

Mechanisms of nutritional and hormonal regulation of lipogenesis

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Fat build-up is determined by the balance between lipogenesis and lipolysis/fatty acid oxidation. In the past few years, our understanding of the nutritional, hormonal and particularly transcriptional regulation of lipogenesis has expanded greatly. Lipogenesis is stimulated by a high carbohydrate diet, whereas it is inhibited by polyunsaturated fatty acids and by fasting. These effects are partly mediated by hormones, which inhibit (growth hormone, leptin) or stimulate (insulin) lipogenesis. Recent research has established that sterol regulatory element binding protein-1 is a critical intermediate in the pro- or anti-lipogenic action of several hormones and nutrients. Another transcription factor implicated in lipogenesis is the peroxisome proliferator activated receptor γ . Both transcription factors are attractive targets for pharmaceutical intervention of disorders such as hypertriglyceridemia and obesity.

Introduction

In the past several decades, obesity has become extremely common, with prevalence rates skyrocketing among certain groups and communities (Kopelman, 2000). Inasmuch as traditional dietary approaches to combat obesity have largely failed, the scientific community has become increasingly interested in the molecular regulation of triglyceride synthesis and in pharmaceutical approaches to reduce fat storage. Accordingly, a heavy research effort is currently directed towards the identification of molecular targets for fat storage, and on the development of drugs that specifically reduce adipose tissue mass.

Fat accumulation is determined by the balance between fat synthesis (lipogenesis) and fat breakdown (lipolysis/fatty acid oxidation). Lipogenesis encompasses the processes of fatty acid synthesis and subsequent triglyceride synthesis, and takes place in both liver and adipose tissue (Figure 1). Lipogenesis should not be confused with adipogenesis, which refers to the differentiation of

pre-adipocytes into mature fat cells. A comprehensive review on the regulation of adipogenesis has appeared recently (Rosen and Spiegelman, 2000).

Nutritional regulation of lipogenesis

Lipogenesis is very responsive to changes in the diet. Polyunsaturated fatty acids decrease lipogenesis by suppressing gene expression in liver, including that of fatty acid synthase, spot14 and stearoyl-CoA desaturase (Jump *et al.*, 1994). Conversely, a diet rich in carbohydrates stimulates lipogenesis in both liver and adipose tissue, leading to elevated postprandial plasma triglyceride levels. Fasting reduces lipogenesis in adipose tissue, which, combined with an increased rate of lipolysis, leads to net loss of triglycerides from fat cells. In contrast, in liver, because of the large amounts of fatty acids arriving from the adipose tissue, triglyceride synthesis is increased, resulting in a mild form of hepatosteatosis (fatty liver) (Kersten *et al.*, 1999). This happens despite a reduced rate of fatty acid synthesis and decreased expression of numerous genes involved in lipogenesis (Shimano *et al.*, 1999).

It can be reasoned that, somehow, the signal of reduced or excess food intake has to be translated into altered expression levels of lipogenic genes. This concept can be illustrated by examining the effects of fasting, which is associated with a decrease in plasma glucose and an increase in plasma-free fatty acids. Plasma glucose levels stimulate lipogenesis via several mechanisms. First, glucose itself is a substrate for lipogenesis. By being glycolytically converted to acetyl-CoA, glucose promotes fatty acid synthesis. Secondly, glucose induces the expression of lipogenic genes, the mechanisms of which are explained below. Finally, glucose increases lipogenesis by stimulating the release of insulin and inhibiting the release of glucagon from the pancreas.

