Neurobiology of Disease 104 (2017) 1–14

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Agomelatine protects against neuronal damage without preventing epileptogenesis in the kainate model of temporal lobe epilepsy

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ARTICLE INFO

Article history:
Received 4 April 2017
Accepted 20 April 2017
Available online 21 April 2017

Keywords:
Agomelatine
Kainate
Epileptogenesis
Behavior
Neuronal loss

ABSTRACT

Recent studies about the novel antidepressant agomelatine, which is a mixed MT_1 and MT_2 melatonin receptor agonist and $5HT_{2C}$ serotonin receptor antagonist possessing an anticonvulsant and neuroprotective action, suggest that it may have potential to contribute against epileptogenesis and epilepsy-induced memory impairment. In order to ascertain whether protection of some brain structures could suppress epileptogenesis, in the present study, we evaluated the effect of chronic post-status treatment with agomelatine on epileptogenesis, behavioral and neuronal damage induced by kainate acid (KA) status epilepticus (SE). Agomelatine/vehicle treatment (40 mg/kg, i.p.) started one hour after SE and continued up to 10 weeks in Wistar rats. Latency for onset of spontaneous motor seizures (SMS) and their frequency was detected by a 24-h video-recording. Locomotor activity, anxiety and hippocampus-dependent spatial memory in open field (OF), elevated plus maze (EPM), light-dark test (LDT) and radial arm maze (RAM) test, respectively, were evaluated during the last two weeks after SE. Agomelatine significantly decreased the latency for onset of SMS and increased the seizure frequency during the 2nd and the 3rd week of treatment. The MT_1 and MT_2 receptor agonist and serotonin $5HT_{2C}$ receptor antagonist exacerbated the KA-induced hyperlocomotion and impulsive behavior and it was unable to prevent spatial memory impairment of epileptic rats. However, agomelatine induced a neuroprotection in the dorsal hippocampus, specifically in the CA1, septal CA2 and partially in the CA3c region, the hilus of the dentate gyrus, piriform cortex and septo-temporal and temporal basolateral amygdala. Our findings suggest that the beneficial impact against SE-induced neuronal loss exerted by agomelatine is not crucial for the suppression of epileptogenesis and its deleterious consequences in KA model of temporal lobe epilepsy.

1. Introduction

Agomelatine, developed by the pharmaceutical company Servier, was introduced as a new class of antidepressants in Europe in 2009. This drug has been actively studied in recent years by many research groups using different experimental models characterized by cellular, neurochemical and behavioral abnormalities (Boulle et al., 2016; Mairesse et al., 2013; Morley-Fletcher et al., 2011; Rainer et al., 2012). Agomelatine became the focus of increased scientific interest due to its unique pharmacological mechanism of action. This compound can exert chronobiotic efficacy because of its agonism on MT_1/MT_2 melatonin receptors while its antidepressant and anxiolytic effect depends on synergistic activation of melatonin receptors and antagonism of 5-HT_{2C} serotonin receptors (Guardiola-Lemaitre et al., 2014; Stahl, 2014). The beneficial effects of agomelatine against depression, anxiety, memory impairment and sleep disorder have been found both in animal models and in patients (reviewed in: Comai and Gobbi, 2014).

Numerous preclinical and clinical studies are in support of the hypothesis that melatonin can be used in seizure control and epilepsy (Bazil et al., 2000; Borowicz et al., 1999; Lapin et al., 1998; Lima et al., 2011; Rufo-Campos, 2002). In line with experimental results, clinical data confirm a potential efficacy of melatonin as a powerful antioxidant to be applied as an add-on option in the treatment of patients with epilepsy (Gupta et al., 2004). It has been suggested that low plasma levels

Abbreviations: KA, kainate acid; SE, status epilepticus; SMS, spontaneous motor seizures; OF, open field; EPM, elevated plus maze; LDT, light-dark test; RAM, radial arm maze test; PTZ, pentylenetetrazol; SHRs, spontaneously hypertensive rats; TLE, temporal lobe epilepsy; PB, phosphate buffer.

