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**Melatonin**, chemically ***N*-**[**acetyl**](/wiki/Acetyl)**-5-**[**methoxy**](/wiki/Methoxy)[**tryptamine**](/wiki/Tryptamine),[[1]](#cite_note-1) is a substance found in animals, plants, fungi, and bacteria. In animals, it is a [hormone](/wiki/Hormone) that anticipates the [daily onset of darkness](/wiki/Photoperiod);[[2]](#cite_note-2) however in other organisms, it may have different functions. Likewise, the synthesis of melatonin in animals differs from that in other organisms.

In animals, melatonin is involved in the [entrainment](/wiki/Entrainment_(chronobiology)) (synchronization) of the [circadian rhythms](/wiki/Circadian_rhythm) of physiological functions including sleep timing, blood pressure regulation, seasonal reproduction, and many others.[[3]](#cite_note-3) Many of melatonin's biological effects in animals are produced through activation of [melatonin receptors](/wiki/Melatonin_receptor),[[4]](#cite_note-4) while others are due to its role as a pervasive and powerful [antioxidant](/wiki/Antioxidant),[[5]](#cite_note-5) with a particular role in the protection of [nuclear](/wiki/Nuclear_DNA) and [mitochondrial DNA](/wiki/Mitochondrial_DNA).[[6]](#cite_note-6) It is used as a [medication for insomnia](/wiki/Insomnia#Melatonin), however, scientific evidence is insufficient for a benefit in this area.<ref name=Bra2015/> Melatonin is sold [over-the-counter](/wiki/Over-the-counter_drug) in the United States and Canada. In other countries, it may require a [prescription](/wiki/Prescription_drug) or it may be unavailable.

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## Medical uses[[edit](/index.php?title=(none)&action=edit&section=1)]

[thumb|150px|A bottle of melatonin tablets: Additionally, melatonin is available in timed-release and in liquid forms.](/wiki/Image:Walgreens_Melatonin-2010-20-07.jpg)

### Sleep disorders[[edit](/index.php?title=(none)&action=edit&section=2)]

Melatonin has shown promise in treating sleep-wake cycle disorders in children with underlying neurodevelopment difficulties.[[7]](#cite_note-7)[[8]](#cite_note-8) As add-on to [antihypertensive therapy](/wiki/Antihypertensive_drug), prolonged-release melatonin has improved blood pressure control in people with nocturnal hypertension.[[9]](#cite_note-9) People with [circadian rhythm sleep disorders](/wiki/Circadian_rhythm_sleep_disorder) may use oral melatonin to help [entrain](/wiki/Entrainment_(chronobiology)) (biologically synchronize in the correct phase) to the environmental light-dark cycle. Sighted people with these disorders may also use correctly timed [light therapy](/wiki/Light_therapy). Melatonin reduces [sleep onset latency](/wiki/Sleep_onset_latency) to a greater extent in people with [delayed sleep phase disorder](/wiki/Delayed_sleep_phase_disorder) than in people with insomnia.[[10]](#cite_note-10) Melatonin has been studied for [insomnia](/wiki/Insomnia) in the elderly.[[11]](#cite_note-11)[[12]](#cite_note-12)[[13]](#cite_note-13) Prolonged-release melatonin has shown good results in treating insomnia in older adults.[[14]](#cite_note-14) Short-term treatment (up to three months) of prolonged-release melatonin was found to be effective and safe in improving [sleep latency](/wiki/Sleep_onset_latency), sleep quality, and daytime alertness.[[15]](#cite_note-15) Evidence for use of melatonin as a treatment for insomnia is, as of 2015, overall poor;<ref name=Bra2015/> low-quality evidence indicates it may speed the onset of sleep by 6 minutes.<ref name=Bra2015>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> A 2004 review found "no evidence that melatonin had an effect on sleep onset latency or sleep efficiency" in [shift work](/wiki/Shift_work) or [jet lag](/wiki/Jet_lag), while it did decrease sleep onset latency in people with a primary sleep disorder and it increased sleep efficiency in people with a secondary sleep disorder.[[10]](#cite_note-10) A later review[[16]](#cite_note-16) found minimal evidence for efficacy in shift work.

