Chapter

Inflammation: Cause or Consequence of Epilepsy?

Vanessa Lin Lin Lee and Mohd. Farooq Shaikh

Abstract

Epilepsy is the third most common neurological disorder, affecting about 70 million people worldwide. It is defined as a central nervous system disorder which affects the neuronal activity in the brain, causing unprovoked seizures and other behavioral changes. Unfortunately, one-third of epilepsy patients are unresponsive to available therapies and patients who respond to antiepileptic drugs often complain of debilitating side effects. In the effort of devising a suitable therapy for epilepsy treatment, researchers delved into the origin of seizures and the epileptogenic process and found an association between epilepsy and inflammation. Here, we discuss the involvement of inflammatory mediators in the development and progression of seizures and epileptogenesis, supported by clinical shreds of evidence. Subsequently, we discuss the role of inflammation in the generation of seizures, as it is debatable whether inflammation is the cause or consequence of epilepsy, along with experimental models in inflammation and epilepsy research.

Keywords: inflammation, inflammatory mediators, seizures, epilepsy, animal models

1. Introduction

Epilepsy is a brain disorder denoted by the predisposition to generate seizures accompanied by emotional and cognitive dysfunction [1]. Currently, there are estimated to be 50–70 million people worldwide suffering from epilepsy but only about 70% of them respond well to existing antiepileptic drugs [2, 3]. Furthermore, epileptic patients suffer deteriorating quality of life as they face limitations on their physical activities and daily life as well as being subjected to prejudice due to their seizures [4]. This calls for more research to seek for novel and effective therapies for the management and treatment of epilepsy, by first understanding the basis for the onset and progression of seizures.

The exact cause of epilepsy is still unknown, but there are mounting evidence showing that the development of epileptogenesis can be linked to a wide array of factors such as genetic predisposition, developmental disorders and neurological insults [5]. Neurological insults, which contribute towards up to 60% of epilepsy cases, include traumatic brain injuries (TBI), cerebrovascular accidents (CVA), central nervous system (CNS) infections and strokes, where inflammation is one of the key features of epileptogenesis [6]. However, the role of inflammation in epilepsy is still being actively studied, with various arguments on whether inflammation is the cause or consequence of epilepsy [7]. The blood-brain barrier (BBB),
which functions as a protector of the central nervous system, has an important role in regulating the transfer of blood constituents in the brain extracellular space [8]. Increased BBB permeability or BBB leakage is said to be one of the earliest characteristics of the pathophysiology of epileptogenesis [9, 10]. BBB dysfunction may contribute to epileptogenesis via a cascade of events triggered by leakage of inflammatory mediators into the CNS which causes neuroinflammation [11, 12]. Here, we discuss briefly how neuroinflammation is involved in epileptogenesis as well as the status of inflammation in post-epileptic conditions; whether it is the cause or consequence of epilepsy, together with experimental evidences.

2. Inflammatory response in epilepsy

Considering inflammation as one of the culprits of epileptogenesis, neuroinflammation occurs as a result of a cascade of inflammatory pathways. This involves inflammatory and anti-inflammatory molecules as a response to noxious stimuli or immune stimulation; targeted to defend against pathogenic threats. The activation of inflammatory mediators such as interleukins (ILs), interferons (IFNs), cyclooxygenase (COX)-2 and nuclear factor kappa B (NF-κB), and the surplus of downstream inflammatory mediators including IL-1β, IL-6, tumor necrosis factor (TNF)-α and prostaglandin E2 (PGE2) contribute to seizure progression [13, 14]. Inflammatory mediators are produced by the glia, neurons, endothelial cells of the BBB and peripheral immune cells. In the presence of noxious stimuli, cytokines are secreted by immunocompetent and endothelial cells as well as glial and neuronal cells in the CNS. In the presence of noxious stimuli, cytokines are released which enable effective communication between effector and target cells [7, 15].

Both innate and adaptive immunity is known to contribute in the generation of inflammation in the brain via the microglia, astrocytes and neurons [7]. In a non-epileptic condition, innate immunity activation occurs during infection and is instrumental for pathogen recognition as well as removal via homeostatic-type tissue inflammation [16]. In epileptic condition where pathogens are absent, innate immunity signaling is activated by damage-associated molecular patterns (DAMPs) which are secreted by injured or activated neurons, bringing about a phenomenon called ‘sterile inflammation’ [17]. The microglia and astrocytes recognize proteins such as high mobility group box 1 (HMGB1), S100 proteins, adenosine triphosphate (ATP), migration inhibitory factor-related protein 8 (MRP8), which makes are DAMPs, extracellular matrix degradation products and IL-1β to induce inflammation [17, 18]. On top of that, the inflammatory signaling disrupts the BBB integrity by inducing up-regulation of adhesion molecules as well as leukocyte recruitment. These processes reduces seizure threshold and contribute to epileptogenesis and seizure recurrence in epilepsy models [19, 20].

Clinically, it is observed that patients with autoimmune diseases such as systemic lupus erythematosus (SLE), Hashimoto’s encephalopathy, Behcet’s disease, and Sjogren’s syndrome have an increased risk of developing epilepsy [5]. Another example of an autoimmune disease associated with a predisposition to seizures is Rasmussen encephalitis (RE), a rare inflammatory brain disease causing cerebral hemiatrophy, which progressively leads to severe seizures [21]. Patients of RE have higher levels of astrocytosis, proinflammatory mediators as well as lymphocytes and activated microglial cells in the brain [22, 23]. In these cases, usually, immunotherapies are more effective as compared to antiepileptic drugs in the management of epilepsy [24].

