Growth Hormone Secretagogues: Physiological Role and Clinical Utility

Felipe F. Casanueva and Carlos Dieguez

Growth hormone secretagogues (GHSs) are artificial compounds developed to release GH in vitro. GHSs mimic an unknown endogenous factor that activates the GHS receptor in the pituitary and the hypothalamus. With the cloning of the human GHS receptor it has been demonstrated that GHS is a new physiological system that regulates GH secretion along with growth hormone-releasing factor (GHRH) and somatostatin. GHSs administered alone or in combination with GHRH are the most potent and reproducible GH releasers, and are useful tools for the diagnosis of GH deficiency when tested in a variety of pathological conditions, both in children and in adults. As therapeutic agents, they show clinical effectiveness in enhancing GH release after short-term treatment.

Although the first proposal for the existence of a growth hormone (GH)-releasing substance of hypothalamic origin was probably made by Seymour Reichlin in 1959, by 1975 no one had succeeded either in isolating it, or in unambiguously demonstrating its existence. As the hypothalamic growth hormone-releasing hormone (GHRH) proved to be elusive, Cyril Bowers began to use a new approach: the systematic structural modification of enkephalins and *in vitro* testing of the GH-releasing properties of the new compounds[1]. With this approach, the first non-opioid peptides with GH-releasing capabilities were developed. They had the structure Tyr-D-Trp-Gly-Phe-Met-NH_2 or Tyr-D-Phe-Gly-Phe-Met-NH_2 and were devoid of opiate activity, showing low potency *in vitro* and, unfortunately, no activity *in vivo*. The data obtained from complex conformational energy calculations were used to relate structural features to the tested GH-releasing capability of these compounds. Subsequently, a linear empirical approach was undertaken with substitutions of amino acids with specific chemical properties at selected positions of the peptide[2]. These changes improved binding as well as intrinsic activity, leading to the development in 1980 of the first highly potent GH-releasing hexapeptide called GHRP-6 (His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2)[3]. GHRP-6 is a highly potent peptide that specifically releases GH in all species tested so far, including humans, and is endowed with the characteristics of being small, stable, soluble and of low toxicity, as well as of being rapidly and cheaply synthesized. Nowadays, GHRP-6 is the gold standard that all the so-called non-classic GH secretagogues (GHSs) can be compared with (reviewed in Ref. 4).

With the isolation and identification of GHRH in 1982, the interest in GHS faded until it was discovered that it acted through receptors different from those for GHRH (Ref. 3), and that the two compounds had synergistic actions on *in vivo* GH release. These facts indicated that GHRPs were not surrogates of GHRH. The cloning of the receptor for these non-classic GH releasers[5] has demonstrated unambiguously that GHRP-6 and its analogues are artificial activators of a new receptor, the endogenous ligand of which is still unknown. This endogenous ligand, and the synthetic compounds, such as GHRP-6, are all provisionally termed GHSs. The GHS system is a new physiological system that is implicated in the regulation of GH secretion and the GHSs are relevant to clinical practice both as diagnostic and therapeutic agents.

F.F. Casanueva and C. Dieguez are at the Department of Medicine, Endocrine Section (FFC), and Department of Physiology (CD), School of Medicine, University of Santiago de Compostela, Spain.

- **Analogues of GHRP-6**

Based on the structure of GHRP-6 (Fig. 1), a second generation of GHSs was developed, initially the heptapeptide GHRP-1 (Ala-His-D-βNal-Ala-Trp-D-Phe-Lys-NH_2) and, subsequently, GHRP-2 (D-Ala-D-βNal-Ala-Trp-D-Phe-Lys-NH_2) (Ref. 6) and hexarelin (His-D-2Methyl-Trp-Ala-Trp-D-Phe-Lys-NH_2) (Ref.7). Genentech scientists have developed a highly active cyclic analogue of GHRP-2 (called 4b) that is a potent and small GH releaser[8]. In spite of the increased potency reported, these GHSs appear to be similar to GHRP-6 in their type of activity. All of them share the characteristics of being readily absorbed intramuscularly, intranasally and orally and show a high plasma half-life as assessed by plasma clearance. While trying to identify the smallest structure capable of selectively causing the release of GH, R. Smith at Merck developed a small substituted benzo-fused lactam called L-692,429, which has the same biological activities as GHRP-6. L-692,429 was the first non-peptide compound able to release GH, and similar compounds, such as the hydroxypropyl derivative L-692,585, or the spiroindoline L-163,191 (MK-0677) (Fig. 1), with potent *in vitro* and *in vivo* GH-releasing activities, have been tested and have proved to be very effective by the oral route[9].

Currently, most drug companies involved in the GH field, and several independent groups, have developed and tested GHRP-6 analogues which are active by the oral route and have improved potency and bioavailability, such as CP-424391 developed by Pfizer, which is a pyrazolidinone-piperidine with high GH-releasing potency[10].

