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Regulation of Various Disorders by Melatonin: A Review

Indu Rana[1], Dr. Neetu Sharma[2], Harshlata[3], Banita Dhatwalia[4], Vijay Bharti[5]

[1]PG student, Department of Zoology, Abhilashi University, Chail Chowk, Mandi, Himachal Pradesh, India
[2]Associate Professor, Department of Zoology, Abhilashi University, Chail Chowk, Mandi, Himachal Pradesh, India
[3,5]Assistant Professor, Department of Zoology, Abhilashi University, Chail Chowk, Mandi, Himachal Pradesh, India
[4]Research Scholar, Department of Zoology, Abhilashi University, Chail Chowk, Mandi, Himachal Pradesh, India

Corresponding Author: Indu Rana

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ABSTRACT

Melatonin is the natural hormone which is produced by the endocrine gland named as a Pineal Gland. Melatonin is also known as "The Hormone of Darkness". Melatonin hormone is involved in the circadian regulation and ease of sleep. Low secretion of Melatonin affects biological rhythm. Individuals who are exposed to light at night especially night shift workers on a regular basis experiences biological rhythm disruption. In some studies, it stated that a shortened duration of nocturnal sleep is associated with a high risk of breast cancer. It also disturbs the menstrual cycle in females. Research stated some of the diseases such as cancer, Alzheimer's disease, multiple sclerosis, fertility, PCOS, combined with the COVID-19 pandemic has led to greater awareness of melatonin because of its ability to act as a potent antioxidant, immune- active agent and mitochondrial regulator. There are different similarities between melatonin and vitamin D on a wide range of their impact on health. There is widespread concern about Vitamin D deficiency as a "sunlight deficiency" and reduced melatonin secretion as a result of "darkness deficiency" from overexposure to artificial blue light. To reduce melatonin disturbance people, have to change the daily life style to maintain the biological rhythm.

Keywords: Melatonin, Pineal Gland, Natural Hormone, Biological rhythm.

INTRODUCTION

The Pineal gland is defined as the neuroendocrine organ which regulates daily body rhythm by the secretion of melatonin. It helps in regulating the light and dark circadian changes to synchronize the daily physiological activities like feeding, metabolism, reproduction and sleep through the secretion of melatonin.[4] The epiphysis cerebri is another name for the pineal gland. The gland is roughly 0.8 cm long and fashioned like a pine cone. About 0.1 g is its weight in an adult.[14] The pineal gland secretes serotonin melatonin or N,N-dimethyltryptamine and it is photo neuro-endocrine organ situated inside the brain.[12] In vertebrates, the pineal gland, a neuroendocrine organ, centrally synthesizes melatonin in addition to its being generated in peripheral tissues and functioning as an autocrine and paracrine signal. Regardless of the species under consideration, the creation of the pineal hormone melatonin always occurs during the night, and the duration of the secretory episode and its production are directly correlated with the length of the

night.[21] Melatonin exhibits a wide range of other functions, such as immunological control, oncostatic, hypnotic, reproductive, puberty timing, mood disorders, and transplantation. Many diseases, including neurological diseases and breast cancer, have been linked to deficiencies in melatonin synthesis or production.[1] According to Musiek and Holtzman (2016), sleep disturbances are frequently linked to neurological etiology and may be a sign of some neurodegenerative diseases.[19]

Synthesis of Melatonin

According to Borjigin *et al.*, 1999, there are four sequential enzymatic steps involved in the synthesis of melatonin from the amino acid tryptophan. Firstly, tryptophan hydroxylase 1 (TPH1) converts dietary tryptophan to 5-hydroxytryptophan (5-HTP); next, aromatic amino acid decarboxylase synthesizes 5-hydroxytryptamine (5-HT or serotonin); arylalkylamine N-acetyltransferase (AANAT) forms N-acetylserotonin (NAS) and hydroxyindole-O-methyltransferase (HIOMT) produces melatonin (also termed N-acetylserotonin methyltransferase or ASMT).[6]

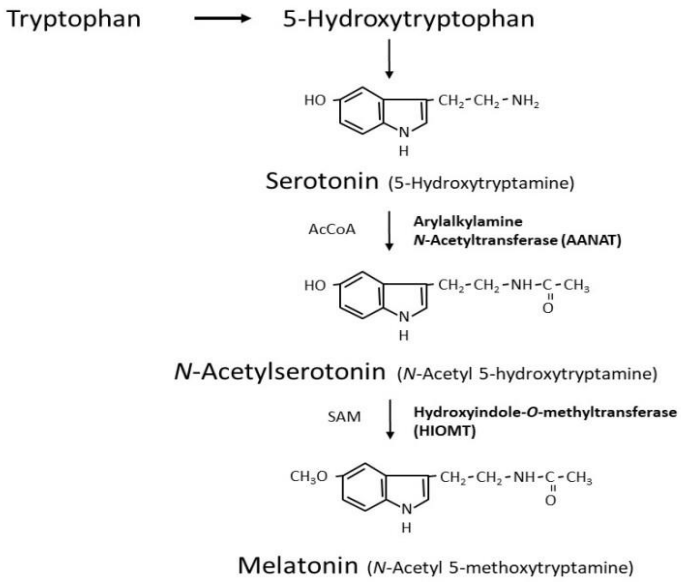

Fig 1: Pathway of Synthesis of Melatonin.[2]

