Review

Cardiac and peripheral actions of growth hormone and its releasing peptides: Relevance for the treatment of cardiomyopathies

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Abstract

Ischemic and non-ischemic cardiomyopathies are associated with significant morbidity and mortality in industrialized countries. Cardiomyopathies of primary origin, and more specifically the dilated form of the disease, have been associated with a number of gene defects in cytoskeletal, membrane, and sarcomeric proteins. Cardiomyopathies of secondary origin such as ischemic cardiomyopathy remain the leading cause of left ventricular systolic dysfunction and heart failure. Among novel strategies to improve cardiac function in heart failure, treatment with growth hormone, insulin growth factor-1 (IGF-1), and natural and synthetic growth hormone-releasing peptides such as ghrelin and hexarelin have been explored. The present review focuses on the issues involved in the use of exogenous growth hormone and its releasing peptides in experimental animal models of chronic heart failure and in clinical studies on cardiomyopathic patients as potential releasing peptides for the treatment of chronic heart failure developing as a consequence of cardiomyopathy.

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1. Introduction

Systolic heart failure (HF) evolves as a consequence of a number of cardiac diseases including hypertension, valvulopathy, ischemic and non-ischemic cardiomyopathies (CM) [1]. Non-ischemic CM are primary myocardial pathologies associated with systolic and/or diastolic dysfunction classified clinically as dilated, hypertrophic, restrictive and arrhythmogenic [2]. Dilated and hypertrophic forms are the most prevalent and lead to significant morbidity and mortality [2]. Dilated CM (DCM) remains the first cause for cardiac transplantation in the USA [3]. DCM, previously largely known as “idiopathic” (IDCM), has been associated with a number of gene defects encoding for cytoskeletal (dystrophin, desmin), cell membrane (β-sarco glycan), sarcomeric (titin, troponin T and actin) and inner nuclear membrane (lamin A/C) proteins [4]. In addition to its genetic and familial origin, CM may occur as a consequence of secondary causes including ischemic, viral, immunologic, inflammatory, metabolic, toxic or neoplastic nature [3]. Among CM of secondary origin, ischemic CM is the leading cause of left ventricular systolic dysfunction and HF [5]. Ventricular remodelling following myocardial infarction (MI) largely account for the decline in left ventricular (LV) function [5,6]. There is a general consensus to treat patients, regardless of the etiology of HF, with a conventional drug regimen including angiotensin-converting enzyme inhibitors, β-adrenoceptor antagonists, diuretics and digoxin [6,7]. However, despite optimal drug dosage, congestive HF (CHF) in cardiomyopathic patients remains a therapeutic challenge with a 3–5 years mean survival time, notwithstanding the origin of the disease [8].

Novel strategies to improve cardiac function in HF have recently included growth hormone (GH), the insulin growth factor-1 (IGF-1) and more recently, GH secretagogues
2. Cardiovascular effects of GH replacement therapy in patients with GH deficiency

One basis for investigating the effects of anabolic agents in CHF relies on the observed benefits of GH replacement therapy in improving cardiovascular performance in GH-deficient patients. Epidemiological studies of GH deficiency (GHD) revealed this clinical condition to be associated with an increased prevalence in cardiovascular mortality, mainly as a consequence of HF [9].

GH replacement therapy in adults with either childhood or adulthood GHD appears to be salutary and is accompanied with an increase in left ventricular mass (LVM) [10,11], an improved LV function [12], a reduced diastolic blood pressure [12] and a rise in exercise capacity [13,14]. Additional benefits of GH replacement therapy include development of a favorable plasma lipid profile [15,16] and a general sense of well-being in patients [17]. Short-term treatment with GH also improves the altered ventricular geometry [9]. The response to GH in GHD patients is time- and dose-dependent, and may take up to 6 months to be fully appreciated [18]. In addition, peripheral vasodilatory effects of GH replacement therapy through normalized/enhanced production of NO, may contribute to the improved cardiac performance observed in patients with GHD [19].

