Review

Melatonin as a potential therapeutic molecule against myocardial damage caused by high fat diet (HFD)

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ABSTRACT

High fat diet (HFD) has been implicated as an independent risk factor for cardiovascular diseases since the second half of the last century. The HFD causes various pathogeneses and progressions of cardiovascular diseases. The oxidative stress and pro-inflammatory reactions induced by the HFD are probably the major risk factors of myocardial damage. In this review we highlight the roles of different dietary fats on cardiovascular diseases and the protective effects of melatonin as a potent antioxidant and anti-inflammation molecule on the pathology induced by HFD. The focus will be given to the molecular mechanisms. The protective effects of melatonin on HFD induced myocardial damage are mediated by multiple pathways. These include that melatonin suppresses the oxidative stress, preserves the normal fat and glucose metabolisms and reduces the pro-inflammatory reactions. Melatonin downregulates the expressions of pro-inflammatory genes of TLR4, NF-κB and NLRP3-Caspase1 but upregulates the expressions of anti-inflammatory genes of Sirt3, CTRP3 and RISK. All of these render melatonin as a powerful protector against cardiovascular diseases caused by the HFD. This review suggests that melatonin can be used as a therapeutic agent in this specific condition.

Key words: High fat diet, melatonin, oxidative stress, inflammation, obesity, heart diseases.

1. INTRODUCTION

Consumption of HFD in different populations has been on the rise for decades due to the currently fast-paced general lifestyle (1-2). Therefore, many persons are habitual to intake of conveniently ready-to-cook and ready-to-eat preserved foods. These foods are generally devoid of balanced nutrition and laden with high amounts of fats. Intake of HFD has been shown to pre-dispose an individual to myriad adverse consequences by affecting important organs and systems (3-4).

Among all organs, heart and liver are the primary targets of HFD. Cardiac tissue has very high demand of energy and relies heavily on a steady supply of free fatty acids (FFAs)

whereas the liver functions as the main site of fat metabolism. This scenario makes these two organs more vulnerable to the supply, utilization and disposal of fats (5-7). Not only have the amounts but also the types of fats been found to play a decisive role in the patho-physiology of many diseases (8-9). Particularly, the trans-fat in processed foods, saturated fatty acids (SFAs) and omega -6 polyunsaturated fatty acids (n-6 PUFAs) tend to increase the risk of metabolic diseases, cancer, heart diseases, altered serum lipid profiles and liver injury (8-9). Among different reasons, their vulnerability to free radical damage and ability to perpetuate the state of oxidative stress make a vicious cycle of oxidative stress and metabolic disturbances. This vicious cycle at a cellular level amplifies the organ and tissue pathogeneses (10-14).

Exploration and identification of proper therapeutic approaches are utmost important to prevent, treat and cure the HFD induced cardiac injury. Many antioxidants are already tested for protection of heart against HFD (15-17). Melatonin (N-acetyl-5-methoxytryptamine), a multitasking molecule with potent antioxidant and anti-inflammatory properties is highly beneficial in cardiac damage caused by other factors (18-20). Its effect on HFD induced cardiac injury will be discussed in the following review.

2. HFD CAUSES DIVERSE PATHOPHYSIOLOGICAL CONDITIONS

Chronic consumption of high amounts of dietary fat has been implicated as causative factor of various diseases (21-23). HFD increases energy intake due to its energy-density and its palatability. This situation precipitates adiposity and then obesity with the imbalance of energy metabolism. Many other consecutive pathologic conditions may arise either as a secondary response to obesity or occur independently (6, 24-25). Thus, HFD may cause various metabolic disorders including hypertension, diabetes mellitus, gall bladder stone and liver diseases (26). HFD consumption as a predisposing factor for the increased risk of different cancers has been hypothesised. The associations between chronic HFD consumption with breast, colon, prostate and ovary cancers have ended up with mixed results (27-30). In addition, non-alcoholic fatty liver disease (NAFLD) and hepatic steatosis are the results of chronic consumption of HFD due to the fact that the fats ultimately accumulate in the liver (31-32). Hepatic steatosis can be caused by oxidative stress induced by HFD. Reactive oxygen species (ROS) generated due to HF metabolism directly injures the hepatocytes, activates redox-sensitive inflammatory processes and develops systemic insulin resistance and finally leads to many obesity related complications (33-37).

Chronic intake of high level of saturated fatty acids increases serum levels of cholesterol fractions, for example low density lipoprotein cholesterol (LDL-c) and precipitates dyslipidaemia (38-40). HFD promotes atherosclerosis and consequent cardiovascular diseases by the elevated circulatory lipids before they are accumulated in liver or adipose tissue (41). HFD dysregulates insulin signalling and induces low grade inflammation with persistent release of pro-inflammatory adipocytokines including tumour necrosis factor alpha (TNFα) and interleukin 6 (IL-6). These factors detrimentally affect many non-adipose target organs and induce tumourigenicity (42-43).

