Melatonin

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INTRODUCTION

Melatonin is a hormone, like the estrogens and testosterone: It is synthesized in the pineal gland and secreted into the blood and cerebrospinal fluid. It conveys signals to distant organs, principally the brain, which affect the synthesis of second messengers and, ultimately, sleep and circadian rhythms. However, unlike the estrogens and testosterone, melatonin is marketed in the United States as a dietary supplement, which implies that people normally obtain this compound from the diet and that melatonin pills simply supplement that which the diet provides. No food has ever been found to elevate plasma melatonin levels; nor is there acceptable evidence that any food actually contains more than trace amounts of the hormone. This entry describes the history of our knowledge of melatonin, the hormone’s synthesis, metabolism, and physiologic regulation, the factors that affect plasma melatonin levels, the known effects of endogenous and exogenous (oral) melatonin, and melatonin’s present usage.

HISTORY OF MELATONIN

Few people would now doubt that the human pineal gland is an important structure, and that it transmits signals to the brain and other organs by secreting a unique hormone, melatonin. However this consensus is only a few decades old. For most of the 20th century, the pineal was generally dismissed as a “vestige” or “third eye” in certain lower vertebrates, which, in humans, died and became calcified early in life. Tumors of the pineal gland were known sometimes to be associated with a reproductive disorder—precocious puberty, especially in boys—and some scientists attributed this phenomenon to the destruction of functioning pineal tissue. However, most concluded that the accelerated sexual maturation simply resulted from increased intraocular pressure.

The modern history of the pineal gland probably began with the discovery, in 1917, that extracts of cow pineals could lighten the skin of frogs. The physiologic significance of this relationship seemed obscure, inasmuch as bovine pineal extracts had no effect on pigmentation in bovines (or humans), and frog pineals lacked detectable skin-lightening ability. However, the finding did indicate that the pineal contained a compound with at least some biological activity, and it provided a way of identifying the active compound, using assays based on the ability of purified extracts to aggregate the melanin granules in the frog’s pigment cells. In 1958, Lerner et al. discovered the compound’s chemical structure to be 5-methoxy-N-acetyltryptamine and named it melatonin.

Around that time, scientists made four seemingly unrelated discoveries, which became coherent, like a partly completed crossword puzzle, once melatonin was identified. In chronologic sequence, these were: 1) the demonstration, by Kitay and Altachi, that surgical removal of the rat’s pineal accelerated the growth of the ovaries, while administration of bovine pineal extracts had the opposite effect; 2) Fiske’s observation that housing rats in a continuously light environment led to decrease in the weights of their pineals; 3) Arieus-Kappers’ discovery that, though the pineal gland originates embryologically as part of the brain, it loses most or all of its CNS connections by birth, and instead receives its innervation from peripheral sympathetic nerves; and 4) the demonstration that both pinealectomy and prolonged light exposure accelerate the growth of the rat’s ovaries to an equal extent, and that both responses are blocked by administering pineal extracts. In 1963–1964, it was shown that melatonin is a true hormone in rats, that it is the gonad-inhibiting substance previously described in pineal extracts, and that its synthesis in the pineal gland is suppressed when rats are exposed continuously to light, the light acting not directly, as on a “third eye,” but indirectly, via the animal’s eyes and sympathetic nerves. (The chemical that mediates the sympathetic nervous signals was shown to be norepinephrine, which stimulates pineal beta-receptors and increases cyclic-AMP production.) The rates at which the rat’s pineal synthesizes
serotonin and melatonin were soon shown to vary with circadian rhythms, and the melatonin rhythm was ultimately found to be generated by intrinsic circadian signals emanating from the suprachiasmatic nucleus (SCN) of the brain,[11] which were controlled primarily by the light–dark cycle.