Moreover, a number of reports suggest that the onset and perpetuation of epilepsy can be driven by inflammation and is not caused by the autoimmune process.
Inflammation: Cause or Consequence of Epilepsy?

Upregulation of proinflammatory markers and inflammation-related microRNAs are found in patients of generalized seizures and temporal lobe epilepsy (TLE) \[25, 26\]. Butler, Li \[27\] reported a significantly greater inflammation intensity and spatial extent using positron emission tomography (PET) scan in post-seizure patients \[27\].

3. Experimental models

Moving forward with the understanding on the clinical association of inflammation with epileptogenesis, researchers sought to decipher the role of inflammation and associated pathways in the genesis of a seizure in the brain. Experimental models of inflammation have been instrumental in understanding the role of inflammation in epilepsy. It is still an ongoing debate as there are two field of thoughts; (1) inflammation acts as the cause of seizures and (2) inflammation is the consequence of seizures \[7\]. Here, we discuss the different types of experimental models and the outcomes of the experimental work, summarized in Table 1.

3.1 Inflammation increases seizure susceptibility

3.1.1 Hyperthermia-induced seizures

Febrile seizures (FS) are common in children aged between 6 months and 5 years and occur in response to fever but without infection of the CNS. Fever is the elevation of the body temperature set point within the hypothalamus which results in an elevation of core temperature and is generated by inflammatory mediators such as cytokines and prostaglandins which then invokes a systemic inflammatory response \[28, 29\]. A widely used hyperthermia-induced seizure model for studying FS is one in which hyperthermia is induced using a regulated stream of mildly heated air to increase the body temperature of neonatal rats aged 10–13 days \[30–32\]. The brain development of rats between 10 and 15 postnatal days best corresponds to the development of brain in human infants when they are most susceptible to FS \[30\]. The ‘ideal’ increase of core temperature in the pups is around 2.9°C, which is reported to be parallel with the temperature increment observed in children experiencing FS \[33\].

In this model, seizures can be confirmed using electroencephalogram (EEG) \[30\]. The behaviors exhibited by the pups, such as biting tonic stiffening, and falling over, are similar to those observed after administration of convulsants. Generalized tonic seizures are rarely observed, however \[30, 32\]. In addition to biochemical analysis, behavioral tests such as the balance beam test and footprint test provide information on the severity and progression of seizures. Research has also shown that in this hyperthermic model, there is a remarkably high release of cytokines within the brain, specifically IL-1β within the hippocampus, and activation of astrocytes, which elevates the brain temperature. This finding is similar to those seen in children suffering from FS \[31\].

3.1.2 Systemic inflammation

Systemic inflammation is believed to have several CNS manifestations, such as fever, locomotor activity reduction and behaviors that are associated with brain hyperactivity during peripheral inflammation \[34\]. In other words, the inflammatory response which can be observed during the manifestation of peripheral inflammatory diseases is similar to the inflammatory response generated in the
It is important to note that systemic inflammation alone is insufficient to induce seizures, and therefore, a double-hit with a proconvulsant is usually adopted in experiments to show that the first hit of existing inflammation predisposes the subject to increased seizure susceptibility in response to a second hit. We discuss two models of systemic inflammation which have been used for the study of epilepsy and seizures.

The first one is a model of inflammatory bowel disease [36–38]. Inflammatory bowel disease is induced in adult male rats by intracolonic administration of 2,4,6-trinitobenzene sulfonic acid (TNBS) to initiate a T helper-1 cell-mediated model of inflammatory bowel disease. A dose of 50 mg/mL, 50 mL per rat, invoked an

---

**Table 1.**

| Types of animal model                     | Dose/method                                                                 | Outcome                                                                                      | References |
|-------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|------------|
| Hyperthermic-induced seizure              | Using a regulated stream of mildly heated air to increase core temperature. | - Mimics febrile seizures in children.                                                        | [28–31]    |
|                                           |                                                                             | - Core body temperature increase by around 2.9°C.                                             |            |
|                                           |                                                                             | - Marked release of cytokines within the brain and activation of astrocytes.                 |            |
| Inflammatory bowel disease model          | Intracolonic administration of 2,4,6-trinitobenzene sulfonic acid (TNBS) at a dose of 50 mg/ml, 50 mL per rat. | - Induces significant inflammatory response within the hippocampus.                          | [32–35]    |
|                                           |                                                                             | - Activation of microglial.                                                                   |            |
|                                           |                                                                             | - Increases levels of TNF-α.                                                                  |            |
|                                           |                                                                             | - Increases susceptibility to PTZ-induced seizures.                                           |            |
| Escherichia coli LPS injection            | Intraperitoneal injection of 5 mg/kg or peritoneal infusion of 2.5 mg/kg/day for 7 days. | - Increases plasma levels of IL-1β, IL-6 and TNF-α.                                          | [36–38]    |
|                                           |                                                                             | - Increases body temperature slightly (by 0.9°C).                                            |            |
|                                           |                                                                             | - Increases seizure susceptibility.                                                           |            |
| Kainic acid injection                     | Intraperitoneal injection of 2 mg/kg in rat neonates, 15 mg/kg in adult rats and 20 mg/kg in mice, 6 mg/kg in zebrafish. | - Induces limbic seizures characterized by a seizure scale devised by Racine.               | [39–44]    |
|                                           |                                                                             | - Seizures induced resemble human temporal lobe epilepsy.                                     |            |
|                                           |                                                                             | - Leads to neuronal cell death and induction of proinflammatory gene expression.             |            |
| Pilocarpine injection                     | Subcutaneous or intraperitoneal injection of 340–350 mg/kg in rats, 30 mM in zebrafish larvae. | - Induces status epilepticus, followed by recurrent spontaneous seizures.                    | [45–50]    |
|                                           |                                                                             | - Causes extensive neuronal cell loss, astrogliosis, and mossy fiber sprouting in hippocampus. |            |
|                                           |                                                                             | - Developmental exposure to pilocarpine shows very little effect to startle response.        |            |
| Serum albumin injection                   | Intracerebroventricular injection of 1.9 mM in rats.                         | - Mimics BBB breakdown following seizures.                                                    | [51]       |
|                                           |                                                                             | - Increased IL-1β immunoreactivity.                                                          |            |
|                                           |                                                                             | - Astrocyte dysfunction.                                                                     |            |
|                                           |                                                                             | - Significant increase in interictal spikes and neuronal excitability.                       |            |
|                                           |                                                                             | - Reduction in seizure threshold.                                                            |            |

