Melatonin and Its Effects on the Human Body

Subjects: Medicine, Research & Experimental

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Melatonin is the main hormone that regulates the sleep cycle, and it is mostly produced by the pineal gland from the amino acid tryptophan. It has cytoprotective, immunomodulatory, and anti-apoptotic effects. Melatonin is also one of the most powerful natural antioxidants, directly acting on free radicals and the intracellular antioxidant enzyme system. Furthermore, it participates in antitumor activity, hypopigmentation processes in hyperpigmentary disorders, anti-inflammatory, and immunomodulating activity in inflammatory dermatoses, maintaining the integrity of the epidermal barrier and thermoregulation of the body.

melatonin photoprotection skin aging sleep disorders allergy allergic rhinitis atopic dermatitis chronic urticaria androgenetic alopecia melasma

1. Introduction

Melatonin is a hormone that plays many useful roles in organisms and can also be used for therapeutic purposes.

It is one of the most powerful natural antioxidants, directly acting on free radicals and the intracellular antioxidant enzyme system [1]. It also has cytoprotective, immunomodulatory, and anti-apoptotic effects [2]. One of melatonin's most important roles in humans is the initiation and maintenance of the sleep cycle. Due predominantly to this positive influence on sleep, melatonin can be used as a therapeutic supplement and in the treatment of various diseases accompanied by sleep disturbances.

2. The Melatonin Molecule and Its Effects on the Human Body

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone that plays a central role in the sleep cycle. It is mostly produced by the pineal gland from the amino acid tryptophan, and it is secreted into the blood and cerebrospinal fluid [1][3]. Other tissues aside from the epiphysis also produce melatonin, including the retina, bone marrow, gonads, and gastrointestinal mucous, as well as the skin, but the role of melatonin in these tissues is still largely unknown [1].

The process of melatonin synthesis is complex. The pineal gland is a neuroendocrine gland located in the brain that contains melatonin-producing cells (pinealocytes). The synthesis of melatonin begins with the amino acid

tryptophan, which, with the action of the enzyme tryptophan hydroxylase, is transformed into 5-hydroxytryptophan. This is then transformed into serotonin. Serotonin is acetylated (with the enzyme arylalkylamine N-acetyltransferase) into N-acetylserotonin, which is then converted into melatonin [1]. The process of melatonin synthesis in the pinealocytes of the pineal gland is under the control of the suprachiasmatic paraventricular nuclei of the hypothalamus; however, melatonin synthesis is primarily controlled by the circadian system rhythm, by which melatonin is produced daily in synchronization with the light-dark cycle [1].

In 1975, it was discovered that the production of melatonin in humans follows the circadian rhythm and that nighttime concentrations of plasma melatonin are ten times higher than daytime concentrations [1]. Light (most often from the blue spectrum) inhibits melatonin synthesis in such a way that it activates the breakdown of melanopsin (a photopigment that absorbs light in retinal ganglion cells) and inhibits melatonin synthesis via the retinohypothalamic pathway [4][5]. Darkness leads to the activation of postganglionic sympathetic neurons, which affects the secretion of noradrenaline and enables the further synthesis of melatonin. At the same time, the enzyme that participates in the synthesis of melatonin, N-acetyl-transferase, is activated [1]. Therefore, melatonin is not stored inside the pinealocytes and is released in the form in which it was synthesized. Melatonin is a lipophilic molecule that easily diffuses into the cerebrospinal fluid of the central nervous system during the night, as well as into the bloodstream. In the bloodstream, melatonin is mostly bound to albumins (approximately 70% of total melatonin), and a smaller part of the molecule is found in its free form [6]. In the liver, melatonin is metabolized into 6-hydroxymelatonin by cytochrome P450 and conjugated into 6-sulfatoxymelatonin, which is subsequently excreted through urine [7].

In humans, melatonin achieves its effects via G-protein coupled membrane receptors, nuclear receptors, calmodulin, and antioxidant properties. Membrane receptors are located in the cerebrum and peripheral organs (spleen, thymus, lymphocyte cells, etc.) [2]. There are two membrane receptor types: the high-affinity Mel1a receptors (ML1, ML1a, MT1, and MTNR1A) (which are primarily located at various sites in the brain and skin) and low-affinity affinity Mel1b receptors (MT2, ML1b, and MTNR1B), also located at various sites in the brain [2]. Concerning signaling, post-receptor signaling mechanisms are performed via the inhibition of adenylate cyclase and the reduction of cAMP, as well as Mel1b receptors inhibiting guanylate cyclase and reducing cGMP [2]. Regarding nuclear receptors, there are two receptor types: the orphan receptor retinoid Z receptor (RZR)- β and the retinoic acid-related orphan receptor (ROR)-α, β, and γ [2]. They are necessary for the mast cells' function and their role in inflammation, immune response, cell proliferation, and apoptosis mechanisms [2]. Moreover, they can be associated with the transcription of nuclear factor-κB (NF-κB) as the post-receptor signaling pathway [2]. Genetic processes are very important for these mechanisms. During inflammation, NF-κB induces endogenous melatonin synthesis from inflammatory cells for mast cell regulation (by stimulating the arylalaminamine-acetyltransferase enzyme) [2]. Stimulation of mast cells is important for melatonin to have an effect: While melatonin administration in the presence of unstimulated mast cells does not affect the endogenous melatonin level, in the presence of stimulated mast cells, it inhibits NF-κB and reduces the endogenous melatonin level in a dose-dependent manner. It could be a mechanism that can stop inflammatory responses [2].

