Role of melatonin on calcium signaling and mitochondrial oxidative stress in epilepsy: focus on TRP channels

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Abstract: Calcium ion ($Ca^{2+}$) accumulation and excessive oxidative stress in the hippocampus and brain cortex have long been known as major contributors to the etiology of epilepsy. I have reviewed the role of $Ca^{2+}$ signaling through cation channels and mitochondria-mediated oxidative stress on epilepsy in human and animals. A review of the relevant papers and results from recent studies were obtained from PubMed and the Science Citation Index. Current literature findings indicate that melatonin and agomelatine reduce activation of hippocampal transient receptor potential (TRP), glutamate receptors, and voltage-gated calcium channels that are critical for the development of abnormal $Ca^{2+}$ homeostasis and oxidative stress and associated mitochondrial dysfunction. In addition, low doses of melatonin induce anticonvulsant action through increase of GABA levels in the hippocampus and brain cortex. The accumulating evidence implicates a modulator role of melatonin on excessive oxidative stress products, plus mitochondrial and $Ca^{2+}$ dysregulations in epilepsy. The evidence indicates that modulation of oxidative stress and neuronal $Ca^{2+}$ handling occurs through effects on TRP channels, suggesting an increasingly viable approach for therapeutic interventions against epilepsy.

Key words: Calcium ion, epilepsy, oxidative stress, melatonin, transient receptor potential channels, mitochondria

1. Introduction
The incidence of epilepsy is high in neurological disorders and approximately 50 million subjects suffer worldwide from the disease. A major event in the etiology of epilepsy is increased excitability of neurons in various brain regions (Naziroğlu et al., 2013a; Yürekli and Nazıroğlu, 2013; Méndez-Armenta et al., 2014). There are different forms of epilepsy with varying etiology. Hence, the molecular pathways involved in the etiology of epilepsy are still unclear, although numerous studies of the subject have been performed (Naziroğlu et al., 2013a; Yürekli and Nazıroğlu, 2013; Méndez-Armenta et al., 2014). Treatment of epilepsy is only partially possible due to its unclear etiology. Currently available antiepileptic drugs provide only partial control of seizures (Cárdenas-Rodríguez et al., 2013; Demirci et al., 2013). The molecular targets of most of these antiepileptic drugs are ion channels such as glutamate receptors and oxidative stress-dependent activated transient receptor potential (TRP) channels that are thought to be partially responsible for epileptic seizures (Yılmaz et al., 2011; Nazıroğlu et al., 2012b; Nazıroğlu and Övey, 2015). For these reasons, the discovery of novel drugs to treat epilepsy would be highly desirable.

Oxidative stress is characterized as an imbalance between antioxidant defense systems and reactive oxygen species (ROS) and nitrogen reactive substances (Nazıroğlu, 2007). ROS production is a physiological process because ROS are generated during many aerobic physiological processes such as mitochondrial electron transfer and phagocytic action. The hippocampus has an important role in the etiology of epilepsy. Different brain areas including the hippocampus are ultimately susceptible to oxidative injury induced by extensive ROS production because they have relatively poor enzymatic antioxidant defense (Nazıroğlu, 2007). Sensitive targets of ROS in lipids are polyunsaturated fatty acids (PUFAs), and the brain contains a high amount of PUFAs (Özmen et al., 2007). The hippocampus is protected from oxidative damage by antioxidants (Nazıroğlu et al., 2015; Övey and Nazıroğlu, 2015). Enzymatic antioxidants such as glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) and nonenzymatic antioxidant defense systems such as vitamin E and glutathione exist in the hippocampus in order to scavenge ROS (Nazıroğlu, 2011, 2012). One of the main nonenzymatic antioxidants in the hippocampus is melatonin (N-acetyl-5-methoxytryptamine), which is a hormone produced and released by the pineal gland.
in association with the suprachiasmatic nucleus (Lee et al., 2006; Turgut et al., 2006). Intracellular ROS are scavenged by melatonin and its metabolites (Espino et al., 2012; Bejarano et al., 2014). Melatonin has been reported to modulate the L-type voltage-gated calcium channel (VGCC) channelopathies (Lee et al., 2006; Nazıroğlu, 2009; Choi et al., 2014), oxidative stress-activated TRPV1 and TRPM2 channels (Reuss et al., 2010; Nazıroğlu et al., 2012a), and glutamate receptors (Molina-Carballo et al., 2007). It is well known that the GABA neurotransmitter has an important role in the induction of epilepsy. Increased activation of glutamate receptors, VGCCs, and TRP channels are accompanied by a decrease in GABA level.