The apparent benefits of GH on the cardiovascular function of patients with GHD gave rise to extensive clinical and experimental studies of the effects of GH and GHS on the cardiovascular function in different pathological settings.

3. GH and GHS in experimental heart failure

Experimental models have explored the effects of exogenous GH and/or IGF-1, and more recently of GHS, on cardiac function and survival in ischemic and non-ischemic CM models. Whereas the effects of GH on ischemic CM progression has mainly been investigated in the context of post-ischemic cardiac failure in the rat, its effects on nonischemic CM progression have essentially relied on the use of models of genetically inherited CM in hamsters and more recently, of genetically engineered CM mice [20].

3.1. Effect of GH/IGF-1 on post-myocardial infarction heart failure

As shown in Table 1, initial studies investigating the effects of early GH treatment on ventricular remodelling post-MI in rats reported a reduction of ventricular aneurysms 25 days post-infarction, following a 3-day treatment with recombinant human GH (rhGH) (0.17 mg/kg daily) beginning the day of left coronary artery ligation (LCAL) [21]. The beneficial effects of GH were attributed to the preservation of the collagen network. These results contrast with those of Bollano et al. (2001) who did not find a difference in aneurysms after a 9-day treatment with GH at a 10-fold higher dose [22]. Additional studies showed the benefits of an early treatment with GH, inducing ventricular hypertrophy and improving function following LCAL in rats. A 3-week treatment with 3 mg/kg rhGH, starting the day after LCAL, caused a beneficial hypertrophy of the non-infarcted myocardium, along with a reduction in LV dilation and vascular resistance that led to an improved cardiac performance [23]. A 4-week treatment with rhGH (0.67 mg/kg), initiated immediately following LCAL, improved considerably cardiac function, in association with reduced pathological remodelling [24]. In a larger animal model, recombinant bovine GH (rbGH) elicited a dose-dependent cardiac hypertrophy following infarction, associated with an increased cardiac level of IGF-1 [25]. In contrast, an early treatment with rhGH (3 mg/kg per day for 3 weeks), starting 3 days post-surgery, attenuated LV remodelling without induction of LV hypertrophy in rats with large MI, an effect associated with an improved myocardial energy status, a decreased myocardial and plasma catecholamines and brain natriuretic peptide levels [26].

Beneficial effects of early combined treatment with IGF-1 and GH post-infarction have also been reported, as shown in Table 1. Early treatments with IGF-1 and/or GH, initiated 24–72 h after LCAL had no effect on the extent of MI [23,27]. However, a beneficial effect on infarct size was observed after initiating treatment with rhGH (1 mg/kg twice daily) as early as 20 min post-surgery [28]. These investigators observed that a 2-week treatment with GH reduced infarct size by 18% and increased survival by 36% up to 52 weeks post-MI. However, others failed to observe beneficial effects of early recombinant rat GH (rGH) administration in rats with large MI [29] or in CHF in volume-overloaded rats (rhGH, 2 mg/kg per day for 4 weeks), although renal function was improved, possibly as a consequence of the enhanced renal nitric oxide (NO) system activity [30]. Others reported that rGH administration (0.8 mg/kg daily for 4 weeks) did not further stimulate the renin system or sodium retention post-MI in rats [31].

