MINIREVIEW

Growth Hormone-Induced Alterations in the Insulin-Signaling System

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Growth hormone (GH) counteracts insulin action on lipid and glucose metabolism. However, the sequence of molecular events leading to these changes is poorly understood. Insulin action is initiated by binding of the hormone to its cell surface receptor (IR). This event activates the intrinsic tyrosine kinase activity residing in the β-subunit of the IR and leads to autophosphorylation of the cytoplasmic portion of the β-subunit and further activation of its tyrosine kinase towards several intermediate proteins, including the family of IR substrates (IRS) and the Shc proteins. When tyrosine phosphorylated, these cellular substrates connect the IR with several downstream signaling molecules. One of them is the enzyme phosphatidylinositol (PI) 3-kinase. The insulin antagonistic action of GH is not a consequence of a direct interaction with the IR. Instead, long-term exposure to GH is, in general, associated with hyperinsulinemia, which leads to a reduction of IR levels and an impairment of its tyrosine kinase activity. The signals of GH and insulin may converge at post-receptor levels. The signaling pathway leading to activation of PI 3-kinase appears to be an important site of convergence between the signals of these two hormones and seems to be mediated principally by IRS-1. Rodent models of chronic GH excess have been useful tools to investigate the mechanism by which GH induces insulin resistance. Decreased IR, IRS-1, and IRS-2 tyrosyl phosphorylation in response to insulin was found in skeletal muscle, whereas a chronic activation of the IRS-PI 3-kinase pathway was found in liver. The induction of the expression of proteins that inhibit IR signaling such as suppressors of cytokine signaling (SOCS)-1 and -6 may also be involved in this alteration. Interestingly, the modulation of insulin signaling and action observed in states of GH excess, deficiency, or resistance seems to be relevant to the changes in longevity associated with those states. [Exp Biol Med Vol. 227(3):149–157, 2002]

Key words: aging; diabetes; growth hormone; insulin receptor substrate; insulin signaling

With the development of biotechnology, growth hormone (GH) became available in large supplies, and its therapeutic use has expanded (1, 2). Consequently, the interest in understanding its metabolic effects has increased significantly in the recent years. Although GH is known to modulate tissue sensitivity to insulin, the sequence of molecular events leading to these changes is poorly understood. In this minireview, we will summarize the observations made in several studies in which the interaction between the insulin and GH signaling pathways has been analyzed. The differences between *in vitro* and *in vivo* findings will be highlighted. We will also focus on the changes induced by chronic GH excess in the proximal steps of the insulin signaling system, discussing some potential mechanisms by which GH antagonizes insulin action at the molecular level. Moreover, we will discuss the evidence supporting the hypothesis that the effect of GH on longevity may be based on its ability to modulate insulin signaling and action. The sequence of presentation will be the following: 1) Early events of insulin signal transduction; 2) Effects of GH on carbohydrate and lipid metabolism; 3) Effects of GH on the insulin receptor: discrepancy between *in vitro* and *in vivo* findings; 4) Shared signaling events between insulin and GH as a potential mechanism of GH-induced insulin resistance; 5) Effects of GH excess on post-receptor insulin signaling events *in vivo*; 6) Effects of disruption of the GH receptor and GH deficiency on post-receptor insulin signaling events *in vivo*; 7) The correlation between lifespan and the modulation of

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insulin signaling and sensitivity exerted by GH; and 8) Conclusions.

