The paper by Plump et al. (1) is a multifaceted investigation of adrenal metabolism of cholesterol in mice deficient in either of the 2 major apolipoproteins of high density lipoproteins (HDL), apo AI, and apo AII. This investigation addresses a number of very relevant questions, among them: (*a*) what is the role of HDL in the delivery of cholesterol to endocrine tissues for steroid production? (*b*) is there a difference in the ability of apo AI and apo AII to modulate cholesterol flux between HDL and adrenal tissues? and (*c*) what is the mechanism by which the cholesterol transfers to the tissues?

HDL consist of a mixture of particles that differ in size and composition. The basic structure of these particles is a lipid core comprised of cholesteryl ester surrounded by a surface coat of unesterified cholesterol, phospholipids, and apoproteins. The major apoproteins are apo AI and apo AII. Although it has been appreciated for a long time that HDL particles have a number of important physiological functions, emphasis has been placed on their role in the transport of excess peripheral cell cholesterol back to the liver for excretion, a process termed "reverse cholesterol transport." It is believed that peripheral cell cholesterol homeostasis is, in part, maintained by the influx of cholesterol from low density lipoproteins (LDL) and efflux to HDL (2). In addition, a role of HDL in the delivery of cholesterol to tissues has been demonstrated, particularly to the liver and endocrine tissues (3, 4).

Closely linked to the general role of HDL in cholesterol flux is the controversial question of the importance of apo AI and apo AII in modulating the flux of cholesterol between HDL and cells. Investigations have focused primarily on cholesterol efflux and, depending on the experimental system, have yielded contradictory results. The present paper very elegantly addresses the role played by HDL in the delivery of cholesterol to the adrenals and, by comparing the metabolism of cholesterol in adrenal tissues of mice deficient in either apo AI or apo AII, clearly demonstrates impaired adrenal cholesterol levels and depressed steroid production in mice lacking apo AI. The important control in this experiment is that although mice deficient in apo AII have similar total HDL cholesterol levels as the apo AI–deficient animals, they demonstrate nearly normal adrenal cholesteryl ester accumulation. Thus, these results obtained by Williams and colleagues represent one of the most dramatic examples of a difference between HDL particles that differ in apoprotein composition in modulating cholesterol flux (1).

The unesterified cholesterol on the surface of HDL can readily exchange with cell membranes (2), and it has been demonstrated that the cholesteryl ester of lipoproteins can also be incorporated into cells. This uptake of cholesteryl ester can occur upon the internalization of the lipoprotein, such as with LDL uptake mediated by the LDL receptor; however, it can also occur without the uptake of the entire lipoprotein particle (5). The mechanism by which the highly insoluble cholesteryl ester within the core of the lipoprotein moves from the donor lipoprotein to the cell membrane remains an intriguing mystery. Although "cholesteryl ester selective uptake" can be mediated by a variety of lipoprotein donors and occurs in a variety of tissues, studies have indicated that HDL is particularly active in this transfer (6) and the liver and adrenals are the major organs for this incorporation (3). The mechanism for selective uptake of cholesteryl ester from HDL and the close association of this process with the presence of apo AI–containing HDL in the mouse models remains to be resolved, and a number of alternative mechanisms can be suggested. An obvious possibility is a receptor-mediated process involving the interaction of the HDL particle with receptors on the cells. This process could be a traditional protein–protein interaction between the apo AI and the putative receptor or could be a less specific protein–lipid interaction. In the latter case the protein might be the apo AI interacting with the lipid domains within the plasma membrane, or alternatively, a cell receptor interacting with the lipid component of the HDL. A particularly exciting candidate is the recently reported SR-B1 receptor that can bind HDL with high affinity and is expressed in liver and steroidogenic tissues (7). The presence of this receptor on cells has recently been shown to facilitate the selective uptake of HDL cholesteryl ester (7). The specificity of this receptor appears to be rather broad; of particular interest is its ability to bind protein-free liposomes containing anionic phospholipids (8). Thus, one can speculate that the apo AI–containing HDL have an array of surface phospholipids that promote binding to the SR-B1 receptor and that this binding enhances the retention of the lipoprotein particles within the microvillar channels in the adrenal (9). The phospholipids on the HDL containing only apo AII may not be appropriate for the required binding to the SR-B1 receptor.

The mechanism by which the cholesteryl ester transfers from the lipoprotein to the cell membrane and the role played by apo AI remain to be resolved. To what extent similar phenomena are operating in the liver and endocrine tissues also has to be established. Finally, the studies in this report are conducted in mice, an animal with high HDL and low LDL, and it must now be established if the data can be extrapolated to humans who have much higher concentrations of LDL. The authors discuss this question and provide evidence indicating that the data generated from mice are relevant to humans. This paper (1) offers an excellent example of a study that has taken a broad experimental approach to address a fundamental question. The authors have used molecular biological approaches, electron microscopy, and a variety of biochemical assays to document the importance of apo AI in providing cholesterol for steroidogenesis. As with any good investigation, the results highlight additional questions that remain to be resolved.

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