Discovering orphans’ sweet secret:
NR4A receptors and hepatic glucose production

Aberrant hepatic gluconeogenesis contributes importantly to hyperglycemia in type II diabetic patients. A study by Pei et al. (2006b) identifies NR4A orphan nuclear receptors as a novel branch of cAMP-dependent regulators of hepatic glucose production under healthy and diabetic conditions.

With around 200 million people affected worldwide, the incidence of type II diabetes has reached pandemic dimensions. As a hallmark of the type II diabetic phenotype, peripheral insulin resistance promotes chronic hyperglycemia, which represents a major cause of vascular complications and relies substantially on unrestricted de novo glucose synthesis (gluconeogenesis) in the liver of these patients. In this metabolic setting, a concomitant predominance of counterregulatory hormones—in particular, pancreatic glucagon acting via the intracellular cAMP pathway—further aggravates hepatic glucose production (Saltiel, 2001). Deciphering how counterregulatory hormones regulate hepatic glucose output represents a major challenge for the identification of potential new therapeutic targets. Recent work by Pei and colleagues (2006b) advances our understanding of gluconeogenic control by investigating the role of NR4A orphan nuclear receptors in liver metabolism.

In healthy subjects, gluconeogenesis is synergistically triggered through rising plasma levels of glucagon and glucocorticoid hormones during fasting to ensure a constant glucose supply for extrahepatic tissues. Gluconeogenic pathway activity is mainly determined through transcriptional induction of rate-limiting key enzyme genes, such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) (Saltiel, 2001).

cAMP-element-binding protein (CREB) has been identified as a critical transcriptional checkpoint for the induction of hepatic gluconeogenesis in response to cAMP. Mice lacking hepatic CREB activity show substantially diminished blood glucose levels and reduction of gluconeogenic enzyme gene expression. Indeed, CREB action accounts for the synergistic activation of the gluconeogenic program by glucagon and glucocorticoid signals through the transcriptional induction of the nuclear-coactivator PGC-1α. PGC-1α, in turn, coactivates the glucocorticoid receptor nuclear receptor HNF-4 as well as the forkhead transcription factor Foxo1 on PEPCK and G6Pase gene promoters, thereby establishing the major regulatory axis of cAMP-dependent glucose production in the liver (Herzig et al., 2001; Puigserver et al., 2003; Yoon et al., 2001). However, PGC-1α-deficient hepatocytes still exhibit a certain degree of cAMP-inducible gluconeogenic activity, suggesting that control over this pathway by cAMP does not depend exclusively on this coactivator (Lin et al., 2004).

Expression of orphan nuclear receptors of the NR4A family (Nurr1, Nurr77, and Nor1) is rapidly induced upon a variety of external stimuli and has been shown to control cell proliferation, apoptosis, and neuronal differentiation. In contrast to classical ligand-activated nuclear receptors, studies to date have offered only very limited insights into the function of these factors for energy metabolism (Maxwell and Muscat, 2006). Coincident with the notion that NR4A transcriptional activities are largely determined by their expression levels (Maxwell and Muscat, 2006), Pei and colleagues (2006b) found that all NR4A family members are induced upon cAMP treatment of isolated hepatocytes as well as in livers of fasted and glucagon-challenged mice in a CREB-dependent manner. These findings prompted the authors to explore a potential role of NR4A receptors in cAMP-dependent hepatic energy metabolism. Indeed, NR4A overexpression in hepatocytes substantially enhances the expression of multiple genes within the gluconeogenic pathway, most notably enolase 3 and fructose-bisphosphatase 1 and 2 (FBP1/2). Remarkably, the authors were able to distinguish three distinct sets of glucone- regulatory targets in the liver, responding to NR4A, PGC-1α, or both in an additive manner, arguing for a distinct, complementary mode of action of NR4A factors apart from the established CREB-PGC-1α axis. Consistently, NR4A receptors do not influence expression of PGC-1α itself or its target gene PEPCK, nor does PGC-1α function as a physical NR4A cofactor in transcriptional activation studies (Pei et al., 2006b). The NR4A nuclear-receptor family, therefore, represents a novel, PGC-1α-independent branch of cAMP/CREB-mediated glucose metabolism in the liver (Figure 1).

Remarkably, Pei and colleagues (2006b) observed a substantial induction of NR4A mRNA expression levels in type 1 and type 2 diabetic mouse models. Furthermore, acute ablation of NR4A liver function in type II diabetic db/db mice by adenoviral delivery of a dominant-negative Nur77 decreased expression of gluconeogenic target genes and restored elevated glucose levels to near normal (Pei et al., 2006b), suggesting an instrumental role of the hepatic CREB/NR4A pathway in the manifestation of diabetic hyperglycemia.

Apart from hyperglycemia, a subacute inflammation represents an additional characteristic feature of insulin-resistant type II diabetes, driven at least in part by the proinflammatory response of macrophages (Saltiel, 2001). In this respect, previous results from the Tontonoz lab demonstrated that NR4A receptors induce the production of proinflammatory cytokines in these cells (Pei et al., 2006a). A prodiabetic liver function of NR4A receptors might, therefore, also point to a more general role of these factors in the promotion of the type II diabetic phenotype.

Some questions arise. What is the mode of cooperativity between the NR4A and PGC-1α pathways? The distinction between individual liver targets argues for specific promoter-dependent setups rendering a gene responsive to NR4A, PGC-1α, or both. Noteworthy, PGC-1α has been shown to coactivate Nurr1 in other cell types (Nervina et al., 2006), an effect not observed by Pei and colleagues (2006b), further strengthening...
the case for a cell- or promoter-specific connection between NR4A and PGC-1α.

What is the connection to insulin signaling? Insulin exerts a dominant-negative effect on gluconeogenesis in response to exogenous glucose, and defects in hepatic insulin signaling lead to hyperglycemia and impaired glucose tolerance (Michael et al., 2000). It will be interesting to determine whether the NR4A pathway is actively inhibited by insulin as shown for PGC-1α (Puigserver et al., 2003) or just passively shuts off in response to declining cAMP levels upon food consumption. Finally, what is the molecular mechanism of NR4A upregulation in diabetic mice? Given the causal relationship between elevated NR4A levels and hyperglycemia, the mechanisms of NR4A receptor induction under these conditions are of particular importance for putative therapeutic intervention strategies. In any case, potential therapeutic benefits of NR4A inhibition in the liver for counteracting diabetic hyperglycemia would need to be balanced by possible effects on other metabolic pathways in or outside of the liver, or by effects on apoptosis or cell proliferation.

In conclusion, the recent paper by Pei and colleagues (2006b) provides an important insight into novel aspects of signal-dependent control of glucose metabolism connected to diabetic pathophysiology. The discovery of the NR4A branch of cAMP-mediated metabolic control will provide a sweet incentive for investigators to follow up on this issue.

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Selected reading


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Figure 1. cAMP controls hepatic gluconeogenesis via two distinct transcriptional effector pathways

Pei and colleagues (2006b) show that the cAMP-responsive transcription factor CREB promotes hepatic glucose output through the independent induction of coactivator PGC-1α and NR4A orphan nuclear receptors. PGC-1α and NR4A receptors, in turn, stimulate the expression of common as well as distinct targets within the gluconeogenic pathway to trigger hepatic glucose release during fasting and under diabetic conditions.