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The role of the growth hormone–insulin-like growth factor axis in glucose homeostasis

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Abstract

Homeostatic mechanisms normally maintain the plasma glucose concentration within narrow limits despite major fluctuations in supply and demand. There is increasing evidence that the growth hormone (GH)–insulin-like growth factor (IGF) axis may play an important role in glucose metabolism. GH has potent effects on intermediary metabolism, some of which antagonize the actions of insulin. In contrast, IGF-I has insulin-like actions, which are, in the case of glucose metabolism, opposite to those of GH. There is often deranged glucose metabolism in situations where GH is deficient or in excess. The clinical administration of GH or IGF-I results in altered glucose metabolism and changes in insulin resistance. Despite these observations, the precise role of GH and IGF-I and their interactions with insulin in controlling normal glucose homeostasis are unknown. In diabetes, GH secretion is abnormally increased as a result of reduced portal insulin resulting in impaired hepatic IGF-I generation. Evidence suggests that this may contribute to the development of diabetic microvascular complications. IGF-I 'replacement' in diabetes is under investigation and new methods of delivering IGF-I as a complex with IGFBP-3 offer exciting new prospects.

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Keywords growth hormone, insulin-like growth factor, glucose metabolism, growth hormone deficiency, insulin resistance

Introduction

Normally plasma glucose concentration is maintained within a narrow range despite wide fluctuations in supply and demand. Although under normal physiological conditions insulin is the prime regulator of glucose metabolism, there is increasing evidence that the growth hormone (GH)–insulin-like growth factor-I (IGF-I) axis plays an important contributory role. GH has potent effects on intermediary metabolism, amongst which is the ability to antagonize the actions of insulin. Although GH and IGF-I exert opposite effects on glucose metabolism, the precise role of these two hormones in controlling normal glucose homeostasis is unknown. The purpose of this review is to examine the available evidence to address this question. The data for this review reflect our own clinical and academic interests and experience. We have also undertaken a comprehensive search using multiple electronic databases and hand searches of reference lists of articles.

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Growth hormone and glucose homeostasis

In the 1930s, Houssay and Biasotti observed that hypophysectomy reduced the hyperglycaemia of experimental diabetes in dogs [1]. The diabetogenic factor isolated from pituitaries was found to have growth-promoting activity and was named 'growth hormone' [2]. Confirmation of the diabetogenic properties of GH was made after it was administered in excess to experimental animals and man [3,4]. Following the development of reliable GH assays, human studies showed the importance of GH in glucose metabolism [5]. In both healthy subjects and those with Type 1 diabetes, a pulse of GH increases fasting hepatic glucose output, by increasing hepatic gluconeogenesis and glycogenolysis, and decreases peripheral glucose utilization through the inhibition of glycogen synthesis and glucose oxidation [6–10]. Growth hormone stimulates lipolysis with the release of glycerol and non-esterified fatty acids (NEFA). This provides a further mechanism for the diabetogenic properties of GH through the effect of NEFA to increase hepatic glucose output and decrease peripheral glucose oxidation according to the glucose–fatty acid cycle [11–13].

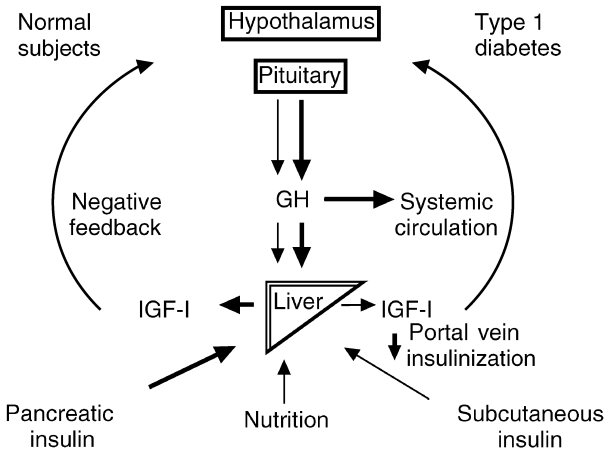

Figure 1 Growth hormone–insulin-like growth factor-I axis in Type 1 diabetes.

GH and diabetes

Growth hormone concentrations are up to two to three times higher in individuals with diabetes compared with healthy subjects (Fig. 1) [14]. This reflects an increase in pituitary secretion, as the metabolic clearance rate of GH in diabetes is normal [15]. A series of studies by Wurzburger *et al.* has shown the importance of portal insulin concentrations in regulating hepatic IGF-I generation and for the normal functioning of the GH–IGF-I axis. GH administration in Type 1 diabetes has little effect on serum IGF-I levels, while residual insulin secretion, as reflected by plasma C-peptide levels, determines the degree of GH hypersecretion [16–19].

