

Review

Melatonin in Aging and Disease — Multiple Consequences of Reduced Secretion, Options and Limits of Treatment

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[Received January 24, 2011; Revised February 7, 2012; Accepted February 7, 2012]

ABSTRACT: Melatonin is a pleiotropically acting regulator molecule, which influences numerous physiological functions. Its secretion by the pineal gland progressively declines by age. Strong reductions of circulating melatonin are also observed in numerous disorders and diseases, including Alzheimer's disease, various other neurological and stressful conditions, pain, cardiovascular diseases, cases of cancer, endocrine and metabolic disorders, in particular diabetes type 2. The significance of melatonergic signaling is also evident from melatonin receptor polymorphisms associated with several of these pathologies. The article outlines the mutual relationship between circadian oscillators and melatonin secretion, the possibilities for readjustment of rhythms by melatonin and its synthetic analogs, the consequences for circadian rhythm-dependent disorders concerning sleep and mood, and limits of treatment. The necessity of distinguishing between short-acting melatonergic effects, which are successful in sleep initiation and phase adjustments, and attempts of replacement strategies is emphasized. Properties of approved and some investigational melatonergic agonists are compared.

Key words: Alzheimer's Disease; Circadian Rhythms; Diabetes; Melatonin; Mood Disorders; Parkinson's Disease; Sleep

The indoleamine melatonin (*N*-acetyl-5-methoxytryptamine) is usually known as the hormone of the pineal gland. This role is of particular importance in a chronobiological context, especially with regard to its effects on the hypothalamic circadian pacemaker, the suprachiasmatic nucleus (SCN). However, its spectrum of functions is considerably broader, in terms of sites of both biosynthesis and action [1-5]. Melatonin is formed in numerous organs and cells, such as the gastrointestinal tract (GIT), bone marrow, several leukocytes, membranous cochlea and, presumably, skin and other regions of the central nervous system. It is frequently overlooked that, in quantitative terms, extrapineal melatonin exceeds by far that found in the pineal and in the circulation. Owing to the size of the organ, the amounts of melatonin present in the GIT are several hundred-fold higher than those in the pineal [6, 7].

Extrapineal melatonin is either poorly released to the circulation or for short periods of time. Relatively high

amounts have been reported to enter the blood from the GIT in response to nutritional factors, as a post-prandial response of short duration [7-9]. These pulses of melatonin are of minor importance to the circadian system, not so much because of its brevity, but rather as a consequence of shape and phase position of the so-called phase response curve (PRC). The PRC describes the resetting of a rhythm by entraining signals in dependence of the phase (i.e., the time point within the circadian cycle) of administration of the signal. Usually, a PRC contains phases in which the rhythm is delayed, others in which it is advanced and also a silent zone in which the rhythm is poorly affected. In humans, the PRC for melatonin has been determined, which mainly reflects the resetting in the SCN [10, 11]. A post-prandial release of melatonin during the day mostly occurs in the silent zone, whereas much stronger effects are observed in phases of pineal melatonin secretion in which the hormone is capable of readjusting the rhythmicity of the

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SCN. In mammals, pineal melatonin biosynthesis and release are, in turn, under the control of the SCN and largely confined to the night. From the pineal gland, melatonin is not only secreted to the circulation, but also, via the pineal recess, to the third ventricle [12-14].

Collectively, all these findings indicate that melatonin serves numerous functions in various organs and that effects at the SCN constitute an important, but by far not the exclusive function. The awareness of this multiplicity of roles and actions gains increasing importance, because melatonin and synthetic melatonergic drugs come more and more into use, e.g., for treating sleep difficulties and mood disorders. These compounds should not be simply regarded as sleeping pills or antidepressants, which might be easily compared with classic drugs for the respective indications. They strongly differ in their mode of action, but, additionally, they exert numerous other effects beyond the reason for treatment. This insight can be of great practical relevance, especially concerning the immunological role of melatonin. Again, the actions are diverse. They comprise antiinflammatory, but also immunoenhancing effects [2-5]. This latter property can be highly undesired in cases of autoimmune diseases and should be regarded as a contraindication for melatonin and melatonergic drugs in these patients. Despite some controversies on this issue and the clearly antiinflammatory actions of melatonin in another context, the methoxyindole obviously aggravates symptoms of rheumatoid arthritis (RA) via stimulation of proinflammatory cytokines [15-17]. Moreover, blood melatonin levels were enhanced in RA patients and the circadian peak of the hormone was advanced [16]. For caveats concerning other diseases, but also adolescents and pregnant women see refs. [18, 19].

The remarkable pleiotropy of melatonin unavoidably leads to a plethora of effects if the hormone or synthetic melatonergic drugs are administered. Many of these actions can be beneficial, but not necessarily all of them. However, the other side of the coin is that a pathological decrease in melatonin formation and secretion has also numerous consequences on the functioning of a body, as will be outlined in this article.

Biosynthesis, Metabolism and Signal Transduction Mechanisms

For the better understanding of several aspects to be discussed, the biosynthetic, catabolic and signaling pathways are briefly described. Melatonin is synthesized from serotonin in two steps, *N*-acetylation to *N*-acetylserotonin (NAS) followed by *O*-methylation (Figure 1). The reverse sequence of these steps is possible, but remains in vertebrates physiologically

irrelevant. Sufficiently high amounts of the precursor serotonin are usually available, but an exception was described for a defect mutation of the sepiapterin reductase gene [20]. The product of this enzyme, tetrahydrobiopterin (BH4), is required by aromatic amino acid hydroxylases. BH4 deficiency causes, beside other effects, poor synthesis of 5-hydroxytryptophan and, thus, serotonin, with the further consequence of a flattened melatonin rhythm [20].

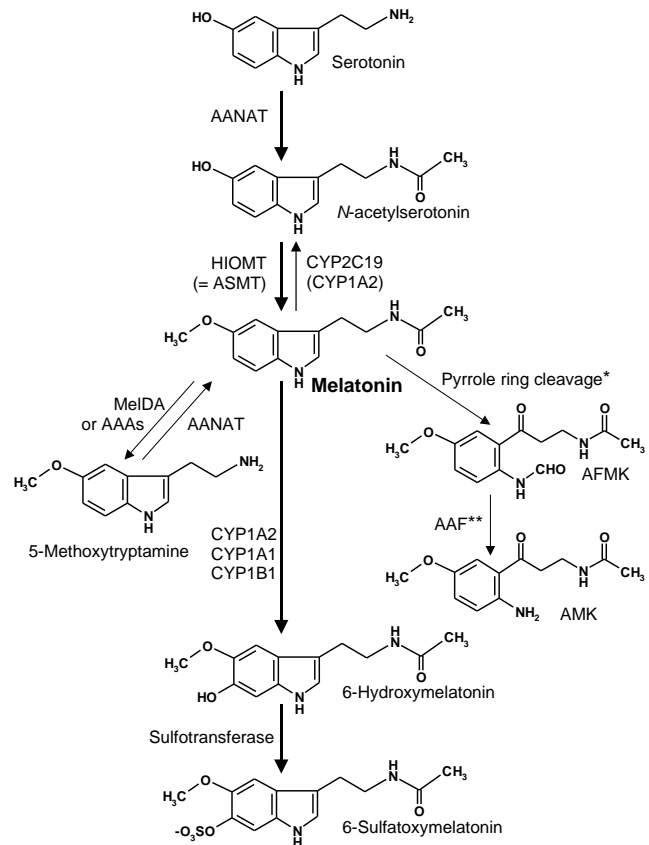


Figure 1: Biosynthesis and catabolism of melatonin. The main pathway is indicated by bold arrows. Abbreviations: AAAs, aryl acylamidases; AAF, arylamine formamidase; AANAT, arylalkylamine *N*-acetyltransferase; AFMK, *N*¹-acetyl-*N*²-formyl-5-methoxykynuramine; AMK, *N*¹-acetyl-5-methoxykynuramine; ASMT, acetylserotonin methyltransferase; CYP, cytochrome P₄₅₀ monooxygenase or dealkylase; HIOMT, hydroxyindole *O*-methyltransferase; MelDA, melatonin deacetylase. * Pyrrole ring cleavage is catalysed by various enzymes, such as indoleamine 2,3-dioxygenase, myeloperoxidase, other peroxidases, and by several reactive oxygen species. ** Alternately, AFMK can be deformedylated by hemoperoxidases and photochemical mechanisms. For further metabolites see ref. [3].

In the pineal gland and several other sites, *N*-acetylation of serotonin is catalysed by arylalkylamine *N*-acetyltransferase (AANAT) [21] and *O*-methylation of NAS by hydroxyindole *O*-methyltransferase (HIOMT, alias acetylserotonin methyltransferase, ASMT). AANAT is usually regarded as the rate-limiting enzyme of melatonin biosynthesis, but this conclusion has been disputed for maximal nocturnal values in the rat pineal, in which a limitation by HIOMT has been reported [22]. The situation may be different in some extrapineal sites of melatonin synthesis. Preliminary data indicate that the steps of *N*-acetylation and *O*-methylation may sometimes be catalysed by alternate acetyl and methyltransferases [4]. The participation of another arylamine *N*-acetyltransferase, NAT-1, was assumed to be involved in cutaneous melatonin synthesis [23, 24]. NAS formation was observed in the skin of C57BL/6 mice [25], which are partially deficient in pineal AANAT because of a point mutation, which leads to a splice variant containing a pseudoexon with a stop codon [26]. However, functionally active splice variants of AANAT were found in leukocytes and bone marrow cells of two pineal melatonin-deficient strains and, to a certain extent, also in their pineals [27]. Therefore, the additional absence of an active HIOMT may strongly contribute to melatonin deficiency in the pineals of the respective mouse strains. The extrapineal cells also contained substantial amounts of melatonin, which was released to some extent into the circulation [27]. Moreover, alternate, cell-specific splicing mechanisms seem to allow extrapineal melatonin synthesis even in mice carrying the mutation described. The important message from these findings is that melatonin can be formed in peripheral organs and cells even if the pineal gland does not produce substantial amounts of its hormone.

