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Minkowski Award, 1967, Stockholm

Dr. E. R. Froesch was born in Zürich in 1929. He obtained an M.D. in Zürich in 1954. From 1954 to 1957 he was Research Fellow and Assistant in Medicine at Harvard Medical School and the Peter Bent Brigham Hospital, Boston, Mass., USA. Between 1970 and 1991 Dr. Froesch was Associate Professor of Pathophysiology in the Department of Medicine and Head of Endocrinology and Diabetology (Metabolic Unit). Since 1991 he has been a Full Professor. Since 1987 Dr. Froesch has been a member of the Council of the Swiss National Science Foundation. The main focus of Dr. Froesch's research activities has been hereditary fructose intolerance; extrapancreatic tumour hypoglycaemia; adipose tissue metabolism and antilipolytic agents; parenteral nutrition; optimal metabolic control of diabetes; description of a new form of familial Cushing's syndrome: micronodular dysplasia (Swiss syndrome, Carney complex); characterization of non-suppressible insulin-like activity (NSILA-S) and NSILA-P); characterization of insulin-like growth factors I and II (IGF I and IGF-II); first studies with biosynthetic IGF I; first studies with rhIGF in man.

Recombinant human insulin-like growth factor-I: a therapeutic challenge for diabetes mellitus

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Summary Insulin-like growth factor I (IGF I) is an endocrine hormone that mediates most of the effects of pituitary growth hormone. Other important regulatory factors of serum IGF I levels are insulin and nutrition. Most of the circulating IGF I is bound to three IGF binding proteins (BP), mostly IGFBP-3, BP-2 and BP-1. IGF I is also produced by many cells in the body where it exerts autocrine and/or paracrine effects. IGF I has a specific receptor on most cells, the so-called type 1 IGF receptor. When IGF I is administered intravenously as a bolus it leads to acute hypoglycaemia in a similar way to insulin and mainly with the insulin receptor. Chronic administration of IGF I to hypophysectomized or diabetic rats leads to prominent anabolic effects and growth. In this manuscript, metabolic and endocrine effects of recombinant IGF I are discussed. Recombinant IGF I therapy increases energy expenditure and lipid oxidation and decreases proteolysis and protein oxidation. These effects occur despite a partial inhibition of insulin and growth hormone secretion. The therapeutic spectrum of recombinant IGF I, consisting of inhibition of catabolism, stimulation of anabolism, decreases of triglyceride and cholesterol levels and a striking increase in insulin sensitivity, renders IGF I a very interesting, powerful tool for insulin-resistant states such as non-insulin-dependent diabetes mellitus. [Diabetologia (1994) 37 [Suppl 2]: S179–S185]

Key words rhIGF I, lipid metabolism, anabolism, energy expenditure, insulin sensitivity, non-insulin-dependent diabetes mellitus.

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Abbreviations: NIDDM, Non-insulin-dependent diabetes mellitus; IGF-I, insulin-like growth factor-I; IGFBP, insulin-like growth factor binding protein; rhIGF-I, recombinant IGF I.

