International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 4, Issue 2, pp: (136-144), Month: October 2016 - March 2017, Available at: www.researchpublish.com

Role of melatonin in Diabetes mellitus, Systemic review

[1]Khaled S.S Shabrawy, [2]Duaa Jihad Zain Basrawi, [3]Rasha Shaker Alkhunizi, [4]Saleh Abdulaziz Alghamdi, [5]Salman Abdulrahman Alolait

Abstract: **Diabetes mellitus is a leading reason for morbidity and death worldwide, with an approximated 346 million grownups being impacted in year 2011. The occurrence is anticipated to double in between years 2005 and 2030. A systematic review of published studies reporting the effects of melatonin on diabetes mellitus was undertaken in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement for systematic reviews of interventional studies. A three staged comprehensive search of the literature was conducted in the following databases; PubMed (U.S. National Library of Medicine, USA), and SciVerse Scopus (Elsevier Properties S.A, USA) for studies published before October 2016. The data discussed in this review shed new light on melatonin as a hormone which acts on diverse physiological processes in mammals and, particularly, on pancreatic islet functions. General agreement exists that the physical effects of melatonin are mediated through the activity of two known membrane receptor isoforms, MT1 and MT2, which belong to the large family of G-protein-coupled receptors. Numerous studies support the notion that activation of either receptor isoform leads to a reduction in second messenger cAMP or, in the case of the MT2, also to cGMP levels, due to a coupling of the receptor with G-proteins which inhibit AC activity.**

Keywords: **Diabetes mellitus, melatonin.**

1. INTRODUCTION

The number of people with diabetes and pre-diabetes are significantly increasing worldwide due to population development, aging, urbanization, unhealthy consuming practices, increasing occurrence of weight problems and physical lack of exercise (1). Diabetes mellitus is a leading reason for morbidity and death worldwide, with an approximated 346 million grownups being impacted in year 2011 (2). The occurrence is anticipated to double in between years 2005 and 2030, with the best boosts anticipated in low- and middle-income establishing nations of the African, Asian, and South American areas (2,3). At present, 80% of the worlds population with diabetes reside in low- and middle-income nations (2,4).

Diabetes is an endocrine illness, include insulin resistance, a lessened pancreatic beta-cell function, unusually high glucagon levels and a minimized incretin result (5). Diabetes is categorized into 2 primary classifications: type 1 (an autoimmune illness of more youthful clients with an absence of insulin production triggering hyperglycemia) and type 2 (a metabolic condition arising from the body's failure to produce sufficient or correctly make use of insulin thus clients have hyperglycemia). Altering way of life patterns such as a propensity to nocturnality and consumption of exceedingly abundant diet plans, trigger disruption of the sleep/wake cycle together with other body clocks (6). Variance in circadian patterns prefers the incident of diabetes (7).

Irregular information have actually been reported worrying the result of pineal hormonal agent on the secretion of insulin, on blood sugar and carb metabolic process. Melatonin (N-acetyl-5-methoxytryptamine), a tryptophan obtained little indolic particle, is primarily produced by the pineal gland in your area in numerous other tissues (8,9). Speculative proofs proposed the diurnal profiles of blood sugar due to melatonin and increased insulin levels in diabetic animals and people (10). Pinealectomy of rodents triggers hyperinsulinemia (11). Diabetes is paired with lower melatonin levels as decrease

in serum melatonin and greater insulin level is observed in type 2 diabetic Goto Kakizaki rats (10). Genome-wide association research studies has actually revealed that details single-nucleotide polymorphisms of the melatonin receptor 2 (MTNR1B) locus is related to an increased blood sugar concentration and type 2 diabetes (12,13,14,15,16,17). Melatonin can be able to bring anti-hyperglycemic result either by enhancing insulin sensitization or by enhancement of insulin secretion, or both.

Melatonin is referred to as the hormonal agent of darkness, is an indoleamine with the chemical name N-acetyl-5-methoxytryptamine. Distributing plasma concentrations are produced by the pineal gland. In mammals, the concentration in plasma throughout night was discovered to be (80 - 100 pg/mL) and low levels throughout the day (10 - 20 pg/mL) (18). It keeps homeostasis in the body, assists change the timing or enhances oscillations of the body clock (19). Its synthesis consisted of 2 actions, at first the conversion of amino acid tryptophan into serotonin (5-hydroxytryptamine, 5-HT), additional acetylation by arylalkylamine N-acetyltransferase (AA-NAT), the rate-limiting action in melatonin biosynthesis, prior to lastly being transformed into melatonin by hydroxyindole-O-methyltransferase (HIOMT) (20). Pinealocytes in the pineal gland produce melatonin. Figure 1 shows melatonin secretion and signaling path through melatonin receptors in keeping body clock within the cell. The pineal gland is triggered or shut off by light direct exposure to the eyes. Throughout the day, melatonin production is prevented while at the night time, it is promoted. when melatonin binds with melatonin receptors it activates G_i and G_q proteins which in turn inhibit adenylate cyclase/cAMP pathway and activates phospholipase C/IP_3 pathway respectively. Due to phosphorylating activity of protein kinases, CREB and MSK1 regulates expression of Clock genes and thus maintain circadian rhythm.

