Regulation of Plasma Triglyceride Utilization

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The uptake of triglyceride fatty acids from the plasma by the extrahepatic tissues is facilitated through hydrolysis of the triglycerides by the enzyme clearing-factor lipase (lipoprotein lipase). The enzyme probably also plays a directive role in determining the pattern of triglyceride fatty acid uptake by the extrahepatic tissues. Thus activities of the enzyme in specific tissues have been shown to change in particular physiological situations and such changes can be correlated with alterations in the uptake of triglyceride fatty acids by these tissues. For example, in adipose tissue, the activity of the enzyme is high in the fed state when triglyceride fatty acids are taken up from the blood for storage. In the starved state, on the other hand, both the activity of the enzyme and triglyceride fatty acid uptake from the blood are markedly diminished. By contrast, uptake of triglyceride fatty acid by heart muscle rises on starvation when the activity of the enzyme in this organ is increased.

Changes in the activity of the enzyme in adipose tissue appear to be under hormonal control, and insulin, catecholamines, glucagon, thyroid-stimulating hormone and adrenocorticotrophin have each been shown to affect its activity under appropriate conditions *in vitro*. It remains necessary to relate these changes *in vitro* to situations *in vivo* where the activity of the enzyme is altered.

The effects of the above hormones on clearing-factor lipase in adipose tissue are opposite in direction to their effects on the lipase concerned with the mobilization of stored triglyceride fatty acids from the tissue. There is some evidence that the hormonal effects on the activity of adipose-tissue clearing-factor lipase, like those on the mobilizing lipase, may be mediated, at least in part, through changes in the concentration of cyclic AMP in the tissue. This mediation could occur through the conversion of one enzyme form into another of higher activity, and there is some evidence that more than one form of the enzyme does exist in the tissue. On the other hand, indirect evidence suggests that, when increases in activity of the enzyme occur, synthesis of new enzyme protein, or of an essential cofactor of the enzyme, may be involved. Clearly these processes could also be under hormonal control.

It is believed that clearing-factor lipase normally functions to facilitate triglyceride fatty acid uptake by adipose tissue by acting at the surface of the endothelial cells, which line the blood capillaries of the tissue. However, the enzyme is also present in fat-cells isolated from the tissue. Some evidence exists that such enzyme may be the precursor of the functional enzyme. This requires a pathway for the

transport of the enzyme from the fat-cell to the luminal surface of the endothelial cell and possibly also a receptor for the enzyme at its functional site of action. Thus enzyme activity in the tissue could be varied through regulation exerted in the fat-cell, at the point of release from the fat-cell, or at any postulated receptor site for the enzyme.

Methods and Problems in the Study of Plasma Triglyceride Metabolism in Man

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Hypertriglyceridaemia in man has not only an academic interest but is also of considerable clinical importance because of its common occurrence in atherosclerotic vascular diseases. This fact makes it important to study the aetiology and the pathogenesis of hypertriglyceridaemia. A basic requirement for this is methods for determination of plasma triglyceride turnover rate in man. Two types of methods for this purpose are reviewed. In the first it is attempted to determine the hepatic secretion rate of triglyceride by multiplying plasma triglyceride concentration difference over the liver by hepatic blood flow. The two major difficulties are the anatomical one and that related to the error in estimation of triglyceride. The latter is highly critical and requires a very precise method with an error less than 1% because of the large hepatic blood flow. Usually the error for a triglyceride determination is around 3–5%. Results with chemical as well as radioisotopic (after intravenous administration of labelled albumin-bound palmitate) measurements are given. In the second method an attempt is made to obtain an estimate—or rather a correlation—of the fractional turnover rate of plasma triglyceride by injecting intravenously a fat emulsion, which behaves very similar to chylomicrons. Our data suggest that the most common pathogenetic mechanism for hypertriglyceridaemia is a decrease of the fractional turnover rate of plasma triglyceride at a normal turnover rate. This indicates that in the majority of cases the aetiology is to be found in the mechanisms regulating peripheral clearance and/or uptake of plasma triglycerides.

