Factors and Mechanisms Involved in Left Ventricular Hypertrophy and the Anti-Hypertrophic Role of Nitric Oxide

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Summary

The left ventricular hypertrophy (LVH) occurs in response to the hemodynamic overload in some physiological and pathological conditions. However, it has not been completely elucidated whether the primary stimulation for the hypertrophy is the mechanical stretching of the heart, neurohumoral factors, or even the interaction of both. These factors are translated inside the cell as biochemical alterations that lead to the activation of second (cytosolic) and third (nuclear) messengers that will act in the cell nucleus, regulating transcription, and will finally determine the genic expression that induces LVH. The LVH is characterized by structural alterations due to the increase in the cardiomyocyte dimensions, the proliferation of the interstitial connective tissue and the rarefaction of the coronary microcirculation. Recently, nitric oxide (•NO) has appeared as an important regulator of cardiac remodeling, specifically recognized as an anti-hypertrophic mediator. Some studies have demonstrated the cellular targets, the anti-hypertrophic signaling pathways and the functional role of •NO. Thus, the LVH seems to develop as a result of the loss of the balance between the pro and the anti-hypertrophic signaling pathways. This new knowledge about the pro and anti-hypertrophic signaling pathways will allow the development of new strategies in the treatment of pathological LVH.

Introduction

According to the World Health Organization (2005) cardiovascular diseases are the leading cause of death in the world. Among these diseases, the left ventricular hypertrophy (LVH) constitutes a very important indicator of cardiovascular morbimortality risk. According to the *"Framingham Heart Study"* [1], the individuals who present LVH, diagnosed through electrocardiographic alterations, presented a six-fold higher risk of death when compared to the general population.

The myocardium of the mammals goes through a hypertrophic growth phase during the post-birth maturation period, which is characterized by an increase in the individual size of the cardiomyocytes without cell division[2]. This pattern of hypertrophic development can be re-initiated in the adult heart in response to hemodynamic and/or neurohormonal alterations[3].

The nitric oxide (•NO) produced in the heart is deemed an endogenous inhibitor of the signaling cascade that induces the heart hypertrophy maladaptation. The first evidence that the •NO can present anti-hypertrophic effects in the heart were obtained in spontaneously hypertensive rats (SHR) under chronic treatment with L-arginine[4]. Subsequently, such role of the •NO was confirmed in mice that hyper-expressed endothelial nitric oxide synthase (eNOS), in which the •NO attenuated the heart hypertrophy induced by the chronic infusion of isoprenaline (ISO)[5], indicating that the endogenous •NO acts as a negative modulator for heart hypertrophy.

The objective of this review is to describe the LVH-inducing hypertrophic and/or proliferative factors, as well as the cell targets, the signaling pathways and the functional role of the •NO as an anti-hypertrophic molecule.

Concept and classification of the left ventricular hypertrophy

The LVH constitutes a set of structural alterations caused by the increased dimensions of the cardiomyocytes, the proliferation of the interstitial conjunctive tissue and the rarefaction of the coronary circulation[6].

When the cardiomyocyte receives a hypertrophic stimulus, this is translated within the cell as biochemical alterations that lead to the activation of second (cytosolic) and third (nuclear) messengers that will act inside the cell, regulating transcription and will finally determine the genic expression that induces LVH (Figure 1).

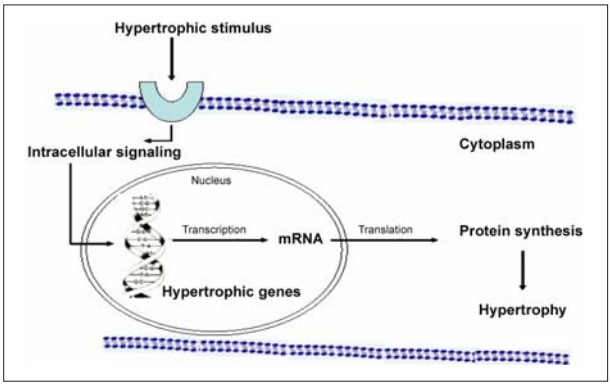

Figure 1 - Translation of the hypertrophic stimulus inside the cardiomyocyte.

Key words

Hypertrophy, left ventricular; nitric oxide; myocytes, cardiac.

