be mediated by the LDLR, since neuroectodermal induction with retinoic acid of P19 mouse embryonic carcinoma cells increases endogenous PCSK9 mRNA expression, without altering LDLR protein abundance nor Sterol Regulatory Element Binding Protein 2 mRNA expression levels (43). Knocking-down PCSK9 is lethal in zebrafish, as a result of defective neurogenesis and total absence of midbrain-hindbrain boundary (43). However, PCSK9 is not necessary for survival in mammals raising the question about a compensatory action of other factors during evolution.

A REGULATOR FOR THE BRAIN

In the brain, PCSK9 potentially interacts with several members of the LDLR family of receptors that transport cholesterol into neurons (i.e. LDLR, the very-low-density lipoprotein receptor (VLDLR), ApoER2, and the LDLR-related protein 1 (LRP1)) as well as with CD36 that transports fatty acids (12). In vitro and in vivo studies conducted in mice provide conflicting evidence on whether PCSK9 targets these receptors for degradation. Since neither plasma lipoproteins nor circulating PCSK9 have the ability to cross the blood-brain barrier (BBB) under physiological circumstances (45–47), only locally expressed PCSK9 may directly modulate cholesterol homeostasis in the developing brain by promoting lysosomal degradation of these receptors (Fig. 2).

LDLR family members have a high affinity for apolipoprotein E (apoE), a major carrier of cholesterol in the brain, allowing transport of apoE-associated cholesterol from pericellular fluids into neurons (44). In vitro, PCSK9 was shown to reduce LDLR abundance in neurons (48). In vivo, LDLR protein levels are significantly higher in the telencephalon and

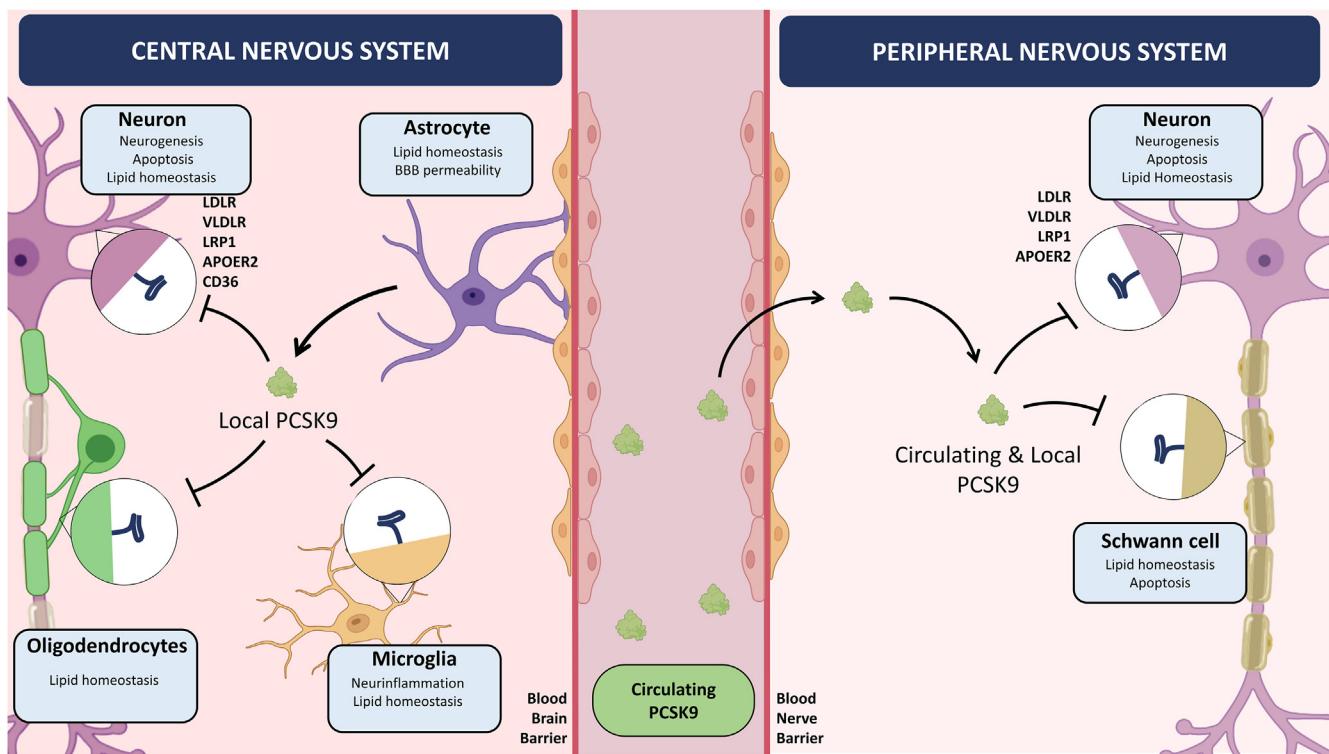


Fig. 2. Proposed roles for PCSK9 in the central and peripheral nervous systems. In the CNS, circulating PCSK9 only directly interacts with vascular endothelial cells and astrocytes as it does not cross the BBB in normal conditions. In contrast, PCSK9 produced locally may act on LDLR, LRP1, VLDLR, and apoER2 are expressed by neurons, astrocytes, and oligodendrocytes as well as on LRPI and CD36 that are expressed by microglia. These receptors are known to modulate lipid homeostasis, neurogenesis, apoptosis, and inflammatory processes in the brain. In the PNS, both circulating and locally produced PCSK9 have the ability to modulate LDLR, LRP1, ApoER2, and VLDLR that are expressed primarily by neurons and Schwann cells and thereby regulate lipid homeostasis and apoptotic processes in peripheral nerves.

cerebellum of PCSK9 knockout mouse embryos, and levels of non-truncated apoE are reduced, compared with wild types (44). However, in adult animals, despite the co-localization of PCSK9 and LDLR transcripts in RE-OP, PCSK9 KO mice do not display significantly different levels of LDLR and apoE proteins in their olfactory bulb or cerebrospinal fluid compared with wild-types (44). Likewise, overexpression or ablation of PCSK9 did not alter LDLR, VLDLR, or ApoER2 expression levels in the hippocampus and cerebral cortex of adult mice (49), nor did they alter the cortical development of the animals (48). Even if knocking-out PCSK9 were to modulate the relative abundance of several lipid species in the cortex and cerebellum of adult mice, these animals do not show any sign of behavioral abnormality (48). In contrast, PCSK9 concentrations are lower in the plasma and amniotic fluid of pregnant female rats as well as in rat embryos with experimentally induced neural tube defects (50) and the plasma of pregnant women with fetuses suffering from open neural tube defects (51).

