Review

Biorhythmic and receptor mediated interplay between melatonin and insulin: its consequences on diabetic erythrocytes

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ABSTRACT

Diabetes *mellitus*, one of the crucial epidemics of this country has snatched the sleep of mankind with a steep slope of 108 million in 1980 to more than 460 million in today's world. The global statistics based on numerological information from World Health Organization (WHO) proposed alarmingly about 642 million affected individuals by 2040. Type 1 diabetes is due to damaged pancreatic β-cells while type 2 diabetes is a result of insulin insensitivity associated with hyperglycaemia. Hyperglycaemia is a principal symptom of diabetes. As a result, the circulatory erythrocytes [red blood cells (RBCs)] become the first and most vulnerable victims to confront such a stressful environment. The RBCs possess many components including haemoglobin, membrane proteins and lipids. They prefer to interact with glucose and form glycated haemoglobin and membrane phospholipid asymmetry which alter RBC adherence. These alterations trigger intracellular reactive oxygen species (ROS) formation and oxidative damage in diabetic erythrocytes. Melatonin, an indoleamine, ameliorates oxidative stress in various tissues and has the capacity of shielding erythrocytes from deleterious stress. A crucial relationship between melatonin and insulin indicates their interplay in occurrence of diabetes. Biorhythm entrained and receptor mediated action of melatonin on pancreatic β-cells in the context of hyperglycaemia are discussed for the first time in the review. Since melatonin protects against erythrocytes, as well as beneficial to diabetes, it is worthy to address proficiency of this indoleamine to the diabetic erythrocytes. In summary, this review has discussed the fostering role of melatonin in hyperglycaemia and encouraged further investigation related to the molecular pathways of melatonin on glucose metabolism.

Key words: diabetes**,** erythrocyte, pancreas, insulin resistance, melatonin, biorhythm.

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1. INTRODUCTION

Diabetes *mellitus* (DM), a curse to the humanity is advancing alarmingly with some worldwide frightening statistics. Prevalence of diabetes emerged as a nightmare in developing countries while 4.2 million deaths have been admitted worldwide in the year of 2019 (1). DM is characterised by elevated blood glucose level either due to destruction of

pancreatic β-cells (Type 1) or due to insulin insensitivity of cells leading to insulin resistance (Type 2) (2).

Confronted endogenous antioxidant system and subsequent profound free radical generation have been an integral part of hyperglycaemia (2), causing associated complications including micro-vascular anomalies, heart diseases, atherosclerosis, stroke, diabetic retinopathy and renal disorders (3). Being the carrier of oxygen, erythrocytes are highly vulnerable to oxidative stress due to absence of nuclei, mitochondria and presence of iron containing heme (4). Oxidative stress has been referred as an intrinsic cause behind diabetes progression and the erythrocytes are evidenced wide spectrum damages due to its long term of exposure to surged glucose level (5). High blood glucose level leads to haemoglobin glycation and subsequent alterations in RBC deformability, adhesion, aggregation promoted-membrane phospholipid asymmetry and thus eryptosis (6). This eryptosis and inhibition of erythropoeisis in diabetics cause development of anaemia (7). Pancreatic β-cells are unarmed to counter enormous intracellular ROS generation, due to their poorly expressed endogenous antioxidant system (8). Additionally, as upregulated insulin production in diabetics requires higher amount of energy to keep β-cells metabolically active, these cells consume more oxygen that make them more prone to ROS generation (9).

While a number of studies claimed the involvement of oxidative stress in pathogenesis of diabetes and its associated complications, scientists have wisely chosen classical antioxidants to conquer such distressing situation. Melatonin, since its discovery, has been proven to act as a companion of cell and tissues (10) while its excellence in abating erythrocyte stress has been recently reported (11). Moreover, as this tiny indoleamine exhibits brilliance in protecting the pancreas from glucotoxicity (12), pancreatitis (13) and other injuries, it seems superior to others when researchers are looking for a potent antioxidant to curb oxidative stress mediated damages in hyperglycaemia.

Circulatory melatonin level and pancreatic insulin secretion exhibit a pivotal inverse relationship (14) which is evidenced from studies depicting decreased insulin secretion with melatonin administration and a daytime escalation in insulin level (15). This axis of melatonin and insulin emerged as a blessing to diabetic patients as evidenced from studies rendering reduced insulin level in pinealectomised rat (16) confirming the vision of diminished melatonin level in diabetic animal model as well as in patients (17). Furthermore, the occurrence of diabetes and related complications rise with aging, correlated with age associated decline in melatonin level (18). All these lead to the conviction of melatonin dependent diurnal rhythm of insulin secretion to preserve functional state of β-cells in order to hinder insulin resistance in diabetic individuals (19), substantiated by the presence of melatonin receptors in pancreatic islets (19, 20). Receptor mediated versatile pathway of melatonin on pancreatic islets (19) gave the ray of hope in rejuvenating β-cells by limiting insulin secretion and thus by delaying the curse of diabetes.