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The growth of the cardiomyocytes in the left ventricular hypertrophy can occur by the addition of sarcomeres in series (volume overload) or in parallel (pressure overload) (Figure 2), allowing the cell to increase in length or in diameter, leading to eccentric or concentric hypertrophy, respectively[7] (Figure 2).

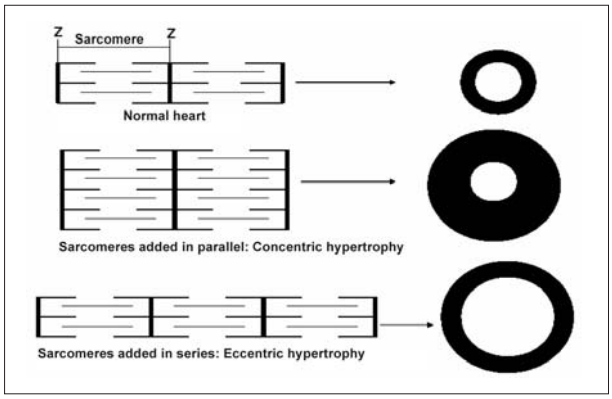

Figure 2 - Differentiation between the eccentric (volume overload) and the concentric (pressure overload) hypertrophy. Sarcomere: space between two Z discs.

According to Kempf and Wollert[7], the hypertrophy caused by hemodynamic overload can lead to adapted (physiological) or maladapted (pathological) hypertrophy. The physiological hypertrophy is the one developed due to a transient hemodynamic overload, such as those observed during cardiac growth at the adolescence, pregnancy and in response to regular exercises, whereas the pathological hypertrophy is the one caused by persistent hemodynamic overload.

Factors that induce left ventricular hipertrophy

Hemodynamic factors

Increase of the metabolic necessity

The work overload is considered the most frequently involved factor in LVH. The increase in the heart activity can be associated to a higher physiological demand, such as when performing physical exercises[8] and chronic anemia states[9]. Thus, as a consequence of the increased necessity to pump more blood to the peripheral sites, there is an adequate adaptation to the new demands.

Pressure and/or volume overload

Pathological conditions, such as arterial hypertension, aorta stenosis or coarctation, called pressure overload; or conditions such as aortic failure or interatrial communication, called volume overload, can promote hypertrophy due to the increased cardiomyocyte volume, together with an increase in size and alteration in the quality of the collagen matrix components[5,7].

The stretching is capable to activate L-type Ca^{+2} channels (LTCC) (Figure 3), Na^{+} channels and Na^{+}/H^{+} exchangers; to inactivate K^{+} channels; to activate adenylate-cyclase and phospholipase C[10] (Figure 3), as well as being associated to the accumulation of phosphate inositols, which act as second messengers[11]. The alterations in the functioning of the ionic channels of the sarcolemma lead to variations in the intracellular ionic concentration, which can represent an initial stimulation to activate the mitogen-activated protein kinase (MAPK). Among the MAPK superfamily, the extracellular-signal regulated kinase (ERK), the c-jun NH_2-kinase (JUNK) and the p38 kinase are mediators of the hypertrophic signaling of the myocardial cells, as they induce the gene transcription associated to hypertrophy[12] (Figure 3). The mechanical stimulation can also activate the integrin receptors, located in the cell membrane between the extracellular matrix (ECM) and the protein complex that form the sarcomere Z line[12]. Signaling proteins, such as the steroid receptor coactivator (Src) tyrosine-kinase and focal adhesion kinase (Fak) are located in this mesh, in addition to others responsible for the start of the integrin-activated signaling process[13] (Figure 3).

The mechanical stimulation also induces the local release of autocrine and paracrine factors through the myocardial cells, such as endothelin 1 (ET1), growth factors and cytokines [fibroblast growth factor (FGF), transforming growth factor β (TGFβ), insulin-like growth factor (IGF) and cardiotrophin-1][12]. These factors can bind to specific membrane receptors and activate calcineurin-, phosphokinase-C and MAPK pathway-coupled intracellular cascades and initiate the cascade of events responsible for the hypertrophic growth of the heart (Figures 3 and 4).

