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MELATONIN: A NEW HORIZON FOR DIABETIC PATIENTS

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ABSTRACT

The global prevalence of Diabetes Mellitus (DM) is increasing in leaps and bounds. The international diabetes federation (IDF) has estimated 592 million people will suffer from DM by 2035. Hence, finding a novel bio molecule that can effectively aid diabetes management is vital, as other existing drugs have numerous side effects. Melatonin, a pineal hormone having anti-oxidative and anti-inflammatory properties, has been implicated in circadian dysrhythmia-linked DM. Reduced levels of melatonin and a functional link between melatonin and insulin are implicated in the pathogenesis of type 2 diabetes mellitus (T2DM). Additionally, genomic studies revealed that rare variants in melatonin receptor 1b (MTNR1B) are also associated with impaired glucose tolerance and increased risk of T2DM. Despite considerable advances in the past few years, obesity and T2DM remain two major challenges for public health systems globally. In the past 9 years, genome-wide association studies (GWAS) have established a major role for genetic variation within the MTNR1B locus in regulating fasting plasma levels of glucose and in affecting the risk of T2DM. Moreover, exogenous melatonin treatment in cell lines, rodent models and diabetic patients has shown a potent effect in alleviating diabetes and other related complications. This highlights the role of melatonin in glucose homeostasis. However, there are also contradictory reports on the effects of melatonin supplementation. Thus, it is essential to explore if melatonin can be taken from bench to bedside for diabetes management. This review summarizes the therapeutic potential of melatonin in various diabetic models and whether it can be considered a safe drug for managing diabetic complications and diabetic manifestations like oxidative stress, inflammation, endoplasmic reticulum stress, mitochondrial dysfunction, metabolic dysregulation etc. However, these studies did not solve the question of whether melatonin is beneficial or detrimental, an issue that will be discussed in the context of the peculiarities of the melatonergic system. Melatonin receptors might have therapeutic potential as they belong to the highly druggable G protein-coupled receptor super family. Clarifying the precise role of melatonin and its receptors on glucose homeostasis is urgent, as melatonin is widely used for other indications, either as a prescribed medication or as a supplement without medical prescription, in many countries in Europe and in the USA.

Keywords: Melatonin, Type 2 Diabetes, Oxidative stress.

INTRODUCTION

DM and related complications are amongst the leading causes of mortality and morbidity world-wide [1]. Our daily life-style gradually progressing towards an exaggerated active night time routine & a sedentary daytime management, leading to acute sleep disturbance. This scenario of disturbed circadian rhythm may be responsible for impaired glucose tolerance and DM. In type 1 diabetes (T1DM), body produces insufficient insulin due to pancreatic β cell damage. Without the presence of insulin many of the body's cells cannot take glucose from blood and therefore body uses other sources of energy. Ketone body is produced by liver as an alternative source of energy which leads to ketoacidosis.

T2DM is characterized by the body not responding efficiently to insulin, termed as insulin resistance. As a result the body is less able to take up glucose from blood.

Circadian rhythm is controlled by the hormone, melatonin. And this property of melatonin may be used as a therapeutic compound for treating DM.

A BRIEF IDEA ABOUT MELATONIN AND ITS FUNCTION

Melatonin is known as the hormone of darkness; an indoleamine with the chemical name N-acetyl-5-methoxytryptamine. In mammals, the concentration in plasma melatonin during night was found to be high (80–100 pg/mL) and low during the day (10–20 pg/mL) [2]. It maintains homeostasis in the body, helps adjust the timing or reinforces oscillations of the biological clock. Its synthesis comprised of two steps - it begins with the conversion of amino acid tryptophan into serotonin (5-hydroxytryptamine, 5-HT), then there is further acetylation by arylalkylamine N-acetyltransferase (AA-NAT), the rate-limiting step in melatonin biosynthesis, before finally conversion into melatonin by hydroxyindole-O-methyltransferase (HIOMT) [3]. Pinealocytes in the pineal gland secrete melatonin. Figure 1 illustrates melatonin secretion and signalling pathway through melatonin receptors in maintaining circadian rhythm within the cell. The pineal gland is activated or deactivated by light exposure to the eyes. During the day, melatonin production is inhibited while at night time, it is stimulated. When melatonin binds with melatonin receptors, it activates Gi and Gq proteins which in turn inhibit adenylate cyclase/cyclic-adenosine monophosphate (AC/cAMP) pathway and activates phospholipase C (PLC)/Inositol Triphosphate (IP3) pathway respectively. Due to phosphorylating activity of protein kinases, cAMP responsive element binding protein (CREB) and Mitogen-activated protein kinase (MAPK) signaling pathway (MSK1) regulate expression of Clock genes and thus maintain circadian rhythm. Melatonin stimulates several antioxidative enzymes - glutathione, catalase superoxide dismutase and acts on bone metabolism.

