Growth hormone secretagogues: recent advances and applications

Michael Ankersen, Thomas K. Hansen, Ian Ahnfelt-Rønne and Anne M. Kappelgaard

The discovery of a new class of compounds that stimulate the release of growth hormone (GH) in a manner distinctly different from growth hormone-releasing hormone (GHRH) is advancing the understanding of the mechanisms that control GH secretion. These compounds, the GH secretagogues, act at both pituitary and hypothalamic levels, and might even elicit effects in the CNS and peripheral systems. A receptor with high affinity for the GH secretagogues has been identified and several observations suggest the presence of additional receptors. The existence of these specific endogenous receptors could indicate that the mechanism of GH release is not yet fully understood. Several potential indications have been explored clinically and, as some of these compounds are orally active, they could offer attractive alternatives to recombinant human growth hormone (hGH) in treating GH disorders such as growth hormone deficiency (GHD), age-related conditions, obesity and catabolic conditions.

The 191 amino acid hormone, hGH, is a pleothrophic hormone interacting with most tissues in the human body. The most prominent effects of GH include promoting growth and having protein anabolic and lipolytic effects. As unlimited supplies of recombinant GH became available in 1985, it has been possible to investigate the metabolic effects of GH rather than just its well-characterized growth-promoting effects. At present, some data suggests a potential beneficial effect of GH treatment in osteoporosis, complicated fracture, cardiomyopathy, obesity and some nitrogen-wasting conditions resulting from, for example, AIDS, chronic dialysis or glucocorticoid treatment[1].

GH is synthesized and released from somatotrophic cells in the anterior pituitary. Both GH synthesis and GH release from somatotrophs are tightly controlled by two hypothalamic hormones, growth hormone-releasing hormone (GHRH, 44 amino acids), which stimulates synthesis and release, and somatostatin (SRIF, 14 amino acids), which inhibits GH release. In addition to the effect of GHRH, a new class of compounds, termed GH-releasing peptides (GHRP) or GH secretagogues, can induce GH release from the pituitary. It is widely believed that GH secretagogues elicit their effects at both hypothalamic and pituitary levels and work synergistically with GHRH (Fig. 1). As hGH cannot be administered orally, it is obviously desirable to develop orally active drugs to induce effects similar to those of GH, possibly by affecting the GHRP pathway. Furthermore, these drugs might produce a GH-release profile that mimics the natural pulsatile pattern of GH release to a better extent than recombinant hGH.

For comprehensive reviews on GH secretagogues, see Refs 2–6. For the purpose of the present review, the terms GHRP and GH secretagogues will be used synonymously.

Growth hormone secretagogues

Whilst working with met-enkephalin analogues, Momany and coworkers discovered a series of compounds that

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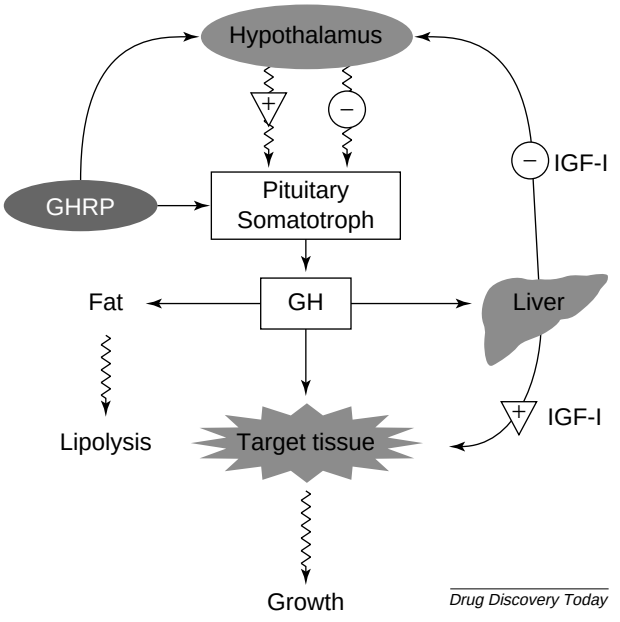

Figure 1. *Regulation of growth hormone release by the pituitary–hypothalamus axis by growth hormone-releasing protein. Abbreviations: GH, growth hormone; GHRH, growth hormone-releasing hormone; GHRP, growth hormone-releasing peptides; IGF-I, insulin-like growth factor I.*

released GH from primary cultures of rat pituitary cells[7]. These compounds release GH in a distinctly different manner from GHRH as demonstrated by the use of specific antagonists of GHRH and GHRP. GHRP is known to act directly on somatotrophs to cause GH release and to potentiate the effects of GHRH. While GHRH increases cAMP levels in somatotrophs, GHRP activates intracellular calcium, depolarizes the membrane and behaves as a functional antagonist of somatostatin. GHRP and GHRH in combination increase cAMP production more than GHRH alone, indicating that these two compounds act synergistically[4].