Chronic consumptions of HFD also cause cognitive defects by impairing recognition memory and spatial learning in both humans and animals (44-45). The effect of HFD on the alterations of circadian rhythm has been studied extensively. HFD alters the circadian rhythm and the levels of circulatory molecules in the body including insulin, glucose and leptin (46-47). Mice fed with HFD have failed to synchronize their endogenous circadian rhythm with changes of environmental light-dark cycle due to the reason that HFD alters the food intake pattern of the rodents. These findings indicate that HFD predisposes organisms to higher than

normal food intake even during the rest phase, thereby, disorganizes their circadian rhythms to induce adverse metabolic consequences (46, 48).

3. HFD LEADS TO CARDIAC INJURIES

Excessive energy intake by consumption of HFD leads to atherosclerosis, cardiac hypertrophy, ischemic damage and ultimately heart failure. Increased levels of dietary fat inhibit the beta-oxidation of free fatty acids and result in accumulation of lipid in the myocardium, cell death and cardiac dysfunction (Figure 1). Such negative alterations in lipid homeostasis adversely affect the metabolic state in an organism (49-51).

Majority of the studies of HFD are usually conducted in genetically knock-out obesogenic rodents; however, HFD also alters the structural and functional integrity of myocardium in wild type rodents. These include degenerative changes in cardiac mitochondria and accumulation of lipids in myocardium (52). Replacement of saturated fat acid (SFA) with n-6 PUFAs significantly increases the thickness of anterior left ventricular wall compared to that of SFA alone treated rodents. An increased body weight and visceral fat associated with HFD predispose the organisms to greater risk of cardio-myopathy (53). Not only the HFD but the types of fats play a major role in initiation and progression of the pathology. For example, the trans-fatty acids, easily available in all kinds of processed foods, provide little healthy benefits, on the contrary, it increases LDL-c fraction, simultaneously reduces the high density lipoprotein-cholesterol (HDL-c). It is also a potent risk factor for inflammatory processes associated with heart disease, stroke, Type 2 diabetes mellitus (Type 2 DM) (54). A meta-analysis of prospective studies reported that every 2% increase in calorie intake from trans-fats would result in a 23% increase of risk for heart diseases (54-55).

Alterations in the levels of LDL-c cannot independently act as an actual measure of coronary heart disease (CHD) risk since a low level of LDL-c achieved with many complex manipulations has failed to mitigate the risk of CHD. Thus, the assessment of a range of low and intermediate density lipoprotein fractions along with the ratio of apo-lipoprotein B to apo-lipoprotein A1 are used for the management and prevention of CHD (56). SFA is a major component of HFD. Due to its pro-atherogenic tendency, SFA is suggested not to be excessive of 10% of daily energy needs (57). Recent studies have reported lack of evidence to establish the causative or protective roles of different dietary fats in heart diseases. However, there is a consensus that replacing SFAs with mono and polyunsaturated fats and high-fibre unrefined carbohydrates significantly reduces the risk of developing cardiovascular diseases (58-59). The idea of Mediterranean diet came to the fore for the first time in the 1960s from the Seven Countries Study (60). Since then numerous studies have proved that monounsaturated fatty acids (MUFAs) and omega-3 polyunsaturated fatty acids (n-3 PUFAs) have significant protective effects against heart disease and stroke since they can effectively reduce atherosclerosis, hypertension as well as dyslipidaemia (61). n-6 PUFAs are also found to protect against heart diseases but they are more prone to oxidative stress related damages (62-63). Evidence, though inconsistent, suggests that due to their pro-inflammatory nature, n-6 PUFAs may predispose to CHD (64-65). Studies have shown that HFD causes both functional impediment and insulin resistance in myocardium (66-67).

4. HFD AND DIABETIC CARDIOMYOPATHY

Clinically, patients with Type 2 DM are twice more likely to develop cardiovascular diseases than the general population (68-69). One of the major mechanisms behind the diabetic cardio-myopathy is oxidative stress. The increased production of ROS and reactive nitrogen species (RNS) coupled with down-regulation of endogenous antioxidant system play a major aetiological role in the complications of Type 2 DM. Nitric oxide syntheses (NOS)

uncoupling, activation of NADPH oxidase and dysregulation of mitochondrial metabolism participate in the development and progression of diabetic cardio-myopathy. HFD results in nutrient overload, alters cellular lipid metabolism and induces hyperglycaemia. Hyperglycaemia in Type 2 DM disrupts the normal function of the mitochondrial electron transport chain (ETC) and elevates superoxide anion ($O_2^{\cdot-}$) free radical production, a vicious cycle of mitochondrial metabolic dysfunction. The availability of FFAs, especially PUFAs, increases in Type 2 DM and this leads to uncontrolled lipid peroxidation. On the other hand, alternative pathways of glucose metabolism are activated. The production of advanced glycation end products (AGEs) and advanced lipo-oxidation end products (ALEs) augment the condition of insulin resistance and pancreatic beta cell dysfunction to perpetuate the state of oxidative stress in diabetic myocardium (68-69) (Fig. 1).

