Melatonin hormone

Research Project

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بسم الله الرحمن الرحيم

وَهُوَ الَّذِي جَعَلَ لَكُمُ اللَّيْلَ لِبَاسًا وَالنَّوْمَ سُبَاتًا وَجَعَلَ النَّهَارَ نُشُورًا (47) الفرقان

Dedication:

To my family

Thanks and appreciation :

Thanks for my teacher Dr.Suharia to help us for finish this research

Contents

The pictures that's used in this research:

Abstract

Melatonin is a chemical with extraordinary phylogenetic conservation found in all known aerobic creatures whose alteration plays an important role in sleep changes with aging. Every day, the late afternoon/nocturnal surge in pineal melatonin helps to synchronize both the central circadian pacemaker found in the hypothalamic suprachiasmatic nuclei (SCN) and a plethora of peripheral cellular circadian clocks. Melatonin is an example of an endogenous chronobiotic substance that can influence the timing and amplitude of circadian rhythms. Moreover, melatonin is also an excellent anti-inflammatory agent, buffering free radicals, down-regulating proinflammatory cytokines, and reducing insulin resistance, among other things. We present both scientific and clinical evidence that melatonin is a safe drug for treating sleep disturbances in the elderly.

Introduction

Melatonin is a hormone that your brain produces in response to darkness. It helps with the timing of your circadian rhythms (24-hour internal clock) and with sleep. Being exposed to light at night can block melatonin production. Research suggests that melatonin plays other important roles in the body beyond sleep.

Naturally-occurring melatonin has been reported in foods including tart cherries to about 0.17–13.46 ng/g,[14] bananas, plums, grapes, rice, cereals, herbs,[13] olive oil, wine,[1] and beer.[2] The consumption of milk and sour cherries may improve sleep quality.[12] When birds ingest melatonin-rich plant feed, such as rice, the melatonin binds to melatonin receptors in their brains.[15] When humans consume foods rich in melatonin, such as banana, pineapple, and orange, the blood levels of melatonin increase significantly.[11]

In some common foods and beverages, including coffee [10] and walnuts,[9] the concentration of melatonin has been estimated or measured to be sufficiently high to raise the blood level of melatonin above daytime baseline values.

Melatonin or 5 methoxy-*N*-acetyltryptamine (Fig. **1**) was discovered and isolated from bovine pineal in 1958 by Aaron Lerner [1]. Melatonin is the main hormone secreted by the pineal gland. Extrapineal sources of melatonin were reported in the retina, bone marrow cells, platelets, skin, lymphocytes, Harderian gland, cerebellum, and especially in the

gastrointestinal tract of vertebrate species [2-9]. Indeed, melatonin is present but can also be synthesized in the enterochromaffin cells; the release of gastrointestinal melatonin into the circulation seems to follow the periodicity of food intake, particularly tryptophan intake [2, 10]. It is noteworthy that the concentration of melatonin in the gastrointestinal tract surpasses blood levels by 10-100 times and there is at least 400 times more melatonin in the gastrointestinal tract than in the pineal gland [2]. Melatonin in the gastrointestinal tract of newborn and infant mammals is of maternal origin given that melatonin penetrates easily the placenta and is after secreted into the mother's milk [11-13]. It has even been suggested that melatonin is involved in the production of mekonium [2]. Melatonin in human breast milk follows a circadian rhythm in both preterm and term milk, with high levels during the night and undetectable levels during the day [14, 15]. No correlation was found between gestational age and concentration of melatonin. It is noteworthy that bottle milk composition does not contain melatonin in powder formula. Also, human colostrum, during the first 4 or 5 days after birth, contains immune – competent cells (colostral mononuclear cells) which are able to synthesize melatonin in an autocrine manner [16].

Melatonin synthesis and secretion is enhanced by darkness and inhibited by light (Fig. **3**) [21]. Luminous information is transmitted from the retina to pineal gland through the suprachiasmatic nucleus (SCN) of the hypothalamus. In humans, its secretion starts soon after sundown, reaches a peak in the middle of the night (between 2 and 4 in the morning) and decreases gradually during the second half of the night [7]. Nearly 80% of the melatonin is synthesized at night, with serum concentrations varying between 80 and 120 pg/ml. During daylight hours, serum concentrations are low (10-20 pg/ml) [20].

