Review

Melatonin as a promising agent alleviating endocrine deregulation and concurrent cardiovascular dysfunction: a review and future prospect

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ABSTRACT

In animals, various endocrine signals modulate the growth and survival mechanisms, and disruption of their homeostasis may potentially cause physiological dysfunctions. Melatonin, a potent antioxidant and neuronal-endocrine hormone, regulates the activities of several other hormones including growth hormones, thyroid hormones, gastrointestinal hormones, and hormones related to reproduction and metabolisms. Specifically, several of these hormones tightly regulate cardiovascular functions. Their imbalance adversely affects cardiovascular integrity while hormonal therapies may aggravate the adverse cardiac events. Therefore, this review focuses on the cardioprotective potential of melatonin in light of endocrine instability-mediated cardiovascular dysfunction. Melatonin can suppress sympathetic overstimulation and reduce the cardiotoxicity of catecholamines and their derivatives. Interestingly melatonin effectively counteracts cardiovascular manifestation of thyrotoxicosis and autoimmune thyroiditis. This activity possibly attributes to its antioxidant property and regulation of iodothyronine-deiodinase activity. A disrupted circadian rhythm accelerates the onset of insulin-resistant diabetes. Melatonin as a circadian synchronizer, potentially preserves the diurnal pattern of insulin secretion and thereby, improves glucose tolerance and GLUT-4 expression in cardiac tissue preventing diabetogenic outcomes. At the molecular level, melatonin enhances tyrosine phosphorylation and subsequent activation of insulin receptor-associated tyrosine kinase. In addition, renin-angiotensin-aldosterone system (RAAS) overactivity can cause cardiac hypertrophy, hypertension, myocardial infarction, and congestive heart disease. Melatonin regulates the RAAS function to lower the non-dipper hypertension. Therefore, it is important to address the potential therapeutic effect of melatonin in endocrine dysfunctions that engender harmful cardiovascular implications.

Keywords: Melatonin, hormones, endocrine dysfunction, cardiovascular disorder, catecholamines, thyroid hormones, insulin, renin-angiotensin-aldosterone system (RAAS)

1. INTRODUCTION

The high prevalence of stress-induced disorders, metabolic impairments, nutritional deficiencies, and endocrine disruptions are threats to human health. The incidents of diabetes,

thyroid disorders, growth abnormalities, endometriosis, and polycystic ovarian disease are cataclysmically rising globally (1). Moreover, conventional medicines for correcting the hormonal imbalances have serious side effects with a noxious impact on human health, especially in the cardiovascular system. The mammalian cardiovascular physiology is tightly regulated by a complex hormonal nexus (2). The cardiomyocytes also exhibit endocrine properties. They produce cardiac-derived natriuretic factors- the atrial natriuretic peptides and brain natriuretic peptides to regulate the extracellular fluid volume, and thus to control blood pressure. Other hormones of cardiovascular origin are adrenomedullin and endothelin 1, both having roles in cardiovascular hemodynamics (3). Additionally, there are a plethora of hormones that directly or indirectly impact cardiovascular health (4).

The increasing evidence substantiates the immense role of endocrine factors in controlling cardiovascular functions. The cardiovascular system ensures uninterrupted delivery of nutrients and oxygen to the whole body even under increased stress (5). The blood supply to the tissues with increased demands is exquisitely regulated by the interplay of hormones (6). Therefore, certain hormones serve as protectors of stress-induced pathogenesis of the cardiovascular system (7, 8). Melatonin is one of them and is a well-known antioxidant and immunoregulative molecule (9-11). By optimizing carbohydrate, lipid, and calcium metabolism, melatonin replenishes cardiac energy deficiency during physiological and pathological stress (12). Melatonin protects against intense exercise-induced oxidative myocardial damage (13). The crosstalk of melatonin with various other hormones either promotes or suppresses their actions to produce the optimal effects (14) and such actions defend against execrable cardiovascular events (15). For example, melatonin has emerged as a potent protector for hypertension, diabetic cardiomyopathy, atherosclerosis, myocardial infarction, and other inflammation-associated cardiovascular diseases (16). Melatonin efficiently scavenges free radicals, suppresses pro-inflammatory cytokines, and prevents apoptotic death of cardiomyocytes (9, 10, 16, 17). Due to its negligible side effects even at high doses, melatonin has been used in various cardiovascular diseases either alone or as adjuvant therapy (18). Endocrine disorders and consequent hormonal disbalance jeopardize cardiovascular integrity (19, 20). Melatonin's ability to synchronize endocrine and metabolic events, especially in the cardiovascular system makes it a beneficial molecule in restoring cardiovascular health amid endocrine disturbances.