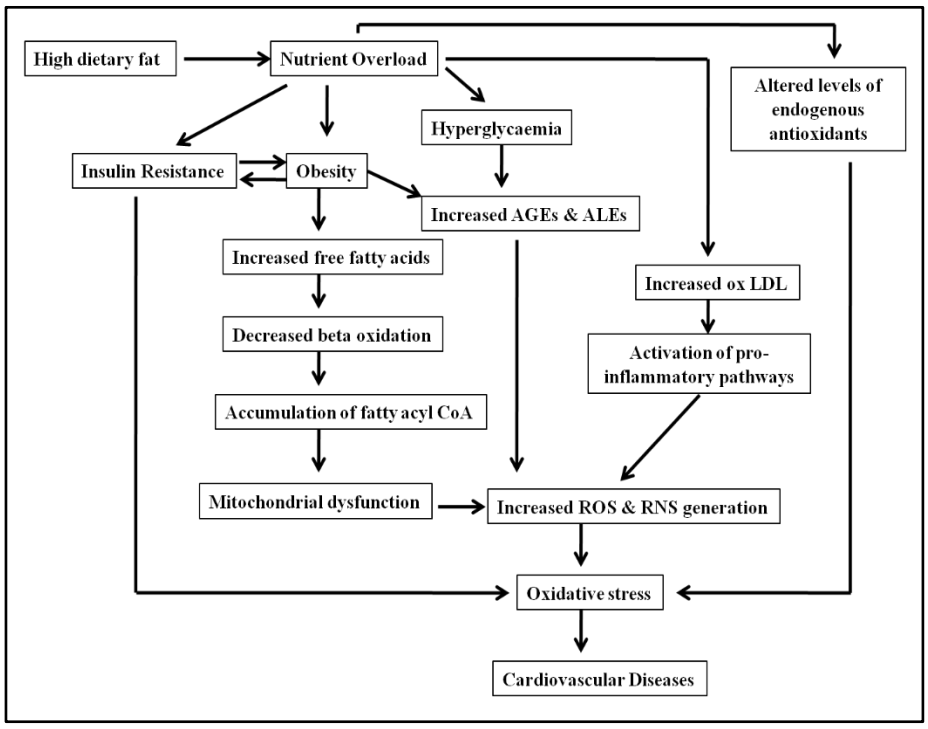

Fig. 1. Role of HFD as a causative factor for cardiovascular diseases.

HFD causes fat overload which directly induces oxidative stress. Fat overload causes obesity and insulin resistance. Increased levels of free fatty acids and blood glucose increase advanced glycation end products (AGEs) and advanced lipo-oxidation end products (ALEs) which in turn induce mitochondrial dysfunction and oxidative stress. Increased levels of oxidised low density lipoprotein (LDL)activates pro-inflammatory pathways and concurrent reduction in endogenous antioxidant activities augment the oxidative stress and result in various metabolic diseases including cardiovascular diseases

5. HFD INDUCES FREE RADICAL GENERATION IN CARDIAC TISSUE

Chronic intake of HFDs elevates production of ROS and induces oxidative stress (22). HFD attenuates the activities of the cellular free radical scavenging enzymes and increases the generation and accumulation of ROS. During myocardial ischaemia ROS is generated from damaged electron transport chain (ETC) and a series of metabolic enzymes including NADPH oxidase, endothelial nitric oxide synthase (eNOS), xanthine oxidase, cytochrome P450 mono-oxygenase, etc. A lack of co-factors for eNOS and $O_2^{\cdot-}$ associated inactivation of NADPH oxidase underlies the development of endothelial dysfunction leading to I/R injuries

(70-73). HFD significantly alters the protein levels of different antioxidant enzymes and jeopardizes their antioxidant activities (74). Excessive energy intake by means of HFD directly increases the levels of FFAs in the serum which stimulates the mitochondrial metabolic pathways to increase production of acetyl CoA and NADH. This, in turn, stimulates the activity of mitochondrial respiratory chain and generates an excess of $O_2^{\cdot -}$. Under the activity of superoxide dismutase (SOD), some $O_2^{\cdot -}$ is converted to hydrogen peroxide (H_2O_2). The over-produced $O2^{\cdot -}$ and H_2O_2 with released transition metals will undergo Haber-Weiss or Fenton reactions to generate hydroxyl radical ($HO^{\cdot}$) which is the most reactive radical to induce cardiac damage (74-76). The pathways of ROS production and oxidative stress induced by HFD are illustrated in Figure1. The chronic exposure of myocytes to ROS causes arrhythmias, hypertrophy, apoptosis, necrosis and fibrosis (77-78). Studies on the effect of different fat sources on ROS generation show that oxidative stress is higher and free radical scavenging capacity was lower in rats fed on HFD comprising of saturated fats. The amount and type of dietary fat modify the fatty acid composition of cardiac mitochondrial membranes which can alter mitochondrial function and impact disease progression (55, 79).

