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# Metabolic Parameters and Orexigenic/Anorexigenic Factors of Obesity in Prader-Willi Syndrome

Elena Bogova\*, Natalya Volevodz, Valentina Peterkova and Ilin Alexander

Endocrinology Research Centre, Institute of Pediatric Endocrinology, Moscow, Russian Federation

\*Corresponding author: Elena Bogova, Endocrinology Research Centre, Institute of Pediatric Endocrinology, Moscow, Russian Federation, Tel: +7-925-882-05-48; E-mail: eabogova@gmail.com

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## Introduction

Prader-Willi syndrome (PWS) is a complex multisystem genetic disorder that arises from lack of expression of paternally inherited imprinted genes on chromosome 15 [1]. PWS is the most frequent cause of syndromic obesity occurring in 1 out of 10000–30 000 live births [2]. It is a neurodevelopmental disorder, characterized by neonatal hypotonia and failure to thrive, followed by a rapid weight gain between the ages of 1 and 6 years, leading most PWS subjects to develop morbid obesity and therefore premature mortality from its complications. The PWS phenotype includes multiple characteristics, most of which are central of origin (temperature dysregulation, high pain threshold, behavioral abnormalities, hypothalamic hypogonadism, growth hormone deficiency, central hypothyroidism, central adrenal insufficiency). Obesity, mostly due to an insatiable appetite, represents one of the most serious symptoms of PWS, leading to develop premature mortality from its complications. Therefore, we tried to investigate more deeply distinctive features of obesity and appetite regulation in PWS patients.

We evaluated metabolic parameters of obese children with genetically confirmed PWS who were non-treated with growth hormone (GH) and compared the data with age, sex and BMI-matched non-PWS obese controls (OC). We also measured levels orexigenic (increasing appetite) and anorexigenic factors (decreasing appetite) to understand their role in PWS. It is assumed, that 'PWS region' (15q11-q13) contains genes, which are overly expressed in the hypothalamus and encode for proteins critical to brain development, function and also the appetite regulation. The mechanism of satiety/hunger is under neuroendocrine control of central and peripheral peptides (Figure 1).

## Subjects and Methods

17 obese (BMI SDS=3,66 [2.99 ÷ 4.57]) non-treated with GH children with PWS (6 boys, 11 girls) at a median age of 9,9 years

[6.5 ÷ 13,9] were compared with 15 obese children (OC) of similar age (9.8 [6.5 ÷ 12.0] years), gender (4 boys, 11 girls) and BMI (3.21 [2.76 ÷ 3.62] SDS). All children included in the study were pre-pubertal (Tanner stage 1).

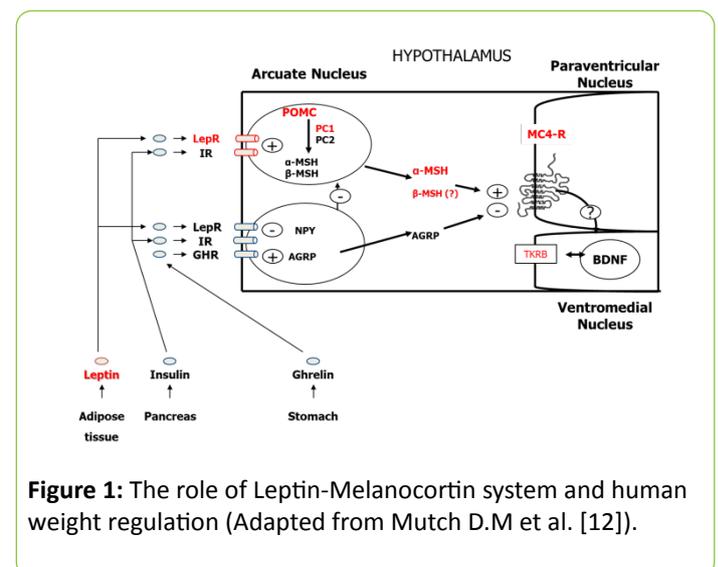


Figure 1: The role of Leptin-Melanocortin system and human weight regulation (Adapted from Mutch D.M et al. [12]).

