Growth Hormone & IGF Research 52 (2020) 101319

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

Mechanisms of putative IGF-I receptor resistance in active acromegaly

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ARTICLE INFO

Keywords:
Active acromegaly
IGF-I
Insulin
S-Klotho
IGF-I receptor
IGF-I receptor resistance
Impaired glucose tolerance
Diabetes mellitus

ABSTRACT

Acromegaly is a disease characterized by overproduction of growth hormone (GH). As a consequence of excessive GH secretion, circulating insulin-like growth factor-I (IGF-I) is elevated in active (untreated) acromegaly. IGF-I is often used as a marker of disease activity and growth hormone status in acromegaly. Although IGF-I can directly improve insulin sensitivity and glucose uptake in muscles, the excessive GH secretion in active acromegaly frequently leads to insulin resistance, glucose intolerance and even diabetes. In this review evidence will be discussed that in active acromegaly chronically elevated IGF-I, insulin and soluble Klotho (S-Klotho) levels play a pathophysiological role in the development of IGF-I receptor (IGF-IR) resistance. It is postulated that as soon as circulating IGF-I, insulin and S-Klotho rise above a certain level the IGF-IR becomes relatively resistant to actions of IGF-I. The development of a degree of IGF-IR resistance for metabolic actions may help to explain why in active acromegaly diabetogenic effects of GH predominate and are not completely counteracted and neutralized by elevated circulating levels of IGF-I. Further studies are necessary in order to support this hypothesis.

1. The GH-IGF-I axis in healthy subjects

In healthy subjects GH is released from somatotroph cells of the anterior pituitary in a pulsatile fashion and activates the growth hormone receptor (GHR) which is present at the cellular surface of target tissues such as liver, muscle, adipose tissue, bone and kidney [36]. Release of GH is primarily regulated by growth hormone-releasing hormone (GHRH; positive regulation), and somatostatin (negative regulation) [36]. GH produced by the pituitary is the main regulator of circulating insulin-like growth factor-I (IGF-I), which is particularly produced by the liver [36,56]. A complicated system of short and long feedback loops negatively regulates GH secretion in the healthy state [36] (Fig. 1). It has been found that IGF-I itself might exert negative feedback on GH secretion at the level of the hypothalamus and at anterior pituitary [5,7] (Fig. 1). Pituitary cells contain specific receptors for IGF-I [45]. IGF-I inhibits basal and GHRH-stimulated GH release from cultured pituitary cells after 24 h of incubation [5]. Furthermore, IGF-I stimulates the release of somatostatin from hypothalamic tissue [5]. GH signaling is initiated by binding of GH to the GHR. One GH molecule binds to two GHR molecules that exist as preformed homodimers. After GH binding to the GHR, the intracellular domains of the GHR dimer undergo rotation, which brings together the two intracellular domains of the GHR [14]. A number of signaling proteins and pathways activated by GH have been identified, including Janus Kinases (JAKs), signal transducers and activators of transcription (Stats), the mitogen activated protein kinase (MAPK) pathway, and the phosphatidylinositol 3′-kinase (PI3K) pathway [33]. Although these signal transduction pathways have been well characterized, the manner by which GH activates these pathways and the downstream signals induced by these pathways are not completely understood [33]. The suppressor of cytokine signaling (SOCS) family of proteins plays an important role in the negative regulation of GH signaling [33]. Other important mechanisms whereby GH signaling is thought to be negatively regulated is through protein tyrosine phosphatases (PTPs) and ubiquitin-dependent GHR endocytosis [33]. Precise regulation of GH signaling is important for the proper maintenance of body growth and metabolism.

2. The IGF-I receptor and IGF-I receptor resistance

The IGF-IR is a heterotetrametric transmembrane protein composed of two α and two β subunits. Binding of IGF-I to the alpha subunit of the IGF-IR is followed by autophosphorylation of tyrosine residues on one β subunit. The activated receptor recruits then phosphorylated intracellularly substrates as the insulin receptor substrate proteins (IRSs) and SH2-containing collagen-related proteins (SHC). Tyrosine phosphorylation of the IRSs in turn activates then the phosphatidylinositol 3-kinase (PI3K-Akt) pathway, which is predominantly involved in metabolic actions (Fig. 2). Tyrosine phosphorylation of SHC induces downstream signaling activation through the Ras/Raf/MEK/Erk

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https://doi.org/10.1016/j.ghir.2020.101319
Received 18 March 2020; Received in revised form 31 March 2020; Accepted 1 April 2020
Available online 06 April 2020

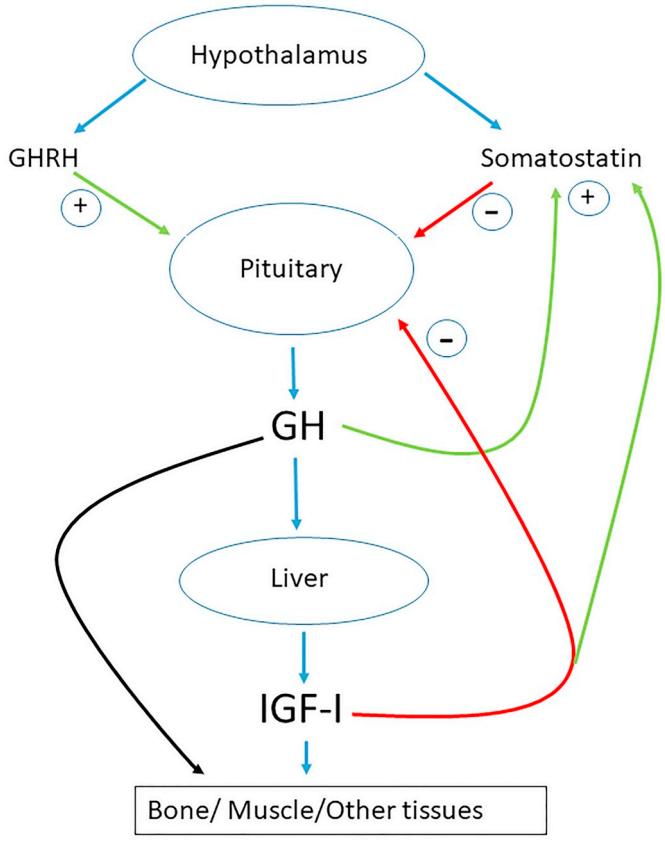

Fig. 1. The regulation of the GH-IGF-I axis. Growth Hormone Releasing Hormone (GHRH) released by the hypothalamus stimulates Growth Hormone (GH) in the pituitary gland. GH secretion by the pituitary is the primary regulator of insulin-like growth factor-I (IGF-I) production in the liver. IGF-I produced in the liver inhibits GH release via negative feedback on the pituitary and via stimulation of somatostatin release in the hypothalamus. There is also direct negative feedback by which GH stimulates hypothalamic somatostatin release. Green: positive feedback; Red: negative feedback. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

pathway which is predominantly involved in mitogenic (growth-promoting) actions (Fig. 2).