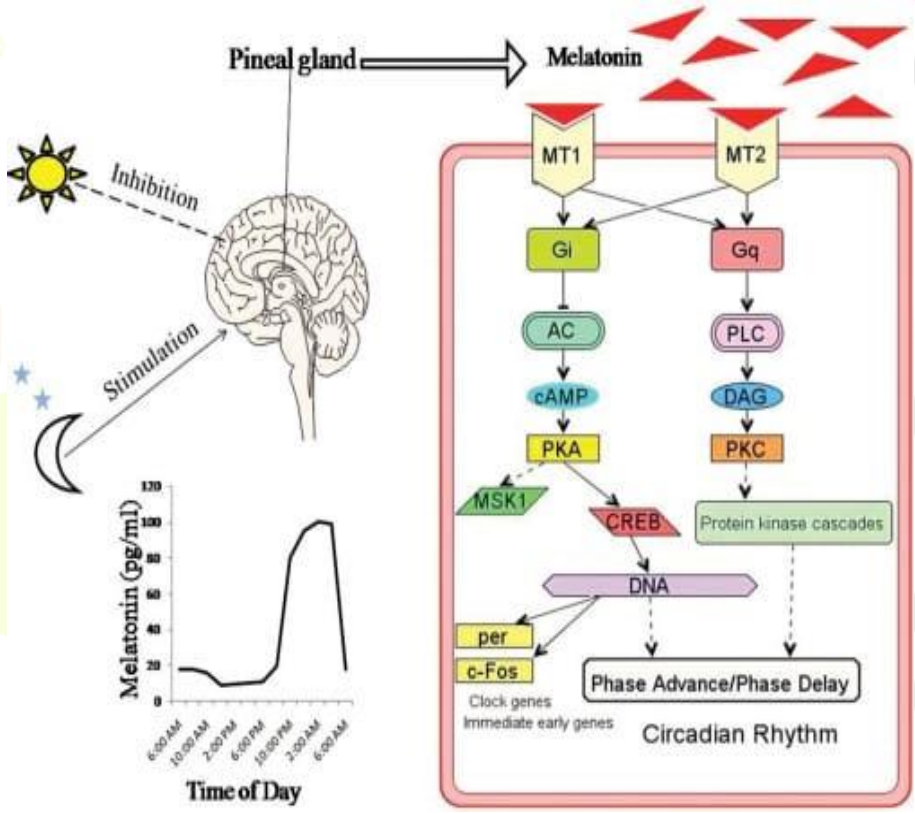

fig. 1: schematic representation of the melatonin secretion and signaling mechanism in maintaining circadian rhythm within the cell [4]. graphical representation of variation in melatonin level at different time of the day MT1: melatonin receptor type 1A; MT2: melatonin receptor type 1B; Gi: guanine nucleotide binding protein (adenylate cyclase inhibitor); Gq: phospholipase C activator; AC: adenylate cyclase; PLC: phospholipase C; cAMP: cyclic adenosine monophosphate; DAG: diacyl glycerol; PKA: protein kinase A; PKC: protein kinase C; MSK1: MAPK signaling pathway; CREB: cyclic AMP responsive element binding protein; Clock genes include Per, Cry, Dec, Rev-erba, Bmal1, Clock, Dbp; -------> -indirect effect[4].