PWS patients were genetically confirmed (methylation-specific PCR). Subjects with chronic secondary illnesses such as diabetes mellitus, liver or kidney disease or active malignancy, or those taking investigational drugs were excluded. Subject characteristics and comparisons are shown in Table 1.

Physical examination included determination of height and weight. Standing height was determined by a Harpenden Stadiometer (Holtain Limited, Crymych, Dyfed, UK).

Body weight was measured to the nearest 0.1 kg, by using a standard equipment. BMI was defined as weight in kilograms divided by the square of height in meters. Standards for age- and gender-specific height (Tanner J.M, Whitehouse R.H, 1976) and BMI percentiles (Cole T.J., 2000) were used for a calculating

standard deviation score (SDS) as well as for classifying the children as non-obese (BMI<2.0 SDS) or obese (BMI>2.0 SDS).

**Table 1:** Characteristics of PWS and OC.

Characteristics	PWS (n=17)	OC (n=15)	p
Age (years)	9.9 [6.5 ÷ 13.9]	9.8 [6.5 ÷ 12.0]	p=0.82
Males/females	06/11	04/11	p=0.85
Tanner stage	1	1	p=0.4
SDS BMI	3.66 [2.99 ÷ 4.57]	3.21 [2.76 ÷ 3.62]	p=0.2
SDS height	-0.02 [-1.29 ÷ 0.49]	1.74 [1.06 ÷ 2.65]	p=0.0001*
Fat mass (%)	53.05 [48.75 ÷ 56.5]	42.2 [40.5 ÷ 45.0]	p=0.04*
Lean mass (%)	46.95 [43.5 ÷ 51.25]	57.8 [55.0 ÷ 59.5]	p=0.04*

All blood samples were collected in the morning after a 12-h overnight fast. Laboratory measurements included serum glucose, leptin, insulin, insulin-like growth factor 1 (IGF-1), lipids (total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides), aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting and postprandial serum brain-derived neurotrophic factor (BDNF) and plasma ghrelin. Insulin and IGF-1 concentration was measured by chemiluminescent immunometric assay, using Cobas 6000 (Roche) and Liaison (Dia Sorin) analyzers. Leptin levels were determined by enzyme immunoassay using. Homeostasis model insulin resistance index (HOMA-IR) was calculated using fasting insulin and glucose concentrations (fasting glucose x fasting insulin/22,5). Fasting and postprandial (on 60 min and 120 min) plasma total ghrelin and serum BDNF levels were measured during mixed meal testing (370 kcal: 20% protein, 50% carbohydrate and 30% fat), using commercial enzyme

immunoassay kits (Phoenix Pharmaceuticals inc. and R&D systems). Blood samples for ghrelin evaluation were collected in EDTA-containing vacutainer tubes with aprotinin and stored at 70 C up to 1 month.

Body composition was evaluated by dual-energy X-ray absorptiometry (DEXA).

Statistical analyses were performed by using Statistica for Windows v.8.0. Data are presented as the median and interquartile range. Manne-Whitney test used for comparing 2 groups. P values at the standard 0.05 level were used to determine the statistical significance.

## Results

The details of the patients' measurements are described in Table 2.

