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Metabolic Actions of IGF-I in Normal Physiology and Diabetes

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Synopsis

Insulin-like growth factor-I (IGF-I) is closely related to insulin but has distinct metabolic actions. IGF-I is an important stimulant of protein synthesis in muscle but it also stimulates free fatty acid utilization. Important indirect effects of IGF-I that influence metabolism include suppression of growth hormone secretion and at supraphysiologic concentrations suppression of insulin secretion. IGF-I actions are regulated by IGF binding proteins and in obesity and metabolic syndrome there is major dysregulation of IGF binding protein secretion resulting in alterations in the concentration of free IGF-I and IGF-I actions. In type 1 diabetes, IGF-I synthesis is markedly impaired and in type 2 diabetes multiple changes occur in IGF-I actions including sensitization to its mitogenic actions in some target tissues. Administration of IGF-I to patients with extreme insulin resistance results in improvement in glycemic control and IGF-I has been shown to be associated with lowering glucose and enhancing insulin sensitivity in both type 1 and type 2 diabetes. However diabetics are also quite sensitive to stimulation of side effects in response to IGF-I and this has greatly limited its usefulness as a hypoglycemic agent. IGF-I coordinately links growth hormone and insulin actions as well as having direct effects on intermediary metabolism.

Keywords

Fat metabolism; growth; insulin resistance; growth hormone

Introduction

Insulin-like growth factor-I (IGF-I) has significant structural homology with insulin. The structural conservation is due to the fact that proinsulin, IGF-I and IGF-II evolved from a single precursor molecule approximately 60 million years ago. The function of that single precursor molecule was to provide a chemical signal for cells within primitive organisms to establish that adequate nutrient was present not only for basal metabolic needs but also for protein synthesis and cell proliferation. At the time vertebrates appeared this system evolved into one with more complexity in order to be able to store calories as fat. At that time insulin diverged from IGF-I and the pituitary gland appeared along with growth hormone. The function of these three hormones were linked to be able to regulate both nutrient availability during periods of starvation and repletion as well as continuing to provide adequate signals and substrate for growth. As such the regulation of synthesis and secretion of these three

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hormones is directly linked to nutrient intake. Since insulin, IGF-I and IGF-II evolved from a single precursor they continue to share significant structural homology however there are also distinct differences. The primary domains within IGF-I and insulin that determine receptor binding have significant amino acid differences that account for major differences in affinity for their respective receptors (1). Similarly the IGFs have the unique characteristic of being able to bind to IGF binding proteins which is determined by a specific amino acid sequence and in positions, 3, 4, 15, 16 of N terminus of IGF-I molecule and homologous substitutions in IGF-II (2). These structural differences provide important distinction for the regulation of IGF-I and insulin bioavailability and thus indirectly regulate their effects on metabolism.

IGF-I and insulin have distinct receptors. Both receptors are tyrosine kinase containing receptors and they show 48% amino acid sequence homology (3). In spite of these similarities the ligand binding specificity is strict. The affinity of the IGF receptor is 1000 fold greater for IGF-I than insulin and the insulin receptor has a 100 fold greater affinity for insulin compared to IGF-I. Insulin and IGF-I receptor densities vary widely among cell types i.e. mature differentiated hepatocytes and adipocytes have abundant insulin receptors whereas they have almost no IGF-I receptors. Conversely cell types such as vascular smooth muscle cells have abundant IGF-I receptors and minimal insulin receptors. This difference in receptor distribution accounts for many of the differences in insulin and IGF-I actions. Growth hormone has an entirely different structure and its receptor belongs to the cytokine receptor family (4). Growth hormone has a major regulatory influence on the metabolic actions of both IGF-I and insulin and functions in several important ways that are quite distinct from insulin and IGF-I to modulate nutrient availability that is necessary for both balanced tissue growth and maintenance of normal intermediary metabolism. Therefore coordinate regulation of the metabolic actions of these three hormones provides an important basis for understanding their individual effects on intermediary metabolism and how they function coordinately to maintain nutrient balance.

Nutrient regulation of IGF-I secretion

As can be predicted from the phylogenetic development of IGF-I the primary variable regulating plasma IGF-I concentrations is nutrient intake. Both total caloric and protein intake are important regulatory variables (5). The effect of caloric intake is such that if caloric intake is reduced by approximately 50% there a significant reduction in IGF-I secretion. The effects of protein are more graded in that even small reductions result in changes in IGF-I (6). For each 25% reduction in protein intake there is an equivalent reduction in IGF-I. The majority of the IGF-I in plasma (estimated at 80% based on mouse genetic manipulation studies) is derived from hepatic synthesis (7). Both protein and energy participate in the regulation of hepatic synthesis with energy regulating IGF-I gene transcription and protein functioning primarily to regulate mRNA stability and translation. A concomitant effect of changes in carbohydrate intake is the indirect effect that occurs as a result of changes in insulin secretion. If carbohydrate is provided at a level of less than the equivalent 700 kcal/day then even supplemental fat intake will not restore a normal IGF-I. This is because IGF-I synthesis in the liver is also regulated by insulin (8). This is best demonstrated by measuring serum IGF-I concentrations in untreated type I diabetics. When they receive insulin they have a substantial increase in serum IGF-I (9). Studies in experimental animals have also shown that blocking insulin action in the liver lowers serum IGF-I. Therefore carbohydrate intake functions not only to increase the total amount of energy that is available thereby increasing IGF-I synthesis but also by a direct effect of insulin on IGF-I gene transcription in particular the ability of growth hormone to stimulate IGF-I gene transcription (8).

