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الميلاتونين : مراجعة لنشاط هذا الهرمون وتأثيراته على صحة الانسان

م.ماهر عبد الستار إبراهيم
maibraim68@uomosul.edu.iq
م.م.انتصار احمد سليمان
entesar.ahmed@uomosul.edu.iq
م.م. شيماء ميسر نايف
shaymaa.nayf@uomosul.edu.iq
م.م. عمر مؤيد ياسين شندالة
جامعة الموصل / كلية الطب

المستخلص:

أسيتيل-٥-ميثوكسي تريبتامين، المادة الكيميائية الأساسية التي تُكوّن الميلاتونين، هو هرمون يُنظّم الدورة اليومية. ينتج جسم الإنسان الميلاتونين طبيعيًا. يرتفع إنتاج الميلاتونين مساءً، مما يُؤدي إلى حالة من اليقظة خلال النهار والنوم ليلًا. فضلا عن تفاعله مع مستقبلات الميلاتونين (MT1 وMT2) يُعدّ الميلاتونين مضادًا قويًا للأكسدة، ويلعب دورًا في تنظيم دورة الخلية. الميلاتونين مادة كيميائية شائعة موجودة في جميع الكائنات الحية تقريبًا، بما في ذلك البكتيريا والبشر. في الفقريات، يُنتَج الميلاتونين مركزيًا بواسطة الغدة الصنوبرية، وهي عضو عصبي صماء، فضلا عن إنتاجه في الأنسجة الطرفية وعمله كإشارة ذاتية الإفراز وإشارة نظيرة إفرازية. بغض النظر عن الأنواع قيد الدراسة، يُنتَج هرمون الغدة الصنوبرية الميلاتونين دائمًا ليلًا، ولطول الليل تأثير مباشر على كل من إنتاج هذا الهرمون ومدة إفرازه. النشاط التكاملي الهرموني الجهازي الأساسي للميلاتونين، الذي يرتبط تركيبه ارتباطًا وثيقًا بدورة الضوء والظلام، هو مزامنة التكيفات الفسيولوجية والسلوكية مع النهار والفصول الجيوفيزيائية. انتظام إنتاجه اليومي، والفرق بين تركيزات الليل والنهار، وأساليب عمله المصممة خاصة، جميعها تؤثر على الإشارة اليومية. يُهيئ الميلاتونين استجابات التكيف النهاري من خلال تأثيرات مستقبلية تظهر فقط خلال النهار، عندما لا يكون موجودًا، ويُنسق فسيولوجيا

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التكيف الليلي من خلال تأثيرات فورية خلال فترة إفرازه اليومية. وبالمثل، يُهيئ الجهاز العصبي المركزي والجهاز الصماء للفصول القادمة من خلال التاريخ السنوي لمدة إفراز الميلاتونين اليومي.

الكلمات المفتاحية: الميلاتونين، أمراض هرمون الميلاتونين، الغدة الصنوبرية

Melatonin: A Review of The Hormone's Activity and its Effects on Human Health

Maher A. Ibrahim / Lecturer
maibraim68@uomosul.edu.iq
Assistant Lecturer/ Entesar Ahmed Sulliman
entesar.ahmed@uomosul.edu.iq
Assistant Lecturer/Shaimaa Muyasser Nayif
shaymaa.nayf@uomosul.edu.iq
Omar M. Shindala / Assistant Lecturer
University of Mosul/ College of Medicine

Abstract:

N-acetyl-5-methoxy tryptamine, the basic chemical that makes up melatonin, is a hormone that regulates the circadian cycle. Naturally, the human body produces melatonin. Melatonin production rises in the evening, resulting in a state of wakefulness during the day and sleep at night. In addition to interacting with melatonin receptors (MT1 and MT2), melatonin is a potent antioxidant and plays a part in cell cycle regulation. A common chemical found in practically all living things, including bacteria and humans, is melatonin. In vertebrates, melatonin is centrally generated by the pineal gland, a neuroendocrine organ, in addition to being produced in peripheral tissues and functioning as an autocrine and paracrine signal. Regardless of the species under consideration, the pineal hormone melatonin is always generated at night, and the length of the night has a direct impact on both the production of this hormone and the duration of its secretory events. The primary hormonal systemic integrative activity of melatonin, whose synthesis is closely correlated with the light/dark cycle, is to synchronize physiological and behavioral adaptations to the geophysical day and season. Its daily production regularity, the difference between day and