The adult brain vastly relies on endogenous synthesis for its cholesterol needs since the BBB is virtually impermeable to circulating lipoproteins (52) and since, unlike oxysterols, cholesterol molecules do not cross the BBB (53). Cells of the CNS, including neurons,

synthesize cholesterol. However, adult neurons gradually lose this ability and become dependent on cholesterol supplied by astrocytes (15, 54, 55). Lipid homeostasis in astrocytes is central to brain health. Thus, recent studies have shown that abnormal lipid accumulation in astrocytes can lead to the formation of lipid-accumulated reactive astrocytes, promoting recurrent neuronal firing and ultimately leading to neuronal loss (56). Lipoproteins and their receptors play important roles in the regulation of neurobehavioral function and energy balance in the brain (57). Brain lipid homeostasis is thus subject, to some extent, to the action of local and/or circulating PCSK9 on neurons and astrocytes that are in direct contact with the cerebrovascular endothelium.

PCSK9 IN THE PERIPHERAL NERVOUS SYSTEM

To date, the expression of PCSK9 in the peripheral nervous system is not firmly established. The only piece of evidence of PCSK9 expression in peripheral nerves is the observation that PCSK9 transcripts are expressed in a rat Schwann cell line (1). Given that some neurons of the CNS express PCSK9, it cannot be ruled out that PCSK9 is also produced in neural and/or glial cells of the PNS. According to the Genotype-Tissue Expression

(GTEX) portal, PCSK9 is synthesized in human tibial nerves at levels deemed physiologically relevant (58). PCSK9 could potentially impact lipid metabolism locally in the peripheral nervous system and thus modulate peripheral nerve physiology.

A distinct feature of peripheral nerves is that they are located outside of the BBB. The blood–nerve endothelial barrier has distinct permeability characteristics (59) making peripheral nerves more susceptible to the action of systemic PCSK9 and hence to PCSK9 inhibitor treatments (Fig. 2). Incidentally, a recent case has reported a patient with a history of prediabetes and dyslipidemia treated with PCSK9 inhibitors who developed peripheral neuropathy (60). The patient started evolocumab treatment due to statin intolerance. While on PCSK9 inhibitor, the patient developed symptoms of chronic inflammatory demyelinating polyneuropathy characterized by bilateral thigh pain, weakness, and numbness. The symptoms improved after stopping evolocumab but resumed a few weeks later after the patient had been injected with the other PCSK9 inhibitor, alirocumab. There is no other report of an association between PCSK9 inhibitor use and demyelinating polyneuropathies. Of note, even if several cases of statin-induced peripheral neuropathy have been reported, there is no evidence for a causal relationship between statin treatment and peripheral neuropathy (61). In addition, a positive association was found between corneal nerve loss and circulating PCSK9 (62), and PCSK9 inhibitors treatment resulted in fibers regeneration in familial hypercholesterolemic patients with corneal small nerve fibers degeneration (63). Randomized trials with these drugs do not show any significant musculoskeletal and neurodegenerative side effect (64), even if several members of the LDLR family of receptors are duly expressed in peripheral nerves and mediate important interactions between Schwann cells and axons as well as Schwann cell response to injury in vivo. (65, 66).

Peripheral axons are more vulnerable compared to the brain due to their polarity, length, and the absence of an impermeable blood–nerve barrier. Schwann cells and the lipid-rich myelin sheath are essential for adequate homeostasis of peripheral nerves. It is therefore likely that PCSK9 could play a role in the regulation of lipid metabolism in the PNS in normal or pathological conditions. The importance of lipoprotein uptake for the maintenance of PNS lipid homeostasis is further highlighted by the abundance of lipoprotein receptors in peripheral nerves. Schwann cells express LDLR (67), LRP-1 (66), and ApoER2 (65). These receptors have also been identified in the dorsal root ganglia along with the VLDLR (68) (Fig. 2).

PCSK9 AND STROKE

An obvious detrimental role for PCSK9 on brain health is by increasing LDL-C levels which accelerates

intracranial atherosclerosis (in particular of large vessels) leading to ischemic strokes. This was evidenced in carriers of PCSK9 gain-of-function mutations (69, 70). In line with these observations, PCSK9 inhibition with evolocumab reduced ischemic strokes and major cardiovascular events in the total population of the FOURIER trial as well as in the key subgroup of patients with prior ischemic strokes (71). Whereas PCSK9 loss-of-function mutations carriers with lifelong reductions in LDL-C and coronary heart disease incidence, were not initially found at significantly reduced risk of stroke (3, 72), a much larger study of the UK Biobank database described the first genetic evidence of a protective effect of the R46L loss-of-function mutation on PCSK9 on ischemic stroke (73).

