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Epilepsy and Inflammation in the Brain: Overview and Pathophysiology

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The possibility that inflammatory processes in the brain contribute to the etiopathogenesis of seizures and the establishment of a chronic epileptic focus is increasingly recognized as a result of supportive evidence in experimental models and in the clinical setting. Prototypical inflammatory cytokines (such as IL-1beta) and "danger signals" (such as HMGB1 and S100beta) are overexpressed in human and experimental epileptogenic tissue, prominently by glia. Neurons and endothelial cells of the blood–brain barrier contribute to inflammatory processes. All these cell types also express receptors for inflammatory mediators, suggesting that inflammatory molecules in the brain exert both autocrine and paracrine activation of intracellular signaling cascades; thus, they may act as soluble mediators of cell communication in diseased tissue.

In experimental models, seizures also trigger brain inflammation in the absence of cell loss; in human epileptogenic tissue, the type of neuropathology associated with chronic seizures contributes to determine the type of cells expressing the inflammatory mediators, and the extent to which inflammation occurs.

Inflammatory molecules, such as IL-1beta and HMGB1, have proconvulsant activity in various seizure models, most likely by decreasing seizure threshold via functional interactions with classical neurotransmitter systems. These findings reveal novel glioneuronal communications in epileptic tissue that highlight potential new targets for therapeutic intervention.

Inflammation has been implicated in the progressive nature of neurodegenerative diseases (1), and inflammatory processes are now considered key contributors to acute and chronic neurodegenerative disorders, such as ischemic stroke and Alzheimer's disease (2). In the last decade, experimental and clinical findings support a crucial role of inflammatory processes in epilepsy (3), in particular in the mechanisms underlying the generation of seizures. Since inflammation represents a homeostatic response to brain injury or pathological threats, its involvement in epilepsy should be envisaged when the extent or duration of inflammatory processes in brain tissue is exceeding the homeostatic threshold.

Sources and Targets of Cytokines and Inflammatory Mediators in Epileptic Tissue

Experimental evidence in rodents demonstrates that seizures induce high levels of inflammatory mediators in brain regions involved in the generation and propagation of epileptic activity. In particular, a rapid-onset inflammatory response is triggered in glia by seizures induced by chemoconvulsants or electrical stimulation (4–11). Prototypic inflammatory cytokines—such as interleukin(IL)-1β, IL-6 and TNF-α—are upregulated in activated microglia and astrocytes, and then trigger a cascade of downstream inflammatory events that also involves neurons and endothelial cells of the blood-brain barrier (BBB) (i.e., activation of NFkB, COX-2, complement system, chemokines, acute phase proteins) (3,10,12). The rapid release of high-mobility-group box 1 (HMGB1) from neurons, microglia, and astrocytes following proconvulsant injuries, and its activation of Toll-like receptor (TLR) signaling in astrocytes and neurons has been proposed as a crucial event for initiating brain inflammation and decreasing seizure threshold (13). HMGB1 is considered to be a danger signal released from injured or stressed cells to alert the microenvironment of an immediate or ongoing injury. Its interaction with cognate TLR4 triggers innate immune mechanisms in tissue and activates the related inflammatory events (14). Penetration into the brain parenchyma of leukocytes has also been described after seizure occurrence (10,15–19; for review, see 3), likely as a consequence of activation of innate immunity in the brain (i.e., microglia and astrocytes derived inflammatory mediators) and upregulation of adhesion molecules in endothelial cells of the BBB.

