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Growth Hormone Signaling in the Regulation of Acid Labile Subunit

Jin Wook Kim* and Yves R. Boisclair[1]

Division of Applied Life Sciences (Institute of Agriculture and Life Science), College of Agriculture and Life Sciences
Gyeongsang National University, Jinju 660-701, Korea

ABSTRACT : The past decades have seen enormous advances in our understanding of how GH acts. GH is a pituitary-derived polypeptide hormone that has diverse physiological effects including the regulation of bone growth, carbohydrate and lipid metabolism. The effects of GH are mediated directly and indirectly through IGF-I. In addition, GH stimulates the hepatic production of ALS. In postnatal life, IGF-I and -II circulate as 150 kDa ternary complexes consisting of one molecule each of IGFBP-3 or IGFBP-5, IGF-I or IGF-II and ALS. It is now known that ALS increases significantly the half-lives of the IGFs, IGFBP-3 and -5, and therefore is responsible for maintaining a circulating reservoir for each of these proteins. (**Key Words** : Growth Hormone, Signaling, Acid Labile Subunit)

INTRODUCTION

GH was discovered in 1921. Since then, it has been regarded as the primary factor controlling postnatal growth rate (Le Roith et al., 2001; Lupu et al., 2001). GH also regulates physiological processes including carbohydrate and lipid metabolism in several tissues through the activation of GH receptor (direct action) or the stimulation of IGF-I synthesis (indirect action) (Etherton and Bauman, 1998; Herrington and Carter-Su, 2001; Okada and Kopchick, 2001). GH activity can be regulated at the level of the GHR or intracellular signaling, with catabolic situations such as malnutrition, infection and disease leading to a state of GH resistance (Kopchick and Andry, 2000; Lucy et al., 2001; Zhu et al., 2001). GH resistance is characterized by reduced circulating IGF-I despite unchanged or increased plasma GH. In the vascular system, most of the IGFs circulate in ternary complexes composed of one molecule each of IGF-I or -II, IGFBP-3 or -5 and ALS (Zapf et al., 1986; Baxter, 1988; Twigg and Baxter, 1998). ALS is predominantly synthesized in liver in a GH-dependent manner, and regulates IGF-I actions (Ooi et al., 1998; Woelfle and Rotwein, 2004). Therefore, these two factors, IGF-I and ALS, could be used to assess the efficiency of hepatic GH action. In this review, I summarize what is known about the molecular mechanisms of GH action and ALS regulation.

* Corresponding Author: Jin Wook Kim. Tel: +82-55-751-5413, Fax: +82-55-751-5410, E-mail: jinkim@gnu.ac.kr
[1] Department of Animal Science, College of Agriculture and Life Sciences, Cornell University, Ithaca, New York 14853-4801, USA.
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ACTION OF GH

Growth

Several hormones are important for normal postnatal growth, but it is generally accepted that GH is the most important hormone in this respect. A major portion of the effects of GH on growth is mediated by IGF-I. GH stimulates growth by stimulating liver production of IGF-I, which in turn stimulates longitudinal bone growth in an endocrine manner (Daughaday et al., 1972; Daughaday and Rotwein, 1989). In contrast, GH is not essential for prenatal growth and development, as shown by the existence of normal-sized infants with either congenital absence of the pituitary or deletions of the genes encoding GH or the GH receptor (GHR) (Laron, 1993; Takahashi et al., 1996).

Knock-out of the IGF-I and IGF-I receptor in mice has demonstrated that the IGF-I signaling pathway is very important for tissue development and growth. IGF-I knock-out mice suffer from a 40% growth deficit at birth and nearly all die within a few hours. Surviving mice suffer from severe growth retardation despite markedly increased circulating GH (Baker et al., 1993; Liu et al., 1993; Powell-Braxton et al., 1993; LeRoith, 1996). In addition, when treated with GH, there was no significant effect of GH on

overall body growth or development in these mice (Liu and LeRoith, 1999). Also, IGF-I receptor knock-out mice are affected more profoundly (55% growth deficit at birth) and die of respiratory failure postnatally due to poor muscle development (Liu et al., 1993). Therefore, these studies demonstrate that IGF-I as well as its receptor play critical roles for normal growth and tissue development. To investigate further the relative importance of GH and IGF-I for growth, Lupu and co-workers (2001) compared the postnatal growth of mice lacking the GHR, IGF-I or both. From these studies, they concluded that the independent actions of GH and IGF-I accounted for 14 and 35% of postnatal growth, respectively, whereas the action of GH mediated by IGF-I accounted for 34% of postnatal growth. The unaccounted fraction (17%) represents growth that is completely independent of GH and IGF-I (Lupu et al., 2001). Therefore, GH and IGF-I promote postnatal growth by both independent and dependent manners.

In postnatal farm animals, it is evident that GH stimulates IGF-I synthesis, and that a positive relationship exists between body weight gain and plasma IGF-I (Etherton and Bauman, 1998; Bauman, 1999; Renaville et al., 2002). In growing pigs, exogenous porcine GH increased growth and protein deposition (Chung et al., 1985; Etherton et al., 1987; Evock et al., 1988). Consistent with IGF-I mediating the effect of GH, the miniature *Bos Indicus* cattle strain has low plasma IGF-I and a 30% growth deficit. Moreover, GH treatment fails to increase plasma IGF-I and has no positive effects on growth in these animals (Hammond et al., 1991; Liu et al., 1999; Kitagawa et al., 2001).