Serum concentrations of melatonin vary considerably with age, and infants secrete very low levels of melatonin before 3 months of age. Melatonin secretion increases and becomes circadian along with child development: Sadeh [19] reported an association between melatonin secretion and organization of sleep-wake rhythm from 6 months of age. However, more recent studies suggest that melatonin rhythm is set around 3 months of age in typical development, at the same time that infants begin to have more regular sleep–wake cycles associated with nighttime sleep lasting 6-8 h [25]. In 3-years-old children, a stabilization of the sleep-wake rhythm is observed, which corresponds to a regular melatonin secretion rhythm [16]. Nocturnal concentration peaks are the highest between the 4^{th} and 7^{th} years of age [17], and then decline progressively [18].

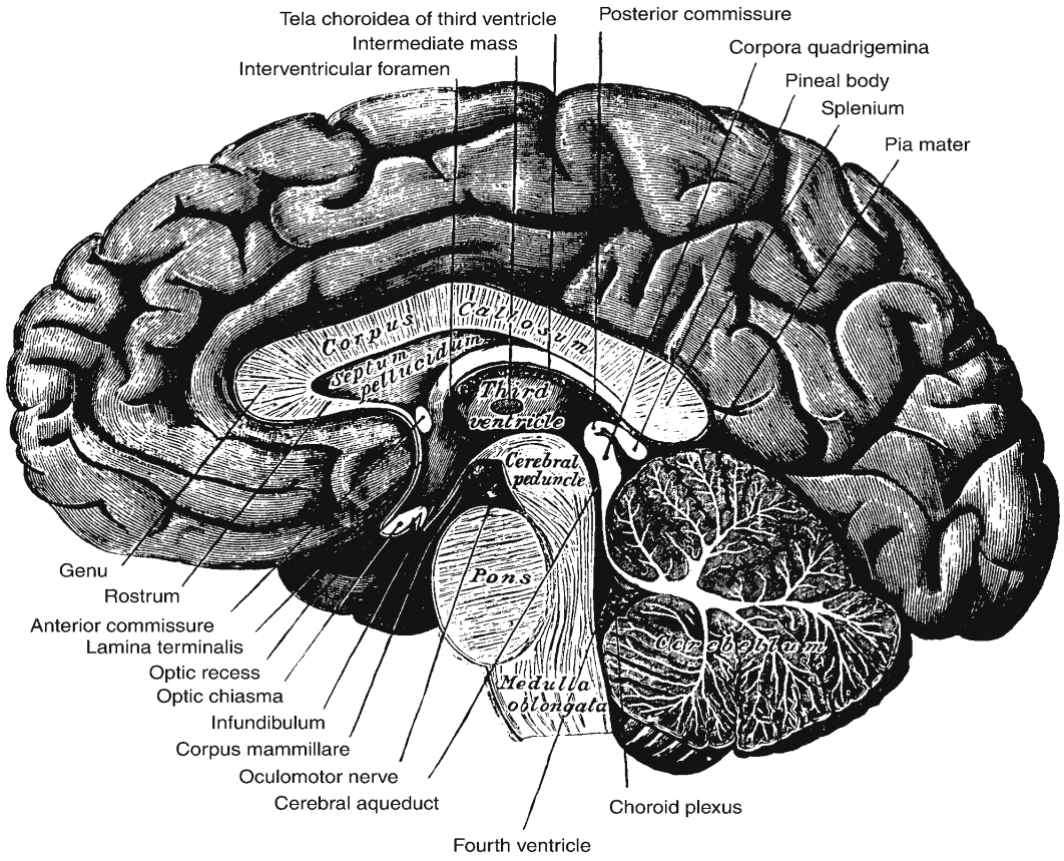

Fig. 1. Median sagittal section of brain. (Reproduced from Gray, 1985)

The aim of our study :

1- Measures of melatonin are considered the best peripheral indices of human circadian timing based on an internal 24-hour clock.

