

Do minocycline and other suppressors of microglia reactivity have a future in prevention or treatment of epilepsy?

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SUMMARY

Introduction. An increasing body of evidence points to an important role of neuroinflammatory processes in the pathomechanism of epilepsy. This hypothesis is mainly supported by data showing an increase of pro-inflammatory cytokine levels and glia activation in animal models of epilepsy and in brain tissue of epileptic patients. On the other hand, less emphasis has been put on pharmacological verification of this hypothesis.

Aim. The aim of this review is to summarize current knowledge on potential usefulness of microglia regulators and anti-inflammatory agents in designing antiepileptic/antiepileptogenic drugs, with the primary mechanism of action based on the inhibition of neuroinflammation.

Methods. We reviewed PubMed and MEDLINE databases to select publications in the topic: epilepsy, neuroinflammation, microglia and microglia regulators with antiepileptic properties. We searched the databases up to April 2017 with no date restrictions.

Review and Discussion. In the present paper, we will discuss new concepts of epileptogenesis which focus not only on changes in neurons but also take into consideration the role of activation of glial cells: microglia and astrocytes. Neuroinflammation, mainly through increased production of pro-inflammatory factors such as cytokines or chemokines, may play an important role in the development of epilepsy. Drugs regulating glial cells activation and consequently inflammatory status in the central nervous system have beneficial effects in different animal models of epilepsy as well as in clinical study in patients. The most promising compound seems to be minocycline which in some studies has been shown to possess antiepileptogenic action. On the other hand, some antiepileptic drugs exhibit marked anti-inflammatory potency.

Conclusions. There are much data to suggest that there is significant opportunity for designing new antiepileptic drugs whose primary mechanism of action entails the inhibition of neuroinflammatory processes.

Key words: epilepsy • neuroinflammation • microglia • anti-inflammatory/antiepileptic drugs

INTRODUCTION

An increasing body of evidence points to an important role of neuroinflammatory processes in the pathomechanism of epilepsy (Kwon et al., 2013). This hypothesis is mainly supported by data showing an increase of pro-

inflammatory cytokine levels and glia activation in animal models of epilepsy and in brain tissue of epileptic patients (Aloisi, 2001). On the other hand, less emphasis has been put on pharmacological verification of this hypothesis.

AIM

The aim of this review is to summarize current knowledge on potential usefulness of microglia regulators and anti-inflammatory agents in designing antiepileptic/antiepileptogenic drugs, with the primary mechanism of action based on the inhibition of neuroinflammation. Modulatory effects of already marketed antiepileptic drugs on neuroinflammation and possible significance of this component in their efficacy and undesired effects will be also briefly discussed.

METHODS

We reviewed PubMed and MEDLINE databases to select publications in the topic: epilepsy, neuroinflammation, microglia and microglia regulators with anti-epileptic properties.

REVIEW AND DISCUSSION

New concepts of epileptogenesis

Epileptogenesis can be defined as a dynamic and progressive process evoking changes in excitability and transformation of neuronal networks, which finally lead to repeated and spontaneous seizures (Majkowski, 1994; Lowenstein, 1996). This process includes neurogenesis, gliosis, axonal sprouting, dendritic plasticity, blood-brain barrier (BBB) damage, neuroinflammation, and the reorganization of extracellular matrix as molecular structure of neurons (Pitkänen and Lukasiuk, 2009; Pitkänen and Lukasiuk, 2011). In contrast to older views on pathomechanisms of epileptogenesis and epilepsy which took into account biochemical and morphological alterations almost exclusively in neuronal system, more recent hypotheses emphasize a key role of the interaction between glia and neuronal cells in these phenomena (Vezani, 2015). These new hypotheses are strongly supported by advances in our understanding of gliotransmission. Calcium-dependent gliotransmission in concert with neuronal activity participate in creating excessive hypersynchronization and epileptogenic circuits (Carmignoto and Haydon, 2012). Glutamate released from neurons activates metabotropic glutamate receptors in astrocytes, thereby increasing intracellular calcium ion influx in these cells. The increase in cytosolic calcium level can in turn enhance glutamate release from astrocytes, which affects neuronal excitability (Carmignoto and Haydon, 2012). Besides glutamate, gliotransmitters comprise many other neuronally active modu-

