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Title: A Novel Human Peptide that Reduces Adipocyte Uptake of Long Chain Fatty Acids

ABSTRACT: Obesity and its co-morbidities, including insulin resistance, type 2 diabetes, fatty liver, and the metabolic syndrome, have reached epidemic proportions. Our translational obesity research program has long been interested in alterations of fatty acid transport and metabolism in these conditions, and in differences in gene expression between obese and normal fat that explain these alterations. We recently used whole genome microarrays to identify individual genes and biological pathways the expression of which is altered in omental and subcutaneous fat samples from obese patients. Of the ca. 55,000 human genes and ESTs queried in these experiments, the one with the most highly regulated expression in obese fat was Spexin, a novel peptide of unknown function, the expression of which had not previously been reported in fat. We found that Spexin message is highly expressed in omental & subcutaneous fat from normal weight patients, but is greatly reduced (~15-fold) in obese fat samples ($p<0.00292$). Serum Spexin peptide levels are approximately 10X lower in obese than in non-obese patients ($p<0.0002$), and Spexin and Leptin levels in sera from obese patients & normal weight controls are strongly negatively correlated ($r=-0.92$). When administered at 10 µg/ kg body weight/day IP to C57BL/6J mice, Spexin reduced food consumption, body weight and adipocyte uptake of fatty acids in mice with HFD-induced obesity, while control HFD mice continued to gain weight. Lower doses virtually abolished weight gain on this diet. Preliminary metabolic studies in rats and mice suggest that Spexin increases locomotor activity and energy expenditure while decreasing food intake, without disturbing normal diurnal feeding patterns and in the absence of any evidence of toxicity. These results lead us to hypothesize (1) that Spexin plays a key role in the regulation of feeding behavior and body weight; and (2) that the absence of Spexin expression in the obese state is associated with increased food consumption, adipocyte uptake of fatty acids, and weight gain in HFD-fed obese mice. The long-term objective of this proposal will be to better define the mechanisms by which Spexin induces weight loss, and to evaluate its potential as an agent for treatment of obesity.

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