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Carbohydrate responsive element binding protein (ChREBP) and sterol regulatory element binding protein-1c (SREBP-1c): two key regulators of glucose metabolism and lipid synthesis in liver

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Abstract

In mammals, the regulation of hepatic metabolism plays a key role in whole body energy balance, since the liver is the major site of carbohydrate metabolism (glycolysis and glycogen synthesis) and triglyceride synthesis (lipogenesis). Lipogenesis is regulated through the acute control of key enzyme activities by means of allosteric and covalent modifications. Moreover, the synthesis of most glycolytic and lipogenic enzymes is regulated in response to dietary status, in which glucose, in particular, is a crucial energy nutrient. This latter response occurs in large part through transcriptional regulation of genes encoding glycolytic and lipogenic enzymes. In the past few years, recent advances have been made in understanding the transcriptional regulation of hepatic glycolytic and lipogenic genes by insulin and glucose. Although insulin is a major regulator of hepatic lipogenesis, there is increasing evidence that glucose also contributes to the coordinated regulation of carbohydrate and lipid metabolism in liver. Here, we review the respective roles of the transcription factor sterol regulatory element binding protein-1c (SREBP-1c) in mediating the effect of insulin on hepatic gene expression, and the role of carbohydrate responsive element binding protein (ChREBP) in regulating gene transcription by glucose.

Keywords: Glucose signaling; Carbohydrate metabolism; Lipogenesis; Transcription factor

1. Introduction

In mammals, the liver is the principal organ responsible for the conversion of excess dietary carbohydrate into triglycerides. Glucose can be metabolized in the liver to provide substrates, such as acetyl CoA, for fatty acids synthesis (Fig. 1). Then fatty acids are incorporated into triglycerides that function as a long-term energy reservoir. In addition, excess carbohydrate also results in the activation of several genes encoding glycolytic and lipogenic enzymes involved in carbohydrate and lipid metabolism, including glucokinase GK [1] and liver pyruvate kinase (L-PK) [2] for glycolysis, ATP citrate lyase, acetyl CoA carboxylase (ACC) [3] and fatty acid synthase (FAS) [4] for lipogenesis, glucose 6-phosphate dehydrogenase (G6PDH) and 6-phosphogluconate dehydrogenase (6PGDH) for the pentose phosphate pathway, thereby promoting long-term storage of carbohydrate and triglycerides [5] (Fig. 1).

Absorption of carbohydrate in the diet is concomitant with increases in the concentrations of substrates such as glucose but also with changes in the concentrations of insulin. Until recently, it was thought that insulin was the main regulator of glycolytic and lipogenic gene transcription. However, it has been shown, using primary cultured hepatocytes, that nutrients themselves play an important role in the regulation of gene transcription, independently of this hormone (review in [6,7]) and it has been proposed that two signaling pathways elicited in response to dietary carbohydrates play a synergic role in regulating lipogenic gene expression (ACC and FAS) [7,8]. The transcriptional induction of ACC and FAS requires both glucose metabolism and insulin and we and others have shown that the role of insulin is to induce GK gene expression which is then essential for subsequent glucose phospho-

