Decreased half-life of insulin-like growth factor I in Rabson–Mendenhall syndrome

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Summary: Rabson–Mendenhall syndrome is an autosomal recessive disorder of insulin signalling caused by mutations in the insulin receptor gene. Affected patients are insensitive to exogenous insulin. Insulin-like growth factor I (IGF-I), whose receptor is similar to the one for insulin and is not impaired in this condition, is not always effective in these patients. To understand the reason for this failure, IGF-I concentrations were measured in a patient after subcutaneous injection of 0.1 and 0.2 mg/kg of rhIGF-I. IGF-I concentrations increased only transiently because of the short half-life (1.3–3 h, compared to a normal range of 17–22 h). No correlation was found between IGF-I concentrations and glucose or insulin concentrations. The short half-life of IGF-I may contribute to treatment failure in patients with inherited insulin-resistant syndromes.

Mutations in the insulin receptor gene cause a spectrum of inherited insulin-resistant syndromes ranging from the extremely severe leprechaunism (McKusick 246200), with death in infancy, to type A insulin resistance, which usually becomes evident after puberty. Rabson–Mendenhall syndrome (McKusick 262190) has an intermediate phenotype with survival beyond 1 year of age but death usually before puberty (Longo et al 1999). Affected children have intrauterine and postnatal growth restriction, dysmorphic features and abnormal glucose homeostasis and fail to respond to exogenous insulin (Longo et al 1994, 1999).

Insulin-like growth factor I (IGF-I) and insulin have structurally similar tyrosine kinase receptors. A few studies have evaluated the effect of IGF-I on glucose metabolism and growth in insulin-resistant patients. Intravenous injection of IGF-I has an acute hypoglycaemic effect (Quin et al 1990; Schoenle et al 1991), while subcutaneous rhIGF (0.2–0.3 mg/kg) has only a minor acute effect and no chronic
effect on glycaemic levels (Kuzuya et al 1993). Lack of acute or chronic effects of rhIGF-I on glucose concentrations and growth has been reported for other patients with inherited insulin resistance (Backeljauw et al 1994; Longo et al 1994). More recently, a very high dose of IGF-I (1.6 mg/kg), given by a combination of subcutaneous injection and continuous subcutaneous infusion, improved growth and glycaemic levels in one patient with leprechaunism (Nakae et al 1998). To determine the reason for the discrepancy among these studies, we evaluated the pharmacokinetics of rhIGF-I in a patient with Rabson–Mendenhall syndrome.

PATIENT AND METHODS

Patient Atl-2 with Rabson–Mendenhall syndrome was a compound heterozygote for two mutations, I1115T and R1131W, in the portion of the gene encoding the tyrosine kinase domain of the insulin receptor (Longo et al 1994, 1999). The patient died at 7 years of age following intractable diabetic ketoacidosis (Longo et al 1999).

The patient was 3 years 9 months old at the time of this study. The protocol was approved by the Human Investigation Committee and conducted in the Clinical Research Facility of Emory University. Prior to this study, determinations of IGF-I concentrations in this patient indicated very low levels (<10 ng/ml). Injection of saline or GH failed to modify IGF-I concentrations (Longo et al 1994). rhIGF-I (0.1 and 0.2 mg/kg) was injected subcutaneously on separate days. IGF-I, IGF-BP3 and insulin were measured using standard procedures by reference laboratories (Longo et al 1994, 1999). Correlation between parameters was performed by regression analysis, with significance determined by analysis of variance.

RESULTS AND DISCUSSION

rhIGF-I administered subcutaneously in a single dose of 0.1 or 0.2 mg/kg raised IGF-I concentrations from 5–6 ng/ml (normal per age 45–230 ng/ml) to 181 and 259 ng/ml, respectively (Figure 1A). The half-life of rhIGF-I was between 1.3 and 3 h, significantly shorter than 17–22 h in normal individuals (Grahnen et al 1993) and 5.7–6.9 h in patients with Laron dwarfism (Grahnen et al 1993), but similar to 1.5 h previously reported in one patient with leprechaunism (Nakae et al 1998).

IGF-I circulates in the plasma bound to specific binding proteins, which prolong its half-life (LeRoith and Butler 1999). Short-term treatment with rhIGF-I did not modify the concentrations of IGF-BP3, the major IGF-I binding protein, which remained < 0.3 mg/L in our patient (normal range 0.9–4.1 mg/L) during repeated measurements (n = 9). Therefore, the abnormally short half-life of IGF-I in our patient with extreme insulin resistance is likely related to the low concentrations of IGF-BP3. This, in turn, is due to GH resistance (Longo et al 1994; Psachchou et al 1993), possibly caused by the lack of the facilitating effect of insulin on GH signalling in the liver (Longo et al 1994).

The reduced concentration of IGF-BP3 should have increased the concentrations of free IGF-I. However, there was no significant correlation between IGF-I and glucose concentrations (p > 0.05, Figure 1C) or insulin concentrations (Figure 1B).