6. HFD AND INFLAMMATION

The changes in the redox state of myocardium result in the activation of many redox-sensitive transcription factors and signalling molecules to initiate an inflammatory cascade. Activation of the nuclear factor kappa B (NF-κB) family of transcription factors as a response to stressful conditions attributes them as a central mediator in inflammatory and stress responses in mammals. In addition, the alterations of toll-like receptor-4 (TLR4) and the mitochondrial protein of sirtuin family, Sirt3, have been implicated responsible for inflammatory responses (80-82). HFD causes a systemic elevation of the NF-κB and TLR4 activity in rodents (76-78). Activation of the NF-κB results in the release of pro-inflammatory cytokines IL-6 and TNFα along with C-reactive protein (CRP) (83-84). In obese associated with HFD, the white adipose tissues (WAT) store excessive fat and also prefer to release several pro-inflammatory adipo-cytokines including adiponectin, IL-6, TNFα, leptin, plasminogen activator inhibitor I. This causes chronic local and systemic inflammation that leads to macrophage infiltration and monocyte-macrophage system mediated immune responses in the myocardium (85-86). In contrast, HFD associated metabolic complications and inflammatory cascade in both rodents and humans have been attenuated by the anti-inflammatory interleukins IL-4, IL-10 and peroxisome proliferator activated receptor gamma (PPARγ) receptor (87). Arachidonic acid, an n-6 PUFAs in the diet, acts as the precursor of eicosanoids which is the parent molecule of several fat-derived inflammatory mediators including prostaglandins, thromboxanes and leukotrienes. It is known that the pro-inflammatory effect of prostaglandin E2 is derived from arachidonic acid (88-89). Interestingly, dietary omega-3 fatty acids attenuate the tissue levels of arachidonic acid and thereby mitigate the production of eicosanoids and inflammation cascade (61). In order to combat such inflammatory reaction melatonin, due to its anti-inflammatory and broad spectrum antioxidant properties, may serve as a potential therapeutic agent.

7. PROTECTIVE EFFECTS OF MELATONIN ON OBESITY AND METABOLISM

Altered metabolic parameters are involved in the patho-physiology of many diseases. Metabolic disorders are positively associated with cardiovascular diseases (90). Melatonin performs immense role in balancing energy metabolism and retarding obesity. Many studies have documented that melatonin effectively reduces HFD induced body weight gain. (91-93).

Extensive studies have been conducted to determine the effects of melatonin on obesity and obesity related secondary metabolic conditions including Type 2 DM, cardiovascular diseases and metabolic syndrome in genetically modified Zücker diabetic fatty (ZDF) rats or wild type animals (94). Various animal studies have shown that melatonin inhibits body weight gain or obesity without altering food intake and physical activity (94-97). Melatonin achieves this by recruiting the metabolically active brown adipose tissue (BAT) and promoting thermo genesis (94). The mechanism is that melatonin up-regulates the expression and activity of the uncoupling protein 1 (UCP1) which is only located in the mitochondria of BAT. UCP1 uncouples the processes of oxidative-phosphorylation by shutting the chemical energy to heat production. In this way, UCP1 activation can dissipate the excessive energy from the HFD (94). Melatonin administration to both ZDF and wild type rats at a dose of 10mg/kg for 6 weeks induces browning of inguinal WAT (95) which contributes to melatonin's role in reducing body weight and increasing energy expenditure. Oral melatonin also lowers the levels of IL-6, TNF-α and CRP in ZDF rats fed with HFD. This result indicates that melatonin ameliorates insulin resistance and subsequent metabolic cascade by mitigating the pro-inflammatory state and oxidative stress (96). Mitochondria are the major cellular organelles susceptible to metabolic and oxidative stress. Melatonin is a mitochondrial targeted antioxidant (78, 97) and its cellular protective effects are primarily mediated by targeting on the mitochondria (78, 97). This notion is further confirmed by the study of Jimenéz-Aranda *et al*. (97). Melatonin improves mitochondrial function in inguinal white adipose tissue of Zücker diabetic fatty rats. Oral melatonin significantly improves blood glucose homeostasis in ZDF rats by improving insulin action and beta-cell function. The results are similar to those of oral hypoglycaemic agents like metformin and stiagliptin suggesting a possible pharmacologic application of melatonin in future (98).

