IGF-I treatment of insulin resistance

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Abstract

Severe insulin resistance resulting from known or putative genetic defects affecting the insulin receptor or post-insulin receptor signalling represents a clinical spectrum ranging from Donohue's and Rabson–Mendenhall syndrome, where the genetic defect is identified, through to the milder phenotype of type A insulin resistance, where a genetic defect can only be detected in around 10% of cases. Paradoxically, subjects with these conditions may present with hypoglycaemia due to mismatch of post-prandial glucose excursion and compensatory hyperinsulinaemia. Ultimately, treatment with insulin and insulin sensitisers will be unsuccessful and subjects may succumb to diabetes or its complications. Recombinant human IGF-I alone or combined with its binding protein (IGFBP-3) provides an alternative therapy as IGF-I receptor shares structural and functional homology with the insulin receptor and recombinant human insulin-like growth factor I (rhIGF-I) therapy could improve glucose disposal by signalling through the IGF-I receptor, whilst reducing the adverse effects of high insulin concentrations. There are also data which indicate that IGF-I signalling through the IGF-I receptor on the pancreatic β -cell may be important in maintaining insulin secretion. Pilot studies confirmed that rhIGF-I could reduce glucose and insulin levels in subjects with type A insulin resistance and those with Rabson–Mendenhall syndrome with sustained beneficial effects on HbA1c. Continued study has confirmed efficacy of rhIGF-I when combined with IGFBP-3 in the treatment of Donohue's and type A insulin resistance subjects. Observations that IGF-I treatment can improve C-peptide levels in these subjects may indicate that it might be more valuable as a first line intervention to preserve β -cell function, rather than its current use as a medication of last resort in subjects where all other therapies have failed.

European Journal of Endocrinology 157 S51–S56

Introduction

Insulin resistance has been defined as a need for greater than normal amounts of insulin to elicit a quantitatively normal response (1). However, this definition does not reflect the possibility, which can exist in some rare conditions, that the insulin resistance may be selective and only relate to particular functions of insulin. The definition proposed by Kahn in 1976 is probably more appropriate as it states that insulin resistance exists whenever normal concentrations of insulin produce less than normal biological responses with respect to

- 1) Glucose uptake
- 2) Suppression of hepatic glucose production
- 3) Decreased lipolysis
- 4) Increased lipogenesis
- 5) Prevention of proteolysis.

Insulin resistance is a feature of normal pubertal development, where it largely relates to impairment of insulin-stimulated muscle glucose uptake (2). The resulting compensatory hyperinsulinaemia may inhibit proteolysis and contribute to anabolism during puberty (3). Similarly, the insulin resistance that develops during prolonged fasting or starvation may relate to growth hormone-induced lipolysis (4), reflecting the importance of survival advantage of changing from the use of glucose as the primary energy substrate to the mobilisation of fat for energy needs. The insulin resistance of starvation is mediated through counter-regulatory hormones such as growth hormone and cortisol, and pathological conditions leading to excess of either of these hormones will lead to insulin resistance (5).

Insulin resistance is also a feature of obesity in the normal population, where it has been linked to the increased deposition of visceral fat and increased rates of lipolysis (6, 7). Increased release of non-esterified fatty acids, particularly from the visceral fat depot, can lead to intramyocellular and intrahepatic fat deposition

This paper was presented at the Ipsen symposium, 'The evolving biology of growth and metabolism', Lisbon, Portugal, 16–18 March 2007. Ipsen has supported the publication of these proceedings.

(8, 9). It is the build up of that ectopic lipid or, perhaps more particularly, the failure to effectively metabolise the lipid that leads to insulin resistance (10). Visceral fat is also a source of a wide range of peptides, which can affect insulin sensitivity and lead to generalised inflammation, which may also be part of the pathogenesis of insulin resistance of obesity (see Weiss chapter; this issue S39–S45).

