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Biological Effects of Growth Hormone on Carbohydrate and Lipid Metabolism

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Abstract

This review will summarize the metabolic effects of growth hormone (GH) on the adipose tissue, liver, and skeletal muscle with focus on lipid and carbohydrate metabolism. The metabolic effects of GH predominantly involve the stimulation of lipolysis in the adipose tissue resulting in an increased flux of free fatty acids (FFAs) into the circulation. In the muscle and liver, GH stimulates triglyceride (TG) uptake ,by enhancing lipoprotein lipase (LPL) expression, and its subsequent storage. The effects of GH on carbohydrate metabolism are more complicated and may be mediated indirectly via the antagonism of insulin action. Furthermore, GH has a net anabolic effect on protein metabolism although the molecular mechanisms of its actions are not completely understood. The major questions that still remain to be answered are (i) What are the molecular mechanisms by which GH regulates substrate metabolism? (ii) Does GH affect substrate metabolism directly or indirectly via IGF-1 or antagonism of insulin action?

Keywords

GH; metabolism; carbohydrate; lipids; insulin resistance

INTRODUCTION

The first published data on the metabolic effects of growth hormone (GH), which can be dated back to 1948, suggested that GH preferentially induces metabolism of fat and inhibits proteolysis in fasted mice[1]. However, until this date the molecular mechanisms of its action have not been completely resolved. It is now clear that GH may affect substrate metabolism either directly or indirectly via insulin-like growth factor-1 (IGF-1) or the antagonism of insulin action. Thus, in this review we will summarize some of the possible mechanisms by which GH affects substrate metabolism based on studies conducted on rodents and humans. We will also identify the various questions that remain to be answered on this topic.

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The mammalian *GH* gene (also called *GH-normal* or *GH-N*) belongs to a gene cluster that includes the genes for prolactin and some placental lactogens, and is primarily expressed in the somatotroph cells of the anterior pituitary gland2. GH secretion occurs in a pulsatile fashion owing to the action of two hypothalamic factors, growth hormone releasing hormone (GHRH) which stimulates GH secretion, and somatostatin which inhibits GH secretion3. GH secretion is also stimulated by ghrelin, an endogenous GH secretagogue that is primarily secreted by the gastrointestinal tract4. In the circulation, GH is bound to the growth hormone binding protein (GHBP) which is a soluble truncated form of the growth hormone receptor (GHR). GHBP is generated either as an alternative splice form of the GHR transcript (in rodents) or by limited proteolysis of the GHR protein (in humans)5. Thus, GH in the circulation exists as bound and free forms, the predominance of each being dependent on the pulsatile pattern of its secretion.

GH secretion exhibits sexual dimorphism; it is secreted more frequently in females than in males. While this could reflect the differential effects of sex steroids on GH secretion and action (reviewed in6, 7), recent data suggest the existence of sex-specific differences in the GH/IGF-1 axis at birth8. Moreover, inter-species differences in circulating GH profiles have been observed in mammals. In males, GH secretion occurs nocturnally in humans and in 3-4 hour intervals in rodents; while in females, rats have residual GH levels between periods of GH secretion which are absent in humans and mice9.

IGF-1, along with IGF-2, belongs to a family of insulin-like growth factors (IGFs) that share close structural homology to the precursor form of insulin (pro-insulin)10. In the circulation, IGF-1 primarily exists in a ternary complex along with the IGF binding protein-3 or -5 (IGFBP-3 or -5) and the acid-labile sub-unit (ALS), while it can exist in a binary complex with the other IGFBPs (IGFBP-1, -2, -4, -6) in the circulation as well as the peripheral tissues. These binary and ternary complexes modulate the bioavailability of circulating IGFs (reviewed in11). However, a small fraction (less than 5%) of circulating IGF-1 may also exist as free IGF-1.

The somatomedin hypothesis, in its original form, stated that GH promotes somatic growth indirectly via the production of a secreted factor called somatomedin-C (IGF-1)12. It was believed that the liver is the primary source of IGF-1. However, since then this hypothesis has been revised to accommodate data demonstrating that the liver is not the only source of IGF-1. In fact, IGF-1 synthesized by extra-hepatic tissues can exert GH-independent autocrine/paracrine effects in the local environment. GH is also known to have IGF-1-independent effects (reviewed in13). Apart from its effects on growth and development, IGF-1 also has insulin-like effects on metabolism14-16. Furthermore, IGF-1 negatively regulates GH secretion through feedback mechanisms17, 18. Thus, perturbations of IGF-1 levels are often accompanied with altered GH levels and *vice versa*.