IGF-IR resistance has been previously reported in a variety of clinical conditions. Some rare conditions are associated with genetic IGF-I resistance [24]. Disease states such as diabetes, severe insulin resistance, chronic renal insufficiency and HIV infection may cause acquired IGF-IR resistance [24]. Acquired IGF-IR resistance may present at the pre-receptor level through decreased bioavailability of IGF-I (for example by circulating inhibitors of IGF-I action) [24]. It is also possible that IGF-IR resistance is caused by defects of the IGF-IR self (by decreased number and/or affinity for IGF-I) or by post-receptor defects in the intracellular signaling pathways of the IGF-IR [24]. IGF-IR resistance may have different effects in various cells and organs, depending on the cell-predominant enzymatic machinery. In addition, in the setting of resistance by defects of the IGF-IR self, one would expect that circulating IGF-I levels are elevated if classical negative feedback regulation is operative [24].

3. Metabolic effects of growth hormone and insulin-like growth factor-I

Metabolic effects of GH and IGF-I are essentially different. Whereas GH leads to a decreased glucose uptake, elevated insulin secretion, reduced insulin sensitivity and an increased lipolysis, IGF-I leads to an increased glucose uptake, a reduced insulin secretion, enhanced insulin sensitivity and neutral effects on lipolysis (Table 1). In healthy subjects metabolic effects of GH and IGF-I are well in balance whereas in active (untreated) acromegaly insulin antagonistic and diabetogenic effects of GH on glucose metabolism predominate over IGF-I (Table 2). As a direct consequence active acromegaly eventually may progress to impaired glucose tolerance and diabetes by inducing a decreased glucose uptake and an increased glycogenolysis and gluconeogenesis (Table 2).

4. Growth hormone, total IGF-I and acromegaly

Acromegaly is a disease characterized by overproduction of GH which is most commonly due to a pituitary adenoma. In active acromegaly, cellular responses elicited by high GH levels overwhelm intracellular mechanisms attenuating GH signaling [33,38]. Due to excessive GH secretion, circulating (immunoreactive) IGF-I concentrations are elevated in active acromegaly [2]. Diagnosis of acromegaly requires elevated circulating total IGF-I concentrations [47]. At present measurement of circulating total IGF-I concentrations is considered the most sensitive and specific test to diagnose acromegaly. In addition, total IGF-I concentrations are used as a marker of disease activity and GH status. It is further used to judge the effectiveness of therapeutic intervention [6]. However, measurement of total IGF-I does not always seem to adequately reflect disease activity of active acromegaly [27]. This has been explained, at least partly, by the fact that GH levels of 80–100 micrograms/L maximally activate IGF-I production in humans and that higher GH levels in general do not further increase in IGF-I production [32]. Another reason may be that in contrast to IGF-I bioactivity measured by the insulin-like growth factor-I receptor kinase activation assay (IGF-IR KIRA assay) total IGF-I levels measured by immunoassays do not produce reliable information about modulating effects of insulin-like growth factor binding proteins (IGFBPs) or IGFBP-proteases on IGF-IR stimulating activity [26]. Furthermore, it could be that there is a degree of IGF-IR resistance in active acromegaly (see below).

5. Is acromegaly also a condition with acquired IGF-IR resistance?

In healthy subjects, as above discussed, IGF-I synthesis is stimulated by GH and an increase in circulating IGF-I plays a central role in the negative feedback regulation of GH secretion. Previously it has been found that IGF-I itself might exert negative feedback on GH secretion at the level of the hypothalamus and at anterior pituitary [5,7] (Fig. 3). Concentrations of IGF-I in blood are determined- like many other circulating hormones- by a balance between IGF-I secretion into the circulation on the one hand and disappearance and breakdown of IGF-I from the circulation on the other hand. It has been further reported that in active acromegaly, compared to normal subjects, the amount of circulating free/unbound IGF-I is higher [4,54]. Continuous exposure to elevated hormone levels may cause a reduction in the number of receptors by promoting internalization as well as degradation of hormone occupied receptors [50]. When a hormone stimulates its target cell, simultaneously by negative feedback, it may reset the responsiveness of the target cell to subsequent doses of hormone, resulting in a functional hormone resistance [25,50]. Desensitization, the ability of a stimulatory ligand to reset the responsiveness of its target cells to its stimulating actions is widespread [50]. For example, patients with type 2 diabetes with continuous exposure to elevated insulin levels develop a degree of insulin resistance [35]. In this respect IGF-I and the IGF-IR may show similarities to insulin and the insulin receptor: thus in active acromegaly chronic exposure to elevated IGF-I levels may reset responsiveness of the IGF-IR and induce a degree of IGF-IR resistance. Indeed, it has been found that chronic and prolonged stimulation with IGF-I may induce functional IGF-IR resistance in vitro through a negative feedback loop [20]. In the setting of IGF-IR resistance in the pituitary/hypothalamus, negative feedback by IGF-I on the pituitary