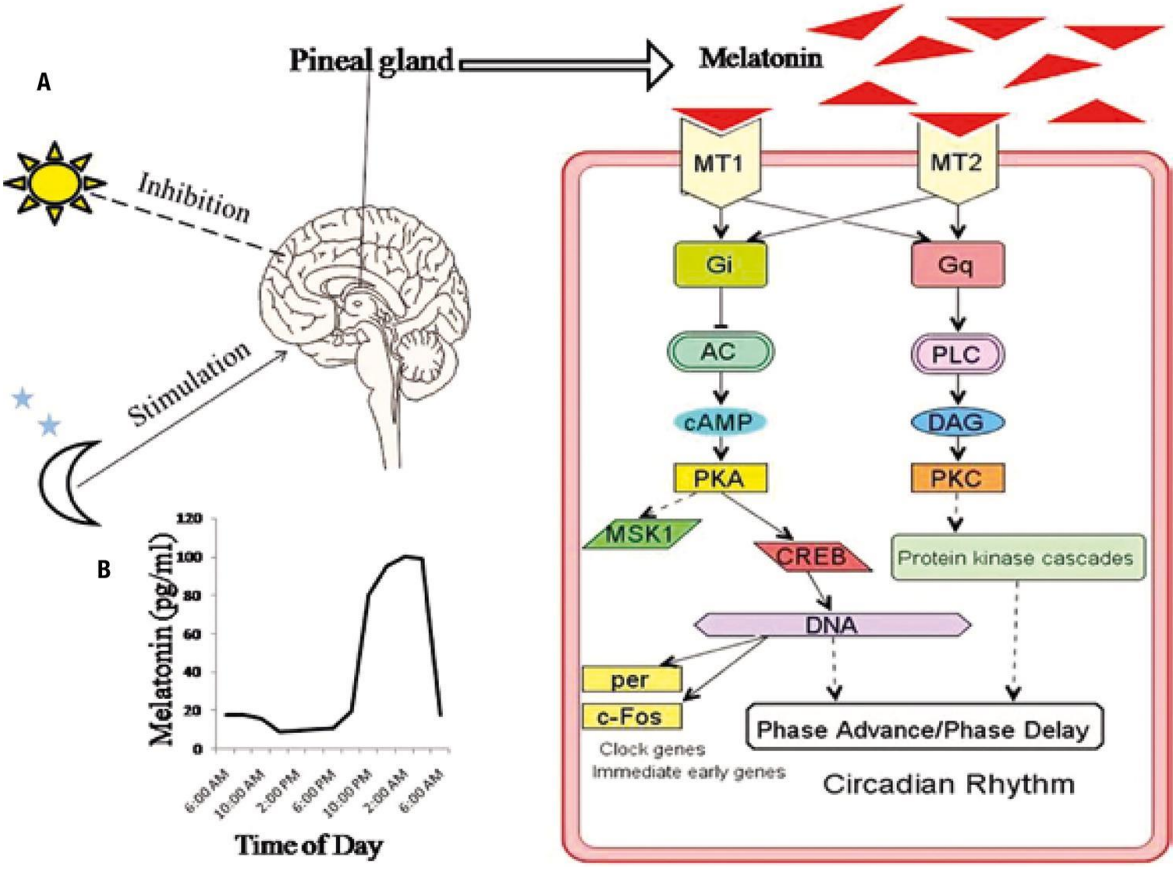

Figure 1: (A) Schematic representation of the melatonin secretion and signaling mechanism in maintaining circadian rhythm within the cell. MT1: melatonin receptor type 1A; MT2: melatonin receptor type 1B; Gi: guanine nucleotide binding protein (adenylate cyclase inhibitor); Gq: phospholipase C activator; 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. (B) Graphical representation of variation in melatonin level at different time of the day.

We aimed by this systematic review to overview the roles of melatonin effects and relation to the diffrent types of diabetes and evaluate the previous evidance based studies which were concerned about this topics, therefore we consider the updated evidance in our study.

2. METHDOLOGY

A systematic review of published studies reporting the effects of melatonin on diabetes mellitus was undertaken in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement for systematic reviews of interventional studies (21). A three staged comprehensive search of the literature was conducted in the following databases; PubMed (U.S. National Library of Medicine, USA), and SciVerse Scopus (Elsevier Properties S.A, USA) for studies published before October 2016.

During the first stage the above databases were searched using the following search criteria. The PubMed database was searched using the MeSH (Medical Subject Headings) term diabetes mellitus and keywords melatonin, diabestes mellitus, diabetes type 2 and. The Web of Science database was searched using search terms diabetes mellitus, melatonin, and melatonin therapy in article topic. In the SciVerse Scopus database the search terms diabetes mellitus and melatonin in article title, abstract or keywords was used as the search criteria. Results were not limited to studies on humans but also studies of rats were included, published in English. conference proceedings, editorials, commentaries and book chapters/book reviews were excluded.

In the second stage the total hits obtained from searching the databases using the above search criteria was screened by reading the article title and abstracts. Studies not satisfying the inclusion criteria were excluded at this stage. In the third stage individual manuscripts were screened, and those not satisfying inclusion criteria were excluded. To obtain additional data a manual search of the reference lists of articles selected in stage three was performed. Wherever possible forward citations of the studies retrieved during the literature search was traced and screened for possible inclusion.

