Hypothesis: Extra-hepatic acromegaly: a new paradigm?

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Abstract
Medical treatment of acromegaly with long-acting somatostatin analogs (LA-SMSA) and the GH receptor antagonist, pegvisomant (PEGV), has made it possible to achieve normal serum IGF1 concentrations in a majority of patients with acromegaly. These two compounds, however, impact the GH–IGF1 axis differently, which challenges the traditional biochemical assessment of the therapeutic response. We postulate that LA-SMSA in certain patients normalizes serum IGF1 levels in the presence of elevated GH actions in extra-hepatic tissues. This may result in persistent disease activity for which we propose the term extra-hepatic acromegaly. PEGV, on the other hand, blocks systemic GH actions, which are not necessarily reliably reflected by serum IGF1 levels, and this treatment causes a further elevation of serum GH levels. Medical treatment is therefore difficult to monitor with the traditional biomarkers. Moreover, the different modes of actions of LA-SMSA and PEGV make it attractive to use the two drugs in combination. We believe that it is time to challenge the existing concepts of treatment and monitoring of patients with acromegaly.

Introduction
Acromegaly is a rare disease, most often caused by a GH-producing tumor of the anterior pituitary (1). Available treatment modalities to date aim at normalizing serum insulin-like growth factor 1 (IGF1) levels via reduction of either GH overproduction or GH actions (2–5). The obvious advantage is that the efficacy of different treatments can be easily compared by means of serum IGF1 measurements, as this is more practical than frequent GH measurements. This also applies to comparisons between the effects of long-acting somatostatin therapies (LA-SMSA) and the GH receptor (GHR) antagonist, pegvisomant (PEGV). This approach, however, is based on the assumption that serum IGF1 levels adequately and uniformly reflect disease activity. This assumption, however, is not necessarily valid. In this paper, we address the relationship between the GH–IGF1 axis with a specific emphasis on the significant differences in the modes of action of LA-SMSA and PEGV. In doing so, we will introduce the novel hypothetic paradigm of hepatic and extra-hepatic acromegaly and its potential clinical implications.

The effects of GH are tissue specific and concentration dependent
The physiological effects of GH versus IGF1 remain controversial. Historically, it has been difficult to isolate the individual effects of GH and IGF1 at the tissue level during physiological conditions. But the fact that GH possesses a diabetogenic or ‘anti-insulin’ activity (6), while IGF1 (as the name implies) is similar to insulin in its actions, clearly demonstrates that physiological differences exist between the actions of the two peptide hormones. Below, we cite results of animal studies that address specific effects of GH and physiological effects of GH versus IGF1.

Animal studies of the actions of GH versus IGF1
Since GH is a diabetogenic molecule, it would not be predicted to be used as a pharmaceutical to treat type 2 diabetes. Yet its lipolytic and anti-lipogenic actions could have potential positive outcomes in type 2 diabetic individuals. Two reports have documented beneficial effects of GH on glucose metabolism in type 2 diabetic patients (7, 8).

A mouse model attempting to determine the effect of GH on diet-induced type 2 diabetes parameters has been presented (9). In this model, male C57BL/6J mice were placed on a high-fat diet to induce obesity and type 2 diabetes. During the studies, mice were treated with various doses of GH. Body weight and composition, fasting blood glucose, insulin and IGF1 levels, glucose tolerance, liver triacylglycerol, tissue weights, and blood chemistries were determined. Several important findings were reported (9). First, a GH dose-dependent decrease
in fat and an increase in lean mass were found. These effects on body composition were seen at the highest two doses of GH administered, even though only the highest dose of GH resulted in elevated circulating IGF1 levels. These results indicate that certain effects of GH are independent of circulating IGF1 levels. Second, the increase in lean mass was observed before the decrease in white adipose tissue (WAT); thus, physiological effects of GH were not observed at the same time points. Third, GH-induced WAT loss was specific to subcutaneous and mesenteric fat. This result agrees with previously published work in which subcutaneous WAT depots were found to be increased in mice that lacked GH action (10–12). Thus, these data further support the notion that ‘not all WAT depots are treated equally’ in terms of GH action and should be evaluated independently in studies with GH or other treatments.