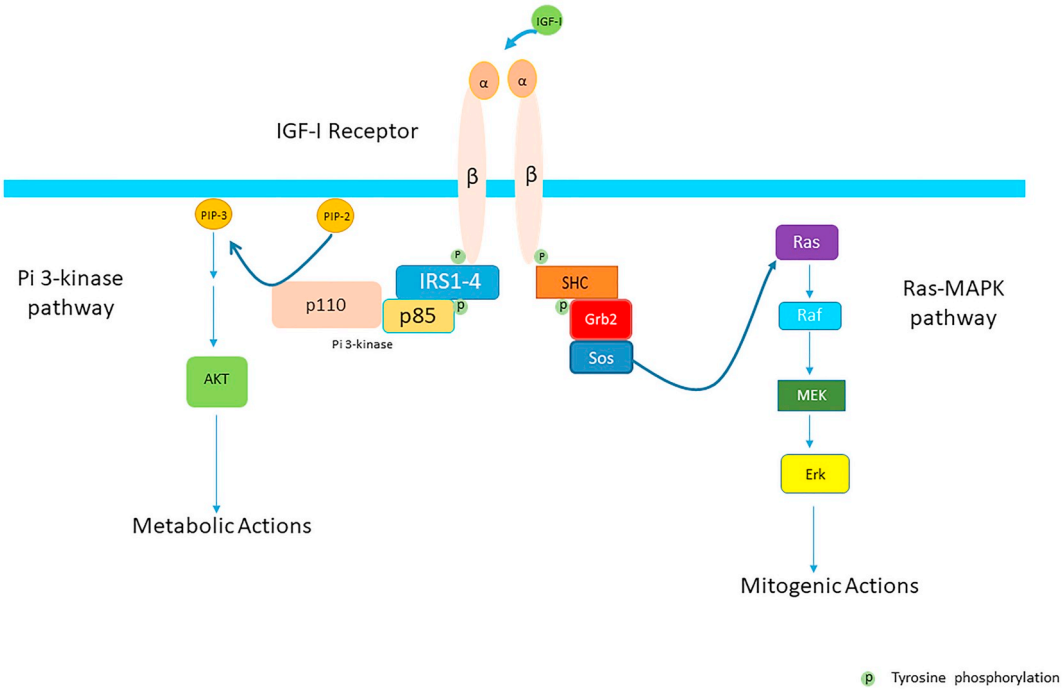

Fig. 2. Signaling pathways of the IGF-I receptor activated by IGF-I. Binding of IGF-I to the α subunit of the IGF-I receptor stimulates phosphorylation of tyrosine residues of the β subunit which then induces phosphorylation of the Insulin Receptor Substrates (IRS 1–4) and SHC, which are docking proteins for activating of the phosphatidylinositol 3-kinase (PI3K-Akt) pathway or the Ras/Raf/MEK/Erk pathway, respectively. The PI3K-Akt pathway is predominantly involved in metabolic actions (glucose uptake, insulin sensitivity) whereas Ras/Raf/MEK/Erk pathway is predominantly involved in mitogenic effects (proliferation, growth).

Table 1
Metabolic effects of Growth Hormone (GH) and Insulin-like Growth Factor-I (IGF-I).

	GH	IGF-I
Glucose uptake	↓	↑
Insulin secretion	↑	↓
Insulin sensitivity	↓	↑
Lipolysis	↑	No effect
Protein synthesis	↑	No effect or ↑
Protein breakdown	↑	No effect
Net protein balance	↑	No effect or ↑

↑ Stimulating.
↓ Inhibiting.

Table 2
In healthy subjects metabolic effects of growth hormone (GH) and insulin-like growth factor-I (IGF-I) are well in balance whereas in active (untreated) acromegaly insulin antagonistic effects of GH on glucose metabolism predominate over IGF-I.

	Healthy subjects	Active acromegaly
GH levels	Normal	Increased
IGF-I levels	Normal	Increased
Negative feedback of IGF-I on GH secretion	Normal	Decreased
Insulin levels	Normal	Increased
glucose uptake	Normal	Decreased
Glycogenolysis	Normal	Increased
Gluconeogenesis	Normal	Increased

gland and hypothalamus would be ineffective, resulting in elevated GH levels and, subsequently, further elevation of IGF-I levels [24].

In this paper we discuss the possibility that in (untreated) active acromegaly chronically elevated IGF-I, insulin and S-Klotho levels induce a degree of IGF-IR resistance: we hypothesize that as soon as circulating IGF-I, insulin and S-Klotho levels rise above a certain level (desensitization threshold), the IGF-IR becomes functionally resistant to actions of IGF-I. When this hypothesis is correct, elevated circulating IGF-I, insulin and S-Klotho levels may be drivers of (acquired) IGF-IR resistance in active acromegaly. In the paragraphs that follow, I will present further data and arguments to support this hypothesis.

6. Arguments for IGF-IR resistance in acromegaly

6.1. IGF-I and IGF-IR expression

In several animal models it has been found that IGF-IR expression in muscle is negatively correlated to IGF-I levels, at least at the mRNA level: bGH giant mice are mice with transgenic overexpression of bovine GH. They showed twofold higher GH levels as well as high hepatic IGF-I expression and serum IGF-I levels relative to controls but low mRNA expression of the IGF-IR [42]. In contrast, dwarf GHR −/− mice, mice which lack the GHR showed the opposite picture: the diminished GH signaling led to very low IGF-I levels and increases expression of the IGF-IR [42]. Furthermore, GHR and IGF-IR mRNA expression measured by real-time RT-PCR was significantly lower in human somatotroph tumors of acromegaly patients than in normal pituitary tissue [28]. In addition, immunostaining showed that the reduced expression of mRNA for both the IGF-R in somatotroph tumors was also reflected in lower protein expression of the IGF-IR [28]. Diminution of IGF-IR auto phosphorylation following chronic stimulation by high IGF-I levels may be a mechanism that enables the body to avoid overstimulation by IGF-I [20]. It has been reported that high IGF-I itself rapidly downregulates the IGF-IR expression following binding to the IGF-IR [11,48]. Chronically elevated IGF-I levels in active acromegaly may be thus in part due the fact that less IGF-I is cleared from the circulation by receptor-mediated mechanism. Moreover, high IGF-I levels may change post-receptor signaling of the IGF-IR. Chronic IGF-I stimulation may induce both internalization of the IGF-IR to the lysosome and degradation of insulin receptor substrates (IRS) proteins, thereby the downregulating the Akt (=protein kinase B) pathway,