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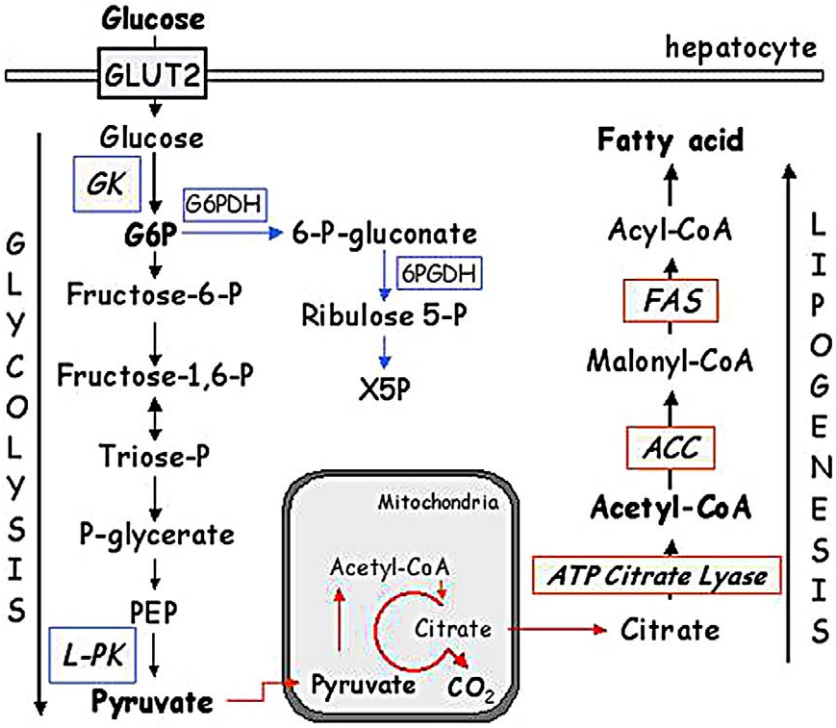

Fig. 1. Glycolytic and lipogenic pathways in the liver. Metabolic flux in the liver reflects the net activities of several major pathways, including glycolysis and lipogenesis. The major function of glycolysis in liver is to provide carbons from glucose for de novo lipid synthesis (lipogenesis). With the exception of hepatic glucokinase, which is exclusively induced by insulin in hepatocytes, all enzymes indicated in this figure are induced at a transcriptional level in response to high glucose and insulin concentrations. Abbreviations used are: GK, glucokinase; L-PK, liver pyruvate kinase; G6PDH, glucose 6-phosphate dehydrogenase; 6PGDH, 6-phosphogluconate dehydrogenase; ACC, acetyl CoA carboxylase; FAS, fatty acid synthase.

rylation into glucose 6-phosphate (G6P) allowing glucose to exert its transcriptional effect [6,9]. To illustrate this point, when GK is expressed constitutively, the induction of L-PK gene occurs in the absence of insulin [10,11], demonstrating that glucose metabolism is necessary for the induction of most of these genes.

2. Role of SREBP-1c on glycolytic and lipogenic gene expression

A pathway by which insulin can control this process has been discovered through the study of the transcription factor sterol regulatory element binding protein (SREBP). Although, SREBP was first discovered as a transcription factor that controls genes involved in the biosynthesis of cholesterol [12], more recently the SREBP-1c isoform has emerged as a major mediator of insulin action on hepatic GK [13,14] and lipogenic gene expression [15]. To illustrate this point, Kim et al. [14] have recently identified two functional sterol regulatory elements (SRE) in the rat GK promoter. The authors demonstrate that SREBP-1c can bind to these SREs and activate the GK promoter. The physiological in vivo interaction between the SREBP-1c protein and SREs of the GK promoter was confirmed by chromatin immuno precipitation (ChIP) assay using primary cultures of hepatocytes, demonstrating the direct involvement of SREBP-1c on GK gene expression. SREBP-1c is also able to induce lipogenic genes by its capacity to bind to SREs present in their promoters [16–18] (Fig. 2 and Table 1). SREBP-1c itself is rapidly induced by insulin in primary cultures of hepatocytes [19], providing a pathway for insulin mediation of lipogenic gene expression [20]. In addition, transgenic mice that overexpress SREBP-1c in the liver exhibit liver steatosis and increased mRNA of most lipogenic genes [21,22]. Consistent with these observations,

