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## Pathophysiological and pharmacological modulation of melatonergic system

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### ABSTRACT

Pineal gland once considered as rudimentary or vestigial, has become a principal endocrine gland that regulates the body's internal environment, after the discovery of melatonin - a hormone produced by it. Melatonin is also synthesized from extra-pineal sites such as retina, skin, platelets, bone marrow, and gastrointestinal tract. The chronobiological property of this hormone in maintaining the circadian rhythm by synchronizing with the dark-light cycle is well-established. Melatonin also possesses anti-inflammatory, anti-depressant, anti-oxidant, oncostatic, immunomodulatory, antiepileptic, and glucose-regulating properties. These pleiotropic effects of melatonin on diverse organ systems either through a receptor or non-receptor mediated pathways are under investigation. This review highlights the pathophysiological and pharmacological actions of melatonin along with melatonergic agonists in "real life" clinical practice.

**Keywords:** Melatonin, Pineal gland, Pleiotropy, Melatonergic drugs

### INTRODUCTION

Melatonin (N-acetyl-5-methoxytryptamine), a hormone of the pineal gland, is a key chronobiological regulator involved in the maintenance of circadian rhythm and sleep-wake cycle. Retina, skin, lymphocytes, bone marrow, and gastrointestinal tract are some of the extra-pineal sources of melatonin. After melatonin's discovery in the pineal tissue, the pineal gland which was once considered as rudimentary or vestigial has turned out to be a focal point which regulates the performance of many of the internal organs. Many of the biochemists and physiologists worked tremendously to bring out the knowledge of biosynthesis and physiological functions of melatonin.

Being considered as the "hormone of darkness," melatonin has generated an enormous amount of interest in researchers as the therapeutic modality for various disorders of sleep.

Melatonin was also found to have other varied biological functions leading to anti-inflammatory, antioxidant,

analgesic, antiepileptic, and other beneficial effects suggesting the potential for a range of clinical uses.<sup>1,2</sup>

### PINEAL GLAND

Pineal gland also known as "pineal body," "conarium," "epiphysis cerebri," or "epiphysis;" is so named because of its resemblance to the shape of the pine cone. Herophilus, the Greek anatomist, around 300 B.C., located and titled the pineal gland as a sphincter which regulates the flow of thought. Early Latin anatomists considered it as a master gland that controls the endocrine system, including the pituitary gland and termed it as "*glandula superior*" whereas pituitary as "*glandula inferior*."

In the 17th century, Rene Descartes, a French philosopher and mathematician called it as "the seat of the human soul."

H.W. De Graff and E. Baldwin Spencer, in 1886, discovered independently that the pineal is a rudimentary eye,

possessing retinal cells, and globular lens like mass similar to the external eyes and called it as “third eye” or “eye of intuition.”

In 1958, Aaron B. Lerner isolated the hormone produced by the bovine pineal gland, which induced contraction of stellate amphibian melanophores (surface pigmentation cells). Hence, melatonin was so named deriving “melas” from melanin and “tonin” as the hormone contracted the melanophores. Axelrod and Wurtman, in 1965, ascribed the term “neuroendocrine transducer” to the pineal gland and also postulated that melatonin was secreted in response to changes in environmental lighting which is known as the “melatonin hypothesis.”<sup>3</sup>

Pineal, a tiny grey-white structure (100 mg) is the smallest organ of the body located as part of the epithalamus within the cranium. It is an unpaired cerebral structure lying closely related to the roof (posterior wall) of the third ventricle of the brain. Pineal gland is situated in the center of the brain from all of the quadrants, and it is positioned such a way that it lies in line with the midpoint between the eyebrows.<sup>4</sup>

Pineal gland is composed of “pinealocytes” which constitute the parenchymal part and also the supporting neuroglial cells. Pinealocytes are star-shaped, neuron-like epithelial cells arranged in clusters (alveoli) and have numerous microtubules, extensive smooth surfaced endoplasmic reticulum, and a few small granules. These cells secrete melatonin and other indolamines known as the pineal peptides. Glial cells are elongated cells that run between the nests of pinealocytes within the pineal stroma. As the pineal gland lacks the endothelial blood-brain barrier, it is termed as a “circumventricular organ” with profuse blood supply.