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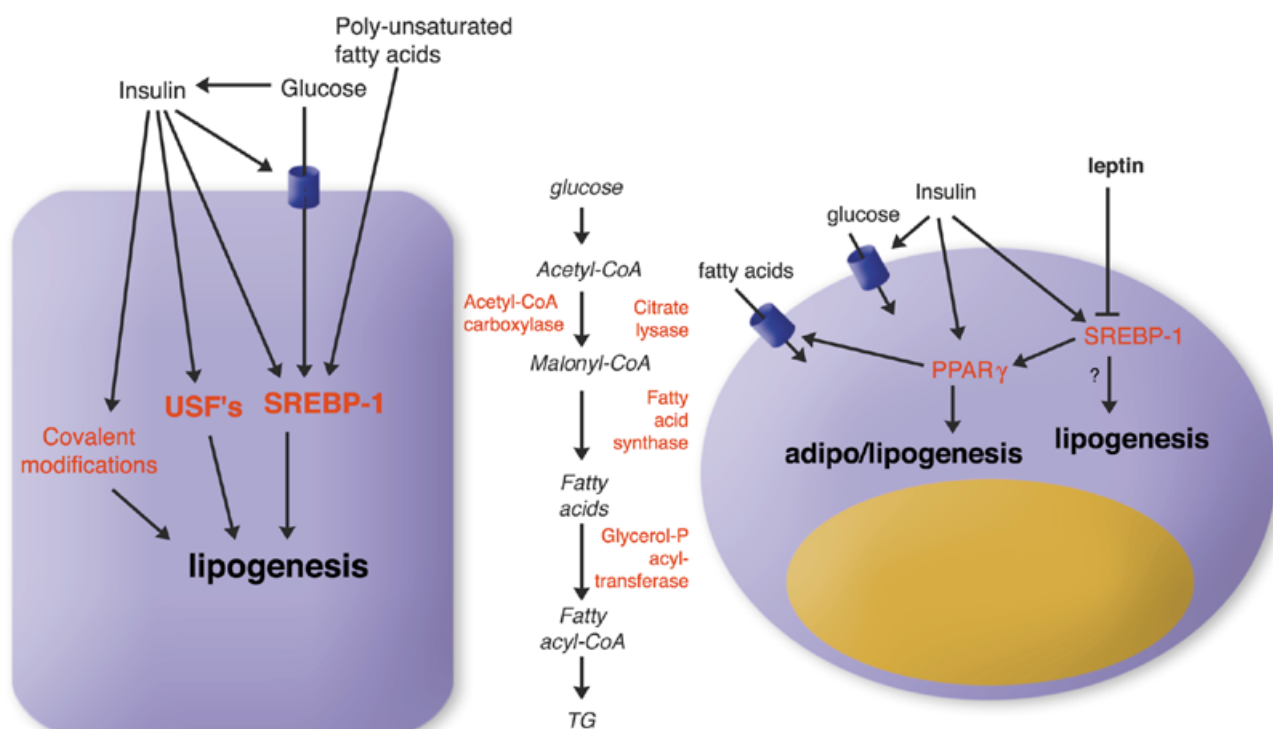


Fig. 1. Regulation of lipogenesis in hepatocytes (left) and adipocytes (right). The effects of nutrients and hormones on the expression of lipogenic genes are mostly mediated by SREBP-1 and, in adipose tissue, by PPAR γ . Lipogenesis entails a number of discrete steps, shown in the middle, which are controlled via allosteric interactions, by covalent modification and via changes in gene expression.

Hormonal regulation of lipogenesis

Fasting is associated with significant changes in plasma hormone concentrations, such as a decrease in plasma insulin and leptin, and an increase in plasma growth hormone and glucagon. Insulin is probably the most important hormonal factor influencing lipogenesis. By increasing the uptake of glucose in the adipose cell via recruitment of glucose transporters to the plasma membrane, as well as activating lipogenic and glycolytic enzymes via covalent modification, insulin potently stimulates lipogenesis (Figure 1). These effects are achieved by the binding of insulin to the insulin receptor at the cell surface, thus activating its tyrosine kinase activity and inducing a plethora of downstream effects via tyrosine phosphorylation (Lane *et al.*, 1990; Nakae and Accili, 1999). Insulin also has long-term effects on the expression of lipogenic genes (Assimakopoulos-Jeannet *et al.*, 1995), probably via the transcription factor sterol regulatory element binding protein-1 (SREBP-1) (Figure 1 and see below). In addition, insulin causes SREBP-1 to induce the expression and activity of glucokinase, thereby increasing the concentration of a glucose metabolite that supposedly mediates the effects of glucose on lipogenic gene expression (Foretz *et al.*, 1999a).