Investigation of the pattern of expression of cytokine receptors in seizures has given information on the cell populations targeted by the cytokines. IL-1R1, which mediates the biological responses to IL-1β, is rapidly increased in neurons after seizures, as well as later in astrocytes (8, 15), thus indicating both paracrine and autocrine actions of IL-1β acting as a soluble mediator of glioneuronal communications in epileptogenic tissue. Strong IL-1β and IL-1R1 immunoreactivity is

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found also in perivascular astrocytes and in endothelial cells of the microvasculature; these changes are associated with evidence of albumin extravasation in brain tissue reflecting BBB breakdown (15). Cytokines can indeed affect the permeability properties of the BBB via disruption of the tight-junction organization or production of nitric oxide and activation of matrix methalloproteinases in endothelial cells (for review, see 2). Alterations in BBB permeability favors neuronal hyperexcitability (for review, see 20), by resulting in albumin extravasation and its astrocytic uptake; this phenomenon compromises astrocytes ability to buffer extracellular K^+ and to reuptake extracellular glutamate (21–23; for review, see 24). The extent of BBB leakage positively correlates with the frequency of spontaneous seizures in rats suggesting a reciprocal cause–effect relationship (25).

Inflammation in Human Epileptic Brain

The activation of both innate and adaptive immune systems has been described in human epilepsy. The analysis of brain specimens from drug-refractory epileptic patients showed upregulation of IL-1β and HMGB1 and their receptors IL-1R1 and TLR4, in glia and neurons in epileptogenic tissue. This suggests that the activation of these signaling pathways occurs in human epilepsy (13, 15, 17, 18, 26, 27).

Moreover, upregulation of complement system and COX-2 were also shown in parenchymal brain cells (28–30). Noteworthy, in epilepsy associated with malformations of cortical development, a positive correlation was found between the percentage of IL-1β-positive brain cells and the frequency of seizures prior to surgical resection (27). Cells of adaptive immunity were detected in some but not all types of epilepsy; for example, a notable absence of lymphocytes was described in temporal lobe epilepsy specimens (15), and this is clearly different from Rasmussen's encephalitis or from epilepsies associated with malformations of cortical development where these cells were found often in close apposition with degenerating or dysmorphic neurons (17, 18, for review, see 31).

The finding that inflammatory events persist during epileptogenesis in experimental models—thus outlasting the initial precipitating event (e.g., status epilepticus, prolonged febrile seizures) (6, 15, 32)—suggests that inflammatory processes may precede the onset of epilepsy in humans, possibly playing an etiopathogenetic role in the occurrence of spontaneous seizures. The use of transgenic mice overexpressing TNF-α or IL-6 indicates that a chronic inflammatory state in the brain can indeed predispose to the occurrence of seizures (33–36). Further, long-term increase in brain excitability was demonstrated in rodents after systemic administration of lipopolysaccharide (LPS), a proinflammatory agent mimicking bacterial infection that induces both systemic and brain inflammation (37).

Functional and Pharmacological Studies in Experimental Models

The role of inflammatory molecules in seizures has been investigated using genetically modified mice with perturbed inflammatory systems or by pharmacological means to specifically block inflammatory pathways. The application of proinflammatory molecules—such as IL-1β (11, 38), HMGB1 (13), complement system component (39), or specific prostaglandins (28, 40) in rodent brains—can result in receptor-mediated proconvulsant effects. In contrast, the intracerebral injection of specific antagonists of some of these proinflammatory molecules (or interference with related intracellular signaling pathways) mediates powerful anticonvulsant effects (4, 13, 38, 41–45). As an example, the injection of IL-1β in rodent brain increases seizure frequency induced by the glutamate analog kainic acid or the $GABA_A$ antagonist bicuculline (11, 45). Importantly, the intracerebral injection of the endogenous receptor antagonist of IL-1β, IL-1ra, mediates powerful anticonvulsant effects (41, 45); furthermore, transgenic mice overexpressing IL-1ra in astrocytes have a reduced susceptibility to seizures (45), demonstrating that IL-1β contributes to seizures in these models. Accordingly, selective blockade or gene deletion of interleukin-converting enzyme (ICE or caspase-1)—the enzyme that produces the biologically active form of IL-1β—reduces seizures significantly in acute models and in chronic epileptic mice (46, 47).