Metabolic effects

The biological effects of GH involve multiple organs and all major classes of nutrients (lipid, protein and carbohydrate). It is well established that GH decreases fat deposition and increases fat mobilization (Houseknecht et al., 1995). The alteration of lipogenesis and lipolysis appears to be a direct action of GH on adipose tissue (Bauman and Vernon, 1993; Etherton et al., 1993). GH treatment reduces the lipogenic response of adipose tissue to insulin *in vitro* (Walton and Etherton, 1986; Walton et al., 1986; Walton et al., 1987) and *in vivo* (Dunshea et al., 1992; Etherton et al., 1993). This results from decreased gene transcription and activities of key lipogenic enzymes such as fatty acid synthase, acetyl-CoA carboxylase and glucose-6-phosphate dehydrogenase (Magri et al., 1990; Mildner and Clarke, 1991; Vernon et al., 1991; Harris et al., 1993; Liu et al., 1994a; Lanna et al., 1995). GH effects on lipid mobilization are also observed when energy intake is restricted (Machlin, 1972; Eisemann et al., 1986; Peters, 1986). GH increases the lipolytic effects (elevated plasma NEFA and glycerol) to cathecholamines in farm animals (McCutcheon and Bauman, 1986; Peters, 1986; Sechen et al., 1990b). This response appears to be mediated in part via the inhibitory G (Gi) protein which mediates the anti-lipolytic effects of adenosine. GH counteracts the effects of adenosine, and therefore causes increased catecholamine-mediated lipolysis (Doris et al., 1994; Lanna et al., 1995; Doris et al., 1996).

GH also increases hepatic gluconeogenesis in dairy cows (Pocius and Herbein, 1986; Knapp et al., 1992) and growing pigs (Gopinath and Etherton, 1989). It is thought that GH treatment attenuates the ability of insulin to decrease gluconeogenesis (Gopinath and Etherton, 1989). This may be important in lactating dairy cows because a decreased response to insulin would allow the liver to increase its rate of gluconeogenesis, and supply extra glucose to the mammary gland.

The administration of GH induces amino acid uptake by skeletal muscles (Kostyo, 1968) and increases whole body protein synthesis (Wolf et al., 1992) and nitrogen retention (Horber and Haymond, 1990). The increase in protein accretion is largely the result of increased protein synthesis, whereas protein degradation remains unchanged in ruminants and pigs (Eisemann et al., 1986; Eisemann et al., 1989; Seve et al., 1993; Boisclair et al., 1994). GH effects on protein synthesis may be mediated by IGF-I, and there is a correlation between plasma IGF-I and protein accretion rate in growing animals (Campbell et al., 1991), but not in neonatal animals (Burrin et al., 1997; Davis et al., 1997).

GH effects on the mammary gland have been extensively studied in farm animals. Milk yield responses to GH have been observed in pigs, sheep, goats and cows (Bauman and Vernon, 1993; Zhou et al., 2006). The mechanisms underlying these effects of GH are not clear. GH is not lactogenic when added to bovine mammary slices cultured *in vitro* (Goodman et al., 1983). Moreover, GH did not bind to membranes prepared from the bovine mammary gland (Gertler et al., 1984; Akers, 1985; Keys and Djiane, 1988; Glimm et al., 1990). Thus, it is believed that effects of GH on the mammary gland are mediated via IGF-I. Bovine mammary epithelial cells have an abundance of IGF-I receptors and IGF-I is a potent mitogen in these cells (Cohick, 1998; Weber et al., 2000). Indeed, close arterial infusion of IGF-I increased milk secretion in goats within 2-4 h (Prosser et al., 1990), although a 24 h infusion of IGF-I was not galactopoetic in goats (Prosser et al., 1995). In contrast, GHR mRNA has been shown in the bovine mammary gland (Glimm et al., 1990; Hauser et al., 1990; Glimm et al., 1992; Ropke et al., 1994). GHR is predominantly localized in the epithelium of ducts and alveoli, and is increased post partum (Sinowatz et al., 2000). This result suggests that GH may have direct effects on epithelial differentiation and milk secretion. In lactating cows treated with GH, milk yield responses are positively

correlated with plasma IGF-I concentration (Etherton and Bauman, 1998). In dairy cows after peak lactation, the typical milk yield increment with GH treatment is 10-15%. The fat, protein and lactose content of milk are not altered in well-fed cows (Chalupa and Galligan, 1989; Barbano et al., 1992).

GH SIGNALING

Growth hormone receptor (GHR)

The GH receptor is a single transmembrane protein of approximately 620 amino acids with a ligand binding extracellular domain (N terminus) of 246 residues, a short, transmembrane domain of 24 residues, and a large intracellular domain (C terminus) of 350 residues. The exact number of amino acids varies slightly from species to species. The receptor is initially synthesized as a pre-protein of ~640 amino acids, containing a short signal peptide (Edens and Talamantes, 1998; Schwartzbauer and Menon, 1998; Kopchick and Andry, 2000).

To date, the amino acid sequence of the GHR has been published for nine species. The human GHR is 84% identical to the rabbit receptor (Leung et al., 1987), ~70% identical to the rodent receptor (Baumbach et al., 1989; Mathews et al., 1989; Smith et al., 1989) and 76% identical to the bovine receptor (Hauser et al., 1990). GHR in most species has a molecular weight (Mr) of 110 to 140 kDa, although the Mr based on amino acid sequence is 70 kDa (Cramer and Talamantes, 1993). The difference between observed and predicted molecular weight reflects glycosylation.

