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The effects of growth hormone on adipose tissue: old observations, new mechanisms

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Abstract

The ability of growth hormone (GH) to induce adipose tissue lipolysis has been known for over five decades; however, the molecular mechanisms that mediate this effect, as well as the ability of GH to inhibit insulin-stimulated glucose uptake, have been scarcely documented. In this same timeframe, our understanding of adipose tissue has evolved to reveal a complex structure with distinct types of adipocytes, depot-specific differences, a biologically significant extracellular matrix and important endocrine properties mediated by adipokines. All of these aforementioned features, in turn, can influence lipolysis. In this Review, we provide a historical and current overview of the lipolytic effect of GH in humans, mice and cultured cells. More globally, we explain lipolysis in terms of GH-induced intracellular signaling and its effect on obesity, insulin resistance and lipotoxicity. In this regard, findings that define molecular mechanisms by which GH induces lipolysis are described. Finally, data are presented for the differential effect of GH on specific adipose tissue depots and on distinct classes of metabolically active adipocytes. Together, these cellular, animal and human studies reveal novel cellular phenotypes and molecular pathways regulating the metabolic effects of GH on adipose tissue.

Introduction

Since the 1980s, the global prevalence of obesity has significantly increased in adults and children, which is associated with excess morbidity and mortality. Obesity is a complex trait

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Author contributions

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that is influenced by diet, physical activity, age and genetics[1,2]. The storage and release of triglycerides from adipose tissue are important processes involved in the development of obesity and are controlled by afferent signals including a variety of hormones, for example, catecholamines, growth hormone (GH) and insulin.

GH is a peptide hormone that is secreted by somatotrophs in the anterior pituitary gland and has a variety of tissue-specific effects, including anabolic effects on muscle and bone and catabolic action on white adipose tissue[3]. Of note, the ability of GH to induce lipolysis in adipose tissue and affect fat volume and distribution is well accepted[3]; however, the molecular mechanisms that underpin these effects are still not firmly established. In addition, the effect of GH on inhibiting the action of insulin (that is, the diabetogenic effect of GH) has been known for more than half a century; yet, the molecular mechanisms supporting this effect in humans are only now being elucidated[4,5]. Clinical evidence demonstrates that GH regulates insulin sensitivity in humans as a direct result of its induction of lipid catabolism in adipose tissue, which liberates free fatty acids (FFA)[6]. Moreover, in patients with GH deficiency, insulin resistance caused by GH treatment is reversed by pharmacological blockade of lipolysis[7,8].

In this Review, we summarize the lipolytic effects of GH in adipose tissue with emphasis on studies in humans. We will also discuss experimental data in mice and cultured cells, emerging data documenting the underlying molecular mechanisms and the growing understanding of how these factors might be influenced by the cellular composition and location of adipose tissue.

An overview of lipolysis

Lipolysis is a catabolic branch of the fatty acid cycle that provides fatty acids in times of metabolic need. Fatty acids are essential as energy substrates and for the synthesis of most lipids. However, despite their fundamental physiological importance, oversupply of FFAs cause lipotoxicity, which can disrupt the integrity of membranes, alter cellular acid–base homeostasis and elicit the generation of harmful bioactive lipids[9]. Furthermore, the high concentrations of circulating FFAs and triglycerides observed in obesity and lipodystrophy cause insulin resistance in skeletal muscle and decreased glucose tolerance[10–13]. Importantly, GH is now known to regulate the balance of fatty acid esterification and triglyceride lipolysis, thereby having a central role in regulating whole body metabolism and glucose homeostasis[3,14].

Adipose tissue lipolysis of stored triglycerides to FFAs and glycerol is coordinated by a number of proteins, including several enzymes and lipid droplet-associated proteins (Figure 1). Lipolysis involves the action of three different lipases: adipose triglyceride lipase (ATGL); hormone-sensitive lipase (HSL); and monoacylglycerol lipase (MGL). ATGL, which is associated with lipid droplets and encoded by *PNPLA2*, is the rate-limiting enzyme for lipolysis and catalyzes the first step of hydrolysis of triglyceride to diacylglycerol[15–19]. Various other proteins are also involved in the lipolytic machinery. For example, in adipocytes, CGI-58 is an activator of ATGL. Under basal conditions, Perilipin A (PLIN1), a major lipid droplet coat protein in mature adipocytes, prevents the access of CGI-58 to

ATGL, thereby decreasing lipolysis[18,20–22]. Upon β-adrenergic stimulation, protein kinase A (PKA) activation results in phosphorylation of PLIN1, causing the release of CGI-58 that then binds and stimulates ATGL on lipid droplets[20,23]. In addition, PKA phosphorylates HSL, which then translocates to lipid droplets and together with ATGL and MGL leads to acute activation of triglyceride hydrolysis.

ATGLis also regulated by two inhibitory proteins: G0S2 and FSP27. For example, G0S2 binds directly to ATGL and attenuates ATGL-mediated lipolysis via inhibiting its triglyceride hydrolase activity[24]. Furthermore, FSP27 is a lipid droplet-associated protein that regulates lipid droplet dynamics[25–29] and lipolysis, through direct interaction with ATGL to inhibit its catalytic capacity[30]. In addition, FSP27 also transcriptionally represses ATGL expression during insulin signalling (Figure 1)[31].

The lipolytic effects of GH in humans

Historical perspectives.

Maurice Raben was among the first to purify and test pituitary-derived human GH in human s and he noted that the rise observed in serum FFA levels after treatment was “perhaps the most sensitive response to GH of any yet described”[32]. Interestingly, he studied treatment responses in adult volunteers, including elderly patients with panhypopituitarism, where a single physiological dose of GH could induce a lipolytic[33]. Raben also demonstrated that the lipolytic effect induced by GH treatment is suppressed by food intake and amplified by fasting[33], which suggests a physiological role of GH to partition substrate metabolism between fat mobilization and protein synthesis that is dependent on ambient nutrient status. In addition, Raben hypothesized that the suppressive effect of food intake on GH-induced lipolysis provided a mechanism of control “not requiring a change in GH secretion” and that GH was present “at all times”[33].

The advent of a GH radioimmunoassay disproved Raben’s GH secretion hypothesis and demonstrated that serum levels of GH are secreted in a pulsatile manner, especially during night time and after exercise[34,35]. Furthermore, serum GH levels were suppressed postprandially and elevated during fasting[36], which is consistent with the aforementioned lipolytic effects. Experimental studies on the metabolic effects of GH and insulin in human volunteers[6] confirmed the lipolytic action of GH and demonstrated that GH-induced lipolysis was accompanied by increased FFA uptake and oxidation in skeletal muscle *in vivo*. Moreover, GH treatment was shown to acutely and directly induce resistance to insulin-stimulated glucose uptake in human skeletal muscle[37]. As the circulating pattern of insulin inversely correlates with that of GH (that is, high insulin levels postprandially and low levels during fasting), the following hypotheses were proposed: first, in the immediate postprandial period, insulin acts alone to increase the storage of glucose and other nutrients; second, in the fasting state, GH acts alone to facilitate mobilization and oxidation of endogenous lipid stores; third, in between these two phases, GH and insulin might act in synergy to promote protein anabolism[6]. This model has largely stood the test of time, even though we now know that the anabolic effects of GH largely depend on the concerted actions of GH, insulin and insulin-like growth factor 1 (IGF1)[3].