Although there is dispute about the relative importance of different hormones in the causation of the 'dawn phenomenon', there is evidence that nocturnal GH hypersecretion plays an important role in the early morning reduction of insulin sensitivity and rise in plasma glucose [20,21]. Patients with Type 1 diabetes who are GH-deficient do not exhibit the 'dawn phenomenon', and a single bolus of GH to these individuals decreases morning insulin sensitivity. The mechanism is probably not simply secondary to an increase in NEFA, because insulin sensitivity decreases even if the lipid concentrations are maintained at a constant level with a heparin infusion [22].

Growth hormone and the microvascular complications of diabetes

In 1953, Poulsen presented the case of a woman with Type 1 diabetes and background diabetic retinopathy, which regressed after she developed panhypopituitarism after post-partum pituitary necrosis [23]. Subsequently in the 1960s, pituitary ablation was shown to result in a regression of diabetic retinopathy, which could be related to the degree of GH deficiency [24]. These observations led to the hypothesis that GH may be involved in the development on angiopathic diabetic complications [25,26]. Theoretically, this susceptibility may be further augmented in Type 1 diabetic patients by the supra-physiological levels of insulin in the retina, nerve and kidney produced by insulin injections into the systemic rather than portal circulation. Although effective, pituitary ablation was associated with significant morbidity and mortality and was superseded by retinal photocoagulation [27]. Patients with Type 1 diabetes and GH deficiency had decreased rates of retinopathy, supporting a role for GH development of microvascular complications [28]. There is, however, no evidence that GH replacement therapy causes an increased incidence of retinopathy in GH-deficient patients with or without diabetes [29]. Furthermore, many other growth factors, including IGF-I, have been implicated in the development of microangiopathic complications [30–32]. This remains a controversial area, as some advocate a protective role for IGF-I in the development of microangiopathic complications of diabetes [33]. According to this hypothesis, IGF-I replacement therapy in patients with diabetes will restore the normal feedback control on GH hypersecretion and thus reduce the risk of developing microvascular complications as well as glycaemic control.

Growth hormone excess

Animal models

Transgenic animals, which over-express GH, have added to our understanding of the role of the GH–IGF axis in glucose metabolism [34,35]. These animals develop insulin resistance, marked hyperinsulinaemia, hyperglycaemia, and hypertriglyceridaemia in association with a number of molecular abnormalities. The number of hepatic insulin receptors is reduced to around 50% of normal in transgenic animals, although the affinity of the receptor is unaffected [36,37]. The phosphorylation status of the insulin receptor and the insulin receptor substrate-1 (IRS-1) is increased so that the insulin receptor and IRS-1 are maximally activated in the resting state [38,39]. The basal association of phosphatidylinositol 3-kinase (PI3-kinase) with IRS-1, as well as PI3-kinase activity, are also increased to maximal levels. This maximal activation of the insulin receptor under basal conditions has the effect of making the tissue insensitive to further stimulation by insulin *in vivo*.

The transgenic animals have modified expression of several genes coding for proteins regulating carbohydrate metabolism. Glycogen synthase and glycogen phosphorylase activity in muscle and liver of transgenic mice is reduced and remains unchanged in liver after feeding [34]. There are also decreases in glucokinase and GLUT-2 mRNA concentrations [34].

The effects of GH on insulin signalling are directly related to the hyperinsulinaemia. If this is normalized by the administration of streptozotocin, the number of insulin receptors and the insulin-stimulated auto-phosphorylation activity of the insulin receptor return to control values [40].

Human studies

Acromegaly

Patients with acromegaly develop insulin resistance and hyperinsulinaemia, while up to 40% become diabetic [41,42]. Glucose intolerance usually resolves rapidly after normalization of GH concentrations with surgery or radiotherapy [43], but remission of diabetes may take several years [44]. The effect of somatostatin analogue therapy on glucose metabolism is more inconsistent [45]. Although somatostatin analogues effectively reduce GH secretion and IGF-I production, insulin secretion is also reduced and so therapy may be accompanied by either improvements or deterioration in glucose tolerance, depending on the relative effect on each of these hormones. The GH receptor antagonist, pegvisomant, results in an improvement in insulin resistance in acromegaly [46]. As this compound results in a decrease in IGF-I levels, it is possible that pegvisomant may worsen insulin resistance in patients with diabetes who already have low serum IGF-I. Antagonizing GH action in Type 1 diabetes may also result in more hypoglycaemic episodes, with increased hypoglycaemia unawareness, as occurs in patients with Type 1 diabetes and GH deficiency [17].

Adult growth hormone deficiency

There has been a considerable advance in the understanding of glucose metabolism in adults with GH deficiency (GHDA). GHDA is commonly associated with a decrease in serum IGF-I and so it is unclear whether the insulin resistance of GHDA is secondary to decreased IGF-I concentrations or is a direct consequence of reduced GH action. However, serum IGF-I concentrations in GHDA may overlap with the age-matched normal range for IGF-I. A further understanding of the relative contributions of GH and IGF-I to glucose metabolism could be gained by assessing whether insulin sensitivity in GHDA is related to the pretreatment IGF-I concentration.

