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Pathophysiological Cascade of Events Leading to Epilepsy: Role of Inflammation

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Authors' contributions

This work was carried out in collaboration among all authors. Author HZA is the first and corresponding author designed the review and wrote the first draft of the manuscript. Authors HSAEKE and FOK managed the literature searches and critically revised the intellectual content. All authors read and approved the final manuscript.

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ABSTRACT

Epileptogenesis is an alteration modification of the typical brain structure, yielding a brain drained by recurring seizures. Such a process is usually precipitated by neurodegeneration, disruption of blood-brain barrier (BBB), the amygdala, the glutamatergic system, oxidative stress, and epigenetic modification deoxyribonucleic acid (DNA). Since there is no efficient method yet, to modify or control this disorder's pathway due to its unclear pathology, novel therapeutic approaches are needed. The risk to develop epilepsy, aggravate the frequency of seizures have been strongly linked to peripheral inflammatory disorders in humans as well as animal studies, with the latter demonstrating a specific association between peripheral inflammatory bowel disorders and peripheral injection of the Toll-like receptor 4 (TLR4) ligand lipopolysaccharide (LPS) and the increased seizer's frequency and their induced injuries. Understanding the exact function and role of the chemical mediators and receptors involved in the neuroinflammatory reaction could help elucidate their contribution to the pathogenesis of epilepsy.
These inflammatory markers include interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α), which are expressed in activated microglia and astrocytes; they trigger the complement

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system, nuclear factor-kappa b (NF-κB), cyclooxygenase-2 (COX-2), chemokines, and acute-phase proteins. The neural tissues and the endothelial layer of the BBB neurons are involved in these inflammatory reactions. The high-mobility-group Box 1 (HMGB1) fast release from microglia, neurons, and astrocytes after exposure to pro-convulsant insult and Toll-like receptor activation (TLR) signaling in astrocytes and neurons has been proven to be significantly involved in triggering brain inflammation and reducing the seizure threshold. The current review aims to determine the effect of anti-inflammatory drugs on the epilepsy foci rather than treating the symptoms. Such understanding could be the basis of developing a new treatment that could be effective for cases refractory to the current treatment.

Keywords: Epilepsy; HMGB1; celecoxib; VPA; TNF-α; (IL)-1β; IL-6; anti-oxidative; anti-inflammatory.

1. INTRODUCTION

Epilepsy is a common disorder of the central nervous system posing serious morbidities and a considerable death rate [1]. It is commonly presented as recurring, unprovoked convulsions caused by excessive and hypersynchronous electrical activities in the brain. The clinical picture of these seizures depends on the site of origin and the propagation of the brain's abnormal electrical discharge [2]. It ranges from a temporary loss of consciousness, an involuntary abnormal motor activity which could be minor limited to a certain body part or major involving the whole body [3].

Epilepsy is highly prevalent worldwide, with the developing countries demonstrating a higher incidence than that of the developed countries because of the poor obstetric services and the higher risk of brain trauma and infections [4]. In addition to that, the treatment is out of reach to around 80-90% of epilepsy cases [5,6]. It affects more than 50 million people with a prevalence of 6.54 per 1000 in Saudi Arabia's kingdom [7,8].

Men are at a slightly higher risk of developing epilepsy than women [1]. Children are more prone to develop epilepsy, especially after brain insults. Around 50% of epileptic patients had their first seizure during childhood, and 50% of these epileptic children had their first seizure during infancy (less than one-year-old) [5]. The children's immature brain is more susceptible to developing seizures than the adults' mature brain and is commonly more severe and precipitated by triggers that are also different from those of the mature brain. The physiologically immature ion homeostasis and other developmental characteristics alongside the aforementioned factors make treating childhood epilepsy challenging [5,6].

2. PATHOPHYSIOLOGY OF EPILEPSY AND EPILEPTOGENESIS

2.1 Etiology

The etiology is well identified in 40% of the epileptic cases like brain trauma, brain ischemia, prolonged acute symptomatic seizures like status epilepticus or complex febrile convulsions, intracerebral hemorrhage, neurodegenerative disorders, brain infections, or brain tumors. Etiologically, epilepsy could be categorized into idiopathic, acquired (symptomatic), and cryptogenic (presumed symptomatic) [9,10,11]. Idiopathic epilepsy starts early in life (childhood) without any brain insults and is not accompanied by any other neurologic signs or symptoms, so most researchers assume genes abnormalities. On the other hand, acquired and cryptogenic epilepsy starts after a single or multiple insults affecting the brain structure, which could be clearly identified in the former and unidentifiable in the latter [12].

2.2 Types of Seizures

According to the International League against Epilepsy, seizures include two major types. Generalized seizures in which both brain hemispheres are involved, and partial (focal) seizures (the commonest type), which starts in one brain hemisphere, mostly the temporal lobe giving rise to what is known as the temporal lobe epilepsy (TLE) [13]. TLE, is the most studied in research for being the hardest to control. Such latter fact has been attributed to the temporal lobe's complex nature, including highly susceptible structures to epileptogenic insults like the hippocampus amygdala and the piriform cortex. Many researchers have been spending great effort, especially on animal models, to unveil the pathogenesis of epilepsy, optimize the antiepileptic or disease-modifying therapy and minimize antiepileptic drug resistance [13].