2. MELATONIN AS A HORMONE

Melatonin is a ubiquitous, amphiphilic indolamine produced from the pineal gland and many other extrapineal tissues (21). In 1917, McCord and Allen demonstrated that the secretion from pineal tissues of tadpoles lightened their skins (22). More than forty years later, Lerner *et al*. isolated the principal component of the pineal gland responsible for this bleaching effect (23). This substance is N-acetyl-5-methoxytryptamine or melatonin. Thereafter, all enzymes responsible for melatonin synthesis have been identified in the pineal gland (24). The precursor of melatonin is tryptophan, which is first converted into 5-hydroxytryptophan by tryptophan hydroxylase and the 5-hydroxytryptophan is decarboxylated to 5-hydroxytryptamine (or serotonin) by aromatic amino acid decarboxylase (AADC), and then, forms melatonin under the activities of enzymes AANAT and ASMT, subsequently (14). Melatonin acts as a hormone (25) and also as a paracoid, autocoid, and tissue factor (26). The pineal melatonin is transported via cerebrospinal fluid and blood to various tissues of the body and its lipophilic character enables it to cross the membrane barriers of the cell and the cellular compartments (21). By acting on its membrane receptors, MT1 and MT2, melatonin instigates a myriad of physiological activities (27) including developmental (28), metabolic (29), circadian (30), and reproductive (31) activities. Besides membrane receptors, melatonin seems also to bind to

orphan nuclear receptors- RZR/ROR. Melatonin also exhibits receptor-independent actions including its antioxidant activity, which is considered to be the original function of melatonin (21). Additionally, melatonin is called "the messenger of darkness" or "the signal of sleep" since melatonin has a circadian rhythm with a peak at night and a low level during the day, thus promoting the sleep-wake cycle (32). Its nighttime level is about 10-40 times higher than that during the day (33). This circadian rhythm can be disrupted by the nighttime bright light exposure (34). In humans, the foetus synthesizes little melatonin but maternal melatonin can be transported to the foetus through the placenta and the neonates can obtain melatonin from the breast milk. Thereafter, the neonates start to synthesize melatonin at the age of 9-12 weeks (35, 36). After the age of five years, melatonin production decreases gradually with age (37).

The argument of melatonin being exclusively a hormone has been challenged since the non-receptor mediated free radical scavenging function of melatonin is considered to be its primary function from the emergence of aerobic lifeform (38, 39). Melatonin possesses pleiotropic effects that discern it from other classical hormones. However, such claims do not exclude melatonin from hormonal category. The physiological role of melatonin in the mammalian body well justifies the classical definition of a hormone, which are communicative molecule synthesized by endocrine organs of the pineal gland and being transported through the circulation to distant organs where they accomplish their specific physiological activities (26). Besides, melatonin is synthesized in various extrapineal locations, including the retina, cerebral cortex, striatum, gut, liver, spleen, thymus, testis, placenta, and cardiac and skeletal muscles (40). Melatonin has been detected in almost all body fluids such as saliva, bile juices, breast milk, cerebrospinal fluid, synovial fluid, and amniotic fluid (41). The concentration of melatonin in biological fluids, as in plasma and saliva, oscillates in a circadian pattern (42).

3. FUNCTIONAL INTERPLAY BETWEEN MELATONIN AND OTHER HORMONES

The growth, development, and survival of multicellular organisms are not only controlled by genetic and nutritional factors but are also tightly integrated by endocrine signals. Disrupted interplays among hormones, growth factors, and their cellular responses are responsible for the genesis of diabetes, obesity, metabolic syndrome, ischemic heart disease, and heart failure (43-45). Melatonin is a key player in the central serotonergic pathway controlling growth hormone synthesis (46). Animal experiments and clinical studies have shown that pinealectomy retards the overall growth and development of sexual organs (47, 48). Activation of the rate-limiting enzyme of melatonin synthesis, serotonin-N-acetyltransferase (SNAT), increases pineal melatonin production during darkness (49). Blinding and persistent darkness reduce the growth hormone production in the pituitary gland resulting in body growth retardation, decreased tibial length, receding weight of accessory organs, and underdevelopment of the gonads. However, pinealectomy reversed these effects- promoted weight gain and restored pituitary hormone levels (50). Evidence obtained from *in vitro* studies in chick embryo muscle cells has demonstrated that melatonin either directly or by its interaction with growth factors promotes cellular growth initially at low doses, whereas prolonged supraphysiological dose inhibits it (51, 52). Indeed, melatonin precursors have a divergent response in different poultry breeds. In birds like turkey and quail, growth hormone concentration in blood escalates in response to serotonergic signals (53). Conversely, increased serotonin concentration corresponds to augmented somatostatin secretion, which has an inhibitory effect on growth hormone release in chickens (53). Melatonin's effects on growth and development are also mediated by its influence on thyroid hormone levels. Melatonin impacts thyroid hormone concentration in a seasonal manner. Melatonin suppresses T4 levels across the year, while it promotes T3 secretion during longer days and reduces its blood

