Growth hormone and its modulation

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List of abbreviations used throughout this article

| Abbreviation | Description |
|--------------|-------------|
| EGF          | epidermal growth factor |
| FGF          | fibroblast growth factor |
| GH           | growth hormone |
| GHRH         | growth hormone releasing hormone |
| IGF-1        | insulin like growth factor-1 |
| PDGF         | platelet derived growth factor |
| PRL          | prolactin |
| SS           | somatostatin |
| TRH          | thyroid stimulating hormone releasing hormone |
| TSH          | thyroid stimulating hormone |
| T_{3}        | triiodothyronine |

The importance of anterior pituitary growth hormone (GH) in the stimulation of tissue growth in general has been appreciated for many years [1,2] but recent technological advances relating to the isolation, characterisation and study of specific genes have increased our understanding of the way in which the GH gene is regulated. Nearly 50 years after growth was stimulated in dogs by injection of bovine GH [1], a similar phenotypic effect was produced in mice by microinjection of a metallothionein-GH or GHRH [3,4] fusion gene into the pronuclei of fertilised mouse eggs. This illustrates that although the physiological questions remain unchanged, the technological tools now available to answer them have revolutionised our experimental and therapeutic approaches.

In this review we will summarise our understanding of the neuroregulation of GH secretion and somatroph cell growth as well as its relevance to various clinical abnormalities. In particular, we will discuss the altered GH secretion which occurs in conditions such as acromegaly, diabetes mellitus and GH deficiency states associated with short stature and the new pharmacological approaches to the treatment of these diseases.

**GH secretion and actions**

GH is a polypeptide hormone with a molecular weight of about 21,500. It exists in the circulation in variable states of polymerisation and hence has a variable biological activity. GH shows an episodic, pulsatile pattern of release throughout the day which is greater in females than in males. However, the most striking feature of GH secretion in man is the slow wave sleep-related (stage 3/4) nocturnal surge of GH release which is a definite, sleep-entrained circadian rhythm [see reviews 5-7]. GH is also released in various stressful conditions and by exercise but circulating levels are very much influenced by the metabolic status of the individual. The successful cloning of the human GH gene has led recently to the availability of synthetic human GH which is presently undergoing clinical trials in the treatment of short stature.

GH has two major groups of actions within the body: 1. It stimulates general tissue growth through the mediation of IGF-1 (formerly known as somatomedin-C and produced largely in the liver in response to GH stimulation) and it has important actions in the control of body metabolism. It stimulates lipolysis with increased production of non-esterified and free fatty acids; it is ketogenic and causes carbohydrate intolerance, ultimately leading to frank diabetes mellitus in states of excess GH production or administration. In both these groups of actions, feedback control at hypothalamic and pituitary levels is exerted by GH itself, by IGF-1 and also by various metabolic factors such as free fatty acids and glucose [5-7]. In consequence, the GH secretory status of any individual at a given point in time is a reflection of the interplay of all these factors acting via their respective feedback control loops.

**Control of GH synthesis and release**

Hypothalamic control of GH synthesis and release is mediated by two hypothalamic peptides, somatostatin (SS) which is inhibitory and GH releasing hormone (GHRH) which is stimulatory. SS was first isolated, characterised and synthesised by Brazeau et al. in 1973 [8] and at that time was shown to be a cyclic tetradecapeptide. Several other molecular forms of SS have been described subsequently, the most important of which appears to be a 28-amino acid N-terminal extension of the tetradecapeptide SS-14 [9]. SS itself is species-nonspecific and has a very short plasma half life of about 3 to 4 minutes. In contrast, GHRH has only recently been characterised. It was isolated independently and simultaneously from pancreatic tumours in two patients with

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Table 1. Role of GHRH and somatostatin in GH secretion [7].

- Acute administration of GHRH or somatostatin both in vivo and in vitro causes rapid, dose-related and specific release or inhibition of GH in a variety of mammalian and nonmammalian species.