MELATONIN RECEPTOR AND ITS CLASSIFICATION

Melatonin receptors belong to a family of receptors referred as G protein coupled receptors (GPCR). Melatonin mediates circadian rhythms and other physiological functions via membrane receptors on the cell surface. Melatonin is considered as a membrane-permeable substance owing to its chemical structure so it has both receptor-independent and receptor-dependent effects. All of its cellular MT1 actions and effects are likely transmitted via two known GPCR isoforms, denoted melatonin receptor type 1 (MT1) and melatonin receptor type 2 (MT2) previously known as Mel1a and Mel1b [5]. The two receptors exhibit a high degree of homology [5]. There are mainly two types of melatonin receptors found in humans, melatonin receptor 1 (MT1; MTNR1A) and melatonin receptor 2 (MT2; MTNR1B).

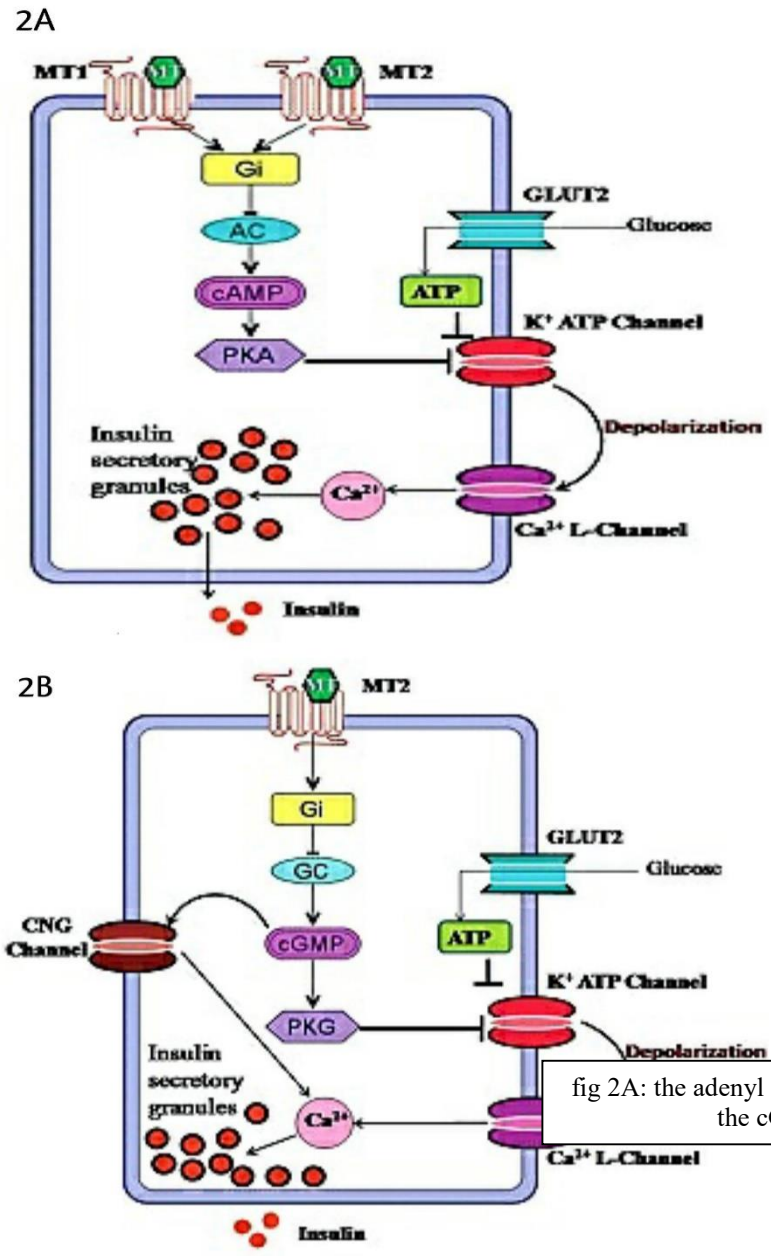

fig 2A: the adenyl cyclase/cAMP pathway 2B: the cGMP pathway

MELATONIN SIGNALLING AND INSULIN SECRETION

The intracellular signal transduction pathways of the pancreatic β-cell influenced by melatonin via MT1 and MT2-membrane receptors include cAMP, cyclic guanosine monophosphate (cGMP) and IP3 signaling pathways (Figure 2). Due to melatonin there is reduction in cAMP production in pancreatic islets and rat insulinoma β-cell line INS1, as well as forskolin-stimulated insulin secretion from isolated pancreatic islets of neonate rats [6]. The insulin and cAMP levels were stimulated by forskolin, an adenylyl cyclase activator [7]. The Giα-protein-inhibitor pertussis toxin (PTX) abolished the effect of melatonin on the levels of cAMP and insulin as well [7]. These results confirmed that melatonin