The Metabolism of Plasma Cholesterol

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Cholesterol in the plasma is carried in the lipoproteins, the β -lipoproteins carrying 60–70% of the total cholesterol in normal human plasma. About

two-thirds of the plasma cholesterol is esterified with fatty acids. The plasma free cholesterol is exchangeable with free cholesterol in many tissues, including erythrocytes, liver, intestinal wall, skin and arteries. Since the rate of equilibration between plasma and tissue cholesterol differs in different tissues, there are several exchangeable pools of cholesterol within the whole body. There is also a net transfer of cholesterol from the plasma into the liver, followed by excretion into the duodenum via the bile, either without metabolic change or after conversion into bile acids. The cholesterol excreted into the duodenum is partially reabsorbed, the unabsorbed fraction leaving the body in the faeces. Cholesterol in the plasma also exchanges with the pools of cholesterol from which steroid hormones are formed in the gonads and adrenal cortex. There is therefore a continual net loss of cholesterol from the plasma owing to faecal excretion and conversion into bile acids and steroid hormones. This loss is replaced by absorption of dietary cholesterol and by endogenous synthesis.

Cholesterol ingested in the food mixes with that excreted into the duodenum and is partially absorbed from the jejunum via the lymphatic system after incorporation into chylomicra, largely in esterified form. Chylomicron cholesterol is removed by the liver and hydrolysed enzymically to free cholesterol. The free cholesterol is then incorporated into lipoproteins and released into the circulation.

The plasma cholesterol of endogenous origin is formed mainly in the liver, but some is also contributed by other tissues, particularly the small intestine. In man, the newly formed cholesterol is incorporated into lipoprotein and released into the circulation, where it is esterified with long-chain fatty acids by a plasma enzyme (lecithin-cholesterol acyltransferase), which transfers the fatty acid residue on C-2 of the plasma lecithin to plasma free cholesterol. In keeping with this mode of synthesis, in human plasma the composition of the fatty acids of the cholesteryl esters in all lipoprotein fractions is similar to that of the fatty acids attached to C-2 of lecithin and is different from that of the cholesteryl esters of human liver. In rats, lecithin-cholesterol acyltransferase is present in plasma and is probably responsible for the formation of the cholesteryl esters in the high-density lipoproteins, but the cholesteryl esters in the very-low-density lipoproteins of rat plasma are believed to be formed in the liver and small intestine.

The plasma cholesteryl esters are hydrolysed enzymically in the liver, the resulting free cholesterol following the same fate as that resulting from hepatic synthesis and from the hydrolysis of chylomicron cholesteryl esters.

From this simplified description it will be seen that the body contains a mass of exchangeable

cholesterol in both free and esterified forms, and that randomization of cholesterol throughout the whole mass takes place by two processes: direct exchange of free cholesterol between plasma and the various tissue pools, and indirect exchange due to hydrolysis of esterified cholesterol in the liver, followed by re-esterification. In man, re-esterification of the plasma cholesterol takes place entirely in the plasma, as shown below:

(FC = free cholesterol; EC = esterified cholesterol)

In rats, the plasma cholesteryl esters are formed partly in the liver and partly in the plasma and intestine. In man, the fractional rate of turnover of the whole mass of exchangeable cholesterol is 1–2%/day (equivalent to the removal and replacement of about 1 g of exchangeable cholesterol/day) and the fractional rate of turnover of the pool of plasma cholesteryl esters is about 2%/h.

Nutritional and Endocrine Factors Influencing Plasma Triglyceride Metabolism

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Patients with atherosclerotic heart disease are metabolically heterogeneous; amongst their commonest abnormalities is endogenous hypertriglyceridaemia (Carlson, 1960). This form of hyperlipidaemia usually is manifested as an increase in the group of very-low-density lipoproteins in plasma, though other dyslipoproteinaemias may occur. The mechanisms of hypertriglyceridaemia are poorly understood, and are discussed in relation to conditions frequently associated with it.

1. About 50% of hypertriglyceridaemic patients show a greater than normal rise of plasma triglyceride on isocaloric high-carbohydrate diets; this response, carbohydrate inducibility, is a graded phenomenon (Glueck, Levy & Fredrickson, 1969). Carbohydrate restriction decreases plasma lipids in this group. Insulin response to oral glucose is high in some patients but is not consistently abnormal (Glueck *et al.* 1969). In the rat, insulin may increase hepatic secretion of triglyceride into plasma, but more certainly enhances both major stages of triglyceride removal from the circulation, inducing