Early Events of Insulin Signal Transduction

In the last two decades, dramatic progress has been made in the understanding of the signaling pathways by which insulin exerts its biological actions (3, 4). The analysis of the phenotype of insulin receptor (IR)-knockout mice indicated that the IR is the master switch of the signaling pathway of insulin (5) (Fig. 1). After insulin binds to the α-subunit of the IR, the tyrosine kinase activity residing in the β-subunit becomes activated, leading to autophosphorylation of tyrosine residues in several regions of the cytoplasmic portion of the β-subunit and further activation of its tyrosine kinase towards several intermediate proteins, such as the family of IRS proteins and Shc (3, 4). At present, it is established that the family of IRS proteins has at least four members in mammals: IRS-1 and IRS-2, which are the best characterized members of this family and are widely expressed; IRS-3, which is restricted to adipose tissue and β-cells; and IRS-4, which is expressed in thymus, brain, and kidney (4, 6–8). Tyrosine-phosphorylated IRS proteins, Shc, and the IR itself bind several Src homology 2 (SH2) domain-containing proteins, which further propagates downstream signals. Phosphatidylinositol (PI) 3-kinase is one of the SH2 domain-containing proteins (Fig. 1). When tyrosine phosphorylated, the IRS proteins bind the p85 subunit of PI 3-kinase (p85), thereby activating this enzyme (3, 4, 8, 9). There is substantial evidence that PI 3-kinase is required for many, if not all, insulin actions, including stimulation of glucose transport, activation of glycogen synthase, and inhibition of hepatic gluconeogenesis through the regulation of phosphoenolpyruvate carboxykinase (9). Protein kinase B, also known as Akt/PKB, has been implicated as a downstream protein kinase mediating insulin responses, including insulin-induced glucose uptake and glycogen synthase activation (10).

Activation of the Ras-Raf-mitogen-activated protein kinase kinase (MEK)-extracellular-signal-regulated kinase (ERK) pathway is another major mechanism of insulin action and results in the activation of mitogen-activated protein (MAP) kinase (4). Although it has been shown that IRS-1 participates in this pathway, several reports indicate that the transforming protein Shc (Src homology 2/α-collagen related) is the main signaling molecule involved (4, 11, 12). During stimulation of cells with several growth factors, including insulin, Shc is tyrosine phosphorylated and binds to the SH2 domain of the growth factor receptor bound protein-2 (Grb2). Through this interaction, Shc plays a role in the activation of the MAP kinase cascade by insulin (4, 11, 12).

Effects of GH on Carbohydrate and Lipid Metabolism

Growth hormone has both acute and chronic effects on carbohydrate and lipid metabolism. The acute effects of GH