### Jet lag and shift work[[edit](/index.php?title=(none)&action=edit&section=3)]

Melatonin is known to aid in reducing the effects of [jet lag](/wiki/Jet_lag), especially in eastward travel, by promoting the necessary reset of the body's sleep-wake phase. If the timing is not correct, however, it can instead delay adaption.[[17]](#cite_note-17) Melatonin appears also to have limited use against the sleep problems of people who work rotating or night [shifts](/wiki/Shift_work).[[16]](#cite_note-16)

### Headaches[[edit](/index.php?title=(none)&action=edit&section=4)]

Tentative evidence shows melatonin may help reduce some types of headaches including [cluster headaches](/wiki/Cluster_headaches).[[18]](#cite_note-18)

### Cancer[[edit](/index.php?title=(none)&action=edit&section=5)]

A 2013 review by the National Cancer Institutes found evidence for use to be inconclusive.[[19]](#cite_note-19) A 2005 review of unblinded [clinical trials](/wiki/Clinical_trial) found a reduced rate of death, but that blinded and independently conducted randomized controlled trials are needed.[[20]](#cite_note-20)

### Gallstones[[edit](/index.php?title=(none)&action=edit&section=6)]

Melatonin presence in the [gallbladder](/wiki/Gallbladder) has many protective properties, such as converting cholesterol to bile, preventing oxidative stress, and increasing the mobility of gallstones from the gallbladder.[[21]](#cite_note-21)

### Protection from radiation[[edit](/index.php?title=(none)&action=edit&section=7)]

Both animal[[22]](#cite_note-22) and human[[23]](#cite_note-23)[[24]](#cite_note-24) studies have shown melatonin to protect against radiation-induced cellular damage. Its metabolites and it protect organisms from [oxidative stress](/wiki/Oxidative_stress) by scavenging [reactive oxygen species](/wiki/Reactive_oxygen_species) which are generated during exposure.[[25]](#cite_note-25) Nearly 70% of biological damage caused by ionizing radiation is estimated to be attributable to the creation of free radicals, especially the [hydroxyl radical](/wiki/Hydroxyl_radical) that attacks DNA, proteins, and cellular membranes. Melatonin has been described as a broadly protective, readily available, and orally self-administered antioxidant that is without major known side effects.[[26]](#cite_note-26)

### Tinnitus[[edit](/index.php?title=(none)&action=edit&section=8)]

Tentative evidence of benefit exists for treating [tinnitus](/wiki/Tinnitus).[[27]](#cite_note-27)

### Psychiatry[[edit](/index.php?title=(none)&action=edit&section=9)]

Melatonin might improve sleep in [autistic](/wiki/Autism_spectrum) people.<ref name=asd>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Children with autism have abnormal melatonin pathways and below-average physiological levels of melatonin.<ref name=melatoninlevels>[Template:Cite journal](/wiki/Template:Cite_journal)</ref><ref name=melatoninlevels2>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Melatonin supplementation has been shown to improve sleep duration, sleep onset latency, and night-time awakenings.[[28]](#cite_note-28)[[29]](#cite_note-29)[[30]](#cite_note-30) However, many studies on melatonin and autism rely on self-reported levels of improvement and more rigorous research is needed.

While the packaging of melatonin often warns against use in people under 18 years of age, available studies suggest that melatonin is an efficacious and safe treatment for insomnia in people with ADHD. However, larger and longer studies are needed to establish long-term safety and optimal dosing.[[31]](#cite_note-31) Melatonin in comparison to placebo is effective for reducing preoperative anxiety in adults when given as premedication. It may be just as effective as standard treatment with midazolam in reducing preoperative anxiety. Melatonin may also reduce postoperative anxiety (measured 6 hours after surgery) when compared to placebo.[[32]](#cite_note-32) Some supplemental melatonin users report an increase in vivid dreaming. Extremely high doses of melatonin increased [REM sleep](/wiki/REM_sleep) time and dream activity in people both with and without [narcolepsy](/wiki/Narcolepsy).<ref name=Lewis>[Template:Cite book](/wiki/Template:Cite_book)</ref>

