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Chapter

Control of Liver Gene Expression by Sex Steroids and Growth Hormone Interplay

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Abstract

Sex steroids have important physiological actions, which are not limited to reproductive organs, in both females and males. They exert important physiological roles, including the regulation of somatotropic-liver axis, intermediate metabolism, or gender dimorphism. This is in part because the liver is a sex steroid-responsive organ where sex steroid- and growth hormone (GH)-dependent signaling pathways connect to regulate complex gene expression networks. Sex steroids can impact liver gene expression by a direct, through hepatic estrogen receptor (ER)α and androgen receptor (AR), or indirect mechanisms, by modulation of pituitary GH secretion and/or interaction with the GHR-STAT5b signaling pathway. Therefore, deficiency of sex steroid- and GH-dependent signaling pathways might cause a dramatic impact on mammalian liver physiology. In this chapter, we will focus our attention on main concepts and paradigms involved in the role and interplay between sex steroid- and GH-dependent signaling to regulate gene expression networks in the mammalian liver. A better understanding of how sex steroids and interactions with GH-STAT5b signaling pathway influence physiological and pathological states in the liver will contribute to improve clinical management of patients with disorders in body growth, development, and metabolism.

Keywords: estrogens, androgens, GH, liver, gene expression

1. Introduction

The liver is as sex steroid-responsive organ [1–13]. The natural estrogen, 17β-estradiol (E2), and androgens, testosterone (T)/dihydrotestosterone (DHT) have physiological actions, which are not limited to reproductive organs, in both females and males. The nonreproductive actions of sex steroids have relevance in liver physiopathology [1–7, 14–18]. The effects of E2 and T/DHT on liver gene expression can be direct, through their hepatic receptors, or indirect, by modulating growth hormone (GH) actions centrally [1, 2], regulating pituitary GH secretion, and, peripherally [5, 7, 19, 20], by modulating growth hormone receptor (GHR)-dependent signaling which can be exemplified by (1) E2 modulating GH actions in the liver through induction of suppressor of cytokine signaling (SOCS) 2 which in turn negatively regulates GHR signal transducer and activator of transcription (STAT)5b signaling pathway and (2) the positive interplay between T/DHT and GH to enhance somatic growth and liver composition in men. Accordingly, deficiency of E2-ERα [4, 18, 19, 21, 22],

androgen/AR [6, 7, 21–25] or GH-GHR [26–32] signaling pathways in adults causes a similar metabolic-like syndrome (i.e., fatty liver, adiposity, insulin resistance), a phenotype that might be ameliorated by E2/T or GH replacement. Therefore, the interplay between sex steroids and GH is clinically relevant because of its importance in the regulation of endocrine, metabolic, and gender-differentiated actions on the mammalian liver [33]. A better understanding of this complex sex steroid-GH interplay in physiological and pathological states will contribute to prevent health damage and improve clinical management of patients with growth, developmental, and metabolic disorders. In this review, we will summarize the role of sex steroid- and GH-dependent signaling pathways on liver gene expression.

2. The liver is as sex steroid-responsive organ

Sex steroids can regulate liver gene transcription through direct and indirect mechanisms.

2.1 Direct regulation of liver gene expression by sex steroids

The liver is a direct target of sex steroids through several receptors and tissue-specific mechanisms [34–36]. The direct interaction between E2 and the transcription factors ERα and ERβ mediates the classical estrogen signaling, which is responsible for most estrogenic effects [35]. ER dimers directly bind DNA, specifically to estrogen-responsive elements located in the ER target gene-regulatory regions, followed by transcription activation. Furthermore, E2 can regulate the expression of its target genes by the interaction between ERs and other transcription factors, such as STAT5. Non-genomic mechanisms, via membrane ERs that activate downstream kinase pathways, have also been described to trigger E2-dependent effects. For instance, the orphan membrane G protein-coupled receptor (GPR)-30 was shown to mediate a rapid estrogen signaling, although conflicting results on this receptor have been reported [37]. Lastly, estrogenic effects are closely related to ER tissue expression. ERα expression has been reported in the bone, reproductive tissues, white adipose tissue, liver, and kidney, whereas the ovary, gastrointestinal tract, lung, bladder, prostate, hematopoietic tissue, and central nervous system are the main ERβ-expressing tissues. This indicates that selective ERα agonists might be used for treating ERα-related liver diseases [38]. Similarly to classical E2 signaling, most of the known androgenic effects are mediated via direct interaction of T/DHT with the DNA-binding transcription factor AR which plays an important role in regulating androgen-dependent gene expression [34, 36]. AR regulates the transcription of a variety of target genes through the interaction with different positive regulators (co-regulators) that provide tissue specificity of androgen actions. In addition, androgen/AR can signal by non-genomic mechanisms. Palmitoylation of AR determines its localization to the membrane, where it can be found in lipid raft membrane [39, 40]. Interestingly, membrane-localized AR can modulate both rapid androgen-mediated G-protein signaling and rapid EGF receptor activation followed by Akt and MAPK signaling pathways and subsequent nuclear AR-mediated effects. T conversion into E2 by aromatase may also play a relevant role to regulate the effects of androgens on body growth and composition.

2.2 Indirect regulation of liver gene expression by sex steroids

Indirect mechanisms, related to the influence of sex steroids on pituitary GH secretory pattern [1, 2] and/or interaction with the GHR-STAT5b signaling pathway in target tissues [5, 7, 19, 20], play a relevant role to regulate the effects of sex steroids on the liver.