There is, however, evidence to suggest that acute decreases in GH and IGF-I concentrations are not associated with insulin resistance. If the GH receptor antagonist, pegvisomant, is administered, GH action is blocked and serum IGF-I concentrations are rapidly reduced. Under these circumstances, insulin sensitivity remains unchanged [47].

GHDA is associated with changes in body composition which lead to a reduction in lean body mass and increase in fat mass, predominantly central adiposity. It appears that the central obesity has an aetiological role in the development of insulin resistance and hyperinsulinaemia in GHDA, as fasting insulin and C-peptide concentrations correlate positively with body mass index, waist to hip ratio and central fat mass [48]. A significant difference in insulin sensitivity remains between GHDA and normal controls, however, even after corrections are made for body fat.

The molecular mechanisms underlying the insulin resistance of GHDA remain unclear. GHDA has decreased glycogen stores and a 50–64% reduction in insulin-mediated glucose utilization (Fig. 2) [49–51]. Glycolytic flux and glycogen synthesis are normal at baseline, but insulin activation of these pathways is reduced [50]. The decreased activation of muscle glycogen synthase by insulin accounts for the reduced muscle glycogen content. Insulin-induced muscle hexokinase activity is attenuated in GHDA, leading to normal or reduced concentrations of glucose-6-phosphate despite increased intramuscular cellular glucose levels [50]. In addition to these peripheral abnormalities, there are defects in pancreatic β-cell function; given the degree of insulin resistance, insulin and C-peptide secretion is often inappropriately low [52].

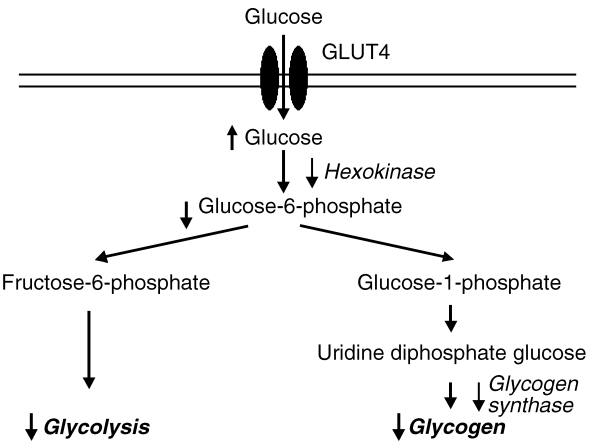

Figure 2 Abnormalities in insulin-stimulated glucose metabolism in growth hormone deficiency.

Effect of GH replacement therapy in GHDA

The acute and chronic effects of rhGH replacement on glucose metabolism in adults have been reported in a number of GH trials (Table 1) [52–60]. In the short term, there is a reduction in insulin sensitivity in association with an increase in plasma glucose and insulin concentrations. Long-term, insulin sensitivity gradually improves in association with an increase in lean body mass and reduction in fat mass. There are, however, discrepancies between studies, but these may reflect duration of GHDA, differences in body composition and the effect of ageing on insulin resistance [61].

There are data from post-marketing surveillance studies looking at any adverse effects of long-term rhGH replacement. The two largest are the KIMS (Pharmacia and Upjohn International Metabolic Database) database and HypoCCS (The hypopituitary control and complications study) run by Eli Lilly. KIMS is a pharmaco-epidemiological survey of rhGH replacement in GHDA and currently comprises over 6000 patients, with a total of 10 000 patient years follow-up (mean duration of replacement 2.8 years). The majority of the 32 individuals, who have developed diabetes in the KIMS database, were obese or had a family history of diabetes, while one had impaired glucose tolerance prior to starting rhGH replacement therapy. The number developing diabetes is in line with the expected increase in diabetes that would be seen with increasing age in the general population and, considering the

Table 1 Growth hormone (GH) trials examining the effect of rhGH on glucose metabolism

Trial	rhGH dose	Method	Duration	Effect of GH on glucose metabolism	Study
DBPC crossover study	0.25 IU/kg per week	Clamp	6 weeks 6 months	Glu and Ins ↑ and Si ↓ Glu and Ins, Si →	[53]
Open study	0.25 IU/kg per week	IVGTT	4 weeks 3 months	Glu, Ins and C-pep, 1st and 2nd Ins secretion after 1 week ↑ Ins-mediated Glu disposal and Glu decay ↓. Fractional Ins MCR → Glu, Ins and C-pep ↑. All other variables →	[54]
DBPC	2 IU/m^2 per day	OGTT	4 months	Glu, Ins and C-pep ↑, Si & Sg ↓	[52]
Open label	1.6 IU/day	IVGTT and HOMA	30 months	3/11 developed IGT. Si ↓, Ins ↑, Ins and C-pep MCR ↑	[55]
DBPC	0.07 IU/kg per day	Fasting isotope study	1 month 6 months	Glu, Ins and C-pep ↑, Glucose Ra ↑, glucose MCR ↑ Glu, Ins and C-pep ↑, Glucose Ra unchanged, glucose MCR ↑	[56]
Open	0.125 IU/kg per week	IVGTT	12 months 18 months	HbA_{1c} ↑ Glu and Ins, HbA_{1c}: no change from baseline values. Sg ↑ and Si ↓	[57]
Open	0.01–0.05 IU/kg per day	OGTT	12 months 48 months	Glu and Ins ↑. AUC for Glu and Ins ↑ Glu N, Ins ↑ (but lower than 1 year value) AUC for Glu and Ins N	[58]
Open	0.025 IU/kg per day	Fasting data	120 months	Glu, Ins and C-pep the same compared with untreated GHDA. No healthy control group	[60]
Open		OGTT	84 months	Glu and Ins → in rhGH-treated group. Si ↓ and Ins AUC ↑ in untreated patients. Comparison with GHDA not treated with GH or only treated for < 18/12	[59]