After melatonin is synthesized, it enters the bloodstream and travels to every bodily fluid, including the urine, saliva, amniotic fluid, semen, and breast milk. Urine contains the byproducts of melatonin's fast metabolism, which primarily occurs in the liver. The primary metabolite of it, 6-sulfatoxymelatonin, is found in the urine and blood. Melatonin is converted by the brain into N1-acetyl-N2-formyl-5-methoxykynuramine. Excreted through the urine, this compound is then demethylated to N1-acetyl-5-methoxykynuramine.[23]

Circadian Rhythm

Melatonin, the pineal hormone, controls the circadian rhythm, promotes sleep, inhibits the growth and spread of cancer, and strengthens the immune system. Biological rhythm, or circadian, disruption occurs in those who are often exposed to light at night, such as night shift workers. This disruption includes nocturnal melatonin suppression, circadian phase shifts, and sleep disruptions. These people not only have immune systems that are weakened, but they also have a higher chance of getting several cancers. According to certain research, having less nocturnal sleep may increase the chance of developing breast cancer.[5]

At least 10% of Western populations suffer from clinically serious sleep problems, while at least one-third of the population experiences excessive daytime sleepiness or

sleep disturbances on a daily basis. Several of these sleep disorders necessitate intricate treatment plans that combine pharmaceutical and non-pharmacological therapies.[11] By the end of the 20th century, technology had given individuals access to more nighttime lighting options, such as computer screens, cellphones, tablets, e-readers, televisions, and computer screens. Presently, nighttime light pollution affects over 80% of people worldwide, with 99% of them residing in the US or Europe. In fact, the artificial night sky glow is so intense that approximately 80% of North Americans and two-thirds of Europeans are unable to see the Milky Way.[27]

Significantly, 15–20% of people in industrialized nations work nights; these people are the classic "canaries in a coal mine" for the effects of circadian rhythm disruption on health. When compared to their colleagues who work day shifts, night shift workers experience several health inequities. For example, they have higher rates of certain cancers.[30]

Various disorders by Melatonin

- **Alzheimer's disease:** Alzheimer's disease (AD) is a globally common neurodegenerative disease, which is accompanied by alterations to various lifestyle patterns, such as sleep disturbance. The pineal gland is the primary endocrine organ that secretes hormones, such as melatonin, and controls the circadian rhythms. The decrease in pineal gland volume and pineal calcification leads to the reduction of melatonin production.[27]
- **Parkinson disease:** A neurodegenerative condition that manifests as both motor and nonmotor symptoms is called Parkinson disease (PD). The pathogenesis of Parkinson's disease (PD) involves several mechanisms, including as α-synuclein aggregation, autophagy, oxidative stress, inflammation, and neurotransmitter alterations.[28]
- **Hypertension:** Although less than one-third of individuals achieve good blood pressure control, hypertension is a leading cause of cardiovascular mortality globally. For hypertension and nocturnal hypertension, oral melatonin is a viable substitute therapy.[17]

