REVIEW

The role of growth hormone in diabetes mellitus


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Summary

The insulin and growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis are two endocrine systems that are interlinked at many levels. GH is one of the glucose counter-regulatory hormones, rising in response to hypoglycaemia, it has both intrinsic hyperglycaemic actions and causes insulin resistance. Both IGF-I and its receptor have high structural and functional homology to insulin and its receptor. Insulin can regulate IGF-I production, acting on the GH receptor or at a post-receptor site. Conversely IGF-I is thought to have a permissive effect on the pancreatic insulin response to glucose.

Growth is compromised in poorly controlled diabetic children; however, a causal link with altered GH/IGF-I levels has not been proven. Insulin-dependent diabetes clearly causes derangements in the GH/IGF-I axis. In poorly controlled diabetics GH levels are invariably raised whilst normal or low levels of IGF-I are found, indicating a dissociation between the two factors. Altered IGF-binding protein levels are also found, with high levels of small binding protein and low levels of large binding protein. These derangements are probably the result of interactions at many levels although the exact mechanisms are not fully understood.

Raised GH levels could result from altered hypothalamic/pituitary control or reduced feedback inhibition. The latter could, in turn, result from low IGF-I levels, reduced availability of IGF-I to relevant receptors or increased levels of inhibitors (possibly the small binding protein). Low IGF-I levels could be directly due to deficient insulin levels or simply to lack of available circulating binding protein.

Alternative or altered molecular forms of circulating GH in diabetes seem unlikely on present evidence.

That GH has an effect on glycaemic control is most evident from the abnormal glucose tolerance seen in acromegalics, but is also seen with physiological GH variations such as during the pubertal growth spurt. In diabetics the derangements to the GH/IGF-I axis, caused by poor metabolic control, leads to aggravation of the metabolic problems.

Altered GH/IGF-I levels have been implicated in the long-term complications associated with diabetes, and whilst GH/IGF-I are not essential for the early changes involved in these complications they may still play an important role in their development, especially proliferative retinopathy.

Introduction

Diabetes is a heterogeneous disorder in which impaired insulin secretion and/or varying degrees of insulin resistance result in abnormalities of carbohydrate, protein and lipid metabolism. The hyperglycaemic actions of insulin are counterbalanced in vivo by the hyperglycaemic actions of a number of other hormones including glucagon, catecholamines, growth hormone (GH) and cortisol. These hormones, which stimulate and support endogenous, primarily hepatic, glucose production and suppress peripheral glucose utilization, are involved in the prevention of and recovery from excessive falls in blood glucose concentrations.

Growth hormone, as one of the hormones of glucose counter-regulation, rises in response to hypoglycaemia. Despite an early and transient insulin-like (i.e. hypoglycaemic) effect, the principle actions of the hormone are hyperglycaemic (Davidson, 1987). GH stimulates hepatic glucose production independently of any change in insulin or glucagon levels. At the periphery, increases in concentrations of GH stimulate lipolysis, releasing glycerol as a fuel for gluconeogenesis and free fatty acids which inhibit glucose oxidation, slowing glucose utilization (Randle, Garland, Hales & Newsholme, 1963). GH also stimulates ketogenesis, making available a non-

Glucose fuel for cerebral metabolism during times of glucose lack. These actions of GH do not appear to be essential in the immediate recovery from acute hypoglycaemia but the occurrence of hypoglycaemia in states of GH deficiency (Bougnères, Artavia-Loria, Ferre et al. 1985) bear witness to the role of the hormone in the chronic maintenance of normoglycaemia. Conversely, GH excess is associated with abnormal glucose tolerance and increased GH levels may contribute to the metabolic derangements of diabetes mellitus.

Growth hormone is produced, stored and secreted by the somatotrophs of the anterior pituitary gland within which it is by far the most plentiful hormone. Pituitary GH secretion is under the dual control of two hypothalamic factors which act via the hypothalamic-hypophysial portal system to stimulate (GH-releasing hormone (GHRH)) or inhibit (somatostatin) GH release. The somatogenic actions of GH in the peripheral tissues are then thought to be mediated by insulin-like growth factor-I (IGF-I, somatomedin C). GH regulates the ubiquitous production of IGF-I from a variety of tissues, but it remains unclear whether IGF-I then acts either locally in an autocrine or paracrine manner or as a true endocrine hormone after entering the circulation. IGF-I circulates at very high levels, 55% of which is calculated to be of hepatic origin (Underwood, D’Ercole, Clemmons & Van Wyk, 1986). Virtually all IGF-I found in the circulation is bound to specific binding proteins, the majority to a large saturated 150,000 dalton complex but in addition to smaller unsaturated proteins in the 35,000–50,000 dalton range.

