Pharmacology & Therapeutics 135 (2012) 337–354

Contents lists available at SciVerse ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: L.H. Lash

Regression of pathological cardiac hypertrophy: Signaling pathways and therapeutic targets

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ARTICLE INFO

Keywords:
Angiogenesis
HIF-1
LVADs
PKG-1
VEGF
VEGF receptors

ABSTRACT

Pathological cardiac hypertrophy is a key risk factor for heart failure. It is associated with increased interstitial fibrosis, cell death and cardiac dysfunction. The progression of pathological cardiac hypertrophy has long been considered as irreversible. However, recent clinical observations and experimental studies have produced evidence showing the reversal of pathological cardiac hypertrophy. Left ventricle assist devices used in heart failure patients for bridging to transplantation not only improve peripheral circulation but also often cause reverse remodeling of the geometry and recovery of the function of the heart. Dietary supplementation with physiologically relevant levels of copper can reverse pathological cardiac hypertrophy in mice. Angiogenesis is essential and vascular endothelial growth factor (VEGF) is a constitutive factor for the regression. The action of VEGF is mediated by VEGF receptor-1, whose activation is linked to cyclic GMP-dependent protein kinase-1 (PKG-1) signaling pathways, and inhibition of cyclic GMP degradation leads to regression of pathological cardiac hypertrophy. Most of these pathways are regulated by hypoxia-inducible factor. Potential therapeutic targets for promoting the regression include: promotion of angiogenesis, selective enhancement of VEGF receptor-1 signaling pathways, stimulation of PKG-1 pathways, and sustention of hypoxia-inducible factor transcriptional activity. More exciting insights into the regression of pathological cardiac hypertrophy are emerging. The time of translating the concept of regression of pathological cardiac hypertrophy to clinical practice is coming.

Contents

Abbreviations: ACE, angiotensin converting enzyme; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CCS, copper chaperone for superoxide dismutase; CK, creatine kinase; Cu,Zn-SOD, Cu,Zn-superoxide dismutase; ECM, extracellular matrix; ERK, extracellular regulated protein kinases; FA, fatty acid; GC, guanylyl cyclase; GC-A, guanylyl cyclase-A; GMP, guanosine monophosphate; GSK-3, Glycogen synthase kinase 3; HIF-1, hypoxia inducible factor-1; HRE, hypoxia-responsive element; LVADs, left ventricular assist devices; MAPK, mitogen-activated protein kinase; MMPs, matrix metalloproteinases; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T cells; PCP, pro-collagen N- and C-proteinases; PCr, phosphocreatine; PDE5A, phosphodiesterase 5A; PE, phenylephrine; PKG-1, cyclic GMP-dependent protein kinase-1; MRA, magnetic resonance angiography; pVHL, von Hippel–Lindau protein; RGS2, regulator of G protein signaling 2; SERCA2a, sarco(endo)plasmic reticulum Ca^{2+}-ATPase 2A; TAC, transverse aorta constriction; TGF-β, transforming growth factor-β; TIMP, tissue inhibitors of metalloproteinase; TNF-α, tumor necrosis factor-α; TRPC, transient receptor potential canonical; VASP, Vasodilator-stimulated phosphoprotein; VEGF, Vascular endothelial growth factor; VEGFR-1, VEGF receptor-1; VEGFR-2, VEGF receptor-2.

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doi:10.1016/j.pharmthera.2012.06.006

1. Introduction

The simple definition of cardiac hypertrophy is the enlargement of the heart. This enlargement results from the growth of the adult heart in response to an increase in load. Physical exercise and pregnancy can lead to cardiac hypertrophy along with normal or enhanced contractile function (Weeks & McMullen, 2011), which is defined as physiological cardiac hypertrophy and is reversible. In response to chronic pressure or volume overload under certain disease conditions such as hypertension, valvular heart disease, and coronary artery disease, the heart becomes hypertrophic (Opie et al., 2006; Weeks & McMullen, 2011). But this hypertrophy is associated with further development to cardiac dysfunction or heart failure, so that it is defined as pathological cardiac hypertrophy, which has been considered to be irreversible.

The traditional view of the irreversibility of pathological cardiac hypertrophy has recently been challenged. Clinical observation of left ventricular assist devices (LVADs) for bridging to transplantation has shown that some pathological changes in the heart can be reversed after a certain period of LVAD support. In some cases, the pathological cardiac hypertrophy can be reversed and the contractility of the heart can be recovered (Li et al., 2008; Moens et al., 2008; Cai et al., 2009). These observations provide a novel therapeutic option for heart failure patients, namely LVAD therapy for heart failure (Baughman & Jarcho, 2007; Maybaum et al., 2007; Birks et al., 2011; Strueber et al., 2011). Experimental studies have produced strong evidence that shows improvement of angiogenesis in hypertrophic heart can lead to regression of pathological cardiac hypertrophy and the prevention of heart failure (Jiang et al., 2007; Zhou et al., 2008, 2009a). With regard to this, the role of the trace element copper in the regulation of hypoxia-inducible factor-1 (HIF-1) transcriptional activity and the subsequent effects on the expression of genes involved in angiogenesis has become an interesting field of cardiac research (Feng et al., 2009; Xie & Kang, 2009; Borkow et al., 2010; Xie & Collins, 2011). Experimental studies have shown that supplementation with physiologically relevant levels of copper can reverse heart hypertrophy and improve cardiac function in a mouse model of pressure overload-induced pathological cardiac hypertrophy (Jiang et al., 2007).