Table 1.
Animal models in epilepsy studies.
acute form of localized inflammatory colitis. To study the susceptibility to seizures, a convulsant, pentylentetrazole (PTZ) was given through intravenous infusion to induce seizures. In this study by Riazi et al. [38], they found that TNBS-treated rats express increased susceptibility to PTZ-induced seizures that strongly correlates with the severity and progression of intestinal inflammation. The TNBS-treated rats present a prominent and reversible inflammatory response within the hippocampus along with microglial activation and TNF-α level elevation [38]. The inflammatory colitis model is also used by Rao, Medhi [39] to establish the correlation between systemic inflammation and seizures. They induced colitis using a method described by MacPherson and Pfeiffer [40], which is the application of acetic acid on the colonic lumen of adult rats. They too found that systemic inflammation can be associated with a decreased threshold to PTZ-induced seizures [39].

The second model of systemic inflammation is bacterial lipopolysaccharide (LPS) injection. In adult rats, an intraperitoneal injection of LPS results in an increase in body temperature elicited by an inflammatory response, which mimics febrile seizures, though a second-hit with a pro-convulsant drug, usually kainic acid, is usually required to generate febrile convulsions. LPS increases rat’s body temperature by 1–1.5°C, which mimics fever and amplifies the convulsant actions of KA [41]. Single intraperitoneal injection of *Escherichia coli* LPS at 5 mg/kg or infusion of at a dose of 2.5 mg/kg/day into the peritoneal cavity of adult rats for 7 days via an osmotic mini-pump is sufficient to induce peripheral inflammation [42, 43]. In mice, a single dose of 1 mg/kg of LPS i.p. is sufficient to elicit effects on body temperature and seizure susceptibility [44]. Seizure susceptibility is then tested using an intraperitoneal injection of KA (10 mg/kg) or PTZ (10 mg/mL) after 2 hours [43, 44]. LPS infusion is reported to increase plasma levels of IL-1β, IL-6 and TNF-α. This means that the systemic inflammation induced by LPS infusion brings about the activation of microglia, enhancement of pro-inflammatory cytokines production and tissue oxidative stress in the hippocampus [43, 45]. As a result, LPS administration increases body temperature slightly and reduces PTZ-induced seizure susceptibility in a dose-dependent and time-dependent manner. Recent studies have shown that LPS acts as an activator for Toll-like receptor 4 (TLR 4) and induces seizures. The probable mechanism in explanation to this is that LPS mimics the actions stressed or damaged neurons which releases endogenous ‘danger signals’ via a protein called HMGB1. After being released from neurons, HMGB1 communicates with TLR4 to induce seizures, which activates a positive feedback cycle, by stimulating activated astrocytes and microglia for additional release of HMGB1.

### 3.2 Inflammation as a consequence of seizures

#### 3.2.1 Kainic acid (KA) injection

KA is an agonist for α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and KA receptor. AMPA is a subtype of ionotropic glutamate receptor. Systemic and intracerebral injections of KA induce progressive limbic seizures, which resemble human temporal lobe epilepsy, in rats [46]. These peak in status epilepticus (SE) where, in limbic structures (i.e. hippocampal CA1 and CA3, and the hilus of dentate gyrus) of the brain, reactive oxygen species (ROS) production and mitochondrial dysfunction lead to neuronal cell death [47]. Moreover, the delayed release of proinflammatory gene expressions, such as TNF-α, IL-1β, IL-6, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), is believed to promote prolonged neurodegeneration [48]. For these reasons, KA is used for various studies into neurological disorders including inflammation and epilepsy.
Kainic acid injection into hippocampus of rats increases the number of IL-1ß, IL-6 and TNF-α positive cells in the hippocampus, indicating inflammatory response [49, 50]. There is also a higher number of GFAP-positive cells which shows that kainic acid promotes gliosis, also an indicator of neuroinflammation. Chen, Zhu [49] found that kainic acid administration causes swelling and deformities of endothelial cells and their nuclei in cerebromicrovessels. The BBB integrity is also destroyed following kainic acid injection with signs of vacuolation, perivascular edema and membrane damage [49].