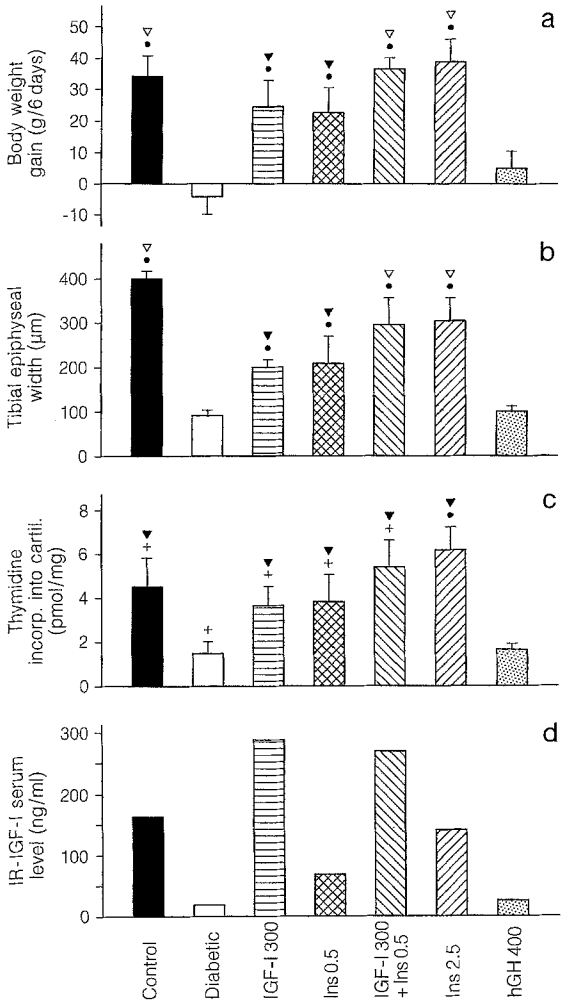

Fig. 1 a–d. Stimulation of growth indices in diabetic rats by insulin, IGF-I and human growth hormone (hGH). (**a**) Gain in body weight; (**b**) tibial epiphyseal width; (**c**) thymidine incorporation; (**d**) immunoreactive IGF-I concentration. Hormones were administered over 6 days by osmotic minipumps in the following daily amounts: insulin, 0.5 IU ($n=5$) and 2.5 IU ($n=6$); hGH, 400 mU ($n=5$); rhIGF-I, 150 µg ($n=4$) and 300 µg ($n=11$); a combination of 300 µg rhIGF-I and 0.5 IU insulin ($n=6$). Controls: non-diabetic rats of the same age. Bars represent means. Student's *t*-test was used for statistical analysis. All values in each panel were tested against the value of the untreated diabetic rats; ●, $p<0.001$; +, $p<0.01$. All values of each treatment group were also tested against each other: ▼, no significant difference against values designated by ▼; ▽ no significant differences against values designated by ▽; ▽ vs ▼ $p<0.05$–0.001. In the radioimmunoassay for IGF-I, human [^{125}I]IGF-I served as a tracer and human IGF-I for standard dilutions. Rat IGF-I levels are, therefore, equivalents of human IGF-I and should not be considered as absolute values. It is impossible to distinguish between endogenous rat IGF-I and infused rhIGF-I. The rats were rendered diabetic by an i.v. injection of 110 mg streptozotocin/kg body weight and were used if their body weight remained constant during the second and third week after streptozotocin. Data derived from [5] with permission

In my Minkowski Lecture in 1967 I presented results of experiments on the inhibition of lipolysis with analogues of nicotinic acid in which a short-lived inhibition of non-esterified fatty acid release was followed by an overshooting lipolysis which explains why these drugs could not possibly function as therapeutic agents to equilibrate glucose metabolism in diabetic subjects [1, 2]. At the end of the lecture I cautiously ventured the guess that human IGF I, then called non-suppressible insulin-like activity, might one day become a useful adjuvant therapy to conventional insulin therapy in diabetes mellitus, because it is much more active on muscle than on adipose tissue when compared to insulin. When the Minkowski Prize winners met again in 1984 we had made considerable progress along these lines and were able to compare insulin with recombinant IGF I in their effects on the hypophysectomized rats and also streptozotocin-diabetic rats [3]. By that time, we and others had proven that IGF I was the mediator of the growth-promoting effects of growth hormone [4] and that IGF I could substitute for insulin in promoting growth in growth-arrested, severely-diabetic rats [5] (Fig. 1). It was clear even then that IGF I was the major anabolic agent for the tissues involved in longitudinal growth mediating the effects not only of growth hormone but also those of insulin [6].

Serum concentrations of IGF I are dependent on the growth hormone, insulin and nutritional status of animals and man [7]. When growth hormone in hypophysectomized animals or insulin in diabetic animals were lacking, administration of recombinant IGF I restored growth and weight gain. However, it was clear even then that, although rhIGF I by no means normalized glucose, lipid, and protein metabolism in diabetic rats [5], it was, nevertheless, a potent growth-promoting hormone. Meanwhile it was recognized that the insulin receptor does not mediate processes that have to do with growth and differentiation. When insulin is used in very large doses in cell culture systems, it is a potent mitogen and also a differentiation-enhancing hormone [8], however, most of the effects of these pharmacological doses of insulin are mediated by the type 1 IGF I receptor. Conversely, IGF I does have hypoglycaemic effects when it is administered in a bolus fashion and these effects of IGF I on glucose metabolism are mediated mostly via the insulin receptor [9–11].