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Starting with the compound NNC 26-0194 [3-(4-imidazolyl) propionyl-D-Phe-Ala-Trp-D-Phe (CH_2NH) Lys-ol], Novo Nordisk researchers have developed NNC 26-0161 (ipamorelin) and NNC 26-0703 (Fig. 1)[11]. Ipamorelin is able to induce a massive release of GH, being active by the intravenous (i.v.) and oral routes and, interestingly, also by the transdermal route[12]. Although their chemical structures vary and hence so do their pharmacokinetic properties and biological activity, all these artificial GHSs probably act on the same kind of receptor. However, the dissociation between GH-releasing capability and binding to the cloned receptor, and the differential distribution of binding sites for different compounds[13] indicate that GHS receptor subtypes exist.

- **Pituitary Actions of GHSs**

There is no doubt that all GHSs act directly on the pituitary[6,14]. It would be surprising if they did not, considering that their development was guided by their *in vitro* GH-releasing capability. After activating their specific receptor, GHSs elicit GH secretion through a different intracellular signalling system than that used by GHRH. In fact, it is well established that GHRH activates the cAMP–PKA (cAMP-dependent protein kinase) pathway in somatotropes, and by a poorly understood mechanism causes a persistent rise in intracellular Ca^{2+} as a result of Ca^{2+} influx through voltage-dependent Ca^{2+} channels, while some of the effects of somatostatin are mediated via its inhibition of cAMP formation[15,16]. On the other hand, binding of GHS to its receptor leads to an inhibition of K^+ channels, which results in a sustained depolarization of the somatotropes. This depolarization results in the entry of Ca^{2+} through voltage-gated L- and T-type channels[15]. There is considerable controversy regarding the possibility that GHS may also cause a rise in intracellular Ca^{2+} by redistribution from internal stores, probably mediated by the generation of inositol trisphosphate. Thus, it appears that GH secretion is related directly to the intracellular free Ca^{2+} concentration