The finding that GH can affect body composition independent of elevations in total serum IGF1 levels is important. However, we must point out that these GH-dependent changes in body composition may be due to the autocrine/paracrine actions of IGF1 and not the direct action of GH. The importance of the autocrine or paracrine production of IGF1 has been documented in the liver-specific IGF1 gene-deficient mouse (13).

Other mouse studies attempting to discriminate the effect of GH versus IGF1 were carried out nearly 20 years ago. These studies showed that animals that have high GH and IGF1 levels display glomerulosclerosis; however, glomerulosclerosis is not observed in mice with increased levels of IGF1 alone (14, 15).

A continuation of these studies was carried out employing transgenic mice that express analogs of GH. For example, when a bovine (b) GH analog containing the following changes (L121P and E126G) is expressed in the transgenic mice, the resulting animals are of normal size with normal levels of IGF1; yet they display kidney glomerulosclerosis as severe as mice that express wild-type bGH (16). These data suggest that GH can affect the kidney independent of increases in IGF1.

Additionally, diabetic kidney disease can be induced in mice using streptozotocin. This kidney pathology was not seen in mice that express a GHR antagonist (17, 18) or in mice injected with PEGV (19). Important in this latter study was the fact that kidney pathology was prevented by PEGV, even in the absence of a decrease in serum IGF1 (19). Again, this implies that GH has a direct effect on the kidney independent of serum IGF1 levels.

The above data derived from mouse models of GH action suggest that GH can have temporal and tissue-specific effects independent of elevations of serum IGF1.

The relationship between portal insulin and GH sensitivity of the liver

Human and other mammals are capable of prolonged fasting because they can recruit and utilize lipid stores when they exhaust readily available carbohydrates (20–22). Prolonged fasting is associated with a gradual decline in hepatic IGF1 production, which makes teleological sense due to the insulin-like effects of IGF1. A study by Leung et al. suggests that GH-induced hepatic IGF1 production is regulated by portal insulin levels (23). They reported that insulin promotes the translocation of the hepatic GHR to the surface.

When portal insulin levels are high, the liver becomes GH sensitive, regardless of the cause of the elevation in insulin production (23). In addition, portal insulin also inhibits hepatic IGFBP1 production, which may increase the bioavailability of circulating IGF1 (24, 25).

In conclusion, high portal insulin levels increase liver GH sensitivity (via up-regulation of surface GHRs) and, therefore, ultimately increase liver IGF1 production with concomitant increases in serum IGF1 levels. In contrast, low portal insulin levels reduce the sensitivity of liver for GH and, therefore, reduce serum IGF1 levels.

Why do acromegaly patients have elevated IGF1 levels

Acromegaly patients have elevated IGF1 levels as a consequence of GH hypersecretion (1). In addition, the elevated GH levels stimulate lipolysis and induce resistance to the effects of insulin on glucose metabolism in liver and muscle. The net result is a hypermetabolic state characterized by elevated levels of glucose, free fatty acids, and insulin (26, 27).

The GH-induced hyperinsulinemia, in turn, is likely to further stimulate hepatic IGF1 production and to lower IGFBP1 levels (28, 29). The importance of this effect is supported by the observation that prolonged fasting-induced hypoinsulinemia can completely normalize serum IGF1 levels in acromegaly patients (30).

In conclusion, acromegaly patients have elevated serum IGF1 levels because of the pathological hypersecretion of GH by the pituitary tumor, which is aggravated by the accompanying hyperinsulinemia.

How somatostatin analogs work

Somatostatin analogs (SMSA) bind to somatostatin receptors of which subtypes 2 (sst2) and 5 (sst5) are the most important ones for mediating the actions of the available LA-SMSAs (31–33). Because of the expression of sst2 and sst5 on the somatotroph cells, pathological GH secretion can be inhibited by SA, which translates into reduced hepatic IGF1 production (31–34). When this reduction is sufficient to normalize IGF1 levels, the treatment is traditionally considered adequate (31, 35–37).

However, SMSA also binds to sst2 and sst5 receptors on the pancreatic islet, which will reduce glucagon and insulin secretion (38, 39). This occasionally results in a worsening of the glycemic control in acromegaly.
patients during long-term LA-SMSA (40). Moreover, a suppression of insulin secretion by SMSA also selectively results in hepatic GH resistance, which itself decreases hepatic IGF1 production (23). Therefore, the ensuing reduction in circulating IGF1 does not necessarily reflect GH activity in peripheral tissues.

