

# Melatonin

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## Melatonin

**Primary Disciplinary Field(s):** Endocrinology, Neurobiology, Pharmacology, Chronobiology

### 1. Core Definition

Melatonin, chemically known as N-acetyl-5-methoxytryptamine, is a naturally occurring neurohormone predominantly synthesized and secreted by the pineal gland in the brain. Its primary and most extensively studied role revolves around the regulation of the body's internal clock, known as the circadian rhythm, which orchestrates the fundamental sleep-wake cycles. Beyond this critical function, melatonin is recognized for its multifaceted physiological effects, encompassing potent antioxidant capabilities, modulation of the immune system, and potential involvement in dreaming processes. While often associated with sleep, its systemic presence and diverse receptor interactions throughout the body underscore its significance as a broad-spectrum signaling molecule influencing numerous biological processes, extending well beyond mere somnolence to cellular protection and metabolic regulation.

This ubiquitous molecule is not exclusive to humans; it is found in virtually all living organisms, from bacteria and algae to plants, fungi, and animals, suggesting a deeply conserved evolutionary role in fundamental biological processes. In plants, for example, melatonin acts as a growth regulator and a stress protectant, analogous to its antioxidant functions in animals. The production and release of melatonin in humans are intricately linked to the ambient light-dark cycle, with secretion peaking during periods of darkness and diminishing in the presence of light, thereby serving as a crucial biochemical signal reflecting environmental illumination. This light-dependent regulation positions melatonin as a key mediator between the external environment and the internal physiological state, profoundly influencing behavior, metabolism, and overall health.

### 2. Etymology and Historical Development

The journey to understanding melatonin began in the mid-20th century, though the pineal gland, its primary production site, has been a subject of speculation for millennia. Ancient philosophers, notably Descartes, referred to the pineal gland as the "seat of the soul," reflecting an early, albeit unscientific, recognition of its unique position within the brain. Modern scientific inquiry into the pineal gland intensified in the 19th and early 20th centuries, with researchers observing its involvement in processes like skin pigmentation in amphibians and seasonal reproduction in mammals, hinting at a secretory function.

The pivotal breakthrough occurred in 1958 when Dr. Aaron B. Lerner and his colleagues at Yale University successfully isolated and identified the compound from bovine pineal glands that caused frog skin to lighten. They named this substance "melatonin," a portmanteau derived from the Greek words "melas" (black) and "tonos" (tension), referring to its ability to lighten amphibian skin, which

was a significant finding at the time. This discovery opened the door to extensive research into melatonin's chemical structure, its biosynthetic pathway, and its diverse physiological actions, shifting the understanding of the pineal gland from a vestigial organ to a central endocrine regulator.

Subsequent decades of research meticulously unraveled melatonin's role in regulating circadian rhythms, demonstrating its potent effects on sleep, seasonal breeding, and various neuroendocrine functions. Key to this understanding was the elucidation of its light-dependent synthesis and release, firmly establishing melatonin as the body's primary darkness signal. This historical progression from ancient philosophical musings to precise biochemical identification underscores the evolution of neuroendocrinology and chronobiology, fields that continue to uncover the profound and far-reaching implications of melatonin for human health and disease.

### 3. Biosynthesis and Regulation

The biosynthesis of melatonin is a meticulously regulated process beginning with the essential amino acid tryptophan, which is converted through a series of enzymatic steps primarily within the pineal gland. Tryptophan is first hydroxylated to 5-hydroxytryptophan, which is then decarboxylated to form serotonin, a crucial neurotransmitter. Serotonin then undergoes two enzymatic modifications to become melatonin: it is N-acetylated by serotonin N-acetyltransferase (AANAT) to N-acetylserotonin, and subsequently O-methylated by hydroxyindole-O-methyltransferase (HIOMT) to melatonin. The activity of AANAT is considered the rate-limiting step in this pathway, and its regulation is critical for controlling melatonin production.

