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Central and peripheral regulation of the GH/IGF-1 axis: GHRH and beyond

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Abstract

The regulation of growth hormone (GH) synthesis and secretion by somatotroph cells of the anterior pituitary is a highly complex process, mediated by a variety of neuroendocrine and peripheral influences. In particular, a key role is played by the hypothalamic peptides growth hormone-releasing hormone (GHRH) and somatostatin, which regulate the somatotroph axis with opposite actions, stimulating and inhibiting GH release, respectively. Since the discovery of GHRH about 50 years ago, many pathophysiological studies have explored the underlying intricate hormonal balance that regulates GHRH secretion and its interplay with the somatotroph axis. Various molecules and pathophysiological states have been shown to modulate the release of GH, GHRH, somatostatin and GH secretagogues. Collectively, the available evidence demonstrates how a vast number of neural and peripheral signals are conveyed and integrated to orchestrate a finely tuned response of the somatotroph axis that adapts to the body's varying needs for growth, metabolism, and repair. The present review aims to summarize the available evidence regarding the key regulators involved in the modulation of the somatotroph axis in humans, presenting detailed molecular insights on the signaling cascades at play. The interplay between different mechanisms governing somatotroph secretion is highlighted, underscoring the nuanced interdependence that maintains homeostasis and facilitates the body's ability to respond to internal and external stimuli.

Keywords Growth hormone-releasing hormone · Somatostatin · Growth hormone · Insulin-like growth factor 1 · Somatotroph axis · Pathophysiology

Abbreviations

ACTH	Adrenocorticotropic hormone
cAMP	Cyclic AMP
CRH	Corticotropin-releasing hormone
ERK	Extracellular-signal-regulated kinase
GABA	γ-Aminobutyric acid
GH	Growth hormone
GHR	Growth hormone receptor
GHRH	Growth hormone-releasing hormone
GHS	Growth hormone secretagogue
IGF-1	Insulin-like growth factor 1
IRS	Insulin receptor substrate
JAK	Janus kinase
L-DOPA	L-3,4-dihydroxyphenylalanine
MAPK	Mitogen-activated protein kinase
MEK	Mitogen-activated protein kinase kinase

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mRNA	Messenger RNA
mTOR	Mammalian target of rapamycin
NPY	Neuropeptide Y
PI3K	Phosphoinositide 3-kinase
STAT	Signal transducer and activator of transcription

1 Introduction

Growth hormone (GH) is a key hormone in promoting growth, metabolism, and cell regeneration, and is finely modulated by growth hormone-releasing hormone (GHRH) alongside other factors such as somatostatin, above all [1–3]. However, these pathways represent only the final part of a much more intricate network of central and peripheral signals that dynamically integrate, modulating the secretory activity of the somatotroph axis [1–3]. Their specific interplay is a subject of interest due to its implications in both normal physiological states and pathological conditions [1–3].

This review aims to synthesize the current body of knowledge about GHRH and its role in the regulation of GH secretion. By examining the molecular mechanisms implicated in the modulation of this axis, we seek to provide a comprehensive overview of its functioning in response to various physiological and pathological contexts.

2 GH structure and signaling

GH, also known as somatotropin, is a peptide hormone composed of a single chain of 191 amino acids with a molecular weight of approximately 22 kDa [2]. Produced and secreted by the somatotroph cells of the anterior pituitary gland, it exerts several biological actions across various target tissues throughout the body, including liver, fat and muscle, among others [1–3]. GH signal transduction is mediated by its binding to a cell-surface receptor, the GH receptor, which prompts the initiation of specific signaling cascades [1–6].

Several intracellular pathways are activated following interaction between GH and its receptor. Among these, a relevant role is played by the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway [4–6]. The activation of this pathway, in fact, leads to the transcription of various GH-responsive genes, which vary among target tissues [4–6]. Among these, insulin-like growth factor 1 (IGF-1), produced primarily in the liver, mediates many of the growth-promoting effects of GH, acting both locally and systemically to stimulate cell growth and survival [4–6]. Of note, the interaction between GH and its receptor also activates other intracellular signaling pathways, including the mitogen-activated protein kinase (MAPK)–extracellular-signal-regulated kinase (ERK) pathway and the phosphoinositide 3-kinase (PI3K)/Akt pathways, contributing to the diverse effects of GH on metabolism, cell proliferation, and cell differentiation [6–10] (Fig. 1).

3 Regulation of GH secretion by GHRH and somatostatin

The regulation of GH secretion is a finely tuned process governed by a complex interplay of central and peripheral stimuli [1–3]. Nevertheless, the vast majority of these signals ultimately exert their actions through the modulation of GHRH and somatostatin release by the hypothalamus, which represent the key, classical regulators of somatotroph axis signaling under normal physiological conditions.

GHRH is a hypothalamic peptide that plays a primary role in stimulating GH secretion from the anterior pituitary gland [2, 3]. It is produced by neurosecretory cells that predominantly originate from the arcuate nucleus of the hypothalamus and project their axons to the median eminence, where they terminate at the capillaries of the hypothalamic-pituitary portal system [11–13]. GHRH binds to specific receptors on somatotroph cells in the pituitary, triggering intracellular signaling pathways that involve the stimulation of the adenylate cyclase and the reduction of intracellular cyclic AMP (cAMP), which ultimately lead to an increase of GH synthesis and secretion [3, 11–13]. Moreover, apart from promoting GH release, GHRH also stimulates somatotroph cell proliferation, as evidenced by observations linking both decreased and increased GHRH production or activity with somatotroph hypoplasia or hyperplasia [11, 13, 14].

Somatostatin, also produced by the hypothalamus, acts as a counterbalance to GHRH by inhibiting GH secretion [2, 3]. It is produced by neuroendocrine neurons of the ventromedial nucleus of the hypothalamus, which – similarly to GHRH-producing neurons – project their axons to the median eminence, where somatostatin is released into the hypothalamic-pituitary portal system. In the anterior pituitary gland, somatostatin binds to somatostatin receptors on somatotroph cells, suppressing the release of GH through the inhibition of adenylate cyclase activity and reduction of intracellular cAMP levels [15–17]. Moreover, it also acts as a regulator of cell growth, by reducing somatotroph cell proliferation [18–20].

