Review

Melatonin as a protective adjunct to the renin angiotensin system imbalance induced cardiovascular pathogenesis: A review

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ABSTRACT

The renin-angiotensin system has emerged as a key modulator of cardiomyopathies, with both local and central effects on the cardiac tissue. With the increase in incidences of cardiac disorders worldwide, the roles of the renin-angiotensin system on the cardiomyopathies have been revealed by scientists. Recent reports suggest that this system might regulate the synthesis of melatonin. This has drawn the interest of scientists globally since melatonin has remarkable protective effects on cardiomyopathies caused by atherosclerosis, cardiac ischemia, and myocardial infarction. Thus, understanding the interactions of melatonin with various components of the renin-angiotensin system becomes a necessary step for devising a targeted therapy for the various cardiomyopathies. This review has summarized the major effects of various components of the renin-angiotensin system on the cardiac tissue and the interaction of this system with melatonin. The role of melatonin in mediating cardioprotective effects by inhibition of certain components of this system has also been discussed.

Key words: renin-angiotensin system, melatonin, cardiovascular diseases

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1. INTRODUCTION

The renin-angiotensin system (RAS) is one of the most important hormonal systems in human body. It serves as one of the major regulators of cardiovascular homeostasis (1). This system has endocrine, paracrine and autocrine effects on several organs, exerting organ-specific actions that summate to induce precise effects on the cardiovascular system (2). Under physiological conditions, the RAS regulates blood volume and systemic vascular resistance which, in turn, modulate cardiac output and arterial pressure, respectively. It consists of classical and counter-regulatory pathways that counter-balance each other's effect in maintaining cardiovascular homeostasis (3). The functional imbalance between the classic ACE/Angiotensin II/AT1R and the counter-regulatory ACE2/Ang 1–7/Mas1R (and AT2R)

pathways is a crucial risk for the development of cardiovascular dysfunctions (4). It has also been observed that various components of the RAS are upregulated during certain pathophysiological conditions including hypertension, cardiac ischemia and acute myocardial infarction which cause severe cardiovascular disorders (5–7). The intracardiac RAS exerts an important role in the development of cardiac ischemia/reperfusion injury (7). Accumulating evidence further suggests that permanent or sustained activation of RAS is involved in cardiac and vascular remodeling that results in ventricular hypertrophy and fibrosis (8). Studies on RAS for more than a century have revealed its importance in maintaining cardiovascular health and this has led researchers to come up with solutions to combat its dysregulation. The development of RAS inhibitory drugs has revolutionized the treatment of cardiovascular diseases and are now amongst the most commonly prescribed medicines for about three decades (9). These include angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, renin inhibitors and mineralocorticoid receptor- antagonists. Large-scale clinical trials have provided reliable evidence on cardioprotection achieved through RAS blockade which has popularized their use clinically. Further studies on RAS inhibitors have proposed the concomitant use of two or more types of these inhibitors. However, the clinical trials on both mono or dual RAS blockade therapies have shown that the patients may be predisposed to risks of hypotension, hyperkalemia and acute renal damage (10–12). The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) had issued restrictions on dual RAS inhibitory therapies that were later approved by the European Commission in 2014 (10). The search for a better solution led us to an interesting report that suggests that melatonin in combination with an angiotensin II receptor antagonist, losartan, yielded better results than losartan alone in treating hypertension (13). Another clinical trial also indicated that melatonin, through its multifaceted functions enhanced the efficacy of RAS inhibitors in the treatment of heart failure (14). Melatonin is well known for its marvelous cardioprotective abilities. However, little data is available on melatonin's interaction with the RAS in various cardiovascular pathologies. This interaction deserves further attention for a better understanding of the physiological changes occurring in cardiovascular anomalies. In this article, we have tried to explore the interaction between melatonin and the RAS in myocardial infarction. Extensive excavation in this area might broaden the prospects of melatonin therapy in clinical practices. Melatonin, being a natural antioxidant endogenously present in the body, comes with very little or no side effects. It also has an important role in preventing myocardial damage following ischemia reperfusion injury. Thus, future clinical studies aiming for better outcomes in treating cardiovascular diseases might consider incorporating melatonin therapy alongside RAS inhibitors.