Structure of GH secretagogues

Because the original GHRPs (Box 1) showed very low oral bioavailability, there was an extensive search for new compounds with improved pharmacokinetic profiles. In 1993, researchers at Merck (Rahway, NJ, USA) reported the first non-peptidyl GH secretagogue, L692429 (Ref. 8). Although its *in vitro* potency was significantly lower than GHRP6, the appealing non-peptidyl structure of L692429 attracted much attention and encouraged a number of academic and industrial research groups to develop orally active GH secretagogues.

Box 1. Some of the most prominent members of the original class of GH-releasing peptides[2]

Ala-His-D-2Nal-Ala-Trp-D-Phe-Lys-NH_2 (GHRP1)

D-Ala-D-2Nal-Ala-Trp-D-Phe-Lys-NH_2 (GHRP2)

His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2 (GHRP6)

Based on the structure of GHRP-6, L692429 was identified through rational screening[4]. The structure of L692429 principally consists of three parts: the benzolactam moiety found in cholecystokinin (CCK) receptor-antagonists and angiotensin-converting enzyme (ACE) inhibitors, the tetrazol-biarylic moiety found in angiotensin receptor-antagonists and a β-amino acid as the N-terminal. This interesting structure highlights the hypothesis first stated by Evans, that certain 'privileged' structures are ligands for more than one receptor[9].

A systematic investigation of L692429 has led to the production of several analogues with improved potency for GH release from rat pituitary cells, including the hydroxylpropyl analogue, L692585 (Ref. 10) and the naphtolactam, NNC260610 (Ref. 11), which showed a 10–20-fold increase in potency. However, none of these compounds showed acceptable oral bioavailability for clinical development (<5%), and different chemical entities were sought[12].

Patchett, Nargund and colleagues[13] discovered a new structural class of GH secretagogues by screening compounds produced from a project aimed at derivatizing 'privileged' structures for broad testing in receptor assays. This strategy led to the spiroindane derivative, MK0677, which was the first GH secretagogue with high *in vivo* potency and good oral bioavailability (>60%) in beagle dogs, and has now undergone several clinical studies (see later). Several analogues closely related to MK0677 have been reported, including L163833 (Ref. 14) and CP424391 [Carpino, P.A. *et*

Box 2. Amino acid sequence of some of the highly potent peptidyl GH secretagogues

H-His-D-(2-CH_3)-Trp-Ala-Trp-D-Phe-Lys-NH_2 (Hexarelin)

H-Alb-His-D-2Nal-D-Phe-Lys-NH2 (Ipamorelin)

3-Aminomethylbenzoyl-D-2Nal-*N*-CH_3-D-Phe-Lys-NH_2 (NNC260235)

Isonipecotyl-Nal-D-Nal-D-Phe-Lys-NH_2 (G7039)

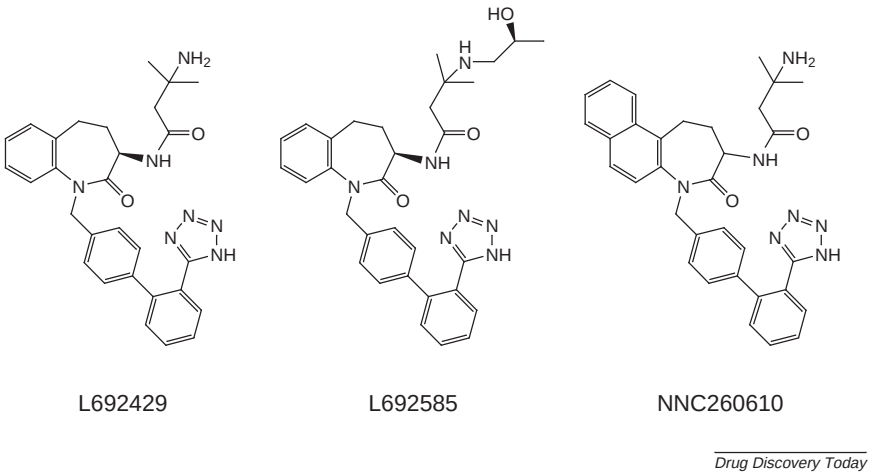

Figure 2. *Chemical structure of some of the benzolactams described as growth hormone secretagogues.*

from GHRP-1 via ipamorelin. NN703 is now in clinical development.

Box 2 and Figures 2–4 show GH secretagogues that have been explored in more detail following the discovery of Bowers and Momany's original GHRPs. A number of structural features are common to most of the compounds[5,22], such as two aromatic groups, one N-terminal amino group and a stereocentre, which is seen in the linear compounds as a D-amino acid and in the benzolactams as an *R*-configuration on the lactam-ring. Although a high degree of structural dissimilarity is present particularly between MK0677 and the peptides and between MK0677 and NN703, this stereocentre is common to all GH secretagogues.

al. (1999) Endo. Soc. Meeting, New Orleans, LA, USA, June)]. Furthermore, a number of tripeptides have been described such as EP51389 (Ref. 15), which like MK0677, has amino isobutyric acid and an aromatic amino acid in the N-terminal position.