Growth hormone (GH) is the second variable that regulates IGF-I synthesis and secretion but for the liver to respond to growth hormone with normal IGF-I synthesis requires adequate nutrition. GH is a potent stimulant of IGF-I synthesis and GH administration to GH deficient animals results in a brisk increase in IGF-I gene transcription in the liver that leads to a major increase in serum IGF-I (10). The increase in serum IGF-I then feeds back on the pituitary gland to suppress GH secretion and maintain homeostasis. IGF binding proteins are another variable which regulates serum IGF-I concentrations. There are six IGF binding proteins (11). IGFBP-3 is the principal binding protein in serum and its concentration is also increased in response to GH and this change accounts for a significant fraction of the increase in total IGF-I that occurs in response to GH. The increase in IGFBP-3 in response to GH is also modulated by changes in nutrition. When IGF-I is bound to IGFBP-3 the binary complex binds to a third protein termed acid labile subunit or ALS. ALS concentrations are also GH dependent (12). This ternary complex prolongs the half life of IGF-I in serum from less than 5 min to 16 hrs. IGFBP-5 is much less abundant then IGFBP-3 but it also binds to ALS and its concentration increases in response to GH. Thus changes in IGFBP-3, IGFBP-5 and ALS all function to increase the serum IGF-I concentration by prolonging its half life. Two other IGF binding proteins, IGFBP-1, and -2 do not bind to ALS and therefore only prolong the half life of IGF-I to periods ranging between 90 min and 2 hr. Therefore they have minimal effects in increasing total serum IGF-I concentrations. However the regulation of serum concentrations of these proteins is important for regulating IGF-I actions. Under normal circumstances IGFBP-3 and 5 are saturated. Therefore abrupt changes in IGFBP-1 and -2 which are not saturated and which occur as a result of changes in either nutrient intake or insulin secretion, can result in major changes in free IGF-I and thereby regulate tissue responsiveness (13). Other hormones that regulate IGF-I bioactivity include cortisol which antagonizes the actions of IGF-I and therefore can result in an increase in serum concentrations, and thyroxine which is necessary for normal IGF-I biosynthesis and which can stimulate an increase in IGF-I concentrations in hyperthyroidism. Estrogens function to antagonize the ability of growth hormone to stimulate IGF-I synthesis in the liver and testosterone alters IGF binding protein concentrations. Additionally the growth hormone analog, human placental growth hormone is an important stimulant of IGF-I synthesis in pregnancy. All of these hormones function coordinately with changes in nutrient intake to modulate the ability of IGF-I to regulate both growth and metabolism.

Metabolic effects of IGF-I

Although IGF-I is classically considered an important growth factor since it stimulates the growth of all cell types it has major metabolic effects. This overarching effect of IGF-I on metabolism is to provide a signal to cells that adequate nutrient is available to avoid apoptosis, enhance cellular protein synthesis, enable cells to undergo hypertrophy in response to an appropriate stimulus and to allow stimulation of cell division. Therefore even in cytostatic adult tissues such as neurons and fused skeletal myoblasts, IGF-I can provide important trophic effects that lead to changes in cellular metabolism. Since IGF-I receptors are ubiquitous, these responses can occur in all cell types. Therefore the signal induced by IGF-I stimulation of its receptor provides a mechanism for coordinating protein, carbohydrate or fat metabolism among various cell types. Importantly each of these processes is regulated coordinately with insulin and in the appropriate target tissue, either insulin or IGF-I may be the primary determinant of each of these processes. Similarly growth hormone functions to coordinately regulate the ability of each of these hormones to modulate all three processes.

Protein metabolism

In cells in tissue culture, IGF-I is a potent stimulant of protein synthesis. This response is modulated by the PI-3 kinase pathway. Following IGF-I receptor activation the receptor tyrosine kinase phosphorylates tyrosines on the adaptor protein termed insulin receptor substrate-1 (IRS-1) (14). This provides a binding site for the p85 subunit of PI-3 kinase which is then activated. Activation of PI-3 kinase results in coordinate stimulation of AKT which then leads to suppression of TSC-2 and activation of mTORC1 complex. This functions to stimulate phosphorylation of p70S6 kinase and E4B1, a translational repressor. These coordinate actions allow major increases in cellular protein synthesis. The process is modulated by the nutrient sensitive AMP kinase which is activated by nutrient restriction and phosphorylates serine 794 on IRS-1 which inhibits its ability to be activated thus leading to PI-3 kinase inhibition and inhibition of IGF-I stimulated protein synthesis (15). In skeletal muscle IGF-I stimulates amino acid transport but it also is a direct stimulant of protein synthesis and an important inhibitor of protein breakdown (16). The atrogin complex whose assembly can be triggered by a variety of catabolic stimuli including glucocorticoid excess is antagonized in the presence of IGF-I stimulation. Conversely mice that have been genetically altered to constitutively activate this complex are resistant to the anticatabolic effects of IGF-I (17). This catabolic response is mediated through MURF1 and atrophy MAF box which is also termed atrogin. These are E3 ubiquitin ligases and their expression increases during disuse atrophy, following glucocorticoid administration or in response to cytokine stimulation. MAF box upregulation can be antagonized by IGF-I treatment leading to inhibition of proteosome formation thus reducing the targeting of proteins for degradation and reducing the rate of catabolism (18). Insulin can have similar physiologic actions. These effects are mediated in part by the ability of AKT to phosphorylate serine 32 on FOXO3A which results in exclusion of FOXO3A from the nucleus. mTOR also blocks MURF1 and MAF box transcription. Studies by Kelly and coworkers have shown that cytokines which are activated in catabolic states and initiate muscle breakdown through MURF1 and MAF box induction can be antagonized in part by IGF-I actions (19). Thus exogenous expression of IGF-I in skeletal muscle of animals can partially reverse the effect of cytokine or glucocorticoid stimulation on catabolism even in insulin resistant states.