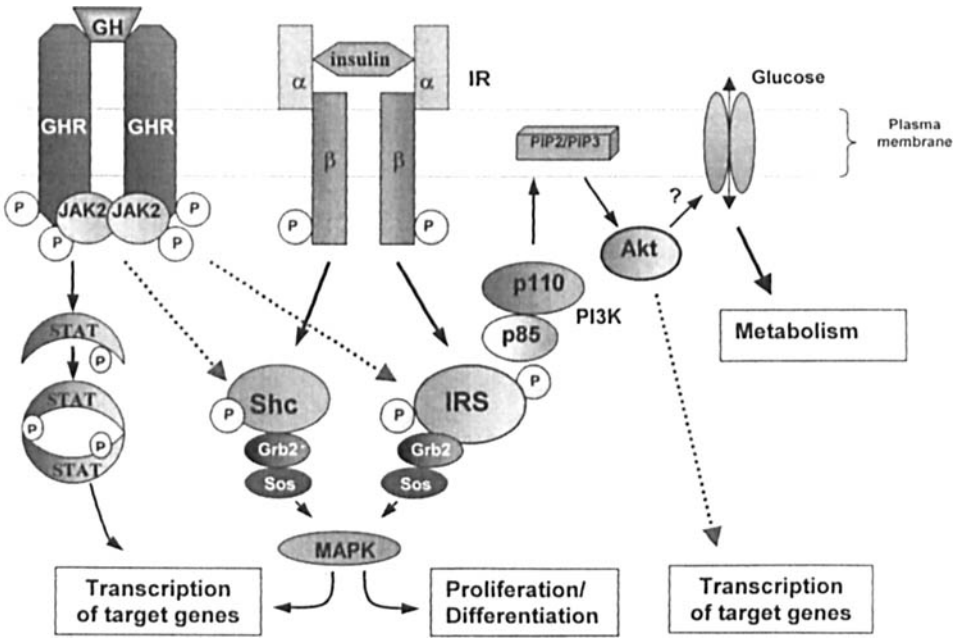

Figure 1. Convergence between insulin and GH signaling. The IR phosphorylates IRS proteins, which in turn bind to the SH2 domains in the p85α regulatory subunit of PI 3-kinase. This results in the activation of the lipid-metabolizing activity residing in its catalytic subunit (p110). The lipid products of PI 3-kinase activation (PIP2 and PIP3) recruit protein kinase B (Akt) to the plasma membrane. This enzyme has been implicated as a downstream protein kinase mediating insulin responses, including insulin-induced glucose uptake and glycogen synthesis. Engagement of Grb2/Sos by tyrosyl-phosphorylated IRSs proteins and Shc is expected to activate $p21^{ras}$ and the downstream MAP kinase cascade. The relative contribution of Shc and IRS proteins to this cascade appears to be cell and tissue specific. GH-induced dimerization of the GHR leads to activation of JAK2 and phosphorylation of several cytosolic proteins, including Shc and the IRS proteins. This signaling crosstalk (represented by dotted lines) is thought to be important for the insulin-like effects of GH and may have a role in its anti-insulin like effects.

are designated as insulin-like because under conditions of deprivation of the hormone such as those seen in hypopituitary subjects and hypophysectomized animals, GH is able to decrease blood glucose concentration, stimulate glucose uptake by skeletal muscle, and stimulate glucose transport and lipogenesis in isolated adipocytes (13, 14). However, these effects are transitory, and their physiological significance is not clear. After a few hours, the chronic anti-insulin effects of GH arise. The insulin antagonistic effects of GH include increased blood glucose concentration, insulin resistance, stimulation of lipolysis, and inhibition of glucose transport (13–17).

The clinical correlates of the insulin resistance produced by an excess of GH have been well documented in individual suffering from acromegaly (18–20), and can be induced by exogenous administration of GH (21–23). The insulin antagonistic effect of GH has also been observed in lower animals under conditions of excessive endogenous GH production (24, 25), after administration of exogenous GH (15–17, 26), as well as in transgenic mice and rabbits overexpressing heterologous GHs (27–30). Moreover, several observations suggest that physiological changes in GH are important in glucose homeostasis. Neutralization of the biological activity of GH by specific antibodies resulted in enhanced insulin sensitivity in rats (31). GH deficiency in humans is associated with increased insulin sensitivity, decreased insulin secretion, and decreased fasting glucose concentrations (32, 33).

Effects of GH on the Insulin Receptor: Discrepancy between *In Vitro* and *In Vivo* Findings

As the IR has a key role in insulin signaling, several studies sought to determine if the insulin antagonistic effect of GH was attributed to a direct effect of the hormone at this level. In early studies, incubation of human monocytes with GH for 3 hr (34) or exposure of IM-9 lymphocytes to the hormone for 24 hr (35) did not alter insulin binding characteristics. Similar studies in adipocytes demonstrated that total insulin binding, IR number, or affinity is not affected after prolonged exposure of these cells to GH, even though glucose metabolism is suppressed (36, 37). Moreover, a synthetic amino-terminal fragment of human GH that was shown to be hypoglycemic and to induce upregulation of IRs *in vivo* failed to interact with the IRs from isolated hepatocytes or liver membranes *in vitro* (38), suggesting that the effects produced by the peptide on glucose and IR levels were indirect.

The analysis of the effects of GH on insulin binding or IR abundance *in vivo* is complex. Several reports suggested that short-term GH excess is associated with impaired hepatic and extrahepatic responses to insulin in the absence of a change in insulin binding, but this observation has not been entirely consistent. When GH was administered to children with hypopituitarism or to normal subjects, no changes in overall insulin binding to circulating blood cells were observed (22, 39, 40). Unaltered insulin binding was also found in skeletal muscle of normal humans after a short-term GH infusion (41). In liver membranes prepared from normal or hypohysectomized rats injected with GH (42), a decreased binding capacity was compensated by an increased binding affinity so that little change in total insulin binding was detected. However, in some studies, decreased insulin binding to circulating blood cells has been found after acute GH administration to normal subjects and GH-deficient children (21, 43).

Excessive endogenous production of GH appears to be associated with downregulation of IRs. Decreased IR binding was found in liver of rats bearing GH-secreting tumors (25, 44). Decreased IR binding and protein levels have been found in liver and skeletal muscle of transgenic mice expressing supraphysiological levels of GH (45–47). Yet results from studies on acromegalic patients contradict this observation because insulin binding was found to be reduced in some studies (48, 49), but unaltered in others (19, 34).

