Published in final edited form as:
Ann N Y Acad Sci. 2011 March ; 1220: 82–92. doi:10.1111/j.1749-6632.2010.05913.x.

Does the pituitary somatotrope play a primary role in regulating GH output in metabolic extremes?

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Abstract

Circulating growth hormone (GH) levels rise in response to nutrient deprivation and fall in states of nutrient excess. Since GH regulates carbohydrate, lipid and protein metabolism, defining the mechanisms by which changes in metabolism alters GH secretion will aid in our understanding of the cause, progression and treatment of metabolic diseases. This review will summarize what is currently known regarding the impact of systemic metabolic signals on GH-axis function. In addition, ongoing studies using the Cre/loxP system to generate mouse models with selective somatotrope resistance to metabolic signals, will be discussed, where these models will serve to enhance our understanding of the specific role the somatotrope plays in sensing the metabolic environment and adjusting GH output in metabolic extremes.

Keywords

growth hormone; somatotrope; fasting; obesity

Introduction

This review will briefly summarize the impact of nutrient deficiency and nutrient excess on circulating GH and insulin-like growth factor I (IGF-I) in humans and other mammals. The mechanisms by which these changes are thought to occur will be discussed, with a particular emphasis on studies exploring the direct effects of systemic signals on somatotrope function. This review is in part an extension of a previous review[1], which examined how GH is regulated under metabolic extremes and how changes in GH modify metabolic function. For an overview of what is known regarding metabolic regulation of somatotropes in non-mammalian species, refer to Gahete et al[2].

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Effects of nutrient deficiency on GH/IGH-I

In humans, circulating GH levels are elevated in response to fasting, diabetes type I and anorexia nervosa[3–5]. Circulating GH levels have also been shown to be elevated in response to fasting, caloric restriction or diabetes type I in a variety of animal models including; pigs, dogs, sheep, goats, cows, rabbits, guinea pigs, and mice as reviewed in Luque et al[6]; with one exception, the male rat, where fasting and diabetes type I suppresses GH secretion[7–9].

Despite an increase in GH levels in the majority of species tested, short term fasting is characterized by a decrease in "free" bioavailable IGF-I, attributed in part to a rise in circulating IGF-I binding protein 1 (IGFBP-1)[10]. More prolonged fasting leads to a reduction of hepatic IGF-I production attributed to a decrease in hepatic sensitivity to GH actions, where GH binding is reduced[11] and GH-mediated phosphorylation of the transcription factor, signal transducer and activator of transcription 5b (STAT5b), is blunted[12,13]. Recent data indicates that the fasting-induced reduction in GH binding may be mediated by a cell surface protein, leptin receptor overlapping transcript (LEPROT), which is induced in response to fasting and is thought to promote internalization and degradation of GH receptor (GHR)[11]. In addition, fasting increases hepatic expression of fibroblast growth factor 21 (FGF21) in animal models and humans[14–16], where FGF21 can directly decrease STAT5b phosphorylation[14]. The fasting induced rise in GH and fall in IGF-I are considered part of the natural adaptive response to nutritional stress[3]. It is believed that the anabolic effects of GH may protect lean muscle mass, while its anti-lipogenic, pro-lipolytic and anti-insulin actions, in the context of low insulin and IGF-I, contribute to the shift in peripheral energy utilization from carbohydrate to fatty acid oxidation, thereby maintaining circulating glucose concentrations for central energy consumption.

Fasting-induced changes in hypothalamic and pituitary expression

In humans, it has been hypothesized that the fasting-induced rise in GH may reflect an increase in hypothalamic GH releasing hormone (GHRH) input and a decrease in somatostatin (SST) tone, as well as an increase in pituitary sensitivity to GHRH and ghrelin and a decrease in the inhibitory effects of SST[4]. These hypotheses are supported by animal studies. In food-restricted sheep, hypothalamic expression of GHRH is increased, and SST is decreased, where the later is reflected by a decrease in SST in the portal vasculature system[17]. Hypothalamic GHRH mRNA levels also increase in the mouse following short-term fasting (12h and 24h)[6], which is associated with a reciprocal shift in the pituitary receptor expression profile (increased GHRH-R and ghrelin receptor [GHS-R] and decreased SST receptor isoform/variants [sst2, sst3 and sst5] mRNA levels[6,18,19] where all of these changes would favor GH release, as illustrated in Fig. 1. Similar changes in pituitary receptor expression have been reported in the fasted and diabetic type I male rat[9,20–23]. These receptor changes may be functional in that the GH response to exogenous administration of GHRH and GHS-R agonists is augmented in fasted rats and dogs[21,24,25]. However, it should be noted, short-term fasting was recently shown to severely blunt the GH response to ghrelin in sheep[26]. These species dependent differences may be, in part, related to species dependent time course in homologous regulation of these receptors, where both ghrelin and GHRH can acutely downregulate the expression of their own receptors, but augment receptor expression after prolonged exposure[27–30].