IGF-I functions both under normal conditions and under conditions of either protein deprivation or when an excess of cytokine stimulation is present to attenuate catabolism. When IGF-I is administered to healthy volunteers it stimulates protein synthesis but if catabolism has not been stimulated it has minimal effects on proteolysis (20). However at high concentrations it can suppress proteolysis even within normally fed subjects. GH administration also results in an increase in protein synthesis but the extent to which GH stimulates this response completely independently of IGF-I has not been determined. Of note administration of a relatively high concentration of IGF-I (10 mcg/kg/hr) to patients with growth hormone receptor mutations resulted in a significant stimulation of protein synthesis (21). However coadministration of growth hormone and IGF-I to normally fed normal subjects does not result in a greater response when compared to the individual response to each hormone given separately. However following caloric deprivation administration of growth hormone and IGF-I results in a synergistic increase in protein balance. In growth hormone deficient adults both GH and IGF-I are anabolic and enhance protein synthesis (22). Insulin can inhibit proteolysis in muscle at very low concentrations but the concentrations that are required to stimulate protein synthesis are higher. Thus it would be reasonable to conclude that IGF-I is the major factor maintaining protein synthesis during relatively long intervals between meals but insulin is a primary factor stimulating anabolism in skeletal muscle following ingestion of a meal that contains a normal protein content.

Both growth hormone and IGF-I have been used experimentally in catabolic illnesses and have been shown to improve nitrogen retention and protein synthesis when administered to patients with severe catabolic conditions such as, burns and renal failure (23, 24). Similarly patients being treated with high doses of corticosteroids respond to IGF-I with induction of an anabolic response (20). IGF-I can also reduce the effect of loss of gonadal function on protein balance. Young men who were administered a gonadotrophin receptor antagonist who became catabolic responded to either GH or IGF-I with a significant increase in protein synthesis although it appeared GH was more potent than IGF-I since it induced an increase in androgen receptor number in skeletal muscle (25).

Fat metabolism

Although mature adipocytes do not express IGF-I receptors, preadipocytes have abundant IGF-I receptors and IGF-I stimulates preadipocyte differentiation (26). However as preadipocytes differentiate, they markedly reduce their IGF-I receptor number and insulin receptors become predominant. Thus in well formed adipose tissue beds, physiologic concentrations of IGF-I are not effective in stimulating changes in lipid synthesis or lipolysis and IGF-I has effects on primary adipocytes only at very high concentrations which are capable of stimulating glucose transport through the insulin receptor. In contrast both GH and insulin are potent modulators of these processes. GH has direct effects on mature adipocytes that result in the release of free fatty acids following triglyceride breakdown and in increased free fatty acid oxidation in liver (27). GH also enhances the lipolytic effect of catecholamines by increasing adrenergic receptor number in adipocytes. In skeletal muscle, GH increases lipoprotein lipase activity thus facilitating free fatty acid utilization. Insulin is a potent stimulant of lipid synthesis and insulin antagonizes triglyceride breakdown. This occurs both in skeletal muscle and liver as well as fat. An increase in free fatty acid flux from adipose tissue to liver can result in insulin resistance in the liver and growth hormone is known to antagonize insulin action through this mechanism (28). IGF-I is a potent stimulant of free fatty acid uptake and oxidation in skeletal muscle. In an interesting mouse model Yakar et al knocked out the IGF-I receptor in skeletal muscle. This also knocked out the insulin/IGF-I hybrid receptor and to some extent reduced the biosynthesis of insulin receptor homodimers. This resulted in the development of type II diabetes over time (29). That this was related to loss of the ability of IGF-I stimulate free fatty acid transport in muscle was strengthened by their observation that the phenotype could be rescued by expressing CD36, a known fatty acid transporter in muscle (30). This led to the conclusion that it is the effect of IGF-I on fatty acid transport in muscle that is mediating this response and that it is so profound that its inhibition can lead to extreme insulin resistance and diabetes. Therefore an important metabolic effect of IGF-I is to reduce flux of free fatty acids through the liver which results in an enhancement of the ability of insulin to suppress hepatic glucose output. Supraphysiologic concentrations of IGF-I also suppresses insulin secretion and this may result in inhibition of insulin's lipogenic effect in fat. Therefore the two major effects of IGF-I that may be enhanced free fatty acid utilization by muscle which results in increased free fatty acid flux in the liver and loss of insulin's lipogenic effect in fat. Suppression of GH by IGF-I also results in decreased free fatty flux in the liver and decreases the amount of substrate available for enhancement of lipid oxidation directly in skeletal muscle thus reducing the total free fatty acid flux. This mechanism probably functions under normal conditions to regulate glucose homeostasis and GH induced insulin resistance. Chronic administration of IGF-I to human subjects has been shown to decrease fat mass rates in GH deficient adults probably secondary to insulin suppression of insulin induced lipogenesis. Chronic administration of IGF-I to patients who had GH receptor defects showed increased lipolysis and lipid oxidation rates and loss of total fat mass (21). The degree of change was similar to the effect of GH when it was administered to GH deficient subjects.

