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Turnover of Plasma Lipoprotein Cholesterol

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The plasma of a normal adult man contains about 200 mg of cholesterol/100 ml. In the fasting state all of this cholesterol is held in solution by association with the plasma lipoproteins. The low-density-lipoproteins carry 60–70% of the total cholesterol in human plasma, but in most non-primate species the bulk of the plasma cholesterol is carried in the high-density lipoproteins. About two-thirds of the total plasma cholesterol is esterified with long-chain fatty acids. In all species the plasma cholesteryl esters contain a high proportion of polyunsaturated fatty acids, but the fatty acid composition of the plasma cholesteryl esters differs markedly from one species to another and, within limits, is dependent on the fatty acid composition of the dietary fat. In man: (1) the predominant fatty acid of the plasma cholesteryl esters is linoleate; (2) the fatty acid pattern is essentially the same in the cholesteryl esters of the high-density, low-density and very-low-density lipoproteins; (3) the fatty acid pattern of the plasma cholesteryl esters is very different from that of the liver cholesteryl esters. In rats: (1) the predominant cholesteryl ester fatty acid in whole plasma is arachidonate; (2) the predominant fatty acid in the very-low-density lipoproteins is oleate and that in the high-density lipoproteins is arachidonate; (3) the fatty acid pattern of the liver cholesteryl esters is similar to that of the very-low-density lipoproteins but differs from that of the low-density and high-density lipoproteins.

All the cholesterol in the plasma is exchangeable, including that in free and esterified form in the different lipoproteins, as is shown by the fact that uniform specific radioactivity of the cholesterol in all these fractions is rapidly achieved when radio-

active free cholesterol is introduced into the circulation. The mechanism by which this exchange takes place is not fully understood, but it is likely that free cholesterol throughout the plasma pool exchanges by direct equilibration. Exchange between free and esterified cholesterol, and between esterified cholesterol in different esters and in different lipoproteins, is thought to occur largely by hydrolysis of plasma cholesteryl esters in the liver, followed by re-esterification (see below) after randomization of the free cholesterol molecules.

Experiments in which the specific radioactivity of the cholesterol in various tissues is measured after a single intravenous injection of radioactive cholesterol, and after prolonged feeding with radioactive cholesterol of constant specific radioactivity, have shown that: (1) the plasma cholesterol exchanges with the cholesterol in some tissues but not in others; (2) the proportion of the tissue cholesterol that is exchangeable differs in different tissues; (3) the rate of exchange varies widely from one tissue to another; (4) the exchangeable cholesterol within a given tissue consists of more than one fraction with different rates of exchange. Since the plasma cholesterol forms part of a heterogeneous pool of exchangeable cholesterol, consisting of many compartments with different rates of equilibration, measurement of the mass of exchangeable cholesterol in the whole body is very difficult. Estimates based on simplified models suggest, however, that a normal man has about 1 g of exchangeable cholesterol/kg body wt.

The exchangeable cholesterol takes part in an enterohepatic circulation in which the plasma cholesterol is excreted via the bile duct into the duodenum, either as cholesterol itself or after conversion into bile acids in the liver. Cholesterol and bile acids are partially reabsorbed from the small intestine, the unabsorbed steroids being excreted in the faeces. There is thus a continual loss of cholesterol from the exchangeable pool. This loss is replaced by absorption of dietary cholesterol and by endogenous synthesis in the liver and other tissues. Excretion of the plasma cholesterol via the faeces accounts for almost all the turnover of the exchangeable pool, but small amounts of exchangeable cholesterol are removed by conversion into steroid hormones in the gonads and adrenal cortex and by desquamation of skin and, perhaps, of intestinal mucosa. Analysis of the plasma disappearance curve of [^{14}C]cholesterol and measurement of the excretion of faecal steroids derived from exchangeable cholesterol agree in showing that the daily turnover of exchangeable cholesterol in an adult human being is about 1 g/day.

Exchange between plasma and tissue cholesterol probably takes place mainly by interchange of free, rather than of esterified, cholesterol molecules.

Since cholesterol is synthesized in many tissues but is removed from the body almost entirely via the liver, there must also be a net transfer of cholesterol from the tissues to the plasma. It is possible that only free cholesterol can be transferred in this way, since cholesteryl esters accumulate in various organs in the rare condition in which there is a deficiency of lysosomal cholesteryl ester esterase.