2- to review highlights the high number and diversity of major melatonin effects and opens important perspectives for measuring melatonin as a biomarker (biomarker of early identification of certain disorders and also biomarker of their follow-up) and using

melatonin with clinical preventive and therapeutic applications in newborns, children and adults based on its physiological regulatory effects.

2.Literature reviews

2.1EFFECTS OF MELATONIN

2.1.1Circadian rhythm

In animals, melatonin plays an important role in the regulation of sleep–wake cycles.[21] Human infants' melatonin levels become regular in about the third month after birth, with the highest levels measured between midnight and 8:00 am.[22] Human melatonin production decreases as a person ages.[23] Also, as children become teenagers, the nightly schedule of melatonin release is delayed, leading to later sleeping and waking times.[24]. When eyes receive light from the sun, the pineal gland's production of melatonin is inhibited and the hormones produced keep the human awake. When the eyes do not receive light, melatonin is produced in the pineal gland and the human becomes tired.

2.1.2Antioxidant

Melatonin was first reported as a potent antioxidant and free radical scavenger in 1993.[25] In vitro, melatonin acts as a direct scavenger of oxygen radicals including OH•, O2−•, and the reactive nitrogen species NO•.[26][27] In plants, melatonin works with other antioxidants to improve the overall effectiveness of each antioxidant.[12]

Melatonin occurs at high concentrations within mitochondrial fluid which greatly exceed the plasma concentration of melatonin.[17][18][19] Due to its capacity for free radical scavenging, indirect effects on the expression of antioxidant enzymes, and its significant concentrations within mitochondria, a number of authors have indicated that melatonin has an important physiological function as a mitochondrial antioxidant.[16][17][18][19][20]

The melatonin metabolites produced via the reaction of melatonin with reactive oxygen species or reactive nitrogen species also react with and reduce free radicals.

2.1.3 Immune system

While it is known that melatonin interacts with the immune system,[29][30] the details of those interactions are unclear. An anti-inflammatory effect seems to be the most relevant[citation needed]. There have been few trials designed to judge the effectiveness of melatonin in disease treatment. Most existing data are based on small, incomplete trials. Any positive immunological effect is thought to be the result of melatonin acting on high-affinity receptors (MT1 and MT2) expressed in immunocompetent cells. In preclinical studies, melatonin may enhance cytokine production and stimulate T cell expansion,[11] and by doing this, counteract acquired immunodeficiences.[10]

2.1.4Weight regulation

A possible mechanism by which melatonin may regulate weight gain is through its inhibitory effect on leptin.[33] Leptin acts as a long-term indicator of energy status in the human body.[9] By suppressing leptin's actions outside of waking hours, melatonin may help restore leptin sensitivity during the daytime by alleviating leptin resistance.[8][35]

2.1.5 Anti-cancer

Melatonin could also increase the infiltration activity of NK cells [**7**]. An animal study showed that a supplement with melatonin augmented NK cell numbers and extended its survival time [**35**]. Melatonin also increased the IL-2 secretion by upregulating the MT1 receptor, increasing NK cell numbers [**23**].