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night concentrations, and specially designed modes of action all influence the circadian signal. Melatonin primes the day adaptation responses through prospective effects that will only manifest during the day, when melatonin is not present, and coordinates the night adaptive physiology through immediate effects during its daily secretory episode. The central nervous and endocrine systems are similarly primed for the upcoming seasons by the yearly history of the duration of the daily melatonin secretory event.

Keywords: Melatonin, Diseases of melatonin hormone, Pineal gland

Introduction

1.Melatonin in Humans:

A substituted indoleamine (N-acetyl-5-methoxytryptamine) produced from tryptophan, melatonin is abundantly present in living, distantly related creatures (Manchester *et al*., 2000). To adjust biological processes to particular times of day or night, circadian clocks have evolved (Pfeffer *et al*., 2018). This clock regulates hormone production, body temperature, and the rhythms of sleep and wakefulness throughout the day. After receiving neurological signals from the retina and communicating the information on photoperiodic status to the cells of the suprachiasmatic nucleus (SCN), the pineal gland produces and releases melatonin, which distributes the time signal throughout the body (Alberts *et al*., 2008). Melatonin production lasts for twenty-four hours every day. However, More is produced and released into the circulation during the night, as seen in Figure (1) (Amaral *et al*., 2018). About 30 grams of melatonin are produced daily by an adult human, and the blood level peaks during the mid-dark phase. The pineal gland does not store melatonin; instead, it is discharged into the bloodstream and rapidly broken down in the liver (Pandi-Perumal *et al*., 2005). Under the action of cytochrome P450 monooxygenases A1 and A2, the liver hydroxylates melatonin at the C6 position. This results in the sulfate derivative, 6-sulfatoxymelatonin, which is subsequently eliminated from the body through urine (Cardinali *et al*., 2013). Melatonin is mostly carried by serum albumin in the circulatory system, while it can also be attached to hemoglobin and albumin. Melatonin's amphiphilic nature makes it simple to pass through morphophysiological and cellular barriers, such as the blood-brain barrier (Cruz *et al*., 2014). Melatonin is generally safe and nontoxic; even at high dosages, a small number of people have had moderate side effects such as headache, nausea, drowsiness, and dizziness (Andersen *et al*., 2016). The fact that human melatonin production declines with age-that is, women already experience a decrease in melatonin at menopause–and that it appears to be particularly low in some diseases, such as AD, cardiovascular problems, and some types of

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cancer, should not be overlooked. Additionally, a higher incidence of cancer and sleeplessness in elderly people has been associated with decreased melatonin production (Pandi-Perumal et al., 2008). The body has a large number of melatonin receptors. The *skin, gastrointestinal tract, reproductive and gestational tissues, immunological and endocrine systems, and the cardiovascular system all contain them (Slominski et al., 2012).* Disorders linked to dopamine may also benefit from melatonin treatment. Research indicates that it alters dopaminergic pathways implicated in human body movement disorders' coordination (Zisapel *et al*., 2001).