## Adverse effects[[edit](/index.php?title=(none)&action=edit&section=10)]

Melatonin appears to cause very few [side effects](/wiki/Adverse_effect_(medicine)) as tested in the short term, up to three months, at low doses. Two systematic reviews found no adverse effects of exogenous melatonin in several clinical trials and comparative trials found the adverse effects headaches, dizziness, nausea, and drowsiness were reported about equally for both melatonin and [placebo](/wiki/Placebo).[[33]](#cite_note-33)[[34]](#cite_note-34) Prolonged-release melatonin is safe with long-term use of up to 12 months.[[35]](#cite_note-35) Melatonin can cause [nausea](/wiki/Nausea), next-day [grogginess](/wiki/Grogginess), and irritability.[[36]](#cite_note-36) In the elderly, it can cause reduced blood flow and [hypothermia](/wiki/Hypothermia).[[37]](#cite_note-37) In [autoimmune disorders](/wiki/Autoimmune_disorders), evidence is conflicting whether melatonin supplementation may ameliorate or exacerbate symptoms due to [immunomodulation](/wiki/Immunomodulator).[[38]](#cite_note-38)[[39]](#cite_note-39) Melatonin can lower [follicle-stimulating hormone](/wiki/Follicle-stimulating_hormone) levels.[[40]](#cite_note-40) Effects of melatonin on human reproduction remain unclear,[[41]](#cite_note-41) although it was with some effect tried as a contraceptive in the 1990s.[[42]](#cite_note-42) Anticoagulants and other substances are known to interact with melatonin.[[43]](#cite_note-43)

## Functions[[edit](/index.php?title=(none)&action=edit&section=11)]

### Circadian rhythm[[edit](/index.php?title=(none)&action=edit&section=12)]

In animals, the primary function is regulation of day-night cycles. Human infants' melatonin levels become regular in about the third month after birth, with the highest levels measured between midnight and 8:00 am.[[44]](#cite_note-44) Human melatonin production decreases as a person ages.[[45]](#cite_note-45) Also, as children become teenagers, the nightly schedule of melatonin release is delayed, leading to later sleeping and waking times.[[46]](#cite_note-46)

#### Antioxidant[[edit](/index.php?title=(none)&action=edit&section=13)]

Besides its function as synchronizer of the biological clock, melatonin is a powerful free-radical scavenger and wide-spectrum antioxidant as discovered in 1993.[[47]](#cite_note-47) In many less-complex life forms, this is its only known function.[[25]](#cite_note-25)Melatonin is an [antioxidant](/wiki/Antioxidant) that can easily cross [cell membranes](/wiki/Cell_membrane)[[48]](#cite_note-48)and the blood–brain barrier.[[5]](#cite_note-5)[[49]](#cite_note-49)This antioxidant is a direct scavenger of radical oxygen and nitrogen species including OH•, O•2−, and NO•.[[50]](#cite_note-50)[[51]](#cite_note-51)Melatonin works with other antioxidants to improve the overall effectiveness of each antioxidant.[[51]](#cite_note-51) Melatonin has been proven to be twice as active as vitamin E, believed to be the most effective lipophilic antioxidant.[[52]](#cite_note-52)An important characteristic of melatonin that distinguishes it from other classic radical scavengers is that its metabolites are also scavengers in what is referred to as the cascade reaction.[[25]](#cite_note-25) Also different from other classic antioxidants, such as vitamin C and vitamin E, melatonin has amphiphilic properties. When compared to synthetic, mitochondrial-targeted antioxidants ([MitoQ](/wiki/MitoQ) and MitoE), melatonin proved to be a better protector against mitochondrial oxidative stress.[[53]](#cite_note-53)

### Immune system[[edit](/index.php?title=(none)&action=edit&section=14)]

While it is known that melatonin interacts with the [immune system](/wiki/Immune_system),[[54]](#cite_note-54)[[55]](#cite_note-55) the details of those interactions are unclear. [Antiinflammatory](/wiki/Antiinflammatory) effect seems to be the most relevant and most documented in the literature.[[56]](#cite_note-56) There have been few trials designed to judge the effectiveness of melatonin in disease treatment. Most existing data are based on small, incomplete clinical trials. Any positive immunological effect is thought to be the result of melatonin acting on high-affinity receptors (MT1 and MT2) expressed in immunocompetent cells. In preclinical studies, melatonin may enhance [cytokine](/wiki/Cytokine) production,[[57]](#cite_note-57) and by doing this, counteract [acquired immunodeficiences](/wiki/Acquired_immunodeficiences). Some studies also suggest that melatonin might be useful fighting infectious disease[[58]](#cite_note-58) including viral, such as [HIV](/wiki/HIV), and bacterial infections, and potentially in the treatment of [cancer](/wiki/Cancer).

