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Review

Role of Vasoactive Hormone-Induced Signal Transduction in Cardiac Hypertrophy and Heart Failure

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Abstract: Heart failure is the common concluding pathway for a majority of cardiovascular diseases and is associated with cardiac dysfunction. Since heart failure is invariably preceded by adaptive or maladaptive cardiac hypertrophy, several biochemical mechanisms have been proposed to explain the development of cardiac hypertrophy and progression to heart failure. One of these includes the activation of different neuroendocrine systems for elevating the circulating levels of different vasoactive hormones such as catecholamines, angiotensin II, vasopressin, serotonin and endothelins. All these hormones are released in the circulation and stimulate different signal transduction systems by acting on their respective receptors on the cell membrane to promote protein synthesis in cardiomyocytes and induce cardiac hypertrophy. The elevated levels of these vasoactive hormones induce hemodynamic overload, increase ventricular wall tension, increase protein synthesis and the occurrence of cardiac remodeling. In addition, there occurs an increase in proinflammatory cytokines and collagen synthesis for the induction of myocardial fibrosis and the transition of adaptive to maladaptive hypertrophy. The prolonged exposure of the hypertrophied heart to these vasoactive hormones has been reported to result in the oxidation of catecholamines and serotonin via monoamine oxidase as well as the activation of NADPH oxidase via angiotensin II and endothelins to promote oxidative stress. The development of oxidative stress produces subcellular defects, Ca^{2+}-handling abnormalities, mitochondrial Ca^{2+}-overload and cardiac dysfunction by activating different proteases and depressing cardiac gene expression, in addition to destabilizing the extracellular matrix upon activating some metalloproteinases. These observations support the view that elevated levels of various vasoactive hormones, by producing hemodynamic overload and activating their respective receptor-mediated signal transduction mechanisms, induce cardiac hypertrophy. Furthermore, the occurrence of oxidative stress due to the prolonged exposure of the hypertrophied heart to these hormones plays a critical role in the progression of heart failure.

Keywords: vasoactive hormones; cardiac hypertrophy; heart failure; oxidative stress; Ca^{2+}-handling abnormalities; extracellular matrix; cardiac dysfunction; ventricular wall tension

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1. Introduction

Heart failure is a major public health problem affecting about 26 million people globally; there are 5.7 million in the United States alone and 670,000 new cases every year [1,2]. This pathological state is associated with cardiac dysfunction, as well as changes in electrical properties and myocardial metabolism, leading to the inability of the heart to pump sufficient blood to meet the oxygen supply and nutrient demands of other organs

in the body [3,4]. Heart failure is characterized by shortness of breath, decreased exercise tolerance as well as fluid retention, and when accompanied by arrhythmias, there occurs a high rate of sudden cardiac death. Several cardiovascular diseases such as coronary artery disease, hypertension, aortic valve stenosis, mitral valve regurgitation, inflammatory disease, genetic cardiomyopathy, diabetes and obesity eventually lead to the development of heart failure [5–7]. The lifetime risk of developing heart failure is 1 in 5 and the long-term survival is very poor; up to one-third of patients die within the first 12 months and about half of them die within 5 years. The mortality due to heart failure in men is about 60% whereas it is about 45% in women [8–10]. Thus, heart failure is a very serious disorder and one of the most common causes of death.

Over the past 60 years, several mechanisms have been proposed to explain the pathogenesis of heart failure [11–16]. These include (a) defects in energy production and utilization, (b) increased preload and afterload, (c) elevated levels of vasoactive hormones and altered signal transductions, (d) the development of intracellular Ca^{2+}-overload and Ca^{2+}-handling abnormalities and (e) cardiac remodeling and subcellular defects. The pathophysiology of cardiac remodeling during the development of heart failure has been reviewed extensively [17–24]. Although all these pathologic mechanisms have been helpful in developing a wide variety of interventions for the therapy of cardiac dysfunction in heart failure, the research based on these issues has not provided sufficient information for distinguishing different types of heart failure such as (a) heart failure with reduced ejection fraction, (b) heart failure with preserved ejection fraction, (c) systolic heart failure and (d) diastolic heart failure [25–30]. It may be noted that heart failure with a reduced ejection fraction is caused by myocardial infarction and is usually associated with loss of cardiomyocytes and replacement fibrosis. On the other hand, heart failure with a preserved ejection fraction is seen in patients with chronic hypertension and chronic diabetes and is associated with cardiomyocyte stiffness and interstitial fibrosis. It can be argued that a description of some other distinctive features of heart failure with a preserved ejection fraction versus that with a reduced ejection fraction would enhance the presentation. Since the exact pathophysiological mechanisms with respect to the involvement of vasoactive hormones in heart failure with preserved ejection fraction are not fully understood at present, it would be prudent to focus the discussion on this topic, mainly on the pathogenesis of heart failure with a reduced ejection fraction.

Since heart failure is usually preceded by cardiac hypertrophy, it is of critical importance that events leading to cardiac hypertrophy be understood to define the progression of heart failure. Furthermore, cardiac hypertrophy under different situations at the initial stages serves as an adaptative mechanism and is considered to be compensatory or physiological hypertrophy. However, if the stimulus is not removed, there occurs a transition from physiological cardiac hypertrophy to pathological hypertrophy. The mechanisms for the transition of physiological (adaptive) cardiac hypertrophy to pathological (maladaptive) hypertrophy as well as the characteristics of both these forms of cardiac hypertrophy are reviewed elsewhere [31–40]. It is emphasized that cardiac hypertrophy, as seen due to exercise, is not always of a pathological nature. Furthermore, the combination of fibrosis and hypertrophy is considered to be a hallmark of pathological hypertrophy as well as cardiac remodeling and dysfunction. It is pointed out there are three types of cardiac hypertrophy that develop to reduce the ventricular wall; these include (a) concentric cardiac hypertrophy, where the muscle mass is increased via the thickening of cardiomyocytes as seen in response to pressure overload; (b) eccentric cardiac hypertrophy, which is associated with an increase in muscle mass via the lengthening of cardiomyocytes as seen in response to volume overload and (c) mixed concentric and eccentric cardiac hypertrophy, where the muscle is increased both via the thickening and lengthening of cardiomyocytes as seen in response to myocardial damage due to myocardial infarction. These structural changes in the size and shape of myocardium in both physiological and pathological forms of cardiac hypertrophy are generally indicated as cardiac remodeling and it is the pathological (adverse) cardiac hypertrophy that results in the development of heart failure.

Several neuroendocrine systems and pathological factors are not only inter-related with each other but are also intimately involved in the development of cardiac hypertrophy as well as the progression of heart failure [18,20,24,35,41–47]. Some of the endocrine systems are shown in Figure 1. It may be noted that myocardial injury due to myocardial infarction is known to result in activations of the sympathetic nervous system (SNS), posterior pituitary, endothelium and platelets, which result in the release of different vasoactive hormones such as norepinephrine, vasopressin, endothelins and serotonin, respectively, whereas the activation of the renin–angiotensin system (RAS) promotes the formation of angiotensin II upon the release of renin from the kidney. These vasoactive hormones have also been shown to induce the development of pathological stimuli, including pressure overload, volume overload, inflammation, increased ventricular wall tension and other abnormalities during the development of cardiac hypertrophy and heart failure. However, only scattered information is available regarding mechanisms for the transition of cardiac hypertrophy to heart failure.

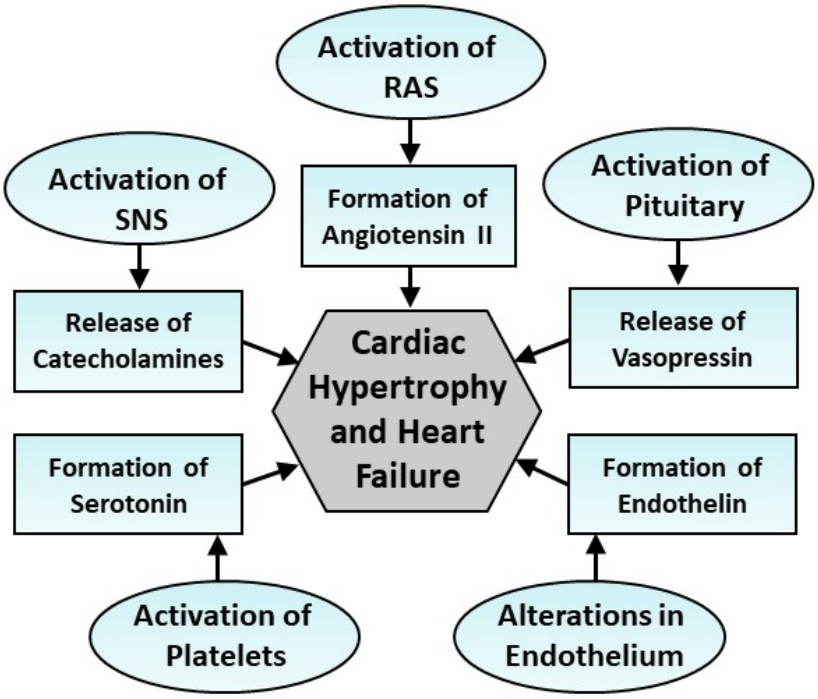

Figure 1. Some endocrine systems involved in the development of cardiac hypertrophy and heart failure through the release of different vasoactive hormones. SNS—sympathetic nervous system; RAS—renin–angiotensin system.

Although plasma levels of several vasoactive neurohumorals and growth factors are elevated in cardiac hypertrophy and heart failure [41–49], mechanisms of their release as well as formation seem to depend upon the type and stage of pathological stimulus. For example, a depression in cardiac output and a decrease in blood pressure due to myocardial infarction, cardiomyopathies and inflammatory diseases stimulate the SNS and peripheral RAS for the release of catecholamines (norepinephrine from the sympathetic nerve endings and epinephrine from the adrenal medulla) and promote the release of renin from the kidney for the formation of Ang II, respectively. Activations of the posterior pituitary for the release of vasopressin and the hypothalamic center for the release of different growth factors are also considered to be due to a decrease in blood pressure. On the other hand, the release of vasoactive hormones and growth factors under conditions of pressure overload and volume overload is considered to occur as a consequence of increased ventricular pressure stress and the activation of afferent nerve fibers connected to different centers in the brain. In addition, increased ventricular wall stress due to hemodynamic overload can be seen to affect vascular endothelium in the heart to release endothelins, mast cells and

serotonergic nerve fibers to release serotonin, sympathetic nerve endings in the ventricle to release norepinephrine and endogenous RAS to release angiotensin II. The activation and aggregation of platelets by circulating norepinephrine and angiotensin II are the major sources of elevated levels of serotonin. These several vasoactive hormones and growth factors are considered to play an important role in the maintenance of hemodynamic homeostasis, the development of cardiac hypertrophy and the progression of heart failure.

It is commonly held that prolonged exposure of the hypertrophied heart to high levels of circulating vasoactive hormones or different pathological stimuli results in the decompensation of the hypertrophied heart for the progression to heart failure. This article, therefore, deals with a comprehensive discussion of signal transduction mechanisms for the development of cardiac hypertrophy as well as an updated description of events that result in the progression of cardiac hypertrophy to heart failure. Although elevated levels of several other hormones such as aldosterone, thyroid hormone, arterial natriuretic peptide (ANP), brain natriuretic peptide (BNP), insulin/insulin-like growth factor and other growth factors and NO are observed in heart failure [48–57], the discussion on these aspects is not included in this review. In fact, this article is intended to focus on the discussion of some vasoactive hormones, which are known to produce hemodynamic overload and increase ventricular wall tension. Since vasoactive hormones are also known to release different proinflammatory cytokines and produce myocardial fibrosis, their participation in the transition from adaptive cardiac hypertrophy to maladaptive hypertrophy will be discussed. Furthermore, in view of the critical role of vasoactive hormones in inducing oxidative stress and Ca^{2+}-handling abnormalities in cardiomyocytes [58–65], it is planned to highlight their involvement in the development of cardiac dysfunction and heart failure.

2. Role of Catecholamines in Cardiac Hypertrophy and Heart Failure

It is now well known that circulating levels of both norepinephrine and epinephrine are increased during the development of heart disease under a wide variety of stressful conditions [66,67]. In the initial stages, elevated levels of plasma catecholamines produce adaptive changes in the heart for maintaining cardiac function; however, at later stages, these hormones result in cardiac dysfunction and cardiomyopathy. Catecholamines have been demonstrated to increase cardiac function and induce cardiac hypertrophy via β-adrenoceptors, activating Gs-protein–adenylyl cyclase complex and promoting the formation of cyclic AMP [17,68–71]. The increased concentration of cyclic AMP activates protein kinase A (PKA) and phosphorylates various intracellular sites to increase Ca^{2+}-movements and protein synthesis in cardiomyocytes. In fact, catecholamines have been reported to stimulate subcellular Ca^{2+}-transport, cardiac gene expression and protein synthesis for the induction of adaptive changes in the heart [72–74]. These alterations through elevated levels of circulating catecholamines in cardiac hypertrophy were attenuated through the β-adrenoceptor blockade as well as Ca^{2+}-antagonists [75]. Furthermore, the inhibition of extracellular signal-regulated kinases (ERK 1/2) was found to abolish the catecholamine-induced cardiac gene expression [74]. It appears that the β-adrenoceptors-PKA-ERK1/2-associated signal transduction system may be involved in the initial hypertrophic response as well as in augmenting cardiac function via catecholamines.

The increase in the cardiac contractile activity and hypertrophic growth action of catecholamines under physiological conditions is mainly modulated through β-adrenoceptor-associated mechanisms [17,76]; however, α-adrenoceptor-associated signal transduction is considered to become more apparent for initiating the progression of cardiac hypertrophy under pathological situations [77]. The activation of α-adrenoceptors via norepinephrine has been shown to stimulate phospholipase C (PLC), which is coupled with G_q-proteins, and results in the production of 1,2 diacylglycerol (DAG) and inositol -1, 4, -5 triphosphate (IP3), the activation of protein kinase C (PKC) and mitogen-activated protein kinase (MAP kinase, ERK1/2). The activation of this signaling pathway is associated with the release of intracellular Ca^{2+} and the induction of hypertrophic response in cardiomyocytes [78]. The development of cardiac hypertrophy in spontaneously hypertensive rats, cardiomy-

opathic hamsters and volume-overloaded rats has been shown to be associated with the activation of PLC [79–81]. Norepinephrine-induced cardiac hypertrophy, gene expression and protein synthesis were attenuated via U73122, an inhibitor of PLC, as well as prazosin, an α-adrenergic receptor blocker [82]. A depression in norepinephrine-stimulated gene expression and protein synthesis in cardiomyocytes via bisindolylmaleimide -1, a PKC inhibitor, and PL98059, an ERK1/2 inhibitor, indicated that PKC-ERK1/2 may be involved in the PLC-associated signal transduction pathway. It is pointed out that the stimulation of protein synthesis in cardiomyocytes has also been reported to occur through phosphatidic acid, a product of phospholipase D activation, for the development of cardiac hypertrophy [83,84]. Thus, phospholipid-mediated signal transduction upon the activation of α-adrenoceptors may represent an important mechanism for the occurrence of cardiac hypertrophy due to catecholamines.

It needs to be emphasized that the actions of catecholamines at the initial stages are beneficial for maintaining cardiac function, but their delayed effects are deleterious [17,66,67]. A schematic representation of events depicting the involvement of both β-adrenoceptors and α-adrenoceptors in causing cardiac hypertrophy and the role of oxidative stress in the occurrence of heart failure at the later stages of catecholamine action is shown in Figure 2. It may be noted that β-adrenoceptor signal transduction is downregulated due to high levels of circulating catecholamines for a prolonged period and, thus, there occurs a depression in Ca^{2+}-transport in cardiomyocytes, leading to the development of cardiac dysfunction [17,72,85]. Such a decrease in subcellular Ca^{2+}-transport via high levels of plasma catecholamines has been shown to be a consequence of the occurrence of oxidative stress [86]. It is also pointed out that oxyradicals are generated during the oxidation of catecholamines through both non-enzymatic and enzymatic mechanisms and under conditions where the endogenous antioxidant pool becomes saturated or depressed, these oxyradicals lead to the development of oxidative stress [87,88]. Catecholamines have also been demonstrated to accumulate in cardiomyocytes, become oxidized through mitochondrial monoamine oxidase and generate oxyradicals [89]. Furthermore, the cardiotoxic effects of high levels of catecholamines are prevented via antioxidants such as vitamin E, vitamin A, vitamin C, N-acetyl L-cysteine and sulfur-containing amino acids [90–92]. It may be noted that in spite of several epidemiological and experimental studies showing the beneficial effects of different vitamins in attenuating cardiovascular disorders, several clinical investigations to determine the therapeutic effects of vitamins such as E or C have shown inconclusive and inconsistent results [91]. Accordingly, it was suggested that antioxidant vitamins may be involved in the prevention rather than the therapy of cardiovascular disease [91]. Nonetheless, different adrenoceptor antagonists have been shown to exert beneficial effects in heart failure not only by exerting antioxidant effects or attenuating cardiac hypertrophy upon blocking α- or β-adrenoceptors but also by lowering the elevated levels of plasma catecholamines upon acting on the sympathetic nerve terminals [93–95]. These observations suggest the involvement of oxidative stress in cardiac dysfunction during the development of catecholamine-induced cardiomyopathy.