Neurohumoral factors

Catecholamines and sympathetic nervous system

The cardiomyocytes express β-adrenergic (β-AR) and α_1-adrenergic (α_1-AR) receptors. The stimulation of the β-adrenergic receptors (β-AR) activates the adenylate-cyclase through the interaction with the stimulatory G protein (Gs), which triggers intracellular cascades that activate protein kinase

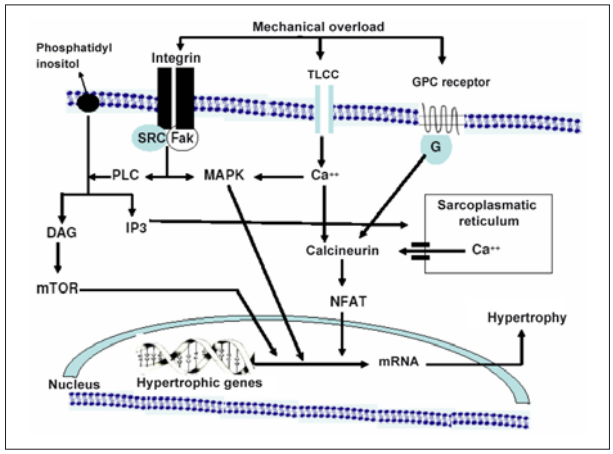

Figure 3 - Hypertrophic signaling pathways in response to mechanical overload. Type L Calcium channels (TLCC), Inositol triphosphate (IP3), Diacylglycerol (DAG), nuclear factor of activated T cells (NFAT), Phospholipase C (PLC), messenger RNA (mRNA), mitogenic-activating protein kinase (MAPK), steroid receptor coactivator (Src) tyrosine-kinase and focal adhesion kinase (Fak), G-protein coupled receptor (GPC receptor), mammalian target of rapamycin (mTOR).

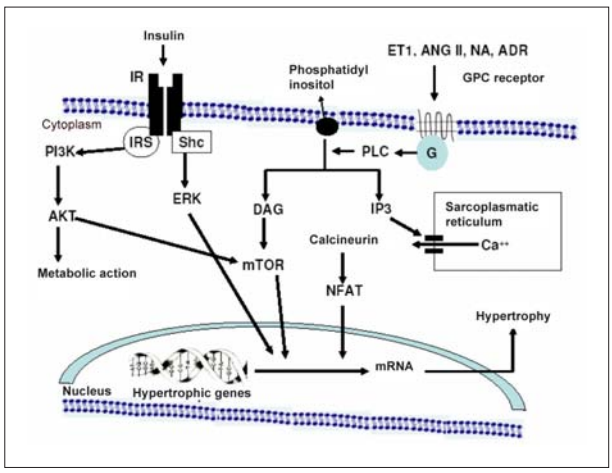

Figure 4 - Hypertrophic signaling pathways in the cardiomyocyte in response to neurohormonal stimulus. Inositol triphosphate (IP3), Diacylglycerol (DAG), nuclear factor of activated T cells (NFAT), Phospholipase C (PLC), messenger RNA (mRNA), extracellular-regulated kinase (ERK), G-protein coupled receptor (GPC receptor), mammalian target of rapamycin (mTOR), Phosphatidyl inositol 3-kinase (PI3K), serine/threonine (AKT) protein kinase, SRC Homology collagen (SHC), Insulin receptor (IR), Insulin receptor substrate (IRS).

A (PKA), also stimulating p38-MPAK[14]. The chronic stimulation of the β-AR by the administration of isoproterenol[15] induces the increase of cardiac mass, cardiomyocytes, myocardial fibrosis and progressive dysfunction, which culminates in heart failure. Acutely, the activation of α_1-AR increases the contractility mediated by the Gq protein activation. The latter induces the phospholipase C activation, which stimulates the hydrolysis of the Phosphatidyl inositol present in the membrane, generating two second messengers, the diacylglycerol (DAG) and the inositol triphosphate (IP3). The IP3 stimulates the release of Ca^{+2} from the sarcoplasmatic reticulum, whereas the DAG activates the protein kinase C (PKC), and the latter induces hypertrophy in culture of neonatal myocytes[16] (Figure 4).

Angiotensin II

Studies by Lindpaintner and Ganten[17] report the synthesis of angiotensin II (Ang II) in myocytes as well as in fibroblasts and myofibroblasts. Its biological effects are basically mediated by the membrane receptors AT1 and AT2.