Potential mechanisms

IGF-I and insulin—Receptors for both IGF-I and insulin are found within the hypothalamus of the rat[31–33] and intraventricular infusion of insulin or IGF-I can decrease GHRH, while increasing SST[34,35]. Therefore the fasting-induced fall in insulin and IGF-I could initiate a reciprocal shift in hypothalamic GHRH and SST neuronal activity. However,

in rats the fasting induced fall in IGF-I and insulin is associated with a decrease in GH pulse release, therefore it is unlikely that these actions are critical for fasting-induced GH changes in this species.

Independent of the central actions of IGF-I and insulin, it has long been recognized that both can directly inhibit somatotrope function by suppressing GH release and synthesis[36–40]. In addition, IGF-I and insulin suppress GHRH-R and GHS-R[37–40] and augment Sst2 expression (unpublished data) in primary pituitary cultures of rats, mice and baboons. The fact that the inhibitory actions of IGF-I on somatotrope function can be mimicked by insulin, at doses not predicted to bind and activate the IGF-I receptor, coupled with the observation that mouse and baboon pituitaries express receptors for both insulin and IGF-I at comparable levels[39,40], supports the hypothesis that the fasting-mediated increase in GH release may be explained, in part, by a decrease in IGF-I and insulin inhibitory tone at the level of the pituitary.

Ghrelin—Another factor thought to regulate the GH-axis in response to fasting, at both the central and pituitary level, is the acylated form of the gastro-intestinal peptide, ghrelin, which has been reported to be elevated in nutrient deficient states (for review see[41–43]). And indeed, central infusion of ghrelin or GHS-R agonists augment GH release[44]. This effect, unlike the well characterized stimulatory effect of ghrelin on food intake, does not require vagal afferents, at least in humans[45] and may be due to a direct stimulatory effect of ghrelin on hypothalamic GHRH neurons, as observed in mice with green fluorescent protein-expressing GHRH neurons[46]. At the level of the pituitary, ghrelin is less effective than GHRH in releasing GH in primary pituitary cell cultures prepared from rats[47,48]. However, ghrelin is as effective as GHRH in releasing GH in primary pituitary cell cultures from mice (unpublished data), pigs[48] and baboons [*Papio anubis*][30], acting through intracellular pathways distinct from GHRH[30,48]. *In vivo*, ghrelin is important in regulating basal GH secretion, based on a study showing mice with an inactivating mutation in GHS-R have reduced GH and IGF-I levels associated with a decrease in pituitary expression of GH, however these changes only modestly alters growth[49]. Ghrelin also contributes to the rise in circulating GH in response nutrient deprivation, based on a recent observation that mice lacking ghrelin O-acylatransferease (GOAT), the enzyme that converts des-acyl ghrelin to acylated ghrelin, show a blunted GH response to caloric restriction with reduced glucose levels, compared to GOAT intact mice[50]. In the same study, circulating GH and glucose levels could be recovered in GOAT knockout mice by infusion of acyl ghrelin. It should be noted that hypoglycemia was not evident until fat mass was less than 2%[50]. Therefore the authors speculate that ghrelin-mediated GH release may be critical in maintaining fasting glucose levels only in severe catabolic states such as anorexia nervosa, consistent with the observations that circulating acyl ghrelin and GH show no association in lean or obese humans in response to short-term fasting where only modest weight loss is observed[51,52].

