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Romanian Prader-Willi Association

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NEUROENDOCRINE MECHANISMS IN PWS PHENOTYPES

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Many of the characteristic PWS phenotypes have a neuroendocrine basis, including genital hypoplasia at birth; childhood development of obesity and then profound hyperphagia (between ages of 1 and 6 years) leading to progressive morbid obesity into adulthood; short stature due to GH deficiency and (predominantly hypothalamic) hypogonadism with incomplete delayed puberty and infertility; developmental delay with mild to moderate mental retardation, abnormal sleep patterns and hypersomnolence.

PWS subjects have delayed meal termination and earlier meal initiation and return of hunger after the previous meal. Given free access to food, PWS subjects will consume approximately three times that of control subjects. The reduced satiation in PWS occurs despite delayed gastric emptying which would be expected to produce the opposite effect.

Subjects with PWS may have marked elevations in the appetite-stimulating stomach-derived hormone ghrelin, for their obesity, though plasma levels do fall appropriately after food. This appears at least partly explained by their preserved insulin sensitivity and relative hypoinsulinaemia, related to reduced visceral adiposity. A role for hyperghrelinemia in the hyperphagia of PWS has yet to be proven. Acute normalisation of ghrelin levels with somatostatin does not reduce food intake in PWS, and chronic studies with longer-acting analogues are ongoing.

For their obesity, subjects with PWS have normal fasting and post-prandial plasma levels of the anorexigenic hormones leptin, PYY, GLP-1 and CCK, and other gut hormones, such as gastrin and GIP. This suggests the absence of a global defect in gut hormone secretion or autonomic efferents to end organs. However, fasting and post-prandial levels of the anorexigenic hormone pancreatic polypeptide (PP) are reduced in PWS.

In addition to these hormonal abnormalities that might contribute to hyperphagia in PWS (hyperghrelinemia, PP deficiency and hypoinsulinaemia), there are likely to be overriding brain defects, particularly hypothalamic, which lead to disordered appetite. The volume and number of oxytocin neurons of the paraventricular nucleus is decreased in post-mortem hypothalami from patient with PWS. No abnormalities in neuropeptide Y, agouti-related protein, pro-opiomelanocortin, growth hormone-releasing hormone, melanin-concentrating hormone receptor 1, or orexin neurons have yet been found that could explain PWS phenotypes.

Recent functional neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) in PWS have revealed abnormal brain activation patterns in corticolimbic structures, such as the amygdala, pre-frontal, orbitofrontal and insula cortex, at rest or in response to food stimuli. These suggest abnormal reward and motivational responses to food that may also contribute to the hyperphagia in PWS. Detailed MR scanning including techniques such as diffusion tensor imaging are also revealing neuroanatomical abnormalities within extra-hypothalamic brain structures in PWS that may play a role in cognitive, behavioural and neuroendocrine phenotypes.

The presence of relative rather than absolute resistance to peripheral satiety signals, and defects within extra-hypothalamic brain structures raises the intriguing possibility of novel therapeutic avenues for PWS, particularly in reducing hyperphagia in PWS.