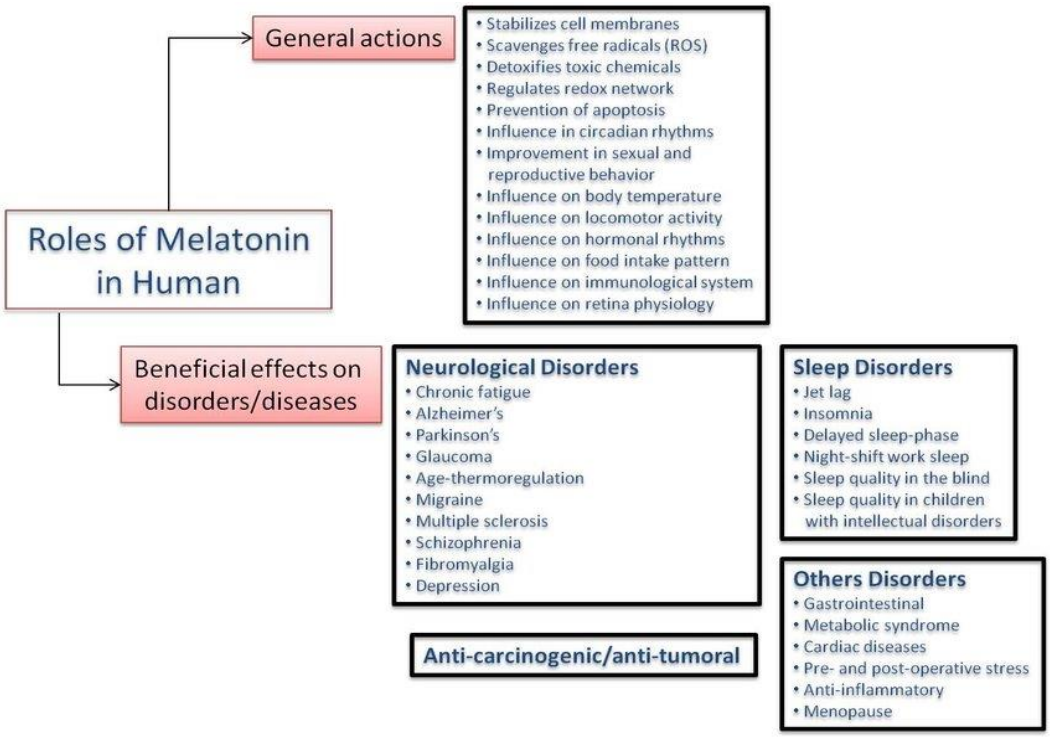

Fig 2: Melatonin's function in human physiology.[3]

- **Insulin Resistance:** Humans use the hormone melatonin, which is generated from tryptophan, as an endocrine signal for exposure to retinal light. It has a role in the control of sleep and circadian rhythm, but in recent years, melatonin's ability to regulate glucose levels has also come to light.[16] Experimental evidence demonstrates that melatonin is necessary for the proper synthesis, secretion, and action of insulin.[22]
- **Breast Cancer:** Significantly, melatonin inhibits the growth of several malignancies, including breast cancer. Melatonin also overcomes medication resistance and reduces aerobic glycolysis in tumours as well as important cell-signalling pathways that are linked to cell survival, proliferation, and metastasis.[15] Rondanelli *et al.*, 2013 conducted a study on the role of melatonin in the prevention of cancer tumorigenesis and in the management of cancer correlated, such as sleep wake and mood disturbances.[25]
- **Prostate cancer:** One of the most prevalent diseases in humans that is detected in men is prostate cancer (PCa). In 2020, there will likely be 33,330 new PCa fatalities and about 191,930 new cases. The human pineal gland is the primary producer of melatonin, a neurohormone that resembles indole and has strong antioxidant properties.[26]
- **Anorexia nervosa:** In clinical settings, anorexia nervosa (AN) is frequently associated with sleeplessness. Patients with AN who self-report their sleep appear to have lower overall sleep duration and poorer quality of sleep.[29]
- **Polycystic ovarian syndrome:** An endocrine condition known as polycystic ovarian syndrome (PCOS) affects 20% of women who are of reproductive age. Menstrual irregularities, obesity, hyperandrogenism, and anovulatory infertility are all linked to melatonin. It has been noted in recent years that PCOS individuals have lower melatonin levels in their follicular fluid.[20]
- **Rabson-Mendenhall:** Insulin receptors are affected by the uncommon autosomal recessive disease known as Rabson-Mendenhall syndrome. Insulin-resistant diabetes mellitus, hyperinsulinemia, acanthosis nigrican, growth retardation, coarse and senile appearance, precocious puberty, dental prematurity, enlarged genitalia, and pineal hyperplasia are the characteristics of this illness.[13]
- **Spontaneous hypothermia hyperhidrosis:** Photoperiod-dependent hormone melatonin controls biological and circadian rhythms and is a well-known sleep aid. Patients who exhibit hyperhidrosis and spontaneous periodic hypothermia should be evaluated for hypermelatoninemia.[9]

Melatonin's impact on insomnia- The definition of insomnia is a chronic inability to fall asleep, stay asleep, or initiate sleep, which leads to poor quality sleep. Individuals who exhibit a propensity for sleep disruptions have hyperarousal, an overactive sympathetic nervous system, and more extreme reactions to stressful situations.[32] Despite having a lower absolute benefit as compared to placebo than other pharmaceutical treatments for insomnia, melatonin may nevertheless be useful in treating insomnia because of its comparatively benign side-effect profile.[10]
It has been demonstrated that melatonin possesses sedative, chronobiotic, antioxidant, and antihypertensive qualities. Additionally, there are clinical and experimental evidences that melatonin has analgesic properties.[31] Melatonin affects several stages of wound healing, including inflammation through controlling the release of inflammatory mediators, cell migration and proliferation through influencing angiogenesis and fibroblast proliferation.[8] Melatonin regulates the survival and differentiation of mesenchymal stem cells (MSCs), among its many other roles. MSCs are a diverse population of multipotent components found in tissues like muscle,

adipose tissue, and bone marrow.[18] In oral cavity cells, melatonin exerts both receptor-mediated and receptor-independent effects. The acinar cells of the main salivary glands and the gingival fluid produce melatonin into the saliva. Melatonin's anti-inflammatory and antioxidant properties are probably the main factors influencing its functions in the oral cavity.[24]