3. RESULTS AND DISSCUSION

Our search identified more than 310 studies disccusing the relation between melatonin and diabetes mellitus we included 38 studies in our review at the final stagy or our search stratgy. Data have been collected concerning melatonin signaling by means of MT1 receptors in β-cells and islets, the practical value and signaling of the MT2 receptor still stays mainly enigmatic. Stumpf et al. (51,52) were the very first to show that melatonin hinders the cGMP path in INS-1 rat insulinoma β-cells. This procedure includes modulation of protein kinase G (PKG) activity by means of soluble guanylate cyclases (sGCs), which is a recognized function of MT2 receptors (53). A current research study (54) examined MT2 signaling in genetically customized INS-1 cells overexpressing the human MT2 (hMT2) (**Figure2**). The authors verified the repressive, intense action of melatonin on insulin secretion, which, in their cellular system, was mostly due to MT2-driven decrease of cAMP and cGMP levels, with an unfavorable effect on insulin secretion. Knockdown of the MT1 receptor in INS-1 cells considerably decreased the repressive result of melatonin and showed that, a minimum of in rodent β-cells and islets, most of melatonin-elicited impacts are sent by means of the MT1 isoform (55). At the end of the cAMP signaling waterfall, melatonin likewise adversely regulates CREB phosphorylation in INS-1 cells (56). Type of receptors differs from types to types. From the research studies carried out in low vertebrates, birds and reptiles, it is reported that there are 3 receptors MT1, MT2 and Mel1c. In mammals, MT1 and MT2 are plainly revealed from the research studies (22), another G-protein combined receptor 50 (GPR50) is the ortholog of Mel 1c (23). Melatonin villain luzindole and guanosine 5-O- (3-thiotrisphosphate) analogue of guanosine 5-triphosphate (GTP), on pancreatic neonatal rats, both which obstruct the impact of melatonin on insulin secretion. This is validated using molecular strategies by another research study, showing that melatonin receptor mRNA similar to that cloned from the rat brain is revealed in pancreatic tissue of newborn rats (22). Hence, showing that a melatonin receptor was found on neonate rat pancreas and melatonin has impact over it. It is apparent that melatonin apply its impact through G protein paired receptors, i.e., MT1 and MT2. The research studies reported that melatonin (MT1) receptors on beta cells, promote Gi-coupled adenylate cyclase activity, consequently adversely regulating incretin-induced increases in cAMP (22). MT2 receptors hinder cGMP signalling path and as a result insulin secretion (23). Melatonin causes phosphorylation of tyrosine moieties of IRS1 and 2 in rat islets and INS-1 cells triggering the protein kinase B and mitogen activated protein kinase (MAPK) path (24). It is

mentioned that there is boost in the insulin secretion and minimize in melatonin synthesis (24). In line with some research studies, alternative of melatonin appears to stop the age boost of insulin (25). This provides strong proof that alternative of melatonin assists to avoid diabetes. Current examinations exposed, single nucleotide polymorphisms (SNPs) in the gene (MTNR1B) of MT2 at a locus rs10830963, a close link is associated in prognostic danger to establish T2DM, in a European (26), and Han Chinese people (27). SNPs at a locus rs10830961 and rs4753426 of the very same gene is connected accountable for greater fasting plasma glucose concentration and lowered insulin release in German mate research study (28).

There is beneficial proof that the body clock of melatonin affects insulin secretion and the endocrine pancreas (29,30). A lot of research studies conclude that the pineal gland has a suppressive impact on the activity of the β-cell, (**Figure2**) due to the fact that melatonin decreases insulin levels in rats (31,32,33) and these results remain in contract with a decrease in glucose tolerance (34,35). Based upon these findings, and the awareness that an increased insulin level puts in a repressive impact on the pineal gland and melatonin (36,37), a practical antagonism in between insulin and melatonin needs to be presumed. This truth is a lot more striking when taking into consideration that high levels of insulin have actually constantly been determined when melatonin concentration was decreased, i.e., throughout the day; contrary to the circumstance of low levels of insulin in addition to high melatonin and glucose levels throughout the night (38). In accordance with these outcomes are rat research studies which showed that the synthesis of melatonin decreases with increasing age, whereas the synthesis of insulin and leptin boosts (31), which melatonin has the ability to stop the age-related insulin boost (33). Complementary to these findings are publications reporting that melatonin levels are decreased in diabetic hamsters (36,37,39). On the other hand, there is proof for a diabetes-preventing impact of melatonin, whereas pinealectomy increases the danger (40,41). More information show that melatonin straight affects both glucose metabolic process and insulin secretion from the β-cell (42,43,44,45).