lators, e.g. D-serine, adenosine triphosphate (ATP), adenosine, g-amino-butyric acid (GABA) and tumor necrosis factor- α (TNF- α). It should be emphasized that astrocytes synthesize GABA from putrescine, then this inhibitory amino acid is released via the reverse action of GABA-transporter 2 (GAT2) and GABA-transporter 3 (GAT3) and exerts tonic suppressive effect on firing of neuronal circuits (Heja et al., 2012). It has been postulated that epileptic seizures result from high-frequency pathological calcium waves produced by astrocyte syncytium (Heinemann et al., 1999). This effect leads to synchronization of neuronal discharges and enhanced release of excitatory neurotransmitters which, further stimulates generation of calcium waves in astrocytes. Thus, the extent and characteristics of astrocytic syncytium will determine the type of epileptic fits (White et al., 1986; Heinemann et al., 1999). A substantial body of evidence supports an important role of astrocytes in the pathomechanism of epilepsy. Astroglial syncytium in the hippocampus following seizure-induced injury has been well described (Borges et al., 2003). Astrocytes synchronize action potentials and preserve ionic homeostasis via redistribution of potassium ions from fields with high neuronal activity to the areas where concentrations of these ions are low, and take up water through potassium channel (Kir4.1) and aquaporin-4 water channel (AQP4). Moreover, they remove excitatory transmitters from extrasynaptic space, take part in glucose metabolism and regulate blood vessel tension. It has been found that "epileptic" tissue from patients with TLE (Temporal Lobe Epilepsy) or from animal models of TLE showed changes in expression, localization and function of astroglial potassium channels, especially Kir4.1, compromising potassium ion buffering capacity. Furthermore, changed water channel expression, dysfunctional glutamate transporters and glutamine synthase have also been detected in the epileptic tissue (Steinhäuser et al., 2012; Seifert and Steinhäuser, 2013). Experimental AQP4 „knock-out” animals expressed more frequent and severe kainate-induced seizures (a TLE model) than wild type animals (Lee et al., 2012). Astroglial and transforming growth factor β (TGF- β 1) signaling pathway can also play a crucial role in epileptic changes related to BBB damage (Heinemann et al., 2012). Besides, Eid et al. (2008) suggested that loss of glutamine synthase activity, which metabolizes glutamate in astrocytes could contribute to early stages of epileptogenesis. Of other gliotransmitters, the role of

adenosine insufficiency in seizures should be emphasized. Specifically, it has been shown that local disturbances in adenosine homeostasis in mice with subclinical focal seizures induced generalized seizures (Li et al., 2008). Adenosine, a putative endogenous anticonvulsant is metabolized by adenosine kinase (ADK). Interestingly, epileptogenesis was observed to be associated with astrogliosis and overexpression of ADK, which led to reduction in adenosine level and generation of focal seizures. ADK-overexpressing transgenic mice are more susceptible to seizures and seizure-induced brain injury, whereas ADK inhibitors suppressed seizures. Moreover, intrahippocampal implants of stem cells devoid of ADK prevented epileptogenesis (Boison, 2008). Microglia cells originating from erythromyeloid progenitors are resident immune cells of the central nervous system (CNS) with phagocytic capacity (Ginhoux et al., 2010). Their function depends on specific phenotypes and activity states. M1 microglia originally respond to the injury and infection, and act as the first line to defend tissue and promote the destruction of pathogens. They also induce neurotoxicity due to the release of pro-inflammatory factors and various neurotoxic mediators. After the onset of classical activation, an anti-inflammatory and repair phase is rapidly initiated that leads to wound healing and brings back tissue homeostasis. M2 microglia are the major effector cells with the potential to dampen pro-inflammatory immune responses and promote the repair genes expression (Tang and Le, 2016). Classically activated microglia M1 express TNF- α interleukin-1 β (IL-1 β), interleukin-18 (IL-18) and inducible nitric oxide synthase (iNOS) which has pro-inflammatory effect. The alternatively activated M2 were characterized by expression of AR-1, interleukin-1 receptor (IL-1R α), IL-4 and IL-13 genes which inhibited inflammation. The M2 phenotype called “acquired deactivation” showed enhanced expression of IL-4R α , IL-10 and TGF- β 1 genes and also had anti-inflammatory effect, whereas microglia M2 with enhanced expression of brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), nerve growth factor (NGF), found in inflammatory zone 1 (FIZZ) and chitinase 3-like 3 (YM-1) genes take part in tissue reparation. The functional role of microglia consists not only in disposing of dead cells and cell debris during inflammation but also in taking in and removing less active synapses in the healthy brain (Paolicelli et al., 2011; Schafer et al., 2012). Recently, microglia have been shown to phago-

cytose apoptotic newborn cells in the subgranular zone of the dentate gyrus regulating, in this way, neurogenesis in the adult brain (Sierra et al., 2010). Thus, microglia communicating with neuronal cells via cytokines, purines, prostaglandins, nitric oxide, BDNF and other mediators, appear to play an essential role in regulating synaptic reorganization and maintaining neuronal circuit homeostasis. Resident microglial and astroglial cells show antigen-presenting properties and produce pro-inflammatory cytokines, such as TNF- α , IL-1 β and interferon- γ (IFN- γ), as well as chemokines, promoting T lymphocyte infiltration into the damaged brain tissue (Aloisi, 2001). A large body of evidence indicates an autoimmune mechanism of epilepsy (Fang et al., 2017). An involvement of microglia and lymphocytes T in Rasmussen’s disease has been well documented (Varadkar et al., 2014). Other epileptic syndromes induced by humoral response of the immune system, e.g. antibodies against glutamate receptor subunits and other neuronal proteins have also been described (Matsuura et al., 2017).

