The Biological Effects and Clinical Uses of the Pineal Hormone Melatonin

Timothy C. Birdsall, ND

Abstract

Melatonin, the primary hormone of the pineal gland, acts as a powerful "chronobiotic," maintaining normal circadian rhythms. In patients with sleep disorders and exogenously-generated desynchrony of circadian rhythms such as occurs in jet lag, oral administration of melatonin can provide the necessary resynchronization of those cycles, at dosages ranging from 0.3 to 8 mg. Synthesis of melatonin from the amino acid tryptophan has been shown to be decreased by exposure to magnetic fields and by the aging process. Melatonin also possesses potent free radical scavenging properties and has been recognized as exerting direct inhibition of cancer growth. Various cancer types have been shown to be responsive to oral melatonin (10 to 50 mg daily), including breast cancer, non-small-cell lung cancer, metastatic renal cell carcinoma, hepatocellular carcinoma, and brain metastases due to solid tumors. Melatonin has also been reported to lower total cholesterol and LDL levels in rats, and abnormally low melatonin levels have been theorized to be a factor in multiple sclerosis, sudden infant death syndrome, coronary heart disease, epilepsy, and postmenopausal osteoporosis. These reports, while preliminary, serve to further illustrate the wide range of potential effects exerted by melatonin.
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Biosynthesis and Physiologic Role of Melatonin

Synthesis of melatonin, the primary hormone of the pineal gland, displays a pronounced circadian rhythm. The production of melatonin (N-acetyl-5-methoxytryptamine) from the amino acid tryptophan (Figure 1) is primarily nocturnal and is controlled by exposure to cycles of light and dark, independent of sleep. The synthesis of melatonin is inhibited by exposure to light and stimulated during periods of darkness by way of a multi-synaptic neural pathway connecting the pineal gland to the external environment via the retina. [1] (Figure 2.)

This sympathetic innervation, through the hypothalamic suprachiasmatic nuclei, upper thoracic pre-ganglionic neurons and post-ganglionic fibers from the superior cervical ganglion has been shown to be essential to normal production and circadian cycling of melatonin. Diabetic patients with autonomic neuropathy have been found to have lower 24-hour melatonin levels and a lower nocturnal melatonin peak when compared to diabetics with an intact autonomic system. [1] This is consistent with earlier findings in patients with abnormal pre-ganglionic [2] and post-ganglionic [3] sympathetic enervation, as well as those with cervical spinal cord