GHR transcripts have been detected in a variety of tissues including liver, muscle, kidney, lung, mammary gland, placenta and adipose tissue, with the highest level of expression in liver (Edens and Talamantes, 1998; Schwartzbauer and Menon, 1998). By northern analysis, the GHR mRNA migrates at ~4.6 kb, although the exact size varies slightly from species to species. In all species, the major GHR transcripts are twice larger than the minimum 1.9 kb necessary to encode ~640 amino acid receptor. The majority of the excess size is due to the presence of an approximately 2 kb of 3'-untranslated region (Leung et al., 1987; Agarwal et al., 1994).

The transcription of the GHR gene is controlled by multiple promoters in human, rat, mouse, sheep and cattle (O'Mahoney et al., 1994; Heap et al., 1995; Menon et al., 1995; Zou et al., 1997). In cattle, there are three promoters (P1, P2 and P3) that transcribe three major classes of GHR transcripts, referred to as GHR1A, GHR1B and GHR1C, respectively (Heap et al., 1995; Schwartzbauer and Menon, 1998; Jiang et al., 1999; Jiang et al., 2000). The mRNA variants are produced by the alternative splicing of exon 1A, 1B or 1C onto a core transcript containing exons 2 to 10. All GHR mRNA classes encode identical proteins (Edens and Talamantes, 1998).

The GHR1A mRNA is expressed exclusively in liver where it accounts for ~50% of total hepatic GHR mRNA (Kobayashi et al., 1999; Jiang and Lucy, 2001b; Lucy et al., 2001). The promoter responsible for GHR1A synthesis (P1 promoter) is positively regulated by the hepatic nuclear factor 4, HNF-4 (Jiang and Lucy, 2001a) and STAT5 (Jiang et al., 2007). The P2 promoter transcribes GHR1B mRNA in a variety of tissues. GHR 1B mRNA accounts for ~35% of total GHR mRNA in liver and ~70% in other tissues (Heap et al., 1996; Jiang and Lucy, 2001b). The ubiquitous transcription factor, Sp1 is required for efficient activity of the P2 promoter. Sp1 acts by binding to a GC box containing element in the proximal region of the P2 promoter (Jiang et al., 2000). The GHR1C mRNA is also synthesized in a variety of tissues by the P3 promoter. GHR1C mRNA accounts for ~15% of total GHR in liver and ~30% in other tissues (Jiang et al., 1999; Jiang et al., 2000). The transcription factor responsible for the ubiquitous activity of the P3 promoter remains to be identified.

Kim et al. (2004) have reported that the bovine hepatic GHR protein can be measured by immunoblotting for the first time and reduced GHR1A abundance is partly responsible for the decline of GHR protein abundance in periparturient liver. Moreover, insulin and feed restriction regulates the efficiency of GH signaling in liver and adipose tissue of dairy cows by acting as a rheostat of GHR synthesis (Rhoads et al., 2004; Rhoads et al., 2007).

Propagation of GH signaling

Recent reviews have described the multiple transduction pathways used by GH (Carter-Su et al., 2000a; Herrington et al., 2000; Kopchick and Andry, 2000; Zhu et al., 2001). GHR dimerization is a key requirement for receptor activation and leads to the activation of Janus kinase 2 (JAK2). JAK2 is a member of the Janus family of mammalian tyrosine kinases, which is comprised of four cytoplasmic tyrosine kinases : JAK1, JAK2, JAK3 and TYK2 (Imada and Leonard, 2000; Zhu et al., 2001; Sodhi and Rajput, 2007). All four kinases have a pseudokinase domain (JH2; catalytically inactive) and a C-terminal kinase domain (JH1). Pseudokinase domain serves as a negative regulator, and maintains JAK2 inactive in the absence of cytokine stimulation (Saharinen et al., 2000). JAK2 has no SH2 domain (binding phosphorylated tyrosine residue) or SH3 domain (binding proline-rich domain). JAK2 associates with the GHR via interactions between the N-terminal region of JAK2 and Box 1 (proline rich element) of GHR. This is followed by JAK2 phosphorylation of key tyrosine residues on itself (autophosphorylation) and on the GHR. Thus, phosphorylated JAK2 and GHR provide

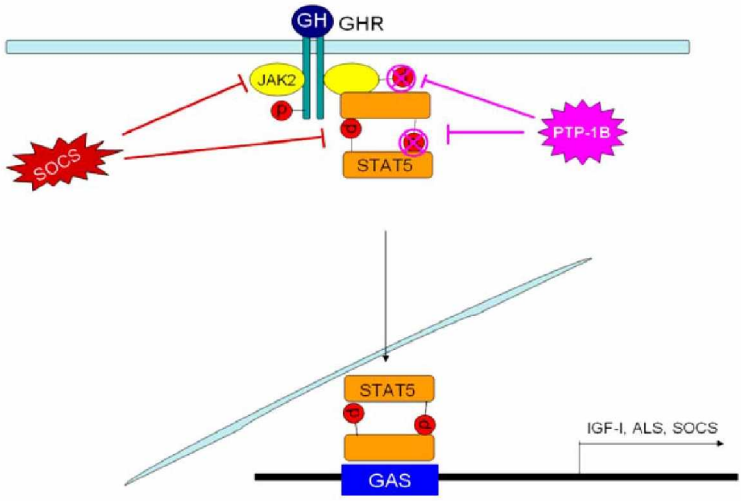

Figure 1. JAK-STAT pathway. GH binds a GHR dimer. JAK2 associates with GHR and phosphorylates GHR to provide multiple binding sites for STAT5. Phosphorylated STAT5 is dimerized and translocates into the nucleus where it binds to *cis*-element (GAS). Eventually, target genes such as IGF-I, ALS and SOCS are expressed. Termination occurs by SOCS as a competitor for binding to tyrosine residue of GHR, and by PTP-1B for dephosphorylating to tyrosine residue of JAK2.

multiple sites for signal molecules to bind via SH2 domain.

