Review

The role of the melatoninergic system in epilepsy and comorbid psychiatric disorders

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Contents

Abbreviations:

suprachiasmatic nuclei (SCN)

hypothalamic-pituitary-adrenal (HPA)

serotonin reuptake inhibitor (SSRI)

serotonin-norepinephrine reuptake inhibitor (SNRI)

open field (OF)

elevated plus maze test (EPM)

light-dark test (LDT)

novelty suppressed feeding test (NSFT)

benzodiazepine (BZ)

hole-board test (HBT)

kainic acid (KA)

major depression disorder (MDD)

forced swim test (FST)

tail suspension test (TST)

glucocorticoid receptor (GR)

carbamazepine (CBZ)

status epilepticus (SE)

pentylenetetrazole (PTZ)

N-methyl-D-aspartate (NMDA)

maximal electroshock seizure (MES)

spontaneously hypertensive rats (SHRs)

attention deficit hyperactivity disorder (ADHD)

Abstract

There is emerging evidence of the beneficial role of the melatonin system in a wide range of psychiatric and neurologic disorders, including anxiety, depression, and epilepsy. Although melatoninergic drugs have chronobiotic and antioxidant properties that positively influence circadian rhythm resynchronization and neuroprotection in neurodegenerative disorders, studies examining the use of melatonin for epilepsy's comorbid psychiatric and neurological symptomatology are still limited. Preclinical and clinical findings on the beneficial effects of the melatonin system on anxiety, depression, and epilepsy suggest that melatoninergic compounds might be effective in treating comorbid behavioral complications in epilepsy beyond regulation of a disturbed sleep–wake cycle.

Introduction

Secretion of the hormone melatonin is under the control of the main circadian clock, located in the suprachiasmatic nuclei (SCN) of the hypothalamus. Although the circadian synchronizing activity of melatonin is effective at specific time-points in diurnal and nocturnal species, the highest secretion of melatonin in all species, whether diurnal or nocturnal, occurs during the dark phase (peak at 2.00 a.m.), with the lowest occurring during the light phase (Arendt, 1998). Furthermore, melatonin deficit after pinealectomy was found to cause a phase shift without abolishment of the circadian rhythm of the rest–activity cycle (Cheung and McCormack, 1982).

The presence of melatonin receptors in the SCN and the pineal gland determines the bidirectional relationship between these structures. Melatonin receptor expression is under the control of light, and secretion of endogenous ligand follows a circadian rhythm (Salva and Hartley, 2012). While melatonin synthesis is regulated by the SCN clock, the hormone directly affects the activity of the SCN through activation of melatonin receptors (Pèvet et al., 2002). Therefore, treatment with drugs targeting the two main types of melatonin receptor in the SCN, namely MT_1 and MT_2 receptors, might affect the circadian regulatory mechanism.

Clinical studies have revealed that anxiety and depression are the most common behavioral complications in patients with epilepsy (Kanner and Nieto, 1999; Paradiso et al., 2001). These comorbid disorders are characterized by disturbed circadian rhythms of a number of parameters as well as dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Maes et al., 1993; Mazarati et al., 2008; Pariante and Lightman, 2008; O'Toole et al., 2014). Furthermore, close relationships between the sleep–wake cycle and the diurnal rhythmicity of seizure activity (Quigg, 2000), as well as between seizure susceptibility and HPA axis activity (O'Toole et al., 2014), have been found.

Mostly prescribed for resynchronization of disturbed biological rhythms in a variety of pathological conditions, melatonin has low toxicity, neuroprotective effects, and a powerful antioxidant action. The chronobiotic activity of the hormone has been validated for cardiovascular, immune, digestive, and temperature regulation (Pevet and Challet, 2011). The MT_1 and MT_2 receptor agonist and serotonin-2C ($5\text{-}HT_{2C}$) antagonist agomelatine, developed by the pharmaceutical company Servier, was introduced as a new class of antidepressant in Europe in 2009, and has been intensively studied in different neurodegenerative disease models (Dastgheib and Moezi, 2014; Descamps et al., 2014; Stahl, 2014). Stimulation of the melatonin system was found to positively influence symptoms of depression, which is commonly linked with anxiety and a disturbed sleep–wake cycle. Experimental and clinical data revealed that while melatonin alone does not have any clear-cut antidepressant or anxiolytic action, agomelatine does exert antidepressant and anxiolytic effects because of its dual pharmacodynamic activity as a melatonin receptor agonist on the one hand and a $5\text{-}HT_{2C}$ receptor antagonist on the other (Bourin et al., 2004; Millan et al., 2005; Papp et al., 2006). Like melatonin, the efficacy of agomelatine is associated mostly with its capacity to correct abnormal circadian fluctuations in many physiological functions (Mairesse et al., 2013; Castanho et al., 2014).