It is clear that the primary source of circulating ghrelin is the gastrointestinal tract, however ghrelin is also produced within the pituitary[6,53–56] and in neurons within the hypothalamus[6,55–57]. In fact, fasting enhances pituitary expression of ghrelin, as well as increasing hypothalamic and pituitary expression of GHS-R[6,56]. Therefore it is possible that local changes in ghrelin synthesis and sensitivity may play a significant role in promoting GH release in response to fasting. In addition, the hypothalamus and pituitary express GOAT, and transcript levels in both tissues are increased in the fasted mouse[56], favoring the possibility that local conversion of des-acyl to acyl ghrelin could take place to promote GH secretion.

Other signals—The acute rise in glucocorticoids, in response to fasting, may also directly contribute to changes in somatotrope function because glucocorticoids can increase GH,

GHRH-R and GHS-R mRNA levels in primary pituitary cell cultures from rats and baboons, while having a predominately inhibitory effect on SST receptor expression[40,58–61]. In vivo, adrenalectomy dramatically blunts the fasting-induced rise in pituitary GHRH-R expression, but does not alter the fasting-induced increase in GHS-R expression, suggesting factors other than glucocorticoids are involved in this response[62].

Effects of nutrient excess (obesity) on GH/IGF-1

In humans, circulating GH levels are negatively correlated with body mass index[63,64]. Obese patients also show a blunted or absent response to all known GH stimuli[65–71], where in some cases these changes can be difficult to differentiate from organic GH deficiency (GHD)[71]. Significant weight loss (by exercise/diet or gastric bypass), results in the recovery of circulating GH concentrations[72,7374]. Therefore, the metabolic alterations associated with weight gain are thought to be the precipitating events leading to suppression of the GH-axis.

The mechanisms by which obesity leads to a decline in GH output are poorly understood. Multiple theories, based on clinical and animal studies, provide evidence implicating defects in hypothalamic input (suppressed GHRH and enhanced SST) and/or defects in somatotrope function, where both central and pituitary changes may be mediated by changes in circulating FFA, glucocorticoids, ghrelin, IGF-I or insulin, as previously reviewed[63,64]. All of these factors may ultimately contribute to obesity-associated GH-deficiency, depending on the experimental model or severity of the condition. However, examination of the GH-axis of the *ob/ob* and diet-induced (high-fat fed) obese mouse revealed obesity can be associated with a defect in somatotrope function (i.e. decreased expression of GH, GHRH-R and GHS-R), independent of changes in hypothalamic GHRH and SST expression[75]. Although we cannot rule out the possibility that GHRH and SST release may be modified, independent of changes in their gene expression, these results serve to minimize the role of a GHRH/SST imbalance in precipitating somatotrope defects in the obese state. These findings are consistent with an earlier observation showing normal male rats, which become obese after feeding a cafeteria-style diet, had normal hypothalamic GHRH and SST expression, but were insensitive to GHRH challenge[76]. Also, the fact that 8-day treatment with GHRH alone, or in combination with arginine (to suppress endogenous SST release), failed to restore the GH response of obese patients[77], supports the theory that obesity-associated defects in somatotrope function may be directly mediated by systemic signals acting directly to inhibit somatotrope function, as illustrated in Fig. 1.

Potential mechanisms

Insulin and IGF-I—In obesity, low GH levels are paradoxically associated with normal levels of total IGF-I but bioavailable IGF-I is elevated, attributed to a direct inhibitory effect of insulin on IGFBP1 production by the liver[10,78]. Therefore, it is hypothesized that in the obese state, more IGF-I is available to directly inhibit somatotrope function, leading to a reduction in GH synthesis and release. And indeed, the inhibitory impact of IGF-I on GHRH-stimulated GH release was reported to be preserved in obese patients[79].

In addition to the direct inhibitory effect of IGF-I on somatotrope function, obesity-associated hyperinsulinemia might also directly contribute to somatotrope dysfunction since several reports have shown a negative correlation between circulating insulin levels and GH[65,74,75,80]. In order for insulin to contribute to somatotrope dysfunction in the obese state, the pituitary must remain responsive to insulin, despite systemic insulin resistance. This appears to be the case in diet-induced obese mice, where the pituitaries remain responsive to the acute *in vivo* actions of insulin, as assessed by phosphorylation of Akt, despite systemic (skeletal muscle and fat) insulin resistance[75].