Neuroinflammation and epilepsy

Neuroinflammation is thought to be a complex immune response of the nervous system to viral and bacterial infections, autoantibodies, toxins, hypoxia, trauma, excitotoxic and other damaging agents. Both innate and adaptive immune system, represented by resident glia and peripheral leukocytes infiltrating brain tissue, respectively, are involved in neuroinflammatory processes. In chronic neurological disorders, neuroinflammation can be perceived as an adaptive reaction which curbs the extent of tissue damage, helps to maintain homeostasis and facilitates regeneration. On the other hand, exaggerated inflammation can exacerbate pathological changes in the (CNS) and contribute to aggravation of neurological diseases, including epilepsy (Legido and Katsetos, 2014). Epileptogenic insults activate microglia and astrocytes leading to increased production of pro-inflammatory agents, thus further enhancing neuroinflammation (Vezzani, 2015). Indeed, in brain tissue of epileptic patients, an increase of inflammatory agents, such as IL-6 and IL-1 β , complement cascade factor C1q and TNF- α was detected (Lorigados et al., 2013; Wyatt et al., 2017). Also in animal models of epilepsy and/or status epilepticus, release of pro-inflammatory cytokines, e.g. IL-1 β , TNF- α and platelet activating factor (PAF) was enhanced. A role of other inflammatory agents, especially fractalkine,

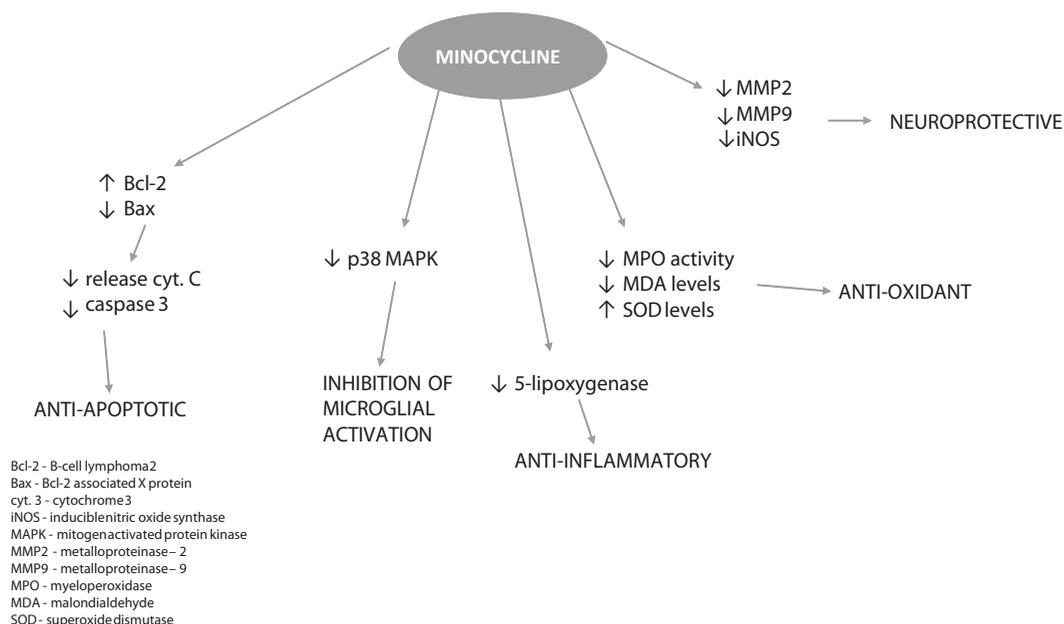


Figure 1. Biochemical mechanisms of anti-oxidant, anti-inflammatory, antiapoptotic and neuroprotective properties of minocycline.

