TRANSGENIC UNACYLATED GHRELIN OVEREXPRESSION MODULATES ADIPOCYTE ACTIN CYTOSKELETON REMODELLING AND EXPANSION IN HIGH-FAT DIET INDUCED OBESITY IN MICE

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Background and Aims: Adipose tissue is key player in the development of obesity and obesity-related complications. Recent evidence shows that adipocyte size regulation through actin cytoskeleton remodeling is mechanistically interlinked with disrupted cell metabolism, including reduced mitochondrial function and insulin signaling. The unacylated form of the hormone ghrelin (UnAG) is a novel whole-body and tissue-specific metabolic modulator. Its impact on adipocyte expansion and metabolism is unknown.

Methods: We investigated the effect of cardiac transgenic UnAG overexpression (Tg; 30-fold increase in plasma UnAG) vs. wild type (Wt) on body weight gain, adipose tissue (epididymal pads) mass, adipocyte size (average area and frequency distribution) as well as actin-mediated remodeling machinery (Arp2, Cofilin1, Profilin2, by western blot) in male 6 week-old mice fed with high-fat (HF; 60% fat) or control diet (Con) for 16 weeks (n=6/group).

Results: HF-induced body weight gain and adipose tissue mass were comparable between TgHF and WtHF, as was cumulative food intake (all p=NS). However, HF-induced increase in actin-mediated remodeling machinery markers was completely prevented (Cofilin1 and Profilin2) or markedly reduced (Arp-2; $p<0.05$) in Tg mice. In excellent agreement, TgHF had lower increase of adipocyte size ($p<0.05$), which was in fact comparable to WtC (p=NS).

Conclusions: While not affecting obesity-associated fat mass, in mouse adipose tissue UnAG overexpression importantly prevents obesity-induced actin cytoskeleton remodeling activation and adipocyte expansion, with the potential to negatively modulate adipose tissue metabolic derangements. These findings support the hypothesis that UnAG could potentially lower the risk of metabolic complications in obese patients.