Further evidence of GH-induced lipolysis in humans.

Regarding the mechanisms whereby GH increases lipolysis *in vivo*, experimental studies in human volunteers demonstrate that this effect of GH is blocked by treatment with acipimox, an antilipolytic agent that suppresses cAMP formation and ultimately the lipolytic action of HSL by inhibition of the niacin receptor[7,8]. Furthermore, these human studies also show that suppression of lipolysis with acipimox abrogated the antagonistic effects of GH on insulin-stimulated muscle glucose uptake[7,8]. In addition to effects on lipolysis, GH treatment for 5 weeks in female individuals with obesity suppresses the activity of lipoprotein lipase, an enzyme that plays a part in lipid clearance from the blood stream by hydrolyzing triglycerides from circulating chylomicrons and VLDLs[38]. However, short-term GH treatment in young lean male individuals has no effect on the turnover rate of VLDL-associated triglycerides[39]. Taken together, these findings suggest that in humans, GH actively increases circulating FFA levels by increasing lipolysis and by inhibiting FFA uptake into adipose tissue. Theoretically, novel compounds could be developed that specifically target the lipolytic and anabolic effects of GH, respectively.

Patients with GH-deficiency and acromegaly.

The physiological and clinical significance of the lipolytic effects of GH have been tested in adult patients with GH-deficiency (GHD) during fasting[40] as well as during a hypoglycaemic clamp[41]. Interestingly, these studies show that GH is critical for lipid mobilization and utilization when glucose availability is limited. Also well-documented is that long term GH replacement in patients with GHD induces sustained lipolysis and a gradual reduction in fat mass towards normal levels (Figure 2)[42].

By contrast, long-term and unregulated GH excess might cause glucose intolerance, as seen in patients with active acromegaly[43]. Interestingly, active acromegaly is also associated with reduced fat mass, increased lean body mass and increased serum FFA levels. Disease control reverses insulin resistance[43] and this effect occurs together with an increase in fat mass and a decrease in lean body mass[44]. The insulin antagonistic effect of GH exposure is rapidly reversible and preceded by elevations in serum FFA levels, as demonstrated in a study in adult patients with GHD where GH was infused at different time points relative to the assessment of insulin-stimulated glucose uptake (Figure 3)[45]. Thus, a causal link between the lipolytic effects of GH and the antagonistic effects GH has on insulin-stimulated glucose uptake is undisputed, but the underlying molecular mechanisms are not yet fully settled.

In contrast to what has been reported in humans with insulin resistance induced by lipid infusion[46], no evidence has been obtained from human studies that GH inhibits insulin signalling through insulin receptor substrate 1 (IRS1)-associated phosphatidylinositol 3-kinase (PI3K) and AKT[47,48]. Of note, this mechanism of action for insulin resistance has been reported in GH-treated rodents[49,50]. However, a study in healthy human volunteers has shown that GH infusion is accompanied by elevated serum FFA levels and suppresses pyruvate dehydrogenase activity, which indicates that substrate competition between glucose and lipid intermediates at the entry point of the citric acid cycle could be one causative mechanism of GH-mediated insulin resistance[51].

These metabolic effects of GH also raise the question whether targeting the GH receptor (GHR) with either exogenous GH or the GH antagonist pegvisomant would prove useful for the treatment of insulin resistance and/or obesity. Indeed, a meta-analysis of studies of GH treatment for obesity in adults demonstrate a moderate but statistically significant reduction in adipose tissue mass, in particular visceral fat, together with a more favorable lipid profile and an increase in lean body mass as compared with placebo[52]. However, the analysis also shows that GH treatment concomitantly increases fasting levels of plasma glucose and insulin[52]. Conversely, pegvisomant treatment might be hypothesized to improve insulin sensitivity, which was reported in young patients with type 1 diabetes mellitus treated with pegvisomant for 4 weeks[53]. However, the treatment was associated with a pronounced reduction in serum IGFI levels towards the range seen in hypopituitarism, which is not surprising given that GH stimulates IGF1 production[53]. In patients with type 2 diabetes mellitus (T2DM) (without acromegaly), no experimental data are available, but pegvisomant therapy is likely to increase fat mass, which is not favorable in the context of T2DM. As such, it might be premature to conclude a role for either GH or pegvisomant beyond the licensed indications.

Taken together, over 50 years of research in healthy human volunteers and patients with GHD or acromegaly document a potent lipolytic effect of GH, which predominates in the fasting state and constitutes a physiologic mechanism to provide energy from fat depots. However, unregulated and sustained GH excess might cause elevated circulating FFA levels, resulting in overt glucose intolerance. The molecular mechanisms responsible for the lipolytic effects of GH remain unresolved although, as described below, current studies provide evidence of relevant pathways[54,55].

GH-induced intracellular signalling

GH exerts its intracellular effects by binding to preformed, single-pass transmembrane receptor dimers on the cellular surface. Within adipose tissue, GHRs are expressed on preadipocytes, mature adipocytes and the assorted cells (including, fibroblasts, immune cells, and endothelial cells) that comprise the stromal vascular fraction[56]. The GHR does not have kinase activity; however, GHR is constitutively associated with two non-receptor tyrosine kinases, Janus kinase 2 (JAK2) and SRC kinase[57]. An important 2008 study showed that an agonist-induced conformational change in the GHR can determine the choice of the intracellular signalling pathway[58]. For example, GH binding to the GHR leads to a conformational change of the receptor, which unmasks the catalytic domains of JAK2 and enables transphosphorylation of adjacent JAK2 molecules[59]. Independent of JAK2, GH binding to the GHR also leads to autophosphorylation of SRC kinase[58,60]. Of note, the profound effects of GH on all tissues, including adipose tissue, is largely dependent on GH-induced activation of JAK2 and SRC kinase pathways. As discussed later, JAK2 and SRC signalling downstream of GH activate different signalling pathways and differentially regulate physiological processes within adipose tissue. Therefore, the ability of GH to activate specific pathways downstream of GHR binding holds interesting therapeutic potential.

Researchers investigating GH signalling pathways have extensively studied phosphorylation and activation of the signal transducer and activator of transcription (STAT) family of transcription factors downstream of JAK2[61–64]. After GH binding to GHR and JAK2 transphosphorylation, JAK2 phosphorylates the GHR at several tyrosine residues leading to the recruitment and phosphorylation of several STAT proteins, including STAT1, STAT3, and STAT5[65,66]. The phosphorylated and dimerized STAT proteins then translocate to the nucleus, where they bind to gamma-activated site (GAS) DNA motifs to regulate the expression of GH target genes. Of the various STAT proteins, two isoforms of STAT5 exist and appear to mediate the majority of the biological effects of GH[65]. These isoforms, STAT5A and STAT5B, have over 90% sequence homology[67]. In humans, STAT5B is the major mediator of GH action. Moreover, in both humans and mice, mutation or ablation of STAT5B leads to GH insensitivity[68–71].