IL-1R/TLR, HMGB1, and RAGE is being investigated (Vezzani, 2015). In neuroinflammatory hypothesis of epilepsy, much attention is paid to the interaction not only between astrocytes, microglia and neurons, but also to the interaction of glia with endothelial cells which are an essential part of BBB. Results of experimental studies showed that excessive permeability of BBB could promote development of epileptic focus, whereas inhibition of leukocyte infiltration to the brain prevented seizures, at least in the animal model of limbic epilepsy (van Vliet et al., 2015). Other pre-clinical data suggest that seizures can accelerate inflammatory processes in the brain through enhancement of pro-inflammatory protein gene transcription or posttranslational changes regulating cytokine release. Besides the classical cytokines, also pro-inflammatory chemokines, which are chemotactic factors controlling leukocyte migration to the brain parenchyma, may be involved in epileptogenesis (Fabene et al., 2010). On the other hand, there are also reports which postulate that the mechanisms of epileptogenesis can be independent of immune and inflammatory processes (Park et al., 2015). Despite these controversies and limited experimental data, one can suggest that, at least in some forms of epilepsies or steps of epileptogenesis, neuroinflammation can play a significant role.

Antiepileptogenic effects of minocycline

It has been proven that activated microglia M1 release pro-inflammatory cytokines, such as IL-1 β , IL-6 and TNF- α decrease seizure threshold and provoke seizures in several animal models. At least some of these changes can have functional significance, because an IL-1 β antagonist decreased intensity of seizures. Apart from antagonists of a particular pro-inflammatory cytokine, less selective substances which attenuate microglia M1 activity can be considered as potential anticonvulsants. Minocycline is a tetracycline antibiotic, which besides its antibacterial action is known to inhibit microglia activity (Mishra and Basu, 2008), and possess anti-apoptotic, anti-inflammatory and anti-oxidant properties (Figure 1). The above-mentioned effects provide a rationale for using minocycline in the treatment of some neurological disorders connected with enhanced microglia reactivity, e.g. chronic pain and epilepsy. Indeed minocycline was shown to be effective in suppressing seizures in several acute and chronic animal models of seizures (Table 1). Wang et al. (2012) compared anticonvulsant effect of three tetracycline antibiotics possessing anti-apoptotic and anti-inflammatory action, i.e. minocycline, doxycycline and tetracycline, in animal models of acute seizures. It was found that all studied antibiotics abrogated partial seizures in the mouse 6-Hz seizure test, however, high doses

Table 1. Different effect of minocycline administration in animal models of epilepsy

Epilepsy model	Effect	Type of treatment (dose, route of administration)	Reference
The maximal electric shock (MES), 6 Hz (minimal clonic seizure) test, subcutaneous Metrazol (scMET) administration	<ul style="list-style-type: none"> abolished partial seizures in a model of 6 Hz seizure test no effects in the maximal electric shock (MES), and subcutaneous Metrazol models 	Intraperitoneal injection; doses: 75 mg/kg, 100 mg/kg, and 150 mg/kg	Wang et al., 2012
Amygdala kindling	<ul style="list-style-type: none"> reduced afterdischarges and seizures duration 	Intraperitoneal injection; doses: 12.5, 25 and 50 mg/kg	Beheshti Nasr et al., 2013
Subconvulsive dose of pentylenetetrazol (PTZ; 37.5 mg/kg)	<ul style="list-style-type: none"> decreased development of seizures and their duration prevented increases in expression of NMDA and GABA receptor subunits, prevented increases in TNF-α expression 	dose: 25 mg/kg	Ahmadirad et al., 2014
Kainic acid (0.4 μ l, 1 mg/ml injection to hippocampus)	<ul style="list-style-type: none"> reduction of seizure-related cell death inhibition of caspase-dependent and independent apoptotic pathways 	Intraperitoneal injection; dose: 45 mg/kg	Heo et al., 2006
Kainic acid (20 mg/kg, intraperitoneal injection)	<ul style="list-style-type: none"> reduced early life seizure-induced microglial cell activation prevented the priming effect of early-life seizures 	Intraperitoneal injection; dose: 20 mg/kg (6-day treatment)	Abraham et al., 2012
Kainic acid (30 mg/kg, intraperitoneal injection)	<ul style="list-style-type: none"> inactivated microglial cells increased the number of newborn cells in dentate gyrus 	Intraperitoneal injection; dose: 75 mg/kg first injection, after 50 mg/kg (4-day treatment)	Luo et al., 2016
Kainic acid (2 mg/kg, intraperitoneal injection)	<ul style="list-style-type: none"> augmented sympathetic responses 	Intrathecal infusion; dose: 100 μ g/10 μ l	Bhandare et al., 2015
Lithium-pilocarpine (lithium chloride 127 mg/kg 18 h before pilocarpine 40mg/kg, intraperitoneal injections)	<ul style="list-style-type: none"> inhibited microglial activation inhibited of interleukin-1β and tumor necrosis factor-α production of in the hippocampal CA1 and the adjacent cortex no effect on astrocytic activation prevented the neuronal loss reduced the frequency, duration, and severity of spontaneous recurrent seizures 	Intraperitoneal injection; dose: 45 mg/kg (14-day treatment)	Wang et al., 2015
Electrical stimulation	<ul style="list-style-type: none"> no effect on the development of spontaneous seizures reduced hyperactivity, hyperlocomotion and the spatial learning deficits observed in the post-status epilepticus period protected neurons in the piriform cortex and the hilus, but not in the hippocampal pyramidal layer 	Intraperitoneal injection; 0–1 day dose: 50 mg/kg (twice a day), 2–13 day dose: 25 mg/kg (once daily)	Russmann et al., 2016
Theiler's murine encephalomyelitis virus infection	<ul style="list-style-type: none"> reduced number of the viral infection-related seizures 	Intraperitoneal injection; 0–8 day dose: 50 mg/kg (twice a day)	Libbey et al., 2011
Theiler's murine encephalomyelitis virus infection	<ul style="list-style-type: none"> reduced infiltration of macrophages into the CNS reduced the number of mice with acute seizures 	Intraperitoneal injection; dose: 50 mg/kg (twice a day)	Cusick et al., 2013
Tuberous sclerosis complex (TSC)	<ul style="list-style-type: none"> prevented the increase in number and cell size of microglia no effect on astrocyte proliferation, cytokine/chemokine expression and the progression of seizures 	Intraperitoneal injection; dose: 50 mg/kg for 1 week/4 weeks or up to 12 weeks 1 mg/kg, 10 mg/kg or 50 mg/kg for 1 week	Zhang et al., 2016

