

Inflammatory response in epilepsy is mediated by glial cell gap junction pathway (Review)

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Abstract. Epilepsy is a common neurological disease that affects more than 50 million people worldwide. Neuroinflammation plays an important role in epilepsy. Activation of the immune system and an excessive inflammatory response can increase the frequency of seizures and increase the susceptibility to epilepsy. Therefore, anti-inflammatory therapies may have antiepileptic effects. Connexin 43 (Cx43) is a major component of astroglial hemichannels and gap junctions. Gap junctions are important for the direct exchange of substances and information between cells, as well as regulating the neuroinflammatory response, changing neuronal excitability, neuronal apoptosis, and synaptic remodeling. Cx43-mediated gap junction pathway can be crucial in epilepsy-induced neuroinflammatory cascades. Further, pro-inflammatory cytokines may in turn directly affect the expression of the Cx43 protein in astrocytes. Therefore, examining the association between neuroinflammation and epilepsy can be instrumental in uncovering the pathogenesis of epilepsy, which can lead to the development of novel and more effective antiepileptic drugs.

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Abbreviations: Cx43, connexin 43; ATP, adenosine triphosphate; IL, interleukin; TNF, tumor necrosis factor

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1. Introduction

Epilepsy is a common neurological disease that affects >50 million people worldwide. Approximately 30% of epileptic patients are resistant to various antiepileptic drugs and eventually develop refractory epilepsy (1,2). Although novel treatment strategies have been developed over the past few years, certain cases of refractory epilepsy cannot be controlled yet (3). In addition, most available treatments are focused on decreasing seizures by inhibiting the excitability of the nervous system (4). Therefore, the development of new antiepileptogenic therapies that can resolve seizures is imminent (5). Recent studies reported that neuroinflammation plays an important role in the development of epilepsy and abnormal neural circuits (6-11). Further, anti-inflammatory therapies were reported to have possible antiepileptogenic potential (12,13). Therefore, uncovering the role of inflammatory reactions in epilepsy can lead to the development of more effective and novel antiepileptic drugs which can decrease the disability rate and improve the quality of life in epileptic patients.

2. Inflammatory reaction in the central nervous system

The central nervous system can be termed as an 'immunity exemption zone' because the blood-brain barrier restricts the entry of various substances in the blood circulation (14-17). However, accumulating evidence indicates that the immune exemption of the central nervous system is relative (18,19). Engelhardt *et al* (20) reported that although immature T cells cannot pass through the blood-brain barrier, activated T cells can directly attach to the surface of the cerebral vascular endothelium and pass through the blood-brain barrier in the direction of blood flow. After crossing the blood-brain barrier, T cells can mediate inflammation in the central nervous system (20).

The central nervous system has a special 'immune defense line'. Cells involved in the brain's inflammatory reaction include the microglia, astrocytes and endothelial cells. Microglia are the immune sentinels of the central nervous system; they can be activated by injury stimuli and induce the corresponding inflammatory reaction, which maintains homeostasis in the central nervous system (21). The number of microglia is relatively small, accounting for ~5% of the