In spite of several studies showing protective effects of melatonin on erythrocytes which are under hyperglycaemia induced oxidative stress (21), the specific pathways involved in such protection remain unknown, especially, in the context of RBC possessing both glucose and melatonin receptors (22). This review will emphasize the possible pathways of melatonin's protective action on diabetic erythrocytes and its relationship to curb the development of diabetes *mellitus* as well as its common complications.

2. MORPHOLOGICAL ALTERATIONS OF ERYTHROCYTES ASSOCIATED WITH DIABETES *MELLITUS*

Insulin resistance, being the foremost cause behind development of type 2 diabetes *mellitus*, leads to gradual accumulation of free glucose molecule in blood stream as cells

became incapable in use of glucose as energy source. This glucose assembly affects the health of blood stream residing erythrocytes leading to extensive structural and functional alterations (23) as depicted in Figure 1.

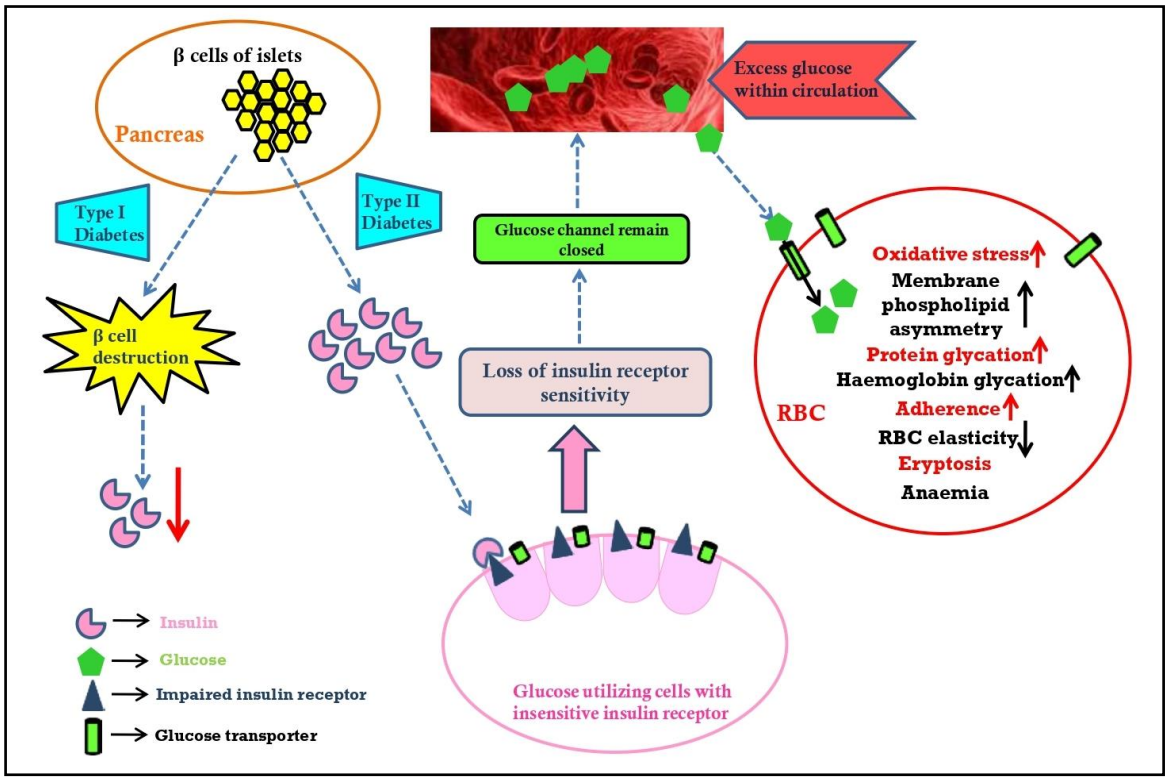

Fig.1. Illustration of alterations of diabetic erythrocytes confronted with high glucose level either due to pancreatic β-cell destruction (Type 1 diabetes *mellitus*) or due to loss of insulin receptor sensitivity leading to insulin resistance (Type 2 diabetes *mellitus*).