Another important difference between insulin and IGF I is their mode of secretion. Whereas insulin is mostly secreted through a regulated secretory pathway and only by one cell, namely the beta cell, IGF I is synthesized and produced by many cells in the body and by a constitutive secretory pathway [12]. Circulating IGF I stems mostly from the liver [12], and is bound mainly to the 150 kDa binding protein complex, a heterotetrimer, consisting of a subunit of IGFBP-3, an acid-labile subunit and one molecule of

IGF I or IGF II. In this form the half-life of IGF I is between 12 and 16 h [13]. Two other binding proteins, BP-1 and BP-2, with molecular sizes of around 35,000 have an apparent half-life of between 30 and 60 min and, in contrast to the 150 kDa complex, can cross the capillary barrier so that IGF I bound to BP-1 and BP-2 can get in contact with the type 1 IGF receptor [14].

Another complication with respect to the physiology of IGF is the fact that many cells in the body can produce and secrete IGF I in their surroundings so that IGF I may act in an autocrine/paracrine manner [15]. This is also true for the binding proteins so that the regulation of differentiation and growth processes has endocrine, paracrine and autocrine aspects which are extremely difficult to sort out [16].

In this manuscript I shall concentrate on the effects of recombinant IGF I in normal subjects, NIDDM patients, insulin-resistant type A diabetic patients, and growth hormone-deficient subjects.

Acute effects of recombinant IGF I on glucose metabolism of normal subjects

IGF I has been administered as an intravenous bolus to several species including normal human subjects. In each case, IGF I leads to acute hypoglycaemia which is indistinguishable from insulin-induced hypoglycaemia [17]. The recovery from hypoglycaemia is also similar and the symptoms of hypoglycaemia are essentially the same. Hypoglycaemia in this situation is due to cross-reaction of free IGF I with the insulin receptor. This can be said with certainty since bolus injections of IGF I have also been administered to insulin-resistant subjects with functionally deficient insulin receptors. In these subjects, two consecutive boluses of IGF I were able to reduce blood glucose from an average of 12–3.5 mmol/l within 6 h [18]. Glucose assimilation was enhanced by IGF I but the rate was not comparable to that observed in normal subjects after insulin or IGF I injection. Therefore, functional insulin receptors are a prerequisite for the rapid hypoglycaemic effect of insulin. Therefore, it appears that the type 1 IGF receptor does not utilize the same transduction system with respect to glucose transport as the insulin receptor. Type 1 receptors are particularly abundant on muscle, i.e. the main organ of glucose storage under insulin stimulation. Therefore, the clear-cut difference between the behaviour of type A insulin-resistant patients and normal subjects strongly suggests that subjects who have a competent type 1 IGF receptor but no functional insulin receptor cannot immediately react to IGF I or insulin because the signal transduction system behind these receptors is different.

Infusion of IGF I over several hours leads to an inhibition of proteolysis and, at higher doses, to increased glucose assimilation by muscle and inhibition of lipolysis [19–21]. These effects of IGF I obtained under euglycaemic clamp conditions are mostly mediated via the insulin receptor but for some, such as the inhibition of proteolysis, the type 1 IGF receptor may well be responsible. The question regarding receptor mediation of IGF effects can be better answered by long-term experiments with IGF I administration.

Endocrine effects of rhIGF I during prolonged therapy

When IGF I reaches the bloodstream slowly by way of an insulin pump as a continuous subcutaneous infusion or by two daily subcutaneous injections hypoglycaemia does not occur when the dosage is below 10 μg per kg of ideal body weight per hour.

IGF I inhibits insulin secretion in normal subjects [17, 22], NIDDM diabetic subjects [23], insulin-resistant type A diabetic subjects [18] as well as in patients with pituitary insufficiency (M Hussain, personal communication). During IGF I administration to normal subjects, fasting and postprandial insulin levels are decreased by approximately 50 % but the reaction of the beta cells to an intravenous or oral glucose load remains rapid [22, 24]. Therefore, glucose tolerance remains normal. Since in all test situations the ratio of blood glucose to serum insulin was increased, this finding was interpreted to mean that during IGF I administration some tissues exhibited increased insulin sensitivity. Another direct endocrine effect of rhIGF I is the partial inhibition of growth hormone secretion [17]. Fasting levels of growth hormone are decreased by IGF I administration, nocturnal peaks of growth hormone are blunted and during arginine stimulation the growth hormone response is partially inhibited [24]. The inhibition of growth hormone secretion by rhIGF I may contribute to increased insulin sensitivity during rhIGF I administration.

