Rationale and problems of melatonergic treatment

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Summary

Melatonergic treatment can be successful under conditions of (i) decreased melatonin levels caused by aging and various diseases, (ii) circadian perturbations or dysfunction, including mood disorders with an etiology of circadian malfunction, (iii) sleep difficulties, and (iv) some metabolic disorders concerning energy metabolism and insulin resistance. In addition to melatonin, which is available as immediate- and prolonged-release formulations, several synthetic melatonergic drugs have been developed. Properties of melatonin are compared with those of β-methyl-6-chloromelatonin (TIK-301), piromelatine, agomelatine, ramelteon, GR 196429 and tasimelteon. The article emphasizes the necessity of distinguishing between promising approaches based on short but repeated actions and others aiming at a substitution therapy, which is not easily achieved. Short actions on sleep initiation and circadian phase shifting are already successful with low doses of melatonin. Such a chronobiotic approach may be also possible in bipolar and seasonal affective disorders. Longer actions are required for promoting sleep maintenance. Prolonged-release melatonin and agonists having a longer half-life in the circulation can be used, however, with a moderate outcome. Direct antidepressant actions are observed with compounds combining properties of melatonergic agonists and 5-HT_{2C} serotonergic antagonists. Moreover, agonists that may be suitable for improving metabolic disorders including insulin resistance are discussed.

Key words: Aging; agomelatine; circadian dysfunction; melatonin; piromelatine; ramelteon; sleep; tasimelteon; TIK-301.

Introduction

Melatonergic treatment can be recommendable under conditions of reduced melatonin secretion or circadian dysfunction, which may comprise age-related degenerative processes in the retina, in the suprachiasmatic nucleus (SCN) or its input or output connections, deviations of the circadian spontaneous period, perturbations of the rhythm by nocturnal light or uncoupling between autonomous/semiautonomous clocks within the multioscillator system (Hardeland and Coto-Montes, 2010; Hardeland, 2012a; Hardeland et al., 2012).

Decreases in melatonin secretion are regularly observed in the course of aging, though with considerable inter-individual variability. In some elderly persons, the nighttime values are almost indistinguishable from those obtained during daytime, whereas other individuals maintain a fairly well pronounced rhythm with only moderate reductions of nocturnal values (Karasek and Reiter, 2002; Hardeland et al., 2011; Hardeland, 2012b). Age-related reductions of melatonin can have different causes, such as a progressive deterioration of the SCN or the neuronal transmission to the pineal, or, sometimes, pineal calcification.

Various, remarkably different diseases are known to also decrease melatonin formation and release. These include several neurodegenerative disorders including Alzheimer's disease (AD) and other types of senile dementia, hypothalamic hamartomas, craniopharyngiomas, various stressful conditions, migraine and other forms of pain, cardiovascular diseases, cases of cancer, endocrine and metabolic disorders, such as diabetes type 2 and acute intermittent porphyria, as summarized elsewhere (Hardeland et al., 2011, Hardeland, 2012a). Especially, under conditions of neurodegenerative changes, reduced melatonin secretion may also favor the development of other diseases or aggravate preexisting health problems.

Melatonin can be beneficial in various disorders and diseases. However, in this article, applications under acute conditions, such as stroke, cardiovascular infarction and sepsis, or attempts of slowing neurodegenerative processes shall not be discussed. The focus will rather be put on interventions for which melatonergic drugs have been developed.

In the last years, melatonergic treatment has been vividly discussed with regard to its suitability for supporting sleep. Insomnias represent frequent disorders associated either with aging or with neurological conditions, especially mood disorders. Melatonin is known to facilitate sleep onset. However, it poorly improves sleep maintenance (Hardeland, 2009a, 2012a, b). The major obstacle for the use of the natural hormone as a clinically efficient drug

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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 (Claustrat et al., 2005; Hardeland, 2009a). As a solution to this problem, controlled-release formulations of the natural hormone have been developed or, alternatively, synthetic drugs with a substantially longer half-life. The properties of these melatonergic agonists, their advantages and disadvantages, and the limits of treatment will be discussed in this article.

Approved and some investigational melatonergic agonists

A selection of melatonergic agonists is presented in Fig.1. It contains the drugs approved by FDA or EMEA as well as several investigational drugs that have been clinically tested or possess properties of particular interest. Numerous other investigational drugs have been developed (Rivara et al., 2008; Hardeland, 2010), which cannot be considered here for reasons of space.