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Available online on ScienceDirect (www.sciencedirect.com).

http://dx.doi.org/10.1016/j.nbd.2017.04.017
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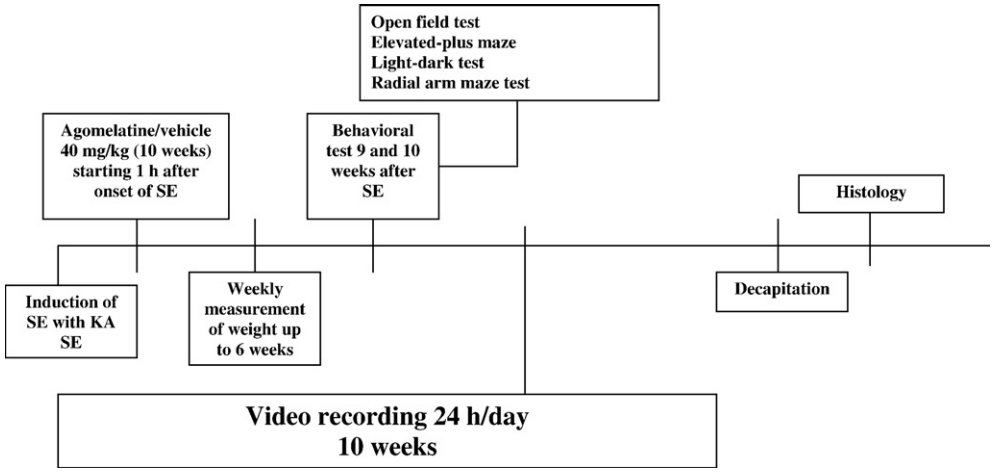

Fig. 1. Schematic illustration of the experimental protocol.

of melatonin in patients with epilepsy is a prerequisite for enhanced seizure activity while its delivery as an adjuvant to a conventional anticonvulsant therapy may be protective against repetitive seizures (Bazil et al., 2000). Previously, we found that a long-term treatment with melatonin after kainate (KA)-induced status epilepticus (SE) exerts strain-specific beneficial effects against the deleterious consequences of epileptogenesis (Tchekalarova et al., 2013; Petkova et al., 2014). Thus, this hormone was able to attenuate the progression of seizure activity and mitigate neuronal loss in the hippocampus and piriform cortex of spontaneous hypertensive rats (SHRs) with epilepsy (Petkova et al., 2014). However, unlike epileptic Wistar rats (Tchekalarova et al., 2013), melatonin failed to affect disturbed diurnal behavioral rhythms and impairment of spatial memory positively in a model of essential hypertension (Petkova et al., 2014) suggesting strain-specific activity. In addition, we have found a strain-dependent beneficial effect of chronic melatonin infusion against the KA-induced oxidative stress in the hippocampus (Atanasova et al., 2013). Status epilepticus-induced excessive release of free radicals is accepted as a prerequisite for the propagation and development of the epileptogenic process (Shin et al., 2011). The kainate acid-induced KA causes increased intracellular calcium leading to cascade of damaging processes such as mitochondrial membrane rupturing, release of proapoptotic factors and free reactive oxygen species (ROS), up-regulation of various enzymes leading to neuronal apoptosis (Srivastava et al., 2008). Several recent reports indicating the antioxidant effects of agomelatine in animal models suggest that this drug could be as potent as melatonin against seizure-induced oxidative stress (Demirdaş et al., 2016; de Mello et al., 2016; Yapca et al., 2014).