Finally, in 1975, it was shown that melatonin production in humans also exhibits a pronounced circadian rhythm,[12] causing nocturnal plasma melatonin levels to be at least tenfold higher than those observed in the daytime. Moreover, this rhythm was not simply a response to the environmental light–dark cycle, since if people were suddenly placed in an environment that was dark between 11 A.M. and 7 P.M. (instead of the usual 11 P.M. to 7 A.M.), it took their melatonin rhythms 5–7 days to re-entrain. The view thus became canonized that the pineal is a “neuroendocrine transducer”[13] that tells all mammals when it is dark outside by raising plasma melatonin levels. The uses to which the body puts this information vary considerably among species: In diurnal, but not nocturnal, animals, melatonin promotes sleep onset and maintenance; in animals that breed seasonally, melatonin influences the choice of breeding season (i.e., spring or fall); and in those like humans and rats, which breed throughout the year, melatonin’s reproductive effects can be minimal.

Much subsequent pineal research has concerned the human brain’s responses to melatonin. The most compelling evidence now available supports two such uses, discussed below: the involvement of nocturnal melanin secretion in initiating and maintaining sleep, and control by the day/night melatonin rhythm of the timing of other 24-hr rhythms. It is melatonin’s effect on sleep that underlies most of its current use as a “dietary supplement.” Some additional possible benefits of melatonin supplementation have been proposed (e.g., as an antioxidant, or to slow aging, or to suppress cancer growth and hypertension). However, evidence supporting these effects is sparse.

Evidence is even more sparse that there is any rational basis for calling melatonin a “dietary supplement.” For melatonin to earn this appellation, it would have to be shown that at least some of the melatonin in human plasma derives from food sources, and that “supplementary” exogenous melatonin simply adds to what the foods provide. But as described below, there is no satisfactory evidence, based on contemporary analytic techniques, that any actual foods contain more than trace amounts of melatonin—if that—and no evidence at all that eating any food elevates human plasma melatonin levels. Melatonin is a hormone, like thyroxine and estrogens, and should be labeled and regulated as such. Only its extraordinary lack of overt toxicity apparently keeps the FDA from insisting that it undergo such regulation.

**MELATONIN SYNTHESIS AND METABOLISM: NEURAL AND PHOTIC CONTROL**

Almost all the melatonin formed in mammals is synthesized within the pineal gland, starting with the uptake of the amino acid tryptophan from the plasma. Since the pineal lies outside the blood–brain barrier, this process—in contrast to tryptophan’s uptake into the brain—is not subject to competition from other circulating neutral amino acids. The tryptophan is first 5-hydroxylated (by the enzyme tryptophan hydroxylase) and then decarboxylated (by the enzyme aromatic L-amino acid decarboxylase) to form 5-hydroxytryptamine or serotonin (Fig. 1).[9]

During daylight hours, the serotonin in pinealocytes tends to be stored, and is unavailable to enzymes (monoamine oxidase and the serotonin-forming enzymes) that would otherwise act on it. With the onset of darkness, postganglionic sympathetic outflow to the pineal increases, and the consequent release of norepinephrine onto pinealocytes causes stored serotonin to become accessible for intracellular metabolism. At the same time, the norepinephrine activates the enzymes (especially serotonin-N-acetyltransferase (SNAT), but also hydroxyindole-O-methyltransferase (HIOMT)), that convert serotonin to melatonin (Fig. 1).[9,10] Consequently, pineal melatonin levels rise manyfold. (Pineal levels of 5-methoxytryptophol, the corresponding deaminated and O-methylated metabolite of serotonin, also rise[11] even though formation of this compound is independent of SNAT.)

The melatonin then diffuses out of the pineal gland into the bloodstream and cerebrospinal fluid.[10,11] rapidly raising human plasma melatonin levels from about 2-10 to 100–200 pg/ml.[12] Melatonin is highly lipophilic, because both the ionizable groups in serotonin—the hydroxyl and the amine—have been blocked by its O-methylation and N-acetylation (Fig. 1). Thus, it diffuses freely across cell membranes into all tissues, and travels in the blood largely bound to albumin.

Most of the melatonin in the circulation is inactivated in the liver, where it is first oxidized to 6-OH-melatonin by a P450-dependent microsomal oxidase and then largely conjugated to sulfate or glucuronide before being excreted into the urine or feces.[13] About 2-3% is excreted unchanged into the urine or saliva, enabling measurements of urinary or salivary melatonin to be used as rough estimates of plasma melatonin levels. (Salivary melatonin apparently corresponds to the 25–30% of blood melatonin that is not bound to albumin.)