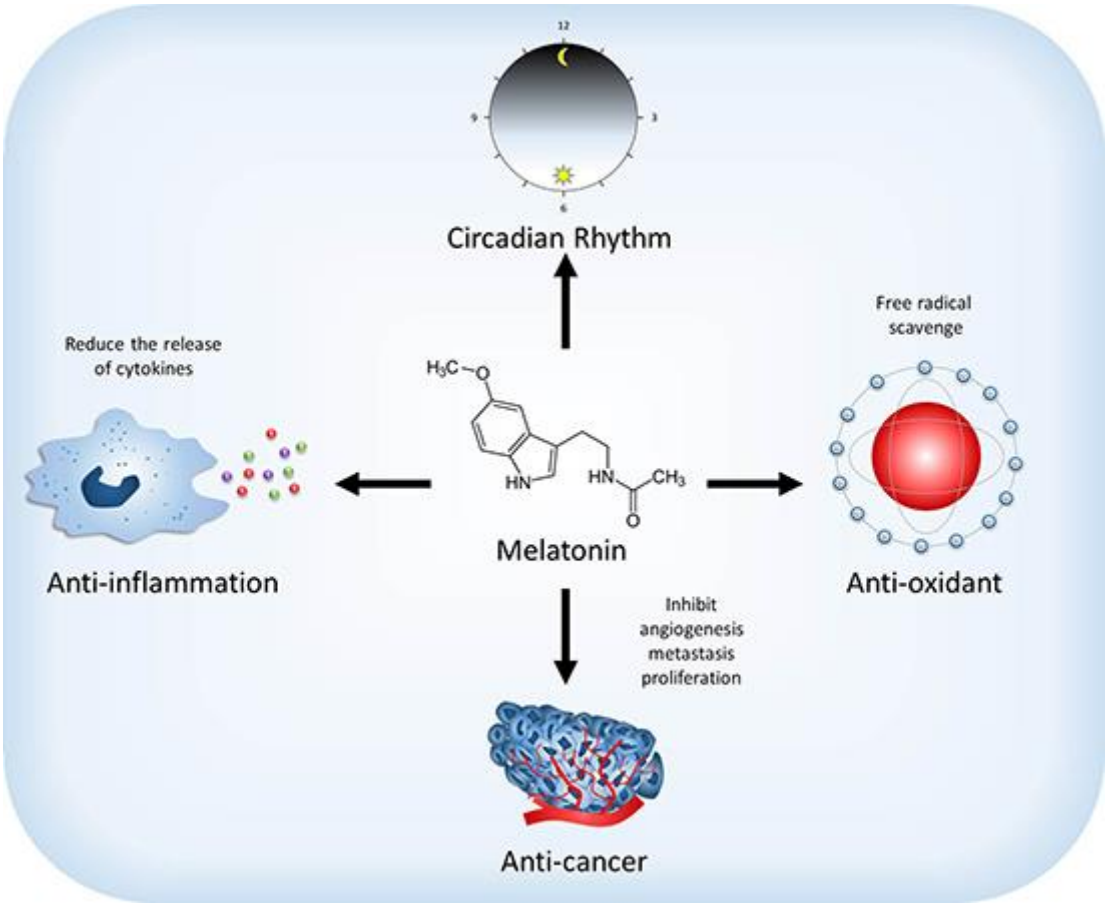

Fig.2 Effect of melatonin on the physiological and pathological functions.

2.2Biochemistry

2.2.1Biosynthesis

Overview of melatonin biosynthesis

In animals, biosynthesis of melatonin occurs through hydroxylation, decarboxylation, acetylation and a methylation starting with L-tryptophan.[36] L-tryptophan is produced in the shikimate pathway from chorismate or is acquired from protein catabolism. First L-tryptophan is hydroxylated on the indole ring by tryptophan hydroxylase to produce 5-hydroxytryptophan. This intermediate (5-HTP) is decarboxylated by pyridoxal phosphate and 5-hydroxytryptophan decarboxylase to produce serotonin.

Serotonin is itself an important neurotransmitter, but is also converted into N-acetylserotonin by serotonin N-acetyltransferase with acetyl-CoA.[36] Hydroxyindole O-methyltransferase and S-adenosyl methionine convert N-acetylserotonin into melatonin through methylation of the hydroxyl group.[6]

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.[5][34]

It has been hypothesized that melatonin is made in the mitochondria and chloroplasts.[33]

2.2.2 Regulation

In vertebrates, melatonin secretion is regulated by activation of the beta-1 adrenergic receptor by norepinephrine.[31] Norepinephrine elevates the intracellular cAMP

concentration via beta-adrenergic receptors and activates the cAMP-dependent protein kinase A (PKA). PKA phosphorylates the penultimate enzyme, the arylalkylamine N-acetyltransferase (AANAT). On exposure to (day)light, noradrenergic stimulation stops and the protein is immediately destroyed by proteasomal proteolysis.[30] Production of melatonin is again started in the evening at the point called the dim-light melatonin onset.