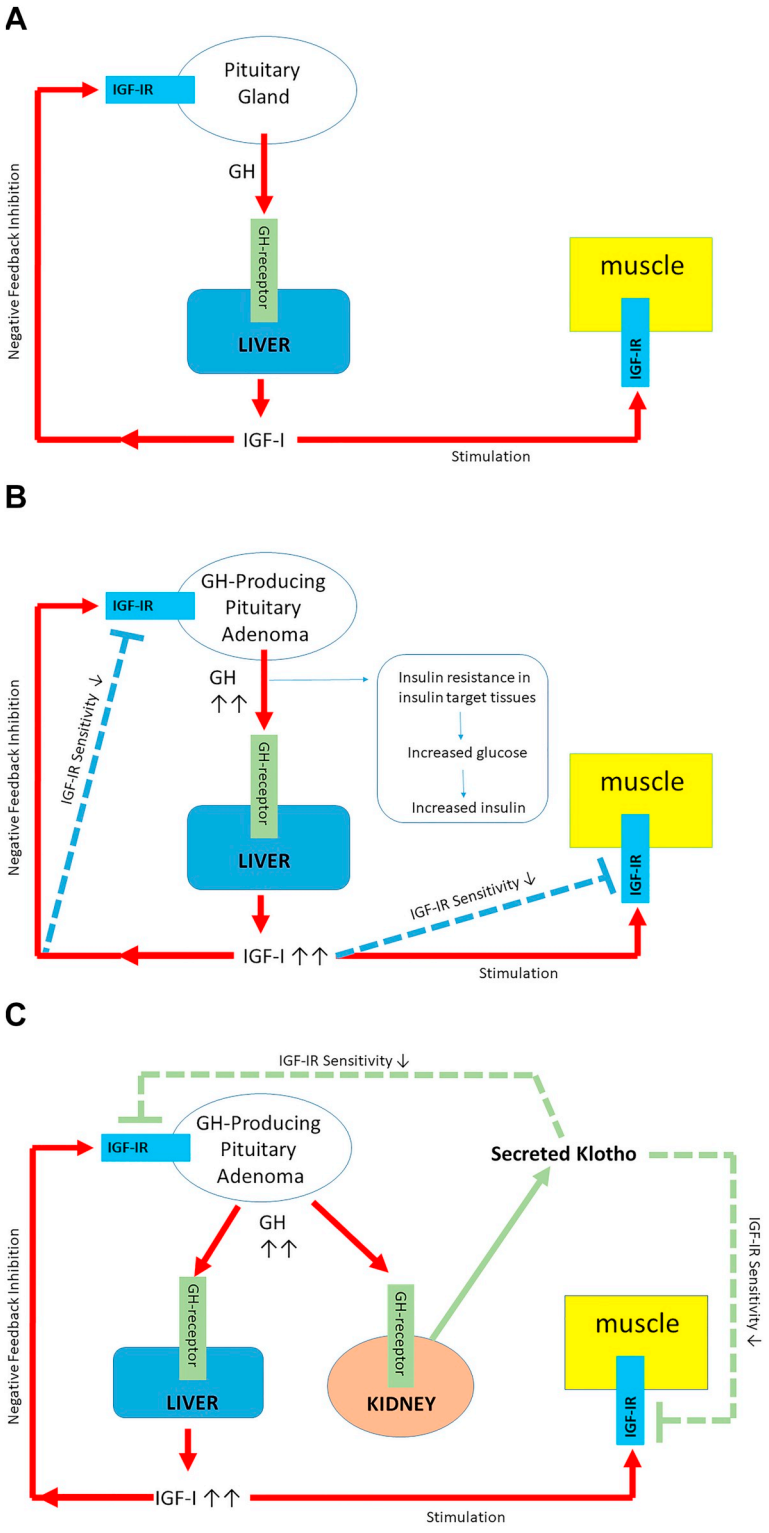

Fig. 3. A. In healthy subjects growth hormone (GH) secreted by the pituitary stimulates hepatic insulin-like growth factor-I (IGF-I) production in the liver and release to the circulation. The circulating IGF-I exerts a homeostatic feedback inhibition on GH secretion by the pituitary and hypothalamus. In addition, circulating IGF-I stimulates the IGF-IR in muscles and other extrahepatic tissues. B In active (untreated) acromegaly there is usually overproduction of growth hormone (GH) by a pituitary adenoma. As a consequence of excessive GH secretion, circulating insulin-like growth factor-I (IGF-I) concentrations are increased. Increased IGF-I levels per se may induce a degree of IGF-IR resistance. In the presence of IGF-IR resistance at the pituitary (and hypothalamus), the IGF-I-induced feedback inhibition of GH secretion is ineffective, leading to increased circulating GH and IGF-I levels. The high circulating IGF-I levels have also reduced effects in muscles and other tissues through the (IGF-I -induced) (relative) IGF-IR resistance. The high GH secretion can lead to insulin resistance, hyperglycemia and hyperinsulinemia. C Circulating levels of S-Klotho levels in acromegaly depend on GH to a comparable extent as IGF-I. When there is overproduction of growth hormone (GH) by a pituitary adenoma Soluble Klotho (S-Klotho) levels are markedly increased in active (untreated) acromegaly. Circulating S-Klotho is most likely of renal origin, but the exact mechanism by which excess GH results in increased release of kidney-derived S-klotho has not yet been elucidated. S-Klotho is also a protein that has been reported to inhibit IGF-IR signaling by inhibiting tyrosine phosphorylation and its downstream signaling proteins (i.e. IRS) (see also Fig. 4). Thus increased S-Klotho levels may induce a degree of IGF-IR resistance. As a consequence the IGF-I-induced feedback inhibition of GH secretion at the pituitary (or hypothalamus) level is reduced, leading to elevations in GH and IGF-I. In addition, the increased circulating IGF-I levels have reduced effects in muscles and other tissues through the S-Klotho-induced IGF-IR resistance.

which - as above discussed- is predominantly involved in metabolic actions [20]. Recently it has been suggested that depletion of insulin receptor substrate-1 (IRS-1) by prolonged IGF-I stimulation accelerates IGF-IR endocytosis and thereby induces a shift from sustained to transient Akt signaling [20]. In the presence of a degree of IGF-IR resistance of the pituitary (and hypothalamus), the IGF-I-induced feedback inhibition of GH secretion will be reduced, leading to increased GH and IGF-I (Fig. 3B). When there is an IGF-I -induced degree of IGF-IR resistance of the Akt pathway, high circulating IGF-I levels will have little or reduced metabolic effects in muscles, but the high GH secretion as consequence of the ineffective negative feedback of IGF-I on the pituitary gland, can lead to insulin resistance, hyperglycemia and hyperinsulinemia (Fig. 3B).

6.2. *Insulin and IGF-I receptor signaling*

Hyperinsulinemia and insulin resistance are important metabolic hallmarks of acromegaly and they are strongly related to disease

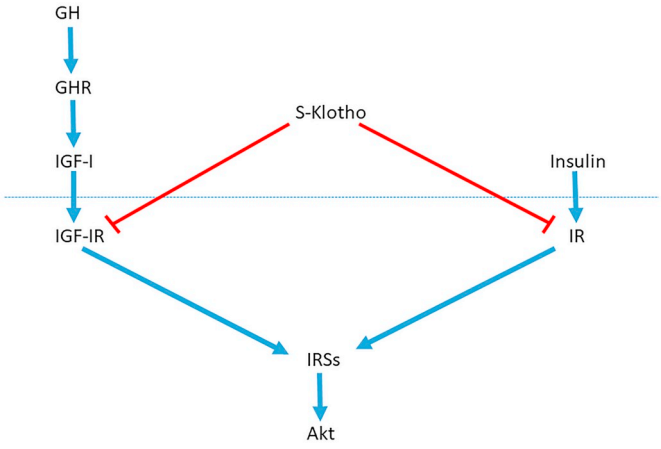

Fig. 4. Elevated Soluble Klotho (S-Klotho) levels in active acromegaly may contribute to (some degree of) insulin-like growth factor-I (IGF-IR) resistance and Insulin Receptor (IR) resistance at the receptor and post-receptor level. Phosphorylation of the IGF-IR by IGF-I and phosphorylation of the IR by insulin is reduced by S-Klotho. As a consequence Insulin Receptor Substrates (IRSs) and the Akt pathway, which is predominantly involved in metabolic actions, will be less stimulated.

activity [58]. Stimulation of the insulin receptor by insulin leads to a decrease in intracellular IRS-1 levels [13]. Since IGF-I can also signal through IRS−I, this may contribute to impaired IGF-I stimulated AKT pathway [13]. In addition, it has been found that insulin after binding to the insulin receptor may induce heterologous desensitization of the signaling of the IGF-IR by downregulating β-arrestin-1 and inhibition of IGF-I-stimulated MAP kinase phosphorylation [13]. Thus hyperinsulinemia may reset the responsiveness of the IGF-IR and this may be another mechanism responsible for (some degree of) IGF-IR resistance at the post-receptor level in active acromegaly. It has been further suggested that serine phosphorylation of IRS-1 is another mechanism of the body to inhibit excess insulin- and IGF-I-mediated Akt1 signaling in active acromegaly [12]. In favor of this latter possibility, it has been found that elevated insulin and IGF-I in bGH giant mice increase serine phosphorylation of IRS-1 in skeletal muscles and it has been suggested that this may act to inhibit exaggerated glycolytic muscle growth in environments of chronic GH/IGF-I excess [12].