GHDA, GH-deficient adults; DBPC, double-blind placebo-controlled study; OS, open study; clamp, hyperinsulinaemic-euglycaemic clamp; IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test; Glu, fasting plasma glucose; Ins, fasting plasma insulin; C-pep, C-peptide; AUC, area under the curve; Si, insulin sensitivity; Sg, glucose effectiveness; MCR, metabolic clearance rate; HOMA, homeostasis model assessment of insulin sensitivity; Ra, glucose appearance.

concomitant risk factors, the incidence may be less than would be expected for an age and weight-matched population [62,63]. HypoCCS consists of 1881 rhGH-replaced patients (mean duration of replacement 2 years) and a control group of 352 GHDA patients not receiving GH, and has shown no increase in the incidence of diabetes compared with the control group [64].

Metabolic syndrome

The 'metabolic syndrome' is a cluster of cardiovascular risk factors including central obesity, dyslipidaemia, hypertension, insulin resistance and Type 2 diabetes [65]. There are similarities between the metabolic syndrome and untreated GHDA, including central obesity and insulin resistance, which suggest that abnormalities of GH secretion may be important in the metabolic aberrations of the metabolic syndrome [66].

Central adiposity is associated with a blunted secretion of GH [67]. Although this could be a consequence of obesity, the reduction in GH secretion may have causal effects. We have shown that GH secretion is related more to age and fitness than adiposity itself, suggesting that the changes in body composition with age may be a consequence of the GH hyposecretion rather than *vice versa* [68]. In a further study, the administration of GH (9.5 μg/kg) to 30 centrally obese men for 9 months led to a reduction in total body fat, in particular abdominal subcutaneous and visceral adipose tissue, in association with an improvement in insulin sensitivity, through an increase in the glucose disposal rate [69].

Insulin-like growth factors and glucose homeostasis

Insulin-like growth factor-I is a single chain peptide, which has structural homology with pro-insulin. Although IGF-I is synthesized widely [70], the majority of circulating IGF-I is derived from the liver [71]. Its synthesis is regulated by GH, insulin and nutritional intake [72–74]. It has profound effects on the regulation of proliferation and differentiation of many cell types, as well as metabolic effects, which are similar to those of insulin, including actions on glucose metabolism (Table 2).

Animal studies

IGF-I transgenic animals

The issue of possible functional redundancies in the insulin and IGF systems *in vivo* has been addressed using knockout mice for genes encoding IGF-I or the IGF-I receptor [75–77]. The severity of the phenotypes, however, has prevented in depth examination of glucose metabolism in these mice, as 95% die. If the mice, which lack IGF-I, IGF-II or the IGF-I receptor, survive, they do not develop diabetes or ketoacidosis [78].

There have been further insights by specifically manipulating the IGF-I gene in different tissues [79,80]. If the gene for IGF-I is specifically knocked out in the liver, serum IGF-I concentrations fall to 15–25% that of wild-type animals, whilst GH increases six-fold. The liver IGF-I-deficient animals

Table 2 Comparison between insulin and insulin-like growth factor (IGF)-I

		Insulin	IGF-I
Structure		Single-chain polypeptide	Single-chain polypeptide
Weight, kD		5807	7500
Chromosome		19	12
Binding proteins		None	6 high affinity 4 low affinity IGFBP related peptides
Receptor		Transmembrane glycoprotein	Transmembrane glycoprotein
Post receptor Signalling		IRS-1 Tyrosine kinase	IRS-1 Tyrosine kinase
Metabolic actions			
Glucose	Hepatic glucose production	⇓⇓	⇓
	Peripheral utilization	⇑ (only at high doses)	⇑
Protein	Protein synthesis	→	⇑
	Protein degradation	⇓	→
Free fatty acids	Lipolysis	↓	?↓

have similar glucose concentrations during fasting and following glucose challenge to normal animals but are hyperinsulinaemic and insulin-resistant. Interestingly, the mice lacking liver IGF-I were leaner than wild-type mice [79]. Although these data show a role for IGF-I in glucose homeostasis, it remains unclear whether the insulin resistance results directly from a reduction in serum IGF-I, indirectly through GH hypersecretion or via changes in body composition.