Several GHRP-6-derived compounds with improved metabolic stability were identified, including hexarelin, ipamorelin[16], NNC260235 (Ref. 17), G7039 and G7502 (Ref. 18). G7502 represented a new class of small truncated analogues with the minimum pharmacophoric requirements of two aromatic groups and an amino group, and was active in rats with an intravenous ED_{50} of 0.8 mg kg^{-1}. The oral bioavailability of G7502 has not been reported, but a close analogue, NNC260323, showed moderate oral bioavailability in rats (<20%)[17]. Although NNC260323, which was identified via the 'rule of five'[19], showed only moderate potency *in vitro*, it created the structural basis for a new class of small compounds with high *in vivo* potency and good oral bioavailability in dogs. This class of compounds, represented by NNC260722 (Ref. 20) and NN703 (Ref. 21), was developed by a step-by-step peptidomimetic strategy

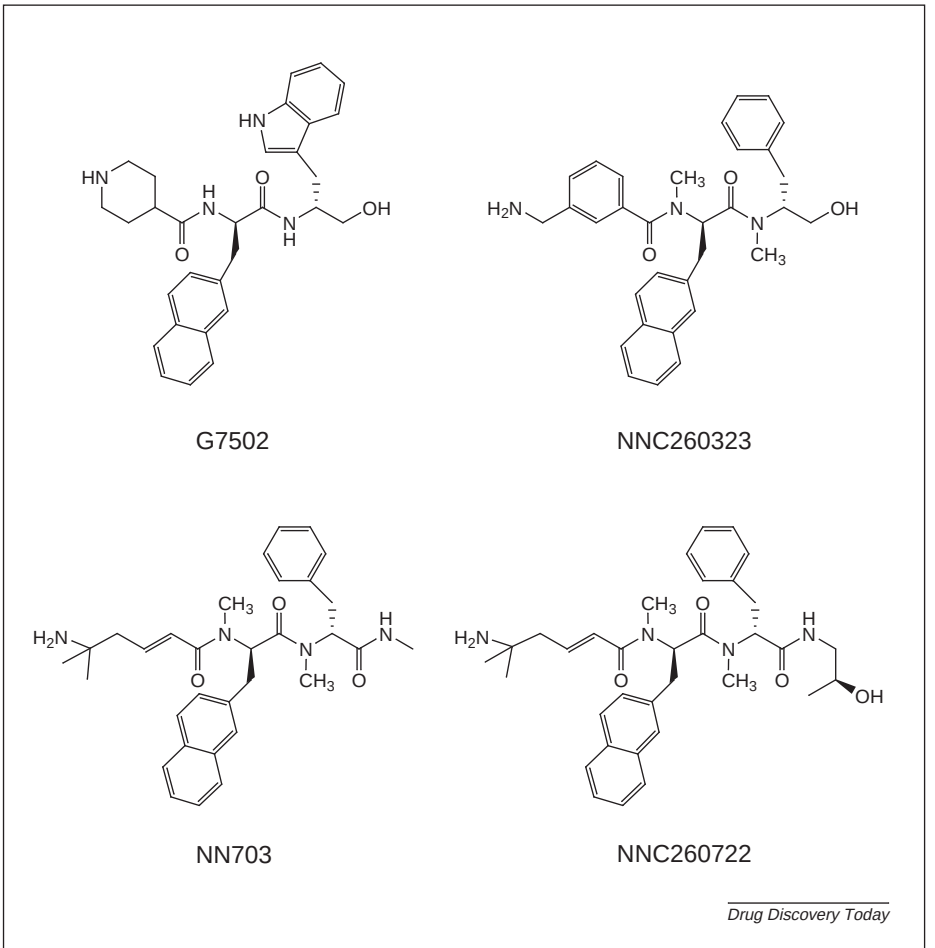

Figure 3. *Peptidomimetic growth hormone secretagogues based on two aromatic D-amino acids as the core fragment.*