It is thought that hyperinsulinemia, insulin resistance, glucose intolerance and type 2 diabetes in active acromegaly are induced by the prolonged exposure to high GH. For sure, hypersecretion of GH is an important mediator of hyperinsulinemia and insulin resistance. Chronic GH excess acts at several levels to block insulin actions and this induces hyperglycaemia by increasing endogenous glucose production and decreasing peripheral glucose disposal in muscle [9]. Chronic GH excess may induce a reduction in the number of insulin receptors at the cell surface and an impairment of the kinase activity of the insulin receptors [3,16]. Although the GH receptor lacks intrinsic tyrosine kinase activity, it stimulates the activity of JAK-2, a tyrosine kinase that associates with the cytoplasmic domain of the activated GH receptor. It has been suggested that activation of JAK-2 might result in tyrosine phosphorylation of IRS-1 and possibly other proteins in the insulin signaling pathway and thereby account for the insulin-like actions of GH [51,61]. Chronic GH excess may lead to an increased phosphorylation status of the insulin receptor and IRS-1 so that the insulin receptor and IRS-1 are maximally activated in the resting state [17,18]. The basal association of phosphatidylinositol3-kinase (PI-3 kinase) with IRS-1, as well as PI-3 kinase activity, is also increased to maximal levels. The maximal activation of the insulin receptor under basal conditions has the effect of making the insulin receptor insensitive for further stimulation by insulin [3,16]. As a consequence chronic exposure to GH excess is associated with a decreased response to insulin stimulation in terms of IRS-I phosphorylation and PI-3 kinase activity in skeletal muscle [16]. In the adipocytes chronic GH treatment causes insulin resistance by uncoupling activation of PI-3 kinase and its downstream signals [53]. In the liver GH excess leads to chronic activation of the IR/IRS-1/PI-3 kinase pathway, thus blocking insulin-induced activation [16]. Thus despite hyperinsulinemia peripheral glucose uptake in muscles and other insulin-dependent tissues is reduced whereas also the ability of insulin to suppress gluconeogenesis is significantly reduced [9]. A similar mechanism may be active for elevated circulating IGF-I levels and the IGF-IR.

6.3. IGF-I receptor and Klotho

Klotho is a transmembrane protein mainly expressed in the kidneys, choroid plexus and various endocrine-related tissues including the pituitary [46]. Klotho is an essential cofactor for the binding of fibroblast growth factor 23 to its receptor, serving as a major regulator of phosphate metabolism [30]. It is also a potent inhibitor of the insulin and IGF-I signaling [1,31,60]. In addition to its local effects Klotho can be cleaved by two specific proteases (ADAM 10 and 17), shed and released from the cell membrane to act as a circulating hormone (Soluble Klotho (S-Klotho)) [29]. Insulin has been shown to activate both of these proteases [8]. Currently GH and IGF-I are the biochemical markers used to confirm active acromegaly and also for assessing the activity of acromegaly [57]. However, recent data show that serum levels of S-Klotho levels in acromegaly depend on GH to a comparable extent as IGF-I. Excessive GH secretion results in markedly increased circulating S-klotho levels in (untreated) active acromegaly [41] and they decrease rapidly following adenoma removal suggesting a causal relation between GH-producing adenoma and high serum levels of S-Klotho in active acromegaly [41,52]. Therefore circulating S-Klotho has been introduced as a novel biomarker for the activity of GH-producing adenoma [41]. Elevated circulating S-Klotho is most likely of renal origin, but the exact mechanism by which excess GH results in increased release of kidney-derived S-klotho has not yet been elucidated [49]. It has been further found that S-Klotho can inhibit the activation of the IGF-IR in a dose-dependent manner [31,59]. Thus elevated S-Klotho levels in active acromegaly may contribute to (some degree of) IGF-IR resistance [57]. As a consequence the IGF-I-induced feedback inhibition of GH secretion at the pituitary (or hypothalamus) level is reduced, leading to elevations in GH and IGF-I (Fig. 3C). Interestingly, S-Klotho is a protein that has been reported also to inhibit IGF-IR and insulin receptor signaling by inhibiting tyrosine phosphorylation of both receptors and their downstream signaling proteins (i.e. IRS) [31,60] (Fig. 4). Thus due to S-Klotho-induced IGF-IR resistance elevated circulating IGF-I levels in active acromegaly have reduced effects in muscles and other tissues.

6.4. Hyperglycemia and IGF-IR resistance

Chronic hyperglycemia probably plays also a role in the development of IGF-IR resistance in active acromegaly. In cells exposed in vitro to normal glucose, stimulation of the IGF-IR and its kinase results in phosphorylation IRS-1 [38]. As above discussed, this is an important adaptor protein that couples IGF-I stimulation of the IGF-IR to downstream activation of the PI-3 kinase signaling pathway. However, following exposure to hyperglycemia it has been reported that IGF-I responsiveness was reduced and IRS-I was down regulated [38].

7. GH hypersecretion and functional IGF-IR resistance in active acromegaly

Persistent GH hypersecretion in active acromegaly together with highly elevated IGF-I implies impaired negative feedback by IGF-I. In support of this, it has been reported that negative feedback regulation is greatly attenuated in active acromegaly [23]. The possibility that loss of

IGF-I feedback at the level of the pituitary/hypothalamus plays a pathophysiological role in GH hypersecretion in acromegaly is supported by in vitro data [23]. Furthermore, it has been suggested that a decrease in number of IGF-IRs on somatotroph adenoma cells contributes to GH hypersecretion in acromegaly or that alternatively, post-receptor abnormalities play a role in IGF-IR resistance [23]. Development of a degree of IGF-IR resistance (mediated by elevated IGF-I, insulin and S-Klotho levels) in active acromegaly may function as a safety valve of the body that counteracts overstimulation by IGF-I of the IGF-IR in order to avoid too large changes of the homeostasis [20].