An overload of intracellular Ca\textsuperscript{2+} has an important role in epileptic seizures. Mitochondrial function is essential for neuronal survival because neurons critically depend on ATP synthesis produced by mitochondrial oxidative phosphorylation (Espino et al., 2012; Bejarano et al. 2014). Mitochondrial depolarization depends on intracellular Ca\textsuperscript{2+} and is fueled by Ca\textsuperscript{2+} entry from the extracellular space via TRP and N-methyl-D-aspartate (NMDA) channels when triggered by neuronal activity (Kumar et al., 2014; Tök et al., 2014; Yüรรึker et al., 2015). In addition to epileptic seizures, an overload of intracellular Ca\textsuperscript{2+} concentration in epilepsy induces ROS production, apoptosis, and caspase activations (Figure). Melatonin reduces ROS production and intracellular Ca\textsuperscript{2+} concentration through regulation of cation channels, preventing apoptosis (Molina-Carballo et al., 2007; Choi et al., 2014).

Current knowledge regarding the functional importance of melatonin for cation channels, oxidative stress, and mitochondrial depolarization of the hippocampus and brain cortex in epilepsy is still relatively sparse. Studies utilizing pharmacological usage of melatonin indicate that this antioxidant is not only an important element of hippocampal and brain cortex functions but may also play a protective role in epilepsy. In the review, I report on the most recent findings about the protective functions of melatonin against oxidative stress, mitochondrial functions, and calcium signaling through TRP channels in the hippocampus and brain cortex of epileptic animals and humans and discuss the possibility of its use as a potential drug for the treatment of epilepsy.

2. Melatonin, epilepsy, and Ca\textsuperscript{2+}

Epilepsy affects about 2%–3% of the population worldwide. It is characterized by seizure symptoms such as loss of consciousness, increased motor activity, and sensory phenomena occurring in brutal and short attacks according to the three forms of epilepsy characterized as idiopathic, symptomatic, and cryptogenic (Shorvon, 2011; Nazıroğlu, 2015). The genesis of epilepsy is associated with increased excitability of brain areas through an excessive depolarization of the brain areas (Nazıroğlu, 2015). Some of the factors that are thought to contribute to the genesis of the three epileptic forms include overload of Ca\textsuperscript{2+}, genetic defects, and oxidative stress (Méndez-Armenta et al., 2014; Romá-Mateo et al., 2015).

The intracellular Ca\textsuperscript{2+} concentration has an important influence on numerous physiological functions such as generation of action potentials, synaptic transmission, plasticity, and cell survival in neurons (Nazıroğlu, 2012; Kumar et al., 2014). Cation channels play a significant role in modulating intracellular Ca\textsuperscript{2+} concentrations in all cells, including neurons, because Ca\textsuperscript{2+} passes the cell membranes to enter the cytosol by way of these channels (Nazıroğlu, 2012; Kumar et al., 2014).

It is well known that physiological activity-dependent processes such as neurotransmitter release, cell death, and cytosolic signaling processes are also regulated by Ca\textsuperscript{2+} influx through neuronal VGCCs (Kumar et al., 2014). In healthy neurons, calcium channels regulate and activate homeostatic signaling processes. In presynaptic neurons, VGCCs are opened by action potential-induced depolarization and neurotransmitter release is dependent upon the Ca\textsuperscript{2+} influx that induces local domains of high Ca\textsuperscript{2+} concentration. In postsynaptic neurons, many signaling processes are regulated by changes in cytosolic Ca\textsuperscript{2+} concentration following Ca\textsuperscript{2+} entry through receptor-operated channels and L-type VGCCs. In epilepsy, the increased rate of action potential results in overload of Ca\textsuperscript{2+} entry through activation of VGCCs, although some antiepileptic chemicals such as pregabalin and topiramate induce antiepileptic effects though regulation of VGCCs (Nazıroğlu et al., 2009; Cárdenas-Rodríguez et al., 2013; Demirci et al., 2013), plasma membrane Ca\textsuperscript{2+}-ATPase activity (Nazıroğlu et al., 2008), and oxidative stress (Kutluhan et al., 2009). In addition, the antiepileptic drug melatonin also has a regulator role on VGCCs in both presynaptic and postsynaptic neurons. It was reported that inactivation of VGCCs and glutamate receptors in rat pinealocytes was induced by downregulation of melatonin (Kim et al., 2008; Choi et al., 2014). In addition, neurotransmitter release in rat hippocampus and PC12 neuronal cells was regulated by melatonin treatments (Choi et al., 2014). In an experimental temporal lobe epilepsy model, hippocampal injury and epileptic seizures were reduced by melatonin treatment (Tchekalarova et al., 2013).