Insulin, one of the key regulators of carbohydrate and lipid metabolism, is a peptide hormone synthesized by the β-cells of the pancreatic islets. Insulin is stored in secretory vesicles and is released into the bloodstream in response to increased glucose influx19. Insulin secretion is also regulated by several factors such as glucagon-like peptide-1 (GLP-1) and free fatty acids (FFAs). In the circulation, insulin stabilizes blood glucose levels in an endocrine manner by stimulating glucose uptake by various tissues and suppressing hepatic glucose production (HGP). It also stimulates lipogenesis and represses lipolysis and proteolysis (reviewed in20).

Signal Transduction

An in-depth discussion of all the signaling pathways activated by GH, IGF-1 and insulin is beyond the scope of this review. However, we summarize the predominant intracellular signals transduced by GH, insulin and IGF-1. GH signals via the GHR which is a member of the cytokine receptor superfamily. While the traditional view of the initiation of GH signaling is

that one molecule of GH binds two GHR monomers and induces their dimerization, recent data show that GHR in fact exists as preformed dimers which bind GH21-23. Nevertheless, GH binding to the GHR results in activation of adjacent Janus kinase 2 (Jak2) molecules, cytoplasmic tyrosine kinases associated with the GHR, by trans-phosphorylation. Activated Jak2 phosphorylates the GHR on tyrosine residues, which in turn recruits members of the signal transducer and activator of transcription (STAT) family of transcription factors. Of the various STAT proteins, i.e. STAT 1, 2, 3, 4, 5a, 5b and 6, STAT5b has been widely associated with GH action; although STAT 1, 3, and 5a have also been shown to be recruited by the GHR24, 25. Phosphorylation of the STATs by Jak2 results in their dissociation from the receptor, homo- or hetero- (in the case of STAT 1 and 3) dimerization, and translocation to the nucleus where they modulate the transcription of target genes such as *IGF-1, ALS, and SOCS (*suppressor of cytokine signaling). SOCS proteins represent a family of negative regulators that, among other effects, terminate the GH signal cascade26. Apart from the Jak2/STAT pathway, the GHR can also bind the Src tyrosine kinase and signal via other intermediates as well (discussed below and reviewed in27).

Insulin and IGF-1 bind to their cognate receptors (the insulin receptor (IR) and the IGF-1 receptor (IGF-1R) respectively), which belong to the family of receptor tyrosine kinases. While the receptors have highest affinity for their respective ligands, the IR can also bind the IGFs and the IGF-1R can bind insulin, albeit with lower affinities. Ligand binding induces activation of the receptors by trans-phosphorylation and recruitment of adaptor proteins such as insulin receptor substrates (IRSs) and Src homology/collagen protein (SHC). The adaptor proteins subsequently activate the phosphatidylinositol-triphosphate kinase (PI3K) and/or mitogen-activated protein kinase (MAPK) pathways. These two pathways mediate the various metabolic and mitogenic responses elicited by insulin and IGF-1 (reviewed in20). The insulin/IGF-1 signal cascade is down-regulated by inhibitory serine phosphorylations of the adaptor proteins, or by the dephosphorylation of the receptor by tyrosine phosphatases (reviewed in28).

Several studies have shown the existence of crosstalk between the pathways activated by GH, insulin and IGF-1. GH can activate the MAPK pathway via several mechanisms that can be dependent on or independent of Jak2[29-32]. GHR can also activate the PI3K pathway via phosphorylation of IRS-1 and/or IRS-2[29, 33, 34]. Furthermore, GHR, Jak2, and IGF-1R have been shown to physically interact *in vitro*[35]. Conversely, the IR phosphorylates STAT5b both by direct association and via activation of Jak2[36]. Moreover, SOCS-1 and SOCS-3 can terminate insulin signaling by inhibiting the tyrosine phosphorylation of the IRS proteins or by triggering the proteasomal degradation of the IRS proteins[37, 38]. Thus, the GH, insulin and IGF-1 signaling pathways seem to converge at a level downstream of the receptors, and possibly at the level of the receptors as well. This interplay of the signaling pathways is also reflected in the effects that GH has on substrate metabolism, as will be discussed in the forthcoming sections.