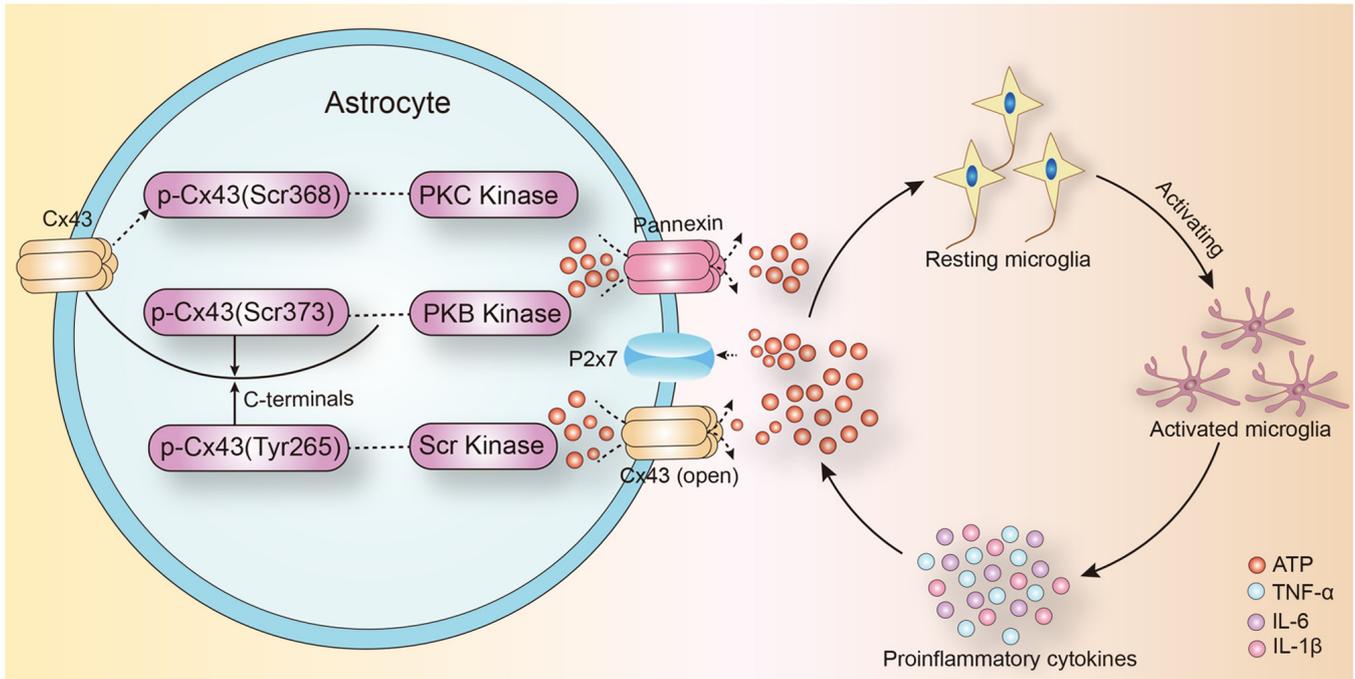


Figure 1. Proposed role of Cx43 pathway and ATP in inflammatory activation of microglia in epilepsy. Under physiological conditions, Cx43 is phosphorylated and the channel is closed. Cx43 is dephosphorylated by a variety of protein kinases or protein phosphatases in epilepsy. The change in Cx43 conformation leads to abnormal opening of the channels. The release of the intracellular ATP mediates the activation and differentiation of microglia into proinflammatory phenotypes, and mediates the process of neuroinflammatory response in epilepsy. Cx43, connexin 43; TNF, tumor necrosis factor; IL, interleukin; ATP, adenosine triphosphate.

glial population (22-24). Following infection or damage to the central nervous system, the resting microglia acquire antigenicity, their shape becomes extended, and they are activated into macrophages to participate in the inflammatory reaction together with T cells inoculated within the blood circulation (25). However, hyperactivated microglia are important sources of pro-inflammatory factors as well as oxidative stress, and can cause neurotoxicity.

Astrocytes are also important contributors to the inflammatory reaction in the nervous system (26,27). Astrocytes can play a role in neuronal migration movement, maintain the potassium concentration in the central nervous system, regulate neuronal excitability, and present antigens to autoreactive T cells.

Microglia are activated leading to the production of inflammatory factors following trauma or other injuries. Activated microglia can release cytotoxic substances and cytokines (28). Further, tissue injury could lead to the infiltration of circulating immune cells (29). Additionally, brain tissues are also exposed to systemic inflammatory response, which further aggravates the immune response and leads to secondary neuronal damage (30).

3. Role of the inflammatory reaction in the development of epilepsy

Activation of the immune system and an excessive inflammatory response play crucial roles in the development of chronic seizures (31-33). Moreover, neuronal inflammation associated with inflammatory cytokines signaling pathways may trigger epileptogenesis (34). Of note, patients diagnosed

with relapsing remitting multiple sclerosis with epilepsy showed more extensive cortical inflammation compared with patients diagnosed with relapsing remitting multiple sclerosis without epilepsy (35). Therefore, examining the association between neuroinflammation and epilepsy can help uncover the pathogenesis. Clinical and animal studies suggested that the immune response is triggered during the pathophysiology of epilepsy and that the inflammatory reaction within the brain may be involved in the development of epilepsy (36,37). Further, the dysregulation of immunoinflammatory reactions during the pathological course of epilepsy was associated with seizure-induced plasticity (10). Rana and Musto (37) reported that neuronal inflammation generated by neural death and astrocytes proliferation was associated with the microglial activation in damaged areas such as the amygdala, piriform and hippocampus in a rat model of lithium-pilocarpine-induced epilepsy (38). This dysfunction can facilitate the occurrence of epileptic seizures or epilepsy-induced neuronal damage (39). Indeed, inflammatory reactions were found to increase the propensity for seizures, change neuronal excitability, damage the blood-brain barrier, and mediate neuronal apoptosis and synaptic remodeling by activating intracellular signaling pathways (40). Seizures can activate microglia and neurons in the brain, and produce a series of inflammatory reactions without additional exogenous stimuli (32,33). Consequently, microglia and neurons secrete large amounts of pro-inflammatory factors and prostaglandins, and activate the complement system, which ultimately promotes neuronal death and synapse regeneration, leading to chronic spontaneous seizures (10,39).