Disturbance of the circadian rhythm of melatonin synthesis, and its relationship with changes in HPA axis activity, has been studied in patients with depression (Beck-Friis et all., 1985, Claustrat et al., 1984). Several studies have reported that melatonin deficit due to pinealectomy exacerbates epileptogenesis and is associated with neuronal loss in particular brain structures, such as the hippocampus and amygdala (De Lima et al., 2005; Janjoppi et al., 2006; Yildrim et al., 2013); moreover, a deficit of melatonin can negatively affect the HPA axis (Weidenfeld et al., 1993). Indeed, exogenous melatonin has been shown to abolish the circadian pattern of spontaneous epileptic seizures and to exert beneficial effects on seizure

frequency, neuronal damage, status epilepticus (SE)-induced oxidative stress, and behavioral complications concomitant with epilepsy (Tchekalarova et al., 2013, Petkova at el., 2014; Atanasova et al., 2013). Therefore, chronobiotic melatoninergic drugs may be used to reverse two contributors to the development of comorbid psychiatric complications – depression and anxiety – desynchronizing the rhythms of a number of physiological parameters and attenuating the hyper-activated HPA axis seen in epilepsy.

The important role of the MT_1 receptor for maintenance of HPA axis activity has been confirmed recently with MT_1 receptor knockout mice, which have a blunted circadian fluctuation in diurnal corticosterone levels (Comai et al., 2015). Targeting this receptor has beneficial effects that might indirectly influence pathological hyperexcitability, oxidative stress, and imbalance of excitatory/inhibitory neurotransmission in the brain, which have been associated with disturbances in behavioral responses, memory deficit, neuronal death, and plastic changes in the hippocampus.

This review summarizes current findings on the role of the melatoninergic system in neurodegenerative disorders, with a focus on anxiety, depression, and epilepsy. We hypothesize that melatoninergic drugs targeting MT_1 and MT_2 receptors as well as possessing an antagonistic effect on the 5-HT_{2C} receptor subtype can be used as an effective add-on therapy in epilepsy for the treatment of comorbid anxiety and depression.

1. The melatonin system and anxiety

Although patients with panic disorder have decreased plasma melatonin at night (McIntyre et al., 1987; Cameron and Nesse, 1988), anxiogenic stimuli have been reported to evoke secretion of melatonin from the pineal gland in mice (Golombek et al., 1996). Several clinical reports have confirmed the impact of perioperative treatment with melatonin as an anxiolytic

(Caumo et al., 2007; Khezri et al., 2013; Yousaf et al., 2010). Evidence suggests that agomelatine may be considered an alternative for the treatment of anxiety disorder (Stein et al., 2008), having a comparative, or higher, efficiency than the selective serotonin reuptake inhibitor (SSRI) class, serotonin-norepinephrine reuptake inhibitor (SNRI) class, and sertraline (reviewed in De Berardis et al., 2013).

Experimental studies have revealed that melatonin exerts a modest activity in different tests for anxiety in rodents (Table 1). The first report on the efficacy of melatonin to alleviate anxiety in experimental animals was that of Golus and King on the open field (OF) test (1981). Although there is a discrepancy among reports on the effective dose and time of delivery (evening vs. morning), there is consensus that melatonin's effects are strongly dependent upon the timing of its administration (Golombek et al., 1993; 1996; Loiseau et al., 2006; Papp et al., 2006, Tian et al., 2010), suggesting a primary role for melatonin receptors in mediating the chronobiotic properties of the hormone.

Administration of this hormone to rats two hours before or during the dark phase produced a dose-dependent anxiolytic effect in the elevated plus maze (EPM) test, the light-dark test (LDT), ultrasonic vocalization, and the Vogel test (Kopp et al.; 2000; Loiseau et al., 2006; Papp et al., 2006; El Mrabet et al., 2012). In contrast, acute administration of melatonin in the morning was found to be ineffective in most anxiety tests (Golombek et al., 1993; Loiseau et al., 2006; Millan et al., 2005; Papp et al., 2006). However, agomelatine and the melatonin agonist Neu-P11 exhibited potent anxiolytic effects independent of the timing of administration (Millan et al., 2005; Papp et al., 2006, Tian et al., 2010). Although these new drugs were shown to have slightly weaker effects than the classical anxiolytics diazepam and buspirone (Tian et al., 2010), they do not produce sedation (Papp et al., 2006). The melatonin antagonist S22153 was shown to block the activities of melatonin and agomelatine when the latter were administered in the evening but not in the morning (Papp et al., 2006), confirming

the assumption that the anxiolytic effects of the two drugs are mediated by melatonin receptors. However, the lack of a time-dependent effect on anxiety with agomelatine suggests a role for 5-HT_{2C} receptor antagonism, whereas the lack of a chronobiotic activity for Neu-P11 might be due to its interaction with GABAergic (Laudon et al., 2008) or 5-HT (Tian et al., 2010) pathways. Agomelatine's dual action on melatoninergic and serotoninergic components determines a broader anxiolytic efficacy and lack of chronobiotic dependence compared with melatonin.

