site significantly decreased the promoter activity in mouse hepatoma cells (Hepa1-6) and mouse primary hepatocytes, and the promoter carrying the mutated HNF-1 site was not transactivated by co-transfected HNF-1 in a non-hepatic cell line. These findings indicated that HNF-1 was essential and critical factor for the basal expression of Angptl8 in murine liver. In fact, knockdown of Hnf-1 using siRNA method in mouse Hepa1-6 and mouse primary hepatocytes reduced Angptl8 protein levels. We also performed Electrophoretic mobility-shift assays and confirmed the direct binding of Hnf-1 to its *Angptl8* promoter binding motif. To elucidate whether refeeding could enhance HNF-1, we checked the expression levels of Hnf-1 in mouse liver. Hnf-1 expression levels of both mRNA and protein were increased after short-term refeeding, paralleling the enhanced expression of the Angptl8. Moreover, insulin-stimulated primary hepatocytes showed increased expression of Angptl8 protein, but knockdown of Hnf-1 completely abolished this enhancement by insulin. Chromatin immunoprecipitation (ChIP) analyses confirmed the recruitment of endogenous Hnf-1 to the *Angptl8* promoter region and it was strongly induced by insulin. Conclusion: HNF-1 plays essential role in hepatocyte-specific and refeeding-induced rapid increases in *Angptl8* expression via insulin.

Adipose Tissue, Appetite, and Obesity

NOVEL MECHANISMS CONTROLLING ADIPOSE TISSUE PHYSIOLOGY AND ENERGY BALANCE

Hepatic GH Receptor Signaling Directly Suppresses Hepatic Steatosis and** De Novo **Lipogenesis, Independent of Changes in Plasma IGF1 and Insulin

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A reduction in GH, as well as IGF1, is associated with non-alcoholic fatty liver disease (NAFLD). However, the relative contribution of changes in circulating GH and IGF1, to hepatic triglyceride accumulation (steatosis), remains to be clearly defined. To study the direct actions of GH on hepatocyte metabolism, we have utilized a mouse model of adult-onset, hepatocyte-specific, GHR knockdown (aHepGHRkd; 10–12 week-old, $GHR^{fl/fl}$ male mice, treated with AAV8-TBGp-Cre). In this and previous reports, we have observed that aHepGHRkd male mice rapidly develop steatosis (after 7 days) associated with enhanced *de novo* lipogenesis (DNL; measured by deuterated H_2O labeling, 10h after 0800h food removal), and low ketone levels, suggestive of reduced hepatic β-oxidation. Of note, aHepGHRkd also reduces plasma IGF1 levels to >80% of GHR-intact controls ($GHR^{fl/fl}$ mice treated with AAV8-TBGp-Null), leading to a rise in GH, due to loss of IGF1 negative feedback to the pituitary/hypothalamus. This reciprocal shift in IGF1/GH is associated with an increase in insulin levels. Therefore, it is possible that the steatosis that develops in aHepGHRkd mice is the consequence of systemic insulin resistance supplying excess substrates (glucose and NEFA) for hepatic lipogenesis. However, inconsistent with this theory is the fact that glucose and NEFA levels are not altered after aHepGHRkd. To tease out the indirect (perhaps driven by high insulin levels) vs. direct effects of GH on hepatocyte lipid accumulation, male aHepGHRkd mice were injected with a vector expressing rat IGF1 (AAV8-TBGp-rIGF1). Reconstitution of hepatocyte IGF1 in aHepGHRkd mice, raised plasma IGF1 and normalized GH, insulin and ketone levels, but hepatic steatosis and DNL remained greater than that of GHR-intact controls, indicating GH directly suppresses hepatic fat accumulation. RNAseq analysis of livers from aHepGHRkd mice showed expression of genes related to carbohydrate metabolism (*Gck*, *Khk*) and fatty acid synthesis (*Fasn*, *Srebf1, Usf1*), processing (*Scd1*) and uptake (*Cd36*) were increased, while genes related to gluconeogenesis (*Pck1, Fbp1, G6pc*) were reduced. Remarkably, IGF1 reconstitution had no major impact on the hepatic transcriptome of aHepGHRkd mice, with the exception of reducing the expression of *Srebf1*, consistent with the reduction in circulating insulin levels. Interestingly, carbohydrate-responsive element-binding protein (CHREBP) levels, but not mRNA levels, were greater in aHepGHRkd mice with or without IGF1 reconstitution, consistent with upregulation of CHREBP target genes (*Khk* and *Fasn* among others). Taken together, these results suggest GH directly regulates steatosis, at least in part, by suppressing carbohydrate-driven DNL, where additional studies are underway to test this hypothesis.

Adipose Tissue, Appetite, and Obesity

NOVEL MECHANISMS CONTROLLING ADIPOSE TISSUE PHYSIOLOGY AND ENERGY BALANCE

HepatocyteGHR/STAT5b Signaling Protects Against Liver Injury in NAFLD/NASH Mice Models Independent of Steatosis

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Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of pathologies ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) that can lead to cirrhosis and hepatocellular carcinoma. Clinical and mouse studies indicate GH-signaling is reduced in NAFLD. We reported that chow-fed mice, with adult-onset, hepatocyte-specific GH receptor knockdown (aHepGHRkd) develop steatosis, and with age, a mild NASH-like phenotype. In the present study, we sought to determine if aHepGHRkd accelerates the development of steatosis and fibrosis in the context of diets shown in wild-type male mice, after 6 months of feeding, to produce mild NASH (60% fat [lard] + sucrose in the drinking water [HFS] or a severe NASH-like phenotype (40% fat,