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Review

Cross-regulation of hepatic glucose metabolism *via* ChREBP and nuclear receptors ☆

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ABSTRACT

There is a worldwide epidemic of obesity and type 2 diabetes, two major public health concerns associated with alterations in both insulin and glucose signaling pathways. Glucose is not only an energy source but also controls the expression of key genes involved in energetic metabolism, through the glucose-signaling transcription factor, Carbohydrate Responsive Element Binding Protein (ChREBP). ChREBP has emerged as a central regulator of *de novo* fatty acid synthesis (lipogenesis) in response to glucose under both physiological and physiopathological conditions. Glucose activates ChREBP by regulating its entry from the cytosol to the nucleus, thereby promoting its binding to carbohydrate responsive element (ChoRE) in the promoter regions of glycolytic (L-PK) and lipogenic genes (ACC and FAS). We have previously reported that the inhibition of ChREBP in liver of obese ob/ob mice improves the metabolic alterations linked to obesity, fatty liver and insulin-resistance. Therefore, regulating ChREBP activity could be an attractive target for lipid-lowering therapies in obesity and diabetes. However, before this is possible, a better understanding of the mechanism(s) regulating its activity is needed. In this review, we summarize recent findings on the role and regulation of ChREBP and particularly emphasize on the cross-regulations that may exist between key nuclear receptors (LXR, TR, HNF4α) and ChREBP for the control of hepatic glucose metabolism. These novel molecular cross-talks may open the way to new pharmacological opportunities. This article is part of a Special Issue entitled: Translating nuclear receptors from health to disease.

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1. Introduction

In mammals, the liver is responsible for the conversion of excess dietary carbohydrates into triglycerides (TG), through *de novo* lipogenesis. Appropriate control of lipogenesis is crucial since excess fatty acid storage leads to hepatic steatosis and other related metabolic diseases [1]. Increased lipogenesis results from transcriptional activation of many genes encoding glycolytic and lipogenic enzymes including glucokinase (GK) [2], liver-pyruvate kinase (L-PK) [3], acetyl CoA carboxylase (ACC) [4], fatty acid synthase (FAS) [5] and stearoyl CoA desaturase (SCD1) [6]. Uptake of glucose by liver is concomitant with increased concentrations of substrates such as glucose but also in the ratio of pancreatic hormones: insulin/glucagon. Until recently, it was thought that insulin and glucagon were the main transcriptional regulators of glycolytic and lipogenic gene expression (respectively up and down regulators).

The transcriptional effect of insulin is mediated by sterol regulatory element binding protein-1c (SREBP-1c) [7], a transcription factor from the basic-helix–loop–helix leucine zipper (bHLH/Zip) transcription factor family. SREBP-1c induces lipogenic genes by its capacity to bind a sterol response element (SRE) present in the promoter of its target genes [8]. SREBP-1c is not only regulated by itself but also by liver X receptors (LXRs) [9]. LXRs are ligand-activated transcription factors that belong to the nuclear receptor super-family. LXRs, which activity is controlled by cholesterol metabolites called oxysterols, are important regulators of the lipogenic pathway, since LXRs are central for the transcriptional control of SREBP-1c by insulin [10] and lipogenic genes such as FAS and SCD1 [11]. Transgenic mice that overexpress SREBP-1c in liver or mice gavaged by an agonist of

Abbreviations: ACC, acetyl-CoA carboxylase; ABCC1 and G1 (ABCG1), ATP-binding cassette transporters C1; bHLH-ZiP, Basic-helice–loop–helice leucine zipper; ChREBP, carbohydrate responsive element binding protein; ChoRE, carbohydrate responsive element; CEH, chick embryo hepatocytes; CAR, constitutive androstane receptor; CBP, CREB binding protein; dn-Mlx, dominant negative form of Mlx; ERα, estrogen receptor α; FAS, fatty acid synthase; FXR, farnesoid X receptor; GK, glucokinase; G6P, glucose 6-phosphate; G6Pase, glucose 6-phosphatase; G6PDH, glucose 6 phosphate dehydrogenase; GSM, glucose-sensing module; GRACE, glucose response conserved element; GSD-1, glycogen storage disease type 1; HNF4, hepatocyte nuclear factor 4; LBD, ligand binding domain; L-PK, liver-pyruvate kinase; LXR, liver X receptor; LXRE, liver X receptor element; LID, low glucose inhibitory domain; Mlx, Max-like protein X; MCR, Mondo Conserved Region; NES, nuclear export signal; NLS, nuclear localization signal; PTU, propylthiouracil; PKA, protein kinase; PPARs, peroxisome proliferator-activated receptors; PP2A, phosphatase 2A; PXR, pregnane X receptor; RTQ-PCR, real time quantitative polymerase chain reaction; RXR, retinoid X receptor; TH, thyroid hormones; TR, thyroid hormone receptor; SRE, sterol regulatory element; SREBP-1c, sterol regulatory element binding protein-1c; SCD1, stearoyl CoA desaturase 1; STZ, streptozotocin; TH, thyroid hormones; TG, triglycerides; VDR, vitamin D receptor