As mentioned earlier, phosphorylation and activation of SRC kinase through the GHR is independent of JAK2[60,72]. Activated SRC kinase phosphorylates Protein Kinase C (PKC) and activates the extracellular signal regulated kinases (ERK1 and ERK2) and MAPK signalling pathways[72]. Through the MAPK–ERK pathway, GHR can also activate the PI3K–AKT pathway via phosphorylation of IRS1 and/or IRS2, as evidenced by studies in mice[57]. Of note, AKT-mediated activation of PDE3B would be expected to inhibit GH-induced lipolysis. However, our new observations show that a single bolus of GH is sufficient to repress PDE3B mRNA levels in subcutaneous adipose tissue of human volunteers (unpublished observation). Interestingly, bovine GH (bGH) transgenic mice have increased adipose tissue expression of the p85α regulatory subunit of PI3K, whereas the opposite is found in GH-deficient mice[49]. In bGH-expressing mice, the increased expression of p85α regulatory subunit homodimers can enable them to bind and sequester IRS1[73], thereby preventing the activation of PI3K and resulting in insulin resistance. However, as stated earlier, studies in humans have demonstrated that GH-induced insulin resistance is independent of effects on MAPK–ERK and PI3K signalling pathways[45,47,48,74,75]. Thus, GH-induced intracellular signalling substantially alters the physiology of adipose tissue through its actions on various metabolic pathways (Figure 1).

When evaluating the role of GH in any metabolic pathway, the interplay between GH and IGF1 must also be considered. In 1985, Howard Green and colleagues proposed “a dual effector theory of GH action”, in which GH induces preadipocyte differentiation, whereas IGF1 stimulates clonal expansion of the differentiated adipocytes[76]. Thus, GH and IGF1 have well established and distinct functions in adipose tissue. Importantly, there are other well-known activities that clearly differentiate GH versus IGF1 actions: first, GH is diabetogenic, whereas IGF1 is not[6]; second, GH stimulates glomerulosclerosis**[G]**, whereas IGF1 does not[77]; and third, growth in mice is differentially influenced by the two hormones. For example, one report shows that GH contributes 14%, IGF1 contributes 35%, GH and IGF1 together contribute 34% and other factors contribute 17% to total mouse growth[78]. In the context of this Review, it is important to note that GH is lipolytic, whereas IGF1 is not. Thus, the role of IGF1 in lipolysis is not discussed; however, an indirect role of IGF1 on lipolysis is possible via an influence on adipose tissue structure and function (for example, adipokine expression, senescence, fibrosis and depot differences). Future studies are

necessary to delineate the specific molecular targets specifically effected by either GH or IGF1 actions in adipose tissue.

Mechanisms of GH-induced lipolysis

Studies in humans, mice and cellular models have elucidated some of the molecular mechanisms of GH-induced lipolysis. For example, GH treatment in cultured adipocytes or patients with obesity has been shown to increase phosphorylation and activation of HSL to stimulate lipolysis[79,80]. During weight loss in patients with obesity, GH administration regulates HSL activity in adipose and muscle tissue[80]. In rat adipocytes, GH treatment decreases the levels of inhibitory G protein coupled receptor alpha subunits, resulting in a decrease in sensitivity to anti-lipolytic agents[81,82]. Also, GH treatment of human adipose tissue represses lipoprotein lipase activity both *in vivo*[80] and *in vitro*[38,83] (not shown in Figure 1). Interestingly, in adults with GHD, 1 month of GH treatment down-regulates mRNA expression of CIDEA[84], a lipid droplet protein that protects against lipolysis[84,85]. Furthermore, G0S2 expression in adipose tissue is suppressed during fasting, where both GH secretion and lipolysis are elevated[86], but it is unclear if this effect is directly mediated by GH[84,86,87]. Finally, either STAT5 or JAK2 ablation specifically in adipose tissue of mice decreases lipolysis[88–90]; however, this effect is not specific to GH-induced lipolysis, and the detailed molecular mechanisms underlying this reduction are unknown. The net effect is that GH strongly induces lipolysis in adipose tissue (Figure 1). Importantly, the above studies warrant further identification of the precise molecular pathways and lipolytic signals that are triggered by GH.

Studies from our research groups have identified a molecular mechanism that links GH-mediated lipolysis and insulin resistance in human adipocytes. In this work, we carried out experiments in human volunteers, mouse models and cultured cells to demonstrate that GH suppresses the expression of FSP27 at both the mRNA and protein level[54,55] (Figure 1). Of note, FSP27 levels are associated with insulin sensitivity in humans with obesity[26,85,91], and nonsense mutation of FSP27 in humans leads to increased lipolysis, hypertriglyceridemia and insulin resistant diabetes mellitus.[92]. In addition, adipose tissue-specific disruption of FSP27 causes insulin resistance in high fat diet-fed mice[93].

The expression of FSP27 is regulated by peroxisome proliferator-activated receptor gamma (PPARγ)[28,85,94]. Our studies[54,55] tested the hypothesis that GH transcriptionally controls the lipolytic flux of FFAs by affecting PPARγ activity to downregulate FSP27 in adipocytes. Indeed, GH-induced modulation of FSP27 expression is mediated through activation of both MEK–ERK and STAT5-dependent intracellular signalling pathways, which interact to differentially manipulate the activity of PPARγ on the FSP27 promoter[54]. For example, GH induces MEK–ERK activation, which causes PPARγ inactivation. As a counter-regulatory mechanism, GH induces phosphorylation of STAT5, which directly activates PPARγ. However, the GH-induced MEK–ERK pathway is the dominant pathway, leading to PPARγ inactivation, decreased FSP27 expression and thereby increasing lipolysis and insulin resistance[55] (Figure 1). More studies are required to dissect the molecular interaction between FSP27 and PPARγ and to identify any additional mechanistic pathways that are regulated by GH to induce lipolysis.

Previous in vitro studies in human HEK293 cells have demonstrated that MAPK pathway activation decreases PPARγ transcriptional activity via MEK–ERK activation[95], which leads to PPARγ downregulation[95]. Furthermore, many studies have linked PPARγ Ser^{273} phosphorylation with the development of insulin resistance in mice[96–98]. Interestingly, overexpression of FSP27 in cultured primary human adipocytes as well as exposure to a GHR antagonist, pegvisomant, can block MEK–ERK-mediated phosphorylation of PPARγ at Ser^{273}, which stabilizes PPARγ in the nucleus and prevents GH-induced lipolysis and insulin resistance[54,55]. Thus, these studies identify a novel molecular MEK–ERK–PPARγ–FSP27 pathway that regulates GH-induced lipolysis and insulin resistance. In addition, the findings suggest that pegvisomant treatment maintains insulin sensitivity in patients with acromegaly, at least in part, through its regulation of FSP27 expression. Furthermore, the MEK–ERK and PPARγ-dependent mechanism suggests several molecular targets of intervention to reduce GH-dependent lipolysis. Many of these targets already have pharmacological agents in clinical use, including: MEK inhibitors (Trametinib), PPARγ agonists (Thiazolidinediones) and anti-lipolytic agents (Acipimox)[8].