**Table 2:** Measurements of PWS and OC.

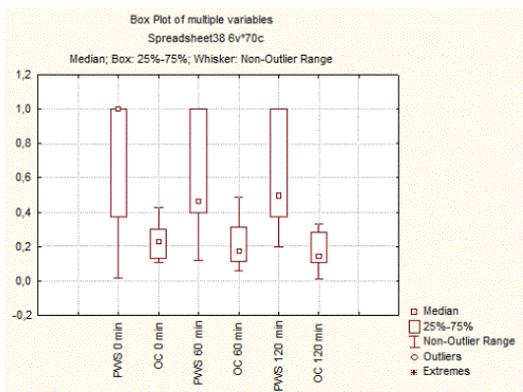
Characteristics	PWS (n=17)	OC (n=15)	p
Leptin (ng/ml)	85.05 [43.7 ÷ 117.45]	37.2 [27.7 ÷ 44.90]	p=0.02*
IGF-1 (ng/ml)	84.5 [52.7 ÷ 173.3]	238.2 [221.9 ÷ 323.8]	p=0.0003*
Insulin (U/l)	9.7 [5.4 ÷ 15.45]	12.6 [8.2 ÷ 18.5]	p=0.38
Glucose (mmol/l)	4.55 [4.0 ÷ 5.0]	4.75 [4.2 ÷ 5.1]	p=0.37
HOMA-IR	1.44 [1.04 ÷ 2.05]	2.74 [1.9 ÷ 3.95]	p=0.01*
Cholesterol total (mmol/l)	4.9 [4.3 ÷ 5.6]	4.06 [3.7 ÷ 5.1]	p=0.08
LDL (mmol/l)	3.18 [2.45 ÷ 4.0]	2.8 [2.0 ÷ 3.1]	p=0.13
HDL (mmol/l)	1.1 [0.87 ÷ 1.5]	0.97 [0.88 ÷ 1.2]	p=0.42
Triglycerides (mmol/l)	0.8 [0.7 ÷ 1.1]	1.05 [0.95 ÷ 1.25]	p=0.07
ALT (U/l)	25.75 [18.0 ÷ 42.7]	18.15 [18.0 ÷ 22.0]	p =0.1
AST (U/l)	27.0 [24.5 ÷ 36.15]	23.5 [21.0 ÷ 25.0]	p=0.05

When compared to OC, PWS children of similar age, sex and BMI had lower height SDS (-0.02 [0.49 ÷ 1.78] vs. 1.74 [1.06 ÷ 2.65], p=0.0001) and IGF-1 levels (84.5 [52.7 ÷ 173.30] vs.

(238.2 [221.9 ÷ 323.8], p=0.0003). Body composition studies showed increased body fat in PWS children in comparison with control group of OC (53.05 [48.75 ÷ 56.5] vs. 42.2 [40.5 ÷ 45.0]%,

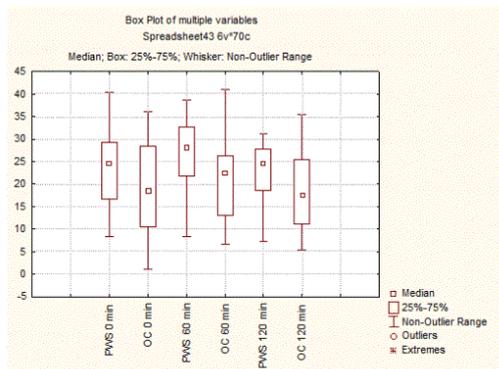
$p=0.04$ , respectively), and decreased lean mass (46.35 [42.7 ÷ 49.85] vs. 57.80 [55.0 ÷ 59.5]%,  $p=0.04$ ). Relative to OC, leptin levels were nearly 2-fold higher in PWS (85.05 [43.7 ÷ 117.45] vs. 37.2 [27.7 ÷ 44.9] ng/ml,  $p=0.02$ ); in contrast, there were no significant differences in total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, AST, ALT levels between two groups. HOMA-IR was lower in PWS compared with OC (1.44 [1.04 ÷ 2.05] vs. 2.74 [1.9 ÷ 3.95],  $p=0.01$ ), suggesting that PWS children are more insulin sensitive.

Fasting ghrelin concentration (1.0 [0.5 ÷ 1.0] vs. 0.23 [0.13 ÷ 0.30] ng/ml,  $p=0.028$ ) and postprandial ghrelin levels on 60 and 120 min (0.47 [0.4 ÷ 1.0] vs. 0.18 [0.11 ÷ 0.31],  $p=0.00039$  and 0.5 [0.37 ÷ 1.0] vs. 0.14 [0.11 ÷ 0.28] ng/ml,  $p=0.000025$ ) were significantly higher in PWS children in comparison with OC (Figure 2).



**Figure 2:** Fasting and postprandial ghrelin levels (ng/ml) in PWS and OC during mixed meal test.

There were no significant differences in basal (22.8 [15.7 ÷ 29.19] vs. 18.42 [10.40 ÷ 28.50] ng/ml,  $p=0.54$ ) and postprandial anorexigenic BDNF levels on 60 and 120 min between PWS and OC (27.7 [21.4 ÷ 30.27] vs. 22.53 [13.02 ÷ 26.20],  $p=0.43$  and 24.62 [18.56 ÷ 27.75] vs. 17.53 [11.08 ÷ 25.50] ng/ml,  $p=0.21$ ) (Figure 3).



