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Review

Physiology and pharmacology of melatonin in relation to biological rhythms

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Abstract:
Melatonin is an evolutionarily conserved molecule that serves a time-keeping function in various species. In vertebrates, melatonin is produced predominantly by the pineal gland with a marked circadian rhythm that is governed by the central circadian pacemaker (biological clock) in the suprachiasmatic nuclei of the hypothalamus. High levels of melatonin are normally found at night, and low levels are seen during daylight hours. As a consequence, melatonin has been called the "darkness hormone". This review surveys the current state of knowledge regarding the regulation of melatonin synthesis, receptor expression, and function. In particular, it addresses the physiological, pathological, and therapeutic aspects of melatonin in humans, with an emphasis on biological rhythms.

Key words:
melatonin, AANAT, melatonin receptors, pineal gland, retina, circadian rhythm, light, photoperiod, circadian rhythm sleep disorders

Introduction

Melatonin was originally discovered fifty years ago by the American dermatologist Aaron Lerner and his co-workers as an amphibian skin-lighting factor present in extracts of bovine pineal glands. Lerner named the molecule melatonin because it induces contraction of stellate amphibian melanophores [170]. Subsequently, melatonin was reported to be present in a wide spectrum of organisms, including bacteria, fungi, plants, protozoa, invertebrates [118, 120] and vertebrates (see below), including man. The fact that melatonin is an evolutionarily highly conserved molecule speaks in favor of its important physiological role(s).

In vertebrates, melatonin is produced predominantly by the pineal gland (reviewed in [12, 160, 251]). Extrapineal sites of melatonin production include the retina, Harderian gland, gut, bone marrow, platelets, and skin (e.g., [47, 63, 76, 136, 296]). However, with the exception of the retina, the physiological significance of these extrapineal sites is still a matter of debate. In the vast majority of species examined, the synthesis of melatonin is significantly lower in the retina than in the pineal gland. In the pineal gland, melatonin is synthesized by pinealocytes, whereas in the retina, it is produced by photoreceptor cells [12, 53, 136, 160, 306, 355].

Melatonin produced by the pineal gland is released into the cerebrospinal fluid and the circulation, and exerts various biological actions upon reaching melatonin receptor-rich target tissues. Although the eye contributes significantly to circulating melatonin levels [25, 73, 81, 317, 318] in a few species (i.e., sea bass, frog, quail, and pigeon), it is generally accepted that melatonin synthesized by the retina acts primarily within the eye [136, 246].

Melatonin biosynthesis

Melatonin is synthesized from a dietary amino acid precursor, L-tryptophan, *via* the following pathway:

L-Tryptophan
↓ tryptophan hydroxylase (TPH; EC 1.14.16.4.)
5-Hydroxytryptophan
↓ aromatic aminoacid decarboxylase (AADC; EC 4.1.1.28)
5-Hydroxytryptamine (Serotonin; 5-HT)
↓ serotonin N-acetyltransferase (arylalkylamine N-acetyltransferase; AANAT; EC 2.3.1.87)
N-Acetyl-5-hydroxytryptamine
↓ hydroxyindole-O-methyltransferase (HIOMT; EC 2.1.1.4)
N-Acetyl-5-methoxytryptamine (**melatonin**)

The rate of melatonin formation depends on the activity of two enzymes: serotonin N-acetyltransferase (AANAT) [136, 153] and, to a lesser extent, tryptophan hydroxylase (TPH), which controls the availability of serotonin [52, 309]. In addition, it has been demonstrated that some nutritional factors, such as the availability of tryptophan, folate, and vitamin B6, could also influence melatonin production [96, 195, 323, 368].

Tryptophan hydroxylase (TPH)

The mitochondrial enzyme TPH transforms tryptophan to 5-hydroxytryptophan, and requires a pteridine cofactor, tetrahydrobiopterin (BH4), for its catalytic action. The localization of TPH is restricted to serotonin-synthesizing tissues, including the pineal gland and retina [61, 203, 305, 308]. Once thought to be a single gene product, TPH is now known to exist in two isoforms. TPH1 is found in the pineal gland and gut, whereas TPH2 is exclusively expressed in the brain [269, 305]. In the pineal gland and retina, the expression of TPH mRNA and/or TPH activity fluctuates in a clock-driven circadian rhythm, with high values occurring during the night [61, 90, 305, 308]. The nocturnal increase in the enzyme activity requires *de novo* protein synthesis [308]. Exposure to light during the night causes a rapid reduction in nocturnal TPH activity [91, 308].

Serotonin N-acetyltransferase (AANAT)

Serotonin N-acetyltransferase (AANAT) is considered a key regulatory enzyme in the melatonin biosynthetic pathway (reviewed in [64, 153]). In line with this assumption, changes in melatonin content and secretion reflect oscillations in AANAT activity (e.g., [12, 152, 153, 359, 363]). Due to its role in melatonin biosynthesis, AANAT has been named "the melatonin rhythm enzyme" [153]. Northern blot analysis revealed the presence of high AANAT mRNA levels in the pineal glands and retinas of vertebrates [62, 136, 277]. In the retina, AANAT mRNA has been observed primarily in photoreceptor cells [28, 65, 186] and, at significantly lower levels, in the inner nuclear layer and the ganglion cell layer [28, 186]. These findings suggest that, in addition to photoreceptors, other retinal cells may also possess a limited capacity to produce melatonin (reviewed in [136]).

A single *Aanat* gene has been found in mammalian, avian, and anuran genomes [64]. Teleost fish have been reported to have two genes: *Aanat-1* (homologous to the non-fish *Aanats*) and *Aanat-2*, primarily expressed in the retina and pineal gland, respectively (e.g., [87, 367]). Vertebrate AANATs belong to a superfamily of GCN5-related N-acetyltransferases (GNAT), and require acetyl coenzyme A (AcCoA) as an acetyl group donor [64, 153]. The enzyme has a high affinity for arylalkylamines, such as tryptamine and serotonin, and has a very low activity with regard to arylamines, such as phenylamine [89, 155]. Vertebrate AANATs are comprised of a catalytic core and regulatory regions. The former binds arylalkylamines and AcCoA and facilitates the transfer of the acetyl group, while the latter contains phosphorylation sites critical for activation and stabilization of the catalytic core. Phosphorylation of these sites promotes binding to 14-3-3 proteins, which reduces the K_m for the arylalkylamine substrates and also protects the enzyme from proteosomal proteolysis [64]. Pineal AANAT activity in

mammals is controlled by a circadian clock located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. In the pineal organs of birds and lower vertebrates and in the vertebrate retina, AANAT is regulated by a circadian clock located in the pinealocytes and photoreceptors, respectively (reviewed in [64, 136]).

Melatonin catabolism

Melatonin produced by the pineal gland is released into the circulation and gains access to various fluids, tissues and cellular compartments. Because this highly lipophilic hormone is not stored in the pineal gland, the profile of its plasma levels reflects pineal activity (reviewed in [12]). More than 90% of circulating melatonin is deactivated by the liver. Melatonin is first hydroxylated at the 6-position by a hepatic cytochrome P450, predominantly the CYP1A2 isoform [85, 200, 292]. 6-Hydroxymelatonin is then conjugated with sulfate and, to a lesser extent, with glucuronic acid, and the formed conjugates are excreted in urine [12, 19, 158, 169, 294]. In some mouse strains, melatonin has been shown to be metabolized to 6-glucuronylmelatonin rather than 6-sulfatoxymelatonin (aMT6s) [148, 199]. Very small amounts of free 6-hydroxymelatonin are excreted unchanged in the urine; other minor metabolites have also been identified [12]. Urinary aMT6s excretion closely reflects the plasma melatonin profile and is frequently used for evaluation of melatonin rhythm, especially in humans [11, 12, 39]. The metabolism of melatonin is rapid, and its half-life in humans following exogenous administration is short, ranging between 10 and 60 min [97, 165, 331].

