

Estrogens in the Control of Growth Hormone Actions in Liver

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1. Introduction

The liver responds in a sex-specific manner to Growth Hormone (GH) and sex hormones. GH is the main regulator of body growth, somatic development, body composition, and sex-differentiated functions in liver (Butler and Le Roith, 2001; Mode and Gustafsson, 2006; LeRoith and Yakar, 2007; Lichanska and Waters, 2008; Vijayakumar et al., 2010). GH is mainly produced in the pituitary gland and acts distantly on target tissues through the activation of the transmembrane GH receptor (GHR). The liver shows the highest levels of GHR expression and, therefore, is a major target for GH, but virtually all human tissues are responsive to GH. GH regulates glucose, lipid, amino acid, and endo-xenobiotic metabolism. The sex-specific secretion release from pituitary has been shown to have a great impact on hepatic transcriptional regulation (Flores-Morales et al., 2001b; Tollet-Egnell et al., 2001; Tollet-Egnell et al., 2004; Lichanska and Waters, 2008; Waxman and Holloway, 2009). Global expression analysis of GH actions in liver using microarrays clearly indicates that most of the known physiological effects of GH can be explained through its effects on the transcription of specific genes. To this end, GH is known to activate a network of transcription factors in liver that include, among others, nuclear receptors/transcription factors such as Hepatocyte Nuclear Factors (4 α , 6, 3 β), Peroxisome Proliferator-Activated Receptor alpha (PPAR α), Constitutive Androstane Receptor (CAR), Farnesoid X Receptor (FXR), Small Heterodimer Partner (SHP), Sterol Regulated Element-Binding Protein (SREBP), CRBP, C/EBP β , and Signal Transducer and Activator of Transcription (STAT)-5b. The latest is of particular importance in the regulation of endocrine, metabolic, and sex-differentiated actions of GH in liver (Udy et al., 1997; Wiwi and Waxman, 2004; Waxman and O'Connor, 2006; Vidal et al., 2007).

17 β -Estradiol (E2), a major natural estrogen in mammals, has physiological actions which are not limited to reproductive organs in both females and males (Simpson et al., 2005). Estrogens exert their physiological effects through two estrogen receptor (ER) subtypes, ER α and ER β , which belong to the nuclear receptor family of ligand-activated transcription

factors (Heldring et al., 2007). Moreover, together with a mechanism based in ligand-activated transcription, estrogens can modulate gene expression by a second mechanism in which ERs interact with other transcription factors through a process referred to as transcription factor cross-talk. Estrogen may also elicit effects through non-genomic mechanisms, which involve the activation of protein kinase cascades via membrane-localized ERs (Revankar et al., 2005). Recently, an orphan G protein-coupled receptor (GPR)-30 in the cell membrane was reported to mediate non-genomic and rapid estrogen signaling. Therefore, the mechanisms involved in ER signaling are influenced by cell phenotype, the target gene, and the activity or the crosstalk with other signaling networks. Biologically and clinically relevant are potential interactions of estrogens with GH-regulated endocrine, metabolic, and sex-differentiated functions in liver. Estrogens can modulate GH actions in liver by acting centrally, by regulating pituitary GH secretion, and, peripherally, modulating GH signaling. Most previous studies have focused on the influence of estrogen on pituitary GH secretion (Kerrigan and Rogol, 1992; Wehrenberg and Giustina, 1992) but there is also strong evidence that estrogen modulates GH action at the level of GHR expression and signaling. Particularly, E2 has been shown to induce Suppressor of Cytokine Signalling (SOCS)-2, a protein inhibitor for cytokine signalling, which in turn negatively regulate GHR-Janus Kinase (JAK)-2-STAT5 pathway (Leung et al., 2004). Finally, the liver is a direct target of estrogens because it expresses ER α (Heldring et al., 2007) which is connected with liver development (Fisher et al., 1984), regulation of hepatic metabolic pathways (D'Eon et al., 2005; Ribas et al., 2010; Faulds et al., 2011), growth (Vidal et al., 2000), protection from drug-induced toxicity (Yamamoto et al., 2006), hepatocarcinogenesis (Bigsby and Caperell-Grant, 2011), fertility (Della Torre et al., 2011), as well as lipid metabolism and insulin sensitivity (Simpson et al., 2005; Foryst-Ludwig and Kintscher, 2010).

Therefore, estrogen-GH interactions are relevant because physiological roles these hormones have in mammals, and the widespread use of estrogen and estrogen-related compounds in human. These have been supported from clinical observations where administration of pharmacological doses of estrogens to human impairs GH-regulated endocrine and metabolic functions in liver (Meinhardt and Ho, 2006). Thus, deficiency of GH or E2 activities as well as estrogen-GH interactions may cause a dramatic impact in liver physiology during development as well as in adulthood. In this chapter, we will address the roles of these hormones in liver physiology as well as data of how estrogens modulate GH actions in liver. A better understanding of estrogen-GH interplay will lead to improved management of children with growth and developmental disorders and of adults with GH deficiency.

2. Regulation of pituitary GH secretion

GH is a polypeptide mainly secreted from the somatotrophs within the anterior pituitary gland. In addition to the pituitary, GH is produced in extra-pituitary tissues (e.g., placenta, mammary tissue, pineal gland, brain, lymphocytes) which indicates that GH has local paracrine-autocrine effects, distinct from its classic endocrine somatotrophic effects (Waters et al., 1999). The regulation of pituitary GH secretion involves a complex neuroendocrine control system that includes the participation of several neurotransmitters and the feedback of hormonal and peripheral (metabolic) factors (Le Roith et al., 2001; Kaplan and Cohen, 2007) (Figure 1).

