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Effect of Melatonin and Time Restricted Feeding in the Diabetic Rats

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ABSTRACT

In this review we focus on two particular approaches to resetting glucose level rhythm city in the context of restricted feeding (TRF; access to food is restricted for specific time intervals during the day without calorie restrictions) and melatonin, it's a hormone produced predominantly in the pineal gland. Its release is triggered by the loss of light exposure to the retina. Hence, melatonin indicates the time of day, or ambient light, to various organs and tissues in the bodyit is hereby a ''Zeitgeber,'' entraining circadian rhythm. Indeed, control of circadian rhythm at several levels, including the pancreatic βcellexplore the possibility of pursuing circadian realignment via nutritionally inspired interventions Therefore understanding the health-promoting roles of regulating (i.e., restoring) circadian rhythms, thus suppressing harmful effects of circadian deregulations, would likely improve treatment. This review study the effects of time restricted feeding and how it affects the secretion of melatonin, which in turn improves the secretion of insulin in diabetic mice in high-fat diets, with studying many aspects and their effect on the production of melatonin such as light, dark, temperature and interference with met form in and time restriction feeding it has been argued that studies are warranted to determine whether there is any use in restoring circadian rhythms in diabetic patients, what therapeutic goals should be targeted, and how these could be achieved.

KEY WORDS: Melatonin, Time restriction feeding ,Diabetes ,Circadian rhythms

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INTRODUCTION

WHO (2016) reported that about 1.5 million people worldwide were dead due to diabetes. About 2.2.Amillion deaths were happened due to cardiac problems associated with diabetes and 3.7 Million deaths were due to blood glucose level fluctuations. It was found that about 43% of the deaths due to diabetes occur under the age of 70. In 2014, over 422 Million people in the world were found with diabetes. It was estimated in 2012 that diabetes is the eighth major reason of death in both male and female and fifth major reason of death in women. Lower limb amputation is higher (10, 20 times) in diabetic patients.
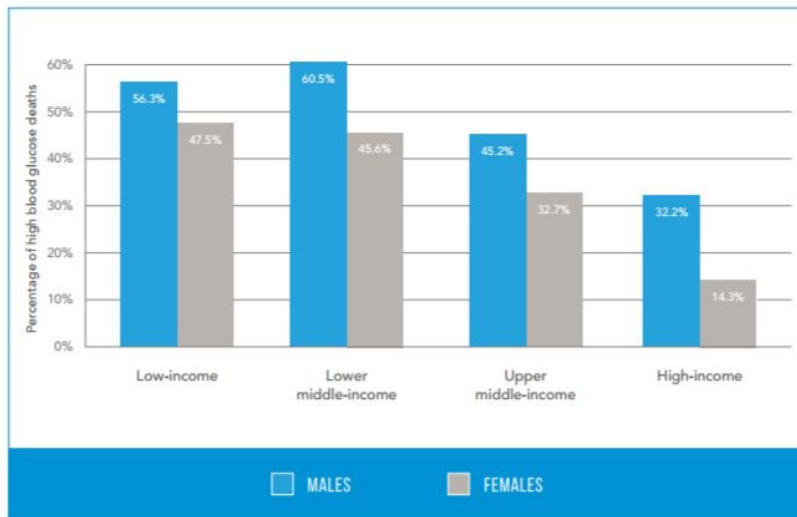

Figure 1: Graph showing the mortality rate people with diabetes.(WHO,2016)