Ghrelin—Ghrelin also appears to play a role in releasing GH under fed conditions, where acyl ghrelin levels were shown to be positively correlated with GH pulse release in healthy subjects when supplied regular meals[51]. In obesity, total ghrelin levels (des-acyl plus acyl)) are reduced[63,75,81,82]. However, more recent studies indicate that acyl ghrelin is selectively elevated in obesity[83,84]. Therefore circulating ghrelin is unlikely to be a key player in obesity-associated GH suppression, but is hypothesized to directly contribute to hyperphagia and fat accumulation[85].

Adipokines—The most studied of the adipokines, in relationship to GH output, is leptin where circulating levels increase in obesity and decrease in response to fasting. Curiously, leptin has been shown to stimulate GH release *in vivo* and this action has been associated with increased GHRH and/or suppressed SST output depending on the species and nutritional status studied, as previously discussed[86,87]. Leptin receptors are also located on pituitary somatotropes, and leptin can directly stimulate GH release from primary pituitary cell cultures with species- and dose-dependent effects differences on GH, GHRH-R and GHS-R expression[86–89]. Therefore, the rise and fall of leptin in nutrient extremes are unlikely to explain changes in GH production under these conditions, however leptin may play a role in informing the somatotrope when nutrients are replete, as discussed in the last section of this review. Two other adipokines, resistin and adiponectin have also been shown to acutely stimulate GH release from primary pituitary cell cultures[90,91], however circulating levels of these adipokines are oppositely controlled in fasting and obesity, where resistin levels follow those of leptin, but adiponectin levels are elevated in fasting and suppressed in obesity. Therefore, further studies are required to appreciate the intricacies of adipose regulation of somatotrope function.

Circulating nutrients—In the obese human[80] and mouse[75] GH output is negatively correlated with glucose, as well as insulin. Certainly, acute hyperglycemia leads to suppression of GH via central activation of SST neuronal activity[92] and high glucose can suppress GHRH-stimulated GH release in primary pituitary cell cultures[93,94]. Therefore, it is possible that chronic hyperglycemia, associated with obesity/diabetes type II may signal through similar pathways to reduce GH output. FFA can also block basal GH release and suppress GH, GHRH-R and GHS-R expression in primary pituitary cell cultures from baboons and other species as reviewed in Luque et al[40]. An inhibitory effect of FFA on GH output *in vivo* is supported by the observation that oral administration of acipimox, to block lipolysis and lower circulating FFA, enhanced GHRH-stimulated GH release in obese patients[65]. However, based on the fact that in obese patients, acipimox treatment or a euglycemic insulin clamp, lowered FFA and glucose levels to that observed in similarly treated lean controls, but did not normalize insulin levels or the GH response to GHRH[65], the authors concluded that hyperinsulinemia is a major determinant of GH suppression in the obese state. It should also be noted that circulating FFA increase in response to fasting, in part due to the lipolytic effect of GH[95], and therefore are unlikely to play a dominant inhibitory role on GH release.

New tools

Although many hormones and nutrients can directly regulate somatotrope function and may in fact mimic the effect of metabolic extremes on GH output, as reviewed above, this does not prove that these direct actions are critical for the changes in GH output observed *in vivo* (*i.e.* exclude the contribution of altered hypothalamic signals). In order to circumvent this problem, our laboratory has developed and validated a mouse model that allows for somatotrope-specific gene modification by the Cre/loxP system[96]. Specifically, 310 bp 5' of the initiation codon of the rat GH gene (rGHp) was used to drive somatotrope-specific, *Cre* recombinase expression. This promoter was selected based on previous reports showing it

was effective in targeting transgene expression to the somatotrope in other genetically engineered mouse models[97,98]. Since their development, the rGHpCre transgenic mice have been backcrossed and maintained in a C57Bl/6 background, where this strain has been favored in studies of hormonal regulation of metabolic function. To date, we have used the rGHpCre mice to generate somatotrope-specific knockouts of the IGF-I, insulin and leptin receptors and the data accumulated thus far is summarized below.

