Melatonin: the sleeping hormone

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Pineal gland – “epiphysis cerebri” lies in the center of human brain. Phylogenetically, pineal gland became prominent in vertebrates—both aquatic and terrestrial. Pineal gland was thought to control circadian rhythms and play a role as “zeitgeber”—a German word for the natural phenomenon of cyclicity. The signals from the retina are relayed to the supra-chiasmatic nucleus (SCN) which is the circadian clock. From the SCN, signals are relayed to the superior cervical ganglion and to the pineal gland. The possibility of other pathways is supported by finding that mice deficient in rods, cones, and melanopsin systems show no light suppression of the pineal melatonin synthesis pathway [1].

Pineal gland secretes melatonin and smaller quantities of many hormones including a putative β -carboline molecule pinoline. Melatonin ($C_{13}H_{16}N_2O_2$) levels are high at night and low at sunrise. Around 3 months of age melatonin secretion begins to establish circadian rhythm in life as the infant starts cyclical sleep. Entrainment happens every morning and evening to reset the clock. The retinal ganglion cells express melanopsin—a photopigment. The cues for pinealocytes come from melanopsin in the retina. Unlike the rods and cones, melanopsin is predominant in peripheral retina. The function of melanopsin appears independent of the rods and cones [2]. Or in other words, even in the absence of rods and cones the circadian entrainment exists. These physiological pathways give some credence to the concept of “vision beyond eyesight”. Circadian rhythms run free in totally blind in

contrast to the entrained. Trilateral retinoblastoma consists of retinoblastoma bilaterally along with pinealoblastoma. These findings lend support to the common progenitor cell origin. Interestingly, mutations in PAX genes cause the absence of pineal gland as well as aniridia [3], indicating connections to the ancient belief of third eye.

Melatonin is stored as serotonin precursor in pinealocytes until night time. Starting from dawn, the next steps of acetylation and methylation takes place. Melatonin is amphiphilic in nature. It is destroyed in the liver. All commercially available melatonin is synthesized and even the smallest available dose raises the levels to supraphysiological concentrations. Pineal gland calcification is seen in more commonly in Caucasians and this increases with aging. Pineal gland is shown to play a key role in the sense of direction. A study showed that subjects with pineal calcification lost their sense of direction. Similar observations were made in pigeons. Those with pineal calcifications lost their priming ability [4]. Melatonin is claimed to be beneficial in atopic dermatitis, neuroprotection, and ADHD. However, FDA approval is in animal husbandry for melatonin implants in minks to accelerate priming and molting [5]. There are inconclusive data on the effects of geomagnetic manipulation of the pineal gland to induce or suppress melatonin secretion or on sense of direction.

Melatonin effects beta cell insulin release through Melatonin 1 (MTNR1) and MTNR2 receptors. Mutations in MTNR 2 have recently been shown to increase the risk of diabetes [6]. Sleep deprivation can quickly reduce insulin sensitivity [7]. A meta-analysis showed an U-shaped association of diabetes with hours of sleep, i.e., those sleeping few hours and more hours having an increased risk [8]. Overall, the studies are indicating the association of poor sleep with detrimental effects on diabetes [8–10]. At a physiological level, melatonin decreases both insulin secretion and sensitivity. Melatonin also increases glucagon secretion [11].

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In this issue of the Journal, Rezvanfar and his team report results of an intervention study of melatonin in type 2 diabetics [12]. The researchers showed an improvement in glycemic control and HDL cholesterol. Large data on the effects of melatonin on lipids in vitro and experimental animals is available with very few well-conducted clinical trials. The indication from these studies is that the atherogenic lipid profiles benefit favorably. In the light of existing data [13], the current findings on lipids are not surprising.

The studies of melatonin on glycemic control are riddled with contrasting results in both experimental animals and humans. The field lacks robust human data. Some intervention studies showed benefits while others did not. A double blind cross-over trial in diabetics with insomnia used prolonged-release melatonin at 2 mg/d dose. A benefit was noted at 5 months but not as early as 3 weeks [14]. Melatonin administration has also been shown to worsen glycemia [15].

Genome-wide association studies (GWAS) have identified mutant alleles close to the MTNR1 gene for progression of normoglycemic status to prediabetes and prediabetes to diabetes [16]. MTNR2 mutations increase the risk for type 2 diabetes [6]. These receptor mutations and their link to glucose homeostasis were reviewed recently [17, 18].

Some of the caveats in the current study need to be highlighted. The study was blind designed to the patients. Melatonin was given after 12 weeks of placebo. This is not a cross-over trial. There is a huge variability in fasting glucose at baseline. The subjects were of average weight; the body mass indices were not shown. We assume that melatonin used was not a long acting preparation. Importantly, there is a significant reduction in HbA1c during the placebo period ($P < 0.01$) and a similar significant reduction in HDL cholesterol. It is possible that this effect could have been carried forward into the second phase of this study, representing a mere placebo effect.

Data are not available on the nocturnal profile of melatonin in the supplemented diabetics. As discussed above, melatonin is known to cause resistance to glucose induced insulin secretion, and this is more prominent in people with MTN receptor mutation. How is it possible to have an improved glycemic control with lessened insulin concentration? Some of the mechanisms: (1) with phase advancement of sleep rhythms, cortisol secretion may remain low early and possibly prolonged low phase. (2) Peripheral action and sensitivity and effects on other counter hormones: 3) we can also hypothesize that the benefits of melatonin exist outside alpha and beta cell.

This study was carried out in Arak, Iran, which is geographically located between the Caspian Sea and Persian Gulf. Fluoride levels in drinking water vary from suboptimal to toxic ranges in these areas. High environmental fluoride levels were reported from this area [19]. Fluoride accumulates in excessive concentration in the pineal gland. However, pineal calcification may not alter the melatonin or its

photoperiodism. A baseline melatonin levels in the study population would have also helped to know whether the populations are melatonin depleted.

How to interpret and go forward from here? The study population is small and limited to a geographic area. Broader conclusions cannot be drawn from these data. We need a full profile of the melatonin, glucose, insulin, and counter hormone levels during such studies with the additional use of methods like Homeostatic Model Assessment and Insulin Resistance (HOMA-IR). The other simpler option could be using the continuous glucose monitoring with intravenous melatonin administration. The physiological relationship is such that the insulin levels go down while melatonin goes up during the night. Future studies addressing insulin, melatonin levels, and circadian rhythms in patients with pancreatectomy and pinealectomy/calcified pineal glands are all needed. We do not have any data on insulin sensitivity as a continuous variable in blind persons. Likewise, its role in pituitary and other tissues is underexplored. There is also paucity of data on what melatonin does in type 1 diabetes.

Melatonin remained a sleeping hormone so far. The field is rapidly evolving and soon its receptor agonists and antagonists will surface and hopefully we will be able to target these to the potential advantage to treat metabolic disorders.

While appears safe, a case control trial on melatonin has not been conducted so far despite its metaphorical popularity. At this point in time, the current findings are interesting but need long term physiological data to recommend melatonin use in diabetes practice.

Compliance with ethical standards

Conflicts of interest None.

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