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Regulation of skeletal growth and mineral acquisition by the GH/IGF-1 axis: Lessons from mouse models

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ABSTRACT

The growth hormone (GH) and its downstream mediator, the insulin-like growth factor-1 (IGF-1), construct a pleotropic axis affecting growth, metabolism, and organ function. Serum levels of GH/IGF-1 rise during pubertal growth and associate with peak bone acquisition, while during aging their levels decline and associate with bone loss. The GH/IGF-1 axis was extensively studied in numerous biological systems including rodent models and cell cultures. Both hormones act in an endocrine and autocrine/paracrine fashion and understanding their distinct and overlapping contributions to skeletal acquisition is still a matter of debate. GH and IGF-1 exert their effects on osteogenic cells via binding to their cognate receptor, leading to activation of an array of genes that mediate cellular differentiation and function. Both hormones interact with other skeletal regulators, such as sex-steroids, thyroid hormone, and parathyroid hormone, to facilitate skeletal growth and metabolism. In this review we summarized several rodent models of the GH/IGF-1 axis and described key experiments that shed new light on the regulation of skeletal growth by the GH/IGF-1 axis.

1. Introduction

The skeleton is a rigid connective tissue that except for providing protection and support for the body also functions as an endocrine organ and interacts with other internal organs via secretion of hormones and micronutrients. Both long and flat bones of the skeleton are vital tissues containing osteocytes, the bone resident cells, and osteoblasts, the bone matrix-lining cells. During life, bones undergo processes of modeling (shaping) and remodeling (damage correcting), mediated by osteoblasts and osteoclasts, the bone resorbing cells. Bones are composed of two major compartments: the cortical bone, which is a compact dense structure of mineralized collagen; and the trabecular compartment, which is spongy, less compact, and is irregular in structure. Cortical bone has two surfaces: the periosteum, which is a fibrous layer with osteogenic potential allowing radial bone growth (also called periosteal bone apposition); and the endosteum, which borders with the marrow. Longitudinal bone growth occurs at the growth plates via endochondral ossification where pre-chondrocytes/resting cells first differentiate, proliferate, undergo hypertrophy, and subsequently mineralize. Both the periosteum and the endosteum layers contain blood vessels and nerve fibers connecting them to other organs in the body.

Bone metabolism refers to the complex functions of the skeleton in maintaining whole body homeostasis. Bone acts as a calcium and phosphate reservoir and responds to hormonal stimuli to release or deposit minerals according to systemic needs. Releasing of alkaline salts from bone buffers the blood, and absorbing/depositing heavy metals and other extraneous elements assists in whole body detoxification. Bone matrix functions as a repository for cytokines and growth factors that are released upon bone resorption and act locally in their microenvironment. Lastly, bone acts as an endocrine organ releasing fibroblast growth factor-23 (FGF23), a peptide regulating phosphate metabolism; osteocalcin, a hormone contributing to glucose/lipid metabolism; and sclerostin, a hormone regulating bone formation whose functions in other organs are yet to be discovered. There are several hormones/growth factors that regulate bone metabolism. These include the 1) parathyroid hormone (PTH), which regulates calcium and phosphate metabolism via its receptors (PTH1Rs) found

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on osteoblasts, osteocytes, cells of the intestine, and the kidney; 2) calcitonin, a peptide secreted from the thyroid and neuroendocrine cells that inhibits bone resorption; and 3) vitamin D, a secosterol hormone, which promotes calcium absorption by the intestine and decreases calcium and phosphorus excretion by the kidney. During development, linear and radial bone growth and modeling are regulated mainly by the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis and sex steroids, which also protect the skeleton from age-related bone loss.

Summary of the literature about the GH/IGF-1 axis is overwhelming. The effects of these two hormones on cellular proliferation, differentiation and function have been tested in almost all cell systems and in numerous animal models. Thus, we have reviewed herein only a limited number of papers. We focused on regulation of skeletal growth by the GH/IGF-1 axis in mouse models, and emphasized specifically in vivo findings obtained from wild-type, global gene ablation, as well as data from cell-specific inactivation of GH/IGF-1 and members of its axis in mice.

2. The GH/IGF-1 axis

The GH/IGF-1 is an anabolic, pleotropic axis that includes several members; The GH releasing hormone (GHRH) that regulates GH secretion, GH, the GH receptor (GHR), IGF-1, and the IGF-1 receptor (IGF-1R). Downstream mediators of the GHR, such as the Signal Transducer and Activator of Transcription 5 (STAT5), Janus kinase 2 (JAK2), and the suppressors of cytokine signaling 1–3 (SOCS1-3) are often included in that axis. Incorporated also are the IGF-binding proteins (IGFBPs) and the acid labile subunit (ALS) that carry IGF-1 in circulation, prolong its half-life, and regulate its bioavailability.

