Editorial comment

Lipid metabolism

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Abbreviations

HSPG	heparan sulfate proteoglycans
PPAR	peroxisome proliferator-activated receptor
SAA	serum amyloid A
SR-B1	scavenger receptor class B type 1

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The demonstration by Monty Krieger's laboratory of the important role played by the scavenger receptor class B type 1 (SR-B1) in selective cholesteryl ester uptake from HDL has revived tremendous interest in the pathway of reverse cholesterol transport as a potential anti-atherogenic pathway (for a recent review see Trigatti *et al.* [1]). Others are now actively investigating the regulation of HDL cholesteryl ester uptake by SR-B1, including the interaction between SR-B1 and other known mediators of HDL metabolism. SR-B1 is expressed in many tissues but primarily in the liver and steroidogenic tissues.

One such recent paper comes from the group of Santamarina-Fojo (Lambert *et al.* [2•]), who examined the importance of hepatic lipase in facilitating selective clearance of HDL components from the circulation. In addition to the confirmed role of catalytically active hepatic lipase in HDL metabolism, catalytically inactive hepatic lipase has more recently been shown to function as a ligand for cell surface proteoglycan and receptor-mediated lipoprotein uptake. That group used an in-vivo approach, examining the metabolism of radiolabelled HDL cholesteryl ether as a marker of HDL cholesteryl ester, as well as the clearance of apolipoproteins AI and AII in hepatic lipase-deficient mice. They showed similar apolipoprotein AI and AII clearance in hepatic lipase-deficient versus C57BL control mice, but markedly delayed in-vivo clearance and diminished hepatic accumulation of HDL cholesteryl ether in the former, despite similar hepatic SR-B1 expression. Their study emphasized an important interaction between hepatic lipase and SR-B1 in the selective uptake of HDL cholesteryl ester. Previous in-vitro work from the group demonstrated that, for maximum efficiency of selective cholesteryl ester uptake, both the lipolytic function as well as the ligand-binding roles of hepatic lipase are required. Studies still need to be performed to investigate the relative importance of the lipolytic versus the ligand-binding activities of hepatic lipase in facilitating selective cholesteryl ester clearance *in vivo*. Further proof of the activity of hepatic lipase in this process could be established in experiments that reintroduce either catalytically active or catalytically inactive hepatic lipase into hepatic lipase-deficient mice. Interestingly, as mentioned above, the authors did not establish a role for hepatic lipase in the clearance of the apolipoprotein moieties of HDL, apolipoproteins AI and AII. This does not exclude an important role for hepatic lipase in the clearance of HDL apolipoproteins AI and AII, such as in cases in which the HDL particle is triglyceride rich. Triglyceride enrichment of HDL occurs in clinically prevalent hypertriglyceridaemic states. In addition, marked overexpression of hepatic lipase has previously been shown to reduce plasma HDL apolipoprotein AI and AII concentrations. The precise biochemical mechanism whereby hepatic lipase facilitates SR-B1-mediated selective cholesteryl ester uptake remains to be determined.

There has been tremendous interest in understanding the control of insulin sensitivity and lipoprotein metabolism by peroxisome proliferator-activated receptor (PPAR) nuclear transcription factors. The γ subtype has been felt to play an important role in insulin signalling, whereas the α subtype is felt to play a role in the regulation of lipoprotein metabolism. Interest in these receptors has also been stimulated by the recent recognition that two classes of therapeutic agents exert their clinically beneficial effects through their binding to PPAR. It has been assumed that the thiazolidinedione class of insulin-sensitizing agents (the 'glitazones') exert their effects predominantly by their ability to act as PPAR-γ agonists, whereas the fibrate class of lipid-lowering agents are PPAR-α agonists. A recent study by Guerre-Millo *et al.* [3•] examined the in-vivo effects of pure PPAR-α agonists in improving insulin sensitivity and reducing adiposity. The investigators examined the capacity of three highly selective PPAR-α agonists in two rodent models of high fat-induced (C57BL/6 mice) or genetic (obese Zucker rats) insulin resistance. They showed that these agents markedly lowered hyperinsulinaemia by improving insulin action and, when present,

