HDL: Close to Our Memories?

Anatol Kontush, M. John Chapman

The last decade has witnessed an explosion in studies of the role of lipoproteins in brain function. Neurons require a continuous supply of lipids for membrane synthesis and acetylcholine production. Indeed, the brain is a site of intense lipid turnover—even though the central nervous system (CNS) accounts for only 2.1% of body weight, it contains 23% of total body cholesterol. Lipid metabolism in the brain is tightly controlled locally, as plasma lipoproteins are shielded from the brain by the blood-brain barrier. Although neuronal cells are capable of de novo synthesis of a wide spectrum of molecular species of lipids, they rely heavily on exogenous sources and readily bind and internalize lipoproteins of the extracellular fluid. Equally, neurons need to dispose of excess lipids; lipoprotein-mediated lipid transport is therefore bidirectional and includes cellular efflux of cholesterol.

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Human cerebrospinal fluid (CSF) primarily contains spherical lipoproteins of approximately 10 to 12 nm in diameter with hydrated density in the range 1.063 to 1.25 g/mL, thereby resembling HDL in human plasma. Lipid concentrations in CSF are however much lower (eg, 300- to 400-fold for total cholesterol and phospholipids) as compared to the plasma compartment. Apolipoproteins (apo) E and A-I are the major apolipoproteins in human CSF (typical concentration range: 0.1 to 0.4 mg/dL), with apoA-II, A-IV, J, D, C-II, C-III, C-IV, and H equally present. Importantly, CSF lipoproteins carry amyloid-β (Aβ), a 39- to 43-aa peptide produced in neuronal cells, which is the major component of senile amyloid plaques.

The metabolism of CSF lipoproteins remains poorly characterized but seems to be distinct from that of plasma lipoproteins. ApoE-rich HDL are synthesized locally in CNS and secreted by astrocytes as discoidal complexes enriched in free cholesterol. High apoE content targets these lipoproteins to cellular apoE receptors, particularly LDL receptor–related protein, which is abundantly expressed on the surface of neurons. By contrast, apoA-I–rich CSF lipoproteins are most probably derived from plasma HDL that enter the CNS by crossing the blood-brain barrier, and as apoA-I is not synthesized in the CNS. Similar to plasma HDL, CSF lipoproteins can be remodeled by lecithin-cholesterol acyltransferase and phospholipid transfer protein; by contrast, cholesteryl ester transfer protein (CETP) is absent from CSF.

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prevalent in AD. However, none of these studies infers causality because, as Singh-Manoux et al rightly point out, plasma lipid levels can be considerably modified over the development of dementia, making the time point of the measurement critically important.

The key question that was not addressed by the authors is, therefore: which mechanisms underlie these effects? Singh-Manoux et al11 mention vastly different neuroprotective properties of HDL which include accelerated maturation of synapses, maintenance of synaptic plasticity, improved metabolism of $\beta$ b, and increase in hippocampal volume, later adding antiinflammatory and antioxidative activities to the list—just to illustrate how complex and variable biochemical mechanisms potentially linking HDL to AD might be.

The complexity of the mechanistic relationship between HDL and brain function is immediately apparent when we look at $\beta$ b metabolism, the major pathway involved in the pathogenesis of AD. Brain HDL can exert several neuroprotective effects acting only via this pathway (Figure). First, as neuronal production of $\beta$ b frequently parallels membrane content of cholesterol, HDL can suppress $\beta$ b production by decreasing cellular cholesterol through the activation of reverse cholesterol transport mediated by ABC transporters.16 Second, HDL can directly bind excess $\beta$ b and thereby inhibit its oligomerisation,17 the latter representing a major step in the transformation of the monomeric nontoxic peptide to the aggregated neurotoxic form that can account for memory impairment.18 As HDL transports $\beta$ b in both CSF and plasma,19 elimination of the excess peptide from the brain may follow. In addition, HDL might also remove $\beta$ b that accumulates in the vessel wall during the course of VD19; by analogy with reverse cholesterol transport, such a process can be termed “reverse amyloid transport.” Third, oxidative stress induces enhanced production of $\beta$ b as a potentially protective response (monomeric $\beta$ b is a particularly strong chelator of prooxidant transition metal ions in their free form)20; in turn, HDL can decrease oxidative stress21 and thereby indirectly decrease $\beta$ b production. Fourth, HDL can act on astrocytes to attenuate a local inflammatory reaction.

In all of these scenarios, it remains unclear as to how low levels of HDL-C measured in plasma can be translated into defective functionality of HDL in the brain. ApoA-I, the major component of plasma HDL implicated in cellular cholesterol efflux and other biological activities of HDL, might represent a potential link.22 Plasma levels of HDL-C and apoA-I are strongly correlated in the general population23; it is therefore possible that levels of apoA-I decrease in parallel with those of HDL-C in subjects with memory deficit. Cholesterol removal from neuronal cells together with reduced neuroinflammation, both mediated by apoA-I that has crossed the blood-brain barrier, might then mechanistically underlie the relationship between low HDL-C levels and memory deficits observed.11

Finally, classical inhibition of large-vessel atherosclerosis by HDL is another interesting possibility, as vascular pathology may play a common role in initiating neurological deficits in AD and VD.

The authors rightly list a number of limitations of their study, including its observational nature, potentially incomplete adjustments for confounders (such as smoking habits, alcohol use and physical exercise, all of which can strongly impact on HDL-C levels), above-average socioeconomic status of the participants, and potential survival and selection bias attributable to follow-up. This list should be further extended to include the absence of the distinction between fasting and nonfasting subjects as well as between men and women. Indeed, HDL-C levels strongly depend on sex and can be altered in the postprandial state.24 The low proportion of women in the study population (<30%) questions the applicability of the results to females. In addition, a more traditional presentation of plasma lipid levels as continuous, instead of categorical, variables could have provided more detailed information on their relationships to memory deficits. Next, decreasing cardiovascular risk concomitant with increasing HDL-C levels and decreasing total cholesterol with age observed in this study11 is not a straightforward finding, but most probably related to the 3.7-fold elevated use of lipid-lowering drugs; such a limitation should have additionally decreased the number of subjects displaying decreasing concentrations of HDL-C on follow-up, thereby reducing statistical power.

Finally, the absence of data on the incidence of diabetes and obesity in the Whitehall population is regrettable. Type 2 diabetes shares metabolic features with AD, as the number of pathways shared by these 2 major pathologies is evolving progressively; for example, elevated levels of insulin result in elevated generation of $\beta$ b peptide.25 As subgroup levels of HDL-C are a hallmark of Type 2 diabetes,26 the increasing prevalence of this disease in low HDL-C subjects might well underlie the association with memory decline observed by Singh-Manoux et al.11 Whatever the case, the link between
Type 2 diabetes, low HDL-C, and memory decline is worthy of further study.

It is tempting to speculate that increasing levels of HDL-C, or “good cholesterol”, might protect our good memories and the authors do not escape this temptation. However, unfortunate results in large interventional trials with dietary antioxidants suggest that we should remain extremely cautious when proposing therapeutic intervention on the basis of observational studies which do not imply causation. This is particularly true for a study with a number of important limitations such as that of Singh-Manoux et al. For example, a close look at their data shows that whereas falling HDL-C over the time of the study was associated with deterioration of memory, increase in HDL-C concentrations was not associated with improved memory as compared to their stabilization (Table 4). As a minimum, such observational studies which do not imply causation. This is when proposing therapeutic intervention on the basis of observational studies which do not imply causation. This is particularly true for a study with a number of important limitations such as that of Singh-Manoux et al..

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