The plasma cholesteryl esters turn over as a result of continual hydrolysis and resynthesis. In man the fractional rate of turnover of the total esterified cholesterol in the plasma is such that about 100 mg is renewed/h. In human plasma all the cholesteryl esters (irrespective of their fatty acid moiety) turn over at the same fractional rate, but the cholesteryl esters in the high-density lipoprotein turn over more rapidly than do the low-density-lipoprotein cholesteryl esters. In man the plasma cholesteryl esters do not originate in the liver but are formed in the plasma by the action of lecithin (phosphatidylcholine)-cholesterol acyltransferase, which transfers the fatty acyl residue on C-2 of the plasma lecithin to free cholesterol in the high-density lipoproteins. The cholesteryl esters so formed are then transferred to the low-density and very-low-density lipoproteins, possibly by exchanging with triglyceride. In the familial disease in which the acyltransferase is absent from the plasma no cholesteryl esters are present in the plasma in the fasting state. As expected, in human plasma the composition of the fatty acids in the cholesteryl esters is similar to that of the fatty acids on C-2 of lecithin. In rats the cholesteryl esters of the high-density lipoproteins are formed by the acyltransferase reaction, but the cholesteryl esters of the very-low-density lipoproteins (which have a fatty acid pattern different from that of the C-2 of lecithin) are probably formed in the liver and small intestine.

The turnover of the plasma cholesterol is influenced by dietary, genetic and other factors. A diet rich in polyunsaturated fats lowers the concentration of the plasma cholesterol, possibly by promoting its catabolism and excretion. Cholestyramine lowers the plasma cholesterol concentration by stimulating the formation of bile acids. This results in increased hepatic synthesis of cholesterol. There is thus an increase in both the fractional and the absolute rate of turnover of the plasma cholesterol. Other drugs alter the turnover of the plasma cholesterol by interfering with the intestinal absorption of cholesterol, by inhibiting its endogenous synthesis, by stimulating the excretion of the plasma cholesterol, or by a combination of these effects. The raised plasma cholesterol concentration in familial hyper- β -lipoproteinaemia is associated with a diminished fractional rate of turnover of the plasma cholesterol, as shown by the presence of a subnormal faecal

clearance rate (ml of plasma cleared of cholesterol via the faeces/day), but a normal absolute rate of turnover. In this disease there is also a subnormal fractional rate of turnover of the apoprotein of the low-density lipoproteins. These findings are consistent with defective removal of low-density lipoproteins, but other interpretations are equally plausible.

The Mechanism of Removal of Lipoprotein Triglyceride from the Plasma

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The major physiological importance of the plasma lipoproteins derives from their function as carriers of triglyceride, most of which is present in the plasma in the chylomicrons and very-low-density lipoproteins, derived respectively from the intestine and the liver. The turnover time of the plasma chylomicron and very-low-density-lipoprotein triglyceride is much shorter than that of other lipoprotein lipid: its half-life in the rat, for example, is only a few minutes. Moreover, although the rate of influx of triglyceride into the plasma may increase markedly in particular physiological circumstances (for instance, during the absorption of dietary fat), the triglyceride concentration in the plasma normally increases only moderately: that is, the rate of removal rises to balance the increased rate of entry.

It can be concluded that a mechanism for the rapid removal of triglyceride from the plasma exists and that this is not saturated under normal conditions. It is now established that this removal mechanism involves hydrolysis of the chylomicron and very-low-density-lipoprotein triglyceride by the enzyme clearing-factor lipase (lipoprotein lipase). It appears that this hydrolysis occurs at or close to the luminal surface of the capillary endothelial cells and that the free fatty acids released then pass across the endothelial cells into the tissues. Particular lipoprotein peptides in the chylomicrons and very-low-density lipoproteins may well play a specific role in the association of these complexes with the enzyme at the endothelial cell surface. Though most of the triglyceride fatty acids removed from the blood are taken up by the extrahepatic tissues by the action of clearing-factor lipase, the possibility of some uptake by the liver by a different process cannot be excluded.

Changes in the extent of uptake of plasma triglyceride fatty acids by particular tissues occur when the physiological state changes: for example, starvation results in a fall in uptake by adipose

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