Lipoprotein lipase in the physiological system

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Lipoprotein lipase (EC 3.1.1.34) catalyses the hydrolysis of plasma triacylglycerols and thereby enables the transfer of triacylglycerol fatty acids from the circulation to various extrahepatic tissues. The enzyme is synthesized in the parenchymal cells of a number of tissues including adipose tissue, heart and mammary gland, and is then secreted and transported to its functional site on the luminal surface of the capillary endothelial cells (Robinson, 1970; Nilsson-Ehle et al., 1980).

Tissue-specific changes in lipoprotein lipase activity

Adaptive changes in lipoprotein lipase activity occur in different tissues in response to variations in the physiological state. These changes correlate with altered rates of triacylglycerol fatty acid uptake into the respective tissues. Thus circulating triacylglycerol fatty acids are effectively directed to various body sites in a manner appropriate to the prevailing physiological conditions.

This direct role of lipoprotein lipase is typified by reciprocal changes in the activity of the enzyme between different tissues. For example, when rats are fasted, the activity of lipoprotein lipase decreases in white adipose tissue (Pav & Wenkeova, 1960; Wing & Robinson, 1968a; Reichl, 1982) and concomitantly increases in heart and skeletal muscle (Borenztajn et al., 1970; Rogers & Robinson, 1974). Furthermore, when rats in a variety of nutritional states are compared, adipose tissue lipoprotein lipase activity is inversely correlated with the activity of the enzyme in heart and skeletal muscle (Cryer et al., 1976).

These dietary-induced tissue-specific variations in lipoprotein lipase activity result in the preferential uptake of circulating triacylglycerol fatty acids by adipose tissue for storage when animals are in the fed state, and by heart and muscle for oxidation during periods of fasting.

Reciprocal changes in tissue-specific lipoprotein lipase activity also occur during cold exposure: where the activity of the enzyme increases, in heart and decreases in epididymal adipose tissue (Rault et al., 1974; Rogers & Robinson, 1974). In addition such treatment also results in a dramatic increase in the activity of the enzyme in brown adipose tissue (Radomske & Orme, 1971; Matsushita et al., 1980). Thus during cold exposure, the lipoprotein lipase activities of white and brown adipose tissue change in a reciprocal fashion, consistent with the thermogenic role of the latter tissue in oxidizing fatty acids to provide heat (Nedergaard & Lindberg, 1982).

Perhaps the most striking of the tissue-specific changes in lipoprotein lipase activity is that which occurs in the mammary gland during the pregnancy-lactation-involution cycle. The activity of the mammary gland enzyme is extremely low throughout pregnancy but increases dramatically to a very high level just before parturition. This elevated level persists throughout lactation and then decreases at the onset of involution (McBride & Korn, 1964; Scow et al., 1977). Prevention of suckling during lactation reduces the activity of mammary gland lipoprotein lipase to a low level and concurrently increases the activity in adipose tissue (Hamosh et al., 1970; Scow et al., 1977).

The lipoprotein lipase activity of rat uterus increases several-fold in the later stages of pregnancy, co-incident with a reduction in the activity of the enzyme in the adjoining parametrical adipose tissue. This further example of reciprocal control of the enzyme between tissues results in a preferential uptake of triacylglycerol fatty acids by the uterus at the expense of adipose tissue before parturition, thus providing the uterus with fuel for contraction and/or substrate for prostaglandin synthesis (Gray & Greenwood, 1983).

The above examples of tissue-specific changes in lipoprotein lipase activity serve to illustrate the important role of this enzyme in the metabolic adaptation to variations in physiological state. In addition to those tissues already mentioned, lipoprotein lipase is also present in lung (Zemplenyi & Graffnerter, 1958), monocyte-derived macrophages (Khoos et al., 1981; Chait et al., 1982; Iverson et al., 1982; Mahoney et al., 1982) and aortic smooth-muscle cells (Vance et al., 1982). The lipoprotein-lipase-dependent uptake of lipid into monocyte-derived macrophages may play a role in the conversion of these cells to foam cells during atherosclerotic plaque formation (Lindqvist et al., 1983).

Although lipoprotein lipase is usually regarded as an extrahepatic enzyme, a transient appearance of the enzyme has been detected in the liver of the newborn rat, consistent with the postulated function of this tissue as a temporary lipid store in the neonate (Llobera et al., 1979).

Regulation of lipoprotein lipase activity in rat epididymal adipose tissue

The foregoing discussion has reviewed the changes which occur in the lipoprotein lipase activities of a number of tissues in response to various physiological conditions. It is evident that the regulation of such changes is a complex process, especially when the reciprocal nature of the tissue-specific events is considered. The control of the enzyme in white adipose tissue has been studied in some detail and the results of such work are summarized below.