2.3 Neurotransmitters and Receptors in Epileptogenesis

Among the most studied neurotransmitters are Glutamate and γ-aminobutyric acid (GABA), which have been implicated in the neuronal hyperexcitability of epilepsy when they are out of balance as Glutamate is responsible for neural excitation. Simultaneously, GABA is responsible for neural inhibition via neural hyperpolarization and generation of inhibitory presynaptic potentials [14]. One of the proposed mechanisms explaining the role of glutamate in epileptogenesis is the up-regulation of its receptors, which are classified into ionotropic (ligand-gated cation channels) receptors: α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA), N-methyl-D-aspartic acid (NMDA) and kainate, and metabotropic (G protein-coupled) receptors. Other mechanisms include increased extracellular level, abnormalities in glutamatergic transporters, and autoimmune disorders. The aforementioned mechanisms' net result is heightened glutamatergic activity, which increases the neural excitability and epileptic discharges, causing a phenomenon called 'paroxysmal depolarizing shift'[14,15]. On the electroencephalogram, it appears as an interactive pulse. It is associated with depolarization caused by a giant synaptic excitatory potential with a burst discharge characteristic caused by the initial activation of AMPA receptors followed by NMDA receptors [7]. Two types of GABA receptors have been reported to be involved in the GABAA and GABAB receptors' epileptogenic process[14]. GABAA receptors (ligand-gated ion channels) enhance chloride influx initiating fast inhibitory presynaptic potentials. GABAB receptors (G-protein-coupled receptors) enhance potassium conductance and decrease calcium influx initiating slow inhibitory presynaptic potentials. Inhibition or loss of the GABAergic action elevates the risk of emergence of excitatory postsynaptic potentials and synchronizing burst discharges, which trigger epileptic foci. Changes that could affect the GABAergic system include altered GABA receptors, impaired synthesis, or GABA release or neuronal loss [15,16].

Epileptogenesis could also be modulated by other neurotransmitters like noradrenaline, dopamine, and serotonin (5-hydroxytryptamine), a tryptophan-derived monoamine neurotransmitter. The nervous system has many serotonin receptors located on the cortical and/or hippocampal neurons, like 5-HT1A, 5-HT2C, and 5-HT7. Animal studies have demonstrated serotonin's role in epilepsy as shown in genetical epilepsy- prone rat model of audiogenic seizures, which were significantly affected by the depletion of serotonin and the mutants' mice that lacked the 5-HT1A or 5-HT2C receptor subtypes and demonstrated a lower seizure threshold. Human research also demonstrated a lower 5-HT1A receptor binding in the epileptogenic zone of TLE cases. In general, serotonin's role in neuronal excitability is mostly evident in the inhibitory effect of 5-HT1A receptors on the hyperpolarized glutamatergic neurons, the depolarizing effect of 5-HT2C receptors on GABAergic neurons, and the neuronal inhibitory effect of 5-HT3 and 5-HT7 receptors [10,17].

Noradrenaline is a product of dopamine. This catecholamine has two sources: the adrenal medulla (hormone) and the noradrenergic neurons of the central and sympathetic nervous systems (neurotransmitter) [16]. It has been demonstrated that endogenous noradrenaline acts as an anticonvulsant in epilepsy via preventing the formation of epileptic circuits and modifying the epilepsy-induced neuronal changes, its depletion heightens the risk to develop seizures as well as the post-seizure neuronal damage in the limbic region in rats [8].

2.4 Cellular Changes in Epilepsy

Some authors have proposed that epilepsy could result from new brain circuits, a process referred to as aberrant hippocampal neurogenesis. Many brain gross and cellular structure changes, and its neurochemicals have been detected to follow brain insults and acute convulsions. Cellular changes include forming new neurons, generating new granule cells with hilar basal dendrites, and abnormal migration of these cells into the dentate hilus and the dentate molecular layer. Such events could trigger aberrant circuits and excitatory loop formation, causing the generation and propagation of epileptiform activities [18].

2.5 Fever and Febrile Seizures

Fever is one of the symptoms that reflect the body response to many inflammatory, infectious, and stressful stimuli; it could trigger seizures (febrile convulsions) in up to 14% of Japanese young children and only 3 to 5% the western world young children. The pathogenesis of these seizures is still vague, although some studies