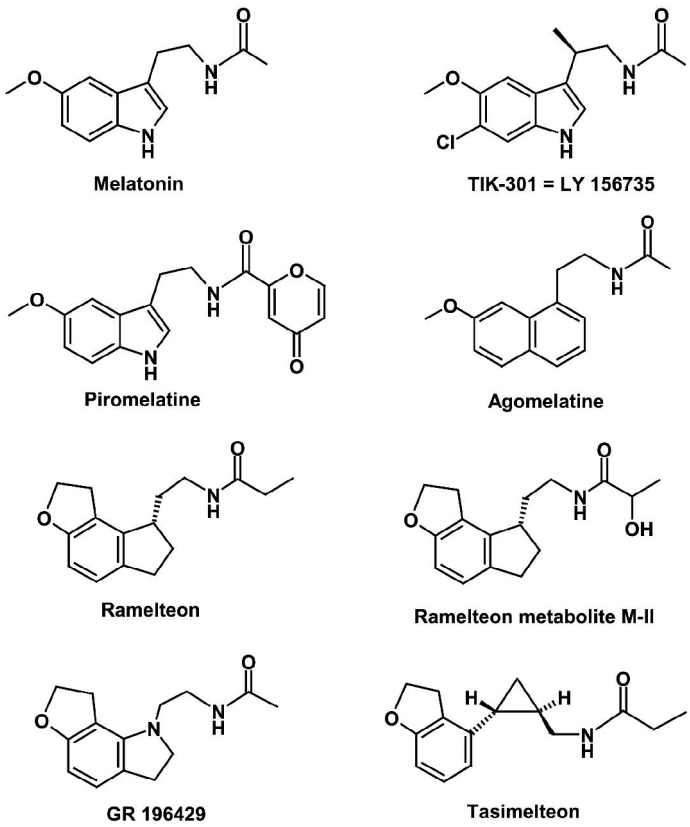

Fig. 1. A selection of melatonergic agonists.

Several prolonged-release formulations of melatonin have been tested. Among these, a controlled-release tablet (Circadin®) has been developed by Neurim, Israel and UK, and is also provided by Lundbeck and Nycomed. This drug has been approved by EMEA for the treatment of insomnia in patients aged 55 years and over. It was licensed on the combination of improvement of sleep quality and next-day feeling. The pharmacokinetics revealed considerable interindividual variation, which has been discussed elsewhere (Hardeland, 2009a).

The drug most closely related to melatonin is β-methyl-6-chloromelatonin, referred to in the literature as TIK-301 or, earlier, as LY 156735. The compound had been originally developed by Eli Lilly, and is now under production and study by TIKVAH. TIK-301 has received an orphan drug designation by the FDA to be used for treatment of sleep disorders in blind individuals. Despite its chemical similarity, TIK-301 shows significant deviations from melatonin concerning receptor affinities. Whilst melatonin exhibits pK_i values around 10.09 and 9.42 for MT_1 and MT_2 receptors, respectively, these are about 10.09 and 10.38 for TIK-301 (for pK_i values of these and other drugs, see Hardeland 2010; Hardeland 2012a). Therefore, the affinity to MT_2 is considerably higher, whereas that to MT_1 is practically identical with that of the natural hormone. With regard to the more and more emerging functional differences between MT_1 and MT_2 receptors, TIK-301 may become of interest for future applications aiming at a stronger stimulation of MT_2 signaling. Another property, which was first described for agomelatine, concerns the combination of melatonergic signaling with serotonergic inhibition. TIK-301 was reported to be an even more potent antagonist of 5-HT_{2C} and 5-HT_{2B} receptors than agomelatine (Landolt and Wehrle, 2009). As will be discussed below, TIK-301 may, therefore, possess direct antidepressive properties, as described for agomelatine, an assumption which would require clinical confirmation. Although the chlorine at ring atom 6 prevents hydroxylation of TIK-301 by CYP isoenzymes in this position, the half-life of TIK-301 is only moderately extended to about 1 h (Mulchahey et al., 2004).

Another indolic agonist carrying an unusual substitution at the ethylamine nitrogen is piromelatine, developed by Neurim, Israel, first introduced into the literature under the provisional name Neu-P11 (She et al., 2009). Relevant pharmacological, toxicological and metabolism data remain to be disclosed. According to doses applied, receptor affinities seem to be lower than those of melatonin. A property of interest concerns insulin signaling. In an insulin resistance model, the drug was reported to be more potent than melatonin in inducing the expression of insulin receptor substrate 1 (IRS-1) and in reducing its Ser307 phosphorylation (Yin et al., 2008).

