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PATHOPHYSIOLOGY AND PHARMACOLOGICAL INTERVENTION IN THE TREATMENT OF CARDIAC HYPERTROPHY

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ABSTRACT

Cardiovascular disorders are the major cause of mortality and morbidity. One of the major disorders that are associated with mortality is cardiac hypertrophy. Cardiac hypertrophy is basically the enlargement of the heart muscles characterized by increased thickness of the heart muscle. Depending upon the various factors it may pathological and physiological. Cardiac hypertrophy develops in response to hemodynamic overload that is a major predictor for the development of coronary heart disease and heart failure. Pressure overload induces concentric hypertrophy characterized by wall thickening without significant chamber enlargement. During embryogenesis heart growth occurs primarily via proliferation of cardiac myocytes. However, soon after birth, cardiac myocytes withdraw irreversibly from the cell cycle and subsequently growth of the heart occurs mostly through hypertrophy. However, the factors that are responsible in the progression of cardiac hypertrophy are still not clear. Hence, the present review has been designed to study the various pathophysiological mechanisms and the pharmacological interventions in the management of cardiac hypertrophy.

Introduction

Cardiovascular disease is the main cause of mortality [1] and the term cardiovascular disease comprises of broad spectrum of cardiac and circulatory pathologies [2]. Cardiac hypertrophy has been defined as an increase in cardiomyocytes size that may be beneficial, adaptive (physiological) or maladaptive (pathophysiological) phenomenon to compensate the hemodynamic stress that arises due to pressure or volume overloads [3-4]. Pressure overload results in concentric hypertrophy characterized by wall thickening without significant chamber enlargement [4].

Further, soon after birth, cardiac myocytes withdraw irreversibly from the cell cycle and subsequently growth of the heart occurs mostly through hypertrophy [5]. Compensatory hypertrophy occurs in response to exercise and pregnancy [6]. During pregnancy and exercise, the heart undergoes hypertrophic growth and eccentric hypertrophy to compensate the increase in cardiac output [3]. Eccentric hypertrophy characterized by enlargement in the heart chamber with a proportional change in wall thickness [4]. In high dynamic exercise, like running, eccentric hypertrophy is developed in response to high cardiac output due to volume overload whereas in static exercise, like weightlifting [7-8], chemical changes are developed that mark the initiation of hypertrophy [3]. Pathological hypertrophy occurs in response to abnormal stress. When maladaptive remodelling of reactive hypertrophy, persists for a long time along with ventricular dilation, it results in cardiac enlargement, wall thinning and wall stress [6]. Moreover, it is followed by the loss of cardiac myocytes function ultimately leading to irreversible functional cardiac deterioration, heart failure and death. Furthermore, cardiac hypertrophy includes alterations in intercellular matrix leading to interstitial fibrosis and loss of β-adrenergic receptor responsiveness [6]. Further, Phosphofructokinase and lactate dehydrogenase, key regulators of glycolytic metabolism, were also found to be upregulated in pathological hypertrophy induced by hypertension [9-10]. It has been well reported that physiological hypertrophy is reversible and commonly occurs during maturation, pregnancy and exercise without any morbid effects on cardiac function [11-12]. Thus the present review has been designed to delineate pathophysiology and pharmacological intervention in the management of cardiac hypertrophy.

Pathophysiology and Signalling pathways

Cardiac hypertrophy is thickening of the myocardium which causes a marked reduction in size of the heart chamber, including the left and right ventricles and commonly occurs because of increased hemodynamic demand. Cardiac hypertrophy is generally aggregated by hypertension

[13], heart valve stenosis [14] and heart failure [13]. The renin angiotensin system (RAS) had been reported play a pivotal role in the pathogenesis of hypertension, a major inducer of hypertrophy shown in fig-1. [15]. It has been well reported that heart failure too plays an important role in pathogenesis of hypertrophy [16]. Both cyclooxygenase-2 (COX-2) and PI3K/Akt have also been associated in the progression of cardiac hypertrophy [17] and overexpression of COX-2 leads to cardiac deterioration [18-19-20]. Peroxisome proliferator-activated receptors (PPAR's) are also implicated in the pathogenesis of cardiac hypertrophy [10]. PPARα is a target of ERK1/2 which gets activated in settings of pathological cardiac hypertrophy [21]. However, the role of PPARγ in the pathogenesis of cardiac hypertrophy is not well understood [22]. Further, various studies indicate the pivotal role of calcineurin in the development of pressure overload-induced cardiac hypertrophy [23-24]. NGF1A-binding protein (Nab1) is a transcriptional repressor which appears to be a specific regulator of pathological cardiac hypertrophy [10-25].