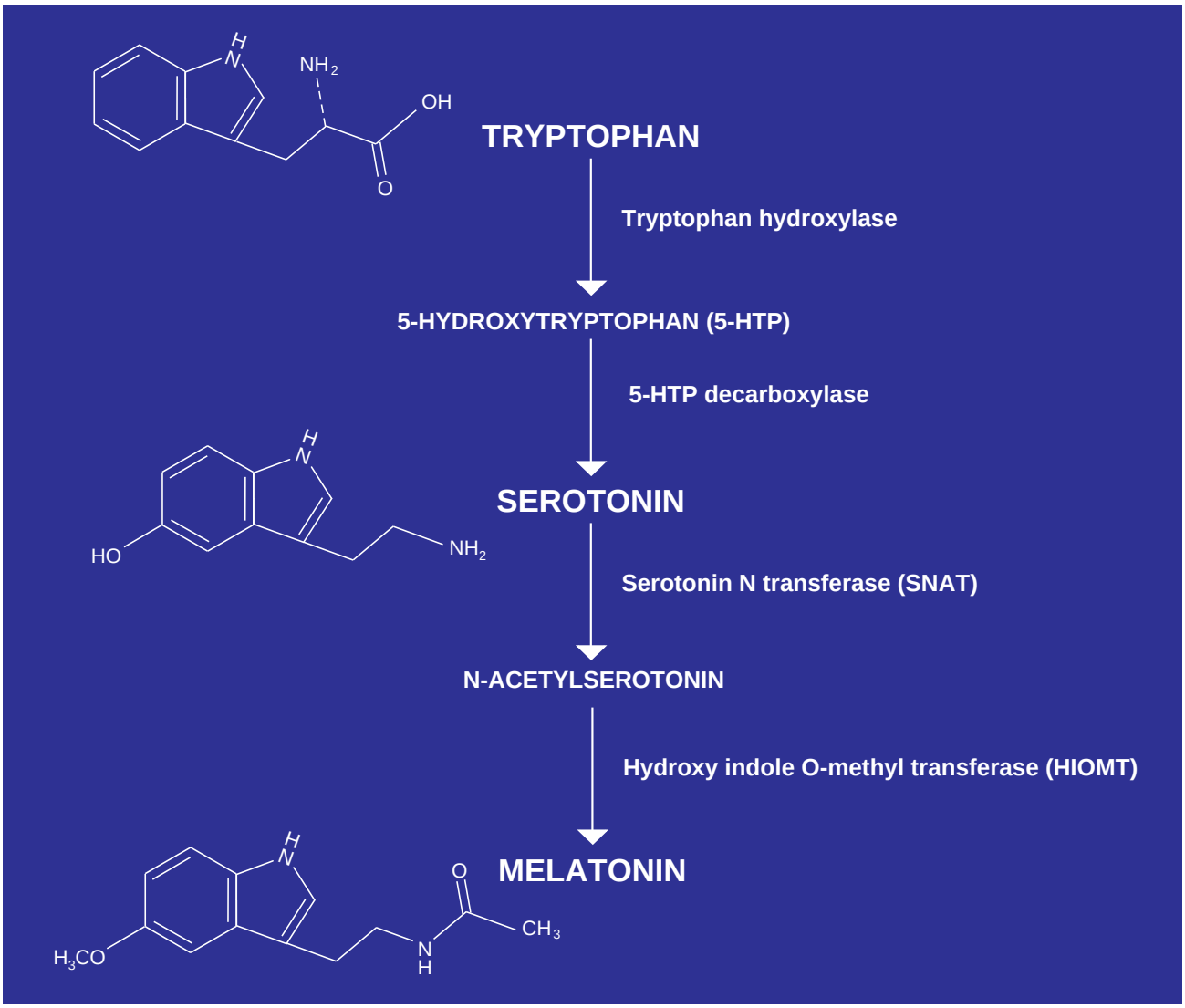

FIGURE 1. Biosynthesis of melatonin

damage resulting in sympathetic dysfunction.[4,5] Further evidence of the importance of this retino-pineal pathway is provided by observations that persons who are blind frequently have profound circadian rhythm disturbances [6] which can be at least partially corrected by exogenously administered melatonin. [7,8]

Melatonin Influences on the Neuroendocrine-Reproductive Axis

In animals which have a seasonal breeding pattern, melatonin levels may play a role in signaling changes in reproductive hormone levels. In long-day breeders, such as rodents, melatonin secretion increases as the days lengthen, inhibiting gonadotrophin releasing hormone secretion, thus decreasing gonadotrophin levels. [9] What is perhaps less expected is that melatonin also effects reproductive hormonal levels in non-seasonal breeding mammals such as humans, although its precise role remains unclear. In a short-term study, Terzolo and associates evaluated the effects of melatonin administration on prolactin secretion. Using a double-blind, placebo-controlled, cross-over protocol, seven women

were administered either 4 mg melatonin or placebo in the mid-follicular phase (days 8-10) of their menstrual cycle. Prolactin levels were then monitored for the next 6 hours. The researchers found that melatonin administration increased mean prolactin levels (551 vs. 281 mIU/l, $p<0.05$), maximal prolactin secretion (716 vs. 324 mIU/l, $p<0.001$), and lowest prolactin secretion (572 vs. 216 mIU/l, $p<0.001$). No short-term effects were found on leutinizing hormone or thyroid stimulating hormone, [10] although animal studies have found that melatonin administration decreases serum T4 levels and T3 uptake. [11]

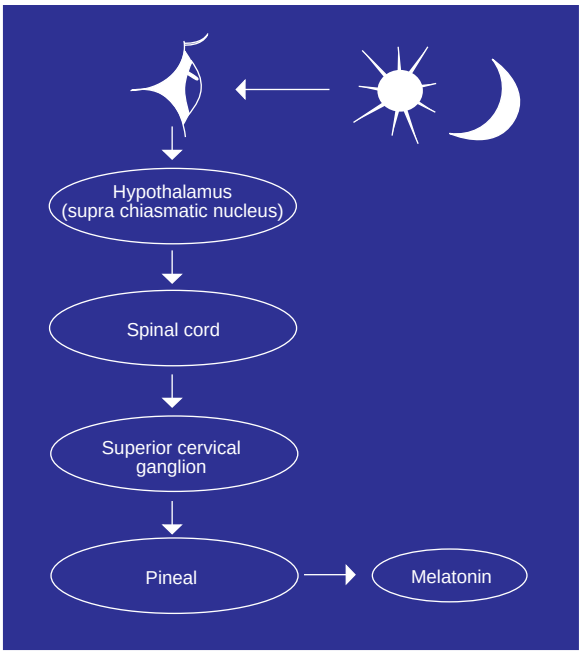

FIGURE 2. Neurologic pathway connecting the pineal gland to the retina.