Several studies have indicated that the anti-anxiety activity of melatonin depends on the type of experimental test employed: indeed, melatonin was shown to be effective in the Vogel test, but not in the EPM test (Loiseau et al., 2006), which implicates positive responses against a 'trait', but not 'state' anxiety (Papp et al., 2006). Genetic studies on MT_1 and MT_2 receptor knockout mice confirmed the principal role of both receptors in anxiety responses (Weil et al., 2006; Comai et al., 2014; 2015). Interestingly, these knockout mice exhibited anxiety-resistant behavior in the OF test, in contrast to the anxiogenic activity shown in the novelty suppressed feeding test (NSFT) (Comai and Gobbi, 2014; Comai et al., 2015); the authors suggested that NSFT was a more specific test for validating anxiety-like behavior in genetically manipulated animals. Moreover, whereas hyperactivity of $MT_1^{-/-}$ mice produced false-positive hypoanxiety behavior with the EPM test (Comai et al., 2015), knockout of the MT_2 receptor reflected on decision-oriented behavior (Comai and Gobbi, 2014). A previous study by the same research group supports the principal participation of the MT_2 receptor in anxiety (Ochoa-Sanchez et al., 2012). Furthermore, the MT_2-selective partial agonist UCM765 was reported to be an effective anxiolytic compound even at a low dose, and did not produce side effects, such as sedation and abuse.

Studies on how melatonin deficit produced by pinealectomy affects the level of anxiety are controversial. Some authors indicate no influence of pinealectomy with the EPM test

(Appenrodt and Schwarzberg, 2000; Juszcak et al., 1996; Karakaş et al., 2011), whereas others report increased anxiety with the burying behavior test (Bustamante-García et al., 2014), the OF test, and the EPM test (El Mrabet et al., 2012). This inconsistency could be due to differences in the testing period. Indeed, it has recently been demonstrated that anxiety levels return to normal three months after removal of the pineal gland, suggesting involvement of a compensatory, extra-pineal, melatonin system (Nenchovska et al., 2014).

A bulk of data in the literature shows that benzodiazepine (BZ) receptors are also involved in the emotional effects of melatonin, and that melatonin can modulate the GABA-BZ receptor complex. Exogenous melatonin has been demonstrated to enhance GABA-induced chloride influx and GABA turnover rate (Rosenstein and Cardinali, 1986; Rosenstein et al., 1989), as well as changing GABA-BZ binding to brain membranes (AcuÑa-Castroviejo et al., 1986; Niles et al., 1987). The combination of either melatonin or agomelatine with diazepam is unable to enhance the myorelaxant activity of the BZ drug, confirming the pharmacodynamic nature of their relationship (Loiseau et al., 2006), but melatonin does potentiate diazepam's anxiolytic action, as indicated by several anxiety tests on mice and rats (Guardiola-Lemaître et al., 1992; Loiseau et al., 2006), and exerts a dose-dependent effect in the conflict test in rats (Naranjo-Rodriguez et al., 2000). Furthermore, the anxiolytic activity of melatonin is antagonized by pretreatment with the BZ antagonist flumazenil in the EPM procedure in rats (Golombek et al., 1993), the hole-board test (HBT), LDT, and free-exploratory tests in mice (Pierrefiche et al., 1993; Kopp et al., 1999). In contrast, the anxiolytic profile of agomelatine seems to be different from that of BZs (Papp et al., 2006, Millan et al., 2005), and the potential role of 5-HT_{2C} receptor antagonism underlying the anxiolytic activity of the former is still uncertain and needs further study.

Melatonin restored anxiety to a normal level after application of different aversive stimuli, such as administration of lipopolysaccharide (Nava and Carta, 2001), diazinon (Ahmed et al.,

2013), or doxorubicin (Aziriova et al., 2014), and upon long-term restrain stress in mice (Kumar et al., 2014). Continuous administration of melatonin had disease-modifying effects on neuronal damage and behavioral disturbances in different models of neurodegenerative disorders: long-term melatonin treatment (4 mg/kg/day, via drinking water for 29 days) attenuated behavioral complications associated with increased motor activity and anxiety in a mouse model of ischemic stroke (Kilic et al., 2008), but repeated melatonin administration was unable to prevent kainic acid (KA)-induced epileptogenesis in Wistar rats and spontaneously hypertensive rats (SHRs), although it did exert neuroprotection in specific brain areas and restored the anxiety response during the chronic epileptic phase (Tchekalarova et al., 2013; Petkova et al., 2014).

2. Melatonin and depression

Patients with major depression disorder (MDD) are characterized by a low melatonin level at night, a disturbed HPA axis, and a phase shift in circadian melatonin and cortisol rhythms (Beck-Friis et al., 1985; Nair et al., 1984). Although agomelatine is as effective as other classic antidepressants in the acute phase of MDD, insufficient data on its efficacy for relapse prevention and its hepatotoxic side-effects hampers its use as a first-choice therapeutic for MDD (Gahr, 2014). Overall, assessment of melatonin could be effective in acute tests for the screening of antidepressants as well as in chronic models of depression. However, clinical data have not revealed clear-cut evidence that melatonin, per se, is able to prevent depressive symptoms in MDD. Indeed, long-term treatment with a combination of melatonin and low doses of the 5-HT_{1A} receptor agonist buspirone exerted a beneficial activity and few side effects in patients with acute MDD (Fava et al., 2012). It seems that the beneficial effect of melatonin treatment as an adjuvant to other antidepressants is associated with its ability to synchronize disturbed circadian rhythms in patients with depression and a deficit of melatonin

secretion (Haimov et al., 1995; Garfinkel et al., 1995; Jan et al., 2001; Mittal et al., 2010; Wade et al., 2010).

