Invited Review

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Melatonin agonists for treatment of sleep and depressive disorders

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Abstract

Melatonin the hormone secreted by the pineal gland has been effective in improving sleep both in normal sleepers and insomniacs and has been used successfully in treating sleep and circadian rhythm sleep disorders. The lack of consistency in the reports published by the authors is attributed to the differential bioavailabilty and short half-life of melatonin.

Sleep disturbances are also prominent features of depressive disorders. To overcome this problem, melatonergic agonists with sleep promoting properties have been introduced in clinical practice. Ramelteon, the MT_1/ MT_2 melatonergic agonist, has been used in a large number of clinical trials involving chronic insomniacs and has been found effective in improving the total sleep time and sleep efficiency of insomniacs and has not manifested serious adverse effects.

The development of another MT_1/MT_2 melatonergic agonist agomelatine with antagonsim to 5-HT_{2c} serotonin receptors has been found useful not only in treating sleep problems of patients but also as a first line antidepressant with earlier onset of actions in patients with major depressive disorder. An agonist for MT_3 melatonin receptor has also been found effective in animal models of depression.

Key words:
Agomelatine; Antidepressant; Insomnia; Major depressive disorder; Melatonergic agonist; Melatonin

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Introduction

Melatonin or N-acetyl-5-methoxytryptamine is secreted mainly from the pineal gland of vertebrates including humans. However, synthesis also occurs in different parts of the body, such as the eyes, skin, gastrointestinal tract, lymphocytes, bones, and ovaries [1-3]. It participates in several important physiological functions of the body, including sleep regulation, circadian rhythm regulation, and regulation of human mood, immune regulation, oncostatic and antioxidative functions, [4, 5]. Melatonin exerts most of its physiological actions by acting through melatonin membrane receptors MT_1 and MT_2. These receptors are G-protein linked receptors that inhibit adenyl cyclase [6, 7]. MT_1 receptors also activate protein kinase C-β, while MT_2 receptors inhibit guanylate cyclase pathway [8].

Since melatonin is a short-lived molecule, its physiological actions have also been found to be limited in duration, particularly with regards to its effects on sleep regulation. Hence it was felt that a melatonin molecule with a longer half-life would have a better opportunity to activate melatonin receptors for influencing sleep properties and for promoting sleep efficiency [9]. Melatonin has been used successfully in the treatment of insomnia and circadian rhythm sleep disorders [10, 11]. Since sleep disturbances constitute the main symptom of depressive disorders, and disturbances of melatonin secretion have been documented in patients with major depressive disorders, melatonin has been tried in the treatment of depression [12]. Many antidepressants that are currently in use have been shown to have adverse effects on sleep, and

insomnia has been found to worsen with antidepressant drugs like selective serotonin reuptake inhibitors (SSRIs) [13]. Recently a novel melatonergic antidepressant agomelatine with both MT_1/MT_2 melatonin receptor agonist properties, and with selective antagonism to $5\text{-}HT_{2c}$ has been developed by Servier (Suresnes Cedex, France). Similarly ramelteon, with high selectivity for MT_1 and MT_2 melatonin receptors with significant effects on sleep, has been developed by Takeda Pharmateuticals (Tokyo, Japan). These two melatonergic drugs have revolutionized the treatment of insomnias and depressive disorders.

Ramelteon

Ramelteon, *i.e.* N-{2-[(8S)-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl}propanamide, is the first FDA approved selective melatonin receptor agonist and has the chemical formula $C_{16}H_{21}NO_2$ with a molecular weight of 259.34 Da. Receptor binding studies have shown that ramelteon has high selectivity for MT_1 and MT_2 receptors with little affinity to MT_3 receptors [4]. The selectivity of ramelteon for MT_1 has been found >1000 fold over that of MT_2 receptors. It is well known that melatonin exerts its hypnotic effects through the activation of the MT_1 and MT_2 melatonin receptors [8, 15]. Although both MT_1 and MT_2 receptors are involved in the regulation of sleep, the selectivity of MT_1 receptors by ramelteon suggests that it targets sleep onset more specifically than melatonin [16]. Ramelteon has been found to have no affinity for benzodiazepine, dopamine, opiate, or serotonin receptor binding sites [17]. Hence this drug has advantages over other hypnotic drugs in not causing rebound insomnia, withdrawal symptoms, and dependence which are common with the activation of benzodiazepine, opiate, or dopamine receptors [18].