The effect of late treatment (initiated 4 to 6 weeks after LCAL) with GH and/or IGF-1 on heart function and survival, has also been studied as shown in Table 1. A 2-week treatment with rhGH (2 mg/kg daily), starting 4 weeks after LCAL, was able to prevent the reduction in cardiac index observed in untreated rats, despite similar extent of MI between groups [32]. GH-treated rats had reduced systemic vascular resistance (SVR) and increased $dP/dt$, which might have contributed to the benefits of treatment. Reduced SVR, possibly as a consequence of an increased...
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<td>SD rats</td>
<td>LCAL*</td>
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<td>0.5 U (0.17 mg)**/kg/day × 3 days, day of LCAL</td>
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<td>LCAL</td>
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<td>Grimm, 1998 [24]</td>
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<td>Duerr, R.L., 1995 [27]</td>
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<td>rhIGF-1</td>
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<td>LCAL</td>
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<td>Improved systolic function</td>
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<td>Duerr, R.L., 1996 [35]</td>
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<td>Shen, Y.T., 1998 [37]</td>
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<td>Rapid pacing</td>
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*Abbreviations: SD—Sprague Dawley; rbGH—recombinant bovine GH; rhGH—recombinant human GH; rrGH—recombinant rat GH; rhIGF-1—recombinant human IGF-1; rpGH—recombinant porcine GH; CO—cardiac output, **1 mg rhGH IRP 88/624 = 3 U (Growth Hormone Research Society recommendation, 1997).
production of NO, contributed to the overall beneficial cardiovascular effect of rhGH (1.1 mg/kg) or rhIGF-1 (3 mg/kg) treatment, initiated 4 weeks after LCAL in rats for a period of 2 weeks [33]. Additional studies have confirmed that late treatment with rhGH improved systolic function, despite the absence of cardiac hypertrophy [34].

Combined administration of 3 mg/kg rhIGF-1 daily and 0.1 mg rhGH twice a day for four weeks, starting 4 weeks after LCAL, increased cardiac output in treated rats, probably due to the massive reduction in SVR [35]. However, no significant increase in cardiac index was found with combined GH/IGF-1 treatment, except in rats with larger infarct size. The beneficial effect of rhGH on ventricular contractile function post-MI has been confirmed in vitro, where cardiomyocytes isolated from rats treated with 3.5 mg/kg daily for 2 weeks, 4 weeks after LCAL, displayed improved contractile reserve and intracellular calcium transients [36].

Although contradictory observations of early or late GH treatment on cardiovascular performance in experimental studies might be related to the heterogeneous origin of HF [30], the different dosing regimens and duration of treatment may also have a significant impact on these divergent observations. A clear limitation of all these experimental studies with GH and/or IGF-1 is their short duration. One of the restrictions is due to the use of rhGH in rats and the production of anti-GH antibodies. Therefore, the long-term effects (either beneficial or deleterious) remain unknown in these models.

3.2. Effects of GHS in cardiac cachexia and heart failure

An alternative approach for increasing systemic levels GH, possibly in a more physiological manner, is the administration of GHS [38], of which ghrelin is the endogenous representative [39]. Ghrelin, a 28-amino acid peptide n-octanoylated at serine 3, exerts its neuroendocrine effects through stimulating 7 transmembrane G protein-coupled receptors (GHS-R1a) [39]. As shown in Table 2, ghrelin, in a chronic HF model in rats, improved LV function and attenuated the development of LV remodelling and cardiac cachexia at a dose of 100 μg/kg twice daily for 3 weeks [40]. These effects were attributed to both GH/IGF-1-dependent and GH-independent vasodilatory effects of ghrelin. Using a similar experimental model, Tivesten et al. showed that hexarelin, at a dose of a 100 μg/kg daily for 14 days, improved cardiac performance as shown by an increased stroke volume and reduced total peripheral resistance [41]. In additional studies, ghrelin or hexarelin, in contrast to the non-peptidic MK-0677 GHS analogue, decreased myocardial ischemic injury in isolated working rat heart models [42,43]. In dogs rendered cardiomyopathic following chronic pacing and subjected to acute ischemia by
transient coronary occlusion, growth hormone-releasing peptide (GHRP)-6, at a dose of 0.2 mg/kg for 3 weeks, increased survival rate without any hemodynamic changes in contrast to GH, suggesting that these effects are mediated by GHS receptors rather than through the GH axis. Overall, GHS exert beneficial effects on cardiovascular function in experimental models of ischemia-reperfusion injury and CHF which are, at least in part, mediated via GH-independent pathways.