That insulin secretion is managed by circadian systems is supported by research studies of human beings with circadian misalignment, who are reported to reveal extensive perturbations of glucose and insulin levels (46). The idea is supported by the presumption that there is a circadian clock in pancreatic islets (47). There are indicators that the diurnal secretion of melatonin is modified in diabetes, especially when neuropathy is apparent (48). Peschke et al. (10) reported minimized flowing melatonin levels and raised insulin levels in type 2 diabetic clients, with a statistically considerable unfavorable connection in between both particles. Nighttime melatonin levels are minimized in the Goto-Kakizaki (GK) rat, a design of type 2 diabetes (10). The quantities of mRNA of the melatonin manufacturing enzymes, such as HIOMT, are modified under diabetic conditions. In addition, the concentrations of all precursors of melatonin, consisting of tryptophan and serotonin, are decreased in the pineal glands of diabetic GK rats, and the pineal glands of diabetic GK rats consist of less noradrenaline and produce less melatonin in response to noradrenaline in vitro (49). Confusingly, animal designs of type 1 diabetes, i.e., streptozotocin- and alloxan-treated rodents, show either raised (50) or reduced (51) levels of melatonin. These observations recommend a practical correlation in between melatonin and insulin, and might suggest a decrease of melatonin in the genesis of diabetes (10). In this context, unique outcomes have actually reported that melatonin-enhanced insulin receptor kinase. Melatonin villain luzindole and guanosine 5-O-(3-thiotrisphosphate) analogue of guanosine 5-triphosphate (GTP), on pancreatic neonatal rats, both of which obstruct the result of melatonin on insulin secretion. Hence, showing that a melatonin receptor was found on neonate rat pancreas and melatonin has impact over it. Based on these findings, and the awareness that an increased insulin level puts in a repressive result on the pineal gland and melatonin (36,37), a practical antagonism in between insulin and melatonin has actually to be presumed. In accordance with these outcomes are rat research studies which showed that the synthesis of melatonin decreases with increasing age, whereas the synthesis of insulin and leptin boosts (31), and that melatonin is able to stop the age-related insulin boost (33). These observations recommend a practical correlation in between melatonin and insulin, and might suggest a decrease of melatonin in the genesis of diabetes (10). activity increased insulin receptor substrate 1 (IRS1) phosphorylation, thus suggesting the potential existence of a signalling pathway cross-talk between melatonin and insulin (52). Furthermore, melatonin also increased the activity of phosphatidylinositol 3-kinase (PI-3-kinase), whereas 3',5'-cyclic adenosine monophosphate-activated protein kinase (AMPK), another important glucose transport stimulatory mediator (*via* an insulin-independent pathway), was not influenced by melatonin application (53). Therefore, melatonin stimulates glucose transport to skeletal muscle cells through the IRS1/PI-3-kinase pathway, which implies, at the molecular level, a putative role in glucose homeostasis and possibly in diabetes (53). Additionally, it was speculated that

aging and the exposure to light at night, both of which lower melatonin levels, may contribute to the incidence and/or development of diabetes (53).

