Melatonin – the chronobiological "clock" hormone

The rhythm of darkness

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Nature's own cycles dictate the biological rhythms of all living organisms. A key role in the complex circadian system is played by melatonin, the "hormone of darkness"

Melatonin is a compound widely found in nature, occurring in certain single-cell organisms, certain plants, in some invertebrates, and in all vertebrates. In vertebrates the main source of melatonin is a small gland localized in the centre of the brain, called the pineal gland (*corpus pineale*). Melatonin is also synthesized in the retina, and (in some species) in the Harderian gland and in the intestine – where its function remains unknown. Melatonin is known as the "hormone of darkness", since it is produced in the pineal gland and retina during the night, but very little is synthesized during the day. Pineal melatonin is produced in a circadian rhythm and plays dual role in the body: on one hand it transfers information from the biological clock to the tissues, while on the other it regulates the operation of the clock itself.

Biosynthesis of melatonin

Melatonin is a derivative of serotonin, produced from an amino acid precursor (L-tryptophan) in a four-stage process. The rate-limiting step in the melatonin biosynthetic pathway is the stage of serotonin acetylation, catalyzed by a specific enzyme – serotonin N-acetyltransferase (also known as aryla-

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In infants born at full term, the melatonin rhythm first appears only after 3 months. Over the human lifespan the amplitude of the melatonin rhythm, i.e. the difference between day and night levels, first increases gradually (with the largest increase being observed between the 3rd and 7th year) and subsequently declines – first rapidly and then (after age 20) more mildly

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Melatonin secreted by the pineal gland regulates circadian rhythms in mammals

lkylamine N-acetyltransferase; AANAT). This enzyme is most active only at a specific time of day (when there is no light in the environment), and is present exclusively in cells that produce melatonin. Melatonin synthesized in the pineal gland is released in a pulsating manner into the bloodstream and cerebrospinal fluid, and after reaching target tissues expressing specific melatonin receptors (named MT_1, MT_2 and MT_3) the hormone exerts various physiological actions.

Clock and calendar

Research carried out in various centers, including work by our own teams, has shown that in a majority of animal species as well as in humans the circadian rhythm of melatonin is generated by an endogenous biological clock. Regardless of the nature of a given species' lifestyle (nocturnal, diurnal, or mixed), the melatonin level and the activity of the AANAT enzyme always peak at night (or in the dark phase of an artificial light-dark illumination cycle), and the longer the nighttime period the longer the duration of high melatonin production (called a "melatonin window"). Interestingly, melatonin rhythm is also observed in a signal-less environment (i.e. constant darkness). These unique properties of the melatonin-generating system indicate that the hormone acts as the body's time-keeper: the presence of the hormone signals nighttime, while its absence (or low level) signals daytime. Depending on the time of day, a rising concentration of melatonin presages the onset of night, while drops in the hormone content signal the coming daytime. Melatonin likewise acts as a biochemical calendar: the gradual broadening or narrowing of the "melatonin window" informs the body about the changing of the seasons: autumn → winter and spring → summer.

Light's twofold impact

Light is the most important environmental factor that regulates melatonin biosynthesis. Its impact is of a twofold nature: on one hand it exerts a rapid inhibiting effect (the "acute effect"), and on the other it has a synchronizing effect that shifts the phase of the melatonin circadian rhythm.

Exposure to light of the proper intensity at night causes rapid reduction in the concentration of the hormone circulating in the organism's fluids: this, called the acute effect, stems from a sudden reduction in AANAT activity in the pineal gland under the influence of the light signal. The strongest inhibition of the melatonin-generating system is exerted by blue light (460–480 nm), a somewhat lesser effect is caused by green light (500–560 nm), and the smallest by red light (>600 nm). Our research has shown that radiation in the near ultraviolet range (UV-A, 320–400 nm) also inhibits melatonin synthesis in the pineal gland and retina.

The synchronizing effect of light results from its primary impact on the operation of the biological clock, which is responsible for the melatonin rhythm. Exposure to light at night causes a phase shift in the circadian melatonin rhythm, without at the same time affecting the length of the cycle. The extent of the light-induced phase shifts depends on the duration of the light stimulus, on its intensity, and on variations in tissue, species, and individual sensitivity. Light does not act directly on the biological clock; rather,

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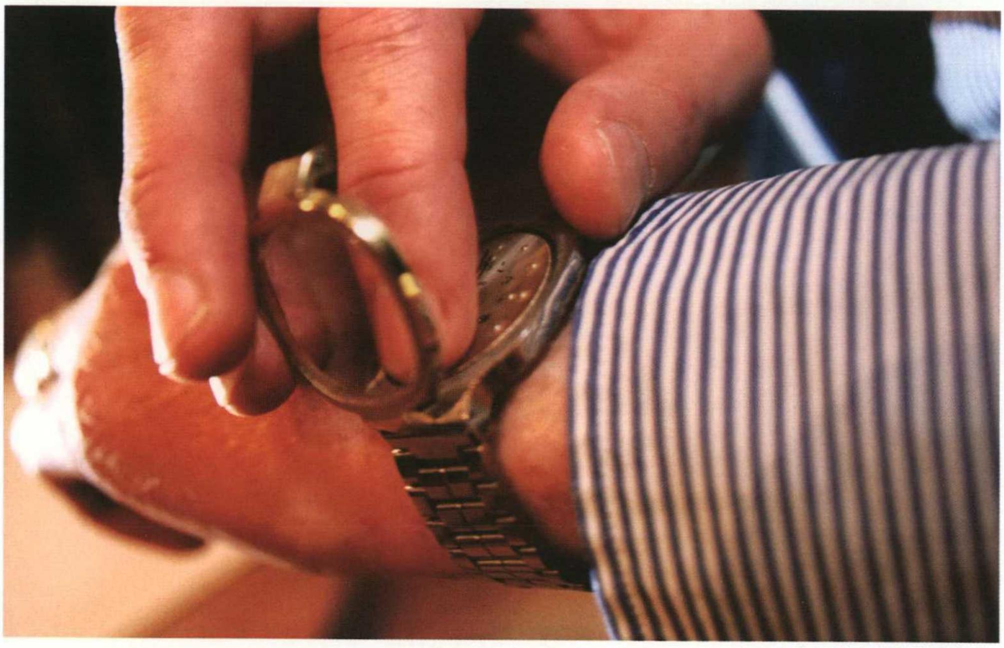
Research has recently uncovered the presence in the retina of intrinsically light-sensitive cells that contain a newly discovered visual pigment called melanopsin. They work like "photon counters," registering changes in the intensity of radiation over time. It is suggested that due to the work of these cells, blind individuals with damage to their classical photoreceptors continue to have their biological clock synchronized by environmental light signals



