A Sweet Path to Insulin Resistance Through PGC-1\(\beta\)

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Fructose is a highly lipogenic dietary nutrient that has been implicated in the pathogenesis of hyperlipidemia and insulin resistance. In this issue, Nagai et al. (2009) provide in vivo evidence that pinpoints transcriptional coactivator PGC-1\(\beta\) as a key factor in mediating the metabolic response to fructose intake.

The consumption of the Westernized diet is a major factor that contributes to the global epidemic of the metabolic syndrome and type 2 diabetes. Dietary intake of fructose, which is commonly derived from sweeteners based on sucrose or high-fructose corn syrup, was estimated to increase by 20\%–40\% over the last three decades (Havel, 2005). Numerous studies in humans and animal models have implicated fructose in the pathogenesis of insulin resistance and dyslipidemia, in particular hypertriglyceridemia (Havel, 2005; Rutledge and Adeli, 2007). Fructose is absorbed by enterocytes through GLUT5, a fructose-specific hexose transporter, and reaches the liver through the portal circulation. Compared to glucose, fructose is more potent in the stimulation of de novo hepatic lipogenesis and VLDL secretion (Hellerstein et al., 1996), which subsequently impact on systemic energy metabolism and insulin sensitivity. The exact molecular pathway that mediates the effects of fructose on hepatic lipogenesis and insulin resistance remains unclear. A new study in this issue (Nagai et al. 2009) revealed the transcriptional coactivator PPAR\(\gamma\) coactivator-1\(\beta\) (PGC-1\(\beta\)) as a missing link between fructose intake and metabolic disorders.

The lipogenic activity of fructose is achieved through its effects on the metabolic flux as well as the induction of a genetic program that supports lipogenesis. In the liver, fructose enters the glycolytic pathway downstream of phosphofructokinase, a rate-limiting enzyme in glycolysis, and generates carbons for the synthesis of fatty acids and triglycerides. As a result, high levels of fructose intake provide an essentially unregulated source of acetyl-CoA for hepatic lipogenesis. On the other hand, fructose intake also activates the expression of lipogenic genes (Nagai et al., 2002), which involves the induction of sterol regulatory element binding proteins (SREBP), particularly SREBP1c, a major transcriptional regulator of lipogenic gene expression (Horton et al., 2002).

The PGC-1 family of transcriptional coactivators regulates glucose, lipid, and mitochondrial oxidative metabolism in response to nutritional and hormonal signals (Finck and Kelly, 2006; Lin et al., 2005a). These coactivators physically interact with selective transcription factors as well as cofactors and induce the transcription of target genes through remodeling of local chromatin structure. A case in point is PGC-1\(\beta\), which coordinates hepatic lipogenesis and lipoprotein metabolism through coactivating several transcription factors, including SREBPs, the liver X receptor (LXR), and forkhead transcription factors, including SREBP1c promoter is reduced when PGC-1\(\beta\) is knocked down in response to dietary saturated fats. Further, adenosin-mediated expression of PGC-1\(\beta\) in the liver induces triglyceride synthesis and VLDL secretion, leading to hypertriglyceridemia in transduced rats. These effects of PGC-1\(\beta\) on lipid metabolism are reminiscent of the metabolic consequences of high-fructose feeding. Using an antisense oligonucleotide (ASO) strategy, Nagai et al. (2009) demonstrated that PGC-1\(\beta\) is an important regulator of hepatic lipogenesis and VLDL secretion in response to short-term high-fat feeding (Lin et al., 2005b). While PGC-1\(\beta\) ASO appears to also decrease fasting plasma glucose and insulin levels in the context of high-fat feeding, it has modest effects on hepatic glucose production and whole-body glucose utilization. These findings place PGC-1\(\beta\) at a unique regulatory point that is apparently required for mediating the adverse metabolic effects of dietary fructose, but not dietary fats.

Parallel to the improvement of metabolic parameters, PGC-1\(\beta\) ASO suppresses the lipogenic response to high-fructose feeding in the liver. The induction of SREBP1a, SREBP1c, and fatty acid synthase by fructose is attenuated in rats receiving PGC-1\(\beta\) ASO treatments. Since LXR and SREBP1 regulate the transcription of SREBP1c itself, Nagai et al. used chromatin immunoprecipitation (chip) to demonstrate that the occupancy of these two transcription factors on the SREBP1c promoter is reduced when PGC-1\(\beta\) is knocked down. It is likely that PGC-1\(\beta\) knockdown reduces the transcriptional activity of LXR and SREBP1, resulting in repressive chromatin...
environment on the SREBP1c promoter and decreased recruitment of these factors to their respective binding sites. Additional chIP experiments using antibodies against PGC-1β and various histone marks should provide further insights into this pathway. The findings are somewhat paradoxical as PGC-1β does not appear to directly regulate the expression of SREBP1c in previous gain-of-function studies (Lin et al., 2005b). This dilemma raises the possibility that the inhibition of SREBP1 expression by PGC-1β ASO could be secondary to altered hormonal milieu, particularly insulin, which is a potent activator of SREBP1c gene expression.

It is remarkable that PGC-1β ASO drastically enhances glucose uptake by white adipose tissue when the rats were fed a fructose-rich diet. This appears to be an important contributor to the improvement in whole-body glucose utilization. Interestingly, the total levels as well as the membrane pool of GLUT4 protein are significantly elevated in the white fat following PGC-1β ASO treatments. While the exact molecular mechanisms are currently unknown, these surprising findings could potentially reveal a novel link between PGC-1β and the regulation of GLUT4 protein turnover and/or translation.

An unresolved issue is how PGC-1β interacts with dietary fructose to bring about the desirable responses. In this regard, PGC-1β knockdown apparently causes hepatic insulin resistance in the rats fed a regular chow. A plausible explanation for these findings is that PGC-1β ASO impairs mitochondrial function in the liver, in particular the expression of genes involved in fatty acid β-oxidation, and causes hepatic insulin resistance. However, similar decreases were also observed in PGC-1β ASO-treated rats fed a high-fructose diet. This discrepancy raises an intriguing possibility that PGC-1β may serve as a nodal point that modulates the interaction between dietary nutrients and the metabolic regulatory programs. The findings by Nagai et al. support the emerging role of gene/environment interaction in modulating the metabolic phenotype and disease pathogenesis. Thus, perturbations of the same regulatory motif may produce vastly different metabolic responses, depending on the specific combinations of dietary nutrients.

REFERENCES