close to those considered toxic had to be used. On the other hand, these antibiotics showed no effects in the maximal electroshock seizure (MES) model and subcutaneous Metrazol tests (Wang et al., 2012). A support for antiepileptogenic properties of minocycline came from experiments with electrically and chemically-induced kindling. Thus, intraperitoneal injection of minocycline at doses of 25 and 50 mg/kg significantly reduced afterdischarges and duration of seizures induced by amygdala kindling in rats (Beheshti et al., 2013). Also, pretreatment but not posttreatment with minocycline at a dose of 25 mg/kg decreased development and duration of seizures induced by administration of a sub-threshold dose of pentylenetetrazol (PTZ; 37.5 mg/kg) in mice on every other day. Moreover, in this model, minocycline prevented the increases in expression of not only NMDA and GABA receptor subunits, but also an important inflammation marker, i.e. expression of TNF- α receptor in the hippocampus and piriform cortex (Ahmadirad et al., 2014). Kainic acid-induced seizures are an established animal model of temporal lobe epilepsy associated with neuronal degeneration mainly in the limbic system structures. When kainic acid was co-administered intrahippocampally with minocycline in mice, the seizure-related cell death was reduced. Further biochemical analysis revealed that blockage of both caspase-dependent and -independent apoptotic pathways played an important role in the neuroprotective mechanism of minocycline effects (Heo et al., 2006). Minocycline was also successfully employed in the kainic acid model for providing evidence on the role of the innate immunity in mediating the long-term epileptogenic effects of early-life seizure. Animals pretreated with kainic acid to induce status epilepticus not only responded with greater microglial activation to “the second hit” of KA, but showed a shorter latency to express seizures (Abraham et al., 2012). Status epilepticus is known to stimulate neurogenesis in dentate gyrus resulting in the increase in newborn granule cells which were characterized by abnormal maturation, anomalous axonal sprouting and ectopic localization (Jessberger et al., 2007; Kron et al., 2010; Parent et al., 2006; Scharfman et al., 2000). The functional significance of the above neuroplastic changes remains unknown. Nevertheless, Jung et al. (2004) found that eradication of newborn granule cells after status epilepticus attenuated spontaneous recurrent seizures, whereas Jakubs et al. (2006) postulated that the newborn granule cells were built in the dentate circuitry and