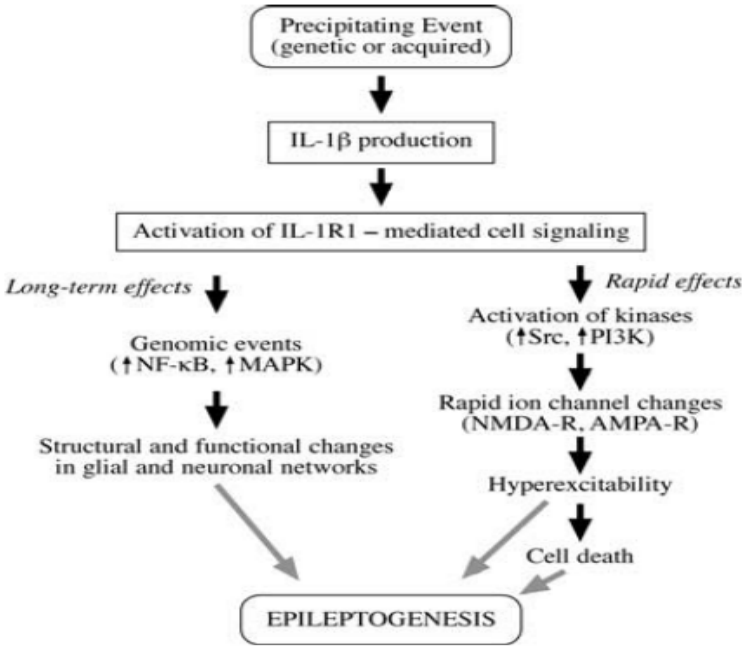

Fig. 1. IL-1β and Epileptogenesis. This figure illustrates the events occurring in the CNS as a result of IL-1β triggered release by a precipitating event. Brain IL-1β is mainly produced by glia (microglia and astrocytes); endothelial cells of the BBB, neurons, and lymphocytes are additional sources [13]

have implicated the IL-1β produced from peripheral and potential brain sources, which are up-regulated in the CSF of these cases [19]. Other studies have implicated genetic variances enhancing the expression of IL-1β. The role of genes has been proven in some studies conducted on animal models as a rat study demonstrating hyperthermia's inability to provoke convulsions in subjects with ablated IL-1R1 gene. Other studies have shown that intra-cerebral application of IL-1β in immature rodents reduces the threshold for induction of experimental febrile convulsions. It has been reported that hyperthermia triggers IL-1β synthesis in the hippocampal tissue, which is involved in the origin and spread of febrile convulsions. Most Experimental febrile convulsions studies have reported long-lasting changes in the expression of many intrinsic neuronal genes, which triggers seizures [20]. Fig. 1 demonstrates the role of IL-1β in the aforementioned alterations as its acutely up-regulated production induced by hyperthermia significantly enhances neuronal excitability causing evident changes to some gene transcription [13].

2.6 Glutathione (GSH) in Epilepsy

GSH plays a significant role in activating the antioxidant enzymes; abnormal GSH levels or activity led to the imbalanced antioxidant system and accumulated oxidants linked with the development and progression of some neuronal disorders like epilepsy [21].

3. INFLAMMATORY PATHWAY AND EPILEPTOGENESIS

It is understood that brain inflammation plays a crucial role in epileptogenesis. Although local inflammation is intended to protect tissue after insult, normal cell function is altered by aberrant inflammatory responses [22]. They can lead to significant effects, such as destruction of the blood-brain barrier, which can ignite seizure production and lead to intractable epilepsy. Inflammatory cytokines (including IL-10, IL-1β, IL-1Ra) partially mediate the pathogenic mechanisms operating in this process, including disturbance in ion channels' role and abnormal absorption and excitatory release neurotransmitters such as glutamate [23]. Brain cyclooxygenases (COX1 and COX2), called

prostaglandin-endoperoxide synthase (PTGS), are up-regulated and caused by seizures as the rate-limiting enzymes that catalyze the metabolism of arachidonic acid to prostaglandins [15].

3.1 Cytokines

Cytokines are polypeptide mediators well known to be involved in immune and inflammatory reactions. They recently have been implicated in the pathogenesis of epilepsy, especially interleukin (IL)-1β, IL-6, interferon (IFNγ), cyclooxygenase (COX)-2, nuclear factor kappa B (NF-κB), tumor necrosis factor-α and prostaglandin E2 (PGE2), which have been proven to be up-regulated in the brain regions harboring epileptic foci [16].

The inflammatory cytokines claimed to play a role in epilepsy pathology are produced by the glial cells, mainly microglia, and astrocytes, the non-neuronal cells of the central nervous system [17]. When these cytokines are secreted, a cascade of downstream inflammatory events follows recruiting neurons and activating adaptive immune response [18].

3.2 Role of Cytokines in Epilepsy

The exact role played by the inflammatory cytokines in epilepsy has yet to be determined. Some of the proposed theories claim that they produce toxic mediators causing apoptotic neuronal death, increase the blood-brain barrier (BBB) 's impermeability (BBB), and alter the neuronal excitability linked to IL-1β as it activates NMDA receptor, which enhances NMDA-mediated ion calcium influx into neurons. A similar role to that of IL-1β has been linked to the tumor necrosis factor-α and its role in down-regulating the GABA receptors in which the inhibitory synapse strength decreases [13,19]. The cytokine-mediated disruption of the BBB contributes to the epileptogenic activity via allowing more albumin, which binds to transforming growth factor-β receptor initiating a cascade of events leading to hyper-excitable neurons [19].

3.3 Cerebral Inflammatory Reaction and Immune System

Both innate and adaptive immune systems mediate cerebral inflammatory reaction through the astrocytes, microglia, and neurons [20]. Exposure of the body to noxious stimuli like infection the innate immune reaction rapidly recognizes the pathogen and removes it via homeostatic-type tissue inflammation. While in epilepsy, there is no pathogen (sterile inflammation), so the innate immune reaction is triggered by damage-associated molecular patterns (DAMPs) which are released by injured or activated neurons as in cases of ischemic or traumatic brain injuries, chronic neurodegenerative disorders, autoimmune disorders affecting the CNS, or during seizures [20,21].