As the age progresses, along with the involution of the size of the pineal gland there is also deposition of calcium and magnesium salts within the substance of the gland leading to the formation of the so-called “pineal sand” or “brain sand.” These radiopaque calcium concretions aid in the radiographic detection of space-occupying lesion within the skull, as the calcified pineal gland gets displaced due to the presence of such lesions.<sup>5</sup>

## PATHOPHYSIOLOGICAL FUNCTIONS OF MELATONIN

Melatonin is a master hormone, involved in numerous aspects of biological and physiological regulations of the body.

Melatonin is an indole hormone synthesized from the aromatic essential amino acid tryptophan. Figure 1 portrays the synthetic pathway of melatonin.<sup>6</sup>

As shown in the Figure 1, melatonin is formed from serotonin by *N*-acetylation and *O*-methylation and the conversion of serotonin to *N*-acetylserotonin is the rate limiting step. The

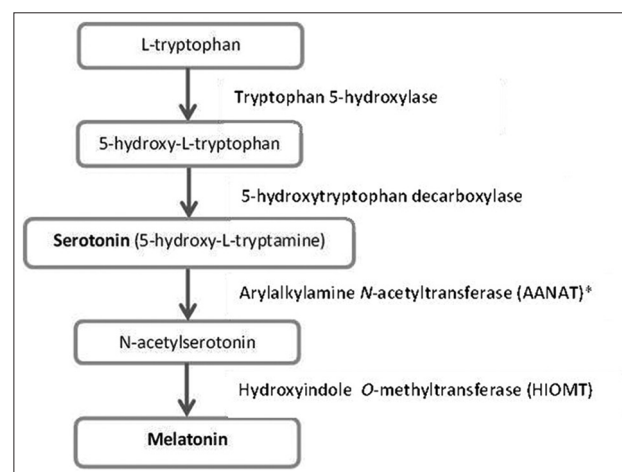
enzyme involved in this acetylation process is arylalkylamine *N*-acetyltransferase (AANAT), which is aptly called “the timezyme” as it determines the circadian rhythm. The gene coding for AANAT is directly influenced by the photoperiod and also the mRNAs encoding for these enzymes involved in the synthetic pathway of melatonin are expressed with a day/night rhythm.<sup>1,6,7</sup>

As discussed above melatonin biosynthesis is synchronized to the light/dark cycle by the suprachiasmatic nucleus (SCN). SCN, the internal “biological clock,” gets photic input from the external environment via the retinohypothalamic tract. From the SCN, the circadian signal is relayed through the paraventricular nucleus of the hypothalamus, the intermediolateral gray column of thoracic spinal cord (segments 1 and 2), and the superior cervical sympathetic ganglia (SCG). Noradrenaline released from the post-ganglionic fibers of the SCG act on the beta-adrenergic receptors present on the pineal gland resulting in the activation of AANAT.

But at daylight, this noradrenergic stimulation of the pineal gland ceases. The production of melatonin again starts in the evening called as the dim-light melatonin onset. In the retina, melanopsin-containing retinal ganglion cells detect the 460-480 nm of the visible spectrum, which corresponds to the blue light. Hence, blue portion of the spectrum and also the beta-adrenergic receptor blockers delink the synthetic pathway of melatonin.

Synthesis of melatonin also depends on the availability of tryptophan, folic acid, and pyridoxine; the last two act as co-factors for the enzymes involved in the synthesis.<sup>5,7-9</sup>

Melatonin released into the circulation immediately after production. The plasma profile of melatonin truly reflects the pineal gland activity, as there is no storage in the pineal gland. As discussed in the above sections, melatonin secretion occurs at night with peak plasma levels around 3-4 a.m. with undetectable daytime levels. The circulating



**Figure 1: Biosynthesis of melatonin (\*rate limiting enzyme).**

daytime serum levels of melatonin in healthy adults do not usually exceed 20 pg/ml while the values at night time may range from about 20 to 170 pg/ml.<sup>7,8</sup>

Nocturnal plasma melatonin concentrations are much higher in children than adults, and the levels decline with age. The average nocturnal plasma melatonin levels are as follows:

- 1-3 years of age : 250 pg/ml
- 8-15 years of age : 120 pg/ml
- 20-27 years of age : 70 pg/ml
- 67-84 years of age : 30 pg/ml.

