Regulation of hepatic triacylglycerol synthesis and lipoprotein metabolism by glucocorticoids

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The excessive synthesis and storage of triacylglycerol (triglyceride) has a number of clinical implications. It is obviously the main symptom of obesity where excess lipid is stored in adipose tissue. Abnormal accumulations of triacylglycerols can also be manifested as a fatty liver, e.g. as a result of the ingestion or inhalation of toxic compounds and damage to the liver. These conditions are often associated with an increase in the rate of triacylglycerol synthesis in the liver and are aggravated if the ability to secrete the triacylglycerol in very-low-density lipoproteins (VLDL) is impaired. If the increased synthesis of triacylglycerol results in a greater secretion of VLDL, then this implies that the flux of cholesterol into low-density lipoprotein (LDL) should also be increased. This is because cholesterol is secreted as part of the VLDL particle to facilitate the transport of triacylglycerol. When the triacylglycerol is removed from the VLDL by the action of lipoprotein lipase (EC 3.1.1.34), the cholesterol appears in the circulation in low-density lipoproteins. It therefore seems important to understand how the body controls triacylglycerol metabolism and to identify the mechanisms by which the synthesis of triacylglycerols in the liver becomes raised.

At present this knowledge is incomplete, but it has become evident from animal work that the availability of glucocorticoids is an important factor [1, 2]. Although the control of glucocorticoid metabolism in experimental animals is probably different from that in man, nevertheless their effects on metabolism are likely to be similar. High concentrations of circulating cortisol are associated with excessive fat deposition in Cushing's syndrome and in obesity in experimental animals [3]. Most human obesity is not associated with gross elevations of serum cortisol concentrations, but obesity may involve an increased sensitivity to glucocorticoid action [3]. These hormones facilitate the action of insulin in stimulating the synthesis of fatty acids [4,5]. Their effects on the synthesis of triacylglycerols in liver seem to be more direct and the available evidence indicates that they stimulate the synthesis of the enzyme phosphatidate phosphohydrolase [1, 2]. The microsomal and soluble phosphatidate phosphohydrolase (Fig. 1) have a regulatory function, particularly in enabling the liver to synthesize increased quantities of triacylglycerol. This enzymic adaptation therefore partly explains why injections of corticotropin or glucocorticoids stimulate hepatic triacylglycerol synthesis [2, 6] and produce a fatty liver [7, 8]. Glucocorticoids also promote the secretion of VLDL [9, 10].

The influence of glucocorticoids on the activity of phosphatidate phosphohydrolase is particularly apparent in stress conditions. This activity can increase in starvation [11, 12], mildly ketotic diabetes [13], severely ketotic diabetes [14], hypoxia [15], after surgical stress including subtotal hepatectomy [12], and after hydrazine injection [16, 17]. It may seem paradoxical that the capacity of the liver to synthesize triacylglycerols should increase in conditions where the concentrations of circulating glucagon, catecholamines and glucocorticoids increase relative to insulin. The liver receives a large supply of fatty acids from adipose tissue and decreases its own synthesis of these acids. The latter event is accompanied by a decreased concentration of malonyl-coenzyme A (CoA), a key intermediate in this process, which also inhibits β-oxidation.
FIG. 1. Fatty acid metabolism in severe ketotic diabetes or severe stress. The direction of fatty acid metabolism in severe diabetes or stress where the concentration of insulin to glucagon, catecholamines, corticotropin and glucocorticoids is very low is shown. The enzyme activities that are referred to are indicated by: (1) glycerophosphate acyltransferase (EC 2.3.1.15); (2) carnitine palmitoyltransferase (EC 2.3.1.21); (3) phosphatidate L-α-phosphohydrolase (EC 3.1.3.4); (4) lipoprotein lipase (EC 3.1.1.34).

[18] through its action on carnitine palmitoyltransferase. Lack of insulin has also been reported to decrease the activity of glycerophosphate acyltransferase, particularly that in the mitochondrial fraction [19]. These changes promote the partitioning of fatty acids into β-oxidation and ketogenesis rather than into esterification (Fig. 1). However, the supply of fatty acids to the liver often exceeds its need for energy production via β-oxidation, and the excess acids and their acyl-CoA esters are potentially toxic. Their conversion into triacylglycerols enables them to be stored temporarily in a safe form and allows CoA to be regenerated. This explains why these stress conditions are often accompanied by a fatty liver.

The liver can also secrete this triacylglycerol provided that lipoprotein synthesis is not inhibited as it may be in some toxic conditions. This VLDL secretion can increase in ketotic diabetes [20] and, since insulin is required for the activity of lipoprotein lipase in adipose tissue, triacylglycerol clearance is decreased and a hypertriglyceridaemia results (Fig. 1). The action of insulin in increasing lipoprotein lipase activity in adipose tissue can be potentiated by glucocorticoids [21]. By contrast, the lipoprotein lipase activity in heart appears to be maintained primarily by glucocorticoids and insulin may promote this action [22]. This ability of the heart to oxidize and esterify fatty acids is also high in ketotctic diabetes [23]. In this condition the liver is supplying energy to the heart in the form of triacylglycerols and ketones, and to the brain as glucose and ketones. In this instance the control of hepatic phosphatidate phosphohydrolase by glucocorticoids appears to resemble their control of some enzymes of gluconeogenesis.

The diurnal peak of corticosterone in rats occurs about 4 h before the maximum food intake [24]. This peak is probably responsible for the increased synthesis of phosphatidate phosphohydrolase, so that its activity is greatest when the liver increases its synthesis of fatty acids. Nutrients such as glycerol, sorbitol, fructose and ethanol stimulate hepatic triacylglycerol synthesis. When these are given as acute loads to rats, they provoke a much larger glucocorticoid response than does the equivalent load of glucose and they do not increase insulin concentrations [25]. The effect of the former nutrients again increases phosphatidate phosphohydrolase ac-
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Glucocorticoids increase the activity and concentration of L-α-phosphatidate phosphohydrolase (EC 3.1.3.4) in the liver. This enzyme has an important regulatory function and this change facilitates the increased synthesis, accumulation and secretion of triacylglycerols by the liver. The increased production of very-low-density lipoprotein also means that the ultimate flux of cholesterol into low-density lipoproteins is increased.

If insulin concentrations are low, or if there is insulin insensitivity, then the clearance of circulating triacylglycerol by adipose tissue decreases and a hypertriglyceridaemia may result.

The clearance of triacylglycerols by the heart can increase in relative terms, since its lipoprotein lipase activity is maintained by glucocorticoids rather than by insulin.

Changes in glucocorticoid status may be significant in determining the effects on metabolism of stress, diabetes, smoking and the consumption of diets deficient in ascorbate or rich in sucrose, sorbitol, ethanol and fat.

It is proposed that changes in glucocorticoid status that could occur in these conditions could contribute to the development of fatty livers.
maturity onset diabetes, obesity and atherosclerosis.

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