Of note, the regulation of GH secretion by GHRH and somatostatin is further tuned through precise feedback mechanisms, acting on three levels [1] (Fig. 2). Ultrashort-loop feedbacks are those in which a given hormone regulates its own secretion; such mechanisms have been shown for somatostatin [1, 21] and GH release [1, 22–24], while evidence for GHRH is less conclusive [1, 25]. Short-loop feedbacks designate the regulation of hypothalamic hormones by

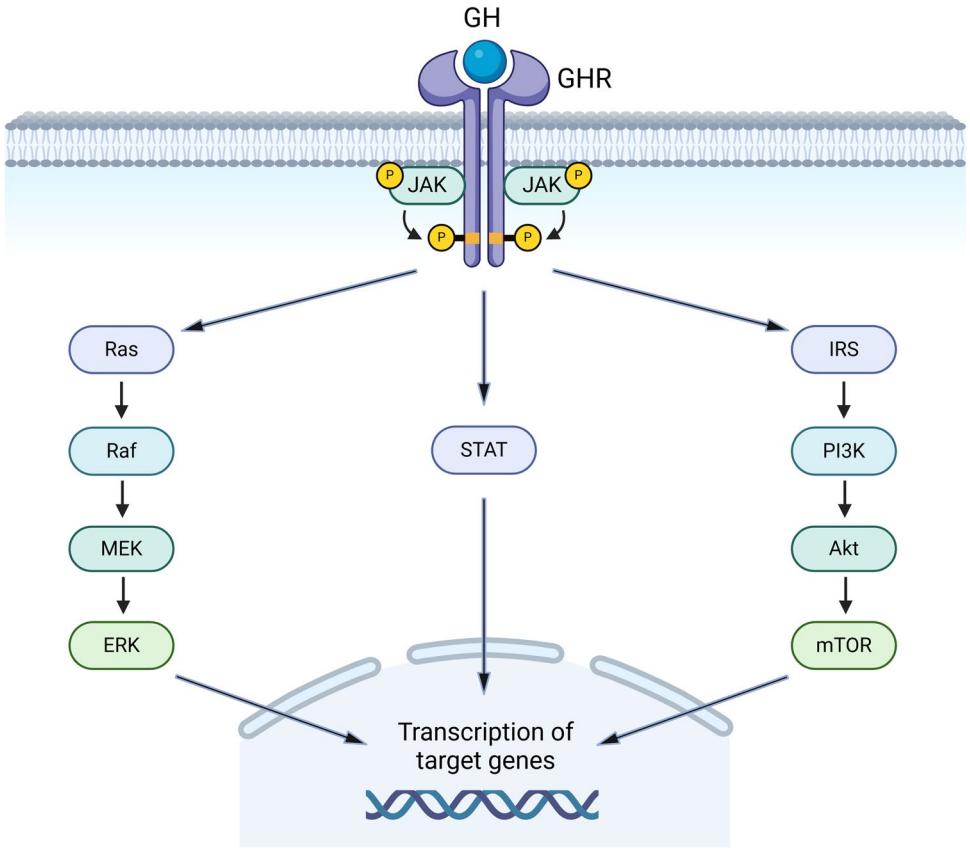

Fig. 1 Signaling pathways of growth hormone. Created with Biorender.com. Abbreviations: ERK, extracellular signal-regulated kinase; GH, growth hormone; GHR, growth hormone receptor; IRS, insulin receptor substrate; JAK, Janus kinase; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; STAT, signal transducer and activator of transcription

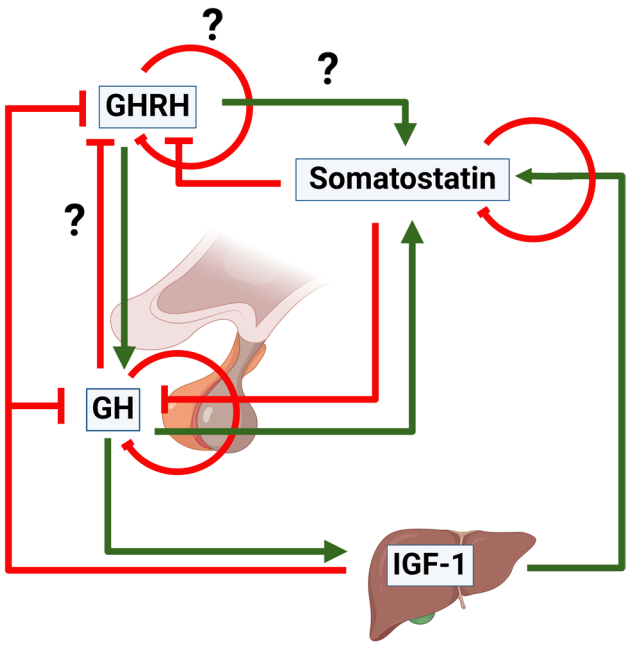

Fig. 2 Overall regulation of the somatotroph axis. The role of the two main regulators of GH secretion (i.e., GHRH and somatostatin) is highlighted. Ultrashort-loop, short-loop and long-loop feedback mechanisms are also represented. Created with Biorender.com. Abbreviations: GH, growth hormone; GHRH, growth hormone-releasing hormone; IGF-1, insulin-like growth factor 1

pituitary hormones or other hypothalamic hormones; in this sense, GH acts in the hypothalamus to promote the release of somatostatin [1, 26, 27] and possibly suppress the release of GHRH [1, 28, 29]; in addition, an intra-hypothalamic cross-talk between somatostatin and GHRH release has been proposed, with somatostatin inhibiting GHRH activity and, possibly, GHRH stimulating somatostatin release [1, 3, 30]. Finally, a long-loop feedback from IGF-1 is also present; in fact, IGF-1, produced by the liver in response to GH, favors the secretion of somatostatin, while concomitantly suppressing GHRH and GH release [1, 31–34].

4 Neuroendocrine/neurohormonal regulators of the somatotroph axis

4.1 Ghrelin

Ghrelin is a 28-aminoacid neuroendocrine peptide, first isolated in 1999 by Kojima and colleagues from the rat stomach [35, 36]. Although ghrelin is primarily released by gastric cells, smaller amounts are also produced by several other organs in the body, including the intestines, pancreas, kidneys, immune system, placenta, testes, and lungs. Additionally, ghrelin-immunoreactive neurons are present in certain regions of the brain, such as the arcuate and ventromedial

nuclei of the hypothalamus, as well as in the cerebellum and brainstem [36–38].

Ghrelin exhibits strong GH-releasing activity and, along with other growth hormone secretagogues (GHSs), acts through the GHS receptor type 1a, a G protein-coupled receptor, involving a downstream cascade that ultimately results in the release of calcium ions from intracellular stores with consequent increase of GH secretion [39–41]. Specifically, ghrelin stimulates GH release by acting directly on both the hypothalamus and the pituitary, although its primary effect appears to be at the hypothalamic level. Additionally, ghrelin has been shown to promote the release of prolactin and adrenocorticotropic hormone (ACTH) from lactotroph and corticotroph cells in the anterior pituitary [37].