Noteworthy, adenosine triphosphate (ATP) was shown to activate the sterile inflammatory process through interactions

with purinergic receptors (40). The ATP-gated ionotropic P2X7 receptor (P2X7R) can mediate the regulation of neuroinflammation and immune reactions in the central nervous system (41). Neuronal injury was reported to activate microglia and increase the expression of P2X7R (42,43). Monif *et al* (44) reported that the overexpression of P2X7R is sufficient to drive microglial activation. Moreover, the Fas ligand derived from microglia exacerbates P2X7-mediated microglial activation and triggers a vicious cycle of neuronal death (45,46). Low concentrations of ATP act as chemotactic agents for microglia recognition and migration to guide them to the site of injury (47). ATP-stimulated and P2X4R-mediated microglial activation might have an initial protective effect. Activated microglia can remove potentially necrotic cell debris and promote tissue repair, thereby contributing to neuroprotection. Further, activated microglia release neurotrophic factors through activated P2X4Rs and contribute to neuronal survival (48). P2X7R-activated microglia in neuron-microglia co-culture protect neurons from glutamate toxicity primarily by releasing tumor necrosis factor (TNF)- α . The depletion of microglia can lead to an increase in the levels of cytokines and chemokines such as interleukin (IL)-1 β , TNF- α , cytokine-induced neutrophil chemoattractant 1 and monocyte chemoattractant protein-1 in the brain, which aggravates brain damage (49). In later stages of brain injury, ATP can stimulate the overexpression of microglia P2X7R, leading to microglia activation and proliferation, as well as cell death (50). Over-activated microglia upregulate the expression of surface immunomodulatory proteins and release of neurotoxic proinflammatory factors such as IL-1 β , IL-6, and TNF- α , which can promote further activation of microglia. Long-term inflammatory reactions result in neuronal death that affects both healthy and damaged cells (51,52).

The expression of connexin 43 (Cx43) in astrocytes is affected by inflammatory cytokines (53). Treatment with IL-1 β , for 24 h, inhibited the gap junction communication between the human embryonic astrocytes and decreased Cx43 mRNA and protein expression (54). IL-1 β had a transient inhibitory effect on gap junction communication between primary astrocytes, and this inhibitory effect was produced through p38-dependent signaling pathway (55). Therefore, Cx43-mediated gap junction communication in astrocytes is closely correlated to the inflammatory response in the central nervous system. They regulate inflammation in the brain and selectively regulate the opening of gap junction communication by intracranial inflammatory factors (Fig. 1).

4. Regulation of astrocyte glial junction in epilepsy

Cx43 is a major component of astroglial hemichannels and gap junctions (56). Gap junctions play an important role in neuroinflammatory reactions (52). However, the impact of astrocyte Cx43, its hemichannel, and gap junctions on regulating the neuroinflammatory response in epilepsy is still unclear.

Astrocytes are the largest glial cell population in the central nervous system. Cx43 is a gap junction protein that is mainly expressed in astrocytes and mediates over 95% of the gap junction communication in the brain (57). Under physiological conditions, gap junctions allow the exchange of

small molecules (<1.5 kDa) between cells. ATP mediates the migration of activated microglia to the injured area, especially in the initial phase of inflammation (41). Further, extracellular ATP induces the release of endogenous ATP from microglia and attracts distant microglia to the injury site, which leads to the promotion of the inflammatory cascade. ATP released by astrocyte hemichannels establishes an ATP gradient in the extracellular environment that can trigger microglial activation (58,59). Increased extracellular ATP concentration in the injury site mediates the activation of microglia around the lesion (60). Of note, the local injection of ATP mimicked the traumatic brain injury-induced microglial activation and the administration of the gap junction channel blocker, carbenic acid, significantly inhibited the microglial activation (61,62). Following injury, extracellular ATP is released from the open hemichannels and mediates a rapid reaction to microglial damage (63). Jesus *et al* (64) demonstrated that targeted knockout of astrocyte Cx43 expression decreased proinflammatory cytokine levels in the brain following lipopolysaccharide injection. In addition, hemichannel modulators like Cx43 mimetic peptide and Cx43 antisense oligonucleotides could inhibit the inflammatory response mediated by microglial activation following spinal cord injury (65). Taken together, it is plausible that astrocyte gap junction channel can act as a 'switch' in the inflammatory signaling cascade by promoting the release of ATP into the extracellular space. The inflammatory response can affect neuronal excitability, neuronal apoptosis and synaptic remodeling. These factors can lead to the development of abnormal neural excitability, which contributes to the pathogenesis of epilepsy. At the same time, pro-inflammatory cytokines can directly affect the expression of Cx43 protein in astrocytes (Fig. 1).

5. Conclusion

The occurrence, development and maintenance of epileptic seizures progress through a complicated process. The neuro-inflammatory reaction can aggravate epilepsy and maintain recurrent episodes by increasing neuronal excitability, mediating neuronal apoptosis and remodeling the synapses. Therefore, controlling the neuroinflammatory reaction can mitigate the downstream cascade. The gap junction pathway mediated by astrocyte Cx43 can play a crucial role in controlling the epilepsy-induced neuroinflammatory cascade. Therefore, Cx43 can be a potential target for managing epileptic inflammatory reactions. Studies that examine the correlation between neuroinflammation and gap junctions will lead to a better understanding of epilepsy pathogenesis and can uncover new treatment targets.

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Authors' contributions

CX and JX searched for literature; GW and JW wrote this review; JL and XW revised this review. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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