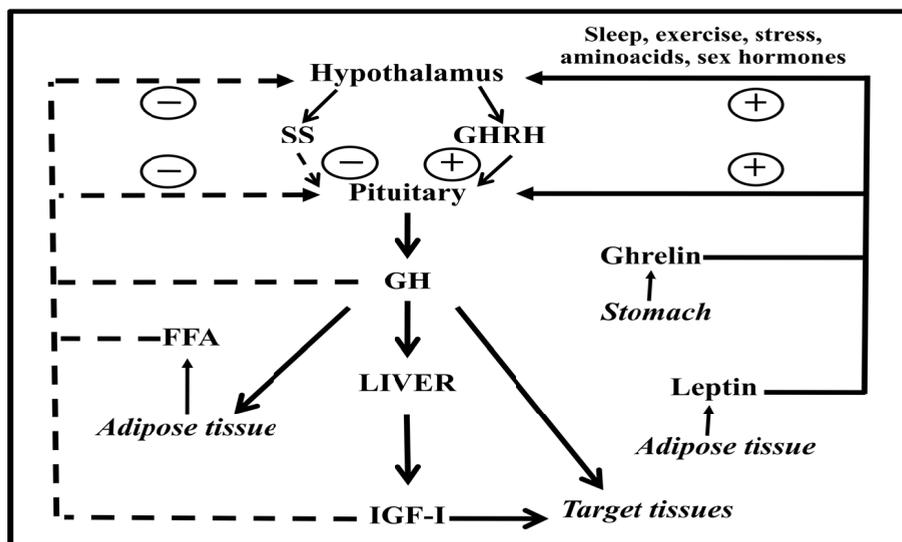


Fig. 1. **The somatotrophic axis.** The synthesis and release of GH from the pituitary are controlled by two hypothalamic hormones: GHRH and SS. GHRH is negatively (dashed lines) regulated by feedback from blood GH and IGF-I concentrations. FFA also inhibits whereas leptin and ghrelin stimulate GH release. Sex hormones and other factors also act centrally to stimulate GH release. Circulating GH acts directly on many organs to stimulate IGF-I production, with IGF-I production in the liver providing the main source of blood IGF-I. As illustrated, GH also has direct effects on many target tissues (adipose, kidney, bone, pancreatic), which can be independent of IGF-I action.

GH secretion from pituitary gland is regulated by two major hypothalamic peptides: GH releasing hormone (GHRH) and the inhibitory hormone Somatostatin (SS). The balance of these stimulating and inhibiting peptides is in turn, indirectly, affected by many physiological stimulators (e.g., exercise, nutrients, sleep, thyroid hormones, and sex hormones) and inhibitors (e.g. glucocorticoids, Insulin-like Growth Factor (IGF)-I and GH). The final integration of these signals occurs in the hypothalamus. Pituitary GH secretion is mainly reduced by negative feedback of two circulating signals: pituitary GH itself and liver-derived IGF-I produced by GH. The liver-derived IGF-I is a key negative regulator of pituitary GH secretion by acting directly on the somatotroph and on hypothalamic neurones. In addition to hypothalamic (GHRH, SS) and endocrine (IGF-I, GH) factors, other peripheral (metabolic) factors influence pituitary GH release: insulin, glucose, amino acids, free fatty acids (FFA), leptin, neuropeptide Y, and ghrelin. These factors are primarily related to or derived from the metabolic status of the organism, which is consistent with the role of GH in regulating substrate metabolism, adiposity, as well as growth, and appear to coordinate the metabolic status of the organism with GH secretion. This is exemplified by adiposity which is a powerful negative regulator of GH secretion and probably contributes to the age-related decline in GH status. FFA can act directly on the pituitary to inhibit GH release, which is postulated to complete a feedback loop, since GH stimulates lipid mobilization. In addition, adipocytes produce the hormone leptin which, in contrast to FFA, stimulates GH secretion in rodents at the level of the hypothalamus (Carro et al., 1997).

Finally, ghrelin is another GH-secretory factor that is highly expressed in the endocrine cells of the stomach. Currently, synthetic analogs of ghrelin are used to induce pituitary GH secretion (Howard et al., 1996). However, endogenous ghrelin may have little effect on GH secretion in mice, given that body growth and serum IGF-I levels are largely unaffected in ghrelin and ghrelin receptor knockout (KO) mice (Zigman et al., 2005). On the other hand, selective lack of ghrelin receptor signaling in humans may lead to a syndrome characterized by short stature (Holst and Schwartz, 2006) and ghrelin analogs have been shown to be effective in enhancing serum IGF-I levels in humans (Svensson et al., 1998).

Sex steroids are also physiological regulators of pituitary GH secretion. Both neonatal and post-pubertal sex steroids control the ability of the hypothalamus to drive the sexually dimorphism of pituitary GH secretion in adulthood (Kerrigan and Rogol, 1992; Wehrenberg and Giustina, 1992). Sexually dimorphism in rodents seems to be regulated by estrogen secretion in adult females and by androgen secretion neonatally and during adulthood in males. Essentially, estrogen increases and androgen decreases basal GH levels. These effects seem to be mediated by changes in hypothalamic release of SS and GHRH. These patterns are ultimately determined by neonatal exposure to testosterone, which imprints the male program of neuroendocrine control of the pulsatile pituitary GH secretion that is first seen at puberty, when the adult pattern of GH secretion becomes evident, and continues through adulthood. If such an androgen re-programming does not occur, the secretion pattern will remain as the feminine pattern (continuous GH secretion). In post-pubertal rats, the blood male pattern consists of high amplitude pulses (near 200 ng/ml) spaced near 3-4 hours apart with no measurable trough levels. In contrast, the female pattern is of lower amplitude pulses (25-50 ng/ml) and continuous; so, GH is always present. The sexually dimorphic pattern of GH secretion is also seen in humans, but not as marked as in the rat. Interestingly, depletion of liver-derived IGF-I in male mice causes a feminization of some of the GH-regulated sexually dimorphic markers of liver functions. This suggests that liver-derived IGF-I may suppress basal GH secretion in male rodents and contribute to masculinization of liver functions. Loss of the feedback effect exerted by IGF-I on the hypothalamic-pituitary system results in increased GH secretion, including elevated baseline GH levels between pulses which resemble a female pattern of pituitary GH release.

3. Positive and negative regulation of GH signaling

The GHR belongs to type I cytokine receptor, a family of receptors without intrinsic kinase activity (Lanning and Carter-Su, 2006). Figure 2 shows the traditional view of the initiation of GH signaling: one molecule of GH binds two GHR monomers and induces their dimerization. GH binding to the GHR results in activation of adjacent JAK2 molecules, cytoplasmic tyrosine kinases associated with the GHR, by trans-phosphorylation. Activated JAK2 phosphorylates the GHR on tyrosine residues, which in turn recruits members of the STAT family of transcription factors. Since the JAK family of proteins consists of only four members (JAK1, 2 and 3, and TYK2), multiple cytokines activate the same JAK. Specificity of action, accordingly, does not reside in the JAKs, but in their downstream phosphorylation targets such as the STATs. Of the various STAT proteins (STAT 1 to 4, 5a, 5b, and 6), STAT5b has been widely associated with GH biological actions; although STAT1, 3, and 5a have also been shown to be recruited by the GHR. STAT phosphorylation by JAK2 results in their dissociation from the receptor, homo- or hetero- (in the case of STAT1 and 3) dimerization, and translocation to the nucleus where they modulate the transcription of target genes such as IGF-I,

ALS, or SOCS-2 (Rowland et al., 2005; Vidal et al., 2007). The STATs represent one of at least three major pathways in GH-induced signaling; others include the MAPK and PI3K pathways (Figure 3). However, to date, there is no convincing evidence linking the MAPK, ERK or PI3K pathways with GH-induced IGF-I regulation, at least in humans. Accordingly, GH-induced MAPK signaling has proven to be insufficient to compensate for the lack of STAT5b activation in patients with homozygous mutations of STAT5b or with GHR mutations, or deletions resulting in isolated failure of STAT5b activation.