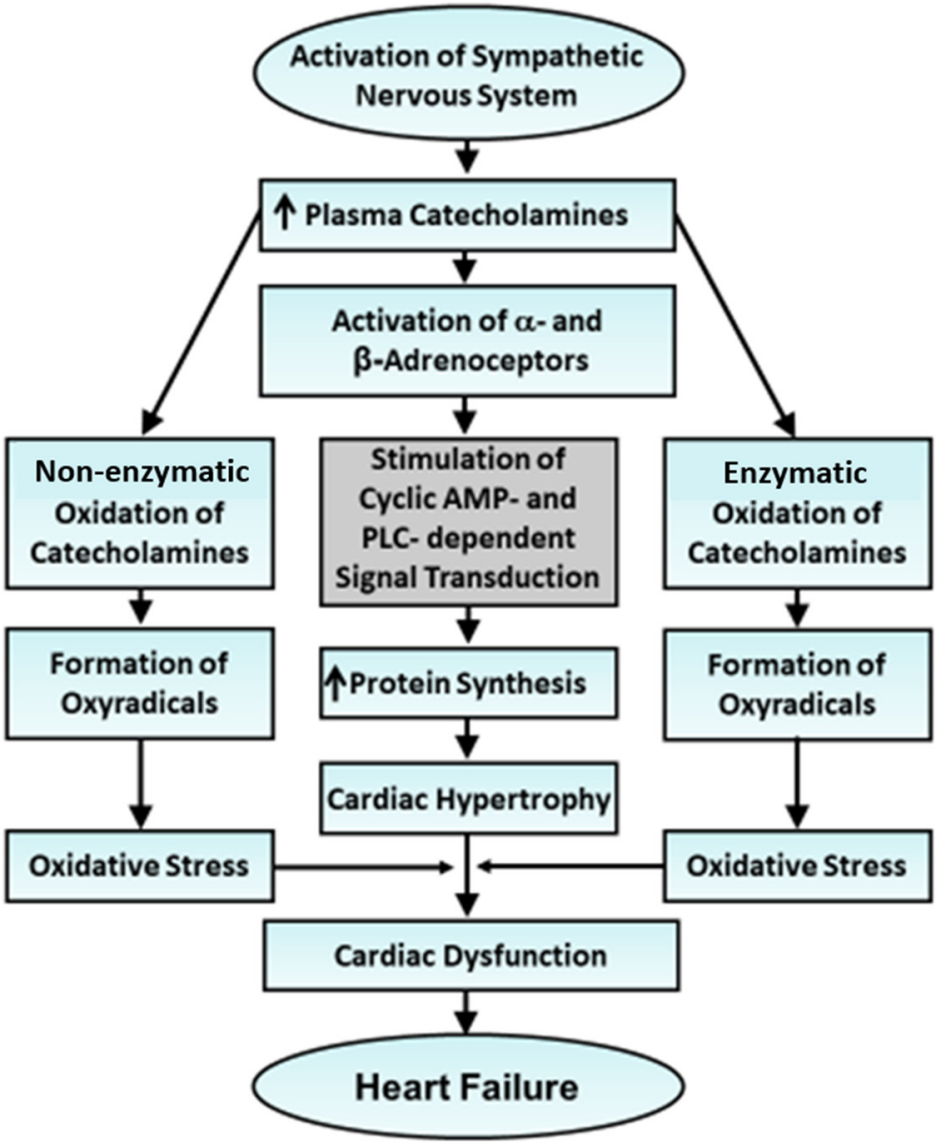

Figure 2. Role of the sympathetic nervous system in the development of cardiac hypertrophy and progression of heart failure. PLC—phospholipase C. Low concentrations of plasma catecholamines upon the activation of adrenoceptors induce cardiac hypertrophy, whereas high concentrations upon oxidation for a prolonged period result in heart failure.

3. Role of Angiotensin II in Cardiac Hypertrophy and Heart Failure

Over the past six decades, extensive research has been carried out to understand the involvement of angiotensin II (Ang II) in the development of hypertension, cardiac hypertrophy and heart failure [96–104]. Ang II is a multifunctional hormone, which is formed in both peripheral (circulating) and local (tissue) RAS. The generation of Ang II in the peripheral RAS is associated with the release of renin from the kidneys via a reduction in blood flow, the formation of Ang I from angiotensinogen in the liver by renin and the conversion of Ang I to Ang II in the lung with the angiotensin-converting enzyme (ACE). Although all components of the RAS are expressed in various organs, ACE is mainly localized on fibroblasts as well as the endothelium; chymase is also involved in the conversion of Ang I to Ang II in the heart. Thus, under a wide variety of pathophysiological conditions, the circulating levels of Ang II are elevated upon the activation of the peripheral RAS via reduced blood flow to the kidneys, whereas the activation of the cardiac RAS is stimulated by increased ventricular wall tension to maintain hemodynamic homeostasis.

Several excellent reviews concerning the pathophysiological implications of the activated RAS as well as the mechanisms of Ang II action on the cardiovascular system are available in the literature [105–110]. Although the exact time course for the activation of the RAS due to any pathophysiological stimulus still remains to be established, it seems that the activation of the RAS may lag behind that of the SNS because of the time required for the synthesis of Ang II from angiotensinogen in the peripheral RAS as well as the development of the ventricular wall tension for the release of Ang II from the cardiac RAS.

The elevated levels of Ang II not only produce vasoconstriction, cardiac hypertrophy and heart failure but are also involved in release of catecholamines from the sympathetic nerve terminals and the adrenal medulla for raising blood pressure, the release of aldosterone from the adrenal cortex for salt and fluid retention and the release of autocrine factors such as transforming growth factors (TGF-β) and interleukin (IL-6) for inflammatory responses [100–102,104,107]. The cardiovascular effects of Ang II are mediated by two types of receptors, namely AT_1R and AT_2R. The interaction of Ang II with AT_1R induces prohypertensive, prohypertrophic and proinflammatory actions, whereas the interaction of Ang II with AT_2R has been shown to produce antihypertensive, antihypertrophic and anti-inflammatory effects [102,104,111–114]. Both Ang I and Ang II are metabolized to Ang (1–9) and Ang (1–7) with ACE2, the homologue of ACE, which is known to activate MAS receptors (MASR) and produce antihypertensive, anti-inflammatory and antihypertrophic actions [115–117]. Since the effects of AT_1R activation are antagonized by the effects of AT_2R activation and MASR activation, an imbalance between the adverse actions of AT_1R activation and the beneficial effects of AT_2R activation as well as MASR activation has been suggested to determine the acceleration and progression of heart disease [104,118,119]. Although AT_1R, AT_2R and MASR are G_q- protein-coupled receptors [120,121], the sequence of their activations during the development of cardiac hypertrophy and heart failure has not yet been established.

The activation of the peripheral RAS has been shown to increase the level of plasma Ang II rapidly and stimulate AT_1R in vascular smooth muscles to elevate blood pressure and produce a hypertrophic response [102,104]. The elevated blood pressure is considered to increase afterload on the heart and, thus, increase the left ventricular wall tension to activate the local RAS and release Ang II. Thus, Ang II from both peripheral and local sources activates AT_1R in cardiomyocytes to stimulate myocardial metabolism and cardiac function in addition to inducing signal transduction for the process of cardiac hypertrophy. In the early stages, the activation of AT_1R is associated with the incorporation of different amino acids and the stimulation of a signal transduction mechanism for the synthesis of proteins and the development of adaptive cardiac hypertrophy [102,104,122,123]. The Ang II- AT_1R hypertrophic signal transduction includes the activation of sarcolemmal PLC, resulting in (i) the formation of DAG, the stimulation of PKC and the activation of MAP kinase and (ii) the formation of IP_3, the release of Ca^{2+} from the sarcoplasmic reticulum and the activation of Ca^{2+}-calmodulin kinase for the occurrence of cardiac hypertrophy. It is noteworthy that AT_1R is coupled with NADPH oxidase (NOX)-2 in the sarcolemmal membrane, whereas the production of small amounts of oxyradicals upon activating AT_1R is considered to change the redox status of cardiomyocytes and promote the hypertrophic signal transduction pathway for the induction of adaptive cardiac hypertrophy [102,104].

Since Ang II is known to activate AT_2R and its metabolite, Ang (1–7) activates MASR to produce antihypertrophic responses for limiting the development of cardiac hypertrophy induced through AT_1R activation [102,104]; the net growth of myocardium due to Ang II is considered to be a balance between the effects of AT_1R activation and AT_2R as well as MASR activations. Several immediate early genes including c-fos, c-jun and c-myc are also induced through the activation of AT_1R for the development of cardiac hypertrophy [122–124]. The activation of AT_1R in the adrenal cortex by Ang II has also been documented to release aldosterone and promote cardiac hypertrophy as a consequence of increasing the preload on the heart due to its sodium retention and fluid-accumulating effects [103,104,125]. Thus, the development of adaptive cardiac hypertrophy via Ang II not only involves

the AT_1R-mediated signal transduction pathway but is also a consequence of increased ventricular wall tension due to hemodynamic overload. It should also be noted that Ang II has been shown to release proinflammatory cytokines such as interleukin (IL)-6, IL-1β and tumor necrosis factor (TNF)-α and anti-inflammatory cytokines including IL-10 and transforming growth factor (TGF)-β from macrophages and neutrophils [13,104,126,127]. These proinflammatory cytokines are known to promote the accumulation of collagen in the extracellular matrix and fibrosis in cardiomyocytes. The progressive Ang-II-induced activation of different isoforms of NOX has also been reported to exhaust the antioxidant reserve and increase the concentration of oxyradicals [102,128–134] in cardiomyocytes. Such an effect of Ang II has been shown to be associated with the occurrence of apoptosis and fibrosis. Thus, it appears that both myocardial inflammation and high levels of oxyradicals may be involved in the transition of adaptive cardiac hypertrophy to maladaptive cardiac hypertrophy due to elevated levels of Ang II.

It is now becoming clear that acute exposure to Ang II is associated with the development of adaptive cardiac hypertrophy in which cardiac function is either unaltered or augmented, whereas prolonged exposure of the heart to Ang II results in the transition of adaptive cardiac hypertrophy to maladaptive cardiac hypertrophy, in which cardiac function is depressed; thereafter, a progression to a major health hazard occurs, namely heart failure. A simplified schematic representation of some major events occurring during the development of Ang II-induced cardiac hypertrophy and heart failure is shown in Figure 3. Although the exact mechanisms associated with the progression of heart failure subsequent to various pathological conditions are of a complex nature and not fully understood, the involvement of Ang II in this process is evident from the fact that various blockers of the RAS and AT_1R antagonists are well known to produce significant beneficial effects [103,104]. Furthermore, a progressive increase in the degree of oxidative stress has been claimed to be associated with the progression of heart failure [102,128–134]. There are four major mechanisms that have been identified in the production of oxidative stress due to prolonged exposure to Ang II [101–164]. These include (i) the activation of NOX-2 and NOX-4 during the hypertrophic process; (ii) the exhaustion of antioxidant reserve due to the continued activation of AT_1R and the depressed activity of nuclear factor erythroid-2 elated factor 2; (iii) the stimulation of NOX-4 in mitochondria upon the entry of Ang II in cardiomyocytes and (iv) the induction of functional hypoxia in the hypertrophied myocardium due to the inadequate development of capillaries in comparison to cardiomyocytes growth. The excessive development of oxidative stress in cardiomyocytes has been reported to adversely affect the function of different subcellular organelles and result in Ca^{2+}-handling abnormalities, metabolic alterations, changes in cardiac gene expression and the impairment of cardiac performance [58–62,101–104,134]. Although the role of cardiac inflammation cannot be ruled out, the evidence available in the literature strongly supports the view that oxidative stress plays a crucial role in the progression of heart failure due to prolonged exposure to Ang II.

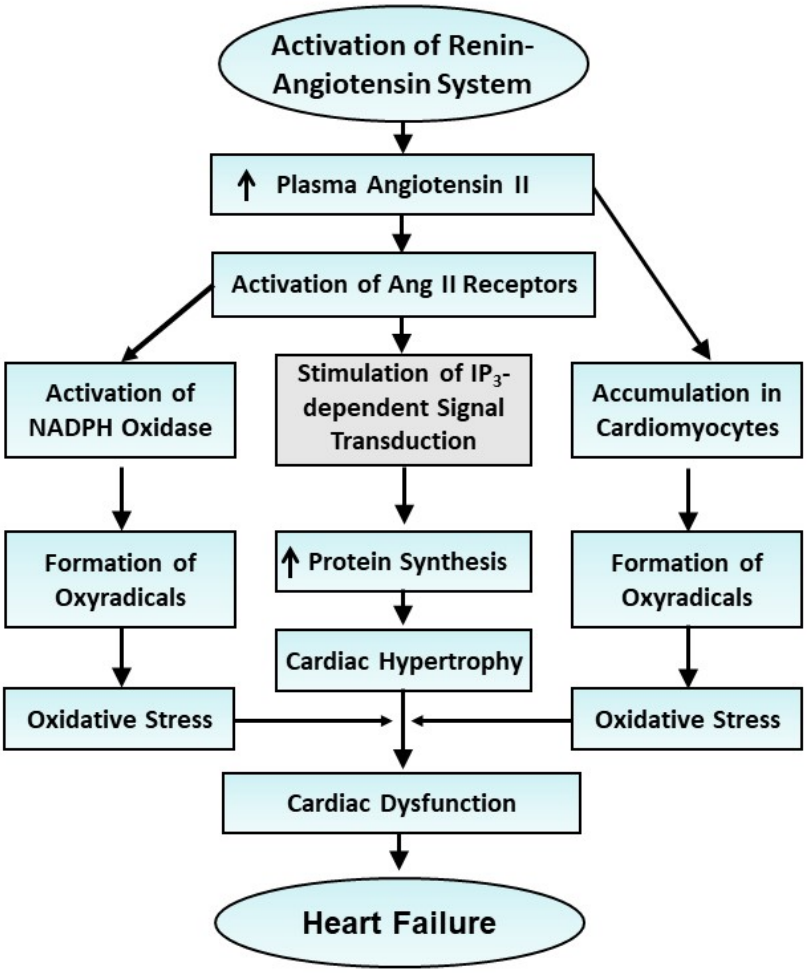

Figure 3. Role of the renin–angiotensin system in the development of cardiac hypertrophy and the progression of heart failure. Ang II—angiotensin II. Elevated plasma levels of angiotensin upon the activation of Ang II receptors induce cardiac hypertrophy, whereas the prolonged activation of NADPH oxidase results in heart failure.

4. Role of Serotonin in Cardiac Hypertrophy and Heart Failure

Serotonin (5-hydroxytryptamine; 5-HT) is a monoamine, which is present in platelets, mast cells and sympathetic nerve terminals in the heart [135,136]. The release of this hormone upon the aggregation of platelets as well as the degranulation of mast cells has been shown to produce vasoconstriction, smooth muscle cell proliferation, coronary spasm, tachycardia, inotropic effect, cardiac hypertrophy and fibrosis [137–141]. Although there are several families of serotonin receptors present in the cardiovascular system, the vasoconstriction and hypertrophic effects of this hormone are mainly mediated via 5-HT_{2A} and 5-HT_{2B} receptors [142–144]. The activation of 5-HT_{2A} receptors, which are coupled with PLC through $G_{\alpha q}$ proteins, has been shown to stimulate PKC due to the formation of DAG and induce a hypertrophic response involving MAP kinase [145]. Furthermore, the activation of these receptors with serotonin has been demonstrated to accumulate IP_3 upon the hydrolysis of phosphoinositide for releasing Ca^{2+} from the intracellular pool [146–148]. Although the stimulation of both SNS and RAS is also known to activate platelets and release serotonin, plasma levels of serotonin are increased due to ischemia-reperfusion, atherosclerosis, coronary artery disease and heart failure [149–154]. Accordingly, the serotonin-5-HT_{2A} signal pathway is considered to regulate cardiovascular function in both health and disease [149–156].

Several antiplatelet agents such as aspirin, clopidogrel and cilostazol, either alone or in combination, have been reported to produce beneficial effects in diverse cardiovascular dis-

eases including pulmonary hypertension [157,158], coronary artery abnormalities [159–163] and ventricular arrhythmias and atrial fibrillation [155,156,164]. Furthermore, the 5-HT_{2A} receptor antagonist, ketanserin, has been shown to improve hemodynamic and neurohumoral alterations in patients with heart failure [165,166]. Sarpogrelate, another 5-HT_{2A} receptor antagonist, was also demonstrated to mitigate cardiac remodeling as well as subcellular remodeling in heart failure due to myocardial infarction [167,168]. Sarpogrelate has been reported to suppress Ang II-, endothelin-1- or phenylephrine-induced cardiac hypertrophy in cultured cardiomyocytes in addition to attenuating systolic dysfunction in mice subjected to transverse aortic constriction [169]. Since sarpogrelate was found to inhibit the effects of different stimuli other than serotonin, it has been suggested that this agent may affect some hypertrophic signaling other than that associated with 5-HT_{2A} activation [169]. Nonetheless, these observations support the view that serotonin is involved in the pathogenesis of cardiovascular abnormalities, and it appears that various antiplatelet agents and 5-HT_{2A} antagonists may not be specific for acting on the same site in the hypertrophic signal transduction pathway for serotonin.

