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MELATONIN AND DIABETES MELLITUS: A RECENT UPDATE

MANOJ KUMAR NANDKEOLIAR
Professor, Department of Biochemistry, School of Medical Sciences and Research and Sharda Hospital, Sharda University, Greater Noida, Uttar Pradesh, India.

PRADEEP KUMAR
M.Sc Medical Biochemistry Final Year, Department of Biochemistry, School of Medical Sciences and Research and Sharda Hospital, Sharda University, Greater Noida, Uttar Pradesh, India.

THURAYA ABDULLSALAM AA ALAZAZI
PhD Scholar, Department of Biochemistry, School of Medical Sciences and Research and Sharda Hospital, Sharda University, Greater Noida, Uttar Pradesh, India.

NIRUPMA GUPTA
Professor, Department of Anatomy, School of Medical Sciences and Research and Sharda Hospital, Sharda University, Greater Noida, Uttar Pradesh, India.

BHASKAR CHARANA KABI *
Professor, Department of Biochemistry, School of Medical Sciences and Research and Sharda Hospital, Sharda University, Greater Noida, Uttar Pradesh, India.
*Corresponding Author Email: bhaskarkabi@hotmail.com

Abstarct

The pineal gland, situated within the hypothalamus, secretes melatonin, a hormone that governs the circadian rhythm of sleep and wakefulness. Multiple types of tissues include melatonin receptors, notably melatonin receptor 1 and melatonin receptor 2, which have an impact body weight and energy expenditure. Melatonin, which is generated from tryptophan, shows a rise during the night that helps with sleep and has antioxidant effects. It affects the synthesis of glucagon and insulin via interacting with insulin receptors in pancreatic tissues. Research indicates that melatonin performs a crucial part in the control of blood sugar levels, and a lack of melatonin is linked to the onset of type 2 diabetes. One aspect of melatonin's effect on diabetes is its capacity to protect against oxidative damage. Another factor to consider is its possible contribution to the onset of diabetes and the disruption of circadian insulin control. Diabetes patients see a notable reduction in melatonin levels in their blood, highlighting the importance of melatonin in the progression of diabetes.

INTRODUCTION

The pineal gland is situated in the hypothalamus of the brain and its function is affected by the level of light it receives. The gland secretes the hormone melatonin [1,2]. Melatonin is a neuroendocrine hormone that is produced by the gland on a daily basis Termed as the "darkness hormone," its production is increased when there is a lack of light [3]. The primary role of this is to control the regular sleep-wakecycle and the circadian biological rhythm of the human body [4]. Recent study suggests that melatoninhas antioxidant and anti-inflammatory properties. A functional association in between melatonin and insulin and a decrease in melatonin levels are associated to the pathophysiology of diabetic kidney disease [5,6]. The maximum concentration melatonin is found successively in the cytosol, mitochondria, cellmembranes, and nuclei of the brain. Given that mitochondria

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production of significant amount of Reactive Oxygen Species (ROS), it is reasonable to infer that antioxidants like meiztonin are effective in reducing the overall oxidative stress. Furthermore, research has shown that melatonin has impressive. effectiveness as an antioxidant that selectively targets mitochondria. The low efficacy of traditional antloxidants, even when administered in large quantities, can be related to their challenge in infiltrating mitochondria. Thus, melatonin has the capacity to greatly improve the efficacy of therapy by exerting anti-oxidative actions [7].

Melatonin Receptors and its Classification

Multiple physiological tissues, including pancreatic islet cells, include melatonin receptors, indicating that melatonin has substantial effects on energy expenditure and the regulation of body weight [8]. G protein coupled receptors are a class of receptors that include melatonin receptors. In humans, there are two primary melatonin receptors: MT1 (also referred to as melatonin receptor A) and MT2 (sometimes referred to as melatonin receptor B) [9,10].

