Melatonin and Health: Insights of Melatonin Action, Biological Functions, and Associated Disorders

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KEY POINTS FROM THIS ARTICLE:

1) "Melatonin is [an] ubiquitous molecule with wide distribution in nature and is produced by many living organisms."

2) "In human beings, [the] pineal gland is the major site for melatonin production and to lesser extent by retina, lymphocytes, bone marrow, gastrointestinal tract, and thymus."

3) Melatonin is a neurohormone that is released into circulation where it "penetrates all tissues of the body." **[Important]**

4) "Melatonin synthesis and secretion is suppressed by light and enhanced by dark."

- "Melatonin production and release peak during the dark hours and fall during the day in all species studied."

5) Melatonin exerts its effects through the melatonin receptors which are expressed by many organs.

6) "Melatonin helps to regulate sleep patterns and circadian rhythms."

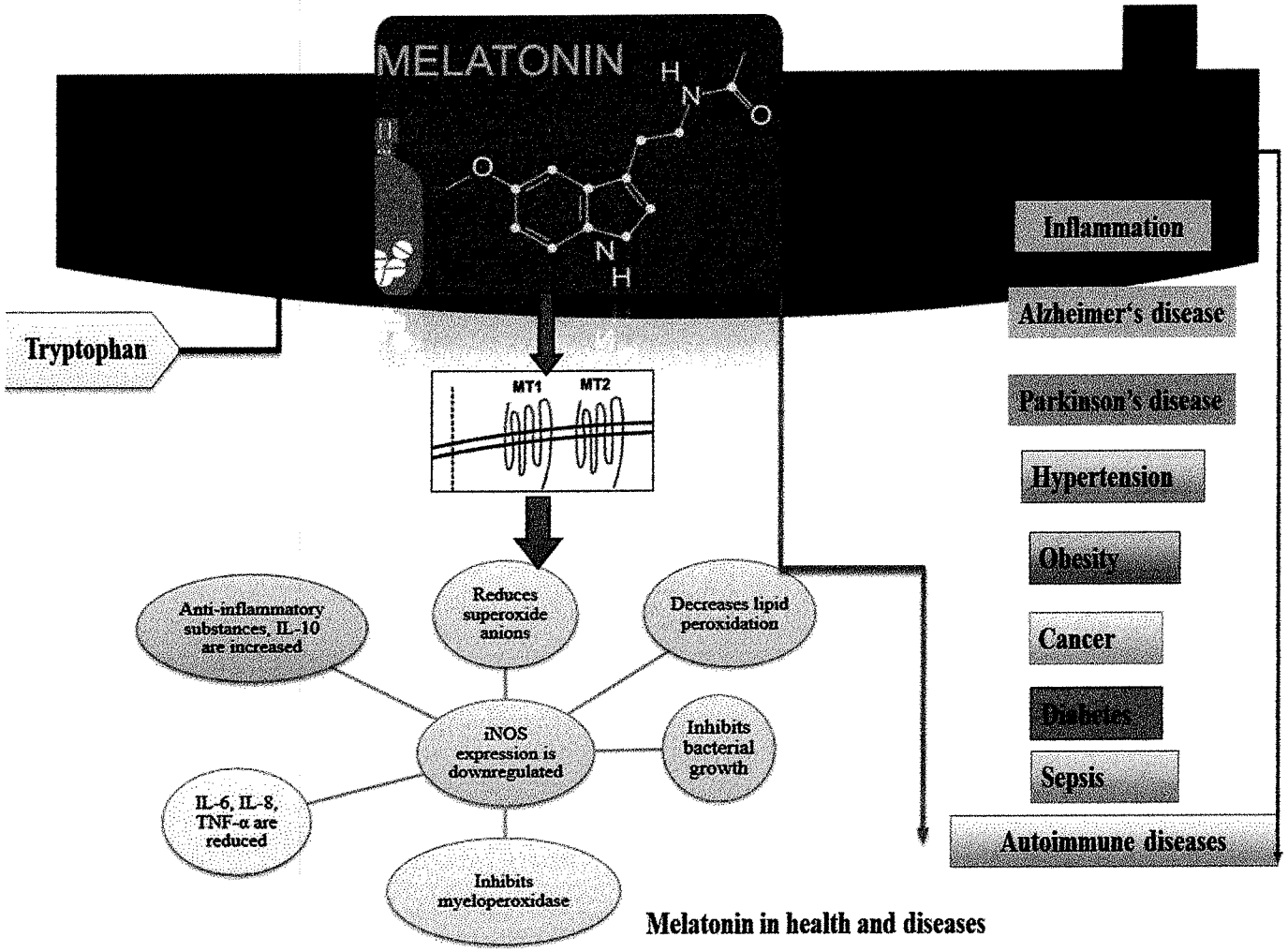
7) "Melatonin acts as an antioxidant and scavenges excessive free radicals generated in the body."

8) Other benefits of melatonin include immune regulation, reproduction, puberty timing, and mood disorders.

9) "Deficiencies in the production or synthesis of melatonin have been found to be associated with onset of many disorders like breast cancer and neurodegenerative disorders."