Erythrocytes have to squeeze through narrow capillaries (24) to deliver oxygen in every part of the tissues to meet their oxygen demand (25). To carry out this function RBCs solely depend on the unique architecture of cytoskeletal membrane (26). Membrane phospholipid asymmetry, a key feather of functional erythrocytes, has been interrupted in diabetic RBC (27). A seesaw style ratio of saturated and unsaturated fatty acid content in RBC membrane has been suggested and this ratio is elevated in hyperglycaemic patients (28). Significantly abated values in RBC diameter and concave depth have been reported in diabetics (29) and decreased roughness of diabetic erythrocytes has been visualized by both scanning electron and atomic force microscopies (29), a determinant of RBC health condition (30). High membrane fluidity has been observed in early young RBCs of diabetic patients compared to healthy subjects (31, 32). Increased sphingomyelin and phosphatidylcholine ratio (6) with collaterally decreased cholesterol and phospholipid ratio (33), as evidenced by spin labelling of fatty acids (34) may be the cause of altered diabetic erythrocyte membrane fluidity. Morphological reshuffling of RBCs has also been evidenced in diabetics solely due to membrane cholesterol modifications (35). Distinct membrane lipid conformation in type 1 and type 2 diabetics in comparison to healthy individuals has further confirmed the notion of modified lipid raft in hyperglycaemia (36). A strong correlation between diabetes and erythrocyte membrane alterations has been reported (37). The membrane phosphatidylcholine is more susceptible to phospholipase A2 treatment in diabetics (27). Dense fibrin deposition in diabetic patients was reported in iron induced blood coagulation study (38). Moreover,

significant morphological and ultrastructural alterations are identified in type 2 diabetics, with dysregulated inflammatory markers, which were ameliorated by use of iron chelators (39). A protective role of iron chelators in combating escalated inflammation associated with type 2 diabetes straightens the argument that hyperglycaemic pathology involves oxidative stress (40).

3. DIABETES *MELLITUS* AND ERYTHROCYTE OXIDATIVE STRESS- A CRUCIAL LINK

Studies have uncovered a potential association between the progression of type 2 diabetes *mellitus* and the degree of erythrocyte oxidative stress. How lipid peroxidation induces modulation in RBC membrane composition has been elucidated in diabetic subjects (41). Phosphatidylserine (PS) exposure in the outer membrane of a cell has been recognised as a convincing apoptotic marker that triggers subsequent apoptotic pathway. High blood glucose content is considered as a prime factor to lead erythrocytes toward eryptosis with PS exposure and these features promote the erythrocyte removal from circulation through macrophage activation (42). Microvascular difficulties associated with non insulin dependent diabetes *mellitus* (NIDDM) has been found with increased lipid peroxidation and depleted antioxidant enzyme activities in erythrocytes (43). The exhausted endogenous antioxidant system is the principal cause behind oxidative injury which leads to the surged atherosclerotic anomalies, a leading cause behind death of diabetics (44). Studies have also confirmed the presence of conjugated diene in RBC membrane of diabetes patients as a stress indicator (45). Reduction of oxygen by increased blood glucose also caused deleterious ROS formation, particularly the hydrogen peroxide (46, 47). Since the high blood glucose level compromises endogenous antioxidant level, diabetic patients are highly susceptible to oxidative stress (48). Theoretically, antioxidants will provide beneficial effects to the diabetics. Indeed, vitamin E supplementation has been selected in revamping malondialdehyde and glutathione of RBCs in diabetics, affirming the prevalence of oxidative stress (49). The disrupted vitamin E concentration in type 2 diabetic patients (50) supports the finding of erythrocyte catalase deficiency in individuals with diabetic risk factors (51). Compromised SOD activity (50) and SOD inactivation by glycosylation and loss of Cu^{2+}, the prime cofactor for functional SOD, in hyperglycaemics has been reported by Hamden *et al*. (52). In addition, glycation product induced binding of diabetic erythrocytes to vessel wall further confirms of the oxidative stress that leads to versatile diabetic complications (53). Oxidative stress mediated ultrastructural alterations in erythrocytes then trigger increased prevalence of inflammation (39) and this has been observed in diabetic patients with disassembled RBC membrane spectrin network (54). Collectively, substantial evidence strongly indicates the high vulnerability of hyperglycaemic RBCs to oxidative stress compared to healthy control (55), even as *in vitro* studies, more damages were found in diabetic RBCs exposed to hydrogen peroxide than those of healthy control RBCs (56, 57).