2. COMPONENTS OF THE RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system consists of numerous key modulators that exert the multifaceted effects of this system. The primary mediators of the classical pathway include renin, the active form of prorenin, angiotensin I & II, angiotensin-converting enzyme and aldosterone. The mediators of the counter-regulatory pathway include angiotensin 1-7, angiotensin 1-9, and the angiotensin-converting enzyme 2. The intracardiac RAS components are localized in the atria and ventricles, valves, coronary arteries, myocytes and fibroblasts (15, 16). The discovery of major regulatory roles of local and circulating RAS pathways in the development and aggravation of various cardiovascular pathologies has further advanced this particular area in recent years. A growing evidence suggests that cardiac RAS is abnormally upregulated following myocardial infarction. The roles of the main components of RAS played in myocardial infarction are discussed below.

2.1. Renin.

The classical RAS cascade begins with the action of renin. Renin is an aspartyl protease enzyme that controls the initial rate-limiting step of converting angiotensinogen to angiotensin I. Renin has been detected in cardiac atria, ventricles and also in ventricular myocytes of neonatal and adult rat primary cell culture (17). In humans, renin mRNA can be found in right and left atrium, right ventricle, endothelium, capillaries of myocardium and vascular smooth muscle cells of coronary arteries and veins (18). It has been noted that overexpression of renin results in increased production and release of angiotensin II (17). In the normal myocardium, renin synthesis is nearly undetectable but in experimental models of myocardial infarction, a significant increase in the expression of renin has been reported which may indicate its involvement in the progression of injury in the infarcted myocardium (19, 20).

2.2. Angiotensinogen.

Cardiac angiotensinogen is an α2 class glycoprotein synthesized in the cardiac muscles and is cleaved by renin into angiotensin I. Gene expression of angiotensinogen has been detected in the myocyte, fibroblast and the heart of humans, dogs, rats and mice (16). In the adult human heart, angiotensinogen is primarily distributed in the atrial muscles, fibres of the conducting system and a small amount in the subendocardial layer of the ventricles (21). The scanty presence of angiotensinogen in the ventricles may be physiologically relevant because an increase in its level has been associated with increased production of angiotensin II and ventricular hypertrophy suggesting the fact that angiotensinogen may be the rate-limiting component of the intracardiac RAS activation (22).

2.3. Angiotensin I.

Angiotensin I or pro-angiotensin is a peptide consisting of ten amino acids, formed by the cleaving action of renin on angiotensinogen. It is the precursor of angiotensin II and angiotensin 1-9. Cardiac angiotensin I is known to be synthesized in the cardiac tissue. It has been reported that angiotensin I is synthesized in vascular muscle cells (8).

2.4. Angiotensin converting enzyme (ACE).

Angiotensin converting enzymes are metallopeptides in nature. They are found very commonly distributed on the endothelial and epithelial cell surfaces (7). In humans, ACE has been localized in the endothelium of the aorta and pulmonary artery, but were absent in the cardiac valves. Primarily, ACE are expressed in the cardiac fibroblasts and endothelial cells. In comparison, murine ACE has also been localized in the cardiac valves along with the coronary vessels, great vessels, endocardium and epicardium (16). ACEs are mainly of two types – ACE1 and ACE2. While ACE1 is well known for it's role in converting angiotensin I to angiotensin II, ACE2 was discovered in 2000 (23). Being a carboxypeptidase, ACE2 breaks down angiotensin II to generate angiotensin 1-7 and angiotensin I to angiotensin 1-9 which are supposedly cardio-protective in nature (24). ACE1 also degrades bradykinin into it's inactive form (25). Upregulation of ACEs has been observed in the cardiac tissue following myocardial infarction. The highest ACEs activity has been reported in the scar tissues of infarcted hearts (17). In pathological conditions, increased ACE1 activity is instrumental in the development of left ventricular hypertrophy (25). On the other hand, in a

rat model of myocardial infarction, ACE2 upregulation ameliorates cardiac dysfunction and associated left ventricular remodeling (24).