Chronic treatment with exogenous GH appears to induce no changes in insulin binding or IR protein levels. Adipocytes isolated from pigs after a 7-day treatment with GH exhibited unaltered insulin binding (50). Similarly, IR levels were unchanged in liver and skeletal muscle of rats treated chronically with GH (51). However, in a single study, chronic treatment with GH was found to be associated with an increase in the abundance of IR in muscle (52). The divergence in the results found in these studies may reside in the different circulating concentrations of insulin attained. There is considerable evidence that insulin is the main modulator of its own receptor (35, 53), and results from our previous studies demonstrate that the inverse relationship between insulinemia and IR levels is maintained even in the presence of very high GH levels (54).

The effects of GH on IR autophosphorylation and tyrosine kinase activity appear to be indirect and to result from hyperinsulinemia that develops after chronic exposure to excessive GH levels. This is supported by results from studies in cultured cells showing that exposure to GH did not change IR tyrosine phosphorylation (55). Short-term administration of GH to normal subjects resulted in similar observations because no change in IR kinase activity in skeletal muscle was found (41). Tyrosine kinase activity of the IR was also unaltered in adipocytes isolated from pigs treated with GH for a short period (50). However, in conditions associated with prolonged exposure to chronic GH excess, changes in the autophosphorylation or kinase activity of the IR have been found. In rats treated chronically with GH, insulin-induced IR tyrosine phosphorylation was unaltered in liver (51), but was reduced in skeletal muscle (51, 52, 56). Conditions of chronic excessive endogenous GH production such as those associated with the presence of GH-secreting tumors have been found to result in increased levels of IR autophosphorylation and tyrosine kinase activity in liver under basal conditions (44). Similarly, increased

in vitro basal autophosphorylation and tyrosine kinase of IRs purified from liver (46, 54), as well as increased basal IR tyrosine phosphorylation in liver and skeletal muscle *in vivo* were found in transgenic mice overexpressing GH (47, 57). Moreover, similar to the alterations found in rats treated chronically with GH, reduced insulin-stimulated phosphorylation of the IR was found in skeletal mice of GH-transgenic mice (47). These results suggest that one of the mechanisms by which chronic GH excess produces insulin resistance may be the induction of an increase in the basal phosphorylation of the IR in liver, leading to loss of sensitivity to insulin in this tissue, together with reduced IR phosphorylation and tyrosine kinase activity in skeletal muscle.

Shared Signaling Events between Insulin and GH: Potential Mechanisms of GH-Induced Insulin Resistance

Although GH does not interact directly with the IR, several downstream insulin signaling events are affected when cultured cells are exposed to GH, suggesting that the signals of GH and insulin may converge at post-receptor levels (58–61). The GH receptor (GHR), unlike the IR, lacks intrinsic tyrosine kinase activity (60–62). In response to GH, the non-receptor tyrosine kinase Janus 2 (JAK2) becomes rapidly phosphorylated and activated while associated with the GHR (63). Following the activation of JAK2, several intracellular proteins, including the cytoplasmic domain of the GHR and JAK2 itself, undergo tyrosine phosphorylation (60, 61). Several signaling cascades are initiated following these primary tyrosine phosphorylation events (60, 61). Of potential relevance to its physiological insulin-antagonistic action, GH has recently been shown to promote tyrosine phosphorylation of IRS-1 and IRS-2 and their association with PI-3 kinase in a broad range of GH-responsive cell types (64–68) (Fig. 1), as well as in liver and other GH target tissues of the intact rat (69, 70). This phenomenon is mediated by JAK2, and does not involve direct interaction of the IRS proteins with the GHR (69–71) (Fig. 1). GH has also been shown to utilize Shc (Fig. 1). Treatment with GH induces phosphorylation of Shc in 3T3-F442A fibroblasts (72, 73), and also in GH target tissues of the intact rat (70). However, it must be considered that the physiological relevance of these observations is not clearly defined. Thus, GH was shown to induce phosphorylation of these substrates in fasting conditions (69, 70), but failed to stimulate IRS-1 or Shc phosphorylation under fed conditions *in vivo* (74). Furthermore, the extent of PI 3-kinase stimulation by GH was only a fraction of that observed after insulin infusion under the same conditions (69).