There are changes in apoptotic factors such as glutamate-mediated excitotoxicity leading to changes in cytosolic Ca\textsuperscript{2+} metabolism, mitochondrial membrane abnormalities, and induction of oxidative stress in epilepsy (Nazıroğlu and Övey, 2015). At the cellular level, a large Ca\textsuperscript{2+} influx via VGCCs and NMDA-dependent calcium
channels results in huge seizure activities (Naziroğlu, 2009; Vimala et al., 2014). Following melatonin treatment in epilepsy, decrease in intracellular Ca\(^{2+}\) concentration through inhibition of VGCCs, TRP channels, and NMDA receptors promotes biochemical antioxidant cascades, resulting in decreased neuronal cell death (Yamamoto and Mohanan, 2003; Naziroğlu et al., 2015). This latter aspect will be the focus of the remaining sections of this review.

3. Melatonin and TRP channels

Molecules of the TRP family contain several transmembrane domains with four hydrophobic pores, which are located between the fifth and sixth transmembrane domains. In most TRP channels Ca\(^{2+}\) must cross the cell membrane through these pores nonselectively. There are 30 known mammalian TRP channels but new members of the family continue to be discovered. The activation and inhibition mechanisms are very different within the subfamilies. For example, TRPM8 is activated by menthol and environmental noxious cold (<15 °C), while TRPV1 channels are activated by different stimulants, including environmental high temperature (≥43 °C), oxidative stress, capsaicin, and inflammation (Naziroğlu, 2011; Naziroğlu et al., 2012b; Naziroğlu and Demirdaş, 2015). TRPA1 is activated by cinnamaldehyde of cinnamon oil, wasabi, garlic, and environmental vehicle exhaust gas (Kozai et al., 2014).

Expressions of the channels also differ in different tissues of body. For example, TRPV1 and TRPM2 channels are mostly expressed in the brain and neurons, while TRPC1 channels are mostly expressed in the cardiovascular system (Shenton and Pyner, 2014; Zhang and Liao, 2015). TRP channels have different cellular polymodal integrators that are sensitive to environment factors (Naziroğlu et al., 2012; Naziroğlu and Demirdaş, 2015).

There are limited reports on interactions between TRP channels and melatonin, but what is known is summarized in Table 1. Photosensitive retinal ganglion cells in the eye have an important role in regulating melatonin synthesis. Photosensitive retinal ganglion cells express melanopsin as a putative opsin-family photopigment and TRPC5 channels are regulated in the photosensitive retinal ganglion cells by melanopsin (Panda et al., 2005).

Excessive ROS production and intracellular Ca\(^{2+}\) concentration overload induce apoptosis and depolarization of mitochondrial membranes through activation of poly(ADP-ribose) polymerase-1 (PARP-1) enzyme activation and gating of mitochondrial permeability transition pores (Figure) (Naziroğlu, 2007). The regulator role of melatonin in apoptosis and mitochondrial depolarization was reported in human neutrophils (Espino et al., 2010, 2011a, 2011b). In a recent study we also reported the modulator role of melatonin on the apoptosis level and TRPM2 channel activity in a transfected Chinese hamster ovary cell line (Celik and Naziroğlu, 2012).

Electromagnetic radiation frequencies such as those used for mobile phones (900 MHz) and Wi-Fi (2.45 GHz) induce many toxic effects on neurons in animals and human. One of the toxic effects is oxidative stress. TRPM2 channels are activated by increased level of oxidative stress and ADP-ribose. Dorsal root ganglion (DRG) neurons have a modulator role in peripheral pain pathways. In a previous study, we investigated the