Circulating melatonin is rapidly metabolized in the liver by the cytochrome enzymes (especially, CYP1A2). Hydroxylation and conjugation with sulfate or glucuronic acid results in the formation of 6-hydroxymelatonin, 6-sulfatoxymelatonin (6-MTS), and 6-glucuronylmelatonin. Urinary excretion of 6-MTS closely parallels the plasma melatonin profile and is frequently used for evaluation of nycthemeral melatonin rhythm. Metabolism of melatonin in other areas like brain and retina varies considerably.<sup>5,7,9</sup>

Melatonin carries the timing signal that coordinates endocrine and other internal events with the light-dark cycle in the environment. Hence, melatonin functions as a robust biochemical neurotransducer that controls circadian rhythmicity and seasonality. The rhythmic secretion of melatonin can be used as a marker of the endogenous circadian clock.

Melatonin acts mostly through G-protein-coupled plasma membrane receptors, *viz.*, MT<sub>1</sub> (formerly Mel 1a, encoded by MTNR1A gene) and MT<sub>2</sub> (Mel 1b, encoded by the MTNR1B gene) are the two functional melatonin membrane receptors. MT<sub>1</sub> receptors are seemed to be involved in the sleep-promoting effects of melatonin while MT<sub>2</sub> receptors appear to play a significant role in the resynchronizing activity (rhythm-regulatory effect/phase shifting effect) of melatonin and seem to be involved in the pathophysiology and pharmacology of sleep disorders.

Besides the SCN, melatonergic receptors are also present in the retina, other areas of brain, pituitary, duodenum, colon, cecum and appendix, gallbladder epithelium, parotid gland, pancreas, ovaries, coronary, cerebral and peripheral arteries, breast epithelium, myometrium, placenta, kidney, adipocytes, platelets, and various immune cells.

Activation of melatonergic receptors on the pituitary gland and the ovaries appears to play a role in regulating the release of reproductive hormones in females. Therefore, melatonin influences to a large extent the timing, length, and frequency of menstrual cycles in women.

Pineal gland calcification also occurs by deposition of fluoride salts within the substance of the pineal gland. It was identified that pineal gland contains the maximum fluoride content when compared to other soft tissues. A preliminary study on prepubertal female gerbils showed that over-

accumulation of fluoride in the pineal gland resulted in decreased pineal melatonin synthesis and an accelerated onset of sexual maturation. A report from the National Research Council summarized that fluoride exposure results in altered melatonin production and altered timing of sexual maturity in human beings also.<sup>10</sup>

Deficiency or dysfunction of melatonin signaling is observed in various disease states such as dementia, certain mood disorders, severe pain, rheumatoid arthritis, migraine, cancer, and Type 2 diabetes mellitus.

Since the regulatory system of melatonin secretion is intricate, involving central and autonomic pathways, there are many pathophysiological conditions in which melatonin secretion can be disturbed. The resulting changes could increase the risk of developing a disease, add to the severity of existing symptoms, or change the course and outcome of the disorder. Hence, it is evident that melatonin deficiency or dysfunction could lead to a plethora of consequences far beyond the known sleep difficulties.<sup>1,7,9,11,12</sup>

## MELATONIN - PHARMACOLOGICAL AND CLINICAL ROLE

Melatonin functions as a chronobiotic that participates in the organization, control, and stabilization of the circadian system by way of its sleep-promoting effects. It shortens sleep latency and lengthens the duration of sleep. Hence, melatonin has been used for the treatment of age-related insomnia, as well as of other primary and secondary insomnias. It has been utilized in several countries for circadian rhythm disorders (like delayed sleep phase syndrome), jetlag, shift work disorder, and sleep-wake cycle disturbances in blind people.