Somatotrope-specific knockout of IGF-I and insulin receptors

The use of the Cre/loxP system to explore the differential effects of IGF-I and insulin on somatotrope function is particularly relevant given the fact that 1) circulating concentrations of IGF-I and insulin track together in metabolic extremes, 2) pituitaries express comparable levels of insulin receptors (INSR) and IGF-I receptors (IGF-IR) and 3) insulin and IGF-I at high concentrations can activate each others receptors and stimulate common intracellular signaling pathways. Therefore, rGHpCre mice were crossbred to mice carrying a loxP-modified IgfIr allele ($IgfIr^{fl/fl}$, developed by Jens Bruning, Univ. of Mainz[99]) and/or mice carrying a loxP-modified Insr allele ($Insr^{fl/fl}$, developed by Dr CR Kahn, Joslin[100]), generating somatotrope-specific knockouts of IgfIr ($IgfIr^{rGHpCre}$), Insr ($Insr^{rGHpCre}$) or both receptors ($IgfIr/Insr^{rGHpCre}$). Preliminary findings of the phenotype of these mouse models were recently reported at the 2010 Endocrine Society meeting[101] and the ICN2010[102], where a full characterization of the GH- and metabolic-axis of the $IgfIr^{rGHpCre}$ mice has been previously reported[103]. Knockout of either the IgfIr or Insr alone did not alter pituitary morphology or cell composition, while $IgfIr/Insr^{rGHpCre}$ pituitaries were smaller than homozygous floxed, Cre negative controls, which appears to be due to cell size, not cell number. $IgfIr^{rGHpCre}$ and $Insr^{rGHpCre}$ mice showed modest elevations in GH, that were most pronounced in $IgfIr^{rGHpCre}$ mice. Body weight of $IgfIr^{rGHpCre}$ and $Insr^{rGHpCre}$ mice did not differ from controls up to 3 months, however $IgfIr^{rGHpCre}$ mice had reduced fat mass[101,103]. Knocking out both receptors ($IgfIr/Insr^{rGHpCre}$) had an additive stimulatory effect on GH that was sufficient to clearly elevate IGF-I and increase growth[101]. The additive effect of knocking out both receptors on GH/IGF-I production indicates IGF-I and insulin signal through separate systems to inhibit somatotrope function, which was confirmed *in vitro* by knocking out the IGF-I and insulin receptors in primary pituitary cell cultures of $IgfIr^{fl/fl}$ or $Insr^{fl/fl}$, using a Cre recombinase adenoviral vector[101]. The fact that somatotrope-specific loss of both IgfIr and Insr, *in vivo*, elevated GH levels indicates negative feedback to hypothalamus is not sufficient to compensate, suggesting the somatotrope serves as the primary sensor of circulating IGF-I and insulin. Therefore, studies are ongoing to determine if somatotrope-specific loss of these receptors modifies fasting and obesity-induced changes in GH output.

Somatotrope-specific knockout of the leptin receptor (Lepr)

The rGHpCre transgenic mice have also been crossbred to mice carrying a loxP-modified Lepr allele ($Lepr^{fl/fl}$, developed by Dr. Streamson C. Chua, Albert Einstein College of Medicine[104]) generating mice with somatotrope specific knockout of the Lepr[87]. Consistent with the stimulatory effect of leptin on GH release observed in primary pituitary cell cultures of a number of mammalian species[86,88,89], including baboons (unpublished data), the loss of the Lepr was associated with a significant decrease in circulating GH levels and a reduction in the proportion of GH immunopositive cells. However the total pituitary cell number and gross pituitary morhphology was not altered, suggesting leptin regulates GH secretion in the adult, but not somatotrope development. Interestingly, the decline in GH did not impact early growth curves but did result in an increase in body weight later in life due to excess fat accumulation, with no significant change in lean mass, consistent with the impact of adult onset GH deficiency on body composition. These observations provide further evidence that the somatotrope plays an important role as a metabolic sensor, where

hypothalamic signals are unable to compensate to normalize GH output. These results also indicate that leptin plays a role in informing the somatotrope of nutrient excess, where leptin-mediated maintainance of GH release could serve to keep excess fat accumulation in check.