In contrast to ischemic strokes, only one study has investigated a link between PCSK9 and brain hemorrhage, showing no significant association (73). Nevertheless, PCSK9 inhibition has been proposed to precipitate hemorrhagic cerebral infarcts and to associate with increased cerebrovascular-related mortality (72, 74, 75), as a result of very low LDL-C levels, reduced platelets reactivity (via CD36), and lower blood coagulability (via LRPI) (76, 77). *In vivo* studies designed to investigate this possibility did not show any difference between PCSK9 knockout and wild-type mice in terms of cerebral infarct size following a transient MCAO procedure. PCSK9 KO and control mice also displayed similar hemorrhagic transformations following reperfusion post-MCAO (44, 74). These studies were however performed in young and otherwise healthy animals which do not recapitulate the pathophysiological conditions of ischemic strokes (aging population, diabetes, and hypertension). In that respect, aging PCSK9 KO mice accumulate cholesterol in pancreatic islets and display impaired glucose-stimulated insulin secretion irrespective of gender and diet as well as signs of glucose intolerance (78). Given that hyperglycemia and diabetes alone worsen ischemic strokes outcome in terms of prevalence, severity, and complications, and negatively impact on the integrity of the BBB, the initial hypothesis has been revisited: under acute hyperglycemic conditions, PCSK9 KO mice exhibit more intracerebral hemorrhages than wild-type mice following an MCAO procedure (79). Likewise, compared with placebo, PCSK9 inhibition with monoclonal antibodies increased cerebral hematoma volume following induction of experimental intracerebral hemorrhage using collagenase in a mouse model harboring a lipoprotein profile similar to that of humans (80). Lowering PCSK9 and LDL-C therefore appears beneficial in the context of ischemic stroke but further investigations are needed to test whether PCSK9 inhibition impacts hemorrhagic stroke.

PCSK9 AND NEUROCOGNITION

Impairment of neurocognitive function has been an important concern for the clinical development of

PCSK9 inhibitors. In the initial trials of these drugs, the incidence of neurocognitive adverse events (including delirium, cognitive and attentional disturbances, dementia, thought and perceptual disturbances, and psychiatric disorders) was very low (<1%) but slightly higher albeit non-significantly in the treated groups compared with placebo (0.9% vs. 0.3% for evolocumab) (81) (1.2% vs. 0.5% for alirocumab) (82). However, the combined analysis of both studies indicated an increased occurrence of neurocognitive side effects in patients treated with PCSK9 inhibitors (83). But the analysis of larger groups of patients enrolled in those trials over longer follow-up periods did not show significantly more neurocognitive adverse events associated with these therapies (10, 84, 85). Furthermore, there was absolutely no correlation between the occurrence of neurocognitive side effects and the degree of LDL-C reduction achieved with these drugs (64).

Likewise, studies conducted in PCSK9 loss-of-function mutations carriers did not show any sign of neurocognitive impairment or decline over time (86), indicating that lifetime exposure to low levels of PCSK9 and thus of LDL-C does not impact neurocognitive function. Of note, PCSK9 loss-of-function mutations were found associated with depression in Mendelian randomized analyses using the British Biobank cohort (87) and in a genome-wide association study (88).

PCSK9 AND ALZHEIMER'S DISEASE

Considering that PCSK9 was initially found in apoptotic neurons, its implication in neurodegenerative diseases, in particular in Alzheimer's disease (AD) has been extensively scrutinized (1). AD is characterized by the accumulation in the brain of toxic β -amyloid peptides arising from the cleavage of amyloid precursor proteins by β -site amyloid precursor protein cleaving enzyme (BACE1). *In vitro*, PCSK9 overexpression reduced BACE1 expression whereas PCSK9 inhibition increased the levels of BACE1 and A β deposition (89). A series of experiments conducted in rat stroke models found a negative association between the expression of PCSK9 and the formation of amyloid plaques (90). However, another study failed to identify a direct effect of PCSK9 on BACE1 expression or A β levels in mice (49).

A second putative pathway that may link PCSK9 inhibition to AD includes its inhibitory effects on the LDLR family of receptors as well as on the scavenger receptor CD36 in the central nervous system (91). Thus, PCSK9 inhibits the expression of the LRP8 (also known as apoER2), a receptor involved in signaling pathways governing the survival of neurons (39). In addition, genetic variants in the LRP8 locus associate with an increased risk of AD (92). Likewise, two other PCSK9 targets, LRPI and CD36, have been proposed to play a role in A β clearance (91). Thus, endothelial expression

of LRPI promotes the clearance of A β across the BBB in vivo, a process directly modulated by PCSK9 inhibitor treatment (93, 94), and the expression of CD36 parallels the ability of microglia to perform A β clearance (95). The ability of PCSK9 to modulate the abundance of these receptors in the CNS is still unknown. Another mechanistic pathway linking PCSK9 to AD, as shown in vitro, would be through canonical inhibition of local LDLR expression, resulting in decreased astrocyte-to-neuron cholesterol transport and reduced neuronal cholesterol content, thereby increasing A β neurotoxicity (96). Presumably, by reducing LDL-C, PCSK9 inhibitors may also lower the inflammatory processes within cerebral blood vessels and thus mitigate the progression of AD (97).

In that respect, PCSK9 concentrations were found higher in the cerebrospinal fluid as well as brain autopsies of AD patients compared with controls (98), but similar observations have been made for other neurodegenerative diseases (99). Noteworthy, there is no consensus for an association between PCSK9 genetic variants and AD, given that PCSK9 loss of function mutations carriers are at neutral risk of developing AD (86, 100, 101).

The impact of PCSK9 in other neurodegenerative diseases such as Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, and Huntington's disease with severe neuronal apoptosis has not been investigated despite the recognized association between lipid metabolism and the severity of these diseases (102–105). In a mouse model of multiple sclerosis, PCSK9 did not alter the progression of the disease or the associated immune responses (106). Yet, more work is needed to assess any potential impact of PCSK9 on these pathologies.

CONCLUSION

The best-characterized function of PCSK9 is its inhibitory action on hepatocyte-derived LDLR and thereby its established role in the systemic control of blood cholesterol. Despite its initial identification in the brain, the precise roles of PCSK9 in the nervous system remain elusive. *In vitro*, *in vivo*, epidemiological, and genetic studies indicate that PCSK9 possesses neurobiological regulatory properties of relevance in pathophysiological conditions of the nervous system. If so, it remains to be established whether these disorders are influenced by PCSK9 expressed locally in nervous tissues or systemically by circulating PCSK9. It is also important to decipher the precise molecular and cellular pathways acted upon by PCSK9 in these tissues. Important efforts should therefore be deployed to unravel the yet unknown functions of PCSK9 in the central and peripheral nervous systems. PCSK9, the youngest member of the family of proprotein convertases, has made history in cardiology but still raises

many hopes of new clinical applications beyond cardiovascular health. 