2.2.1 Sex steroids regulate the pattern of pituitary GH secretion

Regulation of pituitary GH release depends of two hypothalamic peptides: a positive regulator, GHRH, and the inhibitory hormone somatostatin (SS) [41, 42]. The balance of these peptides is in turn, indirectly, affected by many physiological inhibitors (i.e., GH, IGF-1, glucocorticoids) and stimulators (i.e., sleep, nutrients, exercise, thyroid hormones, sex hormones) of pituitary GH secretion. The final integration of these signals occurs in the hypothalamus. Not only hypothalamic and endocrine factors but also other peripheral elements, mostly metabolic, affect pituitary GH production. These include glucose, fatty acids, amino acids, insulin, leptin, neuropeptide Y, and ghrelin, among others, and are dependent on the metabolic condition of the organism. This is consistent with the GH role in the regulation of somatic growth and composition. A good example to explain the close relationship between GH and the metabolic status is the feedback loop among pituitary and adipose tissues. Adiposity is a powerful negative regulator of pituitary GH secretion. In contrast, GH induces fatty acid mobilization from adipose tissue to reduce adiposity, and circulating fatty acids inhibit pituitary GH secretion. On the contrary, other metabolites such as leptin (also produced in the adipose tissue) [43] and ghrelin (from the stomach) [44] stimulate pituitary GH secretion. Furthermore, sex steroids can also regulate pituitary GH secretion. It has been described that neonatal and postpubertal sex steroids regulate the hypothalamus on its generation of the gender dimorphism of the pituitary GH secretion seen in adulthood. This could explain the gender dimorphism seen in liver physiology [1, 13]. In rodents, gender dimorphism is thought to be controlled by E2 secretion in adult females, whereas it is mediated by T secretion in neonatal and adult males. T neonatal exposure determines adult neuroendocrine control of the pulsatile pituitary GH secretion, which is first seen at puberty, when the GH secretion pattern is perceptible and continues throughout adulthood. In postpubertal rats, the male pituitary GH secretion pattern has been shown to be episodic with peaks every 3–4 hours and no measurable trough levels. As consequence, activation of GHR-STAT5b pathway is episodic as well, and phases with low levels of circulating GH are required to achieve maximal activation of STAT5b-mediated transcription. Conversely, female rat GH secretion is continuous, with higher basal levels and smaller intermittent peaks, and they show reduced STAT5b activation compared with males. Interestingly, depletion of liver-derived IGF-1 (LID mice) [45] or SOCS2 deletion [46] in male mice or exposition of adult male rats to E2 [47] causes liver feminization of some of the GH-regulated biomarkers of gender dimorphism. Therefore, maximal GHR-STAT5b activation occurs at puberty, and suppression occurs during aging or in mutants with defects in GHR signaling. Additionally, xenobiotics (i.e., chemicals, endocrine disruptors) can perturb the hypothalamo-pituitary-liver GH axis and disrupt GHR-dependent activation (masculinization) or suppression (feminization) of STAT5b function in the liver [48, 49]. Other factors that can affect liver STAT5b function include fasting, caloric restriction, and infections. Exposure to DHT and thyroid hormones can cause liver masculinization, whereas glucocorticoids, FGF15, and angiotensin II cause liver feminization [47, 49]. Interestingly, liver feminization has been consistently observed in mouse models of obesity and diabetes. Finally, feminization of the male liver has been also associated with activation of constitutive androstane receptor (CAR) or peroxisome proliferator-activated receptor (PPAR)α, two xenobiotic-responsive receptors, or increased expression of PPARγ but not other lipogenic transcription factors linked to the fatty liver [47–49]. Relevant, GH-activated STAT5b in the liver is also commonly altered by diverse xenobiotics and provides a linkage between chemical exposure and hepatotoxicity.

2.2.2 Sex steroids interact with GHR-STAT5b signaling pathway

E2(ERα)- and T(DHT)/AR-dependent signaling might modulate liver gene expression by interacting with GHR-STAT5b signaling pathway. The level of cell surface GHRs can be influenced by transcriptional, translational, and posttranslational factors (e.g., nutritional status, endocrine context, IGF-1, developmental stage, sex steroids) which, thereby, regulate cell sensitivity to GH actions. In addition, E2 can inhibit GHR-JAK2-STAT5 signaling pathway through induction of SOCS2 and SOCS3 expression which in turn negatively regulates GHR signaling pathway in the liver [19]. Recently, we have shown that subcutaneous administration of nearly physiological doses of E2 to hypothyroid male rats dramatically influenced the hepatic transcriptional program (e.g., genes related to endocrine, metabolic, and gender-differentiated functions) in response to pulsatile (male pattern) GH administration [54]. The effects were associated with increased mRNA expression of several negative regulators of GHR-JAK2-STAT5b signaling pathway (e.g., SOCS2) [54]. It is thought that other negative regulators of JAK/STAT signaling may also contribute to the interaction between E2 and GH in the liver. Indeed, ERα has been shown to stimulate protein inhibitor of activated STAT3 (PIAS3) expression which in turn inhibits STAT3 DNA binding. Intriguingly, as mentioned above, a direct ER-STAT5 interaction might directly control STAT5-dependent transcriptional activity in the liver [50].