Within the brain, melatonin is degraded *via* oxidative pyrrole-ring cleavage. N^1-Acetyl-N^2-formyl-5-methoxykynuramine (AFMK), a product of this reaction, is subsequently deformylated by either arylamine formamidase or hemoperoxidase to N^1-acetyl-5-methoxykynuramine (AMK) [12, 267].

Metabolic breakdown of retinal melatonin is different from that of the melatonin synthesized by the pineal gland. Initially, aryl acylamidase (aryl-acylamide amidohydrolase) catalyzes the deacetylation of melatonin to 5-methoxytryptamine. Subsequently, 5-methoxytryptamine is metabolized *via* the same pathway as indoleamines and catecholamines, with deamination by monoamine oxidase to form 5-methoxyindole acetaldehyde, and its further oxidation to 5-methoxyindoleacetic acid or reduction to 5-methoxytryptophol [110].

Melatonin synthesis is controlled by an endogenous circadian clock and environmental light

The melatonin rhythm: a chemical expression of darkness

The most striking features of the melatonin-generating system are its daily variation and sensitivity to light, which suppresses its activity. Regardless of whether a given species is active during day-time (diurnal), night-time (nocturnal), or exhibits a crepuscular activity pattern, melatonin levels are high during the dark phase of any natural or imposed light-dark (LD) illumination cycle (reviewed in [12, 251]). An exception to this "high-at-night' rule is the retina of some salmonoid fish, where melatonin levels are high during the day or no significant differences between day and night levels have been found [31, 133]. These species-specific variations in melatonin rhythm profiles may have developed as a result of changes in regulatory mechanisms during the course of evolution [133].

The rate and pattern of the nocturnal increase in melatonin production depend on species and tissues, among other factors. Three different basic patterns of pineal melatonin production have been described in mammals [326]. Type A, which is generally uncommon among animals, but is demonstrated in the Syrian hamster, Mongolian gerbil, and the house mouse, is characterized by a discrete melatonin peak occurring late in the night (or in the dark phase of the LD cycle). After midnight, melatonin levels quickly increase to peak values, and soon thereafter, before the time of lights on, they decline to day-time values. Type B represents the most common pattern of nocturnal pineal melatonin formation, and is characterized by a midnight melatonin peak. In animals with this pattern (e.g., rat, guinea pig, ground squirrel) and in man, pineal melatonin levels gradually rise, beginning at about the time of lights off, reaching a peak around the middle of the night, and then decline slowly during the second half of the night to reach

low day-time values near the time of lights on. A similar pattern is exhibited by some avian species [358, 363]. Animals with a type C pattern are also common. The type C pattern is characterized by a prolonged peak of melatonin levels for virtually the entire night; thus, peak melatonin production is reached soon after the onset of darkness. These high levels of the hormone are maintained for most of the night and decrease before lights on. This pattern of nocturnal melatonin synthesis is present in animals such as sheep, deer, cat, and the Djungarian hamster.

Rhythmic variations in melatonin and/or AANAT activities are circadian in nature, as they persist under constant darkness (DD) in most species. Both melatonin and AANAT activity are low during the subjective light phase, and are high during the subjective dark phase of the cycle (e.g., [2, 12, 53, 160, 194, 358, 364]). Circadian fluctuation in melatonin release has also been observed in flow-through cultures of chick pinealocytes [227] and in frog and mammalian retinas [53, 313, 314], indicating the presence of an intrinsic circadian clock in these tissues. Under DD, the amplitude of the melatonin/AANAT activity rhythm progressively dampened. This dampening was predominantly due to a decrease in enzyme activity and melatonin production during the subjective dark phase (both in the pineal gland and retina), and – in the retina only – to an increase in AANAT activity and melatonin synthesis during the subjective light phase [2, 53, 194, 361, 364]. The melatonin rhythm is usually undetectable in mammals kept in constant illumination of sufficient intensity [4, 37, 42]. By contrast, in the pineal gland of galliforms, melatonin levels, expression of AANAT mRNA, and AANAT activity rhythmically oscillate, albeit at a low amplitude, for a few days under continuous light (LL) [28, 194, 364].

The shape of the melatonin rhythm changes with season

Rhythmic melatonin production in various taxonomic classes of vertebrates is modified by seasonal changes in day length (photoperiod) [7, 8, 14, 73, 83, 100, 101, 132, 324, 325, 359]. Namely, the duration of elevated pineal/plasma melatonin levels increases proportionally to the length of the night. In some species the photoperiod may also affect the amplitude of the melatonin rhythm. A few reports indicate that humans are also able to respond to environmental day length by altering melatonin secretion [48, 128, 196, 285, 336]. It is believed that the pineal gland, through the secretion of melatonin, is essential for photoperiodic time measurement and allows organisms to anticipate and adapt to changes in environmental conditions (see below) (reviewed in [12, 109, 121, 182]).

Light regulates melatonin synthesis

Light is the dominant environmental factor that controls melatonin biosynthesis both in the pineal gland and the retina. In birds and lower vertebrates, the pineal organ is directly light-sensitive (reviewed in [159]). In addition, it has recently been demonstrated that light perceived by the retina only regulates melatonin production in the chicken pineal gland [263, 352, 357]. The mammalian pineal gland has lost photosensitivity during the course of evolution, and information about environmental lighting conditions is imposed on the gland *via* a complex multisynaptic pathway (reviewed in [159, 160]). A light signal perceived by the retina is transmitted primarily through the retinohypothalamic tract to the SCN, the site of the master circadian clock. The SCN subsequently conveys the signal to the pineal gland *via* the dorsomedial hypothalamic nucleus, the upper thoracic cell columns of the spinal cord, the superior cervical ganglia, and finally the postganglionic adrenergic fibers innervating the pineal gland. Changes in levels of noradrenaline (NA) released from these fibres ensure proper translation of the light information (*via* the circadian clock) into melatonin synthesis by the pineal gland (reviewed in [144, 152]).

Light exerts two distinct effects on melatonin production. First, the exposure to light at night rapidly decreases AANAT activity, melatonin, and aMT6s [2, 37, 41–43, 126, 146, 148, 180, 297, 307, 356, 358, 362]. This suppressive effect has been shown to result from illumination with full spectrum white light, monochromatic visible light, as well as with near-ultraviolet radiation (UV-A). The amount of light required to suppress melatonin production during the night varies from species to species, with the time of night, and with previous light exposure [37, 42, 43, 124, 125, 173, 212, 287]. The magnitude of the light-evoked changes in nocturnal AANAT activity, melatonin, and aMT6s was dependent on the duration and intensity of the light pulse, its wavelength (blue and red light being the most and least potent, respectively), tissue, and species examined [41–43, 152, 307, 356]. Light-at-night did not alter AANAT mRNA

levels in the pineal gland or retina of the chicken [28], indicating that rapid light-induced changes in the enzyme activity reflect changes at the protein level. In addition to this acute suppressive action, appropriately timed pulses of light reset the circadian oscillator that generates the melatonin/AANAT activity rhythm in a phase-dependent manner. Light pulses beginning late in the subjective day and early in the subjective night delay the phase of the melatonin/AANAT activity circadian rhythm, while pulses beginning during the second half of the subjective night produce a phase advance of the rhythm [12, 53, 146, 150, 175, 306, 332, 357]. These time-dependent effects can be summarized as a phase response curve (PRC) [141]. The human PRC to light [150, 217] is about 12 h out of phase with the PRC to melatonin [49, 175]. In some reports, pulses of light given during the subjective day did not produce phase shifts (reviewed in [12, 53, 306]); however, in humans there is some controversy as to whether or not such a "dead zone" exists [49]. There is also clear evidence for the participation of two "oscillators" in the production of phase shifts in both animals and humans [68]. For example, phase-advancing morning light has a greater effect on the melatonin/AANAT rhythm decline, while evening phase-delaying light has a greater effect on the melatonin/AANAT rise [134, 336].