- Rats treated with anti-GHRH antibodies or treated neonatally with monosodium glutamate (which reduces GHRH in the median eminence) show an abolition of pulsatile GH secretion and a decrease in somatic growth, whereas rats treated with anti-somatostatin analogues show an increase in basal and stimulated GH levels and increased body weight.

- GHRH and somatostatin are present in portal vessels at concentrations which stimulate or inhibit GH release and GH gene transcription. GHRH levels are increased whereas somatostatin levels are reduced at the time of the expected GH secretory episode.

- Chronic administration of GHRH to intact rats or humans leads to an increase in GH and IGF-1 levels as well as somatic growth. Chronic administration of somatostatin inhibits basal and stimulated GH release.

- Elevation of plasma GHRH levels (ectopic GHRH producing tumours or transgenic mice expressing the GHRH gene) elevates GH levels and increases somatic growth.

- Specific high affinity low capacity GHRH and somatostatin receptors are present on membranes of anterior pituitary cells.

Table 2. Extrapituitary effects of GHRH.

| Tissue          | Response                                      |
|-----------------|-----------------------------------------------|
| Central nervous system | Increase in the amount of time spent in slow-wave sleep |
| - Increase in locomotor activity |
| - Increase in feeding |
| - Stimulation of somatostatin release from the hypothalamus |
| - Increase in the activity of dopaminergic neurones in the arcuate nuclei |
| - Stimulation of calcitonin and neurotensin release from a neural-crest derived cell line |
| Digestive tract | Stimulation of bombesin secretion from the stomach |
| - Stimulation of gastrin release from the stomach |
| - Stimulation of epithelial cell proliferation in the rat digestive tract |
| - Reduced antral motor activity |
| Pancreas | GHRH 1-40, but not 1-44, causes a dose-dependent stimulation of insulin, glucagon and somatostatin secretion |
| - Increased amylase release |
| Other tissues | Stimulation of glucose transport in adipocytes |

Acromegaly in whom the disease state was secondary to ectopic production of a GH stimulator [10,11]. It has now been demonstrated clearly that this original pancreatic material is identical to the human hypothalamic GHRH. The peptide is much larger than SS and three major forms have been described, consisting of 44, 40 and 37 amino acids [12]. It is species-specific but shows 67 per cent homology with rat GHRH [7]. The evidence for physiological roles for SS and GHRH in the control of GH secretion is documented in Table 1. Furthermore, data gleaned over the last few years have clearly shown that in addition to their role in the control of GH secretion, both GHRH and SS exert many other effects in different tissues (Tables 2 and 3).

Table 3. Inhibitory actions of somatostatin.

| Tissue          | Response                                      |
|-----------------|-----------------------------------------------|
| Anterior pituitary | Secretion of GH and TSH and occasionally PRL and ACTH |
| Pancreas (islets) | Secretion of insulin, glucagon and pancreatic polypeptide |
| Pancreas (exocrine) | Secretion of water, bicarbonate and enzymes |
| Stomach | Acid and pepsin secretion and gastric emptying |
| Intestine | Amine and peptide hormone secretion, absorption of triglycerides, sugars, amino acids, and other nutrients, mesenteric blood flow |
| Gall bladder | Bile flow |
| Kidney | Renin secretion, aldosterone response to angiotensin II |
| Parathyroid | Parathyroid hormone secretion |
| Salivary gland | Salivary flow |
| Platelets | Aggregation |
| CNS | Inhibition of firing but sometimes excitation. Decreased feeding |
| Thyroid | Calcitonin secretion |

In recent years, considerable attention has focused on the neuronal pathways which mediate the control of synthesis and release of hypothalamic SS and GHRH with the consequent net effects on GH secretion from the anterior pituitary [7]. All the classical neurotransmitter pathways including catecholaminergic, serotoninergic and GABAergic have been implicated in GH control.