Moreover, melatonin can also regulate leptin and adiponectin levels thus contributing to energy expenditure, metabolism and weight management. It has been observed that blood glucose level and leptin are significantly decreased with melatonin in the animals fed with HFD (91). These variations may be due to a number of reasons including type of diet, feeding state and different strains and species. Interestingly, melatonin activates the same signalling pathway of leptin (99) and performs an immense role in weight management as leptin. Melatonin also increase another important adipokine, adiponectin, which regulates both glucose and lipid metabolism (100). Melatonin significantly decreases total triglyceride, total cholesterol, LDL-c, while significantly increases HDL-c in animals fed with HFD (74, 92-93, 101). Besides mitigating the altered metabolic parameters, melatonin also attenuates oxidative stress stemming from obesity (102). Feeding rats with HFD (35% fat) significantly reduces the nocturnal melatonin peak. This observation suggests that HFD-induced obesity is somehow associated with physiological melatonin levels. The low melatonin level reduces the energy expenditure and subsequent body weight gain in animals fed with HFD (103).

8. MELATONIN ATTENUATES OXIDATIVE STRESS AND APOPTOSIS IN CARDIAC TISSUE INDUCED BY HFD

Melatonin not only neutralizes ROS and RNS but also stimulates many important antioxidant enzymes (104). It is well documented that melatonin can ameliorate oxidative stress mediated cardiac damage (20, 104-106). A few studies have explored the protective effects of melatonin on HFD induced cardiac injury (74, 107). This is evidenced by significantly reduced lipid peroxidation (LPO), protein carbonyl (PCO), hydroxyl radical and enhanced glutathione (GSH) in cardiac tissue of HFD fed animals (74). Long term administration of HFD escalates ROS/RNS generation which is responsible for apoptosis in myocardium. Melatonin suppresses ROS/RNS generation and subsequently inhibits apoptosis

in myocardium of high fat fed animals (Figure 2). Interestingly, melatonin selectively suppresses the activity of iNOS while promotes the activity of eNOS (108). In addition, melatonin up-regulates the expression of important anti-apoptotic protein, B-Cell lymphoma 2 (Bcl-2) (107).

9. PROPOSED MOLECULAR MECHANISMS OF MELATONIN'S PROTECTION ON CARDIAC INJURY CAUSED BY HFD

9.1. Inhibition of NLRP3 inflammasomes and TLR4/NF-κB.

Atherosclerosis is one of the key features related to cardiovascular diseases. HFD plays crucial role to promote atherosclerosis. Inflammation along with vascular endothelial dysfunction leads to atherosclerosis. NLR family, Pyrin domain containing 3 (NLRP3) inflammasomes mediates endothelial inflammation and initiates artery atherosclerosis (109). A consequence of NLRP3 activation is IL-1β generation which initiates the inflammatory cascade. Melatonin down regulates NLRP3 expression in the site of atherosclerotic lesions (105-106). When apo-lipoprotein E knock out ($ApoE^{-/-}$) mice are fed with HFD atherosclerosis is observed. However, melatonin treatment significantly ameliorates the size and vulnerability of the plaque observed in the mice (110). Mechanistic study indicates that the protective effects of melatonin are derived from the deactivation of NLRP3 via activation of sirtuin-3 (Sirt3) and mitophagy (110-111). The study has found that melatonin does not up regulate Sirt3 expression but enhances Sirt3 activity which is the primary mechanism of melatonin's protection on the atherosclerosis. Additionally, this study also explored the important mitophagy indices like microtubule-associated protein, 1A/1B light chain 3 (LC3), translocase of outer membrane (TOM20) and Parkin expression. It is found that melatonin increases the LC3II/I ratio and Parkin expression whereas decreased the mitochondrial protein TOM20.These findings reveal that melatonin activates the mitophagy within atherosclerotic lesion to attenuate the pathology. This study provides novel therapeutic approach for atherosclerosis (110). TLR4/NF-κB pathway recently has gained attention among different signalling pathways which are involved in atherosclerosis. HFD up regulates expressions of TLR4, myeloid differentiation primary response 88 (MyD88) and NF-κB, while down regulating IkB expression (Figure 2). HFD increases the plasma concentration of Ox-LDL which is a promoter of TLR 4/NF-κB Pathway and melatonin administration suppresses the expression of TLR4, MyD88, and NF-κB p65 expressions and influences the expression of IkB. Thus, melatonin eliminates the pathological alterations caused by HFD (111). The results suggest the therapeutic potential of melatonin on atherosclerosis and vascular endothelial dysfunction (VED) induced by HFD and inflammation (111).