Serotonin not only exerts vasoconstriction and raises blood pressure but is also known to act as a growth factor, stimulating mitogenesis and migration of arterial smooth muscle cells [143,144,170,171]. It produces cardiostimulatory effects [172,173] and is involved in the development of cardiac hypertrophy as well as heart failure [151,155,156]. The plasma levels of serotonin are correlated with the progression of heart failure involving CaMK II/HDAC 4 signal transduction [150,174–177]. The activation of 5-HT_{2A} receptors for the induction of cardiac hypertrophy was observed to be associated with the ERK ½-GATA4 signal pathway [169]. Elevated levels of plasma serotonin were also reported in patients with diastolic heart failure and ischemic heart disease and were formed to activate different receptors such as 5-HT_{2B} and 5-HT_4 [178–184]. Serotonin has also been shown to play an important role in regulating cardiac development and function through the involvement of HT_{2B} receptors, and in fact, the overexpression of 5-HT_{2B} receptors has been demonstrated to induce cardiac hypertrophy [185,186]. The interleukin-18-induced cardiac hypertrophy was inhibited via pretreatment with the 5-HT_{2B} receptor antagonist, SB215505, as well as siRNA for the 5-HT_{2B} receptor [187]. It may also be noted that aspirin, an antiplatelet agent, has been reported to attenuate the right ventricular hypertrophy due to pulmonary hypertension [158], whereas another antiplatelet agent, cilostazol, was shown to depress myocardial infarction-induced right ventricular hypertrophy [167,168]. Thus, it appears that the involvement of serotonin in the induction of cardiac hypertrophy and heart failure due to different types of pathological stimuli may be associated with different types of serotonin receptors as well as signal transduction pathways.

In view of the participation of platelets as a major source for the release of serotonin during the development of cardiac hypertrophy and heart failure, a graphic presentation of signal transduction events associated with pathological situations is given in Figure 4. Elevated levels of serotonin upon activating its receptors and signal transduction pathway promote protein synthesis and induce cardiac hypertrophy. Serotonin-induced vasoconstriction and increased blood pressure can be seen to increase hemodynamic overload on the heart and, thus, would also promote the occurrence of cardiac hypertrophy. Since monoamine oxidase-A (mainly present in mitochondria) is involved in the degradation of serotonin and the production of oxyradicals and H_2O_2 [188], it is suggested that serotonin will not only change the redox status of cardiomyocytes for promoting cardiac hypertrophy upon producing a small amount of oxyradicals at initial stages but will also produce oxidative stress, intracellular Ca^{2+}-overload, apoptosis and necrosis for the induction of cardiac dysfunction and heart failure [89,188–190].

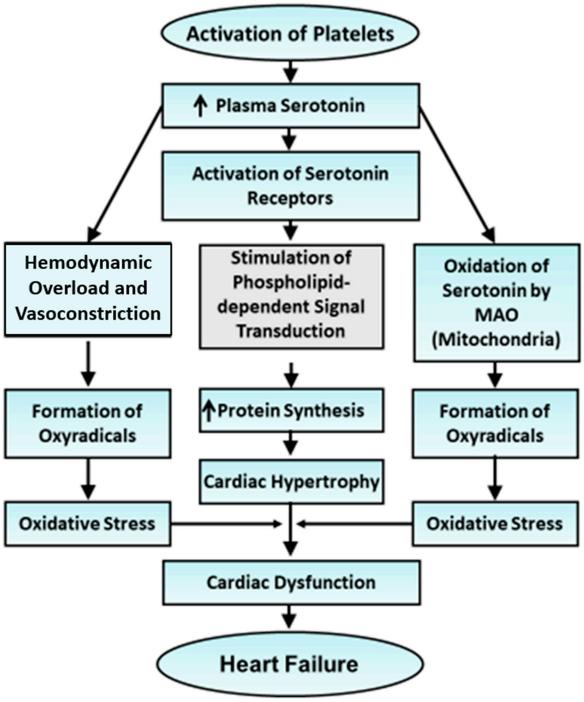

Figure 4. Role of the activation of platelets in the development of cardiac hypertrophy and progression of heart failure. MAO—monoamine oxidase. Cardiac hypertrophy is induced by the activation of serotonin receptors, whereas its transition to heart failure occurs due to the oxidation of serotonin by MAO.

5. Role of Endothelin-1 in Cardiac Hypertrophy and Heart Failure

Following the discovery of endothelin in 1988 [191] and the identification of endothelin-1 as the most potent vasoconstrictor [192,193], extensive research has been carried out to understand the role of endothelin-1 in cardiovascular health and disease. Several excellent reviews in the area of endothelin-1 molecular biology, pathophysiology and pharmacotherapy have appeared in the literature [194–200]. This hormone is produced mainly in the vascular endothelium and is known to increase blood pressure, exert a positive inotropic effect and produce cardiac hypertrophy. In addition, endothelin-1 influences salt and water retention homeostasis due to its interactions with angiotensin II, aldosterone and vasopressin [195]. This hormone is released from the endothelium through hemodynamic shear stress in the ventricle as well as through hypoxia, vasoactive hormones, growth factors and inflammatory cytokines [196]. Low concentrations of endothelin-1 are considered to maintain cardiovascular homeostasis, whereas the excessive production of this vasoactive hormone has been demonstrated to result in hypertension, cardiac hypertrophy and heart failure [195,196]. The cardiovascular effects of endothelin-1 are mediated by two types of receptors, namely ET_A and ET_B [201]. While the activation of ET_A is associated with vascular constriction and cell proliferation as well as myocardial cell growth and cardiac hypertrophy, the activation of ET_B has been shown to produce vasodilatory and antiproliferative effects [201]. Thus, the net effect of endothelin-1 on the cardiovascular system seems to be dependent upon the activity ratio of ET_A/ET_B.

ET_A receptors are present on both vascular smooth muscle cells and cardiomyocytes, whereas ET_B receptors are present on endothelial cells [196,202,203]. Endothelin-1 has been shown to produce smooth muscle contraction by activating ET_A receptors, whereas it promotes the production of NO in endothelial cells upon the activation of ET_B receptors [204,205]. Furthermore, endothelin-1 has been observed to increase contractile force in the heart by activating ET_A receptors [206]. Both ET_A and ET_B receptors are coupled to PLC through G_q-proteins [207,208]. The activation of ET_A in smooth muscle cells and cardiomyocytes results in a hypertrophic response involving PLC-PKC-MAP kinase-mediated

signal transduction mechanisms [194,199]. The activation of PLC has also been shown to increase the intracellular concentration of Ca^{2+} for the occurrence of vasoconstriction and cardiostimulation as well as apoptosis [194,195]. In addition, the activation of ET_A receptors through endothelin-1 is associated with the stimulation of phosphoinositide 3-kinase and protein kinase Akt (or protein kinase B) for promoting protein synthesis and protecting against the development of apoptosis [194,209,210]. The mitogenic effects of endothelin-1 for the induction of smooth muscle cell proliferation and cardiac growth are associated with the induction of several proto-oncogenes such as c-fos, c-jun and c-myc [194,199].

There is a growing body of evidence to indicate that endothelin-1 is involved in the pathogenesis of hypertension, cardiac hypertrophy and heart failure [194–196,199,211–216]. The increase in blood pressure due to endothelin-1 can be seen to increase the left ventricular pressure and induce cardiac hypertrophy. It may also be noted that the induction of pulmonary hypertension as a consequence of elevated levels of endothelin-1 would result in hypertrophy of the right ventricle leading to right heart failure [215,216]. The role of endothelin-1 in the development of pulmonary hypertension and right heart hypertrophy is further substantiated by the fact that several ET_A antagonists such as bosentan, macitentan and ambrisentan have been shown to produce beneficial effects in patients with pulmonary hypertension [194,198,217,218]. In addition to hemodynamic overload, endothelin-1 induces cardiac hypertrophy upon binding with ET_A receptors and the stimulation of the PLC-mediated signal transduction pathway [218–221]. It is also pointed out that plasma levels of endothelin-1 have been reported to increase in heart failure due to different pathological situations [222–227]. In fact, there occurs a positive correlation between plasma levels of endothelin-1 and the degree of cardiac dysfunction in heart failure [228]. Furthermore, endothelin-1 has been demonstrated to activate NOX for the generation of oxidative stress via the involvement of the ET_A-proline-rich tyrosine kinase-2 and Rac 1 pathway [229] and, thus, can be seen to induce heart failure. Treatments with ET_A antagonists such as bosentan and BQ-123 have been shown to improve the cardiac function and survival of heart failure subjects [230]. Several endothelin-1 receptor blockers [197,231] and salidroside, an antioxidant [232], have also been demonstrated to inhibit adverse cardiac remodeling in heart failure. A schematic representation of events for the development of cardiac hypertrophy and heart failure due to endothelin-1 is shown in Figure 5.

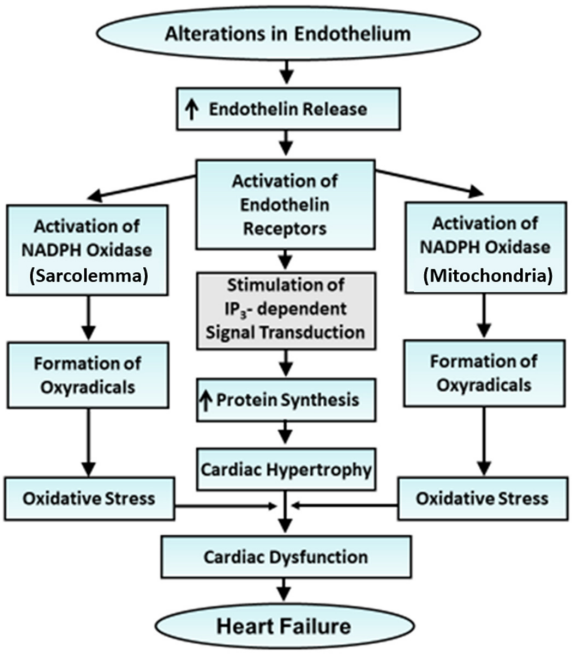

Figure 5. Role of alterations in endothelium in the development of cardiac hypertrophy and progression of heart failure. Cardiac hypertrophy is induced via the activation of endothelin receptors, whereas its transition to heart failure occurs due to the activation of NADPH oxidase.

6. Role of Vasopressin in Cardiac Hypertrophy and Heart Failure

Vasopressin is a nonapeptide hormone with a six-member disulfide ring and a three-member tail with a terminal carboxyl group [233,234]. This hormone is produced in supraoptic and paraventricular nuclei of the hypothalamus and stored in the posterior pituitary. Vasopressin is secreted in response to the activation of both osmotic and non-osmotic receptors for maintaining body fluid homeostasis and peripheral vascular resistance under several pathological conditions [47,197,235–237]. The osmotic secretion of this hormone is regulated by osmoreceptors in the hypothalamus, which sense small changes in plasma osmolarity due to alterations in sodium concentrations and results in the retention of water rather than sodium [238,239]. On the other hand, the non-osmotic release of vasopressin is controlled by baroreceptors in the left atrium, aortic arch and carotid sinus in response to atrial underfilling due to a decrease in cardiac output or peripheral vascular resistance [240]. The synthesis of vasopressin has also been reported to occur in the heart in response to pressure overload [241] but the significance of the hormone action from this source is not clear except that it may exert some local or systemic effect. The activation of the SNS is considered to promote the production of vasopressin [240], whereas Ang II has been shown to affect its release [242].

There are two major G-protein-coupled vasopressin receptors, namely the V_{1a} receptor and the V_2 receptor, which mediate the cardiovascular responses of this hormone in the body [243]. The activation of V_{1a} receptors has been demonstrated to increase contractile force in the heart [244] and produce cardiac hypertrophy [245]. The increase in blood pressure by vasopressin due to its action on vascular smooth muscle cells can be seen to increase the afterload on the heart and promote the occurrence of cardiac hypertrophy. Vasopressin has been reported to cause cardiac growth by promoting protein synthesis in neonatal and adult cardiomyocytes [245,246]. It is pointed out that the interaction of V_{1a} receptors with vasopressin results in the activation of PLC-mediated signal transduction, involving the stimulation of PKC and MAP kinase as well as the increase in the concentration of Ca^{2+} for augmenting protein synthesis in cardiomyocytes and smooth muscle myocytes [247,248]. On the other hand, the activation of V_2 receptors, which are mainly located on the basolateral membrane in the renal medulla, leads to water retention in the body [248,249]. This antidiuretic hormone has also been shown to stimulate adenylyl cyclase, increase the intracellular concentration of cyclic AMP and activate protein kinase A for increasing the rate of insertion of water channel-containing vesicles into apical membrane [250]. Such an action of V_2 receptor activation increases water permeability [249] for increasing fluid accumulation in the body, which is known to produce the preload on the heart. Thus, vasopressin is considered to increase both the afterload and preload on the heart by activating the V_{1a} receptors and V_2 receptors, respectively. This hemodynamic overload on the hypertrophied heart would increase the ventricular wall tension and release endogenous Ang II and norepinephrine, which are known to promote the occurrence of oxidative stress and induce heart failure. Accordingly, it appears that the transition of vasopressin-induced cardiac hypertrophy to heart failure may also occur due to the development of oxidative stress as a consequence of both Ang II and norepinephrine released from endogenous RAS and sympathetic nerve endings in the heart. A schematic representation of events for the induction of cardiac hypertrophy and heart failure due to vasopressin is given in Figure 6.

It has been reported that the plasma levels of vasopressin are elevated during the development of heart failure [251–253]. While the activation of the V_{1a} receptors via vasopressin results in the development of vasoconstriction, hypertension, cardiac hypertrophy and heart failure, the activation of the V_2 receptors is associated with fluid retention, leading to the development of volume overload, venous congestion, edema and lung congestion [254–259]. Vasopressin not only causes water retention but also results in kidney dysfunction in heart failure patients. These abnormalities are associated with the occurrence of hyponatremia, which may limit the use of several agents such as diuretics for the management of heart failure [260–263]. Nonetheless, various therapies based on the antagonist effects of different agents on both the V_{1a} receptor and V_2 receptors have been

developed for the treatment of heart failure [197]. Since these vasopressin blockers improve cardiac function and reduce cardiac hypertrophy, it can be argued that vasopressin plays an important role in the pathogenesis of cardiac hypertrophy and heart failure.

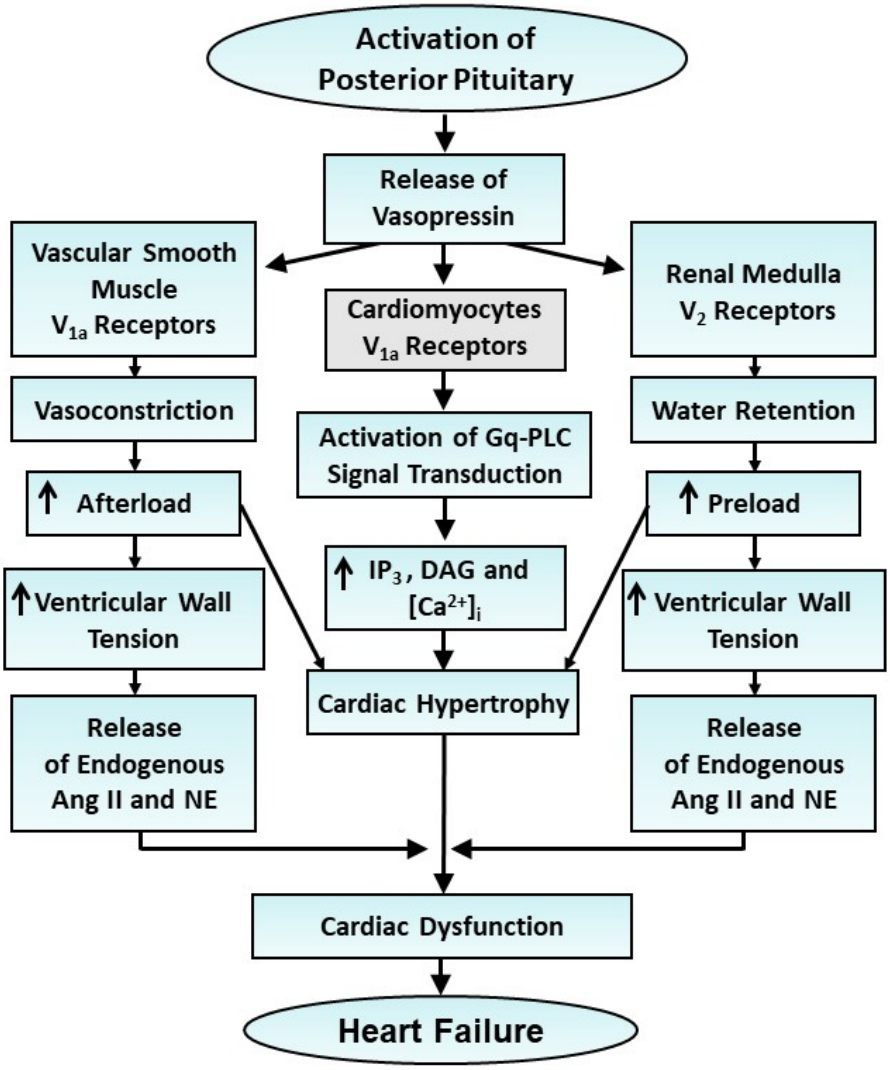

Figure 6. Role of the elevated levels of vasopressin in cardiac hypertrophy as well as vasoconstriction and water retention for the development of increased afterload and preload and subsequent cardiac dysfunction as well as heart failure.