Since IL-1β acts as pyrogen after its central or systemic administration, recent studies have addressed the possibility that the increase in IL-1β during fever evokes seizures in immature rodent brain (48, 49): Intracerebral application of IL-1β reduced the threshold to seizures in two models of febrile convulsions caused by hyperthermia (48) or by LPS (49). Moreover, mice with a deletion of the IL-1R1 gene were resistant to induction of hyperthermia-induced seizure, thus demonstrating the significant contribution of IL-1β (48).

Role of Cytokines in Neuronal Excitability

In addition to the classical induction of NFkB-mediated gene transcription described during peripheral inflammation, nonconventional intracellular signaling pathways are activated by proinflammatory mediators in the epileptogenic tissue. These novel mechanisms are likely to contribute to neuronal hyperexcitability underlying seizures, mediating at least part of the inflammation related glioneuronal interactions that have a role in decreasing seizure threshold.

For example, recent evidence demonstrates that IL-1β activation of neuronal IL-1R1 induces Src kinase-mediated tyrosine phosphorylation of the NR2B subunit of the N-methyD-aspartate (NMDA) receptor, a key glutamate receptor involved in seizures. As a consequence of this action, NMDA receptor-mediated Ca^{2+} influx into neurons is enhanced by IL-1β, and this effect plays a role in promoting excitotoxicity (50) and seizure generation (38). This mechanism is also shared by HMGB1, another proinflammatory molecule that is implicated in experimental seizure precipitation and recurrence (13).

Activation of other kinase families (e.g., MAPK, PKA, PKC) by proinflammatory molecules has been implicated in rapid posttranslational changes in voltage-dependent Ca^{2+}, Na^+, and K^+ ion channels with significant impacts on neuronal excitability (28, 51).

IL-1β can also inhibit the astrocytic reuptake of glutamate (52, 53) and increases its glial release possibly via TNF-α production (54), resulting in elevated extracellular glutamate levels. It has been recently reported that the astrocytic glutamate release may have a role in the genesis or strength of seizure-like events (55, 56).