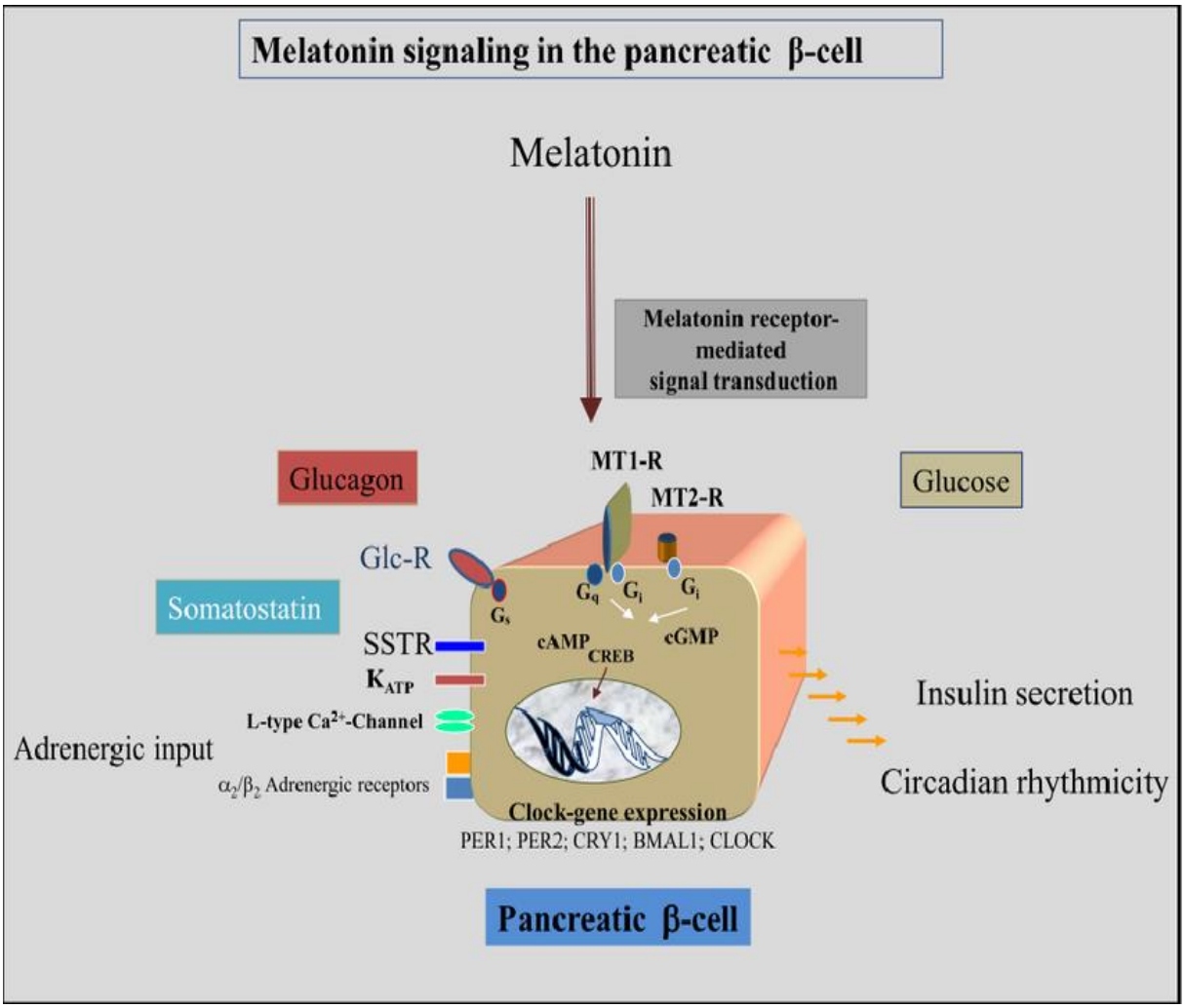

Figure2: The pineal hormone melatonin acts on the pancreatic β -cell via two receptor isoforms (MT1 and MT2) which transmit their signals through guanosine triphosphate (GTP)-binding proteins (G-proteins). The inhibitory action of melatonin on insulin secretion is transmitted by activation of the Gi-protein signaling cascade involving cyclic adenosine monophosphate (cAMP) (MT1-dependent signaling) or cAMP and cyclic guanosine monophosphate (cGMP) as second messengers (MT2). Melatonin downregulates adenylate or guanylate cyclase activity, leading to reduced second messenger levels and attenuated protein kinase A (pKA) or protein kinase G (pKG) activity. Consecutively insulin secretion is reduced. As a secondary effect, phosphorylation and activation of the cAMP-modulated transcription factor cAMP response element-binding protein (CREB) is downregulated. In addition, the MT1 receptor is also known to alternatively couple to Gq-proteins and thus modulates cell-internal IP3 and Ca 2+

One of our identified studies showed that the the insulin receptor mRNA of the pineal gland was found to be reduced in type 2 diabetic rats, suggesting a functional interrelationship between melatonin and insulin (10). In this context, recent results are important which reported that melatonin-enhanced insulin-receptor kinase activity increases insulin-receptor substrate-1 (IRS1) phosphorylation, suggesting the potential existence of signaling pathway cross-talk between melatonin and insulin, possibly also in the pinealocytes (50,57). The insulin-melatonin interactions are summarized in a synoptic presentation (**Figure 3**, left side). In a relatively early stage of type 2 diabetes, insulin secretion is increased and melatonin is decreased a pattern that is observed in rats and humans. It was hypothesized that catecholamines, especially norepinephrine, which decrease insulin levels and stimulate melatonin synthesis, trigger the antagonistic insulin-melatonin interactions (58,59).