Studies using radioactively labeled melatonin of high specific activity have identified three probable melatonin receptors, two of which have been cloned using human sources.[17] These macromolecules are
Fig. 1 Metabolism of tryptophan to melatonin in the pineal gland. (Reproduced with permission from Zhdanova, I.V.; Wurtman, R.J. in Endocrinology: Basic and Clinical Principles; Conn, P.M., Melmed, S., Eds.: Humana Press, Inc.: Totowa, NJ, 1997; 281.)

Concentrated, respectively, within the suprachiasmatic nucleus of the hypothalamus, the pars tuberalis of the pituitary, and cardiac blood vessels (mT1), in the retina and hippocampus (mT2), and in kidney, brain, and various peripheral organs (mT3). Their affinities for melatonin are enhanced by several G-proteins. Activation of the mT1 and mT2 receptors by melatonin suppresses cAMP production. The mT2 site is shared 95% homology with a detoxifying enzyme, quinone reductase 2; its effects on specific signal transduction pathways await identification. Because of melatonin’s unusual lipid solubility, its receptors could be located intracellularly, in contrast to the plasma membrane receptors characteristic of neurotransmitters; indeed, a nuclear binding site has been identified. The mT1 receptors in the SCN allow melatonin to inhibit the firing of SCN neurons during the night—an action that might contribute to melatonin’s sleep-promoting effects. The SCN’s mT2 receptors apparently mediate melatonin’s effects on the SCN’s own circadian rhythms, as well as on other rhythms that this brain region controls.

In all species examined thus far, melatonin secretion manifests a characteristic circadian rhythm, causing plasma levels to be low during the daylight hours, ascend after the onset of darkness, peak in the middle of the night between 11 P.M. and 3 A.M., and then fall sharply before the time of light onset. (It is interesting that high nocturnal plasma melatonin levels characterize both diurnally active species, in which these levels promote sleep onset and maintenance, and nocturnally active ones, in which melatonin has no obvious relationship to sleep.) While this rhythm is normally tightly entrained to the environmental light cycle, it does persist when people are placed for a few days in a dark room, and it does not immediately phase-shift when the light schedule is altered, indicating that it is not simply generated by the light–dark cycle but also by cyclic endogenous signals, probably from the SCN. These reach the pineal via a retina-hypothalamic tract, the superior cervical ganglia, and postganglionic sympathetic fibers that re-enter the cranial cavity. In certain fish, birds, and reptiles, pineal glands also contain true photoreceptors, and generated (or even cultured) glands can sustain circadian rhythms in melatonin synthesis that can be entrained by the light–dark cycle; in contrast, light has no known direct effects on melatonin synthesis in humans and other mammals.

**PLASMA MELATONIN LEVELS**

Plasma melatonin normally reflects the amounts secreted by the pineal gland, the flux of melatonin into and out of tissues, melatonin’s destruction in the liver, and its secretion into urine and saliva. Since melatonin is now also available as a dietary supplement, plasma levels can reflect consumption of the exogenous compound as well. Available evidence does not support the view that humans derive any plasma melatonin from foods. Several laboratories have described a compound in dietary fruits or vegetables (e.g., tomato) that they concluded was melatonin. But in only one of these studies was the identity of the melatonin unambiguously confirmed by gas...
chromatography-spectrometry (GCMS), and in that study, the melatonin concentrations determined by GCMS were very low (less than 20 ng per kg of fruit), and the "concentrations...indicated by RIA were 6-100-fold higher than...by GCMS for the same extracts, suggesting...contamination by an immunological interference." Of perhaps greater relevance, no investigator has ever presented evidence that feeding any amount of any food to humans can raise plasma melatonin levels.

Usually, the principal factor affecting plasma melatonin levels is its rate of secretion, which varies with the circadian rhythm described above and as a function of age (Fig. 2). Nocturnal melatonin levels are also affected by drugs that interfere with the transmission of neurotransmitter signals to pineal cells (like propranolol, a beta-blocking agent), those that inhibit melatonin's metabolism (like 8-methoxypsoralen), and a few drugs that lack clear links to melatonin's synthesis or metabolism (e.g., caffeine, ethanol, ibuprofen, and indomethacin, which decrease melatonin).