played a compensatory role in restoring seizure inhibition. Thus, it is believed that the selective annihilation of status epilepticus-induced newborn granule cells is critical for homeostasis of the dentate circuitry. Recently, Luo et al. (2016) reported that microglia removed excess newborn cells in the subgranular zone of the dentate gyrus after kainic acid-induced status epilepticus in mice via primary phagocytosis. Moreover, they found that minocycline-induced silencing of microglia maintained the increase in the number of newborn cells in dentate gyrus in this model of epilepsy (Luo et al., 2016). It was also shown that inflammatory cytokine secretion from microglia mitigated progenitor cell proliferation after status epilepticus (Matsuda et al., 2015). These studies support the hypothesis that the selective elimination of newborn granule cells after status epilepticus by microglia is pivotal to the homeostasis of dentate circuitry. Besides kainic acid, pilocarpine-induced seizures in mice and rats are the most popular model of temporal lobe epilepsy. Systemic administration of pilocarpine at high doses or lithium and pilocarpine evokes recurrent limbic seizures followed by silent 2–3 week period (epileptogenesis), after which spontaneous seizures occur (epilepsy). In order to find out whether inflammatory signaling elicited by prolonged seizures can be implicated in neuronal injury as well as in the development of spontaneous recurrent seizures, Kwon et al. (2013) employed a cocktail of anti-inflammatory drugs to modify seizure-related changes in the pilocarpine model. Interestingly, in immature rats the administration of either IL-R antagonist, COX-2 inhibitor or minocycline alone had no effect on morphological and behavioral changes in this model, whereas binary combinations of these drugs reduced development of spontaneous recurrent seizures and curtailed CA1 hippocampal neuronal damage and mossy fiber sprouting. The authors concluded that targeting multiple inflammatory signaling pathways for a limited time after status epilepticus may provide a practical approach to neuroprotection and anti-epileptogenic therapy (Kwon et al., 2013). It has been postulated that by activating inflammatory responses and increasing neuronal excitability in the cardiovascular nuclei of the medulla oblongata, seizures can lead to sudden unexpected death in epilepsy (SUDEP). Intrathecal infusion of the microglia antagonists, minocycline and doxycycline augmented sympathetic responses to kainic acid-induced seizures. It was suggested that the protective effect of microglia oc-

curs when the cells assume an M2 phenotype and express factors, such as TGF- β and IL-10 that promote neuronal quiescence (Bhandare et al., 2015). In a rat lithium-pilocarpine model of temporal lobe epilepsy, minocycline administered once daily at 45 mg/kg for 14 days following status epilepticus suppressed the microglial activation and elevated production of interleukin-1 β and TNF- α in the hippocampal CA1 and adjacent cortex, without affecting astrocytic activation. Furthermore, minocycline counteracted the neuronal loss and reduced the frequency, duration, and severity of spontaneous recurrent seizures (Wang et al., 2015). It is of note that rats which develop chronic epilepsy following pilocarpine-induced status epilepticus reveal a set of interictal disorders consistent with depressive-like behavior. It was reported that pilocarpine-induced seizures led to induction of IL-1 β and IL-6 expression and further up-regulation of indoleamine 2,3-dioxygenase 1 (IDO1), a rate-limiting enzyme in tryptophan metabolism, in the hippocampus. The blockade of this enzyme activity by minocycline indirectly protected the animals from development of depressive-like behavior but failed to influence spontaneous seizures. It was concluded that minocycline can indirectly normalize kynurenine/tryptophan and serotonin/tryptophan ratios and that brain IDO1 activity plays a key role in epileptic rats with epilepsy-associated depressive-like behavior (Xie et al., 2014).

Another interesting animal model of epilepsy is based on seizures induced by the Theiler's murine encephalomyelitis virus infection accompanied by enhanced production of interleukin-6. It was reported that C57BL/6 mice treated with minocycline, which affects monocytes/macrophages, microglial cells, and polymorphonuclear leukocytes, manifested a significantly reduced number of the viral infection-related seizures (Libbey et al., 2011). Further study showed that in the mice which developed seizures, the pathological changes in minocycline-treated and IL-6-deficient chimeric mice were very similar (Libbey et al., 2011a). The same research team demonstrated that the complement system within the CNS played a crucial role in the induction of acute seizures during viral encephalitis. They observed that mice deficient in complement component C3 within the CNS, but not in the periphery, developed significantly less behavioral seizures following TMEV infection (Libbey et al., 2010). Although TNF- α and IL-6 have been linked to the development of acute seizures in the Theiler's murine encephalomyelitis vi-

rus-induced encephalitis, the immune cells which were mostly implicated in this effect remained largely unknown. However, the study by Cusick et al. (2013) shed some light on this problem by demonstrating that minocycline or wogonin was able to reduce both infiltration of macrophages into the CNS and the number of mice with acute seizures in Theiler's murine encephalomyelitis virus-induced encephalitis. These results support the hypothesis that infiltrating macrophages are an important source of IL-6 that contributes to the development of acute seizures (Cusick et al., 2013).