Pre-clinical and clinical data support the notion that the selective MT_1/MT_2 agonist ramelteon, which has a substantially longer half-life than melatonin, might be considered as a drug of choice for the treatment of circadian rhythm sleep disorders (Salva and Hartley, 2012). Despite its chronobiotic activity as a pure MT_1 and MT_2 receptor agonist, ramelteon is unlikely to affect depressive symptoms in MDD (Salva and Hartley, 2012). Currently approved in Europe for the treatment of MDD, agomelatine improves the sleep and clinical symptoms of depressive illness and does not have the side effects on sleep seen with other compounds in use (Arendt and Rajaratnam, 2008; Eser et al., 2007). Preclinical data has revealed that exogenous melatonin is active in routinely used screening tests for antidepressant actions, such as the forced swim test (FST) (Bourin et al., 2004; Brotto et al., 2000; Ergün et al., 2008; Micale et al., 2006; Overstreet et al., 1998; Raghavendra et al., 2000; Shaji et al., 1998; Ramírez-Rodríguez et al., 2014; Zahra et al., 2012;) and the tail suspension test (TST) (Prakhie et al., 1998; Mantovani et al., 2003; Binfarè et al., 2010; Oxenkrug et al., 2010) (Table 2). Agomelatine was reported to be more efficacious than melatonin in the FST on naïve rats and mice (Bourin et al., 2004) as well as on transgenic mice with low glucocorticoid receptor (GR) function (Barden et al., 2005). Moreover, the efficacy of melatoninergic drugs has been shown to be strongly dependent upon sex hormones, species (rats vs. mice), sex (male vs. female), and treatment protocol (chronic vs. acute) (Bourin et al., 2004; Brotto et al., 2000; Païzanis et al., 2010; Raghavendra et al., 2000; Zahra et al., 2012). Indeed, chronic, but not acute, treatment regimens with pharmacological doses of melatonin and agomelatine had an anti-depressant effect in mice (Raghavendra et al., 2000; Bourin et al., 2004), whereas acute and chronic administration of agomelatine were effective in an FST on rats (Bourin et al., 2004). Unlike agomelatine, the activity of melatonin

is strongly dependent on the timing of administration, with an evening antidepressant activity for melatonin receptors and a morning activity for 5-HT_{2C} receptors (Papp et al., 2003). Clinical data has also revealed that the period of delivery of exogenous melatonin is critical for the efficacy of this hormone on the circadian rhythms of sleep and core body temperature (Arendt , 2005).

The antidepressant activity of melatonin and melatonin receptor agonists has been confirmed in a genetic animal model of depression (Flinders Sensitive Line rats) (Overstreet et al., 1998), in $MT_1^{-/-}$ mice on an FST (Weil et al., 2006), and in the chronic mild stress model of depression in mice and rats (Kopp et al., 1999; Papp et al., 2003; Haridas et al., 2013). Furthermore, a recent study on $MT_1^{-/-}$ mice has suggested that the MT_1 receptor is implicated in melancholic depression, and that MT_1 receptor agonists might be considered as potential antidepressant drugs with putative chronobiotic effects (Comai et al., 2015). In contrast, the role of MT_2 receptors in depression is not clear, although there are some indications that the antidepressant-like activity of luzindole is mediated through this receptor sub-type (Sumay et al., 2005).

Melatonin was less effective than fluoxetine in preventing chronic mild-stress-induced complications in the behavior of C3H/He mice (Kopp et al., 1999). Agomelatine had an antidepressant effect in a rat model of prenatal restraint stress, suggesting that it might be considered a “disease-dependent drug” (Morley-Fletcher et al., 2011). The combination of agomelatine with 5-HT agonists/antagonists was more efficacious than the effects of melatonin alone. While the putative role of 5-HT_{2C} receptor blockade in the mechanisms underlying the antidepressant potency of agomelatine is supported by experimental and clinical data, the mechanism of melatonin’s antidepressant activity remains obscure. The antidepressant effect of melatonin in BALB/c mice was suppressed by pretreatment with a 5-HT_{2A}/5-HT_{2C} agonist and BZ receptor antagonist, suggesting involvement of 5-HT and BZ

receptors (Raghavendra et al., 2000; Micale et al., 2006). On the other hand, experimental data has indicated that the effect of melatonin in the TST might be mediated by an interaction with dopamine D_1 and D_2 receptors, NMDA receptors, the L-arginine-NO pathway, and the BZ pathway (Binfarè et al., 2010; Mantovani et al., 2003; Guardiola-Lemaître et al., 1992). The above-mentioned results reveal the complex mechanisms underlying melatonin's antidepressant activity, which need to be explored in more detail.