Another hormone that has an important influence on lipogenesis is growth hormone (GH). GH dramatically reduces lipogenesis in adipose tissue, resulting in significant fat loss, with a concomitant gain of muscle mass (Etherton, 2000). These effects appear to be

mediated by two pathways. In one case, GH decreases insulin sensitivity, resulting in down-regulation of fatty acid synthase expression in adipose tissue (Yin *et al.*, 1998). The details of this mechanism are still unknown, but GH probably interferes with insulin signaling at the post-receptor level. In the second case, GH may decrease lipogenesis by phosphorylating the transcription factors Stat5a and 5b. The loss of Stat5a and 5b in a knock-out model was recently shown to decrease fat accumulation in adipose tissue (Teglund *et al.*, 1998). The mechanism by which Stat5 proteins enhance fat storage remains to be determined.

Leptin is another hormone that may be involved in lipogenesis. There is a growing consensus that leptin limits fat storage not only by inhibiting food intake, but also by affecting specific metabolic pathways in adipose and other tissues. Leptin stimulates the release of glycerol from adipocytes (Siegrist-Kaiser *et al.*, 1997), by both stimulating fatty acid oxidation and inhibiting lipogenesis (Bai *et al.*, 1996; Wang *et al.*, 1999). The latter effect is achieved by down-regulating the expression of genes involved in fatty acid and triglyceride synthesis, as was nicely demonstrated recently by oligonucleotide micro-array analysis (Soukas *et al.*, 2000). Interestingly, another negative target of leptin is probably SREBP-1, suggesting that this transcription factor may be involved in mediating the inhibitory effect of leptin on lipogenic gene expression (Kakuma *et al.*, 2000; Soukas *et al.*, 2000).

A final endocrine/autocrine factor connected with triglyceride synthesis is acylation stimulating protein (ASP). ASP is a small peptide that is identical to C3adesArg, a product of the complement

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factor C3 (Sniderman *et al.*, 2000). ASP is produced by adipose tissue and supposedly acts via an autocrine loop. Numerous *in vitro* studies have shown that ASP stimulates triglyceride accumulation in adipose cells (Sniderman *et al.*, 2000). This is achieved by an increase in triglyceride synthesis, as well as by a simultaneous decrease in adipose tissue lipolysis. Intraperitoneal injection of ASP has been reported to stimulate triglyceride clearance from plasma, indicating that ASP has a similar effect *in vivo* (Murray *et al.*, 1999a). This is supported by studies with female ASP null mice, which display a pronounced reduction in adipose tissue mass despite an increased energy intake (Murray *et al.*, 2000). However, whereas Murray *et al.* (1999b) reported a delayed postprandial triglyceride clearance in ASP null mice, another group failed to find any differences between null and wild-type mice (Wetsel *et al.*, 1999). The reason for this discrepancy is unclear. Very little is known about how ASP stimulates triglyceride synthesis. It probably binds to some kind of cell surface receptor, thereby activating a signaling cascade that involves phosphodiesterase 3 (Van Harmelen *et al.*, 1999).