Synthesis of Melatonin

Tryptophan is the precursor for the synthesis of melatonin. The production of hormones adheres to an inherent circadian pattern that is triggered by the suprachiasmatic nuclei located in the hypothalamus Because of its notable lipophilicity, melatonin may readily traverse cell membranes and reach PAV subcellular compartments like mitochondria. It decreases electron leakage and the production of free radicals while stabilizing the internal membranes of mitochondria. Furthermore, melatonin demonstrates strong direct actions in neutralizing peroxyl radicals. Melatonin, being both a hormone and an antioxidant, is present in nearly all animal tissues, irrespective of the existence of melatonin receptors [11,12]. The production of melatonin is closely linked to light and darkness seen in daily cycle of light. The nocturnal rise in secretion is believed to "promote the initiation of sleep". The light stimulus received by the retina inhibits the secretion of melatonin, resulting in arousal in the morning and heightened alertness throughout the day. The production of melatonin via the pineal gland is started by an endogenous signal from norepinephrine, which is produced by an adrenergic neuron. Small doses of melatonin can promote sleep by lowering body temperature and slowing down breathing. Resetting the circadian rhythm might be advantageous for persons who often alternate between day and night shifts. Animals have been shown to possess many melatonin binding sites, including the MT(1) and MT(2) membrane receptors, which have a significant impact on chronobiology. The G protein-coupled receptors (GPCRs) MT (1) and MT (2) participate in signal transduction [13].

Melatonin and Insulin Secretion

Recent research has discovered the existence of MT1 and MT2 receptors in the pancreatic tissues, islets, and cell lines of humans [14]. Melatonin modulates the intracellular signal transduction pathways of the pancreatic B-cell, namely the cAMP, cGMP, and IP3 signaling pathways, via binding to the MT1- and MT2-membranous

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receptors. The production of cAMP in the pancreatic islets is inhibited by melatonin. Insulin and cAMP levels were raised via the adenylyl cyclase activator. Prior research has demonstrated that receptor antagonists effectively counteracted the suppressive impact of melatonin on cAMP and insulin. The inclusion of pertussis toxin (PTX), which hinders the activity of G-protein, had the same result of cancelling out the impact of melatonin on cAMP and insulin levels. The results suggest that the melatonin hormone inhibits the secretion of insulin induced by cAMP, and this mechanism is aided by MT1 receptors that are associated with G proteins [9], Melatonin stimulates the MT2 receptor, resulting in a reduction in insulin secretion from pancreaticß-cells and suppression of the second messenger, cGMP [15]. Melatonin negatively affects soluble guanylate cyclase, is activated via nitric oxide, through the activation of MT2 receptors: Cyclic GMP activates the protein kinase G. The active protein kinase G has the capacity to directly add a phosphate group to and potentially activate the CCAAT enhancer-binding protein. Furthermore, the MT2-receptor has a suppressive effect on the second messenger, cAMP. Therefore, the influence of receptors on cAMP Response Element can be enhanced via the cAMP and cGMP signaling pathways. The expression of circadian clock genes regulated by pancreas through protein kinase G (PKG) and cyclic guanosine monophosphate (cGMP), which in turn affects the timing and synchronization of secretion cycles. Furthermore, the cGMP signaling cascade specifically affects cyclic nucleotide-gated (CNG) channels and phosphodiesterase's that are unique to cGMP [16]. The pancreatic islets include melatonin receptors, indicating that melatonin may directly affect the manufacture of glucagon or insulin. This clarifies the scientific basis for the claim that lower melatonin levels may have an effect on pancreatic function in diabetics [9]. Immunoprecipitation and immunoblotting tests have demonstrated that melatonin stimulates the tyrosine phosphorylation of the insulin receptor and the insulin growth factor receptor in pancreatic islets. Therefore, melatonin controls the proliferation and differentiation of pancreatic cells. It activates two channels inside the cell that transmit signals [17].