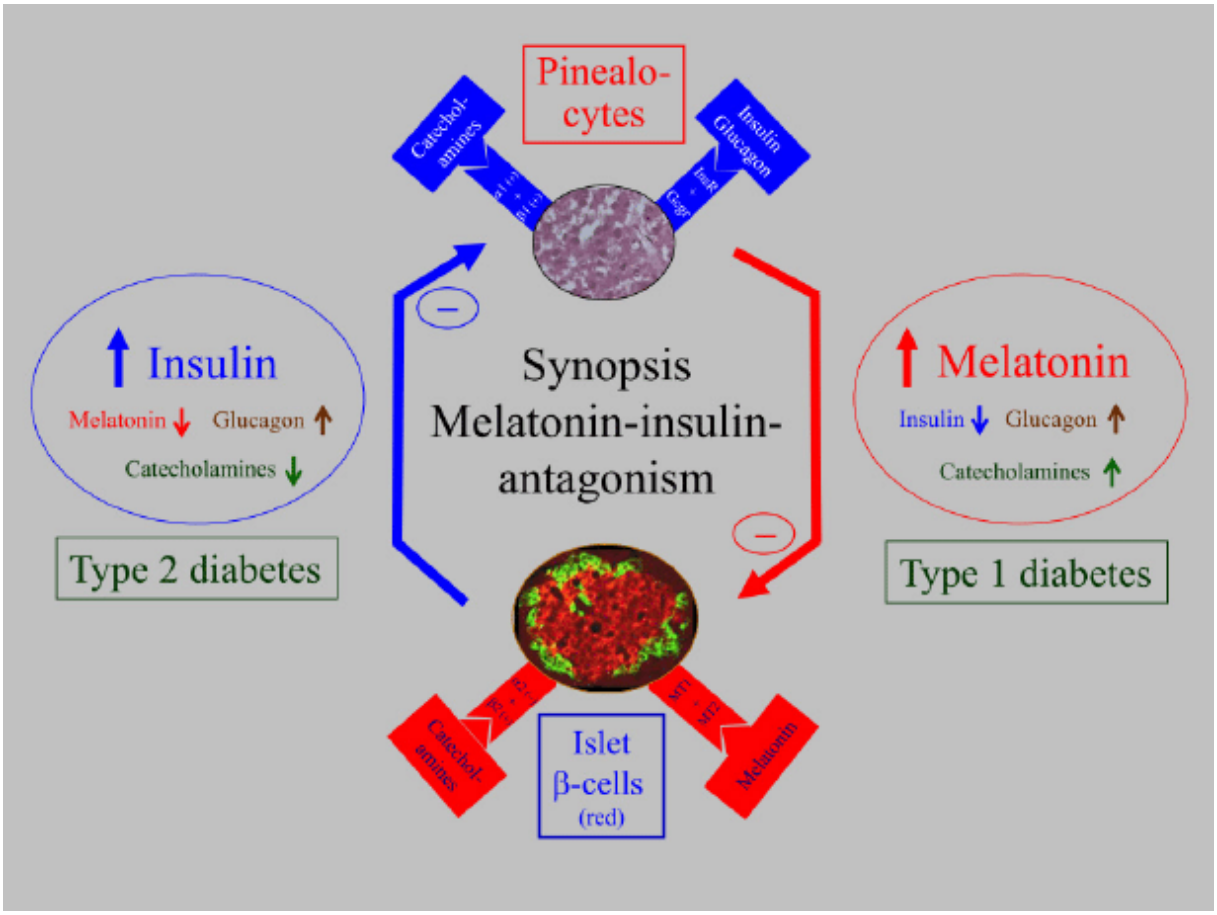

Figure3: Synoptic presentation of the insulin–melatonin antagonism in relation to the importance of melatonin for type 1 and type 2 diabetes, including interactions with glucagon and catecholamines. At a relatively early stage of type 2 diabetes (left side), insulin secretion is increased while melatonin synthesis is decreased. These reactions were observed in type 2 diabetic Goto Kakizaki (GK) rats and humans. In contrast, under type 1diabetic conditions (right side), insulin was greatly reduced and, subsequently, melatonin was significantly increased. These reactions were observed in streptozotocin (STZ)-treated Wistar (WR) rats, as well as in LEW.1AR1-iddm rats, a spontaneous animal model of human type 1 diabetes mellitus.

4. CONCLUSION

Recent advances in the elucidation of melatonin receptor expression, function and signaling have changed this situation dramatically. The data discussed in this review shed new light on melatonin as a hormone which acts on diverse physiological processes in mammals and, particularly, on pancreatic islet functions. General agreement exists that the physical effects of melatonin are mediated through the activity of two known membrane receptor isoforms, MT1 and MT2, which belong to the large family of G-protein-coupled receptors. Numerous studies support the notion that activation of either receptor isoform leads to a reduction in second messenger cAMP or, in the case of the MT2, also to cGMP levels, due to a coupling of the receptor with G-proteins which inhibit AC activity. Within endocrine cells, like the pancreatic β-cells, a reduction in cAMP levels is accompanied by reduced insulin secretion, at least in rodent β-cell lines and islets. In contrast, secretion of glucagon from α-cells is increased, which may indicate a coupling of the melatonin receptor with a different type of G-protein. Thus, the interplay between the different cell types of the pancreatic islet and their respective secretion products needs to be studied in more detail.

REFERENCES

[1] Wild S, Roglic G, Green A, Sicree R, King H. Global Prevalence of Diabetes. Diabetes Care. 2004. pp. 1047–1053.

[2] WHO. Diabetes Fact Sheet. http://www.who.int/mediacentre/factsheets/fs312/en/index.html.

[3] Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27:1047–1053. doi: 10.2337/diacare.27.5.1047.

[4] IDF. Diabetes Atlas - The Economic Impacts of Diabetes.

[5] Bergenstal R, Kendall D, Franz M, Rubenstein A. Management of type 2 diabetes: a systematic approach to meeting the standards of care. II: Oral agents, insulin, and management of complications. Endocrinology 4th ed Philadelphia, Pa: WB Saunders Co. 2001. 822 p.

[6] Bixler E. Sleep and society: an epidemiological perspective. Sleep Med. 2009;10:S3-6.

[7] Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci U S A. 2009;106(11):4453-8.

[8] Reiter RJ. Pineal melatonin: cell biology of its synthesis and of its physiological interactions. Endocr Rev. 1991;12(2):151-80.

[9] Stefulj J, Hörtner M, Ghosh M, Schauenstein K, Rinner I, Wölfler A, et al. Gene expression of the key enzymes of melatonin synthesis in extrapineal tissues of the rat. J Pineal Res. 2001;30(4):243-7.

[10] Peschke E, Frese T, Chankiewitz E, Peschke D, Preiss U, Schneyer U, et al. Diabetic Goto Kakizaki rats as well as type 2 diabetic patients show a decreased diurnal serum melatonin level and an increased pancreatic melatonin-receptor status. J Pineal Res. 2006;40(2):135-43.

[11] Nishida S, Segawa T, Murai I, Nakagawa S. Long-term melatonin administration reduces hyperinsulinemia and improves the altered fatty-acid compositions in type 2 diabetic rats via the restoration of Delta-5 desaturase activity. J Pineal Res. 2002;32(1):26-33.

[12] Staiger H, Machicao F, Schäfer SA, Kirchhoff K, Kantartzis K, Guthoff M, et al. Polymorphisms within the novel type 2 diabetes risk locus MTNR1B determine β-cell function. PLoS One. 2008;3(12):e3962.

[13] Bouatia-Naji N, Bonnefond A, Cavalcanti-Proença C, Sparsø T, Holmkvist J, Marchand M, et al. A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk. Nat Genet. 2008;41(1):89-94.

[14] Lyssenko V, Nagorny CL, Erdos MR, Wierup N, Jonsson A, Spégel P, et al. Common variant in MTNR1B associated with increased risk of type 2 diabetes and impaired early insulin secretion. Nat Genet. 2008;41(1):82-8.

[15] Prokopenko I, Langenberg C, Florez JC, Saxena R, Soranzo N, Thorleifsson G, et al. Variants in MTNR1B influence fasting glucose levels. Nat Genet. 2008;41(1):77-81.