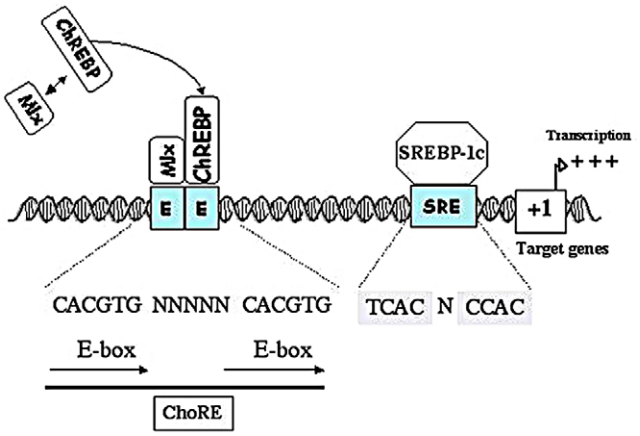

Fig. 2. Schematic roles of ChREBP and SREBP-1c in the regulation of glycolytic and lipogenic gene expression in response to insulin and glucose. Most lipogenic genes (FAS, ACC) have carbohydrate responsive element (ChoRE) for binding the ChREBP–Mlx complex and sterol responsive element (SRE) for binding SREBP-1c, identified through promoter-mapping analysis. The ChREBP–Mlx complex and SREBP-1c act in synergy to induce lipogenic gene in response to high glucose and insulin concentration.

Table 1
Sequence comparison of the different ChoRE and SRE of glycolytic and lipogenic genes

Gene	ChoRE consensus sequence	Position	Ref
Rat L-PK	CACGGGGCACTCCCGTG	–171	[32,33]
Rat FAS	CATGTGCCACAGGCGTG	–7210	[35]
Rat ACC	CATGTGAAAACGTCGTG	–122	[37]
Gene	SRE consensus sequence	Position	Ref
Rat FAS	GTCAGCCCAT	–72	[35]
Rat FAS	GCCACGCCAC	–62	[35]
Rat ACC	GGAGGACCAT	–280	[16,38]
Rat ACC	CTCACGTCGC	–261	[16,38]

SREBP-1c gene knock-out mice have an impaired ability to fully induce lipogenic gene expression after high carbohydrate feeding [23]. The effect of insulin on SREBP-1c was corroborated by in vivo studies showing that SREBP-1c expression were low in livers of diabetic rats, and increased markedly after insulin treatment [24].

Several studies have also suggested that SREBP-1c may be involved in the pathogenesis of hepatic insulin resistance. Indeed, elevated levels of SREBP-1c are observed in liver of insulin-resistant animals [25,26] and a recent study demonstrates that high levels of SREBP-1c exacerbates insulin resistance through inhibition of IRS-2 signaling in liver [27]. In contrast, and from a therapeutic point of view, it is interesting to note that the disruption of SREBP-1c gene expression in *ob*/*ob* mice improves their hepatic steatosis. More importantly, overexpression of the mature isoform of SREBP-1c in livers of streptozotocin-induced diabetic mice leads to increased hepatic glycogen and triglyceride content as well as a marked decreased in hyperglycemia in these mice [28].

All together these results indicate that SREBP-1c plays a major role in the long-term control of glucose and lipid homeostasis by insulin, through the regulation of glycolytic and lipogenic gene expression. However, SREBP-1c activity alone does not appear to fully account for the stimulation of glycolytic and lipogenic gene expression in response to carbohydrate since SREBP-1c gene deletion in mice only results in a 50% reduction in fatty acid synthesis [23]. Indeed, the induction of glycolytic and lipogenic genes in response to a high carbohydrate diet, although significantly diminished, is not completely suppressed in SREBP-1c knockout mice [23]. In addition, we and others have provided evidence that SREBP-1c expression is not sufficient by itself to account for the glucose/insulin induction of glycolytic and lipogenic genes in primary cultured hepatocytes [9,17,29]. We have demonstrated, using hepatic GK knockout mice (hGK-KO) [30], that overexpression of a constitutive active form of SREBP-1c in hGK-KO hepatocytes cultured in the presence of high glucose concentration (25 mM) did not fully induce glycolytic and lipogenic genes compared to what was observed in control hepatocytes [9]. Therefore, glucose metabolism via GK and SREBP-1c exerts a synergistic effect on the expression of glycolytic and lipogenic genes.