Recently, researchers have also demonstrated the presence of melatonin receptors in human prostate epithelial cells. Based on evidence that melatonin administration delayed pubertal development in rats, with the most pronounced effects on prostate development, [12] Laudon and colleagues used radiolabeled melatonin to determine the presence of melatonin receptors on prostate cells surgically removed from patients with benign prostatic hyperplasia.[13] The researchers then grew the cells *in vitro* with and without added melatonin. Melatonin inhibited the growth of the cells and decreased the rate of protein synthesis, even when dihydrotestosterone was also present, raising the possibility that melatonin might regulate androgen responses in the prostate gland itself. [14]

While much more research must be done before firm conclusions may be drawn, it currently appears that significant interactions do exist between melatonin and other hormones. Given these reported effects of melatonin on the neuroendocrine-reproductive axis, clinicians should exercise caution when placing patients on long-term or high-dose melatonin therapy.

Magnetic Field Effects on Melatonin

The synthesis of melatonin has been reported to be affected by exposure to both electric and magnetic fields. The elevated nocturnal formation of melatonin involves an increase in the activity of the enzyme N-acetyltransferase (NAT), which acts on serotonin, converting it to N-acetylserotonin (See Figure 1); this conversion is considered to be the rate-limiting step in melatonin synthesis. Exposure to both static and pulsed magnetic fields has been shown to significantly decrease NAT activity and melatonin levels in the pineal gland of experimental animals. [15-17]

While the effects of magnetic fields on melatonin production on humans have yet to be investigated, given the widely acting nature of melatonin, the implications are profound. A depressed circadian melatonin cycle might be the mechanism by which electromagnetic fields generate a dysfunctional biological response in humans.

Circadian Rhythm and Sleep

To date, the primary physiological role identified for melatonin in humans has been its ability to influence circadian rhythms in the body. When administered in pharmacologic doses, melatonin acts as a powerful "chronobiotic," maintaining synchronicity and preventing desynchrony of circadian rhythms. [18] Because the hours of highest melatonin secretion correlate to normal hours of sleep, the hormone has also been investigated for use in sleep disorders. Recently, Attenburrow et al demonstrated that patients with insomnia have decreased nocturnal melatonin secretion. [19]

In a placebo-controlled trial using 8 subjects with delayed sleep phase insomnia, Dahlitz et al found that melatonin acted as a "phase-setter" for sleep-wake cycles. The subjects were given placebo or melatonin (5 mg daily at 10:00 PM) for 4 weeks with a 1-week washout period between the treatments, and were allowed to awaken naturally. In all 8 subjects, the onset of sleep occurred earlier during melatonin treatment (mean change=82 minutes; $p<0.01$). There was a slight decrease in the total amount of time asleep, but ratings of daytime alertness showed no change. [20] Similar results were obtained by another group of researchers who administered 5 mg of melatonin nightly to 6 subjects with delayed sleep phase insomnia. The onset of sleep was an average of 115 minutes earlier when the subjects were taking melatonin when compared to pre-melatonin findings. [21]

MacFarlane and associates investigated the use of high-dose melatonin in the treatment of chronic insomniacs. In a 2-week study, the researchers administered either 75 mg of melatonin or placebo at 10 PM to a group of 13 insomniacs. Those who received the melatonin had significant increases in their total sleep time as well as daytime alertness, although a majority of the subjects reported no significant improvement in their subjective feelings of well-being. [22]

Low-dose melatonin also has been shown to be effective in treating insomnia. In a recent study, volunteers were either given 0.3 mg or 1.0 mg doses of melatonin or placebo. Both of the dosage levels of melatonin were effective at decreasing the time needed to fall asleep. [23] In another study of 20 male volunteers, 0.1 mg and 0.3 mg doses of melatonin given in the morning generated peak serum levels of melatonin which were within the normal nighttime range for those untreated, indicating that these small oral doses may be effective for replacement therapy in those who are melatonin deficient. [24] Haimov and associates have also reported on the effectiveness of 1-2 mg doses in treating melatonin-deficient elderly insomniacs. [25]