The photoreceptor system or systems mediating the effects of light on melatonin production are yet to be fully elucidated. Studies performed on humans and non-human mammals indicate that a novel photoreceptor system, that is distinct from the classical visual photoreceptors (cones and rods) and is sensitive to the blue portion of visible light (λ_{max} between 446 and 484 nm), is primarily involved in melatonin-related and other non-image forming light responses [41, 55, 188, 197, 257, 307]. It is suggested that melanopsin, a newly discovered photopigment [29, 117], plays a primary role in light-induced melatonin suppression [117].

Molecular and neurochemical mechanisms underlying the clock-controlled and light-driven regulation of AANAT activity

The dynamic changes in AANAT activity are regulated by complex control systems that consist of two basic elements: an autonomous circadian clock and turn-off mechanisms [153]. The circadian clock is composed of transcriptional/translational feedback loops and is entrained to the environmental lighting conditions by light. Turn-off mechanisms are responsible for the rapid suppressive effects of light on AANAT levels and activity. An exception to this model is found in salmonoid fish, in which light is the only mechanism controlling AANAT activity due to the absence of the clock [87]. This exception may also be true in Arctic reindeer [300].

AANAT activity levels may be controlled at several different stages of enzyme synthesis and processing, namely (*i*) at the transcriptional level; (*ii*) through posttranscriptional processes, such as phosphorylation and binding to chaperone proteins; and (*iii*) through regulation of protein degradation velocity by proteosomal proteolysis (see below) (reviewed in [136, 144, 153]).

The importance of transcriptional events in the regulation of pineal AANAT activity varies according to species. An absolute requirement for *de novo* transcription is most evident in the rat. During the light phase, transcripts of the *Aanat* gene are not detectable, whereas the increased release of NA at night induces a potent, ~100-fold increase in AANAT mRNA levels. This increase is followed by a rise in AANAT protein levels within 2–3 h and is accompanied by elevated AANAT activity [40, 205, 262]. On the contrary, in sheep and the rhesus macaque pineal AANAT mRNA levels show relatively little change over the 24-h period, and changes in AANAT activity are primarily regulated at the protein level [65, 66].

In non-mammalian species, the clock and AANAT are located in the same light-sensitive cells, pinealocytes (pineal gland) and photoreceptors (retina). Mechanisms involved in clock-controlled melatonin synthesis have been thoroughly studied in the pineal gland and retina of the chicken. In both tissues the rhythm of AANAT mRNA is translated into rhythms of AANAT expression and activity, followed by melatonin production [60, 62, 135]. The 5'-flanking region of the chicken *Aanat* (*cAanat*) gene contains an E-box element that is thought to mediate its clock-regulated expression. It has been demonstrated that the binding of heterodimers BMAL1/CLOCK and BMAL1/MOP4 to this E-box element enhances transcription of *cAanat* [60]. Furthermore, transcripts of several clock genes (i.e., *Bmal1*, *Mop4*, *Cry1*, and *Per2*) are rhythmically expressed in the chicken pineal gland and retina [60, 62]. *Cry1 and Per2* transcripts increased rapidly in the early morning and were low at night. As

CRY1 inhibits the BMAL/CLOCK-mediated activation of the E-box promoter element, this pattern of timing may, in turn, indicate an involvement of CRY1 in the inhibition of *Aanat* transcription during the day-time. In chicken pinealocytes and photoreceptors, levels of cAMP (a crucial second messenger controlling AANAT levels and stability) are high at night, and are regulated by both the clock and light [58, 231]. The phosphorylation of transcription factors, namely CREB (cAMP regulatory element-binding protein), by cAMP-dependent protein kinase (PKA), augments the E-box-driven increase in AANAT mRNA and protein [60].

In mammals, the clock controlling pineal AANAT is located in the SCN, which receives photic information from the retina *via* the retinohypothalamic tract. The sympathetic neurotransmitter, NA, released from postganglionic fibers that innervate the gland, is central to rhythmic AANAT fluctuations. At night, when the activity of these fibers increases, NA is released and stimulates postsynaptic β_1- and α_1-adrenergic receptors located on pinealocytes. In a process termed "biochemical AND gate", an increase in intracellular Ca^{2+} concentration (resulting from α_1-adrenoceptor stimulation) potentiates the activation of adenylyl cyclase (AC; resulting from β_1-adrenoceptor stimulation) by a mechanism involving protein kinase C and calcium/calmodulin protein kinase. This activation causes a rapid and large increase (~100-fold in the rat) of intracellular cAMP level (reviewed in [152, 157, 277]).

Elevated levels of cAMP, the second messenger that controls melatonin biosynthesis both in mammals and non-mammalian vertebrates, subsequently activate PKA and exert dual actions on AANAT. Thus, during the night in darkness (when cAMP levels are high) AANAT is phosphorylated by PKA and forms a complex with 14-3-3 proteins. Within this complex, AANAT is catalytically activated and protected from dephosphorylation and degradation [99, 153, 244]. Exposure to light lowers cAMP, which leads to dephosphorylation of AANAT and disruption of the AANAT/14-3-3 complex, with a concomitant drop in AANAT catalytic activity and rapid proteasomal proteolysis of the enzyme [86, 102, 135, 244, 264, 278]. In ungulates and primates this is the only cellular mechanism known to control AANAT activity (reviewed in [153]). However, in rodents, birds, and fish, cAMP also controls *Aanat* transcription. This mechanism relies on the PKA-dependent phosphorylation of CREB and operates *via* CREs in the *Aanat* promoter [60, 262, 284, 328]. It is suggested that the termination of cAMP-induced *Aanat* transcription in the rodent pineal gland involves, in part, inducible cAMP early repressor (ICER), which competes with pCREB for binding to CREs [95, 205, 284, 328]. Another hypothetical molecular regulator of *Aanat* expression is the calcium sensor, downstream regulatory element antagonist modulator (DREAM). DREAM is thought to interact with the rhythmic expression of AANAT in the rodent pineal gland by two mechanisms: directly by repression of DRE-containing genes (*Aanat, Icer*) and indirectly by displacing pCREB from CREs [185].

Role of dopamine in regulation of retinal melatonin biosynthesis

Dopamine, the major catecholamine of the vertebrate retina, is localized to a subpopulation of amacrine and/or interplexiform cells, depending on the species, and functions as a biochemical signal for light (reviewed in [342]). It is suggested that the suppressive effect of light on retinal melatonin biosynthesis is mediated, in part, by D_4/D_2-dopamine receptors localized to photoreceptor cells [136, 137, 312, 355, 360, 361, 362]. D_4/D_2-dopamine receptors appear to be involved in the phase-shifting effect of light on the circadian melatonin/AANAT rhythm in the retina of *Xenopus* [53], but not the chicken [351]. D_4-dopamine receptors that regulate melatonin biosynthesis in the retina may be indirectly linked, in a negative manner, to the cAMP generating system [136, 354].