concentration during short photoperiod (55). The increased melatonin production in short photoperiod leads to the inhibition of Tshb (that encodes the β-subunit of thyroid-stimulating hormone) resulting in decreased TSH production. The binding of TSH to its receptor leads to the activation of deiodinase 2 (Dio2), thereby promoting the conversion of T4 to its active form T3. On the contrary, deiodinase 3 (Dio3) impedes T3 activation. The increased melatonin enhances the activity bias from Dio2 towards Dio3, thus antagonizing the action of TSH and subsequent suppression of T3 production (56). In addition to thyroid hormones, melatonin reduced plasma levels of leptin, ghrelin, and galanin, indicating its promising role in regulating appetite (57). Melatonin administration lowered plasma leptin concentration in Siberian hamsters (58). Leptin, on the other hand, directly affected pineal melatonin production (55). Pinealectomized rats had increased blood vasopressin levels while melatonin administration reversed this effect (59). Seasonal shifts alter the duration of nocturnal melatonin secretion and this, in turn, impacts the reproductive physiology of photoperiodic breeders (46). The hypothalamic and pituitary hormones that control the mammalian reproductive cycle exhibit a circadian pattern similar to melatonin. During puberty, the pulse frequency of GnRH, LH, and FSH reaches its peak during the night which correlates to the maximum melatonin level (60). In women, during the ovulation period, the cyclical spike of their gonadotrophin hormone blood level is more pronounced during the late-night period positively related to melatonin production (61, 62). Interestingly, follicular fluid in the preovulatory phase contains a significantly higher concentration of melatonin than that in plasma (63). In both preovulatory follicles and cultured granulosa or luteal cells, melatonin levels are also positively correlated with progesterone concentration (64). A similar synergistic association was observed in the cultured granulosa cells between melatonin and human chorionic gonadotrophin. Melatonin at higher concentrations can induce hCG production in trophoblast cells (65). Melatonin is used for infertility caused by oxidative stress-mediated follicular injury due to its ability to scavenge intra-follicular ROS (66). *In vitro* experiments on uterine smooth muscle cells have demonstrated that melatonin stimulates oxytocin-induced myometrial contraction, thus having a potential role in parturition (67).

4. DISRUPTION IN ENDOCRINE FUNCTION AND ITS EFFECT ON CARDIOVASCULAR HEALTH

Not only does the neurohormonal system immensely regulate cardiovascular homeostasis, but the heart itself has neuroendocrine-like functions and produces several hormones and growth factors. These dynamic interactions between the heart and the endocrine system are essential for the regulation of cardiac metabolism (2). Therefore, alterations of plasma and cellular levels of hormones often lead to an increased risk of cardiac dysfunction and cardiovascular pathologies. Hormones acting on the cardiovascular system exert their effects through both hemodynamic and non-hemodynamic mechanisms (4). The hemodynamic actions involve modulation of peripheral vascular resistance and alteration in cardiac output, while the non-hemodynamic actions may directly affect the cardiovascular tissue through metabolic, inflammatory, and oxidative stress-mediated mechanisms (4). Diabetes, obesity, metabolic syndrome, and thyroid disorders are also associated with hormonal alterations, which subsequently may jeopardize cardiovascular function (20). The obesity-associated neurohormonal disorder leads to hemodynamic changes with increased hypervolemia and hypertension, metabolic changes including insulin resistance, hyperglycemia, dyslipidemia, inflammation, lipotoxicity and mitochondrial dysfunction (68). Hormones including leptin, adiponectin, and insulin can improve myocardial efficiency for energy production by stimulating AMP-kinase (AMPK) activity which enhances glucose metabolism and fatty acid oxidation to replenish cardiac metabolic demand (69).