Such ectopic deposition of fat is an important cause of insulin resistance in syndromes of lipodystrophy (11). There are multiple forms of lipodystrophy and most are very rare. Kobblerling/Dunnigan syndrome (due to a lamin gene defect) is characterised by partial lipodystrophy involving the trunk and the limbs but often sparing the face (12). Patients with this condition, which generally develops around the time of puberty, are unable to deposit fat in the abnormal adipocytes and this leads to severe hepatic fat deposition and insulin resistance. Recently, treatment with recombinant human leptin has proved efficacious in leptin-deficient lipodystrophy by reducing fat intake and perhaps through direct effects on insulin sensitivity (13). Patients with partial lipodystrophy related to mutations of PPAR- γ are also insulin resistant and develop a wide spectrum of abnormalities including hepatic steatosis, hypertension, diabetes and dyslipidaemia (14). PPAR- γ is the cognate receptor for the thiazolidinediones, a class of drugs frequently used in the treatment of type 2 diabetes. These drugs have the ability to redistribute visceral fat to s.c. depots thus ameliorating effects on insulin sensitivity (15). Leptin and thiazolidinediones have been used to try and reverse the insulin resistance in other rare genetic disorders relating to the insulin receptor and impaired insulin action (49).

Primary disorders of insulin action

Severe insulin resistance, secondary to impaired insulin signalling, encompasses a wide range of rare disorders including genetic defects in the insulin receptor and more complex syndromes, associated for example with dwarfism and skeletal dysplasia where the genetic basis is unknown (see Table 1).

The most severe form of insulin resistance occurs in Donohue's syndrome (leprechaunism), where there are homozygous or compound heterozygous mutations in the regulatory or coding domains of the insulin receptor, resulting in what is effectively a functionally null receptor (16). These affected individuals present in the newborn period with severe intrauterine growth retardation, dysmorphic features such as thick lips, upturned nostrils, prominent eyes and low set posteriorly rotated ears. They are born with very little s.c. fat, distended abdomen, enlarged genitalia in the males and cystic ovaries in the females (17). As they effectively have a null mutation of the insulin receptor, insulin levels may exceed 10 000 pmol/l yet, unlike animal

Table 1 Classification of severe insulin resistance.

Aetiology	Clinical syndrome
Mutations of the insulin receptor	Donohue's syndrome (leprechaunism) Rabson–Mendenhall syndrome Type A insulin resistance
Post-binding defects in insulin action	Lipodystrophic disorders (partial or generalised; inherited or acquired) Type C insulin resistance (HAIR-AN syndrome; PCOS)
Anti-insulin receptor antibodies	Type B insulin resistance
Others	Associated with skeletal dysplasia, Alstrom syndrome, myotonic dystrophy

models with similar genetic defects, these babies do not develop diabetic ketoacidosis (18). Indeed, initially the major clinical problem may be hypoglycaemia followed by post-prandial hyperglycaemia. They may require continuous nasogastric glucose infusions, and treatment with insulin or insulin sensitisers rarely reverses the decline towards diabetes. The majority of babies with Donohue's syndrome will die within the first 2 years of life.

Rabson–Mendenhall syndrome is also the result of mutations of the insulin receptor but the features may be much milder, with presentation during childhood with poor growth, insulin resistance, acanthosis nigricans, hirsutism, abnormal nails and dentition, phallic enlargement and occasional pineal hyperplasia (19–21). These patients will eventually develop severe insulin-resistant diabetes requiring very large doses of insulin to achieve normoglycaemia. Death is inevitable from intractable diabetic ketoacidosis or the complications of diabetes.

Type A insulin resistance is at the least severe end of the spectrum and thought to arise from mutations at the insulin receptor or in post-receptor signalling. Severe insulin resistance might be suspected in an insulin-dependent subject requiring more than 200 units of insulin a day but, paradoxically, many of the patients with type A insulin resistance present with hypoglycaemia. They have elevated fasting insulin levels in excess of 150 pmol/l (normal range <60 pmol/l), which may be sufficient to control fasting glucose levels but leads to a mismatch between glucose and insulin post-prandially and thus hypoglycaemia. Type A insulin resistance was originally used to describe lean adolescent females with the phenotype of hyperinsulinism, glucose intolerance or frank diabetes mellitus, acanthosis nigricans, virilisation and polycystic ovary syndrome (22). However, the diagnosis now encompasses both males and females in teenage or early adult years, who are not obese but have severe insulin resistance and acanthosis nigricans in the absence of insulin receptor autoantibodies (19). Despite the common presenting features, this is undoubtedly a heterogeneous group of patients and at present only about 10% have detectable genetic defects in the insulin

receptor (22–24). It is likely that some will have defects in post-insulin receptor signalling (50). These patients are not predisposed to the significantly early mortality seen in the other two groups, but are likely to be at high risk of long-term complications secondary to their hyperglycaemia.