Melatonin receptors

Classification

Melatonin receptors were originally divided into two classes, ML_1 and ML_2, based on their different affinity and binding kinetics for an agonist radioligand 2-[^{125}I]iodomelatonin ([^{125}I]Mel), and differential pharmacological profiles of synthetic ligands. In particular, ML_1 receptors showed a high (in the picomolar range) affinity to [^{125}I]Mel, while ML_2 receptors bound the radioligand with a low (in the nanomolar range) affinity [79]. Since 1994, when the first mela-

tonin receptor was cloned from *Xenopus laevis* dermal melanophores [82], expression cloning has revealed the presence of three different melatonin receptor subtypes with ML_1-like pharmacology: Mel_{1a} (currently known as MT_1), Mel_{1b} (currently known as MT_2), and Mel_{1c} (to date found only in non-mammals) [82, 253, 254]. These cloned melatonin receptors belong to a superfamily of G protein-coupled receptors (GPCR), share high (overall ~55%) homology in their amino acid sequences, and their molecular structures each consist of seven transmembrane α-helices (TMI-TMVII) linked by three alternating intracellular (ic1-ic3) and extracellular (ec1-ec3) loops (reviewed in [80, 252]). Recent site-directed and chimeric receptor mutagenesis studies have identified residues critical for melatonin binding to the MT_1 and MT_2 receptors [23, 104, 157]. An additional cloned melatonin-related receptor (GPR50) has around 40% sequence identity with other melatonin receptors, but is incapable of binding melatonin [255]. At present, this receptor is classified as an orphan GPCR. Human melatonin receptors form a distinct receptor cluster within an α-group of the rhodopsin receptor family of GPCRs [98]. ML_2 receptor (now known as *MT_3*), unlike other melatonin receptors, is not a GPCR. Recent experimental evidence suggests that this melatonin binding protein is the enzyme, quinone reductase 2 [232].

In addition to the membrane-bound melatonin receptors, it has been demonstrated that melatonin binds to receptors from the retinoid-related orphan nuclear hormone receptor family, RZR/RORα and RZR/RORβ [27, 299]. The functional significance of these nuclear melatonin receptors is still a matter of debate.

Distribution

In birds and lower vertebrates, melatonin receptors are widely distributed in the CNS [211, 228, 239, 254]. On the other hand, the distribution of melatonin receptors is more restricted in mammals, and the level of expression is markedly weaker than in non-mammalian species. It has been demonstrated that in mammals, most of the [^{125}I]Mel binding observed by *in vitro* autoradiography and physiological responses to melatonin reflect MT_1 receptors, and this subtype is more prevalent than the MT_2. The highest expression of melatonin receptors in mammals (including man) has been found in the *pars tuberalis* of the anterior pituitary. MT_1 receptors are widely localized in the hypothalamus, including the area of the SCN. The presence of MT_1 mRNA has also been demonstrated in the cerebral cortex, thalamus, hippocampus, cerebellum, cornea, and retina [5, 80, 346]. MT_2 receptors are expressed in the retina, hippocampus, SCN, and cerebellum (human) [5, 80]. Melatonin receptors have also been detected in several peripheral tissues, including the adrenal gland (MT_1), arteries and heart (MT_1, MT_2), lung (MT_1, MT_2), liver (MT_1, MT_2), kidney (MT_1), small intestine (MT_2), skin (MT_1, MT_2), and in T and B lymphocytes (MT_1) [207, 226, 245, 259, 270, 296, 311].

Based on their analogy to other GPCRs, it is suggested that melatonin receptors form both homo- and heterodimers [172]. Their existence in native tissues and their physiological significance awaits further detailed analysis.

Pharmacology

During the last decade, the development of subtype-selective melatonin receptor agonists and antagonists has been facilitated due to the remarkable progress in our understanding of the molecular structure of the receptor protein, and the use of recombinant receptor cellular models in which a homogenous population of a defined receptor subtype can be expressed. However, despite extensive efforts, there are currently no ligands that bind exclusively to either the MT_1 or the MT_2 receptor, although some subtype-selective drugs, particularly for the MT_2 receptor, have been synthesized and analyzed for their biological activity. A recent review by Zlotos [369] provides detailed information on agonists and antagonists of MT_1 and MT_2 melatonin receptors. Examples of the most selective ligands of MT_1 and MT_2 receptors [84, 315, 369] are shown in Table 1. Three high affinity agonists of MT_1/MT_2 receptors, agomelatine, ramelteon, and tasimelteon (Table 2), appear to be of clinical importance in humans (see below; reviewed in [20]).

The pharmacological profile of the *MT_3* melatonin receptor is distinct from that of the MT_1 and MT_2 receptors. 5-Methoxy-carbonylamino-N-acetyltryptamine (5-MCA-NAT), prazosin and N-acetyltryptamine are selective ligands of the *MT_3* receptor. In addition, the melatonin precursor, N-acetylserotonin, activates the *MT_3* receptor, but has negligible activity towards MT_1 and MT_2 receptors (reviewed in [80]).

Tab. 1. Selective ligands of MT_1 and MT_2 receptors

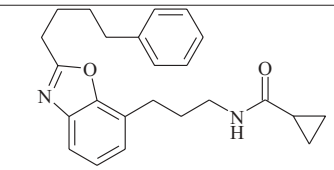
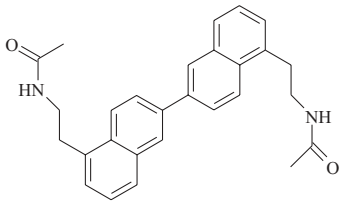
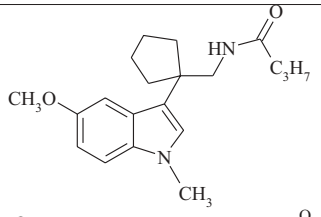
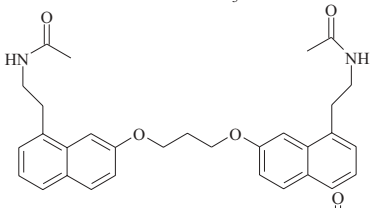
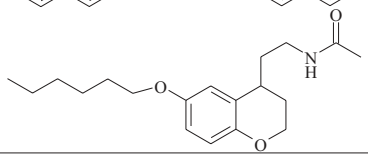
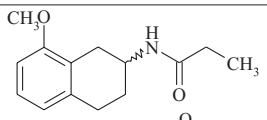
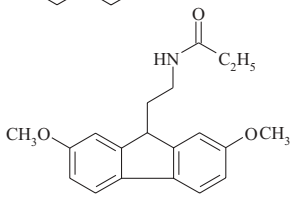
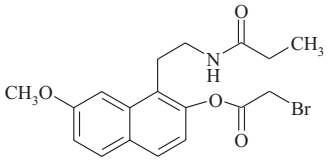
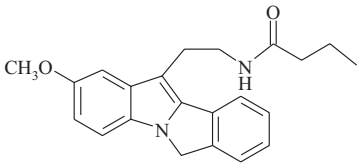
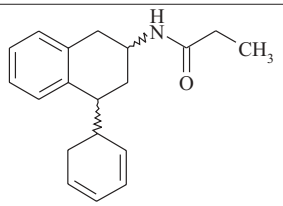
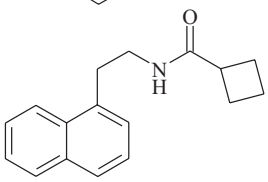
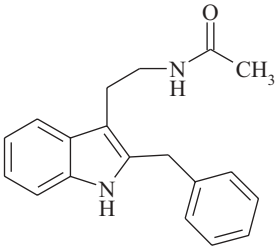
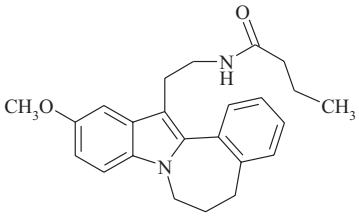
	MT_1-receptor agonists	
	Cyclopropanecarboxy-{3-[2-(4-phenyl-butyl)-benzooxazol-7-yl]-propyl}-amide	
	*N*-{2-[5'-(2-acetylamino-ethyl)-[2,2']bi-naphthalen-5-yl]-ethyl}-acetamide	
	MT_1-receptor antagonists	
	*N*-butanoyl-5-methoxy-1-methyl-β,β-tetramethylene-tryptamine	
	N1-(2-(7-({8-[2-(acetyloamino)ethyl-2-naphthyl}oxy)-propoxy]-1-naphthyl}-ethyl) acetamide	S26131
	*N*-[2-(hexyl-chroman-4-yl)-ethyl]-acetamide	
	MT_2-receptor agonists	
	8-methoxy-2-propionamidotetraline	8M-PDOT
	N-[2-(2,7-dimethoxyfluoren-9-yl)ethyl]propanamide	
	bromoacetic acid 6-methoxy-1-(2-propionylamino-ethyl)-naphthalen- 2-yl ester (irreversibly alkylates MT_2 receptor, and is used for its visualisation *via* affinity gel chromatography)	BMNEP
	[2-(2-methoxy-*6H*-isoindolo[2,1-*a*]indol-11-yl)-ethyl]butyramide	

