Review

Melatonin as a prospective metabolic regulator in pathologically altered cardiac energy homeostasis

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ABSTRACT

A constant energy supply is indispensable for the relentlessly working heart. The unique metabolic flexibility of the cardiac tissue enables it to maintain its energy requirement under variable physiological conditions. However, some physiopathological statuses including aging, ischemia-reperfusion injury, diabetic cardiomyopathy, pathological cardiac hypertrophy, and heart failure frequently cause cardiac dysfunction and detrimental metabolic alteration. If the ATP supply fails to match the requirement of a working heart, the heart loses its functional capacity, resulting in slower recovery. A decrease in energy generation is often the ramifications of myocardial mitochondrial dysfunction and oxidative stress. Melatonin, a broad-spectrum antioxidant molecule has an appreciable role in the maintenance of metabolic homeostasis— from a single cell to an entire organism. Melatonin has the capacity to reduce ROS generation, preserve mitochondrial stability, and restore a robust mitochondrial function for unabated ATP production in cardiac tissues. Additionally, melatonin can promote carbohydrate and fat metabolism to further improve the ATP production in heart. In cardiac cells, melatonin upregulates GLUT4 expression either by impeding oxidative stress or by enhancing AMPK activation which accelerates fatty acid oxidation by upregulating PPAR-α and CPT-1α. Melatonin plays a pivotal role in the maintenance of calcium homeostasis in cardiomyocytes by obviating oxidative stress-mediated disruption of SERCA and NCX proteins. A possible role of melatonin to convert the Warburg effect to oxidative metabolism in pathological cardiac events has been recently contemplated. The current review will discuss the possible role of melatonin protecting against cardiac metabolic imbalances under pathological states.

Key words: Cardiomyopathy, melatonin, carbohydrate metabolism, fat metabolism, calcium homeostasis, mitochondrial dysfunction, oxidative stress.

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1. INTRODUCTION

The ceaseless contractile activity of the heart requires an uninterrupted supply of energy. To fulfil the metabolic demands, the myocardial cells have evolved an ability to utilize a wide range of substrates for energy metabolism (1). This enables the heart to adapt to various physiological challenges during its lifetime from the fetal stage to old age (2). The

fetal heart encounters a low oxygen environment; hence, has a different fuel preference than that of the adult heart (3). While glucose is the substrate of choice for the fetal heart, a neonatal heart relies on fatty acid oxidation for the production of ATP (3, 4). During intense exercise, lactate can emanate as the prime substrate contributing to oxidative metabolism and ATP generation (5). Although such metabolic flexibility of cardiac tissue is essential for the survival, growth, and maintenance of cardiac functions, altered metabolism during pathological circumstances can lead to maladaptive cardiac remodelling (2).

Preservation of cardiac energy metabolism under stressful conditions including cardiovascular disorders, physical exertion, and aging is a huge physiological challenge. Cardiac and other non-cardiac originated disorders such as systemic inflammation or metabolic diseases often converge into a common molecular mechanism that ultimately affects the cardiac metabolism (6, 7). One example is lack of appropriate substrate supply to the cardiac tissue. Normally, 70% of ATP supply in cardiac tissue are derived from fat oxidation and the rest is from glucose metabolism (8). Under stressful conditions, this normal ratio is disturbed by altered substrate availability or by altered functions of mitochondria (2). In either case, the cardiac tissue requires the adaptation to recover energy supply. To our best knowledge, melatonin is such a cardioprotective molecule (9). The circulatory melatonin in blood is mainly derived from the pineal gland of mammals but other tissues and cells can also synthesize melatonin for its local use (10). Cardiac tissue *per se* can generate melatonin and it also extracts a prodigious amount of melatonin from blood (11). Melatonin is synthesized during dark, and light exposure at night suppresses melatonin production. Indeed, the increased nocturnal light exposure in modern humans inevitably lowers their blood melatonin level. This disruption in night-time melatonin production has a strong association with increased heart disease (12). Subjects with lower blood melatonin concentration have higher prevalence to develop myocardial ischemia and coronary heart disease (13). Additionally, patients with coronary artery disease and congestive heart failure had a lower urinary melatonin metabolites (10, 14). Accordantly, most of these cardiac disorders exhibit a deteriorated metabolic profile (15). Melatonin, on the other hand, promotes energy metabolism (12). In the present review, our focus is to gather the available information concerning the roles of melatonin in the restoration of metabolic homeostasis by mitigating the maladaptive metabolic alteration in various cardiopathological conditions.

2. CARDIAC MUSCLE METABOLISM

The heart has been regarded as an “omnivorous organ” because of its excellent potential to utilize a varied range of substrates for energy production (16). The metabolic function of cardiac tissue enables it to produce enormous amounts of ATP, which accounts for 15-20 times the weight of the heart in a day (1). The predominant substrates used by the cardiomyocytes are fatty acids and glucose. However, through strategic flexibility, cardiac cells can quickly adapt to other available substrate, and sustain their robust metabolic performance at various stages of life and under different physiological circumstances (17).

