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Growth hormone induced lipolysis during short- and long-term administration in adult Prader–Willi patients

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Abstract

Prader–Willi syndrome (PWS) is a complex genetic disease, clinically characterised by short stature, abnormal body composition, with more body fat than lean body mass, hyperphagia and obesity. Partial growth hormone (GH) deficiency is common, and GH treatment to PWS children and adults has shown beneficial effects on body composition. In this study, we have evaluated indices of GH's lipolytic effect in 6 PWS adults analysing glycerol, lactate and glucose in dialysate from microdialysis in subcutaneous abdominal adipose tissue. The patients were four men and two women, 19–37 years old; all hypogonadal. BMI was 24.2–49.1, mean 35.9 kg/m^2. All had normal serum insulin levels. They received GH therapy (Genotropin® Pfizer) during 12 months and doses were individually titrated to normal serum IGF-I for age. Immediately before treatment start and at 12 months, 30–36 h after the last GH injection, sampling of dialysate was carried out at night (11 p.m. to 7 a.m.), as well as after intravenously injection of a standardised GH dose (0.8 mg). At baseline individual mean night time glycerol and lactate were similar to levels in adults without PWS (160.7–278.1 μmol/L and 0.80–3.99 mmol/L, respectively), and did not change with 12 months GH treatment. Glucose levels were normal, except in a patient with diabetes, and did not change during the study. Compared to baseline the immediate effect of GH injection resulted in a significant increase in glycerol levels after 12 months. In conclusion, night time lipolytic response in this small group of PWS adults seemed normal and did not change after 12 months GH treatment. On the other hand short-term GH induced lipolysis increased, indicating normal lipolytic response in PWS.

Keywords: Prader–Willi syndrome; Adults; Lipolysis; GH treatment

1. Introduction

Prader–Willi Syndrome (PWS) is a congenital disorder, caused by non-functioning paternal genes in the region q11–13 on chromosome 15 [1]. The prevalence is 1/15.000–1/20.000 newborns. Some of the physical signs include hypogonadism, reduced height and abnormal body composition with reduced lean body mass and increased body fat – the latter often aggravated by excessive eating [1,2]. Most patients have a mild to moderate intellectual disability; and behavioural problems – increasing with age – are common.

Treatment with growth hormone (GH) in children with PWS has not only resulted in improved longitudinal growth, but also an even more impressive positive effect upon body composition [1]. Also in adult PWS, GH treatment has been shown to increase lean body mass and reduce body fat [3]. GH is known to possess very strong lipolytic actions in normal as well as in GH deficient (GHD) subjects [4–7]. This action is most likely

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crucial for the above mentioned beneficial effects observed in the clinic.

Very little is known about the metabolic actions of GH in PWS. Therefore, we decided to study indices of lipolysis in abdominal subcutaneous adipose tissue by means of microdialysis. The aims were to study lipolysis during the night as well as the response to a standardised iv GH injection given in the morning. Investigations were carried out both at baseline and after 12 months of subcutaneous (sc) GH treatment daily.

2. Patients and methods

2.1. Patients and study protocol

The patients were all part of a clinical trial concerning GH's effects in 17 adult PWS [2,3].

Microdialysis was performed as part of the experimental protocol. However, the experimental procedure as described below turned out to be technically and practically difficult in this particular patient group, and incomplete sampling was unfortunately rather frequent. Complete datasets, including full night time and post-GH administration metabolic profiles both before and at 12 months, were available in six patients. It was decided to base the statistical analysis on these patients only. The six patients were four men and two women, 19–37 years old; BMI was 24.2–49.1 kg/m^2. Percent body fat was 40.1–59.1, and serum IGF-I levels 62–173 μg/L (−4.4 to −1.8 SD-scores). All had hypogonadism. The characteristics of the patients are given in Table 1.

All six patients had PWS genotype confirmed with positive methylation test [2], and all had been on a strict diet of 1000 kcal/day for several years. One woman, age 37 years had hyperglycemia and heart failure. GH (Genotropin®, Pfizer Corporation) was given in daily sc injections in the evening and doses were titrated individually to IGF-I levels in healthy subjects of the same age. The GH dose was 1.6 IU/day (0.53 mg) in five patients and 2.4 IU/day (0.8 mg) in one patient at the end of the treatment period.

The study was approved by the Ethics Committee of the Karolinska Institute, Stockholm, Sweden. The patients and their guardians gave their oral and written consent.

2.2. Microdialysis

Microdialysis was evaluated before and after 12 months of GH treatment.

Microdialysis is a sampling technique of substances from the extra cellular fluid [8–10]. Its principle is based on diffusion. The microdialysis probe (CMA, Microdialysis AB, Stockholm, Sweden) has a double lumen plastic cannula, that has a tubular semi permeable membrane with a diameter of 0.6 mm. The probe is continuously perfused with a buffer (Ringer's isotonic solution). Fluid and small molecules will be able to diffuse over the membrane according to the concentration gradient. The length of the dialysis membrane was 30 mm, the flow rate was 0.5 μL/min and the time for collection of each sample was 30 min.

The microdialysis probe was implanted in the abdominal subcutaneous tissue with an introducer. To avoid the immediate effect of the implantation with increased blood flow and oedema, we waited at least 4 h before we started collecting samples for later analysis. Blood flow was not measured.

The probe was inserted at 7 p.m. Night time lipolysis was measured at 30 min intervals from 11 p.m. to 7 a.m. At 7 a.m. injection of 2.4 U (0.8 mg) GH was given intravenously to study the immediate lipolytic effect of GH. Samples were collected until 12 a.m., and glycerol, lactate and glucose were measured in the dialysate fluid [11,12]. The concentration in the sample analysis as percent of the concentration in the tissue was estimated to be 100%.

2.3. Assays

Dialysate concentration of glycerol, glucose and lactate were measured with a commercial method using enzymatic reagents and colorimetric measurements (CMA 600 microdialysis Analyzer; CMA/Microdialysis AB).

Table 1
Characteristics of 6 adult Prader–Willi patients

Gender	Age (years)	BMI (kg/m^2)	Body fat (%)[a]	IGF-I μg/L (SDS)	Glycerol (μmol/L)[b]	Lactate (mmol/L)[b]	Glucose (mmol/L)[b]
Male	22	44.4	58.4	112 (−3.2)	250.6	1.45	4.42
Male	25	24.2	40.1	92 (−3.7)	128.8	3.99	4.86
Male	27	27.5	41.6	123 (−2.5)	160.7	1.35	3.69
Male	32	31.9	53	121 (−2.3)	239.3	0.80	4.71
Female	19	38.1	59.1	173 (−1.8)	218	2.85	3.95
Female	37	49.1	45.7	62 (−4.4)	278.1	1.72	9.14

[a] Measured by dual energy X-ray absorptiometry.
[b] Mean nightly concentration 11 p.m. to 7 a.m. measured in the microdialysate.