Author contributions

A. K. J., R. T., K. C., G. L., and S. B. writing–original draft; A. K. J., R. T., K. C., G. L., and S. B. writing–review and editing; A. K. J., R. T., and K. C. methodology; G. L. and S. B. supervision.

Author ORCIDs

Gilles Lambert  <https://orcid.org/0000-0001-5632-0685>
Steeve Bourane  <https://orcid.org/0000-0002-9805-2196>

Funding and additional information

A. K. J. is the recipient of a PhD scholarship from La Fondation pour la Recherche Médicale, Paris, France, and from the European Union and Région Réunion, Saint-Denis, Réunion; GL is the recipient of a project grant funded by the Agence Nationale de la Recherche, Paris, France [KRINGLE2 ANR-20-CE14-0009]; SB is the recipient of a program grant funded by Inserm, Paris, France [ATIP-AVENIR].

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

AD, Alzheimer's disease; apoE, Apolipoprotein E; ApoER2, ApoE receptor 2; BACE1, β -site amyloid precursor protein cleaving enzyme; BBB, Blood–brain barrier; CHD, Coronary heart disease; KO, knock-out; LDLR, LDL receptor; LRP, LDLR-related protein; MCAO, Middle cerebral artery occlusion; PCSK9, Proprotein convertase subtilisin/kexin type 9; PNS, Peripheral nervous system; RE-OP, Rostral extension of the olfactory peduncle; VLDLR, VLDL receptor.

Manuscript received July 7, 2023, and in revised form August 8, 2023. Published, JLR Papers in Press, August 14, 2023, <https://doi.org/10.1016/j.jlpr.2023.100426>

REFERENCES

1. Seidah, N. G., Benjannet, S., Wickham, L., Marcinkiewicz, J., Jasmin, S. B., Stifani, S., et al. (2003) The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation. *Proc. Natl. Acad. Sci. U. S. A.* **100**, 928–933
2. Abifadel, M., Varret, M., Rabès, J-P., Allard, D., Ouguerram, K., Devillers, M., et al. (2003) Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat. Genet.* **34**, 154–156
3. Cohen, J. C., Boerwinkle, E., Mosley, T. H., and Hobbs, H. H. (2006) Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N. Engl. J. Med.* **354**, 1264–1272
4. Rashid, S., Curtis, D. E., Garuti, R., Anderson, N. N., Bashmakov, Y., Ho, Y. K., et al. (2005) Decreased plasma cholesterol and hypersensitivity to statins in mice lacking Pcsk9. *Proc. Natl. Acad. Sci. U. S. A.* **102**, 5374–5379
5. Lambert, G., Sjouke, B., Choque, B., Kastelein, J. J. P., and Hovingh, G. K. (2012) The PCSK9 decade Thematic review series: new lipid and lipoprotein targets for the treatment of Cardiovascular diseases. *J. Lipid Res.* **53**, 2515–2524
6. Lagace, T. A., Curtis, D. E., Garuti, R., McNutt, M. C., Park, S. W., Prather, H. B., et al. (2006) Secreted PCSK9 decreases the number of LDL receptors in hepatocytes and inlivers of parabiotic mice. *J. Clin. Invest.* **116**, 2995–3005
7. Hooper, A. J., Marais, A. D., Tanyanya, D. M., and Burnett, J. R. (2007) The C679X mutation in PCSK9 is present and lowers blood cholesterol in a Southern African population. *Atherosclerosis* **193**, 445–448
8. Zhao, Z., Tuakli-Wosornu, Y., Lagace, T. A., Kinch, L., Grishin, N. V., Horton, J. D., et al. (2006) Molecular characterization of loss-of-function mutations in PCSK9 and identification of a compound heterozygote. *Am. J. Hum. Genet.* **79**, 514–523
9. Sabatine, M. S., Giugliano, R. P., Keech, A. C., Honarpour, N., Wiviott, S. D., Murphy, S. A., et al. (2017) Evolocumab and clinical outcomes in patients with cardiovascular disease. *N. Engl. J. Med.* **376**, 1713–1722
10. Schwartz, G. G., Steg, P. G., Szarek, M., Bhatt, D. L., Bittner, V. A., Diaz, R., et al. (2018) Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N. Engl. J. Med.* **379**, 2097–2107
11. Ray, K. K., Wright, R. S., Kallend, D., Koenig, W., Leiter, L. A., Raal, F. J., et al. (2020) Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N. Engl. J. Med.* **382**, 1507–1519
12. Seidah, N. G., and Garçon, D. (2022) Expanding biology of PCSK9: roles in atherosclerosis and beyond. *Curr. Atheroscler. Rep.* **24**, 821–830
13. Zaid, A., Roubtsova, A., Essalmani, R., Marcinkiewicz, J., Chamberland, A., Hamelin, J., et al. (2008) Proprotein convertase subtilisin/kexin type 9 (PCSK9): hepatocyte-specific low-density lipoprotein receptor degradation and critical role in mouse liver regeneration. *Hepatology* **48**, 646–654
14. Dietschy, J. M., and Turley, S. D. (2001) Cholesterol metabolism in the brain. *Curr. Opin. Lipidol.* **12**, 105
15. Dietschy, J. M., and Turley, S. D. (2004) Thematic review series: brain lipids. Cholesterol metabolism in the central nervous system during early development and in the mature animal. *J. Lipid Res.* **45**, 1375–1397
16. Calderon, R. O., Attema, B., and DeVries, G. H. (1995) Lipid composition of neuronal cell bodies and neurites from cultured dorsal root ganglia. *J. Neurochem.* **64**, 424–429
17. de Chaves, E. I. P., Rusiñol, A. E., Vance, D. E., Campenot, R. B., and Vance, J. E. (1997) Role of lipoproteins in the delivery of lipids to axons during axonal regeneration*. *J. Biol. Chem.* **272**, 30766–30773
18. Moutinho, M., Nunes, M. J., and Rodrigues, E. (2016) Cholesterol 24-hydroxylase: brain cholesterol metabolism and beyond. *Biochim. Biophys. Acta* **1861**, 1911–1920
19. Mauch, D. H., Nägler, K., Schumacher, S., Göritz, C., Müller, E. C., Otto, A., et al. (2001) CNS synaptogenesis promoted by glia-derived cholesterol. *Science* **294**, 1354–1357
20. Norton, W. T., and Poduslo, S. E. (1973) Myelination in rat brain: method of myelin isolation. *J. Neurochem.* **21**, 749–757
21. Norton, W. T., and Poduslo, S. E. (1973) Myelination in rat brain: changes in myelin composition during brain maturation. *J. Neurochem.* **21**, 759–773
22. O'Brien, J. S. (1965) Stability of the myelin membrane. *Science* **147**, 1099–1107
23. Saher, G., Brügger, B., Lappe-Siefke, C., Möbius, W., Tozawa, R., Wehr, M. C., et al. (2005) High cholesterol level is essential for myelin membrane growth. *Nat. Neurosci.* **8**, 468–475
24. Poitelon, Y., Kopec, A. M., and Belin, S. (2020) Myelin fat facts: an overview of lipids and fatty acid metabolism. *Cells* **9**, 812
25. O'Brien, J. S., Sampson, E. L., and Stern, M. B. (1967) Lipid composition of myelin from the peripheral nervous system. Intradural spinal roots. *J. Neurochem.* **14**, 357–365
26. Norton, W. T., and Autilio, L. A. (1966) The lipid composition of purified bovine brain myelin. *J. Neurochem.* **13**, 213–222
27. Dod, B. J., and Gray, G. M. (1968) The lipid composition of rat-liver plasma membranes. *Biochim. Biophys. Acta* **150**, 397–404
28. Chrast, R., Saher, G., Nave, K-A., and Verheijen, M. H. G. (2011) Lipid metabolism in myelinating glial cells: lessons from human inherited disorders and mouse models. *J. Lipid Res.* **52**, 419–434
29. Lamari, F., Mochel, F., Sedel, F., and Saudubray, J. M. (2013) Disorders of phospholipids, sphingolipids and fatty acids biosynthesis: toward a new category of inherited metabolic diseases. *J. Inher. Metab. Dis.* **36**, 411–425