Insights from mouse models

Extremes in the GH–IGF1 axis in both humans and animal models provide valuable insight as to the actions of GH on adipose tissue *in vivo*. In particular, mouse models, due to their genetic tractability, have been instrumental in deciphering the physiological and metabolic effects of GH action.

Mouse models with altered GH activity.

Different mouse models have been generated with altered GH action (for select examples, see Table 1). For example, mice engineered to express bGH have elevated GH action. For a model of decreased GH action, researchers can utilize GHR antagonist (GHA) mice, which is similar to human congenital GH deficiency, and inducible adult GH deficiency models (aiGHRKO and AOiGHD mice), which are similar to adult human GHD. Finally, mouse models with no GH action are available, either with complete GH-resistance found in GHR gene disrupted (GHR$^{-/-}$) mice or with GH-deficiency found in Ames and Snell dwarf mice (Table 1).

Although comparable human clinical conditions do not exist, tissue-specific mouse lines also allow one to explore the role of GH in selected tissues and/or cell types. Relevant to adipose tissue, two separate adipose tissue-specific GHR gene disrupted or knockout (FaGHRKO and AdGHRKO) mouse lines have been characterized[99,100]. In addition, as the majority of circulating IGF1 is produced by hepatocytes, liver-specific GHR knockout (LiGHRKO) mice allows the evaluation of other tissues, including adipose tissue, under conditions of elevated GH and low IGF-1. This condition resembles a fasting state and enables the *in vivo* molecular dissection of IGF1 independent and dependent roles of the GH signalling axis[101] (Table 1). Of note, several of these mouse lines share features with clinical conditions (for example, bGH mice with acromegalic gigantism and GHR$^{-/-}$ mice with Laron Syndrome. However, in addition to size and species differences, most of the

genetically engineered mice have life-long disruption of the GH–IGF1 axis and/or perturbations in the normal pulsatile action of GH.

In these mouse models, excess GH reduces overall adiposity whereas the opposite condition increases adiposity. For example, adult bGH mice and LiGHRKO mice are leaner than littermate controls, having notably less fat mass for most of their adult lives[101–103]. Conversely, adult mice with decreased GH action (that is, Ames, Snell, GHA, FaGHRKO, AdGHRKO, GHR$^{-/-}$, AOiGHD and aiGHRKO) have increased fat mass[99,102,104–108]. Importantly, body composition trends are age-dependent and sex-dependent, highlighting the need to consider these factors in experimental design. For example, longitudinal body composition analyses in bGH mice show resistance to midlife gains in adipose tissue, but these mice have greater fat mass at younger ages (<3 months of age for males and <4 months of age in females), and bGH female mice have a delayed and less exaggerated difference in body composition as compared with bGH males[103]. In addition, LiGHRKO mice have a very similar trend to bGH mice in fat mass gains[101]. In contrast, Ames and Snell mice have increased adiposity[104,109]; however, this trend is attenuated in Ames mice at older ages[106], whereas GHA mice continue to see fat mass gains with advancing age[110].

Longitudinal body composition data are available for a variety of other lines including GHR$^{-/-}$, FaGHRKO, AdGHRKO and aiGHRKO mice; all lines with reduced GH action in adipose tissue have increased fat mass throughout life, albeit the increase in adipose tissue mass is less exaggerated for females[105,107,110]. Upon challenge with a high fat diet, bGH mice are resistant to obesity, with preferential accumulation of lean tissue instead of adipose tissue[111,112], whereas GHA, Ames and GHR$^{-/-}$ mice are more susceptible to gaining additional fat mass when compared with wild type mice[109,111,113,114]. Interestingly, despite increased obesity, Ames dwarf, GHA and GHR$^{-/-}$ mice are resistant to the detrimental effects of high fat feeding on glucose homeostasis and insulin sensitivity[109,111,113,114], which is consistent with the idea of GH-induced lipolysis as a causative factor for insulin resistance.

Adipokine expression.

Adipokine secretion is altered by GH in both mice and humans, although the molecular pathways have yet to be fully elucidated. Interestingly, GHR$^{-/-}$ mice and patients with Laron Syndrome exhibit increased leptin levels, which mirrors the increase in adipose tissue mass. Similarly, reduced circulating leptin (which inhibits appetite) is observed in bGH transgenic mice and patients with acromegaly[115,116]. Likewise, acute GH stimulation of adipocytes *in vitro* leads to increased leptin secretion in a STAT5-independent manner[117].

Similar to leptin, levels of circulating adiponectin (which regulates glucose and lipid metabolism) are increased in GHR$^{-/-}$ mice and patients with Laron Syndrome[99,118]. Although differences in the literature exist regarding adiponectin levels in patients with acromegaly, GH treatment in human adipose tissue *in vitro* and in rodents *in vivo* leads to reduced adiponectin expression and secretion[119]. This reduced expression of adiponectin can be attributed to a STAT5-mediated transcriptional repression on the adiponectin promoter[120]. By contrast, GH levels are inversely correlated to ghrelin (which increases appetite) levels; that is, GH treatment acutely decreases circulating ghrelin levels in children with GHD, and

remission of acromegaly after surgical therapy increases total ghrelin levels[121,122]. Other adipokines have been evaluated in several of these mouse lines (reviewed in[56]).

Differences in adipose tissue depots.

Adipose tissue is a heterogeneous tissue with well-documented depot differences in cellular developmental origin, proliferative capacity, glucose and lipid metabolism, insulin sensitivity, fatty acid composition, cytokine pattern, thermogenic ability and vascularization. Importantly, key proteins in lipolysis, such PLIN1 and HSL, have expression levels that have been reported to vary not only by depot but also by obesity status[123]. Thus, it might not be surprising that the effect of GH on adipose tissue differs depending on the depot in both humans and mice. Interestingly, the depot most affected seems to vary by species. In humans, the visceral depot is the most affected by alterations in the action of GH, and the greatest reduction of white adipose tissue mass occurs in the visceral depot in patients with active acromegaly[124]. In addition, in humans with GHD, GH treatment decreases total body fat, with the largest decrease observed in the visceral depots[125,126].