KA is widely used in epilepsy studies and models include rodents as well as zebrafish. In rodents, KA works to induce seizures and SE in neonatal and adult rat and mice. In rat neonates, 2 mg/kg of KA injected intraperitoneally was found to induce seizures without mortality while 4 mg/kg of KA was shown to induce mortality in 60% of pups [51]. For adult rats and mice, a single dose of KA at 15mg/kg for rats and 20 mg/kg for mice can be used for inducing seizures [52].

In rat neonates, the phases of convulsions that are generated by KA are automatism (forelimb/hind-limb scratching) and continuous generalized tonic-clonic seizures, with loss of righting reflex, indicating tonic extension and SE. In this model, SE is defined as continuous clonic seizures involving both forelimbs and hind-limbs and continual loss of the righting reflex [51].

In adult rats and mice, seizures are characterized by a seizure scoring scale devised by Racine as follows:

- **Stage 1**: Wet dog shakes, facial clonus and staring.
- **Stage 2**: Head nodding.
- **Stage 3**: Forelimb clonus.
- **Stage 4**: Forelimb clonus with rearing.
- **Stage 5**: Rearing, jumping, falling and SE.

Despite being a relatively new model, zebrafish is acknowledged to be a fairly popular animal model in pre-clinical researches and as a suitable alternative to rodents and other animal models in epilepsy research [53]. KA is used to induce seizures in zebrafish at a dose of 6 mg/kg, injected intraperitoneally. The seizures induced by KA are characterized as follows [54]:

- **Stage 1**: Immobility and hyperventilation.
- **Stage 2**: Whirlpool-like swimming behavior.
- **Stage 3**: Rapid left-to-right movements.
- **Stage 4**: Abnormal and spasmodic muscular contractions.
- **Stage 5**: Rapid, whole-body, clonus-like convulsions.
- **Stage 6**: Death.

SE is represented by seizure scores fluctuating between 4 and 6 for a period of 30 minutes or more [55].

### 3.2.2 Pilocarpine injection

Pilocarpine is a cholinergic (muscarinic) agonist which induces SE, followed by recurrent spontaneous seizures (RSS), in animal models and is widely used to study the mechanisms of SE. It acts on the endothelial muscarinic receptors which compromises the integrity of the BBB [56]. It subsequently causes the influx of proinflammatory cytokines into the brain, which results in neuroinflammation [35]. The hippocampus is notably more vulnerable to pilocarpine-induced neuronal injury because it possesses numerous distinct neuronal circuits which are involved in the generation of seizures [57]. Pilocarpine causes extensive neuronal cell loss in CA1 and CA3 pyramidal cell layers, astrogliosis, and mossy fiber sprouting in the hippocampus [57, 58].

Upon administration of pilocarpine into rats, the levels of inflammatory biomarkers, IL-1ß, TNF-α, NF-κß and COX-2, are elevated in the hippocampus,
indicating the presence of neuroinflammation [59]. During pilocarpine-induced seizures, ROS formation increases and glutathione (GSH) redox status becomes impaired in the hippocampus [60, 61]. The overproduction of ROS leads to an increase in oxidative stress which contributes to cell apoptosis in the brain [62]. Ali, Mahdy [59] reported that pilocarpine injection induces a significant elevation of hippocampal cytochrome c and caspase 3 levels which contributes to apoptosis. This apoptotic cell death is a key feature of hippocampal cell loss induced by SE [59]. Furthermore, apoptosis related proteins such as Bax, Bcl-2 family and caspase-3 can modify the neurotransmission pathways that are independent of cell death in the CNS and have significant contribution in epileptogenesis [63, 64].

Seizures can be induced in adult mice or rats with a subcutaneous or intraperitoneal injection of 340–350 mg/kg of pilocarpine hydrochloride [58, 65]. Pilocarpine treatment sequentially induces the following behavioral changes: akinesia, facial automatisms, forelimb clonus with rearing, salivation, masticatory jaw movements and falling [65, 66]. These behaviors build up progressively into motor limbic seizures that recur repeatedly and rapidly develop into SE, similar to that described in patients of temporal lobe epilepsy (TLE). EEG findings showed a significant surge of theta rhythms and isolated spikes in the hippocampus, synchronization of the hippocampal and cortical activities, isolated electrographic seizures and SE [65]. The electroencephalographical, behavioral, as well as anatomical alterations and characteristics of human TLE are emulated by this model [58].

Besides the rodent models, pilocarpine is also used to induce seizures in zebrafish larvae for anticonvulsant studies. A final concentration of 30 mM of pilocarpine is used with a 1-minute incubation before quantification of larval locomotor activity. Exposure to pilocarpine results in a more subtle convulsive behavior compared to PTZ, such as lurching/head banging, head-to-tail undulations, increased mouth movements, tremor, body contortions and loss of posture [67]. Eddins, Cerutti [68] reported the use of pilocarpine to induce seizures in zebrafish embryos to compare its effects on early exposure to developmental exposure to toxicants. Zebrafish embryos (2-hours post-fertilization) exposed to 100 μM pilocarpine exhibit very little to zero dose–response relationship of developmental pilocarpine exposure with regard to the startle response [68].