**Figure 3:** Fasting and postprandial BDNF levels (ng/ml) in PWS and OC during mixed meal test.

## Discussion

We measured the levels of orexigenic (ghrelin) and anorexigenic factors (leptin, BDNF) in children with PWS and OC with “simple obesity”. PWS patients showed higher fasting and postprandial levels of ghrelin than OC, that might contribute to their hyperphagia and high level of adiposity. Ghrelin is the only known peripheral orexigenic peptide, that stimulates food intake, adipose tissue lipogenesis and inhibits lipid oxidation. It is produced primarily in the stomach and is thought to be a meal initiator: its concentration rises before feeding and decreases to a minimum one-hour after eating. Elevated ghrelin concentrations in PWS patients have been reported in previous studies [3,4], but the results in children are controversial [5,6]. The cause of hyperghrelinemia in PWS is unclear. There are data, suggesting that PWS patients have the increased number of ghrelin-expressing cells in gastric tissue [7]. In addition, relative hypoinsulinemia and/or increase in insulin sensitivity may act as an additive signal to enhance hyperghrelinemia in PWS (as insulin has an inhibitory role on ghrelin secretion) [8]. In our study we found that insulin sensitive index HOMA was higher in patients with PWS than in OC. Proposed reasons for increased insulin sensitivity in PWS include relative lower amounts of visceral fat and growth hormone deficiency. In turn, hyperghrelinemia can promote the different glucoregulatory mechanisms in PWS patients (decreased insulin secretion and increased insulin sensitivity) [9].

The concentration of anorexigenic hormone leptin was higher in patients with PWS in comparison with OC. As is known, leptin is secreted from fat cells (adipocytes) in direct proportion to the amount of stored fat. Therefore, the observed hyperleptinemia reflects the high level of adiposity in patients with PWS [10]. Body composition study showed increased body fat and decreased lean mass in PWS children in comparison with OC, which in combination with short stature and low IGF-1 suggests that PWS patients are growth hormone deficient.

The brain-derived neurotrophic factor (BDNF) is a central anorexigenic factor, known to influence growth, development and survival of neurons and appears to function downstream of the leptin-melanocortin signaling pathway to control appetite (Figure 1). In both animals and humans, diminished BDNF function is associated with hyperphagia and obesity. Hunger suppresses BDNF gene expression in the hypothalamus, whereas feeding does the opposite. BDNF is produced mainly by central nervous system and platelets serve as a reservoir. BDNF peripheral circulation is believed to reflect cerebral BDNF output [11]. We didn't find any difference in the levels of fasting and postprandial BDNF between PWS and OC. However, in the work by Joan C. Han et al. PWS children had lower peripheral BDNF compared to OC, and the authors concluded that BDNF insufficiency could be the potential cause for PWS hyperphagia [12]. The difference in BDNF levels between studies could be associated with leptin content. Leptin levels were similar between PWS and OC in Joan C. Han study in contrast with the observed hyperleptinemia in PWS children in our work. It is known that leptin activates hypothalamic BDNF-expression, so not decreased levels of BDNF in our group of PWS patients could be connected with high leptin content, reflecting their adiposity.

Various peptides and hormones have been studied in patients with PWS, but still there is no precise concern about the mechanism of PWS hyperphagia. Probably not one, but many factors could play a role in heightened appetite of PWS patients.

## Conclusions

Observed PWS children have short stature, low IGF-1 levels and abnormal body composition with increased body fat and decreased lean body mass, resembling patients with growth hormone deficiency. Leptin levels in PWS children are higher than in OC, reflecting the degree of adiposity. HOMA-IR was lower in PWS compared with OC, suggesting that children with PWS are more insulin sensitive than patients with «simple obesity». This could suggest a different role of insulin in the pathogenesis of metabolic alterations in PWS as compared to simple obesity. Fasting and postprandial orexigenic ghrelin levels are significantly higher in PWS children compared to obese controls, indicating the presence of intrinsic hyperphagia in patients with this syndrome. There are no significant differences in basal and postprandial anorexigenic BDNF levels between PWS children and OC, however further research is needed to clarify the role of BDNF and its receptor in weight reduction, energy expenditure, and appetite control in PWS.

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