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through either direct pituitary or hypothalamic actions but the most recent data have highlighted the fundamental importance of hypothalamic cholinergic pathways in the control of GH release in man. Blockade of cholinergic muscarinic receptors with drugs such as atropine or pirenzepine, abolishes the GH response to several GH secretagogues including arginine, L-dopa, exercise, glucagon and, most recently, GHRH [13–15]. We have also demonstrated that cholinergic muscarinic receptor blockade with pirenzepine totally abolishes slow wave sleep-related GH release in normal adult men [16]. It is likely that there is important cholinergic modulation of SS release from the hypothalamus into hypophysial portal blood.

There have also been important advances in the understanding of the intracellular mechanisms involved in GH control. It is now known that GHRH and SS bind to specific plasma membrane receptors and act on membrane-bound adenylate cyclase via stimulatory (N\textsubscript{S}) and inhibitory (N\textsubscript{I}) guanine nucleotide-dependent regulatory proteins. The consequent stimulation or inhibition of cyclic AMP generation leads to appropriate changes in the activity of a cyclic AMP-dependent protein kinase which regulates GH exocytosis via protein phosphorylation. This process is also dependent upon extracellular calcium [17]. In addition, cyclic AMP mediates the regulation of GH gene expression and although the precise intracellular pathways are not yet known, a specific nucleotide sequence has now been identified which may represent a universal cyclic AMP/nuclear protein receptor ‘recognition site’ [18]. In a similar manner, the nucleotide recognition site for glucocorticoids has also been described [19] and the T\textsubscript{c} recognition site encoded in the c-erb-A oncogene has recently been identified [20,21]. Both these hormones are known to have important stimulatory effects on GH gene expression [7].

**Regulation of somatotroph cell growth**

Compensatory growth of the anterior pituitary probably depends upon the interaction between inhibitory target gland hormones, stimulatory hypothalamic regulatory hormones and a variety of growth factors acting in a paracrine or autocrine fashion. It is important to realise that growth factors such as IGF-1 should no longer be regarded simply as ‘circulating mediators’ since their production has been demonstrated in a variety of tissues. It seems likely that the local production, action and metabolism of such factors within tissues is the more important determinant of cell growth. Certainly, recent data have demonstrated that the anterior pituitary produces a variety of growth factors that may well be involved in the regulation of cell growth and function (Table 4). However, their regulation and physiological roles are unknown as are their specific target cells. IGF-1 inhibits GH secretion and GH mRNA levels both basally and after stimulation with GHRH. Furthermore, IGF-1 receptors have been characterised on both anterior pituitary membranes and somatotroph adenoma cells. The IGF-1 gene is expressed in the pituitary as indicated by in situ hybridisation of specific mRNA with IGF-1 cDNA probes [22].

EGF at physiological concentrations, stimulates GH secretion from superfused normal rat adenohypophysial fragments without affecting TSH or PRL secretion [23]. Also, EGF receptors are present on normal rat and human pituitary membranes but not on tumours taken from acromegalic patients [24]. By contrast, in a tumour cell line (GH\textsubscript{4}C\textsubscript{1} cells) EGF increases PRL gene transcription [25], stimulates PRL synthesis and inhibits GH synthesis [26]. Using another tumour cell line (GH\textsubscript{3}/D\textsubscript{1}), Johnson et al. [27] found that EGF alone did not stimulate cell division but inhibited cell growth stimulated by thyroid hormone-induced growth factor. However, their most striking finding was a marked alteration in the morphology of the cells after EGF treatment from a rounded to an elongated form. It has been suggested that EGF-like mitogens act within the pituitary to mediate continued cell turnover and to permit population shifts in response to changes in the peripheral hormonal environment [26].

PDGF inhibits PRL secretion in GH\textsubscript{4} cells and enhances GH release in GC cells. PDGF also affects cellular morphology leading to larger, flattened cells with angular borders which are more tightly adherent to the culture dish [28]. FGF increases the sensitivity of both thyrotrophs and lactotrophs to TRH [29] and inhibits, in a similar fashion to TRH and EGF, cell proliferation in the GH\textsubscript{4}C\textsubscript{1}, cell line [30]. It is now clear that GHRH may play an important role in the regulation of somatotroph cell growth as well as GH secretion. Using autoradiographic detection of \textsuperscript{3}H-thymidine uptake and immunocytochemistry it was shown that nanomolar concentrations of GHRH markedly increased (60%) the total number of somatotrophs. SS caused partial inhibition of this stimulatory effect of GHRH [31]. It has been reported recently that GHRH produced a very rapid activation of the c-fos oncogene in anterior pituitary cells, although this may be more related to cell differentiation than division [32]. Of further interest is the recent report that the c-myc oncogene, which initiates the nuclear events in cell division, is expressed in cultured human adenomatous GH-secreting cells but not in other pituitary cell types studied [33].