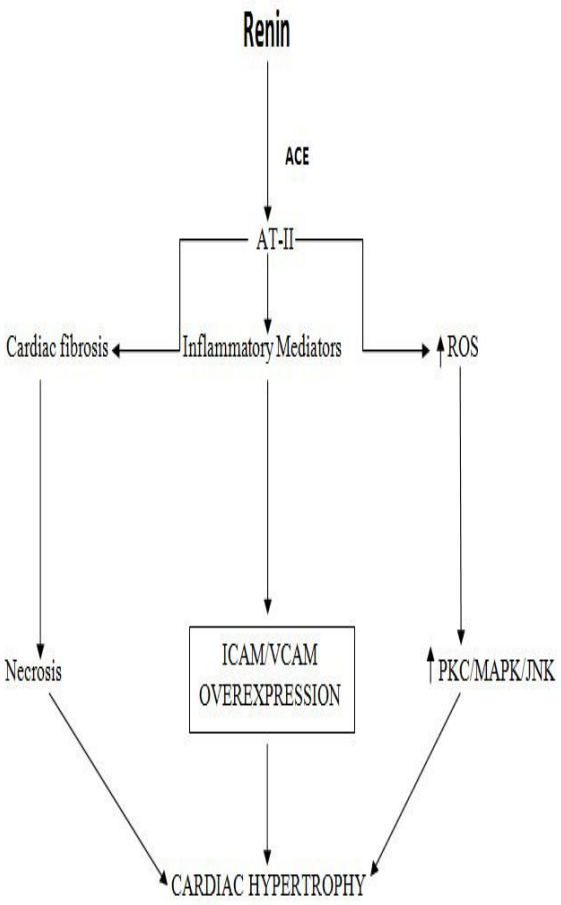

Figure 1. Role of various mediators in mediating cardiac hypertrophy where ACE = Angiotensinogen converting enzyme; ROS = Reactive oxygen species; PKC = Protein kinase C; MAPK = Mitogen activated protein kinase; JNK = Jan nuclear kinase, ICAM = Intracellular adhesion molecule, VCAM = Vascular adhesion molecule.

A recent study has indicated the role of estrogens in both physiological and pathological cardiac hypertrophy indicated in Fig-2 [26-27-28-29]. Cardiac hypertrophy was also observed in patient with hyperthyroidism that results due to increased activity of sympathetic nervous system and increase level of RAS. [10-15]. Increase activity of NADPH oxidase results in cardiac hypertrophy as it is a key source for the generation of reactive oxygen species (ROS) which have been shown to play a portal role in the development of pathological hypertrophy [30-31]. Further, in cardiac hypertrophy there is overexpression of C-reactive protein (C-RP) [32]. Moreover, oxidative and nitrosative stresses plays a vital role in inducing cardiac hypertrophy and result in the generation of reactive oxygen species (ROS). ROS stimulates various signalling pathways like tyrosine kinase Src, GTP-binding protein Ras, protein kinase C, mitogen-activated protein kinase (MAPK), and Jun-nuclear kinase (JNK) [33-34]. Further, Tumor necrosis factor-α (TNF-α), a proinflammatory cytokine has been implicated in the pathogenesis of cardiovascular disorders [35-36-37-38]. However, the prolonged exposure to high levels of TNF-α is associated with cardiac dysfunction and hypertrophy of the heart [39]. The TNF superfamily such as TNF-related apoptosis inducing ligand (TRAIL), osteoprotegrin (OPG), receptor activator of NFκB ligand (RANKL), CD40L and CD27L were upregulated in heart failure patients [40]. These mediators contributed to inflammation, cardiac remodeling and apoptotic cell death in the failing heart [40-41]. The RANKL increased the expression of matrix metalloproteinase (MMP) in cardiomyocytes and produced cardiac remodelling [42]. C-reactive protein (CRP), a cytokine and a member of the class of acute-phase reactants, was significantly elevated during the inflammatory process and was associated with cardiovascular risk and the development of heart failure [43-44].