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<tr>
<td>TRPC3</td>
<td>Photosensitive retinal ganglion cells</td>
<td>Melanopsin is a putative opsin-family photopigment and TRPC3 channel is activated by melanopsin</td>
<td>Panda et al. (2005)</td>
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<td>Apoptosis and Ca(^{2+}) entry through inhibition of TRPM2 channels are modulated by melatonin incubations</td>
<td>Celik and Naziroğlu (2012)</td>
</tr>
<tr>
<td>TRPM2</td>
<td>Rat dorsal root ganglion (DRG) neuron</td>
<td>Wi-Fi frequency-induced oxidative stress level and TRPM2 channel and VGCC activations were reduced by melatonin treatment</td>
<td>Naziroğlu et al. (2012)</td>
</tr>
<tr>
<td>TRPM2</td>
<td>Traumatic brain injury (TBI)-induced rat hippocampus</td>
<td>TBI-induced apoptosis, caspase activation, intracellular ROS production, mitochondrial membrane depolarization, and TRPM2 channel activation were reduced by melatonin</td>
<td>Yürük et al. (2015)</td>
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<td>TRPV1</td>
<td>Rat pineal gland</td>
<td>TRPV1 stimulator capsaicin increased melatonin secretion from perfused pineal glands in a dose-dependent manner</td>
<td>Reuss et al. (2010)</td>
</tr>
<tr>
<td>TRPV1</td>
<td>Rat brain striatum neurons</td>
<td>Oxidative stress and mitochondrial enzyme complex were decreased by agomelatine</td>
<td>Gupta and Sharma (2014)</td>
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TRPC3, transient receptor potential canonical. TRPM2, transient receptor melastatin 2. TRPV1, transient receptor vanilloid 1.
The modular role of melatonin on Wi-Fi-induced oxidative stress in DRG neurons of rats, and Wi-Fi-induced TRPM2 channel activation was reduced in the rat DRG neurons by intraperitoneal melatonin treatment (Nazıroğlu et al., 2012a).

Traumatic brain injury (TBI) is characterized by injury involving mechanical trauma of the hippocampus, which is followed by secondary injury processes including apoptotic cell death, inflammation, oxidative stress, and Ca\(^{2+}\) dysregulation (Esposito and Cuzzocrea, 2010). Melatonin can modulate these processes via regulation of Ca\(^{2+}\) entry in TBI (Esposito and Cuzzocrea, 2010). In a recent study, we observed that TBI-induced apoptosis, caspase 3, caspase 9, intracellular ROS production, depolarization of mitochondrial membranes, and Ca\(^{2+}\) entry through TRPM2 channel activation were modulated in the hippocampus of TBI-induced rats by melatonin treatment (Yürüker et al., 2015).

In addition to capsaicin, vanillin is a selective stimulator of TRPV1 channels. Gupta and Sharma (2014) reported that levels of oxidative stress and mitochondrial enzyme complexes (I, II, and IV) in rat brain striatum were reduced in a rat model of Huntington disease induced by agomelatine treatment. Agomelatine is an agonist of melatonin receptors and vanillin (Aguiar et al., 2012, 2013).

Figure. ROS production can induce seizure activity through direct activation of glutamine synthetase, thereby permitting an abnormal buildup of excitatory neurotransmitter glutamate (Nazıroğlu, 2009). The TRPM2 channel is activated by ADP-ribose and oxidative stress. In addition to capsaicin, the TRPV1 channel is also activated by oxidative stress and is inhibited by capsazepine. Overload of intracellular Ca\(^{2+}\) induces mitochondrial injury and results in a decrease in the activities of mitochondrial complexes and ATP synthesis and a further increase in ROS production, caspase activity, apoptosis, and NMDA, TRPM2, and TRPV1 channel activation in the mitochondria. Hence, the mitochondrial depolarization level depends on Ca\(^{2+}\) in epileptic seizures and is fueled by Ca\(^{2+}\) entry from the extracellular space via TRPM2, TRPV1, and NMDA channels when triggered by neuronal activity. The molecular pathways of TRP channels may be a cause of epileptic seizures and thus represent a fruitful subject for further study.
The neuroendocrine modulator role and the regional distribution of a molecular marker of pineal synaptic ribbons in the pineal gland of rodents were investigated by Reuss et al. (2010). They observed that the TRPV1 stimulator capsaicin increased melatonin secretion from perfused pineal glands in a dose-dependent manner that was blocked by the TRPV1 blocker capsazepine (CPZ).

4. Role of melatonin in mitochondria and oxidative stress in epilepsy

ROS are frequent products of biological redox reactions and invariably those involving one-electron transfer processes. The ROS are produced by many physiological functions, such as phagocytic activity and mitochondrial electron transfer reactions. ROS production in an uncontrolled fashion causes important damage to a wide range of biological molecules, such as DNA, lipids, proteins, carbohydrates, or any nearby molecule causing a cascade of chain reactions resulting in neuronal damage and epilepsy (Nazıroğlu, 2009). Oxidative stress has been implicated in the genesis and progression of epileptic seizures (Nazıroğlu et al., 2008; Kutluhan et al., 2009; Demirci et al., 2013). The ROS in the neurons of epileptic animals and humans are controlled by antioxidants, including melatonin (Table 2).

