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Commentary

COMMENTARY

Lipid-Lowering Drug Effects Beyond the Cardiovascular System: Relevance for Neuropsychiatric Disorders

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In this issue of the *International Journal of Neuropsychopharmacology*, Alghamdi et al. conducted an elegant study investigating the effects of lipid-lowering medications on neuropsychiatric phenotypes using Mendelian Randomization (MR) modeling (Alghamdi et al., 2018). MR is a tool that uses genetic variants to determine potential causal relationships between exposures and outcomes. As such, it has been used to predict causal relationships between risk factors and disease, for example, lipids and cardiovascular disease (Danesh et al., 2007; Do et al., 2013), or exposures to medications and adverse events (Bennett and Holmes, 2017). Alghamdi et al. used genetic risk scores that reflect lipid-lowering effects through HMGCR, NPC1L1, and PCSK9 to mimic the effects of lipid-lowering medications. They then assessed effects on neuropsychiatric symptoms. Their main findings were that both statins and the PCSK9 inhibitor treatment increased the risk of depression, while statins slightly reduced neuroticisms in subjects.

The notion that lipid-lowering drugs might have effects on depression or the brain is not new, and in fact over the past several decades multiple studies have investigated this relationship with mixed results. Some studies show a link between statin exposure and depression while others do not (Olusi and Fido, 1996; Steegmans et al., 1996; Maes et al., 1997; Almeida-Montes et al., 2000; Sarchiapone et al., 2000, 2001; Golomb et al., 2002, 2004; Deisenhammer et al., 2004; Fiedorowicz and Coryell, 2007; Gabriel, 2007). Speculations about the exact mechanisms on how lipid-lowering drugs affect depression include possible effects on serotonin synthesis, neurosteroid homeostasis, and inflammation, all of which have been independently linked to depression (Otte et al., 2016). However, using a genetics-based approach, Alghamdi et al. showed for the first time a new link between PCSK9 and depression. This is potentially important, as PCSK9 recently emerged as a new target for familial hypercholesteremia (Abifadel et al., 2003; Rosenson et al., 2018). This has been followed by the rapid development of anti-PCSK9 therapeutics, which resulted in new ways of powerfully lowering LDL-cholesterol (Praluent (alirocumab), package insert, 2015; Robinson et al., 2015; Sabatine et al., 2015; Farnier et al., 2016, Repatha (evolocumab), package insert, 2017). Interestingly, in the MR study, PCSK9 showed the strongest effect on depression of all the lipid-lowering surrogate targets (HMGCR, NPC1L1, and PCSK9) with an OR of about 1.2. This might reflect a direct genetic link between PCSK9, depression, and LDL-cholesterol regulation. It would be interesting to see how the combination of statins and PCSK9 inhibitors might change the size of the effect, as polypharmacy is becoming more prevalent and several of the PCSK9 clinical trials used a combination of both therapies (Sabatine et al., 2017).

The role of PCSK9 in cholesterol metabolism was initially identified as a gain-of-function mutation in families with a history of familial hypercholesteremia (Abifadel et al., 2003). PCSK9 is predominantly expressed in the liver, where it is synthesized and secreted (Cariou et al., 2015). It primarily targets low-density lipoprotein cholesterol receptors (LDL-R) in liver cells and interferes with the regulation of low-density lipoprotein cholesterol (LDL-C) in the blood (Cariou et al., 2015; Joseph and Robinson, 2015). However, there is emerging evidence that PCSK9 has many different functions, including potential roles in immune function, inflammation, sepsis, neuronal apoptosis, and alcohol use disorder (Bittner, 2016; Dwivedi et al., 2016; Ruscica et al., 2016; Lohoff et al., 2017; Filippatos et al., 2018; Seidah et al., 2018). Although most studies of PCSK9 have focused on the liver,

there is emerging evidence that PCSK9 might also play a critical role in the brain. PCSK9 was previously termed neural apoptosis-regulated convertase-1 (Seidah et al., 2003). There is evidence that PCSK9 is expressed in the hippocampus and cerebellum as well as in endothelial cells among other cell types (Seidah et al., 2014; Ding et al., 2015). Several studies link PCSK9 function to be involved in neuronal apoptosis through a mechanism downstream of oxidized LDL. PCSK9 may also decrease neurite outgrowth through interference with LDL-R neurite induction and has been investigated in Alzheimer's disease (ALZ). In neurons, PCSK9 has been shown to degrade LDL-Rs as well as other apoE-binding receptors (Canuel et al., 2013; Poirier and Mayer, 2013). Thus, PCSK9 may be involved in brain cholesterol trafficking and lipoprotein homeostasis as well as possible ALZ pathogenesis and cognitive decline. Given mounting evidence that organs such as the liver, heart, and brain are much more connected than previously thought (Butterworth, 2013; Bruce et al., 2017; Taher et al., 2017), PCSK9 may play an integral part in the biology of the liver-heart-brain axis and other biological systems.

The interconnection and communication between organ systems is complex and might be partially accomplished by common regulatory genes or elements that can adapt and regulate gene function in various tissue types. Pleiotropy—the notion that a genetic variant can have more than one direct biological effect—is likely present for PCSK9 and would thus raise concerns about the validity or potential bias of using MR to investigate PCSK9 effects. In fact, several findings from MR studies suggest that genetic variants in PCSK9 are associated with increased risk of diabetes (Ference et al., 2016; Lotta et al., 2016; Schmidt et al., 2017), while other MR studies with focus on Parkinson's and ALZ could not confirm a link (Benn, 2017). In light of the many unknown functions of PCSK9, additional research and potentially prospective clinical trials or deep-phenotyping studies are needed to investigate its effects. The assumption of on-target effects is one major limitation of MR studies that needs to be carefully considered given what we do not yet know about the biology of genetic variants. In addition, with recent advances in the field of epigenetics, it is possible that known "functional" genetic variants are further modulated by epigenetic mechanisms such as DNA methylation or histone modifications. MR studies would need to integrate new knowledge of dynamic single nucleotide polymorphism biology via epigenetics into their modeling and promising approaches are being developed to do this (Relton and Davey Smith, 2012; Dekkers et al., 2016). Other limitations for MR studies include limited power, population stratification concerns, and linkage disequilibrium between variants.

The field of medicine is changing and expanding rapidly. Still, the embrace of genomic, transcriptomic, proteomic, and epigenomic approaches may be impeded by the simultaneous segmentation of medicine into subspecialties, which may preclude the detection of the effects of novel therapies in organ systems for which a novel drug was not designed. It is becoming clear that specific organ biology must be considered in the context of the whole body as a system; thus, integrative approaches are needed, for example, tissue interactions in various organs should be studied at the same time. This might be particularly crucial for novel "personalized medicine" derived drugs that tend to have very large effects on a very specific target, such as PCSK9 antibodies for the treatment of high cholesterol. In fact, while PCSK9 inhibitors are one of the prototype compounds that were FDA approved by acting on a surrogate biomarker (i.e., LDL cholesterol), impacts on disease outcomes, so far promising in the cardiovascular realm, need to be carefully evaluated (Nicholls et al., 2016; Sabatine et al., 2017; Rosenson et al., 2018). Meanwhile the impact on other organ systems remains unclear. We are entering an exciting area of medicine where integrative-omics approaches, such as MR studies, have become standard for biomedical investigations and perhaps clinical trials. This could open up important opportunities for augmenting current safety monitoring of clinical trials and could ultimately lead to more rapid development of novel treatments, with a humble understanding of what we know and what we do not know.

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Statement of Interest

None.

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