Transcriptional regulation of lipogenesis

Evidence that has been gathered over the past few years indicates that the effects of various nutrients and hormones on the expression of lipogenic genes are mediated by the SREBPs (Hua *et al.*, 1993; Tontonoz *et al.*, 1993; Yokoyama *et al.*, 1993). SREBPs are transcription factors that regulate the expression of genes connected with cholesterol and fatty acid metabolism. They belong to the group of basic helix-loop-helix (bHLH)-leucine zipper transcription factors, and can be separated into three types: SREBP-2, SREBP-1a and SREBP-1c (also called ADD1). SREBP-1a and -1c, of which SREBP-1c is considered the most physiologically relevant, are products from a single gene that differ in their first exon. Since its discovery in 1993, the molecular mode of action of SREBP-2 has been very well characterized. When levels of free cholesterol in the cell are high, SREBP-2 is present as a large immature precursor bound to the endoplasmic reticulum. When the cellular concentration of cholesterol declines, the precursor molecule is proteolytically cleaved to release a mature fragment that translocates to the nucleus. In the nucleus, mature SREBP-2 binds to a so-called sterol response element in the promoter region of target genes and thereby activates their transcription.

Studies in transgenic mice that overexpress SREBP-2 in the liver suggested that SREBP-2 stimulates the expression of genes involved in cholesterol metabolism, such as the *LDL receptor*, *farnesyl pyrophosphate synthase* and *HMG-CoA reductase* genes. Interestingly, in mice that overexpress SREBP-1a or SREBP-1c in liver, a dramatic build-up of hepatic triglycerides and elevated expression levels of lipogenic genes were observed. This led to the conclusion that SREBP-1 activates genes connected with lipogenesis in liver (reviewed in Horton and Shimomura, 1999).

Surprisingly, the phenotype of SREBP-1 null mice revealed that SREBP-1 probably has a somewhat different role in adipose tissue. In these mice, adipose tissue mass was not affected, nor was the adipose tissue expression of fatty acid synthase and acetyl-CoA carboxylase (Shimano *et al.*, 1997). Further evidence suggesting a different role of SREBP-1 in adipose tissue came from studies with transgenic mice that express SREBP-1c under

control of the aP2 promoter (for adipose tissue-specific over-expression). In white adipose tissue of these mice, expression of genes implicated in cholesterol metabolism was markedly elevated, whereas the expression of genes implicated in fatty acid and triglyceride synthesis remained unchanged (Shimomura *et al.*, 1998). An even more striking and counterintuitive observation in these mice was that their adipose tissue mass was reduced to less than half that of wild-type mice. The explanation behind the diminished fat mass remains elusive, but could be related to decreased expression of the adipogenic transcription factors peroxisome proliferator activated receptor γ (PPAR γ) and CCAAT enhancer binding protein (C/EBP α). Overall, these data suggest that the roles of SREBP-1 in liver and adipose tissue may differ.

It is becoming more and more evident that the induction of lipogenic gene expression in liver by insulin and glucose is mediated by SREBP-1. Indeed, SREBP-1 null mice display impaired up-regulation of lipogenic gene expression on a fasting/refeeding protocol (Shimano *et al.*, 1999). Insulin and glucose affect SREBP-1 transcriptional activity via several mechanisms. First, insulin has been shown to stimulate SREBP-1 mRNA expression in adipocytes (Kim *et al.*, 1998) and hepatocytes (Foretz *et al.*, 1999b), an effect that is probably mediated by the phosphatidylinositol 3-kinase pathway (Azzout-Marniche *et al.*, 2000). In addition, insulin probably increases transcriptional activation by SREBP-1, independently of changes in its mRNA levels, via MAP-kinase-dependent phosphorylation (Roth *et al.*, 2000). Like insulin, glucose stimulates SREBP-1 promoter activity and mRNA expression (Hasty *et al.*, 2000). The relative increase in the nuclear form of SREBP-1 after carbohydrate refeeding (Horton *et al.*, 1998) suggests that insulin and glucose may also stimulate SREBP-1-dependent gene transcription by activating the proteolytic cleavage of membrane-bound SREBP-1. However, a direct effect of insulin or glucose on the proteolytic cleavage of the SREBP-1 precursor could not be demonstrated (Azzout-Marniche *et al.*, 2000; Hasty *et al.*, 2000).

