Effects of Growth Hormone on Metabolism and Satiation in Prader-Willi Syndrome: Translational Research in Prader-Willi Syndrome and Obesity – Part 3.

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Introduction
Prader-Willi syndrome (PWS) is a neurodevelopmental syndrome associated with early-onset obesity. Phenotypic features of PWS include infantile hypotonia, mental retardation, short stature, hypogonadism, and hyperphagia with resultant obesity. A majority of PWS patients have lacked satiety with an insatiable appetite. Approximately 70% of PWS cases are due to a genetic deletion on chromosome 15 (15q11-13), 25% of PWS cases are from a maternal uniparental disomy (UPD) of chromosome 15, and the remaining cases result from genetic imprinting defects. Obesity in PWS patients contributes to their risk for obesity related physical ailments, such as cardiovascular disease, Type 2 diabetes mellitus and hyperlipidemia. PWS is one of the most commonly recognized genetic causes of obesity, and obesity is the most significant health problem in affected individuals. Individuals with PWS usually have growth hormone deficiency. Growth hormone was FDA-approved for use in individuals with PWS in 2000. Growth hormone therapy for PWS individuals has dramatic effects, including an increase in linear growth, muscle mass, and fat utilization, as well as a decrease in total body fat. The hyperphagia component of PWS has been refractory to psychopharmacologic intervention

Experimental
Research subjects will arrive at the NIH funded General Clinical Research Center (GCRC) the night before their study. A complete history and physical examination will be performed, including measurement of weight and height, pregnancy test, and further assessment made as to the presence of any exclusion criteria. Subjects will also be habituated to the MRI scanning procedures by having an anatomical MRI scan (using GE 3.0 Tesla scanner in the McKnight Brain Institute) to exclude any gross neuroanatomical pathology. Subjects will have two fMRI studies (in both fasted and fed states) on two separate days (day 3 and day 5) with a rest day in-between (day 4). The two study days will differ in the caloric size of the meal given (small or large), equal to either 33% (estimated as between 400 and 650 kCal depending on size and sex or 100% of the REE, in a randomized cross-over order.

Results and Discussion
Statistical parametric maps were generated to graphically depict differences between the food versus rest condition for each participant group (Fig 1). Figure 1 shows the regions of activation along with voxels in other regions (eg, visual cortex) with t-score thresholds exceeding 4. Individuals with PWS demonstrated a markedly larger prefrontal cortex response to food pictures than normal weight controls in both the fasting and fed states on the day of the small breakfast. The focus of the BOLD activation in individuals with PWS was more anterior and medial than observed for control participants, whose activity bordered the lateral prefrontal cortex. There was no significant difference between PWS and controls after the large breakfast.

Figure 1. BOLD activation in controls vs. PWS. Individuals with PWS had greater BOLD activation when viewing food pictures than controls in fasted state and after a small breakfast.

Conclusions
Individuals with PWS have a greater BOLD response to food pictures in the fasting state and following a typical-size meal. However, we are able to attenuate the response with a larger meal, suggesting that individuals with PWS have a relative resistance to peripheral satiety signals compared to normal weight individuals. We are measuring hormonal mediators of hunger/satiety and will determine which of these values change between the small and large meals to determine which hormones are the most important in decreasing the appetite of individuals with PWS.

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