hyperglycaemia in both animal models. A limitation of the study was that the investigators did not perform direct in-vivo or ex-vivo tests of insulin action, such as the euglycaemic hyperinsulinaemic clamp or 2-deoxy-glucose uptake by muscle tissues. Fenofibrate treatment prevented the high-fat diet-induced increase in body weight and adipose tissue mass without influencing caloric intake or leptin gene expression. This is in contrast to PPAR-γ agonists, which increase adipose tissue mass. One potential mechanism whereby the fibrates could improve insulin sensitivity is through their ability to increase hepatic fatty acid oxidation. The authors hypothesized that this could potentially reduce fatty acid synthesis and triglyceride secretion in VLDL, thereby reducing muscle fatty acid and triglyceride exposure. Fatty acid flux to muscle and muscle triglyceride content are closely correlated with muscle insulin resistance. Alternatively, PPAR-α agonists may have direct insulin-sensitizing effects.

Genetically engineered mouse models have been used with increasing frequency in recent years to study the mechanisms of diabetic dyslipidaemia. Metabolism of the triglyceride-rich lipoproteins (VLDL and chylomicrons and their respective remnants) has been shown to be abnormal in diabetes. Ebara *et al.* [4••] used mice genetically engineered to express either apolipoprotein B100 or apolipoprotein B48 exclusively, compared with wild-type mice, to examine the effect of streptozotocin-induced diabetes on apolipoprotein B100- and B48-containing lipoproteins. They found an increase in plasma lipids and abnormal fat tolerance in the wild-type mice, with increased lipids and VLDL cholesterol enrichment in the apolipoprotein B48 but not in the apolipoprotein B100 mice. Interestingly, and perhaps in contrast to human diabetic dyslipidaemia, there was no increase in triglyceride and apolipoprotein B production rates, nor was there a reduction in lipase activity or VLDL lipolysis. The investigators also investigated the role of apolipoprotein CIII in the aetiology of this diabetic dyslipidaemia but their data did not support a prominent role for apolipoprotein CIII. The novel finding of that study was that remnant VLDL particle (β-VLDL) clearance was slower in the diabetic animals, with reduced trapping by the liver. They postulated, on the basis of in-vitro findings in cultured hepatoma and endothelial cells, that this was caused by decreased hepatic perlecan heparan sulfate proteoglycans (HSPG). Proteoglycans are felt to play an important bridging function, binding and concentrating remnant lipoproteins in proximity to the LDL receptor-related protein, thereby facilitating LDL receptor-related protein-mediated and perhaps direct hepatic remnant uptake. Perlecan is the principal proteoglycan of Disse's space of the liver, where remnant particles are trapped before their uptake by hepatocytes. Although decreased HSPG has been described previously in diabetes, particularly in relation to diabetic nephropathy and arterial wall abnormalities, this is the first association to be made between alterations of HSPG and diabetic dyslipidaemia. Its relevance for human diabetic dyslipidaemia still needs to be proved, because there are numerous differences between genetically engineered animal models of diabetic dyslipidaemia and type 1 or 2 diabetes in humans.

References

1 Trigatti B, Rigotti A, Krieger M, *et al.* The role of the high-density lipoprotein receptor SR-BI in cholesterol metabolism. Curr Opin Lipidol 2000; 11:123–131.

2 • Lambert G, Amar MJA, Martin P, *et al.* Hepatic lipase deficiency decreases the selective uptake of HDL-cholesteryl ester *in vivo*. J Lipid Res 2000; 41:667–672.

3 • Guerre-Millo M, Gervois P, Raspe E, *et al.* Peroxisome proliferator-activated receptor alpha activators improve insulin sensitivity and reduce adiposity. J Biol Chem 2000; 275:16638–16642.

4 •• Ebara T, Conde K, Kako Y, *et al.* Delayed catabolism of apo B-48 lipoproteins due to decreased heparan sulfate proteoglycan production in diabetic mice. J Clin Invest 2000; 105:1807–1818.