Melatonin and Glucose Homeostasis

Melatonin performs a role in regulating the body's internal clock by binding to melatonin receptors found in several organs outside the brain. The circadian system governs the glucose metabolism, similar to its regulation of other physiological processes [18]. Multiple studies indicate that melatonin has the potential to impact glucose regulation and the secretion of insulin. Patients with T2DM have lower quantities of melatonin in their blood [19], but at the same time, they have higher levels of melatonin membrane receptor [20]. Furthermore, alterations in the melatonin receptor gene have been linked to levels of glucose in the blood during fasting and the probability of developing T2DM [21]. Clinical data show that melatonin helps regulate blood glucose levels, and that the onset of diabetes may be related to melatonin deficiency [22]. The presence or absence of melatonin receptors affects the amounts of pancreatic islet hormones and glucose transporters (Glut1 and Glut 2) in the liver and pancreas, as shown by reverse transcription polymerase chain reaction [23]. The production of glucagon and insulin by the

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pancreatic islet cells is crucial for regulating glucose level in the body. The first rise in glucose level observed following exercise exemplifies the daily fluctuation in plasma glucose concentration. The ingestion of food triggers the release of insulin, leading to daily variation in insulin levels in the bloodstream based on eating patterns. Moreover, scientific investigation has shown that both human and animal pancreatic islet cells exhibit circadian activity [24,25]. The therapeutic relevance of melatonin was established based on data obtained from a specific cohort of postmenopausal women. Insulin sensitivity and glucose tolerance were reduced after taking melatonin [26].

Melatonin and Diabetes

Melatonin has two distinct receptors, MT1 and MT2, which are encoded by MTRN1A and MTRN1B; respectively Melatonin induces the dissociation of the a and B/y subunits of MT1 and MT2. Subsequently, this division initiates the stimulation of subsequent signaling pathways, such as Phospholipase A2 (PLA2), Phospholipase C (PLC), and Adenylyl Cyclase (AC). Studies have demonstrated that disruptions in melatonin signaling have a role in the pathogenesis of Insulin Resistance (IR)-induced T2DM. An etiology of Type 2 diabetes mellitus and obesity is intricately linked to the disturbance of sleep patterns and the circadian rhythm. These findings suggest that individuals with atypical lifestyles, such as those who work night shifts or have unorthodox eating patterns, are at a higher risk of experiencing metabolic problems. The text is wrapped within tags. A study done by Ciaran J. McMullan et.al suggests that inadequate synthesis of melatonin or reduced melatonin signaling may impede insulin sensitivity and contribute to the onset of T2DM [27]. Melatonin modulates insulin secretion and offers protection against reactive oxygen species, which can affect diabetes mellitus and related metabolic disorders. The limited capacity of pancreatic ß-cells to protect themselves from oxidative stress is the reason behind this. Patients with diabetes mellitus exhibited a notable reduction in melatonin levels in their blood [28,29]. Melatonin levels were shown to be lower in diabetics, and a functional relation between melatonin and insulin was discovered. Based on the knowledge that is currently available, melatonin may have a role in the development of diabetes [30]. Melatonin mostly decreased glucose tolerance in human by decreasing insulin secretion in the morning, whereas a decrease in insulin sensitivity was observed in the evening [31]. Moreover, several studies have shown a correlation between sleep disturbances and a enhanced probability of improper glucose tolerance and the onset of T2DM [32,33]. Genome-wide correlation studies indicated that Allelic variances of MT2 affect glycemic traits, such as high fasting blood glucose, reduced insulin production, and susceptibility to T2DM [34]. The presence of a connection between abnormally reduced melatonin levels and diabetes [30,35], suggests that the melatonin signal has a vital function in controlling blood glucose levels and preserving homeostasis [36]. Individuals with type 2 diabetes have a diurnal pattern in gluconeogenesis and endogenous glucose production, resulting in increased levels of fasting blood glucose. This phenomenon is absent in those who are in good health [37]. Hence, melatonin has the ability to influence the onset of diabetes by altering the time of insulin production. The disturbance of the

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regular regulation of insulin release over a 24-hour period is a critical feature of diabetes mellitus [38].

CONCLUSION

According to the report, a correlation exists between diminished melatonin synthesis and an increased susceptibility to developing type 2 diabetes in individuals. Melatonin performs a pivotal function in the development and evolution of diabetes mellitus via regulating insulin secretion, protecting against oxidative stress, and influencing insulin secretion.

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