The major pathway of melatonin catabolism consists of 6-hydroxylation by hepatic monooxygenases, CYP1A2, CYP1A2 and CYP1B1, which allows conjugation with sulfate to give the easily excretable metabolite, 6-sulfatoxymelatonin [2] (Figure 1). For this reason, levels and rhythm of melatonin can be indirectly followed by measuring this urinary product. Surprisingly, formation of 6-sulfatoxymelatonin was also detected in the brain, although the conjugation should disfavor its release from the CNS (for discussion see ref. [28]). In the tissues, alternate pathways of melatonin catabolism exist, but are of minor quantitative importance. Melatonin can be demethylated to NAS by CYP2C19, with eventual contributions by CYP1A2 and CYP1A1 [28]. Deacetylation to 5-methoxytryptamine by a specific melatonin deacetylase or less specific aryl acylamidases is also possible [28, 29]. An entirely different pathway consists of oxidative pyrrole ring

cleavage, which leads to *N*¹-acetyl-*N*²-formyl-5-methoxykynuramine (AFMK). This process can be catalyzed by remarkably many agents and includes various enzymes, especially dioxygenases and peroxidases, and several pseudoenzymatic, free radical-mediated and photochemical reactions (summarized in ref. [30]). AFMK was originally believed to be a major brain metabolite, since it was detected in large amounts after injection of melatonin into the cisterna magna of rats [31]. Although AFMK was reported to be also formed by several cell types, such as macrophages and keratinocytes, as discussed in ref. [28], no substantial amounts of this metabolite were detected in human urine and in various mouse tissues [32]. However, the same study described a new metabolite that might have been formed from AFMK, a finding that may be in accordance with the assumed transitory nature of methoxylated kynuramines (cf. ref. [30]). Nevertheless, AFMK has been detected in the human cerebrospinal fluid of patients with viral meningitis [33]. A negative correlation became apparent to the levels of IL-8 and IL-1 β , which were lower in CSF samples containing over 50 nM AFMK, compared to those between 10 and 50 nM. Notably, these AFMK concentrations are by orders of magnitude higher than nocturnal plasma concentrations of melatonin. In conjunction with antiinflammatory and neuroprotective properties ascribed to AFMK [30, 31, 34], this metabolite remains to be of pathophysiological interest. The same may be valid for several secondary products that derive from AFMK (cf. ref. [30]). Another metabolite formed from melatonin by free radical-mediated reactions is cyclic 3-hydroxymelatonin (c3OHM), which is strongly elevated under conditions of oxidative stress, such as exposure to ionizing radiation [35].

Detailed information about signal transduction pathways is available for the G protein-coupled membrane receptors of melatonin. In mammals, two receptor subtypes are known, MT₁ (alias Mel_{1a}, MTNR1A) [36] and MT₂ (alias Mel_{1b}, MTNR1B) [37]. The classic effect of both receptors is transmitted by pertussis toxin-sensitive G_i proteins. In these case, the α subforms are usually α_{i2} and α_{i3} , which mediate decreases in cAMP and, thereby, in protein kinase A activity and CREB phosphorylation. Meanwhile, additional pathways and regulatory interconnections have been identified, which involve α_q and $\beta\gamma$ subunits, activation of phospholipase C β , protein kinase C, MAP and CaM kinases, upregulation of phosphoinositide 3-kinase (PI3K) and Akt (protein kinase B), regulation of Ca²⁺ and K⁺ channels, and modulation of cGMP (summarized in ref. [38]). MT₁ was shown to be modulated by the PDZ domain protein MUPP1 (multi-PDZ domain protein 1; PDZ = PSD-95/*Drosophila* disc

large/ZO-1 homology) and the melatonin receptor homolog, GPR50, which has no affinity to melatonin, and, perhaps, by heterodimerization with MT₂ [38]. Additional regulatory interconnections seem to exist, in which either circadian oscillator proteins are involved or factors controlling energy metabolism [39]. MT₁ and MT₂ display overlapping, but not identical actions. In a number of cases, they were shown to mutually substitute for each other, but, with regard to other functions, they can behave in an antagonistic way. For instance, MT₁ activation leads to vasoconstriction, but MT₂, present in other parts of the vasculature, to vasodilation [40].

The membrane receptors MT₁ and/or MT₂ have been shown to be present in numerous human tissues, such as duodenal enterocytes, colon, caecum and appendix, gallbladder epithelium, parotid gland, exocrine pancreas, β cells of endocrine pancreas, skin, breast epithelium, myometrium, placenta, granulosa and luteal cells, fetal kidney, cardiac ventricular wall, aorta, coronary and cerebral arteries and other parts of peripheral vasculature, brown and white adipose tissues, platelets, different types of immune cells, and various parts of the CNS and associated tissues (for further details, functions and extensive literature see ref. [5]). This remarkable multiplicity of targets unavoidably leads to highly pleiotropic effects exerted in numerous parts of the body, when melatonin or melatonergic drugs are pharmacologically administered, a fact that is usually not emphasized by vendors of respective pills designed for improving sleep or attenuating depressive symptoms. The highest density of melatonin membrane receptors is found in the SCN, the structure that is responsible for the chronobiotic, i.e., phase shifting effects of melatonin and also for important actions in sleep initiation, as will be discussed in the next section.

Numerous other binding sites of melatonin have been described, in addition to the membrane receptors. However, their physiological relevance in humans is either unknown or controversial. A protein transiently believed to represent a third melatonin receptor and found in the literature under the name "MT₃" has turned out to be an enzyme of xenobiotic metabolism, quinone reductase 2 (QR2) [41-43]. Melatonin also binds to transcription factors belonging to the retinoic acid receptor superfamily, in particular, splice variants of ROR α (retinoic acid receptor-related orphan receptor- α ; human gene ID: 6095), designated as ROR α isoform a (alias ROR α 1), ROR α isoform b (alias ROR α 2) and ROR α isoform d (formerly called RZR α), and the product of another gene, ROR β (alias RZR β ; human gene ID: 6096) [5, 44-46]. ROR α isoforms are almost ubiquitously expressed in the body, whereas ROR β is mainly found in the nervous system. Although many investigators agree about regulation of gene expression

by melatonin via ROR transcription factors, this issue has remained controversial. RORs are chronobiologically important, because they also interact with circadian core oscillators and thereby influence phasing, resetting and period lengths of circadian rhythms. However, it remains to be clarified whether or not these are melatonin-independent actions [39]. Moreover, some RORs seem to have other or additional ligands.

Even less is known about the role of melatonin binding to calmodulin, calreticulin and some other proteins with partial homology to calreticulin, and on binding to the mitochondrial complex I [38]. However, these findings may have the potential of further expanding the pleiotropy of melatonin. Finally, it should be mentioned that melatonin and some of its metabolites are potent free radical scavengers [47-51]. In humans, these actions which do not require receptors and signaling mechanisms are, in quantitative terms, presumably only relevant at high pharmacological doses, whereas receptor-mediated circadian, antiexcitatory, antiinflammatory and mitochondrial effects that reduce radical formation and enhance the expression of antioxidant enzymes physiologically contribute to antioxidative protection [50].

Melatonin and the Suprachiasmatic Nucleus: Output and Input

The SCN receives, in addition to inputs from other brain areas, such as the intergeniculate leaflet, its main information from the eye. The relevant photoreceptors are blue-absorbing melanopsin-containing retinal ganglion cells and green-absorbing cones [52-54]. The photic information entrains the circadian master oscillator system, which is composed of numerous cellular clocks. Within the SCN, groups of cells constitute several, internally coupled oscillatory subsets, which can differ in their resetting by photic and non-photic time cues [55, 56]. Moreover, the left and the right SCN may behave differently in respective experimental protocols and can lead to temporal splitting of rhythmic output functions such as locomotor activity [57]. In other, forced desynchronization protocols, differences between the ventrolateral and dorsomedial SCN zones have been observed in rats [58].

In mammals, the information about the circadian phase is transmitted to the pineal gland through a neuronal connection, via the paraventricular nucleus, a sympathetic connection from the intermediolateral cell column of the upper thoracic cord to the superior cervical ganglion, whose fibers innervate the pineal [59]. Melatonin synthesis is stimulated by β_1 -adrenergic upregulation of cAMP and α_{1B} -adrenergic activation of phospholipase C β that leads to rises in Ca²⁺, protein

kinase C and CaM kinases. These processes are modulated by several peptidergic and glutamatergic mechanisms [3].

The rhythm of melatonin synthesized in and released from the pineal gland is characterized by a prominent nocturnal peak, which also contains temporal information that had originated in the SCN [60]. Insofar, melatonin release represents an output function of the SCN. However, melatonin also acts as an input to the SCN by feeding back to this structure [61]. In the SCN, it mainly exerts two effects. One consists in a suppression of neuronal firing that can be attributed to MT_1 -dependent decreases in cAMP and, presumably, conductivity changes of cation channels. The other one is of chronobiotic nature, i.e., the capability of readjusting the circadian phase in the oscillator system of the SCN, in accordance with the PRC for melatonin. In many mammals, the chronobiotic actions are mediated by MT_2 receptors, but their poor expression in the human SCN may indicate an additional function of MT_1 , as discussed elsewhere [5]. The question of why such a feedback is necessary, although the photic information from the SCN steers the activity of the pineal gland, may find its answer in another effect of light, namely the acute suppression of melatonin biosynthesis [60]. This latter action is more immediate and rapid than a light-induced phase shift of the temporally more inert circadian oscillator that is based on rhythmic gene expression and transcriptional inhibition. Therefore, melatonin contributes to the effective clock resetting by the phase of its rise. However, in modern civilizations, individuals can be exposed to nocturnal light, for reasons of rotatory shift-work or life style. Under these conditions, the acute suppression of melatonin leads to both rhythm perturbations – in addition to those directly induced in the SCN – and melatonin deficiency in circadian phases in which the hormone is required for optimal functioning of the body [39, 62]. The importance of such a lack of melatonin is immediately evident, as soon as one becomes aware of the highly pleiotropic role of the hormone that controls and orchestrates numerous physiological processes [2-5, 39].