Nocturnal melatonin secretion is also suppressed by exposure to environmental lighting, even by a relatively dim 100-200lux, when pupils are dilated.

Melatonin secretion by the human pineal gland exhibits a pronounced age dependence (Fig. 2). Secretion is minimal in newborns, starts during the third or fourth months of life (coinciding with the consolidation of sleeping at night), increases rapidly at ages 1-3 yr, and then declines slightly to a plateau that persists through early adulthood. Nocturnal melatonin secretion then starts a marked continuing decline in most people, with peak nocturnal levels in most 70-yr-olds being only a quarter or less of what they are in young adults. This decline may reflect the progressive unexplained but ubiquitous calcification of the pineal gland and resulting loss of secretory tissue. Obviously, one strategy in using supplemental melatonin is to administer to older people doses that are just sufficient to compensate for this age-related decline.

The first person to examine the effects of exogenous melatonin was the scientist who discovered it, Aaron Lerner; he explored its actions (and possible toxicities) by giving himself 200 mg intravenously per day for five consecutive days. Lerner described feeling "relaxed." Neither he nor the investigators who subsequently gave it (in doses of 10 mg-6.6 g) to 96 other subjects prior to 1977 measured its effects on plasma melatonin levels. However, since most administered doses in excess of 1 g, it can be assumed that massive increases in plasma melatonin ensued. When Waldhauser et al. administered 80 mg doses to two male volunteers in 1987, plasma levels increased more than 1000-fold, and serum prolactin levels rose significantly—an effect not observed with physiologic melatonin doses.

In 1993, Dollins et al. examined the effects of 10, 20, 40, or 80 mg melatonin on various behavioral indices (auditory vigilance; self-reported fatigue, confusion, and sleepiness; reaction times), body temperature, and plasma melatonin levels. All the doses tested produced similar changes in the behavioral assays and in body temperature. And all raised plasma melatonin levels to at least 5000 pg/ml—well beyond the normal nocturnal range of 100-200 pg/ml. Hence, the study was repeated using much lower doses (0.1-10 mg orally). The authors found that oral doses as low as 0.1-0.3 mg caused dose-related decreases in sleep latency and increases in sleep duration and self-reported sleepiness and fatigue, but without reducing body temperature or elevating plasma melatonin levels beyond their normal nocturnal range (Fig. 3). This suggested that nocturnal melatonin secretion—which produces plasma melatonin levels similar to those seen after the 0.3 mg dose—has a physiologic effect on sleep. It also identified the dosage range that investigators needed to use if they wanted to examine melatonin's physiologic effects.

It should be noted that there is considerable person-to-person variability in the bioavailability of melatonin. In one study using single 80 mg doses, there were 25-fold variations in areas under the curve (AUCs) in the five subjects studied. In another, using 0.5 mg oral doses, peak plasma melatonin levels among four subjects varied from 480 to 9200 ng/L. Melatonin's bioavailability was relatively poor—10% to 50%—which the authors attributed to person-to-person differences in first-pass hepatic extraction. Perhaps reflecting such differences in hepatic function, older subjects given a 0.3 mg oral dose of melatonin exhibit considerably greater increases in plasma melatonin levels.
levels, with correspondingly greater variability, than young adults receiving that dose.

These findings all suggest that while a 0.3 mg dose given to young subjects during the daytime, or to older insomnics at night, can, on average, produce normal nocturnal plasma melatonin levels, some individuals may need a little more, or a lot less, melatonin to attain this effect. The pharmacokinetic properties of any oral dosage of melatonin can also vary depending on the lipid solubility of the inert ingredients that accompany it: A preparation containing corn oil plus 0.05 mg melatonin elevated plasma melatonin levels to as high a peak (from 4 to 118 pg/ml)\textsuperscript{[30]}, though for a shorter period, as one containing 0.3 mg melatonin plus microcrystalline cellulose (15–105 pg/ml)\textsuperscript{[29]}.