[16] Sparsø T, Bonnefond A, Andersson E, Bouatia-Naji N, Holmkvist J, Wegner L, et al. G-allele of Intronic rs10830963 in MTNR1B Confers Increased Risk of Impaired Fasting Glycemia and Type 2 Diabetes Through an Impaired Glucose-Stimulated Insulin Release Studies Involving 19,605 Europeans. Diabetes. 2009;58(6):1450-6.

[17] Rönn T, Wen J, Yang Z, Lu B, Du Y, Groop L, et al. A common variant in MTNR1B, encoding melatonin receptor 1B, is associated with type 2 diabetes and fasting plasma glucose in Han Chinese individuals. Diabetologia. 2009;52(5):830-3.

[18] Simonneaux V, Ribelayga C. Generation of the melatonin endocrine message in mammals: a review of the complex regulation of melatonin synthesis by norepinephrine, peptides, and other pineal transmitters. Pharmacol Rev. 2003;55(2):325-95.

[19] Arendt J. Melatonin and the mammalian pineal gland: Springer; 1995.

[20] Axelrod J, Weissbach H. Enzymatic O-methylation of N-acetylserotonin to melatonin. Science. 1960;131(3409):1312.

[21] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535. doi: 10.1136/bmj.b2535.

[22] Reppert SM, Weaver DR, Ebisawa T, Mahle CD, Kolakowski Jr LF. Cloning of a melatonin-related receptor from human pituitary. FEBS Lett 1996;386:219–24.

[23] Duforny L, Migaud M, Thiery JC, Malpaux B. Development of an in vivo adenoassociated virus mediated siRNA approach to knockdown tyrosine hydroxylase in the lateral retrochiasmatic area of the ovine brain. J Neurosci Methods 2008;170:56–66.

[24] Kemp DM, Ubeda M, Habenar JF. Identification and functional characterization of Mel 1a receptors in pancreatic beta cells: potential role in incretin-mediated cell function by sensitization of cAMP signaling. Mol Cell Endocrinol 2002;191:157–66.

[25] Picinato MC, Haber EP, Cipolla-Neto J, Curi R, De Oliveira Carvalho CR, et al. Melatonin inhibits insulin secretion and decreases PKA levels without interfering with glucose metabolism in rat pancreatic islets. J Pineal Res 2002;33(3):156–60.

[26] Sparso T, Bonnefond A, Andersson E, et al. G-allelle of intronic rs10830963 in MTNR1B confers increased risk of impaired glucose-stimulated insulin release: studies involving 19,405 Europeans. Diabetes 2009;58:1450–6.

[27] Ronn T, Wen J, Yang Z, et al. A common variant in MTNR1B, encoding melatonin receptor 1B, is associated with type 2 diabetes and fasting plasma glucose in Han Chinese individuals. Diabetologia 2009;52:830–3.

[28] Staiger H, Machicao F, Schafer SA, et al. Polymorphisms within the novel type 2 diabetes risk locus MTNR1B determine beta cell function. PLoS ONE 2008;3:e3962.

[29] Peschke E, Stumpf I, Bazwinsky I, Litvak L, Dralle H, Mühlbauer E. Melatonin and type 2 diabetes - a possible link? J Pineal Res. 2007;42:350–358.

[30] Peschke E, Frese T, Chankiewitz E, Peschke D, Preiss U, Schneyer U, Spessert R, Mühlbauer E. Diabetic Goto Kakizaki rats as well as type 2 diabetic patients show a decreased diurnal serum melatonin level and an increased pancreatic melatonin-receptor status. J Pineal Res. 2006;40:135–143.

[31] Rasmussen DD, Boldt BM, Wilkinson CW, Yellon SM, Matsumoto AM. Daily melatonin administration at middle age suppresses male rat visceral fat, plasma leptin, and plasma insulin to youthful levels.Endocrinology. 1999;140:1009–1012.

[32] Wolden-Hanson T, Mitton DR, McCants RL, Yellon SM, Wilkinson CW, Matsumoto AM, Rasmussen DD. Daily melatonin administration to middle-aged male rats suppresses body weight, intraabdominal adiposity, and plasma leptin and insulin independent of food intake and total body fat. Endocrinology.2000;141:487–497.

[33] Rasmussen DD, Mitton DR, Larsen SA, Yellon SM. Aging-dependent changes in the effect of daily melatonin supplementation on rat metabolic and behavioral responses. J Pineal Res. 2001;31:89–94.

[34] Dhar M, Dayal SS, Ramesh Babu CS, Arora SR. Effect of melatonin on glucose tolerance and blood glucose circadian rhythm in rabbits. Indian J Physiol Pharmacol. 1983;27:109–117.

[35] Cagnacci A, Arangino S, Renzi A, Paoletti AM, Melis GB, Cagnacci P, Volpe A. Influence of melatonin administration on glucose tolerance and insulin sensitivity of postmenopausal women. Clin Endocrinol (Oxf)2001;54:339–346.

[36] Champney TH, Steger RW, Christie DS, Reiter RJ. Alterations in components of the pineal melatonin synthetic pathway by acute insulin stress in the rat and Syrian hamster. Brain Res. 1985;338:25–32.

[37] Champney TH, Brainard GC, Richardson BA, Reiter RJ. Experimentally-induced diabetes reduces nocturnal pineal melatonin content in the Syrian hamster. Comp Biochem Physiol A Comp Physiol.1983;76:199–201.

[38] Boden G, Ruiz J, Urbain JL, Chen X. Evidence for a circadian rhythm of insulin secretion. Am J Physiol. 1996;271:E246–E252.

