Chapter

Inflammation: Cause or Consequence of Epilepsy?

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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.

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

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. • Core body temperature increase by around 2.9°C. • Marked release of cytokines within the brain and activation of astrocytes.	[28–31]
Inflammatory bowel disease model	Intracolonic administration of 2,4,6-trinitobenzene sulfonic acid (TNBS) at a dose of 50 mg/ml, 50mL per rat.	• Induces significant inflammatory response within the hippocampus. • Activation of microglial. • Increases levels of TNFα. • Increases susceptibility to PTZ-induced seizures.	[32–35]
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. • Increases body temperature slightly (by 0.9°C). • Increases seizure susceptibility.	[36–38]
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. • Seizures induced resemble human temporal lobe epilepsy. • Leads to neuronal cell death and induction of proinflammatory gene expression.	[39–44]
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. • Causes extensive neuronal cell loss, astrogliosis, and mossy fiber sprouting in hippocampus. • Developmental exposure to pilocarpine shows very little effect to startle response.	[45–50]
Serum albumin injection	Intracerebroventricular injection of 1.9 mM in rats.	• Mimics BBB breakdown following seizures. • Increased IL-1β immunoreactivity. • Astrocyte dysfunction. • Significant increase in interictal spikes and neuronal excitability. • Reduction in seizure threshold.	[51]

Table 1.
Animal models in epilepsy studies.

periphery [35]. 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 colitis 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

acute form of localized inflammatory colitis. To study the susceptibility to seizures, a convulsant, pentylenetetrazole (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 at15mg/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-1β, TNF-α, NF-κβ 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.

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Conflict of interest

Authors declare no conflict of interest.

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