DAMPs are typically intracellular molecules released extracellularly or exposed to the cell surface when exposed to troubling cellular stress signals and relay the message of tissue threats to cells carrying their cognate pattern recognition receptors (PRRs), which act as damage sensors. Proteins such as high mobility group box 1 (HMGB1), S100 proteins, adenosine triphosphate (ATP), migration inhibitor protein 8 (MRP8), which generates DAMPs, extracellular matrix degradation products, and IL-1β to cause inflammation, are recognized by microglia and astrocytes [21]. Fabene et al. [19] demonstrated in their study in which they induced seizures using pilocarpine and found an up-regulation of the development of vascular cell adhesion molecules with multiple leukocytes adhering to the endothelium of cerebral blood vessels mediated by leukocyte mucin P-selectin glycoprotein ligand-1 and leukocyte integrins, inflammatory cell adhesion was involved in the epilepsy process, triggering cerebral inflammation, hyper permeable BBB, neuronal hyper-excitability, leukocyte extravasation, and ultimately epileptogenesis [22].

4. IMMUNOLOGICAL PATHWAY

Clinically, the risk of developing epileptic seizures have been found to escalate in patients suffering from autoimmune disorders such as Hashimoto's encephalopathy, systemic lupus erythematosus (SLE), Sjogren's syndrome, Behcet's disease, and Rasmussen encephalitis (RE), which is a rare cerebral inflammatory disorder associated with higher levels of astrocytes, pro-inflammatory mediators, lymphocytes and activated microglial cells in the brain causing cerebral hemiatrophy, which progressively leads to severe seizures. Such cases benefit more from immunotherapies than antiepileptic drugs [23,24]. The risk is also magnified after TBI and is usually accompanied by neurological deficits like cognitive impairment, as reported by others [24,25].

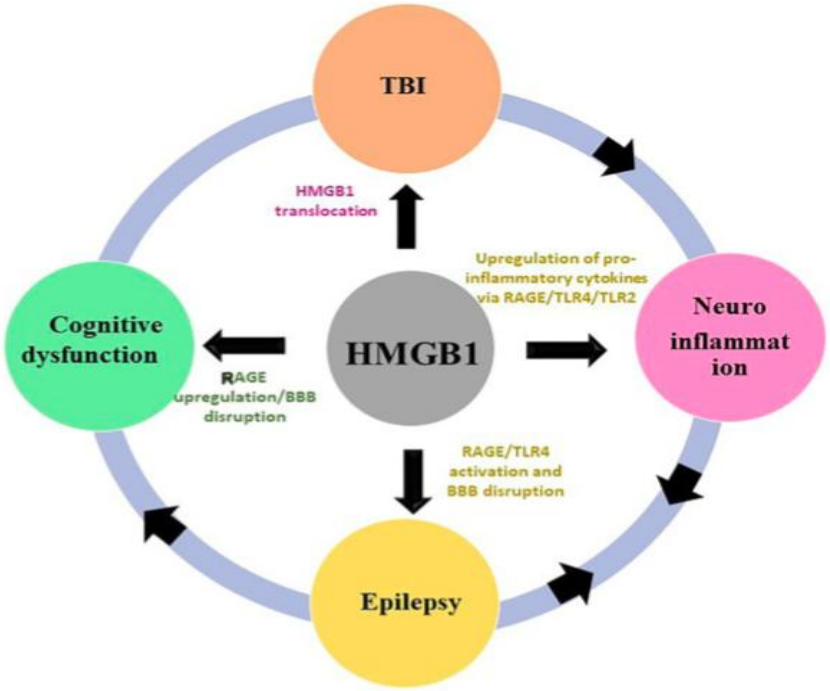

Fig. 2. Interlinkage of HMGB1 with epilepsy, cognitive disorders and neuroinflammatory disorders. The HMGB1 exerts its action via a putative mechanism a putative mechanism outlined in this figure [24]