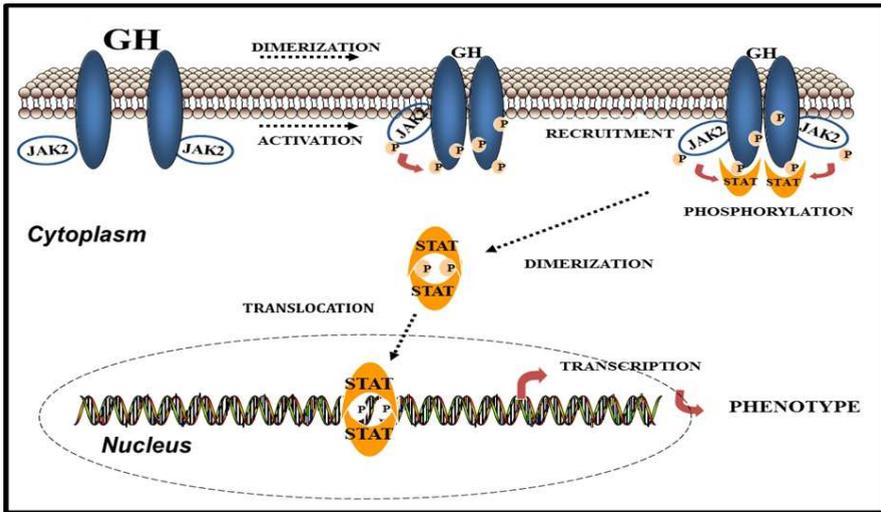


Fig. 2. Activation of GH-GHR-STAT signalling pathway.

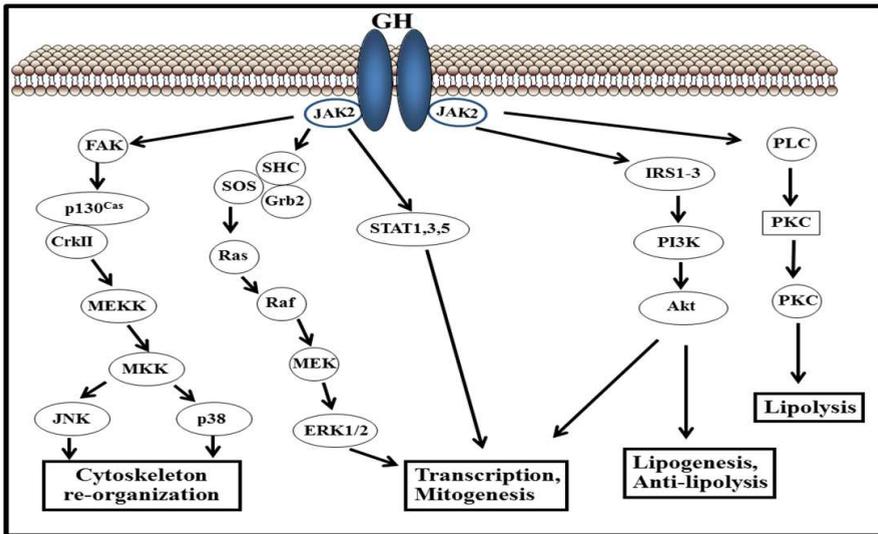


Fig. 3. Schematic representation of GH-activated signaling pathways.

The analysis of molecular mechanisms involved in inactivation of GHR signaling cascades is imperative to GH physiology. The activation of GH-signaling pathways is rapid and transient; the duration of GH-activated signals is a critical component in relation to the biological actions of this hormone. This is clearly illustrated in the case of hepatic GH actions where signal duration regulates gender differences in liver gene expression (Waxman et al., 1995). As mentioned, the male pattern of GH secretion in rats is episodic with peaks every 3-4 hours and no measurable trough levels (Jansson et al., 1985). Consequently, intracellular activation of STAT5 is also episodic and periods with low GH circulating levels are required to achieve maximal activation of STAT5. Female rats, which exhibit a more continuous GH secretion pattern with higher basal levels and smaller and irregular intermittent peaks showed reduced STAT5b activation compared with males (Waxman et al., 1995). These differences in STAT5b activation are responsible for several of the gender differences in hepatic gene expression (Waxman and O'Connor, 2006). Studies on primary hepatocytes and several cell lines have shown that GH-induced JAK2-STAT5b activation is transient, with maximal activation achieved within the first 30 min of stimulation, followed by a period of inactivation (Flores-Morales et al., 2006). This period is characterized by an inability to achieve maximal JAK2-STAT5 activation by GH in the following 3 h, unless GH is withdrawn from the media. The conserved control of GHR-JAK2 activation kinetic in multiple cell models emphasizes the importance of mechanisms of negative regulation for GH actions. Several studies already show that GH action can be modulated through interference with GHR down-regulation. Phospholipase C inhibition (Fernandez et al., 1998), induction of the unfolded protein response (Flores-Morales et al., 2001a), actin cytoskeleton depolymerization (Rico-Bautista et al., 2004), and treatment with $1\alpha,25$ -dihydroxyvitamin D3 (Morales et al., 2002), prolong the duration of JAK2-STAT5 phosphorylation after GH treatment, with little or no effect on its rapid and maximal activation.

The molecular mechanisms for desensitization of GH-dependent signaling pathway play a critical role in GH physiology. Cell surface levels of GHR are the primary determinant of GH responsiveness. The coordination of extracellular and intracellular signals is achieved through inactivation of GHR signals. This mechanism is GH activated and prolonged in time (Kelly et al., 1991). The mechanisms governing GHR expression are complex (Schwartzbauer and Menon, 1998). Transcriptional, translational and posttranslational level factors can influence GHR synthesis and, thereby, regulate cell sensitivity to GH actions. These factors include nutritional status, endocrine context, developmental stage, and, relevant to this review, estrogens (Flores-Morales et al., 2006). Removal of cell surface GHRs by endocytosis is an early step in the termination of GH-dependent signaling. GHR ubiquitination is a key control mechanism in the down-regulation of GH signaling, modulating both GHR internalization and proteasomal degradation. In addition to GHR down-regulation, other mechanisms are needed to complete inactivation of GH signaling. Since activation of GH-dependent signaling pathways is critically based on protein phosphorylation on tyrosine, serine or threonine residues, the obvious mechanism for deactivation of this process is the action of protein phosphatases. Recently, several studies have resulted in the identification of three phosphatases which are involved in the specific inactivation of GHR signaling: SHP1 (SH2 domain-containing protein-tyrosine phosphatase1 or PTP-1); 2) PTP1b; and 3) PTP-H1. Second, Signal Regulatory Protein (SIRP)- α , which belongs to a family of ubiquitously expressed transmembrane glycoproteins, was identified by ability to associate with the SH2 domain of SHP-2, SHP-1, and Grb2 in response to insulin, EGF, and PDGF (Kharitononkov et al., 1997). GH induces JAK2-