\section*{EFFECTS OF MELATONIN}

Because melatonin is available as a dietary supplement and is relatively nontoxic, physicians, researchers, and even consumers are able to administer or consume doses that elevate its plasma levels to hundreds or even thousands of times those ever occurring normally.\textsuperscript{[26,31]} Indeed, even the 1–10 mg doses most commonly marketed raise these levels to 3–60 times their normal peaks (Fig. 3).\textsuperscript{[28]} Not surprisingly, such concentrations produce biological effects, for example, sleepiness, which might or might not also occur physiologically. Does the demonstration that a pharmacologic dose of melatonin produces such an effect indicate that the effect also occurs at normal night-time plasma melatonin levels? Or, by extension, that a deficiency in melatonin (e.g., in older people) can contribute to a related disease process? Alas, no: Enormous melatonin concentrations inhibit the aggregation of A-beta peptides to form amyloid in vitro;\textsuperscript{[32]} however, this no more means that the age-related decline in plasma melatonin causes Alzheimer's disease than that poison ivy dermatitis—which can be treated with cortisone—is a sign of adrenocortical insufficiency.

What evidence must be adduced before one can propose that some effect of a melatonin megadose also occurs in response to secreted melatonin? First, that the effect occurs when plasma melatonin levels rise or fall within their normal range. Second, that administering melatonin in the daytime, in doses that increase plasma melatonin concentrations to—but not beyond—peak night-time levels, also produces the effect. This type of study can sometimes be done in vitro: If melatonin were found to suppress beta-amyloid aggregation at concentrations found nocturnally in plasmas of young people (up to about 1 nM), but not in concentrations more typical of many older people (less than 0.3 nM), this would indeed be suggestive.

Using these criteria, two probably physiologic effects have been associated with melatonin administration—the promotion of sleep onset and maintenance,\textsuperscript{[28]} and the phase-shifting of circadian rhythms, including the rhythm in melatonin itself.\textsuperscript{[33]} Both are produced by physiologic doses, i.e., 0.1–0.3 mg for sleep and 0.5 mg for phase-shifting. Melatonin's actions on sleep include both a direct action (which decreases sleep latency, increases sleep efficiency, and increases total sleep time) and an indirect effect on the daily rhythm in the phasing of sleep onset.

\section*{Sleep}

A 1997 review\textsuperscript{[34]} on melatonin's hypnotic effects listed 24 papers, almost all of which described sedation, fatigue, decreased alertness, increased reaction time, shortened sleep latency (i.e., number of minutes needed to fall asleep), increased sleep efficiency (i.e., percentage of the total sleep period actually spent sleeping), and/or increased total sleep time. A recent (2005) meta-analysis\textsuperscript{[35]} of all the 17 studies (e.g., Refs 38–43), involving 284 subjects, that satisfied inclusion criteria demonstrated a significant decrease in sleep latency and significant increases in sleep efficiency and total sleep duration. The inclusion criteria were that a study include at least six subjects, all adults, be randomized and double-blinded, involve placebo-controlled clinical trials, and use objective measures of sleep evaluation. Studies could utilize crossover or parallel group designs; however, case reports were excluded. Statistical significance was obtained in spite of considerable variations among the studies in melatonin doses and
routes of administration, the general health of the subjects, and the measures used to evaluate sleep.

The effects of exogenous melatonin on sleep have been examined under three types of experimental conditions in relation to the onset or offset of endogenous melatonin secretion.

In some studies, the hormone was administered during the daily light period, such that blood melatonin levels would be transiently elevated but would then return to baseline before the initiation of nocturnal melatonin secretion. Such experiments were used to demonstrate that melatonin decreases sleep latency at any time in the afternoon or evening, and that this effect is independent of an action on sleep rhythms (since no treatment can immediately shift the phase of a circadian rhythm by 8–10 hr).

In others, the hormone was given close enough to the onset of darkness for blood melatonin levels to still be elevated when nocturnal melatonin secretion started. The period during which plasma melatonin levels were continuously elevated would thus be prolonged. Such experiments reflected the use of melatonin to decrease sleep latency and maintain continuous sleep in, for example, a shift-worker or eastbound world traveler who needed to start sleeping earlier.

In yet others, the hormone was given at the end of the light period to older insomniacs with low nighttime plasma melatonin levels. The intent was to prolong the portion of the night during which their plasma melatonin concentrations would be in the same range as those of noninsomniac young adults.