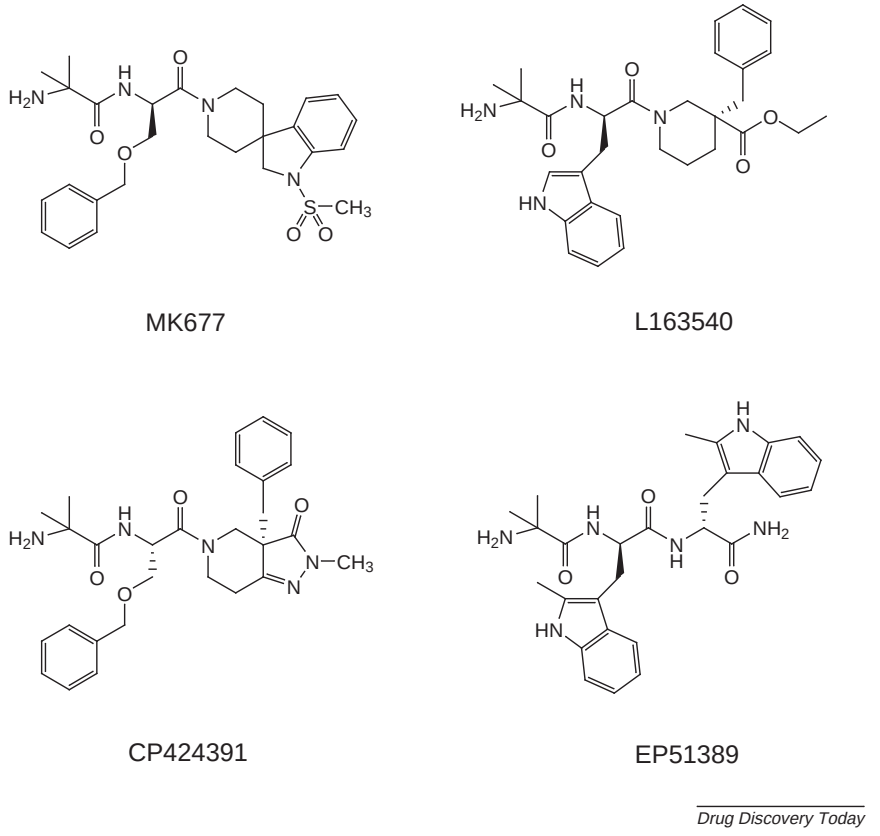

Figure 4. *Peptidomimetic growth hormone secretagogues based on aminoisobutyric acid as the N-terminal.*

Pharmacology of GH secretagogues

The principal screening assay for GH secretagogues has been a functional assay using primary rat pituitary cell cultures[23]. This assay demonstrates GH release in a reliable and dose-dependent manner (indicated in Table 1 as EC_{50}), although it is not applicable to high-throughput screening. As shown in Table 1, most of the described GH secretagogues, with a few exceptions such as L692429 and NNC260323, show EC_{50} values in the low nanomolar range.

Several GH secretagogues have been tested in various animal models, including rats, dogs and pigs. However, the use of different animal models has meant that a direct comparison between the compounds is not possible. Most of the peptides are highly potent in rats, while the smaller analogues have very poor potency, suggesting that the lysine group might be of particular importance in this species. By contrast, most of the smaller analogues are potent in larger animals such as pigs and dogs, with compounds such as MK0677 being efficacious in dogs after oral administration at doses as low as 0.1 mg kg^{-1}. Ipamorelin, hexarelin, GHRP-2 and GHRP-6 are equipotent in pigs after intravenous bolus administration, while MK0677 and NN703 are 10–30-fold less potent[21].

In 1996, Feighner and coworkers[24] cloned a receptor from a pig pituitary library with a high affinity to MK0677. The structure of this G-protein-coupled receptor is highly conserved between species, including humans, will bind MK0677, GHRP-2 and GHRP-6, and has been designated the GHS-R receptor (GHS-1A receptor). The potency of several compounds, with respect to its ability to release GH from rat pituitary cells, has been compared with binding data for the GH secretagogue receptor and with *in vivo* data in pigs, and the data is summarized in Table 2 (Ref. 21).

It is relevant to comment on the discrepancies between the three sets of data. In the function-based *in vitro* assay, MK0677 was slightly more potent than ipamorelin, GHRP-2, GHRP-6, hexarelin and NN703. In the binding studies, MK0677, GHRP-2 and GHRP-6 show binding affinities in the subnanomolar range, whilst ipamorelin and NN703 have a more than 200-fold weaker binding affinity than MK0677. This is not in accordance with *in vivo* potencies in pigs, where ipamorelin, in particular, is much more potent than MK0677. This observation can be explained in several ways. However, in light of a recent publication by Ong, McNicoll and colleagues where an alternative GHRP receptor with high binding affinity to hexarelin, but not MK0677, has been suggested, it is tempting to speculate that the GH-releasing ability of ipamorelin and perhaps also of NN703, is mostly caused by stimulation of this alternative GHRP receptor[25]. As this receptor has not yet been isolated and no binding studies in cell lines have been performed, it might be too early to conclude that more than one receptor subtype of the GH secretagogues exists. However, it is very likely that GH release could be triggered by different intracellular pathways, especially on considering the structural differences of the GH secretagogues. Similarly, it is likely that, for example, MK0677 and its analogues (e.g. CP424391) are one class of

compounds and ipamorelin and its derivatives (e.g. NN703) are another, and that these two classes do not share the same binding modes. The pharmacological consequence of such potentially different modes of binding has yet to be resolved.