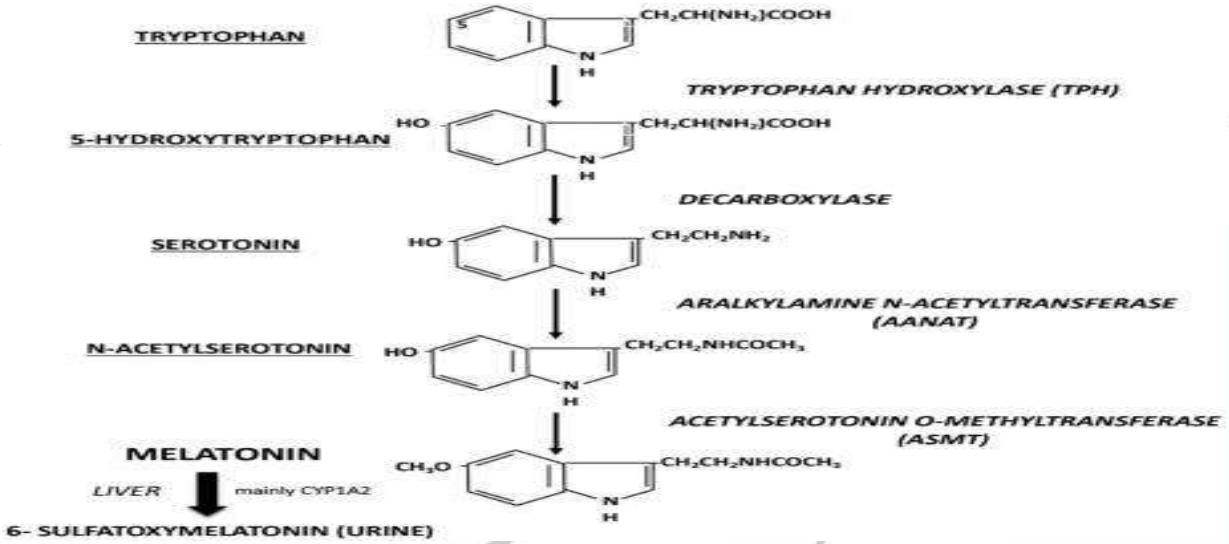

Figure (1): Melatonin synthesis pathway and hepatic metabolization (Amaral *et al*., 2018)

2.Melatonin as an Antioxidant:

The conversion of molecular oxygen to water is a necessary and inevitable process in organisms with aerobic metabolism. The respiratory system receives electrons from mitochondria, the primary source of energy processes, and uses them to create hydroxyl radicals ($OH^{\cdot}$), superoxide radicals ($OOH^{\cdot}$), and hydrogen peroxide radicals (H_2O_2). Reactive oxygen species (ROS) are free radicals that can harm DNA. This has an impact on the oxidation of lipids, amino acids, polyunsaturated fatty acids, and other cofactors as well as the physiology of aging (Hardeland, 2013). The primary response in several neurodegenerative, immunological, inflammatory, and mitochondrial disorders is radical creation (Hardeland, 2005). Another antioxidant that lessens electron leakage from the mitochondrial electron chain is glutathione, which is likewise stimulated by melatonin (Reiter *et al*., 2003). Humans have a 20% oxygen consumption rate in the brain, which leads to oxidative stress and the production of harmful free radical molecules in the body.

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Cell membranes, proteins, and DNA are all harmed by these extremely reactive compounds (Gupta *et al*., 2003).

3. Melatonin and the Brain:

The presence of melatonin in the brain was suspected because it is released into the cerebral ventricles both from the systemic circulation (Young *et al*., 1984). By directly influencing hippocampus neurons, melatonin regulates the creation of memories, which is linked to memory (Comai *et al*., 2014). Antinociceptive, depressive, anxiolytic, and locomotor modulating properties are all exhibited by melatonin (Uz *et al*., 2005). In addition to its anti-tumor, vascular, retinal, osteoblast, seasonal reproductive, ovarian, and neuroprotective effects, melatonin also lowers blood pressure and modulates pain (Li *et al*., 2013). Melatonin regulates the hypothalamus neurons' release of gonadotrophin-releasing hormone (GnRH), which in turn affects the synthesis of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (Dubocovich *et al*., 2003). Additionally, melatonin suppresses the expression of estrogen receptors and the activation of estrogen (Carlberg *et al*., 2000). Neurological conditions like Parkinsonism (Gunata *et al*., 2020), Alzheimer's illness (Vecchierini *et al*., 2021), Traumatic brain damage and brain edema (Dehghan *et al*., 2013), depression (Grima *et al*., 2018), cerebral ischemia (Tang *et al*., 2014), hyperhomocysteinemia (Karolczak *et al*., 2021), glioma (Lai *et al*., 2019), and phenylketonuria (Yano *et al*., 2016) have all been found to respond well to melatonin. Amyloidosis has been demonstrated to be inhibited by melatonin (Shukla *et al*., 2017).