In all these situations, oral melatonin decreased sleep latency and, when tested, increased sleep duration and sleep efficiency. A 0.2 mg dose was either as effective as, or more effective than, higher doses, particularly when the hormone was administered for several days. This dose had no effect on body temperature, affirming that, while pharmacologic doses can cause hypothermia, melatonin’s ability to promote sleep is not mediated by such a change, as had been suggested. The hormone had no consistent effect on sleep architecture (e.g., REM time). Its effects differed from those of most hypnotic drugs, since after receiving melatonin, subjects could readily keep from falling asleep if they so chose, and their cognitive abilities the next morning were unchanged or improved.

In a relatively large (N = 30) study on people who were 50 yr old or older and did or did not suffer from clinically significant insomnia (i.e., sleep efficiencies of 70–80% in the insomniacs vs. 92% in controls), melatonin was found to produce statistically and clinically significant improvements in sleep efficiency among insomniacs (Fig. 4). A 0.3 mg dose caused the greatest effect (P < 0.0001), particularly during the middle portion of the nocturnal sleep period (Fig. 5).

![Fig. 4 Sleep efficiency in subjects with normal sleep (A) and age-related insomnia (B) following melatonin or placebo treatment. *P < 0.05. (Reproduced with permission from Ref.[41].)](image)

No effects were noted in subjects without insomnia, or in latency to sleep onset (which is not abnormal in this population). Dose-related increases in plasma melatonin levels were observed (Fig. 6), the 0.3 mg dose causing peak levels in the range usually observed nocturnally among young adults. When subjects received a higher dose (3.0 mg) but not 0.3 mg, plasma melatonin levels remained significantly elevated during much of

![Fig. 5 Sleep efficiency in insomniacs during three consecutive parts (I, II, and III) of the night, following placebo (light bar) or melatonin (0.3 mg, dark bar) treatment. *P < 0.05. (Reproduced with permission from Ref.[41].)](image)
their normal range, i.e., to 1327 pg/ml. As described above, melatonin can also control the timing of sleep and sleepiness rhythms—an effect readily demonstrated among blind people with free-running melatonin and sleep rhythms but also among sighted individuals.

Melatonin’s ability to phase-shift circadian rhythms underlies its common use to prevent or treat “jet lag”—particularly that associated with eastbound travel (possibly because the melatonin can be taken while the traveler is still awake). A 1999 review cited nine placebo-controlled field studies on this use; in seven, subjective measures of sleep and alertness improved. Adequate data are not available on the relationship between the ability of a particular melatonin dose to treat jet lag and to raise plasma melatonin levels. Some investigators recommend taking the melatonin at a specific time (e.g., at 2 a.m. in the traveler’s new geographic environment); others simply propose "... a pre-flight early evening treatment before an eastbound flight, followed by treatment at bedtime for four days after arrival..." Westbound, the traveler is advised to take the melatonin late in the evening, to sustain nocturnal plasma melatonin levels for as long into the night as possible.

Other Reported Effects

It has been suggested that melatonin is a potent antioxidant, and that supplements of the hormone may protect against such age-related diseases as atherosclerosis, cancer, and Alzheimer’s disease. None of these proposed uses has been tested in a controlled clinical trial and all remain controversial because of lack of confirmation, the enormousness of the melatonin concentrations or doses needed to produce the effect, the failure of the investigators to provide data on actual blood or tissue melatonin concentrations after treatment, and the lack of studies comparing melatonin’s effects with those of known antioxidants such as vitamins C or E. It has usually been possible to demonstrate antioxidant or free radical scavenger effects in vitro; however, these have generally required melatonin concentrations 1000–100,000 times those ever occurring in vivo. Similarly, while high doses of melatonin (10–450 mg/kg body weight parenterally) have sometimes elicited antioxidant effects in experimental animals in vivo, neither their long-term safety nor their effects on the animals’ blood melatonin levels have been characterized. In humans—if not in nocturnally active laboratory rodents—such megadoses might ultimately impair sleep or various circadian rhythms, perhaps by downregulating melatonin receptors.