Table 1. *In vitro* potency and oral bioavailability of a number of selected growth hormone secretagogues

Compound	EC_{50} (nM)	f_{po} (%)	Refs
GHRP-1 (Bowers)	1.1		16
GHRP-2 (Bowers)	1.8		17
GHRP-6 (Bowers)	2.2		18
Hexarelin (Europeptides)	2.3		19
Ipamorelin (Novo Nordisk)	1.3	≈5 (dog)	16
NNC260235 (Novo Nordisk)	0.5	≈10 (dog)	17
G7039 (Genentech)	0.2		18
G7502 (Genentech)	10.6		18
NNC260323 (Novo Nordisk)	265.0	20 (rat)	17
NN703 (Novo Nordisk)	2.7	35 (dog)	21
NNC260722 (Novo Nordisk)	8.9	25 (dog)	20
L692429 (Merck)	60.0	≈4 (dog)	10
L692585 (Merck)	3.0		11
NNC260610 (Novo Nordisk)	8.0		13
MK0677 (Merck)	1.3[a]	>60 (dog)	14
L163540 (Merck)	1.6	29 (dog), 12 (rat)	13
CP424391 (Pfizer)	3.0	44 (dog), 65 (rat)	[b]
EP51319 (Europeptides)			15[c]

[a]See Table 2. [b]Carpino, P.A. *et al.* (1999) Endo. Soc. Meeting, New Orleans, LA, USA, June.
[c]No *in vitro* data has been disclosed on this compound, but the compound has been described to be active in rats after intravenous and oral administration.

Specificity of GH secretagogues

Many studies have addressed the effect of GH secretagogues in various animals and most of these have focused on their specificity towards GH-release. Early studies with L692429 demonstrated a high potency in dogs after intravenous administration[26]. As expected, insulin-like growth factor I (IGF-I) levels were increased (as is the case with GH administration). Adrenocorticotrophic hormone (ACTH) and cortisol levels were also increased, while there were no effects on prolactin, insulin and thyroxine. These increases in ACTH and cortisol have also been seen with some of the other GH secretagogues. For example, a study by the same group with once-daily oral administration of MK0677 over two weeks in dogs showed a sustained release of IGF-I, while both GH and cortisol levels were normalized by the end of the study. This attenuation of GH and cortisol levels after repeated administration might be explained by a negative feedback by IGF-I (Ref. 27). However, it is interesting to note that NN703, in contrast to hexarelin and MK0677, did not dose-dependently increase cortisol (see Fig. 5), suggesting that this phenomenon is not a general class effect of all GH secretagogues, and it could further indicate that this particular subclass of GH secretagogues acts through a different pathway[21].

Central actions of GH secretagogues

The mechanism of action underlying the GH-releasing activity of GH secretagogues seems to involve the antagonism of somatostatinergic pathways at both the pituitary and hypothalamic levels as well as the stimulation of GHRH-secreting neurons[28]. GH secretagogues activate distinct subpopulations of hypothalamic arcuate neurons in GH-deficient rats and mice, as reflected by increased electrical activity in the cell nuclei[29]. In the past three years, it has been suggested that the arcuate neurones activated by systemic or intracerebroventricular injections of GHRP-6 are mainly of the neurosecretory type and contain GHRH or neuropeptide Y (NPY)[30,31]. Some GH secretagogues are not very selective, having a slight stimulatory effect on prolactin, ACTH and cortisol levels as well as influencing the control of sleep and food intake[26,32–34]. These actions could take place through activation of specific receptors at levels other than in the hypothalamic-pituitary system. In agreement with this hypothesis, the binding sites of GH secretagogues have been detected in the forebrain of the rat, pig and human[35–37].

Table 2. *In vitro* potency from a pituitary cell-based assay, *in vivo* potency in pigs and binding affinities at the growth hormone secretagogue receptor in COS-7 cells[17,21]

Compound	EC_{50} (nM)	ED_{50} (nmol kg^{-1})	K_i (nM)
GHRP-2	1.8	0.6	0.6
GHRP-6	2.2	3.9	0.9
Hexarelin	1.8	2.0	1.8
Ipamorelin	1.3	2.3	63.0
NN703	2.7	155.0	50.0
MK0677	0.4[a]	46.0	0.3

[a]The EC_{50} values for MK0677 in this table are not in accordance with Table 1. The data in Table 1 is gathered from different sources, while data in Table 2 is from the same experiment.