30. Tabernero, A., Lavado, E. M., Granda, B., Velasco, A., and Medina, J. M. (2001) Neuronal differentiation is triggered by oleic acid synthesized and released by astrocytes. *J. Neurochem.* **79**, 606–616
31. Orr, S. K., Trépanier, M-O., and Bazinet, R. P. (2013) n-3 Polyunsaturated fatty acids in animal models with neuroinflammation. *Prostaglandins Leukot. Essent. Fatty Acids.* **88**, 97–103
32. Verheijen, M. H. G., Chrust, R., Burrola, P., and Lemke, G. (2003) Local regulation of fat metabolism in peripheral nerves. *Genes Dev.* **17**, 2450–2464
33. Owen, O. E., Morgan, A. P., Kemp, H. G., Sullivan, J. M., Herrera, M. G., and Cahill, G. F. (1967) Brain metabolism during fasting. *J. Clin. Invest.* **46**, 1589–1595
34. Björkhem, I., Leoni, V., and Meaney, S. (2010) Genetic connections between neurological disorders and cholesterol metabolism. *J. Lipid Res.* **51**, 2489–2503
35. Liu, Y., Chan, D. K. Y., Thalamuthu, A., Wen, W., Jiang, J., Paradise, M., et al. (2020) Plasma lipidomic biomarker analysis reveals distinct lipid changes in vascular dementia. *Comput. Struct. Biotechnol. J.* **18**, 1613–1624
36. Verrips, A., van Engelen, B. G., Wevers, R. A., van Geel, B. M., Cruysberg, J. R., van den Heuvel, L. P., et al. (2000) Presence of diarrhea and absence of tendon xanthomas in patients with cerebrotendinous xanthomatosis. *Arch. Neurol.* **57**, 520–524
37. Caruso, P. A., Poussaint, T. Y., Tzika, A. A., Zurakowski, D., Astrakas, L. G., Elias, E. R., et al. (2004) MRI and IH MRS findings in Smith-lemlí-optiz syndrome. *Neuroradiology.* **46**, 3–14
38. Chiang, L. W., Grenier, J. M., Ettwiller, L., Jenkins, L. P., Ficenec, D., Martin, J., et al. (2001) An orchestrated gene expression component of neuronal programmed cell death revealed by cDNA array analysis. *Proc. Natl. Acad. Sci. U. S. A.* **98**, 2814–2819
39. Kysenius, K., Muggalla, P., Mätlik, K., Arumäe, U., and Huttunen, H. J. (2012) PCSK9 regulates neuronal apoptosis by adjusting ApoER2 levels and signaling. *Cell. Mol. Life Sci.* **69**, 1903–1916
40. Bingham, B., Shen, R., Kotnis, S., Lo, C. F., Ozenberger, B. A., Ghosh, N., et al. (2006) Proapoptotic effects of NARC 1 (=PCSK9), the gene encoding a novel serine proteinase. *Cytometry A.* **69**, 1123–1131
41. Wang, L., Wang, Z., Shi, J., Jiang, Q., Wang, H., Li, X., et al. (2018) Inhibition of proprotein convertase subtilisin/kexin type 9 attenuates neuronal apoptosis following focal cerebral ischemia via apolipoprotein E receptor 2 downregulation in hyperlipidemic mice. *Int. J. Mol. Med.* **42**, 2098–2106
42. Piao, M-X., Bai, J-W., Zhang, P-F., and Zhang, Y-Z. (2015) PCSK9 regulates apoptosis in human neuroglioma u251 cells via mitochondrial signaling pathways. *Int. J. Clin. Exp. Pathol.* **8**, 2787–2794
43. Poirier, S., Prat, A., Marcinkiewicz, E., Paquin, J., Chitramuthu, B. P., Baranowski, D., et al. (2006) Implication of the proprotein convertase NARC-1/PCSK9 in the development of the nervous system. *J. Neurochem.* **98**, 838–850
44. Rousset, E., Marcinkiewicz, J., Kriz, J., Zhou, A., Hatten, M. E., Prat, A., et al. (2011) PCSK9 reduces the protein levels of the LDL receptor in mouse brain during development and after ischemic stroke. *J. Lipid Res.* **52**, 1383–1391
45. Chen, Y. Q., Troutt, J. S., and Konrad, R. J. (2014) PCSK9 is present in human cerebrospinal fluid and is maintained at remarkably constant concentrations throughout the course of the day. *Lipids.* **49**, 445–455
46. Dietschy, J. M. (2009) Central nervous system: cholesterol turnover, brain development and neurodegeneration. *Biol. Chem.* **390**, 287–293
47. Nieweg, K., Schaller, H., and Pfrieger, F. W. (2009) Marked differences in cholesterol synthesis between neurons and glial cells from postnatal rats. *J. Neurochem.* **109**, 125–134
48. Pärn, A., Olsen, D., Tuvikene, J., Kaas, M., Borisova, E., Bilgin, M., et al. (2022) PCSK9 deficiency alters brain lipid composition without affecting brain development and function. *Front. Mol. Neurosci.* **15**, 1084633
49. Liu, M., Wu, G., Baysarowich, J., Kavana, M., Addona, G. H., Bierilo, K. K., et al. (2010) PCSK9 is not involved in the degradation of LDL receptors and BACE1 in the adult mouse brain. *J. Lipid Res.* **51**, 2611–2618
50. An, D., Wei, X., Li, H., Gu, H., Huang, T., Zhao, G., et al. (2015) Identification of PCSK9 as a novel serum biomarker for the prenatal diagnosis of neural tube defects using iTRAQ quantitative proteomics. *Sci. Rep.* **5**, 17559