A specific effect of melatonin at the SCN concerns sleep initiation. MT_1 -mediated actions favor the onset of sleep via the hypothalamic sleep switch, a structure characterized by typical on-off responses. On the basis of mutual inhibition, it alternately activates either wake-related neuronal downstream pathways that involve locus coeruleus, dorsal raphe nucleus and tuberomammillary nucleus or, under the influence of melatonin, sleep-related pathways via the ventrolateral preoptic nucleus [63, 64]. The MT_1 -dependent suppression of firing by SCN neurons seems to be decisive for the activation of the sleep-promoting

circuits. However, the sleep-inducing actions of melatonin are more complex and comprise thalamic effects that include thalamocortical interplay and are detectable in the promotion of sleep spindles [18, 65, 66]. Thus, the feedback by melatonin to the SCN and its additional effects in the CNS are important for the onset of sleep, a physiological process that is disturbed in various disorders. A role of melatonin in sleep maintenance may exist as well, but this is not easily demonstrated at physiological concentrations of the hormone, for reasons to be discussed.

Melatonin and the Circadian Multioscillator System

In the literature, chronobiological effects of melatonin have been mostly discussed in relation to the circadian master clock, the SCN. However, the earlier view of a single clockwork exclusively ticking in this central tissue has changed. In fact, numerous peripheral oscillators have meanwhile been identified, which are either directly coordinated by the SCN [67] or may be, sometimes, only loosely coupled to or relatively independent of the master clock [39]. In fact, the existence of peripheral oscillators is not entirely new, since their discovery dates back to 1958 [68], but this and other comparable findings did not seem to be compatible with concepts developed after the identification of the SCN as a circadian pacemaker. To date, extrasuprachiasmatic oscillators have been identified in various mammalian tissues, e.g., intestine, liver, heart, adrenal cortex, pars tuberalis, retina, other CNS areas, and also in cultured cells such as fibroblasts (reviewed in ref. [39]). Circadian oscillations are primarily generated at the cellular level, whereas the coupling of a number of oscillating cells can result in a more stable collective rhythm. With regard to this cellular origin and the expression of clock proteins in many tissues [69, 70], the existence of peripheral clocks can be expected in numerous if not all parts of the body.

The complexity of the circadian oscillator system is even higher, since parallel oscillators are also acting in a single tissue. These are operating on the basis of the alternate use of orthologs or paralogs of core oscillator proteins. For instance, the clock protein PER1 may be replaced by PER2, CRY1 by CRY2, or CLOCK by NPAS2. The consequences can be differences in output functions. Moreover, the expression of a host of additional proteins associated with the core oscillator components can vary between cells, with divergent consequences of feedbacks to the primary clocks [71].

Melatonin has been shown to also influence peripheral oscillators and, moreover, to be important for the phasing and phase coupling of parallel oscillators

within a single tissue. Examples for a role in peripheral oscillators have been found in the murine adrenal cortex and retina. In the adrenal cortex of the melatonin-proficient mouse strain C3H, the core oscillator proteins PER1, CRY2 and BMAL1 oscillate with robust amplitudes, whereas only weak fluctuations and reduced average expression levels are observed in the melatonin-deficient strain, C57BL [72]. In the retinal oscillator, C57BL mice did not show significant rhythms in PER1 and CRY2 levels, whereas robust rhythms were detected in C3H mice [73]. In human adrenal explants, inhibitory effects of melatonin on adrenal ACTH-induced responses of *Per1* mRNA, BMAL1, StAR and β -HSD protein levels as well as cortisol and progesterone production have been demonstrated [74].

In cultured murine striatal neurons, melatonin caused marked decreases in the expression of *Per1* and *Clock* and elevations of *NPAS2*, effects which were abolished in *MT1* knockouts [75]. Effects of melatonin on phase coupling of parallel oscillators were observed in the rat SCN. In pinealectomized animals, the maxima of *Per1* and *Per2* mRNAs showed an unusual temporal phase difference, but became, again, more tightly coupled to approximately normal when these rats were treated with melatonin [76].

Two important messages can be deduced from these findings. (i) Decreases in melatonin, whether caused by aging or diseases, should not only affect a single master oscillator, but also oscillatory subsets within the SCN, and peripheral oscillators as well. (ii) Treatment of patients with melatonin or synthetic melatonergic drugs can exert effects on the internal coupling of rhythms within the SCN and between SCN and peripheral oscillators. Therefore, the pleiotropic actions of melatonin and its synthetic analogs do not only directly up- or downregulate peripheral physiological functions, but also affect their time structure in a complex chronobiological manner.

Reduced Melatonin Secretion During Aging and in Various Disorders and Diseases

In the course of aging, the nocturnal melatonin peak is usually decreasing, though with considerable interindividual variability [77-80]. In several aged individuals, the nighttime values are almost indistinguishable from those obtained during daytime, whereas others maintain a fairly well pronounced rhythm with only moderate reductions of nocturnal values. In individuals with strongly reduced melatonin, daytime values are often decreased, too. Age-dependent impairments of melatonin formation are not only detected in plasma concentrations, but also in human pineal glands [81], saliva [82], cerebrospinal fluid [83,

84], and in urinary amounts of the main metabolite, 6-sulfatoxymelatonin [82, 85, 86]. The high interindividual variability of the decrease in pineal function is also observed in urinary 6-sulfatoxymelatonin levels, which can vary in apparently healthy subjects by a factor of 20 [86]. As long as a melatonin rhythm is detectable, the nocturnal peak of plasma melatonin is frequently phase-advanced in the elderly relative to young individuals [79]. Age-related reductions of melatonin can have different causes, a progressive deterioration (i) of the SCN or (ii) of the neuronal transmission to the pineal, reminiscent of changes observed in neurodegenerative disorders [79, 87-89], or (iii) pineal calcification [90, 91].

In several neurodegenerative disorders, especially Alzheimer's disease (AD) and other types of senile dementia, levels of melatonin are frequently more strongly decreased than in age-matched controls [79, 81, 84, 87-89, 92-95] (Table 1). In many of these patients, the melatonin rhythm is practically abolished. These declines seem to frequently result from SCN degeneration. Reduced melatonin secretion as a result of tissue destruction in the SCN has been also observed in young individuals diagnosed with hypothalamic hamartomas, which may cause precocious puberty [96], or with craniopharyngiomas [97-99].

Cases of degeneration of the SCN, the pineal or their neuronal connections provide an immediately plausible interpretation of reductions in melatonin secretion. However, there are surprisingly many other diseases and disorders in which the pineal hormone is also decreased. These include various neurological and stressful conditions, pain, cardiovascular diseases, cases of cancer, endocrine and metabolic disorders, in particular diabetes type 2 and acute intermittent porphyria [100-142] (Table 1). Further details are discussed in refs. [5] and [39].

A major question arising from these findings concerns the alternative of cause or consequence. In some cases, such as acute pain and stress, a decrease in melatonin is likely induced by these events. The same may occur if a disease is associated with oxidative stress and the easily oxidizable melatonin is destroyed by high amounts of free radicals. Under conditions of neurodegenerative changes, reduced melatonin secretion may favor the development of other diseases. However, the decision is not always that easy and, moreover, both possibilities may exist simultaneously or sequentially, in that an otherwise initiated decline of melatonin further aggravates a disease, e.g., because of a reduction in immunological and antioxidative protection mechanisms. A contribution of low melatonin to disease development or progression may be deduced, with due caution, from the association of various pathologies with gene

polymorphisms related to melatonin. Differences in either rates of melatonin synthesis or signal transduction can lead to the same consequence as an otherwise induced decrease of the hormone. A list of respective gene polymorphisms [103, 143-183] is presented in Table 2. These polymorphisms have been detected in the genes of the melatonin membrane receptors, MT₁ and MT₂, of the enzymes of melatonin biosynthesis, AANAT and HIOMT, and also of the orphan receptor GPR50. This protein, which does not bind melatonin, has been identified as a mammalian ortholog of the non-mammalian Mel_{1c} receptor [184]. It inhibits MT₁ by heterodimerization and prevents G protein coupling [185]. Its precise role in melatonin signaling and the conditions under which GPR50 is upregulated await further clarification. Various metabolic changes have been observed in GPR50 knockout mice [186]. However, GPR50 has obviously additional functions beyond melatonin signaling, since it was found to also interact with the neurite outgrowth inhibitor NOGO-A [187] and

with TIP60, a coactivator of glucocorticoid receptor signaling and histone acetyltransferase [188].

Notably, there is a remarkable overlap of pathologies listed in Tables 1 and 2. Further connections between melatonin and diseases may exist, inasmuch as polymorphisms of clock genes are concerned, which may alter the melatonin rhythm and, moreover, may be differently influenced by melatonin. This might be of particular interest with regard to cancer, as recently discussed [39]. However, it is important to remain aware of the very meaning of associations between diseases and polymorphisms, which mostly do not represent anything else but risk factors. They often become effective in combination with others in multifactorial etiologies and are sometimes only demonstrable in some but not all populations. Nevertheless, the coincident observations of reduced melatonin and unfavorable gene variants in the same disease or disorder are indicative of possible causal relationship that is worth further investigation.