Table 1 continued on the next page

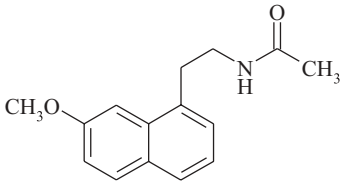
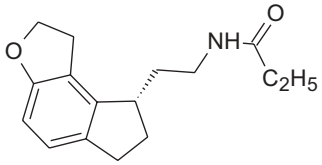
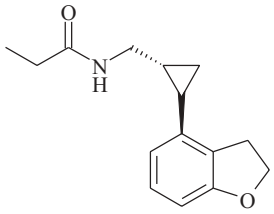
Tab. 1. Selective ligands of MT_1 and MT_2 receptors – continued from the previous page

MT_2-receptor antagonists		
	4-phenyl-2-propionamidotetraline	4P-PDOT
	*N*-(2-(1-naphalenyl)ethyl)cyclobutane-carboxamide	S-20928
	*N*-acetyl-2-benzyl-tryptamine	luzindole
	*N*-[2-(11-methoxy-6,7-dihydro-5*H*-benzo[3,4]azepino-[1,2-α]indol-13-yl)-ethyl]butyramide	K-185

Signal transduction

Depending on the tissue and species, melatonin can activate different second messenger cascades acting on the same receptor subtype. MT_1, MT_2, and Mel_{1c} receptors are primarily coupled, in an inhibitory manner, to the AC → cAMP → PKA signaling pathway, *via* a pertussis toxin sensitive G_i protein (reviewed in [80]). Activated MT_1 receptors, in addition to inhibition of CREB phosphorylation [213, 327], can also inhibit the formation of immediate early gene products, c-Fos and jun B [265]. Stimulation of MT_1 and MT_2 receptors may activate phospholipase C-β (PLC-β), with a concomitant increase of inositol-(1,4,5)-trisphosphate (IP_3)/Ca^{2+} and 1,2-diacylglycerol (reviewed in [5, 80]). In COS-7 cells expressing human MT_1 and MT_2 receptors it has been demonstrated that activation of these receptors stimulates c-Jun N-terminal kinase (JNK) activity *via* pertussis toxin sensitive and insensitive G proteins [57]. Stimulation of the MT_1 receptor has also been associated with increased phosphorylation of mitogen-activated protein kinase MEK1/2, and extracellular signal-regulated kinase ERK1/2 [57, 343]. In addition, MT_1 melatonin receptors increase potassium conductance by activating Kir3 (GIRK) inward rectifier potassium channels [229], and potentiate prostaglandin F2α- and ATP-mediated stimulation of PLC activity [108, 261]. Both processes may involve activation of membrane-bound βγ-subunits released by G_i-proteins. In rat microvascular endothelial cells, melatonin inhibits stimulated nitric oxide production. This effect was mediated by the suppression of Ca^{2+} mobilization from intracellular stores [283]. In human benign prostate cells, melatonin inhibits cGMP and DNA synthesis [106]. Modulation of intracellular cGMP level by cloned Mel_{1b} and Mel_{1c} receptors has also been reported [140, 242].

Tab. 2. High affinity of agonists of MT_1/MT_2 receptors

	N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide	Agomelatine (S20098)
	(S)-*N*-[2-(1,6,7,8-tetrahydro-2*H*-indeno-[5,4-*b*]furan-8-yl)ethyl]-propionamide	Ramelteon (TAK-365)
	(1R-*trans*)-N-[[2-(2,3-dihydro-4-benzofuranyl)cyclopropyl] methyl] propanamide	Tasimelteon (VEC-162)

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Physiological functions of melatonin

Melatonin secretion as a function of day length: a seasonal time cue

The most definitive physiological role of melatonin is to convey information about day length (photoperiod) to body physiology for the organization of functions that vary with season, such as reproduction, pelage (coat growth and color), appetite, body weight, and sleep (reviewed in [12, 109, 121]). Photoperiod is often critical for the timing of pubertal development [94]. As previously stated, melatonin secretion is related to the length of the night: the longer the night, the longer the duration of secretion in most species. This changing duration of secretion is the critical signal timing photoperiodic changes, and it is clear that in photoperiodic mammals and marsupials, an intact innervated pineal gland is essential for the perception of photoperiod change [119, 127, 310]. For example, pinealectomy of sheep leads to desynchronization of their seasonal cycles from the 365 day year, an observation that required heroic experimental work done on pinealectomized and intact sheep for more than 5 years [344].

It is possible to administer melatonin by daily infusion or feeding so as to generate, at will, circulating hormone profiles, with a duration characteristic of particular photoperiods in the intact or pinealectomized animal. In this way it has become apparent that a particular melatonin duration is a necessary and sufficient condition for the induction of a given seasonal response and is equipotent with a particular photoperiod. Specifically, long-duration melatonin is equivalent to short days and short-duration melatonin is equivalent to long days. The interpretation of the signal, as with day length, depends on the physiology of the species in question (for example, long- or short-day breeder). In sheep, melatonin can time the whole seasonal cycle, at least for reproduction, acting as a seasonal zeitgeber for a presumed endogenous annual rhythm [344]. Reproduction in domestic ruminants and the winter coat of animals such as mink, arctic foxes, and cashmere goats has commercial significance, and can be manipulated by photoperiod and melatonin administration [14, 59]. Implanted melatonin induces short-day effects, and a number of commercial preparations of melatonin have been developed to this end [59].

The mechanisms by which melatonin times seasonal rhythms have not been fully elucidated. With regard to changing levels and pulsatility of gonadotrophic hormones, melatonin appears to influence steroid feedback on gonadotrophic regulatory systems in the hypothalamus [32, 204, 210]. There is evidence

for action *via* MT_1 receptors in the premammillary hypothalamus [204]. More is known about the seasonal control of prolactin secretion by melatonin, which is known to occur by a direct action on MT_1 receptors in the *pars tuberalis* of the pituitary [184, 341]. It has been demonstrated that melatonin influences clock gene expression in the *pars tuberalis* [220]. Many clock genes are expressed in this tissue (*Bmal1*, *Clock*, *Per1*, *Per2*, *Cry1*, *Cry2*) with a 24 h rhythmicity that is different from their expression in the SCN. *Per1* is activated at the beginning of the light phase, and C*ry1* at the beginning of the dark phase. Long or short photoperiod information is encoded within the SCN. Melatonin synthesis, driven by the SCN, conveys this photoperiodic information to the *pars tuberalis* by virtue of its pattern of secretion. This, in turn, influences the pattern of expression of the clock genes *Per1* and *Cry1* within the *pars tuberalis,* providing a means of translating the melatonin signal for the control of seasonal prolactin variations [183]. In rodent *pars tuberalis* cells, rhythmic expression of *Per1* appears to be dependent on sensitization of adenosine A_{2b} receptors, which, in turn, depends on melatonin activation of MT_1 receptors [327]. Clearly, it is possible that the melatonin signal is a widespread humoral mechanism related to biological timing that acts through the modification of peripheral clock gene expression.