Insulin has long been recognized as a major regulator of adipose tissue lipoprotein lipase, both in vivo and in vitro. Enzyme activity is increased several-fold by injection of insulin into fasted rats (Borenztajn et al., 1972; Garfinkel et al., 1976) and is strongly correlated with the plasma insulin concentration when rats in a variety of nutritional states are compared (Cryer et al., 1974, 1976). In addition, the activity of the enzyme is low in diabetes (Kessler, 1963; Schmatz & Williams, 1983) and is increased by insulin treatment (Chan & Stern, 1982; Sadur & Eckel, 1982). Insulin has also been shown to increase lipoprotein lipase activity during incubation of epididymal fat-bodies in vitro (Salaman & Robinson, 1966; Hollenberg et al., 1970; Vydelingum et al., 1978; Ashby & Robinson, 1980) and during the differentiotion of pre-adipocytes (Eckel et al., 1978; Spooner et al., 1979; Murphy et al., 1981).

Glucocorticoids have also been implicated in the regulation of adipose-tissue lipoprotein lipase. The activity of the enzyme is increased after glucocorticoid injection in vivo (de Gasquet & Pequignot, 1973; de Gasquet et al., 1975). Also, insulin-induced stimulation of lipoprotein lipase activity during incubation of epididymal fat-bodies in vitro was found to be markedly potentiated by glucocorticoids (Ashby & Robinson, 1980). The physiological significance of these results is supported by the fact that, in the rat, the plasma
concentration of corticosterone rises immediately before the onset of nocturnal feeding and remains high during the fed state (Peret et al., 1973). Thus the dietary-induced increase in the activity of the enzyme may be at least partly attributed to increases in the plasma levels of insulin and corticosterone which occur at, or around, the time of feeding. In addition, gastric inhibitory polypeptide, which is released into the plasma on fat-feeding, has been shown to stimulate adipose tissue lipoprotein lipase in *in vitro* and may thus also play a role in the dietary regulation of the enzyme (Eckel et al., 1980).

Adrenaline and noradrenaline also reduce the activity of the enzyme during incubations of epididymal fat-bodies *in vitro* (Wing et al., 1965; Nikolaï & Pykalisto, 1968; Antonov et al., 1978; Ashby & Robinson, 1980). This effect is mimicked by dibutyl cyclic AMP, suggesting a β-adrenergic mechanism for this process (Wing & Robinson, 1968b; Patten, 1970). The implication that adrenergic nervous stimulation of adipose tissue may be involved in the regulation of the enzyme *in vito* has not, however, been substantiated (Hansson et al., 1981). Although the possibility of regulation of the enzyme's activity by cyclic AMP-mediated phosphorylation has frequently been considered, no evidence for control of this kind has yet been obtained (Steinberg & Khoo, 1977; Robinson et al., 1983).

The changes which occur in the activity of lipoprotein lipase in rat adipose tissue on starvation and in pre-adipocytes during differentiation are associated with parallel changes in the amount of enzyme as estimated by immunotitration (Jansen et al., 1978; Vannier et al., 1982). These results suggest that alterations in the rate of synthesis and/or degradation of lipoprotein lipase may be involved in the regulation of enzyme activity.

The control of lipoprotein lipase synthesis received little attention until recently, largely for methodological reasons. However, in 1983 Vydelingum et al. (1983) measured the incorporation of '*H*-labelled amino acids into lipoprotein lipase, by using antibodies to precipitate the enzyme from adipose tissue extracts. In our laboratory, we have developed an alternative method, based on the use of affinity chromatography on heparin-Sepharose, to quantitatively isolate the enzyme free from other radiolabelled proteins (Robinson et al., 1983; Speake et al., 1985). Application of these methods had indicated that both insulin and glucocorticoids may regulate the activity of the enzyme by stimulating its synthesis. Thus, the incorporation of '*H*-labelled amino acids into lipoprotein lipase, during incubations of epididymal fat-bodies *in vitro*, is stimulated approximately 2-fold by insulin and by 4-5-fold in the presence of insulin plus dexamethasone (Robinson et al., 1983; Vydelingum et al., 1983; Speake et al., 1985). The insulin-induced effect on lipoprotein lipase synthesis could be partly explained by an increase in total protein synthesis in the tissue. However, the additional glucocorticoid-potentiated effect represented a specific increase in the synthesis of the enzyme.