inhibits cAMP stimulated insulin secretion, which are mediated via Gi protein-coupled MT1 receptors. Melatonin activates MT2 receptor that inhibits the second messenger cGMP and suppresses secretion of insulin through pancreatic β-cells [8]. It activates cGMP dependent protein kinase (PK)

G. The activated PKG can directly phosphorylate and potentially turn on CREB and/or C/EBP (CCAAT enhancer-binding protein). The MT2-receptor also affects the second messenger cAMP in an inhibitory manner. Thus, both cAMP and cGMP pathways may have receptor mediated influence on cAMP responsive elements (CREs). Through PKG, cGMP probably modulates pancreatic circadian clock genes (e.g., on heterodimeric, activating bmal1/clock and antagonistic, inhibiting cry/per1 genes) leading to phase-shifting/resetting of secretion rhythms. cGMP signaling cascade also target on cyclic nucleotide-gated (CNG) channels and cGMP-specific phosphor diesterases (Figures 2A and 2B).

2C

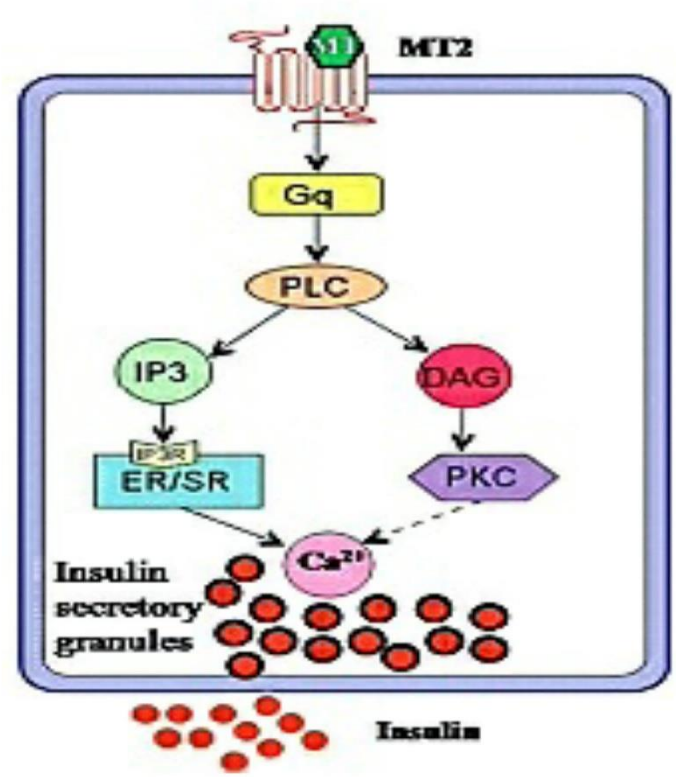

fig 2C: phospholipaseC/IP3 pathway

In the experiment involving INS1 cell line melatonin stimulates IP3 release in a dose dependent manner. During the same time melatonin receptor antagonist luzindole was capable of absolutely inhibiting such IP3-liberating effects of melatonin, hence signifying the role of melatonin receptors [9]. In addition, melatonin induced IP3 liberation that allow Ca^{2+} to flow into the cell from intracellular stores [10], a common mechanism that triggers insulin secretion by pancreatic β-cell. Alternatively, MT2-receptor-dependent signaling pathway of melatonin stimulates phospholipase C via Gq proteins, markedly elevating IP3/Ca^{2+} from intracellular stores [11]. The co-product of PLC activity, diacylglycerol (DAG), may lead to MAPK p38-modulated activation of PKD, PKC and increased vesicle fusion (Figure 2C).

