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 ($ghr^{-/-}$) 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 $ghr^{-/-}$. 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, $ghr^{-/-}$, 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 *$ghr^{-/-}$*, *ghr391* and liver $stat5^{-/-}$ 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 $ghr^{-/-}$ 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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