Endocrine disorders, encompassing both hormonal deficiency and excessively high levels, can forge functional anomalies in the cardiovascular system (20) while treating them with conventional drugs also has some serious cardiovascular side effects. The treatment with growth hormones, prolactin, and adrenocorticotrophic hormones may temporarily preserve cardiovascular functions but may cause permanent cardiovascular damage (20). For instance, a high level of growth hormone-associated acromegaly may cause hypertension, myocardial hypertrophy, valvular dysfunction, arrhythmia, ventricular dilatation, and systolic and diastolic dysfunction (70-72). Patients with acromegaly often develop atherosclerotic lesions. The somatostatin analogues can improve cardiac arrhythmias in patients with acromegaly (73), but they have little effect on atherosclerosis (20). Cushing's syndrome or hypercortisolism, occurring as a manifestation of excessive ACTH stimulation, leads to metabolic upset and consequent development of diabetes, hypertension, and obesity, all of which have cardiovascular consequences (74). Besides, a high blood prolactin level is associated with insulin resistance, abnormal lipid profile, high blood pressure, and other related cardiovascular conditions (75, 76). The cathepsin D-cleaved 16 KDa prolactin fragment is involved in the pathogenesis of postpartum cardiomyopathy (77). Both glucocorticoid and mineralocorticoid deficiencies are linked with abnormal electrocardiographic alterations (78). Likewise, growth hormone deficiency causes a decreased left ventricular mass and a thickened interventricular septum. Growth hormone deficiency is also characterized by dyslipidemia, endothelial dysfunction, and an increased risk of atherosclerosis (79).

5. MELATONIN REGULATES THE ENDOCRINE FUNCTIONS TO PRESERVE CARDIOVASCULAR HOMEOSTASIS

Melatonin exhibits its protective effects on both acute and chronic cardiovascular pathologies including ischemia-reperfusion injury and myocardial infarction (16). The mechanism partially involves the suppression of TLR4 signaling cascades (80) and activation of the Notch1/HES1/AKT/BCL2 pathway which significantly attenuates apoptosis in myocardial infarction (81). Melatonin restores the optimal blood lipid concentration and also curbs ROS-stimulated inflammasome activation, adeptly preventing atherosclerosis. The anti-atherosclerotic activity of melatonin lowers triglyceride levels, averts LDL oxidation, attenuates endothelial dysfunction, and minimizes proinflammatory macrophage polarization (82). Melatonin significantly ameliorates alteration in cardiac metabolomics and energy depletion in case of heart failure (83). Melatonin levels are lower in heart failure patients with hypertensive cardiomyopathy compared to healthy subjects (84). Undoubtedly, melatonin possesses a critical function in cardiac health. Herein, we discuss, the potential involvement of melatonin in restoring cardiovascular function by modulating the endocrine system.

5.1. Protective role of melatonin in catecholamine-stress-induced cardiovascular abnormalities.

Epinephrine, the hormone known for its fight-or-flight response during stressful circumstances, activates the β-adrenoceptors in skeletal muscles, leading to vasodilation and increased blood flow to the muscles (85). On the contrary, epinephrine can also induce vasoconstriction by acting on α_1 and α_2 adrenergic receptors, respectively. These are responsible for the positive chronotropic and ionotropic responses of adrenaline (86). At the molecular level, epinephrine can stimulate SOD activity, thereby promoting the dismutation of superoxide ions into hydrogen peroxide (H_2O_2). The moderate level of H_2O_2 during optimal exercise induces e-NOS-mediated vasodilation in skeletal muscle. Adrenaline at physiological concentration also promotes antioxidant functions. Other adrenergic agonists including

norepinephrine can cause oxidative stress through the autooxidation process (87). Epinephrine at a high concentration can elevate the plasma C-reactive protein (CRP), a hepatic component released during systemic inflammation (88). A high circulatory CRP level is often indicative of deteriorating cardiovascular health (89). The metabolic byproducts of epinephrine such as quinoproteins, adrenochromes, and adrenolutin are possibly responsible for the cardiotoxic repercussions of epinephrine (90). The administration of melatonin in rats ameliorated adrenaline autooxidation-driven cardiac tissue damage through its antioxidant mechanisms (13). Besides, melatonin curbs cardiac norepinephrine turnover and also prevents norepinephrine-mediated lipid peroxidation, glutathione oxidation, apoptosis, and inflammation (91). Melatonin may directly curtail sympathetic activities, thus suppressing the positive chronotropic, ionotropic and hypertensive effects of norepinephrine (92). The antioxidant ability of melatonin is associated with decreased sympathetic tone and an enhanced baroreflex in spontaneously hypertensive rats (SHR). The results suggest an increased NO production in vascular endothelial cells in melatonin-treated SHR groups (93). Melatonin administration preserves optimal heart rate and reduces catecholamine release and β-adrenergic receptor expression to normalize blood pressure in animals (94). The regulation of sympathetic tone by melatonin is partly attributed to its antioxidant function and is comparable to conventional antioxidants such as N-acetylcysteine (95). The sympathetic hyperactivity links between anxiety disorders and the onset of cardiovascular pathologies. A sustained increase in catecholamine levels may contribute to myocardial injury caused by coronary spasms, ischemic damage, and arrhythmia. Interestingly, $\beta_{1,2}$-antagonist, used in the treatment of sympathetic overactivity, has been found to be beneficial in treating physiological distress pertinent to anxiety including hyperventilation, tremors, chest pain, and palpitation (96). In this regard, melatonin exibits a positive impact since it has both sympatholytic and anxiolytic effects. Melatonin has been used to cope with pre- and post-surgery anxiety. The mechanisms involve the interaction with melatonin receptors in the brain as well as modulation of the circadian rhythm, neurotransmitters, and glucocorticoid signaling (97) (Figure1).