The links between insulin and GH in controlling glycaemia have been known for nearly 60 years since it was first shown that hypophysectomy could reduce diabetic hyperglycaemia and induce hypersensitivity to insulin (Houssay & Biasotti, 1930). This interrelationship has been the subject of intensive examination. The role of GH in diabetes is, however, still not fully understood. This is partly because most of the studies have used animal models with experimental diabetes, chiefly the rat. Extrapolation of these findings to the human condition is not always valid and often adds confusion due to the intrinsic differences between the species, particularly in relation to the physiology of GH. Thus GH induces its own receptors in the rat (Baxter & Zaltsman, 1984) but down-regulates its receptors in man (Murphy, Vro Ivsek & Lazarus, 1984). Stress and hypoglycaemia are both accompanied by suppression of GH levels in the rat (Painson & Tannenbaum, 1985) again in contrast to the observed effects in man. Furthermore, experimental diabetes in the rat is characterized by low levels of GH and IGF-I (Tannenbaum, 1981). In man, poorly controlled diabetes is characterized by normal or low IGF-I levels despite raised circulating levels of GH (Tamborlane, Hintz, Bergman et al. 1981; Amiel, Sherwin, Hintz et al. 1984).

The inter-relationships between insulin and GH are more fundamental than their opposing influences on metabolism. The somatogenic actions of GH are, as stated above, now known to be largely mediated by the IGFs: a series of peptides with a high degree of structural homology to proinsulin. Indeed the most prevalent of these in the circulation, IGF-II, is encoded by a gene on chromosome 11 very close to the insulin gene (Van den Brande, Jansen, Hoogerbrugge et al. 1986). The predominant mediator of the somatogenic actions of GH is, however, thought to be IGF-I. IGF-I is capable of binding to the insulin receptor and vice versa. Furthermore, two type of receptors have been identified for the IGFs, the IGF-I receptor being structurally and enzymatically remarkably similar to the insulin receptor. Indeed, as IGF-I has close to 50% amino acid homology with proinsulin, its receptor also has a similar degree of amino acid homology to the insulin receptor (Rechler & Nissley, 1986; Ullrich, Gray, Tam et al. 1986).

**Effects of experimental diabetes on the GH/IGF-I axis**

In addition to the close similarities between insulin, IGF-I and their respective receptors, there are many functional links between the two hormone systems. Whilst insulin stimulation of GH secretion in vivo is largely secondary to the induced hypoglycaemia, insulin has been demonstrated to affect the GH/IGF-I system directly at many levels in experimental models.

High concentrations of insulin and its receptor have been found in the rat hypothalamus, particularly in the ventromedial region, the putative site of glucosensory cells (Van Houten, Posner, Koriwa & Brawer, 1979; Baskin, Porte, Guest & Dorsa, 1983), specific receptors for insulin and IGF-I have been identified on rat anterior pituitary cells (Rosenfeld, Ceda, Cutler et al. 1985) and insulin has been shown to suppress the synthesis and secretion of GH from cultured rat pituitary cells and to suppress their GH mRNA levels (Ceda, Davis, Rosenfeld & Hoffman, 1987; Yamashita & Melmed, 1987). The effect of insulin on rat GH gene expression can, however, be either positive or negative depending on the metabolic state of the cells (Isaacs, Gardner & Baxter, 1987).