Recommended reading

Lambert G, Amar MJA, Martin P, *et al.* Hepatic lipase deficiency decreases the
• selective uptake of HDL-cholesteryl ester *in vivo*. J Lipid Res 2000; 41:667–672.

This study demonstrated an important role for hepatic lipase in facilitating the selective uptake of HDL cholesteryl ester by the scavenger receptor SR-B1. The studies were performed *in vivo* in hepatic lipase-deficient mice. In contrast to the reduction in HDL cholesteryl ester clearance, there was no reduction in HDL apoliprotein AI or AII clearance in hepatic lipase-deficient mice. The importance of the lipolytic versus the non-lipolytic function of hepatic lipase was not examined in this study.

Guerre-Millo M, Gervois P, Raspe E, *et al.* Peroxisome proliferator-activated
• receptor alpha activators improve insulin sensitivity and reduce adiposity. J Biol Chem 2000; 275:16638–16642.

The amelioration of insulin resistance has previously been shown to be mediated by activators of the γ isoform of PPAR. In this study, three highly selective PPARα agonists were tested in two rodent models of insulin resistance, and were shown to lower hyperinsulinaemia by improving insulin action and to improve hyperglycaemia when present. In contrast to the previously demonstrated effect of PPARγ agonists, these agents did not promote weight gain. It is not known whether the insulin-sensitizing action of PPARα activation is a direct effect or indirectly mediated by their ability to promote fatty acid oxidation and reduce plasma triglycerides and fatty acids.

Ebara T, Conde K, Kako Y, *et al.* Delayed catabolism of apo B-48 lipoproteins due
•• to decreased heparan sulfate proteoglycan production in diabetic mice. J Clin Invest 2000; 105:1807–1818.

This is the first demonstration, in a genetically engineered mouse model of diabetic dyslipidaemia, that the reduction in remnant VLDL clearance is associated with a reduction in hepatic perlecan HSPG. There was no increase in VLDL production or reduction in VLDL clearance in this mouse model of diabetes.

Kindy MS, De Beer MC, Yu J, De Beer FC. Expression of mouse acute-phase
• (SAA1.1) and constitutive (SAA4) serum amyloid A isotopes – influence on lipoprotein profiles. Arterioscler Thromb Vasc Biol 2000; 20:1543–1550.

It has been postulated that the acute-phase increase in the serum amyloid A (SAA) family of proteins are responsible for displacing the usual HDL apolipoproteins (particularly apolipoprotein AI) by associating with HDL particles, thereby lowering HDL cholesterol and apolipoprotein AI plasma concentrations during inflammation. In this study, acute-phase *Saa1.1* transgene expression and SAA1.1 adenoviral-mediated protein expression resulted in SAA association with HDL particles but did not significantly alter the apolipoprotein AI or HDL cholesterol levels. This elegant experiment suggests that factors other than increases in acute-phase SAA proteins alone are necessary to alter HDL apolipoprotein AI and HDL cholesterol levels during inflammation. The investigators did, however, demonstrate that adenoviral expression of the constitutive SAA4 protein resulted in larger HDL particles and a marked increase in VLDL levels.

Herrington DM, Pusser BE, Riley WA, *et al.* Cardiovascular effects of droloxifene,
• a new selective estrogen receptor modulator, in healthy postmenopausal women. Arterioscler Thromb Vasc Biol 2000; 20:1606–1612.

Selective oestrogen receptor modulators have the advantage of maintaining the beneficial agonistic effects of oestrogen on bone without the agonistic oestrogen-associated effects on uterine and breast tissue proliferation and neoplasia. The effects of this new class of agents on lipids and the risk of cardiovascular disease has not yet been clearly established. In this study, 24 postmenopausal women were randomly assigned to receive treatment with droloxifene (a new selective oestrogen receptor modulator) compared with conjugated oestrogen for a period of 6 weeks, and markers of cardiovascular risk were examined. Droloxifene and oestrogen had similar beneficial effects on LDL cholesterol, lipoprotein(a), fibrinogen and flow-mediated vasodilation. It did not, however, increase HDL cholesterol or induce oestrogen-like changes in fibrinolytic factors.