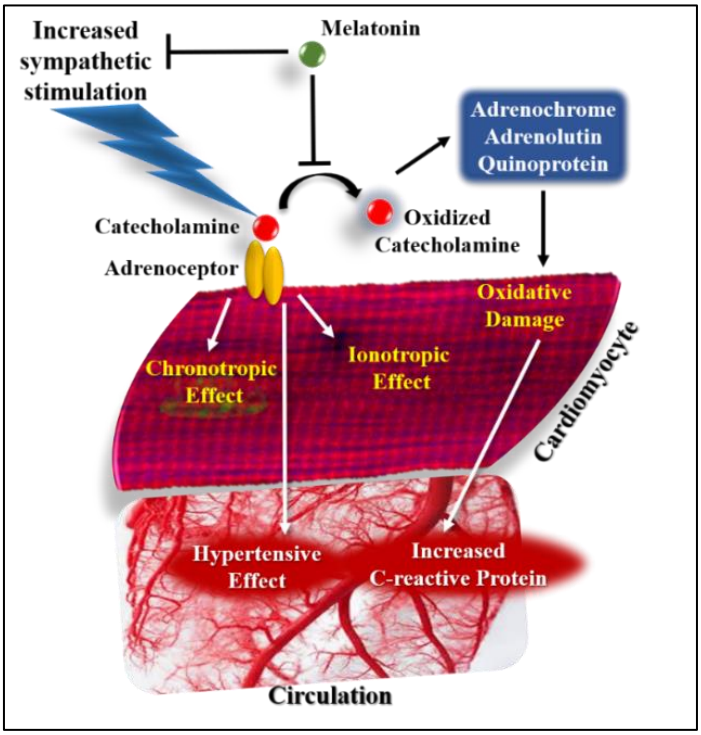

Fig.1. The protective mechanisms of melatonin against catecholamine-mediated cardiac and vascular dysfunctions.

5.2. Melatonin supports cardiovascular health against thyroid hormone imbalance.

Both hyperthyroidism and hypothyroidism cause systemic pathologies including cardiovascular abnormality. Hyperthyroidism and thyrotoxicosis lead to abnormal T3 and T4 concentrations in the blood. Unbridled overproduction of thyroid hormones referred to as "thyroid storm" can be lethal due to their potential life-threatening cardiac complications (20). The cardiac manifestations of hyperthyroidism include decreased systemic vascular resistance, increased cardiac preload, the augmented force of cardiac contraction, tachycardia, systolic hypertension, pulmonary hypertension, and overall increased cardiac work burden (98, 99). In thyrotoxic patients, the resting sinus tachycardia is primarily due to increased sympathetic and reduced parasympathetic activities. Increased sympathetic stimulation and consequent strain on cardiac tissue often lead to cardiac hypertrophy and the eventual hypoxia, coronary spasm, and angina pectoris (99). Patients with hyperthyroidism have cardiac output deficiency in response to stressful events such as exercise or pregnancy. Without proper treatment, it can result in elevated atrial filling pressure and pulmonary edema (100). Hypothyroidism also causes cardiomyopathy, albeit cardiovascular dysfunction includes negative ionotropic and chronotropic effects and diastolic hypertension in patients (101). The hypothyroidism-associated bradycardia and ventricular arrhythmias are caused by impairment in cardiomyocyte K^+ ion channel activity indicated by the longer QT interval in the ECG of these patients (102).