Blue light, principally around 460–480 nm, suppresses melatonin biosynthesis,[4] proportional to the light intensity and length of exposure. Until recent history, humans in temperate climates were exposed to few hours of (blue) daylight in the winter; their fires gave predominantly yellow light.[34] The incandescent light bulb widely used in the 20th century produced relatively little blue light.[32] Light containing only wavelengths greater than 530 nm does not suppress melatonin in bright-light conditions.[33] Wearing glasses that block blue light in the hours before bedtime may decrease melatonin loss.[29] Use of blue-blocking goggles the last hours before bedtime has also been advised for people who need to adjust to an earlier bedtime, as melatonin promotes sleepiness.[28]

2.2.3 Metabolism

Melatonin has an elimination half-life of 20 to 50 minutes.[1][2][3] In humans, melatonin is mainly metabolized to 6-hydroxymelatonin, which is conjugated with sulfate to be excreted as a waste product in urine.[27]

2.2.4 Measurement

For research as well as clinical purposes, melatonin concentration in humans can be measured either from the saliva or blood plasma.[25]

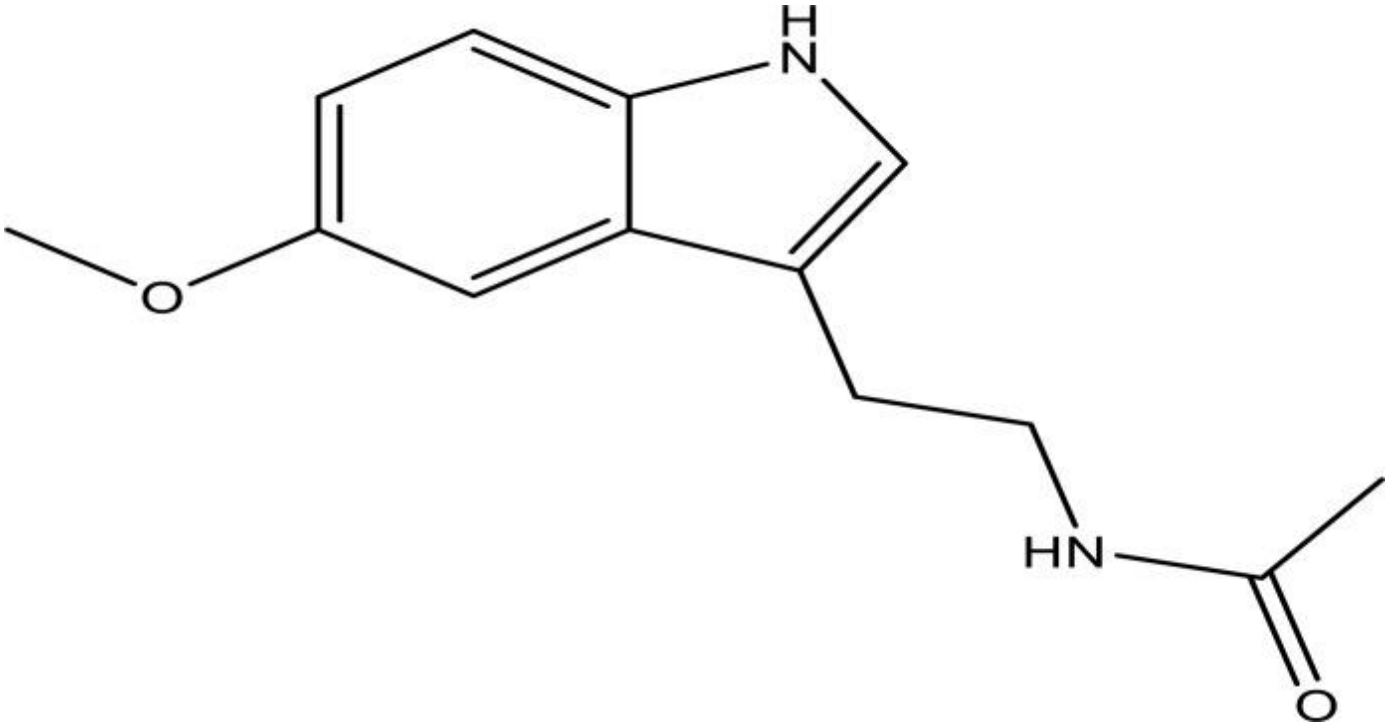

Fig.3. Structure of melatonin

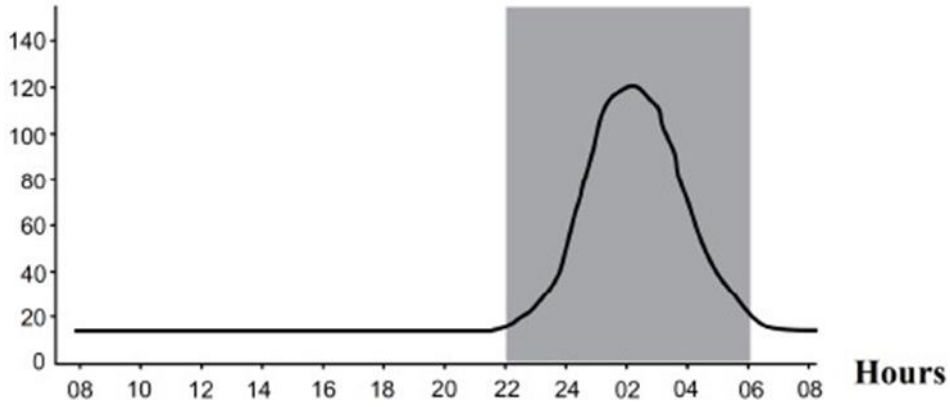

Fig.4.Circadian profile of melatonin plasma concentrations (in grey is represented the period of darkness)

Sleep Disorder and Treatment

Not only should an ideal hypnotic reduce sleep onset latency, but it should also boost total sleep time and sleep efficiency. Furthermore, the ideal hypnotic medicine should not have undesirable side effects such as impaired memory, cognition, next psychomotor slowdown, day hangover symptoms, or the possibility of misuse. Many of these conditions are satisfied by melatonin, as evidenced by various consensus declarations and meta-analysis articles.[39,41-46]