Effects on carbohydrate metabolism

An understanding of the effect of IGF-I on carbohydrate metabolism is dependent upon knowledge of its effects in modulating insulin and GH actions. IGF-I reduces serum GH concentrations and it also reduces GH's direct effects on insulin suppression of hepatic gluconeogenesis and by increasing free fatty acid uptake in muscle it indirectly enhances hepatic insulin action (31). In both fat and liver GH stimulates the synthesis of the p85 subunit of PI-3 kinase (32). This relative increase in p85 leads to suppression of p110 subunit activity thus leading to antagonism of insulin action (33). Therefore IGF-I may indirectly modulate carbohydrate metabolism through both GH suppression and enhancement of insulin action. Following ingestion of a meal there is a significant increase in free IGF-I. This occurs via insulin induced suppression of IGFBP-1 secretion (34). The IGFBP-1 gene is transcriptionally regulated by insulin thus the meal induced increase in insulin leads to an increase in free IGF-I. This change may be adequate to stimulate fatty acid oxidation in muscle and suppress GH and these changes may to occur at physiologic IGF-I levels. Provision of pharmacologic levels of IGF-I to normal subjects results in further changes in carbohydrate metabolism. IGF-I can directly stimulate glucose transport into muscle through either IGF-I or insulin/IGF-I hybrid receptors (35, 36) although this requires relatively high concentrations of free IGF-I. Additionally a high concentration of free IGF-I can directly suppress renal gluconeogenesis in mice (37). Experimental mice in whom the insulin receptor has been deleted show a decrease in blood glucose in response to IGF-I indicating that in part its effect can be mediated directly through stimulation of glucose transport by the IGF-I or the hybrid receptor (38). Experimental mice in which serum IGF-I is lowered by 80% by deleting expression in the liver have impaired glucose tolerance (39). However whether this is a direct effect of reduced IGF-I or due to an increase in GH, it has been difficult to determine because GH levels increase substantially in these mice. Therefore the extent to which the effect of IGF-I on lowering glucose is due to the direct of effect of IGF-I on glucose transport, enhancement of FFA metabolism in muscle or suppression of GH has been difficult to ascertain. In a comparable study we infused a GH receptor antagonist into patients with acromegaly and showed that it improved their insulin sensitivity (40). We then repeated the experiment and added an IGF-I infusion. Although IGF-I was infused at supraphysiologic concentrations, these concentrations were capable of further improving insulin sensitivity and lowering glucose even when the activity of GH had been completely suppressed. Simpson et al showed that following suppression of GH with octreotide in Type I diabetic patients IGF-I could further lower glucose (41). This suggests at least at pharmacologic levels, IGF-I does function to enhance insulin sensitivity and lower glucose independently of its ability to suppress GH. However in GH deficient individuals administration of a physiologic replacement concentration of IGF-I does not change carbohydrate oxidation but in patients with GH receptor mutations it resulted in enhanced carbohydrate oxidation. It also increased hepatic glucose production rates which was probably due to suppression of insulin but, overall normoglycemia was maintained (32). This also supports the conclusion that IGF-I has a glucose lowering effect secondary to its ability to increase fatty acid oxidation in muscle leading to decreased free fatty acid flux to the liver and enhanced insulin suppression of hepatic glucose output. Thus the predominant effect of IGF-I on carbohydrate metabolism appears to be secondary to its effects on lipid metabolism. Because suppression of insulin and GH secretion occurs at pharmacologic levels of IGF-I it is difficult to extrapolate from the results of most published studies and conclude that these effects occur at normal physiologic levels. However GH suppression would be expected to lead to decreased free fatty acid flux in liver and reduced antagonism of insulin action on glucocogenesis.

IGF system component concentrations and their utility in predicting changes in carbohydrate and fat metabolism

