Journal of Clinical Lipidology (2018) ■, ■–■

Journal of Clinical Lipidology

Review Article

PCSK9 and neurocognitive function: Should it be still an issue after FOURIER and EBBINGHAUS results?

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KEYWORDS:
Brain;
Cholesterol;
Cholesterol-lowering treatment;
Neurocognitive function;
PCSK9;
PCSK9 inhibitors

Abstract: The serine protease proprotein convertase subtilisin/kexin type 9 (PCSK9) modulates the levels of low-density lipoprotein cholesterol and cardiovascular risk. Potential risks of adverse neurological effects of intensive lipid-lowering treatment have been hypothesized, as cholesterol is a component of the central nervous system. Moreover, several observations suggest that PCSK9 might play a role in neurogenesis, neuronal migration and apoptosis. In rodents, increased expression of PCSK9 has been detected in specific areas of the central nervous system during embryonic development; also, PCSK9 modulates low-density lipoprotein receptor levels in the ischemic brain areas. Despite a putative participation of PCSK9 in nervous system physiology, the absence of PCSK9 in knockout mice or in humans with loss-of-function mutations of PCSK9 gene has not been linked to neurological alterations. In recent years, some concerns have been raised about the potential neurological side effects of cholesterol-lowering treatments and, more specifically of PCSK9 inhibitors. In this review, the evidence regarding the function of PCSK9 in neuron differentiation, apoptosis, and migration and in nervous system development and latest clinical trials evaluating the effects of PCSK9 inhibitors on neurocognitive function will be described.

Introduction

The discovery and characterization of proprotein convertase subtilisin/kexin type 9 (PCSK9) has introduced a revolution in the understanding of lipid metabolism and has enabled the most important innovation in the treatment of dyslipidemias since the introduction of statins. PCSK9 is an enzyme encoded by the PCSK9 gene in humans on chromosome 1, expressed mainly in the liver, but also in

Declaration of Interest: The authors report no declarations of interest.
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Submitted October 12, 2017. Accepted for publication May 21, 2018.

1933-2874/© 2018 Published by Elsevier Inc. on behalf of National Lipid Association.
https://doi.org/10.1016/j.jacl.2018.05.012

many other cells and tissues. Once secreted in plasma, PCSK9 binds the low-density lipoprotein receptor (LDLR) at the surface of hepatocytes, thereby enhancing its degradation in endosomes/lysosomes, and preventing its recycling resulting in reduced LDL cholesterol (LDL-C) clearance.

The interest in PCSK9 has grown exponentially after the discovery of gain-of-function mutations of the PCSK9 gene, resulting in high plasma levels LDL-C and increased susceptibility to coronary artery disease (CAD).[1] Conversely, PCSK9 loss-of-function mutations lead to lower plasma LDL-C levels and protection from CAD.[2,3] The use of monoclonal antibodies (mAbs) inhibiting PCSK9 reduced LDL-C levels by as much as 60%–70% when administered as monotherapy or as an add-on to other cholesterol-lowering therapies[4] and produced a considerable additional cardiovascular (CV) benefit beyond that achieved by statins and ezetimibe.[5] Hence, anti-PCSK9 mAbs have been welcomed with great enthusiasm with the promise to give a positive response to some unmet clinical needs, that is, (further) reducing plasma LDL-C levels and CAD risk both in patients with high or very-high CV risk and in those not tolerating statins.

Despite these promises have been respected, some concerns have emerged about the potential side effects related to the marked reduction of plasma cholesterol levels and the incomplete knowledge of PCSK9 functions. In this regard the extensive investigation on PCSK9 revealed novel potential functions, including the regulation of cell apoptosis, participation in immunity and neuronal development.[6–10] Recently, the knowledge about the role of PCSK9 in the development and function of the nervous system has been the subject of considerable debate, partly as a consequence of the preliminary observation of an increased risk of neurocognitive events after anti-PCSK9 mAb therapy.[11,12]

A potential relationship between PCSK9 and brain function is not surprising. When it was first discovered in 2003 by Seidah et al.,[13] PCSK9 was described as the ninth member of the secretory subtilase family and called neural apoptosis–regulated convertase 1/proprotein (NARC1). This name has been assigned to show that this protein was expressed in the brain and is capable to modulate cortical neuron differentiation and apoptosis.[10,13] However, the role of PCSK9 in the development and function of the nervous system is still not clear. In this review, we summarize the evidence showing the implication of PCSK9 in nervous system development, and the influence of PCSK9 on neuronal differentiation, migration, and apoptosis. In addition, recent clinical trials investigating the effect of PCSK9 inhibitors on neurocognitive function are discussed.

PCSK9, nervous system development, and neuronal apoptosis

PCSK9 has been postulated to play a role in the development of the central nervous system (CNS). NARC1/PCSK9 is highly expressed in embryonic brain telencephalon neurons.[13] The overexpression of PCSK9, induced by transfection, was associated with an increased recruitment rate of undifferentiated neural progenitor cells.[13] Additional observations suggested that PCSK9 may play an important role in neurogenesis. PCSK9 can be detected in the cerebrospinal fluid, although its concentration is lower than that noticed in the serum.[14] A transient increase in PCSK9 expression has been observed in the telencephalon and cerebellum during the gestational period in rodents.[13] Conversely, PCSK9 expression is low in CNS during adulthood, with the exception of the rostral extension of the olfactory peduncle.[15] These observations suggest that transient PCSK9 expression in the forming telencephalon and cerebellum might be involved in the recruitment of undifferentiated neural progenitor cells toward the neuronal lineage.[15]

PCSK9 expression may be involved in the regulation of cell differentiation in pluripotent mouse P19 embryonal carcinoma cells. It was observed that, after neuroectodermal induction by retinoic acid of P19 cells, PCSK9 expression increased, whereas naive P19 cells exhibited a very low level of PCSK9, suggesting that early PCSK9 may be required to modulate cell differentiation.[16,17] The study of clinical phenotypes associated with the lack of PCSK9 helps to understand its physiological role in various organs.[18] Rousselet et al. found that LDLR levels increased, whereas apolipoprotein E (apoE) levels were reduced during brain development in telencephalon and cerebellum in Pcsk9 –/– mice compared with wild type (WT) animals.[15] This suggests that LDLR protein upregulation in Pcsk9 –/– mice enhances apoE degradation in the developing brain.[15] However, in the adult brain of Pcsk9 –/– mice, LDLR protein and apoE levels were similar to those in WT mice, implying that PCSK9 is not involved in cerebral LDLR degradation.[15] Moreover, adult transgenic mice with overexpressed PCSK9 in the liver do not show hippocampal and cortical LDLR regulation by ectopic PCSK9.[15]

The impact of PCSK9 deficiency on brain recovery after ischemic injury is of great interest.[15] After experimental transient cerebral ischemia, LDLR protein levels decreased 2-fold less in the injured brain area of Pcsk9 –/– mice than WT mice, which suggests that endogenous PCSK9 modulates the levels of LDLR in ischemic brain areas. In the same experiments, apoE protein levels increased similarly in the injured brain areas of WT and Pcsk9 –/– mice compared with the nonlesioned brain areas. These findings suggest that the higher LDLR levels in lesioned brain areas of Pcsk9 –/– mice do not translate into a different amount of apoE cerebral degradation.[15]

Irrespective of whether PCSK9 is directly involved in brain LDLR expression and degradation of cerebral apoE, both in the developing brain and during experimental brain ischemia, these events do not seem sufficient to cause significant consequences.[15] Accordingly, no alterations of brain morphology or changes of markers of cell proliferation/differentiation were observed during brain development