To date, four major signaling pathways mediating GH actions have been studied: 1) signal transducers and activators of transcription (STAT) signaling pathway (Figure 1); 2) mitogen-activated protein kinase (MAPK) pathway; 3) insulin receptor substrate (IRS) pathway; 4) Phospholipase Cγ (PLCγ) pathway. These pathways are characterized by intracellular signaling with multiple points of intersection and convergence, rather than linear paths leading to independent and exclusive cellular events. STAT signaling is the major pathway by which GH actions are transmitted. GH can activate four (STAT 1, 3, 5a and 5b) of the seven known mammalian STATs (Campbell et al., 1995; Smit et al., 1996). The STAT proteins contain many conserved domains including a DNA binding domain, SH2 and SH3 domains, a tyrosine residue serving as a substrate for JAK2 and a transcriptional activation domain. The SH2 domain of STAT binds to the tyrosine phosphorylated GHR cytoplasmic sites on either the GHR (STAT5a and 5b) or JAK2 (STAT1 and STAT3) (Yi et al., 1996). JAK2 phosphorylates STATs on a single tyrosine residue, and then STATs are dimerized via their SH2 domain. Dimerized STATs translocate into the nucleus where they bind to cis-elements in the promoter regions of target genes. The two major classes of cis-elements are γ-interferon-stimulated response element (GAS) binding STAT5a and 5b and interferon-stimulated response element (ISRE) binding STAT1 and 3 (Imada and Leonard, 2000).

The two forms of STAT5 (5a and 5b) are encoded by two different genes, and share 90% homology in their coding sequence (Shuai, 1999; Herrington et al., 2000). STAT5a plays a major role in mediating the effects of prolactin on mammary gland differentiation (Teglund et al., 1998), as shown by failure of mammary gland development and lactation in STAT5a knock-out mice (Liu et al., 1997). STAT5b knock-out mice defects include decreased amounts of adipose tissue, immunological defects, loss of sexually dimorphic body growth rate, and decreased liver gene expression (i.e. IGF-I), indicating that STAT5b plays a key role in GH action (Udy et al., 1997; Teglund et al., 1998; Park et al., 1999). STAT5a/b double knock-out mice combine phenotypes seen in the individual knock-outs (Teglund et al., 1998).

STAT5 has been implicated in the GH-regulation of IGF-I gene transcription. In hypophysectomized STAT5b knock-out mice, GH treatment fails to increase hepatic IGF-I mRNA and plasma IGF-I, suggesting that IGF-I expression is STAT5b-dependent (Davey et al., 2001). Recently, Woelfle and co-workers (2004) used adenovirus-mediated gene transfer in hypophy-sectomized rats to evaluate the role of STAT5b. Animals infected with a dominant negative STAT5b did not have hepatic IGF-I expression even in the presence of GH whereas GH was dispensable in animals infected with a constitutively active STAT5b (Woelfle and Rotwein, 2004). Consistent with a role for STAT5b in GH-dependent activation of IGF-I gene, a functional STAT5 response element was identified in the second intron of the gene (Woelfle et al., 2003).

GH also signals via the MAPK pathway (Okada and Kopchick, 2001; Zhu et al., 2001). This pathway begins with binding of the SHC adaptor protein via its SH2 domain to the tyrosine phosphorylated GHR (Moutoussamy et al., 1998), followed by the tyrosine phosphorylation of SHC by JAK2. Subsequently, phosphorylated SHC interacts with

growth factor receptor-binding protein 2 (Grb2) containing one SH2 domain flanked by two SH3 domains (Okada and Kopchick, 2001; Zhu et al., 2001). The coupling of Grb2 and son of Sevenless (SOS) is mediated via the interaction of SH3 domain of Grb2 with the C-terminal proline rich region of SOS. The assembly of a SHC-Grb2-SOS complex initiates a cascade of interdependent kinase activation (Okada and Kopchick, 2001; Zhu et al., 2001). SOS is a guanine nucleotide exchange factor that activates the small GTP binding protein Ras. Ras located at the plasma membrane then associates with and activates the serine/threonine kinase Raf. Raf, in turn, phosphorylates and activates the dual kinase MEK (phosphorylating serine/threonine or tyrosine), which then phosphorylates and activates MAPK (ERK1/2) (Cobb, 1999; Lewis et al., 1998; Vanderkuur et al., 1997). In the nucleus, ERK1/2 activates p90RSK, which phosphorylates the serum response factor (SRF). ERK1/2 also activates the serine phosphorylation of Elk-1. Both SRF and Elk-1 mediate the transcriptional effects of GH on the c-fos gene by binding to the serum response element (SRE) in the proximal promoter (Rivera et al., 1993; Hodge et al, 1998).