Much of our understanding of how GH affects adipose tissue in a depot-specific manner comes from studies done in mice, where multiple depots can be compared in a single animal. Overall, a reduction in GH action, as seen in $GHR^{-/-}$ and GHA mice, causes a striking and specific enlargement of the subcutaneous fat depot, whereas an excess in GH action appears to decrease the mass of all depots similarly[102,107,110]. Importantly, despite similar reductions in the mass of adipose tissue in these studies[102,107,110], molecular signatures of the adipose tissue depots reveal a more significant genotype effect in subcutaneous depots as compared to other depots. For example, compared with wild type mice, the subcutaneous adipose tissue of bGH mice shows a striking increase in gene expression pathways related to T cell infiltration and activation, but only modest changes are seen in epididymal adipose tissue[127]. Furthermore, $GHR^{-/-}$ mice show subtle but distinctive expression signatures between epididymal and subcutaneous adipose tissue depots[128]. These data confirm that adipose tissue mass alone might not be a sufficient readout of the effect of GH on a specific adipose tissue depot.

Many examples in the literature support depot-specific differences at the cellular or molecular level (reviewed in ref.[56,129]). For example, histological analysis of adipose tissue sections from mouse lines with extremes in GH action show substantial alterations between the different models in morphology and adipocyte size in subcutaneous adipose tissue; however, the epididymal adipose tissue depot is fairly uniform among mouse lines[56]. Furthermore, the capacity of preadipocytes for proliferation and differentiation is dependent on the depot of origin of the isolated cells[130]. Of note, adipose tissue depot differences in insulin receptor, IGF1 receptor and GHR have also been reported, with highest IGF1 receptor (IGF1R) expression in epididymal and mesenteric depots, higher insulin receptor expression in retroperitoneal and mesenteric depots and highest GHR expression in the retroperitoneal depot[131]. This finding is important for the hormone responsiveness of specific depots. In addition, the levels of pregnancy-associated plasma protein-A (PAPPA), which might increase local IGF1 action through its proteolytic activity, are statistically significantly higher in visceral adipose tissue from adipose tissue explants from patients with

obesity and mouse mesenteric adipose tissue samples from wild type, bGH and GHR$^{-/-}$ mice, which could also contribute to depot-specific responses to the GH–IGF1 axis[132,133]. Importantly, adipocyte-specific deletion of GHR versus IGF1R in mice[134] suggests that the depot differences are mainly GH-dependent; that is, GHR deletion specifically in adipocytes using an adiponectin Cre promoter results in an increase in adipose tissue mass with the subcutaneous depot most effected. By contrast, IGF1R deletion in adipocytes is associated with a 25% reduction in adipose tissue mass that is uniform among the depots[134]. Collectively, these observations underscore the need to study more than one adipose tissue depot and other cell types in addition to adipocytes to fully understand the role that GH has on adipose tissue metabolism.

Emerging areas of research

Cellular senescence in adipose tissue.

Senescent cells are cells that undergo irreversible cell-cycle arrest, and the tissue accumulation of senescent cells is common during normal aging and in response to various metabolic stressors such as oncogene activation, DNA and oxidative damage, or metabolic insults like high glucose[135]. In addition to growth arrest, senescent cells produce a senescence-associated secretary phenotype, which is a complex mixture of secreted factors that include proinflammatory cytokines, chemokines, growth factors and proteases[136]. Collectively, the accumulated senescent cells and their secretory products induce a potent proinflammatory state that alters tissue inflammation, angiogenesis and fibrosis[135]. The cellular growth arrest occurring in senescence is seemingly regulated through two main pathways, p16^{INK4a}–Rb and p53–p21^{CIP1} (REF[137]). Importantly, administration of senolytic agents, which selectively eliminate senescence cells, have been shown to improve physical function and increase longevity in mice[138].

Increases in cellular senescence are commonly associated with obesity and type 2 diabetes mellitus[139]. Furthermore, the accumulation of these cells can have a major effect on age-related adipose tissue dysfunction, leading to lipotoxicity and chronic inflammation, irrespective of adipose tissue mass[140,141]. Interestingly, GH action is positively correlated with the accumulation of senescent cells in adipose tissue of mice. More specifically, bGH mice (10 months of age) and GH-injected (19 months of age) mice accumulate more senescent cells and have higher p16^{INK4a} expression in adipose tissue than their littermate controls[142]. Conversely, primary subcutaneous preadipocytes from 18-month old GHR$^{-/-}$, Ames and Snell dwarf mice, exhibit decreased burden of senescent cells and lower p16 ^{INK4a} expression (a marker of senescence) in most adipose tissue depots compared with control littermates[142]. In contrast to 18-month old GH deficient Ames dwarf mice and GHR$^{-/-}$mice, 18 month old GHA mice do not have any change in adipose tissue senescent cell burden despite considerable obesity[143]. This finding suggests that senescent cell burden is more related to aging than to the level of GH action. Alternatively, the protection against generating senescent cells afforded by decreased GH action, low IGF1 or improved insulin sensitivity in the GHA mice is counterbalanced by the extreme obesity of GHA mice with advancing age.

Of note, the p53 tumour suppressor pathway is also upregulated by GH in adipose tissue, and this pathway has been suggested to mediate the insulin resistance seen with acromegaly in bGH mice[144]; however, the influence of p53 on adipose tissue senescence is not established in these studies. Relevant to this Review, an increase in the number of senescent preadipocytes contributes to a decline in insulin responsiveness and increase the overall lipotoxicity in the tissue[145,146]. Taken together, GH-induced alteration in senescent cells probably influences the lipolytic potential of adipose tissue, although this hypothesis has yet to be thoroughly studied.

Adipose tissue fibrosis.

An important non-cellular component of white adipose tissue is the extracellular matrix (ECM), which surrounds individual adipocytes and provides structural support for the tissue. Of note, adipose tissue is one of the few tissues in the body that undergoes constant alterations in cell size, which requires a flexible, accommodating ECM. Therefore, when an excessive accumulation of ECM proteins or fibrosis occurs, the rigid ECM impedes adipocyte growth and promotes local and systemic pathologies, including chronic inflammation, immune cell recruitment, insulin resistance and cell death[147,148]. Interestingly, a 2018 study from our research group showed that GH action is positively correlated with ECM deposition. For example, bGH mice and LiGHRKO have excess fibrosis and collagen deposition in adipose tissue, whereas GHA, AdGHRKO and FaGHRKO mice (Table 1) have reduced collagen content[100,149]. This phenomenon is most prominent in the subcutaneous fat depot and correlated better with GH action rather than IGF1 action. Whether the increase in fibrosis is a direct effect of GH or an indirect effect of the hormone's potent lipolytic action remains to be determined. Regardless, the marked fibrosis in bGH mice probably contributes to the limited ability of these mice to store lipids in adipose tissue and might influence the capacity of a depot for lipolysis.

Intra-depot adipocyte heterogeneity.

In addition to depot specific differences found in adipose tissue, individual white adipocytes within a single depot might differ in insulin-stimulated glucose uptake, maximal lipogenic rate, response to catecholamines, uptake of free fatty acids, as well as regulation of oxidative phosphorylation and glycolysis[149–155]. Indeed, lineage tracing analyses have demonstrated that adipocytes, even within a single adipose tissue, develop from different developmental origins[156,157]. These studies are further supported by genetic mouse models, including ablation of HSL and fat-specific knockout of the insulin receptor, which both lead to a bimodal distribution of adipocyte cell size[158,159]. Similarly, GH excess in bGH mice alters adipocyte size distribution in subcutaneous adipose tissue, yielding a subset of very small adipocytes[149]. Thus, the genetic changes in these mouse models unmask an intrinsic heterogeneity within white adipocytes of a single adipose tissue depot.