8. Elevated IGF-I levels, IGF-IR resistance and effects on metabolism in active acromegaly

As discussed above, compared to GH, IGF-I has divergent effects on carbohydrate and lipid metabolism [37]. Most of the established metabolic effects of GH may be classified as insulin-antagonistic: for example, gluconeogenesis and lipolysis are stimulated by GH [21]. Most metabolic effects of IGF-I can be classified as insulin-like [37]. For example, IGF-I increases glucose uptake of muscles and inhibits gluconeogenesis. In addition, IGF-I can improve insulin sensitivity [9]. In fact GH antagonizes the effects of IGF-I on glucose metabolism [37]. Although IGF-I has been found to be 0.05–0.1 times as potent as insulin in terms of stimulating glucose transport in vitro and inducing hypoglycemia, in vivo its concentration is in healthy subjects approximately 100 times higher compared to that of insulin [34,43,62]. In active (untreated) acromegaly circulating IGF-I levels are usually >2 SD above the upper limit of the normal range. Despite these elevated IGF-I levels and the insulin-like effects of IGF-I, active acromegaly is characterized by hyperinsulinemia, insulin resistance, high plasma glucose concentrations and type 2 diabetes. However, in subjects without acromegaly a potent glucose lowering effect is typically observed after recombinant IGF-I administration, with improved insulin sensitivity and lowering of insulin concentrations [37]. Even though this effect may be (partly) mediated through stimulation of the insulin receptor, experimental mice knockouts of the insulin receptor also show a potent glucose lowering effect of IGF-I, indicative that the hypoglycemic effect of IGF-I is mediated at least in part directly through the IGF-IR [15,37]. In addition, chronic IGF-I stimulation improves insulin sensitivity of skeletal muscle and adipose tissue resulting in increased glucose transport, increased glycogenesis and decreased lipolysis [22]. Administration of IGF-I to subjects with type 2 diabetes results in a marked enhancement of insulin sensitivity and a clear improvement of diabetic control [10,39,40]. When Clemmons et al. previously studied patients with active acromegaly and severe insulin resistance, they observed -as expected- an improvement of insulin sensitivity and glucose control after administration of the GH antagonist pegvisomant [44]. Although insulin resistance that ensues acromegaly was at least partly improved by lowering GH hypersecretion in this latter study, interestingly, a more marked improvement in insulin sensitivity and glucose control was observed when IGF-I was added to pegvisomant [44]. This finding does not only suggest that IGF-I may have insulin-sensitizing actions on top of and independent of its ability to suppress GH secretion, but it also suggests that in untreated acromegaly endogenous markedly elevated circulating IGF-I levels are insufficient to neutralize GH-mediated effects on insulin resistance [9]. Development of a degree of IGF-IR resistance -initiated and sustained by high circulating IGF-I, insulin and S-Klotho levels- could explain why in active acromegaly even IGF-I levels >2SD above the normal range are not able and sufficient to overcome the effects of GH on metabolism and to normalize insulin sensitivity and glucose tolerance. When chronically elevated IGF-I, insulin and soluble Klotho play a pathophysiological role in the development of IGF-IR resistance in active acromegaly, sensitivity of the IGF-IR will be improved by removing elevated circulating IGF-I, insulin and soluble Klotho levels.

Normalization of circulating IGF-I is more frequently achieved by monotherapy with the GH antagonist (pegvisomant) than by somatostatin analogues [19,55]. Moreover, pegvisomant ameliorates all aspects of glucose metabolism, while somatostatin analogues sometimes increase plasma glucose levels [58]. At first glance this suggests, theoretically at least, that medical therapy with pegvisomant is better able to reverse IGF-IR resistance in active acromegaly than somatostatin analogues. However, further studies are needed to elucidate the exact role of pegvisomant and somatostatin analogues on reversal of IGF-IR resistance in active acromegaly.

In conclusion, active acromegaly is characterized by increased GH secretion, elevated circulating IGF-I, insulin and S-Klotho levels. In this paper the hypothesis is born that in active acromegaly chronically elevated IGF-I, insulin and/or S-Klotho levels initiate and sustain a degree of IGF-IR resistance. The development of a degree of IGF-IR resistance (especially for metabolic functions of the IGF-IR) may help to explain why in active acromegaly GH-mediated effects on glucose metabolism predominate over IGF-I and are not prevented and counter-regulated by elevated circulating levels of IGF-I. Further studies are necessary to support this hypothesis.

Funding

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

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Declaration of Competing Interest

The author has no competing interests to declare.

Acknowledgement

The author is grateful to Dr. Aimee J. Varewijck, Dr. Michael P. Brugts and Prof dr. Leo J. Hofland for comments and proofreading the manuscript.

References

[1] L. Abramovitz, T. Rubinek, H. Ligumsky, S. Bose, I. Barshack, C. Avivi, B. Kaufman, I. Wolf, KL1 internal repeat mediates klotho tumor suppressor activities and inhibits bFGF and IGF-I signaling in pancreatic cancer, Clin. Cancer Res. 17 (2011) 4254–4266.
[2] M. Arosio, S. Garrone, P. Bruzzi, G. Faglia, F. Minuto, A. Barreca, Diagnostic value of the acid-labile subunit in acromegaly: evaluation in comparison with insulin-like growth factor (IGF) I, and IGF-binding protein-1, −2, and −3, J. Clin. Endocrinol. Metab. 86 (2001) 1091–1098.
[3] A. Balbis, A. Bartke, D. Turyn, Overexpression of bovine growth hormone in transgenic mice is associated with changes in hepatic insulin receptors and in their kinase activity, Life Sci. 59 (1996) 1363–1371.
[4] A. Barreca, G. Cariola, P. Ponzani, M. Arvigo, L. Foppiani, G. Giordano, F. Minuto, Effect of octreotide on circulating IGF-I chromatographic profile: evidence for an inhibitory action on the formation of the 150-kDa ternary complex, Clin. Endocrinol. 42 (1995) 161–167.
[5] M. Berelowitz, M. Szabo, L.A. Frohman, S. Firestone, L. Chu, R.L. Hintz, Somatomedin-C mediates growth hormone negative feedback by effects on both the hypothalamus and the pituitary, Science 212 (1981) 1279–1281.
[6] A.M. Brooke, W.M. Drake, Serum IGF-I levels in the diagnosis and monitoring of acromegaly, Pituitary 10 (2007) 173–179.
[7] G.P. Ceda, R.G. Davis, R.G. Rosenfeld, A.R. Hoffman, The growth hormone (GH)-releasing hormone (GHRH)-GH-somatomedin axis: evidence for rapid inhibition of GHRH-elicited GH release by insulin-like growth factors I and II, Endocrinology 120 (1987) 1658–1662.
[8] C.D. Chen, S. Podvin, E. Gillespie, S.E. Leeman, C.R. Abraham, Insulin stimulates the cleavage and release of the extracellular domain of klotho by ADAM10 and ADAM17, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 19796–19801.
[9] D.R. Clemmons, Roles of insulin-like growth factor-I and growth hormone in mediating insulin resistance in acromegaly, Pituitary 5 (2002) 181–183.
[10] D.R. Clemmons, A.C. Moses, A. Sommer, W. Jacobson, A.D. Rogol, M.R. Sleevi, G. Allan, Rh/IGF-I/rhIGFBP-3 administration to patients with type 2 diabetes