2.5. Angiotensin II.

Alike angiotensin I, angiotensin II has also been localized in atria and ventricles of various mammals (16). Evidence suggests that angiotensin II is produced in cardiac tissues due to intracellular synthesis. Supporting this fact, intracellular angiotensin II has been found within cardiomyocytes and cardiac fibroblasts (16). Angiotensin II has been identified as a key player in inducing detrimental effects in the cardiac tissue during the insidious process of deteriorating ventricular function in myocardial damage. It can mediate both direct and catecholamine related vasoconstriction in the coronary vasculature (26). It also induces endothelial damage by inducing oxidative stress, triggering inflammatory responses and inhibiting the regeneration of endothelial cells (27, 28). In addition, it is a potent promoter of cardiac fibrosis by stimulating fibroblasts to produce collagen and cause hypertrophy in cardiomyocytes (29). Angiotensin II may also be involved in atherosclerotic progression and in the plaque rupture process which cause severe consequences like myocardial infarction (30).

2.6. Angiotensin 1-7.

Angiotensin 1-7 is a heptapeptide found in the heart and is also formed in the endothelial layer of blood vessels in human. It is formed by the enzymatic action of ACE2 on angiotensin II. In recent years, cardioprotective roles of angiotensin 1-7 have been discovered. It mediates vasodilation in aortic rings and in other vascular beds (31). It opposes the action of angiotensin II in a number of tissues by inhibiting angiotensin II induced cell growth, migration and inflammation, thereby preventing adverse cardiac remodeling and cardiovascular dysfunction (32). Studies have shown that production of angiotensin 1-7 increases significantly in the infarcted heart and it inhibits ventricular hypertrophy induced by myocardial infarction (33).

2.7. Angiotensin 1-9.

Angiotensin 1-9 is a nine amino acid peptide formed by the hydrolyzing action of ACE2 on angiotensin I in the myocardium. Under pathological conditions, there is an increased level of angiotensin 1-9 in heart. Angiotensin 1-9 has a significant biological role in preventing cardiac hypertrophic growth and preserves the left ventricular systolic function following myocardial infarction (32).

2.8. Alamandine

Among the newest identified angiotensin peptides found in the cardiac tissue and plasma, alamandine has emerged as an important member of the counter-regulatory arm of the RAS. Alamandine binds to a novel RAS receptor named Mas related G-protein receptor (MrgD) to produce its biological actions (34). This peptide is synthesized by the action of ACE2 on Angiotensin II and it can also be decarboxylated from Angiotensin 1-7 (35). The structure of alamandine is highly homologous to that of Angiotensin 1-7 and it also shows anti-fibrotic and anti-hypertensive effects (36). Being a part of the counter-regulatory arm of the RAS , it shows cardioprotective effects and may have important roles in ameliorating cardiac pathogenesis (37).

3. MECHANISMS OF RAS ACTING ON CARDIOVASCULAR PHYSIOLOGY

The RAS has always been intricately involved in maintaining the cardiovascular homeostasis of our bodies. Until recently, the proteolytic enzyme renin and angiotensin II are considered to be the key players in both physiological and pathological implications of this system. They belong to the classical pathway for RAS regulation compared to the newly discovered counter regulatory pathway of the same system.

3.1. The classical pathway.

The major member of this pathway is angiotensin II. It mediates its effects by binding to angiotensin I receptor (AT1R). It is well known that upregulation of angiotensin II in myocardial infarction occurs following severe ischemic insult (38). This ischemic insult is a result of plaque rupture or luminal narrowing due to atherosclerosis. In atherosclerotic progression, angiotensin II induces vasoconstriction, endothelial dysfunction, migration and proliferation of vascular smooth muscle cells, hypertrophy of cardiomyocytes and release of pro-inflammatory mediators that aggravate the plaque rupture process (39). Angiotensin II also exerts a positive inotropic effect on cardiomyocytes that might further increase myocardial oxygen demand in ischemic zones thereby inducing ischemic progression (40).

On binding to the AT1R, angiotensin II mediates several signaling cascades which are both G-protein dependent and independent. In addition, angiotensin II also interacts with numerous tyrosine kinases (41). Inspite of the principal target being vascular smooth muscle cells, angiotensin II also exerts its effects on all other vascular cells such as endothelial cells, cardiac myocytes, monocytes and macrophages.