It should be emphasized that not all reports confirmed a potential anti-epileptogenic activity of minocycline. In contrast to chemically induced status epilepticus, minocycline failed to exert anti-epileptogenic effects in a rat with status epilepticus elicited by electrical stimulation. Thus, sub-chronic minocycline administration was not able to block the development of spontaneous seizures, but did reduce hyperactivity and hyperlocomotion and alleviated spatial learning deficits observed in the post-status epilepticus period. Interestingly, in that study, minocycline protected neurons in the piriform cortex and the hilus, but not in the hippocampal pyramidal layer. These findings highlight a significant potential of minocycline to modify development of behavioral co-morbidities following status epilepticus (Russmann et al., 2016). Zhang et al. (2016) evaluated microglial activation in a mouse model of tuberous sclerosis complex (TSC), which is a genetic disorder, characterized by tumor growth in multiple organs and severe neurological disorders, including epilepsy. They found that mice with conditional inactivation of the *Tsc1* gene mostly in glial cells (*Tsc1*GFP CKO mice) showed age-dependent increase in the number of cortical and hippocampal microglia cells correlated with the onset of seizures. Minocycline prevented the rise in the number and size of microglia cells, but had no effect on astrocyte proliferation, cytokine/chemokine expression and seizure progression in *Tsc1*GFP CKO mice. It was concluded that additional studies are needed in other animal models and in human trials to determine whether microglia are critical for epileptogenesis in TSC (Zhang et al., 2016).

Antiepileptic effects of other inhibitors of neuroinflammation

Cyclooxygenase 2 (COX-2) expression in the brain is enhanced by seizures and this enzyme has been implicated in seizures-related neuroinflammatory pro-

cesses. It was reported that a COX-2 inhibitor celecoxib decreased seizure frequency and duration in the pilocarpine model of status epilepticus and attenuated neurodegeneration in that model (Jung et al., 2006). In contrast, parecoxib had no effect on seizure frequency and duration of in the same model, but attenuated seizure intensity (Polascheck et al., 2010). Another COX-2 inhibitor, SC58236 had no effect on seizure development in an electrical model of temporal lobe epilepsy (Holtman et al., 2009). On the other hand, the selective COX-2 inhibitor etoricoxib attenuated development of spontaneous nonconvulsive seizures in WAG/Rij rats, i.e. a well-recognized model of absence epilepsy (Citraro et al., 2015). Antagonists of pro-inflammatory prostaglandin receptors were proposed as an adjunct therapeutic strategy for prevention of neuroinflammation and neurodegeneration evoked by status epilepticus. In particular, a potent and selective antagonist of the prostaglandin E2 receptor subtype EP2 reduced brain inflammation, prevented BBB injury, and had neuroprotective effect in the hippocampus, without acute modification of seizures following pilocarpine-induced status epilepticus (Jiang et al., 2013). Inhibition of leukocyte adhesion using anti-integrin $\alpha 4$ monoclonal antibody reduced seizures frequency, BBB damage, neuronal degeneration and improved behavioral parameters in a model of temporal lobe epilepsy in mice (Fabene et al., 2008). An engagement of complement system-mediated inflammation in the pathomechanism of epilepsy has been recently confirmed by Benson et al. (2015). They found that the pro-inflammatory C5a receptor, C5ar1 was up-regulated following kainate- and pilocarpine-induced status epilepticus in mice. Moreover, the C5ar1 antagonist displayed anticonvulsant activity in several seizure models, and C5ar1-deficient animals showed alleviation of seizures, neuroinflammation and neurodegeneration and decreased mortality following pilocarpine-induced status epilepticus. Collectively, this study suggests that C5ar1 could be a promising target for antiepileptic treatment (Benson et al., 2015). Regarding other anti-inflammatory agents, it has also been suggested that add on glucocorticoids could be of efficacy in controlling pediatric drug resistant seizures (Marchi et al., 2011). It was also reported that pulsatile corticoid therapy as alternative treatment to adrenocorticotropic hormone was effective in West syndrome, whereas in Lennox-Gastaut syndrome corticosteroids had no significant effect on seizures (Haberlandt et al., 2010).

It should be stressed that new potential disease-modifying agents and techniques are entering the epilepsy market. Among them rapalogues, such as everolimus and the antibiotic minocycline are currently under development for specific epileptic syndromes, like tuberous sclerosis or Angelman syndrome (Mula, 2016; Bialer et al., 2015).

Clinical studies of minocycline antiepileptic effects

In contrast to a substantial body of evidence obtained in animal models on seizure suppressing-effects of minocycline underlain by the inhibition of microglial activation and pro-inflammatory cytokine release, only a few data on possible antiepileptic effects of minocycline are available from clinical studies. To this end, in a randomized, double-blind, placebo-controlled crossover study, Lang et al. (2013) found that minocycline at a single oral dose of 200mg prolonged mean cortical silent period after single- and paired-pulse transcranial magnetic stimulation (TMS), but had no effect on other TMS parameters of cortical excitability (Lang et al., 2013). A case study demonstrated anticonvulsant properties of minocycline in a patient with severe symptomatic epilepsy due to an astrocytoma. However, it was also pointed out that minocycline attenuated seizures when administered at rather high doses, close to the toxic range. Furthermore, minocycline belongs to the drugs which readily evoke Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome (Nowak et al., 2012). The interaction of minocycline with anticonvulsant drugs with the exception of gabapentin (GBP), has not been studied (Miranda et al., 2017). Of other immunomodulators, tacrolimus, which via forming complex with immunophilins inhibits functional response to cytokines, showed no effect in the model of temporal lobe epilepsy in rats. On the other hand, Sato et al. (2016) presented the first case report of efficient therapeutic approach using tacrolimus in acute encephalitis with refractory, repetitive partial seizures. It should be mentioned that the patient showed infiltration of many neutrophilic leukocytes, T cells, and microglia in the area exhibiting severe spongiosis and that in contrast to tacrolimus, methylprednisolone pulse therapy and intravenous immunoglobulin administration were only temporarily effective (Sato et al., 2016).