After starting in Wuhan, China in late December 2019, the Corona Virus Disease 2019 (COVID-19) pandemic spread to more than 150 countries on every continent in less than two months. The fact that the epidemic is becoming more severe as people age and that men account for the majority of serious cases is one of its key characteristics. Acute respiratory distress syndrome and multi-visceral failure are brought on by an intense immune response that releases a large number of cytokines, as was the case in the majority of severe cases. The primary neurohormone released by the pineal gland is melatonin. This hormone's production has a circadian rhythm. People over 60 have a noticeable decline in melatonin secretion, which happens progressively with age. The rise in COVID-19-related mortality is inversely correlated with this deprivation. It is assumed that melatonin with its immunomodulatory and antiviral actions plays a protective role against the severity of SARS-CoV-2 infection.[7]

CONCLUSION

The study concluded that Melatonin hormone released by Pineal Gland plays a crucial role in maintaining of sleep wake cycle. The chemical name of melatonin is N-acetyl-methoxytryptamine. Melatonin is a chemical molecule which is found in living organisms including bacteria and humans. It is generated in peripheral tissue and functions as an autocrine and paracrine signal. The people who work more at night *i.e* night shift workers are most commonly affected by sleep disorders. Melatonin also affects menstrual cycle in female. When your nocturnal peak melatonin levels are lower than usual or your overall melatonin output is lower than usual relative to your age and sex, you have hypomelatoninemia. Hypomelatoninemia disorders may include Alzheimer's disease, Parkinson's disease, high blood pressure, Insulin resistance, Obesity, Metabolic syndrome, breast cancer, prostate cancer and increased risk of Type 2 diabetes. The term hypermelatoninemia refers to the overproduction of pineal melatonin and is typically linked to several medical conditions such as anorexia nervosa, polycystic ovarian syndrome, hypogonadotrophic hypogonadism, Rabson-Mendenhall syndrome, and spontaneous hypothermia hyperhidrosis. A few strategies that can help us overcome melatonin issues are to practice meditation, get some sunshine, consume foods high in tryptophan, take a warm bath, minimise artificial light, cut back on using phones after dark, maintain a healthy diet, and avoid excessive stress. We can eat tart cherries, which are heavy in sugar and improve sleep and calorie intake, to raise our melatonin levels. Mangos have the highest concentration of melatonin. Tryptophan and seretonin levels were found to be elevated in mulberries and pineapple. Sweet corn can be used as a rice substitute since it has high quantities of naturally occurring, gluten-free melatonin. The following five fruits: pineapple, berries, bananas, cherries, and kiwis can all help with sleep cycles.

Sr. No.	Diseases	Organ affected	Symptoms	Prevention
1.	Alzheimer's disease	Brain	Memory loss, Poor judgment, Mental confusion, difficulty concentrating.	Diet & supplements, stress management, Exercise and Spiritual fitness.
2.	Parkinson disease	Brain, Cardiac system, heart.	Tremor in hands, arms, legs and jaw or muscle stiffness.	Regular aerobic exercise, consume caffeine, Intake of

				plant food, fruits, vegetable and whole grains.
3.	Hypertension	Eye, Brain, Heart, Kidney and blood vessel.	Severe headache, chest pain, dizziness, difficulty breathing, nausea, vomiting, blurred vision and anxiety.	Diet, maintaining a healthy weight, taking regular exercise, drinking alcohol in moderation and not smoking.
4.	Insulin resistance	Liver, Muscle and Adipose tissue.	Increased thirst, frequent urination, increased hunger, blurred vision and slow healing cuts and sores.	Good sleep, regular exercise, reduce stress, healthy diet and herbs for insulin resistance.
5.	Breast cancer	Breast, Lymph node, Lungs, Liver, Brain, Bones.	Swelling in Breast, skin dimpling, breast or nipple pain, nipple discharge.	Maintain a healthy weight, limit alcohol, Protect yourself from sexually transmitted infection.
6.	Prostate cancer	Prostate gland, Bones, Liver, Lung, Lymph node.	Trouble urinated, blood in the urine, bone pain, unexpected weight.	Low in red and processed meat, limit alcohol, diet high in fruits and vegetable or low in fat.
7.	Insomnia	Brain, Immune system, Endocrine system and circulatory system.	Falling asleep, waking up too early, feeling tired and or sleep during day.	Good sleep, avoid caffein, nicotine and alcohol.

Declaration by Authors

Ethical Approval: Not Required

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