The human life cycle is governed by the 24-h light-dark cycle. Frequent physiological activities like behavioral activity, Sleep cycle, and cardiovascular functions etc., are regulated by this mechanism. [1] The internal system consist of circadian clocks that consists of many transcriptional and translational loops that involve multiple genes (Bmal1, Per(s), Dec(s) and Cry(s)). This is located in the SCN – suprachiasmatic nucleus which is known as the master clock that regulates the activities of all peripheral tissues associated with heart, liver and pineal glands. This biological clock is being altered by nocturnal activities, shift works, and late night dieting. This impairment causes several metabolic dysfunctions [2,3] Constant shifts in the mealtime will result in deviation in carbohydrate and lipid metabolisms. Various studies regarding shifting in feeding time on rats indicated that these rats were prone to diabetes and obesity when compared to control rats [4]
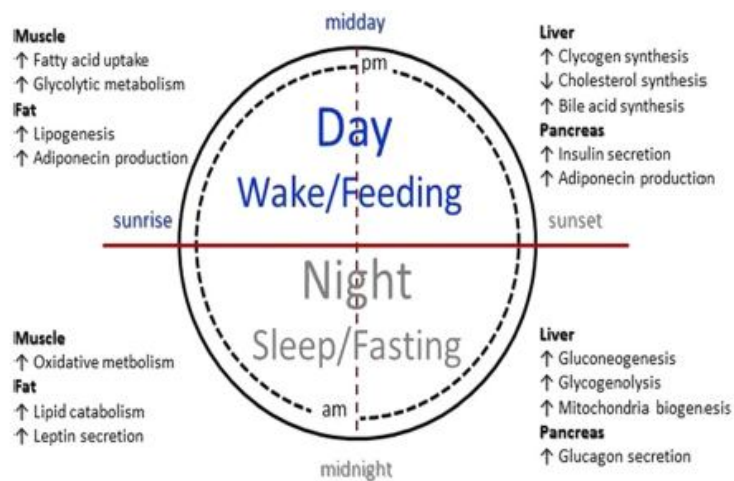
Figure 2: Influence of biological clock over metabolic regulation. (Sunder ram et al., 2014)

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) – and derivative of tryptophan and an endogenous neuro hormone, is secreted from the pineal gland [5]Melatonin was isolated in 1958 by Lerner and his associates, its chemical nature being identified as N-acetyl-5-methoxytryptamine [6] melatonin considered very importantly because of its participation in regulating energy metabolism. They are known for optimizing reproduction and cardiac rhythms. They also act as an efficient scavenger of various reactive oxygen species (ROS) namely peroxyl and hydroxyl radicals. This is distributed all through the cells thus scavenging free radicals that result in damage of tissues[5].
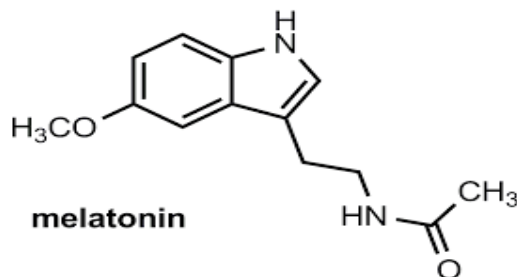

Figure 3: melatonin chemical structure

Melatonin secretion is synchronized to the light/dark (LD) cycle, with a nocturnal maximum (in young humans, about 200 pg/ml plasma) and low diurnal baseline levels (about 10 pg/ml plasma). Studies have supported the value of the exogenous administration of melatonin in circadian rhythm sleep disorders, insomnia, cancer, neurodegenerative diseases, disorders of the immune function, and oxidative damage

Biosynthesis and metabolism of melatonin

In vertebrates, melatonin is primarily secreted by the pineal gland. Synthesis also occurs in other cells and organs including the retina human and murine bone marrow cells, platelets

,gastrointestinal tract, skin or lymphocytes . However, circulating melatonin is derived only from the pineal gland, as shown by its disappearance after pineal removal. Since there is no storage of melatonin in the pineal gland, and since the circulating melatonin is degraded rapidly by the liver, plasma levels of melatonin reflect pineal biosynthetic activity. In bacteria, protists, fungi, and plants, melatonin is synthesized indirectly with tryptophan as an intermediate product of the shikimate pathway. In these cells, synthesis starts with D-erythrose 4-phosphate and phosphoenolpyruvate, and in photosynthetic cells with carbon dioxide. The rest of the synthesizing reactions are similar, but with slight variations in the last two enzymes[19,10]

Biological functions

Melatonin, stimulated by darkness and inhibited by light, is involved in synchronizing the body's hormone secretions and in regulating their levels, setting the brain's internal biological clock and hence controlling circadian rhythms (daily biorhythms) or sleep-wake. Melatonin regulates many neuroendocrine functions and can inhibit secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary gland. When the timing or intensity of melatonin peak is disrupted (as in aging, stress, jet-lag, or artificial jet-lag syndromes), the biological clock is upset and many physiological and mental functions are adversely affected including the ability to think, remember, and make sound decisions can be profoundly hampered. Melatonin also controls the timing and release of female reproductive hormones and hence helps determine when menstruation begins and ends (menopause), and the frequency and duration of menstrual cycles.