2.1. Cardiac metabolism in fetal life.

Relative hypoxia or low oxygen tension in the fetus as compared to adults is imperative for the development of the embryonic heart. This hypoxic state, however, demands an efficient fuel source that can be utilized even at an arterial blood pO_2 of 30 to 20 mmHg, as is found in the fetus (18). Glucose oxidation yields a larger amount of ATP per mole of oxygen consumed than other substrates, and hence it is the preferred substrate in fetal hearts (17). Although small amounts of fatty acids, triglycerides, and ketone bodies are present in the

fetal blood, the paucity of mitochondria in fetal cardiomyocytes and their insufficient fat oxidation capacity make lipid a minor fuel source (2). The relative low oxygen environment activates the transcription factor— the hypoxia-inducible factor (HIf) that promotes angiogenesis, fetal heart remodeling, and modulates the expression of genes related to glucose metabolism (18, 19). The fetal heart stores a large volume of glycogen (about 30% of the total volume of embryonic cardiomyocyte), indicating the significance of glycogen metabolism in the developing heart (20). Intriguingly, glucose no longer remains the substrate of choice in the neonates. As soon as the newborn is exposed to an oxygen-rich environment, the cardiac tissue switches towards the use of fat as the principal fuel source (8).

2.2. Cardiac metabolism during pregnancy.

Pregnancy is associated with altered hormonal status and a consequent changes in the metabolic profile that is manifested in the cardiac tissue. The increased mass of the maternal heart, increased angiogenesis, mild transient cardiac dysfunction, increased stroke volume and cardiac output along with pregnancy-induced tachycardia are the typical features of a pregnancy-related cardiac adaptation (21-23). This metabolic adaptation includes the decreased reliance on the carbohydrate fuel source and increased utilization of other substrates such as lactate, ketone bodies, fatty acids, and triglycerides (24-26). A spike in circulating levels of certain hormones and growth factors, particularly the progesterone and fibroblast growth factor 21 (FGF21) is responsible for the suppression of carbohydrate catabolism and the dominance of fatty acid (you can use Fatty acid or fatty acid, but you need to unify them throughout the text!) metabolism during pregnancy (2). Both progesterone and FGF21 upregulate pyruvate dehydrogenase kinase (PDK) 4 which in turn curbs glucose oxidation while stimulating fatty acid oxidation (27). The carbon atoms of glucose participate in the ancillary anabolic processes, instead of being utilized for ATP generation. Therefore, the pentose-phosphate pathway, sorbitol-aldose reductase pathway, hexosamine biosynthetic pathway, and glycerophospholipid synthesis pathway— may all be upregulated during pregnancy, contributing to pregnancy-mediated myocardial remodeling (2).

2.3. Exercise-induced alteration in cardiac metabolism.

Exercise-induced cardiac metabolic changes can be categorized into — acute and chronic adaptations. They are attributed to the type of exercise, workload, substrate availability, and the hormonal surge in the cardiac tissue in response to exertion. The low to moderate intensity exercises increase myocardial energy demand with the enhanced fat and carbohydrate catabolism (28, 29). Increased workload during exercise episodically elevates the secretion of epinephrine and nor-epinephrine which further enhances oxidative metabolism of glucose, fatty acids, lactate, and branched-chain amino acids (30-33). Epinephrine activates phosphofructokinase (PFK) to accelerate glucose metabolism for ATP production (33, 34). On the other hand, the extremely intense exercises, for example, in weight training or long-duration endurance session will lead to a rise of circulatory lactate and free fatty acids and allocate glucose for the anabolic reactions (35). Exercise-adapted heart, however, has an elevated overall rate of glucose uptake and utilization. Indeed, trained individuals have higher resting glycolytic activity than sedentary individuals (2). Hormones like insulin-like growth factor-1(IGF1) and neurogenin-1 are partly responsible for such exercise-induced cardiac metabolic adaptation. These hormones activate protein kinase B that stimulates the activity of PFK-2 to promote glycolysis and cardiac hypertrophy (36-38). Increased glucose and fatty acid oxidation during exercise also raises AMP/ATP ratio that enhances AMP-dependent kinase (AMPK) activity. AMPK further promotes mitochondrial

biogenesis and downregulates sinoatrial activity, thereby, lowering resting heart rate in exercise adapted state (39, 40). Additionally, glucose-6-phosphate stimulated mTOR (mammalian target of rapamycin) activation has been found to increase cardiomyocyte size (41).