- Melatonin has promising benefits in "treating various diseases like inflammatory, gastrointestinal, cancer, mood disorders, and others."

10) "Melatonin could be used as a potential analgesic drug in diseases associated with pain and it has quite a promising role there."



Graphical Abstract

11) Melatonin is predominantly synthesized and secreted by the pineal gland through hydroxylation of the essential amino acid *tryptophan*.

- Melatonin is also synthesized in very small quantities by the retina, gastrointestinal tract, and lymphocytes.

12) Traces of melatonin have been identified in plants:

- "The levels in these plant parts are too low for supply to human beings."
- "In plants, melatonin presence is universal," but concentrations are small, from picograms to micrograms.
    - The highest listed plant source, by a large margin, is black pepper.

- In plants, melatonin provides reduction of oxidative stress, improves resistance to stress, stimulates immune system, and is an "antistress agent against drought, toxic chemicals, salinity, heavy metal stress, UV radiation, high and low ambient temperatures, water stress, and light-induced stress."

- Melatonin provides plants with antibacterial, antiviral, and antifungal effects.

13) Pineal Gland:

- The pineal gland lacks a blood–brain barrier.

- The pineal gland produces but does not *store* melatonin.

- Melatonin secretion from the pineal gland is controlled by the superchiasmatic nucleus.

14) "Due to high lipid and water solubility of melatonin, its distribution is facilitated through most cell membranes including the blood–brain barrier."

- When released into circulation, [melatonin] easily gains entry into different body fluids, cellular compartments, and tissues.

15) "The melatonin in circulation can travel to all tissues in the body and easily modulate activity of the brain by crossing the blood–brain barrier."

16) Melatonin is *decreased* by:
- Light, especially bright light of > 30lx and wavelength of 460–480 nm (blue]).
- Ibuprofen, Aspirin
- Alcohol
- Smoking

17) Melatonin is *increased* by:
- Vigorous exercise
- Caffeine

18) "Melatonin is a multifaceted hormone exhibiting its effects through endocrine, autocrine, and paracrine modes."

19) Melatonin directly competes with calcium for binding to the intracellular secondary messenger *calmodulin* "which may also be responsible for anti-proliferative effect observed in cancers."

20) "The receptors of melatonin are widely distributed and are found in brain, cardiovascular system, aorta, cardiac ventricular wall, cerebral and coronary arteries, gallbladder, liver, retina, parotid gland, appendix, cecum, colon, skin, pancreas, platelets, immune system cells, kidney, brown and white adipocytes,

breast and ovarian granulosa cells, epithelial cells of prostrate, fetal kidney, and placental myometrium."

21) Melatonin is a strong antioxidant and is directly responsible for scavenging of the free radicals.

- Melatonin binds to the transition metals, preventing the formation of hydroxyl radicals.
- "Melatonin being highly concentrated in mitochondria protects proteins, lipids, and DNA from oxidative damage caused by free radicals." **[Important]**
- "The antioxidant role of melatonin is of paramount importance for mitochondrial activities where free radical production is a natural phenomenon because of cellular respiration." **[Important]**
- "Apart from its antioxidant role, melatonin plays a prime role not only in regulating respiratory chain complexes I and IV but also prevents the mutation and deletion of mitochondrial DNA." **[Important]**
- Melatonin prevents DNA damage.

22) Melatonin and the Brain

- "Melatonin has a diverse role and mostly affects the brain."
- It regulates circadian rhythm, seasonal adaptation, and puberty development.
- "Melatonin is associated with memory by regulating memory formation by directly affecting hippocampal neurons."

23) Melatonin "controls posture and balance of the body."

24) "Melatonin has neuroprotective, blood pressure lowering, modulating pain, vascular, retinal, osteoblast differentiation, seasonal reproductive, ovarian physiology, anti-tumor, and antioxidant properties."

25) "Melatonin has been shown to be very helpful in treating neurological disorders such as Parkinsonism, Alzheimer's disease, brain edema and traumatic brain injury, depression, cerebral ischemia, hyperhomocysteinuria, glioma, and phenylketonuria."

26) A Basic Model:

- "In humans, there is a high consumption of oxygen in the brain i.e., 20% and this increased consumption causes oxidative stress and generates toxic free radical molecules in the body."

- "These high reactive molecules damage DNA, proteins, and cell membrane."

- "The presence of considerable amounts of fat in membrane and myelin sheaths enhance the damage by free radicals thus creating an imbalance between oxidants and antioxidants."

- "The damage by reactive oxygen species (ROS) results in a compromised blood–brain barrier and the enhanced expression of excitatory neurotransmitter glutamate to extracellular space thereby triggers the depolarization."

27) Melatonin supplementation enhances superoxide dismutase (SOD) and glutathione peroxidase (GPx) activity. **[Important]**

- "Melatonin exerts its neuroprotective potential through its antioxidant power."

28) "The onset of stroke results in the massive destruction of cells with enhanced production of ROS and inflammation."

- The neuron survival is dependent on an active energy metabolism; hence, any obstruction in the cerebral flow of blood restricted glucose and oxygen supply that results in ischemic stroke and can have catastrophic implication on neurons.