4. DISTURBED ERYTHROCYTES IN HYPERGLYCAEMIA- AN DEPTH VIEW

When RBCs are exposed to high glucose for long time, they may adapt some pathological alterations by modifying their ultrastructure (58) (Figure 1). For example, unrestrained aggregation and adherence of hyperglycaemia related RBCs to endothelium induce vascular modifications associated with diabetic complications (59, 60). As mentioned above, the ultrastructural alterations of RBCs escalate pro inflammatory cytokine level, reported as a major cause behind such malfunction (6). The adherence comes from interaction between specialized glycation product of diabetic RBC and the specific receptor of endothelium (61),

as reported also by Wautier *et al*. (53). Nitric oxide serves as an anti adherence factor (61) and its formation is inhibited by increased nitro-L-arginine in diabetes which triggers adhesion of diabetic RBC with endothelium (61). Unusual exposure of PS in outer membrane is also a major site of diabetic erythrocytes triggering adherence with cultured endothelium (27) which supports a previous study depicting role of decreased adherence phenomenon in controlled diabetes (62).

Both scanning electron and atomic force microscopic studies have visualized a smoother surface in diabetic erythrocytes than that of healthy RBCs. This indicates diabetic erythrocytes having remarkable alterations in their surface roughness due to modified membrane cytoskeletal as well as superficial protein conformation and arrangements (29). The erythrocytes of diabetic patients have higher Young's modulus, indicative of stiffer RBC (39). In the same study by using scanning electron microscopy the authors observed a remodelling of diabetic RBCs fibrin network, where instead of forming individual visible fibres, fibrin form a continuous layer of finer fibres, giving an embolus image (39). A laser assisted optical rotational cell analyzer detected the extensive evolution of RBC deformability in diabetics (63).

Apart from extensively remoulded membrane lipid asymmetry, the distinct cytoskeletal protein architecture of erythrocytes is the most perturbed area in diabetic RBCs while alterations in molecular level have also been speculated (64). High glucose concentration induced RBC membrane protein (65) and haemoglobin (66) glycation increases RBC fragility (67), hampers protein integrity (68) and leads to diminished RBC life span (37). Bonadonna *et al*. (69) reported high proneness of GLUT1 glycation in diabetic RBCs and this glycation jeopardized glucose uptake and transport across plasma membrane and finally caused cellular damage. Moreover, high glucose concentration adversely affects another membrane protein Band3 menacing the anion exchange capability of RBCs (70).

This lifespan shortened diabetic erythrocytes are the cause of anaemia occurred as a complication of diabetes (71). Presence of hypoxic environment prevailing in chronic hyperglycaemia leads to hindered erythropoietin secretion and thus reduces RBC generation (72). The erythropoietin secretion can also be suppressed by IL6 in diabetes (73) and this suggests a role of inflammation in DM.

5. MELATONIN AS A BROAD SPECTRUM OF PROTECTOR AGAINST DIABETES *MELLITUS*

While oxidative stress is a major cause behind the development of diabetes and its related complications (74, 75), the molecule melatonin has been coined as a potential candidate to target diabetes due to its wide acceptance as a potent antioxidant (10).

5.1. Relevance to type 2 diabetes.

The strong correlation between inflammation induced oxidative stress and hyperglycaemia is evidenced by the increased macrophage infiltration and escalated pro-inflammatory cytokine level which lead to insulin resistance (76), and progress to obesity dependent type 2 diabetes *mellitus* (77). The obesity (78) and hyperglycaemia induced in high fat fed rats were attenuated by melatonin administration (79), indicating a mechanism that melatonin improves glucose equilibrium in animal study (80). Mitigation of IL6, TNF-α mediated low grade inflammation and reduction in release of chronic inflammatory marker CRP are additional mechanisms of melatonin targeting diabetes observed in Zucker diabetic fatty rats, a model for NIDDM (81). The anti-inflammatory role of melatonin is mediated either by binding to its dedicated receptors (81) or by upregulating anti inflammatory adiponectin secretion (80) and