Further effects of insulin are seen in the liver where insulin has been shown to enhance the production of IGF-I (Daughaday, Phillips & Meuller, 1976). Insulin deficiency in diabetic rats has been reported to block the effect of GH on hepatic IGF-I production (Scott & Baxter, 1986). This effect on IGF-I production is
thought to act through one or both of two possible mechanisms. The GH receptor appears to be regulated by insulin (Baxter, Bryson & Turtle, 1980b) in common with other peptide hormone receptors such as Leydig cell luteinizing hormone (LH) receptors (Charreau, Calvo, Tesone et al. 1978) and hepatic glucagon receptors (Bhatena, Voyles, Smith & Racant, 1978). In experimental diabetes the expression of GH receptors is suppressed, this suppression correlates with the degree of insulin deficiency and is reversed by insulin therapy concomitant with a normalization of IGF-I levels (Baxter, Brown & Turtle, 1980a). Insulin may also regulate IGF-I levels by a permissive effect on post GH-receptor events at the transcriptional and/or the translational level (Maes, Underwood & Ketelsleegers, 1986). It remains contentious whether the effects of insulin are on the GH receptors or at a post-receptor site. It is also unclear to what extent these effects are those of insulin per se or are secondary to altered intracellular metabolism resulting from the stimulated uptake of amino acids and glucose. Secondary increases of circulating intermediate metabolites may also contribute to the GH/IGF-I derangements of insulin deficiency. Phillips & Unterman (1984) have reported an inverse correlation between β-hydroxybutyrate and IGF-I levels in insulin-deficient diabetic rats. Acute fasting and malnutrition have effects on IGF-I production analogous to those of diabetes and it has recently been reported that protein deficiency suppresses IGF-I production in rats independently of changes in insulin levels (Maiter, Underwood, Fliesen et al. 1987).

Finally, at least in man, insulin may also have a permissive effect on the actions of IGF-I, thus acromegalias with only moderate increases in IGF-I but with raised insulin have pronounced symptoms of the disease (Zapf & Froesch, 1986). This clinical observation is, however, in contrast to the suggestion, from in-vitro work in rats, that insulin desensitizes effector pathways from the IGF receptors at a post-binding site (Rechler & Nissley, 1986).

The GH/IGF-I axis in human diabetes
Mauriac's syndrome (dwarfism, hepatomegaly and obesity in children with poorly controlled diabetes mellitus and now fortunately rare) is the extreme example of the adverse effects of poorly controlled diabetes upon linear growth (Guest, 1953). Evidence for more subtle growth retardation in diabetic subjects comes from studies in identical twins, discordant for diabetes. The adult height of the probands who developed diabetes before puberty was significantly less than that of their non-diabetic, genetically identical twin (Tattersall & Pyke, 1973). Furthermore, intensive insulin therapy and improved metabolic control causes a sharp acceleration of growth velocity even in non-selected diabetic children with apparently normal stature (Rudolf, Sherwin, Markowitz et al. 1981).

That growth is compromised in insulin-dependent diabetes (IDD) may not seem surprising considering the number of derangements in the GH/IGF-I system that have been reported to occur, but a causal link has not been proven. In poorly controlled IDD, deranged GH/IGF-I levels and growth retardation might both reflect the metabolic deficiencies implicit in poor control which could themselves account for both effects. The growth retardation of diabetes is not an effect of diminished GH secretion. Indeed, GH levels in poorly controlled diabetes are raised above normal despite the prevailing hyperglycaemia. Raised GH levels have been found throughout the day (Hansen, 1972) with increased amplitude and frequency of secretion episodes (Hayford, Danney, Hendrix & Thompson, 1980; Evans, Christiansen, Faria et al. 1987). Moreover, inappropriate or exaggerated GH responses to a whole range of stimuli have been reported, including sleep (Hansen, Ledet & Lundbaek, 1981) and exercise (Tambarlane, Sherwin, Koivisto et al. 1979), hypothalamic stimuli such as dopamine (Lorenzi, Karam, McLlroy & Forsham, 1980), arginine (Burday, Fine & Schalch, 1968) and clonidine (Topper, Gertner, Amiel et al. 1985), and pituitary stimuli such as GHRH (Pietschmann, Schernterhan, Prskavec et al. 1987; Krassowski, Felber, Rogala et al. 1988) and other hypothalamic neuropeptides including thyrotropin-releasing hormone (Ceda, Speroni, Dall'Aglie et al. 1982) and LH-releasing hormone (Giampietro, Ferdeghini, Miccoli et al. 1986). Some controversy exists over the response to GHRH with reports of normal and raised responses. This discrepancy may partly arise from the complication caused by obesity which itself impairs the response to GHRH (Kopelman, Mason, Noonan & Monson, 1988). In addition, a normal response in diabetes should be considered inappropriate since the response in non-diabetes is suppressed by an equivalent induced hyperglycaemia, whereas in diabetics the response is unaltered by similar changes in glycaemia (Press, Tambarlane, Thorner et al. 1984b). As the metabolic clearance rate of GH in diabetes remains unaltered (Navalesi, Pilo & Vigneri, 1975), the increase in GH and its responses to secretagogues reflect increased pituitary output. These derangements are most evident in young poorly controlled IDD particularly during the active phase of growth (Hayford et al. 1980).