Additional studies, by using pulse-chase incubations of epididymal fat-bodies, have indicated that newly synthesized lipoprotein lipase is rapidly degraded in the tissue by a proteolytic mechanism, and that the rate of degradation is significantly increased in the presence of adrenaline (Parkin et al., 1985). The significance of this finding in relation to the well-established high turnover rate of adipose tissue lipoprotein lipase *in vitro* (Wing et al., 1967), and the possible role of postsecretory endocytotic uptake and subsequent lysosomal degradation of the enzyme by adipocytes (Friedman et al., 1982), has yet to be established.

In conclusion, it is clear that adipose-tissue lipoprotein lipase is likely to be regulated by multiple hormonal interactions, and that both the synthesis and the degradation of the enzyme are potential sites of control. Hormonal regulation of the synthesis of the enzyme may occur at both transcriptional or translational levels within the adipocyte. However, regulation of degradation could occur before secretion, or outside the adipocyte at the endothelial cell surface, or after re-uptake by endocytosis. The high rate of turnover will enable the level of the enzyme to respond rapidly to any variations in its rate of synthesis, such as may be brought about by, for example, changes in the plasma concentrations of insulin and corticosterone (see Schimke, 1970).

**Regulation of tissue-specific, reciprocal changes in lipoprotein lipase activity**

Studies have been carried out on the effect of hormones on lipoprotein lipase activity in tissues other than white adipose tissue. Injection of glucagon into fed rats increased the activity of the heart enzyme (Borensztajn et al., 1973), and adrenaline was reported to increase lipoprotein lipase activity in perfused rat hearts (Palmer & Kane, 1983a) and isolated cardiac myocytes (Palmer & Kane, 1983b). Thus the effects of glucagon and adrenaline on lipoprotein lipase are apparently opposite to their effects on the enzyme in white adipose tissue. Injection of noradrenaline into rats stimulated the activity of lipoprotein lipase in brown adipose tissue, mimicking the effects of cold exposure (Carneheim et al., 1984), and again producing an effect opposite to that observed in white adipose tissue.

In lactating rats, hypophysectomy reduced the activity of lipoprotein lipase in mammary gland and increased the enzyme activity in adipose tissue, whereas subsequent injection of prolactin restored both tissue activities to the original levels (Zimder et al., 1974). Administration of oestrogen to non-pregnant rats increased the enzyme activity of mammary tissue and decreased that of adipose tissue (Hamosh & Hamosh, 1975; Kim & Kalkhoff, 1975). Thus it appears that the increase in the plasma concentrations of prolactin and oestrogen before parturition, possibly coupled with the simultaneous decline in the level of progesterone (Spooner et al., 1977), may regulate the mammary and adipose tissue lipoprotein lipase activities in a reciprocal manner.

The mechanism by which a particular hormone increases the activity of the enzyme in one tissue, yet decreases it in another remains obscure. One possibility would be the existence of tissue-specific forms of lipoprotein lipase, and the report by Ben-Zeev et al. (1983), suggesting that the adipose tissue and heart enzymes are coded by different genes, may be of particular relevance in this connection. However, in contrast to earlier work (see Nilsson-Ehle et al., 1980), our recent results (S. M. Parkin & D. S. Robinson, unpublished work) indicate that preparations of the enzyme isolated from rat adipose tissue, heart and mammary gland are identical in terms of their *M* and kinetic properties.

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Genetic variants of the lipoproteins and hyperlipidaemia

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Lipoproteins constitute a complex carrier system of interconverting particles for the transport of triglyceride and cholesterol amongst tissues. The details of this transport system are shown in Fig. 1. Important proteins required for lipid transport are the apolipoproteins, enzymes and lipoprotein receptors. Of the eight apolipoproteins, the amino-acid sequences of six (apo A-I, A-II, C-I, C-II, C-III and E) have been elucidated; and although they were initially considered to serve a structural role in the formation and stabilization of the lipoprotein particle, some of them (e.g. apo A-I, B-100, C-II and E) may have a functional role regulating enzymes or interacting with receptors involved in the catabolic pathways of lipoproteins in peripheral tissues (Galton et al., 1983). The major enzymes involved in lipoprotein catabolism are lipoprotein lipase (EC 3.1.1.34), hepatic lipase (EC 3.1.1.3) and lecithin:cholesterol acyltransferase (EC 2.3.1.43). The latter two are lipolytic enzymes hydrolysing the core triglyceride of chylomicra and VLDL in the capillary bed of many peripheral tissues, and the triglyceride of remnant particles within the liver respectively. The latter is responsible for the esterification of HDL cholesterol in plasma during maturation of the nascent particle. The major receptor proteins are the LDL receptor found on the cell-surface of many peripheral cells (e.g. monocytes, fibro-