mechanisms that differ from those observed in mice with defective lipolysis.

Taken together, the work by Albert et al. underlines the key role of HSL for lipid metabolism, energy homeostasis, and cell signaling in humans. Important questions, however, remain open: Which lipolytic mediators are involved in the regulation of gene transcription by nuclear receptors? What are the (species-specific) mechanistic links between HSL deficiency insulin resistance and diabetes? What is the molecular basis for hepatosteatosis and dyslipidemia in humans lacking HSL? Additional studies in humans and mice with HSL deficiency will answer these questions.

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Insulin-Degrading Enzyme Inhibition, a Novel Therapy for Type 2 Diabetes?

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The insulin-degrading enzyme (*IDE*) has been identified as a type 2 diabetes and Alzheimer's disease susceptibility gene, though its physiological function remains unclear. Maianti et al. (2014) now propose that an IDE inhibitor may be a promising therapeutic strategy for type 2 diabetes.

Insulin-degrading enzyme (IDE) is a highly conserved and widely expressed Zn^{2+} metalloprotease first identified through its action to degrade insulin. IDE also degrades a variety of substrates that share in common small size (<50 amino acids) and a pattern of charged and hydrophobic residues rather than being from a particular family of proteins (Shen et al., 2006). Interest in IDE function was prompted by genome-wide association studies that suggested linkage to *IDE* for both type 2 diabetes (Sladek et al., 2007) and Alzheimer's disease (Bertram et al., 2000), although linkage to the former has not always been replicated. Whether the genetic linkage of *IDE* with type 2 diabetes and Alzheimer's disease is due to loss or gain of function of IDE enzyme activity also remains unclear, though investigators in the Alzheimer's disease field have concluded that inactivation of IDE underlies the association (Farris et al., 2004). Loss of function of IDE has also been implicated in pancreatic β cell failure, as the $Ide^{-/-}$ mouse has impaired insulin secretion (Steneberg et al., 2013), and an inactivating mutation in the *Ide* gene is responsible for failed insulin secretion in the Goto-Kakizaki (GK) rat model of type 2 diabetes (Farris et al., 2004). Moreover, genetic analysis of type 2 diabetes susceptibility variants linked the *IDE* gene to impaired insulinogenic index, a diabetic trait that is a measure of insulin secretion (Dimas et al., 2014). In a recent intriguing *Nature* paper, Maianti et al. (2014) propose that acute inhibition of IDE activity may be a novel therapeutic approach to restore postprandial hyperglycemia in type 2 diabetes (Maianti et al., 2014).

Maianti et al. (2014) performed an impressive chemical and biochemical survey in order to select an optimal small-molecule modulator of IDE. After establishing ideal arrangements of the

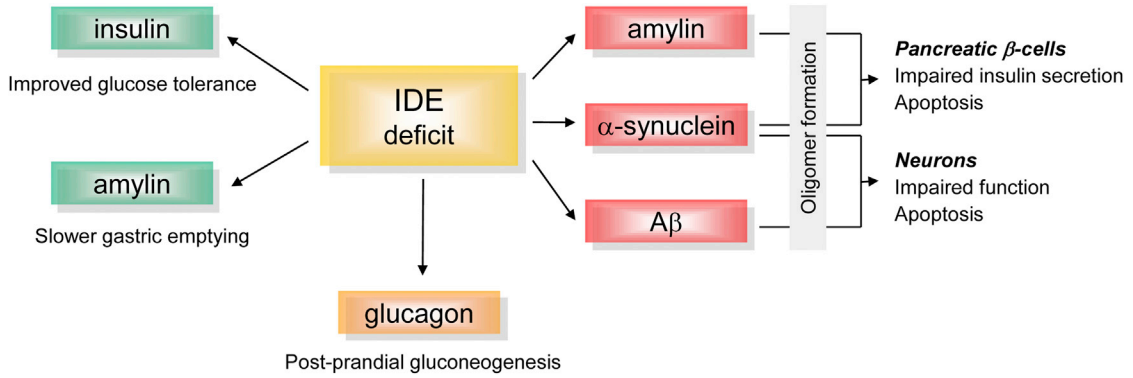

Figure 1. Roles of IDE in Glucose Homeostasis, Gastric Emptying, and Regulation of Amyloidogenic Protein Levels Based on Studies with Pharmacological IDE Inhibition or *Ide* Knockout Mice