3. Melatonin and epilepsy

Melatonin's antioxidant activity and low toxicity makes it attractive to clinicians as a potential adjuvant for epilepsy therapy. Furthermore, studies have reported that the primary beneficial effect of melatonin on seizure activity is due to its ability to synchronize disturbed circadian rhythms in epileptic patients (Fauteck et al., 1999; Peled et al., 2001). Comorbidity of a sleep disorder with epilepsy creates difficulties in choosing an anti-epileptic drug (AED). Indeed, while lamotrigine, levetiracetam, valproate, and gabapentine have been reported to lack or exert few negative effects, other agents such as BZs, barbiturates, and phenytoin aggravate sleep architecture in individuals with epilepsy (reviewed in: Bazil et al., 2003). In line with this, melatonin and melatonin receptor agonists may be suitable for use as add-on treatments with routine AEDs. Indeed, melatonin alleviates sleep disturbances of different etiologies in epileptic children and adults (Coppola et al., 2004; Fauteck et al., 1999; Peled et al., 2001). The improvement in sleep parameters is accompanied by an attenuation of seizure activity in young patients with intractable epilepsy (Elkhayat et al., 2010) and in patients on valproate (Gupta et al., 2005), but melatonin produces an ambiguous, dual effect in epileptic patients with mental complications (Coppola et al., 2004). Furthermore, clinical reports have shown the beneficial effect of melatonin treatment on seizure activity during the day (Goldberg-Stern et al., 2012) and the night (Peled et al., 2001) in patients with intractable epilepsy, a pathology

characterized by an increased post-seizure salivary melatonin level (Bazil et al., 2003). High melatonin levels were also detected in unmedicated patients with complex partial epilepsy, and might represent a compensatory feedback mechanism against the severe epileptic state (Graham et al. 1995). However, increased night-time plasma melatonin has been associated with a higher incidence of seizure attacks at night (Sandyk et al., 1992).

Another important advantage of melatonin as an add-on option for epilepsy is associated with its potent antioxidant properties. Clinical data has shown that melatonin has an antioxidant activity in epileptic patients on carbamazepine (CBZ) (Gupta et al., 2004, 2006). Increased oxidative stress and disturbance of the endogenous antioxidant system can aggravate seizure activity (Yüksel et al., 2000). On the other hand, data has shown that the metabolites of several AEDs behave as pro-oxidant agents with toxic effects (Graf et al., 1998; Niketic et al., 1995; Yüksel et al., 2000). Experiments have confirmed the potent antioxidant activity of melatonin in different pathological states: chronic melatonin infusion (10 mg/kg/day), as well as a cumulative dose of 10 mg/kg, suppressed KA-induced oxidative stress in the hippocampus (Chung and Han, 2003) without preventing the development of SE (Atanasova et al., 2013).

Melatonin has been reported to have an anticonvulsant action in many models of acute seizures, such as those produced by the administration of pentylenetetrazole (PTZ), picrotoxin, bicuculline, pilocarpine, L-cysteine, kainate, 3-mercaptopropionic acid, quinolinate, glutamate (Glu), strychnine, N-methyl-D-aspartate (NMDA), or penicillin, as well as in the maximal electroshock seizure (MES) test in rats, mice, gerbils, and hamsters (Table 3). The anticonvulsant and neuroprotective effects of melatonin have been verified in the chronic amygdala kindling model of partial epilepsy in rats (Mevissen et al., 1998) and the KA model of temporal lobe epilepsy (Tchekalarova et al. 2013; Petkova et al., 2014). Pinealectomy facilitates epileptogenesis in some species and increases seizure activity (De

Lima et al., 2005; Janjoppi et al., 2006; Silva de Lacerda et al., 2007; Yildrim et al., 2013), and melatonin has been reported to either reverse (Yildrim et al., 2013) or to be ineffective (De Lima et al., 2005) in this pinealectomy-induced enhancement of seizure susceptibility.

In addition to the MT receptor-mediated effects of melatonin in seizure models, a number of studies have demonstrated the participation also of GABAergic, 5-HT-ergic, and NO/L-arginine pathways (Bikjdaouene et al., 2003; Dastgheib and Moezi, 2014; Golombek et al., 1992; Ray et al., 2004; Yahyavi-Firouz-Abadi et al., 2007). Melatonin potentiates the effect of several AEDs, such as carbamazepine and phenobarbital (Borowicz et al., 1999; Forcelli et al., 2013), but fails to protect neonatal rats against PTZ-induced seizures, even at the high dose of 80 mg/kg (Forcelli et al., 2013). Although chronic melatonin infusion had an antioxidant effect in Wistar rats and SHRs with KA-induced SE, it was ineffective against the development of SE (Atanasova et al., 2013); however, it did partially blunt pilocarpine-induced SE in pinealectomized rats (De Lima et al., 2005). Moreover, a few reports have raised the point that melatonin can act as an endogenous proconvulsant (Stewart and Leung, 2003; Yehudi and Mostofsky, 1993). These contrasting effects might be associated with Mel_{1b} receptor-mediated suppression of $GABA_A$ receptors in CA1 pyramidal cells (Stewart and Leung, 2003) and involvement of the dopaminergic pathway (Yehudi and Mostofsky, 1993).