Pharmacokinetics of ramelteon

On oral administration, ramelteon is found to be rapidly absorbed with a T_{max} of <1 hour [19, 20]. The absolute bioavailabilty of the oral formulation of ramelteon was found to be <2% (range 0.5% to 12% [19]. It is metabolized mainly in the liver via oxidation to hydroxyl and carbonyl groups and then conjugated with glucuronide [20]. Cytochrome P450 1A2, is the major hepatic enzyme involved in ramelteon metabolism. Four principal metabolites of ramelteon, M-I, M-II, M-III, and M-IV, have been identified. Of these, M-II has been found to occur in much higher concentration with systemic concentration being 20 to 100 fold greater than ramelteon. Ramelteon is rapidly excreted and elimination of ramelteon is significantly higher in elderly than in younger adults [21].

The influence of age and gender on the pharmacokinetics and pharmacodynamics of ramelteon was evaluated following a single dose of 16 mg of ramelteon in healthy volunteers (young 18-34; elderly 63-79 years). Ramelteon clearance was significantly reduced in elderly vs. young volunteers (384 vs. 883 mL/min/kg, respectively; $P<0.01$) and half-life significantly increased (1.9 vs. 1.3 h, respectively; $P<0.01$). Gender did not significantly influence clearance or half-life [21]. The contribution of ramelteon's metabolites on the net pharmacologic activity was also evaluated. Among the four metabolites, the activity of M-II has been shown to be about 30 fold lower than that of ramelteon, but its exposure exceeds exposure to ramelteon by a factor of 30. Hence it is suggested that M-II contributes to net clinical activity of ramelteon [21].

Clinical efficacy of ramelteon

Sleep disruption is documented as the most common complaint seen in the elderly and it is attributed to declining melatonin levels. In administering melatonin to healthy individuals, it was found that 'physiologic' doses of melatonin have little or no effect on nighttime sleep, and high pharmacological doses have been found beneficial in inducing hypnotic activity [22]. With the availability of melatonin receptor agonist with improved solubility and bioavailability, it will be possible to influence sleep propensity even in normal subjects. In a double blind placebo-controlled study conducted for 5 weeks on 829 patients (341 men, 488 women) aged 64 to 93 years, administration of ramelteon in 4 mg or 8 mg doses caused significant reductions on sleep latency starting from the first week onwards [23].

From the study of Roth *et al* [23], it was noted that ramelteon has significant efficacy in promoting sleep in older adult patients with chronic insomnia and was found to be dose independent. A reduction in sleep latency was found to be more pronounced in patients with more sleep difficulties. The absence of dose dependent effects of ramelteon on sleep promotion has prompted the authors to postulate that ramelteon promotes sleep by regulating the normal sleep/wake cycle rather than producing CNS depression as seen with the use of commonly used hypnotic sedatives. In another randomized, double blind, placebo-controlled crossover study

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with polysomnographic monitoring involving 107 patients, it was found that ramelteon in varying doses (4 mg, 8 mg, 16 mg, and 32 mg) caused significant reductions in latency to persistent sleep (LPS) and increased the total sleep time (TST) [24].

It is interesting to note that patients taking ramelteon did not experience the type of sedative feeling as is common with the use of traditional sleep-promoting agents. The incidence of adverse events in the ramelteon-treated group has been found to be similar to placebo-treated patients with most adverse events found to be either mild or moderate [23]. Increase of latency was also reported with 4 mg ramelteon in 100 elderly patients recruited from 17 sleep centres. LPS was shortened (P=0.001) and sleep efficiency was very much improved [25].

The efficacy of ramelteon with different doses was evaluated in another multicenter double blind placebo-controlled study. Ramelteon was administered in both 8 mg/day and 16 mg/day doses on 405 patients suffering from chronic insomnia. Of these, 371 patients completed the double blind study, and 267 completed the single blind follow up. Polysomnography (PSG) was used for sleep evaluation parameters. LPS was significantly reduced with both doses of ramelteon when compared to the placebo. Total duration of sleep also was prolonged with both doses of ramelteon. These effects were maintained throughout the study period (5 weeks) [26]. In a similar study on 289 adults, ramelteon at both 8 mg and 16 mg doses significantly reduced LPS (P=0.004). TST was also significantly increased with ramelteon 8 mg (P=0.009) and ramelteon 16 mg (P=0.043) [27]. In a study conducted by Takeda Pharmaceuticals, ramelteon at 8 mg dose caused reductions in LPS; at the end of week 1, 63% for ramelteon vs. 39.7% for the placebo (P<0.001); at the end of week 3, 63% with ramelteon and 41.2% with placebo (P<0.01); at the end of week 5, 65.9% with ramelteon and 48.9% with placebo (P<0.05). The improvement in LPS was sustained throughout the study [28].

