

## Adipose Tissue, Appetite, and Obesity INTEGRATED PHYSIOLOGY OF OBESITY AND METABOLIC DISEASE

### *Weight Loss With a Novel Peptide YY Analogue for Obesity: A Randomised, Placebo-Controlled Phase I Trial*

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**Background:** Obesity and its co-morbidities remain a prime driver of global morbidity and mortality. Current therapies for obesity are limited in efficacy and durability, have serious adverse effects or are not scalable to the numbers required to treat this widespread disease. Gut hormones such as peptide YY (PYY) have emerged as candidate therapies for obesity which activate natural satiety pathways, reduce food intake and therefore body weight. We report the results from a Phase I trial of a PYY analogue, Y14, in overweight volunteers. **Methods:** In a first time in human Phase I randomized placebo-controlled trial, an extended-release formulation of Y14 with zinc chloride for subcutaneous injection, utilizing various Zn:peptide molar ratios, was tested. Part A of the trial was a partially blinded single ascending dose study. Part B was double-blinded and tested multiple ascending doses given at 7–14 day intervals over the course of 28 days with up to 5 doses given per subject. The primary outcome was the safety and tolerability of extended-release Y14; the secondary outcome was to assess its pharmacokinetics. Exploratory outcomes included the assessment of food consumption, body weight and glucose tolerance in response to 75g oral glucose load after multiple doses of Y14. [ClinicalTrials.gov NCT03673111]. **Findings:** Between Apr 11, 2017, and Dec 24, 2018 44 participants were enrolled into Part A of the trial and 24 into Part B and were included in the full analysis and safety datasets. The multiple doses of Y14 given in Part B led to significant mean placebo-subtracted reductions in body weight of 2.76 to 3.59 kg at 31 days after the first dose, in association with profound reductions in food intake and no evidence of tachyphylaxis. No significant changes in glucose tolerance were detected. The most common adverse events were nausea, vomiting and injection site reactions. No serious adverse events occurred. The pharmacokinetic characteristics of extended-release Y14 were compatible with administration every 7–14 days. **Interpretation:** Our results support the continued development of Y14 as a novel treatment for obesity. **Funding:** UK Medical Research Council Developmental Pathway Funding Scheme.

## Adipose Tissue, Appetite, and Obesity NOVEL INSIGHTS FROM THE CLINIC INTO THE DEVELOPMENT OF METABOLIC DISEASE: CASE REPORTS

### *A Novel Variant of the SH2B1 Gene in an Obese Child With Type 2 Diabetes*

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Obesity in children and adolescents is at epidemic levels in the United States and creates high risk for comorbidities later in life. Childhood obesity is thought to be the result of behavioral and nutritional problems. Although genetic factors may play a role in the etiology of obesity, monogenic forms of obesity are rare. We present a child with obesity, behavioral problems, leptin resistance, and type 2 diabetes who also carries a mutation of Sarcoma Homologous 2B adapter protein 1 (SH2B1). The subject was evaluated at 13 <sup>7</sup>/<sub>12</sub> years old. He had polyphagia, learning disability, aggressive behavior and marked obesity. At ages 9, 11, and 13 years respectively, his BMI was 9%, 16%, and 52% above the 95<sup>th</sup> percentile. At 13 <sup>7</sup>/<sub>12</sub> years old, his height was at the 80<sup>th</sup> percentile and BMI was 66% above the 95<sup>th</sup> percentile. He had marked acanthosis nigricans and he was prepubertal. Fasting blood glucose and insulin levels were 116 mg/dl and 592 mIU/L, respectively. Hemoglobin A1c was 6.5% and metformin therapy was initiated for type 2 diabetes. Fasting leptin level (41.5 ng/mL) was markedly elevated indicating leptin resistance. DNA methylation study excluded Prader-Willi syndrome. DNA sequencing indicated a novel heterozygous c.1555G>T variant of SH2B1 gene, which is predicted to result in the amino acid substitution p. Asp519Tyr. The analysis by PolyPhen-2 and MutationTaster predicts that the variant is a pathogenic mutation affecting protein functions. SH2B1 interacts with JAK2 and may play a role in insulin signaling. Pathogenic heterozygous variants in SH2B1 have been associated with obesity, insulin resistance and maladaptive behavior phenotypes (Pearce et al, 2014). *Sh2b1-null* mice develop severe leptin resistance, obesity, and type 2 diabetes. Our report underscores the importance of investigating monogenic causes of obesity in subjects who present severe obesity, diabetes, and behavioral problems. Additional studies are needed to determine the association between this novel mutation and the clinical features of this patient.

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### *Acquired Brain Injury-Induced Hyperphagia and Obesity, Successfully Treated With a GLP-1 Agonist*

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**Background:** Several Glucagon-like peptides 1 (GLP-1s) were approved since 2005 for the treatment of DM & obesity. Their usefulness in other conditions is not well studied. We present two cases of hyperphagia after TBI successfully treated with GLP-1 agonists. **Clinical cases:** **Case 1:** A 54-year-old female with a history of multiple