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REVIEW

The melatonergic system: effects on sleep and implications for the treatment of psychiatric disorders

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Abstract: The circadian pacemaker or biological clock, located in the hypothalamic suprachiasmatic nucleus, is the generation site of circadian rhythms. The light/dark cycle is the circadian pacemaker's dominant synchronizing agent, though it is also influenced by neurotransmitters and the phase-shifting effects of various chemical and pharmacological components, of which melatonin (N-acetyl-5-methoxytryptamine) is the most well established. In recent years, melatonin and melatonin analogs have been commercialized in many countries, mainly with hypnotic purposes. A new compound, agomelatine, has been recently synthesized and studied. Among melatonin analogs, this drug possesses unique pharmacological and clinical features; it is an antagonist at 5-HT2B and 5-HT2C receptors and has well established antidepressant and anxiolytic properties. Agomelatine opens new perspectives in the chronobiotic treatment of depression. The purpose of the present review was to elucidate the effects of the melatonergic system on sleep and the implications for the treatment of psychiatric disorders.

Keywords: melatonin, agomelatine, circadian rhythms, depression

Introduction: circadian and sleep–wake systems

Many biological functions are regulated by biological rhythms, among which circadian rhythms (Latin: circa, about; dies, day) are the most extensively studied and the best understood. They determine daily rhythmicity in behavior, core body temperature, sleep, feeding, drinking, and hormonal levels.[1,2] These circadian rhythms prepare the organism to anticipate daily changes in the environment and are not simply driven by the 24-hour environmental cycle, since they persist in the absence of time cues.[3]

The circadian pacemaker, or biological clock, is the generation site of circadian rhythms. In mammals, the biological clock is located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, above the optic chiasma. It is noteworthy that most SCN efferent projections remain within the limits of the hypothalamus, and the best studied projection of SCN outside the hypothalamus is a multisynaptic projection to the pineal gland (see later).[4]

SCN neurons isolated and kept in culture for several days still continue to show approximately 24-hour rhythms in action potential frequency. Metabolically, the SCNs show peak activity during the subjective day. This increased level of metabolism is paralleled by the increased electrophysiological activity evident from brain slice recordings.[5]

The mean circadian period generated by the human SCN is approximately 18-24 hours. To remain perfectly entrained to the 24-hour cyclicity of the environment,

the circadian clock uses several internal and external synchronizers that are able to modify the period and the phase of circadian rhythms. The light/dark cycle is the dominant synchronizing agent for circadian rhythmicity. In fact, the human circadian pacemaker is stimulated by light presented in the evening to phase-delay its rhythms and by light stimuli given in the morning to phase-advance.[6,7]

Circadian pacemaker regulation is also determined by neurotransmitter function and the phase shifting effects of various chemical or pharmacological components, including melatonin (N-acetyl-5-methoxytryptamine).[8]

Melatonin physiology

Melatonin is an indoleamine hormone, mainly synthesized in the pineal gland. The biosynthesis of melatonin involves several steps that can be summarized as follows: (1) pinealocytes take up L-tryptophan from cerebral vessels and convert it to serotonin through 5-hydroxylation and decarboxylation, (2) serotonin is converted to *N*-acetyl-serotonin (AANAT) by the rate-limiting enzyme arylalkylamine *N*-acetyl transferase, (3) AANAT is finally converted into melatonin by hydroxyindole-*O*-methyl transferase.[9]

Once synthesized, melatonin is not stored within the pineal gland but diffuses out into the bloodstream, rapidly reaching all body tissues.[10] Circulating melatonin is metabolized by cytochrome P-450 which catalyzes its hydroxylation at the C-6 indole position to yield 6-hydroxymelatonin. This reaction is followed by conjugation with sulfuric acid (or to a lesser extent with glucuronic acid) to produce the principal urinary metabolite, 6-sulfatoxymelatonin. In the brain, melatonin can be metabolized to the kynurenine derivative *N*1-acetyl-5-methoxykynurenine by oxidative pyrrole-ring cleavage, or to a cyclic 3-hydroxymelatonin derivative (1-{3a-hydroxy-5-methoxy-3,3a,8,8a tetrahydropyrrolo[2,3-b]indol-1(2*H*)-yl} ethanone).[4]