The extent of crosstalk between GH and insulin appears to differ according to the tissue and/or metabolic action involved. PI 3-kinase, for instance, appears to be important for the insulin-like effects of GH on lipid metabolism (75), and has also been shown to be necessary for the full activation of MAP kinase and $p70^{s6k}$ by GH (68). Additionally, recent reports indicate that PI 3-kinase mediates GH-regulated gene transcription independently of MAP kinase (76) (Fig. 1). However, studies investigating its involvement in the GH stimulation of glucose uptake or in the GH-induced translocation of GLUT4 glucose transporter led to contradictory results. In Chinese hamster ovary (CHO) cells, the presence of a GLUT4 translocation pathway mediated by GH through the activation of PI 3-kinase and Akt kinase was established (77), wheras in 3T3-L1 adipocytes, GH induced GLUT4 translocation independent of PI 3-kinase and Akt was detected (78). In addition, although GH was capable of inducing tyrosine phosphorylation of IRS-1, -2, -3, and Shc in rat liver *in vivo*, the GH activation of PI 3-kinase in that tissue was determined to be mediated mainly by IRS-1 (69). Moreover, PI 3-kinase was shown to be necessary for the GH stimulation of the proliferation of a pancreatic β-cell line, but this event has been shown to proceed via the JAK2/STAT5 pathway without engaging the Shc or IRS-1 signal transduction pathways (79).

Recent reports have indicated the existence of a second signaling pathway involved in the stimulation of glucose transport by insulin that functions in parallel with PI 3-kinase. This mechanism involves insulin-stimulated tyrosine phosphorylation of the c-Cbl proto-oncogene product (Cbl), which is recruited to the IR by the adapter protein CAP (80). Upon phosphorylation, the CAP-Cbl complex dissociates from the IR and moves to lipid rafts recruiting the CrkII-C3G complex, leading to the activation of the small GTP-binding protein TC-10 (81). Interestingly, GH has also been shown to stimulate the phosphorylation of Cbl as well as the association of Cbl with CrkII in CHO cells (82), indicating an additional potential site of crosstalk between GH and insulin.

The fact that GH is able to use the same signaling molecules as insulin suggests a possible explanation for the insulinomimetic effects of GH on carbohydrate and lipid metabolism. However, it is not clear if this signaling crosstalk may have a role in the physiological insulin-antagonistic action of GH or in the insulin resistance associated with states of GH excess. One mechanism by which GH could produce insulin resistance is by inducing the expression of cellular proteins that inhibit IR signaling. The SH2-domain-containing proteins suppressors of cytokine signaling (SOCS) are negative regulators of cytokine signaling pathways, and their expression is regulated by certain cytokines including GH (83). In a recent study, two members of this family of proteins (SOCS-1 and SOCS-6) were found to interact with the IR and to inhibit insulin-stimulated activation of ERK1/2 and Akt kinase *in vivo* and phosphorylation of IRS-1 by the IR *in vitro* (84). These findings are indicative of a potential role of SOCS proteins in mediating GH-induced insulin resistance. In addition, one mechanism of GH-induced insulin resistance was recently identified at the cellular level by using 3T3-L1 adipocytes. Chronic treatment of these cells with GH resulted in an

increase in the insulin-stimulated IRS-1-PI 3-kinase pathway, but in a reduction in the insulin-stimulated Akt activation as well as in the insulin-induced translocation of Akt from the cytosol to the plasma membrane (85). Thus, GH may induce insulin resistance in adipocytes by uncoupling PI 3-kinase and its downstream signals (85). Whether this alteration is cell specific or a general mechanism by which GH excess impairs insulin action remains to be determined.

It is also important to consider recent results obtained in mice with liver IGF-1 deficiency (86). These results suggest that although GH plays a major role in reducing insulin sensitivity, circulating IGF-1 also participates in the control of insulin sensitivity and action. This implies that IGF-1 plays an important role in the hormonal balance between GH and insulin in addition to its effect on reducing circulating GH levels (86).

Effects of GH Excess on Post-Receptor Insulin Signaling Events *In Vivo*

To our knowledge, the effect of chronic GH excess on insulin signal transduction *in vivo* has been investigated only in two models: rats treated chronically with GH (51, 52, 56) and transgenic mice overexpressing bovine GH (47, 57). In both cases, a state of insulin resistance was detected (28, 51, 52). In addition, long-term exposure to GH in transgenic mice leads to a decrease in the expression of several proteins of importance in carbohydrate metabolism, as well as decreases in both the insulin-mediated activation of glycogen synthase in liver and muscle and in the activation of glycogen phosphorylase in both tissues (28).