In summary, there is a steady accumulation of data which indicate the importance of stimulatory and inhibitory growth factors in the paracrine, and perhaps autocrine, regulation of anterior pituitary cell growth and function. There may well be several more specific pitu-
itary growth factors which will be identified in the near future. Preliminary data are also emerging concerning the patterns of oncogene expression in human pituitary tumours. It is now necessary to relate growth factor production, oncogene expression and hypothalamic regulation to specific anterior pituitary cell populations and human pituitary adenomas.

Clinical relevance

Acromegaly and other disease states

The therapeutic usefulness of SS has been limited by its short plasma half-life and wide variety of inhibitory actions, particularly on the gastrointestinal hormones insulin and glucagon [5]. Furthermore, the promise of long-acting, more selective inhibitory analogues of SS has only recently been fulfilled with the development by Sandoz of an octapeptide (SMS 201-995). This molecule has a prolonged plasma half-life and inhibits GH release somewhat more selectively than that of insulin and glucagon. Our own studies and those of several other groups have now demonstrated that administration of SMS 201-995 subcutaneously on a twice-daily basis reduces GH levels to normal in most acromegalic patients (Fig. 1) which is paralleled by clinical improvement [34]. Although a few acromegalic patients may show a small reduction in tumour size following treatment for several months, the changes are certainly not comparable to the dramatic reduction in size of prolactinomas which is achieved by treatment with dopamine agonist drugs. Despite this however, present data indicate that SMS 201-995 will have an important therapeutic role in acromegalic patients in whom surgery is either contra-indicated or has failed.

In view of the importance of cholinergic mechanisms in the regulation of GH release, we have investigated whether cholinergic blockade may be of benefit in acromegaly. However, such treatment does not alter acutely either basal GH levels or GH responses to GHRH and TRH in the majority of acromegalic patients [35] (Fig. 2). Our hypothesis at present is that cholinergic pathways...
in the hypothalamus exert an inhibitory influence on SS release into hypophyseal portal blood at the median eminence. Hence, blockade of such a pathway in normal subjects with an intact axis will lead to an increase in hypophyseal portal SS levels which will inhibit GH release from the anterior pituitary. In acromegalic patients with a somatotroph adenoma, it is possible that hypophyseal portal SS does not get through to the adenomatous cells because of a microvascular block within the pituitary and in consequence one would see no effect of such agents on GH release in these patients (Fig. 3).

SS is widely distributed throughout the nervous system and other body tissues where it exerts a neurotransmitter or paracrine role respectively [5]. Not surprisingly therefore, the therapeutic potential of SS has been investigated in a variety of other disease states in man (Table 5). In addition to any therapeutic role in acromegaly, SMS 201-995 has also been shown to produce symptomatic relief in patients with vipomas and glucagonomas but the effects on tumour size and metastases are controversial [36]. There is also considerable evidence indicating the benefit of SS in reducing the severity of upper gastrointestinal bleeding, particularly oesophageal variceal haemorrhage [37]. SS also inhibits pancreatic exocrine secretion but therapeutic trials in patients with acute pancreatitis have produced conflicting results. It is particularly difficult to carry out adequately controlled studies in this disease state but an optimistic interpretation of the evidence to date does suggest that in certain patients with acute pancreatitis SS may be of therapeutic benefit [38]. Finally, preliminary data in patients with exfoliative dermatitis associated with psoriasis indicate that SS administration may also be therapeutically beneficial [39].