Serum IGF-I concentrations vary widely among normal human subjects. Age is a major determinant and serum levels are low at birth and rise progressively with a peak during puberty then decrease progressively with the greatest decrease occurring during the second and third decades, but levels continue to decrease throughout the lifespan (42). These changes parallel the age- dependent changes in GH secretion. Changes in the GH dependent IGF binding proteins, IGFBP-3 and -5, as well as the acid labile subunit parallel the changes that occur in serum IGF-I; although changes in IGFBP-3 are significantly less sensitive to changes in GH because IGF-II which is relatively insensitive to changes in GH is a major determinant of serum IGFBP-3 and to some extent ALS (43). Other IGF binding proteins that are non-growth hormone dependent such as IGFBP-1 and 2 have been studied extensively in humans. Insulin is a major suppressor of hepatic IGFBP-1 synthesis therefore changes in IGFBP-1 often reflect changes in either insulin secretion or insulin sensitivity (44). IGFBP-2 changes much less rapidly in response to insulin however chronic changes in insulin availability or insulin sensitivity can lead to changes in IGFBP-2 (45). As noted previously changes in these two proteins can have major effects on the plasma concentration of free IGF-I. Acute changes in several nutritional variables regulate IGF-I secretion and plasma concentrations however chronic changes in dietary intake that lead to changes in fat mass also regulate IGF-I and GH. In general when body mass index rises above 24 there is a substantial increase in serum IGF-I concentrations (46). Studies have shown that this change occurs as a function of enhanced sensitivity to the ability of GH to stimulate IGF-I synthesis (47). This change plateaus with a body mass index of 25 and remains relatively constant until body mass index reaches 36. At that point although the enhanced sensitivity to GH is maintained there is a reduction in GH secretion. Therefore massively obese patients have lower 24 hr blood production rates of GH. This effect becomes predominant with BMI >37 and serum IGF-I concentrations tend to decrease as a function of increasing weight in this subgroup (48). There are also changes in binding proteins that occur as a result of obesity and the net effect is a moderate increase in free IGF-I when body mass index increases above 30 (49). This change in free IGF-I correlates with a lowering of IGFBP-1 which presumably occurs as a result of hyperinsulinemia.

IGF-I and the metabolic syndrome

Several studies have attempted to correlate total plasma IGF-I concentrations with the presence of the metabolic syndrome. In general patients with a low normal IGF-I who are obese and meet other criteria for metabolic syndrome tend to have a worse cardiovascular disease outcome than those with a mid to high normal IGF-I (50). Clearly many of these subjects have insulin resistance. Whether the degree of resistance or the accompanying changes in inflammatory cytokine secretion is the predominant predictor of a poor outcome has not been definitively determined. There are also studies correlating the lower total serum IGF-I concentrations with increased waist to hip ratios or with the development of impaired glucose tolerance both of which predict a worse cardiovascular outcome (51, 52). Therefore although it appears that a lower serum IGF-I predicts a worse cardiovascular outcome the exact parameter that is mediating this increased risk has not been determined. Cytokines that are elevated in these patients such as C reactive protein are known to decrease circulating IGF-I in experimental animals (53) and could contribute to the relationship between low serum IGF-I and the prediction of a poor cardiovascular outcomes.

In patients with type 1 diabetes, the changes in serum IGF-I are relatively straightforward. In poorly controlled type 1 diabetes, the lack of adequate insulinization of the liver leads to a major suppression of IGF-I biosynthesis (54). Thus acute administration of insulin to type 1

diabetics results in a 3–3.5 fold increase in serum IGF-I due to restoration of a hepatic synthesis (9). Administration of insulin via the portal circulation results in a greater increase in serum IGF-I in type 1 diabetes compared to peripheral insulin administration (55). Thus in poorly controlled adolescent type 1 diabetics IGF-I can be low enough that optimal growth is not achieved. That this is rate limiting for growth was shown in experimental animals with diabetes and low IGF-I levels in whom a growth response was achieved when the IGF-I levels were normalized (56). Even though GH concentrations are elevated in these animals they are relatively refractory to the high GH concentrations due to a low serum IGF-I that is inadequate to sustain normal growth. In addition in poorly controlled diabetes there is increased catabolism particularly in skeletal muscle (57). In type 2 diabetes the range of IGF-I concentrations that has been reported is broad (58). This suggests that because of multiple variables that are interacting to control IGF-I concentrations such as increases in inflammatory cytokines, decreases in hepatic insulin action due to insulin resistance, concomitant changes in IGF binding proteins and the effects of obesity upon IGF-I production, that the net effect of all these variables combined is that there is not a uniform abnormality in serum IGF-I concentrations in this disease state.

In contrast to total IGF-I levels, IGFBP levels are significantly altered in type 2 diabetes and these changes result in changes in free IGF-I (59). Recent studies from Sweden in prediabetics suggest that IGFBP-1 is initially lower in subjects who will subsequently develop type 2 diabetes (60). This is due to hyperinsulinism which occurs in the early prediabetic phase of disease. This results in an elevation in free IGF-I however as insulin resistance progresses the liver becomes more resistant to insulin suppression of IGFBP-1 and IGFBP-1 levels rise which is concomitantly accompanied by a decrease in free IGF-I (60). Therefore there may be a natural progression of changes in total IGF-I and free IGF-I that occur as a function of changing insulin secretion and insulin sensitivity over time in type 2 diabetes. That a change in free IGF-I that occurs as function of changes in IGFBP-1 could be clinically significant was shown by administration of IGFBP-1 to experimental animals using concentrations that were sufficient to lower free IGF-I significantly and showing that this resulted in increased serum glucose even in absence of a change in insulin (61). Administration of insulin to type 1 diabetics not only results in a major increase in total IGF-I levels but also free IGF-I levels are increased substantially and IGFBP-1 decreases approximately 5 fold (9). IGFBP-2 is suppressed in obesity and this may contribute to the increase in free IGF-I (62). The suppression of IGFBP-2 in obese subjects may be physiologically relevant since transgenic mice that overexpressed IGFBP-2 are relatively resistant to the development of obesity during high fat feeding suggesting that this protein may have a direct effect on preadipocyte differentiation (63). A further confounding variable is IGFBP-3 proteolysis which occurs in diabetes and results in disproportionate increases in free IGF-I as a function of diabetic control (64, 65).