A tissue-specific regulation of IRS-1 was detected in insulin target tissues of GH-treated rats. IRS-1 protein levels were found unaltered in skeletal muscle (51, 52, 56), but were reduced in liver (51). Overexpression of GH in transgenic mice led to different results, with an increase of IRS-1 levels in skeletal muscle (47), but no significant change in liver (57). Circulating insulin levels in GH-transgenic mice are approximately 7-fold above normal values (46, 54), whereas only a 2-fold increase was detected in GH-treated rats (51). The difference in insulin levels between these two models, as well as differences in the levels and dynamics of GH (continuous endogenous production versus exogenous administration by injection), may account for this discrepancy. In contrast, IRS-2 protein levels were not affected by *in vivo* GH excess in any of the tissues examined (51).

A common finding in these studies was that chronic GH excess resulted in a diminished response to insulin injection in terms of IRS-1 tyrosine phosphorylation in skeletal muscle (47, 51, 52, 56). Downstream signaling events such as the insulin-stimulated p85-IRS-1/IRS-2 association, as well as the insulin-stimulated PI 3-kinase activity were also impaired (47, 51). In contrast, a chronic activation of the IRS-PI 3-kinase pathway reducing the degree of insulin-induced activation was observed in liver of GH-transgenic mice (51). Moreover, increased basal phosphorylation of IRS-1 was detected in both skeletal muscle and liver, which may contribute to the insulin insensitivity seen in those *in vivo* models.

Interestingly, the insulin-stimulated tyrosine phosphorylation of Shc and its association with Grb2 was found unaltered in skeletal muscle of GH-treated rats (56). This suggests that the chronic GH excess results in a selective attenuation of the IRS-mediated signaling pathways of insulin.

Effects of GH Deficiency and of Disruption of the GH Receptor on Post-Receptor Insulin Signaling Events *In Vivo*

A counterpart to the studies described above was provided by results obtained in GHR/GH binding protein gene knockout (GHR-KO) mice, an animal model of the Laron syndrome (87). In these mice, although GH is secreted in large quantities, its biological effects are absent due to the lack of GHR (87). Thus, they are an excellent tool to study how the lack of GH effects influences the insulin signaling system in intact animals. Additional complementary information was obtained by using Ames dwarf mice, which have primary pituitary deficiency consisting of the absence of, or extreme reduction in, anterior pituitary cells that produce GH, prolactin (PRL), and thyrotropin (TSH) (88–90). Both GHR-KO and Ames dwarf mice exhibit a state of hypersensitivity to insulin. Ames dwarf mice have significantly reduced glucose levels and fasting insulin levels and less consistently reduced insulin levels in the fed state (91, 111). GHR-KO mice have reduced plasma glucose and extremely low plasma insulin levels under both fed and fasting conditions (92, 93). Moreover, an increased hypoglycemic response to exogenous insulin has been found in both models (94, 111). Unexpectedly, the increased responsiveness to insulin in Ames dwarfs and in GHR-KO mice appears to result from alterations of the insulin-signaling pathway at different levels. A major elevation in IR levels was the principal change found in GHR-KO mice (93), whereas Ames dwarf mice have a smaller increase in IR and a large increase in the amount of IRS-1 and -2 (111). In good agreement with results obtained in GH-treated rats (56), Shc phosphorylation and protein levels in liver of GHR-KO mice were not affected by the state of GH resistance (93). Moreover, the increase in insulin sensitivity in these models appears not to involve modulation of PI 3-kinase in liver (93, 111). This result is somewhat unexpected due to the fundamental role of PI-3 kinase in insulin action. However, in recent studies it was demonstrated that the states of reduced insulin sensitivity induced by administration of high-fat or high-salt diets are associated with enhanced insulin activation of PI 3-kinase in the liver (95, 96), indicating that the *in vivo* level of insulin-stimulated activity of PI 3-kinase in liver cannot always be considered as an indicator of the insulin sensitivity status.