Ghrelin and GHRH have demonstrated a synergistic effect on GH secretion, suggesting that they operate, at least in part, through distinct mechanisms. However, GHSs depend on GHRH activity to fully exert their GH-releasing effects and likely act by stimulating GHRH-secreting neurons [42, 43]. Indeed, patients with a GHRH receptor deficiency show no increase in GH secretion in response to GHSs stimulation even if they maintain the ability to increase prolactin as well as ACTH and cortisol secretion [44]. Additionally, the GH response to GHSs is significantly inhibited, though not completely abolished, by GHRH receptor antagonists and by hypothalamic-pituitary disconnection [37, 45, 46].

Ghrelin and synthetic GHSs do not reduce hypothalamic somatostatin release; however, it has been shown they can also act as functional somatostatin antagonists at both the pituitary and hypothalamic levels [43, 47, 48]. Evidence for this includes the fact that the GH response to ghrelin and GHSs is not further enhanced by the inhibition of somatostatin release [37, 43]. Moreover, the GH-releasing activity of GHSs is partially resistant to the inhibitory effects of substances that act through the stimulation of hypothalamic somatostatin, as well as to exogenous somatostatin administration [43, 47].

Notably, the GH-releasing effect of GHSs is independent of sex but undergoes significant age-related variations, increasing during puberty, reaching a plateau in adulthood, and subsequently declining with age [37, 43]. The increase GH-releasing effect of GHSs during puberty, for instance, is attributed to the positive influence of elevated serum estrogen levels, which enhance GHS-R expression [37, 49–51]. However, estrogen deficiency alone does not fully account for the diminished GH response to GHS observed in postmenopausal women [52–54]. The primary mechanism underlying the reduced GH-releasing activity of GHSs with aging is likely due to age-related changes in the neural regulation of somatotroph function, including decreased GHRH activity and increased somatostatinergic tone [3, 37, 43, 49]. Additionally, it has been hypothesized, that the age-related decline in GH secretion could be linked to reduced activity of the endogenous GHSs system [3, 37, 55]. An overall summary of the regulation of the somatotroph axis by ghrelin and synthetic GHSs is reported in Table 1.

4.2 Catecholamines

The catecholaminergic system significantly influences the neural regulation of GH release, exhibiting a dual action—both stimulatory and inhibitory—mediated by distinct receptors [56]. Indeed, both adrenaline and noradrenaline exert an important control over GH secretion, with stimulation mediated by α2-adrenergic receptors and inhibition mediated by α1- and β-adrenergic ones [1, 56, 57].

In this regard clonidine, a α2-adrenergic agonist, has shown to stimulate GH secretion [1, 56], while yohimbine, a α2-adrenergic antagonist, is able to block such increase [57]. It is likely that the stimulatory effect is due to both a positive action on hypothalamic GHRH-secreting neurons and, concomitantly, by the inhibition of somatostatin release [56, 58]. Certainly, clonidine has shown to trigger the release of GHRH from perifused rat hypothalamic explants [59], yet it fails to induce GH secretion in rats administered with an anti-GHRH antibody [60]. On the other hand, the inhibitory influence of α1/β-adrenergic receptors is likely to be due to the stimulation of hypothalamic somatostatinergic activity. Indeed, the use of phentolamine and salbutamol (α1- and β2-receptors agonists, respectively), has been shown to blunt the GH response to stimulation with GHRH [1].

Furthermore, the GH response to GHRH is enhanced by propranolol, a non-specific β-adrenergic receptor antagonist which has previously shown to be able to directly inhibit somatostatin release in vitro [1, 61], while it is suppressed by isoproterenol, a β2-adrenergic receptor agonist; this inhibitory effect on GH secretion, however, is reversed by an anti-somatostatin antibody. These observations clearly demonstrate the presence of a delicate balance between stimulatory and inhibitory adrenergic influences on the somatotropic axis [56, 57].

Other relevant catecholamines involved in the control of GH secretion are L-DOPA (L-3,4-dihydroxyphenylalanine), the precursor of catecholamines, and dopamine. Specifically, dopamine has demonstrated to reduce human pituitary GH release stimulated by GHRH in vitro [62]. In normal subjects, however, the acute administration of dopamine agonists such as L-DOPA, apomorphine, dopamine itself, and bromocriptine causes GH release [63, 64] and increases GH response to GHRH secretion [3, 65–67], probably through an inhibitory effect in the hypothalamic release of somatostatin [43]. Of note, this effect is attenuated by the concurrent presence of hyperglycemia [68]; in this context, it is possible that the stimulation of glucoreceptors may partly

Table 1 Summary of the signalling pathways of the main neuroendocrine and hormonal modulators of the somatotroph axis. Abbreviations: CRH, corticotropin-releasing hormone, GABA, γ-aminobutyric acid, GH, growth hormone; GHRH, growth hormone-releasing hormone; GHSs, growth hormone secretagogues; L-DOPA, L-3,4-dihydroxyphenylalanine; mRNA, messenger RNA

Neuroendocrine and hormonal modulators	General actions on somatotroph axis	Relevant pharmacological interactions	Special circumstances and remarks
Ghrelin and synthetic GH secretagogues	↑ GH secretion both directly and through stimulation of GHRH-secreting neurons No effect on somatostatin release but can act as functional somatostatin antagonists	Synergistically ↑ the maximal GH response to GHRH administration GH response is not further enhanced by the inhibition of somatostatin release; likewise, GH-secreting stimulus is partially resistant to the inhibitory effects of substances that act through the stimulation of hypothalamic somatostatin, as well as to exogenous somatostatin administration	Proper GHRH activity is essential for the full expression of GH-releasing effects: as a result, patients with a GHRH receptor deficiency show no increase in GH secretion in response to GHSs stimulation GH response is significantly inhibited, though not completely abolished, by GHRH receptor antagonists and by hypothalamic-pituitary disconnection GH response is sex-independent, but it undergoes marked age-related variations, with a maximum during puberty and adulthood and a subsequent decline with age
Catecholamines	Dual action: both stimulatory (α2-adrenergic receptors) and inhibitory (α1- and β-adrenergic receptors) Likely ↑ GHRH secretion and ↓ somatostatin release	Clonidine (α2-adrenergic agonist) ↑ GH secretion Yohimbine (α2-adrenergic antagonist) ↓ GH release Phentolamine and salbutamol (α1- and β2-receptors agonists) blunt the GH response to GHRH stimulation Propranolol (non-specific β-adrenergic receptor antagonist) enhances the GH response to GHRH administration Isoproterenol (β2-adrenergic receptor agonist) suppresses GH response to GHRH L-DOPA, apomorphine, bromocriptine and dopamine ↑ GH release and ↑ GH response to GHRH secretion in normal subjects Antidopaminergic drugs exhibit variable effects on both basal and GHRH-stimulated GH response; metoclopramide has been shown to either ↑ or not alter the GH response to GHRH, but it does not ↑ basal GH release in young adults	Clonidine ↑ GHRH release from perifused rat hypothalamic explants, yet it fails to induce GH secretion in rats treated with anti-GHRH antibodies The inhibitory effect is reversed by anti-somatostatin antibody pretreatment The concurrent presence of hyperglycemia partly counteracts the effects of catecholaminergic stimuli on GH release Subjects with acromegaly present a paradoxical inhibitory response to L-DOPA, and dopamine agonist treatment ↓ GH secretion Likely sex difference in dopaminergic regulation as significant differences in the GH response to metoclopramide were observed in men and women