Melatonin is primarily synthesized in the pineal gland, but synthesis also occurs in the retina, gastrointestinal tract (GIT), skin, bone marrow, and lymphocytes, thus likely influencing other physiological functions.[11,12]

In lower vertebrates, the pineal gland is photosensitive and is the site of a self-sustaining circadian clock. In humans, the gland has lost direct photosensitivity, but responds to light via a multisynaptic pathway.[13,14] Pineal melatonin exhibits a circadian rhythm with very low levels occurring during daytime and high levels during nighttime, irrespective of whether the species are diurnal, nocturnal, or crepuscular in their activity patterns.[15,16]

The circadian rhythm of melatonin production is regulated by the SCN of the anterior hypothalamus.[17] Nerve fibers from the SCN project through multisynaptic descending pathways that pass through the sub-paraventricular zone, median forebrain bundle, and the reticular formation to the intermediolateral horn cells of the spinal cord.[18] From here, preganglionic fibers reach the superior cervical ganglion, which gives rise to postganglionic fibers that innervate the pineal gland: these postganglionic fibers regulate pineal melatonin synthesis via norepinephrine (NE) release.[19] The light/dark cycle entrains SCN activity by photoperiodic information transmitted through the retinohypothalamic pathway/tract.[20]

The nocturnal increase of melatonin production is due to an increase in AANAT activity via activation of β-adrenergic receptors by NE, which in turn is associated with increases in intracellular cyclic-AMP levels.[21] Cyclic-AMP stimulates AANAT expression and phosphorylation via protein kinase A, which also allows AANAT to be stabilized by binding of 14-3-3 proteins.[22] These processes are inversely affected by the presence and amount of environmental illumination, with immediate degradation of pineal AANAT production following exposure to bright light at night.[23] The expression of specific clock genes in the SCN is also affected by the nocturnal exposure to light.[24] Moreover, the circadian rhythm of AANAT activity in the pineal gland is abolished by lesions of SCN, further demonstrating its dependence on this hypothalamic area.[25]

Circulating melatonin is derived mainly from the pineal gland. Melatonin diffuses easily through all biological membranes and is then metabolized mainly in the liver, where it is first hydroxylated in C6 position and then conjugated and excreted as 6-sulfatoxymelatonin.[26]

Within neurons, melatonin and its metabolites play neuroprotective, metabolic and coordinating roles: they exhibit antioxidant properties, enhance cell viability, inhibit mitochondrial neurodegenerative events and apoptosis, and benefit numerous diseases via their multiple metabolic actions.[27] Its physiological effects are likely to be mediated through activation of distinct melatonin receptors in target tissues.[28,29] The discovery of different melatonin receptors was facilitated by the introduction of the agonist radioligand 2-[125I]-iodomelatonin.[30] Melatonin receptors were originally divided into the MT1 and MT2 classes, based on different affinity and binding kinetics for 2-[125I]-iodomelatonin and on different pharmacological profiles for a conventional series of ligands.[31,32] Both receptor classes

belong to the family of G-protein-coupled receptors linked to the inhibition of adenylyl cyclase. Melatonin binds to these sites with low picomolar (MT1) and low nanomolar (MT2) affinities, respectively.[33] The MT1 receptor-subtype was shown to inhibit neuronal firing in mice SCN slices[34] and to be responsible for cardiac vessel constriction.[35,36] The MT2 subtype regulates the phase-shift of circadian rhythms[37] and inhibits cardiac vessel constriction.[38] A clear functional distinction between these two subtypes needs further investigation.