A naphthalenic melatonergic agonist, agomelatine (Valdoxan®; S20098), developed by Servier, France, has been licensed in Europe by EMEA for the treatment of major depressive episodes (MDE) in adults. Agomelatine has receptor affinities (pK_i 10.21 and 9.57 for MT_1 and MT_2, respectively) slightly above those of melatonin. Its half-life in the circulation is in the range of 1-2 h. Importantly, it displays the additional property as an antagonist of the serotonin receptor 5-HT_{2C}, which has been interpreted as the cause of agomelatine's direct antidepressant actions (Millan et al., 2003; Srinivasan et al., 2009). Importantly, these direct effects 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. Nevertheless, melatonergic properties may still be of relevance for the direct antidepressant efficacy. Recently, the antidepressant action of agomelatine has been interpreted on the basis of a synergistic interaction between melatonergic activation and 5-HT_{2C} inhibition (Racagni et al., 2011).

In various other melatonergic agonists, the methoxy group present in the natural hormone is replaced by a dihydrofuran structure, having the oxygen in the corresponding position. This is the case with the first approved synthetic melatonergic drug, ramelteon (Rozerem®; TAK-375). It was developed by Takeda, Japan, and has been licensed in the USA by the FDA for the treatment of insomnia. Actions and properties of ramelteon have been discussed and reviewed by several authors (e.g., Kato et al., 2005; Pandi-Perumal et al., 2007, 2009a; Simpson and Curran, 2008). This drug is rapidly absorbed by the gastrointestinal tract and its half-life in the circulation is in the range of 1 - 2 h (Karim et al., 2006). Ramelteon is the only melatonergic agonist with considerably higher affinities to both membrane receptor subtypes (pK_i 10.85 and 9.95 for MT_1 and MT_2, respectively), compared to melatonin. The ramelteon metabolite M-II is also depicted, because it contributes substantially to the overall activity of the parent compound. M-II exhibits receptor affinities of about one tenth of those of the parent compound, but its half-life is by 2 - 5 h longer. As a result, its circulating levels are 20 – 100-fold (median 30-fold) higher than those of ramelteon after systemic exposure (Karim et al., 2006).

GR 196429 is an investigational drug with some similarity to ramelteon, but its 5-membered ring that corresponds to the pyrrole in the melatonin molecule contains a nitrogen to which the aliphatic chain is attached. Its receptor affinities are roughly in the range of other agonists (pKi 9.85 and 9.79 for MT_1 and MT_2). GR 196429 is mentioned here because it was reported to increase the amplitude of the melatonin rhythm in rats. However, it showed substantial deviations in the phase resetting properties compared to melatonin and other melatonergic drugs, which would require mechanistic explanations (Hardeland, 2010).

An investigational drug that has been clinically tested is tasimelteon (Rajaratnam et al., 2009). It also carries the dihydrofuran moiety, but the residues attached to the aromate profoundly differ from those of other agonists. A full drug profile is available (Hardeland, 2009b). Like TIK-301, tasimelteon has a somewhat higher affinity to MT_2 (pK_i 9.80) than to MT_1 (pKi 9.45). The half-life seems to be longer than that of melatonin. In monkeys and rats, values around 2 h (between 1 and 3 hours) have been reported. Information on human pharmacokinetics is only partially available. For details see Hardeland (2009b).

Immediate actions of melatonergic drugs

Immediate actions that do not require prolonged bioavailability are mainly relevant in two areas, namely, (i) phase resetting and synchronization of circadian rhythms, also referred to as chronobiotic effects, and (ii) sleep-onset facilitation. In either case, actions at the SCN are of particular significance, although effects at other sites contribute and cannot be neglected.

A short-acting chronobiotic such as melatonin is already capable of inducing phase shifts. Continuous levels of the pineal hormone in the circulation are not required, since circadian oscillators are widely sensitive to a so-called non-parametric resetting (Pittendrigh and Daan, 1976), caused by stimuli in which the relative change is decisive rather than the absolute level of the synchronizer. This conclusion, which had originally been made for the light/dark zeitgeber, is *cum grano salis* also valid for melatonin. However, to fully synchronize a rhythm, repetitions of the signal on consecutive days are usually required. Concerning phase adjustments, the treatment has to consider the fundamental chronobiological rules concerning the phase response curve (PRC). This curve describes the phase-dependence of extent and direction of phase shifts, for a given signal strength. The human PRC for melatonin is known (Lewy et al., 1992; Burgess et al., 2008) and indicates suitable time points for phase shifts of sufficient extent. Readjustment of rhythms by melatonin depends on the administration at an appropriate,

sufficiently sensitive phase within the circadian cycle. In individuals with poorly synchronized rhythms or strongly deviating circadian period lengths, it may be necessary to locate the rhythm's phase position, e.g., by determining the dim light melatonin onset. Depending on the phase position of the circadian cycle, full synchronization may be only achieved after a couple of days. If the rhythm is dysphased because of poor coupling to other synchronizers, it may take additional days until the desired phase is reached. Disregard of these chronobiological fundaments may lead to false conclusions on inefficacy.