7. Perspective and Concluding Remarks

Various cardiovascular diseases such as myocardial infarction, hypertension, diabetes, aortic stenosis and valvular regurgitation, as well as inflammatory and genetic cardiomyopathies, are known to be associated with elevated levels of plasma vasoactive hormones. Although it is generally claimed that different vasoactive hormones such as catecholamines, angiotensin II, vasopressin, serotonin, and endothelins are involved in the pathogenesis of heart failure, the exact mechanisms for their involvement in the development of cardiac dysfunction in various diseases are not fully understood. Since heart failure is mostly preceded by adaptive cardiac hypertrophy, it is not clear how these vasoactive hormones participate in the transition of adaptive cardiac hypertrophy to maladaptive hypertrophy and progression to heart failure. In this article, we have, therefore, updated the existing information and described the evidence that these vasoactive hormones, through acting on their respective receptors, stimulate different prohypertrophic signal transduction mechanisms in cardiomyocytes for the induction of cardiac hypertrophy. The activation of

receptors via different hormones has also been shown to stimulate sarcolemmal NOX2 for the production of oxyradicals and change the redox status of cardiomyocytes, which is considered to promote the hypertrophy process and the development of cardiac hypertrophy. In addition, these vasoactive hormones increase intraventricular pressure, ventricular wall tension and shear stress by inducing marked changes in the hemodynamic overload and inotropic effect on the myocardium. The vasoactive hormones also act on fibroblasts and promote the formation of collagen in the extracellular matrix as well as the development of apoptosis and replacement fibrosis for the occurrence of maladaptive cardiac hypertrophy by elevating the levels of proinflammatory cytokines such as IL-6 and TNF-α in cardiomyocytes. It is, thus, evident that initial events involved in the increase of cardiac muscle mass are associated with adaptive cardiac hypertrophy, whereas those dealing with the development of myocardial replacement fibrosis and the accumulation of collagen in the extracellular matrix are associated with maladaptive cardiac hypertrophy.

Although all vasoactive hormones are known to produce cardiac hypertrophy upon stimulating protein synthesis through their specific but complex receptor-mediated signal transduction mechanisms [31–40], the nature of proteins involved in the growth of cardiomyocytes, smooth muscle cells and fibroblasts seems to depend upon the type of hormonal stimulus as well as clinical stage and experimental models of cardiac remodeling and dysfunction. For example, YAP (yes-associated protein 1) has been demonstrated to activate the nuclear effector of the Hippo pathway by upregulating glucose transporter 1 (GLUT1), promoting glycolysis and inducing the accumulation of serine, aspartate and malate in physiological cardiac hypertrophy [264]. On the other hand, STING (stimulation of interferon gene) has been shown to induce pathological hypertrophy by upregulating inflammatory response and fibrosis upon increasing the expression of phospho-protein kinase RNA-like endoplasmic reticulum (ER) kinase and phospho-inositol-requiring kinase (all indices of ER stress) [265]. Furthermore, pathological cardiac hypertrophy was attenuated with HINT1 (histidine triad nucleotide-binding protein 1) by suppressing the expression of HOXA5 (homeobox A5) and inhibiting protein kinase Cβ type 1 and the MAP kinase/extracellular signal-regulated kinase/ yin yang 1 signal pathway [266]. From such complex observations, it can be appreciated that it is difficult to describe the exact nature of proteins involved in the development of cardiac hypertrophied and failing hearts. Particularly, it is pointed out that more than one vasoactive hormone is involved in initiating the hypertrophic process, which may not only exert their effects due to their own receptor-mediated signal transduction system but there may also occur cross talk between their receptor mechanisms. For example, Ang II has been shown to release catecholamines [267–269] and facilitate the formation of endothelin [270–272] and, thus, the influence of adrenoreceptor and endothelin receptor activations in the development of cardiac hypertrophy due to Ang II cannot be ruled out. Furthermore, Ang II is known to affect different isoforms of NOX, which may result in Na^+ retention by activating the epithelial Na^+-channels in the distal nephron, promoting Ca^{2+}-influx in smooth muscles for increasing blood pressure and inducing inflammation for producing cardiac fibrosis [273–275]. Such indirect effects of Ang II on NOX isoforms with respect to hemodynamic overload and inflammation can also be seen to affect the Ang II-induced pathological cardiac hypertrophy due to its receptor-mediated signal transduction. In addition, it should be mentioned that the pro-hypertrophic, proinflammatory and pro-fibrotic actions of AT_1R receptor activation through Ang II are antagonized via the activation of AT_2R as well as MasR activation via Ang II metabolite, Ang1–7 [101–104]. Thus, any imbalance between the pro- and anti-inflammatory mediators leads to the transition of adaptive cardiac hypertrophy to maladaptive cardiac hypertrophy.

It needs to be emphasized that the vasoactive hormones are not only involved in the genesis of cardiac hypertrophy but are also considered to participate in the progression of cardiac maladaptive hypertrophy to heart failure. For example, both catecholamines and serotonin have been reported to enter cardiomyocytes and produce oxyradicals during their oxidation by mitochondrial monoamine oxidase. On the other hand, angiotensin II

and endothelins generate oxyradicals by activating both sarcolemmal and mitochondrial NOX 4, whereas vasopressin may produce oxyradicals indirectly through mechanisms associated with the release of endogenous norepinephrine and angiotensin II due to increased intraventricular pressure and ventricular wall stress. The excessive generation of oxyradicals through diverse mechanisms such as the activation of xanthine oxidase and impaired electron transport in mitochondria can also be seen to develop oxidative stress in the hypertrophied heart. Furthermore, the depletion or depression in the antioxidant reserve in the hypertrophied heart via vasoactive hormones would favor the development of oxidative stress during the progression of heart failure. It should be mentioned that oxidative stress is known to activate metalloproteinases, produce the breakdown of collagen crosslinks and destabilize the extracellular matrix. In addition, oxidative stress has been reported to depress cardiac genes and activate calpain and other proteases either directly or indirectly through changes in the concentration of intracellular Ca^{2+}; these alterations will induce subcellular defects and Ca^{2+}-handling abnormalities in the hypertrophied heart. The increase in intracellular Ca^{2+} concentration in cardiomyocytes will also induce mitochondrial Ca^{2+}-overload due to the action of different vasoactive hormones. This change will not only impair the process of energy production but will also generate oxyradicals in the myocardium. Thus, oxidative stress may result in the development of cardiac dysfunction and play an important role in the progression of cardiac hypertrophy to heart failure due to vasoactive hormones. It is also pointed out that the failure of several classical treatments such as inhibitors of the RAS and β-adrenoreceptor blockers to improve the long-term outcome of heart failure is due to the fact that such interventions were developed to suppress the effects of a single vasoactive hormone. Accordingly, in view of the involvement of several vasoactive hormones in the development of heart failure, it is suggested that some special combination therapy using different receptor antagonists be designed to improve the treatment of this devastating health hazard.

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References

1. Roger, V.L.; Go, A.S.; Lloyd-Jones, D.M.; Benjamin, E.J.; Berry, J.D.; Borden, W.B.; Bravata, D.M.; Dai, S.; Ford, E.S.; Fox, C.S.; et al. Heart disease and stroke statistics—2012 update: A report from the American Heart Association. *Circulation* **2012**, *125*, e2–e220. [PubMed]
2. Heidenreich, P.A.; Albert, N.M.; Allen, L.A.; Bluemke, D.A.; Butler, J.; Fonarow, G.C.; Ikonomidis, J.S.; Khavjou, O.; Konstam, M.A.; Maddox, T.M.; et al. Forecasting the impact of heart failure in the United States: A policy statement from the American Heart Association. *Circ. Heart Fail.* **2013**, *6*, 606–619. [CrossRef] [PubMed]
3. Jessup, M.; Brozena, S. Heart failure. *N. Engl. J. Med.* **2003**, *348*, 2007–2018. [CrossRef] [PubMed]
4. Stanley, W.C.; Recchia, F.A.; Lopaschuk, G.D. Myocardial substrate metabolism in the normal and failing heart. *Physiol. Rev.* **2005**, *85*, 1093–1129. [CrossRef] [PubMed]
5. Felker, G.M.; Thompson, R.E.; Hare, J.M.; Hruban, R.H.; Clemetson, D.E.; Howard, D.L.; Baughman, K.L.; Kasper, E.K. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N. Engl. J. Med.* **2000**, *342*, 1077–1084. [CrossRef] [PubMed]
6. Janicki, J.S.; Brower, G.L.; Gardner, J.D.; Chancey, A.L.; Stewart, J.A., Jr. The dynamic interaction between matrix metalloproteinase activity and adverse myocardial remodeling. *Heart Fail. Rev.* **2004**, *9*, 33–42. [CrossRef]
7. Parmley, W.W. Pathophysiology and current therapy of congestive heart failure. *J. Am. Coll. Cardiol.* **1989**, *13*, 771–785. [CrossRef] [PubMed]

8. Levy, D.; Kenchaiah, S.; Larson, M.G.; Benjamin, E.J.; Kupka, M.J.; Ho, K.K.; Murabito, J.M.; Vasan, R.S. Long-term trends in the incidence of and survival with heart failure. *N. Engl. J. Med.* **2002**, *347*, 1397–1402. [CrossRef]
9. McMurray, J.J.; Stewart, S. Epidemiology, aetiology, and prognosis of heart failure. *Heart* **2000**, *83*, 596–602. [CrossRef] [PubMed]
10. Lloyd-Jones, D.M.; Larson, M.G.; Leip, E.P.; Beiser, A.; D'Agostino, R.B.; Kannel, W.B.; Murabito, J.M.; Vasan, R.S.; Benjamin, E.J.; Levy, D. Lifetime risk for developing congestive heart failure: The Framingham Heart Study. *Circulation* **2002**, *106*, 3068–3072. [CrossRef]
11. Olson, R.E. Myocardial metabolism in congestive heart failure. *J. Chronic Dis.* **1959**, *9*, 442–464. [CrossRef] [PubMed]
12. Dhalla, N.S.; Saini-Chohan, H.K.; Rodriguez-Leyva, D.; Elimban, V.; Dent, M.R.; Tappia, P.S. Subcellular remodelling may induce cardiac dysfunction in congestive heart failure. *Cardiovasc. Res.* **2009**, *81*, 429–438. [CrossRef] [PubMed]
13. Dhalla, N.S.; Das, P.K.; Sharma, G.P. Subcellular basis of cardiac contractile failure. *J. Mol. Cell. Cardiol.* **1978**, *10*, 363–385. [CrossRef] [PubMed]
14. Pfeffer, M.A.; Braunwald, E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. *Circulation* **1990**, *81*, 1161–1172. [CrossRef] [PubMed]
15. Cohn, J.N.; Ferrari, R.; Sharpe, N. Cardiac remodeling--concepts and clinical implications: A consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J. Am. Coll. Cardiol.* **2000**, *35*, 569–582. [CrossRef] [PubMed]
16. Packer, M. Neurohormonal interactions and adaptations in congestive heart failure. *Circulation* **1988**, *77*, 721–730. [CrossRef] [PubMed]
17. Dhalla, N.S.; Bhullar, S.K.; Adameova, A.; Mota, K.O.; de Vasconcelos, C.M.L. Status of β_1-adrenoceptor signal transduction system in cardiac hypertrophy and heart failure. *Rev. Cardiovasc. Med.* **2023**, *24*, 264. [CrossRef]
18. Dhalla, N.S.; Afzal, N.; Beamish, R.E.; Naimark, B.; Takeda, N.; Nagano, M. Pathophysiology of cardiac dysfunction in congestive heart failure. *Can. J. Cardiol.* **1993**, *9*, 873–887. [PubMed]
19. Opie, L.H.; Commerford, P.J.; Gersh, B.J.; Pfeffer, M.A. Controversies in ventricular remodelling. *Lancet* **2006**, *367*, 356–367. [CrossRef] [PubMed]
20. Mudd, J.O.; Kass, D.A. Tackling heart failure in the twenty-first century. *Nature* **2008**, *451*, 919–928. [CrossRef] [PubMed]
21. Dhalla, N.S.; Shao, Q.; Panagia, V. Remodeling of cardiac membranes during the development of congestive heart failure. *Heart Fail. Rev.* **1998**, *2*, 261–272. [CrossRef]
22. Machackova, J.; Barta, J.; Dhalla, N.S. Myofibrillar remodeling in cardiac hypertrophy, heart failure and cardiomyopathies. *Can. J. Cardiol.* **2006**, *22*, 953–968. [CrossRef] [PubMed]
23. Sabbah, H.N.; Goldstein, S. Ventricular remodelling: Consequences and therapy. *Eur. Heart J.* **1993**, *14* (Suppl. C), 24–29. [CrossRef] [PubMed]
24. Dhalla, N.S.; Dent, M.R.; Tappia, P.S.; Sethi, R.; Barta, J.; Goyal, R.K. Subcellular remodeling as a viable target for the treatment of congestive heart failure. *J. Cardiovasc. Pharmacol. Ther.* **2006**, *11*, 31–45. [CrossRef] [PubMed]
25. Burchfield, J.S.; Xie, M.; Hill, J.A. Pathological ventricular remodeling: Mechanisms: Part 1 of 2. *Circulation* **2013**, *128*, 388–400. [CrossRef] [PubMed]
26. Paulus, W.J.; Tschope, C. A novel paradigm for heart failure with preserved ejection fraction: Comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J. Am. Coll. Cardiol.* **2013**, *62*, 263–271. [CrossRef] [PubMed]
27. van Heerebeek, L.; Borbely, A.; Niessen, H.W.; Bronzwaer, J.G.; van der Velden, J.; Stienen, G.J.; Linke, W.A.; Laarman, G.J.; Paulus, W.J. Myocardial structure and function differ in systolic and diastolic heart failure. *Circulation* **2006**, *113*, 1966–1973. [CrossRef] [PubMed]
28. Selby, D.E.; Palmer, B.M.; LeWinter, M.M.; Meyer, M. Tachycardia-induced diastolic dysfunction and resting tone in myocardium from patients with a normal ejection fraction. *J. Am. Coll. Cardiol.* **2011**, *58*, 147–154. [CrossRef] [PubMed]
29. Shimizu, I.; Minamino, T.; Toko, H.; Okada, S.; Ikeda, H.; Yasuda, N.; Tateno, K.; Moriya, J.; Yokoyama, M.; Nojima, A.; et al. Excessive cardiac insulin signaling exacerbates systolic dysfunction induced by pressure overload in rodents. *J. Clin. Investig.* **2010**, *120*, 1506–1514. [CrossRef]
30. Borbely, A.; van der Velden, J.; Papp, Z.; Bronzwaer, J.G.; Edes, I.; Stienen, G.J.; Paulus, W.J. Cardiomyocyte stiffness in diastolic heart failure. *Circulation* **2005**, *111*, 774–781. [CrossRef]
31. Maillet, M.; van Berlo, J.H.; Molkentin, J.D. Molecular basis of physiological heart growth: Fundamental concepts and new players. *Nat. Rev. Mol. Cell Biol.* **2013**, *14*, 38–48. [CrossRef] [PubMed]
32. Lyon, R.C.; Zanella, F.; Omens, J.H.; Sheikh, F. Mechanotransduction in cardiac hypertrophy and failure. *Circ. Res.* **2015**, *116*, 1462–1476. [CrossRef] [PubMed]
33. Bernardo, B.C.; Weeks, K.L.; Pretorius, L.; McMullen, J.R. Molecular distinction between physiological and pathological cardiac hypertrophy: Experimental findings and therapeutic strategies. *Pharmacol. Ther.* **2010**, *128*, 191–227. [CrossRef] [PubMed]
34. Molkentin, J.D.; Dorn, G.W., 2nd. Cytoplasmic signaling pathways that regulate cardiac hypertrophy. *Annu. Rev. Physiol.* **2001**, *63*, 391–426. [CrossRef] [PubMed]
35. Shimizu, I.; Minamino, T. Physiological and pathological cardiac hypertrophy. *J. Mol. Cell. Cardiol.* **2016**, *97*, 245–262. [CrossRef] [PubMed]