IDE deficit increases the abundance and signaling of the pancreatic hormones insulin, amylin, and glucagon. Increased insulin improves glucose tolerance, and increased amylin levels slow postprandial gastric emptying. On the right is shown that IDE deficit increases levels of amylin, α-synuclein, and Aβ monomers which, via subsequent formation of toxic oligomers, impair secretory function and survival of pancreatic β cells and neurons.

candidate structure, the potent and selective IDE inhibitor 6bK was generated. Administration of a single dose of 6bK in nonfasted mice 30 min prior to an insulin tolerance test confirmed the physiological stability and efficiency of 6bK to inhibit IDE activity in vivo. 6bK was then evaluated in lean- or high-fat-fed mice, given as a single dose 30 min prior to a glucose challenge. Acute administration of 6bK enhanced glucose tolerance to oral glucose, notably to a greater extent in high-fat-fed mice. However, 6bK induced glucose intolerance when glucose was administered by intraperitoneal (i.p.) injection. Measurement of plasma levels of the main glucose-regulating hormones in high-fat-fed mice after i.p. glucose delivery revealed that 6bK not only increased circulating insulin, presumably by decreasing its degradation, but also, as predicted by prior structural and in vitro studies (Shen et al., 2006), increased glucagon and amylin (also known as islet amyloid polypeptide [IAPP]). The latter was shown to delay gastric emptying, contributing to the enhanced glucose tolerance with 6bK. In contrast, 6bK action on glucagon signaling was shown to be responsible for the hyperglycemia that follows i.p. glucose injection. In summary, acute inhibition of IDE activity in obese mice enhanced postprandial insulin and amylin secretion, attenuating the postprandial glycemic excursion presumably by insulin-mediated suppression of hepatic glucose release and amylin-induced delayed gastric emptying (Figure 1).

There is an unmet need for enhanced postprandial glucose control in type 2 diabetes. Therefore, the authors' proposal of an IDE inhibitory therapy, perhaps in combination with a GLP-1-based therapy since GLP-1 suppression of glucagon secretion may offset increased glucagon secretion with IDE inhibition, is an intriguing one. However, there are some important questions that would need to be addressed before serious consideration can be given to this strategy as a therapy. The findings reported by Maianti et al. (2014) draw attention to the uncertainty as to how IDE influences risk for type 2 diabetes or Alzheimer's disease, or indeed a full understanding of its physiological role. For example, does the inhibition of IDE increase insulin levels primarily by decreasing hepatic insulin clearance of insulin, and/or by decreasing degradation of insulin in β cells to increase insulin secretion? Of greater concern, what would be the outcome of long-term use of IDE inhibition on cell viability in tissues that express amyloidogenic peptide substrates of IDE (Kurochkin, 2001)?

Maianti and colleagues (Maianti et al., 2014) considered the potential issue of an adverse effect of IDE inhibition on one such amyloidogenic peptide. They reported that there was no measurable accumulation of 6bK or increase of amyloid β-protein (Aβ) in the brain 2 hr after injection of 6bK. The pancreas did take up 6bK, however, raising concerns about the potential accumulation of misfolded insulin, amylin, α-synuclein, and Aβ in β cells. Indeed, given that IDE has an apparent substrate preference for amyloidogenic proteins (proteins with a propensity to form amyloid fibrils, but of greater concern, also membrane-permeant toxic oligomers) (Kurochkin, 2001), IDE has been proposed to play a role in defending against intracellular accumulation of these proteins, as well as cellular dysfunction and apoptosis that may follow (Figure 1). To this end, inhibition of IDE has been shown to increase β cell vulnerability to human amylin (Bennett et al., 2003). While rodent amylin is not amyloidogenic, rodent models expressing human amylin are available, and human islets can be evaluated after transplantation into immune-tolerant mice. Likewise, it would be important to evaluate the effect of long-term 6bK delivery (more than a single dose) to mice vulnerable to neurodegenerative diseases (e.g., expressing mutant α-synuclein or Aβ). Given that the alternative pathways for clearance of amyloidogenic proteins (i.e., autophagy and ubiquitin/proteasome system) decline with aging (Koga et al., 2011), evaluating the repercussions of long-term administration of 6bK in aged mice would be necessary. Moreover, it remains critical to exclude accumulation of other amyloidogenic proteins expressed in potentially vulnerable tissues, such as atrial natriuretic peptide in cardiac muscle (Kurochkin, 2001), after repeated administrations of an IDE inhibitor.