The Ang II interacts with the AT1 receptor, associated to the G protein, which stimulates phospholipase C. The latter induces the formation of inositol triphosphate as well as of diaglycerol, which causes the increase in the cytoplasmic concentration of Ca^{++}, leading to the activation of protein kinase C (PKC) and of the adenylate-cyclase[18]. The Ang II, through the AT1receptor, is also capable to inducing an activation cascade through the tyrosine-kinases[19]. These tyrosine-kinases regulate intracellular effector pathways, including MAPK, which activate several protein transcription factors in the cardiomyocytes (Figure 4).

The AT2 receptors present a classical transmembrane structure of a G-protein associated receptor[20]. Studies by Senbonmatsu et al [21] have demonstrated that mice with AT2 receptor deletion presented hypertrophy attenuation induced by pressure overload. However, animals with AT1 receptor deletion did not present hypertrophy attenuation induced by pressure overload[22], suggesting that the deficiency of AT1 receptors might be compensated by the AT2 receptors, or that the AT2 subtype can have a predominant role on the trophic effects of Ang II on cardiomyocytes.

Insulin

The insulin binds to the subunit α of the receptor that belongs to the membrane receptor family that has tyrosine-kinase capacity[23], causes a conformational change in the β subunit, which leads to its autophosphorylation. in tyrosine and activates its tyrosine-kinase capacity. Once activated, the insulin receptor (IR) is capable of phosphorylating several intracellular substrates and among them, the insulin-receptor substrates (IRS-1-4), Shc (SRC Homology collagen) and Jak-2[24] (Figure 4). These phosphorylated proteins recruit and activate several intracellular effectors, with different cellular functions[23]. The ERK/MAPK pathway is involved in the control of growth (Figure 4) and of mitogenesis, whereas the activation of phosphatidyl inositol (PI) 3-kinase by the IRS-1 is preferably involved with the metabolic actions of insulin[23,25] (via IRS/PI3K/AKT/mTOR) (Figure 4). In normal situations, the insulin activates the production of •NO in endothelial cells through a phosphatidyl inositol (PI) 3-kinase-dependent mechanism, leading to the increase of the local production of •NO[26] with a consequent vasodilating and anti-apoptotic effect[27].

The insulin induces the phosphorylation in tyrosine of the IRS-1, whereas agents that lead to insulin resistance, such as TNFα, free fatty acids, cellular stress and hyperinsulinemia induce the activation of kinases of serine/threonine that phosphorylate IRS-1 in serine, inhibiting its function[28]. Thus, the reduction in the activation of the phosphatidyl inositol (PI) 3-kinase/Akt pathway in parallel to the preserved activation of the ERK/MAPK pathway in a situation of insulin resistance and hyperinsulinemia are being considered as vital events for the development of cardiac hypertrophy[29] (Figure 4).

Indirectly, insulin can also induce cardiac hypertrophy through the increase in the expression of the mRNA of the AT2 receptors[30] and in the activation of the sympathetic nervous system[3].

Oxidative stress

The imbalance between the production and removal of the reactive oxygen species (ROS) and reactive nitrogen species (RNS) is denominated oxidative/nitrosative stress, respectively. Several physiopathological and genetic situations can induce cardiac oxidative stress, such as the increase in the concentration of AngII[31], hypercholesteremia[32], mechanical stress in the myocardium[33] and inflammatory processes[34].

Hypertension and the mechanical stress in the myocardium induce the increase of ROS in the cardiomyocytes, activating the MAPK pathway[33], which has an important role in cardiac hypertrophy. Additionally, the redox imbalance reduces the bioavailability of •NO in the cardiovascular system[35], altering the balance between the hypertrophic factors (and/or proliferative) and the anti-hypertrophic factors (and/or anti-proliferative) (Figure 5), triggering a myocardial remodeling.

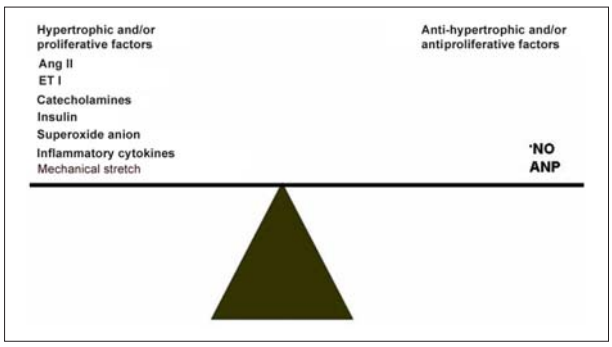

Figure 5 - Balance between the hypertrophic (and/or proliferative) factors and the anti-hypertrophic (and/or antiproliferative) ones. Nitric oxide (•NO); Atrial Natriuretic Peptide (ANP); Angiotensin II (Ang II); Endothelin 1 (ET1).

