

Transcriptomic and lipidomic profiling reveals a functional interplay between sex steroids and Growth Hormone in the Liver

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L. Fernández-Pérez^I, B. Guerra^I, R. Santana-Farré^I, M. Mirecki-Garrido^I, I. García^{II}, J.C. Díaz-Chico^I, A. Flores-Morales^{III}, D. Iglesias-Gato^{III}, M. Díaz^{II}

^IUniversity of Las Palmas de Gran Canaria (ULPGC), Las Palmas de Gran Canaria, Spain, ^{II}University of La Laguna, La Laguna, Spain, ^{III}University of Copenhagen, Copenhagen, Denmark

Gonadal steroids (GS) and GH are critical regulators of body growth and intermediate metabolism in mammals. The metabolic influences of GS and GH deficiency have been well documented in adult men by the developing of chronic illness (e.g., fatty liver, insulin resistance), a phenotype that can be ameliorated by E2/testosterone and GH replacement. The effects of GS on liver might be direct through their respective nuclear receptors. Indirect mechanisms, related to the influence of sexual steroids on the pituitary GH secretion and/or their influence on GHR signaling pathway in the target tissue, might also play a relevant role to regulate liver physiology. The molecular characterization of the hepatic changes induced by GS and how they influence the liver response to GH deserves to be explored. Hypothyroidism-hypogonadism is accompanied by systemic and hepatic metabolic disturbances with features that mimic deficiencies in GH and GS. In this study, the analyses of lipid and transcriptional profiles in hypothyroid-orchidectomized rats were combined to obtain comprehensive information on the GS and GH crosstalk in liver. Testosterone (T) activated, among others, a metabolic transcriptional program linked to glucose and fatty acids and lipid class metabolism. The overall impact of T on hepatic lipid content and transcriptome differed from the effects of E2. The combined administration of T and GH revealed biological processes related to lipid biosynthesis, oxidation-reduction, unsaturated and long-chain fatty acid metabolism. GH showed permissive, additive, or antagonistic effects on T actions on hepatic lipid content. Protein-protein interactions analysis revealed a close interplay among proteins which are central in the metabolism of steroid and fatty acids. These findings highlight the impact of GS-GH interplay on liver metabolism which is relevant for physiological and therapeutic roles of these hormones in human.