VARIANTS OF MTNR1B GENE LEADING TO DM

The effect of melatonin is exerted by two G-protein coupled receptors – MT1A and MT1B. The two distinct receptors have been found to be expressed in human pancreatic islets [12]. Recent genome-wide association studies (GWAS) identified common genetic variants within MTNR1B were associated with higher fasting glucose levels or the increased risk of T2DM [13]. The two common genetic variants: rs1387153and rs10830963 are located near the melatonin receptor gene MTNR1B that encodes the MT2 receptor of melatonin. The variant with the strongest association signal was the single nucleotide polymorphism (SNP) rs10830963 [14]. A meta-analysis revealed that rs10830963 is strongly associated with fasting glucose levels and moderately associated with an increased risk to develop diabetes [15]. The risk allele was also related to impairment of early insulin secretion T2DM by the rs10830963 risk allele [16]. Recently, the associations of rs10830963 with the elevated fasting glucose and risk of T2DM were reported in Asian adults, including Chinese [17], Japanese and Sri Lankan populations [18]. In pregnant Chinese women, the MTNR1B variant rs10830963, rs1387153, rs2166706 and rs1447352 were shown to be associated with gestational glucose intolerance; so MTNR1B is probably involved in the regulation of glucose homeostasis during pregnancy. The role of MTNR1B gene (that codes for MT2 receptor), is important for regulating plasma glucose level & pathogenesis of T2DM. Variants of MTNR1B locus such as rs1387153 and rs10830963 have been associated with fasting glucose & T2DM. MT2 especially acts primarily on the pancreas due to the close association of rs10830963 SNPs causing impaired insulin secretion. The MTNR1B variant manifests increased glucose despite elevated insulin-to-glucagon ratio and predominates in β-cells unlike MTNR1A which is expressed in cells, leading to T2DM.

MELATONIN: A RELIEF FROM OXIDATIVE STRESS CAUSED BY DM

Insulin Resistance in adipocytes increases release of free fatty acids (FFAs) from stored triglyceride and increased oxidation of FFAs in aortic endothelial cells. Stimulation of malonyl co-enzyme A production causes increased production of superoxide by the mitochondrial electron transport chain. Overproduction of superoxide activates a variety of pro-inflammatory signals and inactivates two important anti-atherogenic enzymes-- prostacyclin synthase and endothelial Nitric oxide synthases (eNOS). In two non-diabetic rodent models, inactivation of prostacyclin synthase and eNOS was prevented by inhibition of the rate-limiting enzyme for fatty acid oxidation in mitochondria (carnitine palmitoyl transferase I), and by reduction of superoxide levels [19].

Elevated oxidative stress is a feature found in DM associated with diabetic neuropathy (DN), retinopathy (DR), nephropathy and cardiovascular disease. Reactive oxygen species (ROS) and nitrogen oxidative species are usually produced in

massive amounts via glucose and lipid peroxidation, and this leads to diabetic complications. DM increases Flavin adenine dinucleotide (FADH2) and Nicotinamide adenine dinucleotide (NADH), and inhibits the delivery of protons to complex III of Electron transport chain (ETC). Melatonin is an antioxidant which scavenges ROS and reactive nitrogen species (RNS). It also detoxifies hydroxyl radicals & peroxyl radicals. Melatonin increases secretion of antioxidants enzymes (glutathione, catalase, superoxide dismutase) & down-regulates triacylglycerol, total cholesterol and low-density lipoprotein concentration in Streptozotocin (STZ)-treated diabetic rats [19], [Table 1]

table 1:[20]