A special aspect of phase resetting concerns the existence of numerous autonomous or semiautonomous oscillators outside the SCN within the CNS and in peripheral organs. Although they may differ in terms of their sensitivity to melatonin, the pineal hormone was shown to readjust phase relationships between distinct oscillators. This even includes parallel oscillators within the SCN that are based on the alternate use of homologs or paralogs of core oscillator proteins (reviewed in Hardeland et al., 2012).

In the different tissues, melatonin receptor densities vary considerably. The meaning of these differences for phase resetting remains to be investigated in detail. In the human SCN, MT_1 receptors are highly abundant, especially in vasopressin neurons (Weaver and Reppert, 1996; Wu et al., 2006, 2007). The expression of this receptor subtype was also shown to decrease during aging and, more strongly, in Alzheimer's disease (Wu et al., 2007). Contrary to many other mammals, the MT_2 receptor is, if at all, only poorly expressed in the human SCN (Weaver and Reppert, 1996; Hardeland et al., 2011). Since MT_2 is important for circadian phase shifting in other mammals, this function may have been taken over in humans by MT_1 (Hardeland et al., 2011), an assumption that will require direct confirmation. However, the poor expression of MT_2 may have implications for the medicinal suitability of agonists with preferred binding to this subtype, although these drugs may be very efficient in animal models.

Another area in which only short actions of melatonin are required is sleep-onset facilitation. This can be achieved by relatively low doses of the pineal hormone, down to 0.1-0.3 mg/d of an immediate release formulation (Pandi-Perumal et al., 2007). Sleep initiation is favored by MT_1-mediated actions that influence the hypothalamic sleep switch, a structure that responds in an on-off mode based on mutual inhibition. Either wake-related neuronal downstream pathways are activated, which involve locus coeruleus, dorsal raphe nucleus and tuberomammillary nucleus or, under the influence of melatonin, sleep-related pathways acting via the ventrolateral preoptic nucleus (Saper et al., 2005; Fuller et al., 2006). The MT_1-dependent suppression of firing by SCN neurons is believed to be decisive for the activation of the sleep-promoting circuits. However, the sleep-inducing effects of melatonin are, in fact, more complex and comprise thalamic actions that include a thalamocortical interplay and are detectable in the promotion of sleep spindles (Dijk et al., 1995; Jan et al., 2009; Hardeland, 2009a). Thus, the feedback by melatonin to the SCN is not only important in chronobiotic terms, but also for the onset of sleep. Notably, this process is disturbed in various disorders (Pandi-Perumal et al., 2007; Hardeland, 2009a).

A connection between sleep difficulties and circadian rhythms exists in the so-called circadian rhythm sleep disorders (CRSDs). One type of possible causes is an innate or acquired deviation from an easily entrainable spontaneous period, as present in delayed sleep phase syndrome (DSPS) and familial advanced sleep phase syndrome (FASPS). Polymorphisms in the core oscillator genes *Per2* and *Per3* (*Period 2* and *3*) are associated with some CRSDs, but mutations in other clock genes may also lead to this type of disorder (for discussion see Hardeland, 2009a, 2012a). Insufficient entrainment may also exist in some blind subjects or because of an otherwise impaired light input pathway. As long as both the melatonin signaling pathways and circadian core oscillators are sufficiently operating, CRSDs can be efficiently treated by melatonin. This is similarly possible in blind subjects, which are poorly entrainable via the light/dark zeitgeber (Srinivasan et al., 2006; Skene and Arendt, 2007; Hardeland et al., 2008).

In all these cases, in which only short melatonergic actions are required, for either synchronizing circadian rhythms or purposes of sleep onset, immediate-release formulations of the natural hormone, melatonin, are sufficient. The same can be achieved by synthetic melatonergic drugs (Karim et al., 2006; Pandi-Perumal et al., 2007, 2009a; Rivara et al., 2008; Hardeland et al., 2008; Simpson and Curran, 2008; Rajaratnam et al., 2009; Hardeland, 2009a,b, 2010), but there is no convincing reason for preferring these synthetic compounds for short actions, also with regard to the much higher recommended doses compared to those required for melatonin and to the superior tolerability of the pineal hormone (Hardeland, 2012a, b).