Subsequently, a third, nonmammalian melatonin receptor subtype, MT3 (formerly known as Me1c)[39,40] was cloned, and its binding site was characterized as the hamster homolog of the human enzyme quinone reductase.[41] In addition to membrane melatonin receptors, the nuclear melatonin receptor RZR/ROR is also known.[42]

Tissues endowed with fully characterized functional MT1 and/or MT2 melatonin receptors include: retina, suprachiasmatic nucleus, pars tuberalis, cerebral and peripheral arteries, kidney, pancreas, adrenal cortex, testes, and immune cells.[43] Melatonin acutely inhibits SCN neuronal firing, an effect that is most pronounced at times of high SCN neuronal activity (ie, during daytime, although the effect is also observed at night).[44] Suppression of SCN neuronal activity by melatonin represents a likely mechanism by which the methoxyindole contributes to the regulation of sleep in diurnal species.[45] This effect is presumably linked to the activation of GABAergic mechanisms in the SCN.[46] The acute inhibitory effects of melatonin on SCN multiunit activity are completely absent in MT1 melatonin receptor knockout mice, while the phase-shifting effects of melatonin are preserved. The expression of melatonin receptors in the SCN varies during the circadian cycle, with increased levels at night and lower levels during the day.[47,48] Light-sensitive neurons found in the "core" area of the SCN do not exhibit demonstrable endogenous rhythmicity in melatonin receptor expression, while oscillating neurons are present in the surrounding "shell" group.[49,50]

An important conceptual difficulty in melatonin research concerns its different functional consequences depending on the species' time of peak activity, though it signals darkness in all species.[49] In nocturnal species, melatonin is associated with arousal and physical activity, whereas it is associated with sleep and rest in diurnal species.[51]

Given that the SCN has a similar function in both nocturnally and diurnally active animals, melatonin signal's differential "interpretation" must be downstream of the SCN and possibly involves a counterbalance between melatonin's effects on brain regions involved in certain activities (eg, arousal) and those involved in the suppression of these activities.[51] These "chronobiotic" properties of melatonin may have a significant regulatory influence over many of the body's physiological functions.[52]

Biological rhythms and human pathology

Since antiquity, scientists and philosophers have linked mental disorders to physical and functional changes in the pineal gland, due to its attributed role in humans as the connection between soul and body.[53] Nowadays, ever since an amphibian skin-lightening molecule was isolated and identified as *N*-acetyl-5-methoxytryptamine in 1958,[54] there has been renewed interest for the involvement of the pineal gland and melatonin in human pathology.[55]

It is well known that there is a physiological chronobiological variability between individuals. In qualitative terms, one may distinguish morning people (or morning larks), characterized by tendency to awaken early and experience minimum core body temperature at an early clock time, and night people (or night owls), with opposite features.[56] Advanced sleep phase syndrome is a pathological extreme of the morning lark phenotype, whereas delayed sleep phase syndrome is a pathological counterpart of the night owl phenotype. For both these syndromes, there are familial, genetically determined forms.[57]

Besides these relatively rare syndromes, strictly linked to chronophysiology, many attempts have been made to correlate medical pathologies to circadian-clock and circadian rhythm alterations. For example, it has been suggested that desynchrony between the SCN and the various oscillators in peripheral tissues is involved in cardiovascular diseases.[58] Travel across multiple time zones and shift work are the most common causes of circadian desynchrony. Cardiovascular disease risk factors such as obesity, low high-density lipoprotein cholesterol levels, and high triglycerides are more prevalent among shift workers than day workers.[59] Furthermore, many of these associations increase in aged shift workers. In addition, epidemiological studies have shown that women working night shifts have a significantly higher risk of breast cancer.[60] These reports require more thorough preclinical and clinical studies for confirmation.

Circadian rhythms are altered in many neuropsychiatric states (eg, psychotic disorders, post-infectious illnesses, chronic fatigue states, and chronic pain), but the disease with most prominent clinical circadian disturbances is depression,

with delayed sleep onset, nonrestful sleep, early-morning awakening, daytime fatigue, and blunting or reversal of the normal morning peaks in subjective energy, mood, and alertness.[61,62] Depression is also the most studied among these conditions, and it seems to be related to disruption of the central circadian clock function and not to an alteration in a specific rhythm.[63] Some of the most characteristic circadian alterations in depression include: reductions in the amplitude of diurnal variations in core-body temperature and plasma cortisol concentrations,[64] phase shift of several circadian rhythms (eg, core body-temperature, plasma melatonin, and cortisol concentrations, and sleep–wake timing),[65] increased stage 1 and stage 2 sleep total time, reduced latency to the first rapid eye movement (REM) episode, and decreased time spent in slow-wave sleep.[66] However, the type of rhythm abnormality varies notably in depressed patients, including rhythms' phase advance or delay and increase or decrease in rhythms' amplitude.[64] The complex relation between the endogenous circadian pacemaker and the appearance of depressive symptoms is, therefore, far from being elucidated.[67]