### 3.2.3 Albumin injection

Extravasation of serum albumin into the brain provokes prominent BBB dysfunction through the activation of transforming growth factor beta (TGF-β) receptor (RII) signaling. This causes the astrocytes to fail in buffering extracellular K+ which causes BBB dysfunction [69–71]. BBB dysfunction is a commonly found following seizures or epileptogenic brain injuries [7].

Frigerio et al. [72] described a model using albumin to provoke BBB breakdown, mimicking brain excitability after SE. They showed that a single intracerebroventricular injection of albumin to rats causes the diffusion of albumin into the hippocampus before conveyed into principal neurons. The extravasation of albumin by parenchymal cells at pathological concentration causes the following conditions: (1) down-regulation of Kir4.1 channels and neuroinflammation in glial fibrillary acidic protein(GFAP)-positive astrocytes; (2) brief neuronal hyperexcitability manifested as involuntary epileptic spikes, and amplified KA–induced epileptic activity; and (3) chronic reduction in seizure threshold without causing cell loss or spontaneous epileptic activity [72].

BBB disruption was induced using a single dose of intracerebroventricular injection of 1.9 mM rat albumin into deeply anesthetized adult rats. After the injection, GFAP-positive glial cells and IL-1β staining in the hippocampus were evaluated. It
was found that albumin injection prominently increases IL-1β immunoreactivity in GFAP-positive astrocytes and the number of IL-1β immunopositive cells, indicating the presence of inflammation. Besides that, the production of rapid onset and transient spiking activity in the hippocampus can be found on the EEG analysis of rats injected with rat albumin. This means that the injection of albumin provokes the increase in neuronal excitability. Interestingly, rats presented a significant decline in seizure threshold 3 months after albumin injection. This suggests that acute tissue exposure to albumin induces a long-lasting increase in brain excitability [72].

In short, this model is able to show the pro-ictogenic effect of serum albumin in the brain, mimicking those attained after prolonged seizures and BBB dysfunction. Albumin induces the production of inflammatory molecules and together, they significantly increase brain excitability and seizure susceptibility although insufficient to trigger spontaneous seizures.

4. Conclusion

Inflammation plays an important role in the development of epilepsy and understanding this inflammatory process that happens during epileptogenesis could provide a strong basis for drug development and therapeutic approaches. We briefly highlighted the inflammatory response during epilepsy and some clinical correlation. Besides, we outlined the experimental findings in epilepsy research pertaining to inflammation and hope to clear the doubts as to whether inflammation is a cause or consequence of epilepsy. Evidently, inflammation can be both the cause as well as consequence of epilepsy. Inflammation due to hyperthermia or infection activates the release of inflammatory molecules which increases seizures susceptibility. On the other hand, BBB dysfunction and prolonged seizures cause an influx of inflammatory molecules which causes neuroinflammation to take place.

Anti-inflammatory drugs, such as acetaminophen, celecoxib or aspirin, along with other anti-inflammatory agents such as anti-MGB1 antibodies and COX-2 inhibitors have been shown to possess anti-convulsant properties [73]. Therefore, we suggest incorporating anti-inflammatory drugs into anti-epileptic treatments or therapy could be beneficial in the management of epilepsy and ameliorating comorbidities and side effects that could be exacerbated by neuroinflammation.

Acknowledgements

The authors would like to thank Mr. Brandon Choo Kar Meng for proofreading the manuscript.

Conflict of interest

Authors declare no conflict of interest.
Inflammation: Cause or Consequence of Epilepsy?
DOI: http://dx.doi.org/10.5772/intechopen.83428

Author details

Vanessa Lin Lin Lee and Mohd. Farooq Shaikh*
Neuropharmacology Research Laboratory, Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Bandar Sunway, Malaysia

*Address all correspondence to: farooq.shaikh@monash.edu

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
References

[1] Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. Lancet. 2006;367(9516):1087-1100

[2] Cunliffe VT, Baines RA, Giachello CN, Lin WH, Morgan A, Reuber M, et al. Epilepsy research methods update: Understanding the causes of epileptic seizures and identifying new treatments using non-mammalian model organisms. Seizure. 2015;24:44-51

[3] Thurman DJ, Begley CE, Carpio A, Helmers S, Hesdorffer DC, Mu J, et al. The primary prevention of epilepsy: A report of the prevention task force of the international league against epilepsy. Epilepsia. 2018;59(5):905-914

[4] Johan Arief MF, Choo BKM, Yap JL, Kumari Y, Shaikh MF. A systematic review on non-mammalian models in epilepsy research. Frontiers in Pharmacology. 2018;9:655

[5] Rana A, Musto AE. The role of inflammation in the development of epilepsy. Journal of Neuroinflammation. 2018;15(1):144

[6] Klein P, Dingledine R, Aronica E, Bernard C, Blümcke I, Boison D, et al. Commonalities in epileptogenic processes from different acute brain insults: Do they translate? Epilepsia. 2018;59(1):37-66

[7] Vezzani A, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. Nature Reviews. Neurology. 2011;7(1):31-40

[8] Tomkins O, Feintuch A, Benifla M, Cohen A, Friedman A, Shelef I. Blood-brain barrier breakdown following traumatic brain injury: A possible role in posttraumatic epilepsy. Cardiovascular Psychiatry and Neurology. 2011;2011:765923