The increased GH levels of IDD fail to stimulate IGF-I production effectively, IGF-I levels having been found to be either normal or suppressed in IDD when measured by a variety of techniques (Yde, 1964;
The suppression of IGF-I could mute the growth-promoting activities of GH, permitting utilization of mobilized substrates for fuel homeostasis rather than for cell growth and proliferation. The suppression of IGF-I may relate to the degree of metabolic control of the diabetes, and has been correlated with increases in blood glucose levels (Yde, 1964) and glycosylated haemoglobin (Winter, Phillips, Klein et al. 1979; Blethen, Sargeant, Whitlow & Santiago, 1981). IGF-I levels are also less responsive to exogenous GH in poorly controlled IDD, the blunted IGF-I response being correlated with raised glycosylated haemoglobin and with increased GH responses to clonidine (Lanes, Recker, Fort & Lifshitz, 1985). Improved diabetic control, generally obtained by more effective delivery of insulin, results in suppression of the elevated GH levels and a rise in IGF-I levels (Tamborlane et al. 1981; Amiel et al. 1984) although not all reports support this (Merimee, Gardner, Zapf & Froesch, 1984). The exaggerated GH responses to some stimuli are also reversed following improved control (Tamborlane et al. 1979; Topper et al. 1985).

There are many possible mechanisms for the enhanced GH levels found in diabetes. The simplest, but least likely of these mechanisms is the loss of a possible direct effect of insulin suppressing GH release from pituitary somatotrophs. In diabetics the low functional insulin levels would then result in elevated GH. As stated above there is experimental evidence in rats to support this possibility; however, in the nontumorous pituitary, insulin was much less active than IGF-I which was thought to be a more likely important physiological regulator (Ceda et al. 1987).

A second, also improbable explanation would be a direct effect of glucose on the hypothalamus suppressing somatostatin release (Lewis, Dieguez, Inglesias et al. 1987). In non-diabetic man raised levels of glucose are normally associated with suppressed and not elevated GH, although this relationship may not hold true in diabetes, where the GH response to GHRH is inappropriately high during hyperglycaemia, suggesting a blunting of this regulatory pathway.

A third possible explanation is an effect of the suppressed IGF-I levels, IGF-I having been shown to exert negative feedback control over GH release. IGF-I can act on the hypothalamus, stimulating somatostatin release (Berelowitz, Szabo, Frohman et al. 1981) or suppressing GHRH (Brazeau, Guillemin, Ling et al. 1982), or directly on the pituitary, suppressing GH release (Ceda, Hoffman, Silverberg et al. 1985; Yamashita & Melmed, 1987). The reduced IGF-I levels found in diabetes could thus result in disinhibition and hence raised GH output. This could explain the reported negative correlation between GH and IGF-I levels in diabetes during acute metabolic decompensation (Rieu & Binoux, 1985) and a similar correlation observed in malnourished children (Hintz, Suskind, Amatayakul et al. 1978). It could also explain, in IDD, the association between blunted IGF-I responses and elevated GH responses (Lanes et al. 1985) and the simultaneous fall in GH and rise in IGF-I which occur with improved control (Tamborlane et al. 1981; Amiel et al. 1984). As IGF-I suppresses the pituitary response to GHRH (Ceda et al. 1987), the low IGF-I levels in diabetics could also explain the exaggerated responses found to this and other stimuli. Feedback inhibition by IGF-I has also recently been implicated in the deranged GH control found in obese children. Obese children offer the opposite setting to that in poorly controlled diabetics and are frequently hyperinsulinaemic. Thus IGF-I levels are raised and GH responses to various stimuli are blunted, the blunted response to GHRH correlating with the raised IGF-I levels (Loche, Cappa, Borrelli et al. 1987). As pyridostigmine, a cholinesterase inhibitor enhancing cholinergic tone (known to stimulate GH by inhibiting somatostatin release), was found to reverse the blunted response to GHRH, it was concluded that IGF-I was acting via enhancement of hypothalamic somatostatin secretion (Loche et al. 1987).

