Somatostatin, Growth Hormone, Insulin-like Growth Factor-1, and Diabetes: Friends or Foes?

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Major findings with regard to the somatostatin–growth hormone (GH)–insulin-like growth factor (IGF-1) axis and diabetes are summarized. GH hypersecretion and reduced circulating IGF-1 levels are prevalent in insulin-dependent diabetes. Somatostatin improves metabolism in insulin-dependent diabetics. Insulin resistance and poor metabolic regulation, which may partly be due to hypersecretion of GH, are believed to accelerate the development of diabetic angiopathy. Diabetic hypersomatotrophinemia may be due to hepatic resistance to GH and increased hepatic production of IGF-1–binding protein-1 (IGFBP-1), leading to reduced levels of circulating IGF-1 and further stimulation of GH production. Studies in vitro and in diabetics suggest a causal link between diabetic hypersomatotrophinemia and diabetic angiopathy. In vitro evidence for the involvement of IGF-1 in diabetic angiopathy is reviewed. Also reviewed is evidence, from rat and human studies, of the possible involvement of GH and IGF-1 in diabetic nephropathy. The role of somatostatin in late diabetic vascular complications remains to be elucidated.

A BRIEF HISTORY

THE THREE PARTICIPANTS in the somatostatin–growth hormone (IGF-1)–insulin-like growth factor axis have a fine past, present, and undoubted future role in diabetes research and in intermediary metabolism in general. Important classic studies include the following: Young's demonstration that administration of anterior pituitary extracts precipitated somatotrophic (hyperinsulinemic) and later metasomatotrophic (hypoinsulinemic) diabetes in dogs[1]; Rabinowitz and Zierler's famous hypothesis that insulin and GH alternately and in combination, in a three-phased diurnal cycle, "dominate metabolism,"[2] a theory that was expanded in 1988 by Baxter's group[3,4] after the discovery of the dramatic diurnal fluctuations in serum IGF-binding protein-1 (IGFBP-1); Froesch et al's early work on nonsuppressible insulin-like activity[5] (the IGFs) and their later studies investigating IGF-1 action in man[6,7]; Yde's demonstration that insulin-dependent diabetics often had paradoxical elevations in serum GH during glucose tolerance tests[8]; and Hansen and Johansen's studies showing that insulin-dependent diabetics had a three to four times augmented 24-hour circulating GH level[9]; and that this GH hyperproduction was metabolically dependent so that it ameliorated with some weeks of extremely strict insulin treatment.[10] Yde showed that the sulfation factor (somatomedin C, later IGF-1) was reduced in diabetic serum and inversely related to blood glucose[11]; Lundbaek et al proposed the GH hypothesis, which stated that diabetic GH hyperproduction was a causal factor in diabetic angiopathy[12]; Gerich's and Press's groups elegantly demonstrated that the level of hypersomatotrophinemia found in diabetics under ordinary clinical control was amply sufficient to increase insulin resistance and to accelerate threatening metabolic deterioration[13,14]; and Campell et al[15] and later others found evidence that the nightly GH hyperproduction was involved in the dawn phenomenon. It was only 1 year after the discovery of somatostatin[16] that its extrapituitary effects began to emerge, beginning with inhibition of insulin secretion,[17] and somatostatin became an invaluable tool in assessing hormonal action in many metabolic situations, among them diabetes. It was found that somatostatin administration ameliorated the metabolic aberration in insulin-dependent diabetics,[18] but worsened it in non–insulin-dependent diabetics.

Three large, recent publications on the topic include overviews and original articles.[19-21] The contents of these collections illustrate the explosion of knowledge and the quality of current research, but also that a great deal remains to be discovered.

DIABETIC HYPERSOMATOTROPHINEMIA AND ANGIOPATHY

Today, it would be hard to find anyone who would dispute that the average insulin-dependent diabetic patient releases GH in considerable excess,[9] that this implies augmented insulin resistance,[14] and that, if practicable, it would be expedient to curb the hypersomatotrophinemia, not only from a direct metabolic point of view, but also, in the long run, because insulin resistance and imperfect metabolic regulation are responsible for accelerating the development of diabetic microangiopathy and macroangiopathy.