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light impulses are received by the retina and transmitted via the optic nerve to the main biological clock, which in mammals is located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. Our research has shown that environmental light information is "decoded" in the retina by different neurotransmitter systems for white light (dopamine acting on D1- and D2-dopamine receptors) than for UV-A radiation (glutamate acting on ionotropic glutamate receptors of the NMDA type). Once received by the biological clock itself, information about environmental light is transmitted down-stream to the pineal cells that produce melatonin, known as pinealocytes. A light pulse triggers a cascade of biochemical processes in the pinealocytes that finally leads to a decline in melatonin production.

Feedback

The hormone of darkness is an integral part of the so-called circadian system, which consists of three closely interacting structures: the SCN, the pineal gland, and the retina. Even though melatonin is synthesized in the circadian rhythm generated by the master biological clock (SCN), melatonin likewise itself has a strong influence on how the clock functions.

Melatonin affects the SCN in a twofold way. It acutely inhibits the activity of SCN neurons. In addition, melatonin phase-shifts the circadian rhythm of SCN activity. The inhibitory action of melatonin on SCN neurons makes them more sensitive to any secondary signals of a synchronizing nature, coming from the body itself or its environment (for example, environmental noise which stimulates vigilance). Melatonin's synchronizing effect adjusts the circadian rhythm in accordance to the current environmental rhythm. Overall, two factors interact in regulating the work of the biological clock: light in the daytime and melatonin at night.

An abundant body of experimental data indicates that melatonin exerts these diverse actions by interacting with two different types of receptors present in the SCN. MT_1 receptors are responsible for the acute effect, MT_2 receptors for the synchronizing effect; which in turn triggers two different signaling cascade reactions.

Genes first

The electrophysiological activity of the SCN neurons is genetically conditioned. In individual neurons the duration of the full activity cycle fluctuates broadly from 16 to 32 hours. Interactions within the SCN, however, lead the individual rhythms to become synchronized into a single overall rhythm with a cycle duration of about 24 hours. Full synchronization with the environmental rhythm, as set by the succession of day and night, is related to the light signal that is received by mammals through the retinal photoreceptors. Melatonin secreted at night and released into the bloodstream and cerebrospinal fluid coordinates the circadian activity of the SCN, giving rise to a uniform biological clock rhythm. We should stress that under natural conditions the transition from day to night (and vice versa) is a gradual process, rather than a sudden one (as usually occurs under experimental conditions). During the times of dusk and dawn, the mechanisms appropriate for the oncoming time of day come into effect, and it is during these times - researchers believe - that the role of "rising" and "dissipating" melatonin is most crucial as a signal for the SCN.

A drug for insomnia?

In view of how melatonin affects the activity of the biological clock, the hormone can be described as a chronobiotic agent. Could this property be of therapeutic use? When supplied as exogenous melatonin (in the form of tablets, capsules, linguettes, etc.) it should have effects similar to naturally secreted melatonin. Indeed, highly advanced clinical studies show that melatonin can be an effective drug for the treatment of what are called chronobiological sleep disorders. These include delayed/advanced sleep phase syndromes, sleep disorders that result from shift work, sleep disorders and other biological rhythm disturbances caused by the rapid crossing of time zones on transcontinental flights (known as jet-lag syndrome), and sleep disorders in autistic children, the blind, and geriatric patients (including patients suffering from Alzheimer's disease). However, it must be kept in mind that melatonin is no ordinary sleeping pill. Melatonin can indeed be used as a soporific compound, helping a subject fall asleep. There are also suggestions that the simultaneous stimulation of MT_1 and MT_2 melatonin receptors and $5HT_{2C}$ serotonin receptors form a potentially antidepressive system, which could make melatonin useful in therapy of depression. However, both endo- and exogenous melatonin is rapidly metabolized in the body (a feature that clearly hampers the compound's therapeutic use), and oral delivery of melatonin alters its natural evening-nighttime concentration within the body. Furthermore, being a natural substance, melatonin interacts with all three subtypes of melatonin receptors. As mentioned above, the hormone affects the work of the circadian clock system through interactions with MT_1 and MT_2 receptors in the SCN. The consequences of melatonin's interaction with MT_3 receptors have not yet been fully studied, and so there is a risk that such therapy could have as-yet unknown side effects.

Melatonin is thus not an ideal chronobiotic drug, and an intensive research is now underway for a compound or compounds of a different structure but with a similar profile of action. Such a compound should mimic the pharmacokinetic properties and physiological actions of melatonin without interacting at the same time with MT_3 receptors, and would therefore solely affect the body's internal biological clock. ■

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Melatonin can be an effective drug in the treatment of chronobiological sleep disorders, such as jet-lag syndrome - caused by the rapid crossing of time zones

Further reading:

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