An alternative to this explanation is offered by a recent report that acute GH pretreatment suppressed the subsequent response to GHRH (Ross, Borges, Grossman et al. 1987), suggesting that GH controls its own secretion via a short negative feedback loop, probably acting by stimulating hypothalamic somatostatin release (Sheppard, Kronheim & Pimstone, 1978). If insulin deficiency in diabetes causes GH resistance at the hypothalamus in an analogous manner to that found in the liver, then a resulting fall in somatostatin would lead to enhanced GH output from the pituitary. However, this feedback could also operate through locally produced IGF-I acting in a paracrine manner on the pituitary before increases in circulating IGF-I become apparent. Following GH administration, tissue levels of IGF-I have been shown to peak much earlier than serum levels (Underwood et al. 1986). Supporting the possibility of this short feedback loop, it has recently been shown that cultured rat pituitary cells secrete IGF-I (Fagin, Pixley, Slanina et al. 1987).

A further alternative to this mechanism could operate via either increased levels of uncharacterized IGF-I inhibitors (Phillips, Belosky, Young & Reichard, 1979) or decreased levels of factors potentiating IGF-I activity. With regard to the latter it has recently been reported that the low molecular weight IGF-I binding protein is secreted by a number of cells and can bind to other cells, enhancing the subsequent binding and actions of IGF-I on these cells (Clemmons, Elgin,
Han et al. 1986; Clemmons, Elgin, Busby & McCusker, 1987; Elgin, Busby & Clemmons, 1987). Others have found that this binding protein inhibits IGF-I binding to various cell types (De Vroede, Tseng, Katsoyannis et al. 1986; Rutanen, Pekonen & Makinen, 1988), raising the possibility of a local mechanism to regulate individual tissue responsiveness to IGF-I. Very recent reports suggest that insulin, and not GH, is a potent stimulant of the secretion of this binding protein in vitro (McCusker & Clemmons, 1987) and insulin may also be an important modulator of the binding protein in vivo. Elevated levels have been found in poorly controlled diabetics which were normalized by insulin infusion (Brismar, Gutniak, Werner & Hall, 1987; Povoa, 1987). It is proposed that insulin regulates the clearance of the binding protein from the circulation and hence its availability to tissues. In diabetes, hypoinsulinaemia could therefore result in decreased availability of the binding protein with a consequent impairment of cellular responsiveness to IGF-I. Alternatively, the higher levels of the binding protein found in diabetics may inhibit receptor binding of IGF-I. Either mechanism could then, in turn, result in blunted IGF-I feedback on either the hypothalamus or the pituitary, leading to raised GH output, even with normal IGF-I levels. The significance of these recent findings must await further clarification.

Just as several mechanisms may be involved in the hypersecretion of GH in diabetes, so there is evidence to suggest at least three possible mechanisms for the inappropriately low levels of IGF-I. Since insulin stimulates the expression of GH receptors, insulin deficiency could result directly in a reduction in hepatic GH receptors. Alternatively, insulin deficiency or a secondary metabolic effect could suppress IGF-I production at an intracellular post-GH receptor site. That insulin could be an important regulator of IGF-I production independent of GH is also suggested by some experimental and clinical studies. Thus, in the recovery of man from severe injury, plasma IGF-I levels closely follow those of insulin but are unrelated to GH levels (Frayn, Price, Maycock & Carroll, 1984). Indeed, recent findings in rats also suggest that insulin might be the most important regulator of hepatic IGF-I production (Nicholl, Russell, Schlechter et al. 1987). However, technical problems were encountered with these experiments and, even if confirmed, the inherent species differences in GH/IGF-I physiology would preclude extension of the conclusions to man.

An additional simple explanation for the inappropriately low levels of IGF-I might be the availability of circulating binding protein. Circulating IGF-I is primarily bound to a large 150 000 dalton complex. As unbound IGF-I has a half-life of about 20 min its levels might be dictated by the availability of the binding protein, bound IGF-I is known to have a much longer circulating half-life. Levels of the large binding protein have been reported to be decreased 40% in poorly controlled diabetics (Baxter & Martin, 1986). This, however, only begs the further question as to why levels of a normally strongly GH-dependent binding protein are low when GH levels are raised.

