Good Fats
Lipidomics Approach Identify Novel Regulators of Glucose Homeostasis

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Study Hypothesis
The prevalence of obesity and type 2 diabetes mellitus (T2D) continues to rise worldwide. The key features of T2D are altered insulin secretion and peripheral insulin resistance. The insulin responsive glucose transporter, GLUT4, facilitates glucose uptake into skeletal muscle, cardiac muscle, and adipocytes. GLUT4 has been shown to be downregulated specifically in adipose tissue (AT) but not in muscle in both humans and mouse models with T2D and obesity. In this study, Yore et al used lipidomics analysis in mice overexpressing GLUT4 selectively in AT (AG4OX) to identify a novel class of lipids, the branched fatty acid esters of hydroxyl fatty acids (FAHFAs), with antidiabetic properties. Previous work from this group showed that tissue-specific knockdown of GLUT4 in adipocytes caused insulin resistance, whereas overexpression resulted in enhanced glucose tolerance. In addition, the authors previously established that the transcription factor, carbohydrate-responsive element binding protein, mediated the beneficial effects of GLUT4-mediated glucose uptake in adipocytes by activating de novo lipogenesis. Therefore, the authors hypothesized that FAHFAs, which are overabundant in the AG4OX mice, may be novel regulators of glucose-insulin homeostasis.

How Was the Hypothesis Tested?
The authors began by performing a quantitative lipidomics analysis of AT from AG4OX mice and wild-type mice and identified cluster of ions in the AG4OX mice that did not correspond to any known metabolites. After identifying this novel class of lipids, they investigated the biological properties of the most highly upregulated species, the palmitic acid-hydroxy steric acids (PAHSAs) in mice under various dietary conditions, quantified PAHSAs biosynthetic activity in several tissues and determined whether exogenously delivered PAHSAs would improve glucose tolerance. The authors extended their work into humans, by measuring PAHSAs in serum and AT of insulin-sensitive and insulin-resistant nondiabetic subjects.

Principal Findings
After the initial lipidomics screen, 16 FAHFAs and 8 PAHSA isomers were identified using a targeted MS approach. Tissue analysis revealed that the PAHSAs were distributed in all tissues measured, but appeared 16- to 18-fold higher in subcutaneous and perigonadal AT, 3-fold higher in brown AT, and 2-fold higher in serum of AG4OX mice when compared with wild-type mice. Measurement of PAHSAs in AT depots in mice after high-fat diet feeding and insulin-resistant conditions revealed that most of the isomers were decreased in subcutaneous and brown AT, whereas fasting conditions increased PAHSAs. PAHSAs levels in serum and subcutaneous AT from insulin-resistant human subjects were reduced when compared with insulin-sensitive subjects (n=6–7 per group), and PAHSAs levels correlated with insulin sensitivity as measured by clamp studies. Knocking out carbohydrate-responsive element binding protein in wild-type animals significantly reduced PAHSA levels in subcutaneous and perigonadal AT with no change in serum, thus the reduction in PAHSAs in insulin resistance subjects may be mediated by reduced carbohydrate-responsive element binding protein expression. Oral gavage of 2 isomers, 5- and 9-PAHSA, in insulin-resistant high-fat diet fed mice lowered basal glycemia and improved glucose tolerance as determined by an oral glucose tolerance test, suggesting that PAHSAs enhanced insulin sensitivity. In vitro experiments showed that PAHSAs directly enhanced glucose stimulated insulin secretion and stimulated glucagon-like peptide-1 secretion, implying both direct and indirect mechanism of improved glucose tolerance. To elucidate the mechanism of enhanced glucose tolerance further, both 9- and 5-PAHSA were able to bind and activate GPR120, the long-chain fatty acid receptor, in a dose-dependent manner. The activation of GPR120 signaling has been shown to increase glucose transport and GLUT4 translocation in adipocytes. Finally, they establish anti-inflammatory properties of the PAHSAs by demonstrating their ability to block a lipopolysaccharide-induced interleukin-12 secretion.
and reduce interleukin-1β and tumor necrosis factor-α levels in bone marrow–derived dendritic cells and AT macrophages.

**Implications**
Yore et al have identified a new class of bioactive lipids through metabolomic methods that serve as regulators of metabolic homeostasis. This new class of lipids improves glucose tolerance by enhancing insulin and glucagon-like peptide-1 secretion and has important anti-inflammatory effects. Notably, the FAHFAs are synthesized in vivo and may be the endogenous ligand for GPR120, a G-protein–coupled receptor that is the focus of ongoing investigations for obesity and insulin resistance. Although the regulation and synthesis of the FAHFAs is still unknown, they might serve as a potential therapeutic target for the treatment of type 2 diabetes mellitus and obesity.

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**Disclosures**
None.

**Key Words:** adipose tissue • diabetes mellitus, type 2 • fatty acids • GLUT4 protein • insulin resistance • metabolomics • obesity
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