3. ChREBP, a new transcription factor involved in the stimulatory effect of glucose

With the exception of hepatic GK, which is exclusively induced by insulin [31], most of the glycolytic and lipogenic genes are also regulated by glucose [6,8]. A sequence in the L-PK promoter has been identified for its ability to support a response to glucose [32–34]. This DNA element is designated as a carbohydrate response element (ChoRE) and consists of two 5′-CACGTG type E box motifs separated by 5 pb (Fig. 2). Similar ChoRE have been identified in the promoters of FAS and ACC genes through promoter mapping analysis [35–37] (Fig. 2 and Table 1). In the case of the FAS gene, independent sites for the action of insulin and glucose, respectively, have been identified [17,35,38]. These sites act synergistically to support the actions of glucose and insulin.

Until recently, the mechanism by which excess carbohydrate generates a signal to induce the transcription of glycolytic and lipogenic genes was not known, although it had been established that a metabolite of glucose, and not glucose per se, was responsible for the glucose signal [6]. The recent identification of a glucose-responsive basic/helix-loop-helix/leucine zipper (bHLH/LZ) transcription factor named ChREBP (carbohydrate responsive element binding protein) (also known as WBSCR14 and Mondo B) [39] has recently shed light on the possible mechanism whereby glucose affects gene transcription. ChREBP is known to recognize E box sequences in the promoters of target genes and ChREBP is predominantly expressed in liver [39–41], kidney, white and brown adipose tissue. ChREBP is regulated in a reciprocal manner by glucose and cAMP [42] (Fig. 2). Under basal conditions ChREBP is localized in the cytosol, and its nuclear translocation is rapidly induced under high glucose concentrations. Nuclear translocation of ChREBP is controlled by dephosphorylation of several serine (Ser) and threonine (Thr) residues. Serine residue 196 (SER 196) is the target of protein kinase A (PKA) phosphorylation, and its dephosphorylation allows ChREBP translocation in the nucleus. Two other residues, Ser 568 and Thr 666 are dephosphorylated in the nucleus, thus alleviating DNA binding inhibition. Recently, protein phosphatase 2A (PP2A) was shown to be activated by xylulose 5-phosphate (X5P), a metabolite generated by the pentose phosphate pathway in presence of high glucose, and was likely responsible for both cytosolic and nuclear

dephosphosphorylation of ChREBP [43,44] (Fig. 3). When primary rat hepatocytes are transfected with a ChREBP expression vector, L-PK promoter activity is increased under high glucose conditions, but not under low glucose conditions [39]. Recently, Towle and coworkers presented further evidence concerning the mechanism of action of ChREBP in stimulating glucose-responsive genes [45]. In fact, ChREBP does not act alone, but instead functions in a heterodimeric complex with the bHLH/LZ transcription factor Max-like protein X (Mlx). The binding of ChREBP–Mlx complex is able to discriminate between E box sites that are glucose-responsive and those that are not [45]. Together, these two transcription factors bind to and activate transcription of a number of glycolytic (L-PK) and lipogenic (ACC) genes containing a ChoRE [45]. The fact that ChREBP interacts with Mlx, suggests that a network of transcription factors or co-factors may be required to fully regulate glucose-responsive gene expression in liver (Fig. 2). All of these data suggest that activation of the ChREBP–Mlx complex may be the glucose-dependent mechanism resulting in synergistic induction of fatty acid synthesis by insulin and glucose.