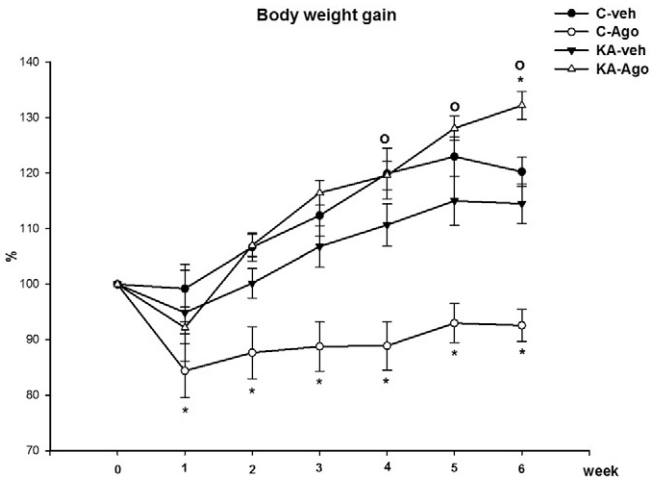

Fig. 2. Effect of kainate (KA)-induced status epilepticus (SE) and treatment with agomelatine on the body weight gain (%). Data are presented as means ± SE, $^{*}p < 0.05$ vs C-veh, $^{o}p < 0.05$ vs Ago-veh. Abbreviations in legends: C-veh (control group treated with vehicle); C-Ago (control group treated with agomelatine, 40 mg/kg for 10 weeks); KA-veh (KA group treated with vehicle); KA-Ago (KA group treated with agomelatine).

Agomelatine was shown to exert an anticonvulsant effect in pilocarpine and pentylenetetrazol (PTZ) seizure test in naive mice (Aguiar et al., 2012). NO/L-arginine pathway was suggested to contribute to the anticonvulsant effect of both agomelatine and melatonin against i.v. injected PTZ in mice (Dastgheib and Moezi, 2014; Yahyavi-Firouz-Abadi et al., 2006). Comparisons of potency demonstrated by agomelatine and melatonin in acute seizure tests support the suggestion that the effect of agomelatine might be due to both to melatonin MT_1/MT_2 and serotonin 5-HT_{2C} receptors (Aguiar et al., 2012; Costa-Lotufo et al., 2002; Yehuda and Mostofsky, 1993). Moreover, the anticonvulsant activity of agomelatine was apparent only after acute but not chronic treatment because of receptor desensitization (Dastgheib and Moezi, 2014). Since the melatonin effect seems to involve a specific mechanism of receptor internalization, it is suggested that the treatment protocol is crucial for an outcome efficacy of that hormone (Delagrange and Guardiola-Lemaitre, 1997; Witt-Enderby et al., 2003).

Neuronal loss in limbic structures, including the hippocampus, is an important indicator for the pathogenesis of neurodegenerative processes. It is accepted that the antioxidant and anti-inflammatory properties of melatonin underlie its protection against various neurodegenerative diseases. The hormone has also been reported to inhibit the apoptotic pathway in models of traumatic brain injury (Ding et al., 2015; Wu et al., 2016). In our previous studies, we reported that long-term treatment with melatonin alleviates the neuronal damage specifically in the CA1 area of the hippocampus and piriform cortex in both normotensive Wistar rats and SHRs with epilepsy (Tchekalarova et al., 2013; Petkova et al., 2014). On the other hand, chronic injection of agomelatine was found to prevent the hippocampus, septal dentate gyrus, temporal piriform cortex and basolateral amygdala from neuronal damage in rats in a model of pinealectomy (Tchekalarova et al., 2016).

Based on previous experimental and clinical studies confirming the anticonvusant potency of agomelatine in several screening seizure tests (Aguiar et al., 2012; Dastgheib and Moezi, 2014), from one site, and that its exerts a positive effect on behavioral abnormalities (Morley-Fletcher et al., 2011), from the other, we can suggest that this drug might represent a promising therapeutic tool targeting comorbid behavioral abnormalities as well as neuronal loss in epileptic state. The KA model of temporal lobe epilepsy (TLE) is proven as a relevant model for study of the pathological consequences of epileptogenesis and discovering a potential therapeutic treatment. In the present study, we aimed to study the ability of chronic agomelatine treatment