Table 1: Diseases and disorders associated with reduced melatonin secretion in humans

Disease/disorder	Comments	References
Alzheimer's disease	Stage dependent decreases down to complete loss of melatonin rhythm	[79, 81, 84, 88, 89, 92-95]
Pick's disease	Two cases only	[92]
Autism spectrum disorders	Decreases in melatonin or urinary 6-sulfatoxy-melatonin frequent, but not generally observed	[100-106]
Schizophrenia	Only in a subpopulation	[107, 108]
Multiple sclerosis with major depression	Not observed in major depression alone	[109]
Primary obsessive compulsive disorder		[110]
Menière's disease	Possibly related to stress by tinnitus and vertigo	[111]
Macular degeneration		[112]
Cases of severe epilepsy	High interindividual variation. However, increases during seizures	[113, 114] [113, 115]
Coronary heart disease, myocardial infarction, cardiac syndrome X		[116-122]
Fibromyalgia	Decreases observed in women Uncertainties concerning levels Pain reduced by melatonin	[123] [124] [124-128]
Neuralgia		[123]
Migraine	Pain reduced by melatonin	[129, 130] [128]
Bulimia		[123]
Critical illness		[131-133]
Postoperative stress	Decreases in patients without complications, but strong increases in those with delirium	[134]
Hypothalamic hamartoma		[96]
Craniopharyngioma		[97-99]
Endometrial cancer		[135]
Non-small cell lung cancer	In part caused by pain?	[136]
Acute intermittent porphyria	Further decreased by seizures	[137, 138]
Hypergonadotrophic hypogonadism		[139, 140]
Diabetes type 2		[141, 142]

Weakening of Clock Functions, Dysphased Melatonin Rhythm and Resetting

Impairments of melatonergic activity have always to be seen in the context of clock functions. This may not only concern the SCN as a master clock, but also peripheral oscillators, although the actual knowledge of chronobiological melatonin effects in the periphery are still insufficient. The need for detailed analyses of peripheral signaling pathways and their metabolic links has been recently addressed [39].

Lowered or dysphased melatonin rhythms can result from functional impairments in the SCN or its input and output connections. On the other hand, reduced melatonin secretion can lead to a poor feedback to the SCN and, thus, failure of dark-induced phase resetting. In either case, a crucial question is that of whether exogenous melatonin or administration of synthetic melatonergic drugs may still be capable of readjusting rhythms under these conditions, with regard to both phase and amplitude.

A weakening of clock functions may have different reasons. Impairments of the visual input should be distinguished from changes in the SCN or output pathways, especially with regard to differences in the chances for a successful treatment. Reductions in the unconscious circadian photoreception can occur in aged people because of pupillary miosis or impaired crystalline lens transmission, specially concerning blue light that is perceived by melanopsin-containing retinal ganglion cells. These changes may already promote circadian disruption, which can lead to sleep problems, contribute to the development of affective disorders, metabolic syndrome, and other systemic diseases [189]. In visually blind people, circadian photoreception can persist if intact melanopsin-containing retinal ganglion cells and the connection to the SCN are retained. In other blind subjects, circadian rhythms including that of melatonin may either poorly couple to or uncouple from external time cues. This results, in the first case, in a so-called relative coordination, in which the rhythms are gradually attracted for several days by an external synchronizer, followed by a sequence of days during which the rhythm is more strongly shifted, or, in the second case, in free-running rhythmicity [190-195]. Failure of entrainment by external time cues is also known under the term 'free-running disorder' (FRD). As long as the neuronal connections between SCN and the pineal gland are functionally active, the rhythmicity of the SCN widely determines the rhythm of melatonin formation and release. However, an additional effect of potentially high significance can strongly modify the melatonin rhythm in sighted subjects, namely, an acute suppression of pineal melatonin by nocturnal light, which has to be

distinguished from the circadian effects [196-199]. This is of particular importance in rotating shift work. Both effects of nocturnal light, circadian disruption and acute suppression of melatonin formation, seem to contribute to health problems observed in shift workers. Rotating shift work as a risk factor for various diseases or disorders, including some types of cancer, cardiovascular diseases, peptic ulcers, obesity and metabolic syndrome, as well as the epidemiological limits for these conclusions have been recently reviewed [39].

The interconnections between the SCN and the pineal gland always have to be seen from two sides. On the one hand, reduced photoreception, SCN dysfunction or impaired pineal innervation can be the cause of dysphased or flattened melatonin rhythms. On the other hand, reduced nocturnal melatonin levels lead to an insufficient feedback to the SCN, in other words, to a poorer resetting by the dark signal. The two-sided relationship between SCN and pineal can gain some complexity under conditions of genetic dispositions for extremely short or long spontaneous circadian periods that lead to difficulties in the proper entrainment to external cycles [39, 200]. In a number of individuals, but not in every case, it is possible to favor synchronization with the external 24-h cycle by enhancing the strength of the resetting signals. This may be bright light, especially in the morning. Alternately, to reinforce the signal darkness, administration of melatonin or synthetic melatonergic agonists in the evening can be effective. From a theoretical point of view, stable synchronization by light or by melatonin is impossible if a 24-h cycle is outside the range of entrainment of the deviant individual cycle. An additional aspect, which deserves future detailed investigation, concerns optimal phase relationships of parallel oscillations in the circadian multioscillator system [39]. Circadian disruption and low nocturnal melatonin seem to promote uncoupling or relative coordination within the multioscillator system. Internal desynchronization of rhythms has, in fact, been observed and discussed as a cause or an indicator of illnesses [39, 201-203].

The pathophysiological deviations related to malfunctioning of the circadian oscillator system seem to be associated with numerous disorders or diseases [5, 39]. However, the probability of developing relevant symptoms may strongly vary, depending on the respective pathology and on differences within populations owing to unequal combinations of risk factors. Among the most frequently observed difficulties, problems of sleep initiation and/or maintenance and mood disorders are of particular interest. Again, it should be emphasized that these disorders, as far as they are related to circadian dysfunction, can either result from deteriorations of oscillators and their neuronal

connections, without a primary contribution of changes in melatonin, or, alternately, from changes in melatonin secretion, with secondary consequences to the clocks. In these two situations, the chances for successfully treating these disorders with melatonin or its analogs may not be identical, but in either case a chance does exist, as long as functional melatonin receptors are expressed in the SCN and other relevant central nervous target areas.

Insomnia represents a complex of diverse disorders, which is experienced in the one or other form by most people during their lives. About 10% of the population are affected chronically and, in this case, the treatment is often challenging [204, 205]. Insomnia is characterized by one or more of the following symptoms: difficulty of falling asleep, numerous nocturnal awakenings, early morning awakenings, reduced total amount of sleep or restorative sleep, with consequences of daytime somnolence, fatigue, irritability, difficulty of concentrating and performing everyday tasks. Importantly, insomnia is associated as a comorbid symptom with other illnesses and disorders. Very frequently, this is observed in mood disorders, but it also occurs in cardiovascular diseases, weight gain and glucose intolerance.

With regard to the diversity of causes of insomnia, subtypes related to circadian dysfunction [85, 206-209] have to be distinguished from sleep difficulties of other etiology. The so-called circadian rhythm sleep disorders (CRSDs) can, again, result from different causes. One of these possibilities is an innate or acquired deviation from an easily entrainable spontaneous period, as present in

familial advanced sleep phase syndrome (FASPS) and delayed sleep phase syndrome (DSPS). Polymorphisms in the core oscillator genes *Per2* and *Per3* (*Period 2* and *3*) have been identified as being causative of some CRSDs [210, 211], but mutations in other clock genes may also lead to this type of disorder. As discussed above, insufficient entrainment may also exist in some blind subjects or because of an otherwise impaired light input pathway. Consequently, free-running or relatively coordinated rhythms lead to sleep difficulties on those days in which a daytime circadian phase is reached at night. Moreover, irregular sleep-wake patterns are associated with low circadian amplitudes [209], especially in elderly patients, in which deteriorations of the SCN [212-214] or decreases in nocturnal melatonin [78, 215] contribute to insomnia or may even be of causal relevance.

The regularly observed association of mood disorders with sleep disturbances has led to numerous assumptions concerning a mechanistic relationship. Some investigators have considered insomnia symptoms as a predictor of a depressive disorder (discussed in ref. [216]). This has been supported by findings showing sleep disturbances or changes in sleep architecture as prodromal symptoms occurring several weeks prior to the recurrence of a depressive episode [217-219]. Although insomnia is a comorbid symptom of most mood disorders, an etiologic relevance of circadian malfunction is only demonstrable or likely in some subtypes of this highly diverse complex of disorders.