Metabolic effects of GH on the adipose tissue

GH exerts a lipolytic effect predominantly in the visceral adipose tissue, and to a lesser extent in the sub-cutaneous adipose tissue, resulting in increased FFA flux from the adipose tissue[39-44]. Moreover, the GH-resistant *GHR* knockout (GHRKO) mice are more susceptible to diet-induced obesity than the *bovine GH* (*bGH*)-transgenic mice that have increased circulating GH levels[45]. The depot-specific effect of GH could be explained by the fact that GH increases lipolysis by increasing adipose tissue hormone-sensitive lipase (HSL) activity46-49, while its effect on HSL mRNA expression is inconclusive 49-51. One of the mechanisms by which GH may increase HSL activity could be via enhanced agonist-induced stimulation of the β-adrenergic receptors (β-AR) which have been implicated in activating the HSL[52, 53]. Moreover, Lonnqvist *et al.* showed that the visceral adipose tissue was more

responsive to β-AR-induced lipolysis than the sub-cutaneous adipose tissue [54]. Lipoprotein lipase (LPL), a component of chylomicrons and lipoprotein particles, mediates the breakdown of circulating TG to FFAs and their subsequent uptake into cells. The effect of GH on lipoprotein lipase (LPL) expression and activity in the adipose tissue is ambiguous, suggesting that GH may not have an appreciable effect on TG uptake in the adipose tissue [46,49,50,55,56].

GH also plays a role in adipocyte differentiation (adipogenesis). Differentiation of small pre-adipocytes into large, mature adipocytes is associated with an increased capacity to store TG and a higher lipolytic ability[57]. Several *in vitro* studies in 3T3-L1 adipocytes have shown that GH may directly induce adipogenesis via activation of STAT5 and its subsequent association with PPAR-γ (peroxisome proliferator-associated receptor-γ), an established adipogenic factor. However, Fleenor *et. al.* showed that GH treatment of 3T3-L1 pre-adipocytes during their differentiation was associated with a concomitant increase in IGF-1 expression; while Kawai *et. al.* demonstrated that STAT5 activation (nuclear translocation) was GH-independent 24 hours after induction of adipogenesis in the presence of GH. These data suggest that while STAT5 may associate with PPAR-γ during adipogenesis, GH may mediate this effect only during the early phase and that other STAT5 activators may come into play during the later phases of adipogenesis[58-60]. This hypothesis is supported by the observation that STAT5 is involved in the development of the immune system and the effects of glucocorticoids on body growth and fatty acid metabolism (reviewed in61). Thus, identifying the alternative stimuli for STAT5 activation during adipogenesis may help clarify the role of GH during the process.

GH represses glucose uptake in the adipose tissue via as yet unclear mechanisms. *In vitro* studies show that GH preferentially down-regulates the glucose transporter-1 (GLUT-1) in the adipose tissue-derived 3T3-F442A cell line[62]. Moreover, treatment of rats with an anti-rat GH antibody increased the membrane localization of GLUT-1 and GLUT-4, most-likely by up-regulating GLUT-1 protein content and altering the sub-cellular localization of GLUT-463. *bGH*-transgenic mice also have increased expression of the p85α regulatory sub-unit of PI3K in the adipose tissue, which has been associated with insulin resistance. Furthermore, the opposite was found in the GH-deficient (GHD) *lit/lit* mice which harbor a mutation in the *GHRH receptor (GHRHR)* gene[64]. Dose-dependent increase in p85α expression was also shown in 3T3-L1 preadipocytes treated with GH[65]. Thus, GH may inhibit insulin action in the adipose tissue, either at the level of glucose uptake or the PI3K.

While several studies have shown that GH has an effect on circulating adipocytokine levels, the net directionality of these effects cannot be concluded. Silha *et. al.* showed that acromegalic patients have lower leptin and higher adiponectin levels when compared to BMI- and insulin-matched control subjects[66]. Conversely, both Lanes *et. al.* and Joaquin *et. al.* showed that GHD individuals have lower adiponectin levels when compared to normal subjects[67, 68]. However, while the former showed normalization of adiponectin levels in GH-treated GHD individuals, the latter did not. This could reflect the fact that Lanes *et. al.* were studying GHD adolescents who had either received GH treatment or were untreated; while Joaquin *et. al.* were analyzing the effects of a 1 year GH-treatment on adult-onset GHD individuals, in tune with the reports of diminishing GH secretion and action with age[69, 70]. However, the studies on humans completely contradict *in vitro* studies as well as *in vivo* observations in GH- transgenic and deficient rodent models which suggest that GH suppresses adiponectin secretion[41, 64, 71, 72]. There is no clear explanation as to the reason for the discrepancy; but inter-species differences in hormone action/ secretion, sampling times, and the fact that alterations in GH levels in rodents lead to systemic differences (such as insulin sensitivity/resistance and altered IGF-1 levels) that cannot be matched to the control group, as in humans, may contribute to this.With respect to leptin levels, Berrryman *et. al.* showed that *bGH*-transgenic mice also have lower leptin levels when compared to control mice; while studies on GHD mouse models did