As discussed above, the major function of angiotensin II is vasoconstriction through classical G-protein dependent signaling cascade. When AT1R is activated by angiotensin II, it couples to G-Protein complexes that in turn activate downstream effectors such as Phospholipase C (PLC), Phospholipase D (PLD) and Phospholipase A_2 (PLA_2) (42, 43). PLC catalyzes the formation of diacylglycerol (DAG) and inositol triphosphate (IP_3) (44) (Figure 1). IP_3 triggers calcium efflux on binding to its respective receptors on the sarcoplasmic reticulum. Calcium binds with calmodulin and activates myosin light chain kinase (MLCK) (44). MLCK enhances actin myosin interaction. Myosin light chain phosphatase (MLCP), on the other hand, counter-regulates the actions of MLCK. Evidences suggest that angiotensin II increases the phosphorylation of a MLCP inhibitor, CPI-17, via PKC (43). Along with this, DAG activates PKC that increases the pH by phosphorylating the Na^+/H^+ pump during cell contraction and also takes part as an effector in the Ras/Raf/MEK/ERK pathway (45–47). On the other hand, PLD hydrolyzes phosphatidylcholine to form phosphatidic acid (PA) and choline (48). PA gets rapidly converted to DAG that facilitates sustained PKC activation (49) which further stimulates muscle contraction, thereby leading to hypertension (50). Angiotensin II-induced phosphorylation and activation of PLA_2 produce arachidonic acid and its metabolites which have pro-hypertensive effects (51). Angiotensin II also promotes the formation of leukotrienes to cause vasoconstriction, inflammation and hypertension (52).

Angiotensin II is also well known to cause oxidative stress. For example, activation of NADPH oxidase by angiotensin II promotes formation of superoxide which is further converted to hydrogen peroxide (53). In addition, superoxide inactivates NO in both endothelial cells and VSMCs (54, 55). Angiotensin II induced excessive ROS generation can activate several transcriptional factors including Nrf2, AP-1, NF-κB and p38MAPK which contribute immensely in the progression of atherosclerosis (56–62). NF-κB activation induces production of cell adhesion molecules such as VCAM-1, ICAM-1, E-Selectin and

chemokines such as MCP-1, IL-6, IL-8,and IL-18 (63). Thus, alterations in ROS signaling induced by angiotensin II promote the release of various cytokines and leukocyte adhesion molecules to cause endothelial damage.

Angiotensin II also mediates activation of MAPK which is then followed by an increase in c-fos and c-jun gene expression along with increased AP-1 activity (64). This signaling cascade ultimately results in cell differentiation, adhesion and migration (65). Angiotensin II also stimulates ERK1/2 which has a significant role in developing hypertension and organ damage (66). Apart from these, it induces ASK-1 which further stimulate JNK and p38MAPK that leads to vascular inflammation (67–69). EGFR pathway is also influenced by angiotensin II. As a result, growth and hypertrophy follows in the atherosclerotic process (70).