Disease	Melatonin Conc.	Duration of Treatment	Exp Model	Outcome	Reference
Diabetes	5mg	15days	Adult male Sprague Dawley derived rat	Decreased glucose level in plasma	Akmali *et al.* 2010 [21]
Diabetes	100mg/kg/day	8weeks	C57/BL6 mice	Improved glucose homeostasis	Sartoli *et al.* 2009 [22]
Diabetes	0.2mg/kg/day	8 weeks	Wister rat	Improved glycemic control	Oliveira *et al.* 2018 [23]
Diabetic cardiomyo-pathy	10mg/kg/day	21 days	Wister rat	Prevented apoptosis of heart	Amin *et al.* 2014 [24]
Diabetic Cardiomyo-pathy	10mg/kg	24weeks	Sprague Dawley rat	Prevented cardiac injury	Xiong *et al.* 2018 [25]
Diabetic Cardiomyo-pathy	10mg/kg	2weeks	Wister rat	Hyperglycemia induces ER stress	Lima *et al.* 2017 [26]
Diabetic Cardiomyo-pathy	10mg/kg	6weeks	Zucker rat	Improved endogenous cholesterol clearance	Agil *et al.* 2011 [27]
Diabetic cardiomyo-pathy	10mg/kg	8 weeks	Wister rat	Ameliorated oxidative stress	Baydas *et al.* 2016 [28]
Diabetic cardiomyo-pathy	20mg/kg	1 week	Sprague Dawley rat	Protected cardiomyocytes from injury	Yu *et al.* 2015 [29]
Diabetic cardiomyo-pathy	10mg/kg	12 weeks	Sprague Dawley rat	Improved atherosclerosis	Tang *et al.* 2019 [30]
Diabetic cardiomyo-pathy	50mg/kg	56 days	Wister rat	Increased production of antioxidant enzyme	Kandemir *et al. 2017* [31]
Diabetic retinopathy	10 mg/kg	4 weeks	Wister rat	Reduced diabetic retinal damage	Masoud *et al.* 2017 [32]
Diabetic retinopathy	0.2 mg/kg	2 weeks	Wister rat	Reduces protein oxidation in retina	Djordjevic *et al.* 2018 [33]
Diabetic retinopathy	10mg /kg	2weeks	Sprague Dawley rat	Reduced diabetic retinal damage	Ozdemir *et al.* 2014 [34]
Diabetic retinopathy	10mg/kg	12weeks	Sprague Dawley rat	Attenuated inflammation by reducing IL-1β, TNFα	Jiang *et al.* 2016 [35]
Diabetic retinopathy	10mg/kg	8 weeks	Sprague Dawley rat	Protective role against hyperglycemia induced keratopathy	Gul *et al.* 2008 [36]

Diabetic retinopathy	20mg/kg	15 days	Wister rat	Maintains catalase retinal activity	Salido *et al.* 2013 [37]
Diabetic neuropathy	10mg/kg	6 weeks	Wister rat	Reduced gliosis in brain	Baydus *et al.* 2016 [28]
Diabetic neuropathy	50mg/kg	45 days	Wister rat	Reduces dopaminergic fiber degradation in hippocampus	Baydus *et al.* 2016 [28]
Diabetic neuropathy	10mg/kg	7 days	Wister rat	Reduces dopaminergic fiber degradation in hippocampus	Metwally *et al.* 2018 [38]
Diabetic neuropathy	20mg/kg	-	Sprague Dawley rat	Increases Nrf2 production	Leeboonngam *et al.* 2018 [39]
Diabetic neuropathy	10mg/kg	6 weeks	Wister rat	Improves nerve conductivity velocity	Ali *et al.*2018 [40]
Diabetic neuropathy	10mg/kg	4 weeks	Wister rat	Improves nerve regeneration	Zangibadi *et al.* 2011 [41]
Diabetic neuropathy	1µM	24 hours	SH-SY5Y cells & mouse hippo-campal cells	Stimulates neuronal cell survival under high glucose condition	Onphachanch *et al.* 2019 [42]
Diabetic neuropathy	10µM	24 hours	Schwann cells	Alleviates high glucose induced apoptosis	Tiong *et al.* 2017 [43]

CONCLUSION

DM is one of the world's leading causes of death which is currently affecting millions of people around the globe. Hence, it is essential to find a biomolecule that could combat diabetic manifestations and their related complications as the current modalities cannot control insulin resistance, loss of β-cell and their dysfunction, oxidative stress, inflammation, and other diabetes-related complications entirely. Melatonin plays a crucial role in glycemic control by reducing Fasting Plasma Glucose. It also ameliorates insulin resistance and enhances insulin sensitivity to cells seen in various rat models. Therapeutic use of melatonin in treatment of diabetes has already studied in various rat models. But there is a scarcity of human trails. So in early future, melatonin can be a key element for diabetes treatment and will open a new horizon for millions of patients suffering from this disease.

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