In [rheumatoid arthritis](/wiki/Rheumatoid_arthritis) patients, melatonin production has been found increased when compared to age-matched healthy controls.[[59]](#cite_note-59)[Template:Relevance inline](/wiki/Template:Relevance_inline)

### Metal chelation[[edit](/index.php?title=(none)&action=edit&section=15)]

*In vitro*, melatonin can form complexes with [cadmium](/wiki/Cadmium) and other metals.[[60]](#cite_note-60)

## Biosynthesis and pharmacology[[edit](/index.php?title=(none)&action=edit&section=16)]

### Biosynthesis[[edit](/index.php?title=(none)&action=edit&section=17)]

[thumb|Overview of Melatonin Biosynthesis](/wiki/File:Mealtonin_biosynth.jpg)

Biosynthesis of melatonin occurs through hydroxylation, decarboxylation, acetylation and a methylation starting with L-tryptophan. [[61]](#cite_note-61) L-tryptophan is produced in the [shikimate pathway](/wiki/Shikimate_pathway) from [chorismate](/wiki/Chorismate) or is acquired from protein catabolism. First L-tryptophan is hydroxylated on the indole ring by tryptophan hydroxylase. The intermediate is decarboxylated by PLP and 5-hydroxy-L-tryptophan to produce serotonin also known as 5-hydroxytryptamine. Serotonin acts as a neurotransmitter on its own, but is also converted into N-acetyl-serotonin by serotonin N-acetyl transferase and acetyl-CoA. Hydroxyindole O-methyl transferase and SAM convert N-acetyl-serotonin into melatonin through methylation of the hydroxyl group.

In bacteria, protists, fungi, and plants, melatonin is synthesized indirectly with tryptophan as an intermediate product of the shikimic acid pathway. In these cells, synthesis starts with d-erythrose-4-phosphate and [phosphoenolpyruvate](/wiki/Phosphoenolpyruvate), and in [photosynthetic cells](/wiki/Photosynthesis) with carbon dioxide. The rest of the reactions are similar, but with slight variations in the last two enzymes.[[62]](#cite_note-62)[[63]](#cite_note-63)

### Mechanism[[edit](/index.php?title=(none)&action=edit&section=18)]

[thumb|Mechanism of Melatonin Biosynthesis](/wiki/File:Melatonin_mechanism.jpg)

In order to hydroxylate L-tryptophan, the cofactor [tetrahydrobiopterin](/wiki/Tetrahydrobiopterin) must first react with oxygen and the active site iron of tryptophan hydroxylase. This mechanism is not well understood, but two mechanisms have been proposed:

1. A slow transfer of one electron from the pterin to O2 could produce a [superoxide](/wiki/Superoxide) which could recombine with the pterin radical to give 4a-peroxypterin. 4a-peroxypterin could then react with the active site iron (II) to form an iron-peroxypterin intermediate or directly transfer an oxygen atom to the iron.

2. O2 could react with the active site iron (II) first, producing iron (III) superoxide which could then react with the pterin to form an iron-peroxypterin intermediate.