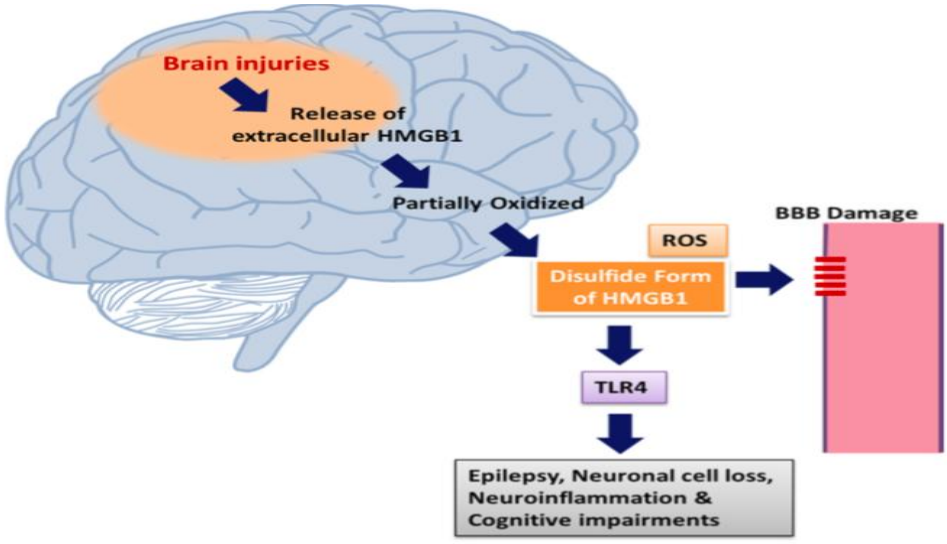

Fig. 3. Role of HMGB1, during brain injuries and epileptogenesis, from the dying cells, neurons and glia. The extracellular HMGB1 is partially oxidized. The disulphide HMGB1 activates TLR4 signaling which mediates pro-inflammatory activities responsible for enhancing the neuronal excitability. The stabilization of HMGB1 in its disulphide form is promoted by the generation of ROS. HMGB1 via activating receptors RAGE and TLR4 cause neuro-inflammatory disorders, loss of neuronal cells, cognitive disorders and epilepsy [24]

5. ROLE OF HIGH MOBILITY GROUP BOX 1 (HMGB 1) IN EPILEPSY

Among the best-characterized DAMPs is HMGB1, which has been believed to be the key culprit for traumatic brain injury (TBI) and the subsequent deterioration in cognitive ability [26]. It is a constitutive protein bound by non-histone chromatin that plays a role in gene transcription, replication of DNA, and repair. PRRs are activated either alone or in combination with other DAMPs by extracellular HMGB1 [27]. Its role in epileptic pathogenesis has recently been the subject of several studies. It has been confirmed that it is involved in breaching the blood-brain barrier and cerebral inflammation induction, but the exact mechanism is not clear. Studies in rats have also closely linked HMGB1 to reduced cognitive abilities related to neuroinflammation, TBI, and epilepsy [28,29] Fig. 2 & 3.

6. CYCLOOXYGENASE (COX) ROLE IN EPILEPSY

Cyclooxygenase (COX) reduces the rate of prostaglandin production, thus targeted by most non-steroidal anti-inflammatory medications. Two COX isozymes are known: COX-1, which is constitutively produced in almost all body tissues, and COX-2, predominantly produced in brain tissues after various insults, thus contributing to the brain inflammation involved in the long-term consequences of such insults [28]. Experimental studies conducted on rat models have shown a significant protective role of selective COX-2-inhibitors against epilepsy and neuronal damage despite the unclear role of COX-2 on the pathogenesis of epilepsy [29]. Because of this neuroprotection role, celecoxib, a selective COX-2-inhibitor non-steroidal anti-inflammatory medication, is currently prescribed as an anti-epileptogenesis disease-modification drug following brain insults like status epilepticus, cerebral ischemic injuries or head trauma. Thus, conditional ablation of forebrain neuronal COX-2 is neuroprotective as it ameliorates the status epilepticus-induced brain inflammation [30,31].

COX-2 is expressed in many types of neuronal tissue and is abundant in the cerebral cortex and hippocampus. It can be induced in migratory immune cells, glia, and neurons by the electrical stimulus, kainite, or pilocarpine-induced seizures. COX-2 is involved in the activation of the astrocytes, brain inflammatory reaction, death of neurons, enhanced neuronal excitability, cellular proliferation, and growth and spread of many tumors [30,31,32]. Inhibition of COX by non-steroidal anti-inflammatory drug drugs decreases neurogenesis and causes a dentate gyrus following acute global ischemia [29,33] Fig. 4.

Brain insult has been shown to activate the microglia, which, via the release of proinflammatory cytokines including COX-2, modulates the migration and differentiation of neural CNS precursor cells ectopic neurogenesis and astrogliosis [34,35].

Epilepsy results from long-lasting plastic changes in the brain tissue, including dispersion of the granule cell layer (GCL), inhibitory interneuronal loss, or axonal or dendritic reorganization [36,37,38]. Status epilepticus does not cause an instant insult to the brain tissues. Instead, the damage occurs over days or even weeks during which the physiology and the morphology of the hippocampus are modified, including locally signaled neurogenesis or gliosis [39,40]. Once these changes are established, spontaneous recurrent seizures (SRS) follow. Epileptic insult stimulates cellular proliferation in the subgranular layer (SGL) or subventricular zone (SVZ). It then produces ectopic granule cells in the hilus, and astrogliosis is reported to trigger epilepsy [41] Fig. 5.

Yamagata et al. [31] were the first to study COX-2-mediated neuroinflammation after a maximal electroconvulsive seizure through the immediate induction of COX-2 mRNA protein in the cerebral cortex of the rat hippocampus. They indicated that the COX-2 produced during the seizure caused prostaglandin development, which caused further brain damage and exacerbated the severity of the disease. According to them, N-methyl-D-aspartate (NMDA) receptor-dependent synaptic activity may control this seizure-mediated COX-2 induction [42,43]. In addition to the hippocampus and cerebral cortex in kainic acid (KA) as well as electroconvulsive shock-induced seizures, several related studies preceded study into other rat brain tissues, striatum, brain stem, and cerebellum, suggesting delayed neuronal damage of an interconnected neuronal network during COX-2 activation [44,45] Fig. 6.