IGFBP changes also correlate with parameters of metabolic syndrome and lower IGFBP-1 levels are present in metabolic syndrome patients with higher CRP. The combination of a high CRP with a low IGFBP-1 value is a strong predictor of the presence of this syndrome (66, 67). Similarly in middle aged men with a low IGF-I and high CRP along with low testosterone predicted the presence of metabolic syndrome with high probability (68). Low IGFBP-2 also predicted the presence of metabolic syndrome and low IGFBP-2 was associated with elevated fasting glucose (61). Whether these factors reflect insulin resistance and the known effect of inflammatory mediators in suppressing IGF-I concentrations and thereby suppressing IGFBP-1 and −2 or whether the primary changes in IGFBP-1 and −2 predispose to the development of obesity and insulin resistance has not been resolved. Studies in transgenic mice overexpressing IGFBP-1 show that this induces hyperinsulinemia and glucose intolerance and that the ability of IGFBP-1 to induce these changes is dependent upon its phosphorylation state which is known to be increased in diabetes (69). Similarly

following weight loss there is a significant increase in IGFBP-1 and IGFBP-2 both in children and adults which correlates with an improvement in insulin sensitivity (70, 71). These findings raise the question as to whether changes in IGF-I or IGFBP-1 and −2 can predict the development of diabetes. Diet induced obesity in experimental animals induces resistance to the vasodilitatory effects of IGF-I. Likewise Zucker rats which are extremely obese are resistant to the glucose lowering effects of IGF-I (72). Since IGF-I modulates the concentrations of IGFBP-1 and −2 it is possible that these values change as a function of early changes in insulin resistance. A recent study utilized IGFBP-1 concentrations to predict the development of type 2 diabetes in women in Sweden. Patients with the lowest fasting IGFBP-1 measurements had high waist circumference and those in the lowest tertile had the highest risk of developing diabetes within 8 years (60). These patients not only have low fasting IGFBP-1 levels but impaired IGFBP-1 suppression after oral glucose loading. Interestingly fasting IGFBP-1 values increased over the 8 year interval suggesting that the subjects developed hepatic insulin resistance. Plasma IGF-I is associated with insulin sensitivity in prediabetic subjects with different degrees of glucose intolerance. During a 4.5 year follow up of 615 subjects who had IGF-I values in the lower half of the normal range had increased predisposition to develop glucose intolerance or type 2 diabetes and this change was independently associated with IGFBP-1 (73). Maternal IGF-I/IGFBP-1 ratios also predict the subsequent risk for gestational diabetes and IGFBP-1 values greater than 68 ng/ml lowered the risk by 57%. A free IGF-I greater than 1 ng/ml lowered the risk by 69% (74). In older individuals (> than 65 years) low IGFBP-1 also predicts an increased risk for glucose intolerance. Subjects with a low IGFBP-2 (10^{th} percentile) had an increased hazard ratio for the development of type 2 diabetes and those with IGFBP-1 above the 90^{th} percentile had a reduced risk. After adjustment for all metabolic parameters, the increased relative risk ratio of a low IGFBP-1 remained present. IGFBP-1 also predicted the development of type 2 diabetes over a 17 year period. Subjects in the lowest quintile had an incidence of 12.6% whereas those in the highest quintile it was 1.5% (66). When corrected for age, gender, CRP and waist circumference, those in the lowest quartile still had an elevated relative risk ratio. Low insulin-like growth factor-II levels also predict weight gain in normal weight middle aged subjects with type 2 diabetes. Those in the highest quartile had a 47% decrease in risk of gaining more than 2 kg for a 5 year follow up period. IGF-I is also negatively correlated with visceral fat mass suggesting that regional distribution in fat may be predicted by IGF-I concentrations (76).

Genetic studies

IGF-I gene polymorphisms and changes in metabolism

A polymorphism due to a CA dinucleotide repeat in a microsatellite that is 1 kilobase upstream from the IGF-I transcription start site results in lower serum IGF-I levels and some investigators have found this is associated with a lower birth weight (77). This occurs in approximately 11% of the Dutch caucasian population. A study of 477 Dutch patients with evidence of ischemic heart disease and 808 control subjects demonstrated an increase relative risk of 1.7:1 for the presence of ischemic disease in noncarriers of this common polymorphism allelle (e.g. 192 based pairs). These subjects were also significantly shorter and had an 18% reduction in serum IGF-I (78). Two other studies conducted in different countries however were not able to reproduce this finding. There is a single nucleotide polymorphism at position −202. A polymorphism involving a tandem repeat and the IGF-I promoter was also associated with an increased risk of development of type 1 diabetes (79). The CA repeats have also been found in intron-1 in pigs and are associated with lower serum IGF-I concentrations and increased fat deposition (80). The CA repeat polymorphisms were also analyzed in a group of young adults. Those with the polymorphism had a lower serum concentration and had 1 kg lower birth weight and 8 mm higher systolic blood pressure at age 36 (81). The CA repeat polymorphisms were also