dependent phosphorylation of SIRP- α , which then enable it to bind SHP2 (Stofega et al., 1998). Overexpression of SIRP- α negatively regulates GH-activated signaling by inhibition of the phosphorylation of JAK2, STAT5b, STAT3, and ERK1-2 (Stofega et al., 1998). Finally, SOCS proteins have been shown key components of negative regulators of GHR-JAK-STAT signaling pathway. The SOCS family comprises at least eight proteins: CIS and SOCS-1 to -7 (Flores-Morales et al., 2006; Rico-Bautista et al., 2006). SOCS proteins have been shown to modify cytokine actions through a classic negative feedback loop. In general, SOCS protein levels are constitutively low, but their expression is rapidly induced by stimulation with different cytokines or growth factors including GH (Alexander, 2002). SOCS proteins bind the receptor/JAK complex and down-regulate JAK-STAT signaling pathway. Particularly, the phenotype of SOCS2 null mice (SOCS2KO) identifies SOCS2 as a key physiological player in the negative regulation of GH signaling (Rico-Bautista et al., 2006). SOCS2KO mice are 30-40% larger than their littermates, with the weight gain due to an increase in bone size and a proportionate enlargement of most organs. Similar phenotypes have been also found in animals overexpressing GH (Kopchick et al., 1999), patients with gigantism (Colao et al., 1997) and in high-growth mice, which have a spontaneous deletion within the chromosome 10 resulting in a disruption and inactivation of the *socs2* locus (Horvat and Medrano, 2001). IGF-I mRNA expression in SOCS2KO mice is significantly increased in some organs, without major changes in hepatic or serum IGF-I content. Other studies have demonstrated that SOCS2 is essential for the regulation of GH actions not directly related to somatic growth. For example, SOCS2 blocks GH-dependent inhibition of neural stem cell differentiation. Consequently SOCS2KO mice have fewer neurons in the developing cortex, whereas SOCS2 overexpression results in increased neural differentiation. Recently, it has also been demonstrated that SOCS2 inhibits intestinal epithelial (Miller et al., 2004) and prostate cell proliferation (D. Iglesias et al, personal communication), which are induced by GH *in vivo*. Evidence also indicates that growth factors (e.g., insulin, chemokines), xenobiotics, and steroid hormones, including estrogens, can induce SOCS expression (Rico-Bautista et al., 2006). Consequently, regulation of SOCS protein expression provides a mechanism for cross-talk where multiple factors can regulate the activity of specific cytokines (Greenhalgh and Alexander, 2004; Leung et al., 2004; Rico-Bautista et al., 2006). Particularly, SOCS2 may be a physiological mechanism by which estrogen signaling pathways influence GH activity: estrogen suppresses GH-dependent JAK2 phosphorylation by increasing the expression of SOCS2 (Leung et al., 2004).

4. Growth Hormone regulates body growth, metabolism, and sexual dimorphism

GH exerts its physiological effects through transcriptional regulation and acute changes in the catalytic activity of several enzymes (Flores-Morales et al., 2001b; Tollet-Egnell et al., 2001; Tollet-Egnell et al., 2004; Lichanska and Waters, 2008; Waxman and Holloway, 2009). Based on gene ontology analysis of liver transcript profiles from targeted disruption/mutation of signaling components of GHR-signaling pathways (Udy et al., 1997) or GHR itself (Lichanska and Waters, 2008), and GH administration to GH-deficient mice and rats (Flores-Morales et al., 2001b; Tollet-Egnell et al., 2001; Olsson et al., 2003; Tollet-Egnell et al., 2004; Rowland et al., 2005; Stahlberg et al., 2005), the main metabolic process affected by GH status is energy/fuel metabolism, particularly lipid/fat metabolism. In addition, carbohydrate, protein, steroid and drug metabolism are also strongly influenced.

These findings in animals together with clinical studies of GH-insensitive mutants have revealed the transcription factor STAT5b is a key GH signaling intermediate for the regulation of postnatal growth, lipid metabolism, and sexual dimorphism of hepatic gene expression. In addition, many transcripts are regulated independently of STAT5b, presumably as a result of GHR-dependent activation of ERK, Src, and PI3K signaling pathways.

4.1 GH and body growth

GH is predominantly linked with linear growth during childhood. The liver is a major target tissue of GH and the principal source of circulating IGF-I. GH-dependent transcription of IGF-I is regulated by STAT5 binding sites in IGF-I gene (Woelfle et al., 2003). Thus, both IGF-I and its transcriptional regulator STAT5 have key roles in mediating the actions of GH on body growth (Le Roith et al., 2001; Kaplan and Cohen, 2007). Importantly, intermittent (male pattern) GH administration to rodents is a more potent stimulus of body growth rate, IGF-I expression, and STAT5b nuclear translocation in liver than is continuous (female pattern) administration. This supports the notion that larger body growth in male compared with female rodents could be due to more effective stimulation of IGF-I and STAT5b mediated transcription. IGF-I proteins are also induced by GH in many tissues and local induction of IGF-I in chondrocytes plays an important role in longitudinal growth (Yakar et al., 1999). GH is, however, more effective than IGF-I because GH exerts additional growth-promoting actions independent of IGF-I (Lupu et al., 2001).

Global disruption of STAT5b in mice cause loss of sexually dimorphic growth characteristics, with affected males reduced to the size of females, and female mice appeared unaffected (Udy et al., 1997). Parallel observations were made with serum IGF-I concentrations, which were reduced by 30-50% in affected male mice, but not in females. However, combined disruption of STAT5a/b significantly reduced body weight gain in females and suppressed body growth more than STAT5b null mice alone in males, approaching that observed either GH or the GHR deficient mice (Rowland et al., 2005). These studies demonstrated that STAT5b is important for male-specific body growth, whereas STAT5a regulates body growth in both sexes. Experiments in mice with SOCS-2 disruption also support that STAT5b is critical for GH-regulated growth in mammals (Greenhalgh and Alexander, 2004). Importantly, SOCS2KO mice have enhanced growth whereas combined STAT5bKO and SOCS2KO mice do not, a demonstration of the necessity of STAT5b for the excess of body growth observed in SOCS2KO mice (Rico-Bautista et al., 2006). In addition to endocrine actions, paracrine involvement of STAT5a/b in the effects of GH on muscle is also evident in the loss of muscle IGF-I transcripts and mass seen with muscle-specific deletion of Stat5a/b (Klover and Hennighausen, 2007). As mentioned above, the growth of female STAT5bKO mice is normal whereas postnatal growth in female GHR-deleted mice is profoundly retarded (Zhou et al., 1997). These data suggest that in addition to STAT5b, other transcription factors are related with growth. This is exemplified by the glucocorticoid receptor (GR) which is a critical co-activator of STAT5b in liver: near 25% of STAT5b-regulated hepatic genes are subject to control by a GR-STAT5b transcriptional complex (Engblom et al., 2007). Importantly, these STAT5b and GR co-regulated transcripts were preferentially enriched in functional groups related to growth and maturation (i.e., IGF-1). Moreover, both direct and indirect interactions between ER and STAT5 (Bjornstrom and Sjoberg, 2005) should be added to the list of mechanisms regulated by nuclear receptors that modulate GH-dependent transcription.