A GH-independent suppressive effect of SMSA on serum IGF1 levels has been documented in two studies in humans (41, 42). Both studies involved administration of octreotide for 7 days during continued GH treatment in adult GH deficiency (GHD) patients. This resulted in a significant 16–18% reduction in serum IGF1 levels with a concomitant reduction in insulin levels and elevated levels of IGFBP1 (41, 42).

In the context of acromegaly, it is therefore plausible that normalization of serum IGF1 levels during LA-SMSA not necessarily implies control of disease activity in peripheral tissues, i.e. a condition for which we propose the term ‘extra-hepatic acromegaly’ (Fig. 1a). This is further supported by a recent report by Rubeck et al. (43). They compared traditional and novel biomarkers and health status in patients with acromegaly treated with either surgery alone or SMSA. They reported that despite similar and normalized IGF1 levels, SMSA treatment compared with surgery alone was associated with less suppressed GH levels and less symptom relief. They concluded that this discordance may be due to specific suppression of hepatic IGF1 production by SMSA (43).

In the absence of a convenient bioassay for disease activity in acromegaly, it is not easy to validate whether extra-hepatic acromegaly is a clinical entity rather than a semantic issue, but it is noteworthy that impaired quality of life (QoL) has been reported in LA-SMSA patients despite normal IGF1 levels (44).

How GHR antagonists work

As described above, the GHR antagonist, PEGV, competitively blocks the GHRs in all peripheral tissues (45–47). Thus, the higher the endogenous GH level, the more PEGV is needed to effectively block GH actions (4). PEGV, however, does not block all tissues equally effective for the actions of GH. Adipose tissue, the kidneys, and skeletal muscle seem to require less PEGV to reduce GH actions compared to the liver where more PEGV is required in order to reduce IGF1 production (19). In further support of this, it was recently reported that short-term PEGV administration in healthy subjects can suppress lipolysis without affecting either circulating or local IGF1 (48).

It is therefore possible that PEGV treatment in acromegaly is subject to tissue-specific differences in a dose-dependent manner. In particular, it is possible that peripheral suppression of GH activity is obtained prior to normalization of hepatic IGF1 production. Such a condition during PEGV therapy could be denoted ‘hepatic acromegaly’, which in essence is reciprocal to the putative conditions during LA-SMSA (Fig. 1b). However, unlike extra-hepatic acromegaly, data in humans are lacking to suggest that hepatic acromegaly indeed does occur during PEGV monotherapy.

Lessons from diabetes type I and II

The effects of restoring portal insulin levels on serum IGF1 have been studied in type I diabetes (49). Only with portal insulin administration, did IGF1 levels increase to within the normal range, which resulted in a decrease in GH levels. However, diabetic patients on conventional insulin therapy had low IGF1 and elevated GH levels (49).

Wurzburger et al. (50) also studied GH-stimulated IGF1 levels in type 1 diabetes. The patients were divided into C-peptide-negative patients without residual β-cell activity and C-peptide-positive patients with preserved β-cell activity. A GH-induced increase in serum IGF1 levels was only observed in patients with remnant β-cell activity (50).
There are similarities between type I diabetes and LA-SMSA-treated acromegalic subjects: both exhibit elevated systemic GH activity together with relative hepatic GH resistance due to low portal insulin levels. The difference is that type I diabetic subjects have low IGF1 levels, while LA-SMSA-treated acromegalic subjects have normal or elevated IGF1 levels. There are also similarities between type 2 diabetes and PEGV-treated acromegalic subjects: both exhibit low systemic GH activity in the presence of relatively high hepatic GH sensitivity due to normal or elevated portal insulin levels.