thus reducing some diabetes related complications including atherosclerosis (82) and neuropathy (83). Generation of excess superoxide anion is an inevitable result of prolonged hyperglycaemia (84), especially in the insulin independent cells like vascular endothelium. In these cells, prolonged hyperglycaemia activates polyol pathway and increases glycation through inhibition of glyceraldehydes 3 phosphate dehydrogenase (85). Under these conditions, melatonin has the capacity to effectively scavenge superoxide anion (86) and counterbalances diabetes associated oxidative stress (21). In high fat diet and low dose sptreptozotocin induced type 2 diabetic rats melatonin treatment at a dose of 10 mg/kg/day for 4 weeks significantly reduced cholesterol content and enhanced the levels of endogenous antioxidants (87). Both immediate and sustained release formula of melatonin are equally efficient in protecting RBCs of diabetics (88). Melatonin improves endothelial function (87) in hyperglycaemia via diminishing the membrane lipid peroxidation (89, 90). Hyperglycaemia is one of the major reasons behind coronary heart disease (91) and atherosclerotic disorders (92) and targeting hyperglycaemia has become an unavoidable area in cardiac treatment. Clinical trials also showed beneficial effects of melatonin on diabetes. For example, in a randomized control trial melatonin supplementation for twelve weeks preserved the redox balance, lipid profile as well as the glycaemic status of type 2 diabetic patients with coronary heart disease (93). The diminutions in stress factors and improved antioxidant status with melatonin administration have been documented in obese women (94) and patients with metabolic syndrome (95). Melatonin also stimulates the hepatic γ-glutamylcysteine synthase activity which accelerates the level of endogenous glutathione in human vascular endothelial cells (96). Additionally, jeopardized mitochondrial metabolic system in type 2 diabetics (97) has further recommended melatonin as an important remedy as the protective role of melatonin against mitochondrial oxidative stress has been documented (98).

5.2. Relevance to type 1 diabetes

The protective effect of melatonin was also observed in streptozotocin induced type 1 diabetic mice (99). In this animal model, ROS mediated cytotoxic effects on β-cells hampers insulin secretion (100). Melatonin supplementation reduced serum glucose and lipid peroxidation levels in both STZ and alloxan induced diabetic mice, respectively (99, 100). The superior effects of melatonin over other substances to scavenge ROS, lower serum glucose and rejuvenate antioxidant machineries has been reported in STZ treated type 1 diabetic Sprague Dawley rat (101). These findings further support the high efficacy of melatonin in mitigating oxidative damages in blood, liver, kidney associated with type 1 diabetes (102-104). An improved lipid profile in experimental type 1 diabetic male and female Wistar rats after melatonin administration has been reported (105, 106) with a concomitant decrease in glycosylated haemoglobin level (106). Melatonin treatment in experimental diabetic mice also enhanced the tolerance of their RBCs to autoxidation (107).

The protective mechanisms of melatonin on hyperglycaemia rely on its antioxidative property (10) and its easy diffusion to cells due to its hydrophilic and lipophilic nature (108). These findings rise craving for studying whether melatonin exhibit any shielding effect towards pancreatic β-cells signifying the presence of melatonin receptors on pancreatic islets.

6. MELATONIN ENTRAINED BIORHYTHM OF PANCREATIC β CELL IN HYPERGLYCAEMIA

Pancreas has been identified as an extra-pineal source of melatonin due to the fact that this organ can synthesize melatonin *de novo* (109, 110), indicative of a direct effect of melatonin

on enzymatic and functional status of pancreatic β-cells. This discovery suggests a correlation between circadian rhythm disturbance and the development of type 2 diabetes *mellitus* (111). It was found that these two events occurred parallelly with the outcome of diminished insulin secretion in pinealectomized rats (112). Melatonin administration normalized the increased plasma glucose and reduced circulatory insulin level in pinealectomized rats (16). Disturbance in sleep duration and quality is one of the causes behind the phenomenon of insulin resistance and the risk factors of type 2 diabetes (111, 113), which supports the finding of Hikichi *et al*., i.e., reduced night-time melatonin secretion in subjects with diabetes and diabetic retinopathy (114). It is known that insulin is a potent inactivator of AANAT (115) which is the rate-limiting enzyme for melatonin synthesis. Its inactivation will result in reduced melatonin production in body. The declined level of nocturnal melatonin has been observed in experimental diabetic Syrian hamster model (14) and this reaffirms the notion of an inverse relationship between melatonin and insulin. To step forward, Csaba *et al*. (116) have raised a question about the linkage between pancreatic islets and pineal gland. To answer this question, Peschke *et al*. reported the existence of melatonin receptor in pancreatic islets and ascertained an inverse association between melatonin and insulin levels (20). In the follow up investigation, Peschke *et al*. further identified that the decreased pineal AANAT activity and plasma melatonin level are associated with upregulated expression of melatonin receptors (MT1) in pancreatic β-cells of type 2 diabetic patients and also of diabetic goto kakizaki rats (17). All results confirmed a decreased melatonin level in diabetes and suggested an involvement of compensatory mechanism behind increased MT1 receptor expression to assure binding with more melatonin. They also reported abated expression of insulin receptors in pineal gland and contended this change as a response to increased plasma insulin level in hyperglycaemia. The similar results were reported by Nishida *et al*. (117) where decreased melatonin level in pinealectomized Otsuka Long-Evans Tokushima fatty rats was associated with elevated triglyceride level and diabetic complications, supporting low level of melatonin in type 2 diabetic patients (118). Collectively, the negative correlation between melatonin and insulin levels (119) and the occurrence of type 2 diabetes indicate the receptor mediated actions of melatonin in alleviating insulin resistance in type 2 diabetes and its secondary complications.