4.2 GH and metabolism

Physiological effects of GH extend beyond the stimulation of linear growth. These include important metabolic actions throughout life. At all ages, GH has anabolic effects and increases muscle size in GH-deficient individuals: GH enhances amino acid uptake into skeletal muscle, increases whole body protein synthesis and enhances positive nitrogen balance, concomitant with the increase in lean body mass (LeRoith and Yakar, 2007; Lichanska and Waters, 2008; Vijayakumar et al., 2010). Thus, GH has a net metabolic effect on protein metabolism, as it stimulates protein synthesis while repressing proteolysis.

The mechanisms of GH actions on lipid metabolism are complex and involve transcriptional and acute changes in catalytic enzyme activities (Flores-Morales et al., 2001b; Tollet-Egnell et al., 2001; Tollet-Egnell et al., 2004; Lichanska and Waters, 2008; Waxman and Holloway, 2009). It is well established that human GH is a lipolytic hormone. Long-term administration of GH includes a decrease in deposition of fat and an increase in fat mobilization, increasing circulating FFA and glycerol levels. GH reduces fat mass, particularly in individuals who have accumulated excess fat during periods of GH deficiency (GHD). Obesity is clinically evident in GHD patients and a decline in GH levels correlates with age-related obesity and lack of GH or GH signaling induces obesity earlier in mice (Corpas et al., 1993; Laron et al., 2006; Cui et al., 2007). GHD in adulthood causes a syndrome characterized by increased visceral adiposity, decreased muscle mass, metabolic disturbances, and increase mortality associated with cancer or vascular complications. This syndrome closely resembles the metabolic syndrome and can be ameliorated by GH replacement (LeRoith and Yakar, 2007; Lichanska and Waters, 2008; Vijayakumar et al., 2010).

The exact mechanisms through which GH exerts lipolytic effects remain to be elicited. GH can induce hepatic LDL receptors and, therefore, increase cholesterol uptake into liver. GH deficiency associates with elevated serum cholesterol and GH replacement therapy normalizes those levels. Serum cholesterol can also be modulated by IGF-I. Specific disruption of IGF-I gene in liver (LID mice) increased circulating cholesterol levels (total and LDL cholesterol) in male and female. These findings concur with the observation that IGF-I treatment decreases serum cholesterol in humans. Interestingly, some studies have reported that LID mice show increased circulating triglycerides levels without changes in liver and muscles triglyceride content. Accumulation of FFA in the adipose tissue is dependent upon lipoprotein lipase (LPL), which hydrolyzes triglycerides into FFA. GH inhibits LPL in adipose tissue, whereas insulin increases activity of LPL. On the other hand, GH increases LPL in muscle, which leads to increased use of FFA by skeletal muscle. Additionally, GH can directly stimulate hydrolysis of triglycerides into FFA and glycerol, which stimulates FFA transport from adipose tissue into the liver and muscle. The increased release of FFA and glycerol transport from adipose tissue then affects liver insulin responsiveness, which leads to insulin resistance and induction of the gluconeogenic enzymes phosphoenol pyruvate carboxy kinase (PEPCK) and glucose-6-phosphatase (G-6-Pase). Therefore, GH increase in hepatic glucose production can be explained primarily through the effects of GH on lipolysis. Interestingly, GH treatment of both healthy and GHD individuals decreased whole-body carbohydrate oxidation and concomitantly increased whole-body lipid oxidation. This opens the possibility that the GH-induced increase in FFA efflux from adipose tissue could, via the provision of substrates for gluconeogenesis, abrogate the need for amino acids and consequently proteolysis. But more direct effects of GH might also have a role in adipocytes. One of the mechanisms by which GH leads to lipolytic effects involve

increased expression of β 3-adrenergic receptor in adipocytes followed by activation of HSL (hormone sensitive lipase). Additional effects include uncoupling of the electron transport chain which enhances mitochondrial heat generation at the expense of energy production from ATP.

As mentioned above, GH stimulates triglyceride uptake in the skeletal muscle and induces LPL activity, thereby promoting lipid store or release energy via either lipolysis or lipid oxidation. However, several factors such as nutrition, exercise, and sex steroid hormone status could modify GH-induced triglyceride storage and lipid oxidation in skeletal muscle. GH also induces triglyceride uptake in liver by increasing LPL and/or HSL expression. GH treatment promotes a state of intrahepatic triglyceride storage. Several studies in bGH-transgenic mice, deficient GHR-JAK2-STAT-5 signaling pathway, GH-treated intact or GH-deficient rats (hypophysectomized or hypothyroid), as well as experiments in PPAR α null mice, have all revealed that GH down-regulates genes involved in lipid oxidation and increases the expression of genes promoting lipogenesis in the liver (Olsson et al., 2003; Wang et al., 2007; Barclay et al., 2011; Sos et al., 2011). On the other hand, an impaired GHR-JAK2-STAT-5 signaling strongly correlates with hepatic steatosis (Fan et al., 2009; Barclay et al., 2011; Sos et al., 2011). Disruption of the hepatic GHR, JAK2 or STAT5 genes in mice resulted in hepatic steatosis due to enhanced lipogenesis and reduced triglyceride secretion. GHR-JAK2-STAT5 signaling deficiency has also been studied by mutagenesis of GHR in mice (Lichanska and Waters, 2008), a model that causes severe obesity in mature mice in proportion to loss of STAT5b activity. Collectively, these experiments have shown that STAT5 regulates several key enzymes or genes otherwise involved in lipid and energy balance. Based on altered transcript expression, several processes have been implicated. For example, up-regulation of some lipogenic genes (e.g., CD36, PPAR α , PGC1 α/β , FAS, SCD1, LPL, VLDLR) may contribute to increased hepatic lipid storage, steatosis, and adiposity in deficient GHR-JAK2-STAT5 signaling models whereas expression of antilipogenic genes such as FGF21 and INSIG2 are decreased. Genetically modified animals and microarray analysis have provided new insights into the long-known anti-adiposity actions of GH and highlighted a key role for STAT5 in these actions. This is supported by original findings that STAT5b-deleted male mice become obese in later life (Udy et al., 1997; Teglund et al., 1998) and that STAT5b deletion in a mature human was associated with obesity (Vidarsdottir et al., 2006). The anti-obesity actions of GH are enhanced by the pulsatility of GH secretion evident in males (Takahashi et al., 1999) because pulsatile STAT5 activation, which is, as mentioned above, so important for sexual dimorphism in hepatic gene expression (including IGF-1). Importantly, these findings suggest that despite normal plasma FFA and minimal adiposity, absent GHR activation could lead to hepatic steatosis because activated STAT5 prevents this pathology (LeRoith and Yakar, 2007).