GH can also activate the IRS signaling pathway. JAK2 is required for GH-dependent phosphorylation of IRS-1, -2, and -3, although neither GHR nor JAK2 contains the NPXY consensus sequence required for IRS association (Argetsinger et al., 1995; Ridderstrale et al., 1995; Argetsinger et al., 1996). It is possible that the interaction between JAK2 and IRS proteins is mediated via a focal adhesion kinase, FAK (Zhu et al., 1998), or other adaptor molecules such as SH2-B, Grb2 or CrkII (VanderKuur et al., 1995; Holland et al., 1997; Thirone et al., 1999; Carter-Su et al., 2000b; Finidori, 2000). Once activated, IRS proteins recruit PI-3 kinase (Argetsinger et al., 1995; Ridderstrale et al., 1995; Argetsinger et al., 1996). PI-3 kinase phosphorylates inositol lipids (phosphatidylinositol and related compounds) to generate the second messengers, phosphatidyl inositol-3, 4-bisphosphate (PIP2) and phosphatidyl- inositol-3, 4, 5-trisphosphate (PIP3) (Leevers et al., 1999). PIP3 recruits PDK-1 (pleckstrin homology domains of 3-phosphoinositide-dependent kinase-1) which in turn activates the serine/threonine kinase, Akt/PKB. GH activates glucose transporter 4 (GLUT4) translocation to the cell membrane in a PI-3 kinase dependent manner, resulting in increased glucose uptake (Yokota et al., 1998; Le Marchand-Brustel et al., 1999). This pathway could explain the acute insulin-like effects of GH in cultured cells. However, GH-mediated PI-3 kinase activation was maintained in IRS-1 deficient cells, in contrast to IGF-I which required IRS-1 to activate PI-3 kinase (Bruning et al., 1997). This indicates that GH also utilizes an IRS-I independent pathway to activate PI-3 kinase. Indeed, the p85 subunit of PI-3 kinase can associate directly with the tyrosyl-phosphorylated GHR, providing a direct alternative route for the activation of PI-3 kinase (Moutoussamy et al., 1998).

Finally, GH stimulates the PLCγ pathway. PLCγ is tyrosine phosphorylated by JAK2 and associates with intracellular portions of GHR (Moutoussamy et al., 1998). PLCγ hydrolyses phosphatidylinositol 4, 5-bisphosphate to produce the second messenger molecule, inositol 1, 4, 5-trisphosphate (IP3) and diacylglycerol (DAG). DAG activates protein kinase C (PKC), which translocates from the cytosol to the plasma membrane (Ron and Kazanietz, 1999; Musashi et al., 2000). Activated PKC is associated with a wide range of downstream events including lipogenesis (Gurland et al., 1990), the increase in intracellular Ca^{2+} concentration (Gaur et al., 1996) and the expression of the c-fos gene (Slootweg et al., 1991; Tollet et al., 1991).

Termination of GH signaling

Hormone signaling is a tightly regulated process. After initial activation, signaling is first attenuated, and finally terminated to avoid the detrimental consequence of excessive stimulation. In the case of GH, two mechanisms accounting for signal termination have been described.

The first mechanism involves a family of proteins called suppressor of cytokine signaling (SOCS). To date, eight members of the SOCS proteins (CIS, SOCS 1-7) have been identified (Krebs and Hilton, 2000; Krebs and Hilton, 2001). All these SOCS proteins have a central SH2 domain and a conserved C-terminal region (SOCS box). SOCS-1, -2, -3 and CIS mRNA are induced by GH in rat liver and hepatocytes (Adams et al., 1998; Ram and Waxman, 1999; Tollet-Egnell et al., 1999), but only CIS and SOCS-2 are induced in the mammary gland from mice (Davey et al., 1999). Moreover, STAT5b is required for the induction of SOCS-2 and -3 in liver (Davey et al., 1999). The phenotype of SOCS-2 knock-out mice is the opposite of that of GH and IGF-I knock-out mice (i.e. increased body weight and length, increased weight of visceral organ weight). Elevated IGF-I was found in the heart, lung and spleen of SOCS-2 knock-out mice (Kopchick et al., 1999; Metcalf et al., 2000). Overall, these data suggest that SOCS-2 is a physiologically relevant attenuator of GH action.

The central SH2 domain of some SOCSs inhibits GH signaling by acting as a competitor for binding to tyrosine residues of the GHR. SOCS-3 does so by binding to the membrane proximal tyrosine residues recognized by STAT5 whereas CIS/SOCS-2 binds to more distal tyrosine residues (Krebs and Hilton, 2000; Krebs and Hilton, 2001). In contrast, SOCS-1 attenuates GH signaling by directly inhibiting JAK2 activity (Ram and Waxman, 1999; Krebs and Hilton, 2000; Krebs and Hilton, 2001). Finally, SOCS proteins may also be involved in proteosomal degradation

of the activated JAK2-GHR complex. This function is suggested by the ability of SOCS box to bind to Elongin B and C, two proteins that associate with the E3 ubiquitin ligase, cullin-2 (Ram and Waxman, 1999; Shuai, 1999). Both JAK2 and SOCS proteins themselves can be ubiquitinated by cullin-2 (Verdier et al., 1998; Bousquet et al., 1999).