The question of whether GH has harmful vascular effects apart from those deriving from its insulin-antagonistic actions, ie, other direct effects or effects mediated through IGF-1, is still unsettled, as is the mechanism behind the diabetic hypersomatrophinemia itself. This is believed to be due to the hepatic resistance to GH demonstrated in catabolic states like fasting, protein malnutrition, and poorly controlled diabetes; it leads to reduced circulating IGF-1, which, by feedback stimulation, increases GH production. Another factor in insulin-dependent diabetes is undoubtedly the increased hepatic production of IGFBP-1, due to portal hypoinsulinemia; this excess further reduces free (bioactive) IGF-1 and further increases the feedback stimulus on GH release.

There is no solid scientific proof, but only circumstantial

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0026-0495/96/4508-1003$03.00/0

evidence, that diabetic hypersomatotrophinism and diabetic angiopathy are related. The same kind of evidence led to the proposal of the GH hypothesis in 1970—primarily the observation that pituitary ablation, whether due to local apoplexia,[22] neurosurgery,[23] or irradiation,[24] ameliorated the progression of retinopathy. As these patients received replacement therapy with adrenal steroids, thyroid hormones, and often sex hormones, the evidence pointed to GH. Compelling evidence was presented by Sharp et al[25] in their follow-up study of more than 100 diabetic patients who underwent pituitary yttrium implantation in the 1960s and early 1970s. The patients were definitely GH-deficient at reexamination, and presented with disappearance of new vessels on the disk and excellent preservation of visual acuity. In addition, these patients had a lower than expected incidence of cardiovascular death. Another possible link was indicated by the demonstration that the capillary hyperfragility associated with long-term diabetes disappeared after hypophysectomy.[26,27] Finally, Ledet, studying cultured aortic smooth muscle cells, found that addition of GH, as well as diabetic serum, stimulated replication, and that the latter effect disappeared with addition of antiserum against GH.[28,29] Ledet's group also demonstrated that GH increased accumulation of basement membrane-like material.[30] It has not been established whether these latter smooth muscle cell effects of GH and diabetic serum are mediated via IGF-1.

IGF-1 AND DIABETIC ANGIOPATHY?

As mentioned in the case of the diabetic, hypersomatotrophinism is believed to be promoted by the low circulating total and free IGF-1 levels characteristic of poorly controlled diabetes. The low levels are due to hepatic resistance to GH and to excessive hepatic production of IGFBP-1. However, it is not known whether peripheral sites of production of IGF-1, and these include the majority of tissues, are also resistant to the actions of GH.

The following observations are relevant when considering the possibility that IGF-1 is involved in diabetic microangiopathy and macroangiopathy (atherosclerosis):

1. Arterial myomedial cells have abundant IGF-1 receptors[31]; this is also the case for cultured cells,[32] while insulin receptors are scant or absent.
2. IGF-1 stimulates DNA synthesis of cultured vascular myomedial cells,[33,34] again more potently than insulin.[34] These points indicate that the atherogenic effects of hyperinsulinemia, if any, are mediated via the IGF-1 receptor.
3. Angiogenesis and vessel proliferation in a variety of circumstances are accompanied by preceding or concomitant immunohistological expression of IGF-1.[35,36]
4. Although the mitogenic effects of IGF-1 may be weaker than those of platelet-derived growth factor and fibroblast growth factor, these factors react synergistically with IGF-1, and this synergism may be necessary to attain a maximal or excessive response by the myomedial cells.[37,38]
5. Vascular smooth muscle cells are themselves capable of synthesizing IGF-1. IGF-1 mRNA has been demonstrated both in vivo and in vitro.[38,39] Other cells present in atherosclerotic lesions, macrophages, and endothelial cells can also express IGF-1.[40,41]
6. IGF-1–binding proteins are secreted from cultured myomedial cells[42]; this may serve to entrap circulating IGF-1 and may possibly enhance cellular binding.[43]

Most of these observations were made using cultured arterial smooth muscle cells. Another much-used model in experimental atherosclerosis research is balloon catheterization (endothelial denudation) of large arteries (aorta, iliac, and carotid) in rats, rabbits, and pigs.