The treatment of any condition resulting in severe insulin resistance is challenging and often unsuccessful. Initially, treatment may consist of the use of insulin-sensitising drugs such as metformin or thiazolidinediones. Eventually, patients end up on escalating doses of insulin with progressive decline in β -cell function, resulting in considerable morbidity and mortality from diabetes and its complications.

Treatment with recombinant human insulin-like growth factor I (rhIGF-I) in severe insulin resistance

Insulin, proinsulin, IGF-I and IGF-II show remarkable structural and in part sequence homology (25, 26). Similarly, the insulin and the type 1 IGF receptor are structurally related and share common post-receptor signalling pathways (27). *In vitro* and *in vivo* both insulin and IGF-I are capable of stimulating glucose uptake, glycogen synthesis and the inhibition of protein catabolism (28, 29). IGF-I has little effect on the adipocyte because there are no IGF-I receptors on that tissue (30). The mature liver also lacks IGF-I receptors but, nevertheless, rhIGF-I has been shown to suppress

hepatic glucose production through unknown mechanisms (31, 32). It was therefore anticipated that rhIGF-I therapy in patients with severe insulin resistance might be efficacious.

The aim of IGF-I therapy in severe insulin resistance would be primarily to stimulate peripheral glucose utilisation and suppress hepatic glucose production, thereby reducing the drive for compensatory hyperinsulinaemia; the high insulin levels acting through the IGF-I receptor being responsible for many of the pathological features including acanthosis nigricans and polycystic ovaries (33, 34). The long-term aim of therapy would be to improve glycaemia, and in the case of Donohue's syndrome, promote linear growth and prolong longevity.

The first reports of the use of recombinant IGF-I therapy in severe insulin resistance were in the early 1990s and largely involved the treatment of patients with type A syndrome. The results of these studies are summarised in Table 2. In 1991, Schoenle *et al.* were the first to demonstrate that a bolus injection of recombinant IGF-I could reduce both insulin and blood glucose levels in patients with severe insulin resistance (35). Subsequently, other groups showed that IGF-I therapy in patients with severe type A insulin resistance could consistently reduce glucose and insulin levels. Kuzuyu *et al.* undertook the longest of these studies, reporting up to 16 months treatment with rhIGF-I in 11 patients, who showed lowering of fasting and post-prandial glucose plus decreases in fructosamine and %HbA1c (36). In all of these early studies, very high doses of rhIGF-I were used and complications

Table 2 Summary design and outcome of studies on recombinant human insulin-like growth factor I (rhIGF-I) treatment in syndromes of severe insulin resistance.

Authors	Trial design	Outcome
Schoenle <i>et al.</i> (35)	Three subjects twice received i.v. doses with rhIGF-I	Immediate slow fall in blood glucose, parallel fall in insulin and C-peptide levels
Morrow <i>et al.</i> (45)	Two subjects received 3–4 weeks treatment with rhIGF-I. Pre- and post-treatment assessment with 24 h glucose and insulin profile, standardised liquid meal, insulin tolerance test, insulin suppression test and i.v. glucose tolerance test	Decreased endogenous insulin levels, normalisation of response to i.v. insulin, reduced steady-state plasma glucose
Zenobi <i>et al.</i> (46)	Two subjects received 10 days treatment with rhIGF-I. Fasting and post-prandial glucose, insulin, C-peptide and proinsulin levels measured pre- and post-treatment	Fasting glucose levels decreased and fasting insulin, C-peptide, and proinsulin levels decreased by ~65% during treatment
Kuzuya <i>et al.</i> (36)	11 subjects received up to 16 months treatment with rhIGF-I. Fasting and post-prandial glucose, fructosamine and %HbA1C were measured pre- and throughout treatment	Lowering of fasting and post-prandial glucose and decreases in fructosamine and %HbA1C
Moses <i>et al.</i> (47)	Six subjects (four out of six subjects had overt diabetes, two with normal glucose tolerance) received 1 months treatment with rhIGF-I. Baseline investigation to quantify carbohydrate tolerance, insulin secretion and insulin action	Three out of four diabetic subjects showed normalisation of fasting and post-prandial glucose levels. Remaining two subjects dramatically decreased insulin and triglyceride levels
Vestergaard <i>et al.</i> (48)	Four subjects received high-dose treatment with rhIGF-I for 2 weeks, three subjects received low dose for 10 weeks. Pre- and post-treatment fasting glucose, insulin, C-peptide and proinsulin plus %HbA1C and fructosamine were measured	High-dose treatment lowered fasting glucose and insulin levels, whereas metabolic and glycaemic effects of 10 weeks low-dose treatment were modest