Exogenous administration of melatonin has shown the phase shift of many physiological parameters like endogenous melatonin, core body temperature, and sleep timing. Timing of melatonin administration has a significant effect on the phase shift. Phase delays occur on morning administration whereas phase advances occur on evening administration of melatonin. Hence, timed intake of melatonin exhibited high efficacy in treating jet lag where there is an acute phase shift of light-dark cycles.

Several studies revealed that affective disorders like major depressive disorders and bipolar disorders are associated with alterations in the circadian rhythm. Therefore, melatonin readjusts this highly variable rhythm existing in these disorders.<sup>13</sup>

The dose of melatonin demarcates the physiological and pharmacological effects of melatonin. Supraphysiological levels of melatonin are attained at "pharmacological" dose, while a "physiological" dose provides plasma levels of the same order of magnitude as that of a usual nocturnal peak.

Exogenous administration of melatonin as a substitution therapy (extended period) for managing sleep-related disorders has its own pitfalls. The first and the most important setback is the rapid metabolism and elimination of melatonin; the half-life varies from <30 mins to about 45 mins (maximally).

Hence, before banking on the therapeutic utility of melatonin on sleep-related disorders, it is a prerequisite to determine whether the melatonergic action is required for a short or longer period. Melatonin is found to promote both sleep onset and sleep maintenance when given at a daily dose range of 0.1-0.3 mg.

In sleep-onset disorders, an immediate-release formulation can be used whereas in disorders related to maintenance of sleep prolonged-/slow-release preparations are more suitable. One such prolonged-release formulation is circadin (2 mg) developed by Neurim Pharmaceuticals, Israel got approval from European Medicines Agency (EMA) in 2007. Based on the on evidence-based treatment of insomnia, parasomnia, and circadian rhythm sleep disorders, the British Association for Psychopharmacology concluded that melatonin is the first-choice treatment when a hypnotic is indicated in patients aged more than 55 years.<sup>1,11,12,14-16</sup> A recent post-marketing surveillance study conducted by Hajak et al.,<sup>17</sup> also proved the efficacy of the prolonged-release melatonin, circadin.

As melatonin receptors are very widely distributed in the body, the possible therapeutic indications of this hormone are diverse. Multicenter randomized controlled trials (RCTs) in a large cohort of patients are necessary to establish the efficacy and also long-term safety of melatonin.

As melatonin is freely available as a food supplement, it has not received regulatory approval from the Food and Drug Administration as a drug. Moreover, drug companies are very much reluctant to work on a non-patentable and so non-profitable compound.<sup>11,14</sup>

### ***Pleiotropic effects of melatonin***

In addition to its chronobiological role, several pharmacological effects of melatonin have been stated including antioxidant, sedative, oncostatic, anxiolytic, antidepressant, anticonvulsant, and analgesic activities. This extensive pleiotropy of melatonin is ascribed either to the receptor- or non-receptor-mediated effects of the hormone. Due to its small size and easy permeability across cell membranes, over and above the specific membrane receptors, melatonin also acts via the nuclear receptors and other intracellular signaling cascades.<sup>18</sup>

### ***Antioxidant***

Melatonin exerts its antioxidant effect by direct scavenging of free radicals (*viz.*, O<sub>2</sub>, O<sub>2</sub><sup>•-</sup>, H<sub>2</sub>O<sub>2</sub>, •OH, and LOO•) and

indirectly by activating major antioxidant enzymes including superoxide dismutase, catalase, and glutathione peroxidase. Other mechanisms include downregulation of pro-oxidant enzymes, reduction of neuronal free radical formation by anti-excitatory actions, reduction of free radical formation by anti-inflammatory actions, reduction of electron leakage by support of mitochondrial electron flux, avoidance of excessive radical formation by optimizing phasing and amplitudes of metabolic circadian rhythms, formation of redox-reactive melatonin metabolites with radical-scavenging properties, and scavenging of low reactive free radicals by melatonin radicals. The term “radical avoidance” is used when melatonin functions by reducing the rate of free radical formation.