Photoperiod *via* melatonin secretion determines the timing of puberty in some species, provided that a sufficient degree of physical maturity has been reached. Interestingly, photoperiod perception by the fetus is present before birth in rodents and ungulates, and ensures a rate of development appropriate to environmental conditions [74, 334]. Melatonin injections given to the mother can dictate the timing of postnatal reproductive development [69, 334]. In rats, injections of melatonin during the late light phase, during a small window in the late dark phase, or even using continuous release implants specifically during the period of pubertal development, will delay reproductive maturity in both males and females. Full sexual maturity is eventually achieved; thus, the system is not permanently compromised [286]. Moreover, melatonin inhibits gonadotropin-releasing hormone (GnRH)-induced luteinizing hormone (LH) release by cultured rat pituitary glands from prepubertal animals [206]. These observations constitute the main evidence for a possible causal role for melatonin in the pubertal development of humans. In fact, the first hypotheses concerning the role of melatonin in humans concentrated on possible anti-gonadotropic effects related to the timing of puberty [151]. However, while it is possible to demonstrate anti-gonadotropic effects of melatonin in humans (attempts were made to develop melatonin in very large doses, in combination with progestin, as a contraceptive [329]), its role in human puberty has not been substantiated.

Actions on SCN neurons and circadian rhythmicity

In mammals, melatonin appears to have a more modest role in the organization of adult circadian physiology. In contrast to seasonal physiology, melatonin appears to be mostly associated with sleep propensity and the core temperature rhythm. Melatonin may be more important in the perinatal period [69]. However, there is convincing evidence that melatonin can indicate the time of day to the circadian system. For example, sleep is worse and the core temperature rhythm amplitude is blunted in the absence of melatonin at night compared to when it is present [75, 272]. There is also evidence for an influence of melatonin on the circadian aspects of systems such as glucose homeostasis [164], the immune system [201], and cardiovascular function [273, 320].

The most direct link between melatonin and the circadian system was shown by *in vitro* experiments on the SCN. In the mammalian SCN, melatonin acutely inhibits neuronal firing [107, 208, 281, 319]. This effect appears to be mediated through stimulation of MT_1 melatonin receptors [139, 187], and is thought to result from the activation of Kir3 potassium channels and an increase in potassium conductance with subsequent neuronal hyperpolarization [319]. In addition, melatonin applied at certain circadian times phase advanced the peak of the circadian rhythm of neuronal firing and other measured SCN outputs [129, 187]. Initially, this phase shifting effect of melatonin was attributed solely to MT_2 receptors [187]. However, more recently it appears that there is redundancy between MT_1 and MT_2 receptors in terms of the regulation of the circadian activity [139].

Regulation of cardiovascular function and temperature

In rat caudal arteries, stimulation of the melatonin MT_1 receptor produced vasoconstriction, while activation of

the MT_2 receptor resulted in vasodilation [103, 207, 322]. The vasoconstrictive action of melatonin appears to be mediated by inhibition of Ca^{2+}-activated large-conductance potassium channels (BK_{Ca}). It is suggested that melatonin-induced vasodilation of arteries and an increase in blood flow in the distal parts of skin regions that are important for heat loss regulation may underlie the hypothermic effects of the hormone [161].

Actions of retinal melatonin

As described above, melatonin synthesized by the retina acts primarily within the eye, where, depending upon the species, it has been shown to control such rhythmic processes as retinomotor movements [243], dopamine synthesis, release, and metabolism (likely through the MT_2 receptor) [3, 77, 78, 233, 258, 353], rod outer segment disc shedding and phagocytosis [53, 339]. It is suggested that in the retina, dopamine and melatonin are components of a mutually interplaying (in a negative manner) system and act as chemical analogues of light and darkness, respectively (reviewed in [136, 342]). Melatonin modulates the glycine currents of retinal ganglion cells [365] and increases photoreceptor susceptibility to light-induced damage [340]. It has also been postulated that in the chicken, melatonin is involved in the regulation /modulation of a- and b-waves of ERG and diurnal ocular growth [241, 246].

Melatonin in humans – physiological, pathological and therapeutic aspects

In humans, melatonin is produced predominantly by the pineal gland, and pinealectomy removes virtually all plasma melatonin [230]. In a "normal" environment, melatonin is secreted during the night in healthy humans, as in all other species. The average maximum levels attained in the plasma of adults are of the order of 60 to 70 pg/ml when measured with high-specificity assays. The concentrations in saliva are approximately one-third of those in plasma. Minimum concentrations in both fluids are usually below 5 pg/ml. The peak concentrations of melatonin in plasma normally occur between 02.00 and 04.00 h. The onset of secretion is usually around 21.00 to 22.00 h and the offset at 07.00 to 09.00 h in adults in temperate zones [12]. The appearance and peak plasma levels of 6-sulfatoxymelatonin (aMT6s) are delayed by 1 to 2 h, and the morning decline by 3 to 4 h [18, 39]. There are strong correlations between the timing and amplitude of the plasma melatonin and urinary aMT6s rhythms, such that aMT6s is a useful measure of circadian phase in field situations. In urine, 50–80% of aMT6s appears in the overnight sample (24.00 to 08.00 h), and levels are low but rarely undetectable in the afternoon and early evening [12]. Possibly the most striking characteristic of the normal human melatonin rhythm is its reproducibility from day to day and from week to week in normal individuals, rather like a hormonal fingerprint [12]. There is, however, a large variability in the amplitude of the rhythm between subjects, and the night time production of the hormone can differ by three orders of magnitude among individuals. A small number of apparently normal individuals have no detectable melatonin in the plasma at all times of day [12]. The melatonin content of pineals obtained *post-mortem* is related to the time of death with, as expected, higher values at night [1, 295].

Factors affecting the melatonin rhythm in humans

Age

The melatonin rhythm appears in humans soon after birth. In healthy full-term infants, rhythmic aMT6s excretion in urine was detected at 5–12 weeks of life [10, 147]. At 24 weeks of age, total aMT6s excretion was 25% of adult levels [147]. The development of melatonin production is markedly delayed in premature infants [10, 147]. The amplitude of the nocturnal peak in melatonin secretion reaches the highest levels between 1 and 3 years old [330]. During the remainder of childhood, nocturnal peak levels drop progressively by approximately 80%. This is likely due to constant melatonin production with increasing size of the human body [38, 330].

Several studies have demonstrated a progressive decline in the amplitude of melatonin rhythm in the elderly, especially in subjects over 70 years of age [38, 130, 202, 218, 293, 330, 345, 366]. A potent reduction in nocturnal melatonin together with an increase in day-time hormone levels has been found in patients with Alzheimer's disease (AD), and these

changes deepened with the progression of AD neuropathy, as determined by the Braak's stages [293, 345]. It is suggested that the circadian system-related behavioral disturbances in elderly patients, including those with AD, might be linked to a diminished melatonin signal [345]. Mechanisms underlying the age-dependent changes in melatonin production remain to be elucidated. Although calcification of the human pineal gland increases with age [111], no relationship between plasma melatonin or aMT6s in urine and pineal calcification has been observed [38]. Other suggested pathomorphological processes include dysfunction of SCN innervation to the pineal gland, degenerative changes in the SCN [368], and insufficient environmental illumination (e.g., [218]), a life condition frequently found in elderly residents of nursing homes.

Blindness

Blind people have varying degrees of visual loss, ranging from some degree of light perception (e.g., counting fingers, see hand movements) to no conscious light perception, i.e., totally blind. Studies have shown that the type of circadian rhythm disorder observed in the blind depends on their degree of light perception [191, 288]. Plasma melatonin profiles in blind people can be categorized into three types: (*i*) entrained with a normal phase, (*ii*) entrained with an abnormal phase, and (*iii*) free-running, with a circadian period (*tau*) different from 24 h [178, 191]. The majority of totally blind subjects have free-running circadian rhythms and suffer from cyclic (non-24 h) sleep-wake disorders. These are characterized by a period of good sleep followed by a period of poor sleep (short night sleep duration) when the melatonin rhythm is in an abnormal phase position (e.g. peaks during the day) [6, 17, 191, 192]. This has been associated with increased napping and reduced alertness and performance during the day [189, 191]. Appropriately timed daily doses of melatonin have been shown to improve night sleep and reduce day-time napping as well as entrain the free-running circadian rhythms [113, 178, 190, 268].