In the lengthy duration of a study conducted on 451 adults with chronic insomnia for six months drawn from 46 centres of USA, Europe, Russia, and Australia, the efficacy of ramelteon (8 mg) was evaluated on sleep measures using PSG. Over the six-month period, ramelteon consistently reduced LPS compared to the placebo. There were no adverse reports, such as next morning residual effects, withdrawal symptoms, or rebound insomnia [29].

In a six-week study conducted on 20 healthy menopausal women, ramelteon at 8 mg doses caused significant improvements in sleep onset latency (SOL), TST, and sleep efficiency; there was no evidence of tolerance or rebound insomnia [30]. In another study conducted on 110 healthy adults with a history of jet lag sleep disturbances who were flown eastward across five time zones from Hawaii to the east coast of the USA, administration of ramelteon in 1, 4, and 8 mg doses 5 minutes before local bedtime caused decrease in mean LPS on nights 2-4 [31].

In a recent study, the efficacy and safety of ramelteon was evaluated in a randomized, double blind placebo-controlled multicenter trial in which administration of ramelteon for 2 weeks reduced mean patient reported sleep-latency (P=0.001) in the first week. It also improved the mean TST [32]. In addition to its effect on nighttime sleep, ramelteon was also effective in improving daytime sleep. This was shown in a study on 14 healthy adults where administration of 8 mg of ramelteon during daytime improved sleep and caused reduction of core body temperature. From this study it is evident that ramelteon could be also effective in treating insomnia associated with circadian misalignment that occurs during circadian rhythm sleep disorders [33].

Safety and adverse effects of ramelteon

Rebound insomnia was evaluated (sleep latency after treatment discontinuation) for each of the seven nights of the placebo run-out period. It was noted that during each of the 7 nights, patients in both ramelteon treatment groups (4 and 8 mg/day) maintained a similar or greater reduction in sleep latency from baseline as compared to those receiving the placebo [23].

In the study of Roth *et al* [23], the withdrawal effects were assessed by changes in BWSQ (The Tyrer Benzodiazepine Withdrawal Symptom Questionnaire) from the week 5 visit and day 7 of the run-out period. No statistically significant differences were observed among the treatment groups for total score. The mean BWSQ score was -0.1 for the ramelteon 4 mg group, -0.2 for the ramelteon 8 mg group, and -0.1 for the placebo group. In another recent study it was noted that ramelteon did not affect alertness or ability to concentrate, indicating no next-morning residual effects [34].

In their continuation study, the same authors conducted randomized, double blind cross-over design involving 26 subjects with mild to moderate

chronic obstructive pulmonary diseseases. Administration of a single bedtime dose of 16 mg caused significant increase in TST (P=0.015) and sleep efficiency (P=0.017) as compared to the placebo [35]. Hence the incidence of adverse effects in ramelteon treated patients in the 5 week study (35 nights) was found to be similar to the placebo treated patients, and these include mild gastrointestinal disturbances, and nervous system effects, such as dizziness, headache, somnolence, depression, fatigue, myalgia, and exacerbated eye pain. Electrocardiography recordings also did not reveal any significant differences [23].

Mechanism of hypnotic action of ramelteon

It is well known that circadian and sleep promoting effects of melatonin are attributed to its action on MT_1 and MT_2 present in the suprachiasmatic nucleus (SCN). Melatonin acutely inhibits SCN neuronal firing, an effect which is most pronounced at times of high neuronal activity (during daytime) although the effect is seen slightly at night as well [36]. Suppression of SCN neuronal activity by melatonin is suggested as the possible mechanism by which melatonin contributes to the regulation of sleep in diurnal species [8]. The role of SCN in the control of sleep has been studied in various species, such as in squirrel monkeys (primates are considered to be closer to humans). Normally the circadian signal produced by the SCN promotes wakefulness during the subjective day and consolidation of sleep at night. SCN lesions result in the disruption of consolidated sleep/wake cycle [37]. Since ramelteon is a selective MT_1 and MT*2* receptor agonist, its effects on sleep were studied in freely moving monkeys. It reduced SOL and increased TST in freely moving monkeys [38].