51. Erol, S. A., Tanacan, A., Firat Oguz, E., Anuk, A. T., Goncu Ayhan, S., Neselioglu, S., et al. (2021) A comparison of the maternal levels of serum proprotein convertase subtilisin/kexin type 9 in pregnant women with the complication of fetal open neural tube defects. *Congenit. Anom. (Kyoto).* **61**, 169–176
52. Björkhem, I., and Meaney, S. (2004) Brain cholesterol: long secret life behind a barrier. *Arterioscler. Thromb. Vasc. Biol.* **24**, 806–815
53. Björkhem, I., Leoni, V., and Svenssonsson, P. (2019) On the fluxes of side-chain oxidized oxysterols across blood-brain and blood-CSF barriers and origin of these steroids in CSF (Review). *J. Steroid Biochem. Mol. Biol.* **188**, 86–89
54. Quan, G., Xie, C., Dietschy, J. M., and Turley, S. D. (2003) Ontogenesis and regulation of cholesterol metabolism in the central nervous system of the mouse. *Brain Res. Dev. Brain Res.* **146**, 87–98
55. Saito, K., Dubreuil, V., Arai, Y., Wilsch-Bräuninger, M., Schwudke, D., Saher, G., et al. (2009) Ablation of cholesterol biosynthesis in neural stem cells increases their VEGF expression and angiogenesis but causes neuron apoptosis. *Proc. Natl. Acad. Sci. U. S. A.* **106**, 8350–8355
56. Chen, Z-P., Wang, S., Zhao, X., Fang, W., Wang, Z., Ye, H., et al. (2023) Lipid-accumulated reactive astrocytes promote disease progression in epilepsy. *Nat. Neurosci.* **26**, 542–554
57. Wang, H., and Eckel, R. H. (2014) What are lipoproteins doing in the brain? *Trends Endocrinol. Metab.* **25**, 8–14
58. Da Dalt, L., Ruscica, M., Bonacina, F., Balzarotti, G., Dhyani, A., Di Cairano, E., et al. (2019) PCSK9 deficiency reduces insulin secretion and promotes glucose intolerance: the role of the low-density lipoprotein receptor. *Eur. Heart J.* **40**, 357–368
59. Malong, L., Napoli, I., Casal, G., White, I. J., Stierli, S., Vaughan, A., et al. (2023) Characterization of the structure and control of the blood-nerve barrier identifies avenues for therapeutic delivery. *Dev. Cell.* **58**, 174–191.e8
60. Franco, D. C., Neupane, N., Riaz, M., Mohammadzadeh, S., and Sachmechi, I. (2019) Chronic inflammatory demyelinating Polyradiculoneuropathy association with low cholesterol levels: a case report in a patient taking PCSK9 inhibitor. *J. Neurol. Res.* **9**, 72–74
61. Pasha, R., Azmi, S., Ferdousi, M., Kalteniece, A., Bashir, B., Gouni-Berthold, I., et al. (2022) Lipids, lipid-lowering therapy, and neuropathy: a narrative review. *Clin. Ther.* **44**, 1012–1025
62. Iqbal, Z., Azmi, S., Ferdousi, M., Kalteniece, A., Adam, S., Ho, J. H., et al. (2020) Obesity related small fibre neuropathy is associated with circulating PCSK9. *Atherosclerosis.* **315**, e162
63. Soran, H., Kalteniece, A., Ferdousi, M., Iqbal, Z., Liu, Y., Baptist, M., et al. (2020) PCSK9 monoclonal antibody treatment promotes small fibre regeneration in heterozygous familial hypercholesterolemia. *Atherosclerosis.* **315**, e215
64. Robinson, J. G., Rosenson, R. S., Farnier, M., Chaudhari, U., Sasiela, W. J., Merlet, L., et al. (2017) Safety of very low low-density lipoprotein cholesterol levels with alirocumab: pooled data from randomized trials. *J. Am. Coll. Cardiol.* **69**, 471–482
65. Pasten, C., Cerda, J., Jausoro, I., Court, F. A., Cáceres, A., and Marzolo, M-P. (2015) ApoER2 and Reelin are expressed in regenerating peripheral nerve and regulate Schwann cell migration by activating the Rac1 GEF protein, Tiam1. *Mol. Cell. Neurosci.* **69**, 1–11
66. Orita, S., Henry, K., Mantuano, E., Yamauchi, K., De Corato, A., Ishikawa, T., et al. (2013) Schwann cell LRPI regulates remak bundle ultrastructure and axonal interactions to prevent neuropathic pain. *J. Neurosci.* **33**, 5590–5602
67. Goodrum, J. F., Fowler, K. A., Hostettler, J. D., and Oews, A. D. T. (2000) Peripheral nerve regeneration and cholesterol reutilization are normal in the low-density lipoprotein receptor knockout mouse. *J. Neurosci. Res.* **59**, 581–586
68. Toma, J. S., Karamboulas, K., Carr, M. J., Kolaj, A., Yuzwa, S. A., Mahmud, N., et al. (2020) Peripheral nerve Single-cell analysis identifies Mesenchymal Ligands that promote axonal growth. *eNeuro.* **7**, ENEURO.0066-20.2020
69. Abboud, S., Karhunen, P. J., Lütjohann, D., Goebeler, S., Luoto, T., Friedrichs, S., et al. (2007) Proprotein convertase subtilisin/kexin type 9 (PCSK9) gene is a risk factor of large-vessel atherosclerosis stroke. *PLoS One.* **2**, e1043