Table 2: Diseases, disorders and metabolic changes associated with gene polymorphisms of melatonin membrane receptors, a receptor homolog and enzymes of melatonin biosynthesis

Disease/disorder	Gene	Refs.
Autism spectrum disorders	<i>HIOMT</i> (= <i>ASMT</i>)	[103, 143, 144]
ADHD (attention-deficit and hyperactivity disorder)	<i>MT₁</i> (= <i>MTNR1A</i>)	[145]
Schizophrenia	<i>HIOMT</i> (= <i>ASMT</i>)	[145]
Major depression	<i>MT₁</i> (= <i>MTNR1A</i>)	[146]
Recurrent depression	<i>AANAT</i>	[147]
BP (bipolar disorder)	<i>HIOMT</i> (= <i>ASMT</i>)	[148]
SAD (seasonal affective disorder)	<i>GPR50</i>	[149, 150]
Rheumatoid arthritis	<i>GPR50</i>	[151]
Adolescent idiopathic scoliosis	<i>MT₂</i> (= <i>MTNR1B</i>)	[152]
(perhaps only in combination with other risk factors)	<i>MT₂</i> (= <i>MTNR1B</i>)	[153]
Coronary artery disease	[154]	[155]
Diabetes type 2, prediabetes	<i>MT₁</i> (= <i>MTNR1A</i>)	[156-180]
Elevated fasting triglycerides	<i>MT₂</i> (= <i>MTNR1B</i>)	[181]
Elevated fasting glucose	<i>GPR50</i>	[181]
Elevated cholesterol	<i>MT₂</i> (= <i>MTNR1B</i>)	[157-160, 162, 167-170, 177-179]
Polycystic ovary syndrome	<i>MT₂</i> (= <i>MTNR1B</i>)	[180]
	<i>MT₁</i> (= <i>MTNR1A</i>)	[182]
	<i>MT₂</i> (= <i>MTNR1B</i>)	[183]

Deviations in the circadian system are likely present in seasonal affective and bipolar disorders, as indicated by polymorphisms in core oscillator genes, such as *Per2*, *Cry2*, *Bmal1* (= *Arntl*) and *Npas2* in winter depression [220-223], *Per3*, *Cry2*, *Bmal1* (*Arntl*), *Bmal2* (*Arntl2*), *Clock*, *Dbp*, *Tim*, *CsnK1ε* and *NR1D1* in bipolar disorder [224-231]. Moreover, DSPS, i.e., a CRSD, was found to be associated with seasonal affective disorder [232]. Since both bipolar and seasonal affective disorders display characteristics of long-period rhythmicity, which can be interpreted in terms of poor coupling of circadian oscillations to external and/or internal rhythms, this is not the case in major depressive disorder (MDD), in which the situation is less clear. On the one hand, it has been concluded that no convincing evidence exists for an involvement of the circadian system [233], but, on the other hand, *Cry1* and *Npas2* polymorphisms were found to be associated with MDD [234]. With regard to the heterogeneity of MDD, a role of circadian rhythmicity cannot be excluded in some of its subtypes.

While the significance of the circadian system for disturbances of sleep and some affective disorders is obvious, the genetic evidence for a role of the melatonergic system is relatively poor. A few hints may exist in findings mentioned in Table 2. Moreover, bipolar disorder was reported to be associated with a polymorphism of the *RORB* gene [235]. This gene encodes the transcription factor ROR β , which is considered as a nuclear melatonin receptor. However, it has remained unclear as to whether the action of ROR β reflects a melatonin-dependent or melatonin-independent input into the circadian clock. Beyond the genetic aspect, there is, however, good reason to conclude that reduced levels of melatonin or impaired melatonergic signaling contribute to low amplitudes and poor coupling of circadian oscillations. Therefore, melatonin and synthetic melatonergic drugs are an option for reversing circadian malfunction, as long as the SCN is functionally intact. This will presumably be of future importance in the treatment of CRSDs and, especially, cyclically occurring affective disorders.

Melatonin and Alzheimer's Disease

Several reasons have given rise to the assumption that melatonin might be beneficial in AD patients. Mainly, these include melatonin deficiency in AD, the malfunctioning of the circadian master clock, and the antioxidant and antiinflammatory actions of melatonin, with regard to oxidative stress and atypical inflammatory processes observed as accompanying symptoms with a presumed contribution to disease progression [236]. Some experimental data in transgenic mice or in vitro had indicated a possibly beneficial role. In the transgenic

mouse model, melatonin treatment starting relatively early in life not only lead to reductions in oxidative damage and in amyloid accumulation but also to an increase in survival [237]. In another study, reductions in neuronal apoptosis and damage to the cholinergic system were reported, which might indicate a support of cognitive functions, and corresponding behavioral improvements [238]. Moreover, melatonin was shown to possess antifibrillogenic properties [239]. However, no substantial benefits were demonstrable after a later onset of treatment [240]. This latter finding is important to humans, as AD is usually diagnosed relatively late in life. Therefore, clinical improvements by melatonin cannot be expected in terms of delay of disease progression or life extension.

With regard to the poor efficacy of other approved treatments in AD, such as cholinergic or memantine therapies [241], and to the unclear early etiology of AD, the findings on melatonin mainly demonstrate that a late onset of therapy is not promising. It remains to be clarified whether new ionophore strategies based on the reduction of metal toxicity and prevention of intracellular metal depletion will be more successful [241-243]. In such a case, melatonin may be re-considered as an adjunctive therapy to improve chronobiological and sleep parameters, as far as they are not accessible to ionophore treatment and remain impaired.

Although a clinical value of melatonin in preventing or delaying disease initiation and progression appears to be questionable, beneficial effects are not generally excluded and have, in fact, been described. These concern AD-associated sleep disorders, behavioral changes, in particular, "sundowning" agitation, and cognitive impairments. However, the findings of several studies are highly divergent. In part, this may be seen on the background of a high interindividual variability among AD patients. In groups with a similar degree of cognitive impairment, degeneration of brain structures related to circadian rhythms and sleep may have progressed to a different extent. As long as the SCN and downstream structures controlling wakefulness and sleep are operating, at least to a certain extent, there remains a chance for improvements of sleep and behavioral functions associated with circadian time patterns. Several smaller studies of variable length, from a few weeks to two or three years, reported improvements in sleep onset, sometimes also in number of awakenings, sleep quality or reduction of daytime somnolence [244-250], in one study using a combined therapy of melatonin in the evening and bright light in the morning [251]. Importantly, sundowning was found to be reduced, in some individuals markedly, by melatonin [244, 246-248, 250], an effect of particular importance with regard to

the caregiver's burden. However, the largest clinical trial [252] did not reveal statistically significant differences in objective measures of sleep. An increase in nocturnal total sleep time and decreased wake after sleep onset, as determined on an actigraphic basis, were only apparent as trends in melatonin-treated cohorts, although melatonin facilitated sleep in a certain number of patients. On subjective measures, however, caregivers' ratings of sleep quality showed a significant improvement in a sustained-release melatonin group relative to placebo. The outcome of this study underlines that the combination of individuals differing in extent and regional distribution of neurodegeneration results in a statistical heterogeneity problem [236]. What is still helpful in one patient may already be unsuccessful in another one.

Melatonin and Parkinson's Disease

The usefulness of melatonin in Parkinson's disease (PD) is even more controversial than in AD. A particular problem results from the investigators' focus on the stage at which the most severe Parkinsonian symptoms appear, namely, the advanced damage to the nigrostriatum. In numerous preclinical studies, animal models based on the administration of neurotoxins such as 6-hydroxydopamine, 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP), sometimes also rotenone, maneb and paraquat, have been applied with the intention of mimicking the nigrostriatal degeneration. In short-term studies of this type, melatonin consistently reduces the damage caused by these compounds [253-262], which are also oxido- and mitochondrial toxins. Since melatonin is a powerful multifunctional antioxidant, antinitrosant, antinitratant and also mitochondrial modulator [47, 48, 50, 263-271], these effects are not surprising, but rather reflect the counteraction against reactive oxygen and nitrogen species including the reduction of their formation. In more extended investigations, the outcome was contradictory. One study reported protective effects in a chronic model [272], whereas two others did not reveal improvements [273, 274]. Regardless of whether nigrostriatal degeneration can be gradually antagonized in the respective models, these approaches do not consider the etiology of PD, which does not start in the nigrostriatum, but rather in the brain stem or even the spinal cord of subjects which remain asymptomatic for a long period of time [275-277]. Therefore, the prodromal extranigral degenerative changes are neglected in the animal models, although the appearance of Lewy bodies can be traced back to much earlier stages.

With regard to the use of melatonin in PD patients, a potentially serious reason of concern has been advanced

by Willis, who interprets PD as a disease of melatonin-dopamine imbalance or, in another term of his, as a "melatonin hyperplasia" disorder [278]. He also reported that melatonin antagonists are beneficial in PD [279]. This conclusion is not in good accordance with findings on reduced MT₁ and MT₂ expression in the striatum and other brain regions such as the amygdala in PD [280]. No enhanced melatonin secretion was observed in the majority of patients tested [281, 282], but rather, sometimes, reduced amplitudes of the melatonin rhythm [283]. Circadian phase advances of the melatonin rhythm were attributed to the treatment with L-DOPA, but not seen in "de novo" patients [283]. Therefore, the assumption of a pathologic melatonin overproduction is not supported by available data. Findings on the use of bright light to suppress melatonin, which was also reported to be beneficial [284], may be alternately interpreted in terms of a strengthening of the circadian system, apart from the fact that the approach disregards the enhanced "rebound secretion" of melatonin following the transient suppression [282]. With regard to PD etiology, it remains to be demonstrated whether the concept of a melatonin-dopamine imbalance would be applicable to the early stages of the disease, in which the nigrostriatum is not yet affected. To date, it seems that a caveat concerning the treatment with melatonin or melatonergic agonists may be deduced from the reported beneficial effects of melatonin antagonists [279].

Despite the reservations discussed, melatonin and synthetic melatonergic agonists have been considered for treating sleep problems in PD and depressive symptoms that are frequently associated with this disease [282]. Some improvements of sleep have been demonstrated, but usually they remain relatively modest. With regard to depressive symptoms in PD, effects of agomelatine would include non-melatonergic actions [282, 285].