Androgen-mediated signaling has shown to be a critical determinant of body composition in adult men, promoting growth of lean mass and suppressing fat deposition [7, 51], a phenotype that is also induced after GH replacement. Interestingly, the GH-IGF-1 axis has been reported to be positively involved in the growth-promoting and metabolic effects mediated by T [5]. Hence, linear growth in children with GH deficiency receiving GH therapy is further stimulated by androgen treatment, and GH is required for reaching whole androgen growth-promoting effect. T increases growth of boys with hypogonadism and those with hypopituitarism under GH prescription. However, T effects on somatic growth are poor in boys with hypopituitarism without concomitant GH replacement. Therefore, it is evident that T-GH interactions are pivotal on body composition, which is clearly exemplified by adult men with GH deficiency, whose lean body mass remains below average even after adequate androgen replacement. Adults with hypopituitarism that are not being treated with GH therapy do not show any effect of T on circulating IGF-1, since both hormones are required to exert an optimal effect on circulating IGF-1. Furthermore, the fact that the effects of GH treatment are more marked in men than in women confirms that T amplifies the anabolic effects of GH in vivo. Although the study is limited to prostate cancer, there are also evidences that T (DHT)/AR signaling interacts with the GHR-STAT5b signaling pathway [20]. In prostate cancer cells, SOCS2 expression was induced by androgens through a mechanism that required STAT5- and AR-dependent transcription. Consequently, SOCS2 inhibited GH activation of JAK2, Src, and STAT5 as well as both cell invasion and cell proliferation in vitro [20]. Thus, in addition of sex steroid regulation of pubertal growth and gender pattern of pituitary GH secretion, induction of negative regulators of JAK2-STAT5b signaling pathway in vivo is a very relevant mechanism that could explain, in part, how sex steroids modulate hepatic transcriptional program. However, further studies are still needed to better understand molecular interactions between sex steroids and GHR-STAT5b-dependent transcription in the liver.

2.3 The GHR-STAT5b signaling pathway

STAT5 proteins are expressed in many tissues and play critical roles in body growth, immune function, cellular differentiation, adipogenesis, oncogenesis, and,

as mentioned above, gender dimorphism [26–32]. Regarding STAT5 tissue distribution, STAT5a is more prevalent in mammary tissue, while STAT5b expression is more enriched in the muscle and liver.

2.3.1 Positive regulation of GHR-STAT5b signaling pathway

GH activates STAT5b via GHR [52–54]. When GH interacts with a preformed dimmer of identical GHR pairs, a conformational change of GHR and the associated tyrosine kinase JAK2 molecules is displayed, exposing the catalytic domain of JAK2 [53]. Thus, through its pseudokinase domain, JAK2 adjacent molecules are activated by transphosphorylation. Activated JAK2 proteins phosphorylate tyrosine residues on the cytoplasmic domain of GHR, activating downstream JAK2-dependent and JAK2-independent intracellular signaling, including, among others, STAT5b-dependent gene transcription. STAT5b phosphorylation by JAK2 results in their dissociation from the receptor, dimerization, and translocation to the nucleus where they modulate a transcriptional network of genes such as IGF-1, SOCS2, CYP2C12, or HNF6 [54–58]. In addition to tyrosine phosphorylation by JAK2, STAT5 activity is also regulated by the Ras/MAPK and the PI3K/Akt pathways. STAT5 proteins have been shown to be regulated by serine phosphorylation which appears to modulate DNA-binding affinity and contributes to STAT5 transcriptional activity in a promoter-dependent manner [59, 60]. STAT5 can physically interact with p85, the regulatory subunit of PI3K and Gab2, which is also involved in the PI3K/Akt pathway [61]. Centrosomal P4.1-associated protein (CPAP) is a cytosolic protein that is normally associated with centrosomes, and it has been shown to physically interact with the unphosphorylated and phosphorylated forms of STAT5A/B [62]. Fyn, a non-receptor tyrosine kinase, and phosphoinositide 3-kinase enhancer A (PIKE-A) also physically interact with STAT5A, and these interactions might be relevant in adipogenesis [63]. It has been shown the adaptor protein [64], CT10 regulator of kinase-like proto-oncogene (CrKL), can form a complex with STAT5 after stimulation with some cytokines (e.g., GH, GM-CSF, EPO) and this complex can translocate to the nucleus and bind DNA to regulate gene expression [65, 66]. Although less known than GHR, there exist several proteins that have been shown to directly associate with STAT5 to enhance its transcriptional activity. Similar to other transcription factors, STAT5 interacts with proteins in the general transcription factor machinery. This is exemplified by CREB-binding protein (CBP) and p300 which are nuclear coactivators that exhibit histone acetyltransferase activity and have been shown to play a positive role in the transcriptional activation of STAT5. There is evidence that p300/CBP binds to the carboxy-terminal transactivation domain of STAT5 and that p300 is responsible for enhancing STAT5 transcriptional activity. The nuclear receptor coactivator 1 (NcoA-1), also known as steroid receptor coactivator 1 (SRC-1) is a nuclear coactivator known to coactivate various nuclear transcription factors such as STAT3, STAT6, progesterone receptor (PR), glucocorticoid receptor (GR), ERα, thyroid hormone receptor (TR), retinoid X receptor (RXR), hepatocyte nuclear factor α (HNFα), and PPARγ. Interestingly, chromatin immunoprecipitation assays have shown that STAT5A/NcoA-1 complex binds to a STAT5 site in the CIS, a negative regulator of cytokine signaling promoter [67].

2.3.2 Negative regulation of GHR-STAT5b signaling

The equilibrium between positive and negative regulators of GHR-dependent activity is of special concern because even slight imbalance may disrupt the GH activity causing serious diseases. Under physiological conditions, activation of GH-induced JAK2-STAT5b is temporary, with a peak of activation achieved within the first 30 min after GH stimulation, followed by an inactivation step [68].