70. Han, D., Ma, J., Zhang, X., Cai, J., Li, J., Tuerxun, T., et al. (2014) Correlation of PCSK9 gene polymorphism with cerebral ischemic stroke in Xinjiang han and uygor populations. *Med. Sci. Monit.* **20**, 1758–1767
71. Giugliano, R. P., Pedersen, T. R., Saver, J. L., Sever, P. S., Keech, A. C., Bohula, E. A., et al. (2020) Stroke prevention with the PCSK9 (proprotein convertase subtilisin-kexin type 9) inhibitor evolocumab added to statin in high-risk patients with stable atherosclerosis. *Stroke* **51**, 1546–1554
72. Kent, S. T., Rosenson, R. S., Avery, C. L., Chen, Y-D. I., Correa, A., Cummings, S. R., et al. (2017) PCSK9 loss-of-function variants, low-density lipoprotein cholesterol, and risk of coronary heart disease and stroke: data from nine studies of African Americans and Whites. *Circ. Cardiovasc. Genet.* **10**, e001632
73. Rao, A. S., Lindholm, D., Rivas, M. A., Knowles, J. W., Montgomery, S. B., and Ingelsson, E. (2018) Large-Scale Phenome-wide association study of PCSK9 variants demonstrates protection against ischemic stroke. *Circ. Genom. Precis. Med.* **11**, e002162
74. Tran-Dinh, A., Levoye, A., Lambert, G., Louedec, L., Journé, C., Meilhac, O., et al. (2014) Low levels of low-density lipoprotein-C associated with proprotein convertase subtilisin kexin 9 inhibition do not increase the risk of hemorrhagic transformation. *Stroke* **45**, 3086–3088
75. Wang, X., Dong, Y., Qi, X., Huang, C., and Hou, L. (2013) Cholesterol levels and risk of hemorrhagic stroke. *Stroke* **44**, 1833–1839
76. Paciullo, F., Petito, E., Falcinelli, E., Gresele, P., and Momi, S. (2022) Pleiotropic effects of PCSK9-inhibition on hemostasis: anti-PCSK9 reduce FVIII levels by enhancing LRPI expression. *Thromb. Res.* **213**, 170–172
77. Puccini, M., Landmesser, U., and Rauch, U. (2022) Pleiotropic effects of PCSK9: focus on thrombosis and haemostasis. *Metabolites* **12**, 226
78. Páth, G., Perakakis, N., Mantzoros, C. S., and Seufert, J. (2022) PCSK9 inhibition and cholesterol homeostasis in insulin producing β -cells. *Lipids Health Dis.* **21**, 138
79. Nativel, B., Ramin-Mangata, S., Courret, D., Planesse, C., Roche, M., Gallo, A., et al. (2021) PCSK9 (proprotein convertase subtilisin kexin type 9) inhibition in hyperglycemic mice increases the risk of hemorrhagic transformation of ischemic stroke. *Stroke* **52**, e545–e547
80. Schlunk, F., Fischer, P., Princen, H. M. G., Rex, A., Prinz, V., Foddis, M., et al. (2020) Effects of inhibition or Deletion of PCSK9 (proprotein convertase subtilisin/kexin type 9) on intracerebral hemorrhage volumes in mice. *Stroke* **51**, e297–e298
81. Robinson, J. G., Farnier, M., Krempf, M., Bergeron, J., Luc, G., Averna, M., et al. (2015) Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N. Engl. J. Med.* **372**, 1489–1499
82. Sabatine, M. S., Giugliano, R. P., Wiviott, S. D., Raal, F. J., Blom, D. J., Robinson, J., et al. (2015) Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N. Engl. J. Med.* **372**, 1500–1509
83. Lipinski, M. J., Benedetto, U., Escarcega, R. O., Biondi-Zocca, G., Lhermusier, T., Baker, N. C., et al. (2016) The impact of proprotein convertase subtilisin-kexin type 9 serine protease inhibitors on lipid levels and outcomes in patients with primary hypercholesterolemia: a network meta-analysis. *Eur. Heart J.* **37**, 536–545
84. Giugliano, R. P., Pedersen, T. R., Park, J-G., De Ferrari, G. M., Gaciong, Z. A., Ceska, R., et al. (2017) Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. *Lancet* **390**, 1962–1971
85. Janik, M. J., Urbach, D. V., van Nieuwenhuizen, E., Zhao, J., Yellin, O., Baccara-Dinet, M. T., et al. (2021) Alirocumab treatment and neurocognitive function according to the CANTAB scale in patients at increased cardiovascular risk: a prospective, randomized, placebo-controlled study. *Atherosclerosis* **331**, 20–27
86. Mefford, M. T., Rosenson, R. S., Cushman, M., Farkouh, M. E., McClure, L. A., Wadley, V. G., et al. (2018) PCSK9 variants, low-density lipoprotein cholesterol, and neurocognitive impairment: reasons for Geographic and Racial differences in stroke study (REGARDS). *Circulation* **137**, 1260–1269
87. Nelson, C. P., Lai, F. Y., Nath, M., Ye, S., Webb, T. R., Schunkert, H., et al. (2019) Genetic assessment of potential long-Term on-target side effects of PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors. *Circ. Genom. Precis. Med.* **12**, e002196