Table 1 (continued)

Neuroendocrine and hormonal modulators	General actions on somatotroph axis	Relevant pharmacological interactions	Special circumstances and remarks
Acetylcholine	↓ somatostatin release through interaction with muscarinic receptor M1 Likely no direct effect on the adenohypophysis or direct stimulus on GHRH secretion	Pirenzepine (muscarinic cholinergic antagonist) ↓ basal and GHRH-mediated GH release Pyridostigmine and neostigmine (muscarinic cholinergic agonists) ↑ basal and GHRH-mediated GH release Several interactions with other peptides such as ghrelin and various adrenergic substances (such as clonidine and L-DOPA)	Stimulates basal GH secretion and enhances the GH response to GHRH, even in obese subjects, but not in individuals with either acute hyperglycemia or diabetes mellitus The cholinergic stimulatory influence on GH secretion is not sex-dependent but age-dependent and decreases with age The cholinergic interaction with the somatotropic axis varies during the day; if pyridostigmine is administered at night the basal GH secretion as well as its response to GHRH is blunted
Neuropeptide Y	Markedly ↓ GH secretion in rats Possible action of the peptide directly at the pituitary level	Reduces both basal and GH response to theophylline administration	The inhibitory effect is abolished by anterolateral deafferentation of the mediobasal hypothalamus, a procedure that disrupts the somatostatinergic input Possible role of the peptide in the short-loop feedback regulation of GH secretion Inconsistent findings in humans: in healthy subjects no variation in GH levels were reported, while the response in subjects affected by acromegaly was shown to be highly variable Conversely, in patients with prolactinoma GH levels increased in the majority of cases
Galanin	Likely ↓ somatostatin release Not clear if ↑ GHRH secretion in humans	Significant interactions with catecholamines and GABA; catecholaminergic and GABA antagonists suppress galanin-induced GH release	Stimulates GHRH release from hypothalamic explants or slices in vitro The stimulatory effect on GH is abolished with administration of either anti-GHRH or anti-somatostatin antibodies in rats Significantly ↑ GH response to GHRH in both adults and children, but not able to restore a normal somatotropic response to GHRH in patient with Cushing's disease The action of galanin on the GH response to GHRH is significantly influenced by estrogens, with a more pronounced GH peak observed in young women compared to males; this effect is reversed after menopause
Corticotropin-releasing hormone (CRH)	↓ GHRH and ↑ somatostatin release	-	The inhibitory effect is abolished by treatment with an anti-somatostatin antibody in rats Continuous treatment with CRH antagonists increase GHRH expression in rats Simultaneous administration of both CRH and GHRH should be avoided in clinical practice

Table 1 (continued)

Neuroendocrine and hormonal modulators	General actions on somatotroph axis	Relevant pharmacological interactions	Special circumstances and remarks
Glucocorticoids	↑ GH secretion at physiological levels; ↓ GH secretion if glucocorticoid excess (mediated by ↓ GHRH and ↑ somatostatin release)	GH response to arginine, L-dopa and insulin-induced hypoglycemia is impaired in patients with central adrenal insufficiency, with a complete restoration after initiating glucocorticoid replacement therapy	The inhibitory effect of glucocorticoid excess on GH secretion has been demonstrated both for exogenous and for endogenous hypercortisolism Some evidence indicate somatotroph axis suppression also in the context of subclinical forms of cortisol excess in patients with adrenal incidentaloma
Sex steroids	Androgens: ↑ GH secretion (mediated by ↑ GHRH and ↓ somatostatin release) Estrogens: ↑ GH secretion (through somatostatin- and ghrelin-mediated pathways)	Part of the central actions of the androgens is mediated by local conversion to estrogens, as the administration of aromatase inhibitors and/or central estrogen antagonists blunts GH response to testosterone	Apart from stimulating GH secretion, androgens also enhance the peripheral action of GH, increasing the expression of GH receptor in the liver and other target tissues On the other hand, the action of estrogens in modulating GH receptor expression is tissue-specific, notably with a downregulation of signaling in the liver and a reinforcement in the bone
Thyroid hormones	In the hypothalamus: regulate GHRH expression and synthesis In the pituitary: promote the expression of GH, GHRH receptor and GHSs receptor; likely ↑ somatostatinergic tone	Levothyroxine enhances the GH response to GHRH in hypothyroid patients, with the GH response returning to normal two weeks after the initiation of replacement therapy Methimazole treatment normalizes the GH response to GHRH in well-controlled hyperthyroid patients after euthyroidism has been maintained for at least 3 months	GHRH mRNA expression is increased in hypothyroid subjects, while hyperthyroidism acts decreasing GHRH mRNA levels In vitro studies have shown that thyroid hormones may increase the number of somatotroph cells

counteract the effects of catecholaminergic stimuli on GH release [1].

On the contrary, subjects with acromegaly present a paradoxical inhibitory response to L-DOPA in vivo as acute or chronic dopamine agonist treatment is able to inhibit GH secretion [3, 69, 70]. For this reason bromocriptine and cabergoline (the latter as an off-label treatment) are commonly used in patients affected by acromegaly in order to restore IGF-1 levels normal for age [71, 72].

Finally, antidopaminergic drugs exhibit variable effects on both basal and GHRH-stimulated GH response [3]. For example, metoclopramide has been shown to either increase [73] or not alter [74] the GH response to GHRH, but failed to increase basal GH release in young adults [75]. Significant differences in the GH response to metoclopramide were observed in men and women [76], suggesting a sex difference in dopaminergic regulation. An overall summary of the regulation of the somatotroph axis by catecholamines is reported in Table 1.

4.3 Acetylcholine

Beyond being a neurotransmitter, acetylcholine plays a major stimulatory role in the central control of GH secretion [56, 77]. Previous studies have demonstrated that muscarinic antagonists like pirenzepine are able to suppress basal GH secretion, as well as to blunt the GH response to various stimuli, including GHRH [56]. On the other hand, muscarinic cholinergic agonists, such as pyridostigmine and neostigmine, stimulate basal GH secretion and enhance the GH response to GHRH, even in obese subjects (both adults [78] and children [79–81]), but not in individuals with either acute hyperglycemia or diabetes mellitus [82, 83].