mellitus reduces insulin requirements while also lowering fasting glucose, Growth Hormon. IGF Res. 15 (2005) 265–274.
[11] C.A. Conover, D.R. Powell, Insulin-like growth factor (IGF)-binding protein-3 blocks IGF-I-induced receptor down-regulation and cell desensitization in cultured bovine fibroblasts, Endocrinology 129 (1991) 710–716.
[12] L.A. Consitt, A. Saneda, G. Saxena, E.O. List, J.J. Kopchick, Mice overexpressing growth hormone exhibit increased skeletal muscle myostatin and MuRF1 with attenuation of muscle mass, Skelet. Muscle 7 (2017) 17.
[13] S. Dalle, T. Imamura, D.W. Rose, D.S. Worrall, S. Ugi, C.J. Hupfeld, J.M. Olefsky, Insulin induces heterologous desensitization of G-protein-coupled receptor and insulin-like growth factor I signaling by downregulating beta-arrestin-1, Mol. Cell. Biol. 22 (2002) 6272–6285.
[14] F. Dehkhoda, C.M.M. Lee, J. Medina, A.J. Brooks, The growth hormone receptor: mechanism of receptor activation, cell signaling, and physiological aspects, Front Endocrinol (Lausanne) 9 (2018) 35.
[15] G. Di Cola, M.H. Cool, D. Accili, Hypoglycemic effect of insulin-like growth factor-1 in mice lacking insulin receptors, J. Clin. Invest. 99 (1997) 2538–2544.
[16] F.P. Dominici, D.P. Argentino, M.C. Munoz, J.G. Miquet, A.I. Sotelo, D. Turyn, Influence of the crosstalk between growth hormone and insulin signalling on the modulation of insulin sensitivity, Growth Hormon. IGF Res. 15 (2005) 324–336.
[17] F.P. Dominici, D. Cifone, A. Bartke, D. Turyn, Alterations in the early steps of the insulin-signaling system in skeletal muscle of GH-transgenic mice, Am. J. Phys. 277 (1999) E447–E454.
[18] F.P. Dominici, D. Cifone, A. Bartke, D. Turyn, Loss of sensitivity to insulin at early events of the insulin signaling pathway in the liver of growth hormone-transgenic mice, J. Endocrinol. 161 (1999) 383–392.
[19] L.F.S. Grasso, R.S. Auriemma, R. Pivonello, A. Colao, Somatostatin analogs, cabergoline and pegvisomant: comparing the efficacy of medical treatment for acromegaly, Expert. Rev. Endocrinol. Metab. 12 (2017) 73–85.
[20] F. Hakuno, S.I. Takahashi, IGF1 receptor signaling pathways, J. Mol. Endocrinol. 61 (2018) T69–T86.
[21] R.I. Holt, H.L. Simpson, P.H. Sonksen, The role of the growth hormone-insulin-like growth factor axis in glucose homeostasis, Diabet. Med. 20 (2003) 3–15.
[22] R. Jacob, E. Barrett, G. Plewe, K.D. Fagin, R.S. Sherwin, Acute effects of insulin-like growth factor I on glucose and amino acid metabolism in the awake fasted rat. Comparison with insulin, J. Clin. Invest. 83 (1989) 1717–1723.
[23] C.A. Jaffe, W. Pan, M.B. Brown, R. DeMott-Friberg, A.L. Barkan, Regulation of GH secretion in acromegaly: reproducibility of daily GH profiles and attenuated negative feedback by IGF-I, J. Clin. Endocrinol. Metab. 86 (2001) 4364–4370.
[24] S. Jain, D.W. Golde, R. Bailey, M.E. Geffner, Insulin-like growth factor-I resistance, Endocr. Rev. 19 (1998) 625–646.
[25] J.L. Jameson, Molecular mechanisms of end-organ resistance, Growth Horm IGF Res 14 (Suppl A) (2004) S45–S50.
[26] J. Janssen, A.J. Varewijck, M.P. Brugts, The insulin-like growth factor-I receptor stimulating activity (IRSA) in health and disease, Growth Hormon. IGF Res. 48-49 (2019) 16–28.
[27] A. Juul, K. Main, W.F. Blum, J. Lindholm, M.B. Ranke, N.E. Skakkebaek, The ratio between serum levels of insulin-like growth factor (IGF)-I and the IGF binding proteins (IGFBP-1, 2 and 3) decreases with age in healthy adults and is increased in acromegalic patients, Clin. Endocrinol. 41 (1994) 85–93.
[28] B. Kola, M. Korbonits, S. Diaz-Cano, G. Kaltsas, D.G. Morris, S. Jordan, L. Metherell, M. Powell, S. Czirjak, G. Arnaldi, S. Bustin, M. Boscaro, F. Mantero, A.B. Grossman, Reduced expression of the growth hormone and type 1 insulin-like growth factor receptors in human somatotroph tumours and an analysis of possible mutations of the growth hormone receptor, Clin. Endocrinol. 59 (2003) 328–338.
[29] M. Kuro-o, Y. Matsumura, H. Aizawa, H. Kawaguchi, T. Suga, T. Utsugi, Y. Ohyama, M. Kurabayashi, T. Kaname, E. Kume, H. Iwasaki, A. Iida, T. Shiraki-Iida, S. Nishikawa, R. Nagai, Y.I. Nabeshima, Mutation of the mouse klotho gene leads to a syndrome resembling ageing, Nature 390 (1997) 45–51.
[30] H. Kurosu, Y. Ogawa, M. Miyoshi, M. Yamamoto, A. Nandi, K.P. Rosenblatt, M.G. Baum, S. Schiavi, M.C. Hu, O.W. Moe, M. Kuro-o, Regulation of fibroblast growth factor-23 signaling by klotho, J. Biol. Chem. 281 (2006) 6120–6123.
[31] H. Kurosu, M. Yamamoto, J.D. Clark, J.V. Pastor, A. Nandi, P. Gurnani, O.P. McGuinness, H. Chikuda, M. Yamaguchi, H. Kawaguchi, I. Shimomura, Y. Takayama, J. Herz, C.R. Kahn, K.P. Rosenblatt, M. Kuro-o, Suppression of aging in mice by the hormone klotho, Science 309 (2005) 1829–1833.
[32] S.W. Lamberts, P. Uitterlinden, T. Verleun, Relationship between growth hormone and somatomedin-C levels in untreated acromegaly, after surgery and radiotherapy and during medical therapy with sandostatin (SMS 201-995), Eur. J. Clin. Investig. 17 (1987) 354–359.
[33] N.J. Lanning, C. Carter-Su, Recent advances in growth hormone signaling, Rev. Endocr. Metab. Disord. 7 (2006) 225–235.
[34] Y. Le Marchand-Brustel, P. Freychet, Effect of fasting and streptozotocin diabetes on insulin binding and action in the isolated mouse soleus muscle, J. Clin. Invest. 64 (1979) 1505–1515.
[35] C.A. LeDuc, R.L. Leibel, Auto-regulation of leptin neurobiology, Cell Metab. 30 (2019) 614–616.