not show a difference in leptin expression or serum levels when compared to control mice[41, 71, 72]. There is also evidence, in both humans and rodents, suggesting that GH increases circulating resistin levels, which has been associated with insulin resistance[73-75]. Thus, more investigation into the molecular mechanisms by which GH regulates adipokine secretion and/or action is required and may explain the species-specific effects.

Thus, to summarize, GH triggers TG lipolysis mainly in the visceral adipose tissue via the activation of HSL, with little or no effect on LPL, and thus, TG uptake. GH affects adipogenesis via the activation of the STAT5/ PPARγ pathway; however data suggest that GH may play a role only during the early phase of the process. The molecular mechanisms mediating the termination of GH signaling during adipogenesis remain to be elucidated. GH may directly repress glucose uptake or antagonize insulin signaling in the adipose tissue. Moreover, GH lowers serum leptin levels; while its effects on adiponectin are contradictory in humans and rodents.

METABOLIC EFFECTS OF GH ON THE LIVER

Contrary to its effects on the adipose tissue, GH induces TG uptake in the liver by increasing LPL and/or hepatic lipase (HL) expression[55, 56, 76-78]. Moreover, GH treatment induces a state of TG storage in the liver[79]. Three possible mechanisms may be involved in this: (i) the inhibition of intrahepatic TG (IHTG) lipolysis, (ii) the inhibition of lipid oxidation, and (iii) enhanced lipogenesis. There are data in support of all the three hypotheses. *bGH*-transgenic mice have significantly reduced expression for hepatic HSL, suggesting that GH inhibits lipolysis of IHTG[78]. Studies on *bGH*-transgenic, GHRKO, and PPARα$^{-/-}$ mice, and GH-treated rats suggest that GH serves to down-regulate genes involved in lipid oxidation (eg. PPAR-α, acyl CoA oxidase (ACO-1), carnithine palmitoyl transporter-1 (CPT-1)) and increase the expression of genes promoting lipid synthesis (acetyl CoA carboxylase (ACCβ)) in the liver[78, 80-83]. Interestingly, deletion of the *STAT5* gene in the liver resulted in hepatic steatosis as well as increased phosphorylation of STAT1 and STAT3 under basal and GH-induced conditions84. This suggests that GH may stimulate IHTG storage in a STAT5-independent manner. On the other hand, deletion of the hepatic GHR gene in mice also resulted in hepatic steatosis due to enhanced lipogenesis and reduced TG secretion from the liver [89]. However, these effects cannot be completely attributed to GH action on the liver, as these mice had decreased circulating IGF-1 levels and hyperinsulinemia.

GH increases HGP by increasing glycogenolysis; however, it has either a stimulatory or no effect on gluconeogenesis[85-89]. In addition, rats over-expressing the *human GH (hGH)* gene had increased basal hepatic glucose uptake and glycogen content[90]. Moreover, GHD Ames dwarf mice and the GHRKO mice have improved insulin sensitivity and an up-regulation of hepatic insulin signaling, suggesting that GH antagonizes insulin signaling in the liver[81, 91]. Thus, identifying the exact mechanism by which GH modulates lipid metabolism in the liver is complicated by the fact that GH also affects hepatic insulin signaling.

In summary, GH stimulates TG uptake in the liver by inducing LPL/HL expression. GH also promotes IHTG storage by repressing lipolysis, or lipid oxidation, or by promoting lipogenesis. The GH-mediated increase in IHTG storage may occur by mechanisms that involve phosphorylation of STAT1 and/or STAT3. Antagonism of insulin signaling in the liver, and the control of IGF-1 production (which has insulin-like effects on metabolism) further complicate the identification of the molecular mechanisms by which GH mediates these effects. Moreover, GH has a stimulatory effect on HGP which may be a result of its antagonism of insulin action leading to hepatic/systemic insulin resistance.