- An anoxic depolarization and activation of the voltage-gated calcium channels "results in the intracellular accumulation of Ca2+ which initiates cell injury."

- Administration of melatonin results in reduction of cerebral infarction damage.

29) Melatonin also helps in Ca2+ homeostasis and reduction in extracellular glutamate levels. **[Important]**

30) Melatonin and Hypertension

- "Melatonin regulates heart rate and arterial blood pressure (BP) as the receptors for melatonin are identified in heart and different arterial beds."

- Individuals suffering from coronary heart disease show reduced melatonin levels during the night hours.

- "Subjects with hypertension exhibit disturbed day–night rhythms with changes in sympathetic and parasympathetic cardiac tone."

- A 2006 study reported that administration of melatonin (2 mg/day for 4 weeks) at bed time reduced the nocturnal systolic and diastolic BP.

- "The intake of melatonin in individuals with nocturnal hypertension reduced systolic and diastolic blood pressure."

31) Melatonin and Diabetes

- Melatonin has many roles in insulin secretion and glucose homeostasis.
- "The melatonin administration modulates the synthesis of insulin in the pancreatic β-cells as well as enhancing the optimistic insulin effect."

32) Melatonin and Cancer

- "Cancer accounts for the most number of deaths globally after cardiovascular diseases."
- "The availability of data on neoplastic diseases up to now clearly suggests the progression of human cancers not only depends on disease biological characteristics like mutation, overexpression of genes, grading, and histology, but also on the immunobiological response of the patient that includes immune and endocrine system status as well."
- "These studies provided a promising result in the breast cancer cells that express estrogen receptors."
- "The malfunctioning of the immune system does not rely on immune cell activity but also on modulation of neuroendocrine physiology, that is primarily influenced by the pineal system."
- "The pineal gland exerts anti-tumor anti-proliferative functions through secretion of peptide hormones and various anticancer indole molecules and mostly widely the melatonin hormone."
- "The associations between melatonin and cancer have been studied for many decades and a large number of epidemiological studies favor the protective potential of melatonin against cancer."
- "Studies have demonstrated the preventive role of melatonin in different types of cancers."
- "Several other studies reported the protective role of melatonin against mammary cancer."

33) Melatonin and Obesity

- "There is substantial evidence connecting impaired circadian clock and obesity development."

- Melatonin is "effective in circadian rhythm resetting and correcting disorders associated with obesity."
- "Melatonin is hypothesized to play a role in energy metabolism and body weight management."
- Any rise in circulating melatonin levels is related with a loss in body fat mass.

34) Melatonin and Autoimmunity

- "Multiple studies have linked the onset of immune-compromised diseases like rheumatoid arthritis (RA), multiple sclerosis (MS), and systemic lupus erythematosus (SLE) with exogenous and endogenous production of melatonin despite the scarcity of data on the relationship of melatonin to other autoimmune diseases."
- Psoriatic patients have disturbances in melatonin secretion.
- Both endogenous and exogenous melatonin reduces risks of RA.
- In patients with RA, melatonin levels are significantly reduced in plasma.
- Melatonin supplementation effectively lowers production of pro-inflammatory cytokines.

35) Melatonin and Sepsis [systemic infection]

- "Primarily sepsis is a microbial infection that causes systemic inflammation in the host body."
    - "Generally, microbial pathogens like bacteria, viruses, fungi, and other parasites cause it."
- "Melatonin supplementation has been effective in treating septic shock."

36) Melatonin in Mood Disorders

- "The role of melatonin has been [linked to] the development of various mood disorders such as bipolar disorder (BD), major depressive disorder (MDD), and seasonal affective disorder (SAD)."
- "In individuals affected with BD, a marked decrease in secretion of melatonin is seen in depressed stage, and with symptoms remission, it was restored to normal."

37) Melatonin and Other Infections

- "During the past century, melatonin has been considered as a significant antibiotic, anti-parasitic, and antiviral entity."

- "Melatonin supplementation has been found to be quite efficient in treating parasitic infections."

38) Melatonin and Pain

- The antinociceptive property of melatonin is reported in many studies.

- "During tissue damage, a range of inflammatory molecules such as cytokines, prostaglandins, TNF-α, bradykinin, and leukotrienes are released into the blood circulation."

    - These inflammatory substances "promote excitability of neurons involved in pathways of pain transmission."

- During darkness, individuals experienced less pain.

    - "This phenomenon is attributed to elevated levels of melatonin at night."

39) "Melatonin is a quite important hormonal molecule in the biological living world."

We have reviewed these articles on melatonin:

Article Review 39-20:
Melatonin Inhibits COVID-19-induced Cytokine Storm

Article Review 34-22:
Melatonin Synthesis in and Uptake by Mitochondria

Article Review 35-22:
Highlighting Melatonin Use for Treatment for SARS-CoV-2 Infection

Article Review 6-23:
Is Melatonin the "Next Vitamin D"?

Article Review 15-23:
Melatonin for Chronic Whiplash Syndrome