36. Wikman-Coffelt, J.; Parmley, W.W.; Mason, D.T. The cardiac hypertrophy process: Analyses of factors determining pathological vs. physiological development. *Circ. Res.* **1979**, *45*, 697–707. [CrossRef] [PubMed]
37. Dhalla, N.S.; Heyliger, C.E.; Beamish, R.E.; Innes, I.R. Pathophysiological aspects of myocardial hypertrophy. *Can. J. Cardiol.* **1987**, *3*, 183–196. [PubMed]
38. Heineke, J.; Molkentin, J.D. Regulation of cardiac hypertrophy by intracellular signalling pathways. *Nat. Rev. Mol. Cell. Biol.* **2006**, *7*, 589–600. [CrossRef] [PubMed]
39. Sethi, R.; Saini, H.K.; Guo, X.; Wang, X.; Elimban, V.; Dhalla, N.S. Dependence of changes in beta-adrenoceptor signal transduction on type and stage of cardiac hypertrophy. *J. Appl. Physiol.* **2007**, *102*, 978–984. [CrossRef]
40. Oldfield, C.J.; Duhamel, T.A.; Dhalla, N.S. Mechanisms for the transition from physiological to pathological cardiac hypertrophy. *Can. J. Physiol. Pharmacol.* **2020**, *98*, 74–84. [CrossRef] [PubMed]
41. Parmley, W.W. Neuroendocrine changes in heart failure and their clinical relevance. *Clin. Cardiol.* **1995**, *18*, 440–445. [CrossRef] [PubMed]
42. Nicholls, D.P.; Onuoha, G.N.; McDowell, G.; Elborn, J.S.; Riley, M.S.; Nugent, A.M.; Steele, I.C.; Shaw, C.; Buchanan, K.D. Neuroendocrine changes in chronic cardiac failure. *Basic Res. Cardiol.* **1996**, *91* (Suppl. S1), 13–20. [CrossRef]
43. Rouleau, J.L. The neurohormonal hypothesis and the treatment of heart failure. *Can. J. Cardiol.* **1996**, *12*, 3F–8F.
44. Grossman, W. Cardiac hypertrophy: Useful adaptation or pathologic process? *Am. J. Med.* **1980**, *69*, 576–584. [CrossRef] [PubMed]
45. Weber, K.T.; Sun, Y.; Guarda, E. Structural remodeling in hypertensive heart disease and the role of hormones. *Hypertension* **1994**, *23 Pt 2*, 869–877. [CrossRef]
46. Packer, M. The neurohormonal hypothesis: A theory to explain the mechanism of disease progression in heart failure. *J. Am. Coll. Cardiol.* **1992**, *20*, 248–254. [CrossRef] [PubMed]
47. Francis, G.S.; Benedict, C.; Johnstone, D.E.; Kirlin, P.C.; Nicklas, J.; Liang, C.S.; Kubo, S.H.; Rudin-Toretsky, E.; Yusuf, S. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the studies. *Circulation* **1990**, *82*, 1724–1729. [CrossRef] [PubMed]
48. Delcayre, C.; Swynghedauw, B.; Molecular mechanisms of myocardial remodeling. The role of aldosterone. *J. Mol. Cell. Cardiol.* **2002**, *34*, 1577–1584. [CrossRef] [PubMed]
49. Weber, K.T.; Brilla, C.G. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. *Circulation* **1991**, *83*, 1849–1865. [CrossRef] [PubMed]
50. Kenessey, A.; Ojamaa, K. Thyroid hormone stimulates protein synthesis in the cardiomyocyte by activating the Akt-mTOR and p70S6K pathways. *J. Biol. Chem.* **2006**, *281*, 20666–20672. [CrossRef]
51. Pantos, C.; Mourouzis, I.; Cokkinos, D.V. New insights into the role of thyroid hormone in cardiac remodeling: Time to reconsider? *Heart Fail. Rev.* **2011**, *16*, 79–96. [CrossRef] [PubMed]
52. Vasan, R.S.; Sullivan, L.M.; D'Agostino, R.B.; Roubenoff, R.; Harris, T.; Sawyer, D.B.; Levy, D.; Wilson, P.W. Serum insulin-like growth factor I and risk for heart failure in elderly individuals without a previous myocardial infarction: The Framingham Heart Study. *Ann. Intern. Med.* **2003**, *139*, 642–648. [CrossRef] [PubMed]
53. Troncoso, R.; Ibarra, C.; Vicencio, J.M.; Jaimovich, E.; Lavandero, S. New insights into IGF-1 signaling in the heart. *Trends Endocrinol. Metab.* **2014**, *25*, 128–137. [CrossRef] [PubMed]
54. Parodi, E.M.; Kuhn, B. Signalling between microvascular endothelium and cardiomyocytes through neuregulin. *Cardiovasc. Res.* **2014**, *102*, 194–204. [CrossRef]
55. Ruetten, H.; Dimmeler, S.; Gehring, D.; Ihling, C.; Zeiher, A.M. Concentric left ventricular remodeling in endothelial nitric oxide synthase knockout mice by chronic pressure overload. *Cardiovasc. Res.* **2005**, *66*, 444–453. [CrossRef] [PubMed]
56. Yu, C.M.; Sanderson, J.E.; Shum, I.O.; Chan, S.; Yeung, L.Y.; Hung, Y.T.; Cockram, C.S.; Woo, K.S. Diastolic dysfunction and natriuretic peptides in systolic heart failure. Higher ANP and BNP levels are associated with the restrictive filling pattern. *Eur. Heart J.* **1996**, *17*, 1694–1702. [CrossRef] [PubMed]
57. Clerico, A.; Iervasi, G.; Del Chicca, M.G.; Emdin, M.; Maffei, S.; Nannipieri, M.; Sabatino, L.; Forini, F.; Manfredi, C.; Donato, L. Circulating levels of cardiac natriuretic peptides (ANP and BNP) measured by highly sensitive and specific immunoradiometric assays in normal subjects and in patients with different degrees of heart failure. *J. Endocrinol. Investig.* **1998**, *21*, 170–179. [CrossRef] [PubMed]
58. Siwik, D.A.; Pagano, P.J.; Colucci, W.S. Oxidative stress regulates collagen synthesis and matrix metalloproteinase activity in cardiac fibroblasts. *Am. J. Physiol. Cell Physiol.* **2001**, *280*, C53–C60. [CrossRef] [PubMed]
59. Sawyer, D.B.; Siwik, D.A.; Xiao, L.; Pimentel, D.R.; Singh, K.; Colucci, W.S. Role of oxidative stress in myocardial hypertrophy and failure. *J. Mol. Cell. Cardiol.* **2002**, *34*, 379–388. [CrossRef] [PubMed]
60. Keith, M.; Geranmayegan, A.; Sole, M.J.; Kurian, R.; Robinson, A.; Omran, A.S.; Jeejeebhoy, K.N. Increased oxidative stress in patients with congestive heart failure. *J. Am. Coll. Cardiol.* **1998**, *31*, 1352–1356. [CrossRef]
61. Dhalla, N.S.; Elmoselhi, A.B.; Hata, T.; Makino, N. Status of myocardial antioxidants in ischemia-reperfusion injury. *Cardiovasc. Res.* **2000**, *47*, 446–456. [CrossRef] [PubMed]
62. Dhalla, N.S.; Temsah, R.M.; Netticadan, T. Role of oxidative stress in cardiovascular diseases. *J. Hypertens.* **2000**, *18*, 655–673. [CrossRef] [PubMed]
63. Dhalla, N.S.; Saini, H.K.; Tappia, P.S.; Sethi, R.; Mengi, S.A.; Gupta, S.K. Potential role and mechanisms of subcellular remodeling in cardiac dysfunction due to ischemic heart disease. *J. Cardiovasc. Med.* **2007**, *8*, 238–250. [CrossRef] [PubMed]

64. Molkentin, J.D.; Lu, J.R.; Antos, C.L.; Markham, B.; Richardson, J.; Robbins, J.; Grant, S.R.; Olson, E.N. A calcineurin-dependent transcriptional pathway for cardiac hypertrophy. *Cell* **1998**, *93*, 215–228. [CrossRef] [PubMed]
65. Backs, J.; Backs, T.; Neef, S.; Kreusser, M.M.; Lehmann, L.H.; Patrick, D.M.; Grueter, C.E.; Qi, X.; Richardson, J.A.; Hill, J.A.; et al. The delta isoform of CaM kinase II is required for pathological cardiac hypertrophy and remodeling after pressure overload. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 2342–2347. [CrossRef] [PubMed]
66. Rona, G. Catecholamine cardiotoxicity. *J. Mol. Cell. Cardiol.* **1985**, *17*, 291–306. [CrossRef] [PubMed]
67. Adameova, A.; Abdellatif, Y.; Dhalla, N.S. Role of the excessive amounts of circulating catecholamines and glucocorticoids in stress-induced heart disease. *Can. J. Physiol. Pharmacol.* **2009**, *87*, 493–514. [CrossRef] [PubMed]
68. Bohm, M. Alterations of β-adrenoceptor-G-protein-regulated adenylyl cyclase in heart failure. *Mol. Cell. Biochem.* **1995**, *147*, 147–160. [CrossRef] [PubMed]
69. Bristow, M.R.; Feldman, A.M. Changes in the receptor-G protein-adenylyl cyclase system in heart failure from various types of heart muscle disease. *Basic. Res. Cardiol.* **1992**, *87*, 15–35. [PubMed]
70. Stiles, G.L.; Caron, M.G.; Lefkowitz, R.J. β-adrenergic receptors: Biochemical mechanisms of physiological regulation. *Physiol. Rev.* **1984**, *64*, 661–743. [CrossRef] [PubMed]
71. Dhalla, N.S.; Wang, X.; Sethi, R.; Das, P.K.; Beamish, R.E. β-adrenergic linked signal transduction mechanisms in failing hearts. *Heart Fail. Rev.* **1997**, *2*, 55–65. [CrossRef]
72. Panagia, V.; Pierce, G.N.; Dhalla, K.S.; Ganguly, P.K.; Beamish, R.E.; Dhalla, N.S. Adaptive changes in subcellular calcium transport during catecholamine-induced cardiomyopathy. *J. Mol. Cell. Cardiol.* **1985**, *17*, 411–420. [CrossRef] [PubMed]
73. Kallfelt, B.J.; Hjalmarson, A.C.; Isaksson, O.G. In vitro effects of catecholamines on protein synthesis in perfused rat heart. *J. Mol. Cell. Cardiol.* **1976**, *8*, 787–802. [CrossRef] [PubMed]
74. Singal, T.; Dhalla, N.S.; Tappia, P.S. Regulation of c-Fos and c-Jun gene expression by phospholipase C in adult cardiomyocytes. *Mol. Cell Biochem.* **2009**, *327*, 229–239. [CrossRef] [PubMed]
75. Takeo, S.; Elmoselhi, A.B.; Goel, R.; Sentex, E.; Wang, J.; Dhalla, N.S. Attenuation of changes in sarcoplasmic reticular and gene expression in cardiac hypertrophy by propranolol and verapamil. *Mol. Cell Biochem.* **2000**, *213*, 111–118. [CrossRef] [PubMed]
76. Rockman, H.A.; Koch, W.J.; Lefkowitz, R.J. Seven-transmembrane-spanning receptors and heart function. *Nature* **2002**, *415*, 206–212. [CrossRef] [PubMed]
77. Woodcock, E.A.; Du, X.J.; Reichelt, M.E.; Graham, R.M. Cardiac α1-adrenergic drive in pathological remodelling. *Cardiovasc. Res.* **2008**, *77*, 452–462. [CrossRef] [PubMed]
78. Rhee, S.G. Regulation of phosphoinositide-specific phospholipase C. *Annu. Rev. Biochem.* **2001**, *70*, 281–312. [CrossRef]
79. Kawaguchi, H.; Sano, H.; Iizuka, K.; Okada, H.; Kudo, T.; Kageyama, K. Phosphatidylinositol metabolism in hypertrophic rat heart. *Circ. Res.* **1993**, *72*, 966–972. [CrossRef] [PubMed]
80. Sakata, Y. Tissue factors contributing to cardiac hypertrophy in cardiomyopathic hamsters (BIO14.6): Involvement of transforming growth factor-β1 and tissue renin-angiotensin system in the progression of cardiac hypertrophy. *Hokkaido Igaku Zasshi* **1993**, *68*, 18–28. [PubMed]
81. Dent, M.R.; Dhalla, N.S.; Tappia, P.S. Phospholipase C gene expression, protein content and activities in cardiac hypertrophy and heart failure due to volume overload. *Am. J. Physiol.* **2004**, *282*, H719–H727. [CrossRef] [PubMed]
82. Singal, T.; Dhalla, N.S.; Tappia, P.S. Phospholipase C may be involved in norepinephrine-induced cardiac hypertrophy. *Biochem. Biophys. Res. Commun.* **2004**, *320*, 1015–1019. [CrossRef]
83. Dhalla, N.S.; Xu, Y.J.; Sheu, S.S.; Tappia, P.S.; Panagia, V. Phosphatidic acid: A potential signal transducer for cardiac hypertrophy. *J. Mol. Cell. Cardiol.* **1997**, *29*, 2865–2871. [CrossRef] [PubMed]
84. Xu, Y.J.; Yau, L.; Yu, L.P.; Elimban, V.; Zahradka, P.; Dhalla, N.S. Stimulation of protein synthesis by phosphatidic acid in rat cardiomyocytes. *Biochem. Pharmacol.* **1996**, *52*, 1735–1740. [CrossRef] [PubMed]
85. Corder, D.W.; Heyliger, C.E.; Beamish, R.E.; Dhalla, N.S. Defect in the adrenergic receptor-adenylate cyclase system during development of catecholamine-induced cardiomyopathy. *Am. Heart J.* **1984**, *107*, 537–542. [CrossRef]
86. Tappia, P.S.; Hata, T.; Hozaima, L.; Sandhu, M.S.; Panagia, V.; Dhalla, N.S. Role of oxidative stress in catecholamine-induced changes in cardiac sarcolemmal Ca^{2+} transport. *Arch. Biochem. Biophys.* **2001**, *387*, 85–92. [CrossRef] [PubMed]
87. Dhalla, N.S.; Adameova, A.; Kaur, M. Role of catecholamine oxidation in sudden cardiac death. *Fundam. Clin. Pharmacol.* **2010**, *24*, 539–546. [CrossRef] [PubMed]
88. Dhalla, N.S. Formation of aminochrome leads to cardiac dysfunction and sudden cardiac death. *Circ. Res.* **2018**, *123*, 409–411. [CrossRef] [PubMed]
89. Mialet-Perez, J.; Santin, J.; Parini, A. Monoamine oxidase-A, serotonin and norepinephrine: Synergistic players in cardiac physiology and pathology. *J. Neural Transm.* **2018**, *125*, 1627–1634. [CrossRef] [PubMed]
90. Sethi, R.; Adameova, A.; Dhalla, K.S.; Khan, M.; Elimban, V.; Dhalla, N.S. Modification of epinephrine-induced arrhythmias by N-acetyl-L-cysteine and vitamin E. *J. Cardiovasc. Pharmacol. Ther.* **2009**, *14*, 134–142. [CrossRef] [PubMed]
91. Shah, A.K.; Dhalla, N.S. Effectiveness of some vitamins in the prevention of cardiovascular disease: A narrative review. *Front. Physiol.* **2021**, *12*, 729255. [CrossRef] [PubMed]
92. Adameova, A.; Tappia, P.S.; Hatala, R.; Dhalla, N.S. Potential of sulphur-containing amino acids in the prevention of catecholamine-induced arrhythmias. *Curr. Med. Chem.* **2018**, *25*, 346–354. [CrossRef] [PubMed]

93. Babick, A.; Elimban, V.; Dhalla, N.S. Reversal of cardiac remodelling and subcellular defects by prazosin in heart failure due to myocardial infarction. *J. Clin. Exp. Cardiol.* **2012**, *S5*, 1–7.
94. Babick, A.; Elimban, V.; Zieroth, S.; Dhalla, N.S. Reversal of cardiac dysfunction and subcellular alterations by metoprolol in heart failure due to myocardial infarction. *J. Cell. Physiol.* **2013**, *228*, 2063–2070. [CrossRef] [PubMed]
95. Rehsia, N.S.; Dhalla, N.S. Mechanisms of the beneficial effects of β-adrenoceptor antagonists in congestive heart failure. *Exp. Clin. Cardiol.* **2010**, *15*, e86–e95.
96. Peach, M.J. Renin-angiotensin system: Biochemistry and mechanisms of action. *Physiol. Rev.* **1977**, *57*, 313–370. [CrossRef] [PubMed]
97. Wollert, K.C.; Drexler, H. The renin-angiotensin system and experimental heart failure. *Cardiovasc. Res.* **1999**, *43*, 838–849. [CrossRef] [PubMed]
98. Bader, M. Role of the local renin-angiotensin system in cardiac damage: A minireview focussing on transgenic animal models. *J. Mol. Cell. Cardiol.* **2002**, *34*, 1455–1462. [CrossRef] [PubMed]
99. Miura, S.; Saku, K.; Karnik, S.S. Molecular analysis of the structure and function of the angiotensin II type 1 receptor. *Hypertens. Res.* **2003**, *26*, 937–943. [CrossRef] [PubMed]
100. Schlüter, K.D.; Wenzel, S. Angiotensin II: A hormone involved in and contributing to pro-hypertrophic cardiac networks and target of anti-hypertrophic cross-talks. *Pharmacol. Ther.* **2008**, *119*, 311–325. [CrossRef] [PubMed]
101. Bhullar, S.K.; Shah, A.K.; Dhalla, N.S. Role of angiotensin II in the development of subcellular remodeling in heart failure. *Explor. Med.* **2021**, *2*, 352–371. [CrossRef]
102. Bhullar, S.K.; Dhalla, N.S. Angiotensin II-induced signal transduction mechanisms for cardiac hypertrophy. *Cells* **2022**, *11*, 3336. [CrossRef] [PubMed]
103. Bhullar, S.K.; Shah, A.K.; Dhalla, N.S. Mechanisms for the development of heart failure and improvement of cardiac function by angiotensin-converting enzyme inhibitors. *Scr. Med.* **2022**, *53*, 51–76. [CrossRef]
104. Bhullar, S.K.; Dhalla, N.S. Adaptive and maladaptive roles of different angiotensin receptors in the development of cardiac hypertrophy and heart failure. *Can. J. Physiol. Pharmacol.* **2024**, *102*, 86–104. [CrossRef] [PubMed]
105. Touyz, R.M.; Schiffrin, E.L. Signal transduction mechanisms mediating the physiological and pathophysiological actions of angiotensin II in vascular smooth muscle cells. *Pharmacol. Rev.* **2000**, *52*, 639–672. [PubMed]
106. Kim, S.; Iwao, H. Molecular and cellular mechanisms of angiotensin II-mediated cardiovascular and renal diseases. *Pharmacol. Rev.* **2000**, *52*, 11–34.
107. Touyz, R.M.; Berry, C. Recent advances in angiotensin II signaling. *Braz. J. Med. Biol. Res.* **2002**, *35*, 1001–1015. [CrossRef] [PubMed]
108. Mehta, P.K.; Griendling, K.K. Angiotensin II cell signaling: Physiological and pathological effects in the cardiovascular system. *Am. J. Physiol. Cell Physiol.* **2007**, *292*, C82–C97. [CrossRef] [PubMed]
109. Forrester, S.J.; Booz, G.W.; Sigmund, C.D.; Coffman, T.M.; Kawai, T.; Rizzo, V.; Scalia, R.; Eguchi, S. Angiotensin II signal transduction: An update on mechanisms of physiology and pathophysiology. *Physiol. Rev.* **2018**, *98*, 1627–1738. [CrossRef] [PubMed]
110. Verma, K.; Pant, M.; Paliwal, S.; Dwivedi, J.; Sharma, S. An insight on multicentric signaling of angiotensin II in cardiovascular system: A recent update. *Front. Pharmacol.* **2021**, *12*, 734917. [CrossRef] [PubMed]
111. Miyata, S.; Haneda, T. Hypertrophic growth of cultured neonatal rat heart cells mediated by type 1 angiotensin II receptor. *Am. J. Physiol.* **1994**, *266*, H2443–H2451. [CrossRef] [PubMed]
112. Dostal, D.E.; Baker, K.M. Angiotensin II stimulation of left ventricular hypertrophy in adult rat heart. Mediation by the AT1 receptor. *Am. J. Hypertens.* **1992**, *5*, 276–280. [PubMed]
113. Matsubara, H. Pathophysiological role of angiotensin II type 2 receptor in cardiovascular and renal diseases. *Circ. Res.* **1998**, *83*, 1182–1191. [CrossRef] [PubMed]
114. Li, Y.; Li, X.H.; Yuan, H. Angiotensin II type-2 receptor-specific effects on the cardiovascular system. *Cardiovasc. Diagn. Ther.* **2012**, *2*, 56–62. [PubMed]
115. Simões e Silva, A.C.; Silveira, K.D.; Ferreira, A.J.; Teixeira, M.M. ACE2, angiotensin-(1-7) and Mas receptor axis in inflammation and fibrosis. *Br. J. Pharmacol.* **2013**, *169*, 477–492. [CrossRef] [PubMed]
116. Mercure, C.; Yogi, A.; Callera, G.E.; Aranha, A.B.; Bader, M.; Ferreira, A.J.; Santos, R.A.S.; Walther, T.; Touyz, R.M.; Reudelhuber, T.L. Angiotensin(1-7) blunts hypertensive cardiac remodeling by a direct effect on the heart. *Circ. Res.* **2008**, *103*, 1319–1326. [CrossRef] [PubMed]
117. Patel, V.B.; Zhong, J.C.; Grant, M.B.; Oudit, G.Y. Role of the ACE2/angiotensin 1-7 axis of the renin-angiotensin system in heart failure. *Circ. Res.* **2016**, *118*, 1313–1326. [CrossRef] [PubMed]
118. Santos, R.A.S.; Sampaio, W.O.; Alzamora, A.C.; Motta-Santos, D.; Alenina, N.; Bader, M.; Campagnole-Santos, M.J. The ACE2/angiotensin-(1-7)/MAS axis of the renin-angiotensin system: Focus on angiotensin-(1-7). *Physiol. Rev.* **2018**, *98*, 505–553. [CrossRef] [PubMed]
119. Donoghue, M.; Hsieh, F.; Baronas, E.; Godbout, K.; Gosselin, M.; Stagliano, N.; Donovan, M.; Woolf, B.; Robison, K.; Jeyaseelan, R.; et al. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Circ. Res.* **2000**, *87*, E1–E9. [CrossRef] [PubMed]