The parafollicular cells of the thyroid gland can secrete melatonin under the influence of TSH (103). Studies have established a reciprocal relationship between the activities of the pineal and the thyroid gland, whereby pineal melatonin exerts an inhibitory effect on the growth and activity of the thyroid tissue while the thyroid hormones stimulate the growth and function of the pineal gland. The suppressive action of melatonin on thyroid hormone synthesis is possibly mediated by its regulation of iodothyronine-deiodinases. Therefore, melatonin exhibits a cardioprotective effect against hyperthyroidism-associated cardiomyopathy (104). In addition, the antioxidant activity of melatonin protects the thyroid tissue against oxidative stress implicated in autoimmune thyroid disorder. Therefore, melatonin may have a protective role against autoimmune thyroid disease-related cardiovascular complications (105) as illustrated in Figure 2.

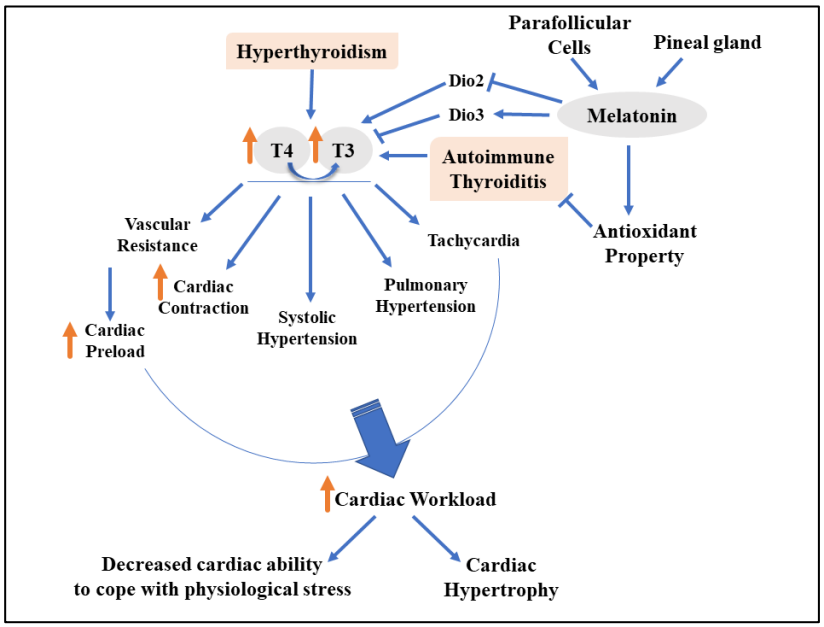

Fig. 2. The potential mechanisms of melatonin protection on hyperthyroidism-induced cardiovascular impairments.

5.3. Effects of melatonin on hormones associated with glucose homeostasis and its role in cardiometabolic disease.

Glucose homeostasis refers to the regulation of glucose metabolism in a way that promotes optimal glucose supply, utilization, and maintenance of a limited glucose pool in the circulation. This requires an orchestrated interplay among several hormones, including insulin, glucagon, growth hormones, catecholamines, glucocorticoids, incretins, and resistins (106). The ability of tissues to perceive and respond to an altered metabolic status and fuel availability varies significantly in conditions like obesity and type 2 diabetes (107). The cardiovascular system is adversely affected by disturbance of glucose homeostasis, as observed in metabolic syndrome (108). Insulin is the most dominant player in the glucose metabolism. Insulin secretion is upregulated by the raised blood glucose level. It promotes hepatic uptake and peripheral utilization of glucose, but antagonizes glucagon action, inhibits lipolysis, and facilitates the protein synthesis pathway (109). However, diabetes entails impairment in glucose regulation and utilization by tissues. Type-I or insulin-dependent diabetes is marked by the destruction of pancreatic β cells with low insulin production, therefore, have dramatically elevated blood glucose levels along with disrupted blood lipid profile in patients with Type-I diabetes. On the flip side, type-I diabetes patients supplemented with insulin often experience episodes of acute hypoglycemia due to the blunted glucagon secretion. Both circumstances may pave the way for baneful cardiovascular complications (110). Unlike type-I diabetes, type-II diabetes is mainly associated with impaired insulin receptor sensitivity in the peripheral tissues. (111).