The first study considering the efficacy of agomelatine in different seizure models in female Swiss mice was published by Aguiar et al. (2012). Similarly with previously reported results on the anticonvulsant effects of melatonin at doses ranging from 40 to 80 mg/kg in PTZ-induced seizures in a variety of species (Bikjdaouene et al., 2003; Moezi et al., 2011; Solmaz et al., 2009; Yahyavi-Firouz-Abadi et al., 2007), the authors showed that agomelatine was active at doses of 25 and 50 mg/kg. Agomelatine was also effective against pilocarpine-induced SE at a dose of 75 mg/kg (Aguiar et al., 2012), while melatonin had an anticonvulsant effect only after repeated injections in this model of epilepsy (Costa-Lotufo et

al., 2002; De Lima et al., 2011). The lack of activity of agomelatine against other convulsants, such as picrotoxin and strychnine, as well as in the MES test, suggests the presence of more-specific mechanisms of action, which need further exploration. The dose-dependent anticonvulsant effect of acute agomelatine administration against PTZ seizure threshold in mice was recently confirmed by Dastgheib and Moezi (2014). However, agomelatine was ineffective in a chronic treatment protocol, a result possibly due to agomelatine-induced receptor desensitization or internalization. In line with this, the receptor-mediated melatonin effect was also found to involve a fine-tuning mechanism of desensitization or internalization, which was strictly dependent upon the treatment protocol (Gerdin et al., 2004; Delagrange and Guardiola-Lemaitre, 1997; Witt-Enderby et al., 2003). Moreover, the anticonvulsant efficacy of agomelatine against i.v.-injected PTZ in mice was reported to involve iNOS or nNOS induction, because selective iNOS and nNOS inhibitors attenuated the effect of agomelatine (Dastgheib and Moezi, 2014). These results concurred with previous findings that the NO/L-arginine pathway was involved in the anticonvulsant effect of melatonin against clonic seizures induced by i.v.-infused PTZ (Bikjdaouene et al., 2003; Yahyavi-Firouz-Abadi et al., 2006).

In conclusion, clinical and experimental findings showing the beneficial effect of melatonin on disturbed circadian rhythms and oxidative stress in epileptic conditions suggest that the targeting of the pathways induced by this hormone may be used to treat epilepsy-related complications. However, because 5-HT_{2C} receptors are also involved in the regulation of seizure susceptibility (Applegate and Tecott, 1998; Isaak, 2005; Upton et al., 1998), further studies on models of chronic epilepsy are required to gain a better understanding of the mechanisms underlying agomelatine’s anti-seizure effect.

4.1. Chronopharmacology of melatonin's effects on epilepsy

Few studies have focused on the chronopharmacology of melatonin in seizure tests and models of epilepsy. Moreover, data is controversial: indeed, exogenous melatonin has been reported to produce an anticonvulsant effect that was either strongly time-dependent (Costa-Lotufo et al., 2002; Golombek et al., 1992; Lapin et al., 1998) or independent from the time of day of administration (Champney et al., 1996; Mevissen et al., 1998). Exogenous melatonin and the secretion of the endogenous hormone at night can both protect neuronal cultures from apoptosis promoted by KA-induced oxidative stress (Manev et al., 1996). Melatonin produced a diurnal variation in susceptibility to PTZ- and 3-MP-induced seizures in hamsters, with the lowest threshold needed to evoke clonic seizures found at night (Golombek et al., 1992). Melatonin administered at a dose of 50 mg/kg i.p. had the greatest effect in the early evening, when the level of endogenous hormone is expected to be the most elevated (Golombek et al., 1992). Melatonin activity seems to be influenced by central BZ antagonism, because Ro 15-1788 and flumazenil blocks its effects. The circadian rhythm of seizure threshold has been documented for different seizure models, including PTZ (Yehuda and Mostofsky, 1993), pilocarpine (Stewart, 2001), and MES test (Löscher et al., 1996). Melatonin was ineffective during the day in rats, but decreased PTZ seizure threshold at night (Yehuda and Mostofsky, 1993).

Clinical and experimental data has revealed the circadian rhythm of seizure activity in patients and in different models of epilepsy (Arida et al., 1999; Raedt et al., 2009; Shouse et al., 1996; Stewart and Leung, 2003). Indeed, there is a prevalence of epileptiform activity during sleep (Asano et al., 2007; Ferrillo et al., 2000; Staba et al., 2002). Rodents are nocturnal animals, and a higher frequency of EEG and video-recorded motor seizures have been monitored in different models of epilepsy when animals are inactive during the light phase (Arida et al., 1999; Bertram et al., 1994; Quigg, 2000; Raedt et al., 2009; Tchekalarova et al., 2013).