Another mechanism involved in the termination of GH signaling is the dephosphorylation of critical tyrosine residues in the activated GHR-JAK2 complex. The SH2 domain-containing phosphatase-1 (SHP-1) directly associates with JAK2 in response to GH (Hackett et al., 1997). GH also induces the interaction between SHP-1 and STAT5b in the nucleus, suggesting that GH-induced SHP-1 might be required for the dephoshporylation of JAK2 and STAT5b (Hackett et al., 1997). SHP-2, another phosphatase has been shown to bind to the GHR and to dephosphorylate GHR, JAK2 and STAT5b (Stofega et al., 2000). Finally, Gu and co-workers showed that the protein tyrosine phosphatase-1B (PTP-1B) associates with JAK2 in a GH-dependent manner and dephosphorylates the tandemly arranged tyrosine residues responsible for JAK2 activation (Gu et al., 2003). Over-expression PTP-1B in H4-II-E cells blunts STAT5-mediated gene transcription in response to GH, suggesting that PTP-1B is one of the phosphatases capable of terminating GH signaling (Gu et al., 2003).

ACID LABILE SUBUNIT (ALS)

As described in previous sections, plasma IGF-I has been used as the endpoint to assess the efficiency of GH action in liver. In plasma, IGF-I is always sequestered in a 150 kDa noncovalent complex. This complex consists of one molecule each of IGF-I or IGF-II, IGF-binding protein (IGFBP)-3 or IGFBP-5 and an acid labile subunit (ALS). In humans and rodents, ALS is synthesized predominantly in liver in a GH-dependent manner (Ooi et al., 1997; Suwanichkul et al., 2000) and therefore could also serve as a reporter of GH action in liver. The next section summarizes what is known about the biology of ALS.

Structure of the ALS gene, cDNA and protein

In the human and mouse, the ALS gene spans ~3.3 kb and is composed of two exons separated by a ~1,100 bp intron (Suwanichkul et al., 2000). Exon 1 encodes only the first 5 amino acids of the signal peptide and contributes the first nucleotide of codon 6. Exon 2 encodes the remainder of the signal peptide (27 amino acids in human, 23 amino acids in mouse) and the entire mature protein (578 amino acids in human, 580 amino acids in the mouse). This genomic structure is conserved in sheep, baboon, rat, pig and cattle (Dai and Baxter, 1992; Delhanty and Baxter, 1996; Rhoads et al., 2000; Lee et al., 2001; Kim et al., 2006). The ALS gene is located on chromosome 16p13.3 in human (Suwanichkul et al., 2000) and on chromosome 17 in mice (Boisclair et al., 1996). Transcription of the gene produces a single ~2.2 kb mRNA in all species studied so far (Dai and Baxter, 1992; Leong et al., 1992; Boisclair et al., 1996; Delhanty and Baxter, 1996; Rhoads et al., 2000; Lee et al., 2001). The ALS cDNA has been cloned in human (Leong et al., 1992), rat (Dai and Baxter, 1992), mouse (Boisclair et al., 1996), baboon (Delhanty and Baxter, 1996), sheep (Rhoads et al., 2000), pig (Lee et al., 2001) and cattle (Kim et al., 2006).

The amino acid sequences deduced from these cDNAs indicate a degree of homology between human and other species ranging from 76% (sheep) to 95% (baboon). Mature ALS contains 6 to 7 asparagine-linked glycosylation sites and 12 to 13 of cysteine residues located in the N-terminal and C-terminal regions. Approximately 75% of mature ALS is represented by 18 to 20 leucine-rich repeat domains of 24 amino acids (Leong et al., 1992; Janosi et al., 1999b). Using computational modeling and rotary shadowing electron microscopy, Janosi et al. (1999b) have predicted that ALS is a donut-shaped structure with an external diameter of 7.2 nm, an internal diameter of 1.7 nm, and a thickness of 3.6 nm. In this model, clusters of negatively charged amino acids (Asp^{55}, Glu^{103}, Asp^{147}, Glu^{171}, Glu^{195}, Asp^{223}, Glu^{287}, Glu^{314}, Glu^{367} and Asp^{411}) are located on the internal face of ALS, and create an overall electronegative surface charge. This property is thought to be important for the interaction with IGFBP-3 and -5 (Firth et al., 1998; Twigg et al., 1998; Janosi et al., 1999a).

Biochemical properties

By SDS-PAGE analysis, the ALS protein migrates at 84 to 86 kDa. After N-glycanase treatment, serum ALS migrates at ~66 kDa (Baxter and Martin, 1989; Baxter et al., 1989; Kim et al., 2006). ALS has a high affinity for binary complexes of IGFs and IGFBP-3, but no affinity for free IGFs and IGFBP-1, -2, -4 or -6 (Baxter et al., 1989; Twigg and Baxter, 1998; Twigg et al., 1998), and low affinity for free IGFBP-3 (Baxter and Martin, 1989; Barreca et al., 1995; Lee and Rechler, 1995a). The binding affinity of ALS for binary complexes containing IGF-I is slightly higher that those with IGF-II (Barreca et al., 1995). ALS is also capable of binding binary complexes of IGFs and IGFBP-5 (Twigg and Baxter, 1998). This is not entirely surprising because IGFBP-5 is structurally similar to IGFBP-3. In plasma, however, ternary complexes containing IGFBP-5 account for only ~10% of all ternary complexes (Mohan et al., 1995). Domain swapping studies indicates that the C-terminal region of IGFBP-3 and -5 are responsible for binding ALS (Hashimoto et al., 1997; Firth et al., 1998; Twigg and Baxter, 1998). This region contains a stretch of positively charged amino acids which are thought to interact

with the negatively charged internal face of ALS. This electrostatic model of interaction is supported by elimination of ternary complex formation when the negatively charged sialic acid chains are removed from ALS (Janosi et al., 1999a).