Regarding the mechanism of acetylcholine stimulation on the somatotropic axis, a direct action at the pituitary level is unlikely, and stimulation of GHRH also appears improbable [1, 56]. Indeed, there is ample evidence supporting the hypothesis that acetylcholine acts by suppressing the release of hypothalamic somatostatin mainly through the interaction with the M1 muscarinic receptor [84]: this is confirmed by the inhibition of somatostatin release from the hypothalamus in culture when exposed to cholinergic agonists [85].

The cholinergic stimulatory influence on GH secretion is age-dependent but not sex-dependent: in this regard, it is likely that as long as the stimulatory effect of cholinergic agonists decreases with age, the somatostatinergic activity increases [56]. Similarly, the action of cholinergic agonists also appears to depend on the time of day they are administered: in this regard, it is possible that somatostatin secretion increases during the night hours, given that basal GH secretion as well as its response to GHRH was blunted if pyridostigmine was administered at night [86, 87].

Lastly, the action of the cholinergic system on the somatotropic axis involves the interaction with other peptides such as ghrelin, which acts as a direct stimulus on pituitary somatotroph cells as well as a stimulus for hypothalamic GHRH [88], and various adrenergic substances (such as clonidine and L-DOPA) [12, 56, 89]. An overall summary of the regulation of the somatotroph axis by acetylcholine is reported in Table 1.

4.4 Neuropeptide Y

Neuropeptide Y (NPY) is a 36 amino-acid peptide that belongs to the family of pancreatic polypeptides, distributed in the intestine and in the central nervous system [90]: in particular, high concentrations of NPY are found within the arcuate, paraventricular, and the periventricular nuclei of the hypothalamus [91].

NPY has been shown to markedly decrease GH secretion and circulating levels of IGF-1 in animals [92, 93], while this effect is abolished by anterolateral deafferentation of the mediobasal hypothalamus, a procedure that disrupts the somatostatinergic input [94]. These findings imply that NPY indirectly affects the pulsatile release of GH by interacting with hypophysiotropic somatostatin neurons situated within the periventricular nucleus [1]. In this regard, it is plausible that NPY is involved in the short-loop feedback regulation of GH secretion [95], given that the vast majority of neurons expressing it in the hypothalamus possess GH receptors [96], and that local injection of NPY inhibits GH secretion whereas the same does not occur with IGF-1 injection [94].

Regarding the response to NPY in vivo, the available studies are limited, and such response has been found to be inconsistent in humans. In particular, while no response was observed in healthy subjects [97], in a study involving 15 acromegaly subjects, the GH response was variable, with an increase in GH levels in 4 individuals and inhibition in 3 [98]. Conversely, a study by the same authors involving 15 patients with prolactinoma demonstrated that intravenous administration of NPY induced a paradoxical increase in GH levels in the majority of cases [99]. It has been suggested that this might depend on the type of adenoma [98]: a stimulatory effect may be present in somatomammotropin adenomas, while an inhibitory effect may be typical of somatotropic adenomas.

In an in vitro study with pituitary adenoma cells from 6 subjects affected by acromegaly, in all cases a reduction in GH secretion was observed [100]. This finding suggests that the inhibitory effect of NPY on GH release from somatotroph adenomas may occur directly at the pituitary level. Furthermore, the authors reported that NPY administration was able to reduce the GH response to theophylline, a methylxanthine derivative previously shown to enhance GH secretion in vitro [101] but not

in vivo [102], primarily influencing intracellular cAMP concentrations. An overall summary of the regulation of the somatotroph axis by NPY is reported in Table 1.

4.5 Galanin

Galanin is a 29- or 30-amino acid neuroendocrine peptide, first isolated in 1983 by Tatemoto et al. from porcin intestine, widely distributed in the central and peripheral nervous systems [103]. Several pieces of evidence have demonstrated an important stimulatory role for galanin in the neural control of GH secretion [56]. Indeed, synthetic porcine galanin has been shown to increase basal GH secretion [104] and enhance the response to its release when co-administered with GHRH [105].

Data available from various preclinical studies suggest that galanin positively influences the somatotropic axis by acting both as a stimulatory factor for GHRH secretion and by reducing somatostatin production [56]. On the one hand, galanin has been shown to stimulate GHRH release from hypothalamic explants or slices in vitro [1, 106, 107]; on the other hand, treatment with either anti-GHRH or anti-somatostatin antibodies is able to abolish galanin-induced GH release in rats [108–110].

Data regarding the exact mechanism of action of galanin in humans, however, are not conclusive, and the prevailing hypothesis at present is for the reduction of somatostatinergic tone at the hypothalamic level [111]. Indeed, galanin has not been shown to have a direct action at the pituitary level but rather in the hypothalamus [112]. Furthermore, the involvement of various neurotransmitters is probable, given the anatomical interactions observed between galanin and hypothalamic neurotransmitters, such as catecholamines or γ-aminobutyric acid (GABA). Additionally, catecholaminergic and GABA antagonists have been shown to suppress galanin-induced GH release [1, 113].

Galanin has demonstrated to significantly increase GH response to GHRH in both adults [105] and children [111, 114], but it has failed to restore a normal somatotropic response to GHRH in patients with Cushing's disease compared to healthy controls [115], unlike what has been demonstrated in rats treated with long-term glucocorticoid treatment [116]. In addition, the action of galanin on the GH response to GHRH appears to be profoundly influenced by estrogens: the GH peak has been shown to be significantly more pronounced in young women compared to males, while it was reversed after menopause [117]. An overall summary of the regulation of the somatotroph axis by galanin is reported in Table 1.

4.6 Corticotropin-releasing hormone

Corticotropin-releasing hormone (CRH) is a 41 amino-acid peptide first isolated from ovine hypothalamus [118] that has shown to decrease GHRH-induced GH release in humans [1, 119, 120] even if this finding was not confirmed in all studies [121]. The exact mechanism of action has not yet been fully elucidated to date, but it is likely to depend in part on both an increase in somatostatin release (as the inhibitory effect of CRH on GH release is abolished by treatment with an anti-somatostatin antibody in rats [122, 123]) and a direct inhibition of hypothalamic neurons secreting GHRH. Indeed, continuous treatment with a CRH antagonist has been able to increase GHRH expression in rats [124]. The evidence of an interaction between CRH and GHRH action also has a significant clinical impact, as simultaneous administration of CRH and GHRH for testing should be avoided in clinical practice [120]. An overall summary of the regulation of the somatotroph axis by CRH is reported in Table 1.