What about combining SMSA and PEGV

Several papers have presented data on combination therapy with LA-SMSA and PEGV. To date, the focus in these reports has been on patients with an insufficient response to LA-SMSA (51, 52), but we believe that combination treatment may offer benefit to other patients. The strongest evidence for this is presented by Neggers et al. (53). They hypothesized that weekly administration of 40 mg PEGV could improve QoL and metabolic parameters in acromegalic patients with normal age-adjusted IGF1 concentrations during LA-SMSA treatment. In a double-blind, placebo-controlled, crossover study, 20 acromegalic subjects received either PEGV or placebo for two consecutive treatment periods of 16 weeks, separated by a wash-out period of 4 weeks. Efficacy was assessed as a significant change in disease-specific QoL between baseline and at the end of each treatment period. QoL was assessed by the acromegaly QoL questionnaire (AcroQoL) and the patient-assessed acromegaly symptom questionnaire (PASQ). Interestingly, the AcroQoL and AcroQol improved significantly after PEGV was added. The addition of PEGV also significantly improved the PASQ and the single PASQ questions dealing with perspiration, soft tissue swelling, and overall health status. By contrast, no significant changes in IGF1 levels were observed during the addition of PEGV. As the age-dependent normal range for IGF1 is still relatively wide, it might be possible, however, that some patients may have a statistically normal IGF1 level that is in fact too high for them. Addition of weekly PEGV might induce a short-lived decline of IGF1 for 2 days, which does not register if the blood is drawn 7 days after PEGV administration, but the clinical effects might be manifested in QoL questionnaires. Thus, low-dose PEGV treatment improved the signs and symptoms of ‘extra-hepatic acromegaly’ without impacting hepatic IGF1 production consistent with our hypothesis of extra-hepatic acromegaly. It is noteworthy that the largest improvement in QoL was observed in patients who also responded to PEGV with alleviation of fluid retention (53). It remains to be studied whether the same favourable effects could be obtained by an increase in the dose of LA-SMSA.

Conclusions and future directions

SMSA have stood the test of time as a safe and effective treatment for acromegaly; however, adequate control of the disease is not always achieved. With the recent introduction of PEGV, it is now possible to obtain biochemical control of the disease in most patients. Thus, now is an appropriate moment for critical evaluation of the proper assessment of the therapeutic outcome with these two different treatment modalities. In particular, we postulate that circulating IGF1 is not necessarily the most reliable biomarker of disease activity. SMSA have at least three tissue-specific effects: i) decreased GH secretion from the pituitary tumor, ii) decreased insulin secretion from the pancreas, and iii) decreased hepatic IGF1 production that may lead to a normalization of serum IGF1 levels despite insufficient control of disease activity in peripheral tissues. The combination of these effects may lead to a state of normalized serum IGF1 levels and residual peripheral disease activity, i.e. extra-hepatic acromegaly. Whether this is of clinical significance and whether it may be overcome by simply increasing the dose of LA-SMSA merits are to be addressed in a controlled clinical trial. It would be obvious to compare the outcome of LA-SMSA in patients who are randomized to dosing according to either serum IGF1 levels or GH levels.

The use of PEGV also is challenging since this treatment is accompanied by a further elevation in GH levels. Moreover, there is evidence to suggest that PEGV in some cases may induce significant blockade of peripheral GH actions prior to blockade of the hepatic GHRs. In this context, it is also noteworthy that the dose requirements of PEGV are subject to a wide inter-individual variation. Novel biomarkers in addition to IGF1 for this individual variation are needed. It also remains to be determined whether assessment of serum PEGV levels would be useful. We believe that patients using combination therapy of SMSA and PEGV should be monitored with more specific ways. This might include procollagen II levels or another parameter that can integrate GH actions on the ‘extra-hepatic’ tissues such as bone.

The fact that LA-SMSA and PEGV exert complementary suppressive effects on the GH–IGF1 axis makes combination therapy with the two modalities an interesting option. Indeed, there is evidence to suggest that combination therapy is superior to monotherapy with LA-SMSA in terms of glucose homeostasis (52) and disease-specific QoL (53). The latter observation also suggests that assessment of QoL could be considered as routine practice during medial therapy. Our hope is that the introduction of the hypothetic paradigm of extra-hepatic acromegaly will challenge basic scientists, clinicians, and pharmaceutical industries to design and perform studies that show that we are wrong, because if we are not, medical treatment of acromegalic patients might need...
a significant update. Last but not least, we believe there is a need for novel biomarkers (either genomic, metabolomic, proteomic, or others), which ideally integrate hepatic as well as peripheral disease activity.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

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