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