Effects of IGF-I administration in animals

When IGF-I is given to rats as an intravenous infusion, it causes hypoglycaemia by stimulating peripheral glucose uptake, glycolysis and glycogen synthesis, but has only a minimal effect on hepatic glucose production [81]. Using a hyperinsulinaemic euglycaemic clamp, IGF-I has been shown to suppress hepatic glucose output, although to a lesser degree than insulin at the doses used, and increase peripheral glucose utilization in dogs [82]. As hepatic expression of the IGF-I receptor is low, it is likely that this effect of IGF-I on hepatic glucose output is by an indirect mechanism.

Effects of IGF-I administration in humans

In 1963, Froesch *et al.* observed that serum had more insulin-like activity than could be explained by the insulin concentration alone [83]. They termed this phenomenon 'non-suppressible insulin-like activity' (NSILA) and went on to describe that, compared with insulin, the hypoglycaemic action of NSILA was more pronounced in muscle than adipose tissue [84]. NSILA was isolated and fully characterized in 1978, shown to be identical to Somatomedin C and termed 'insulin-like growth factor-I' [85].

The effects of an intravenous IGF-I infusion are similar to those described in animals and lead to hypoglycaemia [86]. A single intravenous dose of 100 μg/kg results in the rapid onset of symptomatic hypoglycaemia and is equipotent to 0.15 IU/kg of insulin [87]. A continuous intravenous infusion of IGF-I causes a 50% fall in C-peptide levels despite the maintenance of euglycaemia [88,89]. Insulin sensitivity is increased with respect to glucose by IGF-I through increased peripheral glucose uptake and decreased hepatic glucose production [90,91]. A subcutaneous infusion of IGF-I also causes hypoglycaemia, although the effect is slower in onset than insulin and decreases more slowly after the infusion is stopped because of the presence of the IGF binding proteins. The IGF-I infusion results in lower GH levels, which may also contribute to the improvements in insulin sensitivity.

IGF-I and diabetes

Type 1 diabetes

Insulin regulates hepatic IGF-I production and has an independent effect as well as an additive effect to GH [92,93]. Insulin-deficient diabetic rats have decreased hepatic GH binding whilst *in vitro* insulin has been shown to increase rat hepatocyte GH receptor expression [92]. However, in recent onset or mild streptozotocin-induced diabetes in rats, GH binding may be normal, implying that there may be additional post-receptor defects [94]. Insulin also increases IGF-I mRNA concentrations directly by increasing transcript stability rather than by increasing transcription [95].

Serum IGF-I concentrations are reduced in patients with Type 1 diabetes and are not normalized by intensive insulin treatment [94,96]. As the major source of circulating IGF-I is the liver and IGF-I levels are inappropriately low for the higher GH levels seen in Type 1 diabetes, it is thought that there is an acquired state of hepatic GH resistance. Seven days of rhGH treatment has little effect on IGF-I levels in patients with Type 1 diabetes. This points to the importance of portal insulin for hepatic IGF-I secretion [26]. The route of insulin administration in Type 1 diabetes appears important, as insulin delivered by the hepatic portal route (as occurs normally *in vivo*) is better at normalizing IGF-I levels and hepatic IGF-I expression in diabetic rats than subcutaneous insulin despite there being no difference in glycaemic control [73]. When insulin is given to

patients with Type 1 diabetes by a continuous intraperitoneal infusion using an implantable pump (CPII), portal insulin levels increase and there is near-normalization of IGF-I levels [97]. Low circulating IGF-I may explain the increased GH secretion seen in Type I diabetes through reduced negative feedback control. rhIGF-I replacement therapy in adolescents and adults with Type 1 diabetes results in a reduction in overnight GH secretion, indicating restoration of the normal negative feedback on pituitary GH secretion [98,99]. Thus IGF-I may exert its effect on glucose metabolism directly or indirectly by inhibiting GH secretion.

IGF-I treatment in Type 1 diabetes

There has been interest in treating patients with Type 1 diabetes with IGF-I at a replacement dose to correct the derangements of the GH–IGF axis and to exploit its hypoglycaemic actions. When a single dose of IGF-I (40 μg/kg) was administered to adolescents with Type 1 diabetes, hepatic insulin sensitivity increased and the glucose production rate fell [99,100]. Over 7 days, IGF-I (40 μg/kg bd) increased peripheral glucose uptake and reduced proteolysis, despite a reduction in insulin requirement to maintain euglycaemia [98,101].

After 3 months treatment with 40 μg/kg of rhIGF-I at night, insulin sensitivity and HbA_{1c} improved in adolescents with Type 1 diabetes. This was associated with a reduction in the insulin dose required to maintain glycaemic control [102]. Although these improvements were not maintained over the 6 months of the study, it was thought that the deterioration in control was related to poor compliance with the multi-injection regime rather than a reduction in the biological effect of IGF-I. More recently, the administration of a combination of IGF-I and IGFBP-3 over 2 weeks resulted in improvements in insulin sensitivity together with a reduction in the insulin requirements, without the side-effects that are associated with IGF-I alone [103].