Only one study has described careful dose-response studies on the ability of melatonin to protect
against auto-oxidation and compared melatonin, with known antioxidants. That study, by Duell et al. [31] examined the cell-mediated (by human macrophages) and cell-free (by copper sulfate) oxidation of low density lipoproteins (LDL), a process believed to contribute to atherosclerosis. Melatonin did exhibit weak antioxidant activity, but only at 10,000-100,000-fold physiologic concentrations. In contrast, a vitamin E preparation (alpha-tocopherol) was 50-100-fold more potent than melatonin, and was efficacious at physiologic concentrations. Similarly, vitamin C (ascorbic acid) and tryptophan, melatonin’s indolic circulating precursor (Fig. 1), were significantly more potent than melatonin and were active at physiologic concentrations.

Some investigators suggest—based on small studies on laboratory rodents—that melatonin “maintains juvenile conditions” and is a “geroprotector.” There is no evidence that melatonin has any “antiaging” actions in humans.

In several small studies, melatonin was found to reduce blood pressure when given to normotensive men or women in daytime or the early evening, or to patients with essential hypertension. This possible effect should be explored further.

PRESENT USAGE OF MELATONIN

In the United States, the hormone melatonin is sold, without regulation by the FDA, as a dietary supplement. In most of the rest of the world, it is not sold at all, because it is regulated as a drug and no pharmaceutical company has presented an appropriate regulatory body with a successful new drug application (NDA) for its use. Some countries allow very low doses—less than 100 mg—to be sold without regulatory approval.

Why is melatonin not subject to FDA approval and oversight, while other hormones are subject to such regulation? This is a consequence of the way the Dietary Supplement Health and Education Act of 1994 (Public Law 103–147) has been implemented. That act exempts from FDA regulation a product that is “...intended to supplement the diet that... contains one or more of the following dietary ingredients...,” a list that includes “(D) an amino acid” (e.g., tryptophan), and “(F)...a metabolite...of any ingredient described in clause...(D)” (e.g., melatonin). Not exempted are products like L-dopa that have been “...approved as a new drug...” or “...authorized for investigation as a new drug...” Thyrroxine, estrogens, and testosterone had also been approved as drugs prior to passage of the 1994 Dietary Supplement Act, while melatonin had not; thus, melatonin is treated as a dietary supplement, even though there is virtually no “dietary melatonin” for the “dietary supplement” to supplement.

What have been the consequences of melatonin not being regulated by the FDA? Apparently no deaths to date; if melatonin-related deaths had occurred, the 1994 Act would have allowed the FDA to investigate, and then perhaps to start regulating it. In fact, few serious side effects have been described: A 2001 article described a 35 yr search (1966–2000) of reports on melatonin toxicity using the Medline database. Nine articles were found to describe adverse effects of melatonin; in all cases, the doses administered were in the pharmacologic range (1–36 mg). Individual patients exhibited, autoimmune hepatitis, confusion, optic neuropathy, a psychotic episode, headache, or nystagmus. Four suffered fragmented sleep, four described seizures, and two exhibited skin eruptions. Obviously, no clear pattern of side effects emerges from this review.

In the absence of FDA regulation, companies are able to sell melatonin of uncertain purity, at dosages that are many times those needed for promoting sleep or shifting rhythms, or for restoring normal nocturnal plasma melatonin levels in older people. These dosages can elevate plasma melatonin to levels thousands of times greater than those that ever occur normally, and produce mild but not benign side effects like hypothermia and “hangovers.” Paradoxically, they also may, through receptor downregulation, exacerbate the insomnia that the consumer was trying to treat.

CONCLUSIONS

This entry describes melatonin, a hormone that is presently marketed as a dietary supplement. Melatonin is synthesized at night in the human pineal gland and released into the blood and cerebrospinal fluid. It acts on the brains of humans to promote sleep, and also influences the phasing of sleep and various other circadian rhythms. During the day, plasma melatonin levels are low; at night, they rise 10–100-fold or more in young adults, but by considerably less in older people—who often may have frequent nocturnal awakenings as a consequence. Very small oral doses of melatonin—about 0.3 mg or less—raise daytime plasma melatonin to night-time levels, thus making it easier for people to fall asleep in the afternoon or evening. Such doses can also help older people remain asleep during the night. Melatonin has also occasionally been claimed to confer other medical benefits—e.g., preventing such age-related diseases as atherosclerosis, cancer, and Alzheimer’s disease. The evidence in support of such claims is sparse.
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