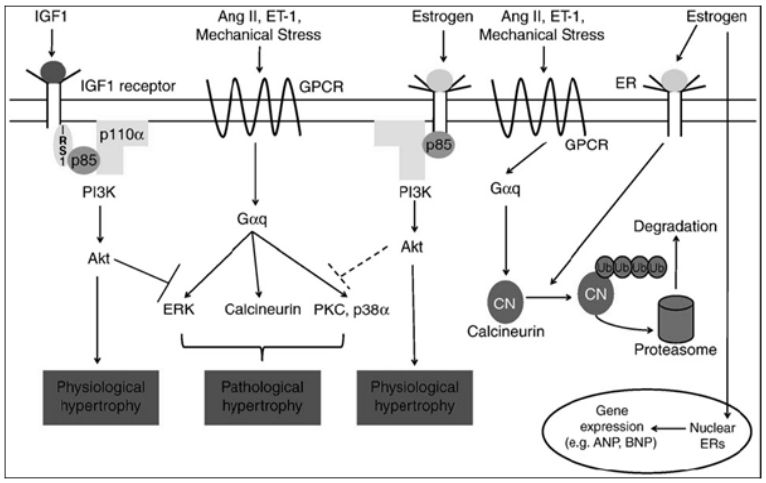

Figure 2. Signaling cascades involved in estrogen-mediated cardiac hypertrophic responses**.**

Ang II: angiotensin II, ANP: Atrial natriuretic peptide, BNP: B-type natriuretic peptide, CN: calcineurin, ER: estrogen receptor, ERK: extracellular regulated kinase, ET-1: endothelin-1, GPCR: G protein-coupled receptor, IGF1: insulin-like growth factor 1, IRS1: insulin receptor substrate 1, PI3K: phosphoinositide 3-kinase, PKC: protein kinase C, Ub: ubiquitin.

Pharmacological interventions (Table 1)

Anti-TNF-α therapy

Pro-inflammatory cytokines has been reported to play a vital role in the development of cardiac hypertrophy and remodelling. In patients with CHF, there is up regulation expression of pro-inflammatory cytokines, including tumour necrosis factor α (TNF-α), interleukins (IL) [45]. Various studies indicated the role of IL-6 in the progression of cardiovascular disease. So, treatment with anti TNF-α attenuates cardiac hypertrophy. Etanercept have been reported to inhibit the TNF-α [46]. Chronic treatments with a low dose of the cholinesterase inhibitor neostigmine or the muscarinic agonist pilocarpine attenuated cardiac hypertrophy and ventricular dysfunction induced by pressure overload. These treatments attenuated the increased TNF-α expression and simultaneously increased IL-10 expression in the hearts with cardiac pressure overload. Moreover, the cholinergic agonist pilocarpine elicits a direct inhibition on increased TNF-α production and hypertrophic responses in primary cultured cardiac cells. Pharmacologically, neostigmine inhibits acetylcholine inactivation and thus prolongs the excitation of cholinergic synapses. Pilocarpine stimulates postsynaptic muscarinic cholinergic receptors. Both agents have been reported to reduce the levels of the pro-inflammatory cytokine TNF-α, increased the levels of the anti-inflammatory cytokine IL-10 and attenuated cardiac hypertrophy [47].

Poly (ADP-ribose) polymerase

Poly (ADP-ribose) polymerase (PARP) is a DNA repairing enzyme present in nuclei and mitochondria of various cells including cardiac myocytes. PARP activation upregulated various transcription factors and hypertrophic genes [48-49], which has been reported to produce pathological cardiac hypertrophy [50]. The PARP-mediated induction of inflammatory cytokines and apoptotic cell death play a major role in the progression of cardiac hypertrophy and decompensated heart failure [50-51]. Inhibition of PARP by 3-aminobenzamide and 5-aminoisoquinolinone markedly prevented pressure over load-induced cardiac dysfunction and pathological cardiac hypertrophy [52-53]. Thus PARP over-activation plays a pivotal role in the transformation of pathological cardiac hypertrophy into heart failure [54].

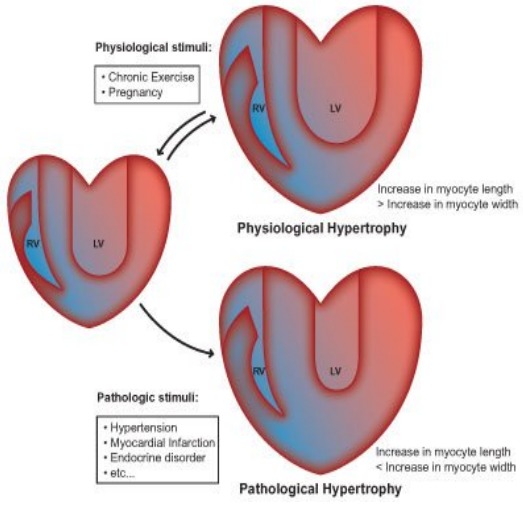

Figure 3. Pathological and physiological hypertrophic responses to stimuli.