7. A BRIEF VIEW ON PATHWAYS INVOLVED IN PROTECTIVE ACTION OF MELATONIN

Literature searching has implanted an idea about erythrocyte modifications in diabetic individuals and the roles of melatonin in ameliorating adverse alterations in diabetic erythrocytes. Moreover, the biorhythmic synchronization of pineal melatonin and pancreatic insulin secretion illuminate the role of melatonin-insulin axis in controlling hyperglycaemic state. But, how this axis and receptor mediated action of the indoleamine shield RBCs from being revamped in hyperglycaemic condition is a concern to explore.

That melatonin promotes pancreatic β-cell survival and subsequent insulin secretion in type 2 diabetic patients confirms the protective effects of melatonin on hyperglycaemia induced β-cell damage and subsequent apoptosis (120, 121). *MTNR1A* mRNA expression in INS-1 cells (122, 123) and expression of both *MTNR1A* and *MTNR1B* in rat and human islets (124, 125) authenticate the assumption of presence of MT1 and MT2 melatonin receptors in pancreatic islets (20). *MTNR1A* and *MTNR1B* mRNA has been elucidated to be predominantly present in α-cells of human pancreatic islets (125) and in β-cells of both human and rodent islets, respectively (126). Though melatonin is easily permeable through lipid bilayer, its cellular actions are predominately mediated by its membrane receptors, MT1 and MT2, two G protein coupled receptors (GPCR) sharing homology in domains to a high

extent (127). This indoleamine executes its function predominantly by inhibiting cAMP level upon binding to its receptor and resulted in reduced insulin secretion (15, 121, 128). MT1 and MT2 knockout mice exhibit insulin resistance owing to diminished insulin sensitivity (129, 130). A loss of function mutation in *MTNR1B* gene has found correlated with the occurrence of type 2 diabetes (131) and carriers of this allele have been identified as diabetes prone individuals (132). A strong correlation between single nucleotide polymorphism (SNP) in *MTNR1B* exon and appearance of higher plasma glucose level (132) along with escalated glycated haemoglobin has been reported (133). MT1 and MT2 exert their cellular effects by binding to inhibitory G proteins (G_i) as pancreatic β-cells have been reported to own G_i2 isoform (134). The binding of melatonin with G_i protein coupled MT1/2 suppresses activity of adenylate cyclase leading to hindered second messenger cyclic AMP (cAMP) generation, protein kinase A (PKA) activation and thus declined insulin secretion from islets (135, 136, 126) (Figure 2).