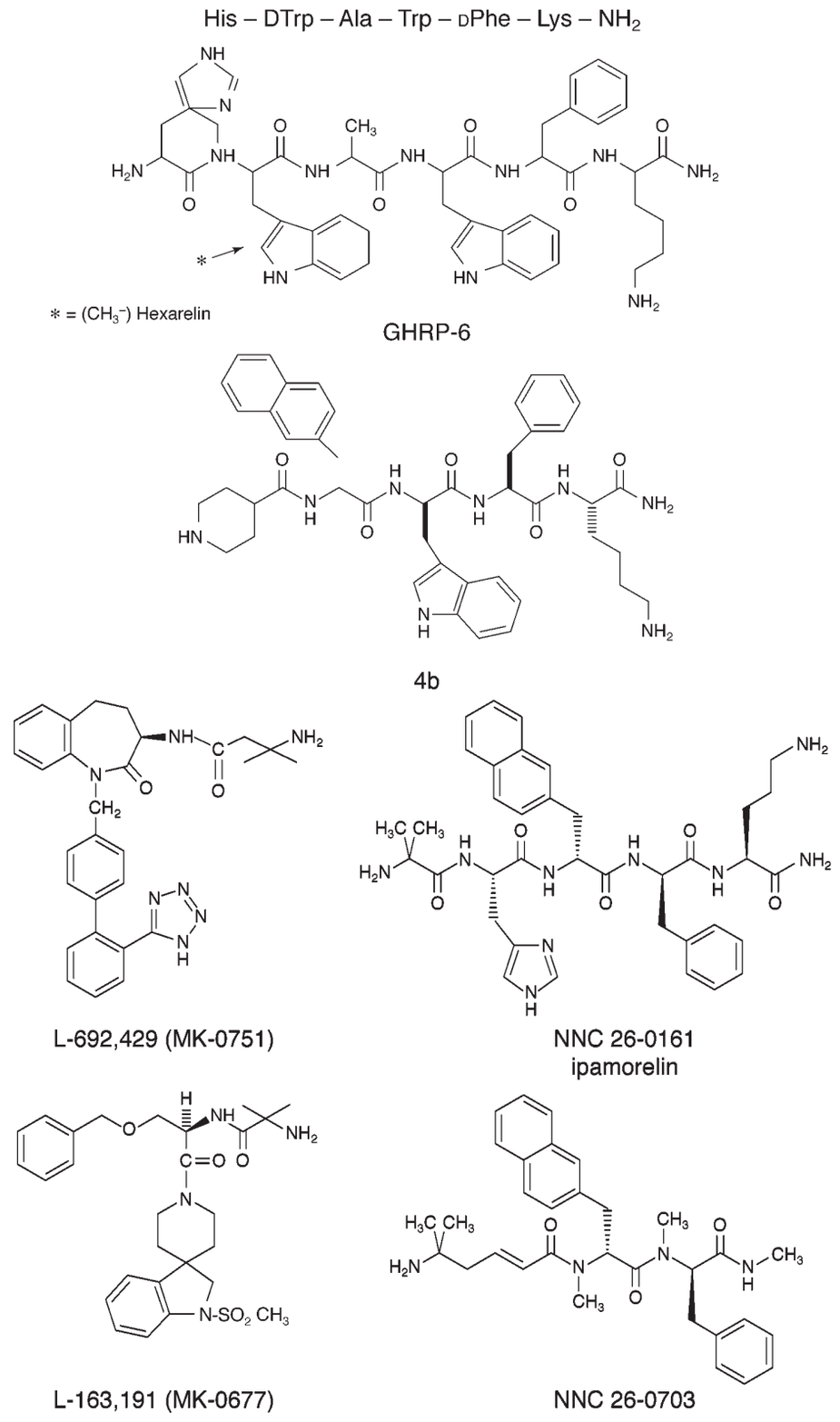

Figure 1. Structure of GHRP-6, which is the standard for the comparison of any other growth hormone secretagogue (GHS). Hexarelin has the same structure as GHRP-6, but with a methyl residue added to the position marked with an asterisk. 4-b is a cyclic analogue of GHRP-2 with a low molecular weight and enhanced potency. L-692,429 was the first substituted benzolactam GHS, and L-163,191 (MK-0677) is a new analogue with enhanced potency. NNC 26-0703 and NNC 26-0161 (ipamorelin) are a new generation of active compounds that selectively release GH. These artificial GHSs have not been discovered but 'invented'; they activate the GHS receptor, the endogenous ligand of which is unknown.

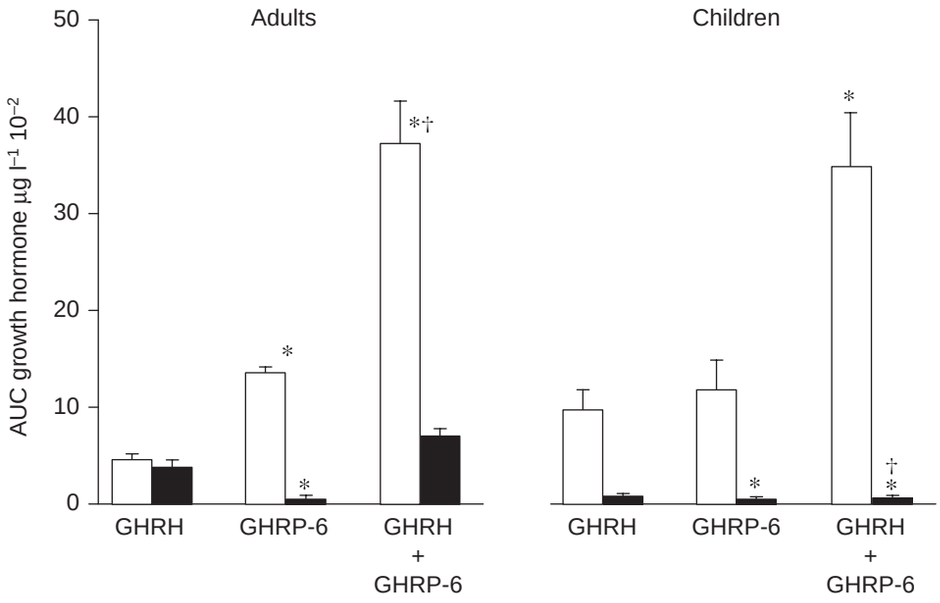

Figure 2. Area under the secretory curve (AUC) (µg l^{-1} 60 min^{-1}) of growth hormone (GH) secretion stimulated on three different days with either 1 µg kg^{-1} intravenous (i.v.) GH-releasing hormone (GHRH), 1 µg kg^{-1} i.v. GHRP-6, or a combination of GHRH and GHRP-6 at the same doses. The groups tested (patients with hypothalamopituitary disconnection, closed bars) were adults with different tumours located in the hypothalamic area, leaving the pituitary intact but blocking the hypothalamopituitary connection. The children had neonatal stalk transection. Controls (open bars) are age- and sex-matched healthy subjects. * = p =<0.05 vs. GHRH; † = p =<0.05 vs. GHRP-6. Redrawn from Refs 25 and 26.

and that both GH releasers (GHRH and GHS) lead to this final and crucial step, although through different intermediate pathways. Considerable cross-talk between the two signalling pathways occurs, as well as a complex participation of ionic channels and pumps[15], which are outside the scope of this review.

GHRH and GHS do not only act through distinct receptors and different intracellular signalling pathways, they also seem to act on different somatotrope subpopulations. With the use of the reverse haemolytic plaque assay, GHRP was shown to increase the number of somatotropes releasing GH, without altering the amount of hormone released by each individual cell[17]. On the other hand, GHRH stimulates both the number of cells secreting GH and the amount of GH secreted per cell. Somatostatin has been reported to decrease the number of cells secreting GH without affecting the amount of GH secreted per cell. With this model in mind, GHS increases, while somatostatin decreases, the number of active somatotropes, probably because these two factors depolarize and hyperpolarize the cell, respectively. On the other hand, GHRH stimulates the amount of secreted GH in the active somatotropes[17].