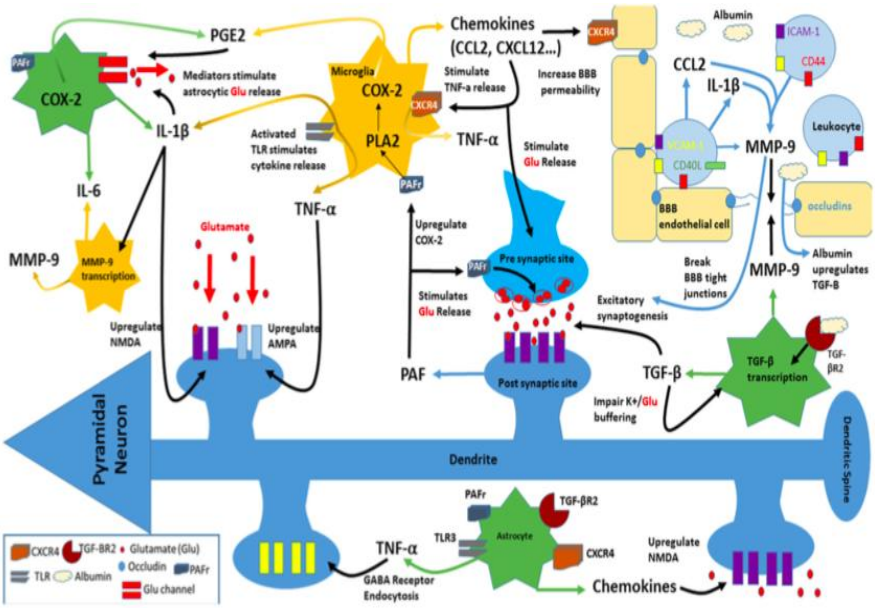

Fig. 4. Sources and targets of unregulated and overlapped components of inflammation in epileptogenesis. Brain insults triggers central inflammatory reactions and disturb the connectivity of hippocampal neurons. Systemic inflammation induces peripheral inflammatory reactions which heighten the up-regulation of inflammatory mediators that impair the physiology of the blood–brain barrier permitting leukocyte infiltration which induce neuronal hyper-excitability and further up-regulation of inflammatory mediators causing hippocampal morphological synaptic changes and finally, epilepsy [29]

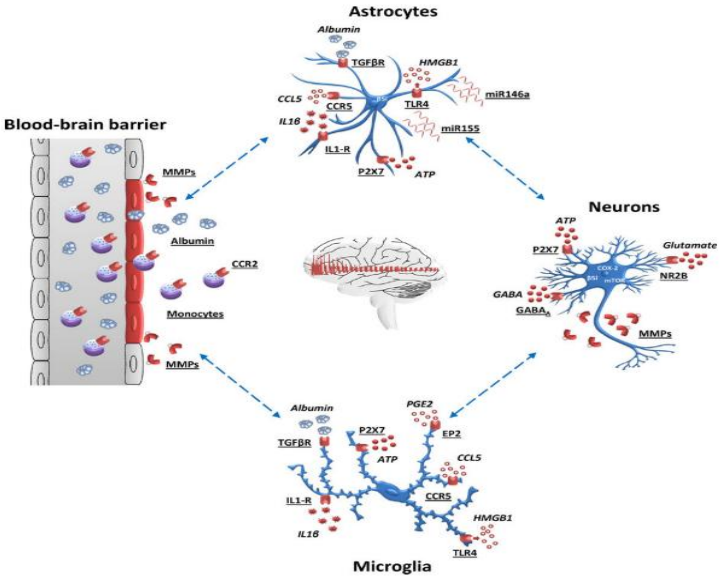

Fig. 5. A cascade of inflammatory reactions involving neurons, astrocytes, microglia, and endothelium. Many inflammatory targets have been reported in previous studies (i.e., cyclooxygenase-2, prostaglandin EP2 receptor, interleukin-1b, HMGB1/Toll-like receptor signaling, P2X7 receptor, immunoproteasome, mTOR, TGFβ, metalloproteinases (MMPs), chemokines). The complement activation (not shown) could also contribute to a sustained inflammatory response, deserving further investigation as a potential target of therapy [25]