This inactivation period is characterized by an inability of GH to promote maximal JAK2-STAT5 activity in the following 3–4 hours, unless GH is removed from the media. The main post-receptor inhibitors of GHR-JAK2-STAT5 pathway are: the SOCS family, protein phosphatases (PTPs), signal regulatory protein (SIRP)-α1, sirtuin 1 (SIRT1), and protein inhibitors of activated STAT (PIAS). In addition, GH-induced STAT5A phosphorylation and STAT5A-dependent transcription might be negatively regulated by transforming growth factor-β (TGFβ) [69], a cytokine that regulates cell growth, proliferation, differentiation, and death. Furthermore, several proteins that have been shown to directly associate with STAT5 can repress its transcriptional activity. This is exemplified by silencing mediator for retinoic acid receptor and thyroid hormone receptor (SMRT) which is a corepressor for various members of the nuclear receptor family. Although STATs are not member of the nuclear receptor superfamily, SMRT was found to interact with STAT5 and repress STAT5-dependent transcriptional activity [70]. Sac3 domain-containing protein (SHD1) is a protein that has been shown to have a role in mitotic progression and interacts with STAT5, and SHD1 can be induced by various cytokines and hormones, suggesting a potential role in modulating STAT5 transcriptional activity [71].

2.4 The SOCS family

The SOCS protein family is characterized by a specific protein structure as all of them have a SH2 domain and SOCS box domain [72, 73]. From a biological point of view, the SOCS box is an ubiquitination-related domain associated with complexes of elongins C and B, cullin-5, RING-box, and ligase E2, so SOCS proteins may act as ubiquitin E3 ligands that degrade proteins by direct interaction with them. An early step in GH-dependent signaling consists of GHR removal through endocytosis and ubiquitination mechanisms [74–78]. In line with this, SOCS2 has been reported to be essential in GHR-JAK2-STAT5b signaling negative regulation [79]. Regularly, SOCS2 protein levels are constitutively low, but GH rapidly induces its expression, with the subsequent SOCS2 binding to GHR complex, which promotes its ubiquitination and proteasomal degradation. Clinically relevant, SOCS2 negatively regulates GH-dependent control of body growth [26] and glucose and lipid homeostasis [46]. In addition, diverse cytokines, sex hormones (E2 and T), growth factors (e.g., insulin), and xenobiotics (e.g., dioxin, statins), can promote SOCS2 expression, generating a cross-talk mechanism through which multiple endo- and xenobiotics can regulate GHR-dependent activities. SOCS2 is responsible, among others, for regulation of the IGF-1 expression in the liver which is mediated by STAT5b [56, 80–83]. Experiments in mice with SOCS2 disruption also support that STAT5b is critical for GH regulation of somatic growth [72, 82]. In the SOCS2-deleted mice, the difference in body weight after weaning was associated with significant increase in bone length and increase in weight of most organs [80]. This phenotype was also associated with increased levels of IGF-1 mRNA expression in several organs [74, 80]. SOCS proteins can bind directly to tyrosine kinases to deactivate them but can also block docking on cytokine receptors to inhibit the activation of STAT in the JAK/STAT pathway [79]. It has been shown that SOCS7 also interacts directly with STAT5 and inhibits prolactin-, leptin-, and GH-dependent activation of STAT5 [84]. Interestingly, the oncogene PIM-1, a serine-threonine-protein kinase 1, might participate in the mechanism of the negative regulation of STAT5 activity by interacting with SOCS1 and SOCS3 [85].

2.5 Protein phosphatases and signal regulatory proteins (SIRPs)

As expected, tyrosine phosphatases such as PTP-1B and PTP-H1 [86] are negative regulators of the GHR-JAK2-STAT5b pathway. The absence (or inhibition) of

these PTPs produces prolonged activation of STAT5 and STAT3, by GH. Relevant in wild-type fasted mice, the GH resistance state develops, which is manifested by disorders in somatotropic axis at the GHR level, whereas in fasted PTP-1B KO mice, despite starvation, GH resistance state does not develop. PTP-1B KO mice are characterized by increased STAT5b tyrosine phosphorylation and augmented level of IGF-1 [87, 88]. The PTP known as Src homology 2 (SH2) containing protein tyrosine phosphatase (SHP-1) was initially described in the hematopoietic system [89]. GH can activate SHP-1 and induce its translocation into the nucleus, where SHP-1 binds to STAT5b and, subsequently, participates in the termination of GH signaling in the male rat liver [90]. The SHP-2 also plays a critical role in the regulation of GHR-dependent signaling [91]. The absence of SHP-2 binding to GHR results in an increased activation of STAT5b-dependent transcription [92]. The clinical role of the SHP-2 in the regulation of the GH signal transduction is confirmed by Noonan [93] and Leopard [94] syndromes. In addition, dual-specificity phosphatases (DUSPs), a family of type-I cysteine-based protein tyrosine phosphatases that act on both tyrosine and serine/theronine residues on a substrate, are also of interest for its ability to interact with STAT5b [95]. However, further studies are required to understand the mechanism of this interaction. Finally, low molecular weight PTPs (LMW-PTPs) are phosphatases that play a role in controlling cell proliferation via the dephosphorylation of tyrosine kinase receptors and docking proteins. These PTPs are also of interest for their interactions with STAT5 and oncogenesis [96, 97]. Finally, SIRPs are glycoproteins which can bind to the SH2 domains of SHP-2 protein [98]. Particularly, SIRPα-1 decreases GH-induced phosphorylation and activities of STAT5, STAT3, and ERK1/2 and, therefore, acts as a negative regulator of GH-dependent signaling.