- **Hypothalamic Actions of GHS**

Receptors for GHSs were initially detected both in the pituitary and in the hypothalamus[18]. However, the concept of a relevant participation of the hypothalamic structures in the GHS-mediated GH secretion came from the observation that GHSs were more effective *in vivo* than *in vitro*. *In vivo*, GHS and GHRH also show a striking synergistic action on GH release: the amount of GH released by the combined administration of GHRH and GHRP-6 is significantly greater than the arithmetical sum of GHRH-mediated GH release plus GHRP-6-mediated GH release[19–21]. In contrast, *in vitro*, GHS and GHRH merely exhibit additive activity[21]. A more direct demonstration of the hypothalamic actions of these compounds is that GHS administration enhances c-*fos* expression in hypothalamic neurones[22,23].

GHSs behave like a hypothalamic neurohormone. In living rats with surgical hypothalamic destruction (deprived of hypothalamic hormones), but with intact pituitaries, the GHRP-6-mediated GH release shows two phases. In the first week after hypothalamic ablation, the GH released by GHS is greater than that seen in sham-operated rats, while 15 days later it is lower[24]. This phenomenon of early supersensitivity and late subsensitivity is typical of a receptor activated by a neurohormone, and has also been seen for GHRH. Similarly, in hypophysectomized rats that have a transplanted pituitary under the kidney capsule, the daily administration of GHRP-6 exerts trophic influences on the transplanted somatotropes, preserving their functionality[24].

One striking point is that to be fully operative, GHSs require the presence of a functional hypothalamus. In patients with intact pituitaries but with a tumoral mass leading to a hypothalamopituitary disconnection (functional stalk section), the release of pituitary hormones after the administration of exogenous releasing hormones is preserved although delayed. In these patients, GH secretion after GHRH is preserved, but GHS-induced GH release is blocked and the synergistic action of GHRH and GHS is absent (Fig. 2)[25]. This is similar to findings in children with neonatal stalk transection[26]. Surprisingly, for agents developed as a result of their *in vitro* action, it seems that the main action of GHSs is exerted at an as yet undetermined structure of the hypothalamus, while the pituitary activity is ancillary.

- **Integrated Model of GHS Action**

On the basis of the present evidence, the widely accepted dual control of GH release, implicating GHRH and somatostatin, must be changed to a trinity that incorporates GHSs (Fig. 3). To explain the integrated model, it should be borne in mind that the endogenous ligand that activates the GHS receptor is unknown. Thus, we are constructing our model based on two as yet unproven assumptions: first, that the endogenous GHS is a peptide and,

second, that it is produced in the hypothalamus, where part of its actions are exerted, and afterwards released into the portal vessels to activate pituitary somatotropes. These concepts are the most probable ones but, as neuroendocrinology is a 'field full of surprises', one should be open-minded regarding alternatives.

Because GHSs are more effective as a result of their hypothalamic action, there are four, not mutually exclusive, explanations for their mechanism of action, namely: (1) exogenous GHSs induce the release of endogenous GHRH; (2) exogenous GHSs inhibit the release of hypothalamic somatostatin; (3) exogenous GHSs, through an autocrine stimulatory mechanism, enhance the release of endogenous GHS; and (4) exogenous GHSs release another unknown hypothalamic factor (Bowers' U-factor) with GH-releasing capability. Let us briefly look at the first option. In sheep, GHRP elevates GHRH levels in hypophyseal portal blood without altering somatostatin levels[27]. In rats, systemic or intracerebroventricular administration of GHRP-6 or L-692,585 enhances the expression of c-*fos*, as well as the electrical activity on the putative GHRH neurones in the rat arcuate nucleus[22]. Although considerable speculation followed the report that pretreatment with anti-GHRH serum blocked GHS-mediated GH release in rats, passive immunization against GHRH blocks GH secretion elicited by all stimuli tested in rats, including somatostatin withdrawal. Thus, the only conclusion that can be drawn from these experiments is that after acute impairment of GHRH action rat somatotropes become blocked to any further stimulus. Furthermore, in infant rats, passive immunization against GHRH does not prevent the action of GHS[28]. On the contrary, the data indicating that GHS action is independent of the release of hypothalamic GHRH can be summarized as follows: (1) the GH response to GHS is considerably greater than that of GHRH (Ref. 28); (2) GHSs can potentiate GH release in response to a maximal stimulating dose of exogenous GHRH (Refs 19,29); (3) in rat hypothalamic explants, GHSs are unable to release GHRH (Ref. 4); (4) hours of infusion of GHRH block the GHRH-mediated GH release without altering the action of GHRP-6 (Refs 30,31); (5) 120 min after a first administration of a saturating dose of GHRH a second dose of GHRH is ineffective, while GHS is fully effective[32]; (6) in acromegalic patients with a mutated G protein and a permanently activated GHRH receptor, exogenous GHRH is unable to enhance GH levels, while GHS is fully active (V. Popovic, unpublished). According to the above reports, it appears that the participation of endogenous GHRH is not necessary to explain the mechanism of action of GHS.