9.2. Activation of CTRP3 expression.

Obesity associated with HFD also causes heart failure with low ejection fraction. Melatonin treatment improves heart failure with increased ejection fraction via up regulation of Complement C1q Tumuor necrosis factor Related Protein 3 (CTRP3) expression. CTRP3 is primarily derived from adipose tissue (107) and executes many functions including increase in cellular differentiations, secretion of adipokines, hepatic lipid oxidation and suppression of inflammation (107). CTRP3 ameliorates hepatic steatosis and consequent insulin resistance induced by HFD (112). CTRP3 can also be generated from cardio-myocytes and hepatocytes. For example, oxidative stress and apoptosis are enhanced in CTRP3 deficient cardio-myocytes (107). Melatonin significantly enhanced the expression of

CTRP3 in adipose tissue of obese mice. HFD significantly lowers circulating CTRP3 while this decline can be restored by melatonin supplementation for 3 weeks (Fig. 2).

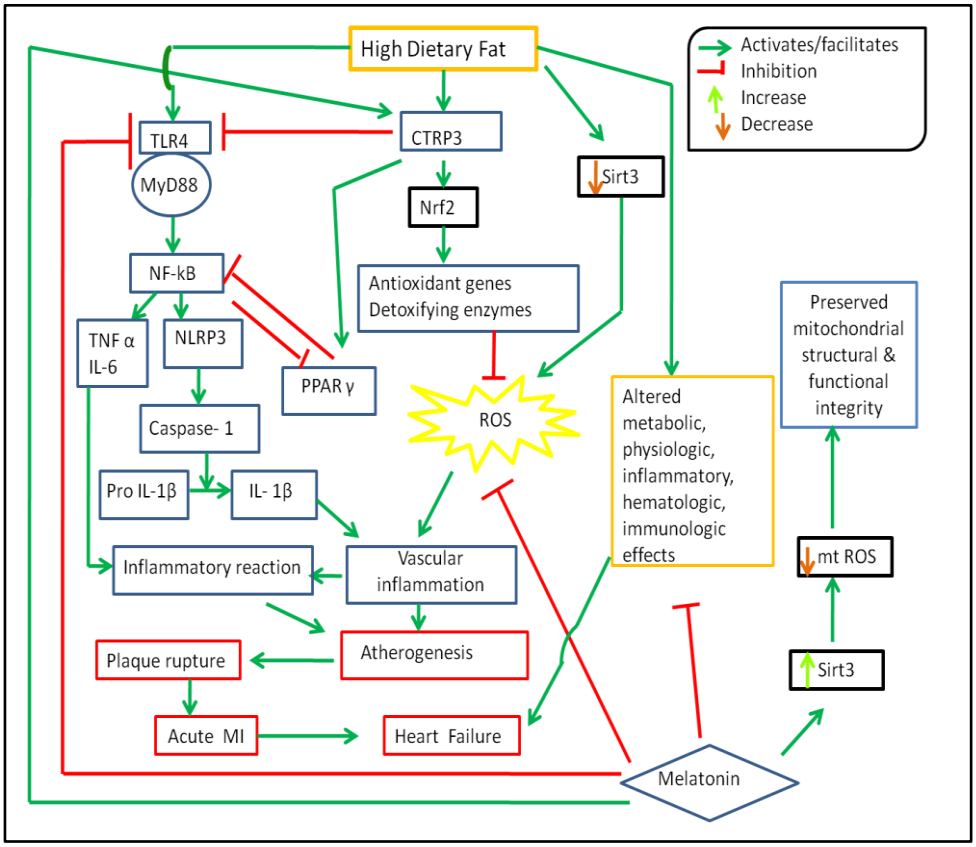

Fig. 2. Schematic diagram representing protective role of melatonin against high fat diet induced cardiac injury through modulation of different signalling pathways.

To determine the CTRP3 contribution in melatonin's protection, circulatory CTRP3 expression was blocked, mice fed HFD and treated with melatonin show aggravated cardiac diastolic function reflected by changed left ventricular end-diastolic pressure (LVEDP), dP/dt. min and the Tau index. The results have confirmed that melatonin preserves the cardiac function in HFD fed mice by enhancing the circulating CTRP3 expression. CTRP3 enhances nuclear factor erythroid related factor 2 (Nrf2) expressions and helps in the translocation of Nrf2 from cytoplasm to nucleus in cardio-myocytes (107). The Nrf2 controls cellular resistance against oxidants by regulating antioxidant responses. Nrf2 also regulates different programmed pathways induced by oxidants (113). As a result, blocking circulating CTRP3 expression also impedes the melatonin's protective effect on oxidative stress induced by HFD. Thus, the action of melatonin is closely associated with Nrf2 through CTRP3 in HFD induced cardiac alterations.