It is unclear whether the improvement in metabolic control is achieved through a reduction in GH secretion or through a direct hypoglycaemic action of IGF-I. In an attempt to address this issue, Simpson *et al.* investigated the effects of IGF-I using an octreotide and glucagon infusion to suppress endogenous GH secretion in patients with Type 1 diabetes. IGF-I administration led to a decrease in hepatic glucose production, an increase in peripheral glucose utilization and an increase in glucose metabolic clearance rate when compared with both GH and placebo, suggesting that IGF-I has an independent effect on glucose metabolism [104].

IGF-I treatment in Type 2 diabetes

Similar trials have been performed to those involving Type 1 diabetic patients, but the doses of rhIGF-I used have been larger. rhIGF-I (80–120 μg/kg bd) results in an improvement in glycaemic control with reduced fasting plasma glucose, insulin and C-peptide concentrations in association with a sustained rise in serum IGF-I to values often above the normal physiological range [105,106]. rhIGF-I therapy was associated with a reduction in fat mass, which may partly explain the improved insulin sensitivity.

The use of high doses of IGF-I has been limited by a significant number of side-effects, particularly jaw ache, optic disc swelling, arthralgia, myalgia and headache [106]. The exact cause of these side-effects is unknown but it has been hypothesized that they result from the high concentrations of free IGF-I that occur after the supra-physiological IGF-I doses [107]. IGF-I was subsequently withdrawn from development as an adjunct to treatment in diabetes. Recently, 2 weeks treatment with combined IGF-I/IGFBP3 in Type 2 diabetes resulted in a reduction in insulin doses and fasting blood glucose concentrations, and an increase in free and total IGF-I concentrations. Notably different from previous studies with IGF-I alone, this was achieved with minimal side-effects [108].

IGF-I treatment in growth hormone deficiency

The metabolic actions of IGF-I have been studied by administering IGF-I to severely GH-deficient young adults [109,110]. IGF-I and GH both increased lean body mass and decreased the percent fat mass, by promoting lipolysis and lipid oxidation. Seven days' treatment with rhIGF-I had no effect on hepatic glucose output, while rhGH increased hepatic glucose output. Both hormones increased lipid oxidation. Interestingly, after 8 weeks of treatment, both hormones increased hepatic glucose output, but in contrast to rhGH treatment, rhIGF-I was not associated with decreased carbohydrate oxidation or increased glucose and insulin concentrations. It is not clear why rhIGF-I should have increased hepatic glucose output in these studies, as the majority of published studies show IGF-I to have either decreased or had no effect on hepatic glucose output.

IGF-I treatment in severe insulin resistance syndromes

Extreme insulin resistance occurs in patients who have primary defects in insulin action at the receptor or post-receptor levels, and may lead to frank diabetes mellitus that does not respond to insulin therapy.

The first report of the use rhIGF-I to treat insulin resistance was in a girl with Type 1 diabetes who required insulin doses of > 2000 IU/h [111]. During an episode of diabetic ketoacidosis, she was treated with intravenous rhIGF-I, which resulted in a rapid lowering of her plasma glucose concentration. After the acute episode, she was treated with weekly subcutaneous rhIGF-I (500 μg/kg) maintaining acceptable glycaemic control. She did not respond to a lower dose, and therapy had to be discontinued because of side-effects. Further studies have corroborated these findings in syndromes of severe insulin resistance with and without receptor abnormalities (Table 3) [112–117]. Although these studies show an improvement in glycaemic control and a reduction in the dose of insulin

Table 3 Studies involving the use of rhIGF-I in the treatment of severe insulin resistance

Diagnosis	IGF-I dose	Duration	Effect	Reference
Rabden–Mendenhall syndrome	100 μg/kg bd		Glu ↓ acutely but not chronically	[112]
Type A insulin resistance			Glu, Ins and C-pep ↓	[113]
Severe insulin resistance	sc rhIGF-I (150 μg/kg)	5 days	Glu, Ins and C-pep ↓ Lipids →	[114]
Type A insulin resistance without IR mutations	100 μg/kg	4 weeks	Glu, Ins, fructosamine ↓. Si ↓ (shown by IVGTT in one patient)	[115]
Severe insulin resistance without IR mutations	100 μg/kg bd	1 month	Diabetic patients (n = 4): HbA_{1c} and ins requirement ↓. Ins ↓ in non-diabetic patients	[116]
11 subjects IR and post receptor defects	100–400 μg/kg bd	Mean 9 months Range 1.5–16 months	Glu and Ins ↓ (acutely and chronic)	[117]

Glu, Fasting plasma glucose; Ins, fasting plasma insulin;. C-pep, C-peptide; Si, insulin sensitivity; IR, insulin receptor.

required, the doses of rhIGF-I used were high, as was the rate of side-effects.