5 Peripheral hormonal regulators of the somatotroph axis

5.1 Glucocorticoids

Glucocorticoids play pivotal roles in regulating various physiological processes, including growth, development, metabolism, and the body's response to stress [125–127]. They interact with the somatotroph axis in a complex manner, influencing GH secretion and action [3, 128].

A biphasic dose-dependent effect on the somatotroph axis has been described [3, 128]. Physiological glucocorticoid levels are required to preserve physiological GH secretion [129–131]; in conditions of glucocorticoid deficiency, in fact, a relative deficiency in somatotroph axis function has been described [129–131], mediated by a lower expression of GHRH receptor on somatotroph cells, ultimately leading to a reduced GH gene transcription and impaired GH secretion [3, 128, 132, 133]. In particular, glucocorticoid deficiency also impairs the response of GH to various stimuli, such as arginine, L-dopa and insulin-induced hypoglycemia, with a complete restoration after initiating glucocorticoid replacement therapy [129–131].

On the other hand, glucocorticoid excess is known to suppress GH secretion as well, mainly by inhibiting GHRH and augmenting somatostatin release from the hypothalamus [3, 128, 134–136]. This inhibitory effect has been demonstrated both for exogenous and for endogenous hypercortisolism [3, 128, 134–136]; moreover, some evidence indicates somatotroph axis suppression also in the context of subclinical forms of cortisol excess in patients with adrenal incidentaloma [137]. Overall, this response

to excess glucocorticoids can be interpreted as part of the body's response to stress, prioritizing glucose conservation and anti-inflammatory effects over growth and anabolic processes. This dual mechanism helps the body to manage energy resources during periods of stress but it can lead to adverse effects on growth and metabolism if glucocorticoid levels remain chronically elevated [3, 128, 138–143]. An overall summary of the regulation of the somatotroph axis by glucocorticoids is reported in Table 1.

5.2 Sex steroids

Sex steroids have differential effects on the somatotroph axis, influencing not only growth and body composition but also gender differences in these areas [3, 144]. Androgens generally stimulate GH secretion and enhance GH action at the target tissues [3, 144–147]. This stimulation contributes to the pubertal growth spurt and the increase in muscle mass typically seen in males during puberty [3, 144, 148, 149]. With regard to the mechanisms mediating this action, androgens exert their effects though multiple pathways; a central effect of stimulation of GH secretion is evident, mostly mediated by a modulation of GHRH and somatostatin release from the hypothalamus [3, 145, 150, 151]. Of note, part of these effects seems to be mediated by local conversion to estrogens through aromatization, as the administration of aromatase inhibitors and/or central estrogen antagonists determine an attenuation in the stimulation of GH secretion by testosterone [144, 145, 152]. Moreover, androgens also enhance the peripheral action of GH, significantly increasing the expression of GH receptor in the liver and other target tissues, thus augmenting its biological effects [144, 153, 154].

Estrogens have a more complex relationship with the somatotroph axis [3, 144]. At physiological concentrations, estrogens can enhance GH secretion by acting both at the level of the hypothalamus and of the pituitary [155, 156]; the activation of estrogen receptor on somatotroph cells reduces the expression of somatostatin receptor, thus enhancing GH release [157, 158]; moreover, estrogens also favor GH release by enhancing ghrelin-mediated pathways [159, 160]. At a peripheral level, estrogens exert a tissue-specific modulation of the expression and function of GH receptor [144]. An inhibition of GH receptor function and signaling is evident in the liver, ultimately leading to a reduction in the synthesis of IGF-1 [161, 162]; this is particularly evident in case of orally administered estrogens, due to the hepatic first-pass effect, and indirectly stimulates GH secretion by reducing the long-loop negative feedback physiologically exerted by IGF-1 [161, 163]. On the contrary, available evidence indicates that estrogens potentiate GH signaling in osteoblasts [164–166]. In fact, the combined administration of GH and estrogen leads to a synergistic stimulation of osteoblast proliferation, with estrogens enhancing the impact of GH on the process of bone formation [164–166]. An overall summary of the regulation of the somatotroph axis by sex steroids is reported in Table 1.

5.3 Thyroid hormones

Thyroid hormones regulate the function of the somatotropic axis through actions at both the hypothalamus and the pituitary gland [167, 168]. In the hypothalamus, the effect of thyroid hormones is most evident on the synthesis and secretion of GHRH: indeed, GHRH mRNA expression is increased in hypothyroid subjects, while hyperthyroidism acts decreasing GHRH mRNA levels [3, 169]. On the other hand, the effect of thyroid hormones on somatostatin is less clear, although they are thought to enhance somatostatinergic tone [168].

In any case, regardless of the type of underlying thyroid dysfunction, spontaneous GH secretion as well as acute GH-secretory responses to the most common physiological and pharmacological stimuli, including GHRH, are blunted in both hypothyroid and hyperthyroid patients [3, 168, 170–172]. Administration of levothyroxine to hypothyroid patients has shown to enhance the GH response to GHRH, with the GH response returning to normal levels two weeks after the initiation of levothyroxine replacement therapy [170]. Similarly, treatment of hyperthyroidism with methimazole led to a normalization of the GH response to GHRH in well-controlled hyperthyroid patients, but only after euthyroidism had been maintained for at least 3 months [173].

In the pituitary, on the other hand, thyroid hormones promote GH and GHRH-R synthesis [174, 175], as well as GHS receptor expression [167]. Moreover, thyroid hormones appear to influence the number of somatotroph cells, as in vitro studies have shown that thyroid hormones may increase the number of somatotroph cells [176], while in vivo studies in rats have associated hypothyroidism with a decreased number of GH secretory cells [177]. An overall summary of the regulation of the somatotroph axis by thyroid hormones is reported in Table 1.

6 Metabolic and other multi-systemic regulators of the somatotroph axis

6.1 Arginine and other amino acids

Amino acids are commonly recognized as building blocks of proteins and metabolic fuels, although their role as neurotransmitters within the central nervous system has been known for many years now [56, 178]. Many of them have shown to stimulate GH secretion, though arginine and

ornithine (its metabolic derivative) are the most potent ones [56, 179–185] (Fig. 3).

In humans, arginine (whether administered intravenously [179] or orally [186], although with a likely lesser effect [187]) increases basal GH secretion; however, it has shown to attenuate GH secretion in trained athletes if taken before exercise [188].

The mechanism of action of arginine does not appear to depend on an increase in GHRH secretion but rather on a direct or indirect action (mediated by nitric oxide) of reducing central somatostatinergic tone [56, 179, 189]. This result is confirmed by the fact that arginine is able to synergistically enhance the maximal GH response to GHRH administration while it does not act synergistically with pyridostigmine, a cholinergic agonist known for its central mechanism of inhibiting somatostatin release from the hypothalamus [190, 191]. Similarly, a direct action on somatotroph cells seems unlikely, as arginine was unable to increase either basal or stimulated GH secretion in rat anterior pituitary cell cultures [179].