A common feature in neuronal diseases is mitochondrial depolarization and injury through excessive production of oxidative stress and overload of Ca\(^{2+}\) entry. Mitochondrial injury induces a decrease in the activities of mitochondrial complexes and ATP synthesis and it induces a further increase in ROS production in the mitochondria. Thus, mitochondrial depolarization is triggered and fueled by Ca\(^{2+}\) entry from the extracellular space via TRP and NMDA channels when triggered by neuronal activity (Nazıroğlu, 2009; Kumar et al., 2014; Tök et al., 2014). Recently we reported that Ca\(^{2+}\) entry is involved in epilepsy and oxidative stress-induced hippocampal and DRG death through activation of TRPV1 channels, and negative modulation of this channel activity by CPZ pretreatment may account for the neuroprotective activity against oxidative stress (Ghazizadeh and Nazıroğlu, 2014). In our recent study we concluded that an overload in Ca\(^{2+}\) entry in the hippocampus of pentylentetrazol (PTZ) and TRPV1 agonist capsaicin-treated rats results in accumulation of ROS and opening of mitochondrial membrane pores that consequently leads to mitochondrial dysfunction, substantial swelling of the mitochondria with rupture of the outer membrane, and release of apoptosis-inducing factors such as caspase 3 and caspase 9 (Ghazizadeh and Nazıroğlu, 2014).

Melatonin is a strong mitochondrial ROS scavenger with minimal cytotoxicity in neuronal diseases including epilepsy (Bejarano et al., 2009; Acuña Castroviejo et al., 2002; Atanasova et al., 2013). It is well known that fat-soluble antioxidants such as melatonin, vitamin A, β-carotene, and vitamin E are primarily retained in cell membranes, including those of mitochondria, and melatonin targets the mitochondria particularly (Ekmeckioğlu, 2006; Martínez-Cruz et al., 2006; Bütün et al., 2015). On the other hand, melatonin possesses redox properties due to the presence of an electron-rich aromatic ring that allows the indole to function as an electron donor. Thus, through efficient removal of ROS, which are mainly formed in the mitochondria, melatonin effectively

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<tr>
<td>Rats</td>
<td>Cytosolic SOD/CuZn and mitochondrial SOD Mn increased but seizures and lipid peroxidation levels decreased in KA-induced epileptic rats</td>
<td>Atanasova et al. (2013)</td>
</tr>
<tr>
<td>Mice</td>
<td>Antioxidant role of agomelatine and melatonin through modulation of GABAergic systems and MT2 receptor in brain of pilocarpine and strychnine-induced epileptic mice</td>
<td>Aguiar et al. (2013)</td>
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<tr>
<td>Mice</td>
<td>Seizures, brain cortex lipid peroxidation, and mitochondrial DNA injury in KA-induced epileptic mice were decreased by melatonin treatment</td>
<td>Mohanan and Yamamoto (2002)</td>
</tr>
<tr>
<td>Rats</td>
<td>Epileptic seizures were not decreased in PTZ- and KA-induced epileptic rats by the melatonin treatment</td>
<td>Xu and Stringer (2008)</td>
</tr>
<tr>
<td>Rats</td>
<td>Latency development and nitroxyl radical level did not decrease in rats with flurothyl-induced seizure by melatonin treatment, although lipid peroxidation level was decreased in the rats</td>
<td>Mareš et al. (2013)</td>
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<tr>
<td>Children (1–16 years old)</td>
<td>Occurrences of epileptiform discharges were decreased in the children by melatonin treatment</td>
<td>Gustafsson et al. (2014)</td>
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PTZ, pentylentetrazol. SOD, superoxide dismutase. KA, kainic acid.
reverses mitochondrial oxidative stress (Ekmekcioglu, 2006; Espino et al., 2012).

Agomelatine is a novel melatonergic antidepressant drug and it is a blocker of melatonin receptors (MT1 and MT2). In addition to its antidepressant role, the drug has anticonvulsant effects (Aguiar et al., 2012). The results of a recent study indicated that agomelatine with or without melatonin exerts antioxidant roles through modulation of GABAergic systems and effects on the MT2 receptor in the brains of pilocarpine- and strychnine-induced epileptic mice (Aguiar et al., 2013).