Clinical pathology

Many clinical attempts have been made to relate circulating melatonin to endocrine diseases and other pathology. The results on the whole are difficult to interpret and inconsistent (see below). Pathological or traumatic denervation of the pineal gland (resulting from the spinal cord injury or bilateral sympathectomy at the second thoracic ganglionic level) abolishes the plasma melatonin rhythm [156, 181, 222, 274]. Liver disease such as cirrhosis, which impairs metabolic function, leads to higher than normal plasma concentrations of melatonin. Furthermore, the time of melatonin rise and the time at which melatonin levels peaked were consistently and significantly delayed in patients with liver cirrhosis [131, 298]. Patients with end-stage chronic renal failure showed increased day-time melatonin and aMT6s levels and the absence of the nocturnal secretory surge of the hormone [198, 321]. An abnormal rhythm of melatonin secretion is a constant feature of Smith-Magenis syndrome, a clinically recognizable rare genetic disease characterized by developmental delay, neurobehavioral abnormalities, and severe sleep disturbances [72]. Surprisingly, little evidence exists for a disturbance of melatonin secretion in narcolepsy [116, 279] or recurrent hypersomnia (Kleine-Levin syndrome) [209]. In delayed sleep phase insomnia (DSPS), delays in the melatonin rhythm are not always found [9, 225]. The range of phase found in normally entrained individuals is large, and it is difficult to define what is and is not an abnormally delayed phase.

Very large pineals (~1 g) have been described in a rare genetic syndrome with insulin resistance [337]. Sudden infant death syndrome (SIDS) is associated with small pineals and decreased melatonin production [304]. SIDS deaths usually occur at night and may be associated with abnormalities of sleep. If melatonin helps to coordinate circadian organization in the developing infant, its underproduction may contribute to the disorder.

Melatonin has been extensively measured in psychiatry to assess biological clock status. There is evidence for a decline in the amplitude of the melatonin rhythm in depression associated with an increase in cortisol, and also possibly an increase in mania, although not all studies are consistent (e.g., [26, 56, 67, 149, 237]). Seasonal affective disorder (SAD) may well relate, at least in some patients, to a delay of the melatonin rhythm, although more complex relationships were recently reported [177, 179]. There is also evidence for abnormal melatonin secretion in patients with pre-menstrual tension [240].

Low melatonin is reported to associate (*inter alia*) with cardiovascular disease and diabetic autonomic neuropathology [234, 316, 347]. Studies of intensive

care unit patients have shown very abnormal melatonin rhythms, but the data are confounded by the concomitant medication.

Cancer

Tumors of the pineal region in children are frequently associated with abnormal pubertal development [22]. In precocious puberty, it was thought that the capacity of the pineal gland to inhibit sexual development was impaired. Much evidence now suggests that precocity is due to the production of human chorionic gonadotrophin (*beta*-hCG) by germ cell tumors of the pineal [333]. There is no consistent information on overproduction or underproduction of melatonin with specific types of pineal tumors.

Considerable effort has been expended investigating melatonin timing and production in prospective and retrospective "field" studies of cancer patients and shift workers (women shift workers may have increased risk of breast cancer) assessed by the urine levels of aMT6s. An increased risk of breast cancer has been attributed to lower melatonin; however, the data are inconsistent and in some cases may be interpreted as an altered timing of the melatonin rhythm rather than reduced production [275, 276].

Pharmacotherapy

Nocturnal melatonin release was decreased by antagonists of β-adrenergic receptors [19, 301, 302]. The non-steroidal anti-inflammatory agents, aspirin and ibuprofen, suppressed night-time plasma melatonin levels [224]. Antidepressant drugs, fluvoxamine (a selective inhibitor of 5-HT re-uptake) and desipramine (an inhibitor of NA/5-HT re-uptake), increased evening plasma melatonin concentrations and prolonged the duration of elevated melatonin secretion, respectively [290]. Desipramine, but not fluvoxamine, increased urinary aMT6s excretion. It is suggested that the observed elevated plasma melatonin following fluvoxamine is caused by the inhibition of CYP1A2-mediated melatonin metabolism [122, 290]. Drugs that stimulate or suppress hydroxylation and conjugation mechanisms or that compete for the same metabolic pathways as melatonin can be expected to affect circulating melatonin concentrations.

Core body temperature and melatonin

The melatonin peak is closely associated with the nadir in core body temperature [51, 247], maximum tiredness/fatigue, and lowest alertness and performance [4]. Causal links are suggested by a number of observations. For example, bright light at night suppresses melatonin, simultaneously increasing body temperature, alertness and performance, and decreasing sleepiness [303]. Exogenous melatonin during the day-time acutely increases sleepiness and decreases core body temperature [163]. This latter observation is dependent on posture. Subjects must be seated or recumbent, and the effect appears to depend on peripheral heat loss [54, 161]. The ovulatory rise in temperature during the menstrual cycle is associated with a reported decline in the amplitude of melatonin [338], and luteal phase melatonin was reported to be higher than follicular phase melatonin [335], but these observations are not consistent [44, 45, 88, 240].

Effects of melatonin on sleep and circadian rhythms

In controlled experimental conditions, it is clear that the evening rise of melatonin corresponds closely to the opening of the "sleep gate" [166], following a period of wake maintenance that has been called the "forbidden zone for sleep" [282]. Few associations have emerged between melatonin production and sleep stages, with the exception of a relationship between the timing of sleep spindles and certain other EEG characteristics and the circadian phase of melatonin [75]. Possibly the best correlative evidence for a role of melatonin in human sleep is the appearance of day-time naps in free-running blind subjects when the peak of melatonin (and of course the temperature nadir) occurs during the day-time [191]. It has been proposed that the sleepiness-inducing properties of melatonin during the "biological day" are dependent on the acute changes induced in the core body temperature [163].

The first evidence for a sleep-promoting effect of melatonin dates from 40 years ago when Aaron Lerner, who first isolated the substance, took a 100 mg dose and described sleepiness afterwards (cited in [171]). Subsequently, a substantial literature generally using much lower doses (0.3–10 mg) has described advance shifts in the timing of sleep after early evening administration, transient sleepiness at several different times of day within 2–4 h of the dose, time-

dependent increases in sleep propensity, and effects on the waking EEG comparable to, but not identical with benzodiazepines (for references see the numerous reviews on this subject, e.g., [13, 46, 272, 291]). Recent evidence supports a phase shifting effect of melatonin on sleep timing, whereby melatonin induced a redistribution of sleep during an imposed sleep opportunity of 16 h without an increase in total sleep time [249].

Phase shifting of human circadian rhythms by melatonin was initially described in humans in the early 1980s. Phase advances were seen after administering 2 mg daily at 17.00 h for one month. There were no significant effects on self-rated mood or on levels of LH, FSH, testosterone, cortisol, growth hormone, or thyroxine. No deleterious effects were reported by the subjects [18]. Advance shifts in sleep, endogenous melatonin, prolactin and core body temperature can be induced by oral administration of melatonin (0.5–10 mg) in the "biological afternoon /evening" (where biological night is the time of endogenous melatonin secretion) [71, 162, 225, 248, 256]. The magnitude of the shift is dose-dependent [71, 280]. Delay shifts can be obtained by early "biological morning" administration, and these time dependent responses have been formalized in terms of a phase response curve (PRC) [49, 174, 175, 215]. Melatonin given ca. 8–13 h before core temperature minimum will phase advance, and melatonin given ca. 1–4 h after core temperature minimum will phase delay.