Studies indicated that deficiency in the secretion of melatonin in rats resulted in increased body mass, insulin resistance, visceral adiposity in association with diabetes due to glucose intolerance, dyslipidemia and cardiac dysfunctions leading to cardiovascular diseases. When these diabetic rats were subjected melatonin administration showed significant reversion of all the symptoms mentioned above Biological rhythms are the major factors affecting the behavioral outcome. These are controlled by proteins and genes regulated by external signals such as light and food. Recent studies prove that the rhythmic signals play a vital role in performing metabolic and immunological functions .The feeding pattern poses a major effect on loco motor activity, synchronization and circadian mechanisms

Studies demonstrated that melatonin has a role in lipid metabolism regulation, including lip genesis, lipolysis, and mitochondrial biogenesis, worked to investigate the effects of melatonin on lipid metabolism during porcine oocyte in vitro maturation. Melatonin treatment significantly enhanced the number of lipid droplets (LDs) and up regulated gene expression related to lip genesis (ACACA, FASN, PPARγ, and SREBF1) Oocytes treated with melatonin formed smaller LDs and abundantly expressed several genes associated with lipolysis, including ATGL, CGI-58, HSL, and

PLIN2. Moreover, melatonin significantly increased the content of fatty acids, mitochondria, and ATP, Overall, melatonin treatment not only altered both the morphology and amount of LDs, but also increased the content of fatty acids, mitochondria, and ATP. In addition, melatonin upregulated mRNA expression levels of lip genesis, lipolysis, β-oxidation, and mitochondrial biogenesis-related genes in porcine oocytes

An abnormal level of melatonin in the blood circulation was found to produce diabetes associated with memory and learning deficiencies, but the action of melatonin in regulating diabetes was unknown. Wongchitrat investigated about the hyperglycemic condition in rats induced by streptozotocin injection (STZ) associated with (HFD) High Fat Diet feeding. This study also focused on the analysis of the function of adult hippocampus based on the effect of melatonin[24]. The study indicated that the High Fat Diet (HFD) feeding and streptozotocin injection caused drastic increase in the blood glucose level. The damage in the memory was found by the results of Morris water maze. The reduction of neurogenesis in hippocampus was concluded by reduction in β-III tubulin immune reactivities, doublecortin (DCX) and nestin associated with decrease in the axon terminal markers, dendritic markers, synaptophysin along with PSD 95 - postsynaptic density 95 and NR2A – a subunit of glutamine receptor. A drastic reverse regulation of melatonin receptors, p-ER insulin receptors IR-β and p-IR-β, simultaneously an increased level of GFAP – gilial-fibrillary acidic protein were found to happen in the STZ-treated and HFD-fed rats. When the rats were treated with melatonin neurogenesis and synaptogenesis were reduced and induction of astrogliosis took place. The results indicated that melatonin had the capacity of reducing pathogenesis of diabetes by reversing insulin signaling pathway dysfunction and reducing synaptogenesis and neurogenesis and correcting the memory impairment.

Light and dark cycle

Light is the dominant environmental factor regulating melatonin biosynthesis, and as such it has two distinct effects on the hormone production. Thus, light causes an acute suppression of NAT (N-acetyl transferees) activity and melatonin content and release[25,26,27,28,29,30] and it resets the phase of the free-running circadian oscillator generating the rhythm of melatonin production [27,31,29,30]. On the other hand, numerous studies performed on various vertebrate species have shown that a short-term exposure to light has no significant effect on both the pineal and retinal hydroxyindole-O-methyl transferees (HIOMT) activity [28,32]

Wu et al., (2014) worked on the investigation of the effect of light over the diabetic animals. The study showed that the individual light/dark reversal (LD) had a similar gene and tissue specific effect on the peripheral clock genes in the circadian phases on both diabetic and control rats. The peak

phases of clock genes *Bmal1, Per1, Per2 and Rev-erb*α of liver and heart were examined showed that there was a slight shift between 0 - 4 h in both control and test rats. After a light/dark reversal of 7 days peak phases of the clock genes of pineal glands were found to be shifted for 8 - 12 h for both diabetic and control rats[33].The individual light/dark reversal resulted in the complete shift of activity rhythm in the control rats. But it was found to be retained in the diabetic rats. This indicated that the activity rhythm was detached from the master clock for the diabetic rats after individual light/dark reversal. After individual light/dark reversal serum glucose level was also found to be high all the day in the diabetic rats without shifting in peak phases. While for the control rats the serum glucose levels were under control during the light/dark reversal and normal conditions. It was indicated that the insulin secretion dysfunction resulted in hyperglycemic condition that led to detached activity rhythm in diabetic rats after individual LD reversal.