Since ramelteon has high selectivity to MT_1 and MT_2 receptors in the SCN with negligible affinity to GABA, benzodiazepine, opiod, muscarinic, dopamine, or histamine receptors, its hypnotic action is attributed mainly to its effect on MT_1/MT_2 receptors in the SCN. It is suggested that ramelteon has the capability of influencing the 'switch' for accelerating the onset of sleep via MT_1 and MT_2 [39]. This sleep switch model was first proposed by Fuller *et al* [40], describing mutual inhibitions among sleep associated activities in the ventrolateral preoptic nucleus, and wakefulness associated activities in locus coeruleus, dorsal raphe, and tuberomammillary nuclei, a system that changes in flip-flop manner.

Agomelatine, the novel melatonergic antidepressant

Agomelatine is a specific agonist of MT_1 and MT_2, and a selective antagonist of 5-HT_{2c} receptors [41, 42]. It is a napthalenic compound chemically designated as N-[2-(7-Methoxy-1-naphthyl)ethyl] acetamide with a selectivity of >100 fold for MT_1 and MT_2 receptors with no significant affinities to muscarinic, adrenergic, dopaminergic or histaminergic receptors. Studies of the interactions of agomelatine with a wide range (>80) of receptors and enzymes have shown that it has negligible affinity to all these receptors except MT_1 and MT_2 receptors [43].

Agomelatine has a short half-life (~2h) in humans. It is absorbed rapidly by the oral route and is metabolized in the liver by three cytochrom P450 (CYP) isoenzymes namely CYPA1, CYPA2, and CYP2C9. 3-hydroxy-, 3-hydroxy 7-methoxy-, and 7-desmethyl-agomelatine (S20098) were identified as the three metabolites of agomelatine [43, 44].

Clinical efficacy of agomelatine in depressive disorders

It is suggested that disruptions in sleep homeostasis constitute one of the main features of depression, and changes in sleep architecture often precede changes in patient's clinical state or can signal relapse [45]. Depressed patients experience difficulty falling asleep, difficulty staying asleep and early morning awakenings. Hence an ideal antidepressant should be able to decrease SOL, wake-time after sleep onset (WASO), and promote a feeling of well-being and alertness during the daytime [46]. Sleep promoting effects of most of the antidepressants, such as tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and SSRIs, have been found to be either limited or non-existent [13]. Since agomelatine has specific actions on MT_1 and MT_2 receptors in the SCN, it has been used successfully in treating patients with major depressive disorder (MDD).

In a large multinational, multicenter (102 centers), placebo-controlled study comprising 711 patients drawn from different European countries (Belgium, France, and the UK) the effects of three doses of agomelatine administered for the duration of 8 weeks (1, 2, and 25 mg/day) was compared with paroxetine 20 mg [47]. Both agomelatine in 25 mg/day dose and paroxetine were found effective in causing clinical remissions. With agomelatine, the HAM-D (The Hamilton Rating Scale for Depression) score decreased from

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27.4 ± 3.1 to 12.77 ± 8.3 (P<0.05). Responder analysis (*i.e.*, 50% or more reduction in the baseline score in HAM-D) showed that agomelatine was significantly better (61.5%) than the placebo (46.3%), while paroxetine showed only 56.3% reduction.

In severely depressed subpopulations, agomelatine caused significant reduction in HAM-D score (from 27.4 ± 3.1 to 13.14 ±8.41) and was found to be better than the placebo (P<0.05) while paroxetine did not differ from the placebo. This finding is very important, since it is very difficult to treat the patients of severely depressed groups. In another multicenter study (21 centers) across Finland, Canada, and South Africa, the effects of agomelatine in 25 mg and 50 mg/day (administered for 6 weeks) was evaluated in patients with MDD. Agomelatine was found effective in causing improvement in the clinical status of patients with severe depression when compared with the placebo (P=0.024). In this study it was also observed that agomelatine had a superior rate of responders (49.1%) over the placebo (34.3%) and it was found to be well tolerated when administered in 50 mg doses to patients who failed to show improvement with 25 mg doses [48].

