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Adropin and insulin resistance: Integration of endocrine, circadian, and stress signals regulating glucose metabolism

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With recent advances in obesity and type 2 diabetes (T2D) therapeutics, some might conclude that all major hormonal pathways governing energy balance and glucose homeostasis have been identified and thoroughly investigated. However, mammalian genomes contain many highly conserved short open frame sequences (sORF) encoding a multitude of secreted peptides that may regulate metabolic homeostasis (1,2), some of which could provide further treatments for obesity and T2D.

The biological activities of the small secreted peptide hormone adropin are indicative of a potentially important regulator of glucose metabolism. The sORF encoding adropin was discovered by Genentech’s Secreted Protein Discovery Initiative (2). The first experiments connecting adropin to metabolism profiled hepatic gene expression in male C57BL/6J mice (3). Expression of the energy homeostasis associated (ENHO) transcript encoding adropin was suppressed with obesity and fasting and rapidly increased when refed after overnight fasting (3,4). These responses suggested involvement in metabolic adaptation to food intake.

Expression profiling using mouse models now suggests a more complex relationship. A variety of metabolic conditions suppress hepatic adropin expression: catabolic states induced by overnight fasting, increased hepatic lipogenesis (e.g., consumption of high-sugar diets or severe hyperphagic obesity syndromes) in hypercholesterolemia, and genetic disruption of the circadian-clock activator BMAL1 (aryl hydrocarbon receptor nuclear translocator-like protein 1) (3–6). Expression of adropin in nonhuman primates indicates that the small secreted peptide hormone adropin regulates glucose metabolism. Here, recent expression profiling data indicating hepatic adropin expression increases with oxidative stress and declines with fasting or in the presence of hepatic insulin resistance and how adropin interacts with the pancreatic hormones, insulin, and glucagon to modulate glycemic control are discussed.
Adropin expression is induced in response to cellular stress. Presumably, normal regulation of adropin in response to oxidative stress, and any potential protective role, are compromised in situations of severe obesity and insulin resistance.

An unexpected observation is a positive correlation between adropin and phosphoenolpyruvate carboxykinase 1 (PCK1), a major control point in gluconeogenesis (4). This relationship was observed in the liver transcriptome in samples collected over 24 hours from mice fed ad libitum or subjected to CR. These data provide a window into the liver transcriptome under conditions ranging from short-term energy deficit between meals in mice subject to prolonged CR, milder energy deficits during the lights-on period when nocturnal mice rest, “normal” voluntary feeding in the dark phase, or recent binge-feeding (mice subject to CR consume 80% to 90% of daily kilocalorie intake within 1 hour of ad libitum food presentation). Overnight fasting of mice housed at room temperature induced a severe catabolic state (9). Although fasting suppresses hepatic adropin expression and increases hepatic glucose production (HGP), this relationship is not observed in mice subjected to a broader range of metabolic conditions involving coactivation of HGP and adropin expression.

Positive correlations with PCK1 and acute responses of liver adropin expression to fasting and refeeding suggest functions related to adapting metabolism to shifts in energy balance. Experiments using adropin knockout mice (AdrKO), mice treated with synthetic adropin, and in primary cultured hepatocytes all suggest adropin inhibits HGP (4,10–13). This effect is bidirectional as liver-specific AdrKO mice exhibited increased glucose excursions following intraperitoneal injections of pyruvate, suggesting increased HGP (4). Adropin appears to “modulate” glucagon receptor signal transduction. Activation of the putative adropin receptor has an inhibitory effect on the induction of cAMP-dependent protein kinase (PKA) signaling by glucagon. This could indicate an inverse relationship between liver adropin expression and the ability of glucagon to increase HGP. Alternatively, adropin has the opposite effect on insulin action, improving hepatic insulin action in conditions of obesity and insulin resistance (12,13).