Antioxidant property is implicated in the usage of melatonin in chronic hemodialysis patients, septic and asphyxiated newborns.<sup>7,15,19</sup>

### ***Immunomodulator***

Melatonin functions as an immune activator in basal or immunosuppressed disease conditions; it has a stimulatory role on innate, cellular, and humoral immunity. On the other hand, melatonin also exerts a negative regulatory function under transient or chronic exacerbated immune response. Hence, it is clear that melatonin acts as an “immune buffer” providing a bi-directional functional link between the neuroendocrine and immune-hematopoietic systems (pineal-immune interconnection). The precise pathophysiological role of melatonin in immune function can be established by developing working models of melatonin knockout animals or by producing highly specific monoclonal antibodies.<sup>7,20,21</sup>

### ***Antineoplastic***

The anti-tumor activity of melatonin is presumed to happen by the following mechanisms:

- Anti-proliferative cytotoxic/cytostatic action
- Inhibition of growth factor receptor activation
- Inhibitory effect on tumor angiogenesis
- Inhibition of tumor growth factor secretion
- Stimulation of the antitumor immunity (immunostimulatory)
- Cytodifferentiating activity
- Anti-inflammatory activity
- Anti-oxidant activity.

Lung cancer patients especially those with non-small cell lung cancer exhibit anomalous variations in the circadian rhythmicity of lymphocytes, hormones, and cytokines which may in turn impair the interplay among different lymphocyte subpopulations and neuroendocrine system components leading to inefficient tumor immune response. Hence, melatonin therapy can be applied in this regard in normalizing the immune response.

Similarly, the selective estrogen receptor modulating and selective estrogen enzyme modulating properties are the most valid explanation of the oncostatic effects of melatonin on hormone-dependent breast cancer.

In addition to the therapeutic role of melatonin in “curative” treatment of various cancers, its potential to counteract the cachectic effects of tumor necrosis factor-alpha can be utilized in “palliative” care of cancer therapy – Thereby, improving the quality of life. Having said so, so far only experimental pieces of evidence are available and more clinical studies are to be undertaken on the treatment (curative and palliative) of human neoplasms with melatonin.

Because of its capacity of acting at different levels and on different tumor targets and on the different molecules involved in promoting tumor cell proliferation and dissemination, melatonin can be considered as a multi-target therapy.<sup>15,22</sup>

### **Microbicidal**

Melatonin has been found to be effective in battling infections caused by various bacteria, viruses and parasites (including *Plasmodium falciparum*). Melatonin potentiates the therapeutic effect of isoniazid by the formation of free radicals or binding with the membranes of mycobacteria. It also inhibits chlamydial infection by G-protein coupled activation of the melatonergic receptors. In other experimental studies in mice, melatonin administration was found to increase the production of interleukin-1 $\beta$  thereby preventing infection with *Venezuelan equine encephalomyelitis virus*. The importance of melatonin as a therapeutic modality in septic shock (with severe respiratory distress syndrome and multiorgan failure) was proven in some of the clinical studies. Very recently, melatonin is being suggested as a treatment for overcoming the highly dreaded modern day epidemic of Ebola virus infection. The pathogenic mechanisms of Ebola such as inflammation, coagulopathy, and endothelial dysfunction can be overcome by the pleiotropic effect of melatonin on these factors, similar to its action on sepsis.<sup>23,24</sup>

### **Antinociception**

Diurnal variation in the perception of pain was the first hint in the application of melatonin as a safe alternative to other analgesics in various types of pain disorders. Numerous clinical trials are underway trying to elicit the clinical role of melatonin in pain-related disorders such as, inflammatory pain, neuropathic pain, migraine, cluster headache, and irritable bowel syndrome. Melatonin exerts its antinociceptive effects by acting on number of receptors such as opioidergic, benzodiazepinergic, muscarinic, nicotinic, serotonergic,  $\alpha_1$ -adrenergic,  $\alpha_2$ -adrenergic, and most importantly the MT<sub>1</sub>/MT<sub>2</sub> receptors present in the dorsal horn of the spinal cord.<sup>15</sup>