As mentioned above, melatonin has significant antioxidant and cytoprotective effects. It is a free radical scavenger and an antioxidant that stimulates superoxide dismutase, glutathione peroxidase, and glutathione reductase enzymes. It also neutralizes molecules such as hydrogen peroxide, oxygen radicals, peroxynitrite anion, nitric oxide, and hypochloride acid [2].

Melatonin also has significant immunomodulatory effects. Its receptors are also present in human lymphocytes, and as explained in the literature data, lymphocytes synthesize melatonin, secrete it, and respond to melatonin [2]. Melatonin also participates in T cell differentiation and activation and promotes the production of IFN-γ and IL-2 (via the membrane and nuclear receptors); thus, it may activate human Th1 cells [2]. As an immunomodulatory hormone, it influences Th1, Th2, Th17, and Treg responses, in a different manner—in the case of immunosuppression, melatonin inhibits the Th1, Th17, and Treg responses, while in the case of immune exacerbation, it stimulates the Treg pathways [2]. Its immunomodulatory mechanism allows the production of various cytokines (such as IL-1, IL-2, IL-6, and IL-10) and it increases T cell activity and regulates cell proliferation; thus, it indirectly increases antibody production. Increased IFN-γ and IL-2 create a positive feedback loop for the synthesis of melatonin and IL-12 (increased IL-2 levels lead to increased Natural Killer (NK) activity) [2].

Melatonin serves an antiapoptotic effect purpose, as has been confirmed in breast cancer. Calmodulin-mediated processing is often associated with breast cancer development, and it has been suggested that melatonin facilitates dephosphorylation and nuclear import of histone deacetylase 4, leading to the inactivation of calmodulin-dependent protein kinase II alpha and apoptosis [2].

Due to the many different roles that it plays in the body, there are also (three) different ways in which melatonin values can be measured/assessed for research purposes—in the blood, urine, or saliva [8][9]. In the blood, the highest melatonin concentrations are reached between 00:00 h and 05:00 h at night, after which they begin to fall again [8]. In the urine, values of 6-sulfatoxymelatonin reflect melatonin levels in plasma, which allows the melatonin concentration in urine to be measured by a less invasive method that is also reliable for assessing both pineal function and melatonin production [7]. Melatonin can also be excreted in saliva, but only in the free form of melatonin that is not bound to albumins [7]. When measuring melatonin, it is important to consider exactly when and how it is measured. According to research the deviation between salivary melatonin and plasmatic melatonin can vary as much as 36% [9]. The concentration of salivary melatonin also depends on the part of the day in which it is measured—values range between 1 and 5 pg/mL, while nighttime values can be between 10 and 50 pg/mL [8].

3. Melatonin as a Therapeutic Option

Melatonin is an important physiological sleep regulator, and adequate production is very important for achieving good-quality sleep. The most common sleep-related disorders include difficulty falling asleep, early waking, and a feeling of fatigue that disrupts daily activities and consequently leads to difficulties in the individual's work and social life [10][11]. Several studies have shown that the exogenous intake of melatonin for diseases accompanied by sleep disorders increases the body's concentrations of melatonin and favorably affects the quality of sleep; therefore, the systemic application of melatonin for sleep disorders has become generally accepted [12][13][14][15][16]

[17][18]. Factors that have a negative effect on melatonin production are aging, the presence of certain diseases (e.g., malignant diseases, diabetic neuropathy, and Alzheimer's disease), and the use of certain drugs (e.g., β-blockers, clonidine, naloxone, and anti-inflammatory drugs). In these conditions, melatonin production is reduced, and individuals often have accompanying sleep disorders [10][11].

The most common indication for systemic use of exogenous melatonin is sleep disorders (insomnia). Melatonin synchronizes circadian rhythms and improves sleep onset, duration, and quality [12]. Melatonin can be taken as a supplement, which is well tolerated and has no known short-term or long-term adverse effects [13][19]. Melatonin is classified as a dietary supplement that is not regulated by the Food and Drug Administration and can be purchased in any dose without a doctor's prescription [13][19]. In Europe, melatonin has been approved for the management of primary insomnia in adults over the age of 55 [13].

There are several ways to administer melatonin, including tablets, oral solutions, sprays for the nose or oral mucosa, and in the form of skin patches, topical creams, or hydrogels [20][21]. The most common side effects of systemic melatonin use are mild and include headache, nausea, dizziness, and drowsiness [20]. However, caution is required in the case of polypharmacy (the simultaneous use of a large number of drugs) since melatonin use can affect the metabolism of drugs that are also metabolized by cytochrome p450 (such as anticoagulants and antithrombotic drugs, anticonvulsants, oral contraceptives, oral hypoglycemics, and immunosuppressants) [20]. According to recent recommendations by an expert group (International Expert Opinions and Recommendations) on the use of melatonin for insomnia, 2–10 mg of slow-release melatonin taken one to two hours before bedtime is recommended [14].

There are also various other indications for melatonin use. For jet lag, a dose of 0.5–1.0 mg of systemic melatonin can be used [15]. Because of its antioxidant and anti-inflammatory properties, melatonin is also used as a natural dietary supplement for athletes for sleep cycle regulation and to protect muscles from oxidative stress [22]. Its effectiveness has also been proven (according to clinical cohort studies) in children with autistic disorders, women with premenstrual dysphoric disorder, hypertensive patients taking beta-blockers, and children with attention deficit hyperactivity disorder (ADHD) [23][24][25][26].

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