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LXRs have an increased expression of most lipogenic genes and develop liver steatosis [12]. Interestingly, mice devoid of SREBP-1c result only in a 50% reduction in fatty acid synthesis [13].

Although insulin is a central regulator of the lipogenic pathway, it is now accepted that glucose also generates an independent signal [14,15]. Glucose should not be uniquely considered as an energy fuel but also as a signaling molecule necessary for *de novo* lipogenesis, acting in synergy with insulin. L-PK gene expression is stimulated by glucose independently of insulin, in primary cultures of hepatocytes expressing GK [16]. Therefore, metabolism through GK is required to initiate glucose signaling [17]. Glucose-regulated genes share a conserved consensus sequence, named carbohydrate response element (ChoRE), which is required for their glucose-responsiveness [18,19]. The identification of ChREBP [20], which belongs to the Mondo family of bHLH/Zip transcription factors, has shed light on the mechanism whereby glucose affects gene transcription [21,22]. ChREBP silencing prevents the glucose-mediated induction of L-PK, ACC and FAS genes in hepatocytes [17]. In a physiopathological context, liver-specific inhibition of ChREBP improves hepatic steatosis and insulin resistance in ob/ob mice [23,24]. Since ChREBP may represent a potential target for lipid-lowering therapies in obesity and diabetes, an accurate knowledge of the mechanism regulating its expression and activity is needed. ChREBP expression can be regulated by key nuclear receptors of energy homeostasis, namely LXR [25,26] and the thyroid hormone receptor (TR) [27,28]. Furthermore, ChREBP interacts with the nuclear receptors HNF4α [29] and COUP-TF II [30] to modulate the transcription of its target genes such as the L-PK. The aim of this review is to report novel findings on the function and the regulation of ChREBP. In particular, we will describe how, depending on the hormonal and/or nutritional status, specific nuclear receptors establish cross-talks with ChREBP to regulate the signaling pathways that control glucose and lipid homeostasis.

1.1. Identification of ChREBP and of its partner Mlx

ChREBP was discovered in 2001 by the group of Uyeda [20] on the basis of complementary studies revealing a glucose response element in the promoter of several lipogenic genes (called ChoRE), and composed of two E box (CACGTG) or "E box like" sequences separated by 5 base pairs [19,31–33]. Using the ChoRE of the glycolytic enzyme L-PK, Yamashita et al. [20] identified ChREBP as a protein enriched in liver nuclear extracts from high carbohydrate diet fed rats. Binding of ChREBP was affected by change of spacing between the two E-box or mutation of the ChoRE. Following these experiments, ChREBP was purified and recognized as the homolog of the human protein named WBSCR14 or MondoB, and known to be deleted in the Williams–Beuren syndrome (WBS) [34]. Seventy-five percent of WBS patients exhibit impaired glucose tolerance or silent diabetes that may be due to a loss of ChREBP [35]. Several features of ChREBP are consistent with a role as a glucose-regulated transcription factor. Its expression is most abundant in liver, small intestine, kidney, white and brown adipose tissue [36], which are the most active sites of *de novo* lipogenesis in the body. ChREBP mRNA has also been detected in distinct brain regions [37] and in rat pancreatic islets [38]. In addition, ChREBP expression is induced in liver in response to high carbohydrate diet, but not in response to polyunsaturated fatty acids diet fed or fasting [39]. Similarly to SREBP-1c, ChREBP is a member of the bHLH/Zip (basic-helix–loop–helix leucine zipper) family of transcription factors, highly conserved among species. ChREBP was first shown to induce the transcriptional activity of the L-PK promoter in hepatocytes cultured under high glucose concentrations [20]. To address the direct role of ChREBP, we used a siRNA approach to down regulate ChREBP expression in mouse hepatocytes. Our studies revealed, for the first time in a physiological context, that ChREBP mediates the glucose effect on L-PK but also on lipogenic genes (ACC, FAS) and that this transcription factor is a key determinant of lipid synthesis in liver [17]. ChREBP was later shown to directly bind the promoter sequences of L-PK and of lipogenic genes using chromatin immunoprecipitation (CHiP) analysis [22]. These results were confirmed by the characterization of mice lacking the ChREBP gene ($ChREBP^{KO}$ mice) [36]. When maintained on a standard diet, $ChREBP^{KO}$ mice display larger, glycogen-laden livers, smaller adipose depots, and decreased plasma free fatty acid levels. Importantly, $ChREBP^{KO}$ mice show impaired glycolytic and lipogenic pathways in liver and exhibit glucose and insulin intolerance.

