with partially hydrogenated corn-oil; 2% cholesterol; 20% fructose [HFCF]). Since aHepGHRkd is associated with a reduction in active STAT5b, aHepGHRkd mice were treated with either a hepatocyte-specific adenoviral-associated vector that expresses constitutively active STAT5b (AAV-TBGp-STAT5b^{CA} = STAT5b^{CA}) or a AAV-Null vector. After only 3 months of feeding either the HFS or HFCF diet, aHepGHRkd, but not GHR-intact controls, mice exhibited clear fibrosis, associated with higher levels of plasma alanine aminotransferase (ALT). STAT5b^{CA} treatment of aHepGHRkd mice reduced fibrosis, as well as plasma ALT. Of note, hepatic TG content did not differ between the treatment groups, within diet. Preliminary studies used GC-MS to reveal aHepGHRkd, in the context of HFS diet, increased hepatic fatty acid ratios indicative of enhanced *de novo* lipogenesis, while STAT5b^{CA} reversed this effect. These results suggest GHR/STAT5b may protect against liver injury not by controlling absolute fat accumulation, but by modifying the fatty acid composition of hepatic lipids. Finally, in order to determine if STAT5b^{CA} could also reverse established diet-induced NASH, wild-type mice were fed the HFCF diet for 6 months and then treated with AAV-STAT5b^{CA} or AAV-Null vectors, and followed for an additional 3 months. Preliminary findings show STAT5b^{CA} modestly reduced liver weight with no changes in TG content. However, STAT5b^{CA} prevented the rise in plasma ALT observed in Null-treated controls. Of note, some mice developed hepatic tumors, where the number and size of visible tumors was reduced by STAT5b^{CA}. Importantly, in all models examined thus far, changes in the liver phenotype could not be clearly attributed to changes in systemic metabolism, supporting a direct action of GHR/STAT5b signaling on liver health. Taken together, these results suggest that enhancing hepatocyte STAT5b activity could prevent/treat diet-induced NASH. How STAT5b mediates these effects, and if there are other players involved, remains to be elucidated.

Adipose Tissue, Appetite, and Obesity

NOVEL MECHANISMS CONTROLLING ADIPOSE TISSUE PHYSIOLOGY AND ENERGY BALANCE

Hypothalamic Glucagon Receptors Regulate Feeding in Mice

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Glucagon is an essential regulator of glucose and lipid metabolism. We have reported that chronic glucagon receptor (GCGR) activation with the highly selective, long-acting GCGR-agonist, IUB288, promotes weight-loss by stimulating energy expenditure and suppressing food intake in diet-induced obese (DIO) mice. Thus, novel therapeutics that include glucagon receptor (GCGR) agonism have emerged as promising candidates for obesity and diabetes. GCGR-stimulated energy expenditure is predominately dependent on hepatic GCGR activation; however, the tissue(s) responsible for GCGR-dependent suppression of food intake have yet to be elucidated. Intriguingly, intracerebroventricularly (ICV) injected glucagon acutely suppresses food intake, suggesting neurons expressing GCGR in the brain mediate the anorectic actions of GCGR activation. Hypothalamic neurons express appetitive neuropeptides, sense nutrients in circulation, and respond to peripheral endocrine signals. Studies herein, utilize mice with hypothalamic *Gcgr*-deficiency (*Gcgr*$^{\Delta Hypo}$) to test the hypothesis that peripherally administered GCGR-agonists (e.g. IUB288) reverse obesity via their actions on hypothalamic GCGRs to suppress food intake and concurrent hepatic effects on energy expenditure. *Gcgr*$^{\Delta Hypo}$ and littermate control mice were fasted overnight to stimulate endogenous hunger signals and test for differential food intake upon refeeding. Interestingly, lean, male *Gcgr*$^{\Delta Hypo}$ mice displayed acute hyperphagia in comparison to control littermates. *Gcgr*$^{\Delta Hypo}$ mice also displayed elevated locomotor activity, an increase in the respiratory exchange ratio, and elevated energy expenditure compared to littermate controls. Furthermore, these metabolic alterations are associated with delayed body weight gain and chronic hyperphagia in *Gcgr*$^{\Delta Hypo}$ mice allowed ad libitum access to a high fat diet for 12 weeks. Consistent with our hypothesis, chronic peripheral administration of IUB288 (14d i.p.) suppressed food intake in DIO male control, but not *Gcgr*$^{\Delta Hypo}$, mice. Altogether, these data suggest that hypothalamic GCGRs mediate the anorectic actions of GCGR activation and play a regulatory role in food take. Moreover, these findings suggest that GCGR-based therapeutics may act on both intake and expenditure components of energy balance to combat obesity.

Adipose Tissue, Appetite, and Obesity

NOVEL MECHANISMS CONTROLLING ADIPOSE TISSUE PHYSIOLOGY AND ENERGY BALANCE

Identification of Key Genes and Pathways for Childhood Obesity Using System Biology Approach Based on Comprehensive Gene Information

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Introduction: Childhood obesity is one of the most important public health issues of the 21st century. Epidemiological studies have suggested that obesity during childhood increases the risk of developing comorbidities, such as type 2 diabetes, later in life. Childhood obesity is a complex disease whose molecular mechanisms are not completely elucidated. In this context, a system biology approach could contribute to the scientific knowledge regarding genetic factors related to childhood obesity onset. **Aim:** To identify molecular mechanisms involved in childhood obesity by implementing a system biology approach. **Methods:** Experimentally validated and computationally predicted genes related to Pediatric Obesity (C2362324) were downloaded from the DisGeNET v7.0 database. The protein-protein interaction (PPI) network was constructed using the STRING v11.0 database and analyzed using NetworkAnalyst v3.0 and Cytoscape v3.8.1. The relevance of each node for the network structure and functionality