Growth hormone action on adipose tissue and liver
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Growth hormone (GH) is an important regulator of adiposity. Mouse models with a loss of GH receptor (GHR) function (ghr<sup>−/−</sup>) develop obesity, conversely, bovine GH transgenic mice (bGH) have decreased adiposity. Mutants with abrogated GHR activation of STAT5 (ghr-391) develop obesity in a similar manner to ghr<sup>−/−</sup>. Here we investigate the role of GH in beige induction of inguinal white adipose (iWAT) using these models and the role of GH in preventing hepatic steatosis.

Method: Transcript and protein analysis of bGH, ghr<sup>−/−</sup>, ghr-391 and iWAT determined the beige phenotype of these mouse models. Plasma and tissue analysis was performed for key beige fat inducer, FGF21. Beige cell induction via FGF21 infusion and β3-adrenergic stimulation was tested in GHR mutants and their wt littermates. Beige induction was measured by transcript and protein analysis and histologically. Hepatic transcript and protein levels were determined in ghr<sup>−/−</sup>, ghr391 and liver stat5<sup>−/−</sup> mice. In vitro studies were undertaken in AML-12 mouse hepatoma cells.

Results: The transcript profile of the iWAT revealed decreased beige adipose markers in GHR mutants, but increased in bGH mice. Proteins such as UCP1 and sub-units of the mitochondrial oxidative phosphorylation complex are increased in bGH and decreased in ghr-391. Despite low circulating and local FGF21 in GHR mutants, FGF21 infusion failed to induce beige adipose in ghr<sup>−/−</sup> and ghr-391 mice. β3-adrenergic stimulation was also ineffective.

Deficiency of GH-STAT5 signalling in the liver resulted in increased lipid synthesis and uptake associated with increased expression of ppar gamma.

Conclusions: GH is important in the development of beige fat and the prevention of hepatic steatosis. Mice with a loss of GHR STAT5 activation are unable to induce beige adipose in iWAT stores even with conventional inducers. Ghr-391 mice indicate STAT5 is critical for GH induction of beige cells. Hence GH is essential to maintain lipid metabolic balance via activation of STAT5.

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