Growth hormone-releasing peptides and the heart: secretagogues or cardioprotectors?

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See article by Iwase et al. [13] in this issue.

Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) are multifunctional hormones with potent cardiotropic effects in prenatal and postnatal cardiac development. Evidence from animal and clinical studies has documented the beneficial effects of the GH-IGF-1 axis on cardiac hypertrophy and contractile function under conditions of GH deficiency, cardiomyopathy and ischemia reperfusion injury [1]. In rats with heart failure due to myocardial infarction, GH and IGF-1 increased cardiac output and decreased systemic vascular resistance [2]. More recently, Sussman’s laboratory demonstrated that cardiac-specific overexpression attenuated dilated cardiomyopathy in tropomodulin-overexpressing transgenic mice and was associated with normalization of left ventricular (LV) mass, increased myocyte number and improved LV end diastolic pressure, \( \frac{dp}{dt} \) and \( \frac{-dp}{dt} \) [3]. A preliminary, uncontrolled clinical trial with seven patients indicated that GH improved myocardial mass and cardiac output and ventricular mechanical work [4]. However, a later double-blind, placebo-controlled trial with a larger number of patients with chronic heart failure due to dilated cardiomyopathy found that recombinant human GH increased LV mass but had no improvement in LV function or clinical status [5]. These conflicting results, along with a report of increased morbidity and mortality of high doses of GH in critically ill patients [6], has led to a search for alternative treatment modalities.

GH-releasing peptides (GHRP) are a heterogeneous group of synthetic peptides that act as potent GH secretagogues on specific G-protein-coupled receptors in the hypothalamus and pituitary. Recently, the myocardium has been shown to express functional GHRP receptors that appear to have distinct binding properties compared to the pituitary receptors [7]. Initial studies by Locatelli et al. [8] documented cardioprotective effects of the GHRP hexapeptide hexarelin in ischemic reperfusion injury in hearts isolated from hypophysectomized rats. Tivesten et al. [9] subsequently showed that a 2-week treatment with hexarelin and GH improved stroke volume and decreased total peripheral resistance in rats subjected to experimental myocardial infarction. In human trials, acute treatment with hexarelin increased the LV ejection fraction in normal and GH-deficient subjects but not in cases of severe dilated cardiomyopathy [10,11]. In patients with coronary artery disease undergoing bypass surgery, the acute administration of hexarelin, but not of rGH or GH-releasing hormone, caused a rapid increase in the LV ejection fraction, cardiac index and cardiac output [12]. However, although these studies suggest GH-independent actions of hexarelin, in some cases, the effects of hexarelin and exogenous GH were similar and the relationship between hexarelin and serum levels of IGF-1 and GH was not completely defined.

In a study published in this issue, Imazio et al. [13] convincingly demonstrate that a 4-week treatment with GHRP-6 attenuates LV dysfunction and dilation in dilated cardiomyopathic hamsters at concentrations that had no effect on serum GH and IGF-1 levels. Interestingly, these studies suggest that GH and GHRP may elicit distinct molecular mechanisms since GH but not GHRP increased wall thickness and the expression of atrial natriuretic peptide, a marker of hypertrophy. Therefore, it is possible that GHRP exerts inotropic responses but does not affect hypertrophic growth. Support for this notion comes from a recent study by Xu et al. [14] who reported a positive inotropic effect of GHRP is associated with the induction of biphasic Ca\(^{2+}\) transients in isolated neonatal and adult rat ventricular myocytes. On the other hand, the ability of GHRP-6 to prevent sudden death in cardiomyopathic dogs subjected to acute myocardial ischemia was associated with increased wall thickness in the non-ischemic zone [15]. Nevertheless, these studies clearly establish a cardioprotective role for GHRP independent of its ability to elicit GH secretion.
Much less is known about the cellular mechanisms that transduce these cardioprotective effects of GHRP. At least two different receptors for this peptide, GHS-R and the b-type scavenger receptor CD36, have been identified in the myocardium [7,16]. GHS-R is a Gq-coupled receptor linked to phospholipase C activation and may mediate the effects of GHRP on cardiac myocyte Ca\(^{2+}\) transients [14]. CD36, which binds exogenous GHRP but not the endogenous GH secretagogue ghrelin, is expressed in coronary vessels and appears to couple to protein kinase C and L-type Ca\(^{2+}\) channels to increase vasoconstriction in response to hexarelin [7,16]. Increased CD36 expression may also account for the cardioprotective effects of hexarelin following ischemia-reperfusion in hypophysectomized rats [17]. On the other hand, ghrelin and des-acyl ghrelin, which doesn’t bind to GHS-R, inhibits cardiac myocyte and endothelial cell apoptosis via ERK1/2- and PI 3-kinase-dependent mechanisms [18]. Thus, it is likely that both receptors subtypes contribute to the cardiac actions of GHRP. Further studies are required to elucidate the cellular signaling pathways that are activated by each receptor and their exact role in the cardioprotective effects of GHRP.

References