An interesting prototype of rhythmicity and seasonality is seasonal affective disorder (SAD). SAD or winter depression has been defined as a seasonal pattern of recurrent major depressive episodes that occur during winter/fall in the absence of seasonal psychosocial stressors, and with full clinical remission in spring/summer.[68] Epidemiological studies show that the incidence of SAD in the general population is 15%–25%.[69] Patients with SAD manifest atypical depressive symptoms such as carbohydrate craving, hypersomnia, hyperphagia, or weight gain.[70]

Melatonin and depression

Literature on melatonin levels in depression is controversial. Wetterberg and co-workers proposed that major depressive disorder (MDD) may be considered a "low melatonin syndrome," thus conceptualizing low melatonin secretion as a biological marker for depression.[71] A number of studies have reported low nocturnal melatonin secretion in depressed patients.[72] However, increases in melatonin secretion have also been observed.[73] These contrasting findings could be accounted for by differences in patterns of depressive symptomatology or of melatonin secretion, inasmuch as there are studies showing increased daytime melatonin secretion in depressed individuals.[73]

The reduced blood melatonin concentrations and the trend towards melatonin rhythms' phase delay reported in affective disorders[74] point to a possible relation, via monoaminergic mechanisms, between antidepressant drugs' efficacy and melatonin secretion.[75] However, the lack of melatonin disturbances noted in other studies suggests that the increase in melatonin could be related to antidepressants' pharmacological effects rather than improvement of depressive symptoms.[76]

Phase delay of the circadian pacemaker relative to timing of the habitual sleep–wake cycle has been postulated to be a major contributing factor in the pathophysiology of SAD.[77]

Melatonin receptor agonists

Melatonin's successful clinical use is limited by its short half-life, which ranges from 20 to 40 minutes.[78] To overcome this drawback, prolonged-release formulations of the natural hormone (eg, Circadin®, Neurim Pharmaceuticals, Tel-Aviv, Israel) and melatoninergic agonists with a longer half-life (eg, ramelteon and tasimelton) have been developed.[4]

Exogenous melatonin has some antidepressant-like actions in animal models.[79] Daily treatment with melatonin reverses the adverse effects of chronic stress in mice.[80] In depressed patients, melatonin administration improves sleep, with only a modest effect on depressive symptoms and without substantially enhancing the effect of existing antidepressant therapies in treatment-resistant depressed patients.[81] It thus appears that melatonin on its own is not sufficient to achieve a robust clinical antidepressant efficacy. Addition of melatonin to present antidepressant therapies can, however, improve overall outcome.[82,83] Indeed, some antidepressants (eg, tricyclic antidepressants, serotonin-specific reuptake inhibitors (SSRIs), and noradrenalin-specific reuptake inhibitors) have negative effects on sleep architecture, reducing the duration of REM sleep and increasing REM latency.[84,85] Because REM sleep is under circadian control, one expects that it could be positively affected by compounds binding to melatonergic receptors.

Pharmacological features of agomelatine

Agomelatine (Valdoxan®/Thymanax®) (S20098, N-[2-(7-methoxynaphth-1-yl)ethyl]acetamide), developed by Servier (Neuilly-sur-Seine, France) and Novartis (New York, NY), was first reported in the literature in 1992.[86] Investigations on agomelatine's action on over 80 receptors and enzymes revealed a high affinity for MT1 (Ki = 0.1 nM) and MT2 (Ki = 0.12 nM) receptors, where it acts as an agonist, and a moderate affinity for 5HT2C (pKi = 6.2 μM) receptors, where it acts as an antagonist.[87,88] Compared with melatonin, agomelatine's binding affinity for MT1 and MT2 is similar.