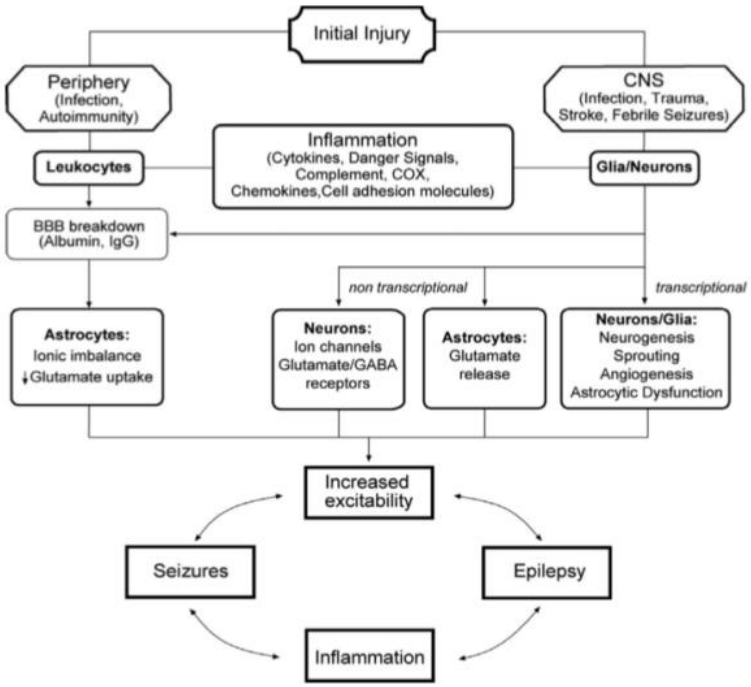

Fig. 6. Pathophysiological cascade of events leading from inflammation to epilepsy [30]

7. CONCLUSION

Several studies on the pathogenesis of epilepsy and its mediators have been performed, aiming to uncover the mystery behind the frequent seizures. The HMGB 1 has had the most focus for being a suspect in this scenario. Although epileptogenesis's definite mechanism is yet to be elaborated, inflammation of the brain tissue has been proven to be a key player. HMGB1 participate in the inflammatory reaction that triggers the epileptic activity, reacting as a pathogenic inflammatory cytokine to the epileptic injury.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

it's not applicable.

ETHICAL APPROVAL

It's not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Banerjee, PN, Filippi D, Hauser WA. The descriptive epidemiology of epilepsy—a review. Epilepsy Research. 2009;85(1):31-45.
2. Baxendale S, Holdsworth CJ, Santoscoy PLM, Harrison MR, Fox J, Parkin CA. Identification of compounds with anti-convulsant properties in a zebrafish model of epileptic seizures. Disease Models & Mechanisms. 2012;5(6):773-784.
3. Mbuba CK, Ngugi AK, Newton CR, Carter JA. The epilepsy treatment gap in developing countries: A systematic review of the magnitude, causes, and intervention strategies. Epilepsia. 2008;49(9):1491-1503.
4. Alaqeel A, Sabbagh AJ. Epilepsy; What do Saudi's living in Riyadh know? Seizure. 2013;22(3):205-209.

5. Bell G, Sander J. CPD—Education and self-assessment the epidemiology of epilepsy: The size of the problem. Seizure. 2001;10(4):306-316.
6. Wahab A, Albus K, Gabriel S, Heinemann U. In search of models of pharmacoresistant epilepsy. Epilepsia. 2010;51:154-159.
7. Britton JW, Frey LC, Hopp JL, St. Louis EK, Frey LC, et al. Electroencephalography (EEG): An introductory text and atlas of normal and abnormal findings in adults, children, and infants [internet]. American Epilepsy Society; 2016.
8. Yin YH, Ahmad N, Makmor-Bakry M. Pathogenesis of epilepsy: challenges in animal models. Iranian Journal of Basic Medical Sciences. 2013;16(11):1119.
9. Rawat C, Kukal S, Dahiya UR, Kukreti R. Cyclooxygenase-2 (COX-2) inhibitors: Future therapeutic strategies for epilepsy management. Journal of Neuroinflammation. 2019;16(1):1-15.
10. Bagdy G, Kecskemeti V, Riba P, Jakus R. Serotonin and epilepsy. Journal of neurochemistry. 2007;100(4):857-873.
11. Tully K, Bolshakov VY. Emotional enhancement of memory: How norepinephrine enables synaptic plasticity. Molecular brain. 2010;3(1):15.
12. Kuruba R, Hattiangady B, Shetty AK. Hippocampal neurogenesis and neural stem cells in temporal lobe epilepsy. Epilepsy & Behavior. 2009;14(1): 65-73.
13. Pack AM. Epilepsy overview and revised classification of seizures and epilepsies. Continuum: Lifelong Learning in Neurology. 2019;25(2):306-321.
14. Clossen BL, Reddy DS. Novel therapeutic approaches for disease-modification of epileptogenesis for curing epilepsy. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2017; 1863(6):1519-1538.
15. Vezzani A, Friedman A, Dingledine RJ. The role of inflammation in epileptogenesis. Neuropharmacology. 2013;69:16-24.
16. Following status epilepticus in rats. Neuropharmacology. 61(5-6):1033-1047.
17. Cherian A, Thomas SV. Status epilepticus. Annals of Indian Academy of Neurology. 2009;12(3):140.
18. Vezzani A, Baram TZ. New roles for interleukin-1 Beta in the mechanisms of epilepsy. Epilepsy currents. 2007; 7(2):45-50.
19. Fabene PF, Mora GN, Martinello M, Rossi B, Merigo F, Ottoboni L. A role for leukocyte-endothelial adhesion mechanisms in epilepsy. Nature medicine. 2008;14(12):1377-1383.
20. Lee VLL, Shaikh MF. Inflammation: Cause or consequence of epilepsy? Epilepsy-Advances in Diagnosis and Therapy: IntechOpen; 2019.
21. Cárdenas-Rodríguez N, Coballase-Urrutia E, Pérez-Cruz C, Montesinos-Correa H, Rivera-Espinosa L, Sampieri A. Relevance of the glutathione system in temporal lobe epilepsy: Evidence in human and experimental models. Oxidative medicine and cellular longevity; 2014.
22. Vezzani A, Granata T. Brain inflammation in epilepsy: Experimental and clinical evidence. Epilepsia. 2005;46(11):1724-1743.
23. Nguyen MD, Julien JP, Rivest S. Innate immunity: the missing link in neuroprotection and neurodegeneration? Nature Reviews Neuroscience. 2002; 3(3):216-227.
24. Vezzani A, Moneta D, Richichi C, Aliprandi M, Burrows SJ, Ravizza T. Functional role of inflammatory cytokines and antiinflammatory molecules in seizures and epileptogenesis. Epilepsia. 2002; 43:30-35.
25. Vezzani A, Ravizza T, Balosso S, Aronica E. Glia as a source of cytokines: implications for neuronal excitability and survival. Epilepsia. 2008;49:24-32.
26. Ravizza T, Terrone G, Salamone A, Frigerio F, Balosso S, Antoine DJ. High mobility group box 1 is a novel pathogenic factor and a mechanistic biomarker for epilepsy. Brain, Behavior, and Immunity. 2018;72:14-21.
27. Paudel YN, Shaikh M, Chakraborti A, Kumari Y, Aledo-Serrano Á, Aleksovska K. HMGB1: A common biomarker and potential; 2018.
28. Aronica E, Bauer S, Bozzi Y, Caleo M, Dingledine R, Gorter JA. Neuroinflammatory targets and treatments for epilepsy validated in experimental models. Epilepsia. 2017;58:27-38.
29. Gumus E, Taskıran AS, Toptas HA, Güney Ö, Kutlu R, Gunes H. Effect of the cyclooxygenase-2 inhibitor tenoxicam on pentylenetetrazole-induced epileptic