3.3. Effect of GH and GHS in cardiomyopathic hamsters

Genetically inherited cardiomyopathies in Syrian hamsters (CMH) may be classified according to their prominent feature, either ventricular dilatation in TO-2 and MS200, both derived from BIO 53.58, or hypertrophy in BIO 14.6 and derived strains including CHF-146, UM-X7.1 and CHF-147, a UM-X7.1 CMH subline. Ryoke et al. have assessed the effect of a 4-week treatment with doses of rhGH (2 mg/kg twice a day for 21 days) in CMH of the CHF 147 line, starting at 4 or 10 months of age. An increase in LV dP/dt max and a decrease in SVR were observed in both groups. In addition, meridional stress of the LV wall at end systole was reduced in 4- but not 10-month old CMH. Meridional stress of the LV wall at end diastole and LVEDP were significantly increased in 10-month old CMH. These observations suggest that GH may exert a beneficial effect, however limited to conditions where diastolic function is not impaired. We have previously assessed the effect of life span therapy with rhGH at a dose of 1 mg/kg per day on the cardiovascular function of UM-X7.1 CMH. Long-term use of rhGH in CMH was not associated with appearance of anti-GH antibodies up to 210 days of treatment. Our results showed that a chronic treatment with rhGH is associated with a reduced cardiac performance and survival at the terminal stage of the disease. The effects of GHS were also investigated in TO-2 CMH, in which a 4-week treatment with GHRP-6 (100 µg/kg daily) improved LV systolic performance and attenuated LV dilation. This beneficial effect was found to be independent of GH/IGF-1 axis.

4. GH and GHS in patients with heart failure secondary to ischemic or nonischemic cardiomyopathy

Clinical studies in patients with GHD, suggested that patients with either ischemic or nonischemic CM may benefit from GH therapy, mainly from reduction of LV maladaptive remodelling and cardiomyocyte loss. However, clinical studies in patients with HF of different etiologies led to conflicting conclusions. As for experimental studies, factors that have possibly contributed to the divergent results include different dosing regimens, the stage of the disease at treatment initiation, the concomitant use of drugs, acquired GH resistance and disease origin.

In nonischemic HF such as IDCM, global, rather than localized ventricular dysfunction as seen in ischemic CM is observed. Studies conducted in patients with CM are summarized in Table 3. The first non-randomized study of rhGH administration (0.05 mg/kg per week for 3 months) in a few patients with IDCM, was reported by Fazio et al. in 1996. GH therapy was associated with an increase in LVM and cardiac output and with a reduced neurohormonal activation, which led to an increased tolerance and a reduced energetic cost at effort in patients. In contrast, Osterziel et al. (1998), in a larger randomized, placebo-controlled study, showed that GH, at a dose of 0.67 mg/day for 3 months, was not beneficial to the cardiac function of patients with IDCM, despite increased LVM and IGF-1 levels. Perrot et al. (2001) observed that elevated IGF-1 circulating levels above 80 ng/ml in response to GH administration led to an increase in LV ejection fraction (LVEF) in patients. Jose et al. (1999) observed an increase in LVM associated with functional improvement following a 6-month treatment with 0.67 mg of rhGH on alternate days. Similar observations were reported recently by Adamopolous et al. (2003), who showed that GH, at a dose of 1.33 mg on alternate days for 3 months, induced an increase in myocardial wall thickness and contractile reserve associated with a decrease in end systolic volume and wall stress in patients with IDCM. These investigators proposed that the potent anti-inflammatory and anti-apoptotic effects of GH may contribute to attenuate maladaptive remodelling in end-stage HF.

The potentially beneficial effect of GH therapy in patients with ischemic HF was initially reported in isolated case reports. Non-randomized studies in a low number of patients showed clinical improvement associated with reduced systolic wall stress and increased exercise performance at dosing regimens ranging from 0.002 to 0.67 mg/kg daily for periods of 3 to 6 months. In contrast, a randomized study in 22 patients with ischemic HF, treated with a maintenance dose of 0.77 mg rhGH per day for 6 months, did not show beneficial effects on either systolic or diastolic function.

Studies conducted in patients with HF of mixed etiologies, showed that GH treatment at a dose of 0.03 mg/kg per week for 1 week, followed by 0.08 mg/kg per week during 3 months, increased IGF-1 levels but did not improve cardiac function. In agreement, Acevedo et al. (2003) did not observe benefits in their patients after 8 weeks of treatment with rhGH at a dose of 0.012 mg/kg/day for 8 weeks. However, Napoli et al. (2002) observed improvement of the endothelial function in 16 patients treated with 1.33 mg GH every second day after a period of 3 months.