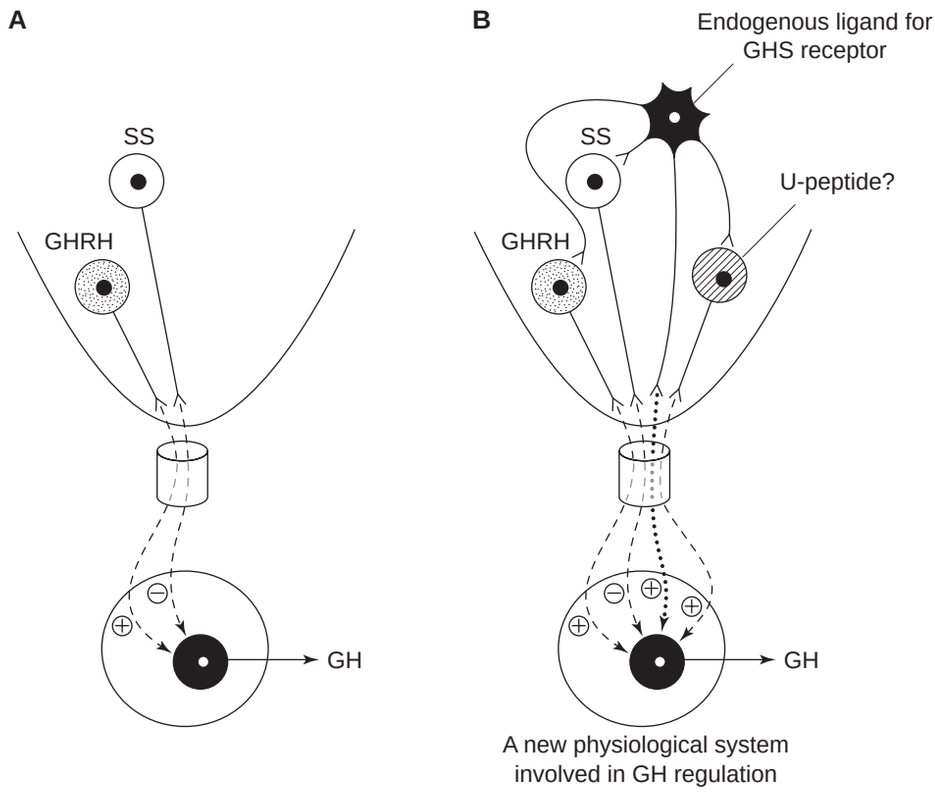

Figure 3. The dual regulation by growth hormone-releasing factor (GHRH) and somatostatin (SS) of GH secretion in humans. (**A**) should be changed to the more complex (**B**) involving GH secretagogue (GHS), the undiscovered endogenous ligand of the GHS receptor.

Although the GHS-mediated GH release is partially insensitive to the inhibitory action of somatostatin[33], the secretagogues do not seem to work by inhibiting hypothalamic somatostatin release[4,20,27,31,34]. In a physiological model, the putative endogenous ligand of the GHS receptor could be envisioned as a secreted factor that would act first at the hypothalamus via paracrine action before acting on the pituitary. The presence of GHS receptors in hypothalamic structures and the evidence that GHS-elicited GH secretion is not mediated by changes in endogenous GHRH or somatostatin, but needs an operational hypothalamus, suggesting that exogenous GHS may induce the release of another hypothalamic factor with GH-releasing capabilities (U-factor)[3]. Although convoluted, this working hypothesis is supported by inferential evidence and needs further testing (Fig. 3).

- **Physiological Studies in Humans**

When administered at the usual dosage, all GHSs are more efficacious than GHRH; that is, they release significantly larger amounts of GH. However, if one takes into account their lower molecular weight, they release less GH per mol of GHS administered, and thus are less potent than GHRH. This theoretical fact is not relevant in

the clinical setting, considering their virtual absence of side effects at the effective doses. While for GHRH 1 μg kg^{-1} is the maximal i.v. dose, for GHSs such as hexarelin the GH-releasing capability can be enhanced by doses of 2 and 3 μg kg^{-1} i.v., and in normal adults, GHS-mediated GH release is dose related[35]. GHSs are effective GH releasers administered by any route tested: i.v., subcutaneous, oral and intranasal[35]. Their reduced bioavailability after oral administration has been partially compensated for by the development of smaller compounds with enhanced potency, such as the non-peptidyl analogues and the new pentapeptides[9,11,36].

- **Interaction of GHS with GHRH**

When GHRP-6 is infused continuously by the i.v. route, in dosages of 1 μg kg^{-1} h^{-1} over 24 to 36 h, the amplitude but not the frequency of the normal spontaneous pulsatile secretion of GH is increased over the entire infusion period. At the end of the infusion period, the GH response to an i.v. bolus of GHRH was increased, while the GH response to an i.v. bolus of GHRP-6 was decreased[31,37]. These facts suggest that at low dosages there is clear homologous desensitization by GHS, but no heterologous desensitization. On the contrary, when saturating doses are used, GHRH does not exert heterologous desensitization, while GHS does. In fact, normal subjects treated previously with the GHS hexarelin showed no GH release when GHRH was administered two hours later, while the contrary order of administration (GHRH followed by hexarelin) did not alter the GH-releasing capability of hexarelin[32]. Interestingly, the heterologous desensitization of hexarelin is seen in a variety of states, but not in patients with anorexia nervosa[38].