Iron (IV) oxide from the iron-peroxypterin intermediate is selectively attacked by a double bond to give a carbocation at the C5 position of the indole ring. A 1,2-shift of the hydrogen and then a loss of one of the two hydrogen atoms on C5 reestablishes aromaticity to furnish 5-hydroxy-L-tryptophan. [[64]](#cite_note-64) A decarboxylase with cofactor [pyridoxal phosphate](/wiki/Pyridoxal_phosphate) (PLP) removes CO2 from 5-hydroxy-L-tryptophan to produce 5-hydroxytryptamine. [[65]](#cite_note-65) PLP forms an [imine](/wiki/Imine) with the amino acid derivative. The amine on the pyridine is protonated and acts as an electron sink, breaking the C-C bond and releasing CO2. Protonation of the amine from tryptophan restores the aromaticity of the pyridine ring and then imine is hydrolyzed to produce 5-hydroxytryptamine and PLP. [[66]](#cite_note-66) It has been proposed that His122 of serotonin N-acetyl transferase is the catalytic residue that deprotonates the primary amine of 5-hydroxytryptamine, which allows the lone pair on the amine to attack acetyl-CoA, forming a tetraherdral intermediate. The thiol from [coenzyme A](/wiki/Coenzyme_A) serves as a good leaving group when attacked by a general base to give N-acetyl-serotonin.[[67]](#cite_note-67) N-acetyl-serotonin is methylated at the hydroxyl position by [S-adenosyl methionine](/wiki/S-adenosyl_methionine) (SAM) to produce S-adenosyl homocysteine (SAH) and melatonin.[[68]](#cite_note-68)[[69]](#cite_note-69)

### Regulation[[edit](/index.php?title=(none)&action=edit&section=19)]

In vertebrates, melatonin secretion is regulated by [norepinephrine](/wiki/Norepinephrine). Norepinephrine elevates the intracellular cAMP concentration via beta-adrenergic receptors and activates the cAMP-dependent protein kinase A (PKA). PKA phosphorylates the penultimate enzyme, the arylalkylamine N-acetyltransferase (AANAT). On exposure to (day)light, noradrenergic stimulation stops and the protein is immediately destroyed by [proteasomal](/wiki/Proteasome) [proteolysis](/wiki/Proteolysis).[[70]](#cite_note-70) Production of melatonin is again started in the evening at the point called the [dim-light melatonin onset](/wiki/Dim-light_melatonin_onset).

Blue light, principally around 460 to 480 [nm](/wiki/Nanometre), suppresses melatonin,[[71]](#cite_note-71) proportional to the light intensity and length of exposure. Until recent history, humans in temperate climates were exposed to few hours of (blue) daylight in the winter; their fires gave predominantly yellow light. The [incandescent light bulb](/wiki/Incandescent_light_bulb) widely used in the 20th century produced relatively little blue light.[[72]](#cite_note-72) Light containing only wavelengths greater than 530 nm does not suppress melatonin in bright-light conditions.[[73]](#cite_note-73) Wearing glasses that block blue light in the hours before bedtime may decrease melatonin loss. Use of blue-blocking goggles the last hours before bedtime has also been advised for people who need to adjust to an earlier bedtime, as melatonin promotes sleepiness.[[74]](#cite_note-74)

### Pharmacology[[edit](/index.php?title=(none)&action=edit&section=20)]

When used several hours before sleep according to the [phase response curve](/wiki/Phase_response_curve) for melatonin in humans, small amounts (0.3 mg[[75]](#cite_note-75)) of melatonin shift the circadian clock earlier, thus promoting earlier sleep onset and morning awakening.[[76]](#cite_note-76) In humans, 90% of orally administered exogenous melatonin is cleared in a single passage through the liver, a small amount is excreted in urine, and a small amount is found in saliva.[[10]](#cite_note-10)

## Animals[[edit](/index.php?title=(none)&action=edit&section=21)]

In vertebrates, melatonin is produced in darkness, thus usually at night, by the [pineal gland](/wiki/Pineal_gland), a small endocrine gland[[77]](#cite_note-77)located in the center of the brain but outside the blood–brain barrier. Light/dark information reaches the [suprachiasmatic nuclei](/wiki/Suprachiasmatic_nucleus) from retinal [photosensitive ganglion cells](/wiki/Photosensitive_ganglion_cell) of the eyes[[78]](#cite_note-78)[[79]](#cite_note-79) rather than the melatonin signal (as was once postulated). Known as "the hormone of darkness", the onset of melatonin at dusk promotes activity in [nocturnal](/wiki/Nocturnal) (night-active) animals and sleep in diurnal ones including humans.