Instead, with respect to 5-HT2C receptors, melatonin has negligible affinity when compared with agomelatine.[87] Though agomelatine receptor binding affinity is at least 100-fold greater for melatonin receptors than for 5-HT2C receptors, it is the 5-HT2C receptor blockade that best explains agomelatine's different efficacy profile from that of melatonin.[88] For instance, when administered in the evening to rats with chronic mild stress, both agomelatine and melatonin show antidepressant-like activity, but only agomelatine exhibits antidepressant-like activity when administered in the morning.[89] The major hypothesis to explain agomelatine's clinical action is that this compound could act synergistically on both melatonergic and 5-HT2C receptors. In-vivo data indicate that agomelatine enhances dopamine and noradrenaline levels in the frontal cortex, but not in the nucleus accumbens or striatum, probably due to blockade of 5-HT2C receptors' inhibitory input to cortical dopaminergic and adrenergic pathways.[90] In addition, 5-HT outflow in the frontal cortex remains unchanged and chronic treatment with agomelatine does not cause any adaptive changes in pre- and post-synaptic 5-HT1A receptors' activity.[91] This is noteworthy, as the lack of effect on 5-HT outflow together with the absence of functional changes in 5-HT1A receptors allow to infer that agomelatine's antidepressant action is not mediated by the same mechanisms as for tricyclics, SSRIs, and monoamine oxidase inhibitors.[92]

Agomelatine is well absorbed following oral administration (intestinal absorption is at least 80%), but due to high first-pass metabolism, mean bioavailability is estimated to be about 3%–4%.[90] Within the therapeutic dose range, systemic exposure to agomelatine increases roughly proportionally to the dose administered; at higher doses, saturation of first-pass metabolism occurs.[91] The bioavailability estimate is twofold higher in women than men.[93] Agomelatine's pharmacokinetics is characterized by a biphasic decrease with mean half-lives ($t_{1/2}$) of 0.2 and 1.4 hours, respectively. Its elimination depends mainly on metabolic clearance, and it is only modestly excreted unchanged in urine.[91] In-vitro studies reveal that agomelatine's major metabolic pathway is the liver's principal CYP1A isoform, CYP1A2, though CYP2C9 and CYP2C19 are also involved. It is generally accepted that agomelatine's metabolites barely contribute to its pharmacological activity.[85]

Agomelatine: clinical features

In addition to its renowned chronobiotic effects, agomelatine also has clinically significant antidepressant and anxiolytic properties.[85]

Agomelatine's antidepressant effects have been investigated in different animal models, including chronic mild stress, forced swimming, learned helplessness, and psychosocial stress models. All studies reported that the drug exerts an antidepressant-like effect.[94] Validated paradigms in rodents have shown that this compound accelerates resynchronization of circadian rhythms of locomotor activity and relevant biological parameters (ie, body temperature and hormone secretions), and its antidepressant effect may also depend on some other noncircadian mechanism, such as increased production of brain-derived neurotrophic factor.[95] Agomelatine's effects in anxiety disorders are less studied in preclinical settings. Nonetheless, some data point to efficacy in these disorders as well.[96] Agomelatine's effects on sleep architecture were evaluated in healthy young individuals using polysomnogram (PSG), and at 5 or 100 mg/day, agomelatine was found to significantly increase REM sleep.[97] In depressed patients, a 6-week administration increased non-REM (NREM) sleep duration as well as sleep quality and continuity, without modifying REM sleep duration.[98] Agomelatine's effects on the cyclic alternating pattern (CAP) in NREM and REM sleep was evaluated on 15 depressed patients using PSG. When compared with baseline data, a significant decrease in CAP time and CAP cycles after 7 and 42 days of treatment was observed.[99] Changes in NREM sleep variables preceded improvements in clinical depression scores. The disappearance of NREM sleep disruption has been suggested as one of the possible mechanisms by which agomelatine exerts its therapeutic effect.