120. Santos, R.A.; Simoes e Silva, A.C.; Maric, C.; Silva, D.M.; Machado, R.P.; de Buhr, I.; Heringer-Walther, S.; Pinheiro, S.V.B.; Lopes, M.T.; Bader, M.; et al. Angiotensin-(1-7) is an endogenous ligand for the G protein-coupled receptor Mas. *Proc Natl. Acad. Sci. USA* **2003**, *100*, 8258–8263. [CrossRef]
121. Kriszta, G.; Kriszta, Z.; Váncsa, S.; Hegyi, P.J.; Frim, L.; Erőss, B.; Hegyi, P.; Pethő, G.; Pinter, E. Effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on angiotensin-converting enzyme 2 levels: A comprehensive analysis based on animal studies. *Front. Pharmacol.* **2021**, *12*, 619524. [CrossRef] [PubMed]
122. Ago, T.; Sadoshima, J. From contractile enhancement to pathological hypertrophy: Angiotenin II-induced Nox2 -mediated reactive oxygen species. *J. Am. Coll. Cardiol.* **2015**, *66*, 273–277. [CrossRef] [PubMed]
123. Hingtgen, S.D.; Tian, X.; Yang, J.; Dunlay, S.M.; Peek, A.S.; Wu, Y.; Sharma, R.V.; Engelhardt, J.F.; Davisson, R.L.; Atef, M.E.; et al. Nox2-containing NADPH oxidase and Akt activation play a key role in angiotensin II-induced cardiomyocyte hypertrophy. *Physiol. Genom.* **2006**, *26*, 180–191. [CrossRef] [PubMed]
124. Looi, Y.H.; Grieve, D.J.; Siva, A.; Walker, S.J.; Anilkumar, N.; Cave, A.C.; Marber, M.; Monaghan, M.J.; Shah, A.M. Involvement of Nox2 NADPH oxidase in adverse cardiac remodeling after myocardial infarction. *Hypertension* **2008**, *51*, 319–325. [CrossRef] [PubMed]
125. De Mello, W.C. Local renin angiotensin aldosterone systems and cardiovascular diseases. *Med. Clin. N. Am.* **2017**, *101*, 117–127. [CrossRef] [PubMed]
126. Tarzami, S.T. Chemokines and inflammation in heart disease: Adaptive or maladaptive? *Int. J. Clin. Exp. Med.* **2011**, *4*, 74–80. [PubMed]
127. Zhang, H.; Dhalla, N.S. The role of pro-Inflammatory cytokines in the pathogenesis of cardiovascular disease. *Int. J. Mol. Sci.* **2024**, *25*, 1082. [CrossRef] [PubMed]
128. Burgoyne, J.R.; Mongue-Din, H.; Eaton, P.; Shah, A.M. Redox signaling in cardiac physiology and pathology. *Circ. Res.* **2012**, *111*, 1091–1106. [CrossRef] [PubMed]
129. Maejima, Y.; Kuroda, J.; Matsushima, S.; Ago, T.; Sadoshima, J. Regulation of myocardial growth and death by NADPH oxidase. *J. Mol. Cell. Cardiol.* **2011**, *50*, 408–416. [CrossRef] [PubMed]
130. Murdoch, C.E.; Zhang, M.; Cave, A.C.; Shah, A.M. NADPH oxidase-dependent redox signalling in cardiac hypertrophy, remodelling and failure. *Cardiovasc. Res.* **2006**, *71*, 208–215. [CrossRef] [PubMed]
131. Sirker, A.; Zhang, M.; Shah, A.M. NADPH oxidases in cardiovascular disease: Insights from in vivo models and clinical studies. *Basic Res. Cardiol.* **2011**, *106*, 735–747. [CrossRef] [PubMed]
132. Zhang, Y.; Murugesan, P.; Huang, K.; Cai, H. NADPH oxidases and oxidase crosstalk in cardiovascular diseases: Novel therapeutic targets. *Nat. Rev. Cardiol.* **2020**, *17*, 170–194. [CrossRef] [PubMed]
133. Sadoshima Lassègue, B.; San Martín, A.; Griendling, K.K. Biochemistry, physiology, and pathophysiology of NADPH oxidases in the cardiovascular system. *Circ. Res.* **2012**, *110*, 1364–1390. [CrossRef] [PubMed]
134. Shah, A.K.; Bhullar, S.K.; Elimban, V.; Dhalla, N.S. Oxidative stress as a mechanism for functional alterations in cardiac hypertrophy and heart failure. *Antioxidants* **2021**, *10*, 931. [CrossRef] [PubMed]
135. Vanhoutte, P.M. Serotonin, hypertension and vascular disease. *Neth. J. Med.* **1991**, *38*, 35–42. [PubMed]
136. Parikh, V.; Singh, M. Resident cardiac mast cells and the cardioprotective effect of ischemic preconditioning in isolated rat heart. *J. Cardiovasc. Pharmacol.* **1997**, *30*, 149–156. [CrossRef]
137. Villalón, C.M.; Centurión, D. Cardiovascular responses produced by 5-hydroxytriptamine: A pharmacological update on the receptors/mechanisms involved and therapeutic implications. *Naunyn Schmiedebergs Arch. Pharmacol.* **2007**, *376*, 45–63. [CrossRef] [PubMed]
138. Jaffré, F.; Bonnin, P.; Callebert, J.; Debbabi, H.; Setola, V.; Doly, S.; Monassier, L.; Mettauer, B.; Blaxall, B.C.; Launay, J.-M.; et al. Serotonin and angiotensin receptors in cardiac fibroblasts coregulate adrenergic-dependent cardiac hypertrophy. *Circ. Res.* **2009**, *104*, 113–123. [CrossRef] [PubMed]
139. Sharma, S.K.; Del Rizzo, D.F.; Zahradka, P.; Bhangu, S.K.; Werner, J.P.; Kumamoto, H.; Takeda, N.; Dhalla, N.S. Sarpogrelate inhibits serotonin-induced proliferation of porcine coronary artery smooth muscle cells: Implications for long-term graft patency. *Ann. Thorac. Surg.* **2001**, *71*, 1856–1864. [CrossRef] [PubMed]
140. Saini, H.K.; Takeda, N.; Goyal, R.K.; Kumamoto, H.; Arneja, A.S.; Dhalla, N.S. Therapeutic potentials of sarpogrelate in cardiovascular disease. *Cardiovasc. Drug Rev.* **2004**, *22*, 27–54. [CrossRef] [PubMed]
141. Nagatomo, T.; Rashid, M.; Abul Muntasir, H.; Komiyama, T. Functions of 5-HT2A receptor and its antagonists in the cardiovascular system. *Pharmacol. Ther.* **2004**, *104*, 59–81. [CrossRef] [PubMed]
142. Barnes, N.M.; Sharp, T. A review of central 5-HT receptors and their function. *Neuropharmacology* **1999**, *38*, 1083–1152. [CrossRef] [PubMed]
143. Saxena, P.R. Cardiovascular effects from stimulation of 5-hydroxytryptamine receptors. *Fundam. Clin. Pharmacol.* **1989**, *3*, 245–265. [CrossRef] [PubMed]
144. Nilsson, T.; Longmore, J.; Shaw, D.; Pantev, E.; Bard, J.A.; Branchek, T.; Edvinsson, L. Characterisation of 5-HT receptors in human coronary arteries by molecular and pharmacological techniques. *Eur. J. Pharmacol.* **1999**, *372*, 49–56. [CrossRef] [PubMed]
145. Fan, G.; Jiang, Y.P.; Lu, Z.; Martin, D.W.; Kelly, D.J.; Zuckerman, J.M.; Ballou, L.M.; Cohen, I.S.; Lin, R.Z. A transgenic mouse model of heart failure using inducible Galpha q. *J. Biol. Chem.* **2005**, *280*, 40337–40346. [CrossRef] [PubMed]

146. Saini, H.K.; Sharma, S.K.; Zahradka, P.; Kumamoto, H.; Takeda, N.; Dhalla, N.S. Attenuation of the serotonin-induced increase in intracellular calcium in rat aortic smooth muscle cells by sarpogrelate. *Can. J. Physiol. Pharmacol.* **2003**, *81*, 1056–1063. [CrossRef] [PubMed]
147. Hamamori, Y.; Yokoyama, M.; Yamada, M.; Akita, H.; Goshima, K.; Fukuzaki, H. 5-Hydroxytryptamine induces phospholipase C-mediated hydrolysis of phosphoinositides through 5-hydroxytryptamine-2 receptors in cultured fetal mouse ventricular myocytes. *Circ. Res.* **1990**, *66*, 1474–1483. [CrossRef]
148. Nosek, T.M.; Williams, M.F.; Zeigler, S.T.; Godt, R.E. Inositol trisphosphate enhances calcium release in skinned cardiac and skeletal muscle. *Am. J. Physiol.* **1986**, *250 Pt 1*, C807–C811. [CrossRef]
149. Shimizu, Y.; Minatoguchi, S.; Hashimoto, K.; Uno, Y.; Arai, M.; Wang, N.; Chen, X.; Lu, C.; Takemura, G.; Shimomura, M.; et al. The role of serotonin in ischemic cellular damage and the infarct size-reducing effect of sarpogrelate, a 5-hydroxytryptamine-2 receptor blocker, in rabbit hearts. *J. Am. Coll. Cardiol.* **2002**, *40*, 1347–1355. [CrossRef] [PubMed]
150. Selim, A.M.; Sarswat, N.; Kelesidis, I.; Iqbal, M.; Chandra, R.; Zolty, R. Plasma serotonin in heart failure: Possible marker and potential treatment target. *Heart Lung Circ.* **2017**, *26*, 442–449. [CrossRef] [PubMed]
151. Vikenes, K.; Farstad, M.; Nordrehaug, J.E. Serotonin is associated with coronary artery disease and cardiac events. *Circulation* **1999**, *100*, 483–489. [CrossRef] [PubMed]
152. Esler, M.; Alvarenga, M.; Barton, D.; Jennings, G.; Kaye, D.; Guo, L.; Schwarz, R.; Lambert, G. Measurement of noradrenaline and serotonin metabolites with internal jugular vein sampling: An indicator of brain monoamine turnover in depressive illness and panic disorder. *Front. Psychiatry* **2022**, *13*, 818012. [CrossRef] [PubMed]
153. van den Berg, E.K.; Schmitz, J.M.; Benedict, C.R.; Malloy, C.R.; Willerson, J.T.; Dehmer, G.J. Transcardiac serotonin concentration is increased in selected patients with limiting angina and complex coronary lesion morphology. *Circulation* **1989**, *79*, 116–124. [CrossRef] [PubMed]
154. Hara, K.; Hirowatari, Y.; Yoshika, M.; Komiyama, Y.; Tsuka, Y.; Takahashi, H. The ratio of plasma to whole-blood serotonin may be a novel marker of atherosclerotic cardiovascular disease. *J. Lab. Clin. Med.* **2004**, *144*, 31–37. [CrossRef] [PubMed]
155. Barta, J.; Sanganalmath, S.K.; Kumamoto, H.; Takeda, N.; Edes, I.; Dhalla, N.S. Antiplatelet agents sarpogrelate and cilostazol affect experimentally-induced ventricular arrhythmias and mortality. *Cardiovasc. Toxicol.* **2008**, *8*, 127–135. [CrossRef] [PubMed]
156. Brasil, D.; Temsah, R.M.; Kumar, K.; Kumamoto, H.; Takeda, N.; Dhalla, N.S. Blockade of 5-HT(2A) receptors by sarpogrelate protects the heart against myocardial infarction in rats. *J. Cardiovasc. Pharmacol. Ther.* **2002**, *7*, 53–59. [CrossRef] [PubMed]
157. Bender, A.M.; Parr, L.C.; Livingston, W.B.; Lindsley, C.W.; Merryman, W.D. 2B Determined: The future of the serotonin receptor 2B in drug discovery. *J. Med. Chem.* **2023**, *66*, 11027–11039. [CrossRef] [PubMed]
158. Shen, L.; Shen, J.; Pu, J.; He, B. Aspirin attenuates pulmonary arterial hypertension in rats by reducing plasma 5-hydroxytryptamine levels. *Cell. Biochem. Biophys.* **2011**, *61*, 23–31. [CrossRef] [PubMed]
159. Virk, H.U.H.; Escobar, J.; Rodriguez, M.; Bates, E.R.; Khalid, U.; Jneid, H.; Birnbaum, Y.; Levine, G.N.; Smith, S.C.; Krittanawong, C. Dual antiplatelet therapy: A concise review for clinicians. *Life* **2023**, *13*, 1580. [CrossRef] [PubMed]
160. Zhao, Y.; Zhou, P.; Gao, W.; Zhong, H.; Chen, Y.; Chen, W.; Waresi, M.; Xie, K.; Shi, H.; Gong, H.; et al. Cilostazol combined with $P2Y_{12}$ receptor inhibitors: A substitute antiplatelet regimen for aspirin-intolerant patients undergoing percutaneous coronary stent implantation. *Clin. Cardiol.* **2022**, *45*, 189–197. [CrossRef] [PubMed]
161. Yang, S.; Kang, J.; Park, K.W.; Hur, S.H.; Lee, N.H.; Hwang, D.; Yang, H.M.; Ahn, H.S.; Cha, K.S.; Jo, S.H.; et al. Comparison of antiplatelet monotherapies after percutaneous coronary intervention according to clinical, ischemic, and bleeding risks. *J. Am. Coll. Cardiol.* **2023**, *82*, 1565–1578. [CrossRef] [PubMed]
162. Linden, K.; Mailey, J.; Kearney, A.; Menown, I.B.A. Advances in clinical cardiology 2019: A summary of key clinical trials. *Adv. Ther.* **2020**, *37*, 2620–2645. [CrossRef] [PubMed]
163. Sikharulidze, I.; Chelidze, K.; Mamatsashvili, I. Cardiovascular event assessment in patients with nonobstructive coronary artery disease undergoing dual antiplatelet treatment. *Georgian Med. News* **2020**, *309*, 43–46.
164. Koh, Y.; Kwok, C.; Voskoboinik, A.; Kalman, J.M.; Wong, M. Serotonin antidepressants and atrial fibrillation burden from cardiac implantable electronic devices. *J. Arrhythm.* **2023**, *39*, 876–883. [CrossRef] [PubMed]
165. Majid, P.A.; Morris, W.M.; Sole, M.J. Hemodynamic and neurohumoral effects of ketanserin, a 5-HT2 receptor antagonist in patients with congestive heart failure. *Can. J. Cardiol.* **1987**, *3*, 70–74. [PubMed]
166. Grobecker, H.; Gessler, I.; Delius, W.; Dominiak, P.; Kees, F. Effect of ketanserin on hemodynamics, plasma-catecholamine concentrations, and serotonin uptake by platelets in volunteers and patients with congestive heart failure. *J. Cardiovasc. Pharmacol.* **1985**, *7*, S102–S104. [CrossRef] [PubMed]
167. Sanganalmath, S.K.; Barta, J.; Takeda, N.; Kumamoto, H.; Dhalla, N.S. Antiplatelet therapy mitigates cardiac remodeling and dysfunction in congestive heart failure due to myocardial infarction. *Can. J. Physiol. Pharmacol.* **2008**, *86*, 180–189. [CrossRef]
168. Sanganalmath, S.K.; Babick, A.P.; Barta, J.; Kumamoto, H.; Takeda, N.; Dhalla, N.S. Antiplatelet therapy attenuates subcellular remodelling in congestive heart failure. *J. Cell. Mol. Med.* **2008**, *12*, 1728–1738. [CrossRef] [PubMed]
169. Shimizu, K.; Sunagawa, Y.; Funamoto, M.; Honda, H.; Katanasaka, Y.; Murai, N.; Kawase, Y.; Hirako, Y.; Katagiri, T.; Katagiri, H.; et al. The selective serotonin 2A receptor antagonist sarpogrelate prevents cardiac hypertrophy and systolic dysfunction via inhibition of the ERK1/2-GATA4 signaling pathway. *Pharmaceuticals* **2021**, *14*, 1268. [CrossRef] [PubMed]
170. Nemecek, G.M.; Coughlin, S.R.; Handley, D.A.; Moskowitz, M.A. Stimulation of aortic smooth muscle cell mitogenesis by serotonin. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 674–678. [CrossRef]