Many animals use the variation in duration of melatonin production each day as a seasonal clock.[[80]](#cite_note-80) In animals including humans,[[81]](#cite_note-81)the profile of melatonin synthesis and secretion is affected by the variable duration of night in summer as compared to winter. The change in duration of secretion thus serves as a biological signal for the organization of daylength-dependent ([photoperiodic](/wiki/Photoperiodism)) seasonal functions such as reproduction, behavior, coat growth, and camouflage [coloring](/wiki/Animal_colouration) in seasonal animals.[[81]](#cite_note-81) In seasonal breeders that do not have long gestation periods and that mate during longer daylight hours, the melatonin signal controls the seasonal variation in their sexual physiology, and similar physiological effects can be induced by exogenous melatonin in animals including mynah birds[[82]](#cite_note-82)and hamsters.[[83]](#cite_note-83) Melatonin can suppress [libido](/wiki/Libido) by inhibiting secretion of [luteinizing hormone](/wiki/Luteinizing_hormone) and [follicle-stimulating hormone](/wiki/Follicle-stimulating_hormone) from the [anterior pituitary](/wiki/Anterior_pituitary) gland, especially in mammals that have a [breeding](/wiki/Reproduction) season when daylight hours are long. The reproduction of [long-day breeders](/wiki/Polyestrous) is [repressed by melatonin](/wiki/Estrous_cycle#Anestrus) and the reproduction of [short-day breeders](/wiki/Polyestrous) is stimulated by melatonin.

During the night, melatonin regulates [leptin](/wiki/Leptin), lowering its levels.

## Plants[[edit](/index.php?title=(none)&action=edit&section=22)]

Until its identification in plants in 1987, melatonin was for decades thought to be primarily an animal neurohormone. When melatonin was identified in coffee extracts in the 1970s, it was believed to be a byproduct of the extraction process. Subsequently, however, melatonin has been found in all plants that have been investigated. It is present in all the different parts of plants, including leaves, stems, roots, fruits, and seeds in varying proportions.[[84]](#cite_note-84)[[85]](#cite_note-85) Melatonin concentrations differ not only among plant species, but also between varieties of the same species depending on the agronomic growing conditions, varying from picograms to several micrograms per gram.[[86]](#cite_note-86)[[87]](#cite_note-87) Notably high melatonin concentrations have been measured in popular beverages such as coffee, tea, wine, and beer, and crops including corn, rice, wheat, barley, and oats.[[85]](#cite_note-85) Melatonin is a poor direct antioxidant, it is, however, a highly efficient direct free radical scavenger and indirect antioxidant due to its ability to stimulate antioxidant enzymes.[[88]](#cite_note-88)[[89]](#cite_note-89)[[90]](#cite_note-90) Thus, melatonin in the human diet is believed to confer a number of beneficial health-related effects.[[85]](#cite_note-85)[[86]](#cite_note-86)[[91]](#cite_note-91) In some common foods and beverages, including coffee[[85]](#cite_note-85) and walnuts,[[92]](#cite_note-92) the concentration of melatonin has been estimated or measured to be sufficiently high to raise the blood level of melatonin above daytime baseline values.

Although a role for melatonin as a plant hormone has not been clearly established, its involvement in processes such as growth and photosynthesis is well established. Only limited evidence of endogenous circadian rhythms in melatonin levels has been demonstrated in some plant species and no membrane-bound receptors analogous to those known in animals have been described. Rather, melatonin performs important roles in plants as a growth regulator, as well as environmental stress protector. It is synthesized in plants when they are exposed to both biological stresses, for example, fungal infection, and nonbiological stresses such as extremes of temperature, toxins, increased soil salinity, drought, etc.[[87]](#cite_note-87)[[90]](#cite_note-90)[[93]](#cite_note-93)

## Exogenous melatonin[[edit](/index.php?title=(none)&action=edit&section=23)]

### Dietary supplement and neurohormone[[edit](/index.php?title=(none)&action=edit&section=24)]

Melatonin is categorized by the US [Food and Drug Administration](/wiki/Food_and_Drug_Administration) (FDA) as a dietary supplement, and is sold over-the-counter in both the US and Canada.[[94]](#cite_note-94) The FDA regulations applying to medications are not applicable to melatonin.[[3]](#cite_note-3) However, new FDA rules required that by June 2010, all production of dietary supplements must comply with "current [good manufacturing practices](/wiki/Good_manufacturing_practice)" (cGMP) and be manufactured with "controls that result in a consistent product free of contamination, with accurate labeling."[[95]](#cite_note-95) The industry has also been required to report to the FDA "all serious dietary supplement related adverse events", and the FDA has (within the cGMP guidelines) begun enforcement of that requirement.[[96]](#cite_note-96) As melatonin may cause harm in combination with certain medications or in the case of certain disorders, a doctor or pharmacist should be consulted before making a decision to take melatonin.[[17]](#cite_note-17) In many countries, melatonin is recognized as a [neurohormone](/wiki/Neurohormone) and it cannot be sold over-the-counter.[[97]](#cite_note-97)

