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Electron Microscopy of Low-density Plasmalipoproteins in Patients with Type IIa Hyperlipoproteinemia

B. Agostini

Max-Planck-Institut für Medizinische Forschung, Abteilung Physiologie, Heidelberg

D. Seidel and H. Wieland

Medizinische Universitätsklinik (Ludolph-Krehl-Klinik), Heidelberg

Analysis of plasmalipoproteins has identified five major types of primary hyperlipoproteinemia [1]. Type IIa hyperlipoproteinemia (essential hypercholesterolemia) is characterized by elevated total plasma cholesterol accompanied by normal plasma triglycerides with an excess of *low-density lipoproteins* (LDL; β-lipoproteins as determined by electrophoresis) of normal lipid-protein composition. This type of hyperlipoproteinemia is of particular interest since it often accompanies tendon xanthomas and accelerated atherosclerosis.

Negative staining has proved a very suitable technique for studying the structure of plasmalipoproteins [2], and aggregates of disc-like lipoproteins have been described in two secondary forms of hyperlipoproteinemia with increased LDL concentrations: cholestasis [3, 4], and familial lecithin: cholesterol acyltransferase deficiency [5]. No significant difference was detected in protein-lipid composition between β-lipoproteins isolated from healthy controls and those from type II patients [1]. However, when observed in the electron microscope the lipoproteins of type IIa are seen to differ from those of healthy controls.

Samples of whole plasma and low-density lipoproteins were isolated by ultracentrifugation at the densities $d = 1.006$ and 1.063 g/ml from fasting healthy controls and well-defined type IIa hyperlipoproteinemics (male and female, age 34–35; cholesterol 474–572 mg-%; triglycerides 75–102 mg-%) and were negatively stained by standard procedures [4, 6]. The stain was applied in an appropriate concentration and a good spreading of the specimen was obtained so as to avoid artifactual clustering. Under these conditions the LDL of normal subjects (Fig. 1a) show a fairly homogeneous population of round particles with a mean diameter of about 200 Å (range 180–220 Å), while those of type IIa hyperlipoproteinemics

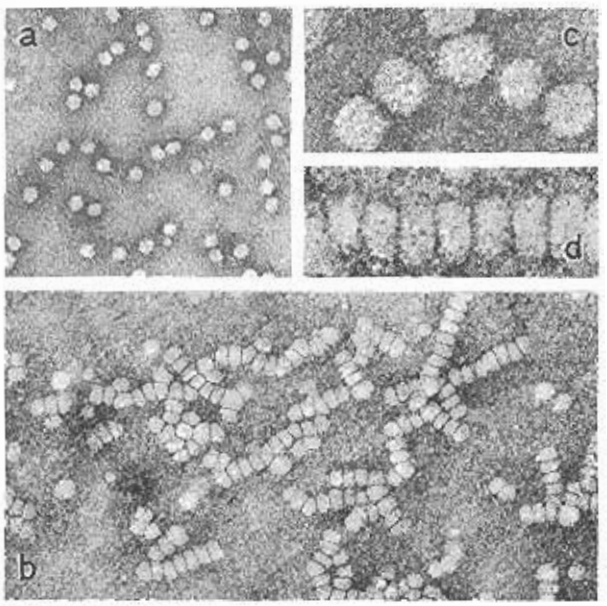

Fig. 1. Electron micrographs of low-density plasmalipoprotein fractions of a healthy control (a and c) and of a patient with type IIa hyperlipoproteinemia (b and d). Negative staining with 1% potassium phosphotungstate. a and b × 100000; c and d × 300000

(Fig 1b) display a striking tendency to form elongated or branched stacks. The particles forming the stacks are ellipsoidal or disc-like with mean minimum and maximum diameters of 150 and 270 Å, respectively. They are not as flattened nor do they flow together like the abnormal LDL particles (LP–X) of cholestatic patients [3, 4] or of patients with familial lecithin:cholesterol acyltransferase deficiency [5]. The fine granular appearance of normal and type IIa LDL particles (Fig. 1a–d) cannot definitively be attributed to the presence of "subunits" as a similar granularity is present all over the micrographs.

Turnover studies of LDL labelled in the protein moiety have shown that the fractional catabolic rate of LDL is significantly lower in type II hyperlipoproteinemics than in controls [7]. We propose to investigate whether and to what extent the structural changes described in this note on the β-lipoproteins in type IIa patients may be caused by a pro-

longed biological half-live of the particles. The structural abnormalities of β-lipoproteins in type II patients may indeed play a role in the accelerated development of atherosclerosis.

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