Is the GH molecule itself different in diabetes? Circulating GH is a heterogeneous family of closely related peptides and several groups have examined this heterogeneity in serum from diabetics to see whether abnormalities could underly the derangements described in this condition. Although a number of GH molecular variants have been described, only two have been found in the circulation in appreciable amounts in man, these being the normal 22 000 dalton (22 kDa) GH and a 20 kDa GH form differing from the former by a 15 amino acid deletion produced by alternative splicing of the GH mRNA. In addition, it is well recognized that circulating GH elutes from gel filtration columns in three size forms with molecular weights of approximately 22 kDa, 45 kDa and 80–90 kDa (known classically as GH, big-GH and big-big-GH respectively). Initial studies of the size variants of GH in diabetes revealed a higher proportion of monomeric GH and a corresponding lower proportion of big-big-GH than in normal man (MacFarlane, Stafford & Wright, 1986a). Monomeric GH has been reported to have a higher affinity for GH receptors than the large molecular weight forms (Gorden, Lesniak, Eastman et al. 1976). Both these findings can now be explained by the recent demonstration of a specific, saturable binding protein for GH in the circulation which accounts for a significant amount, if not all, of the big-big-GH present (Herington, Ymer & Stevenson, 1986; Nixon & Jordan, 1986). Thus the low capacity binding protein limits the levels of the big-big-GH, and hence the proportion of ‘monomeric’ GH increases with increased GH levels. Reduced binding to receptors may be due to competitive binding with the binding protein, or to the receptor binding site on GH being partially blocked by the binding protein. The physiological significance of the circulating binding protein is still not fully understood although a relationship to the GH receptor has been suggested (Daughaday, Trivedi & Andrews, 1987; Leung, Spencer, Cachianes et al. 1987).

Recently, increased amounts of the 20 kDa variant of GH have been reported in diabetic serum (Kreitzer & Chasalow, 1987). This report was, however, based only on differences in immunological properties and, even if confirmed, the significance seems doubtful since original claims for differing bioactivity of this variant, using purified pituitary 20 kDa GH have been
questioned by findings using recombinant DNA-derived 20 kDa GH (Schwartz & Foster, 1986; Ader, Agajanian, Finegood & Bergman, 1987). This suggests that the initial discrepancies may have been due to contaminants present in the final pituitary extracts.

Effects of GH/IGF-I on glycaemic control

Although GH has both insulin-like and anti-insulin-like properties the former are thought not to be important physiologically (Davidson, 1987). The anti-insulin effects of GH include direct stimulation of gluconeogenesis in hepatocytes and, at the periphery, impairment of tissue glucose utilisation. GH stimulates lipolysis, providing glycerol as a substrate for gluconeogenesis and free fatty acids which impair tissue glucose oxidation. GH also has indirect effects through modulating tissue responsiveness to insulin (Davidson, 1987). The resistance to insulin has been shown to be at a site distal to the insulin receptor (Rizza, Mandarino & Gerich, 1982; Rosenfeld, Wilson, Doller et al. 1982).

A further inter-relationship is thought to be a permissive effect of IGF-I on the pancreatic insulin response to oral glucose. Pygmies and hypopituitary dwarfs, both of whom have low IGF-I levels, show blunted insulin responses to glucose (Merimee, Rabinowitz et al. 1968; Merimee, Zapf & Froesch, 1981). GH treatment in the former fails to increase either IGF-I or the insulin response to glucose whilst in the latter GH treatment normalizes both (Merimee, Zapf & Froesch, 1982). This might also explain enhanced insulin responses observed in acromegalics (Fineberg, Merimee, Rabinowitz & Edgar, 1970). In vivo, GH acutely potentiates glucose-stimulated pancreatic insulin secretion and chronically induces β-cell proliferation possibly by regulating islet cell IGF-I production (Swenne, Hill, Strain & Milner, 1987).

The effects of GH are most pronounced in acromegaly where gross increases of GH levels are often associated with abnormal glucose tolerance and insulin resistance which improves when GH levels are lowered (Wass, Cudworth, Bottazzo et al. 1980). In normal man exogenous GH administered to levels within the physiological range causes insulin resistance, impairing the ability of insulin to suppress hepatic glucose production and stimulate peripheral glucose utilization (Rizza et al. 1982). Conversely, GH deficiency causes enhanced sensitivity to insulin (Pearson, Dominguez, Greenberg et al. 1960), which can be reversed by acute but not by chronic GH administration (Lippe, Kaplan, Golden et al. 1981). Similar effects are also seen with physiological variations in GH/IGF-I levels. Thus in puberty, when GH and IGF-I levels rise, insulin sensitivity is impaired (Amiel, Sherwin, Simonson et al. 1986; Bloch, Clemons & Sperling, 1987). This is normally compensated by increased insulin secretion in puberty (Smith, Archibald, Thomas et al. 1988). The normal nocturnal GH pulses of secretion also induce a state of insulin resistance. This occurs several hours later but the causal relationship has been well demonstrated. Abolition of the early nocturnal GH peaks by somatostatin infusion abolishes the early morning rise in plasma glucose, which is restored by infusion of exogenous GH to physiological levels. Early morning hyperglycaemia is prevented by increased pancreatic insulin secretion at this time (Bolli, De Feo, De Cosmo et al. 1984).