In healthy volunteers and in patients with GHD, an acute administration of hexarelin (2 µg/kg) elicited a short-term increase in contractility and LVEF in a GH-independent
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<td>Fazio, 1996 [58]</td>
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<td>Non randomized or controlled, 7 patients</td>
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<td>0.15 (0.05 mg)** to 0.2 U (0.07 mg/kg/week × 3 months)</td>
<td>Reduced LV chamber size; improved hemodynamics and clinical status</td>
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<td>Osterziel, 1998 [60]</td>
<td>DCM</td>
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<td>rhGH</td>
<td>0.5 U (0.17 mg/day up to 2 U (0.67 mg/day × 12 weeks)</td>
<td>Increased LVM but no clinical benefit</td>
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<td>Perrot, 2001 [8]</td>
<td>DCM</td>
<td>Randomized, placebo-controlled, 50 patients</td>
<td>rhGH</td>
<td>0.5 U (0.17 mg/day up to 2 U (0.67 mg/day × 12 weeks)</td>
<td>Increased LVEF (if IGF-1 elevation &gt; 80 pg/ml)</td>
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<td>Jose, 1999 [61]</td>
<td>DCM</td>
<td>Non randomized or placebo-controlled, 6 patients</td>
<td>rhGH</td>
<td>2 U (0.67 mg) on alternate days × 6 months</td>
<td>Increased wall thickness and improved clinical status</td>
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<td>Adamopoulos, 2003 [52]</td>
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<td>Randomized cross-over study 12 patients</td>
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<td>O’Driscoll, 1997 [62]</td>
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</tr>
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<td>Van Thiel, 2004 [53]</td>
<td>Ischemic, LVEF &lt;40%</td>
<td>Randomized, placebo-controlled study 11 patients per group</td>
<td>rhGH</td>
<td>0.5 U (0.17 mg) up to 2 U (0.67 mg)/day × 26 weeks</td>
<td>No beneficial effect</td>
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<tr>
<td>Smit, 2001 [66]</td>
<td>Ischemic, LVEF &lt;40%</td>
<td>Randomized, placebo-controlled study 11 patients per group</td>
<td>rhGH</td>
<td>0.5 U (0.17 mg) up to 2 U (0.67 mg)/day × 26 weeks</td>
<td>No beneficial effect</td>
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<tr>
<td>Isgaard, 1998 [67]</td>
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<td>Randomized, placebo-controlled study 11 patients per group</td>
<td>rhGH</td>
<td>0.1 U (0.033 mg) up to 0.25 U (0.83 mg)/kg (4 U (1.33 mg)/day maximum) × 3 months</td>
<td>No beneficial effect</td>
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<td>Acevedo, 2003 [68]</td>
<td>Mixed, NYHA class III HF</td>
<td>Randomized, placebo-controlled study 10 (GH) patients per group</td>
<td>rhGH</td>
<td>0.035 U (0.012 mg/kg/day × 8 weeks</td>
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<td>Napoli, 2002 [69]</td>
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<td>rhGH</td>
<td>4 U (1.33 mg) every other day × 3 months</td>
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<td><strong>Treatment with GHS</strong></td>
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<td>Bisi, 1999 [71]</td>
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<td>Non randomized or placebo-controlled study 13 patients</td>
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<td>Increased LVEF in ischemic DCM not in DCM</td>
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<td>Enomoto, 2003 [73]</td>
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<td>Randomized order of administration 6 control subjects</td>
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<td>Nagaya, 2001 [74]</td>
<td>Mixed, NYHA class II or III HF</td>
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<td>Ghrelin</td>
<td>0.1 μg/kg/min × 60 min</td>
<td>Decreased mean arterial blood pressure and increased cardiac and stroke volume index</td>
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*Abbreviations: NYHA—New York Heart Association; rhGH—recombinant human GH; **1 mg rhGH IRP 88/624 = 3 U.
manner [70,71]. Similar results were observed in patients with ischemic CM, not with IDCM [72]. Studies with ghrelin showed an improved cardiac performance following acute administration, although this effect was associated with a dose-dependent increase in GH [73]. When administered in healthy volunteers and in patients with HF of different origins, a short-term infusion of ghrelin (0.1 μg/kg/min × 60 min) decreased mean arterial pressure and increased cardiac and stroke volume index, which may be related to a reduced SVR through GHSR-1a in the vasculature [73,74].