Polyunsaturated fatty acids also regulate expression of lipogenic genes. However, in contrast to glucose and insulin, they down-regulate gene expression. This effect is achieved by inhibiting the mRNA expression of SREBP-1 (Kim *et al.*, 1999; Mater *et al.*, 1999; Xu *et al.*, 1999; Yahagi *et al.*, 1999), as well as by inhibiting the proteolytic processing of the SREBP-1 precursor (Thewke *et al.*, 1998).

SREBP-1 clearly plays a pivotal role in mediating the effects of insulin on gene expression, but it is probably not the only transcription factor involved. *In vitro* studies have clearly established the importance of the upstream stimulatory factors (USFs) in the regulation of the fatty acid synthase promoter by insulin. USFs are ubiquitous bHLH-leucine zipper transcription factors that are able to interact as homo- and/or heterodimers with E boxes of CANNTG sequence (Wang and Sul, 1997). Such an E box is present in the promoter of fatty acid synthase. Mutations that weaken binding of USF1 and USF2 to this E box abolish the insulin-dependent activation of the fatty acid synthase promoter. Recent studies with mice lacking USF1 and/or USF2 have provided very compelling evidence that USF1 and USF2 are involved in mediating the stimulatory effect of insulin/glucose on fatty acid synthase expression (Casado *et al.*, 1999). The effects of USFs and SREBP-1 seem to be additive and independent (Latasa *et al.*, 2000). Finally, glucose may regulate

expression of lipogenic genes via a carbohydrate response transcription factor (ChoRF), which has yet to be cloned. Specific response elements that bind this transcription factor have been identified in the promoter of target genes, such as pyruvate kinase (Koo and Towle, 2000).

An important transcription factor in adipose tissue is the nuclear hormone receptor PPAR γ . Despite its name, this protein is not activated by peroxisome proliferators but by fatty acids and their eicosanoid derivatives, as well as by drugs of the thiazolidinedione class (Kersten *et al.*, 2000a). PPAR γ is part of the adipocyte differentiation program, inducing the differentiation of pre-adipocytes into mature fat cells. To date, only a limited number of genes are known to be regulated by PPAR γ in adipose tissue. These encode the adipocyte fatty acid binding protein, lipoprotein lipase, fatty acid transport protein (FATP), acyl-CoA synthetase, phospho-enol pyruvate carboxykinase and the fasting-induced adipose factor FIAF/PPAR γ angiopoietin related PGAR (Kersten *et al.*, 2000b; Yoon *et al.*, 2000). Based on the identities of these genes, coupled with the observation that PPAR γ expression is stimulated by insulin (Vidal-Puig *et al.*, 1997) and by SREBP-1 (Fajas *et al.*, 1999), one would expect PPAR γ to have not only an adipogenic effect, but also a lipogenic effect. This is supported by clinical data, showing that patients taking synthetic PPAR γ activators frequently gain weight (Fuchtenbusch, 2000). Furthermore, heterozygous PPAR γ mutant mice exhibit smaller fat stores on a high fat diet (Kubota *et al.*, 1999; Miles *et al.*, 2000). Inducible and tissue-specific PPAR γ knock-out models should be highly informative in terms of gaining further insight into the function of PPAR γ in mature fat cells. With respect to the liver, although PPAR γ is normally only minimally expressed in hepatocytes, hepatic triglyceride accumulation is associated with a dramatic increase in PPAR γ expression, suggesting that PPAR γ may play a role in stimulating lipogenesis (Chao *et al.*, 2000).

In conclusion, the past few years have brought a deluge of new data about the mechanisms of regulation of lipogenesis by nutrients and hormones. It is now clear that SREBP-1, and to a lesser extent USF1 and USF2, play a pivotal role in mediating the effects of nutrients and hormones on lipogenic gene expression in the liver. In adipose tissue, another transcription factor, PPAR γ , is critical for the regulation of both adipogenesis and lipogenesis. The role that SREBP-1 plays in adipose tissue has yet to be clearly defined. Overall, however, SREBP-1 and PPAR γ have become attractive targets for pharmaceutical interventions of disorders such as hypertriglyceridemia and obesity.

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