Problems of substitution therapy

The relative efficacies have, however, to be judged differently, as soon as additional effects are desired, e.g., concerning the support of sleep maintenance or direct antidepressant actions. The latter aspect will be discussed in the next section. With regard to sleep maintenance, the rationale is to use longer-acting drugs, either a melatonin prolonged-release formulation or a synthetic drug that is more slowly catabolized than the pineal hormone. Higher receptor affinities to both MT_1 and MT_2, which are especially shown by ramelteon, may be welcome, but do not necessarily guarantee better efficacy over time, because of possible receptor internalization and downregulation. These processes have been described, however, mainly in transfected cells (Hardeland, 2009c), and the conditions of physiological or pharmacological feedback reductions of receptor density or sensitivity in intact organisms are poorly understood. Moreover, the roles of additional regulation mechanisms affecting receptor sensitivity, such as interaction with the melatonin receptor ortholog GPR50, homo- and heterodimerizations, and binding of the PDZ domain protein MUPP1 to MT_1 remain to be elucidated under kinetic aspects (Hardeland, 2009c).

All clinically tested melatonergic drugs have been reported to be beneficial with regard to sleep duration, sleep efficiency or sleep quality. Both objective and subjective measures have reached statistical significance in most studies. However, 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 (Pandi-Perumal et al., 2011). It is important to be aware that a statistically significant improvement does not yet imply complete restoration to persistent sleep throughout the night (Erman et al., 2006; Roth et al., 2006; Pandi-Perumal et al., 2011). Similar data have been obtained for the other melatonergic drugs tested for sleep maintenance, as recently reviewed (Hardeland, 2012a). In conclusion, a convincing replacement therapy in melatonin deficiency has not yet been achieved with any of the melatonergic drugs, although they show moderate improvements in sleep efficiency and usually a good outcome concerning sleep initiation. The dose dependence of synthetic drugs has mostly been thoroughly studied, but the respective results show that higher doses do not resolve this problem. Recommended doses of ramelteon are either 4 or 8 mg/d (Erman et al., 2006; Roth et al., 2006; Pandi-Perumal et al., 2007, 2009, 2011; Simpson and Curran, 2008; Hardeland et al., 2008), of agomelatine 25 mg/d (Hardeland et al., 2008; Srinivasan et al., 2009), and clinically tested doses of tasimelteon of 100 mg/d were not superior to 50 mg/d (Hardeland, 2009b; Rajaratnam et al., 2009). The approved standard dose of Circadin® is only 2 mg/d. Whether a replacement therapy will be possible by using much higher doses of melatonin, such as 50 or 100 mg/d, as recently suggested by Cardinali et al. (2011), remains to be demonstrated.

The moderate outcome in the improvement of sleep maintenance indicates that a replacement therapy is not easily achieved with melatonergic drugs. This may be more generally valid and set limits to improvements in other areas such as therapies of neurodegeneration.

Mood disorders: Necessity of distinction between chronobiotic and other effects

With regard to the high incidence of depressive symptoms, antidepressive effects of melatonergic drugs are of high interest. However, it seems to be decisive to not confuse indirect effects achieved by readjusting circadian rhythms with direct antidepressive actions. These latter effects do not reflect a specific property of melatonin. The outcome in animal models of depression has always to be critically interpreted by distinguishing between true antidepressive actions and other explained by sedation and anxiolysis that occur in an antiexcitatory context. Moreover, it is important to consider the complexity of the phenomenon depression, which has numerous different etiologies. Even major depressive disorder (MDD) has to be regarded as a heterogeneous complex of different diseases. Seasonal affective and bipolar disorders seem to represent phenomena associated with circadian dysfunction as indicated by polymorphisms of core oscillator genes and deviations in circadian periods (Hardeland et al., 2011, 2012; Hardeland, 2012a). Melatonin should, thus, be capable of improving symptoms by readjusting the circadian system, an assumption further supported by polymorphisms of genes related to melatonin synthesis and, perhaps, signaling (Hardeland et al., 2012). By contrast, no convincing evidence for the involvement of the circadian system has been concluded to exist in MDD (Lamont et al., 2007), although a few MDD-associated polymorphisms of core oscillator genes have been described and although, sometimes, shifts in the melatonin maximum have been observed (Hardeland et al., 2011; Hardeland, 2012a). This statement may be revisited under aspects of MDD heterogeneity, but, in the majority of cases, direct effects of melatonin cannot be expected.

In conclusion, mood disorders with an etiology of circadian dysfunction offer the possibility of successful melatonergic treatment. This can be assumed for bipolar and seasonal affective disorders. In principle, all approved melatonergic drugs should be capable of improving symptoms by readjusting circadian phase relationships, both internally within the multioscillator system and relative to external time cues. However, the question remains as to whether synthetic drugs are superior to melatonin in this field. Since resynchronization of rhythms requires only short actions, which have to be repeated on consecutive days, the particularly good tolerability of the natural hormone may be in favor of melatonin. On the other hand, the alternative of light treatment should not be neglected in all those cases in which light perception and visual pathways to the SCN are not impaired. Suitable circadian phases for entrainment and the use of light sources emitting sufficient quantities of blue light are required. These spectral properties are decisive to ensure absorption by the melanopsin-containing retinal ganglion cells involved in the transmission to the SCN. In other cases of either blindness or reductions of unconscious circadian photoreception because of pupillary miosis or impaired crystalline lens transmission, melatonin or other melatonergic drugs may be preferred (Hardeland et al., 2012).