The stimulatory effect of arginine on GH response when combined with GHRH is similar in children [192–194] as well as in the elderly [195–197]. This evidence suggests that the age-related decrease in GH secretion and IGF-1 levels is due to hypothalamic pathogenesis, given that it is known that somatostatin secretion increases progressively with age [198, 199], and that the maximal secretory capacity of somatotropic cells does not vary with the years [56, 200]. While age does not influence the effect of arginine, its impact is influenced by sex, being enhanced in women with normal menstrual cycles, likely due to a positive correlation with estrogen levels [56, 187].

Arginine has been shown to potentiate, although not restore, the somatotropic response to GHRH in obese subjects [201–204], but not in individuals with Cushing's syndrome [205]; moreover, restoration of ideal weight was able to significantly increase stimulated somatotropic response [206]. A reduced GH response to GHRH after arginine administration has also been found in diabetic patients, regardless of weight [207, 208], possibly due to the increased hypothalamic somatostatin release mediated by the interaction with free fatty acids [209].

Lastly, research has also explored the interactions between arginine and various neuroactive substances and metabolic inputs. Arginine does not interact with pyridostigmine [191] or ghrelin [210], but it indeed enhances the GH response to galanin, indicating that this neuropeptide may operate, at least partly, through a distinct mechanism [211]. Conversely, the stimulatory impact of arginine

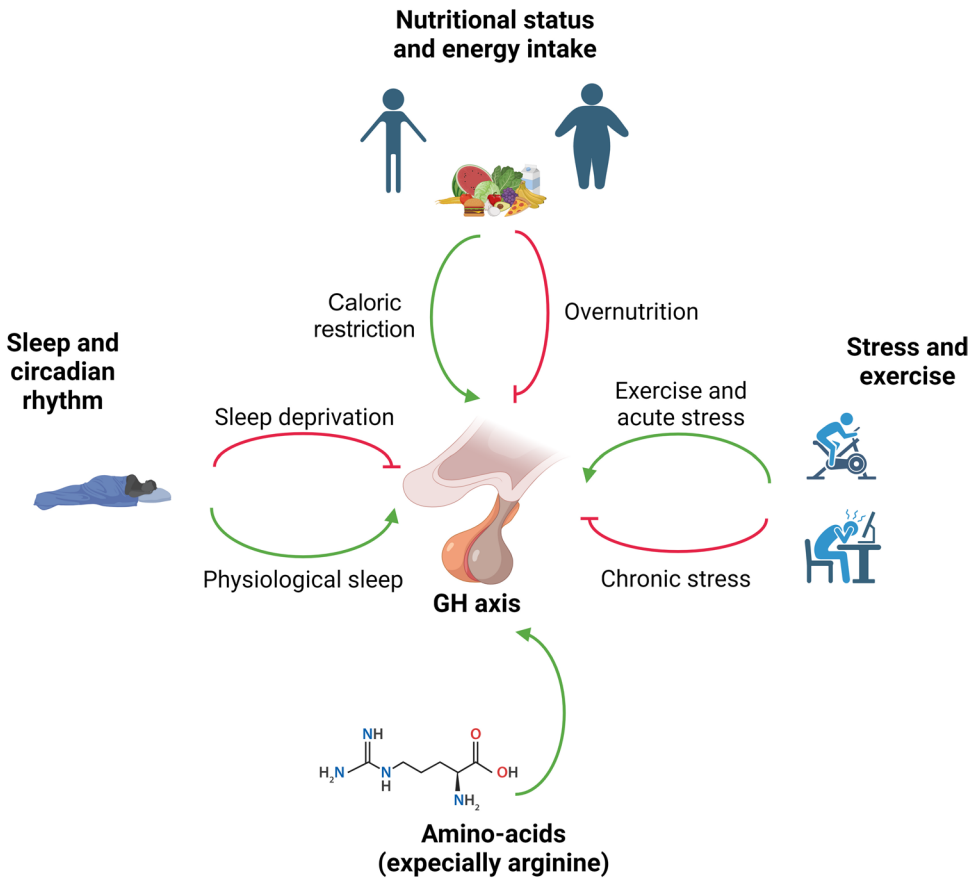

Fig. 3 Integrated modulation of the somatotroph axis in response to major metabolic and multisystemic signals. Created with Biorender.com. Abbreviations: GH, growth hormone

is able to counteract the inhibitory influence of glucose on both basal and GHRH-stimulated GH elevation [212].

6.2 Nutritional status and energy intake

The functioning of the somatotroph axis is significantly impacted by metabolic status and energy intake, reflecting the body's adaptation to nutritional states [213, 214]. Overall, caloric restriction is known to increase GH secretion, whereas overnutrition and obesity are associated with decreased GH levels [213, 214] (Fig. 3). This inverse relationship is thought to be a mechanism by which the body adapts to changes in energy availability, optimizing energy utilization and storage [213, 214].

The stimulatory effect of fasting on somatotroph secretion in humans is consistent with the lipolytic and hyperglycemic properties of GH, promoting endogenous fuel mobilization in contexts of caloric restriction, while trying to preserve lean mass [215–217]. Short-term fasting leads to a notable increase in GH secretion without significantly affecting IGF-1 levels [216]. It has been proposed that central nervous system-mediated mechanisms play a role in altering the secretion of GHRH and somatostatin, contributing to the immediate stimulatory impact of fasting on somatotroph secretion [216]. This effect involves heightened activity of GHRH-secreting neurons and a lengthening of the nadirs of somatostatin-secreting neurons [216]. On the other hand, the adaptation of the somatotroph axis to prolonged fasting is a more intricate process [214, 218–221]. In fact, in conditions of chronic undernutrition, alongside the rise in GH secretion, a condition of peripheral GH resistance emerges, characterized by normal to elevated GH levels coupled with low serum IGF-1 concentrations [214, 218–221]. This resistance appears to stem from the downregulation of the growth hormone receptor (GHR) in the liver, accompanied by alterations in post-receptor intracellular pathways, hindering GH ability to effectively stimulate IGF-1 production, with the possible mediation of low-insulin state [222–225]. Furthermore, the nutritional status itself serves as a regulator of IGF-1 synthesis and secretion from the liver, further contributing to these changes [221, 226].