Metabolic consequences of derangements of GH/IGF-I in diabetes

The above physiological variations in GH also occur in diabetics, but the ability to compensate the induced insulin resistance by increased pancreatic insulin secretion is compromised. Early morning hyperglycaemia (the dawn phenomenon) results (Bolli & Gerich, 1984) and can be ameliorated by suppression of the nocturnal GH surge (Campbell, Bolli, Cryer & Gerich, 1985). Similarly in adolescents, the insulin resistance associated with puberty is unopposed, leading to deterioration of metabolic control (Blethen et al. 1981; Amiel et al. 1986). Thus pubertal diabetics have increased insulin requirements relative to postpubertal diabetics (Sargeant, Achtenberg & Davis, 1980) but have higher glycosylated haemoglobin levels than prepubertal diabetics, suggesting that, despite increasing insulin dosage, glucose control deteriorates for the duration of puberty (Amiel et al. 1986). In diabetic adolescents GH levels are reportedly higher and IGF-I levels lower than in non-diabetics, and the sensitivity to insulin has been reported to be inversely correlated to mean 24-h GH levels but not to IGF-I levels (Amiel et al. 1986). An inverse correlation with log IGF-I levels has been reported by others (Bloch et al. 1987).

In addition to an inability to compensate for normal physiological variations in GH, poorly controlled IDD causes altered GH/IGF-I levels itself, as described above. These, in turn, exacerbate the metabolic derangements of the disease, the initial cause of the elevated GH (Press, Tamborlane & Sherwin, 1984a). A vicious circle is thus created. GH at levels seen in diabetics impairs tissue responses to insulin in normal subjects, but is compensated by hyperinsulinaemia (Metcalfe, Johnston, Nosadini et al. 1981). Administration of GH to well-controlled diabetics leads to marked hyperglycaemia and hyperketonaemia (Press et al. 1984a; Campbell et al. 1985).
This does not exactly simulate the situation in poorly controlled diabetics where IGF-I levels are suppressed, since in well-controlled diabetics exogenous GH leads to raised IGF-I levels (Press et al. 1984a). The effect on glycaemic control is, however, the same, since the insulin resistance is attributed to a direct effect of GH and is not thought to be mediated by IGF-I (Rizza et al. 1982). The hyperglycaemia results from stimulated hepatic glucose production and also from peripheral insulin resistance secondary to the high GH levels (Press, Tamborlane & Sherwin, 1986). It is of interest that improving glucose control inIDD over a period of time partially restores the impaired peripheral (Simonson, Tamborlane, Sherwin et al. 1983) and hepatic (Amiel, Tamborlane, Simonson & Sherwin, 1987) insulin sensitivity, although restoration of normal circulating GH levels is unlikely to be the sole explanation of these observations.

Suppression of GH secretion has been advocated as an adjunctive therapy to insulin in diabetics (Gerich, 1986). This would obviously be inappropriate in the pubertal or prepubertal diabetic, where the adverse effects of GH on metabolic control have been most evident, since growth is already compromised in such subjects. In post-pubertal patients with IDD, somatostatin and its long-acting analogue have been found to suppress GH and glucagon, reduce daily insulin requirements and improve blood glucose profiles (Plewe, Nolken, Krause et al. 1986; Serrano Rios, Navascues, Saban et al. 1986). Conversely, improved glucose control causes a fall in GH, emphasizing that whatever its glycaemic effects the raised GH is a secondary derangement. The benefits of somatostatin in diabetes might be due to effects unrelated to GH suppression, somatostatin having been reported to reduce renal blood flow (Vora, Owens, Luzio et al. 1987) and to impair the clearance of exogenous insulin (Ipp, Sinai, Bar-Oz et al. 1987). Long-acting somatostatin analogues have also been proposed as an adjunct to insulin in the management of adult-onset type II diabetics after secondary failure of oral hypoglycaemic agents. However, in these patients somatostatin acts mainly by inhibiting carbohydrate intestinal absorption (Candrina, Coppini, Guistina & Guistina, 1987). Whilst somatostatin might improve control, the blocking of a counter-regulatory mechanism increases the risks of severe hypoglycaemia (Gil, Pascau, Senen et al. 1987), a common side-effect of insulin treatment (Potter, Clarke, Gale et al. 1982). A promising alternative has been suggested by the demonstration that cholinergic muscarinic receptor blockade with pirenzepine suppresses GH release in normal subjects and patients with IDD, abolishes sleep-induced surges, and yet only slightly inhibits the GH response to hypoglycaemia (Page, Koppeschaar, Dieguez et al. 1987). The effects of pirenzepine have, however, been shown to be transient and are accompanied by rebound GH secretion (Hindmarsh, Pringle & Brook, 1987).