The cellular events taking place after endothelial denudation begin with proliferation of smooth muscle cells and their migration, within a week, to the intima; thereafter, reendothelialization ensues and proliferation diminishes.[44] During the active period, the vascular expression of IGF-1 shows a transient increase from the very low normal levels.[35,45] The somatostatin analog lanreotide diminishes vascular stenosis following experimental endothelial denudation[46,47] and prevents the fourfold accumulation of IGF-1 in the vessel wall.[48] In vitro cultured human smooth muscle cells are stimulated by IGF-1, and the growth response is inhibited by lanreotide.[49] Two controlled trials with subcutaneous infusion of lanreotide in patients subjected to coronary balloon catheterization showed improvements in either clinical events[50] or in coronary arteriography[51] compared with placebo-treated patients, as well as significant increases in serum IGFBP-1 and reductions in circulating total and free IGF-1 (unpublished findings).

GH and IGF-1 have also been suggested to be involved in diabetic nephropathy, at least in the early renal hypertrophy/hyperfunction period. Flyvbjerg et al[52] found that extractable renal IGF-1 accumulated to a peak level 1 to 2 days after administration of streptozotocin in rats and returned to control levels between days 4 and 7, ie, before and during the period when the kidney growth rate was at its greatest. There are several indications that the increase in renal IGF-1 content is a prerequisite for the ensuring kidney hypertrophy; for instance, relationships were found between the amount of accumulated IGF-1, the blood glucose level, and the degree of hypertrophy.[53] Whether the GH/IGF-1 system is also implicated in later stages of diabetic nephropathy is purely speculative. Administration of the somatostatin analog octreotide in streptozotocin diabetic rats not only prevented early renal hypertrophy and prior IGF-1 accumulation,[54] but also the steep increase in albuminuria over 6 months of experimental diabetes.[55,56] But it is far from certain that this latter effect is mediated via the direct causal influence on local or circulating IGF-1.

In insulin-dependent diabetics, Serri et al[57] demonstrated that 3 months' administration of octreotide reduced levels of circulating IGF-1, as well as glomerular filtration rate and kidney hypertrophy. It may be speculated that somatostatin and its analogs will also have reduced the serum concentration of free IGF-1 through their stimulatory effect on IGFBP-1.[58-61] This action has been demon-

strated in normal (unpublished findings) and acromegalic human subjects.[62]

TREATMENT OF THE METABOLIC ABERRATION WITH IGF-1

Some of the same arguments that formed the basis for somatostatin analog administration in diabetic patients, namely, that it appears expedient to reduce hypersomatotrophinemia and thereby the insulin resistance it causes, have inspired trials with IGF-1 treatment in insulin-dependent and non–insulin-dependent diabetics.[63-66] Additional primary aims were to exploit the insulin-like effects of IGF-1, normalize circulating peripheral insulin levels, and, in pubertal diabetics, restore normal growth.

In brief, the few trials so far executed, although all short term, have been encouraging, there have been no significant side effects with the cautious dose regimens applied, and the metabolic and hormonal effects fulfilled expectations.[67] It must be emphasized that the research groups initiating these IGF-1 trials have all stressed the necessity for long-term studies before any firm conclusions can be drawn.

CONCLUSIONS

While it is rather obvious that GH is a foe in diabetes, at least from the metabolic point of view, and therefore (perhaps also more directly) in the context of late diabetic vascular manifestations, it is at present undocumented whether circulating or local IGF-1 has any significant adverse effect in the progression of the latter. As for somatostatin analogs and diabetes, neither is there, at present, any scientifically acceptable proof of important beneficial long-term effects on diabetic complications.

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