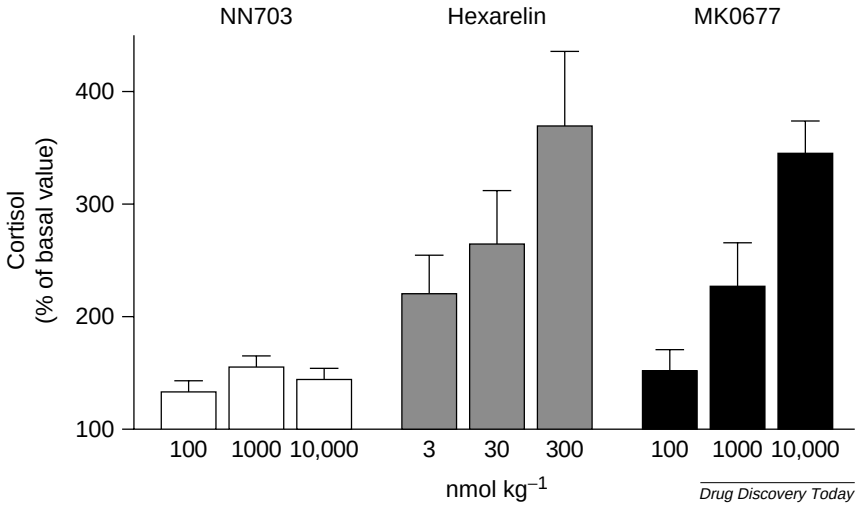

Figure 5. *The release of cortisol by intravenous administration of NN703, hexarelin and MK0677 to pigs. The doses are approximately equivalent to ED_{50}, 10 × ED_{50} and 100 × ED_{50} of the respective compound with respect to growth hormone release (derived from Ref. 21).*

Clinical studies

Clinical research has predominantly been carried out with GHRP-1, GHRP-2, GHRP-6, hexarelin, ipamorelin, L692429 and MK0677. Of these, only MK0677 has shown good oral bioavailability. Table 3 summarizes a number of selected clinical studies performed using various GH secretagogues.

Acute GH release

The acute GH release in humans stimulated by GH secretagogues has been studied extensively following several routes of administration (e.g. parenteral, intranasal, oral). Eighteen healthy men given intravenous boluses of GHRP-6 showed a maximum effect at a dose of 1 μg kg^{-1} (68.7 ± 15.5 ng hGH ml^{-1})[74]. In the same study, submaximal doses of GHRP-6 together with 1 μg kg^{-1} GHRH increased GH levels more than 1 μg kg^{-1} GHRH alone, indicating that GHRP-6 and GHRH stimulate GH secretion synergistically and that GHRP-6 acts through a different mechanism to GHRH (Fig. 6).

This study also showed that prolactin and cortisol levels rose while there were no significant changes in luteinizing and thyroid-stimulating hormone levels. These increased serum prolactin and cortisol levels have also been

Table 3. Dates of selected clinical studies with growth hormone secretagogues in various indications

Compound	Acute GH response	GHD in children	GHD in adults	Elderly	Obese	Catabolic states	Insomnia
GHRP-1	Bowers[38,39] 1992, 1993 Robinson[40] 1993	Laron[41] 1993 Mericq[42] 1995	–	–	–	–	–
GHRP-2	Bowers[39] 1993	Pihoker[43,44] 1995, 1997 Tuilpakov[45] 1995 Mericq[46] 1996	–	–	–	Van der Berghe[47–49] 1996, 1997, 1998	–
GHRP-6	Ilson[50] 1989 Penalva[51] 1993 Maccario[52] 1995	Pombo[53] 1995	Leal-Cerro[54] 1995	–	Cordido[55] 1993	–	Frieboes[33] 1995
Hexarelin	Ghigo[56] 1994	Laron[57,58] 1995, 1997 Loche[59] 1995 Klinger[60] 1996	–	Rahim[61] 1998	–	–	Korbonits[62] 1995
L692429	Gertz[63] 1993	–	–	Aloi[64] 1994	Kirk[65] 1997	Gertz[66] 1994	–
MK0677	Chapman[67] 1996	Yu[68] 1998	Chapman[69] 1997	Chapman[67] 1996 Plotkin[70] 1996	Svensson[71] 1998	Murphy[72] 1998	Copinshi[73] 1997

observed after treatment of healthy and obese subjects with MK0677, but only prolactin levels remained increased after chronic treatment[71]. Studies in healthy elderly humans with once-daily oral administration of 25 mg MK0677 increased the mean 24 h GH concentration by almost 97 ± 23% and serum IGF-I levels were increased from 141 ± 21 ng ml^{-1} into the normal range for young adults (219 ± 21 ng ml^{-1}), these increases being sustained for at least 28 days[67].

