complications. Further studies are necessary to evaluate the effect of the extract on other aspects related to the pathology.

Diabetes Mellitus and Glucose Metabolism

DYSREGULATED METABOLIC RESPONSE

Effects of Sodium Glucose Cotransporter 2 Inhibitor on Renal Renin-Angiotensin-Aldsoterone System

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Objective: The renoprotective effect of sodium glucose cotransporter 2 inhibitor (SGL2i) has been reported in diabetic patients. Local renin-angiotensin-aldosterone system (RAAS) is activated in diabetes mellitus and hypertension. We examined the effects of SGL2i on the RAAS in the obese diabetic rats fed a high salt diet. **Methods:** Zucker-diabetic rats (ZDR) and control rats were fed a high or normal salt diet and were treated with canagliflozin for 8 weeks. Blood pressure (BP), blood glucose (BG), PRA, plasma aldosterone (PAC), urinary albumin excretion (UAE), urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG), gene expression of angiotensinogen in the kidney were measured. **Results:** ZDR febd a high salt diet showed high BP, increased UAE and urinary 8-OHdG and elevated angiotensinogen mRNA levels. Treatment with canagliflozin significantly decreased BP, BG, UAE, urinary 8-OHdG and and renal angiotensinogen mRNA levels compared with control rats (p&lt0.05). **Discussion and Conclusion:** The closer mechanism of renoptotection of SGL2i in diabetes mellitus is unclear. We have reported that the repoprotective effects of type 2 angiotensin receptor antagonist or mineralocorticoid receptor blocker were partly due to the decreased RAAS in the kidney. Decreased renal RAAS by the treatment with canagliflozin may contribute to the renoprotection in DZR.

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DYSREGULATED METABOLIC RESPONSE

Efficient Restoration of Beta Cell Dedifferentiation by Calorie Restriction With High Fat/Low Carbohydrate Diet in Obese Diabetes Model and the Possible Role of GLP-1

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In type 2 diabetes, pancreatic beta cells are gradually 'exhausted' and fall into beta cell dysfunction, which proceeds more severe insulin dependence. Among the proposed mechanisms of beta cell dysfunction such as endoplasmic reticulum stress and oxidative stress, the beta cell heterogeneity has attracted the researcher's interest recently. In 2012, Talchai et al. revealed that the beta cells were dedifferentiated in diabetic mice model, and nowadays it is considered as one form of the beta cell heterogeneity and is observed broadly among diabetic animal models and human patients. Previously we showed that food restriction had the best effect to restore beta cell gene expression in obese diabetic model mice, among the known diabetic treatments which we tested. In the current study, we aimed to unveil the molecular basis in the improvement of beta cell dedifferentiation during the calorie restriction. First, we utilized the high-fat/low carbohydrate diet (HF) or low-fat/high carbohydrate (HC) diet, to determine whether fat restriction or sugar restriction reduces the beta cell dedifferentiation in obese mice. When calorie intake was restricted evenly, both HF diet and HC diet decreased the body weight and hyperglycemia in db/db mice equally. Albeit the same metabolic profile, db/db group fed with HC diet had more enlarged islets and more dedifferentiated beta cell features than db/dbs fed with HF diet, which indicated the compensatory beta cell response in HC diet group. Moreover, HC diet group showed more severe fatty liver than HF diet group, along with the elevated synthesis and accumulation of triglycerides and cholesterol in liver. It is speculated that the insulin resistance in liver might impact on the beta cell dedifferentiation. Next, we analyzed the effect of glucagon-like peptide 1 (GLP-1) on beta cell dedifferentiation, since GLP-1 is secreted more from intestine by protein and fat intake, rather than by sugar intake. Also, increasing number of reports have suggested the improving effect of GLP-1 on beta cell dysfunction and fatty liver. Indeed, GLP-1 administration altered the reduced beta cell/alpha cell ratio in db/db mice, which indicated the restoration of beta cell heterogeneity. We are now investigating if GLP-1 administration reimburse the beta cell dedifferentiation in db/db mice fed with HC diet, to illuminate the role of incretins in beta cell dedifferentiation induced by unbalanced nutrition during diet. Also, we will present the RNA sequencing data of the liver in db/db mice fed with HF and HC diet, to elucidate the key molecules and genes which connect the beta cell function and metabolic state in liver.

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DYSREGULATED METABOLIC RESPONSE

Identification of Sortilin Alternatively Spliced Variants in 3T3L1 Adipocytes

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Type 2 diabetes mellitus (T2DM) is a chronic and progressive metabolic disease with no cure. Adipocytes play a crucial role in glycemic regulation and take up circulating glucose in response to insulin signaling. In T2DM, translocation of major glucose transporter 4 (Glut4) from

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