2.4. Metabolism in senescent heart.

Cardiac mitochondria conduct the oxidative phosphorylation of fatty acids and carbohydrates to provide energy for the maintenance of myocardial contractility and integrity. They also play a crucial role in the dynamics between glucose and fat oxidation, thus contributing to metabolic resilience. However, aging-related fall in mitochondrial number and function lead to decreased flexibility of cardiac tissue for substrate usage (42). The aging heart suffers from the diminished capability to oxidize fatty acids and dependence on pyruvate and lactate metabolism for ATP supply (43). In a senescent heart, defective mitochondria produce more reactive oxygen species (ROS). Oxidative stress further exacerbates myocardial sensitivity to other stressors (42). Increased glucose oxidation in aging hearts is attributed by a decline in PDK4 level in senescent cardiac mitochondria (43, 44). Another significant event in an aging heart is the profuse uptake of fatty acids by the cardiomyocytes due to the increased sarcolemmal expression of fatty acid translocase (or CD36) (45). An augmented lipid accumulation, reduced fatty acid oxidation and increased ROS generation jeopardize the cardiac cells to lipotoxic injury (17).

3. CHANGES IN CARDIAC METABOLISM IN CARDIAC PATHOLOGIES

3.1. Altered energetics during myocardial hypertrophy.

Hemodynamic workload induces mechanical stress in the cardiac muscle, causing the cardiac cells to grow in size leading to myocardial hypertrophy (46). Such changes are accompanied by metabolic alterations that ultimately enable the heart to sustain optimal function in the newly adapted situation (47). This adaptation can occur physiologically in case of exercise training or is pathologically caused by a prolonged hypertensive state. However, physiological and pathological hypertrophies are manifested by dissimilar metabolic features. Physiological cardiac hypertrophy tends to decrease glycolysis and increase glucose oxidation (46). As a result, during ischaemia, the increased glucose oxidation leads to decreased proton build-up and facilitates intracellular pH recovery. This, in turn, favors trans-sarcolemmal H+/Na+ & Na+/Ca2+ exchange and hence minimizes calcium overload. This improves post-ischemic contractile function and efficiency (49). In addition, the rate of fatty acid oxidation is also increased in cardiac physiological hypertrophy and this curbs free fatty acid accumulation and free fatty acid-mediated toxicity, thus having better functional recovery following an ischemic event (46). Conversely, the pathological hypertrophy lacks the ability to withstand acute metabolic distress such as an episode of cardiac ischemia/reperfusion (48). A “Metabolic shift” characterized by decreased fatty acid oxidation and increased glycolytic activity is observed in pathological hypertrophy of the heart. The increased glycolysis, and increased proton accumulation in hypertrophic cardiomyopathy may have detrimental outcomes following ischemic stress (50). Also, the decreased fatty acid oxidation attributed by the suppression of peroxisome proliferator-activated receptor/retinoid X receptor (PPAR-α/RXR-α) pathway is responsible for the accumulation of fatty acid and poor post-ischemic recovery in subjects with pathological hypertrophy (51).

3.2. Myocardial ischemia/reperfusion injury mediated alteration in cardiac metabolism.

Cardiac tissue efficiently works in presence of adequate oxygen and substrates. The contractile activity of cardiomyocytes relies predominantly on the oxidative metabolism of fatty acids and carbohydrates. Inconsistent oxygen supply impairs mitochondrial oxidative function and promote anaerobic metabolism leading to heart in an energy deficient state (52). During an acute ischemia, the energy deficiency may cause cardiomyocyte infarction and death. Following reperfusion, even though the restoration of coronary circulation occurs, the metabolic dysfunction often persists. This condition is termed as myocardial stunning in which the heart is not able to restore its normal contractile efficiency without any irreversible tissue damage caused by ischaemia (53). Reperfusion is also associated with the massive production of ROS that can cause oxidative injury in the cardiac tissue. Oxidative stress and mitochondrial calcium overload that occurs during reperfusion open mitochondrial permeability transition pore (MPTP). The opening of MPTP allows the free flow of protons into and out of mitochondria (54). This leads to the uncoupling of oxidation-phosphorylation and ATP production (54). Heart subjected to ischaemia/reperfusion (I/R) injury replenishes its fuel demands by increasing the rate of anaerobic glycolysis. Nevertheless, increased glycolysis results in excess accumulation of lactate and hydrogen ions (H^+), thus decreasing the intracellular pH of cardiomyocytes (55, 56). During both ischaemia and reperfusion, fatty acid oxidation escalates in cardiac mitochondria at the cost of glucose oxidation (57). Such observations are summarized in Table 1.