Two candidate cell-surface receptors have been identified: an orphan G-protein coupled receptor (GPR19) (14) and a glycosylphosphatidylinositol-anchored neuronal membrane protein that functions as a cell adhesion molecule (NB3/CNTN6) (15). Both are predominantly expressed in the nervous system (16). GPR19 inhibited cAMP signaling in cultured cells (17), whereas Notch signaling was implicated in liver glucose metabolism (18). However, how adropin signaling from the cell surface of hepatocytes affects glucose metabolism needs to be clarified.

Experiments conducted in mouse models support a role for adropin in glucose homeostasis. AdrKO mice exhibited increased HGP assessed by hyperinsulinemic-euglycemic clamp (10). Activation of hepatic protein kinase B (AKT/PKB) signaling by insulin was, however, normal, suggesting a potentially novel and atypical mechanism (10). Whether changes in glucagon signaling observed in liver-specific AdrKO mice explain the phenotype requires further investigation (4). Administration of recombinant adropin to diet-induced obese mice enhances insulin signaling in skeletal muscle and liver (12,19). This effect is observed in perfused hearts ex vivo, suggesting a direct effect of adropin (4,12,20). Adropin treatment is also unique because it was shown to acutely enhance oxidative glucose disposal in diet-induced obese mice (19). Other laboratories have also observed direct effects of adropin in cultured cells and isolated perfused hearts to regulate fuel substrate selection to favor the oxidation of glucose over fat (20–22). Adropin could therefore potentially represent a unique therapy targeting T2D by improving insulin sensitivity while simultaneously enhancing oxidative glucose disposal.

If the mouse data are translatable to humans, low adropin activity should correlate with hyperglycemia. In an NHP model, low plasma adropin concentrations correlate with fasting hyperglycemia and with plasma biomarkers suggesting dysregulation of hepatic lipoprotein metabolism and increased adiposity (7,23). Transcriptomic data in the liver of NHPs suggest adropin expression peaks around mealtime and that it is coregulated with genes involved in glucose metabolism and second messenger signal transduction pathways involving G proteins and receptor tyrosine kinases. In primates, peak hepatic adropin expression may thus anticorrelate and/or coincide with the activation of signal transduction pathways mediating the responses of hepatocytes to endocrine and/or metabolite signals of increased nutrient flux.

Our analysis of relationships between circulating levels of adropin and circulating indices of glucose and lipid metabolism in humans is less clear. Low plasma adropin concentrations correlate with evidence of impaired insulin action in studies of subjects using narrowly defined age, weight, and health criteria for inclusion (5,24). On the other hand, in a larger study with fewer restrictions for inclusion, we reported an inverse relationship with non-high-density lipoprotein cholesterol that could be explained by an inhibitory effect of cholesterol on ENHO expression (6). Fructose consumption rapidly induces insulin resistance and dyslipidemia in humans and rapidly increases plasma adropin concentrations, and this effect was most pronounced in subjects with existing dyslipidemia at baseline prior to sugar consumption (25). As with the early studies of other secreted peptides, issues of assay specificity and validation are significant caveats in the interpretation of the data on plasma adropin concentrations.

To conclude, we have discussed several mechanisms by which adropin acts to regulate glucose homeostasis. Adropin signaling in the liver through an as-yet unidentified receptor interacts with insulin and glucagon to lower HGP. Suppression of adropin expression may contribute to increased HGP in obesity. Data showing enhancement of insulin action and glucose oxidation in cardiac and skeletal muscle also suggest a role in lower glucose (19,20). Clearly,
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further assessment of the clinical relevance of the current findings on regulation of adropin and its physiological actions is warranted. The identity of the cell-surface receptors for adropin and the signal transduction pathways need to be fully explored. Finally, models more relevant to humans (e.g., NHPs) should be used to explore the relationship between low hepatic adropin expression and hyperglycemia.

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The authors apologize that because of space limitations we were unable to cite a number of other important studies on the biology of adropin.

CONFLICT OF INTEREST
The authors declared no conflict of interest.

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