Deep thoughts on lipids and cognition

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Statin benefits on cardiovascular risk reduction appear proportional to the degree of LDL cholesterol (LDL-C) reduction. Despite prior arguments that pleiotropic effects were responsible for the greater therapeutic impact of the statin class [1], recent trials of adjunctive therapy to statins have only further supported LDL lowering as the principle therapeutic mechanism [2,3]. Adding these new drug classes, the most impactful of which may be the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, to statins facilitate the achievement of extremely low LDL-C levels. As cholesterol plays a crucial role in brain development, there has been growing concern regarding the adverse effects of the low LDL-C achieved by these drugs [4[¶]]. Adverse neurocognitive effects have been of keen interest given the progressive increase in life expectancy worldwide and came to the forefront following the Food and Drug Administration report raising concern for statin-related ‘ill-defined memory loss or impairment’ in 2012 [5].

In late 2016, Banach *et al.* [6^{¶¶}] provided a model detailing potential mechanisms whereby statins could affect cognition. First, inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase not only decreases in-situ synthesis of cholesterol in the brain but also causes a significant reduction in isoprenoids (such as farnesyl and geranylgeranyl pyrophosphate), which have important downstream effects [7[¶]]. Second, statin-induced cholesterol depletion has been shown to modulate N-methyl-D-aspartate receptor function in the central nervous system. Finally, statin-induced disruption of lipid and glucose metabolism could affect tau protein phosphorylation, along with stimulating production and reducing clearance of β -amyloid [8[¶]]. Contrary to this reasoning, several recent studies have supported a neuroprotective role; and some researchers have even proposed using statins therapeutically for neurodegenerative diseases [7[¶],9,10]. More importantly, in a comprehensive systematic review (including data from 25 randomized trials), no association was seen between statins and cognitive impairment in both the short and long term [11^{¶¶}].

Although PCSK9 inhibitors employ a different mechanism of action and do not cross the blood-brain barrier, they dramatically lower plasma LDL-C

(by as much as 75%) [12], which could impair cognition. Data from previous small trials have suggested higher rates of adverse neurocognitive effects with PCSK9 inhibitors compared with placebo [13]. Most recently, however, pooled data from 14 such trials found no increase in neurocognitive events in alirocumab-treated patients who achieved LDL-C less than 25 mg/dl compared with patients with LDL at least 25 mg/dl or those treated with placebo [14[¶]]. Amgen recently reported that the EBBINGHAUS cognitive function trial (a 1900 patient subset of the FOURIER trial) found evolocumab to be noninferior to placebo for affecting cognitive function [15,16], though results await peer review. It is also worth noting an earlier study of patients with abetalipoproteinemia and undetectable LDL-C levels, in which neurocognitive dysfunction was not seen [17].

The results of the aforementioned studies are encouraging, especially in light of the additive cardiovascular risk reduction that PCSK9 inhibitors likely provide. Additional long-term outcome trials and postmarket surveillance are warranted, however, to further ensure drug safety. Nonetheless, for high-risk patient populations, the beneficial effects of PCSK9 inhibition appear to clearly outweigh the potential risk of neurocognitive events.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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3. Nicholls SJ, Puri R, Anderson T, *et al.* Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial. *JAMA* 2016; 316:2373–2384.
4. Cartocci V, Servadio M, Trezza V, Pallottini V. Can cholesterol metabolism ■ modulation affect brain function and behavior? *J Cell Physiol* 2017; 232:281–286.

This review emphasizes the function of cholesterol and its metabolism in the central nervous system. By discussing relevant clinical and preclinical studies, it provides insight into the correlations between altered cholesterol metabolism and impaired neurocognitive function. It also reviews animal models in which altering cholesterol metabolism appears to affect neurocognitive function.

5. US Food and Drug Administration. FDA drug safety communication: important safety label changes to cholesterol-lowering statin drugs. February 2012; Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm> [Accessed February 14, 2017]
 6. Banach M, Rizzo M, Nikolic D, *et al.* Intensive LDL-cholesterol lowering ■ therapy and neurocognitive function. *Pharmacol Ther* 2017; 170:181–191.
- A comprehensive review that summarizes available data on neurocognitive side effects resulting from statins and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, while summarizing potential underlying mechanisms. It also reviews studies examining statin or PCSK9 inhibitor administration and cognition, with the conclusion that current published evidence is inconsistent and does not suggest a direct association

7. Ling Q, Tejada-Simon MV. Statins and the brain: new perspective for old ■ drugs. *Prog Neuropsychopharmacol Biol Psychiatry* 2016; 66:80–86.
- This review highlights the properties of statins and their adverse effects on the brain that could be cholesterol-dependent or cholesterol-independent. It also introduces animal models that suggest a potential beneficial effect of statins on several neurodevelopmental disorders. Studies performed on humans, unfortunately, remain inconsistent, and controversial.