[36] M. Lu, J.U. Flanagan, R.J. Langley, M.P. Hay, J.K. Perry, Targeting growth hormone function: strategies and therapeutic applications, Signal Transduct Target Ther 4 (2019) 3.
[37] N. Mauras, M.W. Haymond, Are the metabolic effects of GH and IGF-I separable? Growth Hormon. IGF Res. 15 (2005) 19–27.
[38] S. Melmed, Acromegaly pathogenesis and treatment, J. Clin. Invest. 119 (2009) 3189–3202.
[39] L.A. Morrow, M.B. O'Brien, D.E. Moller, J.S. Flier, A.C. Moses, Recombinant human insulin-like growth factor-I therapy improves glycemic control and insulin action in the type a syndrome of severe insulin resistance, J. Clin. Endocrinol. Metab. 79 (1994) 205–210.
[40] A.C. Moses, S.C. Young, L.A. Morrow, M. O'Brien, D.R. Clemmons, Recombinant human insulin-like growth factor I increases insulin sensitivity and improves glycemic control in type II diabetes, Diabetes 45 (1996) 91–100.
[41] M.C. Neidert, L. Sze, C. Zwimpfer, J. Sarnthein, B. Seifert, K. Frei, H. Leske, E.J. Rushing, C. Schmid, R.L. Bernays, Soluble alpha-klotho: a novel serum biomarker for the activity of GH-producing pituitary adenomas, Eur. J. Endocrinol. 168 (2013) 575–583.
[42] R.H. Nielsen, N.M. Clausen, P. Schjerling, J.O. Larsen, T. Martinussen, E.O. List, J.J. Kopchick, M. Kjaer, K.M. Heinemeier, Chronic alterations in growth hormone/insulin-like growth factor-I signaling lead to changes in mouse tendon structure, Matrix Biol. 34 (2014) 96–104.
[43] K. Rajkumar, M. Krsek, S.T. Dheen, L.J. Murphy, Impaired glucose homeostasis in insulin-like growth factor binding protein-1 transgenic mice, J. Clin. Invest. 98 (1996) 1818–1825.
[44] D.R. Rose, D.R. Clemmons, Growth hormone receptor antagonist improves insulin resistance in acromegaly, Growth Hormon. IGF Res. 12 (2002) 418–424.
[45] R.G. Rosenfeld, G. Ceda, D.M. Wilson, L.A. Dollar, A.R. Hoffman, Characterization of high affinity receptors for insulin-like growth factors I and II on rat anterior pituitary cells, Endocrinology 114 (1984) 1571–1575.
[46] T. Rubinek, I. Wolf, D. Modan-Moses, The longevity hormone klotho is a new player in the Interacion of the growth hormone/insulin-like growth factor 1 Axis, Pediatr. Endocrinol. Rev. 14 (2016) 9–18.
[47] A. Sata, K.K. Ho, Growth hormone measurements in the diagnosis and monitoring of acromegaly, Pituitary 10 (2007) 165–172.
[48] R. Schillaci, M.G. Brocardo, A. Galeano, A. Roldan, Downregulation of insulin-like growth factor-1 receptor (IGF-1R) expression in human T lymphocyte activation, Cell. Immunol. 183 (1998) 157–161.
[49] C. Schmid, M.C. Neidert, O. Tschopp, L. Sze, R.L. Bernays, Growth hormone and klotho, J. Endocrinol. 219 (2013) R37–R57.
[50] M.H. Shanik, Y. Xu, J. Skrha, R. Dankner, Y. Zick, J. Roth, Insulin resistance and hyperinsulinemia: is hyperinsulinemia the cart or the horse? Diabetes Care 31 (Suppl. 2) (2008) S262–S268.
[51] S.C. Souza, G.P. Frick, R. Yip, R.B. Lobo, L.R. Tai, H.M. Goodman, Growth hormone stimulates tyrosine phosphorylation of insulin receptor substrate-1, J. Biol. Chem. 269 (1994) 30085–30088.
[52] L. Sze, R.L. Bernays, C. Zwimpfer, P. Wiesli, M. Brandle, C. Schmid, Excessively high soluble klotho in patients with acromegaly, J. Intern. Med. 272 (2012) 93–97.
[53] A. Takano, T. Haruta, M. Iwata, I. Usui, T. Uno, J. Kawahara, E. Ueno, T. Sasaoka, M. Kobayashi, Growth hormone induces cellular insulin resistance by uncoupling phosphatidylinositol 3-kinase and its downstream signals in 3T3-L1 adipocytes, Diabetes 50 (2001) 1891–1900.
[54] A.J. van der Lely, W.W. de Herder, J.A. Janssen, S.W. Lamberts, Acromegaly: the significance of serum total and free IGF-I and IGF-binding protein-3 in diagnosis, J Endocrinol 155 (Suppl. 1) (1997) S9–13 discussion S15–16.
[55] A.J. van der Lely, J.J. Kopchick, Growth hormone receptor antagonists, Neuroendocrinology 83 (2006) 264–268.
[56] A.J. Varewijck, S.W. Lamberts, P. Uitterlinden, L.J. Hofland, J.A. Janssen, IGF-I bioactivity better reflects growth hormone deficiency than total IGF-I, J. Clin. Endocrinol. Metab. 96 (2011) 2248–2254.
[57] A.J. Varewijck, A.J. van der Lely, S.J. Neggers, S.W. Lamberts, L.J. Hofland, J.A. Janssen, In active acromegaly, IGF1 bioactivity is related to soluble klotho levels and quality of life, Endocr Connect 3 (2014) 85–92.
[58] G. Vila, J.O.L. Jorgensen, A. Luger, G.K. Stalla, Insulin resistance in patients with acromegaly, Front Endocrinol (Lausanne) 10 (2019) 509.
[59] Y. Wang, L. Chen, G. Huang, D. He, J. He, W. Xu, C. Zou, F. Zong, Y. Li, B. Chen, S. Wu, W. Zhao, J. Wu, Klotho sensitizes human lung cancer cell line to cisplatin via PI3k/Akt pathway, PLoS One 8 (2013) e57391.
[60] I. Wolf, S. Levanon-Cohen, S. Bose, H. Ligumsky, B. Sredni, H. Kanety, M. Kuro-o, B. Karlan, B. Kaufman, H.P. Koeffler, T. Rubinek, Klotho: a tumor suppressor and a modulator of the IGF-1 and FGF pathways in human breast cancer, Oncogene 27 (2008) 7094–7105.
[61] T. Yamauchi, Y. Kaburagi, K. Ueki, Y. Tsuji, G.R. Stark, I.M. Kerr, T. Tsushima, Y. Akanuma, I. Komuro, K. Tobe, Y. Yazaki, T. Kadowaki, Growth hormone and prolactin stimulate tyrosine phosphorylation of insulin receptor substrate-1, −2, and −3, their association with p85 phosphatidylinositol 3-kinase (PI3-kinase), and concomitantly PI3-kinase activation via JAK2 kinase, J. Biol. Chem. 273 (1998) 15719–15726.
[62] J. Zapf, C. Hauri, M. Waldvogel, E.R. Froesch, Acute metabolic effects and half-lives of intravenously administered insulinlike growth factors I and II in normal and hypophysectomized rats, J. Clin. Invest. 77 (1986) 1768–1775.