Table 1. Cardiac metabolic homeostasis in different physiopathological conditions

	Physiological cardiac hypertrophy	**Pathological cardiac hypertrophy**	**Aging**	**I/R injury**	**Diabetic cardiomyopathy**
Glycolysis	Decrease (49)	Increase (46)	Increase (43)	Increase (55, 56)	Decrease (58)
Glucose oxidation	Increase (49)	Decrease (46)	Increase (43)	Decrease (57)	Decrease (63)
Fatty acid oxidation	Increase (46)	Decrease (46)	Decrease (43)	Increase (57)	Increase (61)
Cytosolic calcium accumulation	No	Occur (121)	Not clear	Occur (120)	Occur (58, 67)
Mitochondrial proton leak	No	Occur (50)	Occur (74)	Occur (54)	Occur (75)
Lipid accumulation	No	Occur (46)	Occur (45)	Unlikely	Occur (62, 70)
ROS generation	No	Occur (46)	Occur (42)	Occur (54)	Occur (68)

3.3. Diabetes-related cardiac dysfunction and altered cardiac metabolism.

Diabetic cardiomyopathy is referred to the alteration in the structural and functional integrity of cardiac muscle that has its etiological root in diabetes. Diabetic cardiomyopathy is characterized by insoluble collagen deposition in the left ventricular wall, accumulation of epicardial fat with concomitant local inflammation, suppression of sympathetic response, and decreased calcium ion flux in cardiomyocytes (58). The onset and exacerbation of diabetic cardiomyopathy are accompanied by severe perturbations of carbohydrate and fat metabolism as well as calcium homeostasis (7).

3.3.1. Changes in fatty acid metabolism.

In type-II diabetes *mellitus*, the insulin responsiveness of the peripheral tissue decreases, which impels the pancreatic beta cells to produce excessive insulin. Overactivity of the pancreatic tissue, gradually leads to pancreatic dysfunction and insulin secretion drops leading to a hyperglycemic state (59). Deficiency of insulin curtails lipogenesis in adipose tissue, resulting in increased circulatory free fatty acids (FFA) (60). The overproduced FFA stimulates the nuclear receptor PPAR-α which then forms a complex with RXR-α to promote uptake and oxidation of fatty acid in cardiomyocytes (61). Therefore, heart muscles become predominantly reliant on fatty acid metabolism as the source of ATP. Eventually, the supply of lipid substrate exceeds far beyond the fat metabolic capacity of cardiac tissue. This overabundant fatty acid predisposes the cardiac cells to lipotoxicity due to the conversion of long-chain fatty acyl-CoA into toxic intermediates such as ceramide and diacylglycerol (62). These molecules activate protein kinase C (PKC), which in turn phosphorylates insulin receptors, leading to its inactivation to form a vicious cycle in cardiomyocytes (58).

3.3.2. Changes in glucose metabolism.

One of the prominent features of cardiac metabolism in diabetic subjects is the reduction in glucose oxidation (63). Diabetes-induced alteration in glucose metabolism is mechanistically coupled to increased fat oxidation in the diabetic heart. This is evidenced from the fact that suppression of glucose oxidation in diabetic cardiomyopathy occurs prior to the manifestation of insulin resistance, suggesting that increased utilization of fatty acid by the cardiac tissue could be the potential cause of decreased glucose oxidation (64). Oxidation of fatty acid produces acetyl CoA that allosterically inhibits pyruvate dehydrogenase and upregulates PDK4, which ultimately compromises the oxidative metabolism of glucose. Increased citrate concentration, resulting from fat oxidation, can limit the activity of PFK-2, further impairing glycolysis (58). Activation of PKC in cardiomyocytes can impair the translocation of glucose transporter type 4 (GLUT4) into the sarcolemma with the consequent reduction in glucose uptake and induction of apoptosis (65).

3.3.3. Changes in calcium homeostasis.

Rapid transfer of fuel is essential for the optimal operation of various cellular ion transporters including Sarco/endoplasmic reticulum calcium ATPase (SERCA). Glycolysis allows an expeditious supply of ATP to SERCA and therefore maintains an intracellular calcium balance (66). However, suppression of glycolysis in diabetic heart disrupts calcium homeostasis which contributes to the impending cardiac dysfunction (67). Diabetes is associated with the activation of spleen tyrosine kinase (Syk) which promotes mitochondrial ROS generation and is responsible for the pathogenesis of diabetic cardiomyopathy.

Syk-stimulated reactive intermediates have been found to facilitate SERCA peroxidation, which also decreases its activity, leading to a further decline in sarcoplasmic calcium storage and reduce cardiomyocyte viability (68). Such observations are summarized in Table 1.