The influences of light and darkness on circadian rhythms can also be demonstrated by studies conducted in constant environmental lighting conditions. In constant darkness the rhythms free-run in rats . Continuous light treatment induces suppression of melatonin biosynthesis and the circadian rhythm city of loco motor activity is lost in rats. Several other circadian rhythms in rats (e.g. behavioral, temperature and some humoral rhythms) may persist for several weeks depending on the intensity of light . A few papers have demonstrated that have shown that women blind to light have a reduced risk of developing breast cancer. People living in low levels of ambient lighting such as the Arctic also have a lower prevalence of breast cancer. Conversely, women exposed to light at night (night and shift workers) have a higher incidence of breast cancer. A simultaneous decline in serum melatonin levels with increasing tumor growth has been demonstrated in preoperative breast cancer patients.

Major complications of diabetes mellitus were produced by oxidative stress that requires antioxidant therapy. G¨urpınar et al., (2012) investigated on the effect of melatonin in reducing the oxidative stress in the tissue of eye and brain of diabetic rat based on immune histochemical methods. The streptozotocin (STZ) injection at a level of 55mg/kg.IP, was used for the induction of diabetes in rats. Beginning from the sixth week the rats were grouped into 3 groups namely: streptozotocin induced diabetic group along with melatonin (STZ+MLT), streptozotocin induced diabetic (STZ) and control rats (CR).The STZ+MLT rats were subjected to melatonin once a day at a level of 10 mg/kg,IP, for 2 weeks. The results indicated that there was no much difference between the rats with respect to oxidative stress. But Nitric oxide synthases (NOS) activity was comparatively high in the rats without melatonin than STZ+MLT rats. Thus it was concluded that melatonin improvises the histopathological changes associated with oxidative stress and apoptosis in the tissues of eye and brain of diabetic rat.

Wu et al., (2012) found that there was a specific link between the circadian clock and metabolic diseases. Investigated on the behavioral and expression rhythm of the circadian genes of pineal gland and heart muscles in the type 2 diabetic rats under the conditions of both DRF - daytime restricted feeding and NRF - nighttime restricted feeding. During the nighttime restricted feeding similarity was observed between the diabetic rat and the control rat in the conservation of circadian phase of the clock genes of the pineal and heart glands. While in daytime restricted feeding the circadian expression of peripheral clock genes was found to be drastically shifted in the diabetic rats than in the rats used as control. The diabetic rats were observed with completely shifted activity rhythm from dark phase to light phase subsequent to 5 days of daytime restricted feeding pattern, while the control rats possessed a controlled activity rhythm and beneath the SCN – suprachiasmatic nucleus control after subjecting to the same daytime restricted feeding patterns. The serum glucose levels of diabetic rats were also increased which could be controlled by external feeding. Thus it was understood from the results that the circadian rhythms were prone to shift easily by feeding stimuli and daytime restricted feeding patterns had a better effect on the reinforcement of circadian rhythm.

Temperature and Melatonin

The temperature rhythms in mammals were controlled by the circadian pacemaker present in the suprachiasmatic nuclei and it is also regulated by the melatonin a pineal gland hormone. The production of melatonin is altered by type 1 diabetes mellitus.(Ramos-Lobo et al., 2015), worked on the regulation of this circadian rhythm. The rats were subjected to induced diabetes by streptozotocin injection (60 mg/kg). The effect administration of insulin (6U/day) and melatonin (0.5 mg/kg) daily on the of body temperature of the rats were studied. The glycaemia, body weight, body temperature rhythm and its rhythmic patterns were monitored for 55 days. The ANNOVA analysis of the results was performed and Bonferroni post tests were also done. The continuous disruption of temperature rhythm was prevented by the administration of insulin or melatonin treatments. The results revealed that treatment with melatonin and insulin gave better regulation of the temperature rhythm whereas insulin alone showed lesser effect and melatonin alone does not have any effect[4].

METFORMIN AND DIABETES

Rojas and Gomes ,2013 explored the advantages of using metformin for the treatment of type II diabetes. Metformin is an older and most widely accepted ant hyperglycemic drug. This possesses additional features along with glycemic control namely, improvement in hemostasis, endothelial functions, oxidative stress and lipid profiles, also ensures fat redistribution and insulin resistance.