Melatonin is a potent chronobiotic with mild hypnotic properties. Daily dosages of 2–5 mg melatonin, timed to advance the phase of the internal clock through interaction with MT1 receptors in the SCN, sustain circadian rhythm synchronization to a 24-h cycle in sighted people who live in situations that are prone to produce a free-running rhythm.[40] Melatonin synchronizes a person's rhythm after a brief time of free running. By administering melatonin to blind subjects with free-running rhythms, researchers were able to stabilize or entrain, the sleep/wake cycle to 24 hours, resulting in improved sleep and mood.[5] In recent month-long crossover research, 24 healthy older individuals were given a placebo for two weeks and then either 0.3 mg or 5 mg of melatonin 30 minutes before going to bed. The 5 mg melatonin dosage considerably boosted sleep efficiency throughout both biological day and night, mostly by extending the duration of Stage 2 non-REM sleep and somewhat reducing awakenings.[44]

Melatonin therapy helps to minimize variance in sleep start time in normal aged adults and dementia patients with disrupted synchronization of the sleep/wake cycle. Melatonin's phase-shifting effects are also adequate to explain its efficacy as a therapy for circadian-related sleep disorders such as jet lag and delayed phase sleep syndrome.[45,46]

Treatment

Melatonin is surprisingly non-toxic, with a high level of safety. The lethal dose 50 (LD50) of melatonin for intraperitoneal injection in rats (1168 mg/kg) and mice (1131 mg/kg) could not

be attained following oral administration of melatonin (tested up to 3200 mg/kg in rats) or subcutaneous injection of melatonin (tested up to 1600 mg/kg in rats and mice).[94] Unlike many other compounds, the Merck Index (https://www.rsc.org/merck-index) does not include an LD50 for this chemical, and the Merck Safety data sheet specifies an LD50 of >3.2 g/kg for a single oral dosage in rats, indicating that it is not poisonous. Melatonin's extraordinary absence of toxicity in humans up to 100 mg has been demonstrated in dosage escalation trials.[95,96] Large dosages of melatonin have been used in a variety of illnesses with no negative consequences; in people, melatonin has a high safety profile and is generally well tolerated (see ref.[97]). According to a recent study, the number of US individuals aged 65 and over who have used melatonin in the last month has increased threefold over the last two decades.[98]