Correlation between Lifespan and the Modulation of Insulin Signaling and Sensitivity Exerted by GH

Different hypotheses have been proposed to explain the aging process, including a synergistic induction of aging by free radicals, nonenzymatic glycations, and Maillard reactions (97, 98). The exposure to insulin has been proposed as a major factor involved in the regulation of the rate of aging in mammals (99). Moreover, recent studies have provided evidence that the insulin/IGF-signaling system is related to the regulation of aging and lifespan in insects and worms (100–103).

Interestingly, the overexpression of high levels of GH in transgenic mice results in an impairment of insulin signaling and profound insulin resistance and is also associated with a reduction of lifespan (104, 105). In contrast, GH-deficient Ames dwarf mice and GH-resistant GHR-KO mice who exhibit an increase in insulin sensitivity and an enhancement of insulin signaling live much longer than normal mice (106, 107). Increased lifespan has also been found in Snell dwarf mice, who have the same endocrine phenotype as Ames dwarfs (108). However, the status of insulin signaling and action in Snell dwarfs has been barely explored, with results showing increased insulin binding to hepatocytes isolated from these animals suggesting that changes similar to those found in Ames dwarf and GHR-KO mice may be present (109).

Thus, modulation of insulin signaling and action by GH seems to be relevant to the changes in longevity induced by conditions of GH excess or deficiency. The retardation or apparent acceleration of aging induced by changes in GH levels may be a consequence of the compensatory changes in insulin levels in response to GH-related alterations of insulin sensitivity. Exposure to chronic hyper- or hypoinsulinemia may then accelerate or decrease aging, respectively (98, 99). This hypothesis is consistent with the proposed metabolic explanation for the life-prolonging effect of caloric restriction and of mutations decreasing the overall activity of insulin-like receptors in the nematode *Caenorhabditis elegans*. Thus, even though numerous studies indicate that GH and IGF-1 decrease with age and that administration of these hormones ameliorates the deterioration of tissue function associated with aging, results from these murine models of GH excess and deficiency question the anti-aging actions of GH and suggest that the role of GH throughout the lifespan of an individual may be to accelerate rather than prevent aging (110).

Conclusions

The *in vitro* effects of GH on the insulin receptor differ from those detected *in vivo*. GH does not affect IR levels directly, although down- or upregulation of IRs has been a consistent observation in studies of chronic states of GH excess or deficiency. The change in insulin levels associated with these conditions has been shown to be responsible for the observed changes in IR levels.

Chronic GH excess is generally associated with reduced levels of IR and reduced insulin-induced IR phosphorylation in insulin-target tissues. These alterations appear to be the consequence of exposure to high insulin levels and would certainly play a role in the GH-induced insulin resistance.

The signals of GH and insulin seem to converge at the post-receptor level. It is clear that GH is able to use some of the intermediate signaling molecules utilized by insulin, including IRS proteins and Shc, which suggests a possible explanation for the insulinomimetic effects of GH on insulin and lipid metabolism.

The extent of crosstalk between GH and insulin varies in different tissues. IRS-1 appears to be the most predominant intermediate protein involved. PI 3-kinase seems to be an important site of crosstalk between these two hormones.

The physiological significance of this signaling crosstalk is not clear, but it could have a role in the insulin resistance caused by GH excess. Increased *in vivo* basal phosphorylation of IRS-1 in insulin-target tissues has been reported in both GH-treated rats and GH-transgenic mice. Whether this alteration is secondary to hyperinsulinemia or represents the combined effects of increased insulin levels and GH and/or IGF-1, it might be an important contributing factor to insulin resistance resulting in an attenuation of the insulin signal and leading to loss of insulin sensitivity.

GH has been shown to induce the expression of SOCS-1 and -6, two cellular proteins that were shown to inhibit IR signaling. Although the *in vivo* levels of these proteins have not yet been measured in models of GH excess, it is tempting to suggest that they might be involved in the insulin antagonistic action of GH and could have a role in the GH-induced insulin resistance.

The mechanism of induction of insulin resistance by GH may also involve uncoupling between PI 3-kinase and its downstream signaling mediators.

By altering the insulin signaling system and insulin sensitivity, GH may have a role as a modulator of lifespan.

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