Growth Hormone Therapy in Heart Failure

Andrea Salzano, MD[a,b], Alberto M. Marra, MD[c], Roberta D'Assante, PhD[c], Michele Arcopinto, MD[d], Toru Suzuki, MD, PhD[a], Eduardo Bossone, MD, PhD[d], Antonio Cittadini, MD[b,e,*]

KEYWORDS

• Chronic heart failure • Growth hormone • IGF-1 • Anabolic deficiency • Biomarker • Outcomes • Novel therapies • Hormone deficiency

KEY POINTS

- Growth hormone deficiency (GHD) is common in chronic heart failure (CHF) and is associated with impaired functional capacity and poor outcomes.
- Correction of GHD is an innovative therapy that has to be considered in CHF.
- An individualized dose titration of GH should be considered for each patient depending on neurohumoral response, whereas GH therapy should not be administered in patients with advanced CHF.

INTRODUCTION

Despite considerable improvement in the management of heart failure (HF), unsustainable levels of morbidity and mortality coupled with an increasing economic and social burden have been observed over the previous decades.[1] One possible explanation might be that no single pathophysiologic paradigm of HF may completely explain disease progression.

The classical neurohormonal model, rooted on overexpression of different molecular pathways, such as the sympathetic nervous, the renin-angiotensin-aldosterone, and the cytokines system, represented the theoretic background for the implementation of milestone clinical trials, which in turn have dramatically changed the natural history of this disease.[1,2] Nowadays, drugs that contrast the sympathetic nervous system (β-blockers) and the renin-angiotensin-aldosterone pathway (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, angiotensin receptor neprilysin inhibitor, and mineralocorticoid receptor antagonists) are considered the first-line pharmacologic therapy for HF.[3–6]

However, chronic heart failure (CHF) is still burdened by increased mortality, worse than that of many cancers, frequent comorbidities, and, consequently, remarkable associated health care costs.[1] For this reason, other pathophysiologic models to complement the paradigm of neurohormonal hyperactivity were proposed. In this regard, several studies have showed that hormonal deficiencies are common in CHF[7–10] and, more importantly, are significantly related with several indexes of physical performance and survival. The importance of these data led some authors to consider CHF as a multiple hormone deficiency syndrome.[7]

In this context, the reduced activity of growth hormone (GH) and its tissue effector insulin-like

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[a] Department of Cardiovascular Sciences and NIHR Leicester Biomedical Research Centre, University of Leicester, Glenfield Hospital, Leicester, LE3 9QP, UK; [b] Department of Translational Medical Sciences, Federico II University, School of Medicine, Via Pansini 5, Naples, 80131, Italy; [c] IRCCS SDN, Via Gianturco 113, Naples, Italy; [d] Emergency Department, AORN "A. Cardarelli", Via A. Cardarelli, Naples, 80131, Italy; [e] Interdisciplinary Research Centre in Biomedical Materials, Federico II University, Naples, 80100, Italy

* Corresponding author. Department of Translational Medical Sciences, Federico II University, School of Medicine, Via Pansini 5, Naples 80131, Italy.