Hypercholesterolemia

The hypercholesterolemia, in addition to inducing the oxidative stress[32], can alter the function and expression of the K_{ATP} channels in the myocardium[36], inducing cardiac hypertrophy, simply due to the fact that the activation of these channels attenuates the cardiac hypertrophy through the inhibition of 70- KDa S6 Kinase[37], an enzyme that acts as a trigger for protein synthesis in the myocardium remodeling.

Moreover, the hyperlipidemia is associated with the increase in the plasma concentration of ET1, leading to vasomotor alterations[38]. In addition to the vasoconstrictor property, the endothelin activates the hypertrophic signaling pathways in the cardiomyocytes: PKC and MAPK[39].

Cytokines and growth factors induced by the inflammatory process

The trilogy consisting of the inflammatory process[40], endothelial dysfunction[41] and oxidative stress[31], in the cardiovascular environment, is considered the common denominator among the conditions that promote and support cardiac hypertrophy.

The CD40L (ligand) is a transmembrane protein expressed on the surface of lymphocytes, endothelial cells, vascular smooth musculature cells and macrophages. This protein has a pro-oxidative effect and its interaction with its receptor CD40 induces the inflammatory response, favoring the acute coronary syndrome[42]. The interaction between CD40 and CD40L activates the Nfkappaβ[43] pathway, promoting the phosphorylation of IKK (inhibitor of Kappa-β kinase), resulting in the translocation of the nuclear factor Kappa β (NFkappa β) to the nucleus, where it activates the genes involved in cell growth and inflammation[44]. The activation of the NFkappa β participates in the development of cardiac hypertrophy in mice, characterized by the increase in collagen deposit[44].

The activation of the T lymphocytes results in the production of interferon-γ which, in turn, increases the synthesis of inflammatory cytokines, such as TNF-α and IL-1. These cytokines induce the production of large amounts of IL-6, which stimulates the production of inflammatory proteins[45] and cardiac hypertrophy in mice, through its interaction with gp-130 membrane receptors[46]. TNFα induces cardiac hypertrophy *in vivo* by determining the increase in the synthesis of structural and contractile proteins of the cardiomyocytes, as well as by inducing an increase in the expression of AT1 receptors, increasing the effect mediated by angiotensin II in favor of cardiac fibrosis[47].

Nitric oxide/ nitric oxide synthase in the heart

Nitric oxide synthesis

The •NO is produced by enzymes called nitric oxide synthases (NOS). This is a family of complex enzymes that catalyze the oxidation of L-arginine to produce nitric oxide and L-citrulline. Three isoforms of NOS were initially characterized: the neuronal isoforms (nNOS = NOS1), identified in the brain; the induced isoform (iNOS=NOS2) in macrophages; and the endothelial isoform (eNOS=NOS3) in endothelial cells[48] and cardiomyocytes[49]. nNOS and eNOS present constitutive expression [constitutive nitric oxide synthases] and produce low amounts of •NO, when activated by calcium (Ca^{+2})[50]. The iNOS is expressed only in response to pro-inflammatory stimuli and cytokines and can produce large amounts of •NO[50].

In the healthy myocardium, the eNOS is mainly expressed in the coronary vascular endothelium and the cardiac endothelium[51], as well as in the cardiomyocytes[49]. In these cells, the eNOS is located in the caveoli, anchored by caveolin-3 in the plasmatic membrane, near the L-type Ca^{+2} channels[7]. The nNOS is present in the intracardiac nervous ganglia, in the atrial nervous fibers and in some perivascular nervous fibers of the ventricles[52]. Its expression has also been detected in cardiomyocytes and cells from the smooth musculature of small and large coronary arteries of rats[53]. The adult heart does not normally express iNOS. The latter is activated by inflammatory process mediators in many types of cells, including endothelial cells and cardiomyocytes[54]. It can be identified in the cytosol[7], but it has been found in the perinuclear space, Golgi apparatus, mitochondria and plasma membrane[55].