States of overnutrition and obesity, on the other hand, are linked to a reduction in GH secretion [213, 214]. Subjects who undergo refeeding following a period of undernutrition show a suppression of the previously enhanced GH secretion [227, 228]. Excessive food intake in normal-weight individuals can significantly suppress GH release, even before any noticeable weight gain occurs [229]. In subjects with obesity, GH secretion diminishes, and the response of somatotrophs to stimuli is blunted [230–233]. Various theories have been put forth to elucidate the impact of nutritional repletion on GH secretion: alterations in hypothalamic somatostatin and GHRH release have been found [214]; moreover, part of the inhibition of GH secretion may also be mediated by hyperinsulinemia [229, 234, 235]; finally, there is some evidence to suggest that alterations in IGF binding proteins could play a role in modifying IGF-1 bioavailability [218, 230, 236, 237].

Overall, a key factor in the interplay between nutritional status and somatotroph axis regulation is represented by ghrelin. Aside from its role in stimulating GH secretion, ghrelin is a well-known hormone that stimulates appetite and is involved in both hypothalamic and extra-hypothalamic regions that regulate feeding behaviors [238–241]. Levels of circulating ghrelin rise during fasting and decline after meals, with a negative correlation with BMI [239, 242–244]. Various studies have explored the connection between ghrelin and GH in fed or fasted conditions, with a correlation being found in some [245–248] but not all [249–252] cases. Nonetheless, the overall body of evidence supports the role of ghrelin in maintaining viable blood glucose levels under conditions of starvation and fat depletion through GH-mediated mechanisms [243, 248, 253–255].

6.3 Sleep and circadian rhythm

The interplay between sleep, circadian rhythm, and the somatotroph axis is a fundamental aspect of endocrinology that influences metabolism, cognition, and overall health [256]. The pattern of pulsatile burst of GH secretion is notably influenced by sleep and exhibits a strong relationship with sleep patterns [256, 257] (Fig. 3). More specifically, most of the daily GH secretion occurs at night, with a significant surge occurring shortly after the onset of slow-wave sleep [258–260]. This seems to be mainly controlled by the stimulation of GHRH, occurring during a period of relative decrease in somatostatin levels [256, 257]; these pathways help integrating various hypothalamic stimuli related to the control of circadian rhythm, thus synchronizing GH secretion with external light–dark cycles and sleep–wake patterns [256, 257].

Both acute sleep deprivation and chronic sleep restriction have been shown to impair GH secretion [256, 257]. When the timing of the sleep cycle is shifted either later or earlier, the secretion of GH is also shifted to align with the onset of sleep [261, 262]. GH release is minimal or even absent during a night of acute sleep deprivation, while a significant increase is observed during the recovery night, in which GH secretion is even higher in comparison to baseline [263, 264]. Moreover, interestingly, GH pulses during periods of sleep deprivation seem to be more evenly spread throughout the 24-h day, with large pulses occurring during the daytime [264]. A similar reduction in GH secretion is observed during chronic sleep restriction, while the pattern during sleep recovery is slightly different [256, 265, 266]; in fact, during the recovery night, while an increase of slow-wave

sleep compared to pre-sleep-restriction baseline is noted, GH secretion is simply restored to baseline levels, without evidence of higher-than-baseline secretion bursts [256, 265, 266].

The negative consequences of insufficient sleep and/or sleep disorders are well-known, encompassing diminished cognitive functions, exhaustion, emotional disturbances, and worsening of the metabolic and cardiovascular risk profile [267, 268]. Given the involvement of the somatotroph axis in essentially all these functions, a role of GH circadian rhythm disruption in mediating the adverse health consequences of sleep deprivation has been proposed [256], although its specific contribution among all factors involved is difficult to isolate.

6.4 Stress and exercise

Both stress and exercise exert significant, albeit distinct, influences on the somatotroph axis, reflecting the body's adaptive responses to environmental challenges and physical demands [269–271] (Fig. 3).

Stress, whether psychological or physical, initiates a cascade of hormonal responses designed to prepare the body for a "fight-or-flight" reaction [272, 273]. Acute stress can stimulate GH secretion, likely as a part of the acute stress response mechanism, although the response can vary depending on the nature and intensity of the stressor [1, 3, 12, 274]. The activation of the somatotroph axis during acute stress helps mobilize energy resources, enhancing glucose availability and promoting anabolic processes [1, 3, 12, 274]. In contrast, chronic stress may suppress GH secretion [275, 276]. Prolonged exposure to stressors can lead to dysregulation of the somatotroph axis, likely through an increased somatostatin activity and altered sensitivity of the GH axis to GHRH [275, 276], possibly contributing to the overall adverse health outcomes associated with chronic stress [277–279].

Exercise represents a physical stressor that, unlike chronic psychological stress, generally promotes favorable adaptive hormonal responses and outcomes [269]. The response of the somatotroph axis to exercise is complex and influenced by the intensity, duration, and nature of the activity [269, 280]. Acute bouts of exercise can significantly increase GH secretion, even at low intensity [280–283]. This exercise-induced GH surge is thought to be mediated through several mechanisms, including reduced somatostatin inhibition, increased GHRH release, and possibly direct stimulation of the somatotroph axis by other factors such as lactate [283–287]. When evaluating the chronic effects of continuous training, regular exercise has been shown to enhance the sensitivity of the GH axis, resulting in a more pronounced GH response to subsequent exercise stimuli [286, 288, 289].

Overall, thus, the modulation of the somatotroph axis by stress and exercise underscores the adaptability of the endocrine system to environmental and internal challenges. While the axis's response to acute stress is generally beneficial, promoting energy mobilization and tissue repair, chronic stress can lead to maladaptive changes [1, 3, 12, 274–276]. On the other hand, physical exercise seems to exert a favorable role both in the short and in the long term, by inducing GH surges and – more generally – by enhancing the sensitivity of the axis to subsequent stimuli [280–282, 286, 288, 289].

7 Conclusions

In conclusion, GHRH occupies a central role in the intricate regulatory network governing GH secretion in humans. Together with somatostatin, it conveys and integrates a large number of neural and peripheral signals to orchestrate a finely tuned response of the somatotroph axis that adapts to the body's varying needs for growth, metabolism, and repair. Through the lens of pathophysiological interactions and feedback mechanisms, in this review we summarized and highlighted the precise interplay between all key regulators of GH secretion, also providing molecular insights into the signaling pathways involved.

Of note, beyond the pure pathophysiological interest, a precise understanding of the regulatory mechanisms of GHRH/GH signaling is not without practical and clinical implications. GHRH-based dynamic tests have historically provided a reliable diagnostic tool for assessing GH deficiency, with an enduring clinical relevance. More in general, the knowledge of all variables that may possibly influence the somatotroph axis is a key factor for the correct interpretation of any dynamic test used in clinic for the diagnosis of GH hypo- and hypersecretions. In this sense, this review also helps in bridging basic pathophysiological insights with practical clinical considerations, emphasizing the need for a comprehensive understanding of GH regulatory mechanisms for a correct evaluation and interpretation of somatotroph axis function in humans.

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Declarations

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