Oxidative stress contributes greatly to diabetes-related cardiovascular derangements. Therefore, antioxidant therapies play a vital role in managing diabetic cardiomyopathy (106). The rise in circulating oxidative and inflammatory markers as well as the impeded antioxidant defense are observed in type-II diabetes and antioxidant therapy protects these patients against oxidative stress-mediated cardiac and vascular dysfunctions. The misalignment of circadian rhythm is known to accelerate the onset of insulin resistance in diabetes (111). The circadian synchronizer melatonin improves glucose tolerance, insulin sensitivity, and muscle and hepatic glycogenesis, whereas pinealectomy shows diabetogenic consequences (112). The antioxidant activity of melatonin lies at the core of the anti-diabetic efficacy of this pineal component. At the molecular level, melatonin modulates the insulin-signaling pathway by revving up the tyrosine phosphorylation and the activation of insulin receptor-associated tyrosine kinase. Melatonin-stimulated insulin growth factor receptor activation enables the growth and differentiation of cells in the pancreatic islets (113). GLUT4 enables insulin-stimulated transport of glucose into the cardiac cells (114) and depletion of melatonin reduces GLUT4 expression in the cardiac tissue of rodents. Oxidative stress may wreck the transport activity of GLUT4 to reduce the cardiac glucose supply while melatonin can restore GLUT4 expression in cardiac tissue (115). In fact, the action of melatonin on insulin secretion is quite complicated. MT1 and MT2 both are present in pancreatic β cells (116). The MT1 activation curbs insulin secretion by impeding the cAMP/PKA pathway and MT2 activation reduces cGMP production and hence minimizes insulin secretion further. Melatonin induces calcium mobilization in pancreatic cells via the IP3/DAG pathway and thus enhances insulin secretion (117). Such ambiguous actions of melatonin on insulin secretion create an enigma about its effect on glucose homeostasis. In general, melatonin and insulin exhibit inverse circadian patterns, which means that the insulin secretion rate declines in the dark hours and is observed to be lowest late at night. Insulin secretion escalates after midday and peaks in the afternoon. A disruption in nocturnal melatonin production, often instigated by nighttime light exposure, leads to unwanted insulin secretion during the passive phase resulting in insulin resistance

(118). In rats, alteration in light/dark conditions leads to dramatic variation in circulating glucose concentration and is pertinent to the derangement of clock gene functions (117). In pinealectomized and high-fat diet-fed rats and melatonin receptor-deficient mice decreased blood melatonin levels were associated with loss of glucose tolerance and insulin resistance, both of which were abolished upon melatonin administration (119). The potential mechanisms of melatonin in the prevention of insulin resistance are summarized in Figure 3.

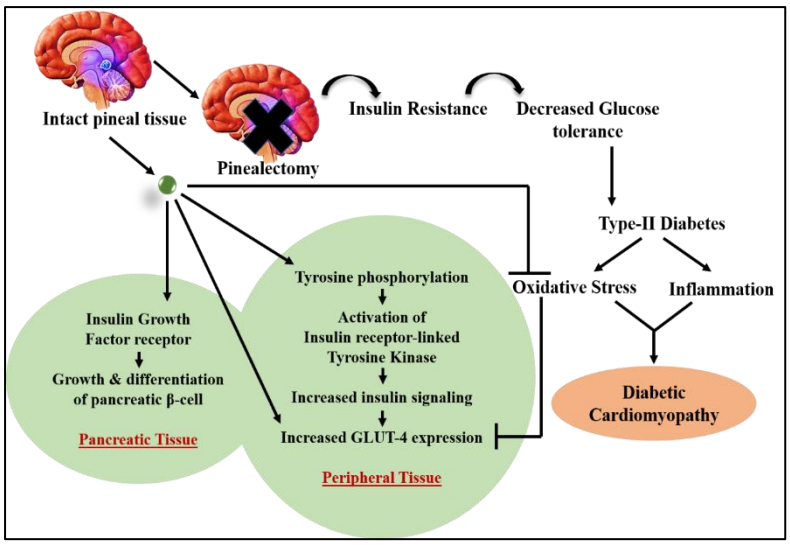

Fig. 3. A mechanistic view of the ameliorative effect of melatonin against insulin resistance and diabetic cardiomyopathy.

5.4. Renin-angiotensin-aldosterone-system (RAAS) in cardiovascular dysfunction and the mitigative effect of melatonin.

The RAAS comprises a cascade of biochemical events that involves multiple organs, including the liver, kidney, lungs, and adrenal gland, that together play a vital role in maintaining hemodynamic stability under physiological conditions. However, overactivation of RAAS has been associated with hypertension, cardiovascular tissue hypertrophy, acute myocardial infarction, congestive heart failure, and stroke (120-123). The classical renin-angiotensin-aldosterone pathway begins with an aspartyl protease, renin, synthesized by the juxtaglomerular cells of the kidney. Renin converts the hepatic-derived angiotensinogen to angiotensin-I (AT-I), the rate-limiting reaction of the series. Angiotensin-converting enzyme (ACE), a metalloprotease primarily produced by the lungs, then cleaves AT-I to its active form angiotensin-II (AT-II), which then exerts a myriad of biological actions in the body (124). In addition to this systemic pathway, several studies have substantiated the presence of the local Renin-Angiotensin System (RAS) that operates through autocrine/paracrine mechanisms rather than the endocrine pathway (125). One such local renin-angiotensin system serves in the brain. Angiotensinogen has been detected in the glial cells of the pineal gland, along with ACE and chymase (126). Pinealocytes harbor angiotensin receptor subtype 1-b (AT-1b). AT-II binds to AT-1b in pineal cells and stimulates melatonin synthesis through its direct influence on the activity of tryptophan hydroxylase (TPH) (127).

