Apolipoprotein M and Sphingosine-1-Phosphate: A Potentially Antidiabetic Tandem Carried by HDL

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The frequent finding of low HDL cholesterol in patients with type 2 diabetes (T2D) or at increased risk for T2D has been traditionally interpreted as the consequence of hypertriglyceridemia and hyperglycemia, which are caused by insulin resistance and hyperinsulinemia (1). However, several observations also point to antidiabetic actions of HDL (1,2). Post hoc analyses of randomized controlled trials showed that inhibitors of cholesteryl ester transfer protein, which increase HDL cholesterol by 25 to 100%, improve the glycemic control of subjects with diabetes and lower the incidence of diabetes in patients who are treated with statins (3). Infusion of artificial reconstituted HDL led to acute decreases in glucose levels and improved insulin sensitivity in subjects with diabetes (4). Mendelian randomization studies generated controversial data, with one study supporting and another disproving genetic causality of HDL for T2D (5,6). Data from genetic mouse models indicate that HDL secures both insulin production in pancreatic β-cells and insulin action in the periphery (2). The clinical exploitation of HDL in the prevention and management of diabetes—for example, the development of drugs that stimulate or mimic the antidiabetic effects of HDL or biomarkers that improve risk prediction—is hampered by the presence of hundreds of different proteins and lipid species in HDL, several of which show antidiabetic properties (7).

In this issue of Diabetes, Kurano et al. (8) provide evidence that at least a part of HDL’s antidiabetic action involves apolipoprotein M (apoM) and its lipid ligand sphingosine-1-phosphate (S1P), two quantitatively minor components of HDL. S1P is the agonist of five G-protein-coupled receptors named S1P1, S1P2, S1P3, S1P4, and S1P5 (9). The presence of apoM is mandatory for the activation of S1P1 by S1P in endothelial cells (9) (Fig. 1). ApoM is one of the most responsive target genes of the transcription factor HNF1α, whose gene is mutated in patients with maturity onset diabetes of the young type 3 (MODY3) (10).

In Apom knockout mice fed with a high-fat diet (HFD), Kurano et al. (8) found plasma levels of S1P decreased and insulin resistance of liver, muscle, and adipose tissue increased. Conversely, HFD-fed mice overexpressing human APOM showed increased plasma levels of S1P, lower blood glucose levels, and less insulin resistance. The glucose-lowering effect of the APOM transgene was abrogated by the treatment with an inhibitor of S1P and S1P3 but not with an inhibitor of S1P2. In liver and skeletal muscle, the phosphorylation of Akt and AMPK, i.e., two well-known downstream targets of S1P1 and S1P3 as well as insulin, was decreased in Apom knockout mice but increased in APOM transgenic mice. Concomitantly, the expression of glucose-metabolizing enzymes was oppositely altered in Apom knockout mice and APOM transgenic mice. Oxygen consumption and the expression of mitochondrial proteins such as Ucp2 were decreased in livers of Apom knockout mice but increased in livers of APOM transgenic mice. Cell culture experiments provided evidence that the activation of S1P1 by apoM/S1P inhibits the degradation of sirtuin 1, which is regulated by AMPK and promotes mitochondrial function (8).

Previous studies have indicated antidiabetic effects of S1P (Fig. 1). Apom knockout mice showed hepatic steatosis (11). Overexpression of the S1P-generating enzyme sphingosine kinase 1 (SPHK1) reduced muscle insulin resistance in HFD-fed mice (12). Kurano et al. (8) did not find any effect of apoM/S1P on β-cell function. However, in a previous study by the same authors, adenovirus-mediated overexpression of APOM in mice enhanced insulin secretion (13). Conversely, reduced S1P production by either pharmacological inhibition of SPHK or knockout of Sphk1 led to decreases in β-cell mass and insulin secretion (14,15). Intraperitoneal S1P administration induced islet β-cell proliferation and abrogated β-cell apoptosis in mice with streptozotocin-induced diabetes (16). Ex vivo, S1P protects β-cells in isolated murine and human islets from IL-1β and glucose-induced apoptosis (17). ApoM and S1P...
can also exert additional indirect antidiabetic effects by inhibiting inflammatory actions of immune cells (9). However, some data contradict the antidiabetic actions of S1P and apoM. Compared with wild-type mice, Apom knockout mice are characterized by larger brown adipose tissue mass, accelerated normalization of postprandial hypertriglyceridemia, and protection from HFD-induced obesity (18). The treatment of mice with fingolimod, which inhibits all five S1P receptors and is in clinical use for the treatment of multiple sclerosis, improved both secretion and peripheral action of insulin as well as HFD-induced hepatosteatosis (19–21). Likewise, genetic interference with S1p2 and Sphk2 in mice resulted in improved β-cell function and insulin resistance (22,23).

When testing the relevance of their findings in humans, Kurano et al. (8) found significantly decreased plasma levels of apoM in patients with diabetes as compared with euglycemic control subjects. However, these differences were rather small. Likewise, correlations between apoM plasma levels and indices of insulin resistance were weak but statistically significant (8). Similar weak associations and correlations of apoM and S1P with T2D and measures of insulin resistance, respectively, were found in some but not all previous studies (9,24). They cannot be interpreted as any indication of causality, as both apoM and S1P levels correlate with plasma levels of HDL cholesterol and apoA-I (25) so that the decrease in HDL particle number in T2D may secondarily cause a decrease in apoM and S1P. In agreement with this, Kurano et al. (8) observed increased rather than decreased plasma levels of apoA-I, apoM, and S1P in mice with diet-induced obesity. However, the decrease of apoM levels in MODY3 patients (10) or the association of single nucleotide polymorphisms of APOM with diabetes (26) may be interpreted as initial hints to causality. Genes contributing to the metabolism, transport, and action of S1P must be tested more comprehensively for their association with diabetes to understand the role of apoM and S1P in human T2D and hence their utility as targets for the management of diabetes. Because S1P plays an important role for the function and survival of many cell types including those of the cardiovascular system and the kidney (9), it will also be interesting to test these genes for their associations with the chronic complications of diabetes.

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