METABOLIC EFFECTS OF GH ON THE SKELETAL MUSCLE

GH stimulates TG uptake in the skeletal muscle primarily by increasing LPL expression; thereby promoting lipid utilization50, 55, 92. The lipids taken up by the skeletal muscle can be either stored as intramyocellular TG (IMTG) or broken down to release energy via either lipolysis or lipid oxidation. Patients with acromegaly have increased IMTG content, as do GH-treated GHD and healthy subjects, supporting the hypothesis that GH induces IMTG storage43, 79, 93, 94. Moreover, GH has either no or a suppressive effect on HSL expression in the skeletal muscle78, 94. Interestingly GH treatment of both healthy and GHD individuals decreased whole-body carbohydrate oxidation and concomitantly increased whole-body lipid oxidation88, 95-97. However, the expression profiles of lipid oxidation genes in the skeletal muscle of GH-treated rodents and humans either support this observation98 or do not78, 95. Thus, it is possible that GH induces TG storage and lipid oxidation in the skeletal muscle in a context-dependent manner (such as nutrition, exercise, and steroid hormone status).

Rats over-expressing the *hGH* have loss of insulin-stimulated skeletal muscle glucose uptake, although there is no convincing evidence to show that GH directly influences GLUT-4 translocation in the skeletal muscle50, 90, 97. Moreover, knockout of the *STAT5* gene in the skeletal muscle does not have a major impact on glucose tolerance and insulin sensitivity in mice99. GH treatment of GHD patients and healthy rats either had no effect, or increased glycogen content respectively in the skeletal muscle100, 101. Moreover, no change in muscle glycogen synthase expression was observed in GH-treated GHD patients50. Thus, GH may have only a minor direct effect on carbohydrate metabolism in the skeletal muscle. In fact, Ames dwarf and GHRKO mice have down-regulated or delayed insulin signaling in the skeletal muscle which may reflect an adaptation to protect against hypoglycemia in the face of improved systemic insulin sensitivity102, 103. However, while these data suggest that GH action in the skeletal muscle may contribute minimally to systemic insulin resistance, Barbour *et. al.* showed increased expression of p85α in *human placental growth hormone (hPGH)* transgenic mice and in liver IGF-1 deficient (LID) mice that have elevated circulating GH levels104. Moreover, treatment of LID mice with a GHRH antagonist reduced p85α expression in the skeletal muscle65.

Ageing-associated muscle wasting (sarcopenia) is often linked to reduced GH and IGF-1 levels as well as a preferential loss of type II (glycolytic) fibers and skeletal muscle atrophy105, 106. GH treatment of wild-type mice induced IGF-1-independent myotube hypertrophy and extension by fusion; this effect was lost in the GHRKO mice107. It has also been shown that GH-induced skeletal muscle differentiation requires intact insulin and IGF-1 signaling in the skeletal muscle108. However, while the former study was conducted on primary myoblast cultures obtained from GHRKO mice, the latter was performed by treating MKR mice, which over-express the dominant-negative form of the IGF-1R in the skeletal muscle, with rhGH. Over-expression of the GHR in C2C12 skeletal muscle cells impaired their differentiation, while increasing their proliferation in response to GH treatment109. These data suggest that GH supplementation in the elderly could prevent the incidence of sarcopenia by either stimulating myofiber proliferation and/or inhibiting fiber apoptosis. However, the data in support of this hypothesis are inconclusive based on studies on aged rodents and humans110-112. Moreover, data from GHD rodents suggest that GH favors the transition from type II (glycolytic) to type I (oxidative) fibers107, 113. Thus, while GH has an effect on myofiber proliferation and/or extension by fusion; it is not yet known if this is a direct effect or an indirect effect mediated by IGF-1.

Taken together, GH increases LPL expression, and consequently, TG uptake in the skeletal muscle and directs it either towards storage as IMTG or towards oxidation; although it is unclear if either of these fates is context-dependent. Moreover, GH action on insulin signaling and

carbohydrate metabolism in the skeletal muscle cannot be clearly defined and may include increasing the expression of p85α, a negative regulator of insulin signaling. Finally, there is very little *in vivo* data on the effect of GH on myofiber proliferation and/or extension although it has been shown to induce a shift in fiber-type from type II to type I fibers. Clarification of these effects would help address the feasibility of using GH to treat muscle-wasting diseases such as sarcopenia.