4.3 GH and insulin sensitivity

The effects of GH on both glucose and lipid metabolism are key components in GH-dependent induction of insulin resistance (LeRoith and Yakar, 2007; Vijayakumar et al., 2010). In liver, GH has a stimulatory effect on glucose production which may be a result of its antagonism of insulin action leading to hepatic/systemic insulin resistance. GH increases glucose production by increasing glycogenolysis; however, it has either a stimulatory or no effect on gluconeogenesis. Over-expressing the human GH gene in rat increases basal hepatic glucose uptake and glycogen content (Cho et al., 2006). In contrast, GHD mice

(Ames) and the GHRKO mice have improved insulin sensitivity and an up-regulation of hepatic insulin signaling, suggesting that GH antagonizes insulin signaling in the liver (Dominici and Turyn, 2002). As mentioned above, GH-induced insulin resistance may develop by the increased FFA mobilization from adipose tissue which can then affect liver insulin sensitivity, and lead to insulin resistance and up-regulation of the PEPCK and G6Pase (Segerlantz et al., 2001; Kovacs and Stumvoll, 2005). However, LID mice showed a 75% reduction in circulating IGF-I levels, 3-4 fold increase in circulating GH levels and insulin resistance, without significant increase in circulating FFA levels. Moreover, while crossing IGF-I specific liver deficient mice with GH transgenic mice, serum FFA levels were significantly increased and there was an improvement in insulin sensitivity during a hyperinsulemic-euglycemic clamp due to higher hepatic, adipose tissue and skeletal muscle glucose uptake (Yakar et al., 2004). This suggests that, in addition to FFA, other factor(s) may also contribute to GH-induced insulin resistance. One candidate is the SOCS family of proteins whose expression is induced by GH (Rico-Bautista et al., 2006). Another mechanism by which GH may induce insulin resistance is by increasing the expression of the p85, a regulatory subunit of PI3K (Leroith and Nissley, 2005; LeRoith and Yakar, 2007). Finally, given the large homologies between the insulin and IGF-I systems, it is not surprising that IGF-I exerts profound effects on carbohydrate metabolism (e.g., insulin-like effects on glucose uptake). Alternatively, IGF-I may enhance insulin sensitivity by suppressing GH release, via negative feedback. Therefore activation of IGF-I signalling adds more complexity for understanding molecular mechanisms involved in GH-induced insulin resistance *in vivo*.

4.4 GH and sexual dimorphism of hepatic physiology

Five decades of research have firmly established the existence of a gonadal-hypothalamo-pituitary-liver axis determining liver sexual dimorphism and the importance of GH secretion patterns (Mode and Gustafsson, 2006). More recently, genomic and bioinformatic technologies have contributed to solve molecular mechanisms involved in hepatic gene regulation (Tollet-Egnell et al., 2000; Flores-Morales et al., 2001b; Tollet-Egnell et al., 2004; Stahlberg et al., 2005; Waxman and O'Connor, 2006; Waxman and Holloway, 2009; Wauthier et al., 2010). As mentioned above, sex hormones imprint a sex-dependent pattern of pituitary GH hormone secretion which is a major player in establishing and maintaining the sexual dimorphism of hepatic gene transcription that emerges in rodents at puberty. Sex-dependent expression and GH regulation characterizes several families of hepatic genes involved in endo- and xenobiotic metabolism as well as relevant metabolic functions (e.g., lipid metabolism); 20-30% of all hepatic genes has a sex-specific expression pattern in rodents (Tannenbaum et al., 2001; Stahlberg et al., 2004; Gustavsson et al., 2010). Most of these hepatic sex differences are explained by the female-specific secretion of GH, through the induction of female-predominant transcripts and suppression of male-predominant. A key player in this scenario is STAT5b. Results from experiments with STAT5b null mice indicated that STAT5b is responsible for the masculinization of the male liver (Udy et al., 1997; Waxman and O'Connor, 2006). STAT5b is more efficiently activated, as other transcription factors such as HNF4 α , by the male GH secretion pattern. STAT5b binding sites have been found in the promoter of several sex-differentiated CYP genes in rat, including Cyp2c12, Cyp2c11, Cyp2a2 and Cyp4a2 (Waxman and Holloway, 2009). Conversely, other transcription factors (e.g., HNF6 and HNF3b) are more efficiently

activated in female liver or by the continuous GH secretion pattern (Mode et al., 1998). Sex differences are not only found in hepatic genes involved in endo- and xenobiotic metabolism but they are also found in GH-regulated lipid metabolism. HNF4 and HNF3b are relevant transcription factors for regulating genes involved in glucose and lipid metabolism (Wolfrum et al., 2004; Sampath and Ntambi, 2005) and most likely they also contribute to sexual dimorphism. Continuous administration of GH has been shown to increase hepatic expression of transcription factor SREBP-1c and its downstream target genes (Tollet-Egnell et al., 2001), as well as hepatic triglyceride synthesis and VLDL secretion (Elam et al., 1988; Sjoberg et al., 1996). As mentioned above, GH actions in liver lead to increased lipogenesis (i.e., induction of SREBP1c) and decreased lipid oxidation (i.e., inhibition of PPAR α), and promote anabolic growth in peripheral tissues (i.e. muscle, bone) (Flores-Morales et al., 2001b; Tollet-Egnell et al., 2004; Stahlberg et al., 2005). Relevant to this review, estrogens cause opposite effects, in comparison with GH, on hepatic lipid metabolism and insulin sensitivity which represents a relevant point of regulatory interactions between estrogens and GH (see below).

5. Estrogens and liver

Estrogens have physiological actions which are not limited to reproductive organs, in both females and males. E2 can modulate GH actions on liver by acting centrally, by regulating GH secretion, and peripherally, modulating GH responsiveness. Importantly, the liver expresses ER α which regulates development (Fisher et al., 1984), hepatic metabolic pathways (D'Eon et al., 2005; Ribas et al., 2010; Faulds et al., 2011), body growth (Vidal et al., 2000), protection from drug-induced toxicity (Yamamoto et al., 2006), hepatocarcinogenesis (Yager et al., 1994; Bigsby and Caperell-Grant, 2011), fertility (Della Torre et al., 2011), as well as lipid metabolism and insulin sensitivity (Simpson et al., 2005; Foryst-Ludwig and Kintscher, 2010). Thus, the liver is a sex steroid responsive organ and represents a site where critical interactions between estrogens and GH could be developed.