3.4. Abnormal energy metabolism in heart failure.

The inability of the cardiac muscle to conduct the systolic and diastolic functions is termed as heart failure which may be caused by an acute myocardial infarction, or pressure overload, or as a result of diabetic cardiomyopathy (69). Depending upon the aetiology, the metabolic profile of the heart failure differs considerably. Heart failure associated with pressure overload and ischemic attack is characterized by increased rates of glucose uptake and glycolysis. Diabetes-induced heart failure, on the other hand, exhibits a higher dependence on fat metabolism and consequent lipotoxicity (70). The myocardial gene expression and protein levels of PPAR-α and RXR-α decrease in heart failure caused by pressure-overload (71). In heart failure associated with insulin resistance, the cardiomyocyte membrane displays a reduced GLUT4 protein and an upregulated expression of CD-36 proteins in the sarcolemma (72, 73), clearly indicating a suppressed glucose oxidation and excess lipid accumulation.

Irrespective of the pathophysiological status and substrates utilized, loss of metabolic flexibility, energy deficit, oxidative stress, and mitochondrial dysfunction (74, 75) seem to be the hallmark of most cardiac disorders. To address this problem, a suitable therapeutic strategy is required to efficiently ameliorate the metabolic disturbances in cardiac tissue associated with different pathological states. Melatonin a tryptophan derivative, appears to have myocardial protective effects (76). Its protective mechanisms will be discussed below.

4. ROLE OF MELATONIN IN METABOLIC HOMEOSTASIS

Melatonin is a potent chronobiotic and is found ubiquitously in nature from microbes to mammals (77). Melatonin regulates metabolism both at the systemic and cellular levels. Maintenance of energy metabolism at the systemic level can be beneficial for the overall health and vitality of the organism. Such protective function of melatonin has been observed in cancer, metabolic syndrome, and cardiovascular diseases (78-80). Pineal gland-produced melatonin is regulated by the hypothalamic suprachiasmatic nucleus that synchronizes melatonin synthesis based on the natural dark/light cycle (81). By transduction of the environmental cues, melatonin's circadian secretion pattern synchronizes the physiological and behavioral processes to attain a metabolic balance in the organisms (82, 83). Studies have demonstrated that melatonin can play a significant role in glucose homeostasis by regulating insulin synthesis and its signalling pathway (79). Binding to MT1 receptor, melatonin stimulates activation of insulin receptor and its downstream phosphorylation cascade. Abolishing melatonin production with pinealectomy downregulated GLUT4 gene expression and protein content in insulin-responsive tissues, including cardiac muscle, while this was rescued by melatonin administration. (84). With the intact pineal gland and normal melatonin production, these animals exhibit high insulin synthesis and sensitivity, enhanced glucose tolerance, elevated glycogenesis, and glycolysis during active phase of the day while during the resting phase of the day they exhibit decreased insulin secretion, increased glycogen secretion, enhanced glycogenolysis, and gluconeogenesis (85) This well-arranged circadian metabolic profile was found to be disrupted with pinealectomy, resulting in insulin resistance during the active phase of the day and insulin sensitivity during the resting period. Such metabolic impairment in pinealectomized animals can be normalized upon adequate melatonin administration (85).

About 90-95% of ATP is produced via aerobic metabolism that takes place within the mitochondria. The mitochondrial oxidative phosphorylation is not an independent mechanism, but is rather combined with the electron transport process. This process builds an electrochemical gradient across the inner mitochondrial membrane, which is not only responsible for ATP synthesis but also for calcium uptake and generation of ROS (86). Adequate amounts of ROS are indispensable for the maintenance of cell signalling process and contribute to cell survival. Cells with endogenous antioxidant molecules can tolerate moderate amounts of ROS. When the cells are exposed to the excessive ROS which is over their antioxidant defense capacity, it will cause the oxidative stress (87). Aging and various pathological conditions weaken the cellular antioxidant defense system, making the cells vulnerable to oxidative stress (42). Melatonin is a potent free radical scavenger and significantly alleviates mitochondrial oxidative stress (88). The antioxidant and anti-inflammatory properties of melatonin have also been suggested to be protective against strenuous exercise-mediated oxidative and inflammatory cardiac damage (89). Experimental evidence indicates that melatonin can suppress cardiovascular dysfunction in developing embryos under hypoxic challenges (90). The role of melatonin as an efficient protector of mitochondrial integrity also comes from its lipophilic nature that shields the mitochondrial inner membrane against oxidative assault (86, 91). Melatonin also preserves mitochondrial dynamics by stimulation of mitofusin-2 activity, the key regulator of mitochondrial fusion and cellular metabolism (91, 92). In addition to membrane stability, melatonin has been reported to restore mitochondrial calcium uptake in rats treated with ruthenium red, which is a mitochondrial calcium transport inhibitor. Adequate calcium concentration in mitochondria preserves the activities of dehydrogenase enzymes. Besides, melatonin prevents ruthenium red and t-BHP-mediated disruption of the mitochondrial antioxidant store (93).