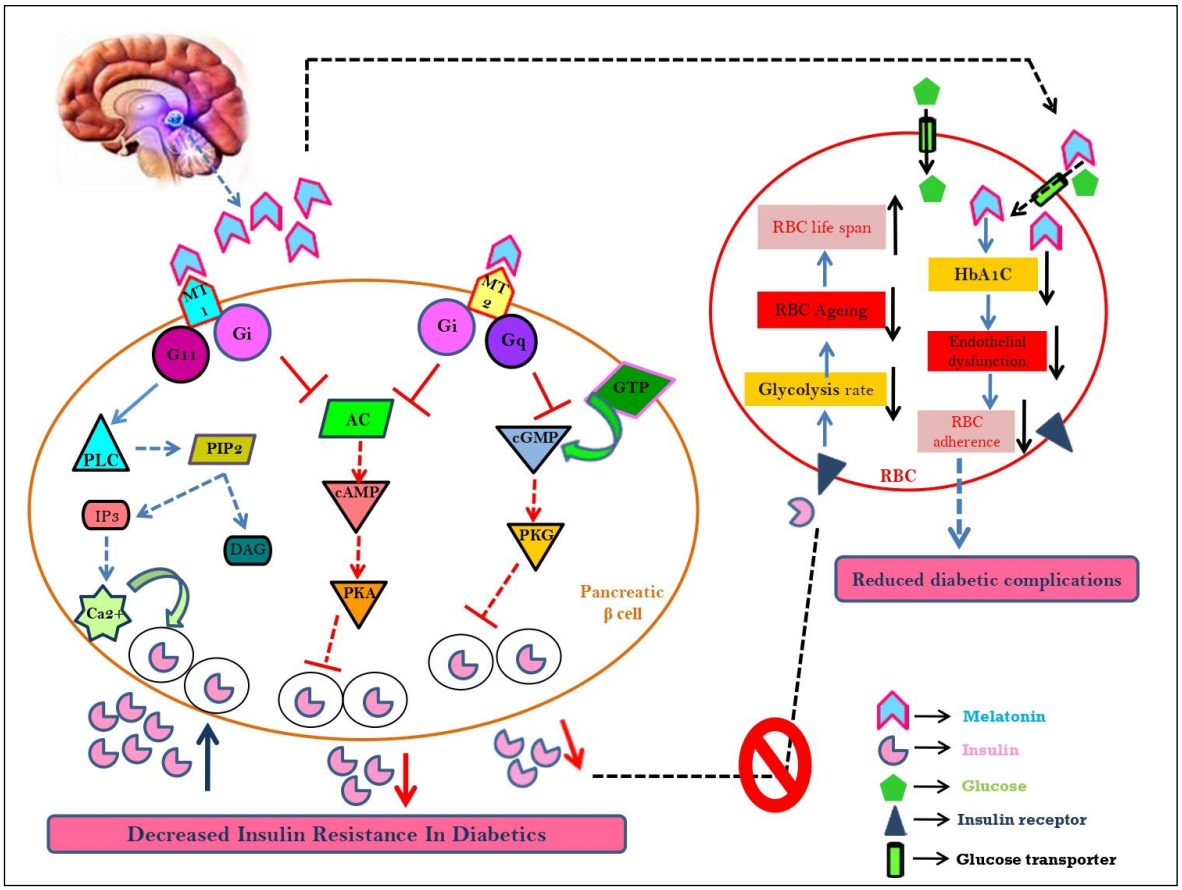

Fig. 2. The illustration of potential interplays between melatonergic system and insulin secretion.

Melatonin upon binding with its receptor MT1 and MT2 on pancreatic β-cell surface triggers some signalling cascades: (a) activations of both MT1 and MT2 bound G_i protein inhibit adenylate cyclise (AC) which in turn suppresses production of cyclic AMP (cAMP) and activation of protein kinase A (PKA) resulting in decreased insulin secretion; (b) MT2 binding to G_q also functions as an inhibitor to insulin secretion by limiting cyclic GMP (cGMP) formation and subsequent protein kinase G (PKG) activation which also leads to reduced insulin secretion; (c) Melatonin upon binding with MT1 (MT2 also may participate) triggers G_{11} mediated hydrolysis of phosphatidyl inositol 4,5- bisphosphate (PIP2) and the

inositol 1,4,5- triphosphate (IP3) generation that trigger calcium (Ca^{2+}) release and leads to vesicular fusion and insulin release. This controlled insulin release by melatonin prevents excessive insulin binding to its receptors on erythrocytes and preserve the sensitivity of RBCs to insulin in diabetic patients; (d) melatonin from circulation also, competes with free glucose molecules to enter RBCs through glucose transporters and reduces RBC glycation and diabetic complications.

Additionally, PKA independent influence of cAMP on insulin secretion by cAMP sensing protein like Epac2 that influences vesicle transport has been inhibited after melatonin binding to its receptor (136). On other hand, melatonin also downregulates the activity of cGMP and thus protein kinase G (PKG) through MT2 receptor to inhibit insulin secretion (135, 136, 126) (Figure. 2). This finding goes parallel with studies reported about diminished cGMP formation either by activation of MT2 (137) or by addition of melatonin to INS-1 cells (138). In spite of a negative correlation between melatonin and insulin, how melatonin receptor knockdown as well as single nucleotide alteration in encoded gene (*MTNR1B*) is integrated with hyperglycaemia is a factor of investigation. The opposite report is that MT1 also couples with another G protein G_q11 (139) which triggers phospholipase C mediated generation of inositol-1, 4, 5-triphosphate (IP3) and diacylglycerol (DAG). IP3 enhances calcium release from internal store and DAG activates protein kinase C/D to accelerate MAPK p38 modulated calcium-driven vesicular fusion and subsequently promotes insulin secretion (135, 136, 126) (Figure 2). This stimulatory activity as evidenced in melatonin mediated release of IP3 in INS1 cells (140) and thus, insulin secretion has been presumed to be mediated by MT2 receptors also (126) which need further confirmation. The reviving effect of MT1 receptor on β-cell insulin secretion may be conveyed by the paracrine action of α-cells of islets in response to melatonin binding at MT1. Glucagon is the secretory product of α-cells and it binds to glucagon specific receptor coupled with G stimulatory (G_s) to stimulate β-cell release of insulin (125,136). Immunohistochemical studies found the only presence of MT2 in β-cell islets of humans (136) which supports the mentioned paracrine effect of glucagon on insulin production due to the observation that both MT1 and MT2 are presence in α-cells (141). Hence, melatonin exerts autocrine action in pancreatic islets to preserve the functions of both α- and β- secretory cells.