Melatonin, Metabolic Syndrome, Insulin Resistance and Diabetes Type 2

This complex of subclinical and clinical disorders and diseases is an emerging field in melatonin research. In part, the interest in the role of melatonin in this area has been newly stimulated by the identification of MT₂ polymorphism as a risk factor for diabetes type 2, as mentioned above. Moreover, melatonin was shown to modulate insulin secretion in various experimental models [286-291]. Concerning the relevance of various signaling pathways see discussion in ref. [39]. The presence of an endogenous circadian oscillator in the islets of Langerhans [292] underlines the importance of chronobiological interpretations in sugar, fat and energy metabolism, in which melatonin may play a role. In perfused rat pancreatic islets, melatonin was shown to

phase shift the rhythm of insulin secretion and to increase its amplitude [293].

With regard to the changes in blood glucose, the mutual paracrine interactions of insulin and glucagon within the pancreatic islet have to be considered. Under conditions of insulin resistance, glucagon secretion is no longer sufficiently inhibited by insulin. Conversely, glucagon stimulates insulin release. In human islets, the activation of glucagon secretion by melatonin via MT_1 can override an insulin-depressing, MT_2 -dependent effect at the β -cell and, thus, leads to enhanced insulin levels [294]. The stimulatory effect of melatonin on glucagon secretion was confirmed in a pancreatic α -cell line [295]. In this context, it is of greatest importance to distinguish between the actions of melatonin in night-active rodents and in humans, and to take notice of the potentially misleading limits of the animal models. Melatonin peaks at night in both nocturnal and diurnal mammals, but unlike rodents, which are active and mainly feed at night, humans are at rest and fasting in this part of the circadian cycle. In humans, glucemia is regulated primarily in the night by gluconeogenesis and reduced glucose utilization. These effects can be induced by nocturnal melatonin which, through stimulation of glucagon secretion, ensures an adequate energy source to the brain [39]. Thus, the well-established suppression of insulin by melatonin observed in rodents is not applicable to humans [39, 294]. From a chronobiological point of view, this is not at all surprising, since the meaning of melatonin for the availability and metabolism of nutrients has to be different in nocturnal rodents and humans. This reservation has also to be made in many other aspects of energy metabolism.

The involvement of melatonin exceeds the effects on insulin and glucagon secretion and extends to prodromal metabolic syndromes, with additional consequences for hypertension, insulin resistance and, perhaps, also obesity. Melatonin's role in metabolic syndrome has been recently summarized [296]. Persistent insulin resistance was induced in rats by pinealectomy [297-299]. In pharmacological settings, melatonin and other melatonergic drugs were shown to antagonize insulin resistance in rats [19, 300]. Correspondingly, knockout of the melatonin MT_1 receptor gene was reported to induce insulin resistance in mice [301]. However, the situation in humans is much less clear. Apart from missing pharmacological support for a relationship between melatonin and insulin sensitivity, the studies on MT_2 polymorphisms (cf. Table 2), which largely agree with regard to elevated fasting glucose in the respective variants [157-160, 162, 167-170, 177-179], mostly do not provide data indicating insulin resistance. Some studies, however conducted in young individuals, explicitly state the absence of an association with insulin

resistance [164, 175, 179]. Instead, reduced glucose-stimulated insulin release has been repeatedly described in subjects carrying these gene variants [157, 159, 165, 302]. A possible indication for an association of an MT_2 variant with insulin resistance has been reported in polycystic ovary syndrome [183]. It seems that additional studies on melatonin receptor variants on subjects of advanced age are required before a final judgment should be made.

The situation is similarly controversial concerning the role of melatonin in obesity. Although melatonin is clearly negatively correlated with the amounts of adipose tissue in nocturnal rodents and can reduce visceral fat masses in these species under various conditions (summarized in ref. [5]), this has not been clearly demonstrated in humans. In some studies, melatonin levels did not substantially differ between obese and normal-weight subjects [303-306], whereas, in others, increased melatonin was reported for some obese individuals [306-308]. Short-term fasting was reported to decrease melatonin [305], which might be in accordance with the latter observations. However, in obese postmenopausal women, melatonin was found to be decreased [309]. Thus, more data on humans appear to be required, and a particular attention should be paid to age and aging. In this context, circadian deviations and chronodisruption have to be also considered, which occur, e.g., in night-eating syndrome, and as far as possible distinguished from obesity alone.

Properties of Melatonin and Synthetic Melatonergic Drugs

The structures of several selected melatonergic agonists are shown in Figure 2. Except for TIK-301 (= β -methyl-6-chloromelatonin), all these compounds represent non-indolic structures. Ramelteon (Rozerem[®]; TAK-375), developed by Takeda, Japan, has been approved in the USA by the FDA for the treatment of insomnia. The ramelteon metabolite M-II is also depicted, because it has melatonergic properties and contributes substantially to the overall activity of the parent compound. Agomelatine (Valdoxan[®]; S20098), developed by Servier, France has been licensed by EMEA for the treatment of major depressive episodes (MDE) in adults in Europe. In addition to these synthetic drugs, a melatonin controlled-release tablet (Circadin[®]), developed by Neurim, Israel and UK and also provided by Lundbeck and Nycomed, has been approved by EMEA for the treatment of insomnia in patients aged 55 years and over. All other compounds are to date investigational drugs, which differ concerning the number and outcome of preclinical and clinical studies.

Table 3: Affinities of melatonin and a few selected melatonergic drugs towards human MT₁ and MT₂ receptors.

Compound	pK _i at MT ₁	pK _i at MT ₂	References
Melatonin*	10.09	9.42	[310]
Ramelteon	10.85	9.95	[310]
Agomelatine	10.21	9.57	[311]
GR 196429	9.85	9.79	[312,313]
Tasimelteon	9.45	9.80	[314]
TIK-301	10.09	10.38	[315,316]
AH-017	8.27	9.16	[313]
UCM765	8.38	10.17	[316,317]
UCM924	6.75	9.27	[317]

*Other, moderately deviating values from different laboratories are summarized in ref. [19]. pK_i values were either directly obtained from respective publications or calculated from published K_i values.

The affinities of the agonists towards human MT₁ and MT₂ receptors [19, 310-317] are summarized in Table 3. The natural hormone has a somewhat higher affinity to MT₁ than to MT₂. This is also the case with ramelteon and agomelatine, but not so with several other compounds. Even TIK-301, which is most closely related to melatonin, has a slightly higher affinity to MT₂. This property is even more expressed in AH-017, UCM765 and UCM924. None of the compounds is strictly selective for one of the two melatonin membrane receptors, but the relative preference for MT₂ is already very pronounced in UCM765 and UCM924, in which the affinities to the receptors differ by almost or even more than two orders of magnitude, respectively. Whether or not this property may turn out to be of value, e.g. in a possible future treatment of disorders and diseases related to MT₂ signaling, remains to be studied.

A major obstacle for the use of melatonin as a clinically efficient drug results from its extremely short half-life in the circulation, which is mostly in the range of 20 - 30 min, sometimes even less, but maximally about 45 min [18, 318]. As a solution to this problem, controlled-release formulations of the natural hormone, such as Circadin[®], have been developed or, alternately, synthetic drugs with a substantially longer half-life. Ramelteon is rapidly absorbed by the gastrointestinal tract (absorption rate: about 84%) and the circulating drug has a half-life in the range of 1 - 2 h [319]. Among the melatonergic agonists, ramelteon is the only one with considerably higher affinities to both receptor subtypes (cf. Table 3). Its metabolism differs profoundly from that of melatonin, although it is also substrate of hepatic cytochrome P₄₅₀ monooxygenases (mainly CYP1A2, CYP2C and CYP3A). Among the metabolites, M-II (cf. Figure 2) is of particular interest, since it also acts as an agonist at MT₁ and MT₂ receptors, with an approximate potency of 10% compared to the parent compound. Despite its lower affinities, M-II is functionally relevant, since its circulating levels are 20 - 100 fold higher than those of ramelteon after systemic exposure. Moreover,

the half-life of M-II is by 2 - 5 h longer than that of the parent compound [319].

The half-life of agomelatine, which has receptor affinities slightly above those of melatonin (Table 3), is also in the range of 1- 2 h. Contrary to melatonin and ramelteon, it displays the additional property as an antagonist of the serotonin receptor 5-HT_{2C}. The inhibition of 5-HT_{2C} signaling has been interpreted as the cause of agomelatine's direct antidepressant actions [216, 321]. These have to be distinguished from indirect melatonergic actions related to adjustments of circadian rhythms, which are effective in subtypes of depression with an etiology of circadian dysfunction. However, a synergistic interaction of melatonergic and 5-HT_{2C} signaling has been recently assumed to explain the antidepressant action of agomelatine [322].

The combination of properties as a melatonergic agonist and serotonergic antagonist has been recently described for TIK-301. This drug was reported to be an even more potent inhibitor of 5-HT_{2C} and 5-HT_{2B} receptors than agomelatine [19, 323]. Therefore, TIK-301 may also possess direct antidepressive properties, comparable to agomelatine, an assumption which would require further clinical substantiation. To date, studies have mainly focussed on soporific effects. The chlorine at ring atom 6 prevents hydroxylation by CYP isoenzymes in this position, i.e., the major catabolic pathway of the otherwise similar melatonin. However, the half-life of TIK-301 has been reported to be in the range of 1 h [315] and is, thus, only moderately extended. TIK-301 has received an orphan drug designation by FDA and can be used for treatment of sleep disorders in blind individuals.

Tasimelteon is another melatonergic drug that has been clinically tested [314], primarily with regard to sleep promotion and, in exploratory and pre-clinical trials, for antidepressive effects. However, no effects on 5-HT_{2C} receptors are known for this compound. The half-life of tasimelteon seems to be longer than that of melatonin; in monkeys and rats, values around 2 h (between 1 and 3

hours) have been reported. For other pharmacokinetic data see ref. [324].