4.Melatonin and Diabetes:

Melatonin's significance has grown due to its function in circadian and sleep regulation. Its significance in glucose tolerance and the risk or treatment of type 2 diabetes (T2D) has, nevertheless, increased recently. This is because of the partially detrimental effects of disrupted circadian rhythms on glucose metabolism and the partial identification of (T2D) risk alleles in (MTNR1B) (Mason *et al*., 2020). Obesity and diabetes have been linked to metabolic syndrome as a result of circadian rhythm disruption (Pulimeno *et al*., 2013). Melatonin's function in insulin secretion and glucose homeostasis has been extensively documented. Patients with type 2 diabetes have been found to have lower levels of melatonin (Prokopenko *et al*., 2009).

5.Melatonin and Cancer:

Over the past century, several studies have evaluated melatonin's oncostatic qualities against a range of cancers, including colorectal, breast, prostate, leukemia, pancreatic, and melanoma. The information currently available on neoplastic diseases makes it abundantly evident that the development of human cancers is influenced by the patient's immunobiological response, which includes the state of the immune and endocrine systems, in addition to the disease's biological features, such as gene overexpression, mutation, grading, and histology (Foon, 1989). These investigations yielded encouraging results regarding estrogen receptor-expressing breast cancer cells. After cardiovascular

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illnesses, cancer is the leading cause of death worldwide. According to statistics, lung cancer kills the most people of both sexes, whereas breast cancer kills the most women and prostate cancer kills the most men (Ferlay *et al*., 2013)(Fitzmaurice *et al*., 2015). In a similar vein, immune system dysfunction depends not only on immune cell activity but also on the pineal system's primary influence on the modulation of neuroendocrine physiology. The pineal gland secretes peptide hormones, many anticancer indole compounds, and most often, the melatonin hormone, which has anti-tumor and anti-proliferative properties (Brzezinski *et al*., 1997).

6. Melatonin and Obesity:

There is strong evidence linking the development of obesity to disruptions in the circadian rhythm. Although there is a reciprocal causal relationship between obesity and chronodisruption (Bray *et al*., 2012), melatonin and its agonist administration are useful in resetting circadian rhythms (Zawilska *et al*., 2009) and treating obesity-related illnesses. Additionally, melatonin or other drugs have been demonstrated to be useful in treating sleeping difficulties, which are among the many comorbidities associated with obesity (Cardinali *et al*., 2011). It is thought that melatonin contributes to energy metabolism and weight control. Melatonin's role in regulating fat mass and metabolism in the bodies of seasonal animals was initially investigated and shown it (Bartness *et al*., 1985), and it was connected to its role as a circadian and seasonal rhythm regulator (Arendt *et al*., 2006).

7.Melatonin and Hypertension:

Obese people are more likely than lean people to have hypertension and melatonin's function in controlling blood pressure has long been a topic of interest for academics (Poirier *et al*., 2006). Melatonin controls heart rate and arterial blood pressure (BP) in mammals (Simko *et al*., 2009). Since melatonin receptors have been found in the heart and several arterial beds (Capsoni *et al*., 1994), Individuals with hypertension show altered sympathetic and parasympathetic heart tone along with disrupted day-night cycles (Nakano *et al*., 2001). People with coronary heart disease, a consequence of hypertension, have lower levels of melatonin at night (Brugger *et al*., 1995). There is compelling evidence that individuals with daytime hypertension have disrupted circadian rhythms (Simko *et al*., 1995). SCN controls the pineal gland's production of melatonin (Buijs *et al*., 2003). Melatonin regulates the synthesis of SCN and other circadian rhythms by giving it feedback through its high-affinity receptors (Shukla *et al*., 2023), and as illustrated in Figure (2) (Konturek *et al*., 2007), The primary pacemaker instantly enhances circadian rhythms through melatonin production during the night, which is also essential for improving blood pressure (Scheer *et al*., 2004) and day-night rhythms (Cipolla-Neto *et al*., 2018).