88. Alghamdi, J., Matou-Nasri, S., Alghamdi, F., Alghamdi, S., Alfadhel, M., and Padmanabhan, S. (2018) Risk of neuropsychiatric adverse effects of lipid-lowering drugs: a mendelian randomization study. *Int. J. Neuropsychopharmacol.* **21**, 1067–1075
89. Jonas, M. C., Costantini, C., and Puglioni, L. (2008) PCSK9 is required for the disposal of non-acetylated intermediates of the nascent membrane protein BACE1. *EMBO Rep.* **9**, 916–922
90. Apajai, N., Moisescu, D. M., Palee, S., McSweeney, C. M., Saiyasiit, N., Maneechote, C., et al. (2019) Pretreatment with PCSK9 inhibitor protects the brain against cardiac ischemia/reperfusion injury through a reduction of neuronal inflammation and amyloid beta aggregation. *J. Am. Heart Assoc.* **8**, e010838
91. Adorni, M. P., Ruscica, M., Ferri, N., Bernini, F., and Zimetti, F. (2019) Proprotein convertase subtilisin/kexin type 9, brain cholesterol homeostasis and potential implication for Alzheimer's disease. *Front. Aging Neurosci.* **11**, 120
92. Ma, S. L., Ng, H. K., Baum, L., Pang, J. C. S., Chiu, H. F. K., Woo, J., et al. (2002) Low-density lipoprotein receptor-related protein 8 (apolipoprotein E receptor 2) gene polymorphisms in Alzheimer's disease. *Neurosci. Lett.* **332**, 216–218
93. Storck, S. E., Meister, S., Nahrath, J., Meinhard, J. N., Schubert, N., Di Spiezio, A., et al. (2016) Endothelial LRPI transports amyloid- β (1-42) across the blood-brain barrier. *J. Clin. Invest.* **126**, 123–136
94. Mazura, A. D., Ohler, A., Storck, S. E., Kurtyka, M., Scharfenberg, F., Weggen, S., et al. (2022) PCSK9 acts as a key regulator of $\text{A}\beta$ clearance across the blood-brain barrier. *Cell. Mol. Life Sci.* **79**, 212
95. Hickman, S. E., Allison, E. K., and El Khoury, J. (2008) Microglial dysfunction and defective beta-amyloid clearance pathways in aging Alzheimer's disease mice. *J. Neurosci.* **28**, 8354–8360
96. Papotti, B., Adorni, M. P., Marchi, C., Zimetti, F., Ronda, N., Panighel, G., et al. (2022) PCSK9 affects astrocyte cholesterol metabolism and reduces neuron cholesterol supplying in vitro: potential implications in Alzheimer's disease. *Int. J. Mol. Sci.* **23**, 12192
97. Altman, R., and Rutledge, J. C. (2010) The vascular contribution to Alzheimer's disease. *Clin. Sci.* **119**, 407–421
98. Picard, C., Poirier, A., Bélanger, S., Labonté, A., Auld, D., and Poirier, J. (2019) Proprotein convertase subtilisin/kexin type 9 (PCSK9) in Alzheimer's disease: a genetic and proteomic multi-cohort study. *PLoS One* **14**, e0220254
99. Courtemanche, H., Bigot, E., Pichelin, M., Guyomarch, B., Bou tolleau-Brettonnière, C., Le May, C., et al. (2018) PCSK9 concentrations in cerebrospinal fluid are not specifically increased in Alzheimer's disease. *J. Alzheimers Dis.* **62**, 1519–1525
100. Benn, M., Nordestgaard, B. G., Frikkie-Schmidt, R., and Tybjærg-Hansen, A. (2017) Low LDL cholesterol, PCSK9 and HMGCR genetic variation, and risk of Alzheimer's disease and Parkinson's disease: mendelian randomisation study. *BMJ* **357**, j1648
101. Paquette, M., Saavedra, Y. G. L., Poirier, J., Thérioux, L., Dea, D., Baass, A., et al. (2018) Loss-of-function PCSK9 mutations are not associated with Alzheimer disease. *J. Geriatr. Psychiatry Neurol.* **31**, 90–96
102. Hurh, K., Park, M., Jang, S-I., Park, E-C., and Jang, S-Y. (2022) Association between serum lipid levels over time and risk of Parkinson's disease. *Sci. Rep.* **12**, 21020
103. Janse van Mantgem, M. R., van Rheenen, W., Hackeng, A. V., van Es, M. A., Veldink, J. H., van den Berg, L. H., et al. (2023) Association between serum lipids and survival in patients with amyotrophic lateral sclerosis: a meta-analysis and population-based study. *Neurology* **100**, e1062–e1071
104. Gafson, A. R., Thorne, T., McKechnie, C. I. J., Jimenez, B., Nicholas, R., and Matthews, P. M. (2018) Lipoprotein markers associated with disability from multiple sclerosis. *Sci. Rep.* **8**, 17026
105. Block, R. C., Dorsey, E. R., Beck, C. A., Brenna, J. T., and Shoulson, I. (2010) Altered cholesterol and fatty acid metabolism in Huntington disease. *J. Clin. Lipidol.* **4**, 17–23
106. Vigne, S., Duc, D., Peter, B., Rebeaud, J., Yersin, Y., Ruiz, F., et al. (2022) Lowering blood cholesterol does not affect neuroinflammation in experimental autoimmune encephalomyelitis. *J. Neuroinflammation* **19**, 42