Melatonin is available as a medicament in both controlled-release and immediate-release formulations. For chronobiotic effects and sleep induction, immediate-release melatonin is the more effective formulation. Melatonin is very widely accessible as an over-The-counter dietary supplement in various countries, and as a food additive in the United States, where an estimated 3.1 million individuals (1.3% of US adults) consume it daily.[99] The manufacturing quality and bioavailability of melatonin and the potential contaminants differ widely in these unlicensed melatonin preparations.[100,101] As a result, although melatonin does not have significant toxicity at the provided levels, it is as yet impossible to make more comprehensive

conclusions about melatonin's potential undesirable side effects and especially those after long-term use.

A report on melatonin prescription stated that it was prescribed in 82% of communities in data obtained from 250 randomly chosen assisted living communities among 5777 inhabitants across seven states in the United States and weighted to an estimated 4043 communities and 152,719 people.[102] Prescriptions were more likely in facilities that had a registered nurse or licensed practical nurse on staff and whose health care supervisor was more supportive of non-pharmacologic approaches.

Adverse effects in melatonin clinical trials for primary or secondary sleep disorders were typically few, mild to moderate in intensity, and either self-limiting or resolved promptly after treatment discontinuation. In a systematic review and meta-analysis of the therapeutic effect of exogenous melatonin on depressive symptoms, 8 out of 19 studies discussed adverse events associated with melatonin administration (eg, headache, daytime sleepiness, dizziness, poor sleep, insomnia, a fuzzy feeling, altered bowel habits, and tachycardia), with six reporting data on adverse events.[103] The average rate of adverse events was 16.41% in the melatonin group and 14.73% in the placebo group. In this set of trials, a meta-analysis revealed no significant difference in adverse events between the melatonin and placebo groups.[103]

A comprehensive study of the negative consequences of oral melatonin supplementation has been conducted.[104] 26 of the 50 publications revealed no statistically significant adverse

events, whereas 24 reported at least one statistically significant adverse event. Adverse effects were typically small, brief, and readily handled, with tiredness, mood, or psychomotor and neurocognitive function being the most often reported. A few studies reported adverse effects including endocrine (eg, reproductive parameters, glucose metabolism) and cardiovascular (eg, blood pressure, heart rate) function, which appear to be regulated by dosage, dose timing, and possible interactions with antihypertensive medications.[104]

Uncontrolled melatonin usage in children has been noted as a growing health issue in the melatonin literature.[107] Between 2012 and 2021, the yearly number of pediatric melatonin ingestions climbed by 530%, with a total of 260,435 ingestions recorded. Pediatric hospitalizations and bad outcomes rose as well, owing mostly to a rise in inadvertent melatonin ingestions in children aged 5 years. Increased usage of over-The-counter melatonin (particularly when consumed like candy) may put youngsters at risk of harmful effects.[107]

Conclusion

Melatonin is a pleiotropic chemical agent with numerous cellular and systemic functions. Its anti-oxidant, anti-inflammatory, anticoagulopathic, and endothelium-protective properties are just a few examples. As far as sleep is concerned, melatonin is not meant for all types of sleep disorders but has a limited scope in adults and children. For example, melatonin is effective in treating circadian desynchronosis (eg, delayed sleep phase syndrome in children; advanced sleep phase syndrome and old-

age insomnia in the elderly, and shift work disorders and transitory jetlag disorder).[108,109] Additionally, other studies point to the fact that melatonin is useful in psychiatric and neurological (eg, autism, neurodegenerative diseases) dysfunctions.[42,110,111]

Melatonin clinical research has expanded beyond therapy of sleep problems into a variety of additional possible applications as our understanding of its physiological activities grows. Aside from the neurodegenerative diseases mentioned above, applications include cardiovascular disorders, cancer adjuvant treatment, side effects of conventional cancer treatments, treatment of liver diseases and injuries, fertility support, post-surgical recovery, gastrointestinal disorders, and many more. To minimize adverse effects and maximize possible advantages in future therapeutic applications, the intricacy of melatonin's interaction with the complete range of human physiological systems must be thoroughly elucidated.

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