[39] 31. Champney TH, Holtorf AP, Craft CM, Reiter RJ. Hormonal modulation of pineal melatonin synthesis in rats and Syrian hamsters: effects of streptozotocin-induced diabetes and insulin injections. Comp Biochem Physiol A Comp Physiol. 1986;83:391–395.

[40] Conti A, Maestroni GJ. Melatonin rhythms in mice: role in autoimmune and lymphoproliferative diseases. Ann N Y Acad Sci. 1998;840:395–410.

[41] Conti A, Maestroni GJ. Role of the pineal gland and melatonin in the development of autoimmune diabetes in non-obese diabetic mice. J Pineal Res. 1996;20:164–172.

[42] Peschke E, Fauteck JD, Musshoff U, Schmidt F, Beckmann A, Peschke D. Evidence for a melatonin receptor within pancreatic islets of neonate rats: functional, autoradiographic, and molecular investigations. J Pineal Res. 2000;28:156–164.

[43] Peschke E, Mühlbauer E, Musshoff U, Csernus VJ, Chankiewitz E, Peschke D. Receptor (MT(1)) mediated influence of melatonin on cAMP concentration and insulin secretion of rat insulinoma cells INS-1.J Pineal Res. 2002;33:63–71.

[44] Kemp DM, Ubeda M, Habener JF. Identification and functional characterization of melatonin Mel 1a receptors in pancreatic beta cells: potential role in incretin-mediated cell function by sensitization of cAMP signaling. Mol Cell Endocrinol. 2002;191:157–166.

[45] Picinato MC, Haber EP, Cipolla-Neto J, Curi R, de Oliveira Carvalho CR, Carpinelli AR. Melatonin inhibits insulin secretion and decreases PKA levels without interfering with glucose metabolism in rat pancreatic islets. J Pineal Res. 2002;33:156–160.

[46] Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci U S A. 2009;106:4453–4458.

[47] Peschke E, Peschke D. Evidence for a circadian rhythm of insulin release from perifused rat pancreatic islets. Diabetologia. 1998;41:1085–1092.

[48] O'Brien IA, Lewin IG, O'Hare JP, Arendt J, Corrall RJ. Abnormal circadian rhythm of melatonin in diabetic autonomic neuropathy. Clin Endocrinol (Oxf) 1986;24:359–364.

[49] Frese T, Bach AG, Mühlbauer E, Pönicke K, Brömme HJ, Welp A, Peschke E. Pineal melatonin synthesis is decreased in type 2 diabetic Goto-Kakizaki rats. Life Sci. 2009;85:526–533.

[50] Peschke E, Wolgast S, Bazwinsky I, Pönicke K, Muhlbauer E. Increased melatonin synthesis in pineal glands of rats in streptozotocin induced type 1 diabetes. J Pineal Res. 2008;45:439–448.

[51] Stumpf, I.; Muhlbauer, E.; Peschke, E. Involvement of the cGMP pathway in mediating the insulin-inhibitory effect of melatonin in pancreatic beta-cells. J. Pineal Res. 2008, 45, 318–327.

[52] Stumpf, I.; Bazwinsky, I.; Peschke, E. Modulation of the cGMP signaling pathway by melatonin in pancreatic beta-cells. J. Pineal Res. 2009, 46, 140–147. \

[53] Brydon, L.; Petit, L.; Delagrange, P.; Strosberg, A.D.; Jockers, R. Functional expression of MT2 (Mel1b) melatonin receptors in human PAZ6 adipocytes. Endocrinology 2001, 142, 4264–4271.

[54] Mühlbauer, E.; Albrecht, E.; Hofmann, K.; Bazwinsky-Wutschke, I.; Peschke, E. Melatonin inhibits insulin secretion in rat insulinoma beta-cells (INS-1) heterologously expressing the human melatonin receptor isoform MT2. J. Pineal Res. 2011, 51, 361–372.

[55] Muhlbauer, E.; Albrecht, E.; Bazwinsky-Wutschke, I.; Peschke, E. Melatonin influences insulin secretion primarily via MT(1) receptors in rat insulinoma cells (INS-1) and mouse pancreatic islets. J. Pineal Res. 2012, 52, 446–459.

[56] Bazwinsky-Wutschke, I.; Wolgast, S.; Muhlbauer, E.; Albrecht, E.; Peschke, E. Phosphorylation of cyclic AMP-response element-binding protein (CREB) is influenced by melatonin treatment in pancreatic rat insulinoma beta-cells (INS-1). J. Pineal Res. 2012, 53, 344–357.

[57] schke, E.; Muhlbauer, E. New evidence for a role of melatonin in glucose regulation.

[58] Best Pract. Res. Clin. Endocrinol. Metab. 2010, 24, 829–841.

[59] Bach, A.G.; Mühlbauer, E.; Peschke, E. Adrenoceptor expression and diurnal rhythms of melatonin and its precursors in the pineal gland of type 2 diabetic Goto-Kakizaki rats.

[60] Endocrinology 2010, 151, 2483–2493.

[61] Peschke, E.; Hofmann, K.; Ponicke, K.; Wedekind, D.; Muhlbauer, E. Catecholamines are the key for explaining the biological relevance of insulin-melatonin antagonisms in type 1 and type 2 diabetes. J. Pineal Res. 2012, 52, 389–396.