5.1 Estrogen receptor signaling

Estrogens exert their physiological effects through two ER subtypes, ER α and ER β , which belong to the nuclear receptor family of ligand-activated transcription factors (Heldring et al., 2007). Structurally, ERs share a common framework with the other members of the nuclear receptor family. The N-terminal A/B domain is the most variable region with less than 20% amino acid identity between the two ERs, and confers subtype specific actions on target genes. This region harbors the activation function-1 (AF-1) that is ligand-independent and shows promoter- and cell-specific activity. The centrally located C-domain harbors the DNA binding domain (DBD), which is involved in DNA binding and receptor dimerization. This domain is highly conserved between ER α and ER β with 95% amino acid identity. The D-domain is referred to as the hinge domain and shows low conservation between ER α and ER β (30%). This domain has been shown to contain a nuclear localization signal. The C-terminal E-domain is the ligand-binding domain (LBD) and the two subtypes display 59% conservation in this region. The LBD contains a hormone-dependent activation function (AF-2) and is responsible for ligand binding and receptor dimerization. The F-domain has less than 20% amino acid identity between the two ER subtypes and the functions of this domain remain undefined. Full transcriptional activity of the ERs is mediated through a

synergistic action between the two activation domains, AF-1 and AF-2. Both ER α and ER β contain a potent AF-2 function, but unlike ER α , ER β seems to have a weaker corresponding AF-1 function and depends more on the ligand-dependent AF-2 for its transcriptional activation function. E2 has a similar affinity for ER α and ER β and they are activated by a wide range of ligands including selective estrogen receptor modulators (SERMS) such as raloxifen as well as many other compounds (Heldring et al., 2007). ER α is mainly expressed in reproductive tissues, kidney, bone, white adipose tissue, and liver, while ER β is expressed in the ovary, prostate, lung, gastrointestinal tract, bladder, and hematopoietic, and the central nervous systems. Therefore, specific actions of estrogens in liver may be reached by using selective ER α agonists (e.g., propyl-pyrazole-triol, PPT) (Lundholm et al., 2008).

Classical estrogen signaling occurs through a direct binding of ER dimers to estrogen responsive elements (EREs) in the regulatory regions of estrogen target genes followed by activation of the transcriptional machinery at the transcription start site (Heldring et al., 2007) (Figure 4). Estrogen also modulates gene expression by a second mechanism in which ERs interact with other transcription factors, like STAT5, through a process referred to as transcription factor cross-talk. Estrogen may also elicit effects through non-genomic mechanisms, which involve the activation of downstream kinases pathways like PKA, PKC, and MAPK via membrane-localized ERs (Revankar et al., 2005). An orphan G protein-coupled receptor (GPR)-30 in the cell membrane has been also reported to mediate non-genomic and rapid estrogen signaling (Dahlman-Wright et al., 2006). Moreover, the mechanisms involved in ER signaling are influenced by cell phenotype, the target gene, and the activity or crosstalk with other signaling networks. Particularly relevant is E2 interaction with GH in the regulation of growth, development, body composition, hepatic metabolism, and sex-differentiated functions in liver (Stahlberg et al., 2004; Stahlberg et al., 2005; Waxman and O'Connor, 2006).

Gender-related differences in body composition are in part mediated by sex steroids modulating the GH-IGF-I axis (LeRoith, 2009; Munzer et al., 2009; Maher et al., 2010a; Maher et al., 2010b; Rogol, 2010; Barclay et al., 2011; Birzniece et al., 2011). This is supported by the observation that gender differences in body composition emerge at the time of pubertal growth. The efficiency of GH activity is also modulated by estrogens in adulthood. This is exemplified by women being less responsive than men to GH treatment (Burman et al., 1997); GH treatment induces a greater increase in lean mass and decrease in fat mass, or a greater increase in indices of bone turnover and in bone mass, in GH-deficient male compared to female patients. Furthermore, pharmacological doses of estrogens exert effects on liver that are somehow different from those caused by physiological E2. Oral administration of pharmacological doses of estrogen to hypopituitary patients inhibits GH-regulated endocrine and metabolic effects: circulating IGF-I levels, lipid oxidation, as well as protein synthesis are suppressed, with a reciprocal elevation of carbohydrate oxidation (Ho et al., 1996; Huang and O'Sullivan, 2009). These effects on metabolism and body composition are attenuated by transdermal administration, suggesting that liver is the major site of regulatory control by estrogen. Estrogens can modulate GH actions on liver by acting peripherally (Figure 4), modulating GH responsiveness, which include changes in hepatic GHR expression and crosstalk with GH-activated JAK2-STAT5 signaling pathway. In addition, direct effects through hepatic ER α play a critical role in liver physiology and pathology. However, the effect of estrogens on GHR is dependent on tissue type and species (Birzniece et al., 2009) (and references within). Estrogens reduce expression of GHR in the

explained by ER α stimulation of PIAS3 expression which binds to and blocks STAT3 DNA-binding activity, suggesting a possible mechanism of STAT3 inhibition requiring PIAS3 as a co-regulator modulating the crosstalk between ER and STAT3. Estrogens can also activate STAT-5 signalling not only in a pituitary but even a JAK2-independent manner. E2 activation of ER followed by direct interaction of ER with STAT5 may also inhibit STAT5-dependent transcriptional activity (Faulds et al., 2001; Wang and Cheng, 2004). Finally, via non-genomic mechanisms, E2-activation of ER α or ER β could induce STAT5 (and STAT3)-dependent transcriptional program in endothelial cells (Bjornstrom and Sjoberg, 2005). These studies have shown a direct interaction between ER and STAT5 but also demonstrate that functional consequence of this cross-talk depends on the precise milieu of the intracellular environment.

5.2 E2 modulates GH promoting of skeletal growth

It is well known that sex steroids and GH interact closely to regulate pubertal growth (Bourguignon, 1991). Many observational studies in children have reported a correlation between IGF-I and sex steroid levels in both sexes during puberty, related closely to a concomitant increase in GH levels. Interestingly, loss of ER α (ERKO), but not ER β , mediates important effects of estrogen in the skeleton of male mice during growth and maturation (Vidal et al., 2000). A phenotype like to ERKO mice can be found for aromatase-deficient (ArKO) male rats (Vanderschueren et al., 1997), which cannot produce estrogens. Thus, some of the effects on skeletal growth seen in ERKO mice may be caused by an inhibition of the GH-IGF-I axis. In contrast, as mentioned above, administration of pharmacological doses of estrogens results in a drastic reduction of circulating IGF-1 which most likely reflects the inhibitory effects of estrogens on hepatic GH-JAK2-STAT5 signalling pathway.