IGF I effects in NIDDM diabetic subjects

rhIGF I was administered over 5 days at a dose of 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$, in two subcutaneous doses at 08.00 and 18.00 hours to eight NIDDM subjects who, at the time of this study, were not receiving any other therapy with the exception of a constant isocaloric diet. As expected the elevated fasting blood glucose levels decreased to normal levels despite the fact that fasting insulin concentrations decreased to 60 % of the initial values [23] (Fig. 2). IGF I also had consistent effects on lipid metabolism. Fasting VLDL triglyceride levels decreased rapidly after initiation of IGF I therapy followed later on by a fall of LDL cholesterol values [25]. HDL levels did not change to any

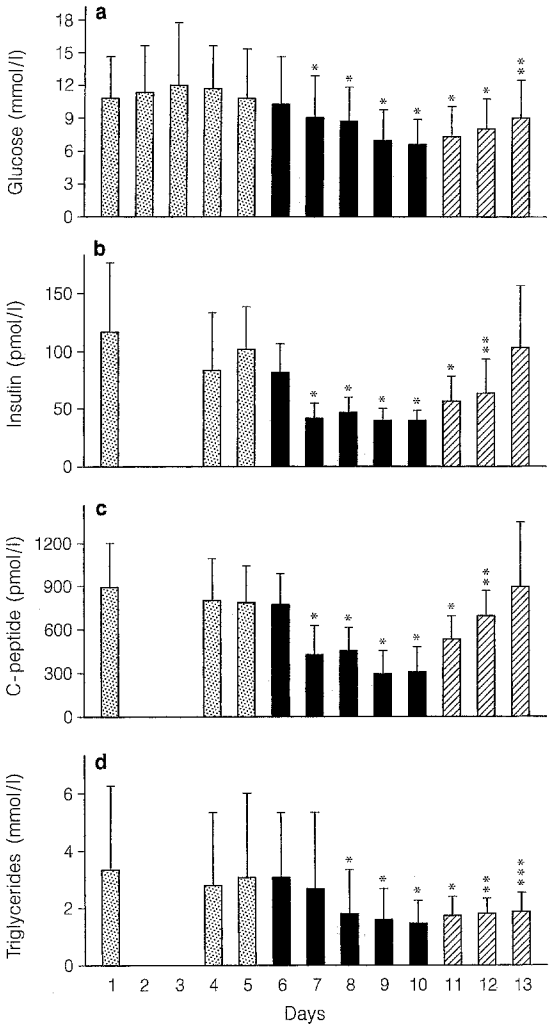

Fig. 2 a–d. Effects of rhIGF-I on fasting glucose, insulin, C-peptide, and triglyceride levels in eight NIDDM patients before, during and after treatment with s.c. 2 × 120 μg rhIGF-I/kg daily. Mean ± SD of plasma glucose (**a**), insulin (**b**), C-peptide (**c**), and total triglyceride levels (**d**) in eight NIDDM patients before (▨), during (■), and after (▨) treatment. $^{*}p < 0.01$, $^{+}p < 0.02$, $^{\#}p < 0.05$ vs control. Paired differences were analysed using the two-tailed Wilcoxon's matched pairs signed-rank test [23]

significant extent. However, LP(a) levels were also decreased [25]. The most likely explanation for these findings is the following: IGF I decreases secretion of insulin into the portal vein so that hepatic VLDL triglyceride synthesis and secretion is diminished. Since VLDL particles are metabolized to LDL particles, the net result of IGF I therapy is a considerable fall of VLDL triglyceride levels and later on also of LDL cholesterol levels. Similar lipid-lowering effects of IGF I administration were also observed in normal subjects but not in patients with type A insulin resistance, presumably because the latter have no functional insulin receptors on hepatocytes so that their lipid metabolism in the liver is independent of the insulin concentration [26].