associated with a lower birth weight and head circumference as well as lower serum IGF-I levels suggesting that this might predict a later development of cardiovascular disease. IGF-I gene polymorphisms have also been associated with the development of retinopathy and nephropathy in patients with established diabetes (82, 83). Polymorphisms in IGFBP-1 have also been associated with a lower body mass index and the presence of type 2 diabetes (84). Four single nucleotide polymorphisms were associated with a lower BMI that was maintained over time and there was a negative relationship between plasma IGFBP-1 concentrations and BMI. Polymorphisms in IGFBP-1 have also been associated with renal protective effects in type 1 diabetes (85). An IGFBP-3 gene polymorphism has been described in the promoter region that accounts for an increase in the serum concentrations of this protein (86). A recent study identified 3 additional polymorphisms and showed that together the 4 polymorphisms account for 6.5% of the variability of IGFBP-3 in the general population (87).

Response of patients with genetic syndromes of severe insulin resistance to IGF-I

Several subgroups of patients with severe insulin resistance have been administered IGF-I in an attempt to achieve improved glycemic control. Patients with severe type A insulin resistance and mutations in the insulin receptor had major decreases in blood glucose as well as insulin and C-peptide levels when administered recombinant IGF-I (88). In a subsequent report, 11 subjects with various types of insulin receptor mutations, were treated up to 16 months with recombinant human IGF-I. Fasting and postprandial glucose as well as fructosamine and hemoglobin A1C were measured and shown to be significantly improved in 6 of 11 of the subjects (89). This degree of improvement was maintained throughout treatment. A subsequent study in patients with severe insulin resistance showed that not only were glucose and insulin concentrations lowered but insulin resistance as measured using a frequently sampled intravenous glucose tolerance test showed significant improvement (90). This was subsequently followed up by another study of 6 subjects, 4 of whom had overt diabetes and received one month of recombinant IGF-I. Glucose tolerance returned to normal in 3 of the 4 diabetic subjects and the remaining 2 subjects showed major reduction in insulin and triglyceride concentrations (91). Two subjects with Rabson-Mendenhall syndrome showed the same benefits in hemoglobin A1C when IGF-I was administered. Children with very severe insulin resistance due to leprechanism usually die within the first two years of life, however, administration of IGF-I to three of these patients has resulted in several years of maintenance of relatively normal glucose levels and normal linear growth. Administration of IGF-I to patients with GH receptor mutations who have extremely low IGF-I concentrations showed that normoglycemia was maintained with suppression of insulin concentrations (92). Hepatic glucose production was increased presumably due to enhanced insulin sensitivity and glucose oxidation rates were decreased. IGF-I has been administered to rare patients with IGF-I gene deletions. In general these subjects have moderate glucose intolerance or overt diabetes and high fasting GH concentrations (93). Administration of IGF-I has normalized glucose concentrations and most importantly normalized insulin sensitivity however since GH is also suppressed it has been impossible to distinguish between the improving insulin resistance due to suppressing GH as compared to enhancing insulin sensitivity directly by IGF-I.

IGF-I and the treatment of type 1 diabetes

Multiple studies have administered IGF-I to type 1 diabetics who are also receiving insulin (94). Many of these studies involved small numbers of subjects although the largest trial had 223 subjects. In that trial the dosages ranged from 20–140 mcg/kg/day. In general hemoglobin A1C has improved and insulin requirements have decreased. In the large study with 223 subjects who received IGF-I for 12 weeks there was a major decrease in insulin requirements and hemoglobin A1C declined by 0.6% (90). Edema, jaw pain, tachycardia

were present in several subjects (95). Additional subjects (n=4) noted worsening of retinopathy which resolved during a follow up period after administration of IGF-I had ceased. IGF-I is also anabolic in these patients and in experimental animals with type 1 diabetes, infusions of IGF-I have been shown to increase long bone growth as well as protein synthesis (56). Studies using a hyperinsulinemic clamp have shown that administration of IGF-I is associated with enhanced insulin sensitivity in type 1 diabetes. Peripheral insulin stimulated glucose disposal increased by approximately 34% during IGF-I administration (96). Concomitantly with the improvement in insulin resistance was a lowering of GH. Therefore the question was raised whether most of the improvement was due to reduced GH secretion. To address this two types of studies were done, Simpson et al infused octreotide simultaneously with recombinant IGF-I. IGF-I was shown to acutely reduce hepatic glucose production and stimulate peripheral glucose uptake (97). Glycerol turnover and free fatty acids were unaffected suggesting to the investigators that the effect was due to IGF-I enhancement of insulin sensitivity and not a reduction in GH. This was further addressed using a GH receptor antagonist. A reduction in the GH effect was clearly achieved with the dosage utilized yet there was no improvement in insulin sensitivity suggesting to the investigators that the effect of IGF-I is also required (98). When IGF-I was given insulin sensitivity improved and LDL, triglycerides and the LDL to APO-B ratio were significantly decreased. In spite of these improvements, significant complications were noted.