5.3 Sexually dimorphic pattern of GH secretion connects sex steroids with liver physiology

Sex steroids are physiological regulators of pituitary GH secretion and, indirectly, regulate sex-specific liver physiology. From neonatal period of life, gonadal steroids play a critical role to maintain liver response to GH in adulthood (Mode and Gustafsson, 2006) (and references herein). Neonatal exposure to androgens is crucial and the full response to androgens in adulthood is dependent on neonatal imprinting by androgens. The male characteristic metabolism in liver in adulthood is dependent on continuous androgen exposure. In female rats, gonadectomy has little impact on hepatic steroid metabolism; estrogen treatment, however, feminizes hepatic metabolism in male rats. The impact of GH secretion patterns on hepatic gene expression has become evident during last decade when DNA microarray technology has made it possible to carry out genome-wide screens of gene expression. These studies have shown that GH- and sex-dependent regulation of hepatic gene expression is not confined to steroid or drug metabolism and a number of other hepatic genes have been found to be up- and/or down-regulated by the different patterns of GH or sex-steroid exposure. GH- and sex-dependent hepatic transcripts encoding plasma proteins, enzymes, transcription factors and receptors involved in the metabolism of proteins, carbohydrates, lipids, or signalling regulation have been identified (Tollet-Egnell et al., 2000; Flores-Morales et al., 2001b; Tollet-Egnell et al., 2004; Stahlberg et al., 2005; Waxman and O'Connor, 2006; Waxman and Holloway, 2009; Wauthier et al., 2010). In addition, a proteomic approach has also been performed by Waxman's group (Wiwi and

Waxman, 2004) to identify GH and sex-dependent nuclear proteins in rat liver. Interestingly, of 165 sexually differentiated spots about 40% underwent a female-like change in male rats upon continuous treatment with GH.

The relationship among the components of GH secretion patterns (interpulse periods, GH concentration, pulse amplitude) and the characteristic sex-dependent expression of a number of genes (Mode and Gustafsson, 2006; Waxman and O'Connor, 2006) has been extensively explored during past years. In general, the GH interpulse periods constitute the major determinant of sex-specific genes; GH concentration and pulse amplitudes are also of different importance for the expression of several sex-characteristic CYP isoforms. In addition, a consensus exists that the response to sex-different GH patterns is the major cause of the "liver sexuality", it is also likely that factors other than the sexually dimorphic pattern of GH secretion are behind some sex differences in rat liver. Potential mechanisms that could contribute to "liver sexuality" are the pituitary-independent effects of estrogens through interaction with ER α or GH-JAK2-STAT5 signalling pathway in liver.

5.4 E2 is a critical regulator of lipid metabolism and insulin sensitivity: Potential crosstalk with GH

Estrogens, acting on both ER α and ER β are recognized as important regulators of glucose homeostasis and lipid metabolism (Simpson et al., 2005; Faulds et al., 2011). Both male and female ER α KO mice develop insulin resistance and impaired glucose tolerance, similar to humans lacking ER α or aromatase. ER α mainly mediates beneficial metabolic effects of estrogens such as anti-lipogenesis, improvement of insulin sensitivity and glucose tolerance, and reduction of body weight/fat mass. In contrast, ER β activation seems to be detrimental for the maintenance of regular glucose and lipid homeostasis. The insulin resistance in ER α KO mice is largely localized to the liver, including increased lipid content and hepatic glucose production. Interestingly, the expression of liver lipogenic genes can be decreased after E2 administration to diabetic Ob/Ob or high-fat diet fed female mice. Similarly, the aromatase knockout (ArKO) mouse, which cannot produce E2, has increased intra-abdominal adiposity and develops steatosis and an impairment of lipid oxidation in liver. Importantly, GH-GHR-JAK2-STAT5 deficiency in adults causes adiposity and hepatic steatosis suggesting that E2 and GH can regulate a common cellular network related with physiological control of lipid metabolism. In our lab, we have shown that subcutaneous administration of nearly physiological doses of E2 to male rats with GH deficiency (hypothyroid rats), dramatically influenced the hepatic transcriptional response to pulsatile GH administration (male pattern). In this model, E2 was able to increase hepatic transcriptional program in relation to lipid oxidation whereas lipid synthesis was decreased. Most relevant, expression of genes related to endocrine, metabolic, and sex-differentiated functions of GH were drastically inhibited by E2.

6. Conclusion

The liver responds in a sex-specific manner to GH and estrogens. GH is a major regulator of growth, somatic development, and body composition. Estrogens have physiological actions which are not limited to reproductive organs in both females and males, and they are recognized as key regulators of liver physiology. Physiologically and therapeutically relevant are estrogen interactions with GH-regulated endocrine (e.g., IGF-I), metabolic (e.g.,

lipid metabolism), and sex-differentiated (e.g., endo- and xenobiotic metabolism) functions in liver. The effects of estrogens are executed not just at the level of pituitary secretion, but also at the level of GHR signalling pathways. In addition, direct effects through hepatic ER α play a critical role in liver physiology and pathology. Thus, estrogens/GH interactions are relevant because physiological roles that these hormones have in mammals, and the widespread use of estrogen-related compounds (i.e., oral contraceptive steroids, hormone replacement therapy, SERM). This is supported from clinical observations where administration of pharmacological doses of estrogen to human impairs the GH-regulated endocrine and metabolic functions. In the general population, the endocrine and metabolic consequences of long-term treatment of women with estrogens or novel estrogen-related compounds are largely unknown. Therefore, this complex interaction deserves further research because its potential impact on GH-regulated body composition and influence on GH efficacy in GH-treated patients.

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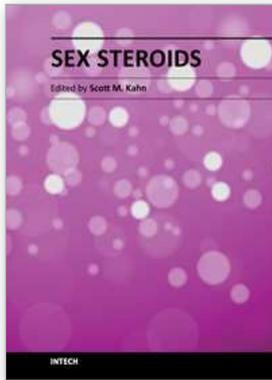
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This book, entitled "Sex Steroids", features a valuable collection of reviews and research articles written by experts in signal transduction, cellular biology, diseases and disorders. "Sex Steroids" is comprised of four sections, "The Biology of Sex Steroids", "Sex Steroids, Memory, and the Brain", "Sex Steroids and the Immune Response", and "Therapy"; individual chapters address a broad range of recognized and predicted functions and applications of sex steroids. "Sex Steroids" is intended to provide seasoned veterans as well as newcomers to this area of research with informative, resourceful, and provocative insights. Readers of "Sex Steroids" should emerge with an appreciation and understanding of the multitude and complexity of biologic processes attributed to these important hormones, and possible future directions of research in this fascinating and ever evolving field.

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