Soon after ChREBP discovery, using yeast two-hybrid system, Towle and co-workers identified a bHLHZiP protein, Mlx (Max-like protein X) that interacts with the bHLHZiP domain of ChREBP [21] (Fig. 1). Mlx is a member of the Myc/Max/Mad family of transcription factors that can serve as a common interaction partner of a transcription factor network [40]. The evidence that Mlx is the functional partner of ChREBP was demonstrated through the use of an adenovirus expressing a dominant negative form of Mlx (dn-Mlx) [41]. The inhibition of Mlx directly interferes with the endogenous ChREBP/Mlx complex and abrogates the glucose-response of the ACC reporter gene in primary cultures of hepatocytes [41]. The response to glucose can be however partially restored when ChREBP is overexpressed. The regulatory domains of the ChREBP and Mlx proteins have been studied in great details over the last years [21,41,42]. According to the model proposed by Ma et al. [42], two ChREBP-Mlx heterodimers bind the two E boxes of the ChoRE to provide a transcriptional complex necessary for glucose regulation. Using a structural ChREBP/Mlx structural model followed by specific mutation experiments, three critical residues (F164, I166 and K170) within the Mlx loop that play a crucial role in the binding of the ChREBP/Mlx complex to the ChoRE have been identified [42]. Therefore, it appears that the Mlx loop region, but not the one of ChREBP, is determinant for mediating the response of glucose. Mlx has a significantly longer loop domain than most other bHLHZiP proteins, allowing it to potentially interact across the interface between heterodimer pairs. It is therefore possible that other proteins, *via* interactions involving the Mlx loop, could assist the binding of the ChREBP/Mlx complex to the ChoRE. It was recently reported that adenoviral overexpression of dn-Mlx in 25-week-old male C57BL/6J mice reduces hepatic TG content and improves glucose intolerance by inhibiting expression of glucose-6-phosphatase (G6Pase) in addition to lipogenic enzymes [59]. A distal promoter region of the G6Pase promoter was previously reported to be glucose responsive in 832/13 INS-1 cells. The fact that ChREBP binds this region in a glucose-dependent manner [43] supports the fact that G6Pase is most likely a direct target of the ChREBP/Mlx complex.

1.2. Regulation of ChREBP activity by glucose

The regulation of ChREBP activity in response to glucose is complex. To date, two mechanisms reporting the glucose-mediated activation of ChREBP have been proposed: one involving on a two-step activation by dephosphorylation on specific residues [44] and one independent involving a dynamic intra-molecular inhibition between two regulatory domains within the ChREBP protein [45] (Figs. 1 and 2). ChREBP is a large protein (864 amino acids and $M_r = 94{,}600$) that contains several important domains including a nuclear localization signal (NLS) near the N-terminus, polyproline domains, a basic loop–helix–leucine-zipper (bHLH/Zip), and a leucine-zipper-like (Zip-like) domain (Fig. 1). Deletion of the NLS impairs ChREBP localization in the nucleus and prevents the glucose-induced transcriptional activation of an L-PK luciferase reporter construct in hepatocytes [46]. By studying the importance of ChREBP regulation by phosphorylation, Yamashita et al. reported that incubation of the protein ChREBP with the catabolic subunit of protein kinase (PKA) and ATP leads to an increase of its phosphorylation rate and a decrease of both nuclear content and DNA binding activity [20]. This effect could be reversed when a PKA inhibitor and/or the phosphatase 2A (PP2A) was added [20]. From these studies emerged a PP2A-dependent model of ChREBP activation and two

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