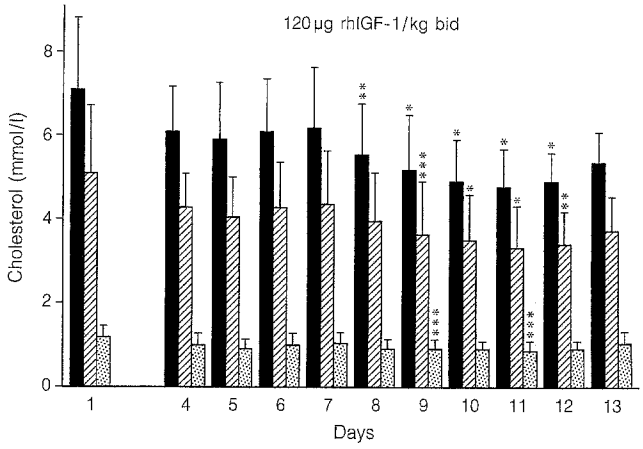

Fig. 3. Total ■ LDL- ▨ and HDL ▨ -C levels before (days 1, 4, 5), during (days 6–10), and following (days 11–13) s.c. rhIGF-I administration at a dose of 2 × 120 μg rhIGF-I/kg daily in eight NIDDM patients. Mean ± SD are given. Symbols and statistical analysis as in Fig. 2 [From 25]

Acute and chronic effects of IGF I in type A insulin-resistant diabetic patients

An acute bolus injection of IGF I was administered to two young type A diabetic females and, as already mentioned, their blood glucose fell very slowly to the normal range at a time when their very high insulin concentrations decreased to 50 % or less compared to the fasting levels [18]. In a 5-day treatment study the markedly elevated fasting blood glucose levels were normalized and postprandial blood glucose levels improved [26]. Again, insulin levels were decreased throughout the study. These results tend to show that IGF I has a beneficial effect on hyperglycaemia in insulin-resistant type A diabetic patients. Japanese patients were treated for a prolonged period of time with relatively high doses of rhIGF I with similar results [27].

Analysis of the mechanism of action of IGF I in normal subjects and in growth hormone-deficient patients

Normal subjects were submitted to an IGF I infusion of 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and a normoglycaemic hyperinsulinaemic clamp was performed on the fifth day of IGF I administration [24]. In these subjects, insulin secretion was inhibited to about 50 % both during fasting and during an i.v. glucose tolerance test. The i.v. glucose promptly stimulated increased insulin secretion and glucose assimilation was the same as without IGF I. However, the subjects were in a new energy balance. During IGF I administration, total energy expenditure was increased by 20 %, protein oxidation decreased, lipid oxidation increased while glucose disposal, oxidative and non-oxidative, remained unchanged. Increased lipid oxidation in these sub-

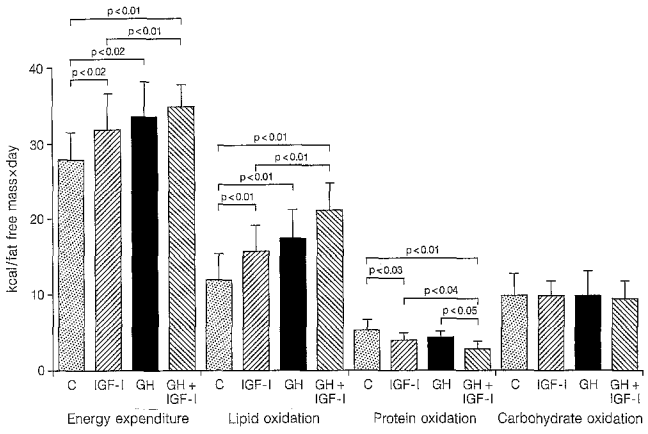

Fig. 4. Basal energy expenditure, lipid, protein and carbohydrate oxidation in eight growth hormone-deficient subjects during the following treatments: c, control; IGF, 10 μg rhIGF-I · kg^{-1} · h^{-1} s.c. infused during 7 days and determinations carried out on day 5; GH + IGF-I, growth hormone pre-treatment as above for 14 days, then IGF-I administered as above together with IGF-I (as above) and determinations carried out on day 5. All data are expressed as mean ± SD. Comparisons were performed by analysis of variance (ANOVA) [From 29]