171. Seuwen, K.; Pouysségur, J. Serotonin as a growth factor. *Biochem. Pharmacol.* **1990**, *39*, 985–990. [CrossRef] [PubMed]
172. Fozard, J.R.; Mwaluko, G.M. Mechanism of the indirect sympathomimetic effect of 5-hydroxytrypt-amine on the isolated heart of the rabbit. *Br. J. Pharmacol.* **1976**, *57*, 115–125. [CrossRef] [PubMed]
173. Sakai, K.; Akima, M. An analysis of the stimulant effects of 5-hydroxytryptamine on isolated, blood-perfused rat heart. *Eur. J. Pharmacol.* **1979**, *55*, 421–424. [CrossRef] [PubMed]
174. Villeneuve, C.; Caudrillier, A.; Ordener, C.; Pizzinat, N.; Parini, A.; Mialet-Perez, J. Dose-dependent activation of distinct hypertrophic pathways by serotonin in cardiac cells. *Am. J. Physiol. Heart. Circ. Physiol.* **2009**, *297*, H821–H828. [CrossRef] [PubMed]
175. Mialet-Perez, J.; D'Angelo, R.; Villeneuve, C.; Ordener, C.; Nègre-Salvayre, A.; Parini, A.; Vindis, C. Serotonin 5-HT2A receptor-mediated hypertrophy is negatively regulated by caveolin-3 in cardiomyoblasts and neonatal cardiomyocytes. *J. Mol. Cell. Cardiol.* **2012**, *52*, 502–510. [CrossRef] [PubMed]
176. Lairez, O.; Cognet, T.; Schaak, S.; Calise, D.; Guilbeau-Frugier, C.; Parini, A.; Mialet-Perez, J. Role of serotonin 5-HT2A receptors in the development of cardiac hypertrophy in response to aortic constriction in mice. *J. Neural. Transm.* **2013**, *120*, 927–935. [CrossRef]
177. Guillet-Deniau, I.; Burnol, A.F.; Girard, J. Identification and localization of a skeletal muscle secrotonin 5-HT2A receptor coupled to the Jak/STAT pathway. *J. Biol. Chem.* **1997**, *272*, 14825–14829. [CrossRef] [PubMed]
178. Kjekshus, J.K.; Torp-Pedersen, C.; Gullestad, L.; Køber, L.; Edvardsen, T.; Olsen, I.C.; Sjaastad, I.; Qvigstad, E.; Skomedal, T.; Osnes, J.; et al. Effect of piboserod, a 5-HT4 serotonin receptor antagonist, on left ventricular function in patients with symptomatic heart failure. *Eur. J. Heart Fail.* **2009**, *11*, 771–778. [CrossRef] [PubMed]
179. Leftheriotis, D.; Flevari, P.; Ikonomidis, I.; Douzenis, A.; Liapis, C.; Paraskevaidis, I.; Iliodromitis, E.; Lykouras, L.; Kremastinos, D.T. The role of the selective serotonin re-uptake inhibitor sertraline in nondepressive patients with chronic ischemic heart failure: A preliminary study. *Pacing. Clin. Electrophysiol.* **2010**, *33*, 1217–1223. [CrossRef] [PubMed]
180. Birkeland, J.A.; Sjaastad, I.; Brattelid, T.; Qvigstad, E.; Moberg, E.R.; Krobert, K.A.; Bjørnerheim, R.; Skomedal, T.; Sejersted, O.M.; Osnes, J.-B.; et al. Effects of treatment with a 5-HT4 receptor antagonist in heart failure. *Br. J. Pharmacol.* **2007**, *150*, 143–152. [CrossRef]
181. Monassier, L.; Laplante, M.A.; Jaffré, F.; Bousquet, P.; Maroteaux, L.; de Champlain, J. Serotonin 5-HT(2B) receptor blockade prevents reactive oxygen species-induced cardiac hypertrophy in mice. *Hypertension* **2008**, *52*, 301–307. [CrossRef] [PubMed]
182. Nigmatullina, R.R.; Kirillova, V.V.; Jourjikiya, R.K.; Mukhamedyarov, M.A.; Kudrin, V.S.; Klodt, P.M.; Palotás, A. Disrupted serotonergic and sympathoadrenal systems in patients with chronic heart failure may serve as new therapeutic targets and novel biomarkers to assess severity, progression and response to treatment. *Cardiology* **2009**, *113*, 277–286. [CrossRef] [PubMed]
183. Hirowatari, Y.; Hara, K.; Shimura, Y.; Takahashi, H. Serotonin levels in platelet-poor plasma and whole blood from healthy subjects: Relationship with lipid markers and coronary heart disease risk score. *J. Atheroscler. Thromb.* **2011**, *18*, 874–882. [CrossRef] [PubMed]
184. Figueras, J.; Domingo, E.; Cortadellas, J.; Padilla, F.; Dorado, D.G.; Segura, R.; Galard, R.; Soler, J.S. Comparison of plasma serotonin levels in patients with variant angina pectoris versus healed myocardial infarction. *Am. J. Cardiol.* **2005**, *96*, 204–207. [CrossRef]
185. Janssen, W.; Schymura, Y.; Novoyatleva, T.; Kojonazarov, B.; Boehm, M.; Wietelmann, A.; Luitel, H.; Murmann, K.; Krompiec, D.R.; Tretyn, A.; et al. 5-HT2B receptor antagonists inhibit fibrosis and protect from RV heart failure. *Biomed. Res. Int.* **2015**, *2015*, 438403. [CrossRef] [PubMed]
186. Nebigil, C.G.; Jaffré, F.; Messaddeq, N.; Hickel, P.; Monassier, L.; Launay, J.M.; Maroteaux, L. Overexpression of the serotonin 5-HT2B receptor in heart leads to abnormal mitochondrial function and cardiac hypertrophy. *Circulation* **2003**, *107*, 3223–3229. [CrossRef] [PubMed]
187. Chen, C.Y.; Leu, J.G.; Lin, K.Y.; Shih, C.Y.; Liang, Y.J. Serotonin receptor subtype-2B signaling is associated with interleukin-18-induced cardiomyoblast hypertrophy in vitro. *Asian Biomed. (Res. Rev. News)* **2022**, *16*, 79–87. [CrossRef] [PubMed]
188. Shih, J.C.; Chen, K.; Ridd, M.J. Monoamine oxidase: From genes to behavior. *Annu. Rev. Neurosci.* **1999**, *22*, 197–217. [CrossRef] [PubMed]
189. Umbarkar, P.; Singh, S.; Arkat, S.; Bodhankar, S.L.; Lohidasan, S.; Sitasawad, S.L. Monoamine oxidase-A is an important source of oxidative stress and promotes cardiac dysfunction, apoptosis, and fibrosis in diabetic cardiomyopathy. *Free Radic. Biol. Med.* **2015**, *87*, 263–273. [CrossRef] [PubMed]
190. Villeneuve, C.; Guilbeau-Frugier, C.; Sicard, P.; Lairez, O.; Ordener, C.; Duparc, T.; De Paulis, D.; Couderc, B.; Spreux-Varoquaux, O.; Tortosa, F.; et al. p53-PGC-1α pathway mediates oxidative mitochondrial damage and cardiomyocyte necrosis induced by monoamine oxidase-A upregulation: Role in chronic left ventricular dysfunction in mice. *Antioxid. Redox Signal.* **2013**, *18*, 5–18. [CrossRef]
191. Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J.R. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature* **1976**, *263*, 663–665. [CrossRef] [PubMed]
192. Inoue, A.; Yanagisawa, M.; Kimura, S.; Kasuya, Y.; Miyauchi, T.; Goto, K.; Masaki, T. The human endothelin family: Three structurally and pharmacologically distinct isopeptides predicted by three separate genes. *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 2863–2867. [CrossRef] [PubMed]

193. Inoue, A.; Yanagisawa, M.; Takuwa, Y.; Mitsui, Y.; Kobayashi, M.; Masaki, T. The human preproendothelin-1 gene. Complete nucleotide sequence and regulation of expression. *J. Biol. Chem.* **1989**, *264*, 14954–14959. [CrossRef]
194. Sugden, P.H. Signaling pathways activated by vasoactive peptides in the cardiac myocyte and their role in myocardial pathologies. *J. Card. Fail.* **2002**, *8*, S359–S369. [CrossRef] [PubMed]
195. Agapitov, A.V.; Haynes, W.G. Role of endothelin in cardiovascular disease. *J. Renin. Angioten. Aldoster. Syst.* **2002**, *3*, 1–15. [CrossRef] [PubMed]
196. Brunner, F.; Brás-Silva, C.; Cerdeira, A.S.; Leite-Moreira, A.F. Cardiovascular endothelins: Essential regulators of cardiovascular homeostasis. *Pharmacol. Ther.* **2006**, *111*, 508–531. [CrossRef] [PubMed]
197. Rehsia, N.S.; Dhalla, N.S. Potential of endothelin-1 and vasopressin antagonists for the treatment of congestive heart failure. *Heart Fail. Rev.* **2010**, *15*, 85–101. [CrossRef] [PubMed]
198. Davenport, A.P.; Hyndman, K.A.; Dhaun, N.; Southan, C.; Kohan, D.E.; Pollock, J.S.; Pollock, D.M.; Webb, D.J.; Maguire, J.J. Endothelin. *Pharmacol. Rev.* **2016**, *68*, 357–418. [CrossRef] [PubMed]
199. Miyauchi, T.; Sakai, S. Endothelin and the heart in health and diseases. *Peptides* **2019**, *111*, 77–88. [CrossRef]
200. Barton, M.; Yanagisawa, M. Endothelin: 30 years from discovery to therapy. *Hypertension* **2019**, *74*, 1232–1265. [CrossRef] [PubMed]
201. Kuwaki, T.; Ling, G.Y.; Onodera, M.; Ishii, T.; Nakamura, A.; Ju, K.H.; Cao, W.; Kumada, M.; Kurihara, H.; Kurihara, Y.; et al. Endothelin in the central control of cardiovascular and respiratory functions. *Clin. Exp. Pharmacol. Physiol.* **1999**, *26*, 989–994. [CrossRef] [PubMed]
202. Hosoda, K.; Nakao, K.; Arai, H.; Suga, S.; Ogawa, Y.; Mukoyama, M.; Shirakami, G.; Saito, Y.; Nakanishi, S.; Imura, H. Cloning and expression of human endothelin-1 receptor cDNA. *FEBS Lett.* **1991**, *287*, 23–26. [CrossRef] [PubMed]
203. Ogawa, Y.; Nakao, K.; Arai, H.; Nakagawa, O.; Hosoda, K.; Suga, S.; Nakanishi, S.; Imura, H. Molecular cloning of a non-isopeptide-selective human endothelin receptor. *Biochem. Biophys. Res. Commun.* **1991**, *178*, 248–255. [CrossRef] [PubMed]
204. Kishi, F.; Minami, K.; Okishima, N.; Murakami, M.; Mori, S.; Yano, M. Novel 31-amino-acid-length endothelins cause constriction of vascular smooth muscle. *Biochem. Biophys. Res. Commun.* **1998**, *248*, 387–390. [CrossRef] [PubMed]
205. Niwa, Y.; Nagata, N.; Oka, M.; Toyoshima, T.; Akiyoshi, H.; Wada, T.; Nakaya, Y. Production of nitric oxide from endothelial cells by 31-amino-acid-length endothelin-1, a novel vasoconstrictive product by human chymase. *Life Sci.* **2000**, *67*, 1103–1109. [CrossRef]
206. Möllmann, H.; Schmidt-Schwedam, S.; Nef, H.; Möllmann, S.; Burstin, J.V.; Klose, S. Contractile effects of angiotensin and endothelin in failing and non-failing human hearts. *Int. J. Cardiol.* **2007**, *114*, 34–40. [CrossRef] [PubMed]
207. Badr, K.F.; Murray, J.J.; Breyer, M.D.; Takahashi, K.; Inagami, T.; Harris, R.C. Mesangial cell, glomerular and renal vascular responses to endothelin in the rat kidney. Elucidation of signal transduction pathways. *J. Clin. Investig.* **1989**, *83*, 336–342. [CrossRef]
208. Takuwa, Y.; Kasuya, Y.; Takuwa, N.; Kudo, M.; Yanagisawa, M.; Goto, K.; Masaki, T.; Yamashita, K. Endothelin receptor is coupled to phospholipase C via a pertussis toxin-insensitive guanine nucleotide-binding regulatory protein in vascular smooth muscle cells. *J. Clin. Investig.* **1990**, *85*, 653–658. [CrossRef]
209. Vanhaesebroeck, B.; Alessi, D.R. The PI3K-PDK1 connection: More than just a road to PKB. *Biochem. J.* **2000**, *346 Pt 3*, 561–576. [CrossRef] [PubMed]
210. Pham, F.H.; Cole, S.M.; Clerk, A. Regulation of cardiac myocyte protein synthesis through phosphatidylinositol 3′ kinase and protein kinase B. *Adv. Enzym. Regul.* **2001**, *41*, 73–86. [CrossRef] [PubMed]
211. Schiffrin, E.L.; Pollock, D.M. Endothelin system in hypertension and chronic kidney disease. *Hypertension* **2024**, *81*, 691–701. [CrossRef] [PubMed]
212. Sakai, S.; Miyauchi, T.; Sakurai, T.; Kasuya, Y.; Ihara, M.; Yamaguchi, I.; Goto, K.; Sugishita, Y. Endogenous endothelin-1 participates in the maintenance of cardiac function in rats with congestive heart failure. Marked increase in endothelin-1 production in the failing heart. *Circulation* **1996**, *93*, 1214–1222. [CrossRef] [PubMed]
213. Teerlink, J.R. The role of endothelin in the pathogenesis of heart failure. *Curr. Cardiol. Rep.* **2002**, *4*, 206–212. [CrossRef] [PubMed]
214. Dmour, B.A.; Costache, A.D.; Dmour, A.; Huzum, B.; Duca, Ș.T.; Chetran, A.; Miftode, R.Ș.; Afrăsânie, I.; Tuchiluș, C.; Cianga, C.M.; et al. Could endothelin-1 be a promising neurohormonal biomarker in acute heart failure? *Diagnostics* **2023**, *13*, 2277. [CrossRef]
215. Mares, A.; Mukherjee, D.; Lange, R.A.; Nickel, N.P. Targeted Therapies in Patients with Pulmonary arterial hypertension due to congenital heart disease. *Curr. Vasc. Pharmacol.* **2022**, *20*, 341–360. [CrossRef] [PubMed]
216. Stewart, D.J.; Levy, R.D.; Cernacek, P.; Langleben, D. Increased plasma endothelin-1 in pulmonary hypertension: Marker or mediator of disease? *Ann. Intern. Med.* **1991**, *114*, 464–469. [CrossRef] [PubMed]
217. Suzuki, T.; Kumazaki, T.; Mitsui, Y. Endothelin-1 is produced and secreted by neonatal rat cardiac myocytes in vitro. *Biochem. Biophys. Res. Commun.* **1993**, *191*, 823–830. [CrossRef] [PubMed]
218. Houde, M.; Desbiens, L.; D'Orléans-Juste, P. Endothelin-1: Biosynthesis, signaling and vasoreactivity. *Adv. Pharmacol.* **2016**, *77*, 143–175.
219. Miyauchi, T.; Yorikane, R.; Sakai, S.; Sakurai, T.; Okada, M.; Nishikibe, M.; Yano, M.; Yamaguchi, I.; Sugishita, Y.; Goto, K. Contribution of endogenous endothelin-1 to the progression of cardiopulmonary alterations in rats with monocrotaline-induced pulmonary hypertension. *Circ. Res.* **1993**, *73*, 887–897. [CrossRef] [PubMed]