9.3. Activation of Sirt3.

Sirt 3 is predominantly found in the mitochondria (114) of metabolically active tissues like heart, liver, brown adipose tissue and it controls mitochondrial metabolism. Deficiency of Sirt3 (in $Sirt3^{-/-}$ mice) escalates the hyperacetylation of mitochondrial protein and aggravates the untoward metabolic changes when treated with HFD (115). Obesity is due to the imbalance between energy expenditure and energy intake. Insufficient fatty acid oxidation leads to fat storage. Thus, the rate of mitochondrial fatty acid oxidation plays a major role in

obesity and metabolic diseases by affecting the total energy balance. Sirt3 deacetylates many enzymes which are responsible for fatty acids oxidation (116). Sirt 3 also regulates enzymes of tri-carboxylic acid (TCA) cycle (117) and different proteins of electron transport chain (116). It is obvious that Sirt3 controls overall activity of mitochondria. HFD causes cardiac remodelling and dysfunction through Sirt3 loss (82) (Figure 2). The reduced Sirt3 expression is accompanied with increased ROS production, reduced capillary density and abnormal hypoxia-inducible factor (HIF) induced signalling in myocardial tissue. The elevated ROS production and aggravated cardiac dysfunction are more severe in Sirt3 knockout mice fed with HFD than that of Sirt3 knockout mice fed with normal diet. The result suggests that the cardiac pathology may not be solely dependent on the loss of Sirt3 but other unknown factors are also involved (82). It has been reported that melatonin ameliorates cardiac dysfunction and remodels the left ventricle in diabetic cardio-myopathic mouse (118). Further investigation indicates melatonin action on (macrophage stimulating 1) Mst1/Sirt3 signalling pathway, that is, melatonin stimulates Sirt3 to inhibit Mst1 phosphorylation. Additional study has confirmed that the cardiac protective effect of melatonin is mediated by Sirt3. Following inhibition of Sirt3, the efficacy of melatonin to protect the cardiac tissue from oxidative stress mediated injury is significantly reduced (119). Currently, there is little direct evidence to show that the protective effect of melatonin on HFD induced cardiac damage is mediated by the Sirt3. However, melatonin indeed can protect the HDF induced heart injury (120) and HFD can suppress Sirt3 (82) while melatonin stimulates Sirt3. Based on these observations, it is likely that the protective effect of melatonin on HFD induced cardiac damage acts on the Sirt3 signalling pathway (Figure 2).

9.4. Activation of RISK pathway.

The protective effects of melatonin on HFD induced cardiac injury may also be from activation of reperfusion injury salvage kinases (RISK) pathway. In HFD fed animals, long term (16 weeks) administration of melatonin not only reduces body weight, visceral adiposity, blood triglyceride, homeostatic model assessment index and lipid peroxidation but also the infarct size in *ex-vivo* perfused hearts (121). The molecular mechanisms are that chronic melatonin treatment activates protein kinase B (PKB), also known as Akt (PKB/Akt) and Extracellular Signal–Regulated kinases p42/44 (ERK p42/p44) and suppresses p38 microtubule associated protein kinase (MAPK) in the heart of HFD fed animals (121). The similar result has also been observed in short term melatonin treatment (6 and 3 weeks) in animals (122). In this study, melatonin confers its protection through baseline activation of signal transducer and activator of transcription 3 (STAT3) and concomitant activation of RISK pathway during reperfusion (122) (Fig. 3). Additionally, these pathways also help to inhibit mitochondrial permeability transition pore (MPTP) opening. Inhibition of MPTP opening can also reduce infarct size (123).

10. MELATONIN PROTECTS CARDIAC MITOCHONDRIA IN OBESITY ASSOCIATED WITH HFD

Oxidative stress induced mitochondrial dysfunction plays a pivotal role in the pathogenesis of different cardiac diseases. These pathogeneses include atherosclerosis, hypertension, ischemia-reperfusion (I/R) injury, cardiac hypertrophy, heart failure (124). The obesity (ob/ob mice) animal model is used to explore melatonin's ability on the morphological and ultrastructural changes of mitochondria in cardiac cells. The pathological alterations of the mitochondria in the ob/ob mice fed with HFD include absence of cristae, increased p62/Sequestosome-1-SQSTM1 (SQSTM1) and decreased Mitofusin 2 (Mfn2)

expressions. Melatonin administration decreases p62/SQSTM1 whereas enhances the Mfn2 expressions and preserves the proper structure of cristae and reduces the over-sized mitochondria (125). In addition, in ob/ob mice melatonin acts on the leptin pathway to alleviates unfolded protein response in a tissue-specific manner, functioning mainly in the restoration of this disturbed ATF6α pathway (126).

