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Hepatic glucose production and storage as a potential strategy for type 2 diabetes treatment – the effect of catestatin – "just another new kid in town"?

In this issue of Acta Physiologica, Bandyopadhyay and colleagues take a novel hormonal approach to target hepatic glycogen synthesis for ameliorating insulin resistance[1]. Insulin resistance is the hallmark of type 2 diabetes (T2D) with insufficient glucose uptake by muscle and fat and unrestrained hepatic glucose production. The result is hyperglycemia. Among the metabolic tissues, the liver is the first organ to develop insulin resistance, followed by skeletal muscle and adipose tissue. In the liver, insulin resistance leads to increased gluconeogenesis and glycogenolysis. In addition, there is relative hyperglucagonemia, further augmenting hepatic gluconeogenesis and glycogenolysis. This glucagon increase may be related to an altered pancreatic alpha – to beta cell ratio, alpha cell resistance to insulin, stress, or stimulatory hormones like epinephrine. These pathophysiological mechanisms make the liver an important additional target for T2D treatment strategies.

Under normal physiological conditions in the interdigestive state the liver tightly controls plasma glucose levels via glycogenolysis and gluconeogenesis, while in the postprandial state glucose is extracted from the portal circulation via conversion to glucose-6-phosphate and glycogen. These processes are modified and influenced by a number of peptides from the gastrointestinal tract, the autonomic nervous system, nutrients, stress mediators and inflammation. Intracellularly, under fasting conditions, inhibition of the serine/threonine protein kinase AKT induces transcriptional activation of the rate limiting enzymes of gluconeogenesis: phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) expressions via inhibition of forkhead box protein O1 (FOXO1) phosphorylation. Inhibition of AKT also reduces phosphorylation of glycogen

synthase kinase 3β (GSK3β) and subsequent impairment of glycogen synthesis, while glycogen phosphorylase (GP) (glycogen degradation enzyme) is activated.

Preceeding this study, the group found in diet-induced obese mice that catestatin attenuates hepatic glucose production via inhibition of inflammation [2].

Catestatin ($CST_{352-372}$) is a peptide of 21 amino acids cleaved by prohormone convertases from chromogranin A (CgA), a 439 amino acid protein, which is widely expressed in endocrine and neuronal tissues including the pancreatic islets [3]. Using a commercial, non-validated, enzyme immunoassay for CST, Simunovic and colleagues found in unprotected serum samples lower catestatin concentrations in obese children (age 14; BMI 30.6) compared to a lean control group (age 14.4 BMI 20,2) (10.03 ± 5.05 vs 13.13 ± 6.25 ng/mL, P= 0.004) [4]. These reported levels in the ng/ml range are very high for a peptide from neuroendocrine tissues and only achieved by leptin or adiponectin from fat stores. Plasma levels are unclear and depend on the different peptides of CgA used as antigen and probably matrix effects, components in the samples that might interfere with antibody binding. Nagasawa et al. e.g. reported fasting plasma levels of a CgA peptide fragment (synthetic human $CgA_{344-374}$ as antigen) of 0.34±0.08 pmol/mL (mean ± SD, n:10) [5].

There are multiple biological effects of CST. Most notably, CST inhibits catecholamine secretion, suppresses inflammation and exerts metabolic effects [5]. Using a high fat diet or a normal chow diet (NCD) on wildtype (WT) and systemic CST knock-out (CST-KO) male mice, Bandyopadhyay et al. treated these mice with CST, either intraperitoneally (ip) or orally (2 ug/g body weight) for 1 hour (acute) or for 15 days (chronic). In WT mice under NCD, acute and chronic CST treatment increased liver and muscle glycogen in both fed and fasting conditions, while CST treatment under DIO decreased lipid density in the liver. Furthermore, CST treatment decreased norepinephrine, epinephrine, and glucagon (only in fasted) in WT mice under NCD, while glycogen content increased about 50% in the fed and 5-fold in fasted mice under DIO. In DIO WT mice, CST treatment dose-dependently decreased blood glucose levels and improved glucose tolerance. In CST-KO mice under NCD, liver glycogen deposition was significantly reduced compared to WT mice and CST treatment restored it. In addition, CST-KO mice had significantly decreased norepinephrine, epinephrine, and glucagon levels compared to WT mice. CST treatment increased liver glucose-6-phosphate levels under NCD in both fed and fasting

mice, however there was no change in DIO fed animals. Furthermore, CST increased uridine diphosphate glucose and glycogen synthase levels in both NCD and DIO mice liver in fasted state. In cultured primary hepatocytes, CST stimulated PI3-kinase activity without affecting the insulin receptor or insulin receptor substrate-1. CST increased pT308–AKT phosphorylation via 3-phosphoinositide-dependent protein kinase-1 (PDK1) and Ser9 GSK-3β phosphorylation, but reduced phosphorylation of glycogen synthase (GYS2), which activates the enzyme producing more glycogen [1; Figure 10].

The current work shows that oral application of CST increases glycogen storage in vivo under normal and high fat diet, and decreases blood glucose levels under high fat diets and lower hepatic lipids. In the isolated hepatocytes, CST decreases phosphorylation of GYS2 under normal diet but not under high fat diet. In the latter, only together with insulin [1: Figure 9E].

How CST mediates these effects requires elucidation. Decreased catecholamines likely contribute to beneficial effects on glucose homeostasis. Additionally, the lipid loading under the high-fat conditions in vivo may affect the zonal oxygenation in the liver, which could alter signal transduction pathways [6]. Interestingly, CST significantly affects gut permeability and the gut microbial population in the CST-KO mice, which could change the metabolic profile of the mice [7].

Overall, these findings are very good news for the potential use of oral CST, especially for subjects with metabolic syndrome with their T2D, obesity, insulin resistance and hypertension. Now, there are four known beneficial effects of CST: 1) Lowering blood glucose; 2) Decreasing catecholamines; 3) Decreasing macrophages/inflammation; and 4) Decreasing gut permeability.

Advancing the studies of oral CST towards human application is the next step.

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