[9] Gorter JA, Van Vliet EA, Aronica E. Status epilepticus, blood-brain barrier disruption, inflammation, and epileptogenesis. Epilepsy & Behavior. 2015;49:13-16

[10] Van Vliet EA, Aronica E, Gorter JA. Blood–brain barrier dysfunction, seizures and epilepsy. In: Seminars in cell & Developmental biology. Academic Press. 2015;38:26-34

[11] Liebner S, Dijkhuizen RM, Reiss Y, Plate KH, Agalli D, Constantin G. Functional morphology of the blood-brain barrier in health and disease. Acta Neuropathologica. 2018;135(3):1-26

[12] Maroso M, Balosso S, Ravizza T, Liu J, Aronica E, Iyer AM, et al. Toll-like receptor 4 and high-mobility group box-1 are involved in ictogenesis and can be targeted to reduce seizures. Nature Medicine. 2010;16(4):413

[13] Huang HL, Lin CC, Jeng KC, Yao PW, Chuang LT, Kuo SL, et al. Fresh green tea and gallic acid ameliorate oxidative stress in kainic acid-induced status epilepticus. Journal of Agricultural and Food Chemistry. 2012;60(9):2328-2336

[14] Teocchi MA, Ferreira AÉD, EPDL d O, Tedeschi H, D’Souza-Li L. Hippocampal gene expression dysregulation of Klotho, nuclear factor kappa B and tumor necrosis factor in temporal lobe epilepsy patients. Journal of Neuroinflammation. 2013;10(1):53

[15] Allan SM, Rothwell NJ. Cytokines and acute neurodegeneration. Nature Reviews. Neuroscience. 2001;2(10):734-744

[16] Ulevitch R, Tobias P. Receptor-dependent mechanisms of cell stimulation by bacterial endotoxin. Annual Review of Immunology. 1995;13(1):437-457

[17] Bianchi MEDAMP. PAMPs and alarmins: All we need to know about
danger. Journal of Leukocyte Biology. 2007;81(1):1-5

[18] Tsan MF, Gao B. Endogenous ligands of Toll-like receptors. Journal of Leukocyte Biology. 2004;76(3):514-519

[19] Vezzani A, Maroso M, Balosso S, Sanchez M-A, Bartfai T. IL-1 receptor/Toll-like receptor signaling in infection, inflammation, stress and neurodegeneration couples hyperexcitability and seizures. Brain, Behavior, and Immunity. 2011;25(7):1281-1289

[20] Vezzani A, Aronica E, Mazarati A, Pittman Q.J. Epilepsy and brain inflammation. Experimental Neurology. 2013;244:11-21

[21] Bien CG, Tiemeier H, Sassen R, Kuczaty S, Urbach H, von Lehe M, et al. Rasmussen encephalitis: Incidence and course under randomized therapy with tacrolimus or intravenous immunoglobulins. Epilepsia. 2013;54(3):543-550

[22] Schneider-Hohendorf T, Mohan H, Bien CG, Breuer J, Becker A, Görlich D, et al. CD8+ T-cell pathogenicity in Rasmussen encephalitis elucidated by large-scale T-cell receptor sequencing. Nature Communications. 2016;7:11153

[23] Cepeda C, Chang JW, Owens GC, Huynh MN, Chen JY, Tran C, et al. In Rasmussen encephalitis, hemichannels associated with microglial activation are linked to cortical pyramidal neuron coupling: A possible mechanism for cellular hyperexcitability. CNS Neuroscience & Therapeutics. 2015;21(2):152-163

[24] Vincent A, Irani SR, Lang B. The growing recognition of immunotherapy-responsive seizure disorders with autoantibodies to specific neuronal proteins. Current Opinion in Neurology. 2010;23(2):144-150

[25] Alsharafi W, Xiao B. Dynamic expression of MicroRNAs (183, 135a, 125b, 128, 30c and 27a) in the rat Pilocarpine model and temporal lobe epilepsy patients. CNS & Neurological Disorders Drug Targets. 2015;14(8):1096-1102

[26] Ishikawa N, Kobayashi Y, Fujii Y, Kobayashi M. Increased interleukin-6 and high-sensitivity C-reactive protein levels in pediatric epilepsy patients with frequent, refractory generalized motor seizures. Seizure. 2015;25:136-140

[27] Butler T, Li Y, Tsui W, Friedman D, Maoz A, Wang X, et al. Transient and chronic seizure-induced inflammation in human focal epilepsy. Epilepsia. 2016;57(9):e191-e194

[28] Gatti S, Vezzani A, Bartfai T. Mechanisms of fever and febrile seizures: Putative role of the interleukin-1 system. In: Febrile Seizures. Massachusetts: Elsevier; 2002. pp. 169-188

[29] Zetterstrom M, Sundgren-Andersson AK, Ostlund P, Bartfai T. Delineation of the proinflammatory cytokine cascade in fever induction. Annals of the New York Academy of Sciences. 1998;856:48-52

[30] Baram TZ, Gerth A, Schultz L. Febrile seizures: An appropriate-aged model suitable for long-term studies. Developmental Brain Research. 1997;98(2):265-270

[31] Dube CM, Ravizza T, Hamamura M, Zha Q, Keebaugh A, Fok K, et al. Epileptogenesis provoked by prolonged experimental febrile seizures: Mechanisms and biomarkers. The Journal of Neuroscience. 2010;30(22):7484-7494