Epilepsy is characterized by cellular changes including greatly increased Ca\(^{2+}\) entry, mitochondrial membrane depolarization, cytosolic enzyme activations, and excessive production of ROS. Melatonin as a strong antioxidant was an effective anticonvulsant in intractable epilepsy patients (Molina-Carballo et al., 1997). Plasma melatonin was also decreased in epileptic patients by epileptic and febrile convulsions (Molina-Carballo et al., 1994). The results of clinical and experimental investigations indicated a close relationship between melatonin and epileptic seizures through modulation of mitochondrial oxidative stress (Mohanand Yamamoto, 2002; Atanasova et al., 2013). It was reported that acute latency for onset of the first seizure, lipid peroxidation in the hippocampus, and mitochondrial Mn SOD were decreased in rats with KA-induced status epilepticus by long periods (10 mg/kg per day for 14 days) of melatonin treatment but the melatonin treatment did not prevent the development of a chronic epileptic state in the rats (Atanasova et al., 2013). High dosage, but for a short period (20 mg/kg for single dose), of melatonin treatment decreased the seizures and attenuated lipid peroxidation in the brain cortex and mitochondrial DNA injury in KA-induced epileptic mice (Mohanand Yamamoto, 2002; Yamamoto and Mohanan, 2003). Anxiogenic activity of diazoxon and the level of brain lipid peroxidation were decreased in rats by oral melatonin (10 mg/kg) treatment, although GSH-Px activity was increased by the treatment (Ahmed et al., 2013). In contrast, epileptic seizures were not decreased in PTZ- and KA-induced epileptic rats by melatonin treatment (20 mg/kg for a single dose), although Trolox, vitamin C, and alpha-lipoic acid induced anticonvulsant activity in pilocarpine-induced epileptic rats (Xu and Stringer, 2008). It was reported that development of latency and the level of nitroxy radical did not decrease in rats with flurothyl-induced seizure by intraperitoneal (100 mg/kg) melatonin treatment, although the lipid peroxidation level was decreased in the rat (Mare\' et al., 2013). The occurrence of epileptiform discharges was decreased in children (1–16 years old) with sleep deprivation by melatonin treatment (Gustafsson et al., 2015).

Melatonin production increased in patients with untreated complex partial epilepsy. Hence, overproduction of melatonin was possibly an attempt by the brain to produce a natural downregulator of cerebral epileptiform activity (Yalin et al., 2006; Vimala et al., 2014). The results of accumulative reports indicate that high doses of melatonin stimulated epileptic seizures through decrease in brain GABA levels, although low doses of melatonin induced anticonvulsant actions through increase in GABA concentrations in the brain cortex and hippocampus. The proconvulsive effects of melatonin are associated with the decrease in brain GABA levels (Molina-Carballo et al., 2007; Banach et al., 2011; Vimala et al., 2014). All in all, these various findings point to a potential role of melatonin in epilepsy.

5. Conclusion and future directions
The current literature provides support for a belief in a modulator role of melatonin in mitochondrial depolarization, intracellular calcium signaling, and oxidative stress in epilepsy and reveals potential novel targets for anticonvulsant drug development. In addition, however, the results of recent studies indicate that high doses of melatonin can be proconvulsant by bringing about a decrease in brain GABA levels. Nevertheless, low doses of melatonin have anticonvulsant activity through increase of GABA levels in the hippocampus and brain cortex. It seems that low doses of melatonin produce anticonvulsant effects by supporting cellular antioxidant systems and GABA levels while protecting against mitochondrial oxidative stress and excessive Ca\(^{2+}\) entry.

Increased Ca\(^{2+}\) entry and excessive oxidative stress play important roles in the induction of epilepsy and some TRP channels such as TRPM2 and TRPV1 are activated by oxidative stress. The results of recent studies report a critical role of melatonin in regulation of oxidative stress in neurons of epileptic animals. Recently we observed a modulatory role of melatonin on inhibition of TRP channels such as TRPM2 and TRPV1 in the DRG neurons and hippocampus of rats ( Naziro\'glu et al., 2012; Yur\'uk et al., 2015). To my knowledge, there is no study on the roles of melatonin in epileptic animals and neurons. Hence, investigation of the role of TRP channels including TRPM2 and TRPV1 channels in epileptic animals would be a very valuable line of inquiry particularly with respect to possible modulation by melatonin.

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