Agomelatine, administered once daily at a dose of between 25 and 50 mg/day, is an effective antidepressant despite its short half-life which, in any case, is longer than that of melatonin.[90] Of the three published placebo-controlled trials supporting drug registration, the absolute difference in response rates (ie, 50% reduction of the 17-item Hamilton Rating Scale for Depression score) between agomelatine and placebo were 14.8% (95% CI 1.5%–27.4%), 15.2% (95% CI 3.3%–26.4%),[98] and 19.0% (95% CI 6.5%–31.5%).[99–102] Further studies versus placebo and comparators have confirmed agomelatine's efficacy in adults of all ages, including the severely depressed and the elderly.[103–109] Whether agomelatine is more effective in patients with specific abnormalities in circadian functions or with more severe sleep disturbances is yet to be established. Improvements on a range of sleep variables, including improved sleep quality (mean difference 5.63, 95% CI 0.85–10.41, $P = 0.021$), reduced wake after sleep onset (mean difference 4.86, 95% CI 0.23–9.49, $P = 0.040$) and fewer insomnia reports (mean

difference 0.37, 95% CI 0.01–0.72, $P = 0.044$), were greater with agomelatine than with venlafaxine.[105] In a long-term prevention of depression relapse trial, agomelatine's relapse rate at 10 months was 23.9% versus 50.0% for placebo (approximate difference of relapse estimates 26.4%, 95% CI 12.7%–39.0%), and the final relapse rate with agomelatine at 24 weeks was 20.6% compared with 41.4% for placebo (a difference of 20.8%, 95% CI 11.0%–30.0%).[110,111] Finally, as opposed to paroxetine, agomelatine does not seem to be associated with discontinuation symptoms.[112]

Because agomelatine does not increase serotonin level, it does not yield side-effects commonly seen with other novel antidepressants (notably, gastrointestinal upset, headaches, sexual difficulties, psychomotor agitation, and weight gain), and there is no risk of other major adverse events (such as serotonin syndrome or serotonin discontinuation symptoms).[110]

In February 2009, agomelatine was approved by the European Medicines Agency for the treatment of MDD and is available in several European countries.[91] Phase III clinical trials of agomelatine for depression (three short-term efficacy and safety trials and one longer-term relapse prevention trial) have also been conducted in the United States, but the results from these studies have not been released, and agomelatine is not yet approved by the United States Food and Drug Administration.[101] There is mounting evidence on its clinical efficacy in anxiety disorders. Besides its effective antidepressant action, agomelatine in fact, also decreases the severity of anxiety associated with depression.[49] Agomelatine's (25–50 mg/d) efficacy in generalized anxiety disorder was assessed in a 12-week double-blind, placebo-controlled study on 121 patients with no comorbid disorders.[113] Agomelatine was more effective than placebo in reducing anxiety (mean change in Hamilton rating scale for anxiety from baseline was 16.6 with agomelatine versus 13.2 with placebo; difference –3.3; $P = 0.04$). Moreover, in the literature there is a case report of social anxiety disorder effectively treated with agomelatine monotherapy[114] and some reports of agomelatine efficacy in obsessive compulsive disorder both in monotherapy[115,116] and in augmentation.[117] However, well performed studies on these disorders are still lacking.

Conclusion

Melatonin is fundamental to the body's homeostatic mechanisms. Melatonin analogs, mainly studied for sleep disorders, may be of potential use as primary or adjunctive drugs for a wide range of neuropsychiatric disorders characterized by persistent circadian disturbance. Agomelatine in particular, combining melatonergic agonism with 5-HT2C antagonism, appears to be promising in the treatment of depression. Because of its specific mechanism of action and potential to help restore circadian function during depressive episodes, this drug might play a unique role in the management of some depressed patients. Moreover, compared with SSRI/serotonin norepinephrine reuptake inhibitors, agomelatine has a favorable adverse effect and safety profile, with lack of clinically relevant weight gain, low risk of sexual dysfunction, low incidence of gastrointestinal reactions, absence of discontinuation symptoms, and overall incidence rates of adverse events that do not differ from placebo. Further studies are needed to examine agomelatine's efficacy in other mood and anxiety disorders, to better understand its role within the neuropsychiatric treatment armamentarium. Agomelatine's effectiveness in elderly patients and those of less than 18 years of age should also be investigated.

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