The availability of antidepressants with activity in severely depressed subpopulations is important from a clinical point of view, since this group is relatively resistant to current drug therapy like SSRIs or SNRIs. The findings of the superior rate of responders treated with agomelatine observed in severely depressed subpopulations (48.7%) seen in the second study supports the inference that agomelatine has the superior therapeutic potential when compared with other currently available antidepressants. In acutely depressed patients with seasonal affective disorder (37 patients with SAD) administration of agomelatine in 25 mg/day for a period of 14 weeks significantly decreased SIGH-SAD (Structural Interview Guide for the HAM-D) and CGI-S and CGI-I scores (Clinical Global Impression of Severity and Improvement) from the second week onwards [49]. In this study the respond rate was found to be 75.7% and remission rate was 70.3%. This study assumes significance, since it reports the longest duration of agomelatine administration with no side effects.

More clinical trials with agomelatine have been reported in recent years. In patients with moderate to severe MDD, agomelatine treatment for 8 weeks significantly reduced HAM-D17 score (P=0.01) throughout the treatment period with 25 mg/day. With 50 mg/day, agomelatine reduced the HDRS score significantly from weeks 2-6, but not at week 8 [50]. In a study involving larger numbers of patients (n=252), administration of agomelatine 25-50 mg/day for 8 weeks to patients with MDD decreased the mean HAM-D17 significantly, and its clinical efficacy was found to be superior to fluoxetine (20-40 mg/day). Post baseline assessment also was found to be higher in the agomelatine group over the fluoxetine group (n=263). From this study it was concluded that agomelatine has superior antidepressant efficacy over fluoxetine in the treatment of patients with severe episodes of MDD [51].

Comparing the clinical efficacy of agomelatine and sertraline on depressive symptoms on 154 MDD patients, it was found that agomelatine improved symptoms of depression (P<0.05) and anxiety (p<0.05) in MDD. In addition, agomelatine also improved sleep latency (P<0.001) and sleep efficiency (P<0.001) from the first to sixth week of treatment. These clinical findings reveal that agomelatine has greater antidepressant efficiency [52]. The conclusion that agomelatine has earlier onset of action with significant clinical efficacy in the treatment of severe depression with no serious side or adverse effect has been supported by a number of review papers published [53-55].

Agomelatine's effects on sleep in depression patients

In depression patients, agomelatine has been found effective in reducing sleep complaints, increasing the duration of slow-wave sleep (SWS) and normalizing sleep architecture [56]. In a six-week blind study conducted on 165 patients, agomelatine at 25 mg/day caused earlier and greater improvements on the criteria of "getting to sleep" (GTS) and the quality of sleep as assessed by Leeds Sleep Evaluation Questionnaire (LSEQ). These changes were evident from the first week of treatment with agomelatine [57]. EEG studies have shown that agomelatine increased sleep efficiency starting from the seventh day of treatment onwards and increased SWS duration and percentage of sleep time on SWS (stages 3 and 4) [58]. Agomelatine is unique in the sense that it improves both the quality of sleep in depression patients and the onset time of antidepressant action [59].

Possible mechanism of therapeutic action of agomelatine

It is well recognized that disruptions in circadian rhythms correlate with clinical severity in depression, and this is attributed mainly to

disturbances in sleep-wake cycles [60-62]. Difficulty in falling asleep, staying asleep, disturbed nocturnal sleep, early morning awakening have all been documented in depressive disorders. Hence the primary aim of any antidepressant treatment is to correct the underlying mechanism of sleep-wake regulation. Agomelatine has been shown to be effective not only in regulating the sleep wake cycle, but also sleep architecture by normalizing the distribution of slow-wave sleep through the night in depressed patients [61]. The therapeutic efficacy of agomelatine is attributed to its actions on MT_1 and MT_2 melatonergic receptors in the SCN and is more effective than melatonin itself because of its higher affinity as well as its antagonistic actions on 5-HT_{2c} receptors [63, 64].