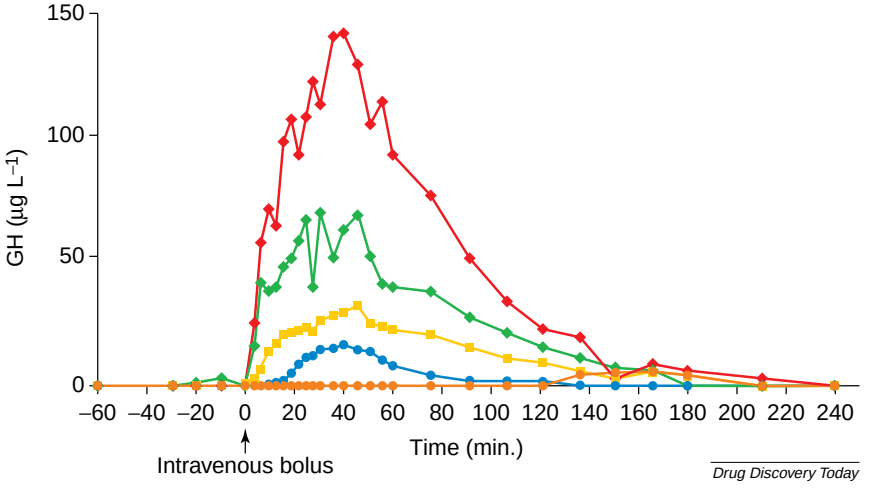

Figure 6. *Comparative growth hormone (GH) responses in individual subjects. GH responses, together with the area-under-the-curve (in μg L^{-1} after 4 h treatment) is as follows: placebo (orange, 540); 0.1 μg kg^{-1} growth hormone-releasing peptide (GHRP; blue, 916); 1 μg kg^{-1} GHRP (green, 5319); 1 μg kg^{-1} growth hormone-releasing hormone (GHRH; yellow, 2590); 0.1 μg kg^{-1} GHRP plus 1 μg kg^{-1} GHRH (red, 10,065) in two normal men (derived from Ref. 74).*

GH deficiency (GHD)

In a long-term clinical study of abnormally short children with intranasal hexarelin (60 μg kg^{-1}), it was shown that the growth velocity increased from 5.3 to 7.4 cm $year^{-1}$. Although the mean hGH levels dropped from 23.5 to 11.3 ng ml^{-1} after seven days, probably because of desensitization, and remained at that level for six months of treatment, it did not affect the observed increase in growth velocity[60].

GHRP-2 given subcutaneously (0.3–3.0 μg kg^{-1} day^{-1}) to prepubertal GHD children over six months increased growth velocity significantly without increasing the corresponding serum IGF-I level[75]. By contrast, oral administration of MK0677 over four days in GH-deficient adults resulted in 24 h hGH and serum IGF-I levels increasing in all the subjects[69]. Whether these differences are because of different selectivities or different pharmacokinetic profiles of these two compounds is unclear.

Elderly

The pulsatile pattern of GH changes dramatically throughout life from being high at birth, slightly decreased during childhood, increased during puberty and slowly declining during adulthood (Fig. 7)[76–81]. The advantage of increasing GH in the elderly has recently been demonstrated in healthy elderly men, where once-daily GH treatment for three months increased lean body mass, muscle mass and thigh strength[82].

GH secretagogues offer a great potential to reverse this decline of GH in aging and a double-blind study of 104 elderly men receiving oral MK0677 over nine weeks revealed significantly increased serum GH, IGF-I and prolactin levels, with cortisol levels remaining unchanged. Increased muscle strength and bone turnover were also noted[70]. However, in a study with hexarelin, no significant effect on body composition was seen over 20 weeks, but it should be noted that serum IGF-I was almost unchanged during the 20 weeks[61].

Obesity

In obese individuals, spontaneous GH secretion is attenuated and can be reversed by weight loss and fasting. When 0.2 or 0.75 mg kg^{-1} L692429 was administered intravenously on three separate occasions after overnight fasting to 12 healthy obese young men, GH release was significantly increased compared with both placebo and 1 μg kg^{-1} GHRH. Whereas in non-obese subjects, the GH effect of L692429 was blunted by feeding, the effect in obese subjects was equally large in fasted and fed conditions, indicating that obesity represents a metabolic condition that is sensitive to GH secretagogues[65]. When obese subjects with a body mass index of >30 kg m^{-2} were treated with MK0677 for eight weeks, the fat-free mass increased by 3 kg in the treated group versus 0.2 kg in the placebo group[83].

Catabolism

Catabolic states are usually precipitated by dietary energy restriction, excessive energy utilization through exercise,