The discovery of ChREBP and its potential role in glucose action prompted us to perform a series of experiments in primary cultures of mouse hepatocytes of both control and

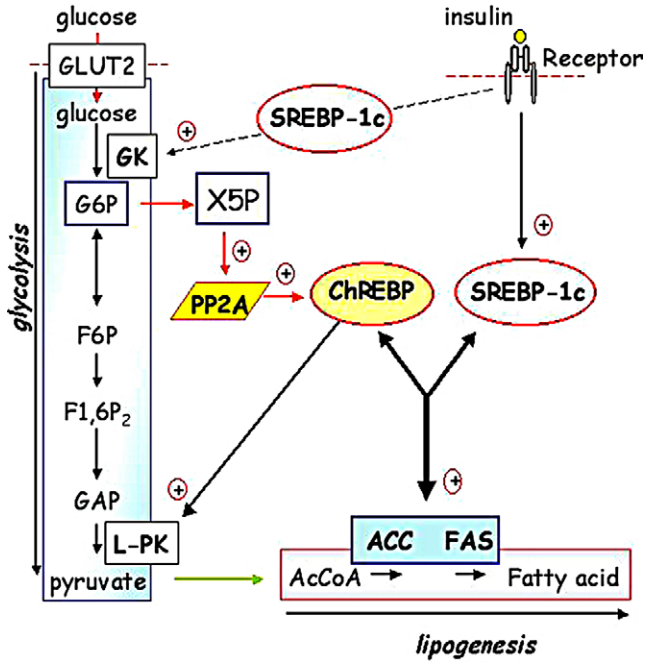

Fig. 3. SREBP-1c and ChREBP act in synergy to regulate glycolytic and lipogenic gene expression. The phosphorylation of glucose in glucose 6-phosphate, by hepatic glucokinase, is an essential step for glucose metabolism as well as for the induction of glycolytic and lipogenic genes. The recent identification of ChREBP has shed light on the possible mechanism whereby glucose affects gene transcription. The activity of ChREBP requires a mechanism of phosphorylation/dephosphorylation which is determined by the relative activity of protein phosphatase 2A (PP2A), regulated by X5P concentrations. SREBP-1c, which is induced by insulin, also plays an important role in mediating insulin signaling on lipogenic gene expression. These two transcription factors work synergistically to induce transcription of the lipogenic genes in the presence of glucose and insulin.

hepatic GK deficient (hGK-KO) mice in order to gain insight into the physiological roles of ChREBP in vitro [9]. We have found that increased glucose metabolism via GK is necessary for both expression and function of ChREBP in primary cultures of hepatocytes. In addition, to address the role of ChREBP in mediating glucose signaling in liver, we have used the small interfering RNA (siRNA) approach to silence ChREBP gene expression in control hepatocytes. Our studies have revealed, for the first time in a physiological context, that ChREBP mediates the glucose effect of both glycolytic and lipogenic gene expression and that this transcription factor is a key determinant of lipid synthesis in liver [9]. At the same time, our results were confirmed by the global inactivation of ChREBP gene expression in mice (ChREBP$^{-/-}$) [41]. In this study, the authors also demonstrate that ChREBP is required for carbohydrate-induced expression of several glycolytic and lipogenic genes and for the synthesis of fatty acids from glucose in vivo. The fact that ChREBP$^{-/-}$ mice are intolerant to glucose and insulin resistant suggests that this transcription factor may also play a role in the pathogenesis of type 2 diabetes.

4. Conclusion

With the discovery of two key transcription factors SREBP-1c and ChREBP, our understanding of the long-term regulation of glucose and lipid metabolism in liver has made considerable progress. Here, we have described the system that prevails in the liver. Together ChREBP and SREBP-1c provide a pair of transcription factors that functions in synergy through distinct binding response elements to coordinately regulate glucose metabolism and lipogenesis (Fig. 3). Such system of regulation provides a means of using glucose for lipid storage only when appropriate conditions (high glucose and insulin concentrations) are met, allowing for a fine utilization of glucose and lipid synthesis. Consequently, the involvement of ChREBP in a physiopathologic context such as diabetes or obesity should be thoroughly analyzed. To gain insight into these possibilities, we are in the process of analyzing the expression of ChREBP in several models of obesity and diabetes.

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