Table 3 Effects of recombinant human insulin-like growth factor I (rhIGF-I)/IGF binding protein-3 (IGFBP-3) complex in a female subject with type A insulin resistance. Therapy was started at 0.5 mg/kg per day and increased up to a total daily dose of 2 mg/kg per day over a 16-week period.

	Pre-treatment	Post-treatment
%HbA1c	8.1	5.0
Intramyocellular lipid	8.6	7.8
Intrahepatic fat	9.4 ± 0.7%	5.9 ± 1.2%

Intramyocellular lipid was quantified using magnetic resonance spectroscopy and hepatic fat using magnetic resonance imaging.

were observed relating to muscle pain, fluid retention, benign intercranial hypertension and worsening retinopathy.

The full therapeutic potential of rhIGF-I therapy in severe insulin resistance has not been explored, because until very recently recombinant peptides were not available for study. A study using rhIGF-I/IGF binding protein-3 (IGFBP-3) in a patient with Donohue's

syndrome reported normalisation of glucose with prevention of postnatal growth failure (37). Recently, we and others have been able to explore the efficacy of IGF-I combined with its principle binding protein IGFBP-3 in a variety of diabetic conditions (38, 39). Combining IGF-I with its principle binding protein prolongs its half life and results in decreased concentrations of free IGF-I and improved tolerability (38, 40). We have preliminary unpublished data from phase 2 clinical trials in subjects with type A insulin-resistant syndrome indicating that treatment with rhIGF-I/IGFBP-3 complex may improve glycaemic control and lead to reductions in HbA1c. Insulin sensitivity improves and there were measurable reductions in intrahepatic and intramyocellular lipid during a 4-month treatment period (Table 3, Figs 1 and 2).

An important observation from these new studies is that IGF-I/IGFBP-3 complex therapy appears to improve β -cell function and improve glucose-stimulated C-peptide responses. This may be the result of reduced glucotoxicity, but recent animal data indicate that IGF-I

Figure 1 Endogenous hepatic glucose production during i.v. glucose tolerance test before and after treatment with IGF-I/IGFBP-3 in a patient with type A insulin resistance.

Figure 2 C-peptide response during i.v. glucose tolerance test in a subject with type A insulin resistance before and after treatment with rhIGF-I/IGFBP-3 complex.

signalling through the IGF-I receptor on the β -cell may have an important role in maintaining β -cell mass and insulin secretion (41–44). This might indicate that early rather than later treatment with recombinant IGF-I may be beneficial and there are two remarkable reports of children with Donohue's syndrome, treated with IGF-I from a very early age, who have shown sustained improvements in insulin sensitivity and growth over several years.

Conclusions

Syndromes of severe insulin resistance are extremely rare and encompass a very wide range of heterogeneous conditions. In some, with severe lipodystrophy, leptin therapy may bring partial benefit but the long-term outcome of such treatment is unknown. In other patients, the use of insulin sensitizers may delay the development of diabetes but inevitably most patients will ultimately require insulin therapy, with escalating doses as β -cell function declines. Treatment with recombinant IGF-I or IGF-I/IGFBP-3 is based on sound physiological principles and appears to be efficacious, at least in the short term. Longer term studies are needed to determine the risk-benefit ratio of such interventions, the ideal doses that should be used and the age at which treatment should be initiated.

Disclosure

This paper forms part of a *European Journal of Endocrinology* supplement, supported by Ipsen. The authors disclose: RM Williams, FM Regan, RK Semple and A McDonald have no potential conflicting relationships with Ipsen. DB Dunger is a member of the Endocrine Scientific Advisory Board for Ipsen. This article was subject to rigorous peer review before acceptance and publication.

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Received 23 April 2007

Accepted 3 May 2007