In a 2019 study, we identified three distinct subpopulations of white adipocytes that have clear phenotypic and functional differences, which we termed Type 1, Type 2 and Type 3 adipocytes[160]. In comparison to Type 1 cells, Type 2 and 3 adipocytes display increased insulin-mediated glucose uptake and tend to have increased *de novo* lipogenesis. By contrast, stimulation of Stat5-Tyr^{694} phosphorylation by GH is highest in Type 2

adipocytes[160]. As insulin and GH positively and negatively regulate adipocyte size, respectively, we hypothesize that the differential responses of these adipocyte subpopulations might, at least in part, contribute to the changes in size distribution observed upon adipose tissue-specific ablation of insulin receptor or in bGH mice. Thus, in addition to depot-specific effects, distinct responses of adipocyte subpopulations might mediate GH action in adipose tissue. Furthermore, a 2019 study utilizing transcriptomic profiling of clonally grown mesenchymal progenitor cells identified four adipocyte subtypes in humans, suggesting that adipocyte subpopulations might also mediate physiological responses in humans[161].

Conclusions

From the historic work in humans showing GH activation of FFA flux, to mechanistic studies that show the inhibiting effect of GH on insulin-induced lipogenesis, to the most recent work depicting the effect of GH effect on FSP27 and PPARγ, we now have a clearer understanding of additional molecular ‘players’ in GH-induced lipolysis. To complement this work, data derived from mice with altered GH action has led to the discovery of differential effects of GH on adipose tissue depots as well as the participation of GH in mediating collagen deposition and senescence, primarily in subcutaneous fat depots. New and exciting data that reveal different populations of adipocytes in white adipose tissue depots and perhaps the ability of GH to target its lipolytic effect to a subpopulation of adipocytes in a given depot are indeed intriguing.

GH is well known to strongly induce whole body lipolysis and the molecular mechanisms responsible for the lipolytic action of GH within the adipocyte are now better understood. However, future studies that consider the surrounding tissue milieu and inherent subcellular differences on these molecular processes should be evaluated. For example, researchers could evaluate the influence of the unique adipokine profile induced by GH on lipolysis, or the responsiveness of distinct adipocyte subpopulations to GH as well as the variation in lipolytic and lipogenic machinery among these subpopulations. Also of interest are GH-induced alterations in senescent cells, the senescent associated secretory proteins, and depot dependent differences in adipose tissue fibrosis. All of these factors probably directly or indirectly influence the balance of adipogenic, lipogenic and lipolytic capacity of adipose tissue. As the pharmacological inhibition of lipolysis restores insulin sensitivity during GH exposure in humans[8] and FSP27 overexpression inhibits GH-induced insulin resistance in human adipocytes, the regulation of GH action in adipose tissue might be a valuable therapeutic target to improve metabolic health in patients with acromegaly.

In this Review, we have updated the decades’ old observation of the effects of GH on adipose tissue and described new molecular and cellular mechanisms. A common denominator of the metabolic effects of GH on adipose tissue lipolysis appears to be insulin antagonism leading to fat loss as well as reduced glucose uptake. Such actions are also potential targets for treating our major health threats of obesity and T2DM.

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GLOSSARY

GH-deficiency	a rare disorder characterized by the inadequate secretion of GH and can be categorized into congenital or acquired, and/or childhood or adult-onset
Acromegaly	a condition caused by hypersecretion of GH from a pituitary tumor that is managed by surgical tumor removal or medical control
Glomerulosclerosis	a degenerative process that involves scarring within the renal glomeruli of the kidney
Laron Syndrome	a rare condition of GH resistance characterized by short stature, which is often caused by mutations in the GHR gene and is inherited in an autosomal recessive manner
Panhypopituitarism	Inadequate production or absence of anterior pituitary hormones. Also known as hypopituitarism
Senolytic agents	small molecules that can selectively target and kill senescent cells

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Key points

- GH exposure in humans potently stimulates the release of free fatty acids (FFAs) from adipose tissue into the circulation after a lag phase of 1–2 hours and with a peak effect after 3–4 hrs.
- This GH-induced increase in circulating FFAs is causally linked to the antagonistic effects of GH on basal and insulin-stimulated glucose uptake.
- Overexpression of FSP27 or exposure to a GHR antagonist, pegvisomant, can block the diabetogenic effects of GH.
- GH-induced activation of the MEK–ERK pathway has a key role in PPARγ inactivation and FSP27 downregulaton, thus increasing lipolysis and insulin resistance.
- GH impacts adipose tissue in a depot-specific manner and influences other features of adipose tissue (for example, senescence, adipocyte subpopulations and fibrosis) all of which could influence lipolysis.