This also decreases the adverse effects in cardiovascular system due to diabetes. The metformin tolerability can be attained by administration of low levels of metformin to higher level dosage[43].

Kurhaluk ,2017 worked on investigate the effects of the oral antidiuretic metformin and the pineal hormone melatonin, administered alone and in combination on oxidative stress and antioxidant enzyme activity in the heart tissue of female Sprague-Dawley rats. The rats were kept on a high fat diet and were subjected to the mammary carcinogenic process induced by N-methyl-Nnitrosourea. The main finding was that metformin and melatonin, in all combinations used, prevented NMU-induced toxicity and oxidative stress. A combination of metformin and melatonin reversed the effect of NMU toxicity on oxidative stress[44]. Melatonin acted significantly stronger than metformin in oxidative stress reduction in the heart tissue, caused by NMU carcinogenesis and a high fat diet.

Melatonin improves the beneficial effects of metformin on insulin sensitivity and body mass gain in high-fat fed Sprague-Dawley rats. Therefore, the combination of melatonin and metformin could be beneficial to develop dual therapies to treat or delay type 2 diabetes associated with obesity[45].

Time restriction feeding and melatonin

Restricted feeding (TRF) is essentially imposing rhythms on nutrient availability. Entrainment by TRF has generated significant interest due to the possibility of synchronizing peripheral clocks without clear influences on (or from) the central pacemaker (SCN) .It has been speculated that restricted feeding (RF) entrains rhythms in peripheral tissues (liver and lung) [48] is likely independent of the SCN. These works challenge the basic hierarchical paradigm that light entrains the SCN which subsequently entrains the peripheral clocks and emphasized the role of RF as an entraining signal. The hypothesis of independently entrained peripheral clocks has been further reinforced by the observation that even lesions in brain nuclei do not eliminate food anticipatory activity, thus pointing to likelihood of a distributed system maintaining and regulating food-anticipatory activities [49,50]. One of the main justifications is that when food accessibility adopts specific rhythmic characteristics so will the physiology and behavior to match nutritional resource availability. It has been shown that feeding mice during the day completely reverses the phase of circadian oscillators (specifically, four clock components, Per1, Per2, Per3, Cry1 ; and the two circadian transcription factors DBP and Rev-erb α) in multiple peripheral cells (liver, kidney, heart and pancreas), but has little if any effect on the central oscillator in the SCN . However, we must point out that RF entrains the rhythm of clock protein Per2 even in the SCN as was shown in studies that eliminated photic stimulation by keeping

mice in constant darkness, or at constant light conditions , thus raising the possibility of peripheral oscillators resetting the central clock.

The awareness of hyperglycemic condition and its regulation by melatonin is growing and so many researchers focused on the analysis of relationship between these two. (Ramos-Lobo)worked on the effect of diabetes over the body temperature rhythms and its control by the combination of insulin and melatonin. (Wu 2012) finalized that there is a relationship between cardiac rhythm and metabolic disorders. This cardiac rhythm could be enhanced with daytime restricted feeding in streptozotocin-induced diabetic rats. G¨urpınar (2012) studied the effect of melatonin over the regulation of oxidative stress in the tissues of brain and eye due to diabetes[5].Wongchitrat (2016) investigated the effects of melatonin treatment on rats with streptozotocin-induced diabetes and high fat feeding pattern[24]. This review study focuses on the Relationship between melatonin and time-restricted feeding in diabetic rats.

FUTURE PROSPECTS

The role of melatonin in control of whole body metabolism and insulin release has been controversial .While most previous studies have suggested an inhibitory effect of melatonin on insulin release , some studies have also shown stimulatory effects. Moreover, both improved and impaired glucose tolerance has been reported after melatonin therapy . The use of different species and experimental models may be a reason for these discrepancies. Another explanation could be that most human studies have not taken into account the genetic background of the study participants, and time of day for experiments has not been standardized. Here, using an array of experimental approaches in vivo and in vitro as well as clinical studies in humans, (Tuomi 2016) arrived at the conclusion that the physiological role of melatonin in islets is to inhibit insulin release, most likely via a reduction in cAMP levels. A melatonin-mediated reduction in nocturnal insulin release, when melatonin levels are high but metabolic demands low, due to cessation of food intake, is perhaps a physiological and protective mechanism against nocturnal hypoglycemia. This explanation prove the role of combine of melatonin and time restriction feeding

ACKNOWLEDGEMENTS

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