EFFECTS OF GH ON PROTEIN METABOLISM

GH has a net anabolic effect on protein metabolism, as it stimulates protein synthesis while repressing proteolysis[96, 114-118]. However, data suggest that the effects of GH on protein metabolism may be mediated by IGF-1[95, 119]. It has also been hypothesized that the GH-induced increase in FFA flux from the adipose tissue could, via the provision of substrates for gluconeogenesis (such as ketone bodies, and acetyl CoA); abrogate the need for amino acids, and consequently proteolysis[120]. This theory has been supported by studies which show that GH increases lipid oxidation in both humans and rodents[88, 95-97]. A possible mechanism of GH-induced protein synthesis was demonstrated in the H4IIE rat hepatoma cell line; GH activated the mTOR signaling pathway, an established pathway involved in protein synthesis[121]. However, a caveat of using rat hepatoma cell lines is that, unlike differentiated hepatocytes, these cell lines express IGF-1Rs as well as IGF-1[122]. Thus, GH exerts a net anabolic effect on protein metabolism either directly or via IGF-1.

GH-INDUCED INSULIN RESISTANCE

GH-mediated induction of insulin resistance is well documented. However, the mechanism by which GH mediates this effect is not completely understood. Here, we suggest some possible mechanisms of GH-induced insulin resistance. GH-induced increase in FFA flux from the adipose tissue has been associated with impaired insulin action at target tissues(reviewed in123). However, LID mice demonstrate a 75% reduction in circulating IGF-1 levels, 3-4 fold increase in circulating GH levels and insulin resistance, without significant increase in circulating FFA levels[104, 124, 125]. Moreover, while crossing LID mice with GHa transgenic mice significantly increased serum FFA levels, there was an improvement in insulin sensitivity during a hyperinsulemic-euglycemic clamp due to higher hepatic, adipose tissue and skeletal muscle glucose uptake125. This suggests that, in addition to FFAs, other factor(s) may also contribute to GH-induced insulin resistance. One candidate is the SOCS family of proteins whose expression is induced by GH. In particular, SOCS-1 and SOCS-3 have been associated with insulin resistance and down-regulation of insulin signaling (reviewed in126). Another mechanism by which GH may induce insulin resistance is by increasing the expression of the p85α regulatory sub-unit of the PI3K, as was shown by del Rincon *et. al.* and Barbour *et. al.* [64, 65]. The PI3K exists as a dimer of two sub-units, the p85 regulatory sub-unit which binds to the IRSs and the p110 catalytic sub-unit. It has been shown that the amount of p85α in a cell may serve as a molecular switch that either enhances or suppresses insulin signaling. When in excess, p85α monomers would competitively bind IRS and block insulin signaling; while in a depleted state, the p110 subunit may still bind other p85 isoforms (like p85β) and enhance insulin signaling[127, 128].

CONCLUDING REMARKS

GH induces lipolysis in the adipose tissue by increasing HSL activity and/ or by influencing differentiation of preadipocytes into adipocytes. Moreover, it represses insulin action in the adipose tissue possibly by (i) inhibiting glucose uptake or (ii) up-regulating the expression of the p85α regulatory sub-unit of the PI3K. Secondary to its effects in the adipose tissue, GH increases TG uptake into the liver by increasing LPL/ HL expression, and induces IHTG storage by several mechanisms including suppressing lipolysis, lipid oxidation, or stimulating

lipogenesis. There is also evidence to suggest that GH may stimulate IHTG accumulation via the activation of STAT 1 and/ or 3. GH also antagonizes insulin signaling in the liver and subsequently mediates an increase in HGP, primarily by stimulating glycogenolysis. Similar to the liver, GH also induces LPL-mediated TG uptake in the skeletal muscle. However, GH has been shown to stimulate both IMTG accumulation and lipid oxidation in the skeletal muscle, although it is still unclear what stimulates these divergent fates. While it is still unclear whether GH influences insulin signaling in the skeletal muscle, p85α may be involved in the process. GH may also play a role in myotube proliferation and extension, as well as in myofiber typing, bringing into question the feasibility of using GH to improve sarcopenia. Finally, GH mediates the conservation of proteins by inhibiting proteolysis and stimulating protein synthesis. However, data indicate that this may be an IGF-1-dependent effect of GH.

The foremost questions that remain to be answered are (i) What is/are the primary molecular mechanism(s) by which GH affects substrate metabolism? (ii) Which of the effects are a direct consequence of GH action and which are mediated indirectly via IGF-1 or antagonism of insulin action? However, as can be appreciated from the review, the interplay between GH, IGF-1 and insulin is extremely complicated and must be completely understood before attempting to answer these questions.

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