Uncontrolled opening of MPTP in mitochondria causes necrosis or apoptosis and cardiac damage (127, 128). Again, HFD can increase calcium ion influx, oxidative stress, mitochondrial dissociation of hexokinase II and mitochondrial fragmentation leading to uncontrolled opening of MPTP especially in ischemia-reperfusion (129). Melatonin prevents MPTP opening either by activation of STAT3 and RISK pathway (122) or by inhibition of cardiolipin peroxidation along with inhibition of mitochondrial NAD^+ and cytochrome c release (130). Melatonin, by exerting a positive influence on different cellular signalling pathways, mitigates mitochondrial oxidative stress thereby helping to maintain the structural and functional integrity of these organelles.

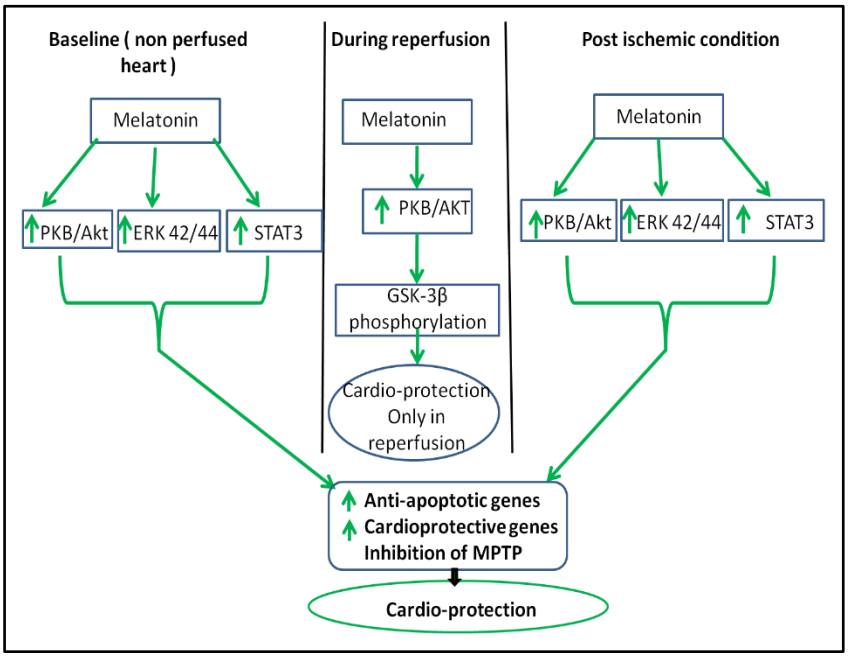

Fig. 3. Schematic diagram representing cardio-protective role of melatonin in control diet and high fat diet fed animals in baseline condition, during reperfusion and post-ischemic condition.

11. CONCLUSION

Cardio-protective roles of melatonin are well documented. In this review we have tried to explore the protective effects of melatonin on cardiac damage caused by HFD. A few studies have already investigated this hot topic. Melatonin efficiently mitigates the altered metabolic parameters induced by HFD in a variety of animal models. These parameters include blood glucose, lipid profile, body weight, circulating leptin, adiponectin level, energy expenditure, glucose and fat metabolism. As a potent antioxidant, melatonin also effectively attenuates cardiac oxidative damage associated with HFD. HFD up regulates the expressions of TLR4, MyD88 and NF-κB, thereby activating NLRP3 inflammasomes. Additionally, by suppressing Sirt3 expression HFD can also activate NLRP3 inflammasomes. Activation of NLRP3 increases caspase-1 activation which ultimately activates IL-1β along with other inflammatory cytokines which causes vascular inflammation, metabolic, physiologic, and

inflammatory. HFD is a promoter of ROS formation to induce oxidative stress in myocardium. The inflammatory reactions and oxidative stress associated with HFD lead to the cardiac damage. Thus, suppressing the inflammatory reactions and reducing the ROS formation are the keys to prevent cardiac injury induced by HFD. Melatonin as potent antioxidant with anti-inflammatory property appears to be the suitable candidate for this purpose. Melatonin increases Sirt3 activity, up regulates CTRP3 expression and preserves structural and functional intactness of mitochondria in HFD fed animals. In addition, by up regulation of RISK pathway, melatonin can activate STAT3 to further protect the cardiac injury induced due to ischemia-reperfusion in HFD fed animals. Moreover, melatonin is present in almost all dietary products including vegetables, fruits, cereals, eggs, fish and meat (131) and various investigations have shown that it is safe for consumption by humans. Consumption of melatonin rich foods can enhance the circulating melatonin levels (132). All these advantages of melatonin have suggested that it will be an effective therapeutic molecule to prevent and treat the cardiac injury associated with HFD.

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AUTHORSHIP

Dr. DB and Dr. AC contributed in conception, revised the manuscript critically and approved it. AG and GB contributed in preparing figures, drafted the manuscript and edited it. Dr. PKP contributed in conception of manuscript and edited it.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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