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Review

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

Jana Tchekalarova[a,*], Slavianka Moyanova[b], Antonio De Fusco[b], Richard Teke Ngomba[b]

[a] Institute of Neurobiology, Acad. G. Bonchev Str., Bl. 23, Bulgarian Academy of Sciences, Sofia 1113, Bulgaria
[b] I.R.C.C.S NEUROMED, Località Camerelle, Pozzilli 86077, IS, Italy

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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 desynchronization 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.

Contents

1. 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, 2005). 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).

Abbreviations: SCN, suprachiasmatic nuclei; HPA, hypothalamic-pituitary-adrenal; SSRI, serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; OF, open field; EPM, elevated plus maze test; LDT, light-dark test; NSFT, novelty suppressed feeding test; BZ, benzodiazepine; HBT, hole-board test; KA, kainic acid; MDD, major depression disorder; FST, forced swim test; TST, tail suspension test; GR, glucocorticoid receptor; CBZ, carbamazepine; SE, status epilepticus; PTZ, pentylenetetrazole; NMDA, *N*-methyl-D-aspartate; MES, maximal electroshock seizure; SHRs, spontaneously hypertensive rats; ADHD, attention deficit hyperactivity disorder.

* Corresponding author. Fax: +359 2 719 109.
E-mail address: janetchekalarova@gmail.com (J. Tchekalarova).

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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 (Pévet et al., 2002). Therefore, treatment with drugs targeting the two main types of melatonin receptor in the SCN, namely MT_1 and MT_2, 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 (Castanho et al., 2014; Mairesse et al., 2013).

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 al., 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 (Atanasova et al., 2013; Petkova et al., 2014; Tchekalarova et al., 2013). Therefore, chronobiotic melatoninergic drugs may be used to reverse two contributors to the development of comorbid psychiatric complications – depression and anxiety – resynchronizing 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 $5\text{-}HT_{2C}$ receptor subtype can be used as an effective add-on therapy in epilepsy for the treatment of comorbid anxiety and depression.

2. 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 (1981) on the open field (OF) test. 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 $5\text{-}HT_{2C}$ 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.