The preserving effects of melatonin on insulin secreting cells of islets are by suppressing their apoptosis and this action will definitely bestow to diabetic patients (142, 143). Though melatonin and insulin has been depicted as predominantly counteracting partners via melatonin receptor mediated action on pancreatic islets, circadian disruption has affirmed to be a dominant cause in hyperglycaemia. Here, melatonin appears as a crucial player in maintaining well being of type 2 diabetics by inhibiting over exhaustion of β-cells (121) and thus preventing the unnecessary insulin secretion which will make cells become insensitive to insulin in a long run. Hence, the presumption of melatonin treatment for insulin resistant glucose utilizing cells will make them less resistance to insulin, especially in type 2 diabetes (144). This action of melatonin provides an opportunity for type 2 diabetic patients to overcome the exhausted β-cells in order to hinder age associated occurrence of diabetes and its complications (145).

8. MELATONIN ENTRAINED DEFENCE IN DIABETIC ERYTHROCYTES

Based on the evidence mentioned above, melatonin seems to serve as a protective cushion for pancreatic tissue by limiting insulin secretion and preserving β-cell function. In this consideration, the efficacy of melatonin in protecting RBCs is addressed since RBCs will not face the long-lasting high glucose environment which is the case in the diabetes with β- cell

dysfunction. The altered erythrocyte environment coupled endothelial dysfunctions are associated with afflicted cardiac injury during ischaemia reperfusion in diabetic patients (146). The stress-related RBC haemolysis and high blood glucose level activate arginase which competes with nitric oxide synthase (NOS) to act upon their common substrate arginine and lead to depletion of nitric oxide (NO) (147). The reduced NO content and elevated ROS enhance RBC adhesion to endothelium with abnormal glycation of membrane proteins cause cardiac functional anomalies. In addition, glycated RBCs in diabetes trigger phagocytosis and lead to elevated susceptibility of atherosclerotic plaque rupture (148) causing atherothrombosis. The influence of insulin on erythrocytes has been affirmed by the presence of the polypeptide specific insulin receptors in these cells (149). These insulin receptors in RBCs are diminished in diabetic patients and this indicates a crucial relationship between hyperglycaemia and erythrocyte response in such state (150). The depletion of insulin receptors in RBCs may be a protective mechanism of erythrocytes in high glucose environment. This assumption is supported by action of melatonin to limit insulin secretion. The self-protective activity of erythrocytes in high glucogenic environment will undermine the adverse effects of insulin which is reported to increase the rate of glycolysis in RBCs (151) and this is also observed in diabetic RBCs (152, 153). The increased glycolysis rate in diabetic RBCs indicates high prevalence of young RBCs (154) and its association with the increased rate of ageing (153) and reduced life span (155) of the diabetic erythrocytes. All of these adverse effects can be protected by melatonin since melatonin hinders insulin secretion, preserves the glycolytic enzymes and prolongs the lifespan of erythrocytes in diabetic patients (Figure. 2). In addition to membrane receptor mediated actions, melatonin can be transported into inside of RBC by glucose transporters (GLUTs) (11, 22) to compete with glucose translocation (156) (Figure 2). In this way, melatonin limits the exposure of erythrocytes, particularly its haemoglobin and its membrane proteins to high glucose for accelerated glycation. The decreased fluidity of diabetic erythrocytes may also be preserved by melatonin since this molecule promotes the membrane fluidity by reducing the membrane lipid peroxidation (157). Both receptor dependent and independent actions of melatonin make this molecule be a potent protector for diabetic erythrocytes.

Hence, we suggest melatonin as a therapeutic alternative for diabetes to rejuvenate the malfunctioned pancreatic β-cells as well as erythrocytes due to the fact that melatonin effectively suppresses the adverse effects associated with high blood glucose.

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AUTHORSHIP

Dr. DB and Dr. AC contributed to conception, revised the manuscript critically and approved it. AB prepared, drafted and edited the manuscript and figures.

CONFLICT OF INTEREST

Authors declare no conflict of interests.

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