Institutionen för kvinnors och barns hälsa

Insulin-like growth factor-I deficiency, insulin sensitivity, and glucose metabolism

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i **Skandiasalen, Astrid Lindgrens barnsjukhus, plan1**

Fredagen den 15 mars, 2013, kl 09.00

av
Klas Ekström
Leg.läkare

Huvudhandledare:
Professor Peter Bang
Linköpings Universitet
Institutionen för klinisk och experimentell
medicin, enheten för vårdvetenskaper

Bihandledare:
Professor emeritus Martin Ritzén
Karolinska Institutet
Institutionen för kvinnors och barns hälsa,
enheten för barnendokrinologi

Professor Claude Marcus
Karolinska Institutet
Institutionen för klinisk vetenskap, intervention
och teknik (CLINTEC),
enheten för pediatrik

Fakultetsopponent:
Professor David Dunger
University of Cambridge
Department of Paediatrics,
Addenbrooke s Hospital, Cambridge, UK

Betygsnämnd:
Professor Hans Arnqvist
Linköpings Universitet
Institutionen för klinisk och experimentell
medicin, enheten för cell biologi

Professor Gunnar Norstedt
Karolinska Institutet
Institutionen för molekylär medicin och
kirurgi (MMK)

Med Dr Maria Halldin Stenlid
Uppsala universitet
Institutionen för kvinnors och barns hälsa

ABSTRACT

In children and adolescents, growth hormone (GH) and insulin-like growth factor-I (IGF-I) act in concert to stimulate linear growth; however, the effects on glucose metabolism are in opposition. GH increases insulin resistance by lipolysis. In contrast, IGF-I stimulates glucose uptake and downregulates GH secretion, thus improving insulin sensitivity. Children with GH receptor mutations , severe primary IGF-I deficiency (PIGFD), lack both the growth-promoting and the metabolic effects of GH and IGF-I, and children with type 1 diabetes mellitus (T1DM), aquired IGF-I deficiency, have low portal insulin concentrations, increased IGFBP-1 levels, hepatic GH insensitivity, low circulating IGF-I, and increased GH secretion, i.e. mechanisms that increase insulin resistance and impair metabolic control (HbA1c). The aims of this thesis were to study the effects of two different rhIGF-I preparations on growth and metabolism in severe PIGFD, and the effects of long-acting insulin glargine and continuous subcutaneous insulin infusion (CSII) on the GH/IGF-I axis as well as the direct effects of rhIGF-I on glucose disposal and tissue IGF-I levels in T1DM. In **Paper I,** we studied the effects of rhIGF-I/rhIGFBP-3 for 17 months and thereafter rhIGF-I for 12 months in two siblings with a GH receptor mutation. We found decreased fat mass, increased lean body mass and improved linear growth in response to both preparations, although rhIGF-I was clearly more efficient. The data on insulin sensitivity (hyperinsulinemic euglycemic clamps) were incongruent. However, decreased overnight insulin secretion, most prominent after rhIGF-I, suggested improved insulin sensitivity. A diurnal rhythm of circulating IGF-I with higher mean levels and suppression of GH secretion was seen on rhIGF-I. In **Paper II,** an observational study of 12 adolescents with T1DM, we studied the effects on the GH/IGF-I axis and metabolic control for up to 12 weeks after changing from NPH insulin to insulin glargine. We found decreased overnight IGFBP-I levels and increased circulating IGF-I levels indicating a more efficient nightly insulin delivery thus suggesting improved hepatic insulin sensitivity and improved hepatic GH sensitivity which was associated with improved HbA1c.In **Paper III,** a parallel multi-centre study lasting 24 months, 72 children and adolescents with newly diagnosed T1DM were randomized to multiple daily insulin injections (MDI) with NPH insulin or CSII and studied regarding the effects on the GH/IGF-I axis and endogenous insulin production. We found decreased fasting IGFBP-1, indicating a more efficient nightly insulin delivery with CSII and thus improved hepatic insulin sensitivity. In addition, the insulin doses were lower in the CSII group indicating improved insulin sensitivity. In **Paper IV,** eight males with T1DM were studied in a randomized single-blind, placebo-controlled, cross-over study. We assessed the effects of a single subcutaneous rhIGF-I injection ($120\,\mu g/kg$) or saline, during a normoinsulinemic euglycemic clamp, on glucose utilization and tissue levels of IGF-I in muscle and subcutaneous fat determined by microdialysis. We found an increase in whole body glucose disposal and a concomitant increase in tissue IGF-I levels during the second hour after injection. **In summary,** this thesis demonstrates that rhIGF-I is superior to rhIGF-I/rhIGFBP-3 in promoting linear growth and also improves body composition and decreases insulin levels more efficiently. A more sustained insulin delivery profile of insulin glargine and CSII improves hepatic insulin sensitivity and insulin glargine increases circulating IGF-I and decreases HbA1c, and the thesis provides evidence that the microdialysis technique can be used to assess biological effects of IGF-I in tissues.
[ISBN 978-91-7549-054-0]