The roles of C-apolipoproteins in the metabolism of triglyceride-rich lipoproteins

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Role of C-apolipoproteins in the metabolism of triglyceride-rich lipoproteins

Dietary triglyceride carried on chylomicrons, and hepatic-synthesized triglyceride carried on very-low-density lipoproteins (VLDL), are hydrolysed at the capillary endothelium of peripheral tissues by lipoprotein lipase (LPL). The enzyme is synthesized in and secreted from tissues such as adipose tissue and skeletal muscle, and migrates to the capillary endothelium. Abnormalities of production and of clearance of triglyceride-rich lipoproteins may result in hypertriglyceridaemia with consequences to the individual.

Polypeptide components of lipoproteins

At least eight apolipoproteins have been identified and their characteristics are given in Table 1. They are distributed non-uniformly throughout the lipoprotein classes. The major apoprotein components of high-density lipoproteins (HDL) are apoproteins A-I and A-II and that of low-density lipoproteins (LDL) is apoprotein B. A third group of apoproteins, the C-apolipoproteins, are associated with HDL, VLDL and chylomicrons and can be structurally divided into apoprotein C-I, C-II and C-III. All the apoproteins have been assigned, with varying certainty, specific functions in lipoprotein metabolism. This editorial will be concerned with the C-apolipoproteins, and their role in the regulation of lipoprotein lipase and the pathophysiology of hypertriglyceridaemia.

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Metabolism of triglyceride-rich lipoproteins

The catabolism of VLDL involves the hydrolysis of triglyceride by LPL followed by uptake of fatty acids and partial glycerides by tissues, together with degradation and loss of phospholipid and loss of C-apolipoproteins. A subfraction of HDL, HDL3, is believed to accept the phospholipid and C-apolipoproteins liberated from VLDL, together with some free cholesterol. By this process it is converted into the lower density subfraction HDL2 (d 1.063-1.125 g/ml) [1, 2]. After delipidation some of the VLDL is converted into LDL, which contains apoprotein B as the only apoprotein component.

It appears that newly synthesized VLDL and chylomicrons do not contain C-apolipoproteins, but acquire them by exchange from HDL, the reverse of the process which occurs during VLDL catabolism.

Function of C-apolipoproteins

A number of studies have shown that apoprotein C-II activates LPL and is essential for maximal hydrolysis of triglycerides containing long-chain fatty acids [3-7]. A severalfold increase in the rate of free fatty acid release by LPL is found after the addition of pure apoprotein C-II to synthetic triglyceride emulsions. Similar increases in activity of LPL are obtained with VLDL, HDL or serum used as a donor of apoprotein C-II. Apoprotein C-II also activates the phospholipase A1, activity of LPL with phosphatidylcholine or phosphatidylethanolamine used as substrates [8, 9]. The precise mechanism of activation of LPL by apoprotein C-II has not been elucidated. However, it appears that the most likely explanation is that the apoprotein reduces the $K_m$ of the enzyme for triglyceride. Schrecker & Greten [10] have shown that apoprotein C-II caused a sixfold
TABLE I. Characteristics of human serum lipoprotein apoproteins

<table>
<thead>
<tr>
<th>Located in</th>
<th>Mol. wt.</th>
<th>Carbohydrate</th>
<th>Function</th>
<th>Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-I</td>
<td>HDL, chylomicrons</td>
<td>28 300</td>
<td>+</td>
<td>LCAT activation</td>
</tr>
<tr>
<td>A-II</td>
<td>HDL, chylomicrons</td>
<td>17 000</td>
<td>±</td>
<td>?</td>
</tr>
<tr>
<td>B</td>
<td>VLDL, LDL</td>
<td>?</td>
<td>5%</td>
<td>(i) Triglyceride transport</td>
</tr>
<tr>
<td>C I</td>
<td>VLDL, chylomicrons</td>
<td>6331 [42, 43]</td>
<td>0</td>
<td>? Activates LCAT</td>
</tr>
<tr>
<td>C II</td>
<td>VLDL, chylomicrons, HDL</td>
<td>8837 [44]</td>
<td>0</td>
<td>Activates lipoprotein lipase</td>
</tr>
<tr>
<td>C-IIH_{1,2}</td>
<td>VLDL, chylomicrons, HDL</td>
<td>8764 [45, 46]</td>
<td>+</td>
<td>? Inhibits lipoprotein lipase</td>
</tr>
</tbody>
</table>