Regulation of ALS

Spatial : ALS is predominantly found in the vascular compartment. The plasma concentration of ALS is 285 nM in human and 570 nM in the rat (Baxter, 1990; Khosravi et al., 1997). ALS has also been found at lower concentration in ovarian follicular fluid (Hughes et al., 1997), synovial fluid (Hughes et al., 1997; Khosravi et al., 1997; Labarta et al., 1997), peritoneal fluid (Khosravi et al., 1997; Labarta et al., 1997) and skin interstitial fluid (Xu et al., 1995; Hughes et al., 1997) in human. In addition, the ternary complexes presumably containing ALS were detected in colostrum, milk, ovarian follicular fluid and mammary lymph in sheep (Hodgkinson et al., 1989). Bovine ALS was detected in plasma at the highest levels followed by ovarian follicular fluid, lymph and colostrums. A portion of colostrums and follicular fluid ALS appears to be synthesized locally as ALS mRNA found in mammary epithelial cells and ovarian follicular cells (Kim et al., 2006).

By northern analysis, ALS mRNA can be detected in liver of the mouse, rat, sheep, pig and primate (Dai and Baxter, 1994; Delhanty and Baxter, 1996; Rhoads et al., 2000; Ueki et al., 2000; Lee et al., 2001) and at low levels in kidney of the mouse (Ueki et al., 2000). In the rat, ALS mRNA was also detected by *in situ* hybridization in kidney (Chin et al., 1994). In pig, using the more sensitive RNase protection assay (RPA), ALS mRNA has been found in muscle, spleen, ovary and uterus (Lee et al., 2001). ALS mRNA was also detected by *in situ* hybridization in granulosa and thecal cells of the pig ovary (Wandji et al., 2000). In cattle, ALS mRNA abundance was five-fold higher in liver than in lung, small intestine, adipose tissue, kidney and heart, but was almost absent in muscle and brain (Kim et al., 2006).

Developmental : ALS could not be detected in human fetal serum at 27 wk of gestation (Lewitt et al., 1995), but is increased five-fold from birth to puberty (Baxter, 1990). Using *in situ* hybridization, ALS mRNA is detected in liver and kidney of embryonic d 20 rats, and is increased dramatically between birth and day 20 (Chin et al., 1994). Hepatic ALS mRNA is increased 10-fold from day 21 to 70 of postnatal age (Dai and Baxter, 1994). In sheep, Rhoads et al. (2000) have shown that the expression of ALS mRNA is detectable by northern analysis at day 130 of prenatal life and is increased dramatically at day 7 of postnatal life. This is consistent with IGF-I circulating as 50 kDa complexes after birth and as 150 kDa complexes within 1 wk of birth (Butler and Gluckman, 1986). In the pig, ALS mRNA was barely detectable in liver on day 75 of gestation, increased on day 112 of gestation and continued to increase after birth (Lee et al., 2001).

Hormonal : Hepatic ALS mRNA abundance was decreased by ~90% in hypophysectomized rats and returned to near normal levels 8 h after GH treatment (Ooi et al., 1997). Using GH deficient rats, circulating IGF-I and IGFBP-3 are less than 10% compared to wild type animals, and there is no formation of ternary complexes (Gargosky et al., 1994). IGF-I treatment increases the binary complex of IGF-I and IGFBP-3, but only GH treatment induces the formation of both the binary and ternary complexes (Gargosky et al., 1994). Renal ALS mRNA was also reduced in hypophysectomized rats and partially restored after GH treatment (Chin et al., 1994). These data suggest that GH is the most important positive regulator of ALS synthesis.

Ooi et al. (1997) identified a GH-responsive element, called ALSGAS1 between nt -633 and nt -625 of the mouse ALS promoter. This element is shown to bind STAT5 in a GH dependent manner and to mediate the effect of GH on ALS gene transcription (Ooi et al., 1997; Ooi et al., 1998). Similar elements are found in human and sheep (Rhoads et al., 2000; Suwanichkul et al., 2000). Hepatic ALS expression is maintained in hypophysectomized rats infected with a constitutively active STAT5b, and eliminated in hypophysectomized rats infected with a dominant negative STAT5b, even after GH treatment (Woelfle and Rotwein, 2004). These data suggest that STAT5b is required and sufficient for effects of GH on ALS transcription.

IL-1β decreases the GH-dependent induction of ALS mRNA in rat primary hepatocytes. This inhibition is mediated by increased SOCS-3 expression (Boisclair et al., 2000). ALS mRNA is also reduced by dexamethasone, cAMP and epidermal growth factor in primary rat hepatocytes (Dai et al., 1994; Delhanty and Baxter, 1998).