The time-dependent nature of melatonin effectiveness has also been demonstrated. Tischinsky and Lavie administered either 5 mg of melatonin or placebo to 18 subjects following an overnight sleep deprivation, varying the time of administration from noon to 9 PM. Melatonin was effective at increasing both the subjective and objective sleepiness of the subjects at all times of administration; however, the time-delay between administration and maximal effect varied linearly from 3 hours 40 minutes at noon, to 1 hour at 9 PM. [26]

Jet Lag

Melatonin administration also has been shown to be effective in minimizing the effects of jet lag in travelers crossing multiple time zones. Use of melatonin has been shown to decrease subjective feelings of jet lag (2.15 vs. 3.40), the time required to establish a normal sleep pattern (2.85 vs. 4.15 days), the time required to not feel tired during the day (3.0 vs. 4.6 days), and the time required to return to normal energy levels (3.25 vs. 4.7 days). [27]

In a placebo-controlled trial, Claustrat and associates demonstrated the effectiveness of a simplified protocol for alleviation of jet lag following intercontinental flights. Thirty-seven subjects were selected who had experienced jet lag on previous eastward intercontinental flights. The subjects, who were flying from North America to France overnight, took 8 mg of melatonin on the day of departure at the time when it would have been 10 PM in France, and then took 8 mg daily for 3 days at bedtime in France. Seven days after the flight, the subjects were asked to fill out a questionnaire rating efficacy, sleepiness, mood, tiredness and efficiency at work. Significant differences were found between melatonin and placebo in overall effectiveness ($p<0.05$), with less morning ($p<0,01$), and evening sleepiness ($p<0.01$). [28]

Melatonin is the major hormonal controller of circadian rhythms in the body, especially those involving sleep/wake cycles. In patients with sleep disorders as well as those with exogenously-generated desynchrony of circadian rhythms such as occurs in jet lag, administration of melatonin can provide the necessary resynchronization of those cycles.

Effects of Aging on Circadian Rhythm

While the 24-hour circadian rhythm of melatonin production is very striking in young animals, including humans, the cycle deteriorates during aging. [29] The normal rhythm of melatonin can be substantially maintained during aging by restricting the food intake of experimental animals; this same treatment increases the life span of the animals. [30] In a group of 71 subjects, ages 19-89, Sharma et al found a significant negative correlation found between mean melatonin levels and age. [31]

Recent studies in mice have strongly indicated that the pineal gland is central to the aging process. [32-34] In 1994, Lesnikov and Pierpaoli reported on a series of surgical experiments involving cross-transplantation of the pineal gland from young-to-old mice, and vice versa. Young (3- to 4-month-old) and old (18-month-old) mice had their pineal gland removed and grafted into mice in the opposite age bracket. A remarkable increase in the rate of aging and death was seen in the young mice grafted with "old" pineal glands, while the old mice grafted with "young" pineal glands showed a very significant delay in aging and an increase in life span (See Table 1). [34]

TABLE 1. Effect of cross-transplantation of the pineal gland in mice. [34]

	Survival in days
Control (sham operated) mice	719 +/- 32
"Old" pineal gland in young mice	510 +/- 36 *
"Young" pineal gland in old mice	1021 +/- 56 **

* $p<0.01$ ** $p<0.002$

Melatonin as a Free-radical Scavenger

In 1993, Tan and associates discovered that melatonin possessed potent free radical scavenging properties both *in vitro* [35] and *in vivo* in rats. [36] When compared to glutathione and mannitol, melatonin was found to be an extremely effective hydroxyl radical scavenger. The concentrations necessary to inhibit hydroxyl radical formation *in vitro* were 21, 123 and 238 μM for melatonin, glutathione and mannitol, respectively, as shown in Figure 3.

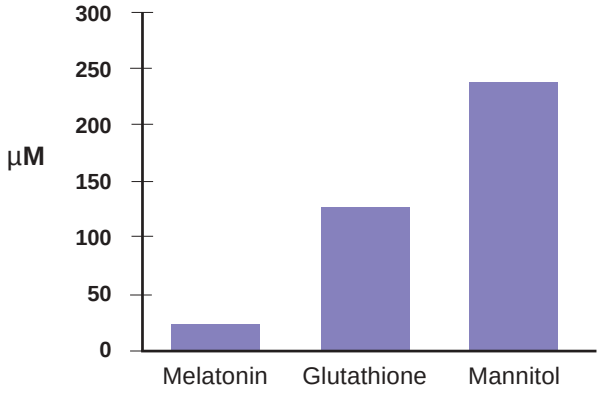

FIGURE 3. Hydroxyl radical quenching. The amounts of melatonin, glutathione and manitol required in μM to inhibit DMPO-OH adduct formation by 50% (IC_{50})[35].