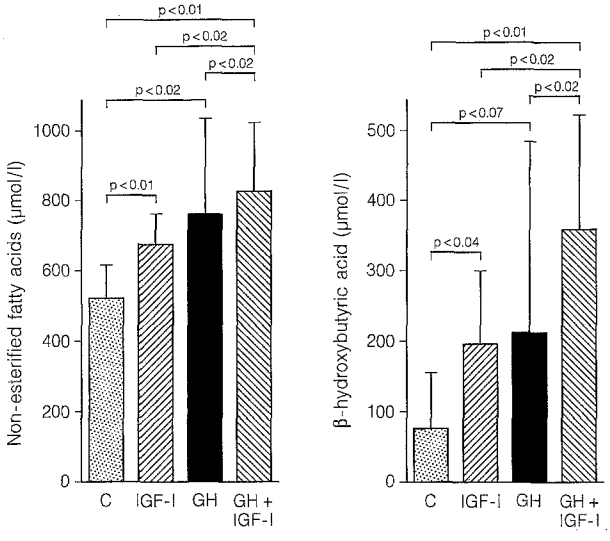

Fig. 5. Non-esterified fatty acid and β-hydroxybutyrate levels in growth hormone-deficient subjects determined on day 5 of treatment periods as described in the legend to Fig. 4. Data and statistical analysis as in Fig. 4 [From 29]

jects during IGF I administration accounts for the increase in total energy expenditure. Elevated levels of non-esterified fatty acids and β-hydroxybutyrate serve as substrates of increased lipid oxidation. Increased non-esterified fatty acid and β-hydroxybutyrate levels under the influence of IGF I administration can best be explained by the decreased insulin levels and the consecutive loosening of the brakes on lipolysis. In this context it is interesting to note that VLDL secretion from the liver is decreased despite increased fluxes of non-esterified fatty acids to the liver, presumably also because of decreased portal insulin levels. The reason for increased energy expenditure under IGF I therapy remains to be elucidated. Several factors may contribute:

1. Increased ATP requirement for protein anabolism.
2. Under the influence of IGF I, the conversion of thyroxine to triiodothyronine is increased.
3. The other constant effect of IGF I is an increase of the heart rate of 10–15 % with a concomitant increase of blood flow.
4. It appears that IGF I reduces the vascular resistance in the kidney, skin, muscle, and other tissues so that heat dissipation may be increased, again explaining some of the increase in total energy expenditure.

The effect of IGF I on vascular resistance in various tissues has not yet been studied in any detail with the exception of the rat which has a glomerular filtration pressure that is not increased by IGF I despite glomerular hyperfiltration [28]. These vascular effects of IGF I are, however, important and need to be studied in detail before IGF I can be considered as a therapeutic peptide. They may be beneficial in some conditions and harmful in others (e.g. diabetic retinopathy).

The role of growth hormone in the changes of glucose and lipid metabolism induced by IGF I

So far, we have focused on the role of IGF I as an inhibitor of insulin secretion to explain changes in glucose and fat metabolism. Another important player is the growth hormone and the fact that IGF I inhibits growth hormone secretion. Therefore, a study was undertaken in eight growth-hormone-deficient adult subjects who received either IGF I alone, growth hormone alone or growth hormone plus IGF I. Both IGF I and growth-hormone stimulated energy metabolism to about the same extent and the effects of both hormones given together were additive (Fig. 4). Both hormones alone increased lipid oxidation, decreased protein oxidation and failed to change glucose oxidation. This means that similar overall effects on substrate oxidation and energy expenditure were observed whether insulin secretion was decreased during IGF I administration or increased during growth-hormone administration. The mechanisms by which the two hormones made non-esterified fatty acids and β-hydroxybutyrate available for increased lipid oxidation are additive (Fig. 5). IGF I decreased insulin secretion so that the brakes on lipolysis were released, whereas growth hormone had a stimulatory effect on lipolysis despite increased insulin levels [24, 29]. When both hormones were given together, these two effects were additive and lipid oxidation was further enhanced. During a normoglycaemic hyperinsulinaemic clamp, insulin sensitivity of the