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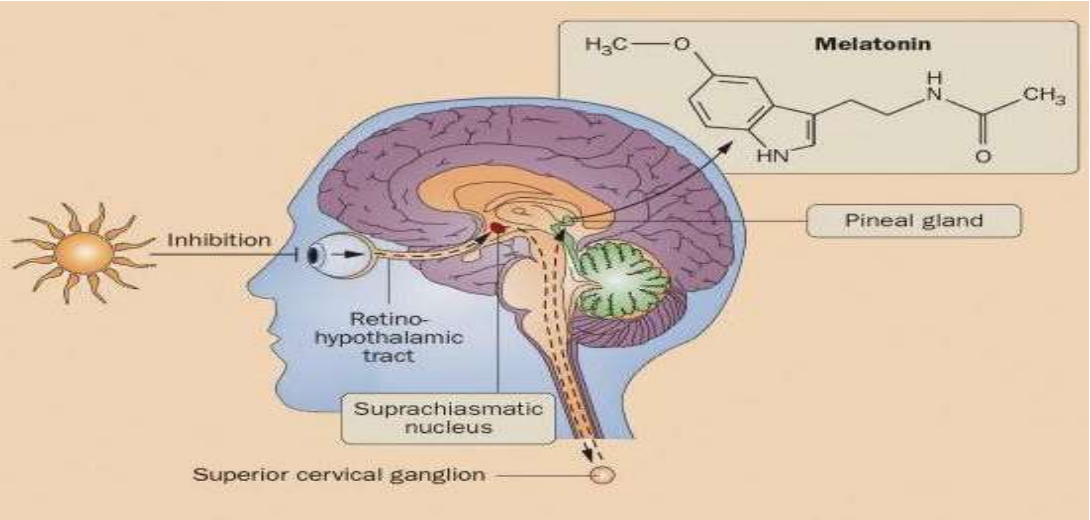
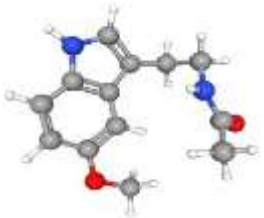
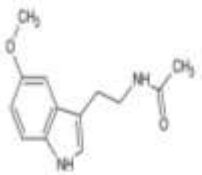


Figure (2): Melatonin, which causes humans to feel sleepy, is freely produced by the pinealgland (Konturek *et al*., 2007).

Table (1): Chemical Identifiers and Properties of Melatonin (Pub Chem. NCBI).

IUPAC name	Synonyms	Other Names		Formula		Molecular Weight	Formula Charge
N-[2-(5-methoxy-1H-indol-3-yl) ethyl] acetamide	Melatonin	5-Methoxy-N- acetyl tryptamine ; N-Acetyl-5-methoxy tryptamine 1-Iodo-5- methoxy naphthalene		C_{13} H_{16} N_2 O_2		232.278 g/mol.	0
Type	Isomeric Smiles	3D structure		2D structure		Melting Point	Mono Isotopic Mass
Non-Polymer	CC(=O)NCCC1=CNC 2=C1C=C (C=C2)OC					Between: 116.5 °C — 118 °C	232.12118 gm./mol.
Aromatic Bond Count	Bond Count	Boiling Point	Solvent	Atom Count	pH	Chemistry Spider ID	Density
10	34	512.8 °C	Water	33	7	872	1.175 m./cm^3

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8.Melatonin and The Immune System:

The immune system and the pineal have a strong relationship (Carrillo-Vico *et al*., 2005) . Immunosuppression is induced in many species by pinealectomy or any experimental procedure that prevents melatonin synthesis and secretion; melatonin treatment reverses this status. The immune system is boosted by melatonin (Carrillo-Vico *et al*., 2006). In vivo, melatonin triggers antibody-dependent reactions, activates cell-dependent cytotoxicity, and stimulates T lymphocytes, monocytes, natural killer cells, and even granulocytes. Melatonin stimulates the synthesis of inflammatory cytokines and nitric oxide in animal models, human research, and in vitro tests. The effects of glucocorticoids on immune function in vitro seem to be modified by melatonin at physiological and pharmacologic dosages. It has been demonstrated that melatonin influences the control of lymphocyte numbers (Lissoni *et al*., 2008). Melatonin receptors have been demonstrated to be expressed on the cell membranes of T cells. Interleukin 2 and interferon γ are among the cytokines secreted along with opioid cytokines when melatonin hits these receptors. Melatonin exposure has been demonstrated to increase the production of interleukin 1, interleukin 6, and interleukin 12 by human monocytes (Lissoni, 1999).

9. Melatonin and Rheumatoid Arthritis:

In northern countries, where the population is exposed to higher melatonin concentrations due to longer nights and longer and heavier winters, rheumatoid arthritis appears to be more prevalent and more severe than in southern Mediterranean countries (Cutolo *et al*., 2005). Melatonin's pro-inflammatory effects during the night may be linked to morning stiffness in rheumatoid arthritis (Cutolo *et al*., 2003) (Cutolo *et al*., 2008). These findings are consistent with melatonin's immune-boosting effects. Compared to healthy controls, rheumatoid arthritis patients have greater nocturnal melatonin levels (Sulli *et al*., 2002). High levels of melatonin have been found in rheumatoid arthritis patients' articular fluid, and melatonin

receptors have been found in the synovial membrane's macrophages. The nighttime and early morning peaks of interferon γ, interleukin 2, interleukin 6, interleukin 12, and tumor necrosis factor α production coincide with the melatonin peak and the lowest point of cortisol secretion (Petrovsky *et al*., 1998). These findings are consistent with the theory that melatonin boosts immune system activation and cytokine production.

10. Melatonin and Bone Remolding:

Bone is a dynamic tissue undergoing remodeling throughout life, and this remodeling requires a balance between deposition of new bone by osteoblasts and resorption of old bone by osteoclasts (Cardinali *et al*., 2003). Bone modeling requires the interaction between multiple bone cells (osteoblasts/osteoclasts/osteocytes) to renew, maintain, or adjust bone strength and/or mineral homeostasis in response to changing environmental influences. There are four distinct phases to this process: activation, resorption, reversal, and formation with resorption and formation taking place via osteoclasts and osteoblasts, respectively (Kotlarczyk *et al*., 2012). Bone remolding processes are mediated by hormones, cytokines, growth factors and other molecules (Ostrowska *et al*., 2003). One of the hormones modulating bone formation and resorption is melatonin. It is hypothesized that melatonin, perhaps through three principle actions, modulates bone metabolism. Firstly, melatonin directly affects the actions of osteoblast and osteoclast. Numerous studies documented that melatonin increases pre-osteoblast/osteoblast/osteoblast-like cell proliferation, promotes the expression of type I collagen and bone marker proteins (e.g., alkaline phosphatase, osteopontin, bone sialoprotein and osteocalcin), and stimulates the formation of a mineralized matrix in these cells (Radio *et al*., 2006) (Satomura *et al*., 2007) (Sethi *et al*., 2010).