How does the regression of pathological cardiac hypertrophy occur under the aforementioned clinical and experimental conditions? Comprehensive understanding of this novel aspect of cardiac research and medicine has not been available, but recent studies have produced some interesting insights. A critical pathway involving cyclic guanosine monophosphate (cGMP)-dependent protein kinase-1 (PKG-1) has been shown to be the major player in the regression of pathological cardiac hypertrophy (Takimoto et al., 2005). It has also been extensively demonstrated that vascular endothelial growth factor (VEGF) plays an essential role in triggering the regression pathway. This pathway is different from that of VEGF-stimulated cardiac hypertrophy in which VEGF is also essential. The regression pathway is mediated by VEGF receptor-1, but the hypertrophic pathway is mediated by VEGF receptor-2. Copper is a critical element in switching the VEGF pathways from VEGF receptor-2-dependent to receptor-1-dependent in the regression of pathological cardiac hypertrophy (Zhou et al., 2009a).

Regression of pathological cardiac hypertrophy opens a new avenue of cardiac medicine. Currently clinical approaches basically focus on prevention of cardiac hypertrophy by blocking the hypertrophic signaling pathways. However, in most cases, pathological cardiac hypertrophy is a secondary development derived from primary cardiac diseases such as hypertension, valvular heart disease, and coronary artery disease. Exploring molecular targets that are involved in the regression of pathological cardiac hypertrophy would generate alternative and probably more effective remedies for heart failure patients.

In this review, a brief summary of biochemical and functional changes in pathological cardiac hypertrophy will be presented to outline the distinct features of this pathological process. This will be followed by discussion of clinical observations and experimental studies demonstrating the use of LVADs in the regression of pathological cardiac hypertrophy. Then, the discussion will be focused on the role of modulation of angiogenesis in the process of the regression, signaling pathways associated with the promotion of the regression, and identification of potential therapeutic targets to promote the regression. Hopefully, this review will provide a timely understanding of the new direction of cardiac research and medicine.

2. Distinct features of pathological cardiac hypertrophy

The distinction between physiological and pathological cardiac hypertrophy is difficult to define from anatomic features; both types of cardiac hypertrophy can be observed in the form of either concentric or eccentric; the former is characterized by an increase in wall thickness with no change or slight reduction in chamber volume and the latter is an increase in chamber volume with no or small change in wall thickness (Mihl et al., 2008). At the cellular level, concentric hypertrophy results from an increase in myocardial cell width due to a parallel addition of sarcomeres in the cell (Libonati, 2011). Eccentric hypertrophy results from an increase in myocardial cell length due to a series of addition of sarcomeres in the cell (Libonati, 2011). Furthermore, increased mitochondrial dynamics in hypertrophic cardiomyocytes is described as an important feature for both types of cardiac hypertrophy. However, there are distinguishable changes between the two types of cardiac hypertrophy. The foremost difference is defined by the functional alteration; physiological hypertrophy is characterized by normal or enhanced cardiac contractile function whereas pathological hypertrophy shows decreased contractility often associated with arrhythmia. The cardiac dysfunction reflects the distinct pathogenesis of pathological cardiac hypertrophy. Experimental approaches have focused on the signaling pathways by which various stimuli can trigger physiological and pathological cardiac hypertrophy. There are many interesting studies and review articles on this topic (Backs et al., 2009; Suckau et al., 2009; Heineke et al., 2010; van Berlo et al., 2010; Zhong et al., 2010; Abel & Doenst, 2011; Luo et al., 2012; Yang et al., 2012), which will not be covered in this review. Some of the key features of physiological versus pathological cardiac hypertrophy are summarized in Table 1.

2.1. Interstitial fibrosis in pathological cardiac hypertrophy

The extracellular matrix (ECM), mainly fibrillar collagen, provides structural integrity to adjoining cardiomyocytes. This not only functions as a structural support for the myocardial tissue, but also facilitates myocyte shortening, which translates into efficient cardiac pump function (Pelouch et al., 1993; Cleutjens & Creemers, 2002; Baicu et al., 2003). The proportional distribution or deposition of fibrillar collagen in the heart is critical for cardiac contractile function. One of the unique features of pathological cardiac hypertrophy is increased interstitial fibrosis, or excessive deposition of fibrillar collagen. This excessive collagen deposition is not found in physiological cardiac hypertrophy. Most studies have demonstrated that in the hypertrophic heart of hypertension patients, there is increased diffuse fibrosis in which types I and III collagens are predominant (Brilla & Maisch, 1994; Diez et al., 2001; Gonzalez et al., 2002; Harada et al., 2007). The excessive collagen deposition is related to changes in the activity of fibroblasts under the condition of pathological stimulations.

Fibroblasts synthesize pro-collagen that is secreted into the interstitial space where it is split by pro-collagen N- and C-proteinases (PCP) in the end-terminal pro-peptide sequences to enable collagen fiber formation (Weber, 1997). Myocardial inflammation is an early