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REVIEW ARTICLE

Sex steroids and growth hormone interactions

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Abstract GH and sex hormones are critical regulators of body growth and composition, somatic development, intermediate metabolism, and sexual dimorphism. Deficiencies in GH- or sex hormone-dependent signaling and the influence of sex hormones on GH biology may have a dramatic impact on liver physiology during somatic development and in adulthood. Effects of sex hormones on the liver may be direct, through hepatic receptors, or indirect by modulating endocrine, metabolic, and gender-differentiated functions of GH. Sex hormones can modulate GH actions by acting centrally, regulating pituitary GH secretion, and peripherally, by modulating GH signaling pathways. The endocrine and/or metabolic consequences of long-term exposure to sex hormone-related compounds and their influence on the GH-liver axis are largely unknown. A better understanding of these interactions in physiological and pathological states will contribute to preserve health and to improve clinical management of patients with growth, developmental, and metabolic disorders.

PALABRAS CLAVE
GH;
E2;
Testosterona;
Hígado;
Metabolismo;
Dimorfismo sexual

Esteroides sexuales e interacciones con la hormona de crecimiento

Resumen La GH y las hormonas sexuales son importantes reguladores del crecimiento y la composición corporal, el desarrollo somático, el metabolismo intermediario y el dimorfismo sexual. Deficiencias en las actividades fisiológicas de estas hormonas, así como las interacciones de las hormonas sexuales con la GH, repercuten en la fisiología hepática tanto durante el desarrollo corporal como en la edad adulta. Las hormonas sexuales pueden actuar

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sobre el hígado por mecanismos directos, a través de sus receptores hepáticos, o indirectos, modulando las funciones de la GH a niveles endocrino y/o metabólico. Las hormonas sexuales pueden modular las acciones de la GH a nivel central, regulando su patrón de secreción hipofisaria, y periféricamente, modulando sus mecanismos de señalización intracelular. Las consecuencias endocrinas y/o metabólicas de la exposición prolongada a compuestos relacionados con hormonas sexuales, así como su influencia sobre el eje GH-hígado son, en gran medida, desconocidas. La comprensión de estas interacciones en diferentes estados fisiológicos y patológicos contribuirá a mantener la salud y mejorar el manejo clínico de los pacientes con transtornos del crecimiento, el desarrollo y el metabolismo.

Introduction

GH is the main regulator of somatic growth, metabolism, and gender-differentiated functions in liver.[1–6] GH is predominantly linked to linear growth during childhood, but continues to have important metabolic actions throughout life. Interestingly, deficiency of GH-GH receptor (GHR),[6] estradiol (E2)-Estrogen Receptor α (ERα)[7–11] or testosterone (T)/Androgen Receptor (AR)[11–15] signaling in adults causes a similar metabolic-like syndrome (i.e., fatty liver, visceral adiposity, insulin resistance, decreased muscle mass), a phenotype that can be ameliorated by GH or sex hormones replacement. E2 and T can modulate GH actions in the liver by acting both centrally, regulating pituitary GH secretion,[16,17] and, peripherally, modulating GH signaling.[18] Most previous studies have been focused on the influence of E2 and T on gender-specific pituitary GH secretion, which has a great impact on hepatic transcriptional regulation. In addition, the liver is a direct target of sexual hormones because it expresses ERα and AR, and the signaling pathways linked to these receptors are connected with lipid and glucose homeostasis,[11] liver growth and regeneration,[19] body growth,[20] drug-induced hepatotoxicity,[21] hepatic carcinogenesis,[22] or fertility.[23] Notably, E2 has been shown to modulate GH actions in the liver through induction of Suppressor of Cytokine Signaling (SOCS)-2, which in turn negatively regulates GHR-Janus Kinase (JAK)-2-Signal Transducer and Activator of Transcription (STAT)-5 signaling pathway. Interactions between T and GHR-JAK2-STAT5b-SOCS2 signaling pathways might also play a relevant role to regulate hepatic metabolism.[24,25] This phenomenon is clinically relevant because its importance in the regulation of endocrine, metabolic, and gender-differentiated actions of GH in the liver. Notably, disruption of the GHR-JAK2-STAT5-SOCS2 signaling pathway is associated with disorders in somatic growth[5,6] and gender dimorphism,[17,26] and with liver diseases such as non-alcoholic fatty liver, insulin resistance, fibrosis, or hepatocellular carcinoma.[27–30] However, the specific roles of the E2/ER and T/AR signaling for the regulation of liver physiology and, particularly, GHR-JAK2-STAT5-SOCS2 signaling pathway are still largely unknown. Furthermore, the novel discovery of JAK2 as a negative regulator of ERα suggests a more complex level of crosstalk between E2/ERα and GH-mediated signaling pathways.[31] In the general population, the endocrine and metabolic consequences of long-term exposition to sex hormones-related compounds and their influence on the pituitary (GH)-liver axis are also largely unknown. In this review, we will summarize the current status of the influence of sex hormones on GH actions in the liver. A better understanding of this complex interaction in physiological and pathological states will contribute to prevent health damage and improve clinical management of patients with growth, developmental and metabolic disorders.

Regulation of pituitary GH secretion

GH is a polypeptide mainly secreted by the somatotroph cells, but also produced in extra-pituitary tissues; therefore, GH also has paracrine-autocrine effects, distinct from its classic endocrine somatotropic effects.[32,33] 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 metabolic factors. Pituitary GH secretion is regulated by two hypothalamic peptides: GHRH and the inhibitory hormone somatostatin (SS). The balance of these peptides is, in turn, indirectly affected by many physiological stimulators (i.e., exercise, sleep, nutrients, thyroid hormones, sex hormones) and inhibitors (i.e., glucocorticoids, IGF-I, GH). The final integration of these signals occurs in the hypothalamus. Pituitary GH secretion is mainly reduced by the negative feedback of two circulating signals: pituitary GH itself, and liver-derived IGF-I stimulated by GH. In addition to hypothalamic and endocrine factors, other peripheral factors influence pituitary GH release (i.e., free fatty acids (FFA), insulin, glucose, amino acids, leptin, neuropeptide Y, 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, and 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: GH can stimulate FFAs mobilization, which inhibit GH release and complete a feedback loop among pituitary and adipose tissue. Conversely, leptin, which is also produced in adipose tissue, and