5. MELATONIN FOR THE OPTIMAL CARDIAC HEALTH

A plethora of animal and clinical studies have confirmed the cardioprotective effects of melatonin (9, 78, 94). Much of the beneficial effects of melatonin on the cardiovascular system is pertinent to its antioxidant and anti-inflammatory actions (88, 95-97). MT1 and MT2 melatonergic receptors are located in the cardiac tissue and coronary arteries which mediate both vasoconstriction and vasodilation functions (10, 98, 99). MT1 solely mediates vasoconstriction while MT2-mediated modulation of vascular tone is complex and depends on the type of blood vessel. For instance, melatonin elicits a vasoconstrictive effect in coronary vessels but vasodilation in the aorta (100). Interestingly, MT2 mediated vascular relaxation involves the synthesis of nitric oxide (NO) in the endothelial cells (101). On the other hand, in coronary arterial smooth muscle cells, MT2 activation leads to decreased NO production and inhibits vascular relaxation (102). Melatonin also imparts its cardioprotective effect through a receptor-independent mechanism which mainly involves neutralization of reactive intermediates and restoration of mitochondrial stability (103). The radical scavenging property of melatonin also prevents oxidative modification of low-density lipoproteins (104). This action minimizes the pathogenesis of atherosclerotic events and therefore, imparts vascular protection (105). In addition, melatonin reduces hypertension, plasma cholesterol level, prevents endothelial leakage, and minimizes inflammatory reactions (78). A robust vascular system ensures a ceaseless supply of blood to the cardiac muscle. However, if the coronary artery is clogged, it can cause ischemic injury (78). Mounting evidence suggests that melatonin safeguards the cardiac cells against ischemia-reperfusion injury by minimizing oxidative stress, inflammation, and apoptosis (106, 107). Melatonin intervention reduced the infarct size caused by regional ischemia-reperfusion in hearts of rats (108). The placental dysfunction (pre-eclampsia) leads to multiple cardiovascular

abnormalities in women with complicated pregnancies and melatonin treatment can rescue these cardiovascular disturbances (109). Moreover, the placenta maintains a constant synthesis of melatonin throughout gestation and is possibly involved in protecting the fetus from oxidative stress-induced developmental complications including hypoxia-related cardiovascular dysfunction (110, 111). Melatonin has been found to alleviate acute physical exertion-mediated oxidative and inflammatory myocardial injury (89). Heat stress produced during vigorous exercise stimulates the sympathomedullary pathway. Melatonin may curb the sympathetic over-activity during increased cardiac workload and can save the cardiac tissue from an imminent ischemic attack (89). Triiodothyronine (T3) induced cardiac hypertrophy was characterized by increased cardiac mass, elevated levels of cardiac oxidative stress markers, and impaired activity of GLUT4 transporter. Treatment with melatonin ameliorated such cardiopathological changes and improved insulin-mediated glucose transport into cardiomyocytes (112).

6. POSSIBLE PROTECTIVE ROLE OF MELATONIN IN ALTERED CARDIAC METABOLISM IN MYOCARDIAL DISORDERS

Melatonin can regulate cellular energy metabolism and protects the cells against toxic free radicals generated as a result of noxious metabolic disorders (85, 86). The cardiac pathological conditions often involve alteration in both glucose and lipid metabolisms. These disorders can be prevented by either endogenously produced and exogenously administered melatonin.

6.1. Melatonin against cardiac mitochondrial stress and lipotoxicity.

Impairment of mitochondrial function in aging hearts promote ROS production and the resultant oxidative stress. Further, aging related cardiomyopathy shows decreased metabolic flexibility, where fatty acid oxidation is highly compromised. This results in FFA accumulation and ROS generation (42). Decreased fat oxidation and ROS production are also implicated in hypertrophic cardiomyopathy and pressure overload-driven heart failure (70, 113). Although fatty acid oxidation rate in diabetic cardiomyopathy is fairly high, an elevated circulatory level of FFA caused by insulin resistance along with an increased expression of sarcolemmal CD36 protein allows lipid accumulation and concomitant lipotoxicity (58). Melatonin efficiently ameliorates oxidative modifications of lipids in cardiac tissue. The potent free radical scavenging and antioxidant properties of melatonin are beneficial in alleviating mitochondrial oxidative burden (114, 115). The amphiphilic nature of melatonin allows its free passage through the cellular membranes and into the mitochondria. Through a receptor-independent action melatonin effectively neutralizes locally accumulated ROS (116, 117). The cardiovascular benefits of regular moderate physical activity are pertinent to a reduction in oxidative stress and increased mitochondrial stability (118). However, the vigorous exercise also can exacerbate oxidative stress-induced cardiac damage. Melatonin decreases cardiac oxidative stress biomarkers which are elevated in response to heavy physical exertion (89). The anti-oxidative effects of moderate exercise in cardiac tissue are comparable to that of melatonin. Additionally, melatonin has been demonstrated to protect against cardiac mitochondrial dysfunction and improves mitochondrial bioenergetics (86). I/R injury is accompanied by perturbed mitochondrial integrity due to the stress-mediated opening of MPTP. Melatonin inhibits reperfusion-associated MPTP opening and minimizes oxidation of cardiolipin, a mitochondrial membrane resident lipid (119). These observations are summarized in Figure 1.