Table 5. Possible clinical uses of somatostatin analogues.

| Tumours | TSH-secreting Carcinoid Small cell carcinoma of lung Medullary carcinoma of thyroid Carcinoma of the prostate Meningioma |
| GI tract | Hormone producing tumours Nesidioblastosis Diabetes—dawn phenomenon Acute pancreatitis Pancreatic surgery Pancreatic duct dilatation Bleeding oesophageal varices Peptic ulceration Ileostomy diarrhea |
| Other | Chronic pain Psoriasis—exfoliative phase |

GH deficiency

GHRH does not have a very promising role in the assessment of hypothalamic-pituitary status in adult subjects. Intra- and inter-individual variation in responsiveness is large and most clinicians still feel that the insulin stress test represents a more adequate investigation of GH reserve since it tests the integrity of the complete hypothalamic-pituitary axis. However, GHRH may be of benefit in the assessment of GH deficiency in children and early results indicate that it may be possible to distinguish between true pituitary GH deficiency and hypothalamic GHRH deficiency [40]. Whilst this is an interesting clinical research problem it is only important therapeutically if treatment with GHRH is contemplated. The treatment of children with short stature has aroused much interest recently because extracted human pituitary GH can no longer be prescribed due to the occurrence of a 'Jacob-Creutzfeldt'-like syndrome in a few patients treated in the distant past with extracted pituitary GH. In consequence, new approaches to the treatment of GH deficiency include the use of synthetic, recombinant human GH and synthetic human GHRH of either 1–29 (fully biologically active) or 1–44 varieties. Recombinant human GH is at least as effective as extracted pituitary GH in stimulating growth in GH deficient children [41]. Furthermore, long-term administration of GHRH has been shown to raise IGF-1 levels and increase tissue growth in up to 60 per cent of children with short stature [42–44]. Quite clearly it is necessary to distinguish between hypothalamic and true pituitary GH deficiencies if these alternative therapeutic approaches are to be used rationally but in the final analysis it seems likely that treatment with recombinant human GH will prove to be the most rational approach since this will stimulate growth in all situations, except in children with Laron's syndrome. At present this approach bypasses the as yet unresolved questions concerning the dosage, timing and route of administration of GHRH in order to produce consistent growth stimulation.

In vitro studies have demonstrated clearly the extreme
sensitivity of the somatroph to even femtomolar concentrations of GHRH although some desensitisation does occur if high enough doses are administered over a long enough period of time [45]. This in vitro desensitisation has at least two components: firstly, there is depletion of readily releasable intracellular stores of GH and secondly, there is almost certainly some uncoupling of the GHRH receptor from membrane bound adenylate cyclase. In the in vivo setting, the situation is more complex because of the long and short inhibitory feedback loops which come into operation. These include the stimulation of hypothalamic SS release by both GH and IGF-1 and also direct inhibitory pituitary actions of IGF-1 on GH release [46]. It is possible that some or all of these latter phenomena explain why not all children with presumed idiopathic GHRH deficiency show a convincing growth response to chronic GHRH administration [43,44].

**Diabetes mellitus**

Why is GH secretion important in the pathophysiology of diabetes mellitus? It has been known for many years that GH secretion is markedly increased throughout the 24-hour period in patients with poorly controlled insulin-dependent diabetes mellitus, and that normal circulating GH levels can be restored by improved glycaemic control. Furthermore, administration of human GH to both normal and diabetic subjects leads to carbohydrate intolerance and impairment of glycaemic control respectively. In a recent study Campbell and colleagues [47] showed clearly that the dawn phenomenon in insulin-dependent diabetics was largely due to nocturnal GH release rather than catecholamines or cortisol. Data presented by Gerich and colleagues [48] have demonstrated improved glycaemic control in insulin-dependent diabetics treated over several days with a long-acting SS analogue, although the frequency of hypoglycaemic episodes was also increased. The circumstantial evidence implicating GH in poor diabetic control is summarised in Table 6.