E-mail address: antonio.cittadini@unina.it

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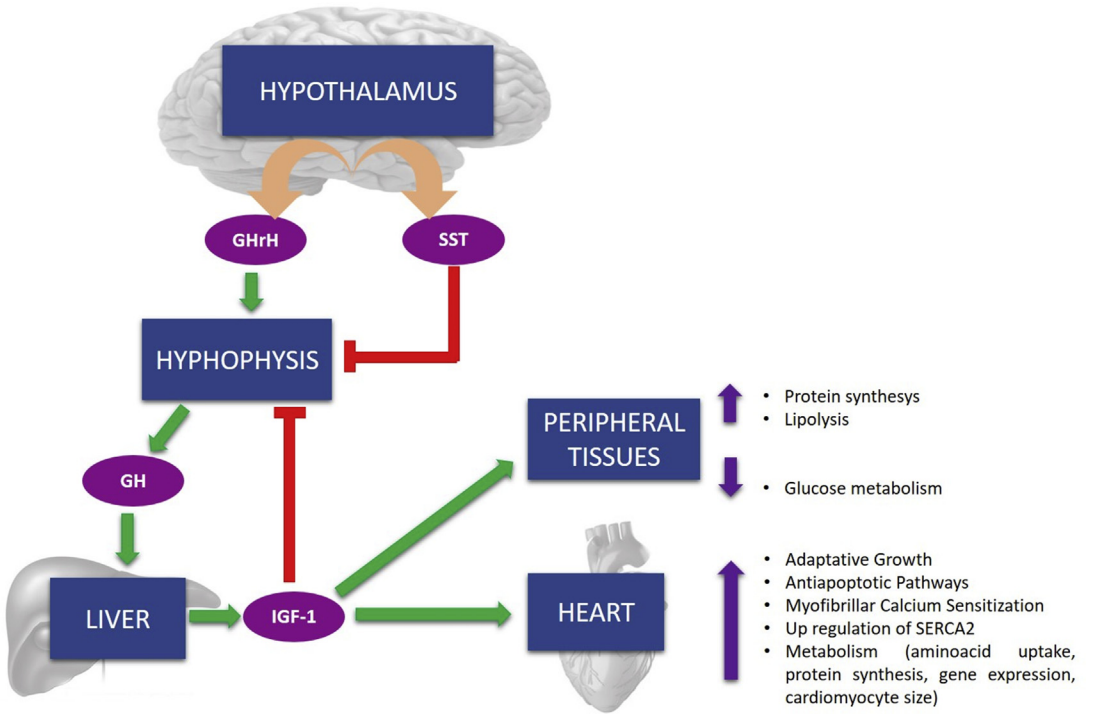

Fig. 1. Pathophysiologic background of hypothalamic-pituitary axis and GH/IGF-1 systemic effects. GHrH, growth hormone–releasing hormone; SERCA2, sarcoplasmic/endoplasmic reticulum Ca2+-ATPase; SST, somatostatin.

growth factor 1 (IGF-1)[11] plays a pivotal role. This review focuses on the involvement of GH/IGF-1 axis in CHF, on the role and prevalence of GH deficiency (GHD) in HF, and on the effects of GH therapy as add-on and replacement in the correction of GHD in HF.

THE EFFECTS OF GROWTH HORMONE/ INSULIN-LIKE GROWTH FACTOR 1 ON THE CARDIOVASCULAR SYSTEM

The pituitary secretion of GH exerts several biologic effects through the interaction between GH and its specific receptors that leads to the hepatic production of IGF-I, its major biologic mediator.[12,13] Through a long-loop feedback, IGF-1 produced in the liver in response to GH prevents GH release (**Fig. 1**).

Among all the anabolic systems existing in nature, the GH/IGF-1 pathway is considered the most powerful. It regulates postnatal growth by increasing muscle mass, bone length, and density during childhood and adolescence. Furthermore, carbohydrates and lipids metabolism are regulated by its effects, mainly on visceral adipose tissue.[14] IGF-1 circulates in blood either free or bound to particular binding proteins that prolong the its half-life.[15] Nevertheless almost 90% of circulating IGF-1 is part of a ternary complex composed of IGF-specific binding protein 3 and acid-labile subunit.[16] Through this complex, IGF-1 is able to reach its target-organs, where the interaction with its own receptor (IGF1R) activates the PI3K/Akt pathway.[17] This complex pathway promotes the main effect of GH: cell growth, enhances glucose transport, inhibits apoptosis, and acts along with interleukin-6 to protect cells from tumor necrosis factor-α cytotoxicity.[15]

The cardiovascular system is an important target of this anabolic axis.[12,18] It is well established that GH plays a pivotal role by regulating cardiac growth, cardiomyocyte size, and metabolism; by stimulating amino acid uptake for protein synthesis[19]; and by promoting the transcription of genes specifically expressed in the cardiac muscle.[19] Moreover, systemic vascular resistance is likely to be reduced by the activation of IGF-1 receptors through the production of nitric oxide. IGF-1 leads to augmented contractility of cardiomyocytes mainly by increasing intracellular calcium concentration and calcium sensitization of the myofilaments and preserves capillary density.[20] Through regulation of the sarcoplasmic/endoplasmic reticulum Ca2+-ATPase (SERCA2), IGF-1 also induces the