Gene modulation studies in rats have divulged an existing relationship between RAS and circadian oscillators to control cardiovascular activities (128). Most of healthy people experience a 10-20% nocturnal drop in blood pressure (BP) compared to the daytime. It is known as the dipping BP pattern. Individuals with circadian desynchronization have non-dipping BP with less than 10% reduction during this resting phase (129). The clock genes

construct the molecular framework of circadian integrators to control cardiovascular functions, while mutations in those genes affect cardiovascular harmony (130). For instance, transgenic hypertensive rats carrying a transfected mouse renin gene exhibited phase delay in their clock gene expression. This results in an inverted blood pressure profile in these transgenic rats with higher diastolic blood pressure at the resting phase (light phase) than the active phase (dark phase) (127). Such reversal of BP profile corresponds to the altered magnitude of aldosterone rhythm. In the transgenic rats, the circulatory aldosterone concentration was found to be ten times higher than that of control animals, and the maximum rise in aldosterone level was observed towards the end of the daytime (passive phase) (131). Such an increase in aldosterone concentration possibly leads to mineralocorticoid receptor resistance, resulting in a hypotensive state during the active phase. Further, studies have demonstrated that non-dipping hypertensive patients experience an impaired melatonin rhythm characterized by a lack of periodic urinary elimination of 6-sulphatoxymelatonin, the primary melatonin metabolite (132). Several lines of evidence have pointed out that melatonin and angiotensin-II control cardiovascular functions in an antagonistic manner. Both melatonin and A-II regulate BP by their direct or circadian mechanisms (16). Besides its direct vasodilation effect, the chronobiotic action of melatonin also restrains non-dipper hypertension, possibly by regulating clock gene expression (133). Unlike A-II, which constricts blood vessels and stimulates vascular sympathetic tone, melatonin imparts a sympatholytic effect (92). As opposed to A-II, melatonin counteracts oxidative stress and suppresses inflammatory damage in the cardiovascular tissues, hence emerging as a potential cardioprotective candidate (16). However, further studies are needed to apprehend the possible interaction between melatonin and the RAS pathway that potentiates or alleviates cardiovascular pathophysiology. Randomized controlled trials have reported that oral administration of controlled-released melatonin provides significant protection from high systolic pressure during the night. However, such clinical evidence must be further validated by a large number of high-quality trials (134).

6. SUMMARY AND FUTURE PERSPECTIVE

In the current scenario, cardiovascular diseases are one of the dreadful medical disasters causing morbidity and fatality at an early age. Many of these cardiovascular events are intimately associated with the functional impairment of the endocrine system. The rising prevalence of endocrine disorders including thyroid dysfunction, diabetes, obesity, and gynecological conditions has dramatically escalated the cardiac health burden, globally. In such cases, it becomes extremely important to identify and delineate a potent therapeutic strategy that can target cardiovascular issues as well as overcome the underlying endocrine challenges. The current review summarizes the available literature that corroborates the beneficial effects of melatonin on hormonal dysregulation-mediated cardiovascular anomalies. Melatonin has the capacity to restore cardiac physiology during stressful events, in thyroid disorder, glucose metabolic imbalance, and RAAS dysfunction. However, there are several unsolved facets concerning the role of melatonin in thyrotoxic heart failure, diabetic cardiomyopathy, acromegalic cardiomyopathy, and endocrine hypertension that are yet to be investigated. Moreover, the possible role of melatonin in obesity-associated endocrine disruptions that have virulent cardiovascular repercussions demands scrupulous study. Endocrine changes during pregnancy impose enormous stress on maternal cardiovascular homeostasis. However, the effectiveness of melatonin therapy in gestational endocrine alterations and associated cardiovascular impairments lacks comprehensive information and could emerge as a novel research area.

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AUTHORSHIP

DB and AC developed the concept, revised the manuscript thoroughly, and approved it. SS contributed to the conception, drafted the manuscript, prepared the figures, and edited the manuscript.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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