[32] Crespo M, DA L-N, Martin M. Cerebellar oxidative stress and fine motor impairment in adolescent rats exposed to hyperthermia-induced
seizures is prevented by maternal caffeine intake during gestation and lactation. European Journal of Pharmacology. 2018;822:186-198

[33] Dupuis N, Auvin S. Inflammation and epilepsy in the developing brain: Clinical and experimental evidence. CNS Neuroscience & Therapeutics. 2015;21(2):141-151

[34] Simard AR, Rivest S. Do pathogen exposure and innate immunity cause brain diseases? Neurological Research. 2005;27(7):717-725

[35] Riazi K, Galic MA, Pittman QJ. Contributions of peripheral inflammation to seizure susceptibility: Cytokines and brain excitability. Epilepsy Research. 2010;89(1):34-42

[36] Pol O, Ferrer I, Puig MM. Diarrhea associated with intestinal inflammation increases the potency of mu and delta opioids on the inhibition of gastrointestinal transit in mice. The Journal of Pharmacology and Experimental Therapeutics. 1994;270(1):386-391

[37] Puig MM, Pol O. Peripheral effects of opioids in a model of chronic intestinal inflammation in mice. The Journal of Pharmacology and Experimental Therapeutics. 1998;287(3):1068-1075

[38] Riazi K, Galic MA, Kuzmiski JB, Ho W, Sharkey KA, Pittman QJ. Microglial activation and TNFalpha production mediate altered CNS excitability following peripheral inflammation. Proceedings of the National Academy of Sciences of the United States of America. 2008;105(44):17151-17156

[39] Rao RS, Medhi B, Khanduja KL, Pandhi P. Correlation of seizures and biochemical parameters of oxidative stress in experimentally induced inflammatory rat models. Fundamental & Clinical Pharmacology. 2010;24(3):325-331

[40] MacPherson BR, Pfeiffer CJ. Experimental production of diffuse colitis in rats. Digestion. 1978;17(2):135-150

[41] Patterson KP, Baram TZ, Shinnar S. Origins of temporal lobe epilepsy: Febrile seizures and febrile status epilepticus. Neurotherapeutics. 2014;11(2):242-250

[42] Yamanaka D, Kawano T, Nishigaki A, Aoyama B, Tateiwa H, Shigematsu-Locatelli M, et al. Preventive effects of dexmedetomidine on the development of cognitive dysfunction following systemic inflammation in aged rats. Journal of Anesthesia. 2017;31(1):25-35

[43] Ho Y-H, Lin Y-T, Wu C-WJ, Chao Y-M, Chang AY, Chan JY. Peripheral inflammation increases seizure susceptibility via the induction of neuroinflammation and oxidative stress in the hippocampus. Journal of Biomedical Science. 2015;22(1):46

[44] Sayyah M, Javad-Pour M, Ghazi-Khansari M. The bacterial endotoxin lipopolysaccharide enhances seizure susceptibility in mice: Involvement of proinflammatory factors: Nitric oxide and prostaglandins. Neuroscience. 2003;122(4):1073-1080

[45] Eun BL, Abraham J, Msna L, Kim MJ, Koh S. Lipopolysaccharide potentiates hyperthermia-induced seizures. Brain and Behavior. 2015;5(8):e00348

[46] Ben-Ari Y, Cossart R. Kainate, a double agent that generates seizures: Two decades of progress. Trends in Neurosciences. 2000;23(11):580-587

[47] Ben-Ari Y. Limbic seizure and brain damage produced by kainic acid: Mechanisms and relevance to human temporal lobe epilepsy. Neuroscience. 1985;14(2):375-403
[48] Rizzi M, Perego C, Aliprandi M, Richichi C, Ravizza T, Colella D, et al. Glia activation and cytokine increase in rat hippocampus by kainic acid-induced status epilepticus during postnatal development. Neurobiology of Disease. 2003;14(3):494-503

[49] Chen Y-C, Zhu G-Y, Wang X, Shi L, Du T-T, Liu D-F, et al. Anterior thalamic nuclei deep brain stimulation reduces disruption of the blood-brain barrier, albumin extravasation, inflammation and apoptosis in kainic acid-induced epileptic rats. Neurological Research. 2017;39(12):1103-1113

[50] Wang Z-h, M-c M, Y-c Y, M-c Y. Asiatic acid and maslinic acid attenuated kainic acid-induced seizure through decreasing hippocampal inflammatory and oxidative stress. Epilepsy Research. 2018;139:28-34

[51] Dhir A, Chavda V. Pre-and post-exposure talampanel (GYKI 53773) against kainic acid seizures in neonatal rats. Pharmacological Reports. 2016;68(1):190-195

[52] Chiu KM, Wu CC, Wang MJ, Lee MY, Wang SJ. Protective effects of bupivacaine against kainic acid-induced seizure and neuronal cell death in the rat hippocampus. Biological and Pharmaceutical Bulletin. 2015;38(4):522-530

[53] Kundap UP, Kumari Y, Othman I, Shaikh M. Zebrafish as a model for epilepsy-induced cognitive dysfunction: A pharmacological, biochemical and behavioral approach. Frontiers in Pharmacology. 2017;8:515