### Food products[[edit](/index.php?title=(none)&action=edit&section=25)]

Melatonin has been reported in foods including cherries to about 0.17–13.46 ng/g,[[98]](#cite_note-98) bananas and grapes, rice and cereals, herbs, plums,[[99]](#cite_note-99) olive oil, [wine](/wiki/Wine)[[100]](#cite_note-100) and beer. When birds ingest melatonin-rich plant feed, such as rice, the melatonin binds to melatonin receptors in their brains.[[101]](#cite_note-101) When humans consume foods rich in melatonin such as banana, pineapple and orange, the blood levels of melatonin increase significantly.[[102]](#cite_note-102) As reported in the *New York Times* in May 2011,[[103]](#cite_note-103) beverages and snacks containing melatonin are sold in grocery stores, convenience stores, and clubs. The FDA is considering whether these food products can continue to be sold with the label "dietary supplements". On 13 January 2010, it issued a warning letter to Innovative Beverage, creators of several beverages marketed as drinks, stating that melatonin is not approved as a [food additive](/wiki/Food_additive) because it is not [generally recognized as safe](/wiki/Generally_recognized_as_safe).[[104]](#cite_note-104)

## History[[edit](/index.php?title=(none)&action=edit&section=26)]

Melatonin was first discovered in connection to the mechanism by which some [amphibians](/wiki/Amphibians) and [reptiles](/wiki/Reptiles) change the color of their skin.[[105]](#cite_note-105)[[106]](#cite_note-106) As early as 1917, Carey Pratt McCord and Floyd P. Allen discovered that feeding extract of the pineal glands of cows lightened tadpole skin by contracting the dark [epidermal](/wiki/Epidermis_(zoology)) [melanophores](/wiki/Melanophores).[[107]](#cite_note-107)[[108]](#cite_note-108) In 1958, dermatology professor [Aaron B. Lerner](/wiki/Aaron_B._Lerner) and colleagues at Yale University, in the hope that a substance from the pineal might be useful in treating skin diseases, isolated the hormone from bovine pineal gland extracts and named it melatonin.[[109]](#cite_note-109) In the mid-70s Lynch *et al.* demonstrated[[110]](#cite_note-110) that the production of melatonin exhibits a circadian rhythm in human pineal glands.

The discovery that melatonin is an antioxidant was made in 1993.[[111]](#cite_note-111)The first [patent](/wiki/Patent) for its use as a low-dose sleep aid was granted to [Richard Wurtman](/wiki/Richard_Wurtman) at [MIT](/wiki/MIT) in 1995.[[112]](#cite_note-112) Around the same time, the hormone got a lot of press as a possible treatment for many illnesses.[[113]](#cite_note-113) *The New England Journal of Medicine* editorialized in 2000: "With these recent careful and precise observations in blind persons, the true potential of melatonin is becoming evident, and the importance of the timing of treatment is becoming clear."[[114]](#cite_note-114)

## Availability[[edit](/index.php?title=(none)&action=edit&section=27)]

[thumb|right|](/wiki/File:Melatonin_prescription.jpg)[University of Helsinki](/wiki/University_of_Helsinki) pharmaceutical laboratory prepared melatonin available upon prescription

Immediate-release melatonin is not tightly regulated in countries where it is available as an over-the-counter medication. It is available in doses from less than half a milligram to 5 mg or more. Immediate-release formulations cause blood levels of melatonin to reach their peak in about an hour. The hormone may be administered orally, as capsules, tablets, or liquids. It is also available for use sublingually, or as transdermal patches.