Disease and catabolic state : Several studies demonstrate that ALS production is reduced during catabolic conditions (Dai and Baxter, 1994; Oster et al., 1995; Bereket et al., 1996; Lang et al., 1996; Frystyk et al., 1999; Fukuda et al., 1999; Moller et al., 2000; Kong et al., 2002a; Kong et al., 2002b). In humans, suffering from burn injury or cirrhosis, ALS synthesis is decreased (Frystyk et al., 1998; Moller et al., 2000). In underfeeding, fasting and diabetes, ALS mRNA and protein are also reduced (Dai and Baxter, 1994; Frystyk et al., 1999). The effects of fasting on ALS production are age-dependent in rats. Fasting for 48 h causes a more pronounced reduction in plasma ALS in juvenile (4 weeks old) than in adult rats (10 weeks old). This reduction is restored within 24 h of re-feeding in the juvenile rats, but persists beyond 48 h in the adult rats (Oster et al., 1995; Kong et al., 2002a).

In almost all of these conditions, the reduction in plasma ALS is associated with the development of hepatic GH resistance. Recent studies show that in human cirrhosis, levels of ALS, IGF-I and GHR mRNA are significantly decreased (Moller et al., 2000; Donaghy et al., 2002). Similar observations have been reported in liver of LPS treated rats (Kong et al., 2002b). These catabolic conditions also increase the secretion of glucocorticoid and production of cellular cAMP (Frystyk et al., 1998; Moller et al., 2000), two factors shown to reduce ALS secretion in primary hepatocytes (Dai et al., 1994; Delhanty and Baxter, 1998).

Function

150 kDa complex : ALS circulates at 2 to 3 fold molar excess over the concentration of IGF-I and IGFBP-3 in humans and rats (Baxter, 1988; Frystyk et al., 1998). As a result, 50% to 60% of serum ALS circulates in free form. This excess is thought to be important in maintaining most of IGFs in ternary complexes. This large excess is needed because ALS has a rather low affinity for binary complexes. IGF-I and ALS are produced by hepatocytes whereas IGFBP-3 is produced in non-parenchymal cells such as Kupffer and sinusoidal endothelial cells (Chin et al., 1994; Scharf et al., 1995; Uchijima et al., 1995). Therefore, the formation of the ternary complexes appears to occur in the vascular system.

Incorporation of IGFs in ternary complexes extends their half-lives from 10 min (free IGF) or 30 min (IGF in binary complexes) to over 15 h (Zapf et al., 1986; Baxter, 1988; Twigg and Baxter, 1998). This reflects the fact that IGFs cross the endothelial barrier when in free form or part of binary complexes, but are unable to do so when in ternary complexes (Binoux and Hossenlopp, 1988). Formation of ternary complexes limits the bioactivity of circulating IGFs. For example, bolus injection of binary IGF-I/IGFBP-3 complexes causes hypoglycemia in hypophysectomized rats with low plasma ALS, but not in intact rats with normal ALS levels (Zapf, 1995). Similarly, non-islet tumor hypoglycemia in human is caused by increased IGF-II present in binary complexes (Baxter and Daughaday, 1991; Zapf et al., 1995). This condition is reversed by chronic GH treatment, which increases plasma ALS and ternary complex formation (Katz et al., 1996).

ALS knock-out models : Recently, Ueki et al. (2000) generated ALS knock-out mice. These mice showed a reduction in circulating IGF-I (62%) and IGFBP-3 (88%). The synthesis of IGF-I and IGFBP-3 in liver and kidney remains unaltered, indicating that absence of ALS caused increasing turnover of IGF-I and IGFBP-3. ALS knock-out mice suffered at 13% growth retardation, but had normal plasma concentrations of glucose, insulin and GH.

Yakar et al. (1999) created a liver-specific IGF-I deficient (LID) mice using the Cre/loxP system. These mice have significantly reduced circulating IGF-I (~75%), five-fold elevated GH and insulin levels, but normal growth. LID mice treated with IGF-I or a GHRH antagonist have increased insulin sensitivity (Yakar et al., 2001). When crossing ALS knock-out and LID mice (ALS×LID), the growth retardation increased to 30% (Yakar et al., 2002). These mice show a dramatic reduction of circulating of IGF-I levels (85 to 90%) and a 15-fold increase of plasma GH (Yakar et al., 2002; Haluzik et al., 2003). Surprisingly, compared with LID mice, ALS×LID mice have improved insulin sensitivity in white adipose tissue and muscle but not in liver. These data suggest that the changes in circulating IGF-I and ALS levels affect glucose metabolism and insulin sensitivity in a tissue specific manner (Haluzik et al., 2003).

An ALS deficient patient has been identified recently. Absence of ALS results from a frame-shift point mutation, which is caused by the deletion of one of five consecutive guanines at positions 1,334 through 1,338 (Domene et al., 2004). This patient shows a marked reduction in plasma IGF-I and IGFBP-3, and high GH concentrations. The concentrations of IGF-I and IGFBP-3 remain unchanged even after GH treatment. The patient has no detectable ternary complexes, reduced binary complexes and increased free IGFs. The phenotype is similar to that of the ALS knock-out mice (a modest growth deficit).

CONCLUSION

It is generally accepted that GH is absolutely required for normal postnatal growth. The effects of GH on growth are mediated in part via hepatic production of IGF-I. Plasma IGF-I forms ternary complexes by associating with IGFBP-3 or -5 and ALS. The ability of GH to stimulate plasma IGF-I and ALS is responsive to many conditions, such as nutrition, disease and physiological state. Two factors such as hepatic GHR abundance and plasma ALS could account for variation in plasma IGF-I in animals.

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