### **Neuroprotection**

As a neuroprotectant, melatonin is indicated as having a positive therapeutic potential against Alzheimer’s disease (AD), Parkinson’s disease, amyotrophic lateral sclerosis, and other types of dementia. The neuroprotective role of melatonin in AD is well studied, and the following mechanisms have been proposed:

- Inhibition of amyloid  $\beta$ -protein deposition
- Inhibition of formation of amyloid fibrils
- Scavenges free radicals induced by amyloid  $\beta$ -protein
- Lipid peroxidation reactions in the neural tissue are inhibited
- Suppresses protein hyperphosphorylation
- Prevents cytoskeletal disorganization.

Melatonin reinforces the mitochondrial homeostasis, thereby preventing neuronal cell death, as intramitochondrial accumulation of amyloid  $\beta$ -protein results in increased electron leakage and consequent decline in adenosine triphosphate production.<sup>25</sup>

Melatonin stabilizes the electrical activity of the central nervous system and causes rapid synchronization of the electroencephalogram. Hence, melatonin in chronic high dose is used as an adjunctive anticonvulsant in intractable seizures.<sup>15</sup>

### **Metabolic function**

Being a multifunctional molecule, melatonin was also found to have putative beneficial effects on body fat mass, energy metabolism regulation, and cardiovascular function. The link between melatonin and cardioprotection is employed in various experimental and clinical studies to examine the favorable effects of melatonin on ischemic heart disease, myocardial infarction, and hypertension. A recent RCT in 2014 conducted by Goyal et al.<sup>26</sup> concluded that melatonin supplementation modestly improved most of the components associated with metabolic syndrome.

## **MELATONERGIC DRUGS**

The lack of receptor (MT<sub>1</sub> and MT<sub>2</sub>) selectivity and shorter half-life of melatonin led to the need for more potent synthetic melatonergic analogs. Ramelteon, agomelatine, and tasimelteon are the melatonergic agonists available in the market.

### **Ramelteon**

Takeda Pharmaceutical Company Ltd., Japan synthesized the first synthetic melatonergic agonist ramelteon (Rozerem), which got approval from the FDA in July 2005 for the treatment of insomnia. Though ramelteon does not exhibit any MT<sub>1</sub> or MT<sub>2</sub> receptor subtype specificity, there is no significant interaction with other receptor systems (except 5-HT<sub>1A</sub>).

Ramelteon shows 3-16 times higher affinity toward melatonergic receptors than melatonin and its higher affinity on  $MT_1$  than  $MT_2$  reflects the fact that ramelteon targets sleep onset more specifically.

The recommended dose of ramelteon is 8 mg taken within 30 mins of going to bed. Peak serum concentrations are achieved within 30-90 mins. The plasma half-life of ramelteon is 1-2 hrs, which is much longer than melatonin.

Similar to melatonin, CYP1A2 is the predominant microsomal enzyme involved in the hepatic metabolism of ramelteon. The commonly seen side effects are headache, dizziness, somnolence, and sore throat.

Unlike benzodiazepines (and other conventional hypnotics), ramelteon does not have abuse or dependence potential to its sedative and hypnotic action. And also there are no next-day hangover effects or withdrawal effects (rebound insomnia) associated with ramelteon, even at higher doses.<sup>1,14,27,28</sup>

### **Agomelatine**

The second melatonergic drug which was introduced in the market was agomelatine (Valdoxan) manufactured by Servier Laboratories in France. Agomelatine is an acetamide naphthalene analog of melatonin approved by EMEA, in February 2009, for use in major depressive disorders including prevention of relapse.

Agomelatine is a unique antidepressant with novel mechanism of action, i.e., by acting as an  $MT_1/MT_2$  receptor agonist and a 5-HT<sub>2C</sub> receptor antagonist simultaneously. Antagonism at the 5-HT<sub>2C</sub> receptor is considered responsible for the antidepressant effect; whereas agonism at the  $MT_1/MT_2$  receptors is related to circadian rhythm regulation necessary for certain subtypes of depression. A synergistic interaction between melatonergic and serotonergic signals has been predicted to be essential for the antidepressant action of agomelatine.