Because of its similarity to melatonin, agomelatine is suggested to inhibit neuronal firing, and this action contributes to the regulation of sleep. MT_1 melatonin receptors in the SCN mediate this effect since this action is absent in MT_1-melatonin receptor knockout mice [65]. Activation of MT_1 receptors in the SCN by agomelatine by attenuating the circadian wake promoting signal can prolong the homeostatic mechanism controlling sleep. It has been demonstrated in animals that that the circadian system plays an important role in the control of the timing of sleep onset, the timing of sleep offset, and the distribution of REM sleep [13].

Since melatonin is the circadian messenger of the circadian pacemaker, and MT_2 receptors in the SCN play a major role in melatonin's phase shifting effects, agomelatine, by influencing MT_2 receptors in the SCN, has a significant role in regulating sleep-wakefulness rhythm. It has been demonstrated that MT_1 melatonin receptor knockout mice exhibit depression-like behaviour, both male and female. MT-/- (melatonin receptor knockout) significantly increased the time spent in immobility in the forced swim test in mice, an indication of depression-like behavior [66]. Because agomelatine has beneficial effects on both sleep and circadian system, its antidepressant effect is attributed primarily to its action on melatonegric MT_1 and MT_2 receptors in the SCN.

Agomelatine's action on 5-HT_{2c} receptors has been demonstrated in the learned helplessness model of animal depression where melatonin alone or a selective 5-HT_{2c} receptor antagonist alone could not mimic the antidepressant-like effects of agomelatine. The stimulation of both melatonergic receptors and the blockade of 5-HT_{2c} seem to be essential for agomelatine's antidepressant effect [64]. Yet selective 5-HT_{2c} antagonists alone have not been demonstrated to be an effective antidepressant in double blind placebo-controlled clinical trials. However, non-specific 5-HT_{2c} antagonists have been shown to be effective in the treatment of depression [67].

Overall decrease of 5-HT_{2c} activity has been demonstrated in the prefrontal cortex of suicide victims with a history of depression, suggesting thereby the involvement of 5-HT_{2c} receptors of the prefrontal cortex in the pathophysiology of depression [68-70]. Agomelatine supremacy over other antidepressants is related to its effects on improving sleep and daytime alertness which are the main complaints of current antidepressant medication [71].

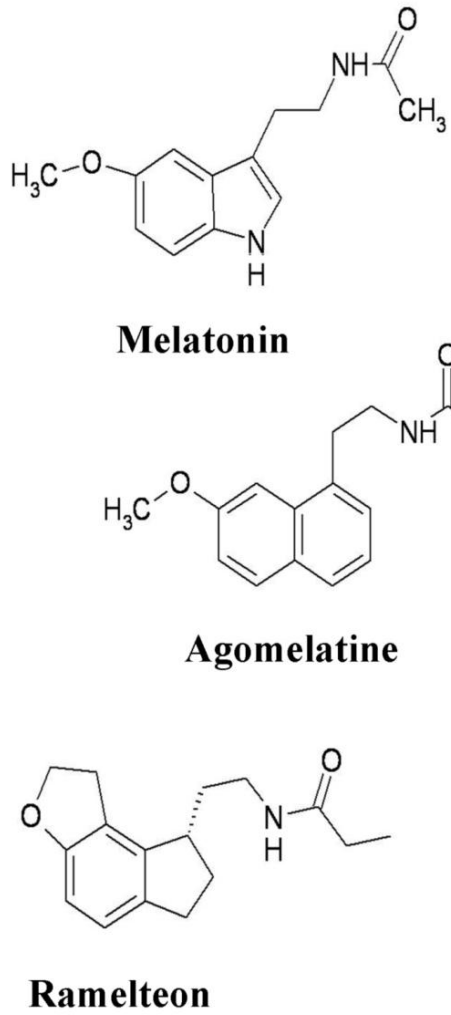

Figure 1. Molecular structures of melatonin, agomelatine and ramelteon.

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Safety and tolerability of agomelatine

Agomelatine has good tolerability and safety, as has been demonstrated in a number of clinical studies [47-49, 58]. In the 14-week study undertaken on the effects of agomelatine on patients with SAD, agomelatine displayed excellent tolerability at a daily dose of 25 mg and was found to be virtually devoid of the side effects typical of other antidepressants, like SSRIs [49]. In fact, long term exposure to agomelatine did not raise any safety problems. The cardiovascular safety of agomelatine has been found to be the same as that of placebo effects, with no changes in heart rate and blood pressure [61].