In addition to these effects, melatonin can clearly maintain synchronization of the circadian clock to 24 h in sighted subjects living in conditions conducive to free-run, and appeared to resynchronize some subjects after a period of free-run [215]. In free-running totally blind people, it has been possible to stabilize the sleep-wake cycle to 24 h with improvement in sleep and mood variables, without necessarily synchronizing strongly endogenous rhythms such as core body temperature [6, 17, 92]. With suitable dose (0.3–10 mg) and timing, however, entrainment/synchronization is possible in most subjects [113, 176, 190, 268]. Success may depend on careful timing either to the advance portion of the PRC or for the treatment to start an hour before preferred bedtime, as the subjects' free-running rhythm approaches a normal phase. Individual sensitivity to melatonin varies and the pharmacokinetics are very different from one individual to another. The lower dose of 0.3–0.5 mg may be more effective than higher doses in many subjects [113, 176]. It is possible that subjects with a very long free-running period will not ever synchronize to melatonin. For example, a free-running subject treated with melatonin daily maintained a consolidated sleep-wake cycle but with persistent free-run in melatonin for at least a year [15, 17], albeit with a shortened *tau*. More recently Hack and colleagues reported a similar case [113].

Melatonin receptor agonists as pharmacological agents for the treatment of circadian rhythm sleep disorders, insomnia and depression

The classical circadian rhythm disorders include: sleep/alertness problems of jet lag and night shift work, delayed sleep phase syndrome (DSPS), advanced sleep phase syndrome (ASPS), and non-24 h sleep-wake disorder of free-running blind subjects (reviewed in [21]). Sleep disorders of the elderly, possibly related to a rhythm disorder, is an important target condition given its prevalence [46, 114].

The most obvious symptom of circadian rhythm disorders is poor sleep. A treatment that is able to shift the biological clock rapidly in all its manifestations would be of substantial benefit to large numbers of people. To date, bright light is the only treatment that at a suitable intensity and duration is able to do this (reviewed in [289]), but clearly cannot be used in the free-running sleep disorder of the blind. Although melatonin has been known to have acute sleep-inducing and phase-shifting effects for many years, a consensus acknowledging its therapeutic benefit has only emerged recently.

Numerous publications have appeared with regard to jet lag and shift work. Two recent meta-analyses of the effects of melatonin have different conclusions with regard to jet lag. One considers that existing evidence shows a robust positive effect [123]. The other, reporting on the use of nutritional supplements, found little evidence for a consistent effect on sleep after time zone change (Agency for Healthcare Research and Quality; (http://www.ahrq.gov/news/press/pr2004/melatnpr.htm). Likewise with regard to shift work the data are inconsistent. Exceptions to these inconsistencies are studies where careful treatment timing was used in the field or in simulation laboratory studies [16, 33, 50, 93]. Timing is critical in order to avoid precipitating phase shifts in the "wrong" direction. Pre-flight treatment with melatonin can be timed to initiate a shift in the right direction (but has rarely been used) [16, 256, 271]. In field studies, individual variability is large and

exposure to conflicting natural bright light is always a problem, although one simulation study has shown that melatonin can partially counter conflicting light [70]. The American Academy of Sleep Medicine has recently published a positive recommendation for the use of melatonin in jet lag, non-24 h sleep-wake disorder, and some other circadian rhythm sleep-wake disorders [221].

The treatment of free-running blind subjects with melatonin has been of particular interest (reviewed in [288]). Refinements of dose, preparation, and the timing of treatment continue to be studied. However, anecdotally many blind subjects are now prescribed melatonin (at least in the UK) with (again anecdotal) clear recognition by the prescribing clinicians of its benefits. Only a small number of subjects have been reported in the literature to date, and large clinical trials would be of great interest.

Results from DSPS have also been consistently good (Agency for Healthcare Research and Quality (http://www.ahrq.gov/news/press/pr2004/melatnpr.htm), and in this case the timing of treatment is relatively easy to predict. Patients are entrained, albeit with a delay, and it is evident that early evening melatonin will induce shifts in the right direction (reviewed in [21]). A recent study has shown the importance of melatonin timing in patients with DSPS [223]. To the authors knowledge there is little information on the treatment of ASPS by melatonin. Hack [112] successfully delayed a blind subject with ASPS by stepwise shifting of melatonin treatment to later times. More studies of this type are needed.

The use of melatonin for elderly sleep disorder (reviewed in [46]) has given somewhat inconsistent results. It is possible that treatment is most effective if the sleep problem is related to rhythm disorder. A "melatonin deficiency" syndrome has been invoked, whereby melatonin treatment of the elderly replaces a deficiency in endogenous melatonin. However, whilst a decline of melatonin in the elderly has frequently been reported, this decline does not necessarily relate to sleep problems [24, 46, 115]. Most recently, careful long-term treatment of elderly dementia patients with light and melatonin has achieved interesting results in terms of the consolidation of activity/rest cycles [260].

A new, prolonged-release melatonin (2 mg) formulation, mimicking the nocturnal melatonin profile, has been found to significantly facilitate sleep onset and improve subjective sleep quality and morning alertness in insomnia patients aged 55 years and older, without producing withdrawal effects upon discontinuation [168]. This drug, under the trade name of Circadin, has been recently approved by the Committee for Medicinal Products in Human Use of the European Medicines Agency as monotherapy for the short-term treatment of primary insomnia in patients who are aged 55 or over.

There has been considerable success treating sleep and behavioral problems in children with severe psychomotor retardation and substantial sleep disorders [138], including those with Smith-Magenis syndrome [72], Rett syndrome [219], and Asperger disorder [236]. However, to what extent this involves changes in the circadian timing system remains unclear.

Of the numerous synthesized ligands of melatonin receptors, at present only two are of therapeutic importance: agomelatine (Valdoxan®, Melitor®) – for the treatment of depression [105] and ramelteon (Rozerem®) – approved by the FDA in 2005 for the treatment of primary chronic insomnia characterized by difficulty with sleep onset (reviewed in [266]). In addition, recent phase II and phase III studies have demonstrated that tasimelteon (VEC-162; a high affinity agonist of human MT_1 and MT_2 receptors), improved sleep latency, sleep efficiency, and sleep maintenance, suggesting that the drug may have therapeutic potential for transient insomnia in circadian rhythm sleep disorders [250].

Ramelteon has a very high affinity for human MT_1 and MT_2 receptors, and a neglible affinity for MT_3 binding sites and for a large number of other receptors, including NA, GABA, glutamate, serotonin, histamine, acetylcholine, dopamine, and opioid receptors [145]. Ramelteon did not appear to significantly alter sleep architecture [350]. The improvement in sleep onset latency with ramelteon treatment is similar to that of melatonin; however, ramelteon does not improve the patient's perceived sleep quality and next day performance compared with placebo [266]. The drug shows no evidence of accumulation after multiple dosings [143] and does not produce next-day residual effects [350]. By contrast to commonly used hypnotic drugs, ramelteon lacks abuse lability and does not impair motor and cognitive function [142].

Agomelatine is a potent agonist of melatonin MT_1 and MT_2 receptors [348] and an antagonist of the serotonin $5\text{-}HT_{2C}$ receptor subtype [216], and is endowed with antidepressant properties (e.g., [30, 167, 238]). Clinical studies of patients with major depressive disorder (MDD) have demonstrated that the

symptoms of depression significantly improved with agomelatine compared with placebo, and agomelatine appears to be as efficacious in treating MDD as other antidepressants but with fewer adverse effects (e.g., [105, 167, 235]). In addition, agomelatine was found to improve sleep quality and the ease of falling asleep, as measured subjectively in depressed patients. Polysomnographic studies have shown that agomelatine decreases sleep latency, decreases waking after sleep onset, and improves sleep stability, as measured by changes in the cyclic alternating pattern [167, 193, 235].

Cancer

For many years, a possible oncostatic effect of melatonin in certain cancers has been investigated (e.g., [34–36, 214, 349]). At present, animal data are supportive of this possibility. It remains to be seen whether these hopes are fulfilled in large human trials. However, given that circadian disruption is strongly associated with increased cancer vulnerability (at least in animals), the chronobiotic effects of melatonin may well prove useful for optimizing defense mechanisms.

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