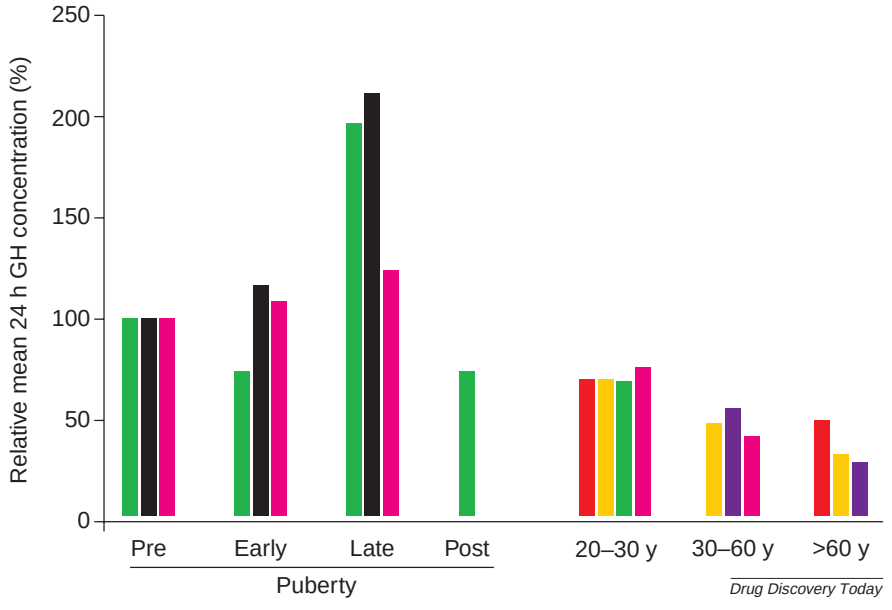

Figure 7. *Influence of age on growth hormone (GH) release given as relative mean 24 h GH concentrations throughout life. Data are collected from different sources[76–81]. Each colour represents a different subject.*

surgery, chronic glucocorticoid treatment and aging. The anabolic properties of GH suggest that it might be useful in the treatment of catabolic disorders, and GH treatment has been shown to partially reverse a number of catabolic conditions including glucocorticoid-induced catabolism[84]. To determine whether GH secretagogues can reverse the steroid suppression of GH, nine young healthy men were treated with prednisolone for four days and then with 0.2 or 0.75 mg kg^{-1} L692429. Under these circumstances, the GH secretagogue reversed the inhibition of GH secretion caused by the high dose of glucocorticoid, and the potential efficacy of GH secretagogues in mild to medium catabolic states induced by chronic steroid treatment is indicated[66,85]. This could have a particularly important role in chronic inflammatory diseases in children, such as asthma, juvenile arthritis or inflammatory bowel disease, which are often controlled by chronic steroid treatment frequently leading to growth retardation.

To investigate whether MK0677 can reverse a diet-induced protein catabolism, a study was carried out with eight healthy men who were calorie-restricted for two weeks and treated with MK0677 for the last seven days. In this study, MK0677 increased GH and IGF-I levels after seven days suggesting that MK0677 reverses diet-induced nitrogen wasting[72].

Sleep enhancement

Most clinical studies carried out so far have in some way been related to results obtained by recombinant hGH, and it is likely that these effects observed with GH secretagogues are caused by release of GH. It is therefore very interesting that GH secretagogues might have a particular influence on the sleep pattern of normal young subjects. After repetitive subcutaneous administration of GHRP-6, there was an increase in stage D2 sleep[33], and after prolonged oral administration of MK0677, there was an increase in the duration of D4 and rapid eye movement sleep[73]. Mild sleepiness has also been reported in a study with hexarelin[62].

Side- and adverse-effect

In animal models, MK0677 and other GH secretagogues[86] significantly increased cortisol and prolactin levels. However, the cortisol release was only transient, returning to normal after four days of once-daily oral administration. Fasting glucose and insulin concentrations also increased after chronic treatment of MK0677, but it is still unclear whether this is of clinical significance, as similar results have been seen with hGH treatments and changes in body composition might eventually counteract the insulin resistance[87].

Future perspectives

Recent advances in the discovery and development of GH secretagogues have provided a better understanding of the chemistry, mechanism and pharmacology behind the secretion of GH. The cloning of a unique G-protein-coupled receptor with high affinity to MK0677 and its presence in the pituitary, hypothalamus and CNS indicates the existence of an endogenous ligand. The recent identification, but not isolation, of a different receptor with high affinity for hexarelin, but not MK0677, suggests the presence of GH secretagogue receptor subtypes. This could explain the discrepancies in potencies in various *in vitro* and *in vivo* models observed for different classes of compounds and the existence of several categories of GH secretagogues. The presence of such receptors in both the brain and the periphery, taken together with the GH secretagogues' effect on sleep and food intake, suggests that

the role of these receptors and their corresponding endogenous ligand(s) could be much more profound than GH release. There have been several attempts to identify an endogenous ligand for the GH secretagogue receptor, but so far without success. The identification of such a ligand will broaden the understanding of GH secretion and other neuroendocrine pathways.

The rapid response to exogenous GH secretagogues in the majority of idiopathic GHD children suggests that this condition could be largely caused by a deficiency in endogenous GH secretagogue production. The same mechanism could underlie some symptoms characteristic of the elderly population who also appear to respond to exogeneous GH secretagogue treatment by marked GH secretion. The development of a selective GH secretagogue for clinical use in these conditions, and possibly also some metabolic diseases such as obesity, osteoporosis and catabolic states, therefore seems to fulfill an unmet medical need.

Conclusion

A large number of growth hormone (GH) secretagogues have been identified. Whether these compounds elicit their effect through the same pathway is unresolved, but with the identification of possibly two receptors and a discrepancy in the potency of different classes of compounds, it seems likely that these compounds do not act in the same way. The discovery of specific orally active GH secretagogues opens up the possibility of initiating treatment for clinical conditions related to GH secretion that have previously met with difficulties in compliance, because of the inconvenience of injectable recombinant human growth hormone.

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