An entirely different situation is present in MDD. With selective melatonergic agonists devoid of additional properties, no profound success can be expected. As mentioned above, agomelatine represents a drug that combines sleep-promoting melatonergic actions with direct antidepressive effects that involve 5-HT_{2C} inhibition or, perhaps, an interaction between MT_1/MT_2 and 5-HT_{2C} signaling. When some authors have criticized the poorer efficacy of agomelatine relative to classic antidepressants, they have missed a clear distinction 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 particularly important because classic antidepressants often induce sleep disturbances (Pandi-Perumal et al., 2006, 2009b; Hardeland et al., 2008; Srinivasan et al., 2009; 2011). It remains to be shown whether TIK-301, which also combines activation of MT_1 and MT_2 receptors with 5-HT_{2C} inhibition (Landolt and Wehrle, 2009), is equally suitable for MDD treatment. The decision may finally depend on aspects of drug interactions, long-term tolerability and non-toxicity, which is still a matter of debate (Hardeland 2012b).

Melatonergic drugs and metabolic disorders

This field of application is still in its infancy. Numerous studies and reviews have already addressed the role of melatonin in the complex of metabolic syndrome, prediabetes, diabetes type 2, general insulin resistance, obesity and associated cardiovascular diseases, including the repeatedly confirmed association of MT_2 polymorphisms with diabetes type 2 (discussed in Hardeland et al., 2012). In the future, more clinical studies will be required for exploring the value of melatonergic drugs in this area. A short note shall be given here regarding properties of the newly developed investigational drug, piromelatine (Neu-P11). This agonist was more potent than melatonin in modulating insulin signaling in rats, normalized the time profiles of circulating insulin after a glucose load, reduced blood glucose, triglycerides and total cholesterol, enhanced HDL-bound cholesterol and inhibited body weight gain and abdominal fat accumulation to an approximately same extent as melatonin (Yin et al., 2008; She et al., 2009; Hardeland, 2010). In a few of these parameters, similar improvements were also obtained with TIK-301 (Rivara et al., 2008).

Conclusion

Melatonergic treatment is recommendable under various conditions. This includes symptoms caused by decreases in melatonin levels because of age or various diseases, sleep difficulties, circadian dysfunction and mood disorders resulting thereof. Other mood disorders such as MDD may be treated with drugs combining melatonergic signaling with 5-HT_{2C} inhibition. In all these cases, it seems to be of utmost importance to not regard the melatonergic drugs just as replacements of other medications classically used as sleeping pills or antidepressants. The chronobiological role of melatonin and the corresponding actions of the synthetic agonists have to be always considered. From a fundamental point of view, clinicians should distinguish between (i) conditions under which only short actions of melatonergic drugs are required, such as sleep-onset facilitation, circadian readjustments including the treatment of those mood disorders with an etiology of circadian dysfunction, and (ii) other conditions which would require prolonged actions of the drug. In the first case, immediate-release formulations of melatonin may be sufficient and a superiority of longer-acting drugs should not be assumed. In the second case, prolonged-release formulations or drugs with a longer half-life in the circulation may be recommendable, but the limits of achieving a replacement therapy should not be overlooked.

References

Burgess HJ, Revell VL, Eastman CI (2008) A three pulse phase response curve to three milligrams of melatonin in humans. *J Physiol.* **586:** 639-647.

Cardinali DP, Srinivasan V, Brzezinski A, Brown GM (2011) Melatonin and its analogs in insomnia and depression. *J Pineal Res.* **52:** 365-375.

Claustrat B, Brun J, Chazot G (2005) The basic physiology and pathophysiology of melatonin. *Sleep Med Rev.* **9:** 11-24.

Dijk DJ, Roth C, Landolt HP, Werth E, Aeppli M, Achermann P, Borbély AA (1995). Melatonin effect on daytime sleep in men: suppression of EEG low frequency activity and enhancement of spindle frequency activity. *Neurosci Lett.* **201:** 13-16.

Erman M, Seiden D, Zammit G, Sainati S, Zhang J (2006) An efficacy, safety, and dose-response study of ramelteon in patients with chronic primary insomnia. *Sleep Med.* **7:** 17-24.

Fuller PM, Gooley JJ, Saper CB (2006) Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. *J Biol Rhythms* **21:** 482-493.