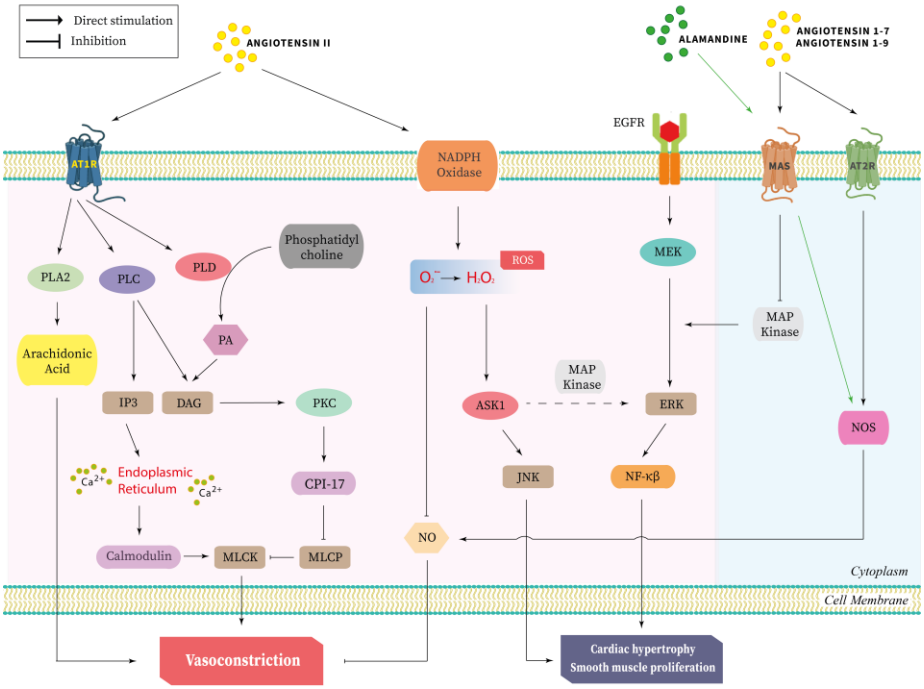

Fig 1: Role of RAS pathways in mediating cardiovascular functions.

The portion highlighted in pink and blue depicts the classical and counter-regulatory pathways of RAS respectively.

3.2. The counter regulatory pathway.

Compared to the classical pathway, a new axis of the RAS with counter regulatory functions has been identified. This axis consists of numerous peptides, enzymes and receptors. The two most important peptides of this axis include angiotensin 1-9 and angiotensin 1-7. In this pathway, AT2R plays an important role alongside another G-protein coupled receptor, the MAS protein. Both angiotensin 1-7 and 1-9 bind to the AT2R, while angiotensin 1-7 has a higher affinity to bind to MAS receptor than it binds to the AT2R (33, 71).

Angiotensin 1-7 activates the phosphatidylinositol-3- kinase Akt pathway. Akt plays a pivotal role in enhancing the vasodilatory functions of endothelial nitric oxide synthase. Also, long term treatment with angiotensin 1-7 prevents the progression of atherosclerotic lesion and improves the endothelial function of nitric oxide via the Mas receptor activation (72). This effect is seemingly mediated through both AT2R and Mas receptor. In contrast, Angiotensin 1-7 has inhibitory effects on MAP kinase pathways in endothelial cells, smooth

muscle cells and cardiomyocytes (73–75). Thus, the hypertrophic, oxidative and proliferative processes induced by angiotensin II are supposedly countereacted by angiotensin 1-7 through inhibition of these MAP kinase pathways. Also, several studies indicate that angiotensin 1-7 has inhibitory effects on smooth muscle cell proliferation and migration as well as on vascular inflammation via Mas receptor-mediated suppression of NF-κB or MAP kinase or both pathways (76). Infusion of angiotensin 1-7 also prevents cardiac remodeling induced by angiotensin II in rats (77). At the cellular level, alamandine, a decarboxylated product of angiotensin 1-7, acts via the MrgD receptor to induce AMPK/NO signaling in order to counteract the vasoconstriction of angiotensin II. It also inhibits the angiotensin II induced upregulation in the expression of PKA that ultimately leads to vasoconstriction (37).

Compared to angiotensin 1-7, angiotensin 1-9 exerts its effects via AT2R alone and inhibition of the Mas receptor has no effect on the biological effects of angiotensin 1-9. Angiotensin 1-9 reduces collagen synthesis which in turn reduces cardiac fibrosis (78). A decrease in Rho kinase activity induced by angiotensin 1-9 attenuates cardiac hypertrophy (23). However, most of the intricate details of this pathway is yet to be unveiled.

4. CARDIOPROTECTIVE ROLES OF MELATONIN

Permanent cardiovascular damage is a chronic process. A prolonged coronary arterial occlusion will result in chronic ischemia that ultimately leads to acute myocardial infarction. The pathological progression of atherosclerosis is accompanied by inflammation, endothelial dysfunction, smooth muscle cell cloning, and thrombosis (79–81). Development of atherosclerotic plaques and their rupture occlude the blood vessels thereby causing the tissue or organ ischemia (82). This is followed by an infiltration of inflammatory cells and inflammatory responses (83, 84). All these lead to a complex process of myocardial tissue remodeling, activation of apoptotic signals, mitochondrial dysfunction and myocardial necrosis (85).

