COMMENT

The Yin and Yang of cholesteryl ester transfer protein and atherosclerosis

Of late, there has been a major renewal of interest into the protective effect of high-density lipoprotein (HDL)-cholesterol on atherogenesis and coronary disease [1,2]. This derives from the ability of HDL to transport cholesterol from peripheral tissue back to the liver [i.e. reverse cholesterol transport (RCT)] and from specific anti-atherogenic properties of HDL, including antioxidant, antithrombotic and anti-inflammatory effects [3,4]. Fundamental to understanding the in vivo metabolism of HDL and its role in atherosclerosis is cholesteryl ester transfer protein (CETP) [5,6].

CETP is a plasma glycoprotein that mediates the transfer and exchange of neutral lipids (cholesteryl esters and triacylglycerol [triglyceride]) between HDL (specifically HDL₃) and apolipoprotein (apo)-B-containing lipoproteins. Because of the relative lipid content of these lipoproteins, the net effect of CETP is to transfer cholesteryl esters from HDL to very-low density lipoprotein (VLDL) and low-density lipoprotein (LDL), and triacylglycerols from VLDL to HDL and LDL. CETP thus contributes to RCT by channelling cholesterol from extra-hepatic tissue to apoB-containing lipoproteins that are subsequently catabolized in the liver, the other route for RCT being via the classical HDL pathway. Moreover, in concert with the enzyme hepatic lipase, CETP converts HDL₃ particles into HDL₂ and apoAI, thus generating the molecular initiators of cellular cholesterol efflux. Great intrigue has surrounded all these functions of CETP, with disparate sources of evidence suggesting that CETP may be both pro- and anti-atherogenic.

Genetic deficiency in CETP, due to missense and nonsense mutations, results in increased plasma levels of HDL-cholesterol in humans. In the Honolulu Heart Study [7], Japanese-American men with a common genetic deficiency in CETP (due to an Asp⁴⁴Gly substitution in exon 15) had moderate increases in HDL-cholesterol to 1.5 mmol/l and a 50% increased risk of coronary heart disease (CHD), in contrast with a decreased risk in those whose HDL-cholesterol was greater than 1.5 mmol/l. In hypertriglyceridaemic individuals in this population, a low CETP genotype, due to an Ile⁴⁰Val mutation, was also associated with increased CHD risk. Combined CETP and hepatic triacylglycerol lipase deficiency was also associated with increased risk of atherosclerosis [8], again possibly due to co-existent hypertriglyceridaemia. Conflicting evidence has also been provided in European studies [9,10], with certain restriction fragment length polymorphisms of the human CETP gene resulting in high plasma HDL-cholesterol concentrations in association with a paradoxical increase in CHD risk in women.

Studies in transgenic mice have also challenged the anti-atherogenic status of CETP. Mice are naturally deficient in CETP, and when atherosclerosis is induced with cholesterol feeding or with apoE or LDL-receptor knockouts, insertion of a simian CETP transgene accelerates progression of atherosclerosis [11,12]. In contrast, in mice overexpressing human apoCIII, the CETP transgene appears to be anti-atherogenic [13]. Hence, in this animal model, it appears that CETP is pro-atherogenic in the setting of increased concentration of LDL-cholesterol or remnants, but anti-atherogenic in the presence of hypertriglyceridaemia, due to accumulation of VLDL. In contrast with mice, rabbits have naturally high plasma levels of CETP. Experiments in cholesterol-fed rabbits have consistently shown that decreased expression of CETP using antisense oligodeoxynucleotides against CETP [14], or inhibition of CETP activity using anti-CETP antibodies [15], increases the plasma concentrations of HDL-cholesterol and results in a marked reduction in aortic cholesterol content.