- **Neurotransmitter and Metabolic Modulation of GHS Action**

GH released by GHS is enhanced by hypoglycaemia[20], or by the reduction of circulating free fatty acids (FFAs)[39]. Unlike GHRH, GHSs are particularly resistant to well-known inhibitors of GH secretion. In fact, hexarelin-mediated GH secretion is reduced but never blocked by a rise in FFAs or by a glucose load, nor by an infusion of somatostatin, atropine, pirenzepine or salbutamol, drugs that are thought to enhance somatostatin secretion by the hypothalamus[40]. GHS-mediated GH release is not reduced by a previous GH rise[32], by short-term glucocorticoid treatment[41] or by abnormal levels of thyroid hormones[42]. GHS-mediated GH secretion is not affected by the time of day that subjects are tested[43]. While GHRH is a very erratic GH stimulator, with large variations between individuals, diverse peaking times and a high number of false negative results being reported, GHSs are potent, synchronized and reproducible, with a virtual absence of non-responders[32]. These observations probably reflect the fact that GHRH-induced GH secretion is influenced by the metabolic and hormonal milieu of the individual, while that induced by GHS is not. In conclusion, one of the most remarkable properties of GHS-mediated GH release is its potency as well as its intra- and interindividual reproducibility[32,43].

- **GH Secretagogues During the Lifespan**

In vitro, functional GHS receptors are detected in the human pituitary as early as the 18th week of gestation[44]. *In vivo*, the GH-releasing activity of GHS is seen from birth[40] and remains elevated throughout infancy[43,45,46]. At puberty, the effectiveness of hexarelin is increased and decreases thereafter[40]. In children, the GHS-mediated GH release is significantly augmented by the administration of oestrogens and testosterone, but not by the non-aromatizable androgen oxandrolone. These results suggest that the action of testosterone is mediated by its previous conversion to oestradiol[43]. In children with short stature, GHSs are potent releasers of GH, and give more reproducible results than any other stimuli[45,46]. Unfortunately, on an individual basis, GHSs were not superior to any of the conventional tests for making a clear-cut diagnosis of GH deficiency.

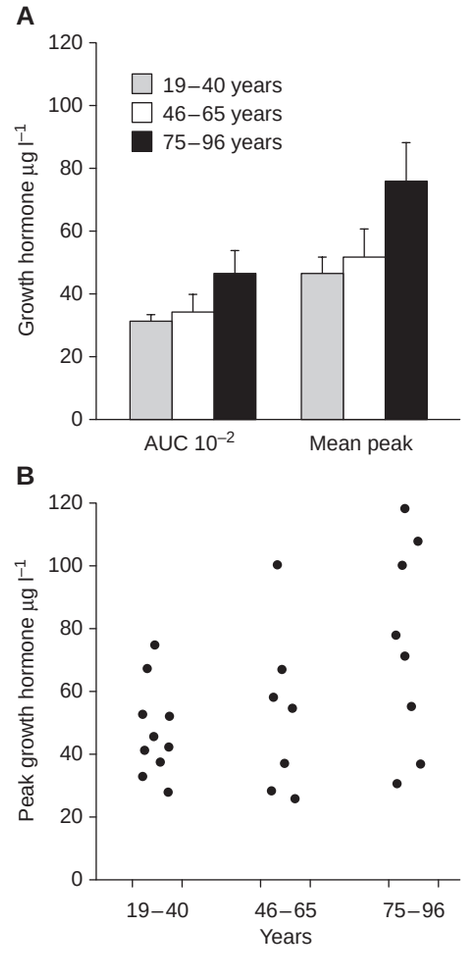

Figure 4. (**A**) Mean + SEM of the area under the curve (AUC) and mean growth hormone (GH) peak in three different groups of healthy subjects with different age intervals, after the administration of GH-releasing factor (GHRH) and GHRP-6 at saturating doses; (**B**) individual peaks after the same stimulus. The GH secretion elicited by this stimulus in subjects over 75 years of age is very well preserved. From Ref. 50 with permission.

GHSs are potent releasers of GH in healthy young males[19,29,47], and in females at any stage of the menstrual cycle[29]. An age-related reduction in the GH-releasing capability of GHS is still under debate[40,48,49]. However, the synergistic effect of GHRH and GHS on GH secretion does not seem to be reduced in very old patients[50], suggesting that the decline in GH secretion in aging might be counteracted by this potent stimulus (Fig. 4).

- **GHSs as Diagnostic or Therapeutic Tools in Pathological States**

As mentioned previously, one of the most striking properties of the GHSs is

their synergistic action when administered in combination with GHRH. Hence, the combined administration of GHRH and GHS is nowadays the most potent and reproducible releaser of GH, being superior even to insulin hypoglycaemia. Obesity is a pathological state characterized by a blocked GH response to all GH stimuli tested so far, a fact that might help to maintain this state (reviewed in Ref. 51). Interestingly, when obese subjects were tested with GHRH and GHS, a large release of GH was observed, indicating that the absent GH secretion in obesity is a functional and potentially reversible state[52]. There is no clear explanation for the fact that the somatotrope cells of obese subjects, with an absence of GH release for years or decades, can suddenly respond normally to this combined stimulus. On the contrary, in another state of blunted GH secretion, chronic hypercortisolism (Cushing's syndrome), a combination of GHRH and GHS was unable to induce a significant release of GH (Ref. 53).