The synthesis and secretion of GH from the pituitary is promoted by GHRH, while inhibition of GH secretion is regulated largely by somatostatin, but also by other central and peripheral signals [1]. Pituitary GH is the prime regulator of IGF-1 production in the liver (Fig. 1). The liver is the major contributor to the circulating pool of IGF-1 (75%) while other tissues such as fat and muscle contribute ~25% of IGF-1 in serum. In the circulation IGF-1 is bound to the IGFBPs and the ALS, which prolong IGF-1 half-life in serum and tissues and determine its bioavailability. IGFBP-3, the most abundant IGFBP in serum, and the IGFBP-5, form ternary complexes with IGF-1 and the ALS which have a half-lives of ~16 h. Binary complexes of IGFBPs and IGF-1 have half-lives of ~90 min, while the half-life of free IGF-1 in serum is only ~10 min. IGF-1 in serum acts in an endocrine fashion and provides negative feedback at the pituitary level to inhibit GH secretion. Importantly, IGF-1, which is produced by virtually all tissues, also acts in an autocrine/paracrine fashion at different local sites of production. IGF-1 binds to its tyrosine-kinase receptor, namely the IGF-1R. Upon binding to its receptor IGF-1 activates receptor autophosphorylation and recruitment of adaptor proteins, such as insulin receptor substrate (IRS) family, and the proto-oncogene tyrosine kinase Src, to activate cellular proliferation, differentiation, and organ function. GH effects on the liver, as well as on other organs, such as muscle, fat, cartilage, and bone, are mediated via the GHR, a cytokine-like receptor found in almost all tissues and which acts in an IGF-dependent or independent manner. Upon GH binding to the GHR, there is a conformational change in the intracellular domain of the receptor [2,3], concomitant phosphorylation of the JAK2 proteins, and transduction of the signal to the STAT5 proteins that activate gene transcription (among them is igf-1). Suppression of this signaling cascade occurs through proteosomal degradation of the receptor, dephosphorylation of the JAK2 proteins [4], and their promotion to proteosomal degradation [5] by the SOCS proteins.

The feedback regulation between serum IGF-1 levels and pituitary GH secretion, as well as the diverse activities of both GH and IGF-1 in multiple tissues, affecting not only body size but also body composition and metabolism, posed many challenges in understanding the relative contribution of each hormone to skeletal growth. Furthermore, based on experimental evidence showing that GH stimulates igf-1 gene expression not only in liver but also in several other tissues, IGF-1 has long been regarded as the mediator of GH effects. However, as will be noted in this review, GH has both IGF-1-dependent and independent effects. Lastly, we mention that interpretation of data on skeletal growth from mouse models of the GH/IGF axis has to be done carefully, taking into account the complex interactions between these two hormones and their pleotropic effects on whole body homeostasis including bone.

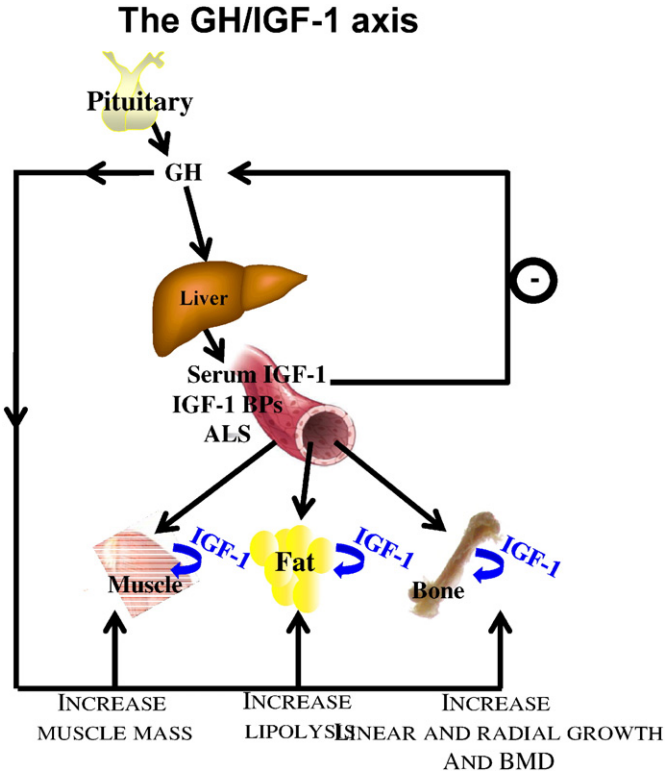

Fig. 1. The GH/IGF-1 axis. GH, secreted from the pituitary, is the prime regulator of igf-1 gene in liver, which contributes ~75% of serum IGF-1. GH acts via its receptor that is found on almost all cells and increase muscle mass, fat lipolysis, linear and radial bone growth, and bone mineralization. IGF-1 in serum is bound to the IGF-BPs and the ALS, which regulate its half-life and deliver it to the tissues leading also to increased muscle mass, and bone mineral content. Serum IGF-1 serves also as a negative regulator of GH secretion from the pituitary. IGF-1 is produced by all tissues and acts in an autocrine/paracrine manner.

3. Global impairment of the GH/IGF-1 axis affects body size and skeletal acquisition

3.1. Excess of GH

The GH/IGF-1 is an anabolic axis and as such, it is expected that models of excess GH/IGF-1 would lead to growth enhancement. Indeed, several models of overexpression of GHRH [6,7], the human (h) [8–14] or bovine (b) GH in mice have demonstrated increased body size and skeletal gigantism [10,15–21]. In this review we will focus on the skeletal phenotype of models overexpressing bGH, which activates the endogenous mouse GHR, as opposed to the hGH transgene, which activates both the GHR and the prolactin receptor. All studies of transgenic mice with excess endogenous or transgenic bGH reported increases in bone size (length and diameter) and overall increases in bone mineral density (BMD). However, detailed analyses of skeletal properties revealed that systemic GH overexpression resulted in sex-specific and age-specific effects on the skeleton and impaired bone architecture and mechanical properties [15,17,19,21]. Overexpression of the hGHRH [20] resulted in systemic stimulation of endogenous GH and IGF-1 leading to initial increase in bone mass. However, later on, excess