Despite the controversies surrounding the role of CETP in atherosclerosis, several pharmacological inhibitors of CETP activity have been developed for potential therapeutic use. A promising compound is JTT-705. This is a thioester that forms disulphide bonds with CETP and when taken orally can inhibit CETP activity in rabbits by 95%. An earlier study by Okamoto et al. [16] showed that oral administration of 255 mg/kg JTT-705 to rabbits with diet-induced hypercholesterolaemia increased HDL-cholesterol by 90%, decreased non-HDL-cholesterol by 40% and, after 6 months, decreased atherosclerotic lesions by 80%. The study reported by Inazu et al. [17] in this issue of Clinical Science aimed to extend these promising earlier observations by examining the dose-dependent effects of JTT-705 on aortic atherosclerosis in rabbits with a more severe degree of hypercholesterolaemia. Using similar experimental methods, an apparently well-powered study and an appropriate interventional design, the authors found no effect of JTT-705 at low (100 mg/kg) or high (300 mg/kg) doses on aortic cholesterol content in cholesterol-fed Japanese white rabbits. This occurred in spite of a significant increase in HDL-cholesterol by 200% and up to 70% inhibition of CETP activity. These results need to be interpreted on the basis that the experimental diet used induced a much higher level of plasma cholesterol of 14.3 mmol/l compared with
4.9 mmol/l in the previous report by Okamoto et al. [16]. Moreover, the higher dose of the CETP inhibitor used by Inazu et al. [17] induced hypertriglyceridaemia and, significantly, the progression of aortic lesions was positively related to plasma concentration of non-HDL cholesterol. Also, the effects of the therapeutic intervention were studied over 3 months compared with 6 months in the previous study by Okamoto et al. [16].

So what can be concluded at this stage concerning the role of CETP and its inhibitors in regulating atherosclerosis? The simple answer is that the roles are conditional on the metabolic setting, environmental and racial factors and on the species under investigation. The human population genetic data suggest that CETP deficiency is anti-atherogenic provided that it induces a substantial increase in HDL-cholesterol. The mouse transgenic data suggest that CETP is anti-atherogenic in the presence of hypertriglyceridaemia and a saturated RCT pathway operating via the HDL route. The rabbit transgenic data suggest that CETP is anti-atherogenic in the presence of hypertriglyceridaemia and a saturated RCT pathway operating via the HDL route. The rabbit transgenic data suggest that CETP is anti-atherogenic in the presence of hypertriglyceridaemia and a saturated RCT pathway operating via the HDL route. The rabbit transgenic data suggest that CETP is anti-atherogenic in the presence of hypertriglyceridaemia and a saturated RCT pathway operating via the HDL route.

In conclusion, inhibition of CETP may be anti-atherogenic, particularly in the presence of mild-to-moderate hypercholesterolaemia. The study of Inazu et al. [17] has implications for patients with heterozygous familial hypercholesterolaemia and is consistent with their previous report [18] showing that such patients with a combined genetic deficiency in CETP and a moderate increase in HDL-cholesterol to 1.6 mmol/l were not protected from coronary artery disease. It is noteworthy that the only published trial to date with JTT-705 in humans was carried out in patients with mild hyperlipidaemia in which a relatively high dose of 900 mg/day over 4 weeks resulted in a significant 37% decrease in CETP activity with a reciprocal 34% increase in HDL-cholesterol [19]. Given the putative priming effect of the metabolic background, one could conclude that CETP may be chiefly pro-atherogenic in the setting of moderate hypercholesterolaemia and possibly combined hyperlipidaemia, but anti-atherogenic in hypertriglyceridaemia with a saturated or compromised HDL RCT pathway. These and related hypotheses, including the effects of co-existent insulin resistance, nevertheless, require testing with CETP inhibitors in clinical and surrogate end-point trials in defined patient groups.

From a wider perspective, inhibition of CETP activity is only one of many approaches for improving HDL metabolism. RCT is a multi-stage process that may be therapeutically manipulated at several levels by, for example, stimulating the synthesis or activities of apoAI, the ABCA1 transporter, the scavenger receptor (SR-B1), lecithin-cholesterol acyl transferase and hepatic biliary excretion of cholesterol [3,20]. ApoB transport also regulates lipid-transfer activity [3,6]. Hence the therapeutic success of CETP inhibitors in clinical practice is also likely to depend on the optimal regulation of other stages of RCT, as well as on therapeutic control of defective apoB metabolism with conventional approaches, including lifestyle modification, statins and fibrates. Preliminary results in human subjects testify that CETP inhibitors are well tolerated [19], but evidently more extensive safety data will be required prior to inclusion of these agents on the clinical menu of lipid-regulating-lowering drugs.

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REFERENCES


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