Patients with acromegaly show an enhanced secretion of GH when they are stimulated with GHRH, GHS or a combination of GHRH and GHRP-6; however, the synergistic action of GHRH and GHS is not seen in these patients[54]. These results suggest that tumoral somatotrope cells respond normally to these secretagogues. In patients with macroprolactinoma, the action of GHS upon GH secretion is severely impeded, and no prolactin (PRL) release occurs. On the other hand, when the macroadenoma disappears as a result of dopaminergic agonist treatment, the GH-releasing capability returns in most patients[55]. It is not known whether the reversal of impaired GH responses to GHS in these patients is due to restoration of the hypothalamopituitary connection or to normalization of elevated PRL levels, as suggested by similar findings in women in early postpartum[56].

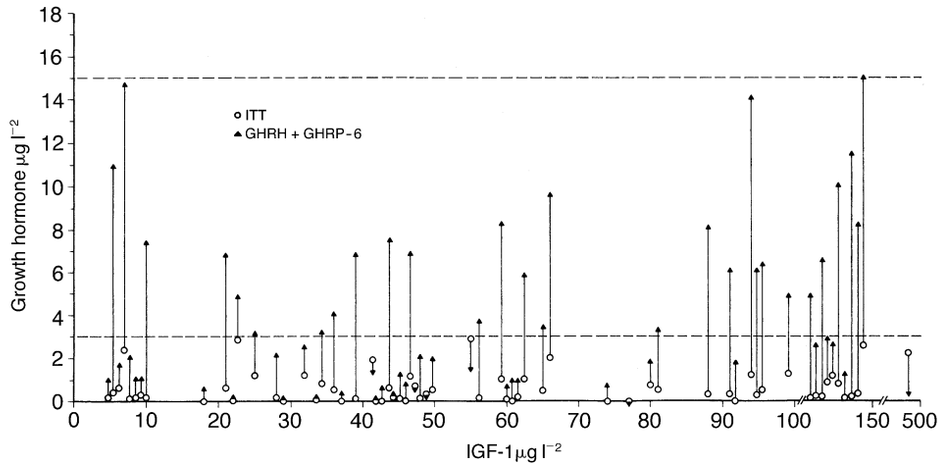

Figure 5. A large group of adult patients with organic hypothalamopituitary disease who were diagnosed as having severe growth hormone (GH) deficiency by an insulin hypoglycaemia test (ITT)-mediated GH peak ≤3 μg l^{-1} that appear plotted against the respective IGF-1 basal value (open circles). After testing with a combination of GH-releasing hormone (GHRH) and GHRP-6, some of them experienced an increased release of GH (arrows) that was always under the cutoff point of 15.0 μg l^{-1} for this test (V. Popovic, unpublished).

- **GH Deficiency in Adults**

The problem of adults with GH deficiency has received considerable attention in the past few years, as it is associated with alterations in body composition, increased prevalence of cardiovascular morbidity and shortened life expectancy[57,58]. Adults with GH deficiency benefit greatly from replacement therapy with GH, but in the present shortage of funding for health care, administrators demand strict biochemical criteria of GH deficiency before allowing subsidized treatments. The diagnosis of GH deficiency in adults shares the uncertainty of the diagnosis in children, and a reliable specific biochemical test is needed[59]. As GH secretion elicited by the combined administration of GHRH and GHS is minimally affected by age, is not affected by sex or adiposity and as, unlike hypoglycemia, it is devoid of potential side effects, it might be a useful test in adults with suspected GH deficiency[60]. In fact, in a large group of adult patients with GH deficiency, the GHRH and GHRP-6 combination was a more effective diagnostic tool than insulin-induced hypoglycaemia (Fig. 5) (V. Popovic, unpublished).

- **Side Effects**

Contrary to other hypothalamic releasing peptide analogues, no unpleasant or serious side effects have been reported for GHSs. Although all GHSs are highly specific for GH release, it was found that the administration of both peptidyl and non-peptidyl compounds induces slight but consistent increases in PRL and in adrenocorticotrophin (ACTH)/cortisol, and in some cases dehydroepiandrosterone (DHEA) (Refs 40,61). However, low-dose GHS administration can still lead to massive GH release with no significant effects on cortisol or PRL, suggesting that these side effects might be a result of GHS binding to low-affinity receptors. It has been argued that the transient cortisol rises might be compared with the frequent cortisol rises that occur in everyone's life with no detrimental effects. Nevertheless, the unwanted rise in cortisol levels is under scrutiny, and might lead to the development of some GHSs being discontinued. The new and selective GHSs with no ACTH- or PRL-releasing capability, such as ipomorelin[62], will circumvent these problems.