**GH/IGF-I and diabetic complications**

Poor glycaemic control has frequently been implicated in the development of the long-term complications of diabetes (neuropathy, nephropathy, retinopathy and premature atherosclerosis). The raised GH levels generally found in poorly controlled diabetes have been linked to these complications, especially proliferative retinopathy (Merimee, Zapf & Froesch, 1983; Gerich 1986). It has long been known that hypophysectomy can arrest or slow down the progression of proliferative retinopathy (Kohner, Hamilton, Joplin & Fraser, 1976) and that GH-deficient dwarfs usually lack microvascular complications (Merimee, 1978). Whilst it has been shown that GH is not essential for the early changes involved in these complications it is still thought that GH may play an important role in their development (Rabin, Bloomgarden, Ferman & Davis, 1984; Salardi, Cacciari, Ballardini et al. 1986).

There are many potential mechanisms through which GH could play a role in the development of diabetic complications. GH has been shown to have direct in-vitro effects on arterial medial cell growth (Ledet, 1976), arterial production of procollagen type I and fibronectin (Ledet & Vuust, 1980) and in-vivo correlations have been found between GH levels and factor VIII-related antigen, plasminogen activator (Sundkvist, Almer, Lilja & Pandolfi, 1984) and platelet release of prostaglandin E (Colwell, Halushka, Sarji et al. 1976). It has been suggested that whilst hepatic resistance to GH develops in diabetes, other tissues retain their sensitivity to GH, thus contributing to the development of vascular complications (Baxter et al. 1980b). However it has generally been found that retinopathy is associated with elevated GH and IGF-I levels (Ashton, Dornan, Pocock et al. 1983; Merimee et al. 1983). This implies that hepatic sensitivity to GH is also normal at this time in these patients. This might represent a later stage of the disease process, with prolonged diabetes or its treatment reverting the original hepatic resistance to GH. Alternatively, it might represent a different response in a subset of the heterogeneous diabetic population. Hyperinsulinaemia is a common occurrence in IDD where normoglycaemia is attempted (Rizza, Gerich, Haymond et al. 1980). This might be expected to improve hepatic sensitivity to GH and hence raise IGF-I levels, the mitogenic effects of which could then aggravate the progression of vascular complications.

There have been reports of circulating GH having enhanced receptor activity in some diabetics (MacFarlane, Stafford & Wright, 1986b) and that
IGF-I is disproportionately raised in relation to GH in some diabetics with advanced retinopathy (Merimee et al. 1983). This might indicate the presence of a GH variant with enhanced bioactivity which could contribute to the development of diabetic complications.

Conclusions

An important role for insulin in the growth process is becoming increasingly clear, similarly the role of GH in metabolic control, especially in relation to diabetes, is receiving increasing attention.

IDD clearly causes derangements in the GH/IGF-I axis. Increased GH causes insulin resistance, adversely affecting diabetic control. This should be considered in treating young diabetics in whom insulin requirements need adjusting during the pubertal growth spurt when GH levels are raised. However, a more general implication is the effect of raised GH caused by poor metabolic control leading to the creation of a vicious circle in diabetics that are metabolically hard to control.

Adjunctive therapy in diabetics to suppress GH levels might prove beneficial, although more work is required to clarify this. The major drawback of such therapy is the increased risk of hypoglycaemia caused by negating a counter-regulatory hormone. Somatostatin appears to reduce insulin requirements but its benefit probably arises from effects other than inhibition of GH secretion. Other agents such as cholinergic receptor blockers could prove more appropriate but further development is needed, particularly regarding the long-term use of such agents.

Whilst poor metabolic control and insulin deficiency cause the initial derangements of the GH/IGF-I axis, the effects of prolonged treatment with frequent episodes of hyperinsulinaemia also should be considered. Frequent hyperinsulinaemia could result in potentiation of the mitogenic activity of the GH/IGF-I axis which, in turn, could contribute to the vascular complications associated with long-term diabetes. Adjunctive therapy might eventually prove to delay such complications.

REFERENCES


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