Glucagon-like peptide-1

Both pre-clinical and clinical studies indicate that proglucagon-derived peptide, Glucagon-like peptide-1 (GLP-1), exerts favourable actions on cardiovascular function [55]. GLP-1 receptor (GLP-1R) is expressed in the heart [56] and GLP-1R agonists directly activate cardiomyocyte signaling pathways [57]. Moreover, it has been well documented that Glucagon-like peptide-1 receptor (GLP-1R) agonists are used to treat type-2 diabetes and transient GLP-1 administration improved cardiac function in humans following acute myocardial infarction (MI) and percutaneous revascularization [58]. Liraglutide increased cyclic AMP formation and reduced the extent of caspase-3 activation in cardiomyocytes in a GLP-1R-dependent. Various studies indicated the Liraglutide drug administration induced changes in the expression of cardioprotective proteins in the normal non-atherosclerotic murine heart characterized by phosphorylation of Akt and GSK3β and increased expression of Nrf2, PPAR-β/δ and HO-1 [58].

Antioxidant

EPIGALLOCATECHIN-3-GALLATE

Epigallocatechin-3 gallate (EGCG) is the major catechin derived from green tea, has been found to have protective effects on the cardiovascular system [59]. It has been reported to have anti-inflammatory effects [60], lower serum cholesterol levels and thus implicated in the management of reducing atherosclerosis [61]. EGCG was found to have antioxidant properties [62] and is thus implicated in the management of oxidative stress-related diseases such as ischemic heart diseases (IHD). Further, cardiac hypertrophy results in the increase in blood pressure and wall stress which is regulated by a number of intracellular signal transduction pathways including mitogen-activated protein kinase (MAPK), Janus kinase/signal transducers, activators of transcription (JAK/ STAT), calcineurin, serine/threonine kinase, Akt and its downstream target, glycogen synthase kinase-3β [63]. The platelet derived growth factor (PDGF)-BB which is inhibited by EGCG induce intracellular Ca^{2+} increase and extracellular signal regulated kinase (ERK) activation in vascular smooth muscle cells (VSMCs) [64] and that EGCG could prevent Ang II-induced VSMCs hypertrophy through blocking c-Jun N-terminal kinases (JNKs) [65]. Moreover, EGCG inhibit the PI3K/Akt and Erk1/2 pathways. Therefore it seems that EGCG can inhibit the signal pathways that regulate cardiac hypertrophy.

Tetrandrine

Tetrandrine is a bisbenzylisoquinoline alkaloid isolated from the Chinese medicinal herb-root of *Stephania tetrandra S Moore*, which was traditionally used as an anti-inflammatory, antipyretic and analgesic herb ([66-67]. Tetrandrine, a naturally occurring calcium antagonist having properties like anti-inflammatory, antioxidant and anti-fibrogenetic, has

been used clinically in the management of cardiovascular diseases such as hypertension and arrhythmia and cardiac hypertrophy [68].

Table 1. Novel pharmacological interventions that prevent the progression of pathological cardiac hypertrophy and heart failure.

Sr.no	Drug	Pharmacological class	Mechanism of drug in pathological cardiac hypertrophy
1	Etanercept	TNF-α-inhibitor	TNF-α-inhibition
2	Neostigmine, Pilocarpine	Cholinomimetic	Downregulation of TNF-α expression
3	3-aminobenzamide	PARP inhibitor	PARP-inhibition
4	Liraglutide	Glucagon-like peptide	Reduction in caspase-3 activation
5	Epigallocatechin-3-gallate	Antioxidant	Inhibition of MAPK
6	Tetrandrine	Antioxidant	Inhibition of cardiac fibrosis and ERK ½ signaling pathway

Conclusion

Cardiac hypertrophy has been regarded as a major risk factor. But no reasonable pharmacological interventions have been developed for the treatment of cardiac hypertrophy. Hence, better understanding of the signalling pathways can open the new vista for the development of new drugs.

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