Nitric oxide: anti-hypertrophic molecule

The two main endogenous substances involved in the anti-hypertrophic role of the heart are the atrial natriuretic peptide (ANP) and •NO. The ANP secreted by atrial granules in response to acute or chronic atrial stretching, has an anti-hypertensive, anti-hypervolemic and anti-hypertrophic function through the activation of guanylate-cyclase and the consequent increase in the levels of cyclic guanosine monophosphate (cGMP)[56].

The production of •NO in the cardiomyocytes is highly compartmentalized[57], as the result of the location of NOS. Due to the high natural reactivity of •NO, its synthesis close to its target aids its accessibility to the intracellular processes for a coordinated signaling. Regardless of the functional specificity of the cNOS in the cardiomyocytes, the •NO has an anti-hypertrophic effect *in vivo*, considering that nNOS- or eNOS-deficient mice developed spontaneous cardiac hypertrophic and that those animals with both nNOS and eNOS deficiency developed a more severe hypertrophy[58].

The well-defined intracellular target of the •NO is the soluble guanylate-cyclase (sGC), which has a heme group that acts as

an acceptor of •NO and catalytically converts the guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP). Several studies have shown that the •NO promotes an anti-hypertrophic effect through the negative modulation of the pro-hypertrophic pathways[7], with the cGMP-dependent pathway having a central role in this effect.

The increase in the cGMP in the intracellular environment inhibits, through the protein-kinase G (PKG) enzyme, the signaling network of the different pro-hypertrophic pathways that involve MAPK[59]. This •NO/cGMP/PKG pathway develops an important role in the negative regulation on cardiomyocyte hypertrophy induced by AngII, ET1, insulin and growth factors, inhibiting the MAPK/ERK signaling, decreasing the transcription of genes associated to hypertrophy[60].

The •NO/cGMP/PKG pathway, in addition to inhibiting MAPK, also reduces the hypertrophic response induced by the mechanical overload and cytokines, inhibiting the following processes: 1) the calcineurin/nuclear factor of activated T cells (NFAT) pathway, through the decrease in the calcium inflow through the L-type calcium channels (LTCC)[59]; 2) the expression of the hypertrophic genes, such as cyclin D[61]; and 3) the activation of the NFkappa β transcription factor[44]. This pathway (•NO/cGMP/PKG) also interacts in an inhibitory way with the β-adrenergic stimulation pathways. The PKG induces a negative inotropic effect in the heart by: 1) phosphorylating troponin I, decreasing the sensitivity of the myofilaments to calcium; 2) inhibiting the calcium release from the sarcoplasmatic reticulum through the phosphorylation and inhibition of the IP3 receptors present in its membranes[62]. There is evidence that the •NO blocks the action of phospholipase C, inhibiting the release of calcium mediated by inositol triphosphate (IP3)[63]. All these effects can decrease the concentration of intracellular hypertrophic messengers activated by the adrenergic stimulation.

As for the K_{ATP} channels and ventricular hypertrophy, the •NO/cGMP pathway activates the K_{ATP} channels of the sarcolemma[64], with probable inhibition of the 70-KDa S6 Kinase, attenuating the hypertrophic response in hyperlipidemic models[37].

In addition to its anti-hypertrophic effects, the •NO has a dose-dependent pro-apoptotic effect on cardiomyocytes. Thus, low •NO concentrations inhibit the cardiomyocyte hypertrophy, whereas high •NO concentrations are required to induce the activation of caspases, DNA fragmentation and apoptosis[65]. The apoptosis stimulated by •NO in adult cardiomyocytes is associated to the alteration in the expression of pro-apoptotic genes of the Bcl-2 family, Bax and Bak, which have a crucial role in the determination of a cell's destiny, partly due to the alteration in the permeability of the mitochondrial membrane[66].

There is abundant evidence that •NO is the effector of cytokine-mediated apoptosis and the activation of pro-apoptotic genes, such as, for instance: 1) the capacity of the cytokines to induce the •NO production in cardiomyocytes is proportional to their capacity to activate programmed cell death (apoptosis); 2) iNOS antagonists prevent the production of •NO, of apoptosis and block the expression of Bcl-2 and Bak[67].