2.6 Sirtuins

Human sirtuins are a family (from SIRT1 to SIRT7) of nicotinamide adenine dinucleotide (NAD+)-dependent enzymes that regulate a varied metabolic pathway [99]. SIRT1 plays a critical role in the organization and stabilization of the genome, response to stress, glucose homeostasis or cell differentiation, cell survival, inflammation, mitochondrial biogenesis, and oxidative damage. Interestingly, SIRT1 inhibits GH-induced IGF-1 mRNA expression in the liver, decreases lysine acetylation on STAT5, and inhibits the GH-induced tyrosine phosphorylation [100]. SIRT1 might be involved in GH resistance state. In fasted mice, SIRT1 protein level was increased, and SIRT1 inhibition restored lysine acetylation of STAT5 and STAT5 phosphorylation to basal levels, which reversed the GH resistance state [100]. The inhibitory effect of SIRT1 has been also observed on STAT3 protein activity in the liver. Resveratrol, an estrogenic/antiestrogenic stilbene and stimulator of SIRT1, also caused inhibition of STAT5 and STAT3 activities [101–104].

2.7 Protein inhibitors of activated STAT (PIAS)

PIAS proteins play an important role in the modulation of multiples signaling pathways which include to the AR-mediated transcription [105, 106]. STAT protein may be modulated by PIAS proteins in varied ways: (1) the interaction of PIASs with STATs may be type-dependent (e.g., PIAS1-STAT1, PIAS3-STAT3); (2) the PIASs can inhibit STAT-induced gene expression by DNA-binding inhibition (e.g., PIAS1-STAT1) or without DNA-binding inhibition (e.g., PIAS4-STAT1); and (3) PIAS proteins are expressed in different tissues. Relevant, intranuclear prolactin/cyclophilin B complex might act as a transcriptional inducer by interacting directly with STAT5, resulting in the removal of the PIAS3, thereby enhancing STAT5 DNA-binding

activity and prolactin-induced STAT5-dependent gene expression [107]. However, the role of PIAS proteins in somatotropic-liver axis has not been thoroughly investigated.

2.8 STAT5 interacts with Oct-1 to regulate cell cycle

Cyclin D1 is involved in regulation of the cell cycle and is a STAT5 target gene [108]. Octamer-binding protein 1 (Oct-1) is a transcription factor ubiquitously expressed in the nucleus that contains POU (pituitary-specific, octomer transcription factor, Unc-86) domain, a DNA-binding domain that recognizes the octamer motif. Oct-1 physically interacts with STAT5A in the nucleus, and this interaction is necessary for activating the cyclin D1 promoter and regulating D1 expression.

2.9 STAT5 associates with steroid receptors

PR and GR physically interact with STAT5. PR interacts with STAT5A in the cell nucleus, and STAT5A functions as a coactivator in the regulation of several PR target genes (i.e., RANKL, Wnt4, Areg) [109]. The GR has been shown to physically interact with both STAT5A and STAT5B in a variety of cell types including mammary gland, adipocytes, and hepatocytes. GR acts as a coactivator of STAT5 during mammary gland and somatotropic-liver axis development [110, 111]. Interestingly, GR acts as a positive regulator (coactivator) for STAT5b transcriptional activity in the promotion of body growth and sexual maturation. In fact, mice with inactive GR, specifically in the liver, have impaired body growth, suggesting the importance of GR in hepatocytes for GH-dependent postnatal growth. In addition, genes whose expression was similarly altered by GR and STAT5 deletions in mice included male-predominant genes, GH-responsive genes, steroid dehydrogenases, ribosomal protein genes, or IGF-1 and ASL, two genes which are involved in promoting body growth and gender dimorphism. In addition to GR acting as a positive activator of STAT5 transcriptional regulation, STAT5 has a role in repressing GR-mediated gene transcription [112, 113].

2.10 Epigenetic modulation of STAT5 transcriptional activity: a cross talk with xenobiotics

Finally, STAT5-dependent gene expression might also be regulated by epigenetic mechanisms [114–116]. Lysine-specific demethylase 1 (LSD1) and histone deacetylase 3 (HDAC3) are epigenetic modifiers that are typically associated with the modulation of histone activity. Nevertheless, the biological impact of the LSD1/HDAC3/STAT5A interaction network remains unclear, and further studies are required in order to elucidate the function of these interactions [117]. Enhancer of zeste homolog 2 (EZH2) is a histone-lysine N-methyltransferase enzyme involved in the methylation of DNA, and studies in different tissues have shown that EZH2 can also modulate several activities of STAT5 [118].

3. STAT5b in liver physiology

Target disruption or mutation of the GHR-JAK2-STAT5b signaling pathway together with clinical studies of GH-resistant mutants has shown that this pathway is a key in GH regulation of target genes associated with postnatal body growth, lipid and glucose metabolism, gender dimorphism, and liver pathophysiology (e.g., fatty liver, insulin resistance, fibrosis, hepatocellular carcinoma) [26–32].

3.1 Postnatal body growth

GH modulates postnatal growth [42]. The liver is the main source of circulating IGF-1, and STAT5b directly controls GH-dependent transcription of IGF-1 [26]. How GH treatment is administrated determines GH actions on the liver. In rodents, it has been reported that intermittent (male pattern) GH administration more potently stimulates body growth rate, IGF-1 expression, and STAT5b activity in the liver than continuous (female pattern) GH administration. However, GH is more efficient than IGF-1 since GH triggers additional growth independent of IGF-1. As pointed above, not only STAT5b but also other transcription factors that interact with STAT5b can influence body growth, including GR, a critical coactivator of STAT5b in the liver [119], or ER, which interacts with E2 and STAT5 [50]. Besides endocrine actions, paracrine effects of STAT5 in GH activity on muscle have been described, since a reduction of IGF-1 transcripts in the muscle and a loss of mass in muscle-specific deletion of STAT5a/b were reported [120].