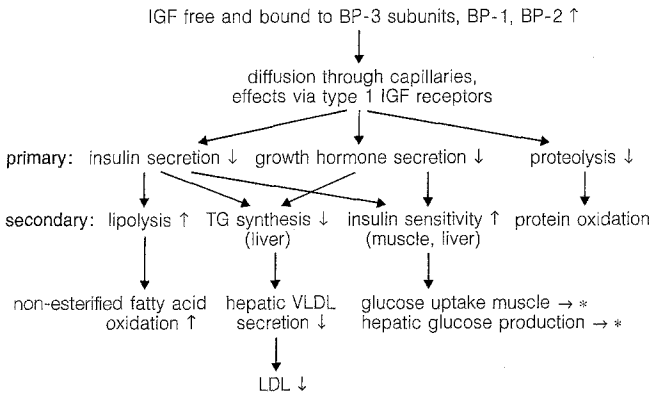

Fig. 6. Metabolic and endocrine sequalae of IGF-I therapy

growth-hormone-deficient subjects was assessed in all three hormone treatment situations and compared with the control period. Insulin sensitivity was increased by IGF I, decreased by growth hormone and again increased by IGF I when given together with growth hormone. Therefore, IGF I increases insulin sensitivity by decreasing fasting and postprandial insulin levels and by increasing the sensitivity of muscle to insulin, whereas growth hormone decreases insulin sensitivity of the liver, muscle and adipose tissue as demonstrated by increased non-esterified fatty acid and glucose levels despite high insulin levels.

Side-effects of IGF I

By dosing IGF I correctly, the danger of hypoglycaemia can be excluded. Nevertheless, IGF I does have side effects when administered in the doses which we have mostly used ($10\ \mu g \cdot kg^{-1} \cdot h^{-1}$). At higher doses, fasting hypoglycaemia and impaired glucose tolerance has been noted [30]. Normal subjects, diabetic patients and hypopituitary patients tend to retain water and gain weight under the influence of IGF I. Fluid retention occurs on days 3–4 of treatment and is usually limited to between 1 and 1.5 kg. Fluid retention, mostly in the skin, appears to be responsible for the weight gain. Some subjects had a somewhat puffy face but none had pitting oedema. One normal subject and one hypopituitary subject complained of slight headache. Some patients complained of pain over the parotid glands when they started eating.

As these changes point to a hyperperfusion of the skin, kidney and other tissues, we have investigated fluorescein distribution in the retina after i.v. injection and in the skin during IGF I administration and have found increased fluorescein diffusion in both tissues. Earlier we reported on renal plasma flow and glomerular filtration rate without an increase of microalbuminuria [31]. In the rat, IGF I administration leads to glomerular hypertrophy without glomerulosclerosis [28]. These effects of IGF I need to be more closely investigated since it could well be that increased capillary circulation might also be accompanied by leakage.

Conclusions (Fig. 6)

The insulin-like activities of IGF I which are typically seen in the acute experimental situation when IGF I crossreacts with the insulin receptor are not observed when IGF I is administered chronically. In contrast, IGF I partially inhibits insulin and growth hormone secretion and thereby leads to increased insulin sensitivity. We have, therefore, investigated the effects of IGF I administration on glucose and lipid metabolism in normal subjects and NIDDM subjects. In the latter, hyperglycaemia was improved, insulin sensitivity increased and VLDL triglyceride and LDL cholesterol levels decreased. In insulin-resistant type A diabetic patients, IGF I administration led to an improvement of fasting glucose levels and some improvement of postprandial glucose concentrations, again at markedly decreased insulin levels.

IGF I had the anticipated protein-sparing effect. Further investigations in normal subjects and in growth hormone-deficient patients showed that IGF I increases total energy expenditure. Under the influence of IGF I and decreased insulin concentrations, non-esterified fatty acid and β-hydroxybutyrate concentrations were increased and served as substrates for increased lipid oxidation. When IGF I was administered together with growth hormone, these effects on energy expenditure and lipid oxidation were additive and protein oxidation was further reduced. In conclusion, we may speculate that IGF I would be the ideal peptide for the treatment of NIDDM subjects leading to decreased insulin secretion and normalization of hyperglycaemia, whereas for the catabolic patient the combination of IGF I and growth hormone would probably be appropriate, since the protein-sparing effect of these two hormones is additive.

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