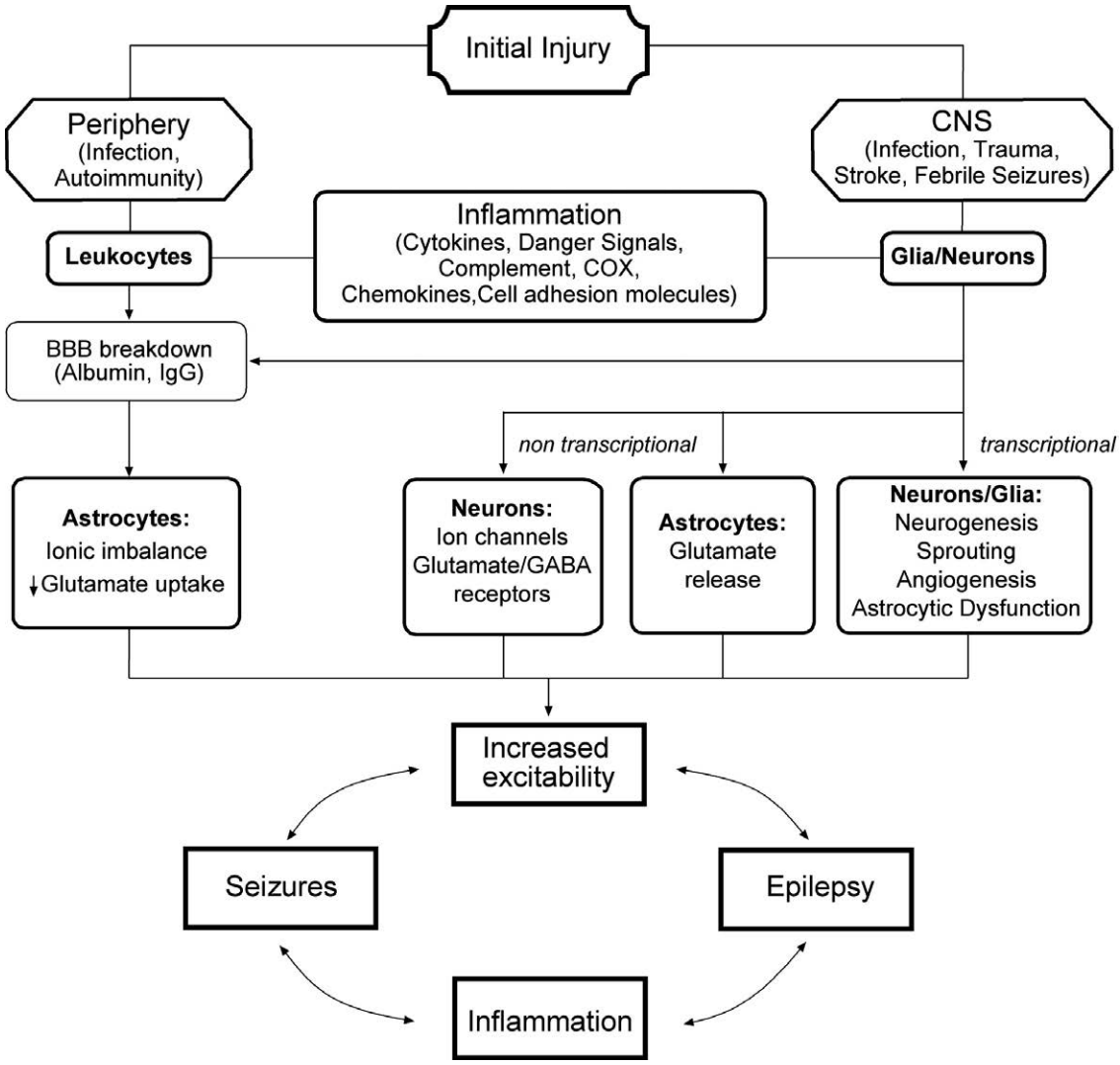

Figure 1. Pathophysiological cascade of events leading from inflammation to epilepsy. See Conclusion section for explanation.

These neuronal and astrocytic effects of IL-1β underlie its proconvulsant activity via an increase in glutamatergic transmission. IL-1β can also inhibit GABA-mediated Cl^- fluxes, thus possibly reducing inhibitory transmission (57, 58).

Long-term transcriptional events may also occur due to the presence of inflammatory molecules in the brain, which would result in activation of genes involved in plasticity phenomena underlying epileptogenesis (3, 59).

Conclusions

Various brain insults—such as neurotrauma, stroke, infection, perinatal injury, febrile seizures, and status epilepticus—can induce inflammation in the brain (31), and these injuries in humans represent risk factors for the development of epilepsy. This evidence suggests that an epileptogenic event, even if subclinical, occurring at birth or during the lifetime may initiate a cascade of chronic inflammatory processes in the CNS that contributes to the onset of epilepsy (Figure 1).

The initiation of an inflammatory response in the brain can be envisaged as a consequence of an intrinsic "injurious" event, or the initial challenge may originate within peripheral lymphoid tissues; for example, when epilepsy evolves after systemic infectious diseases, encephalitis, or in prolonged seizures associated with fever. Experimental studies show that once seizures develop, they can contribute to perpetuate inflammation in the brain via mechanism(s) which are being investigated (13).

In the clinical setting, steroids and ACTH display anticonvulsant activity and may control seizures that are otherwise refractory to classical antiepileptic drugs (3), and these effects, at least in part, may be mediated by their anti-inflammatory properties. Further investigations into the role of cytokines—and more broadly into inflammatory mediators—in epilepsy may add important insights not only into the mechanisms of seizure generation but also for the development of innovative strategies to block activation of

inflammatory signaling in diseased conditions, thus highlighting potential new targets for therapeutic intervention, particularly for epileptic patients not responding to conventional antiepileptic drugs.

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