(0, 1, 2, differ in sialic acid content)

| D          | HDL     | 22 700 | —     | — | Regulates hepatic clearance of chylomicron remnants | Liver |
| E          | VLDL, HDL | 33 000 | —     | — | | |

reduction in the apparent $K_m$ of human post-heparin plasma LPL towards a synthetic triacylglyceride emulsion. Similarly Fielding [11] obtained a threefold reduction in $K_m$ for rat heart LPL. There was no change in $V_{max}$. Similar decreases in $K_m$ have been found when apoprotein C-II is incorporated into apoprotein C-II-deficient VLDL [12] prepared from the plasma of subjects with inherited apoprotein C-II deficiency. The reduction in $K_m$ could arise from either an increase in the amount of enzyme bound to the lipoprotein-medium interface, or by an increase in the affinity of the enzyme for triglyceride after it has bound to the interface.

The LPL-activating property of apoprotein C-II has been localized to a specific region of its primary structure. The molecule contains 78 amino acids, and residues 55-78 contain the determinants for activation. Other regions of the molecule interact with phospholipid, but only synthetic peptides containing sequence 55-78 activate LPL to the same degree as native apoprotein C-II, both in synthetic emulsions and in apoprotein C-II-deficient VLDL [13, 14].

Apoprotein C-I has been shown to be an activator of lecithin–cholesterol acyltransferase (LCAT). It causes a tenfold increase in activity when phosphatidylcholine vesicles are used as a substrate [15]. At present it is not clear if this is of physiological importance since LCAT is also activated by apoprotein A-I, the major apoprotein of HDL. There have also been unconfirmed reports that apoprotein C-I can activate a second LPL fraction, which is released into plasma by lung heparin [16, 17].

Apoprotein C-III is the most abundant of the C-apoproteins. It contains 79 residues and occurs in three isomorphs depending on the number of sialic acid residues attached to galactose and galactosamine at threonine 74, apoproteins C-III_{0}, C-III_{1} and C-III_{2}, containing respectively zero, 1 and 2 mol of sialic acid/mol of peptide [18]. All three isomorphs have been demonstrated to be inhibitors of LPL activity in synthetic emulsions [4, 19]. The inhibitory effect of apoprotein C-III may be the result of absorption of the peptide to the surface of the substrate particle and interference with enzyme binding.

Pathophysiology of hypertriglyceridaemia

Defects in the catabolism of triglyceride rich lipoproteins by LPL give rise to reduced clearance of serum triglycerides and consequently result in hypertriglyceridaemia. For example, the rare familial type I hyperlipoproteinaemia results from impaired clearance of chylomicrons secondary to an absence or deficiency of LPL [20, 21]. The LPL deficiency can be demonstrated by a lack of enzyme activity in post-heparin plasma, or in adipose tissue biopsy specimens. In some cases of type V hyperlipoproteinaemia a similar enzyme defect leads to accumulation of chylomicrons and VLDL. In these cases the enzyme activity is reduced but not absent. This condition may be familial but is more often acquired, for example in diabetes mellitus.

There have been a number of recent reports of individuals with gross hypertriglyceridaemia who have normal levels of LPL but who produce triglyceride-rich lipoproteins with an abnormal C-apoprotein composition, which are poor substrates for the enzyme and consequently show impaired catabolism. Patients have been discovered whose triglyceride-rich lipoproteins lack apoprotein C-II, and who have gross fasting
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hyperchylomicronaemia which could be corrected by the supply of C-II-peptides through the transfusion of blood or plasma [22]. Family studies have shown this apoprotein C-II deficiency to be inherited as an autosomal recessive, obligate heterozygotes having 30–50% of normal levels of apoprotein C-II and normotriglyceridaemia [23, 24]. Although it is clear that C-II activation of LPL is of physiological importance, since an absence of the apoprotein results in defective triglyceride clearance and marked hypertriglyceridaemia, it is unlikely that the quantity of apoprotein C-II per VLDL particle is normally rate limiting for VLDL clearance as long as it is above a minimum value of approximately 10% of that in normal VLDL. This is apparent from studies in vivo and in vitro with C-II-deficient VLDL [12, 14, 22], which have shown that increasing the apoprotein C-II content to approximately 10% resulted in normal substrate behaviour with LPL, and normal clearance of circulating triglyceride-rich lipoproteins. Homozygotes with apoprotein C-II deficiency had triglyceride-rich lipoproteins which in vitro failed to activate LPL, and which were poor substrates for the activated enzyme.