The recommended daily dose is 25 mg at bedtime and can be increased to a maximum of 50 mg after 2 weeks if no improvement occurs. Agomelatine is helpful in restoration of the sleep-wake cycle and also in stabilizing the impaired sexual function which occurs with untreated depression.

A meta-analysis of 20 trials by Taylor et al.,<sup>29</sup> in 2014, reported that agomelatine is an effective antidepressant with similar efficacy to standard antidepressants. Agomelatine is also found to be useful in jetlag-associated depressive disorder, seasonal affective disorder, migraine, bipolar disorder and general anxiety disorder in few of the nascent clinical trials.<sup>1,28,30</sup>

### **Tasimelteon**

On January 31st, 2014, FDA approved tasimelteon (Hetlioz) the first orphan drug for the treatment of non-24 hrs sleep-wake disorder (N24HSWD) in subjects suffering from total blindness. N24HSWD is a chronic disorder characterized by de-synchronization of the internal circadian clock with that of sleep-wake cycle occurring in 70% of the totally blind people. Complete blindness leads to lack of perception external photic cues resulting in N24HSWD.

Tasimelteon is given at a dose of 20 mg/day, prior to bedtime, at the same time every night. It has moderately more affinity toward  $MT_2$  than  $MT_1$  receptors. Headache is the most common adverse effect reported.<sup>1,31</sup>

TIK-301, another  $MT_1/MT_2$  receptor agonist, received orphan drug designation by FDA for the treatment of sleep disorders in blind individuals and currently under clinical trial. TIK-301 also exhibits 5-HT<sub>2C</sub> and 5-HT<sub>2B</sub> receptor antagonism, which has to be further explored for possible antidepressant effects.

Melatonin receptor antagonists are tried only in preclinical studies. They are as follows:

- Luzindole (N-0774) : in depression
- S22153 : in circadian rhythm entrainment experiments
- ML-23 : in Parkinson's disease.

### **FUTURE PERSPECTIVES**

As discussed so far, although melatonin displays multitude of functions within the human body, only its role in entrainment of the circadian rhythm is known fully. For this reason, most of the pharmaceutical companies focused on the development of melatonergic drugs for the treatment of circadian pathologies.

None of the melatonergic drugs available in the market are selective to a specific type of melatonergic receptor. Hence, it is high time to work on subtype-specific melatonergic drugs thereby resulting in more controlled pharmacodynamics effects.

4-phenyl-2-propionamidotetralin, acetamide, and allyl carboxamide are some of the selective  $MT_2$  melatonergic ligands.

Neu-P11 is an  $MT_1/MT_2$  receptor agonist and a 5-HT<sub>1A/1D</sub> receptor antagonist found to promote sleep, improve insulin sensitivity and exert antidepressant and anxiolytic activities in rats. M3C, a new 1-N substituted melatonin analog, has been assumed to have anxiolytic property.

Various animal studies have reported that selective  $MT_2$  receptor agonism results in the promotion of non-rapid eye

movement sleep. Based on this evidence, two MT<sub>2</sub> selective partial agonists UCM765 and UCM924 are under development.

Although receptor selective actions are very much necessary, the recent concept of “polypharmacology” has challenged this opinion. In polypharmacology, multiple therapeutic targets are aimed to attain a superior efficacy and safety.<sup>1</sup>

## CONCLUSION

Though melatonin was discovered 50 years ago, its role in human pathophysiology is getting more diversified along the years. Therapeutic role of melatonin is also expanding in line with the increase in beneficial pleiotropic effects.

Melatonin should be considered as more than an endogenous synchronizer in modifying disease states, as in most of these diseases the role of circadian organization is yet to be fully understood.

Hence, this “sleeping pill” if used wisely following well-designed experimental and confirmatory clinical trials, can go a long way in becoming – the universal panacea!

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