Growth Hormone and Diabetes in Man

Old Concepts—New Implications

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Interest in the relationship between pituitary growth hormone (GH) and diabetes mellitus and its vascular complications has been revived during the last few years. Discoveries of a hormone that regulates growth hormone secretion (growth hormone release-inhibiting hormone, somatostatin) and of the substances that stimulate the biological action of GH in the tissues, the somatomedins, have added to this development. Keener insight into the biological effects of GH has also been gained. This will be a short review of the fundamentals that led to the proposal that GH may be involved in the development of diabetes and, perhaps, its vascular complications. It will also describe how recent observations and discoveries are allowing new approaches to these old concepts.

The role of the hypophysis in experimental diabetes in animals was discovered by Houssay and Biasotti in 1930 when they demonstrated that the severity of diabetes decreases following extirpation of the gland and increases again after implantation or injection of its pars distalis. Young, in 1937, was able to produce diabetes in intact dogs by the administration of crude anterior pituitary extracts. In 1949, Cotes et al. and, independently, Houssay and Anderson demonstrated that growth hormone was the active substance in pituitary extracts which induced diabetes in animals. The cycle of experimental evidence giving to growth hormone the role of a diabetogenic substance was completed when it was demonstrated that (1) hGH given to hypophysectomized nondiabetic patients induced a condition similar to the idiohypophysial diabetes of the laboratory animal (Ikkos and Luft 1960a); (2) hGH caused deterioration of the disease when given to diabetic patients, most obviously in hypophysectomized juvenile diabetics, where administration of a very small amount of the hormone was accompanied by a dramatic response in terms of hyperglycemia, glucosuria, and metabolic acidosis (Ikkos and Luft 1960b); (3) intravenous glucose tolerance decreased in the majority of normal subjects after a few days of hGH administration and reached diabetic levels only in a minority of these (Ikkos et al. 1962).

Against the background of this knowledge the obvious question was whether GH might be considered to be a *primary* factor in the development of diabetes in man or of diabetic vascular disease.

Growth hormone as a primary factor in the development of diabetes

One finding is inconsistent with the concept of GH as a primary factor in this respect—the fact that diabetes or glucose intolerance occurs only in a minority of acromegalic patients which may produce large amounts of hGH for many years. A clarification on this point was presented by Luft and Cerasi (1968). In acromegalic subjects with *normal* glucose tolerance, plasma insulin showed an immediate and, when compared with normal subjects, grossly exaggerated rise in response to glucose infusion. Successful treatment of the acromegaly in these patients was always accompanied by normalization of the insulin response. In acromegalic patients with *decreased* glucose tolerance the plasma insulin response to glucose infusion was of the type seen in nonacromegalic diabetic patients, i.e. delayed and decreased (Luft et al. 1967). After suc-

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cessful treatment of the disease in these subjects, the low and delayed insulin response remained even when the glucose tolerance was normalized.

The authors concluded that hGH is diabetogenic only in such instances where the β-cells of the pancreas have an inherited (?) inability to respond to the insulinogenic effect of hGH and to produce insulin in an adequate manner. In the terms of Cerasi and Luft (1967, 1973) the latter "low insulin responders" would be those subjects with a diabetic "anlage" or prediabetics. It should be emphasized that what the authors discussed was a diabetic state connected with overproduction of hGH. They therefore added that "it remains to be shown whether the normal secretion of hGH with its daily fluctuations may be of any significance for the precipitation of diabetes in prediabetic individuals."

Growth hormone and the development of diabetic vascular disease

This question was considered for the first time twenty years ago by Luft and Olivecrona when they introduced hypophysectomy in the treatment of diabetes with vascular complications (Luft et al. 1952, 1955). These authors stated in their early presentations that the rationale of the intervention was to remove the secretion of GH, one of the hormones that, according to animal work, could have an unfavorable influence on the diabetic state. The beneficial influence of pituitary removal on diabetic vascular disease (mainly retinopathy) as reported later by numerous authors, might be considered to favor this hypothesis (for review, see Goldberg and Fine 1969).