Effect of anticonvulsants on neuroinflammation

Antiepileptic drugs are often, though with disputable ef-

ficacy, administered in order to prevent epilepsy development following traumatic brain injury frequently associated with gliosis and neuroinflammation (Glushakov et al., 2016; Salazar and Grafman, 2015). Recently, Lu et al. (2015) demonstrated that a novel deuterium-containing analog of (+)-N-methyl-3-ethoxymorphinan inhibited non-convulsive seizures and curtailed hippocampal astrocyte activation and perilesional microglial reactivity in a rat model of penetrating ballistic-like brain injury (Lu et al., 2015). Combined low dose diazepam and allopregnanolone (a neurosteroid possessing anticonvulsant efficacy in animal models of epilepsy), but not diazepam alone even at high doses, was shown to decrease microglial activation and protect mice against tetramethylenedisulfotetramine-induced seizures (Bruun et al., 2015). Magnesium sulfate has been the drug most commonly used for the management of severe preeclampsia and eclampsia in past decades but its mechanism of action remains unclear (Li et al., 2016). Using a rat model of severe preeclampsia Johnson et al. (2014) found that magnesium sulfate treatment increased pentylenetetrazole seizure threshold and decreased neuroinflammation, without affecting BBB permeability. It was concluded that abatement of neuroinflammation played a role in the mechanism by which magnesium sulfate prevented eclampsia during severe preeclampsia (Johnson et al., 2014). An in vitro study revealed that micromolar concentration of carbamazepine (CBZ) selectively suppressed lipopolysaccharide-induced microglial iNOS expression through the down-regulation of protein kinase Akt in microglial BV-2 cells. Those authors postulated that the anti-neuroinflammatory effect of carbamazepine played a key role in its therapeutic efficacy in the treatment of both epileptic and non-epileptic disorders, e.g. inflammatory hyperalgesia (Wang et al., 2014). Dambach et al. (2014) evaluated direct effects of valproic acid (VPA), CBZ, phenytoin (PHT), and GBP on glial viability, gap junctional network, microglial activation, and cytokine expression in an in vitro astroglia/microglia co-culture model. Of these drugs, VPA resulted in a highly significant microglial activation, whereas CBZ had an opposite effect. Furthermore, high doses of GBP and PHT enhanced anti-inflammatory cytokine TGF- β 1 release. It was concluded that antiepileptic drugs with anti-inflammatory glial properties might be beneficial for alleviation of seizures caused by persistent brain inflammation (Dambach et al., 2014). GBP administration during the latency period after lithi-

um/pilocarpine-induced status epilepticus reduced reactive gliosis and decreased neuronal loss in the adult rat hippocampus. Also in an in vitro study, GBP attenuated glutamate-induced dendritic loss and reactive gliosis in dissociated mixed hippocampal cell culture (Rossi et al., 2013). Stienen et al. (2011) studied the effects of levetiracetam on neonatal rat astrocytes co-cultured with activated microglia or treated with the pro-inflammatory cytokine IL-1 β to provoke inflammatory responses. They found that levetiracetam normalized the impaired astrocyte membrane resting potentials, and induced TGF- β 1 expression in inflammatory and control co-cultures. Moreover, anti-TGF- β 1 antibody abolished the facilitating effects of levetiracetam on the generation of astrocyte voltage-gated currents in the inflammatory co-cultures. These data indicate that levetiracetam inhibits seizure-like phenomena in astroglial syncytium and stabilizes neuronal-glial interactions (Stienen et al., 2011).

CONCLUSIONS

The above data suggest that there is significant opportunity to design new antiepileptic drugs, with their mechanism of action comprising not only the regulation of ion channels, and other neuronal proteins, but also the inhibition of neuroinflammatory processes. A great challenge for designing new pharmacotherapies of epilepsy would be related to combining connectomics, chemogenetics and inhibitors of neuroinflammatory processes. Assuming that epilepsy reflects periodical activity of pathologically formatted neuronal network, it would be logical to disconnect the aberrant innervation and retrieve the physiological ones.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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