5. Effect of GH/IGF-1 and GHS in regulating cardiomyocyte apoptosis

Cardiomyocyte loss through apoptosis has been shown to occur during the progression of cardiomyopathy and HF in animal models and humans, and has recently been recognized to contribute to cardiovascular dysfunction and remodelling [75,76]. Apoptosis may contribute to the loss of cardiomyocytes and the subsequent myocyte slippage underlying heart dilation [77], and may play a role in the transition to HF [78]. Cardiomyocyte loss through apoptosis can be induced through two independent pathways. The first pathway is mediated by external elements that bind to members of a receptor family known as death receptors, to which Fas and TNFR1 belong. Specific binding to these receptors lead to the activation of caspase 8, which in turn activates caspase 3. Fas ligand as well as anti-Fas antibodies elicit cardiomyocyte apoptosis in culture [79], and an increase in soluble Fas and apoptotic cardiomyocyte cell death have been reported, both in patients with IDCM [80] and experimental models of CM [81]. The second pathway is induced by the release of cytochrome c into the cytosol from the mitochondria by members of the apoptosis-regulating protein family. Studies have shown that the accumulation of cytosolic cytochrome c occurs in ischemic and IDCM hearts, leading to the activation of caspase 3 [82].

IGF-1 and GH have been shown to inhibit apoptosis in rat cardiomyocytes [81]. At the cell membrane, activated IGF-1 receptors stimulate downstream effectors such as PI3-kinase (PI3K) leading to the activation of Akt by phosphorylation [83] and to the accumulation of nuclear phospho-Akt [84,85]. PI3K/Akt phosphorylation of eNOS, a source of cardioprotective and anti-apoptotic NO [86], may provide an additional mechanism through which GH exert anti-apoptotic effect. Interestingly, GH has been shown to induce eNOS expression in endothelial cells [87]. If these observations extend to cardiomyocytes, it may provide an additional mechanism through which GH exert anti-apoptotic effect.

In vivo, IGF-1 attenuated myocardial apoptosis in dogs with CHF, which may have contributed to restore ventricular wall thickness [88]. In transgenic mice overexpressing muscle-specific IGF-1, angiotensin II-induced reduction in phospho-Akt and caspase 3 activation is prevented [89]. Supporting a role for GH in regulating apoptosis in patients with IDCM and HF, addition of GH to the pharmacotherapy was associated with a reduction in apoptotic factors including Fas and Fas ligand [52].

Both ghrelin [90] and hexarelin [91] inhibited apoptosis induced by the cytotoxic agents TNFα and doxorubicin in cardiomyocytes and H9c2 cells. Anti-apoptotic effects may be mediated through the activation of the ERK-1/2 and PI3K/Akt survival signaling pathways, or alternatively by stimulating the biosynthesis of antioxidant proteins, suggesting that the cardioprotective effect of GHS could be explained, at least in part, by their anti-apoptotic properties.

6. Concluding remarks

Although promising effects of GH/IGF-1 were observed in experimental HF models, the only significantly positive clinical outcome was the improvement of cardiovascular function in patients with GHD. The lack of significant benefits of GH/IGF-1 therapy in human patients with HF secondary to CM of different origins might be related to the clinical stage at the onset of therapy, the dosing regimen and duration of treatment. Further studies are required for the optimization of GH/IGF-1 therapy in patients with CM. The GH-independent effect of GHS for the treatment of CM might be related to their role in the prevention of apoptosis associated with the development of HF.

References

References


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