8. Sato N, Morishita R. The roles of lipid and glucose metabolism in modulation ■ of β -amyloid, tau, and neurodegeneration in the pathogenesis of Alzheimer disease. *Front Aging Neurosci* 2015; 7:199.

A review that describes the impact of lipid and glucose metabolism on the pathogenesis of the Alzheimer disease. Disruption of the homeostasis of lipid and glucose metabolism affects production and clearance of β -amyloid and tau phosphorylation, which could induce neurodegeneration.

9. Jiao X, Ashtari N, Balaei MR, *et al.* Mevalonate cascade and neurodevelopmental and neurodegenerative diseases: future targets for therapeutic application. *Curr Mol Pharmacol* 2017; 10:115–140.
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11. Ott BR, Daiello LA, Dahabreh IJ, *et al.* Do statins impair cognition? A ■ systematic review and meta-analysis of randomized controlled trials. *J Gen Intern Med* 2015; 30:348–358.

This is a systematic review and meta-analysis including data from 25 placebo-controlled RCTs (involving 46 836 patients) and examining cognitive outcomes in statin-treated healthy individuals and patients with cognitive impairment. The review found no statistically significant effect of statins on cognition. This was true regardless of duration of therapy, sample size, location, cognitive health status, or whether the statin studied penetrated the blood–brain barrier.

12. Robinson JG, Nedergaard BS, Rogers WJ, *et al.* Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. *JAMA* 2014; 311:1870–1882.
13. Robinson JG, Farnier M, Krempf M, *et al.* Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015; 372:1489–1499.
14. Robinson JG, Rosenson RS, Farnier M, *et al.* Safety of very low low-density ■ lipoprotein cholesterol levels with alirocumab: pooled data from randomized trials. *J Am Coll Cardiol* 2017; 69:471–482.

This analysis pooled data from 14 trials of the PCSK9 inhibitor, alirocumab, added to background lipid-lowering therapy. Duration of treatment ranged from 8 to 104 weeks. Among the 3340 alirocumab-treated patients, 25% had two consecutive LDL-C less than 25 mg/dl measurements, and 9% achieved LDL-C less than 15 mg/dl. Reported adverse events were similar in all three groups (LDL-C < 15 mg/dl, LDL-C < 25 mg/dl, and LDL-C $\geq$ 25 mg/dl). In propensity-matched analyses, rates of specific adverse events including neurological and neurocognitive effects were not significantly different in patients with very low LDL-C levels.

15. Amgen. Amgen Announces Repatha® (Evolocumab) significantly reduced the risk of cardiovascular events in FOURIER outcomes study. February 2017; Retrieved from <https://www.amgen.com/media/news-releases/2017/02/amgen-announces-repatha-evolocumab-significantly-reduced-the-risk-of-cardiovascular-events-in-fourier-outcomes-study>. [Press Release] [Accessed February 19, 2017]
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17. Hooper AJ, Burnett JR, Watts GF. Contemporary aspects of the biology and therapeutic regulation of the microsomal triglyceride transfer protein. *Circ Res* 2015; 116:193–205.

A review that describes the role of PCSK9 in lipid regulation and highlights a mechanism whereby inhibition could potentially benefit patients with sepsis. PCSK9 ultimately decreases LDL-receptors in the liver, thereby hindering clearance of LDL-C from the circulation. LDL-receptors have been shown to be responsible for removal of pathogenic lipids, such as lipopolysaccharide (LPS), from the circulation. By decreasing PCSK9 levels, PCSK9 inhibitors enhance LPS clearance and may ameliorate detrimental sepsis-mediated inflammatory responses.

FURTHER RECOMMENDED READING

Wellington CL, Frikke-Schmidt R. Relation between plasma and brain lipids. *Curr Opin Lipidol* 2016; 27:225–232.

A nice review of lipid metabolism and its derangements that may affect the development of various neurological disorders, such as the Alzheimer disease. Important pathways and potential targets for therapy are discussed.

Momtazi AA, Banach M, Sahebkar A. PCSK9 inhibitors in sepsis: a new potential ■ indication? *Expert Opin Investig Drugs* 2017; 26:137–139.