Future directions

As loxP-modified models become available, the specific roles that systemic hormones and nutrients play in directly regulating somatotrope function and subsequent GH output, in the context of metabolic extremes, will be revealed. A similar strategy can be applied to understand the relative contribution of hypothalamic neurons (such as GHRH and SST) at sensing systemic metabolic changes and altering GH secretion, however this will require the development of mouse models with neuron-specific Cre-recombinase expression. This basic strategy can be refined to include models of inducible, tissue-specific Cre-recombinase expression, which will allow for temporal regulation of gene modification[105,106] and avoid the potential confounding effects of early gene modification on cell-specific development. Since GH has profound effects on carbohydrate, lipid and protein metabolism[107], use of the Cre/loxP system will greatly expand our understanding of the mechanisms by which changes in metabolic function alters GH output and will in turn aid in the understanding and treatment of metabolic diseases.

Acknowledgments

Grants: The original work conducted by our laboratory and discussed throughout this review was supported by the "Programa Ramon y Cajal del Ministerio de Educación y Ciencia (RYC-2007-00186) and the BFU2008-01136/BFI grant (to RML), Spain" (to RML), FI06/00804 (to JCC), R03 HD059066, 1R01HD059056 and core facilities funded by NCRR P20 RR020146 and P30 NS047546 (to GVC), and grants from the University of Illinois at Chicago Campus Research Board, Veterans Affairs Merit Award and R01DK030677 (to RDK).

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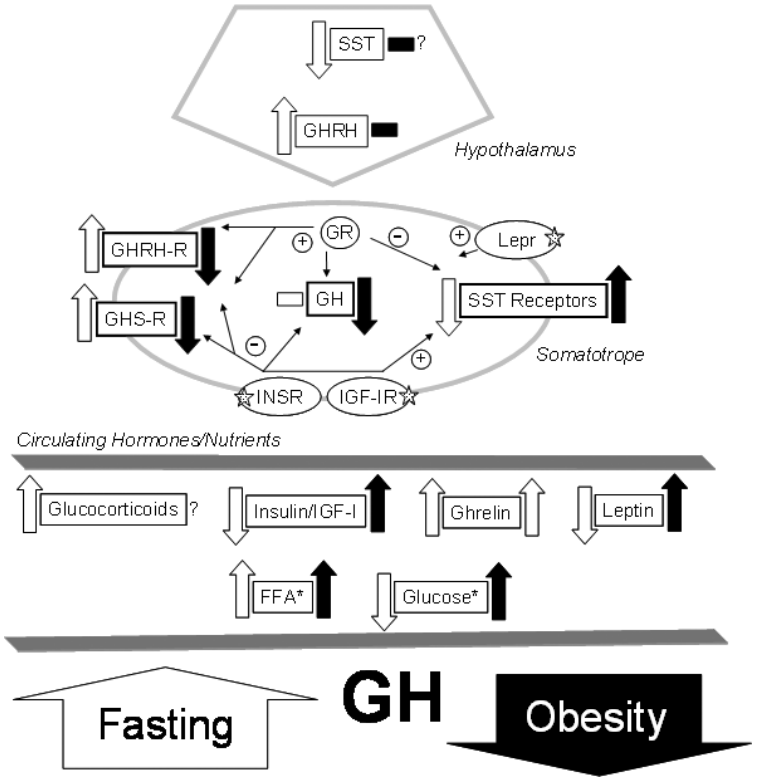

Figure 1.

The impact of metabolic extremes on GH-axis function. The directional impact of metabolic extremes on hypothalamic and somatotrope gene expression important in GH-axis function, as well as circulating factors important in these changes are illustrated by block arrows (up or down) and horizontal blocks (no change). Open (white) blocks represent the impact of fasting, while solid (black) blocks indicate the impact of obesity. Fine arrows connect receptor activation to positive or negative regulation of genes within the somatotrope, as determined by experiments conducted in primary pituitary cell cultures. Question marks (?) denote signals or endpoints in which conflicting or incomplete data has been generated. Five-point stars (☆) indicates receptor genes which have been selectively inactivated using the Cre/loxP system. *, Both free fatty acids (FFA) and glucose negatively impact somatotrope function, but the mechanism of action remains to be clarified. Abbreviations – somatostatin (SST), GH releasing hormone (GHRH), GHRH receptor (GHRH-R), leptin receptor (Lepr), insulin receptor (INSR), insulin-like growth factor I (IGF-I), IGF-I receptor (IGF-IR). This figure represents a modification of a figure published in a previous review (1).