With development of this impressive new tool, Maianti et al. (2014) have opened the opportunity for new lines of investigation to shed insight into both

how IDE functions in health and its linkage to diabetes, as well as whether the postulated role of IDE as a defender against amyloidogenic protein-induced toxicity is valid.

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Another Shp on the Horizon for Bile Acids

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Bile acid metabolism is tightly controlled due to the toxic effects of bile acid overload. In this issue, research from the Feng lab reports Shp2 as a novel integrator of hepatic bile acid and FGF15/FGF19 signaling, adding another layer of complexity to the control of bile acid biosynthesis.

Bile acids (BAs) are end products of cholesterol metabolism but also well-recognized signaling molecules. They are synthesized from cholesterol in the liver, secreted from hepatocytes into bile, and stored in the gallbladder. After ingestion of a meal, bile is secreted into the small intestine, where BAs contribute to the solubilization and absorption of lipids and fat-soluble vitamins. The majority of BAs are reabsorbed in the terminal ileum and transported back to the liver via the portal vein in a process defined as enterohepatic circulation (Thomas et al., 2008). BAs that escape intestinal absorption are excreted in the feces, thus removing the excess cholesterol from the body. Despite their essential functions, high levels of BAs and cholesterol contribute to multiple human metabolic diseases, including cholecystolithiasis (gallstones), hepatic cholestasis, and atherosclerosis, emphasizing the need for a tight regulation of BA synthesis. In this issue of *Cell Metabolism*, Li and coauthors (Li et al., 2014) identify Shp2 as a novel coordinator of BA homeostasis in the liver, adding an additional layer of complexity to this process.

Besides their role in dietary lipid absorption, BAs function as signaling molecules that activate specific receptors, including the nuclear farnesoid X receptor (FXR or NR1H4) and the G protein-coupled receptor TGR5 (Thomas et al., 2008). FXR is the major regulator of the negative feedback loop that controls BA synthesis. Indeed, BA-activated FXR induces hepatic expression of the small heterodimer partner (SHP or NROB2), an atypical nuclear receptor that suppresses BA biosynthesis by inhibiting the expression of *Cyp7a1*, which encodes for the rate-limiting enzyme of this pathway. A second mechanism for the inhibition of BA production involves intestinal BA-FXR signaling. Activation of enteric FXR by BAs leads to a robust induction and secretion of fibroblast growth factor 15/19 (FGF15 in mouse and FGF19 in human) (Inagaki et al., 2005). FGF15/19 is released into the circulation and binds to the FGFR4/β-Klotho complex on the hepatocyte cell membrane, triggering an intracellular signaling cascade that represses *Cyp7a1* mRNA expression and BA synthesis. Although the precise molecular mechanisms are not yet completely characterized, several lines of evidence indicate that both the liver receptor homolog 1 (LRH-1 or NR5A2) and the hepatocyte nuclear factor 4α (HNF4α or NR2A1) are crucial transcriptional activators of the *Cyp7a1* promoter and are required for FGF15/19 and SHP to repress *Cyp7a1* (Kir et al., 2012; Nitta et al., 1999; Stroup and Chiang, 2000). It has been proposed that BA-induced FGF15/19 increases the stability of hepatic SHP by inhibiting its proteasomal degradation in an extracellular signal-regulated kinase (ERK)-dependent manner (Miao et al., 2009), yet other studies suggest that FGF15/19 treatment does not alter the affinity of SHP, HNF4α, and LRH-1 to the *Cyp7a1* promoter (Kir et al., 2012).

Within this scenario, Li et al. identified the Src-homology 2 domain-containing