The introduction of a radioimmunoassay for hGH in plasma has opened new possibilities for investigation of the eventual relationship between hGH and diabetic vascular disease. One question has been whether a generally increased serum level of hGH occurs in diabetic patients or if such subjects demonstrate an abnormal hGH response to agents or measures that are known to stimulate hGH release. The data obtained are conflicting. Thus, Molnar et al. (1968) indicated that blood of juvenile diabetics may contain more immunoreactive hGH than that of nondiabetics, and Prange-Hansen in a series of orderly papers (1970-1973) came to the following conclusions: diurnal plasma hGH levels are higher in male and female diabetics than in control subjects and show wide fluctuations; the fasting pre-exercise hGH level is higher and the exercise response occurs earlier and is greater in diabetics than in normal subjects. On the other hand, Tchobroutsky et al. (1966) and Burday et al. (1968) were unable to demonstrate enhanced GH response to arginine infusion and insulin-induced hypoglycemia in diabetic subjects. Furthermore in a recent paper, Konez et al. (1973), on the basis of studies on hGH secretion after double stimulation with arginine in diabetic and control subjects, concluded that no quantitative difference existed but suggested an impaired sensitivity or defective mechanism of GH secretion in diabetic subjects.

Thus, increased levels of hGH seem to occur in the plasma of diabetic patients. The inconsistency in the data above may be ascribed mainly to the selection of patient materials used. In this connection the data of Hansen (1974) seem to be relevant—the plasma and urinary hGH levels were significantly higher before than during initial insulin treatment of diabetes. Furthermore, since even minor fluctuations in blood glucose concentration are of significance for the hGH level in plasma (Luft et al. 1966), it seems likely that diabetic patients may be exposed to elevated hGH concentrations.

Is there any relationship between such an eventual increase in plasma hGH and the development of diabetic vascular disease? This old hypothesis, suggested by Luft and Olivecrona in the early 1950's, has been revived during the last few years. It is mainly Lundbaek (1973) and his group that have been its advocates. To the best of our knowledge, direct evidence for the above relationship is still lacking. Of interest in this connection are two recent reports. Firstly, Knopf et al. (1972) have shown that fasting levels of hGH "are significantly greater in diabetic females with retinopathy when compared with female diabetics without retinopathy and with normal subjects." However, they also indicated that the blood glucose control was more important than the degree of retinopathy for plasma hGH. Secondly, Merimee et al. (1973) found a considerably lower frequency and degree of micro- and macroangiopathies in subjects with isolated hGH deficiency, carbohydrate intolerance and hyperlipoproteinemia than in a matched group of diabetic patients. The authors concluded from their data, consistency with the hypothesis that chronic deficiency of hGH deters the development of both micro- and macroangiopathic changes "to a clinically detectable state." On the other hand, if hGH were the *primary* factor in the development of diabetic angiopathy, it is difficult to understand how patients with long-standing acromegaly with concomitant diabetes, can be so relatively free of the typical signs of such angiopathy.

In this connection, the findings of Lewis and col-

laborators (1973) are of special interest. These authors recently reported the isolation from human pituitaries of a protein closely related to but different from GH on the basis of (total) amino acid composition and electrophoretic behavior. They consider this peptide to be a much more powerful diabetogenic agent than GH itself based on the peptide modification of glucose tolerance responses in dogs. Obviously, it will be of interest to ascertain whether this diabetogenic factor of pituitary origin is measurable in the peripheral blood of diabetic subjects, in relation to the degree of their disease, and whether its secretion would be inhibited by somatostatin.

Thus, while there is no doubt that GH is a diabetogenic hormone, its place in the development of diabetes in man and even more so in that of diabetic microangiopathy, is still uncertain.

During the last few years some new insight has been gained regarding the control of the secretion of GH and its mode of action at the periphery. In the following, we shall give a brief account of these new developments, as they may establish connections between GH and diabetes.