3.2 Lipid and glucose metabolism

Energy/fuel metabolism, and particularly lipid metabolism, is the main metabolic process affected by GH status [26, 47, 121, 122]. GH promotes protein synthesis and inhibits protein degradation in muscle, bone, and other large tissues, thereby blocking glucose and amino acid catabolism and placing lipids as the main source of energy. GH exerts these actions by inhibiting insulin actions and leading fatty acid mobilization from adipose tissue and liver [26, 27]. In adipose tissue, GH poses lipolytic effects and reduces fat mass. This is especially evident in individuals that show an excess of fat accumulated during periods of GH deficiency [26–28]. Furthermore, GH displays triglyceride synthesis and secretion in the liver, and, besides increasing lipogenesis (e.g., SREBP1), GH inhibits PPARα expression and reduces lipid oxidation [47, 123]. In the skeletal muscle, GH drives triglyceride uptake and lipid oxidation, effects that can be reverted by external factors such as nutrition, exercise, or sex steroid hormones. In adulthood, GH can unleash a metabolic syndrome (i.e., increased visceral adiposity, fatty liver, decreased muscle mass, metabolic disturbances) that can be ameliorated by GH replacement therapy. In rodents and humans with fatty liver and adiposity, an ineffective GHR-JAK2-STAT5 signaling has been reported, which is attributed to increased lipogenesis and reduced triglyceride secretion, as well as lowered lipolysis [28, 29, 124]. In fact, it has been shown that STAT5b-deleted male mice become obese in later life [125] and that deletion of STAT5b in a mature human is associated with obesity [126]. In contrast, ablation of SOCS2, with subsequent increased STAT5 signaling, was shown to protect mice from high-fat diet-induced liver steatosis [46]. These evidences highlight two physiological aspects of GHR-STAT5b signaling: (a) STAT5b is essential in the regulation of key enzymes or genes otherwise involved in lipid and energy balance. Clinically relevant is that GH anti-obesity actions increase with the male pattern of pituitary GH secretion because of pulsatile STAT5 signaling and (b) absent GHR signaling, and therefore reduced STAT5 activation, provokes the fatty liver even with normal plasma levels of free fatty acids and minimal adiposity. Interestingly, agonists of liver X receptor (LXR), which cause hepatic steatosis [127], can inhibit GH-STAT5 activation through the induction of sterol regulatory element binding protein 1 (SREBP1) [128]. SREBP1, a LXR target gene, downregulates STAT5b gene transcription and stimulates STAT5b protein degradation. These findings highlight the molecular interactions of LXR with GH-STAT5 signaling in the liver.

GH activates the production of glucose in the liver by promoting glycogenolysis; however, GH can exert either a stimulatory or no effect on gluconeogenesis, due to GH antagonism of insulin action that triggers hepatic/systemic insulin resistance [27]. Furthermore, IGF-1 has an important role on carbohydrate metabolism and may increase insulin sensitivity by suppressing GH release. Therefore, activation of IGF-1 signaling increases the degree of complexity in understanding the molecular mechanisms involved in GH-induced insulin resistance in vivo. GHRKO and GH-deficient mice show improved insulin sensitivity and upregulated hepatic insulin signaling, thereby suggesting that GH locally antagonizes insulin signaling in the liver [129]. However, human GH gene overexpression has been shown to increase basal hepatic glucose uptake and glycogen burden in rats [130]. GH-induced insulin resistance may emerge from the increased mobilization of free fatty acids from peripheral adipose tissue. This can be affecting liver insulin sensitivity, leading to insulin resistance and upregulation of gluconeogenic genes (e.g., glucose-6-phosphatase, phosphoenolpyruvate carboxykinase), essential to glucose homeostasis in the liver. Intriguingly, LID mice have been shown to present a 75% reduction in circulating IGF-1 levels, three- to fourfold increase in circulating GH levels, and insulin resistance, without significant enhanced circulating free fatty acid levels. This suggested a possible local cross talk between GH and insulin signaling systems within the hepatocyte. Additionally, crossbreeding between LID mice and GH transgenic mice resulted in significantly increased serum free fatty acid levels and improved insulin sensitivity due to higher glucose uptake in hepatic, skeletal muscle, and adipose tissues [131]. Besides free fatty acids, the SOCS family of proteins, whose expression is induced by both GH and insulin in the liver, has also been suggested to contribute to insulin resistance [79, 128]. Recently, we have reported that SOCS2 deletion protected mice against the fatty liver, but, paradoxically, worsened insulin resistance was observed in high-fat diet-fed mice [46]. In contrast, SOCS2 deletion was shown to protect adult male mice against streptozotocin-induced type I diabetes [132].