- **GHSs as Future Therapeutic Agents**

Currently, considerable effort is being devoted to clearly evaluating the potential therapeutic implications of GHSs. They may become effective, safe drugs for enhancing circulating levels of GH in patients with intact hypothalamopituitary function. As these secretagogues act directly on the hypothalamopituitary unit to release GH,

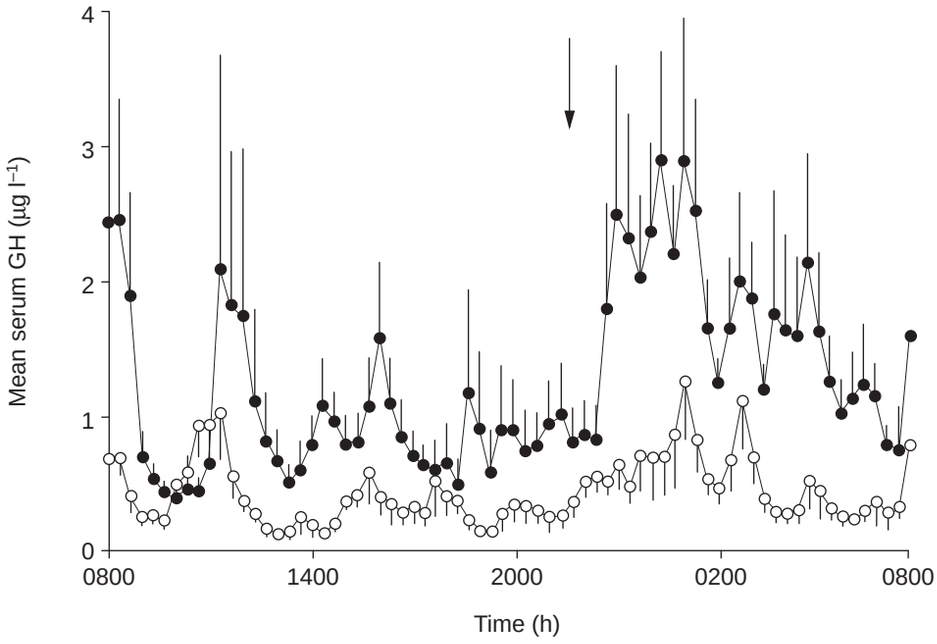

Figure 6. Mean serum growth hormone (GH) concentrations in older subjects after two weeks of treatment with placebo (open circles), or 25 mg day^{-1} MK-677 (closed circles). The evening treatment time (between 2200 and 2300 h) is indicated by an arrow. Redrawn from Ref. 65.

they do not bypass the feedback loop controlling the GH–IGF-I (insulin-like growth factor I) axis[63]. For this reason, administration of GHSs is preferable to the direct administration of GH because this should induce a more physiological profile of GH secretion[31,37].

Potential targets include children with GH deficiency[64]. In recent studies on prepubertal children with short stature, intranasal hexarelin administration for periods of up to eight months caused a rise in IGF-I plasma levels and an increase in linear growth velocity[46]. Furthermore, oral administration of MK-0677 for periods ranging from five to 15 days to normal young adults with GH deficiency led to an increased secretion of GH in a 24 h period and a rise in IGF-I levels (Fig. 6)[36,65]. Similarly, GHRP-2 infusion increased spontaneous GH secretion (sixfold), as well as serum IGF-I in critically ill patients, opening up the possibility of using these compounds to counteract the maintenance of fat depots and to reverse protein hypercatabolism in prolonged severe illness[66]. Furthermore, the full recovery of GH secretion in aged subjects after several days of treatment with GHS (Ref. 36), the reversal of diet-induced catabolism[67] and its effectiveness in obese subjects in whom two-month treatment with GHS led to increased GH secretion, fat-free mass and energy expenditure[68,69], makes the GHSs useful therapeutic alternatives in deleterious situations that affect large segments of the population, such as obesity and aging.

Potentially, GHS could be used in all pathological states in which the administration of medium GH doses have been shown to be effective. Such indications include: infertility and ovulation induction; mild catabolic states; patients undergoing chronic glucocorticoid treatment; patients with chronic renal failure, wound and fracture healing; osteoporosis; and obesity. In addition to nutrition, GHSs might become an alternative to exogenous GH as anabolic agents in catabolic states, such as AIDS or strokes, particularly if the orexigenic action of these secretagogues[70] is confirmed. The action of GHSs on specific heart diseases is most promising[13,71]. Their capability to fulfil these expectations in the clinical setting will be explored in the next few years. The existence of different subtypes of GHS receptors with different tissue distributions[13,18] could make it possible to develop selective drugs that can stimulate the desired target while leaving other tissues untouched. This might be one of the most promising actions of GHSs.

• Conclusions

With the cloning of the GHS receptor, the early vision of Cyril Bowers in which GH-releasing hexapeptides were considered to represent a new physiological system implicated in the regulation of GH secretion has been confirmed. GHSs, administered alone or in combination with GHRH, are effective probes for understanding the normal and pathological regulation of GH in humans, and they might become safe and effective tests for the diagnosis of GH deficiency in both children and adults. Although long-term studies under strictly controlled conditions and with more subjects over longer periods are needed to determine dosages and to optimize administration, the data available suggest that the administration of selective GHSs in therapeutic schedules should not be associated with significant side effects. This illustrates the important potential of this new class of GHSs in the clinical setting.

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