A non-familial and acquired severe depletion of apoprotein C-II associated with hypertriglyceridaemia has been reported [25, 26]. Enzyme-binding studies in vitro with this patient’s triglyceride-rich lipoproteins suggested that hypertriglyceridaemia may have been related to impaired enzyme-substrate binding as well as to a failure of enzyme activation. The primary abnormality may have been an auto-immune reaction as part of multiple myeloma, against the lipoprotein, and possibly against apoprotein C-II specifically. Temporary reversal of the hypertriglyceridaemia in this patient followed infusion of normal plasma or blood and lasted 7–10 days, and long-term reversal of the hyperlipidaemia followed adequate treatment of the myeloma.

Enzyme-binding studies in vitro have provided further evidence of the concept that altered proportions of C-apoproteins carried on triglyceride-rich lipoproteins may result in impaired enzyme-substrate interactions. A further variant of VLDL has been reported where apoprotein C-II has been present in excess in a subject with severe hypertriglyceridaemia [27, 28]. Although the triglyceride-rich lipoproteins were able to activate LPL normally, paradoxically there was chylomicronaemia, the lipoproteins being poor substrates for the enzyme. The abnormal morphology of the particles demonstrated on electron microscopy may reflect altered three-dimensional lipoprotein structure, perhaps caused by interaction of the lipoprotein–triglyceride with excess surface-active apoprotein C-II [29].

A preliminary study, using isoelectric focusing techniques, of VLDL-apoproteins in untreated gouty men has shown a significant reduction in the relative proportion of apoprotein C-II, independent of the patients’ lipid status and drinking habits (D. G. Macfarlane, personal communication). Alterations in apoprotein C-III content of VLDL may be an important cause of defective clearance by LPL. A variant triglyceride-rich lipoprotein with an increased content of apoprotein C-III₂ peptide has been found in some patients with severe hypertriglyceridaemia [30–32] and also in subjects with chronic renal failure [27, 33]. Of the three isoforms of apoprotein C-III differing in their sialic acid content, C-III₁ is the predominant isoform in normal subjects and also in most individuals with hypertriglyceridaemia. The variant lipoprotein with increased content of the more sialylated form of C-III, i.e. C-III₂, behaves as a poor substrate for purified LPL. It is possible that the decreased interaction of the variant lipoprotein with LPL results in decreased clearance and hence contributes to the hypertriglyceridaemia.

Clinical consequences

Severe type I or type V hypertriglyceridaemia is associated with acute complications with eruptive xanthomata, abdominal pain and pancreatitis, and lipaemia retinalis is present. Severe hypertriglyceridaemia increases blood viscosity and is associated with altered platelet function [34, 35]. Hypertriglyceridaemia has been shown to be an important risk factor in the genesis of coronary artery disease [36–38]. Much of the effect of hypertriglyceridaemia as a coronary risk factor may not be primary but may be secondary to association of hypertriglyceridaemia with other risk factors such as hypercholesterolaemia, obesity and diabetes [36, 38]. More recently an important negative association has been found between HDL and coronary heart disease [39–41], and also an inverse relationship between HDL and VLDL [39]. The relationships between the triglyceride-rich lipoproteins and the metabolism of LDL and HDL are likely to be important in the genesis of vascular disease, and indeed the probable integration of the metabolism of the different lipoproteins matches the epidemiological relationships found between HDL and VLDL and between HDL and LDL [39].
It has become clear that the regulation of lipoprotein metabolism is complex and the apoproteins are important modulators of the process. Errors and alterations in apoprotein content have greatly increased our understanding of these pathways, and this is particularly so for the C-apoproteins of triglyceride-rich lipoproteins. Further development in this understanding can be expected to occur in the next few years.

References


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