To confirm this effect *in vivo*, Tan et al utilized the chemical carcinogen safrole, which damages DNA by creating a huge oxidative onslaught. Rats were injected with an amount of safrole adequate to produce considerable hepatic DNA damage. Those that had been pretreated with melatonin showed from 41% to 99% reduction in DNA damage, depending on the dose of melatonin administered. These results indicate that melatonin is "highly protective" of DNA when it is exposed to oxidative free radical assault. [36]

Melatonin and Cancer

In addition to its role as a free-radical scavenger, melatonin has been recognized as exerting direct inhibition of cancer growth. This has been shown *in vitro* in certain human breast cancer cell lines such as MCF-7[37] as well as in animal models. [38] Timing of the melatonin dosage appears to be important, even in the *in vitro* studies, with the most effective protocol being a diurnal cycle mimicking the physiological rhythm of melatonin secretion. [37] Various cancer types have been shown to be responsive to melatonin, including breast cancer, [37,39] non-small-cell lung cancer, [40] metastatic renal cell carcinoma, [41] hepatocellular carcinoma, [42] and brain metastases due to solid tumors, [43] at levels between 10 and 50 mg daily.

In a study of 14 metastatic breast cancer patients who had not responded to initial therapy with tamoxifen, 20 mg of melatonin was administered daily in the evening along with tamoxifen. A partial response was seen in 28% of these patients whose disease would have otherwise been expected to progress rapidly. In those who responded clinically, significant declines also were found in serum levels of the tumor growth factor IGF-1 ($p<0.001$). This response was irrespective of estrogen receptor status. [39]

One of the cancers least responsive to conventional cancer therapy is non-small-cell (NSC) lung cancer. In a randomized study, 63 consecutive NSC cancer patients with metastatic disease that did not respond to initial therapy with cisplatin were placed on either melatonin (10 mg daily at 7 PM) or supportive care alone. Mean survival time was significantly higher for those in the melatonin group than for those receiving supportive care alone (7.9 +/- 1 vs. 4.1 +/- 0.5 months, $p<0.05$). [40]

In patients with advanced solid tumors, one of the most clinically unfavorable events is the development of brain metastases. In these patients, few treatment options are available, and survival time is often less than 6 months. Fifty consecutive cancer patients with brain metastases whose disease had progressed under initial therapy were randomized to receive either supportive care alone or supportive care plus melatonin (20 mg daily at 8 PM). The survival at 1 year (9/24 vs. 3/26, $p<0.05$), mean survival time (9.2 +/- 0.9 vs. 5.5 +/- 0.7

months, $p<0.05$), and time free from brain progression (5.9 +/- 0.8 vs. 2.7 +/- 0.6 months, $p<0.05$) were all significantly higher in the group receiving melatonin. [43]

Other Effects

In addition to the above well-documented research on melatonin, several other published studies deserve mention. Melatonin has been reported to lower total cholesterol and LDL levels in rats, [44] and abnormally low melatonin levels have been theorized to be a factor in multiple sclerosis, [45,46] sudden infant death syndrome, [47] coronary heart disease,[48] epilepsy, [49] and postmenopausal osteoporosis. [50] While these reports are preliminary at best, they do serve to further illustrate the wide range of potential effects exerted by melatonin.

Conclusion

Melatonin is the primary hormonal determinant of normal circadian rhythms, and derangements in circadian rhythms can often be traced to inadequate or desynchronous melatonin secretion which may be corrected with melatonin supplementation. In addition, melatonin is a potent free-radical scavenger, and because melatonin production decreases with age, might also be an important factor in the aging process. Direct inhibition of cancer growth has been observed with melatonin supplementation, and a wide variety of cancer types have been found to be responsive to this therapy, including breast cancer, non-small-cell lung cancer, metastatic renal cell carcinoma, hepatocellular carcinoma, and brain metastases due to solid tumors. Evening doses of melatonin as low as 0.3 mg have been shown to be adequate in improving sleep quality, while 10 to 50 mg daily have been used in the treatment of advanced cancer.

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