6.2. Melatonin against energy deficit in cardiac tissue.

Pressure overload-driven cardiac hypertrophy and heart failure as well as aging-related cardiomyopathy are marked by decreased fat oxidation capacity. Indeed, the metabolic profile of aging-associated heart failure likely switches back to the fetal-like metabolic status with increased glycolysis rather than fat metabolism (120). In an aging heart, augmented glucose oxidation yields acetyl CoA which is the substrate of malonyl CoA. Increased malonyl CoA inhibits carnitine palmitoyl-CoA transferase 1α (CPT-1α), the rate-limiting enzyme of fatty acid oxidation (121-123). In the low-energy state, increased AMP/ATP ratio stimulates AMPK which activates PPAR-α, the enzyme responsible for CPT-1α expression (124, 125). Melatonin stimulates the expression of PPAR-α, and CPT-1α— proteins essential for fatty acid metabolism (126). Melatonin also promotes AMPK activation and therefore, it augments fat catabolism in cardiac tissue (127). However, information on metabolic modulation by melatonin in the cardiac tissue of aging animals is lack and demands extensive research. GLUT4 is responsible for insulin-mediated uptake of glucose into the cardiomyocytes and oxidative stress may impair this transport function (128). Melatonin proficiently prevents oxidative stress-induced downregulation of the GLUT4 gene in cardiomyocytes (112). In an energy-deficient heart, melatonin-stimulated AMPK activation may also aid in increased GLUT4 and PFK-2 expression, facilitating glucose uptake and metabolism (125). Such responses of melatonin in cardiac tissue are similar to that of an exercise-adapted heart. Hypertrophic cardiomyopathy, heart failure, ischemia-reperfusion injury, and diabetes-induced cardiac impairment are all associated with decreased mitochondrial oxidative phosphorylation and enhanced glycolysis, a phenomenon called the Warburg effect which is mostly exhibited by but not limited to the cancer cells (129). Melatonin abolishes the Warburg effect in cardiomyocytes (130). This action of melatonin may involve to inhibit PDK (130, 131). Therefore, melatonin plays a pivotal role in liberating the heart from energy deprivation under pathological stress and all this evidence is indicative of a possible therapeutic application of melatonin in promoting cardiac metabolic flexibility.

6.3. Melatonin improves cardiomyocyte calcium homeostasis.

The contraction and relaxation of cardiac muscle are highly dependent on the sarcoplasmic reticulum (SR) calcium storage. Pathological cardiac hypertrophy, ischaemia, and diabetic cardiomyopathy markedly disturb the SR calcium pool and often result in cytosolic calcium overload (58, 132, 133). One major factor attributing to loss of calcium homeostasis is the vitiated functioning of SR membrane resident calcium handling protein— SERCA and sarcolemmal sodium-calcium exchanger (NCX). Melatonin attenuates cardiomyocyte calcium imbalance by modulating the expression and activities of these proteins (132). In diabetes-induced cardiac dysfunction, melatonin proficiently extenuates Syk activity thus facilitate mitochondrial complex-I activity and prevents ROS production and SERCA peroxidation (68, 134). Such observations are summarized in Figure 1.

7. SUMMARY AND FUTURE PERSPECTIVE

Melatonin as a chronobiotic signal molecule coordinates the diurnal metabolic activity in organisms. Thus, reduced melatonin in some pathological conditions causes metabolic disturbances including altered glucose and fatty acid metabolism. For example, heart diseases are often associated with reduced melatonin level and increased oxidative burden manifested by the mitochondrial dysfunction, the opening of MPTP, proton leakage, and cytosolic calcium overload in the cardiomyocytes (91, 92, 119, 132). Melatonin efficiently protects

mitochondria from oxidative damage and facilitates ATP synthesis. In aging-associated cardiac anomaly, pressure-overload driven myocardial hypertrophy, and heart failure, melatonin enhances fatty acid oxidation by the activation of AMPK pathway and promotes glucose uptake and utilization in cardiomyocytes. While in some cardiac disorders, anaerobic glycolysis seems to become the preferred pathway for ATP generation, melatonin converts this anaerobic glycolysis to oxidative phosphorylation by inhibiting PDK activity. To overcome energy deficiency induced by the ischemic and diabetic cardiomyopathy, the heart attempts to accumulate fatty acids for energy production. Accumulation of the fatty acid further suppresses glucose oxidation, and eventually, the amount of fatty acid in the cardiac cell overpasses its fat oxidation capacity. The accumulated lipid is prone to peroxidation and the resultant lipotoxicity, thus, further disrupts the metabolic energy balance of mitochondria. Melatonin potentially breaks this vicious cycle by stimulating glucose oxidation and preventing oxidative modification of lipids.