The most notable effect of agomelatine is its effect on sexual function. Many antidepressants that are currently in use cause increased impairment of sexual function, which has had a negative impact on the quality of life [72]. Most antidepressants, such as monoamine oxidase inhibitors (MAOIs), TCAs, SSRIs, and SNRIs, have been shown to affect all phases of sexual activity, including desire, arousal, orgasm, and ejaculation [61, 73, 74]. But patients treated with agomelatine experienced significantly less sexual dysfunction than those treated with the placebo.

It is also noteworthy that there was no discontinuation syndrome with agomelatine as there were no significant or apparent differences between the continuation and discontinuation groups after either one week or two weeks [75]. The complete absence of discontinuation symptoms with agomelatine makes it the drug of choice in the treatment of depression. There were also no reports on the adverse effects of agomelatine on renal or hepatic functions [48]. Some of the side effects noted with agomelatine administration on depressed patients include headache, anxiety, abdominal pain, and diarrhea, which were in fact less than that of the placebo [47].

The unique property of agomelatine which makes it the antidepressant drug of choice is the absence of sleep disturbances that are most marked with the use of other antidepressants, such as TCAs, SSRIs, and SNRIs [76, 77]. The improvement in sleep disturbances in depressed patients with the use of antidepressants is thus considered to be crucial in the treatment of depression. Agomelatine stands unique in this aspect as it does not require co-administration of any hypnotic drug during its clinical use in depression [78].

Therapeutic potential of melatonin MT_3 receptor agonist

The other melatonin binding site that has been identified in the brain and other tissues is MT_3, previously described as MT_2 receptor in the brain [79]. MT_3 melatonin binding site has been recently purified from hamster kidney and has been identified as the human homolog of quinine reductase [80].

A specific radioligand, 2-[^{125}I]-MCA-NAT (2-[^{125}I]iodo-5-methoxycarbonylamino-N-acetyltryptamine), that binds with MT_3 receptor has been characterized. By using this, the molecular identity between quinone reductase 2 (QR2) and MT_3 has been recently identified [81]. Polymorphism of QR2, caused by deletion/insertion of 29 base-pair nucleotides in the promoter regions of the QR2 gene has been shown to result in Parkinson's disease or schizophrenia [82, 83]. Elevated QR2 activity is postulated as one of the probable reasons for the occurrence of Parkinson's disease or schizophrenia. Hence inhibition of this enzyme or MT_3 melatonin receptor by a suitable ligand might be useful in the treatment of these disorders.

Quinone-reductases generally act as specific antioxidants and protect against oxidative stress caused by transfer reactions of electrons of quinones. QR2 is also involved in regulating intraocular pressure. In this context, it has been found recently that topical application of the melatonin agonist 5-MCA-NAT reduced intraocular pressure in glaucomatous monkey eyes by its interaction with QR2 enzyme (MT_3 receptor) [84]. Recently the antidepressant effect of QR2 was assessed by using a tail suspension test in rats, and it was found that QR2/MT_3 agonist 5-MCA-NAT decreased the duration of immobility whereas its antagonist prazosin attenuated the antidepressant effect of N-acetylserotonin (NAS) suggesting thereby that modulation of QR2/MT_3 might contribute to the mechanism of the antidepressant effect [85].

Concluding remarks

Although melatonin exhibits hypnotic properties, and has been used in the treatment of elderly insomniacs or in patients with depression or in any other patients with medical illnesses, the inconsistency of the results of its investigators has resulted in the application of melatonin agonists in the treatment of sleep disorders. It is also well known that depressed patients often have great difficulty in getting into sleep, and most

antidepressants that have been in use have caused either little improvement in sleep parameters or more often have worsened the sleep complaints seen in depression. As melatonin happens to have both sleep-promoting and chronobiotic properties, the use of melatonergic antidepressants has been tried, and this has been found effective in treating patients with depressive disorders in multicenter-multinational studies in Europe. Indeed agomelatine has been found effective in sleep in treating patients with MAD. Similarly ramelteon, an MT_1/MT_2 melatonergic agonist, has been found more effective in improving sleep efficiency in elderly insomniacs. Ramelteon also has been used for treating circadian sleep rhythm disorders like jet lag. A MT_3 melatonin receptor agonist is also being investigated for antidepressant properties.

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