Similar higher seizure susceptibility during the inactive period was found in rats subjected to amygdala kindling-induced epileptogenesis (Weiss et al., 1993). Recently, we demonstrated that the administration of melatonin flattens the circadian periodicity of spontaneous seizures in Wistar rats and SHRs with KA-induced temporal lobe epilepsy (Tchekalarova et al., 2013, Petkova et al., 2014). The effect was greater in SHRs, and possibly related to decreased seizure frequency during the light phase.

The circadian periodicity of endogenous melatonin secretion might also influence the diurnal pattern of seizures. Yalýn et al. (2006) reported that melatonin level and its circadian rhythm do not differ between patients with nocturnal or diurnal complex partial seizures. This finding suggests that seizure periodicity does not depend on fluctuations in melatonin release. Melatonin receptor expression follows a circadian pattern and depends on exposure to either light or melatonin. Furthermore, the administration of melatonin produces a phase shift in circadian fluctuations. It is accepted that this chronobiotic activity of the hormone is due to the specific and divergent roles of MT_1 and MT_2 receptors in the central biological clock, located in the SCN at the anterior hypothalamus (Liu et al., 1997).

Studies have demonstrated that humans and experimental animals with epilepsy are characterized by shifted or disrupted circadian rhythms in cortisol release (Bazil et al., 2003), temperature (Quigg, 2000), motor activity (Stewart and Leung, 2003), and sleep architecture, for example decreased REM sleep (Bastlund et al., 2005; Manni and Terzaghi, 2010). Fluctuations of the melatonin level in the sleep–wake cycle have been shown to correlate with a propensity for epileptic activity in patients with complex partial epilepsy (Graham et al. 1995) or following seizures (Bazil et al., 2003), suggesting a compensatory, melatonin-mediated feedback mechanism against severe epilepsy. Studies on the circadian rhythm of melatonin release during epilepsy are missing. Work is needed to understand whether and

how melatonin release and the expression of MT receptors in various brain structures are altered during or related to the circadian pattern of spontaneous seizures.

4.2. Melatonin and depression/anxiety comorbidities in epilepsy

Behavioral complications, such as depression, anxiety, memory deficit, and attention deficit hyperactivity disorder (ADHD), are common concomitances in epilepsy. The predisposition of patients with psychiatric complications for seizures and of patients with epilepsy to develop behavioral complications are both well documented (Adelöw et al., 2012; Forsgren and Nystrom, 1999; Hesdorffer et al., 2012). Although data favors the hypothesis that epilepsy and its behavioral comorbidities have a common underlying mechanism, and that morphological, biochemical, and behavioral changes caused by one disorder may provoke another, the exact pathogenesis of behavioral comorbidities in epilepsy remains obscure, and there is a lack of standard screening and treatment approaches (Ott et al., 2003). Over the last decade, several laboratories have validated animal models of comorbidity, such as depression and ADHD (Koh et al., 2007; Ma and Leung, 2004; Mazarati et al., 2008; Pineda et al., 2010; 2014). We have recently reported on strain-related behavioral differences, using the KA-induced epilepsy model, which is also considered a model of depression comorbidity (Tchekalarova et al., 2010). The intact SHR is characterized by typical behavioral, electrophysiological, and biochemical abnormalities – which are also evident in epileptic rats – such as attention deficit, impulsiveness, deficient sustained attention, and monoamine deficits in the frontal cortex and hippocampus, suggesting that this strain might be used also as a relevant model of ADHD comorbidity (Tchekalarova, 2014). In addition, we recently demonstrated that long-term treatment with melatonin for KA-induced epileptogenesis produces different effects in Wistar rats and SHRs; the finding supported the hypothesis that

the underlying mechanisms of behavioral comorbidities in epilepsy differ in these two rat strains (Tchekalarova et al., 2013; Petkova et al., 2014). Indeed, while seizure frequency in epileptic SHRs remained significantly decreased even after discontinuation of melatonin, in Wistar rats the anticonvulsant effect of melatonin was evident only during the treatment period. In addition, whereas the administration of melatonin to Wistar rats produced a beneficial effect on behavioral and biochemical complications, such as hyperactivity, anxiety, depression, memory deficit, and low hippocampal 5-HT (Tchekalarova et al., 2014), long-term treatment failed to positively affect the behavioral and memory deficits or improve the disturbed diurnal behavioral rhythms in epileptic SHRs (Petkova et al., 2014). However, melatonin was neuroprotective in the CA1 hippocampal area and the piriform cortex in both rat strains, suggesting a positive relationship between anti-seizure efficacy and neuroprotection.

So far, the efficacy of agomelatine for depression, anxiety, memory deficit, and sleep disturbances has been proven in humans and in animal models (reviewed in Vimala et al., 2014). Experimental and clinical studies on the anticonvusant potency of acute agomelatine administration on several seizure tests (Aguiar et al., 2012; Dastgheib and Moezi, 2014) and the positive effect on behavioral disturbances suggest that this agent might have beneficial effects also in epilepsy for comorbid depression, anxiety, and sleep disturbances.