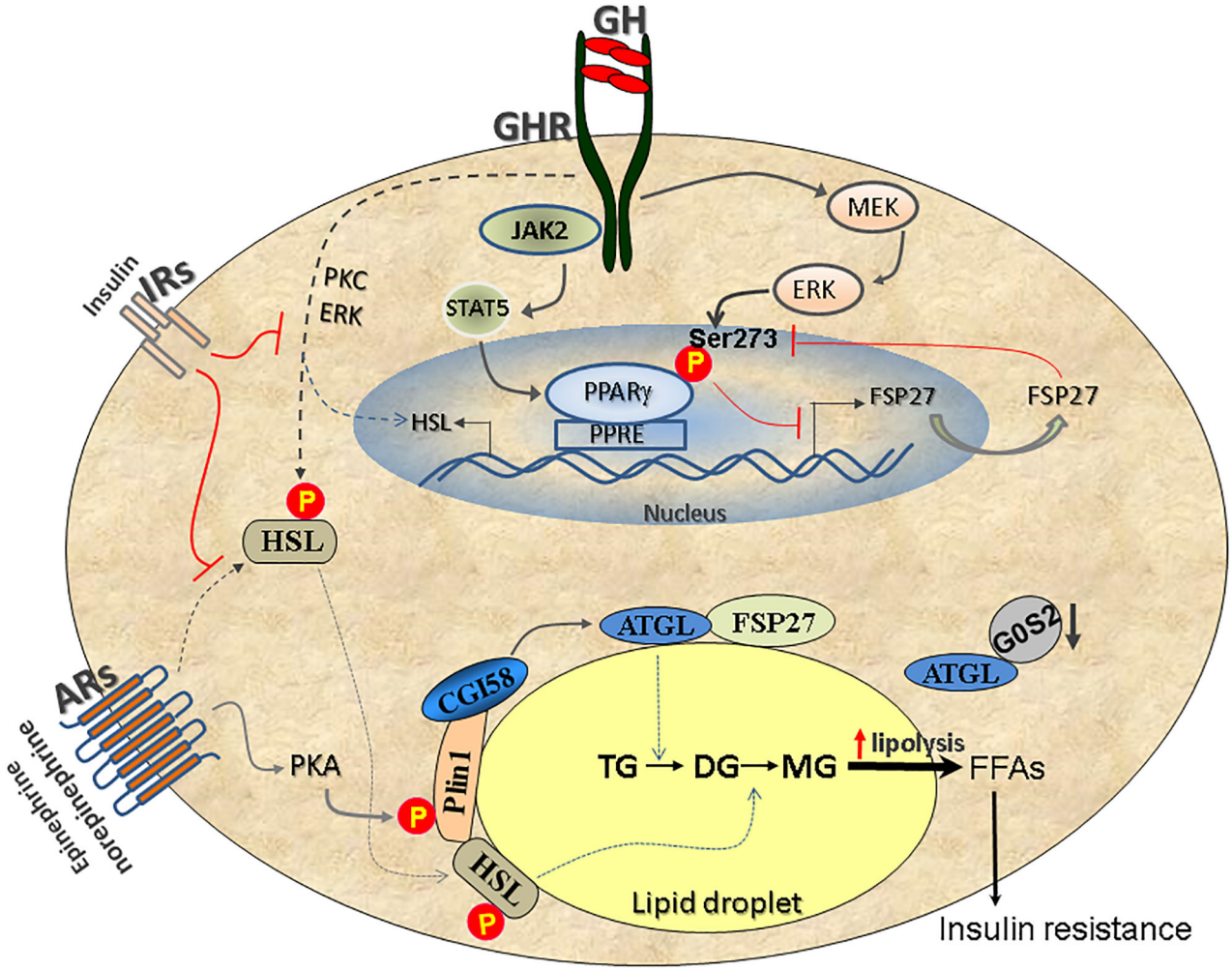

Figure 1: GH-induced lipolysis and insulin resistance.

GH-induced signaling activates the MEK–ERK pathway, which causes phosphorylation of PPARγ at Ser273. This event results in PPARγ inactivation and FSP27 downregulation. The decrease in FSP27 expression leads to increased lipolysis and higher circulatory free fatty acids (FFAs), a hallmark of insulin resistance and type 2 diabetes mellitus. PPARγ-regulated FSP27 feeds-back to stabilize PPARγ in the nucleus. Parallel to the above pathway, GH binding to its receptors also activates STAT5, which is a positive regulator of PPARγ, but the MEK–ERK activation pathway predominates to inactivate PPARγ. In addition, GH induces lipolysis by activating HSL and by increasing the de novo expression of HSL mRNA via the activation of PKC and ERK. Adrenergic signaling via adrenergic receptors (ARs) has a parallel role in the stimulation of lipolysis via activating the lipolytic cascade involving the lipases ATGL, HSL and MGL. Finally, insulin signalling via insulin receptors (IRs) inhibits lipolysis by suppressing GH-induced PKC and ERK activity as well as the adrenergic pathway.

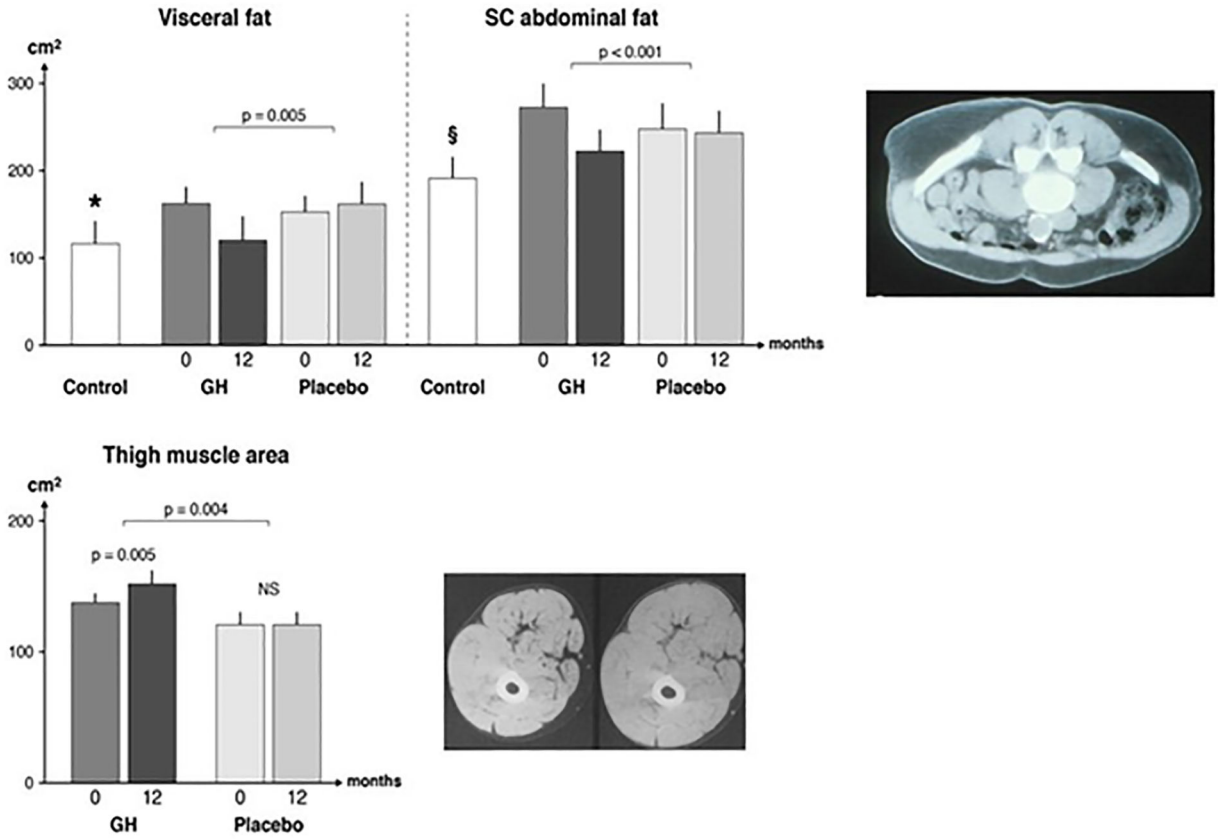

Figure 2: Body composition assessed by CT in adults with GH-deficiency.

Patients with GH-deficiency participated in a double-blind parallel study receiving either GH or placebo. The patients were studied at baseline (0) and after 12 months treatment (12). The results were compared with a reference population ($n = 29$) matched for age and sex (control). The P values denote a comparison of changes between the GH and placebo groups, respectively. Visceral fat lower in the reference group as compared to all patients at baseline, as shown by * ($P = 0.02$). Subcutaneous fat was lower in the reference group as compared to all patients a baseline, as shown by § ($P = 0.03$). The data were originally presented in[42]. The CT images are representative scans from the mid-umbilical region before (upper) and after (lower) GH treatment (upper panel). This scan derives from a separate trial[125] and is reproduced with the permission from the principal investigator. The lower panel includes a representative CT scan from the first study[42] before (right) and after (left) GH treatment. Upper CT image panel reproduced with permission[125]. Lower CT image panel reproduced with permission from REF[42].