Since administration of relatively high doses IGF-I suppress IGFBP-1 and -2 they result in a disproportionate increase in free IGF-I. To try to obviate the effects of excessive free IGF-I in inducing side effects the combination of IGF-I plus IGFBP-3 has also been administered to type 1 diabetics (99). Pharmacologic studies have shown that when this combination is given the rate of appearance of free IGF-I is substantially reduced suggesting that it could lead to fewer side effects (100). Administration of the combination to a group of adult type 1 diabetics resulted in 52% reduction in insulin levels with a 23% reduction in glucose after a 2 week treatment period (99). The prevalence of side effects was reduced. In another study 15 adolescents were administered the combination in doses between 0.1 and 0.8 mg/kg/day. They showed a 41% reduction in overnight insulin requirements and a dose dependent reduction in hepatic glucose production (101). Insulin sensitivity was also improved with the 0.4 and 0.8 mg/kg/day dosages. Overnight GH secretion was reduced substantially suggesting this may be one mechanism by which insulin sensitivity was improved. Therefore this approach offers a possible future therapeutic option.

IGF-I administration to type 2 diabetics

Several studies with small numbers of patients were initially performed in subjects with type 2 diabetes. Most of these were of short duration (102). Studies that were 7 days or less showed decreases in glucose, endogenous insulin and C-peptide secretion and in some cases an improved area under the curve after oral glucose administration. In most of these studies high doses, (e.g. 240–360 mcg/kg/day) were administered and were associated with edema, headaches and arthralgias. A longer study wherein IGF-I was administered to 12 subjects for 6 weeks using the dosage of 80 mcg/kg b.i.d. showed a 3.4 fold enhancement in insulin sensitivity (103). Similarly when 160 mcg/kg/day dose was administered to type 2 diabetics and hepatic and peripheral insulin sensitivity were measured they were shown to be improved after 7 days (104). These findings suggested that IGF-I was capable of enhancing insulin sensitivity in type 2 diabetes. Since most of these subjects are obese and have very low GH concentrations it is highly likely this is due to an effect on free fatty acid metabolism in muscle and suppression of renal gluconeogenesis and not simply suppression of GH secretion.

A large clinical trial in which doses of 10–80 mcg/kg/day were administered to 212 subjects for 12 weeks showed that there was a dose dependent reduction in hemoglobin A1C as well as mean daily blood glucose (105). As in previous trials doses of IGF-I 40 mg/kg bid or greater were accompanied by a significant side effect profile and the number of side effects increased as the dosage increased. For example in the 80 mcg/kg bid dose group the number of subjects having significant side effects was ~30%. This study was followed by a large trial in which IGF-I was administered to type 2 diabetics who were being given insulin concomitantly for 12 weeks. Hemoglobin A1C was decreased by an additional 0.8% over that which could be achieved with more intensive insulinization suggesting that it could be used as an adjunct to insulin therapy in type 2 diabetes (106). Administration of IGF-I combined with IGFBP-3 has also been effective in type 2 diabetics. When 48 subjects were treated with this regimen, fasting and postprandial blood glucose fell significantly by 35–40% (100). These subjects were being administered insulin and therefore they were able to be maintained on lower insulin doses. Insulin requirements decreased in the 4 groups by 54–82% and fasting glucose decreased by 32–37%. The administration of the combination was associated with fewer side effects but a significant minority of patients had edema, athralgias and headaches. This suggests that the degree of increase in free IGF-I that has to be achieved to improve glycemic control is such that even when IGF-I is administered with its binding protein in order to obtain a clinical improvement in insulin sensitivity the concentration of free IGF-I that has to be achieved will induce side effects in a substantial number of patients. These studies suggest that high concentrations of the IGF-I increase insulin sensitivity in type 2 diabetes but the window between therapeutic utility and toxicity is relatively small.

Summary

IGF-I is ancestorally related to proinsulin and therefore retains some physiological effects that complement the ability of insulin to stimulate glucose uptake. Furthermore the actions of IGF-I are coordinately regulated with GH thus enabling organisms to breakdown fat and utilize this as a substrate to meet the energy needs that are required for new growth as well as to coordinate their effects for stimulation of protein synthesis and an anabolic response. Therefore IGF-I plays an integral role in coordinating the response to nutrient intake and in initiating the appropriate metabolic changes that enable cells to tolerate a variety of stressful stimuli and resist apoptosis as well as initiate the tissue repair response that occurs after injury. Furthermore it plays an important role in facilitating adaption to major changes in nutrient intake. In this way IGF-I coordinates the response of the three hormones to form a functional unit thereby coordinating nutrient availability and tissue growth. In obesity and metabolic syndrome as well as in patients with overt diabetes the metabolic actions of IGF-I are altered significantly. Similarly its ability to coordinate its functions with those of GH and insulin is impaired in this pathophysiologic state and this constitutes an important component of the maladaptive response of all 3 hormones to metabolic stress.

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KEY POINTS

- IGF-I is an important stimulant of protein synthesis in muscle but it also stimulates free fatty acid utilization.
- IGF-I actions are regulated by IGF binding proteins and in obesity and metabolic syndrome there is major dysregulation of IGF binding protein secretion resulting in alterations in the concentration of free IGF-I and IGF-I actions.
- In type 1 diabetes, IGF-I synthesis is markedly impaired and in type 2 diabetes multiple changes occur in IGF-I actions including sensitization to its mitogenic actions in some target tissues.