GH has also been implicated in the more chronic microvascular complications of diabetes mellitus, once again on the basis of circumstantial evidence. It has been known for some years that ablative pituitary surgery can

| Table 6. Evidence that GH plays a role in poor diabetic control. |
|---------------------------------------------------------------|
| 1. In poorly controlled insulin-dependent diabetes mellitus (IDDM), GH levels are increased particularly at night. |
| 2. Although this increased GH release is reduced by improved control, administration of hGH to well controlled patients causes deterioration in control. |
| 3. Nocturnal GH release rather than cortisol or catecholamines is largely responsible for the dawn phenomenon in IDDM. |

| Table 7. Evidence that GH may play a role in the development of diabetic microvascular disease. |
|---------------------------------------------------------------|
| 1. Hypophysectomy can halt the progression of proliferative retinopathy. |
| 2. Patients with diabetes and retinopathy usually have higher GH and IGF-1 levels than patients without retinopathy. |
| 3. Diabetic dwarfs with GH deficiency usually lack microvascular complications. |
| 4. GH and other growth mediators can exert direct, deleterious effects on the arterial wall. |

![Fig. 4. Effect of atropine on GH responses to GHRH and insulin-induced hypoglycaemia in normal subjects. Atropine, ●; placebo, ○.](image-url)
cause regression of proliferative retinopathy and sparing of deterioration in visual acuity in patients with insulin-dependent diabetes mellitus [49]. Evidence compatible with the hypothesis that GH may be implicated in this problem is documented in Table 7.

Two major points deserve emphasis. Firstly, GH hypersecretion may be both the cause and the consequence of poor metabolic control and secondly, GH may play an important permissive role in the development of acute metabolic and chronic microvascular complications of this disease.

However, there are problems associated with the inhibition of GH release in diabetes mellitus. Ablative pituitary surgery causes brittleness of control and inhibition of GH release with SS or its longer acting analogues may increase the frequency of hypoglycaemic episodes. These findings highlight the importance of GH as a counter-regulatory hormone and thus that it would be desirable to find a way of inhibiting GH release which spares counter-regulatory GH responses to hypoglycaemia. We have demonstrated that cholinergic muscarinic blockade only minimally inhibits the GH response to insulin hypoglycaemia [50], whereas it virtually abolishes the GH response to GHRH (Fig. 4). It is possible therefore that anti-cholinergic therapy of this type may prove useful, and certainly nocturnal GH release in patients with insulin-dependent diabetes mellitus is also abolished by pirenzepine administration as in normal subjects [51] (Fig. 5). Our working hypothesis at present (Fig. 6) which takes into account the relative sparing of the GH response to hypoglycaemia by cholinergic muscarinic antagonism, is that the hypothalamic somatostatinergic neurone is regulated by both the ambient glucose concentration and acetyl choline in a non-competitive manner. However, falling glucose concentrations can override the inhibitory cholinergic pathway causing a reduction in SS release into hypophyseal portal blood.

**Summary**

Our knowledge of the mechanisms involved in the regulation of somatotroph cell growth is scanty and much work is still needed to elucidate the role of different growth factors and the mechanisms involved in oncogene activation in both normal and tumour cell growth. However, there are several recent, important clinical ramifications from our improved understanding of GH neuroregulation. The use of long-acting SS analogues is valuable in the treatment of acromegaly, probably in acute variceal haemorrhage and it also produces symptomatic improvement in patients with vipomas and glucagonomas. GHRH may be of value in the treatment of
short stature due to hypothalamic GHRH deficiency but further definitive studies are now required to provide convincing evidence that this line of treatment is of greater benefit than the use of synthetic recombinant human GH. Inhibition of GH release may be of value in prevention of both acute and chronic complications of insulin-dependent diabetes mellitus. The use of cholinergic muscarinic receptor blockade in this context may be particularly useful because of a probable sparing of the counter-regulatory GH response to hypoglycaemia. In view of the relative ease with which nocturnal GH secretion can be abolished, we think it reasonable to consider the possible existence of a permissive or mediating role of GH in other disease states, either directly or by maintaining production of either local tissue or circulating growth factors or both.

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