[54] Mussulini BH, Vizuete AF, Braga M, Moro L, Baggio S, Santos E, Lazzarotto G, Zenki KC, Pettenuzzo L, da Rocha JB, de Oliveira DL. Forebrain glutamate uptake and behavioral parameters are altered in adult zebrafish after the induction of Status Epilepticus by kainic acid. Neurotoxicology. Apr 19, 2018

[55] Sierra S, Alfar JM, Sanchez S, Burgos JS. Administration of docosahexaenoic acid before birth and until aging decreases kainate-induced seizures in adult zebrafish. Brain Research Bulletin. 2012;88(5):467-470

[56] Kharatishvili I, Shan ZY, She DT, Foong S, Kurniawan ND, Reutens DC. MRI changes and complement activation correlate with epileptogenicity in a mouse model of temporal lobe epilepsy. Brain Structure and Function. 2014;219(2):683-706

[57] Pestana RR, Kinjo ER, Hernandes MS, Britto LR. Reactive oxygen species generated by NADPH oxidase are involved in neurodegeneration in the pilocarpine model of temporal lobe epilepsy. Neuroscience Letters. 2010;484(3):187-191

[58] Hadera MG, Smeland OB, McDonald TS, Tan KN, Sonnewald U, Borges K. Triheptanoin partially restores levels of tricarboxylic acid cycle intermediates in the mouse pilocarpine model of epilepsy. Journal of Neurochemistry. 2014;129(1):107-119

[59] Ali AE, Mahdy HM, Elsherbiny DM, Azab SS. Rifampicin ameliorates lithium-pilocarpine-induced seizures, consequent hippocampal damage and memory deficit in rats: Impact on oxidative, inflammatory and apoptotic machineries. Biochemical Pharmacology. 2018;156:431-443

[60] Liu J, Wang A, Li L, Huang Y, Xue P, Hao A. Oxidative stress mediates hippocampal neuron death in rats after lithium–pilocarpine-induced status epilepticus. Seizure. 2010;19(3):165-172

[61] Liu Y-F, Gao F, Li X-W, Jia R-H, Meng X-D, Zhao R, et al. The anticonvulsant and neuroprotective effects of baikaln on pilocarpine-induced epileptic model in rats. Neurochemical Research. 2012;37(8):1670-1680
[62] Méndez-Armenta M, Nava-Ruíz C, Juárez-Rebollar D, Rodríguez-Martínez E, Yescas Gómez P. Oxidative stress associated with neuronal apoptosis in experimental models of epilepsy. Oxidative Medicine and Cellular Longevity. 2014;2014:12

[63] Jiao S, Li Z. Nonapoptotic function of BAD and BAX in long-term depression of synaptic transmission. Neuron. 2011;70(4):758-772

[64] Kudryashova I, Onufriev M, Kudryashov I, Gulyaeva N. Caspase-3 activity in hippocampal slices reflects changes in synaptic plasticity. Neuroscience and Behavioral Physiology. 2009;39(1):13

[65] Cavalheiro EA. The pilocarpine model of epilepsy. The Italian Journal of Neurological Sciences. 1995;16(1-2):33-37

[66] Brandt C, Töllner K, Klee R, Bröer S, Löschler W. Effective termination of status epilepticus by rational polypharmacy in the lithium–pilocarpine model in rats: Window of opportunity to prevent epilepsy and prediction of epilepsy by biomarkers. Neurobiology of Disease. 2015;75:78-90

[67] Vermeosen K, Serruys A-SK, Loyens E, Afrikanova T, Massie A, Schallier A, et al. Assessment of the convulsant liability of antidepressants using zebrafish and mouse seizure models. Epilepsy & Behavior. 2011;22(3):450-460

[68] Eddins D, Cerutti D, Williams P, Linney E, Levin ED. Zebrafish provide a sensitive model of persisting neurobehavioral effects of developmental chlorpyrifos exposure: Comparison with nicotine and pilocarpine effects and relationship to dopamine deficits. Neurotoxicology and Teratology. 2010;32(1):99-108

[69] Cacheaux LP, Ivens S, David Y, Lakhter AJ, Bar-Klein G, Shapira M, et al. Transcriptome profiling reveals TGF-β signaling involvement in epileptogenesis. Journal of Neuroscience. 2009;29(28):8927-8935

[70] David Y, Cacheaux LP, Ivens S, Lapilover E, Heinemann U, Kaufer D, et al. Astrocytic dysfunction in epileptogenesis: Consequence of altered potassium and glutamate homeostasis. Journal of Neuroscience. 2009;29(34):10588-10599

[71] Ivens S, Kaufer D, Flores LP, Bechmann I, Zumsteg D, Tomkins O, et al. TGF-β receptor-mediated albumin uptake into astrocytes is involved in neocortical epileptogenesis. Brain. 2006;130(2):535-547

[72] Frigerio F, Frasca A, Weissberg I, Parrella S, Friedman A, Vezzani A, et al. Long-lasting pro-ictogenic effects induced in vivo by rat brain exposure to serum albumin in the absence of concomitant pathology. Epilepsia. 2012;53(11):1887-1897

[73] Paudel YN, Shaikh MF, Shah S, Kumari Y, Othman I. Role of inflammation in epilepsy and neurobehavioral comorbidities: Implication for therapy. European Journal of Pharmacology. 2018;837:145-155