Metabolic factors that lead to obesity in mice with complete deletion of somatotrope leptin receptors (somatotrope null LEPR exon 1)

Leptin receptor signaling has been shown to be important for appetite control, energy expenditure, and development. Our lab is interested in the role of leptin in pituitary somatotrope regulation. Mice with somatotrope-specific deletion of exon 17 of the LEPRb isoform, which encodes the JAK binding site, grow normally but are growth hormone deficient (GHD) and obese as adults (Childs et al, 2011). The present study tested mice with somatotrope-specific deletion of exon 1 of LEPR to determine if loss of all isoforms of the receptor (Cohen et al, 2001) would produce a more significant phenotype.

Homozygous floxed exon 1 LEPR mice (J. Friedman) were crossed with mice bearing Cre-recombinase driven by rGH promoter (R. Kineman; Luque et al, 2007). Organ genotyping showed no evidence of extra-pituitary Cre-recombinase. Somatotrope LEPR Exon 1-null deletion mutants grew normally but showed evidence of increased abdominal fat mass by MRI as early as 2 months, before they exhibited increased body weight. Percentages of immunolabeled growth hormone cells were reduced by 34.2% in deletion mutants. To evaluate the metabolic status of the mice before they became obese, mutant and littermate control male mice were placed in a Comprehensive Laboratory Animal Monitoring System (CLAMS; Oxymax, Columbus Instruments). At 2.5-4 months of age, pre-obese deletion mutant males had significantly higher respiratory quotients (p<.0342) and were less active in both dark (19% lower, p<.006) and light (16% lower, p<.017) cycles. Mutants ate 21% more food/feeding bout than controls during the dark cycle (p< .003), but not more food overall. Serum leptin was within the normal range for control mice. Sleep analyses showed that mutants sleep 30% less overall (p<.032) with no difference in the dark phase but 37% lower in the light phase (p<.019). In addition, serum assays (Millipore) showed 25% increases in adiponectin (p< .048) which is produced by adipocytes, and is a sign of adipogenesis. In addition, the lipogenic protein, glucose dependent insulinotropic peptide (GIP) was significantly increased (by 57%, p<.032). The proinflammatory cytokine, interleukin-6 (44%, p<.024) was lower, which correlates with higher adiponectin. The enhanced carbohydrate oxidation (RQ), lower activity and disrupted sleep are primary contributors to the increased fat mass. The findings indicate the importance of leptin signaling to somatotropes as they optimize body composition.

References: Childs GV et al., Endocrinology 2011; 152:69
Luque RM, Endocrinology 2007; 148:1946

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