4. Molecular mechanisms linking epilepsy and comorbid anxiety and depression: the potential of targeting the melatonin system

Basic molecular mechanisms of the melatonin system that might be considered as possible targets:

i) Melatonin-mediated restoration of a disrupted hypothalamic-pituitary-adrenal axis – Clinical data and experimental models have shown that the HPA axis is hyperexcited in

epilepsy (Culebras et al., 1987; Mazarati et al., 2009; O'Toole et al., 2014) and in depression (Cai et al., 2013; Chen et al., 2015) and that melatonin can correct glucocorticoid-induced HPA axis disruption (Konakchieva et al., 1998). Because stress responses are regulated by the hypothalamic paraventicular nucleus (Laryea et al., 2013), and MT_2 receptors are present in this area (Lacoste et al., 2015), we may speculate that melatonin could correct HPA axis disruption by acting on these receptors.

ii) Melatonin and GABA neurotransmission – Enhancing GABAergic responses in the brain is a common therapeutic approach for epilepsy, anxiety, and other neurological conditions. Melatonin exerts its activity either through a non-receptor-mediated mechanism (Li et al. 2001) or by binding to the $GABA_A$ receptor (Niles and Peace, 1990), which enhances its affinity for the agonist (Wu et al. 1999). Furthermore, enhancement or attenuation of $GABA_A$ receptor-mediated currents strongly depends on (MT_1 or MT_2) receptor activation (Wan et al. 1999). Because of the marked side effects of GABAmimetic drugs, there is a tendency in clinical practice to replace them with melatonin agents.

iii) Melatonin and the serotonin receptor – MT_2 receptors are involved in the pathophysiology and pharmacology of sleep disorders, anxiety, and depression, and selective MT_2 receptor agonists have hypnotic and anxiolytic properties (Comai et al., 2014). Serotonin disturbances are involved in depressive (Meltzer, 1989) and epileptic (Richerson et al., 2011) conditions. A novel finding is the presence of MT_2/5-HT heteromers in the brain (Kamal et al., 2015). Melatonin could act throught this heteromer to modulate epileptic seizures and depressive-like comorbidity. Therefore, this heteromer could further explain similar actions between melatonin and agomelatine.

5. Conclusions and future perspectives

Disturbance of the circadian rhythms of a number of physiological functions is relatively frequent in many neurodegenerative disorders, including depression, anxiety disorder, and epilepsy (Gorwood, 2012; Quigg, 2000; Turek, 2007). A bidirectional link between circadian rhythm and these disorders has been suggested (Salva and Hartley, 2012; Yalyn et al., 2006; Yousaf et al., 2010). Agents that synchronize circadian fluctuations are considered to possess chronobiotic activity (Pévet et al., 2002).

The rationale of using drugs that stimulate prolonged melatonin release (circadian), such as ramelteon (an MT_1 and MT_2 receptor agonist) and agomelatine (a melatonin receptor agonist and a $5HT_{2C}$ receptor antagonist), as adjuvants to anticonvulsant therapy in epilepsy is two-fold. First, treatment with melatonin-related drugs in epilepsy can have beneficial effects on sleep cycle synchronization, thereby exerting indirect improvements in comorbid depression and anxiety, as well as controlling seizure frequency. The presence of melatonin receptors in the SCN suggests that circulating melatonin agonists affect circadian rhythm regulation. Clinical reports have revealed that although melatonin can synchronize circadian rhythm, limiting therapeutic targeting only to MT_1 and MT_2 receptors is not sufficient to treat depressive symptoms (Dalton et al., 2000; Serfaty et al., 2010). A combination of chronobiotic (melatonin receptors) and antidepressant ($5HT_{2C}$ antagonism) effects is proven to be a more effective therapeutic strategy for depression (Kasper and Hajak, 2013). Studies indicated that agomelatine has a beneficial influence on a group of patients with sleep problems (Kasper and Hajak, 2013; Sansone and Sansone, 2011). Besides, studies have documented general improvements in the quality of life of epilepsy patients on melatonin add-on therapy, which could be related to melatonin's chronobiotic activity (Jones et al., 2005). Second, melatonin is proven to possess neuroprotective (Manev et al., 1996; Mevissen et al., 1998; Tchekalarova et al., 2013) and antioxidant activities through scavenging of free radicals and potentiation of the activity of endogenous antioxidant enzymes (Yonei et al., 2009). Most AEDs directly target the receptors of glutamate and/or GABA, thereby causing a number of side effects. Melatonin appears to diminish the glutamate-targeting effect, while enhancing GABA activity through indirect fine-tuning mechanisms targeting melatonin receptors, promoting an inhibition of seizures with fewer side effects. Over recent years, agomelatine has become the focus of interest because of its combined chronobiotic (melatonin receptor agonism) and antidepressant (5-HT_{2C} receptor antagonism) effects. The few experimental

studies reporting an anticonvulsant effect for agomelatine in acute seizure tests give encouraging signs and suggest that this drug represents a promising therapeutic tool for the targeting of circadian desynchronization, oxidative stress, and comorbid depression and anxiety in epilepsy.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgements

We sincerely thank Michael Latronico for his expert assistance in the editing of the manuscript. The work was funded by…

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