The regulation of melatonin synthesis is exquisitely sensitive to environmental light cues, a process orchestrated by the suprachiasmatic nucleus (SCN), often referred to as the "master clock" of the circadian rhythm, located in the hypothalamus. Retinal photoreceptors detect light and transmit this information to the SCN via the retinohypothalamic tract. During the day, light exposure stimulates the SCN, which then sends inhibitory signals to the pineal gland, effectively suppressing AANAT activity and, consequently, melatonin production. Conversely, as darkness falls, the SCN's inhibitory output diminishes, allowing for the disinhibition and activation of AANAT, leading to a significant increase in melatonin synthesis and secretion.

This intricate neuroendocrine pathway ensures that melatonin levels in the bloodstream exhibit a distinct diurnal rhythm, with low concentrations during daylight hours and a sharp increase commencing shortly after dusk, peaking in the middle of the night, and gradually declining towards morning. This precise timing of melatonin release acts as a powerful endocrine signal that informs the body about the environmental light-dark cycle, thereby synchronizing numerous physiological and behavioral processes to the 24-hour day. Disruptions to this delicate regulatory mechanism, such as those caused by artificial light exposure at night or irregular sleep patterns, can lead to

desynchronization of circadian rhythms, potentially contributing to various health issues.

#### 4. Key Physiological Functions

Beyond its well-established role in synchronizing the circadian rhythm, melatonin exerts a wide array of fundamental physiological functions that contribute significantly to overall health and cellular homeostasis. One of its most robust and universally recognized actions is its potent antioxidant capacity. Melatonin directly scavenges free radicals, including reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are implicated in cellular damage and the aging process. Uniquely, melatonin and its metabolites are also capable of activating antioxidant enzymes, thereby amplifying the body's intrinsic defense mechanisms against oxidative stress. This powerful antioxidant profile contributes to its broad cytoprotective effects across various tissues and organs, shielding them from damage induced by environmental toxins, inflammation, and metabolic byproducts.

Melatonin also plays a crucial role in modulating the immune system. It possesses immunomodulatory properties, influencing both innate and adaptive immune responses. Receptors for melatonin are found on various immune cells, including lymphocytes, macrophages, and natural killer cells, indicating its direct involvement in immune regulation. Depending on the physiological context, melatonin can either stimulate or suppress immune functions, often working to optimize the immune response and mitigate excessive inflammation, which can be damaging. Its ability to support the immune system makes it a subject of interest in conditions ranging from infectious diseases to autoimmune disorders, where immune dysregulation is a central feature.

Furthermore, melatonin has been implicated in various other vital bodily functions. Its neuroprotective effects are increasingly recognized, primarily owing to its antioxidant and anti-inflammatory properties, which are crucial for safeguarding neuronal health against neurodegeneration. While less understood and requiring further research, some evidence suggests melatonin's involvement in dreaming, potentially influencing the quality and vividness of dreams. Melatonin also interacts with the reproductive system, influencing seasonal breeding in many species, and in humans, it may play a subtle role in puberty and reproductive health, though its precise mechanisms are still under investigation. Collectively, these diverse functions highlight melatonin as a critical orchestrator of biological processes far beyond its sleep-inducing reputation, underpinning its importance for maintaining physiological balance and protecting against cellular insults.

#### 5. Therapeutic Applications and Clinical Relevance

The extensive physiological functions of melatonin have led to its widespread exploration and use in various therapeutic contexts, addressing a broad spectrum of ailments and conditions. Its most

recognized clinical application is in the management of sleep disorders, including primary insomnia, jet lag, and shift work sleep disorder, where it helps to resynchronize the body's circadian rhythm and facilitate sleep onset. For individuals experiencing disrupted sleep patterns due to external factors or internal clock dysregulation, melatonin supplementation can provide a gentle, physiological approach to restoring regular sleep cycles, mimicking the natural darkness signal the body typically receives.

Beyond sleep, the neuroprotective and antioxidant properties of melatonin make it a promising candidate for neurological conditions. Research suggests a crucial role in conditions such as Alzheimer's disease, Parkinson's disease, and other neurodegenerative disorders where oxidative stress and inflammation are key pathological drivers. Melatonin's ability to cross the blood-brain barrier and its direct scavenging of free radicals offer a potential mechanism to mitigate neuronal damage and slow disease progression. Furthermore, its influence on mood regulation has led to investigations into its efficacy for seasonal affective disorder (SAD) and other forms of depression, particularly those linked to circadian disruption or seasonal changes in light exposure.