Somatostatin

The ultimate controller of the adenohypophysial secretion of GH appears to reside in the ventral hypothalamus in the form of one or more hypophysiotropic peptides as is now well known to be the case for other pituitary hormones such as thyrotropin, TSH and the gonadotropins LH and FSH. In the case of GH the nature of the hypothalamic GH-releasing factor is still unknown, though the presence of a GH-releasing activity is unquestionable in crude hypothalamic extracts. It was while searching for such a GH-releasing factor in side-fractions remaining from our earlier isolation program of the TSH-releasing factor and the LH/FSH-releasing factor when we realized that some of these fractions (of the hypothalamic extracts) were powerful inhibitors of the secretion of radioimmunoassayable GH. The inhibitory activity was shown to be due primarily to a polypeptide named *somatostatin* (or somatotropin release-inhibiting factor) with the primary sequence Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH (Brazeau et al. 1973, Burgus et al. 1973). Both the linear (reduced) and the cyclized (oxidized) form of the peptide have biological activity. Somatostatin is a powerful inhibitor of spontaneous or stimulated secretion of immunoassayable GH *in vitro* or *in vivo* in all circumstances and all species studied so far, including man. For instance, somatostatin, now available by total synthesis in large quantities, inhibits the secretion of GH acutely stimulated in man by administration of L-dopa, arginine, or by insulin-hypoglycemia, physical exercise, or as it occurs in slow wave sleep (Siler et al. 1973, Hall et al. 1973, Prange-Hansen et al. 1973, Parker et al. 1974). Somatostatin also and regularly lowers the elevated resting plasma GH levels in all acromegalics tested so far (Hall et al. 1973, Yen et al. 1973, Hall and Luft 1974).

Early studies on the mechanism of action of somatostatin show it to act in inhibiting the secretion of GH directly at the level of pituitary cells, distally to the locus of action of c-AMP, to be unaffected by inhibitors of RNA-directed DNA synthesis (actinomycin D) or of protein synthesis (cycloheximide) (Vale et al. 1972). In animals as in man, the onset of action of somatostatin in inhibiting secretion of GH is extremely rapid ($<$ five minutes); its biological half-life is also extremely short ($\leq$ five minutes). A long-acting preparation of somatostatin will thus be necessary for any (long term) clinical use. In animal studies, complexing somatostatin with protamine zinc has yielded preparations with sustained ($\geq$ sixteen hours) biological activity (Brazeau et al. 1974).

Somatostatin may thus be the ideal therapeutic tool to lower chemically the concentration of circulating GH. Chronic administration of long-acting preparations of somatostatin should also prevent the abnormally elevated GH responses observed in diabetic patients after meals or exercise (Prange-Hansen et al. 1973, Prange-Hansen 1970). Thus the hypothalamic inhibitor may represent a physiologically significant approach to replace the more drastic procedure of hypophysectomy proposed long ago by Luft and Olivecrona (see above) as a means of suppressing the secretion of GH in patients with diabetic retinopathy and other microangiopathies. Whether somatostatin will be of use in this respect is, of course, for further study and will not be known until several years of both fundamental and clinical investigations are completed.

When discussing the eventual clinical application of somatostatin, other biological actions of the hormone must be considered. Recently it was reported that when injected in unanesthetized baboons, somatostatin not only lowered plasma GH levels but produced a moderate but statistically significant hypoglycemia (lowest level at ca. thirty minutes), *preceded* by a dramatic fall (lowest level at ca. five minutes) in glucagon and plasma insulin levels (Koerker et al. 1974, Ruch et al. 1973). Similar results have since been observed in normal and acromegalic subjects in regard to effects of somatostatin

on plasma insulin and glycemia levels (Yen et al. 1973, Alberti, et al. 1973, Hall and Luft 1974). Also, in juvenile diabetics, somatostatin lowers blood glucose and glucagon levels (Gerich et al. 1974). There is evidence from studies using direct perfusion of somatostatin in isolated dog or rat pancreas that this effect on the secretion of glucagon and insulin takes place directly at the level of the α and β cells (Koerker et al. 1974, Efendić et al. 1974).