11. Melatonin and Osteoporosis:

Osteoporosis was defined as "a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" by the World Health Organization (Lippuner, 2012). It has been a major public

health problem for healthy adults over the age of 55 years and with a major prevalence in women. About 50% of women will go on to develop an osteoporotic fracture, compared to 25% of men (Gallagher *et al*., 2010). Without an intervention strategy, it is likely that the amount of people with osteoporosis will increase threefold over the next 25 years because of an increase in the aging population worldwide (Elffors *et al*., 1994). The possible etiologic role of melatonin in osteoporosis. Nocturnal plasma melatonin levels decline with age. It has also been reported that melatonin secretion decreases sharply during menopause, which is associated with post-menopausal osteoporosis (Vakkuri *et al*., 1996) (Bellipanni *et al*., 2001). A correlation between decreased plasma melatonin levels and an increased incidence of bone deterioration as seen in post-menopausal women has been examined (Ostrowska *et al*., 2001). Melatonin significantly reduced the number of apoptotic cells in nucleus pulposus and epiphyseal cartilage of the spinal column and the expression of inducible nitric oxide synthase (iNOS), which increased after ovariectomy. iNOS plays a pivotal role in the pathogenesis of osteoporosis. It generates nitric oxide, a free radical contributing to the imbalance between bone resorption and formation caused by estrogen depletion (Oktem *et al*., 2006).

12. Melatonin and the Teeth:

Melatonin concentrations change in a specific manner during the lifespan of human (Karasek, 2007). Melatonin is a lipophilic hormone that crosses the placenta barrier easily, thus, prenatally, the fetal obtain melatonin from mothers (Tamura *et al*., 2008). During the first two weeks of life, melatonin could be detected in infant blood, but there was no daily rhythm. During the first two weeks of life, melatonin could be detected in infant blood, but there was no daily rhythm (Kennaway, 2000) (Kivela *et al*., 1990). The nocturnal rise of melatonin concentrations appears in the sixth to eighth week of life, and its circadian rhythm seems to be well established around three months of age (Attanasio *et al*., 1986). From about six years old, permanent teeth begin to replace the deciduous teeth until 10 –12 years old. Since the time course of melatonin secretion and the progression of tooth development run in parallel, the possible role of melatonin in tooth development should be

worthy of study. The most striking feature of the melatonin is the circadian rhythm which is controlled by the endogenous circadian clock, suprachiasmatic nucleus (SCN) and environmental light. Many studies also reported that tooth development exhibits circadian rhythmicity (Iinuma *et al*., 2002) (Ohtsuka-Isoya *et al*., 2001). Periodic growth incremental lines are found universally in the dental tissues of animals, especially in the dentine and enamel, which reflect circadian rhythms of tooth growth (Smith, 2006).

13. The Effect of Physical Exercise on Melatonin Production:

One of the main disadvantages in assessing the synchronizing effect of exercise on the human circadian system is the inability to directly measure its phase-shifting effects of the central pacemaker. Instead, the levels of one of the main output signals of the clock, melatonin, are commonly used to report the phase-shifting effects of exercise on the circadian clock. In addition, acute and chronic physical exercise also modifies plasma melatonin levels. In this regard, there is some controversy about the effects of physical activity on the endogenous profile of melatonin secretion. It has been shown that melatonin levels increase (Smith *et al*., 1984) (Carr *et al*., 1981) (Skrinar *et al*., 1986), decrease (Monteleone *et al*., 1990) (Monteleone *et al*., 1992), or remain unaffected by exercise (Miyazaki *et al*., 2001) (Elias *et a*l., 1993). Such conflicting findings may be due to differences in lighting conditions and the time of day at which the study subjects exercised (Paredes *et al*., 2005). There is now evidence that exercise of quite varied durations and intensities can mediate phase shifts in rhythms in secretory products, independent from those of light, in populations differing widely in athletic status and age (Atkinson *et al*., 2007).

14. Melatonin and Ageing:

Aging is associated with manifold changes. These comprise declined secretion of hormones such as melatonin (Bubenik *et al*., 2011) (Hardeland, 2012), reduced activities of aging-related factors such as sirtuin-1 (SIRT1) (Hardeland, 2018), deterioration of the circadian oscillator system (Yamazaki *et al*., 2002) (Hardeland , 2017), multiple alterations in the immune system that is frequently shifted toward the proinflammatory side