3.3 STAT5b is a master regulator for "liver sexuality"

Gender dimorphism in the mammalian liver contributes to gender differences in body growth, intermediate metabolism, and steroid and xenobiotic compound metabolism. Many sex-dependent liver genes are regulated by sex differences in pituitary GH secretion, with STAT5b, proposed to mediate signaling by the pulsatile, male plasma GH profile. Most of the gender dimorphism in the liver can be explained by the female-specific pattern of pituitary gh secretion, through the induction and suppression of female- and male-predominant transcripts, respectively. The 20–30% of rodent hepatic genes have a sex-specific expression pattern. Genome-wide screens of gene expression have shown that several families of hepatic genes involved in endo- and xenobiotic metabolism and metabolic functions (e.g., lipid metabolism) are dependent on GH- and sex-dependent regulation. Moreover, other hepatic transcripts that encode plasma proteins, enzymes, transcription factors, and receptors and are involved in the metabolism of proteins, carbohydrates, or lipids have been found to be up- and/or downregulated by the different patterns of GH or sex steroid activity [47, 55]. A consensus exists that the response to sex-different pattern of pituitary GH secretion is the major cause of gender dimorphism in the liver. Large-scale gene expression study has been conducted using male and female mice, wild type and STAT5b inactivated, to characterize sex differences in liver gene expression and their dependence on STAT5B [26, 55, 133, 134]. Total disruption of STAT5b triggers loss of sexually dimorphic body growth in mice, as evidenced in affected male mice with reduced size (comparable with female size) and female mice unaffected.

Furthermore, a 30–50% reduction in circulating IGF-1 was found in affected male, but not in female mice. Nevertheless, the combined interruption of STAT5a and STAT5b significantly reduced body weight gain in female mice and repressed body growth in male mice more significantly than in male STAT5b null mice, which resemble both GH- or GHR-deficient mice. These findings confirmed the importance of STAT5b in male-specific body growth while exhibiting that STAT5a equally regulates body growth in both sexes. STAT5b is crucial for sex-dependent liver gene expression, a characteristic of approximately 4% of the genome. In male mice, male-predominant liver gene expressions are positively regulated by STAT5b or STAT5b-dependent factors, whereas female-predominant liver genes are repressed in a STAT5b-dependent manner. Remarkably, a number of the STAT5b-dependent male genes encode transcriptional repressors; these may include direct STAT5b target genes that repress female-predominant genes in the male liver. Several female-predominant repressors show enhanced expression in STAT5b-deficient male mice; these may contribute to the major loss of male gene expression found in the absence of STAT5b. Thus, STAT5b is a key player in this scenario, and it is responsible for the masculinization of the male liver [55, 125]. Conversely, other transcription factors (e.g., HNF6, HNF3β) are more efficiently activated in the female liver or by the continuous GH administration [135, 136]. In addition, SREBP1c induction, as well as hepatic triglyceride synthesis and VLDL secretion, and PPARα inhibition can be observed in the liver after continuous GH administration [47, 123]. However, it is likely that other factors are behind some sex differences in the liver. Potential mechanisms that could contribute to this "liver sexuality" are the pituitary-independent effects of sex steroids through interaction with GH-JAK2-STAT5 signaling pathway in the liver.

4. Sex steroids in liver physiology

The transcriptional program regulated by E2/ERα- and T(DHT)/AR-dependent signaling is linked to body growth and composition, drug-induced hepatotoxicity, liver growth, hepatic carcinogenesis, or even control of fertility [3, 4, 6, 7, 14–17, 23]. However, the specific roles of altered androgen/AR signaling dysfunctions, as well as its influence on GHR-dependent signaling, in the pathophysiology of metabolic phenotypes in the liver remain, in comparison with E2/ERα signaling, largely unknown. Conversely, the influence of JAK2 on ERα/AR-dependent transcription might also play a central role in the regulation of liver physiology and suggests a more complex level of cross talk between E2/ERα- or T/AR-dependent signaling and GHR in the liver [137].

4.1 Body growth and composition

The impact of sex steroids on body growth and composition is complex [4, 5, 19, 138]. Increased pubertal growth velocity associated with enhanced GH secretion has generally been attributed to T secretion in boys and to E2 or adrenal androgen secretion in girls. However, recent evidences support that E2 may be the main hormone promoting pubertal growth spurt in both sexes [139, 140]. Intriguingly, the lack of E2/ERα-dependent signaling, but not of ERβ, mediates key effects of estrogens in the skeleton of male mice during growth and maturation. A similar phenotype to ERα null mice can be found in aromatase-deficient (ArKO) male rats, where T cannot produce estrogens. Remarkably, E2 can retrieve skeletal growth rates in the absence of GHR (i.e., GHRKO mice), which is associated with an elevated hepatic and serum levels of IGF-1. This provides a novel mechanism of hepatic IGF-1 production, independent of GHR [139]. In addition, E2 can induce IGF-1 gene expression in the hypothyroid male rat liver, accompanied by low or

undetectable levels of circulating GH [47]. Gender-related differences in body composition during pubertal growth are thought to be partially mediated by sex steroids through GH-IGF-1 axis modulation. Oral E2 administration to postmenopausal women was shown to decrease circulating IGF-1 levels and increase GH expression, whereas transdermal E2 application was reported to elevate both GH secretion and IGF-1 concentrations [141]. Likewise, oral administration of pharmacological doses of estrogen to hypopituitary patients suppressed GH-regulated endocrine and metabolic effects (i.e., circulating IGF-1 levels, lipid oxidation, and protein synthesis). These effects on metabolism and body composition are attenuated by transdermal administration which suggests that these route-dependent effects are consequence of hepatic first pass effect of oral estrogen leading to direct inhibition of GHR-JAK2-STAT5-IGF-1 signaling pathway. This inhibition might be explained by E2 induction of SOCS2 and SOCS3 which are negative regulators of GHR-JAK2-STAT5b signaling in the liver [19]. E2 modulation of GH signaling is also exemplified by GH treatment inducing 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 than female patients [142, 143].