The source content highlights several other conditions where melatonin is believed to play a crucial part or has therapeutic potential. This includes its role in the aging process, where declining natural melatonin levels are thought to contribute to age-related sleep disturbances and increased vulnerability to oxidative damage. Supplementation may therefore offer anti-aging benefits by bolstering antioxidant defenses and improving sleep quality in older adults. Studies have also explored its utility in alleviating headaches, addressing mood disorders, potentially inhibiting cancer cell growth due to its oncostatic properties, managing obesity by influencing metabolic pathways, and reducing symptoms of tinnitus. While many of these applications are still subjects of ongoing research, with varying levels of clinical evidence, the breadth of conditions indicates melatonin's broad physiological impact and its potential as a versatile therapeutic agent in modern medicine. Melatonin levels are also believed to play a crucial role in autism, where circadian rhythm disturbances and sleep problems are prevalent, suggesting that its use could help regulate sleep patterns and potentially improve behavioral outcomes in affected individuals.

## 6. Debates, Limitations, and Side Effects

Despite its widespread use and perceived safety, the therapeutic application of melatonin is accompanied by ongoing debates, limitations, and potential side effects that warrant careful consideration. One significant debate centers on the regulatory status of melatonin. In many countries, particularly the United States, melatonin is sold as a dietary supplement, which means it is not subject to the same rigorous testing and approval processes as pharmaceutical drugs. This lack of strict regulation has led to concerns regarding product quality, purity, and the accuracy of stated dosages in over-the-counter supplements. Studies have frequently revealed discrepancies between label claims and actual melatonin content, with some products containing significantly

more or less than advertised, and others contaminated with undeclared substances.

Another limitation arises from the variability in individual responses to melatonin supplementation. Factors such as genetics, age, existing health conditions, and the specific timing of administration can influence its efficacy. While generally considered effective for specific sleep-wake cycle disorders like jet lag or delayed sleep phase syndrome, its effectiveness for chronic insomnia or other complex sleep disorders can be less consistent. The optimal dosage and timing for different conditions are also subjects of ongoing research, with the concept of a "one-size-fits-all" approach proving largely inadequate given melatonin's complex pharmacokinetics and pharmacodynamics.

Although melatonin is generally well-tolerated at typical doses, potential side effects, though usually mild, can include drowsiness, dizziness, headache, and nausea. Some individuals may experience vivid dreams or nightmares. Concerns exist regarding the long-term safety of chronic high-dose use, as comprehensive studies are still lacking. Melatonin can also interact with certain medications, such as anticoagulants, immunosuppressants, and drugs for diabetes or blood pressure, potentially altering their effects. Furthermore, while beneficial for regulating sleep, inappropriate timing of melatonin intake can paradoxically disrupt circadian rhythms, leading to further sleep disturbances or daytime grogginess. These considerations underscore the importance of consulting healthcare professionals before initiating melatonin supplementation, particularly for individuals with pre-existing medical conditions or those taking other medications, to ensure safe and effective use.

## Further Reading

[Melatonin - Wikipedia](#)

[Pineal Gland - Wikipedia](#)

[Circadian Rhythm - Wikipedia](#)

[Antioxidant - Wikipedia](#)

[Immune System - Wikipedia](#)

[Aaron B. Lerner - Wikipedia](#)

[Suprachiasmatic Nucleus - Wikipedia](#)

[Tryptophan - Wikipedia](#)

[Serotonin - Wikipedia](#)

[Neuroprotection - Wikipedia](#)

[Sleep Disorder - Wikipedia](#)

[Jet Lag - Wikipedia](#)

[Shift Work Sleep Disorder - Wikipedia](#)

[Alzheimer's Disease - Wikipedia](#)

[Seasonal Affective Disorder - Wikipedia](#)

[Melatonin as a promising agent for cancer treatment - PMC](#)

[Tinnitus - Wikipedia](#)

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