The •NO generated by iNOS has been responsible for the induction of apoptosis in different types of cells[67], including cardiomyocytes[68]. After the induction, the iNOS remains activated for 20 hours[69], during which it synthesizes •NO at concentrations that are 1,000 higher than the cNOS[70]and, under conditions of deficient substrate or cofactors, it reduces molecular oxygen to superoxide[7]. The superoxide and the peroxynitrite, formed by the interaction of •NO with superoxide, are highly toxic to the cardiomyocytes[7]. Ing et al[68] and Arstall et al[71] determined that the apoptosis of cardiomyocytes induced by iNOS seems to be independent from sGC and cGMP, but it seems to be predominantly through the formation of peroxynitrite. The iNOS-mediated cytotoxicity was not exclusively confined to neonatal myocytes, but also in adult myocytes, where the endogenous •NO generated by the iNOS after the exposition to the combination of the cytokines INFγ and IL-1β induces apoptosis[71].

Modulators of the bioavailability of nitric oxide

Nitric oxide donors

Among the compounds that present high potential as •NO donors are the low-molecular weight S-nitrosothiols (RSNOs). The RSNOs are endogenous species that were detected in the airway-lining fluid, platelets and neutrophils, where they act in the biological systems as •NO carriers, as free thiols or proteins containing cystein[72].

The exogenous RSNOs are promising drugs to be used in the treatment of diseases that involve dysfunctions in the •NO bioavailability, as they offer advantages on the currently used drugs, due to the fact that they do not induce to tolerance in vascular cells[73], as do the organic nitrate and sodium nitroprussiate.

Clinical studies have shown that the RSNOs can be beneficial in a series of cardiovascular disorders[74]. They can also have access to the intracellular compartment through the catalytic action of the membrane disulphide isomerase, associated to a nitrosylation reaction[74]. The members of this compound class include: S-nitrous-glutathione (GSN), S-nitro-N-acetylpenicillamine (SNAP), S-nitrous-albumin and S-nitrous-N- acetylcysteine (SNAC).

Angiotensin-converting enzyme inhibitors (ACEI)

The angiotensin-converting enzyme (ACE), in addition to generating ANGII, also degrades bradykinin[75]. The bradykinin is an endothelium-dependent vasodilator, stimulating the endothelium to produce •NO. Thus, the ACE inhibitors enhance the bradykinin and have been used due to their beneficial effect of increasing the bioavailability of •NO in the cardiovascular tissue[76]. Additionally, the ANGII can stimulate the production of superoxide, which would reduce the bioavailability of •NO[77], an event that can be blocked by the ACE inhibitors.

Phosphodiesterase inhibitors

Phosphodiesterase inhibitors such as sildenafil, prolong the signaling action of •NO through the inhibition of cGMP hydrolysis. The inhibition of phosphodiesterase by

phosphodiesterase inhibitors prevents the degradation of cGMP into GMP5´, which prolongs the time of action of cGMP, keeping the intracellular concentration of Ca^{++} low in the smooth musculature of vessels and consequent vasodilation[78].

Conclusion

The increase in the cardiomyocyte stretching is the main factor that induces the hypertrophic growth, but circulating substances, such as endothelin 1 (ET1), angiotensin II, insulin and the catecholamines, as well as growth factors and cytokines released locally by the myocardial cells and oxidative stress products, such as the superoxide anion (O_2^{-}), also induce the hypertrophic growth of the cardiomyocytes. These, in turn, activate second messengers such as phospholipase C (PLC), the mitogen-activated protein kinases (MAPK) and calcineurin. These activated proteins promote alterations in the nuclear factors and in the regulation of the hypertrophic genes. Thus, it seems that there is no isolated signaling cascade for each stimulus or response, but that multiples signaling molecules occur and can form a network of cascades with numerous elements, facilitating their crossing-over. Therefore, it becomes evident that the anti-hypertrophic effect of •NO is achieved through the negative modulation of the pro-hypertrophic pathways and that the cGMP-dependent pathway has a central role in this effect. However, •NO does not block just one of the intracellular signaling pathways, which would not be enough to effectively prevent hypertrophic ventricular growth. Therefore, the LVH seems to develop due to the loss of balance between the pro- and anti-hypertrophic signaling pathways. This new knowledge on the pro- and anti-hypertrophic signaling pathways will allow the development of new strategies for the treatment of pathological LVH.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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