In the light of these findings, somatostatin would have three actions which would be convenient for the diabetic: the suppression of the release of GH and glucagon and the hypoglycemic effect. The inhibiting effect on insulin release, as a matter of fact, might not carry any major disadvantage since insulin secretion is already decreased in diabetes. Thus, the manifest diabetic patient, who appears to have abnormally elevated glucagon (Unger et al. 1972, Gerich et al. 1973) as well as GH levels (see above), would probably benefit from the administration of somatostatin.

It may well be that a combined suspension of insulin plus linear somatostatin in adequate ratios will be the best form of its administration since it would compensate for the lack of insulin or the inhibition of its secretion while controlling the abnormally elevated secretion of growth hormone and glucagon. Too many interrelations are known between secretions of growth hormone, glucagon, insulin and the catecholamines in normal physiology as well as in diabetes to permit anything but speculations on what availability of somatostatin will permit.

The somatomedins

It seems well established now, that at least the anabolic and growth promoting action of GH at the tissue level is mediated by local factors or hormones which belong to the family of somatomedins (for a review see Hall and Luft 1974). Several such factors have already been isolated (A, B and C), and all are peptides. At present, we have some data concerning the effect of such peptides on glucose uptake and lipolysis in isolated muscle and fat tissue. Somatomedin stimulates glucose uptake and oxidation in fat cells, one unit* of somatomedin in this respect being equivalent to 30 to 50 μU. of insulin (Hall and Uthne 1971). It also causes inhibition of glycerol release *in vitro* in epinephrine-stimulated fat tissue (Underwood et al. 1972). The stimulatory effect on glucose uptake could also be demonstrated on muscle tissue (Uthne et al. 1974).

*Purified preparations of somatomedin (A) have specific activities of the order of 2,500 U. per milligram.

Thus, the available somatomedins, beside their anabolic effect, seem to carry the early, well known and somewhat puzzling insulin-like action of GH. It has also been claimed that the noninsulin part of the so-called insulin-like activity of plasma (ILA or NILA) might be very closely connected to or identical with one somatomedin (A) (Hall and Uthne 1971).

Therefore, the diabetogenic effect of GH cannot be ascribed to any of the somatomedins studied so far. On the other hand, the discovery of these tissue hormones, which mediate the effect of GH on the periphery, should promote the search for other GH-dependent tissue factors which might carry the specific actions of this hormone. In this connection it may be of some interest that the production of glomerular basement membrane involves the synthesis of glycoprotein (Spiro 1963, 1969), and the effect of GH on pathways which are important to the synthesis of glycoprotein is well established (Winegrad and Borden 1966). Furthermore, the intima of the aorta is rich in sulfonated polysaccharides which can bind low density lipoproteins in serum. These substances are postulated to be involved in the pathogenesis of atherosclerosis (Levy and Day 1970). Hypophysectomy has been shown to decrease the concentration of such sulfonated polysaccharides in the wall of the aorta; these are restored to normal after administration of GH (Brosnan et al. 1971).

If GH is necessary for the ability of certain tissues to synthesize the above crucial proteins—at an increased rate in some vascular disorders—we might suggest a place for GH-dependent tissue hormones in this connection.

CONCLUSIONS

It is well established that GH levels in blood seem to be raised in diabetes mellitus, which has brought up again the old hypothesis regarding the significance of GH in the development of diabetes and its vascular complications.

In the light of old and recent findings, we believe that GH—in normal or increased amounts—should only be regarded as a factor being able to precipitate diabetes in prediabetic individuals. Furthermore, it seems likely that GH, provided diabetes is present, may play a role in the development of the vascular complications.

The discovery of the GH release-inhibiting hormone, somatostatin, might open the way to an objective evaluation of the role of GH in diabetes. It will soon be possible to follow diabetic patients with com-

pletely suppressed GH secretion.

The discovery of GH-dependent tissue hormones, somatomedins, suggests new approaches to the elucidation of the diabetogenic action of GH and, possibly, to its significance in diabetic vascular disease.

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