220. Ito, H.; Hiroe, M.; Hirata, Y.; Fujisaki, H.; Adachi, S.; Akimoto, H.; Ohta, Y.; Marumo, F. Endothelin ETA receptor antagonist blocks cardiac hypertrophy provoked by hemodynamic overload. *Circulation* **1994**, *89*, 2198–2203. [CrossRef] [PubMed]
221. Shubeita, H.E.; McDonough, P.M.; Harris, A.N.; Knowlton, K.U.; Glembotski, C.C.; Brown, J.H.; Chien, K.R. Endothelin induction of inositol phospholipid hydrolysis, sarcomere assembly, and cardiac gene expression in ventricular myocytes. A paracrine mechanism for myocardial cell hypertrophy. *J. Biol. Chem.* **1990**, *265*, 20555–20562. [CrossRef] [PubMed]
222. Hiroe, M.; Hirata, Y.; Fujita, N.; Umezawa, S.; Ito, H.; Tsujino, M.; Koike, A.; Nogami, A.; Takamoto, T.; Marumo, F. Plasma endothelin-1 levels in idiopathic dilated cardiomyopathy. *Am. J. Cardiol.* **1991**, *68*, 1114–1115. [CrossRef] [PubMed]
223. McMurray, J.J.; Ray, S.G.; Abdullah, I.; Dargie, H.J.; Morton, J.J. Plasma endothelin in chronic heart failure. *Circulation* **1992**, *85*, 1374–1379. [CrossRef] [PubMed]
224. Stewart, D.J.; Cernacek, P.; Costello, K.B.; Rouleau, J.L. Elevated endothelin-1 in heart failure and loss of normal response to postural change. *Circulation* **1992**, *85*, 510–517. [CrossRef] [PubMed]
225. Margulies, K.B.; Hildebrand, F., Jr.; Lerman, A.; Perrella, M.A.; Burnett, J.C., Jr. Increased endothelin in experimental heart failure. *Circulation* **1990**, *82*, 2226–2230. [CrossRef] [PubMed]
226. Underwood, R.D.; Aarhus, L.L.; Heublein, D.M.; Burnett, J.C., Jr. Endothelin in thoracic inferior vena caval constriction model of heart failure. *Am. J. Physiol.* **1992**, *263 Pt 2*, H951–H955. [CrossRef] [PubMed]
227. Miyauchi, T.; Yanagisawa, M.; Tomizawa, T.; Sugishita, Y.; Suzuki, N.; Fujino, M.; Ajisaka, R.; Goto, K.; Masaki, T. Increased plasma concentrations of endothelin-1 and big endothelin-1 in acute myocardial infarction. *Lancet* **1989**, *2*, 53–54. [CrossRef] [PubMed]
228. Sakai, S.; Kimura, T.; Wang, Z.; Shimojo, N.; Maruyama, H.; Homma, S.; Kuga, K.; Yamaguchi, I.; Aonuma, K.; Miyauchi, T. Endothelin-1-induced cardiomyocyte hypertrophy is partly regulated by transcription factor II-F interacting C-terminal domain phosphatase of RNA polymerase II. *Life Sci.* **2012**, *91*, 572–577. [CrossRef]
229. Dammanahalli, K.J.; Sun, Z. Endothelins and NADPH oxidases in the cardiovascular system. *Clin. Exp. Pharmacol. Physiol.* **2008**, *35*, 2–6. [CrossRef] [PubMed]
230. Sakai, S.; Miyauchi, T.; Kobayashi, M.; Yamaguchi, I.; Goto, K.; Sugishita, Y. Inhibition of myocardial endothelin pathway improves long-term survival in heart failure. *Nature* **1996**, *384*, 353–355. [CrossRef]
231. Maayah, Z.H.; Ferdaoussi, M.; Boukouris, A.E.; Takahara, S.; Das, S.K.; Khairy, M.; Mackey, J.R.; Pituskin, E.; Sutendra, G.; Paterson, D.I.; et al. Endothelin Receptor Blocker Reverses Breast Cancer-Induced Cardiac Remodeling. *J. Am. Coll. Cardiol. CardioOnc.* **2023**, *5*, 686–700. [CrossRef] [PubMed]
232. Liu, Q.; Luo, Q.; Zhong, B.; Tang, K.; Chen, X.; Yang, S.; Li, X. Salidroside attenuates myocardial remodeling in DOCA-salt-induced mice by inhibiting the endothelin 1 and PI3K/AKT/NFκB signaling pathways. *Eur. J. Pharmacol.* **2024**, *962*, 176236. [CrossRef] [PubMed]
233. Turner, R.A.; Pierce, J.G.; du Vigneaud, V. The purification and the amino acid content of vasopressin preparations. *J. Biol. Chem.* **1951**, *191*, 21–28. [CrossRef]
234. Davoll, H.; Turner, R.A.; Pierce, J.G.; du Vigneaud, V. An investigation of the free amino groups on oxytocin and desulfurized oxytocin preparations. *J. Biol. Chem.* **1951**, *193*, 363–370. [CrossRef] [PubMed]
235. Szatalowicz, V.L.; Arnold, P.E.; Chaimovitz, C.; Bichet, D.; Berl, T.; Schrier, R.W. Radioimmunoassay of plasma arginine vasopressin in hyponatremic patients with congestive heart failure. *N. Engl. J. Med.* **1981**, *305*, 263–266. [CrossRef] [PubMed]
236. Goldsmith, S.R.; Francis, G.S.; Cowley, A.W.; Levine, T.B.; Cohn, J.N. Increased plasma arginine vasopressin levels in patients with congestive heart failure. *J. Am. Coll. Cardiol.* **1983**, *1*, 1385–1390. [CrossRef]
237. Xu, D.L.; Martin, P.Y.; Ohara, M.; St John, J.; Pattison, T.; Meng, X.; Morris, K.; Kim, J.K.; Schrier, R.W. Upregulation of aquaporin-2 water channel expression in chronic heart failure rat. *J. Clin. Investig.* **1997**, *99*, 1500–1505. [CrossRef]
238. Verbalis, J.G. AVP receptor antagonists as aquaretics: Review and assessment of clinical data. *Cleve Clin. J. Med.* **2006**, *73* (Suppl. S3), S24–S33. [CrossRef] [PubMed]
239. Guyton, A.C. The body fluids and kidenys. In *Textbook of Medical Physiology*; Guyton, A.C., Hall, J.E., Eds.; Saunders: Philadelphia, PA, USA, 2006; pp. 291–414.
240. Kamoi, K.; Ishibashi, M.; Yamaji, T. Interaction of osmotic and nonosmotic stimuli in regulation of vasopressin secretion in hypoosmolar state of man. *Endocrinol. J.* **1997**, *44*, 311–317. [CrossRef] [PubMed]
241. Hupf, H.; Grimm, D.; Riegger, G.A.; Schunkert, H. Evidence for a vasopressin system in the rat heart. *Circ. Res.* **1999**, *84*, 365–370. [CrossRef]
242. Brooks, V.L.; Keil, L.C.; Reid, I.A. Role of the renin-angiotensin system in the control of vasopressin secretion in conscious dogs. *Circ. Res.* **1986**, *58*, 829–838. [CrossRef] [PubMed]
243. Baertschi, A.J.; Friedli, M. A novel type of vasopressin receptor on anterior pituitary corticotrophs. *Endocrinology* **1985**, *116*, 499–502. [CrossRef] [PubMed]
244. Xu, Y.J.; Gopalakrishnan, V. Vasopressin increases cytosolic free Ca^{2+} in the neonatal rat cardiomyocyte. Evidence for V_1 subtype receptors. *Circ. Res.* **1991**, *69*, 239–245. [CrossRef] [PubMed]
245. Nakamura, Y.; Haneda, T.; Osaki, J.; Miyata, S.; Kikuchi, K. Hypertrophic growth of cultured neonatal rat heart cells mediated by vasopressin V(1A) receptor. *Eur. J. Pharmacol.* **2000**, *391*, 39–48. [CrossRef] [PubMed]

246. Tahara, A.; Tomura, Y.; Wada, K.; Kusayama, T.; Tsukada, J.; Ishii, N.; Yatsu, T.; Uchida, W.; Tanaka, A. Effect of YM087, a potent nonpeptide vasopressin antagonist, on vasopressin-induced protein synthesis in neonatal rat cardiomyocyte. *Cardiovasc. Res.* **1998**, *38*, 198–205. [CrossRef] [PubMed]
247. Birnbaumer, M. Vasopressin receptors. *Trends Endocrinol. Metab.* **2000**, *11*, 406–410. [CrossRef] [PubMed]
248. Sparapani, S.; Millet-Boureima, C.; Oliver, J.; Mu, K.; Hadavi, P.; Kalostian, T.; Ali, N.; Avelar, C.M.; Bardies, M.; Barrow, B.; et al. The Biology of vasopressin. *Biomedicines* **2021**, *9*, 89. [CrossRef] [PubMed]
249. Nielsen, S.; Kwon, T.H.; Christensen, B.M.; Promeneur, D.; Frøkiaer, J.; Marples, D. Physiology and pathophysiology of renal aquaporins. *J. Am. Soc. Nephrol.* **1999**, *10*, 647–663. [CrossRef] [PubMed]
250. Snyder, H.M.; Noland, T.D.; Breyer, M.D. cAMP-dependent protein kinase mediates hydrosmotic effect of vasopressin in collecting duct. *Am. J. Physiol.* **1992**, *263 Pt 1*, C147–C153. [CrossRef]
251. Riegger, G.A.; Liebau, G.; Bauer, E.; Kochsiek, K. Vasopressin and renin in high output heart failure of rats: Hemodynamic effects of elevated plasma hormone levels. *J. Cardiovasc. Pharmacol.* **1985**, *7*, 1–5. [CrossRef] [PubMed]
252. Atsumi, W.; Tani, S.; Tachibana, E.; Hirayama, A. Combined Evaluation of the plasma arginine vasopressin and noradrenaline levels may be a useful predictor of the prognosis of patients with acute decompensated heart failure. *Int. Heart J.* **2018**, *59*, 791–801. [CrossRef] [PubMed]
253. Beardwell, C.G.; Geelen, G.; Palmer, H.M.; Roberts, D.; Salamonson, L. Radioimmunoassay of plasma vasopressin in physiological and pathological states in man. *J. Endocrinol.* **1975**, *67*, 189–202. [CrossRef] [PubMed]
254. Mu, D.; Cheng, J.; Qiu, L.; Cheng, X. Copeptin as a diagnostic and prognostic biomarker in cardiovascular diseases. *Front. Cardiovasc. Med.* **2022**, *9*, 901990. [CrossRef] [PubMed]
255. Pittman, Q.J. Vasopressin and central control of the cardiovascular system: A 40-year retrospective. *J. Neuroendocrinol.* **2021**, *33*, e13011. [CrossRef] [PubMed]
256. Chiorescu, R.M.; Lazar, R.D.; Buksa, S.B.; Mocan, M.; Blendea, D. Biomarkers of volume overload and edema in heart failure with reduced ejection fraction. *Front. Cardiovasc. Med.* **2022**, *9*, 910100. [CrossRef] [PubMed]
257. Aikins, A.O.; Nguyen, D.H.; Paundralingga, O.; Farmer, G.E.; Shimoura, C.G.; Brock, C.; Cunningham, J.T. Cardiovascular neuroendocrinology: Emerging role for neurohypophyseal hormones in pathophysiology. *Endocrinology* **2021**, *162*, bqab082. [CrossRef] [PubMed]
258. Szczepanska-Sadowska, E. The heart as a target of vasopressin and other cardiovascular peptides in health and cardiovascular diseases. *Int. J. Mol. Sci.* **2022**, *23*, 14414. [CrossRef] [PubMed]
259. Urbach, J.; Goldsmith, S.R. Vasopressin antagonism in heart failure: A review of the hemodynamic studies and major clinical trials. *Ther. Adv. Cardiovasc. Dis.* **2021**, *15*, 1753944720977741. [CrossRef]
260. Kapłon-Cieślicka, A.; Soloveva, A.; Mareev, Y.; Cabac-Pogorevici, I.; Verbrugge, F.H.; Vardas, P. Hyponatraemia in heart failure: Time for new solutions? *Heart* **2022**, *108*, 1179–1185. [CrossRef] [PubMed]
261. Suwanto, D.; Dewi, I.P.; Fagi, R.A. Hyponatremia in heart failure: Not just 135 to 145. *J. Basic Clin. Physiol. Pharmacol.* **2021**, *33*, 381–388. [CrossRef] [PubMed]
262. Şorodoc, V.; Asaftei, A.; Puha, G.; Ceasovschih, A.; Lionte, C.; Sîrbu, O.; Bologa, C.; Haliga, R.E.; Constantin, M.; Coman, A.E.; et al. Management of hyponatremia in heart failure: Practical considerations. *J. Pers. Med.* **2023**, *13*, 140. [CrossRef] [PubMed]
263. Jönsson, S.; Agic, M.B.; Narfström, F.; Melville, J.M.; Hultström, M. Renal neurohormonal regulation in heart failure decompensation. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2014**, *307*, R493–R497. [CrossRef] [PubMed]
264. Kashihara, T.; Mukai, R.; Oka, S.I.; Zhai, P.; Nakada, Y.; Yang, Z.; Mizushima, W.; Nakahara, T.; Warren, J.S.; Abdellatif, M.; et al. YAP mediates compensatory cardiac hypertrophy through aerobic glycolysis in response to pressure overload. *J. Clin. Investig.* **2022**, *132*, e150595. [CrossRef] [PubMed]
265. Zhang, Y.; Chen, W.; Wang, Y. STING is an essential regulator of heart inflammation and fibrosis in mice with pathological cardiac hypertrophy via endoplasmic reticulum (ER) stress. *Biomed. Pharmacother.* **2020**, *125*, 110022. [CrossRef] [PubMed]
266. Zhang, Y.; Da, Q.; Cao, S.; Yan, K.; Shi, Z.; Miao, Q.; Li, C.; Hu, L.; Sun, S.; Wu, W.; et al. HINT1 (histidine triad nucleotide-binding protein 1) attenuates cardiac hypertrophy via suppressing HOXA5 (homeobox A5) expression. *Circulation* **2021**, *144*, 638–654. [CrossRef] [PubMed]
267. Farrell, D.M.; Wei, C.C.; Tallaj, J.; Ardell, J.L.; Armour, J.A.; Hageman, G.R.; Bradley, W.E.; Dell'Italia, L.J.; Hardwick, J.C.; Ryan, S.E.; et al. Angiotensin II modulates catecholamine release into interstitial fluid of canine myocardium in vivo. *Am. J. Physiol. Heart Circ. Physiol.* **2001**, *281*, H813–H822. [CrossRef] [PubMed]
268. Schlaich, M.P.; Kaye, D.M.; Lambert, E.; Hastings, J.; Campbell, D.J.; Lambert, G.; Esler, M.D. Angiotensin II and norepinephrine release: Interaction and effects on the heart. *J. Hypertens.* **2005**, *23*, 1077–1082. [CrossRef]
269. Tallaj, J.; Wei, C.C.; Hankes, G.H.; Holland, M.; Rynders, P.; Dillon, A.R.; Ardell, J.L.; Armour, J.A.; Lucchesi, P.A.; Dell'Italia, L.J. Beta1-adrenergic receptor blockade attenuates angiotensin II-mediated catecholamine release into the cardiac interstitium in mitral regurgitation. *Circulation* **2003**, *108*, 225–230. [CrossRef] [PubMed]
270. Yu, L.; Yang, G.; Weng, X.; Liang, P.; Li, L.; Li, J.; Fan, Z.; Tian, W.; Wu, X.; Xu, H.; et al. Histone methyltransferase SET1 mediates angiotensin II-induced endothelin-1 transcription and cardiac hypertrophy in mice. *Arterioscler. Thromb. Vasc. Biol.* **2015**, *35*, 1207–1217. [CrossRef] [PubMed]
271. Moreau, P.; d'Uscio, L.V.; Shaw, S.; Takase, H.; Barton, M.; Lüscher, T.F. Angiotensin II increases tissue endothelin and induces vascular hypertrophy: Reversal by ET(A)-receptor antagonist. *Circulation* **1997**, *96*, 1593–1597. [CrossRef] [PubMed]

272. Ito, N.; Kagaya, Y.; Weinberg, E.O.; Barry, W.H.; Lorell, B.H. Endothelin and angiotensin II stimulation of Na^+-H^+ exchange is impaired in cardiac hypertrophy. *J. Clin. Investig.* **1997**, *99*, 125–135. [CrossRef] [PubMed]
273. Mironova, E.; Archer, C.R.; Vendrov, A.E.; Runge, M.S.; Madamanchi, N.R.; Arendshorst, W.J.; Stockand, J.D.; El-Aziz, T.M.A. NOXA1-dependent NADPH oxidase 1 signaling mediates angiotensin II activation of the epithelial sodium channel. *Am. J. Physiol. Ren. Physiol.* **2022**, *323*, F633–F641. [CrossRef] [PubMed]
274. Park, J.M.; Do, V.Q.; Seo, Y.S.; Kim, H.J.; Nam, J.H.; Yin, M.Z.; Kim, H.J.; Kim, S.J.; Griendling, K.K.; Lee, M.-Y. NADPH oxidase 1 mediates acute blood pressure response to angiotensin II by contributing to calcium influx in vascular smooth muscle cells. *Arterioscler. Thromb. Vasc. Biol.* **2022**, *42*, e117–e130. [CrossRef] [PubMed]
275. Wang, M.; Murdoch, C.E.; Brewer, A.C.; Ivetic, A.; Evans, P.; Shah, A.M.; Zhang, M. Endothelial NADPH oxidase 4 protects against angiotensin II-induced cardiac fibrosis and inflammation. *ESC Heart Fail.* **2021**, *8*, 1427–1437. [CrossRef] [PubMed]

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