Formerly, melatonin was derived from animal pineal tissue, such as bovine. It is now synthetic and does not carry a risk of contamination or the means of transmitting infectious material.[[3]](#cite_note-3)[[115]](#cite_note-115)

### Prolonged release[[edit](/index.php?title=(none)&action=edit&section=28)]

Melatonin is available as a prolonged-release prescription drug. It releases melatonin gradually over 8–10 hours, intended to mimic the body's internal secretion profile.

In June 2007, the [European Medicines Agency](/wiki/European_Medicines_Agency) approved [UK](/wiki/United_Kingdom)-based Neurim Pharmaceuticals' prolonged-release melatonin medication Circadin for marketing throughout the [EU](/wiki/European_Union).[[116]](#cite_note-116) The drug is a prolonged-release melatonin, 2 mg, for patients aged 55 and older, as monotherapy for the short-term treatment (up to 13 weeks) of primary insomnia characterized by poor quality of sleep.[[117]](#cite_note-117)[[118]](#cite_note-118) Other countries' agencies that subsequently approved the drug include:

* Australian [Therapeutics Goods Administration](/wiki/Therapeutics_Goods_Administration)[[119]](#cite_note-119)\* Chile[[119]](#cite_note-119)\* Croatia[[119]](#cite_note-119)\* Icelandic Medicines Agency[[120]](#cite_note-120)<ref name=Lundbeck>[Template:Cite web](/wiki/Template:Cite_web)</ref>
* [Israeli Ministry of Health](/wiki/Israeli_Ministry_of_Health) (MOH).<ref name=MOH\_APP>[Template:Cite web](/wiki/Template:Cite_web)</ref>
* [Norwegian Medicines Agency](/wiki/Norwegian_Medicines_Agency)[[121]](#cite_note-121)[[122]](#cite_note-122)[[123]](#cite_note-123)\* South Africa<ref name=AdisInsight>[Template:Cite web](/wiki/Template:Cite_web)</ref>
* South Korean [Ministry of Food and Drug Safety](/wiki/Ministry_of_Food_and_Drug_Safety)[[124]](#cite_note-124)<ref name=MFDS\_APP>[Template:Cite web](/wiki/Template:Cite_web)</ref>
* [Swiss Agency for Therapeutic Products](/wiki/Swissmedic) (Swissmedic)[[125]](#cite_note-125)

## See also[[edit](/index.php?title=(none)&action=edit&section=29)]

* [5-Methoxytryptamine](/wiki/5-Methoxytryptamine)
* [6-Hydroxymelatonin](/wiki/6-Hydroxymelatonin)
* [Agomelatine](/wiki/Agomelatine)
* [Health effects of sunlight exposure](/wiki/Health_effects_of_sunlight_exposure)
* [Melatonin receptor agonist#Drug design and development](/wiki/Melatonin_receptor_agonist#Drug_design_and_development)
* [Ramelteon](/wiki/Ramelteon)
* [Sundowning](/wiki/Sundowning)
* [Tasimelteon](/wiki/Tasimelteon)

## References[[edit](/index.php?title=(none)&action=edit&section=30)]

[Template:Reflist](/wiki/Template:Reflist)

## Further reading[[edit](/index.php?title=(none)&action=edit&section=31)]

* [Template:Cite journal](/wiki/Template:Cite_journal)

## External links[[edit](/index.php?title=(none)&action=edit&section=32)]

[Template:Commons category](/wiki/Template:Commons_category)

* [Melatonin MS Spectrum](http://gmd.mpimp-golm.mpg.de/Spectrums/5c07b02a-6ada-4428-9a58-a739a3177f45.aspx)
* [Melatonin entry in TiHKAL • info](http://tihkal.info/read.php?domain=tk&id=35)

[Template:Neurotransmitters](/wiki/Template:Neurotransmitters) [Template:Hormones](/wiki/Template:Hormones) [Template:Antioxidants](/wiki/Template:Antioxidants) [Template:Dietary supplement](/wiki/Template:Dietary_supplement) [Template:Hypnotics and sedatives](/wiki/Template:Hypnotics_and_sedatives) [Template:Insomnia pharmacotherapies](/wiki/Template:Insomnia_pharmacotherapies) [Template:Melatonergics](/wiki/Template:Melatonergics) [Template:Tryptamines](/wiki/Template:Tryptamines) [Template:Authority control](/wiki/Template:Authority_control)

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