Presently several renin-angiotensin inhibitors are available in the market for treating different cardiovascular infirmities. However, most of them have serious side effects that render them unfit for prolonged use. A brief summary of all the drugs prescribed for targeting the RAS pathway is given in Table 1 (86). Amongst the various endogenous molecules that combat the cardiac damage, a certain molecule has intrigued the scientists with it's multidimensional capabilities. This molecule is melatonin, discovered in 1958 from the bovine pineal gland (87). In the past few decades, scientists have revealed various beneficial effects of melatonin in a number of pathological conditions. During myocardial injury, melatonin scavenges the excess of free radicals, ameliorates inflammatory responses and inhibits apoptosis of cardiomyocytes (88). Melatonin can suppress atherosclerotic developments through activation of nitric oxide synthase, nuclear factor erythroid 2 related factor 2, SAFE and RISK pathways (88, 89). It enhances the stabilization of rupture-prone plaques to prevent ischemia (90). The antioxidant actions of melatonin include the upregulation of antioxidant enzymes and coordination with glutathione (redueded form) and NADPH (90). It also exerts anti-inflammatory effects by inhibiting aggregation of inflammatory cells and release of inflammatory cytokines including TNF-α, IL-1β and IL-6 (82). During acute myocardial infarction, cardiomyocytes experience a harsh microenvironment of hypoxia and ischemia that results in an inflammatory chain reaction resulting in myocardial necrosis (82). Apart from oxidative stress and inflammation, the key processes causing myocardial injury during myocardial infarction include mitochondrial injury and apoptosis (82). Melatonin stabilizes the structure and function of mitochondria by regulating mitochondrial oxidative stress, maintaining mitochondrial membrane potential and restoring mitochondrial energy metabolism (91). It also inhibits mitochondria-initiated

apoptosis; to the contrary, it promotes mitochondrial biogenesis, thereby breaking the vicious cycle of cell injury and protecting cardiomyocyte (82).

Table 1: List of drugs inhibiting the RAS pathway.

Type of Drug	Name of Drug	Side Effects
Renin Inhibitors	Aliskiren	Dizziness, palpitation, hyperkalemia, diarrhea, abdominal pain, anemia, angina, gastroesophageal reflux, gout, myositis, renal stone formation, rhabdomyolysis, seizure, hyperuricemia, nocturia
	Remikiren	
	Enalkiren	
	Zankiren	
	Ciprokiren	
Angiotensin converting enzyme Inhibitors	Benazepril	First dose hypotension, renal dysfunction, hyperkalemia, cough, angioedema, hepatotoxicity, skin rashes, dysgeusia, granulocytopenia, proteinuria
	Enalapril	
	Fosinopril	
	Lisinopril	
	Quinapril	
	Ramipril	
	Captopril	
	Moexipril	
	Trandolapril	
	Cilazapril	
Angiotensin II receptor blocker	Azilsartan	Hypotension, hyperkalemia, angioedema, headache, dizziness, weakness
	Candesartan	
	Eprosartan	
	Irbesartan	
	Losartan	
	Olmesartan	
	Telmisartan	
	Valsartan	

5. RAS-MELATONIN AXIS

The relationship of RAS and melatonin has been studied. It was found that the locally synthesized angiotensin could regulate the melatonin synthesis by activating melatonin synthetic enzyme, tryptophan hydroxylase and this action of angiotensin was mediated by AT1 receptors (92). Tryptophan hydroxylase is the first enzyme in the pathway of melatonin synthesis. The occurrence of the local RAS interfering with the synthesis of melatonin indicates the presence of a RAS-melatonin axis to maintain the general homeostasis of the body. A number of clinical trials have shown that patients with coronary heart disease, especially those with higher risks of hypertension and infarction, have a lowered production of melatonin (38).

6. POTENTIAL PROTECTIVE EFFECT OF EXOGENOUSLY PROVIDED MELATONIN ON CARDIOMYOCYTES

Melatonin was first discovered as a hormone of the pineal gland, functional in maintaining the circadian rhythm of the body. Thereafter, its presence was discovered in various other organs of the body and even in unicellular organisms, fungi and plants (93, 94). Since then, it

has emerged as a pleiotropic molecule exerting a variety of biological effects that are both receptor-dependent and receptor-independent. In the past few decades, several studies have successfully established melatonin as a potent cardio-protective molecule and has also identified its wondrous antioxidant capabilities (95, 96). Therefore, impeding the synthesis of this cardio-protective molecule can bring about disastrous consequences leading to cardiovascular pathogenesis. Focusing on the interaction between the RAS and melatonin can bring into the spotlight, newer dimensions of cardiovascular therapy.