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(Ginaldi *et al*., 1999) (DelaRosa *et al*., 2006) (Dewan *et al*., 2012) (Cardinali *et al*., 2008), and many more deviations of cell biological relevance. This is largely based on the pleiotropy of both melatonin (Hardeland *et al*., 2011) and the circadian system (Gachon *et al*., 2004) (Buijs *et al*., 2006) ([Hardeland, 2015). However, these relationships are highly complex, include actions in opposite directions, and cannot be interpreted in reductionist ways. Besides aging, there are many age-related diseases that have as their basis, at least in part, free radical damage. Many of them involve the central nervous system because of its high vulnerability to oxidative attack. Alzheimer's and Parkinson's diseases are examples. Alzheimer's disease is the most common cause of progressive cognitive decline in the aged population. It has been demonstrated that melatonin concentrations are decreased in Alzheimer's patients (Mishima *et al*., 1999). Parkinson's disease is a major neurodegenerative disorder characterized by the progressive deterioration of dopamine-containing neurons in the pars compacta of the substantia nigra in the brain stem (Fearnley *et al*., 1991). Due to the oxidation of dopamine (Fahn *et al*., 1992). There is evidence that melatonin may reduce dopamine auto-oxidation under experimental conditions (Miller *et al*., 1996). Melatonin was also able to overcome increased lipid peroxidation that occurred in the striatum, hippocampus and midbrain after l-methyl-4-phenyl- 1,2,3,4-tetrahydropyridine injection, the most commonly used drug to produce a model of Parkinson's disease (Acuña-Castroviejo *et al*., 1997). Moreover, using another animal model which is a surrogate for Parkinson's disease in humans, namely treatment with 6-hydroxydopamine, melatonin was shown to reduce the cytotoxicity of this agent (Mayo *et al*., 1998). Melatonin has been shown to lower neural damage due to amino levulinic acid characteristic of acute intermittent porphyria, another disease in which free radicals may account for much of its pathophysiology (Cameiro *et al*., 1998).

15. Conclusion:

A lack of melatonin is frequent as people age and is linked to several illnesses with diverse causes. Furthermore, nocturnal light suppresses melatonin secretion, which can be problematic while working shifts. In

terms of the variety of melatonin's effects, melatonin deprivation has an impact on many physiological processes. If subnormal melatonin levels are caused by neurodegeneration in the SCN, which controls the mammalian pineal gland and to which this hormone is feeding back, methylindole injection cannot fully re-adjust the circadian oscillator system. Although it hasn't been shown yet, effects on certain peripheral oscillators are not ruled out. Melatonin may have beneficial effects on other physiological processes that are accessible without the help of the circadian oscillator system but which are not necessarily free of the regular oscillations that occur in the body. Examples include gastrointestinal functioning, immunological modulation, metabolic syndrome correction, and antioxidant protection. However, before prescription, many contraindications or potential causes of concern should be taken into account. These include use during pregnancy, in patients with autoimmune diseases, liver dysfunctions, CYP1A2 inhibitor-containing medications, in children with severe or otherwise uncontrollable cases, and, if the issue is not resolved, in Parkinson's disease and irritable bowel syndrome type II, both of which have been interpreted as disorders of melatonin overproduction. Melatonin, as an endogenous hormone, participates in many physiological and pharmacological processes. The above analyzed data indicate that melatonin may be involved in the development of the hard tissues bone and teeth. Decreased melatonin levels may be related to bone disease and abnormality. Due to its ability of regulating bone metabolism, enhancing bone formation, promoting osseointegration of dental implants and cell and tissue protection, melatonin may be used as a novel mode of therapy for augmenting bone mass in bone diseases characterized by low bone mass and increased fragility, bone defect/fracture repair and dental implant surgery. The aging process is multifactorial, and no single element seems to be of basic importance. It seems, however, that although melatonin cannot be univocally recognized as a substance delaying aging, some of its actions may be beneficial for the process of aging. It is possible that the age-related decline in melatonin secretion may have various consequences including sleep inefficiency, circadian rhythm dysregulation, reduced antioxidant protection, depressed

immune function, and possibly others. However, the precise role of melatonin in the aging process remains to be determined.

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