cytoplasmic locations to the plasma membrane is impaired. Sortilin is an important constituent of Glut4 storage vesicles and interacts with guiding proteins to determine location of Glut4 in the trans-Golgi network. Sortilin levels are shown to affect adipocyte function. Using mouse 3T3L1 adipocytes, we demonstrate that alternative splicing of sortilin pre-mRNA results in an inclusion of an exon (17b) between exons 17 and 18 in the 10CC motif of the VPS10p domain crucial for ligand interaction. $Sort^{17b}$ expression correlates to insulin resistance and over-expression of $Sort^{17b}$ decreases glucose uptake in adipocytes. Using co-immunoprecipitation assays, we demonstrate that Sort17b is a strong binding partner of Glut4. Using bioinformatic analysis, we show that this insertion results in a novel intrinsically disordered region and has potential sites of proteolytic cleavage. Our study is the first to describe sortilin's alternatively spliced variants in adipocytes and their effects on glucose uptake. As a broader approach, the research demonstrates the impact of a post-transcriptional event on the metabolic fate of adipocytes in conditions of insulin resistance.

Diabetes Mellitus and Glucose Metabolism

DYSREGULATED METABOLIC RESPONSE

In Utero Maternal Benzene Exposure Predisposes to the Metabolic Imbalance in the Offspring

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Environmental chemicals play a significant role in the development of metabolic disorders, especially when exposure occurs early in life. We have recently demonstrated that benzene exposure, at concentrations relevant to a cigarette smoke, induces a severe metabolic imbalance in a sex-specific manner affecting male but not female mice. However, the roles of benzene in the development of aberrant metabolic outcomes following gestational exposure, remain largely unexplored. In this study, we exposed pregnant C57BL/6JB dams to benzene at 50 ppm or filtered air for 5 days/week (6h/day from gestational day 1 to birth) and studied male and female offspring metabolic phenotypes in their adult life. While no changes in body weight or body composition were observed between groups, 4-month-old male and female offspring exhibited reduced parameters of energy homeostasis (VO2, VCO2, and heat production). However, only male offspring from benzene-exposed dams were glucose intolerant and insulin resistant at this age. By six months of age, both male and female offspring displayed glucose and insulin intolerance, associated with elevated expression of hepatic gluconeogenesis and inflammatory genes. Additionally, this effect was accompanied by elevated insulin secretion and increased beta-cell mass only in male offspring. Thus, gestational benzene exposure can reprogram offspring for increased susceptibility to metabolic imbalance in adulthood with differential sensitivity between sexes.

Diabetes Mellitus and Glucose Metabolism

DYSREGULATED METABOLIC RESPONSE

Insertion of a Synthetic Switch Into Insulin Provides Metabolite-Dependent Regulation of Hormone-Receptor Activation

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Insulin signaling requires conformational change: whereas the free hormone and its receptor each adopt autoinhibited conformations, their binding leads to large-scale structural reorganization. To test the coupling between insulin's "opening" and receptor activation, we inserted an artificial ligand-dependent switch into insulin. Ligand binding disrupts an internal tether designed to stabilize the hormone's native closed and inactive conformation, thereby enabling productive receptor engagement. This scheme exploited a diol sensor (meta-fluoro-phenylboronic acid at GlyA1) and internal diol (3,4-dihydroxybenzoate at LysB28). The sensor recognizes monosaccharides (fructose > glucose). Studies of insulin signaling in human hepatoma-derived cells (HepG2) demonstrated fructose-dependent receptor autophosphorylation leading to appropriate downstream signaling events, including a specific kinase cascade and metabolic gene regulation (gluconeogenesis and lipogenesis). Addition of glucose (an isomeric ligand with negligible sensor affinity) did not activate the receptor. Similarly, metabolite-regulated signaling was not observed in control studies of (i) an unmodified insulin analog or (ii) an analog containing a diol sensor in the absence of internal tethering. Although as expected CD-detected secondary structure was unaffected by ligand binding, heteronuclear NMR studies revealed subtle local and nonlocal monosaccharide-dependent changes in structure. Insertion of a synthetic switch into insulin has thus demonstrated coupling between hinge-opening and holoreceptor signaling. In addition to this basic finding, our results provide proof of principle for a mechanism-based metabolite-responsive insulin. In particular, replacement of the present fructose sensor by an analogous glucose sensor may enable translational development of a "smart" insulin analog designed to mitigate risk of hypoglycemia in the treatment of diabetes mellitus.

Diabetes Mellitus and Glucose Metabolism

DYSREGULATED METABOLIC RESPONSE

Liver-Specific Kisspeptin Deletion Impairs Energy Metabolism in Mice