The non-renewability of cardiomyocytes makes it essential to attenuate cardiac damage at its earliest and at the most effective manner, in order to improve chances of restoring normal cardiac functions. Melatonin has shown its potential in combating the cardiovascular diseases with various etiologies (95). Melatonin can intereact with a variety of important molecules to modulate different signaling pathways that ultimately accentuate its antioxidant, anti-apoptotic, antifibrotic properties as well as its free radical scavenging activity (97–99). It also has a major role in maintaining mitochondrial biogenesis and thereby, protecting cardiomyocytes (100). Inspite of the extensive knowledge that has already been excavated about this molecule, much is yet to be revealed and addressing the lesser known interactions might develop additional better target-oriented treatment regimes. Exploring the interaction of melatonin with the excessively activated RAS in the context of myocardial infarction might provide novel crucial information to put a brake to this condition.

Melatonin inhibits the production of ROS through various means. Apart from its direct free radical scavenging properties, it is well known for its modulatory hold on the synthesis and activity of antioxidant enzymes. A recent study has also pointed out that melatonin is capable of inhibiting the assembly of the enzyme NADPH oxidase by inhibiting the phosphorylation of the p47 subunit via the PI3K/Akt dependent pathway in microglia, which leads to attenuation of ROS generation (101). However, further study is required to determine whether melatonin is capable of inhibiting ROS generation by downregulating the activity of NADPH oxidase in cardiomyocytes as well.

Melatonin is inherently involved in maintaining the vascular tone through both its receptors, MT1 and MT2, which have complementary roles. The MT2 receptor is involved in mediating vasodilatory effects (102). In order to counteract the vasoconstriction mediated by angiotensin II, melatonin acts through the MT2 receptor and exhibits a crucial role by maintaining the bioavailability of NO which is essential for vasorelaxation of arteries.

While angiotensin II stirs up various inflammatory responses that have been mentioned before, melatonin's anti-inflammatory role has been established through numerous experiments. It reduces NF-κB binding to DNA which downregulates the expression of downstream molecules like IL-1, IL-6, TNF-α, etc (103). It also prevents leukocyte-endothelial adhesion and the production of adhesion molecules that are upregulated by NF-κB thereby curbing down inflammatory responses (104).

Melatonin has both direct and indirect effects on a number of components of the RAS. It inhibits calmodulin which stimulates the expression of ACE2 (96). A study by Chapell et al. has shown that melatonin increases *Agtr1b* and *Mas1* mRNA expression which oppose the vasoconstrictor arm of RAS and facilitate the functions of the counter-regulatory RAS pathway.

7. CONCLUDING REMARKS

As highlighted in this review, cardiovascular diseases are a serious threat to human health in all parts of the world, irrespective of the socio-economic and financial status of the person suffering from it. However, the economic challenge for healthcare systems increase

exponentially with every passing year (105). Multiple dimensions of the disease are capable of giving rise to several manifestations, which might even result in fatal outcomes if not treated in time. In this review, we have focused on the different aspects of the RAS pathway that allows it to play a key role in the etiology and progression of varied cardiovascular diseases along with a detailed discussion on the molecular basis of its effects. We have also discussed the role of melatonin, a hormone dedicated to the regulation of circadian rhythm and antioxidative activity which can actively protect cardiovascular tissues.

To our understanding, cardiac injury is marked by a distinct upregulation of the RAS system. This results in a marked decline in the overall pineal melatonin level, consequently stalling the cardioprotective effects mediated by melatonin. This in turn enhances the overall stress scenario in the cardiovascular tissue to form a vicious never-ending loop of stress generation. Melatonin administration might put an end to this noxious cycle. Thus, it can be suggested that melatonin is an inexpensive as well as a well-tolerated treatment modality for dealing with different cardiovascular diseases.

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AUTHOR'S CONTRIBUTION

Dr. AC and Dr. DB contributed to the conception, critically corrected and approved the manuscript. MD prepared, drafted, and edited the manuscript. RM contributed to the editing of the manuscript and preparing the tables and figures.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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