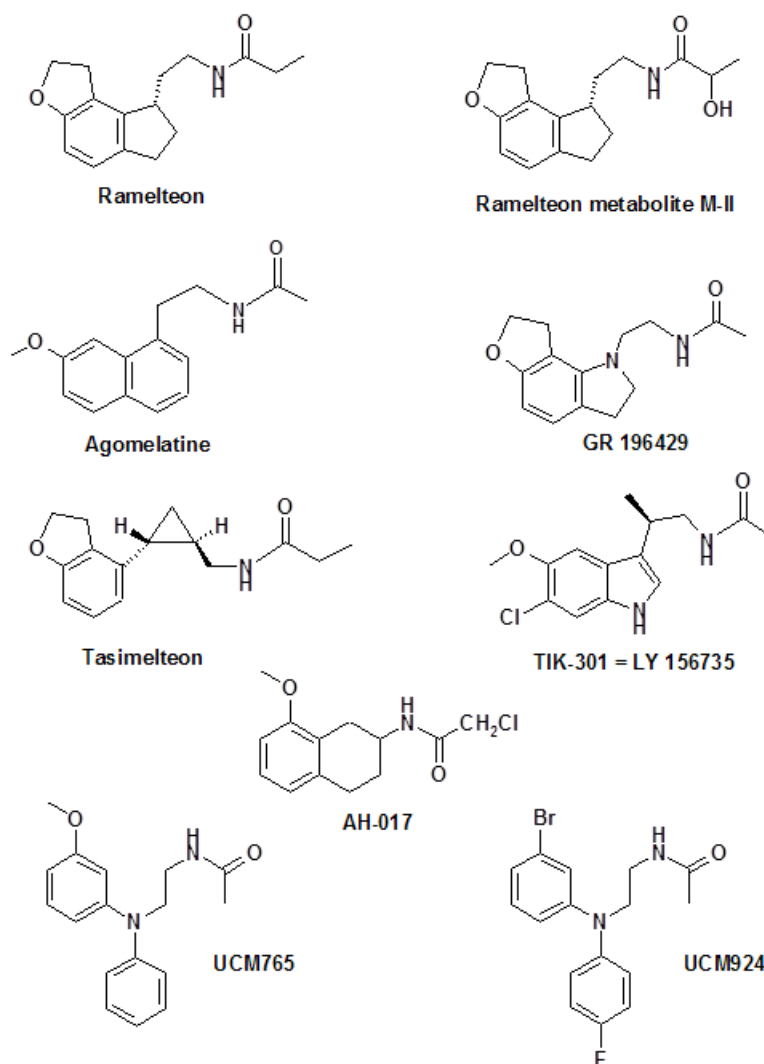


Figure 2: A selection of several approved or investigational melatonergic agonists. For various other agonists see ref. [19].

Pharmacokinetic and, especially, clinical data are poorly available for the other investigational agonists, whereas pre-clinical data on sleep do exist (cf. ref. [19]). GR 196429 and AH-017 were reported to increase the amplitude of the melatonin in rats. Deviations in the phase resetting properties of GR 196429 compared to other melatonergic drugs would require mechanistic explanations [19]. The functional importance and possible value of preferential binding to MT_2 receptors described for AH-017 and, even more, UCM765 and UCM924 await further exploration. This aspect has been

recently addressed in mice, in which UCM765 was shown to stimulate firing of reticular thalamic neurons in an MT_2 -dependent manner, thereby increasing non-REM sleep [325]. These compounds may turn out to be of interest for the treatment of disorders and diseases associated with impaired MT_2 signaling. Finally, it should be noted that the agonist UCM924 was designed to extend the half-life by blocking a preferred hydroxylation site of UCM765 by attaching a fluorine atom, and by preventing *O*-demethylation by substituting the methoxy group by its bioisostere, bromine [317].

Another compound, NEU-P1, has received some attention because it was reported to inhibit weight gain and to improve insulin sensitivity in high-fat/high-sucrose-fed rats [300]. Additional data summarized elsewhere [19] have been published at abstract level and include effects on sleep. Chemical and pharmacokinetic data remain to be disclosed. According to high doses administered to rats, receptor affinities are presumably below those of compounds listed in Table 3.

Options for Treatment Based on Short-term Actions

Instead of repeating the numerous clinical data, especially on sleep parameters, which have been frequently reviewed [18, 19, 127, 128, 216, 236, 245, 246, 282, 285, 326-342], a general outline will be given on the strategies of treatment and their chronobiological rationale.

It is important to distinguish between disorders in which only short actions of melatonin are required and others in which a substitution therapy aims to replace insufficient nocturnal levels of the hormone throughout the night. In the first case, the short-lived natural hormone may suffice for treatment. A short action is sufficient in the case of sleep onset difficulties. Melatonin reduces sleep onset latency, frequently determined as LNA (latency to non-awake) or, by polysomnography, as LPS (latency to persistent sleep), already at low doses of 0.1 – 0.3 mg/d of an immediate release formulation [326]. However, the effects on sleep maintenance remain negligibly low, at these doses. A significant reduction of sleep onset latency has been observed with all synthetic melatonergic agonists so-far tested [18, 19, 314, 326-330, 333, 334, 341, 342]. However, the recommended doses of these drugs are considerably higher, such as 4 or 8 mg/d for ramelteon, despite its higher receptor affinity compared to melatonin, or 25 mg for agomelatine. Therefore, the synthetic drugs are not of advantage, as long as only improvements of sleep onset are intended. Without any doubt, the natural hormone has a preferable profile concerning tolerability and physiological metabolism. Moreover, MT₁/MT₂-independent effects are presumably absent in the synthetic drugs. However, the significance of these actions is still poorly understood.

Short actions are also sufficient if chronobiotic, i.e., phase shifting properties of melatonin are decisive. Resetting of the circadian oscillators is required in cases of rhythm perturbations. These may have been induced either (i) externally by light at night or transmeridian flights, (ii) by clocks poorly coupled to the environmental cycle or (iii) in cases of dysphasing or desynchronization within the multioscillator system. Insufficient coupling may result from flattened

oscillations, especially under conditions of reduced melatonin secretion due to age or disease. For this reason, agents capable of enhancing rhythm amplitudes may become of interest. Phenomena such as relative coordination, internal desynchronization and abnormal phase relationships to external synchronizers or between parallel oscillators have been poorly investigated on a systematic basis, but they seem to be involved in impairments of physical and mental fitness as well as bipolar and seasonal affective disorders [230, 233, 343-347].

As far as circadian malfunctioning is implicated in these latter types of mood disorders, melatonin can be effective in readjusting rhythms and, thereby, improving symptoms. It is important to not confuse such effects with direct antidepressive actions, which are obviously also exerted by agomelatine and TIK-301. Treatments with synthetic melatonergic drugs can be expected to be beneficial on a circadian basis, but neither a higher receptor affinity nor a longer half-life are reasons for assuming a superior efficacy compared to melatonin. A short-acting chronobiotic such as melatonin is capable of inducing phase adjustments, because circadian oscillators are largely sensitive to a so-called non-parametric resetting [348], i.e., by stimuli in which the relative change is decisive rather than the absolute level of the synchronizer.

Concerning phase resetting, the treatment has to consider some fundamental chronobiological rules. Resetting signals are acting according to the respective PRC, as outlined above. The time of melatonin administration according to the human PRC [10, 11] is of utmost importance. Readjustment of rhythms by melatonin will only be achieved if it is given in an appropriate, sufficiently sensitive phase within the circadian cycle. If the rhythm is dysphased because of poor coupling to synchronizers, it may take several days more until the oscillation has attained the desired phase. Disregard of these chronobiological fundamentals can lead to false conclusions on inefficacy.

Melatonin or synthetic melatonergic drugs are not the only means by which circadian rhythms are reset. As mentioned above, this is also possible by light, as long as light perception in the blue range and neuronal connections to the SCN are not impaired. Light therapy is, thus, an option in these cases. In some individuals, a combination of light and melatonin in the different, respective phases may be also suitable or of advantage. However, under conditions of poor accessibility of the SCN to light signals, melatonin may be preferred.

Limits of Substitution Therapies

The short-term melatonergic actions have to be clearly distinguished from a replacement therapy. This would be desired in aged individuals or patients suffering from the various diseases associated with decreases in melatonin levels (cf. Table 1). Because of the short half-life, immediate-release formulations of melatonin cannot afford a satisfactory substitution.

Therefore, synthetic agonists or a controlled-release melatonin formulation such as Circadin[®] should be assumed to be superior. With regard to melatonin's exceptionally good tolerability, the pineal hormone may be tested first [18]. Among the synthetic drugs, ramelteon may be the choice in the USA, because of its approval by the FDA. Agomelatine, which is licensed in Europe, may give comparably good results. However, one should take notice of the restricted approvals of the tablets. Circadin[®] and ramelteon are only licensed for the treatment of insomnia, in the case of the controlled-release melatonin only for individuals of at least 55 years, agomelatine for the treatment of major depressive episodes in adults and TIK-301 for the use in blind people. Therefore, the full spectrum of possible applications is not covered by the approvals. This is particularly valid for agomelatine, which displays all the sleep-inducing and chronobiotic effects known from melatonin [216, 332, 333, 349]. From this point of view, it seems similarly suitable as ramelteon or melatonin.