seizures in rats. Cumhuriyet Tıp Dergisi. 2017;39(4):652-658.
30. Jung KH, Chu K, Lee ST, Kim J, Sinn DI, Kim JM. Cyclooxygenase-2 inhibitor, celecoxib, inhibits the altered hippocampal neurogenesis with attenuation of spontaneous recurrent seizures following pilocarpine-induced status epilepticus. Neurobiology of Disease. 2006;23(2):237-246.
31. Yamagata K, Andreasson KI, Kaufmann WE, Barnes CA, Worley PF. Expression of a mitogen-inducible cyclooxygenase in brain neurons: regulation by synaptic activity and glucocorticoids. Neuron. 1993;11(2):371-386.
32. Rana A, Musto AE. The role of inflammation in the development of epilepsy. Journal of Neuroinflammation. 2018;15(1):144. Available:https://doi.org/10.1186/s12974-018-1192-7
33. Vezzani A. Epilepsy and inflammation in the brain: overview and pathophysiology: epilepsy and inflammation in the brain. Epilepsy Currents. 2014;14(2_suppl):3-7.
34. Gong L, Thorn CF, Bertagnolli MM, Grosser T, Altman RB, Klein TE. Celecoxib pathways: pharmacokinetics and pharmacodynamics. Pharmacogenetics and Genomics. 2012;22(4):310.
35. Kanner AM, Palac S. Neuropsychiatric complications of epilepsy. Current Neurology and Neuroscience Reports. 2002;2(4):365-372.
36. Marchi N, Oby E, Batra A, Uva L, De Curtis M, Hernandez N. In vivo and *In vitro* effects of pilocarpine: Relevance to ictogenesis. Epilepsia. 2007;48(10):1934-1946.
37. Organization WH, Epilepsy GCa, Diseases PfN, Neuroscience Epilepsy IBf, Health WHODoM, Abuse S, Epilepsy IBo, Epilepsy ILa. Atlas: epilepsy care in the world: World Health Organization; 2005.
38. Rafnsson V, Ólafsson E, Hauser WA, Gudmundsson G. Cause-specific mortality in adults with unprovoked seizures. Neuroepidemiology. 2001;20(4):232-236.
39. Sharma AK, Rani E, Waheed A, Rajput SK. Pharmacoresistant epilepsy: A current update on non-conventional pharmacological and non-pharmacological interventions. Journal of Epilepsy Research. 2015;5(1):1.
40. Sperling MR. Sudden unexplained death in epilepsy. Epilepsy Currents. 2001;1(1):21-23.
41. Vezzani A. Pilocarpine-induced seizures revisited: What does the model mimic? Epilepsy Currents. 2009;9(5):146-148.
42. Vezzani A, Friedman A. Brain inflammation as a biomarker in epilepsy. Biomarkers in Medicine. 2011;5(5):607-614.
43. Vezzani A, Maroso M, Balosso S, Sanchez MA, 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.
44. Vidaurre J, Gedela S, Yarosz S. Antiepileptic drugs and liver disease. Pediatric Neurology. 2017;77:23-36.

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