4.2 Lipid and glucose metabolism

Gender dimorphism also affects lipid and glucose metabolism [21, 22, 24]. In human and rodents, E2 physiologically mediates lipid and glucose metabolism. In fact, deficiency of E2/ERα signaling can trigger a metabolic syndrome-like phenotype (i.e., fatty liver, adiposity, insulin resistance) [18, 21, 144]. It has been shown that postmenopausal women are more prone to develop metabolic syndrome than premenopausal women. ERα deficiency or reduced levels of aromatase activity have been reported to promote the development of visceral adiposity, insulin resistance, and hyperinsulinemia both in male humans and mice. In ERαKO and ArKO mice, this metabolic syndrome-like phenotype can be reverted by E2 treatment. The favorable effect of E2 in lipid and glucose homeostasis stabilization is also found in ob/ob and high-fat diet-fed mice, models of obesity and type 2 diabetes. Treatment of ob/ob mice with PPT has been shown to improve glucose tolerance and insulin sensitivity, thus confirming the key role that ERα plays in the control of glucose homeostasis. Estrogenic signaling via GPR-30 has also been connected with glucose homeostasis and insulin production. ERα mainly controls antilipogenesis, reduction of adiposity, and improvement of insulin sensitivity, whereas ERβ may be detrimental for the maintenance of normal glucose and lipid homeostasis. In ERαKO mice, insulin resistance, accompanied by increased lipid content and hepatic glucose production, is mainly localized to the liver. Surprisingly, when hepatic ERα was selectively ablated (LERKO mice), mice did not restore the observed ERαKO mice phenotype (i.e., adiposity, glucose intolerance, insulin resistance), even when challenged with a high-fat diet. This suggests that unidentified compensatory mechanisms may be arising or that hepatic insulin resistance occurs as a secondary effect upon ablation of E2 signaling in other cell types. Intriguingly, selective ablations of ERα in the hypothalamic brain region or in hematopoietic/myeloid cells evoke increased body weight and reduced glucose tolerance. The antilipogenic effects of E2 in the liver are partially a result of the activation of PPARα- and the inhibition of LXRα-dependent signaling pathways, with subsequent increased fatty acid oxidation and inhibition of lipogenic genes (e.g., SREPB1c, Apo E) [47]. Activation of LXRα-dependent signaling enhances triglyceride accumulation in the liver. In contrast, E2/ ERα signaling suppresses lipogenic pathway expression and the fatty liver induced by LXR activation [38]. Similar to E2/ERα deficiency, reduced androgen/AR signaling is associated with a metabolic syndrome-like phenotype

(i.e., truncal adiposity, fatty liver, increased triglycerides/cholesterol, reduced HDL, insulin resistance type 2 diabetes), and this is improved after T replacement therapy [6, 25]. Nevertheless, the specific role of the androgen/AR signaling in liver metabolism regulation is still largely understood. Tissue-specific AR signaling has been shown to be involved in the regulation of lipid metabolism (i.e., inhibits lipogenesis, prevents liver steatosis) and promote anabolic growth in peripheral tissues [25]. Deletion of AR (ARKO) causes late-onset obesity in male mice, whereas the liver-specific ARKO (LARKO) exhibits increased insulin resistance and steatosis, with decreased β-oxidation, upon high-fat diet. Clinically relevant, high insulin resistance and impaired glucose tolerance have also been revealed in men with T deficiency [6]. Furthermore, some AR polymorphisms with reduced AR activity are connected to an excess of body fat and fat distribution pattern in both sexes [36]. Remarkably, T treatment diminishes visceral fat and improves nonalcoholic fatty liver disease in mice and human males [6, 23–25]. However, most E2/ERα actions that regulate body weight and lipid/glucose metabolism equally affect both female and male, thus suggesting that T aromatization in E2, via ERα, might also contribute to energy homeostasis in males. In summary, reduced E2/ERα or T/AR signaling is associated with metabolic disorders, including metabolic syndrome-like phenotype with adiposity and hepatic steatosis, which resembles deficiency of GHR-JAK2-STAT5 signaling. Notably, these metabolic disorders can be partially prevented or ameliorated, by E2/T and/or GH replacement therapies, thus suggesting that these hormones control overlapping cellular networks related with physiological control of lipid and glucose homeostasis.

5. Conclusions

Estrogen/ERα-dependent signaling and androgen/AR-dependent signaling are essential components in liver physiology and pathology in both male and female. Both direct and indirect actions of sex steroids in the liver are physiologically and therapeutically relevant. Particularly relevant are sex hormone interactions with GH-regulated endocrine (e.g., IGF-1), metabolic (e.g., lipid and glucose metabolism), and gender dimorphism (e.g., endo- and xenobiotic metabolism) functions in the liver. Therefore, the pituitary (GH)-gonadal (E2 and T)-liver axis is relevant in physiology and pathophysiology in mammals. Additionally, the endocrine and metabolic consequences of long-term exposition to compounds derived from sex hormones and their influence on the pituitary-liver axis need to be further understood. Thus, going in-depth in the study of this complex interaction in both physiological and pathological states may contribute to prevent health damage and ameliorate clinical outcome of patients with growth, developmental, and metabolic disorders.

Acknowledgements

We thank all the authors who contributed to the understanding of the cross talk between sex hormones and GH signaling in the liver. We apologize to those whose work deserves to be cited but unfortunately are not quoted because of space restriction. The research program in the author's lab was supported by grants-in-aid from the Spanish Ministry of Economy and Competitiveness (MINECO) with the funding of the European Regional Development Fund-European Social Fund (SAF2015-65113-C2-2-R), Canary Islands Government (ACIISI PI2010), and Alfredo Martin Reyes Foundation (Arehucas)-FICIC.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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