In terms of efficacy, all these drugs have been reported to be beneficial concerning sleep maintenance or sleep quality. Although statistical measures have frequently reached significance, the extent of the improvements has remained relatively moderate. In elderly patients with primary chronic insomnia, the efficacy of ramelteon on sleep maintenance was recently found to be highly variable [350]. Despite some statistically demonstrable increases in sleep duration or sleep efficiency, these findings do not imply complete restoration of persistent sleep throughout the night [350-352]. The same can be concluded for the other melatonergic drugs tested for sleep maintenance [314, 316, 324, 340-342, 349, 353, 354]. Therefore, a convincing replacement therapy in melatonin deficiency has not yet been achieved with any of the melatonergic drugs, although they may have a moderate value in sleep efficiency and a good outcome concerning sleep initiation. Whether a replacement therapy will be possible by using much higher doses of melatonin, such as 50 or 100 mg/d, as recently suggested [342], remains to be tested. The standard dose of Circadin[®] is only 2 mg/d. In terms of tolerability and non-toxicity, doses of melatonin can be increased with less concern than in the case of synthetic drugs. Even 300 mg/d enterally have been administered for up to 2 years to ALS patients and found to be safe [355].

Concerning the use of agomelatine, a distinction between types of depression has to be made, as to whether they are based on circadian dysfunction or on other reasons. In the first case, short actions are only required for phase adjustments and, in chronobiological terms, the efficacy of agomelatine cannot be distinguished from those of other melatonergic agonists of similar receptor affinity. In major depressive disorders, symptoms are not primarily of circadian nature and their improvement has been attributed to the inhibition of 5-HT_{2C} receptors or, perhaps, an interaction between MT₁/MT₂ and 5-HT_{2C} signaling [322]. However, these properties are not comparable to effects by classic antidepressants. For this reason, some authors have considered the efficacy of agomelatine to be insufficient in major depressive disorder [356-358]. Another criticism concerned biased publication on the efficacy of this drug [359]. However, it seems necessary to clearly distinguish between modes of action. The advantage of agomelatine does not consist in a superior antidepressive effect, but rather in the combination of antidepressive benefits with sleep improvements. This dual action is important because sleep disturbances are often induced by classic antidepressants [285, 330, 332, 333].

Some other limits for melatonergic treatment can arise from drug interactions. This concerns mainly the synthetic agonists, which may attain undesired high concentrations in the presence of other drugs that inhibit CYP isoforms. For instance, ramelteon is mainly metabolized by CYP1A2, CYP2C9 and CYP3A4, agomelatine by CYP1A1, CYP1A2, and CYP2C9, tasimelteon by CYP1A1, CYP1A2, CYP2D6, and CYP2C9 [18]. Therefore, combined treatment with drugs such as fluvoxamine, ciprofloxacin, mexiletine, norfloxacin, azileuton, fluconazole or ketoconazole has to be avoided. In the case of melatonin, elevations caused by CYP inhibition are presumably relatively harmless, with regard to high doses of the methoxyindole applied in patients, volunteers and numerous pre-clinical experiments, without serious adverse effects. Nevertheless, caution is due with all melatonergic agonists including the natural hormone in autoimmune diseases, because of melatonin's immune modulatory role, in Parkinson's disease, as long as the controversy concerning interpretations by Willis [278, 279] has not been definitely settled, and with regard to reproductive function, especially in juveniles and during pregnancy. Melatonin has been applied in children and pregnant women under some conditions, but this requires a thorough weighing of benefits and possible risks. Concerning the approved synthetic agonists, hepatic and renal impairment, consumption of alcohol and high fat have been also listed as contraindications [326, 330].

Although all clinically tested melatonergic agonists were well tolerable and usually showed side effects in the placebo range during treatments of several weeks or months, the possibility of long-term toxicity seems to require further attention. Several recent papers indicate long-term safety of ramelteon in their titles [360-362], but they mainly address mild adverse events such as nausea and headache, some hepatological parameters, absence of residual effects, rebound insomnia, withdrawal symptoms and dependence for periods of six or twelve months, but do not exclude mutagenic or carcinogenic actions over extended periods of treatment. Studies on hepatotoxicity, micronuclei formation and mutagenicity have to consider not only properties of the parent compound, but also of the main metabolite M-II, which attains, e.g., concentrations in the range of one third of the no-effect level for tumor induction of ramelteon [326, 330]. Toxicological concerns may also exist in the case of agomelatine, which is well-tolerated during short-term treatment, but, being a naphthalenic compound, would require thorough studies on long-term toxicity, including CYP-related hepatic effects and, perhaps, carcinogenicity [18, 19, 330]. With regard to CYP-dependent metabolism, this is less a matter of drug interactions, which have to be avoided or minimized in any case, but that of a possible formation of toxic metabolites, which is a frequent, fundamental problem of naphthalenic substances. The relatively high recommended dose of 25 mg/d should be taken into account. Risks of hepatotoxicity were recently re-addressed and it was criticized that this issue had not been prominently documented in the published studies [357, 359]. Moreover, oncogenicity of very high doses observed in animal experiments should be taken as a caveat [357]. The criteria of long-term safety, including properties of metabolites, have to apply correspondingly to the investigational melatonergic drugs. Their suitability and eventual superiority (i) will less depend on higher receptor affinities, since those of ramelteon may not be easily surpassed, (ii) may be associated with extended half-lives, (iii) might emerge from effects in addition to melatonergic actions, but (iv) requires non-toxicity over extended periods of time.

Conclusion

Progressive reductions of melatonin secretion are one of the hallmarks of aging. Moreover, decreases in circulating melatonin and/or dysfunction of melatonergic signaling are associated with a remarkable number of age-related and other diseases. With regard to the dependence of the mammalian pineal gland on SCN functioning, to the feedback of melatonin to this central pacemaker and to actions of melatonin at peripheral

oscillators, many but, presumably, not all effects of this hormone have to be understood on a chronobiological basis. This is particularly evident in CRSDs, in which melatonin or synthetic melatonergic agonists can be used for circadian phase shifting and, thus, resynchronizing oscillators to favorable phase relationships with external and among internal rhythms, thereby reducing sleep difficulties. Moreover, melatonin is capable of stimulating sleep initiation, via SCN and the hypothalamic sleep switch and, additionally, by acting on other brain areas such as the thalamus. The support of sleep maintenance by the natural hormone or by synthetic melatonergic agonists is also demonstrable but rather limited.

The chronobiotic effects of melatonin and its synthetic analogs seem to be decisive for treating mood disorders with an etiology of circadian dysfunction, such as seasonal affective and bipolar disorders. Agonists that only act via MT₁ and MT₂ receptors may have no or only marginal direct antidepressive effects. Conclusions on anxiolytic or antidepressive actions drawn from experiments in animal models using nocturnally active rodents should be regarded with caution, because melatonin is associated in these animals, contrary to humans, with enhanced neuronal, physical and metabolic activity, and also because sedating effects observed at high doses may be confused with anxiolysis or an antidepressive potential.

However, direct antidepressive effects are demonstrable in melatonergic agonists with additional properties as antagonists of the serotonergic receptor 5-HT_{2C}, such as agomelatine and TIK-301. Whether a synergistic interaction between melatonergic signaling and 5-HT_{2C} inhibition is of importance in these cases, as recently discussed [322], remains to be confirmed in more detailed studies. These drugs offer options for treating types of major depressive disorder, which are not successfully tractable with other melatonergic agonists. They also have the advantage of combining antidepressive actions with sleep-promoting effects, which is important because of sleep disturbances caused by other antidepressants. However, the entirely different mode of actions of these combined melatonergic agonists/serotonergic antagonists does not lead to effects as strong as observed with traditional antidepressants. Therefore, they may not be sufficient for treating severe cases.

Metabolic regulation by melatonin seems to become an important field of future research. Melatonin is obviously involved in the entire complex of obesity, metabolic syndrome, with consequences for cardiovascular diseases, insulin resistance, prediabetic changes and diabetes type II, as shown by deviations of melatonin secretion and signaling and receptor

polymorphisms. This includes a network of interconnected signaling pathways, in which melatonin interacts, e.g., with metabolic sensors such as AMP-activated protein kinase (AMPK) and its downstream factors [5, 39], mechanisms that are also interrelated with circadian oscillators [39]. Moreover, mitochondrial effects of melatonin have to be taken into account, although the role of MT₁/MT₂ signaling is still poorly understood in this area. To date, neither the cell biological basis of these connections nor the clinical experience suffice for recommendations for a use of melatonin or its agonists in this field. Nevertheless, research in this direction seems to be promising.

Although an immense body of knowledge exists on neuroprotection by melatonin in animal and in vitro models, which includes, again, numerous effects such as antiexcitatory, antiinflammatory, direct and indirect antioxidative actions, the application of the pineal hormone or its analogs to humans has remained marginal. In AD, which is also characterized by deteriorations of melatonin secretion and circadian oscillators, some moderate and, sometimes, inconsistent effects have been described concerning sleep. Reductions of sundowning were observed [363] which can be of value especially for caregivers. However, these effects vanish during disease progression, and even the experience with animal models indicates that a late onset of melatonin treatment does not result in substantial benefits. A similarly pessimistic judgment, except for some sleep improvements, has to be given for other neurodegenerative diseases.

However, benefits of melatonin or, perhaps, synthetic melatonergic agonists, may be expected in the area of healthy aging. This should not be confused with life prolongation, which has been demonstrably achieved, in vertebrates, only in senescence-accelerated mice [364], but not to a convincing extent in wildtype animals [365]. Nevertheless, the experience with melatonin-treated rodents indicates an obvious healthier aging [4, 365]. It should be noted that, also in the context of aging, numerous metabolic cross-connections between melatonin and other signaling pathways exist, which include energy sensing, mitochondrial modulation and proliferation, redox sensing and actions of aging suppressor genes [269, 366]. Despite numerous publications that relate melatonin to aging and age-dependent dysfunctions in animal models, the application to humans has, in this field, more or less remained at a stage of discussion or a suggestion [367, 368].

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