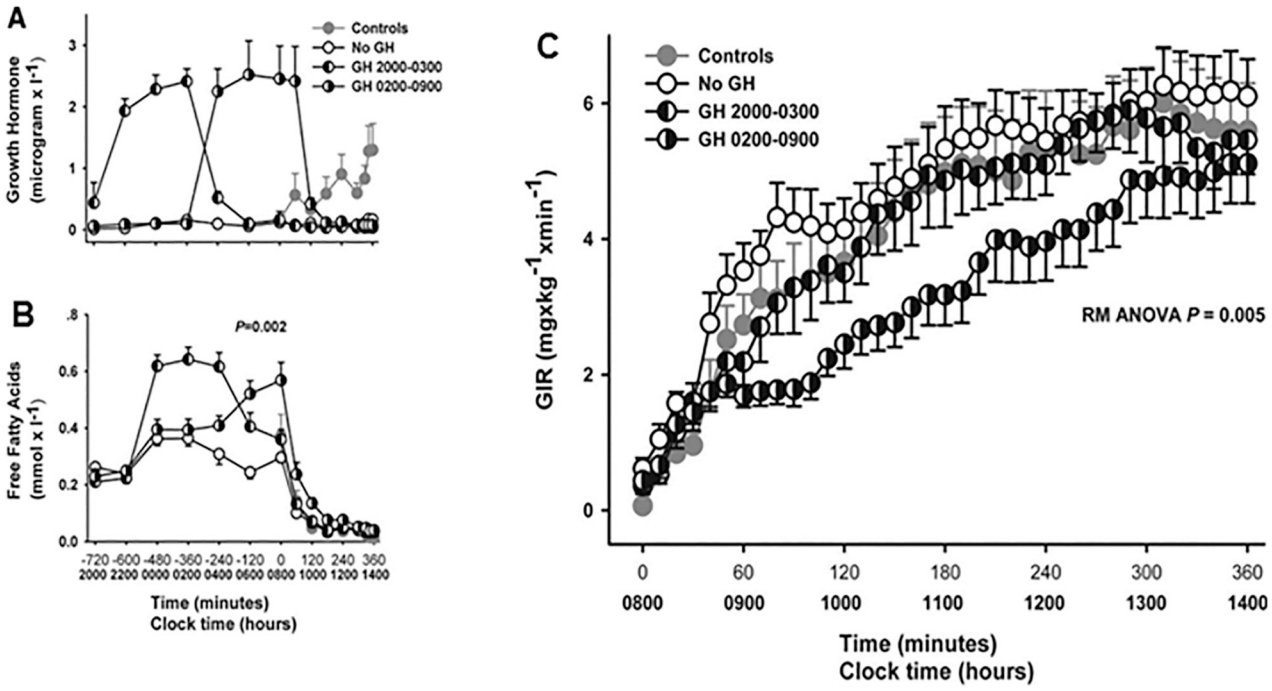

Figure 3: Effects of GH in humans on FFA levels and insulin sensitivity.

Effects of a 7-h GH infusion terminated at either 03h or 09h as compared with no GH in adult hypopituitary patients with GH-deficiency. A reference group (Control) of healthy, age-matched and sex-matched volunteers was studied once without receiving any treatment. Panel a: GH levels. Panel b: FFA levels. Panel c: glucose infusion rate (GIR) as assessed by a euglycemic clamp starting at 08 h. The figure provides evidence that ongoing GH infusion (GH from 02:00 – 09:00) induces insulin resistance as demonstrated by the reduced GIR, and this is temporally associated with elevated FFA levels as shown in panel b. Adapted from a previously published study[45] and used with permission.

Table 1:

Characteristics of mouse lines with altered GH action

Name of mouse line	bGH	LiGHRKO	FaGHRKO	AdGHRKO	AOiGHD	aiGHRKO	GHA	Ames and Snell dwarf mice	GHR$^{-/-}$
GH alteration	Transgenic for bovine GH	Liver specific disruption of GHR	Fat specific disruption of GHR using ap2 promoter driving cre expression	Adipocyte-specific disruption of GHR using adipQ promoter driving cre expression	Adult GH deficiency via somatotroph destruction	Adult GH deficiency via adult inducible deletion of GHR	GHR antagonist gene	Homozygous recessive mutation in Pit-1 (Snell) or prop1 (Ames)	Disruption of GHR gene
General features									
GH action	↑↑	↓ liver; ↑ all extrahepatic tissues	↓ in AT only	↓ in adipocytes only	↓ (10–12 weeks)	↓ (6 weeks)	↓	↓	Absent
GH	↑↑	↑	↔	↔	↓	↑	↑	↓↓	↑
IGF1	↑↑	↓	↑ male	↔	↓	↓↓	↓	↓↓	↓↓
Body weight	↑↑	↓	↑	↔	↔	↓	↓	↓↓	↓↓
Insulin sensitivity	↓	↓	↔	↑	↑	↓	↓↔	↑	↑
Lifespan	↓	↔	↓	N.d.	N.d.	↔ male; ↑ female	↔	↑↑	↑↑
White adipose tissue features									
Mass	↑ young ↓ old	↑ young ↓ old	↑↑	↑↑	↑ (after induction)	↑ (after induction)	↑↑	↑	↑↑
Depot differences	All depots impacted	All depots impacted	All depots impacted	All depots impacted	Sc and Retro	sc	sc	sc	sc
Leptin	↓	↑ female	↑ female ↔ male	↔	↑	↔	↑↑	↑ ↔	↑
Adiponectin	↓	↑	↓ male ↔ female	↓	↔	N.d.	↑	↑	↑↑
Resistin	↓	↑	↔	↓	N.d.	↑ female	↑	↔	↑
Senescence	↑	N.d.	N.d.	N.d.	N.d.	N.d.	↔	N.d.	↓
Fibrosis	↑	↑	↓	↓	N.d.	N.d.	↓	N.d.	↓
Immune Cells**									
M1	↔	N.d.	N.d.	N.d.	N.d.	N.d.	N.d.	N.d.	↑
M2	↑	N.d.	N.d.	N.d.	N.d.	N.d.	N.d.	N.d.	↑
T cells	↑	N.d.	N.d.	N.d.	N.d.	N.d.	N.d.	N.d.	↑

↑, increase; ↔, no change; ↓, decrease; GHR, growth hormone receptor, N.d., no data.

Sc, subcutaneous white adipose tissue; retro, retroperitoneal white adipose tissue; M1, classically activated macrophages; M2, alternatively activated macrophages

* Data obtained from flow cytometry only

Adapted and reused with permission[56] and with data from additional mouse lines[99–101,107,108].