Hardeland R (2009a) New approaches in the management of insomnia: weighing the advantages of prolonged release melatonin and synthetic melatoninergic agonists. *Neuropsychiatr Dis Treat.* **5:** 341-354.

Hardeland R (2009b) Tasimelteon, a melatonin agonist for the treatment of insomnia and circadian rhythm sleep disorders. *Curr Opin Investig Drugs* **10:** 691-701.

Hardeland R (2009c). Melatonin: Signaling mechanisms of a pleiotropic agent. *Biofactors* **35:** 183-192.

Hardeland R (2010). Investigational melatonin receptor agonists. *Expert Opin Investig Drugs* **19:**747-764.

Hardeland R (2012a) Melatonin in aging and disease-multiple consequences of reduced secretion, options and limits of treatment. *Aging Dis.* **3:** 194-225.

Hardeland R (2012b) Neurobiology, pathophysiology, and treatment of melatonin deficiency and dysfunction. *ScientificWorldJournal* **2012:** article no. 640389.

Hardeland R, Coto-Montes A (2010) New vistas on oxidative damage and aging. *Open Biol J.* **3:** 39-52.

Hardeland R, Poeggeler B, Srinivasan V, Trakht I, Pandi-Perumal SR, Cardinali DP (2008) Melatonergic drugs in clinical practice. *Arzneimittelforschung* **58:** 1-10.

Hardeland R, Cardinali DP, Srinivasan V, Spence DW, Brown GM, Pandi-Perumal SR (2011) Melatonin – A pleiotropic, orchestrating regulator molecule. *Prog Neurobiol.* **93:** 350-384.

Hardeland R, Madrid JA, Tan D-X, Reiter RJ (2012) Melatonin, the circadian multioscillator system and health: the need for detailed analyses of peripheral melatonin signaling. *J. Pineal Res.* **52:** 139-166.

Jan JE, Reiter RJ, Wasdell MB, Bax M (2009) The role of the thalamus in sleep, pineal melatonin production, and circadian rhythm sleep disorders. *J Pineal Res.* **46:** 1-7.

Karasek M, Reiter RJ (2002) Melatonin and aging. *Neuroendocrinol Lett.* **23**, Suppl 1: 14-16.

Karim A, Tolbert D, Cao C (2006) Disposition kinetics and tolerance of escalating single doses of ramelteon, a high affinity MT1 and MT2 melatonin receptor agonist indicated for the treatment of insomnia. *J Clin Pharmacol.* **46:** 140-148.

Kato K, Hirai K, Nishiyama K, Uchikawa O, Fukatsu K, Ohkawa S, Kawamata Y, Hinuma S, Miyamoto M (2005) Neurochemical properties of ramelteon (TAK-375), a selective MT_1/MT_2 receptor agonist. *Neuropharmacology* **48**: 301-310.

Lamont EW, Legault-Coutu D, Cermakian N, Boivin DB (2007) The role of circadian clock genes in mental disorders. *Dialogues Clin Neurosci.* **9:** 333-342.

Landolt H-P, Wehrle R (2009) Antagonism of serotonergic $5\text{-}HT_{2A/2C}$ receptors: mutual improvement of sleep, cognition and mood? *Eur J Neurosci.* **29:** 1795-1809.

Lewy AJ, Ahmed S, Jackson JM, Sack RL (1992) Melatonin shifts human circadian rhythms according to a phase-response curve. *Chronobiol Int.* **9:** 380-392.

Millan MJ, Gobert A, Lejeune F, Dekeyne A, Newman-Tancredi A, Pasteau V, Rivet JM, Cussac D (2003) The novel melatonin agonist agomelatine (S20098) is an antagonist at 5-hydroxytryptamine$_{2C}$ receptors, blockade of which enhances the activity of frontocortical dopaminergic and adrenergic pathways. *J Pharmacol Exp Ther.* **306:** 954-964.

Mulchahey JJ, Goldwater DR, Zemlan FP (2004) A single blind, placebo controlled, across groups dose escalation study of the safety, tolerability, pharmacokinetics and pharmacodynamics of the melatonin analog â-methyl-6-chloromelatonin. *Life Sci* **75:** 1843-1856.

Pandi-Perumal SR, Srinivasan V, Cardinali DP, Monti MJ (2006) Could agomelatine be the ideal antidepressant? *Expert Rev Neurother.* **6:** 1595-1608.

Pandi-Perumal SR, Srinivasan V, Poeggeler B, Hardeland R, Cardinali DP (2007) Drug Insight: the use of melatonergic agonists for the treatment of insomnia - focus on ramelteon. *Nat Clin Pract Neurol.* **3:** 221-228.