The mechanisms by which this fall in glucose is achieved have not been studied in humans, but mice, which are genetically deficient for the insulin receptor, provide one possible model [118]. In this model, IGF-I led to phosphorylation of IGF-I receptors and increased PI3-kinase p85 subunit concentrations in the liver and skeletal muscle, suggesting that IGF-I stimulated glucose uptake via the IGF-I receptor in a PI3-kinase-dependent manner. The failure of IGF-I to prevent the death of these animals suggests that IGF-I receptors cannot effectively mediate all the metabolic actions of insulin receptors.

IGF-I treatment and GH insensitivity (Laron) syndromes

The relative contributions of low GH and IGF-I concentrations to the alterations in insulin sensitivity in GH deficiency are difficult to dissect. There are, however, insights from patients with primary GH resistance, secondary to inherited molecular defects of the GH receptor or post-receptor pathways [119]. The clinical course is characterized by progressive obesity, insulin resistance, and a tendency for hypoglycaemia, followed later in life by hyperinsulinaemia, glucose intolerance and even diabetes. In adulthood, β-cell failure may ensue, resulting in insulinopenia and Type 2 diabetes [119].

Circulating GH concentrations are increased and GH therapy produces no clinical benefit. In contrast, IGF-I treatment of children with Laron syndrome can normalize many of these biochemical abnormalities, including glucose intolerance and hyperinsulinaemia. IGF-I treatment may even be complicated by hypoglycaemia [120].

Gene deletion of IGF-I

Woods *et al*. reported a patient with a homozygous partial deletion of the IGF-I gene, resulting in IGF-I deficiency [121]. This child had insulin resistance, hyperinsulinaemia and short stature. IGF-I therapy resulted in a dose-dependent improvement of insulin sensitivity into the normal range and a reduction in basal and stimulated insulin concentrations [122].

IGF binding proteins and glucose metabolism

The IGFs are present in the circulation and throughout the extracellular space almost entirely bound to members of a family of at least six high-affinity IGF binding proteins (IGFBP-1 to -6) [123,124]. Less than 1% of the IGF in the circulation is free, with 90% bound in a stable 150-kD ternary complex comprising IGF-I or IGF-II, IGFBP-3 and an acid-labile subunit. IGFBP-1, -2, -4 and -6 bind most of the remaining IGF in a binary complex of 30–40 kD, while IGFBP-5 is also capable of forming a ternary complex with IGF-I and the acid-labile subunit. All six IGFBPs have negligible affinity for insulin. The IGFBPs co-ordinate and regulate the biological functions of the IGFs, although we have little knowledge about how this works. They transport IGFs and control their efflux from the circulation. The IGFBPs prolong the half-lives of IGFs and regulate their metabolic clearance. Alteration in the quantity and function of the IGFBPs may therefore affect the hypoglycaemic effect of the IGFs.

IGFBP-1

Although not the most predominant IGF-I binding protein, IGFBP-1 is the only binding protein to show rapid regulation of concentration *in vivo*. Under many circumstances, IGFBP-1 is inversely related to insulin concentration [125] and has a diurnal variation, with the highest concentrations being overnight when insulin levels are lowest [126]. IGFBP-1 concentrations are high in Type 1 diabetes and correlate with glycosylated haemoglobin [127]. A bolus of intravenous IGFBP-1 causes hyperglycaemia and prevents exogenous IGF-I from having a hypoglycaemic action in rats [128]. In normal human subjects there is an inverse relationship between IGFBP-1 and free IGF-I levels. Although a single intravenous bolus of IGF-I acutely stimulates IGFBP-1 production [129], continuous subcutaneous administration of IGF-I over 3 days leads to an increase in free and total IGF-I concentrations with a decrease in IGFBP-1 concentrations [130]. These data suggest that IGFBP-1 can acutely regulate bioactivity of IGF-I concentrations and suggest a role for IGF-I in glucose regulation.

There are situations where serum IGFBP-1 is not inversely associated with insulin. One example of this is chronic liver disease, where both insulin and IGFBP-1 concentrations are higher than in normal controls [131]. This may reflect differences in the importance of portal vs. peripheral insulin concentrations. In chronic liver disease, porto-systemic shunts develop, which result in increased peripheral insulin concentrations at the expense of hepatic hypo-insulinaemia. This may explain the observation that IGFBP-1 concentrations are higher in children with portal hypertension compared with those children without portal hypertension [132].

IGFBP-1 transgenic animals

Over-expression of IGFBP-1 in transgenic mice has provided insight into the physiological role of this binding protein in modulating the metabolic effects of the IGFs. In most strains of IGFBP-1 transgenic mice, the animals develop fasting hyperglycaemia, impaired glucose tolerance, and modest insulin resistance in skeletal muscle and hepatic tissue [133,134].