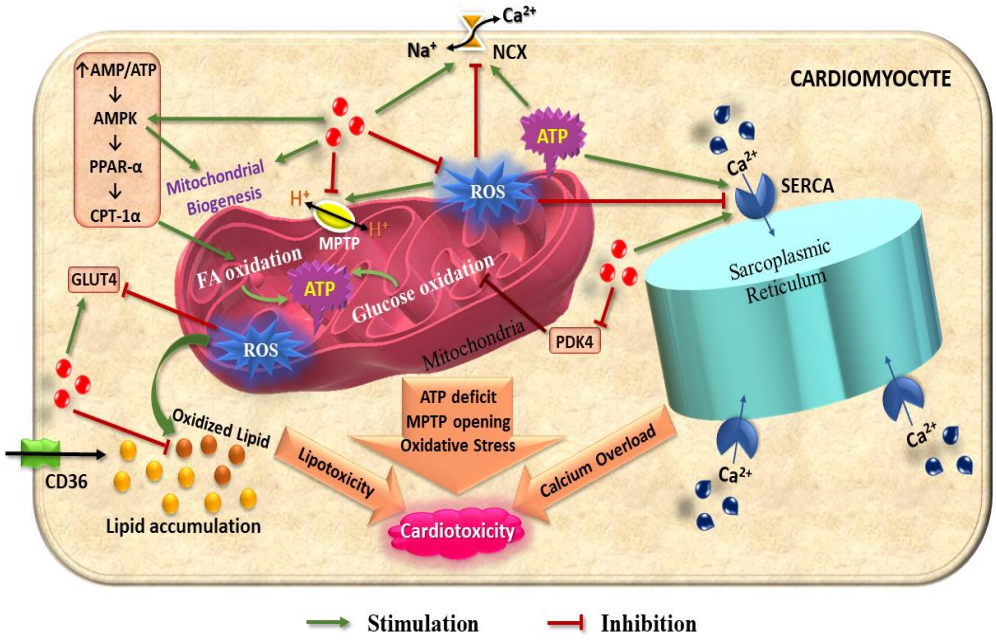

Fig. 1. Role of melatonin in the regulation of metabolic homeostasis in cardiomyocytes.

Melatonin (red spheres) protects the cardiac cell against metabolic energy deficiency possibly by preserving the balance of fatty acid and glucose oxidation in mitochondria. Melatonin by stimulating AMPK upregulates PPAR-α and CPT-1α, which in turn promotes fatty acid oxidation. Further, melatonin inhibits PDK4, thus inhibiting the Warberg effect. Melatonin upregulates GLUT4 which promotes insulin dependent glucose uptake in cardiomyocyte. In conditions where lipid accumulation increases in the cardiac cell, melatonin may prevent lipotoxicity by impeding lipid peroxidation. Further melatonin preserves mitochondrial integrity by annihilating ROS and preventing MPTP opening as well as promotes mitochondrial biogenesis. Melatonin also restores calcium homeostasis by facilitating the activities of the SERCA pump and NCX. Overall, melatonin purportedly protects the cardiac cell from potential toxicity caused by oxidative stress, ATP deficit, calcium overload, and lipid peroxidation under adverse cardiac situations.

AMPK- AMP-dependent kinase; CD36- Fatty acid translocase/cluster of differentiation 36; CPT-1α- Carnitine Palmitoyltransferase-1 alpha; FA oxidation- Fatty acid oxidation; GLUT4- Glucose transporter type 4; MPTP- Mitochondrial permeability transition pore; NCX- Sodium-calcium exchanger; PDK4- Pyruvate dehydrogenase kinase 4; PPAR-α- Peroxisome proliferator-activated receptor-alpha; ROS- Reactive oxygen species; SERCA- Sarco/endoplasmic reticulum calcium-ATPase.

An exercise-adapted healthy heart is characterized by enhanced fat and glucose oxidation, decreased ROS generation, and improved calcium homeostasis. These activities are similar to melatonin as a metabolic stabilizer in the heart. However, extensive study is required to obtain clarity on the involvement of melatonin in the regulation of metabolic pathways during cardiac pathological conditions.

AUTHORSHIP

The concept of the review article was developed by Dr. DB, Dr. AC and SS. Moreover, SS contributed in drafting the manuscript, prepared the figures, and edited it. Dr. DB and Dr. AC also revised the manuscript critically and finally approved it.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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