Pandi-Perumal SR, Srinivasan V, Spence DW, Moscovitch A, Hardeland R, Brown GM, Cardinali DP (2009a) Ramelteon: a review of its therapeutic potential in sleep disorders. *Adv Ther.* **26:** 613-626.

Pandi-Perumal SR, Trakht I, Srinivasan V, Spence DW, Poeggeler B, Hardeland R, Cardinali DP (2009b) The effect of melatonergic and non-melatonergic antidepressants on sleep: weighing the alternatives. *World J Biol Psychiatry* **10:** 342-354.

Pandi-Perumal SR, Spence DW, Verster JC, Srinivasan V, Brown GM, Cardinali DP, Hardeland R (2011) Pharmacotherapy of insomnia with ramelteon: Safety, efficacy and clinical applications. *J Cent Nerv Syst Dis.* **3:** 51-65.

Pittendrigh CS, Daan S (1976) A functional analysis of circadian pacemakers in nocturnal rodents. 4. Entrainment: pacemaker as clock. *J Comp Physiol. A.***106:** 291-331.

Racagni G, Riva MA, Molteni R, Musazzi L, Calabrese F, Popoli M, Tardito D (2011) Mode of action of agomelatine: synergy between melatonergic and 5-HT_{2C} receptors. *World J Biol Psychiatry* **12:** 574-587.

Rajaratnam SMW, Polymeropoulos MH, Fisher DM, Roth T, Scott C, Birznieks G, Klerman EB (2009) Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: Two randomised controlled multicentre trials. *Lancet* **373:** 482-491.

Rivara S, Mor M, Bedini A, Spadoni G, Tarzia G (2008) Melatonin receptor agonists: SAR and applications to the treatment of sleep-wake disorders. *Curr Top Med Chem.* **8:** 954-968.

Roth T, Seiden D, Sainati, S, Wang-Weigand S, Zhang J, Zee P (2006) Effects of ramelteon on patient-reported sleep latency in older adults with chronic insomnia. *Sleep Med.* **7:** 312-318.

Saper CB, Scammell TE, Lu J (2005). Hypothalamic regulation of sleep and circadian rhythms. *Nature* **437:** 1257-1263.

She M, Deng X, Guo Z, Laudon M, Hu Z, Liao D, Hu X, Luo Y, Shen Q, Su Z, Yin W (2009) NEU-P11, a novel melatonin agonist, inhibits weight gain and improves insulin sensitivity in high-fat/high-sucrose-fed rats. *Pharmacol Res.* **59:** 248-253.

Simpson D, Curran MP (2008) Ramelteon: a review of its use in insomnia. *Drugs* **68:** 1901-1919.

Skene DJ, Arendt J (2007) Circadian rhythm sleep disorders in the blind and their treatment with melatonin. *Sleep Med.* **8:** 651-655.

Srinivasan V, Smits MG, Kayumov L, Pandi-Perumal SR, Cardinali DP, Thorpy MJ (2006) Melatonin in circadian rhythm sleep disorders. In: Cardinali DP and Pandi-Perumal SR (Eds.), *Neuroendocrine Correlates of Sleep/Wakefulness*. Springer, New York, pp 269-294.

Srinivasan V, Pandi-Perumal SR, Trakht I, Spence DW, Hardeland R, Poeggeler B, Cardinali DP (2009) Pathophysiology of depression: role of sleep and the melatonergic system. *Psychiatry Res.* **165:** 201-214.

Srinivasan V, Brzezinski A, Pandi-Perumal SR, Spence DW, Cardinali DP, Brown GM (2011) Melatonin agonists in primary insomnia and depression-associated insomnia: are they superior to sedative-hypnotics? *Prog Neuropsychopharmacol Biol Psychiatry* **35:** 913-923.

Weaver DR, Reppert SM (1996) The Mel1a melatonin receptor gene is expressed in human suprachiasmatic nuclei. *Neuroreport* **8:** 109-112.

Wu YH, Zhou JN, Balesar R, Unmehopa U, Bao A, Jockers R, Van Heerikhuize J, Swaab DF (2006) Distribution of MT_1 melatonin receptor immunoreactivity in the human hypothalamus and pituitary gland: colocalization of MT_1 with vasopressin, oxytocin, and corticotropin-releasing hormone. *J Comp Neurol.* **499:** 897-910.

Wu YH, Zhou JN, Van Heerikhuize J, Jockers R, Swaab DF (2007). Decreased MT_1 melatonin receptor expression in the suprachiasmatic nucleus in aging and Alzheimer's disease. *Neurobiol Aging* **28:** 1239-1247.

Yin W, Hou H, Laudon M (2008) NEU-P11, a novel melatonin agonist: effect on glucose transport in a cellular model of insulin resistance. *Sleep* **31:** A26 (abstract 0078).