The effect of IGFBP-1 is to attenuate the hypoglycaemic action of IGF-I. If insulin or des (1–3) IGF-I, an analogue of IGF-I that does not bind IGFBP-1, is infused, there are no differences in the hypoglycaemic response between normal and animals transgenic for IGFBP-1 [133]. Similarly, the glucose response to subcutaneous insulin was similar in transgenic and wild-type mice, suggesting that constitutive over-expression of IGFBP-1 results in impaired glucose tolerance despite normal insulin sensitivity [135]. There is sexual dimorphism in at least one strain of transgenic mice, with male mice having higher stimulated glucose and insulin levels than females [134].

The transgenic animals have increased gluconeogenesis and hepatic insulin resistance, which contributes to the fasting hyperglycaemia [136]. In isolated hepatocytes, the inhibition of glucose production from pyruvate by insulin is decreased in transgenic mice compared with wild-type animals [136]. Furthermore, serum from transgenic mice results in more glucose production by hepatocytes than serum from wild-type mice [136].

IGFBP-2 transgenic animals

Transgenic mice, which over-express IGFBP-2, have reduced fasting serum glucose and insulin concentrations, but post-prandial concentrations are unaffected by the genotype [137].

Non-islet cell tumour hypoglycaemia

Non-islet cell tumour hypoglycaemia (NICTH) is a rare endocrine paraneoplastic syndrome, which is characterized by recurrent fasting hypoglycaemia in the absence of insulin and C-peptide [138,139]. The precise cause of the hypoglycaemia in NICTH remains unclear (Fig. 3). IGF-II is normally synthesized as pro-IGF-II and this is processed in a stepwise fashion to form the mature protein. In NICTH, there is abnormal processing of

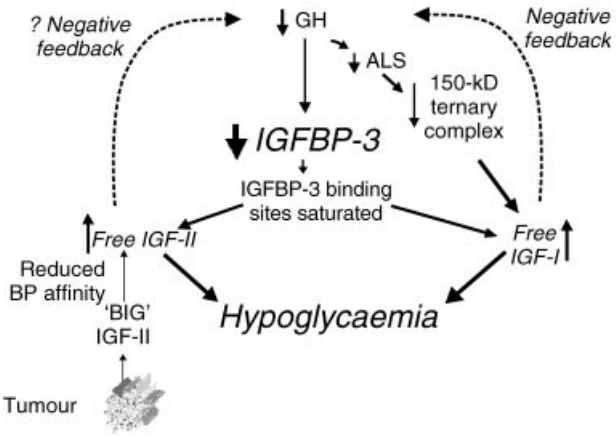

Figure 3 Mechanism for hypoglycaemia in non-islet cell tumour hypoglycaemia.

IGF-II and larger isoforms of IGF-II, known as 'big IGF-II', are invariably released into the circulation. Big IGF-II binds with lower affinity to IGFBP-3 and the acid-labile subunit and consequently has higher bioavailability and bioactivity [140,141]. The switch from IGF-II to big IGF-II appears to be a key step in causing hypoglycaemia as IGF-II is over-expressed in a number of tumours, such as the embryonic Wilm's tumour, without the development of hypoglycaemia [142]. The hypoglycaemia may result through a direct hypoglycaemic action of big IGF-II and indirectly through suppression of GH secretion [143–146]. The reduction in GH secretion results in a reduction of IGF-I, IGFBP-3 and acid-labile subunit (ALS). The reduction in IGFBP-3 and ALS is associated with increased free IGF-I concentrations, which may also contribute to the hypoglycaemia [147]. GH administration in NICTH leads to increased IGFBP-3 and ALS production and has been used to treat the hypoglycaemia of NICTH successfully both in the short term [148] and long term [145]. The massive over-production of big IGF-II may also lead to saturation of IGF-I binding sites of the IGFBPs with a consequential further increase in free IGF-I.

Conclusions

Although the relative contributions of GH and IGF-I to normal glucose homeostasis are difficult to study, there is evidence from patients, animal models and cell cultures to indicate a role for both GH and IGF-I in normal glucose homeostasis. The biological reason for the need for GH and IGF-I may be to allow partitioning of glucose to metabolically active tissues at a time of need and to organize energy storage at times of substrate excess. This is of particular importance in skeletal muscle, which is responsible for 80% of post-prandial glucose transport. Furthermore, as GH has powerful lipolytic properties, this provides glycerol as a gluconeogenic substrate and NEFA as an alternative substrate to glucose at times when glucose or glycogen may be in short supply, such as during fasting or exercise.

The GH–IGF axis is deranged in patients with diabetes and this probably contributes to both the metabolic disturbance and the susceptibility to microvascular complications. Treatment with IGF-I results in improvements in metabolic control but its use has been limited by side-effects. More recently, the combination of IGF-I and IGFBP-3 has been shown to improve metabolic control but without these side-effects. Further work will be needed to confirm the safety and efficacy of this compound.

While insulin may have the overall responsibility to control glucose concentrations, primarily through its effects on hepatic glucose output, IGF-I acting through both endocrine and local mechanisms may serve to fine tune insulin sensitivity. Finally, the contribution of GH and IGF-I to glucose homeostasis may increase at times where insulin action is reduced, either through insulin deficiency or insulin resistance.

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