



Published in final edited form as:

Curr Opin Pharmacol. 2016 February ; 26: 118–123. doi:10.1016/j.coph.2015.11.002.

Modulation of neuronal excitability by immune mediators in epilepsy

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Abstract

A complex set of inflammatory molecules and their receptors has been described in epileptogenic foci in different forms of pharmaco-resistant epilepsies. By activating receptor-mediated pathways in neurons, these molecules have profound neuromodulatory effects that are distinct from their canonical activation of immune functions. Importantly, the neuromodulatory actions of some inflammatory molecules contribute to hyperexcitability in neural networks that underlie seizures. This review summarizes recent findings related to the role of cytokines (IL-1 β and TNF- α) and danger signals (HMGB1) in decreasing seizure threshold, thereby contributing to seizure generation and the associated neuropathology. We will discuss preclinical studies suggesting that pharmacological inhibition of specific inflammatory signals may be useful to treat drug-resistant seizures in human epilepsy, and possibly arrest epileptogenesis in individuals at risk of developing the disease.

Introduction

Cytokines have been shown to modulate neuronal activity either by promoting the release of neuroactive molecules, such as nitric oxide and prostaglandins, classical neurotransmitters and neurotrophins, from glia or brain endothelium [1,2], or by activating their receptors expressed by neurons [3–5]. Proinflammatory cytokines, such as interleukin(IL)-1 β and tumor necrosis factor (TNF)- α , activate receptor-mediated autocrine and paracrine cell signaling that results in different pathophysiological outcomes depending on the cell type [4]. Cytokines are endowed with a variety of physiological functions, including the modulation of ion channels and the regulation of the strength of synaptic transmission and plasticity [3,5,6]. However, pathological consequences may ensue if they are over-produced, or if tissue exposure to cytokines is too prolonged, such as in neurodegenerative diseases and in epilepsy [7–10].

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In the last decade, preclinical and clinical evidence demonstrated the induction of the prototypical inflammatory cytokines IL-1beta and TNF-alpha, as well as danger signals such as High Mobility Group Box 1 (HMGB1), and their related signaling molecules, in epileptogenic brain tissue surgically resected either from animal models of symptomatic epilepsy or human drug-resistant forms of epilepsy [9,11–13]. Immunohistochemical analysis of these tissues showed increased levels of inflammatory molecules mostly in activated microglia and astrocytes as well as in neurons, as compared to control tissue where these molecules were expressed at low or barely detectable levels. This phenomenon, often defined as *neuroinflammation* [14], raised the key question of the pathophysiological role that these molecules may play in epilepsy. Notably, pharmacological and genetic studies performed in animal models of epilepsy unveiled a direct neuromodulatory function of proinflammatory cytokines, and related effector molecules such as cyclooxygenase (COX)-2 and prostaglandin E2 [15], and the complement system [16–18], resulting in modifications in neuronal excitability. These peculiar central nervous system (CNS)-related properties of inflammatory molecules are different from those underlying their canonical role as mediators of immunity activation in response to pathogens [4].

This review focuses on the neuromodulatory properties of IL-1beta, TNF-alpha and HMGB1, and highlights that dysregulation of their receptor-mediated intracellular pathways in target cells, leads to acute and long-term modifications in neuronal network excitability. These alterations play a significant role in the mechanisms of seizures, the hallmarks of epilepsy that originate from synchronized firing of neuronal populations due to underlying hyperexcitability phenomena. In light of this evidence, targeting these cytokines may represent a novel opportunity for the development of new therapies for epilepsies associated with a pathogenic inflammatory component [9,11,12].

Cytokines and danger signals and epilepsy

The presence of inflammatory molecules in human brain tissue capable of generating spontaneous seizures is a feature of various forms of symptomatic pharmacoresistant epilepsies [9,11]. Studies in animal models have shown that this inflammatory brain substrate is associated with the activation of innate immune responses in glial cells following epileptogenic insults (e.g. neurotrauma, stroke, CNS infections, status epilepticus, febrile seizures, *etc*) or during recurrent seizures. The consequent rapid release of cytokines, chemokines and danger signals activates NFkB-dependent downstream inflammatory cascades involving glia, neurons and the blood brain barrier, and may subsequently lead to brain extravasation of leukocytes [19].

Brain inflammation in epilepsy has been recognized since 1958 in Rasmussen's encephalitis [20], a chronic inflammatory disease of still unknown etiology associated with pharmacoresistant epilepsy. However, its pathophysiological relevance in the mechanisms of seizures and the associated neuropathology has been fully recognized only in the last decade thanks to the evidence that (a) inflammation represents a common substrate of drug-resistant epilepsy of differing etiologies and (b) it can directly affect neuronal excitability [4,21,22] independently of its classical homeostatic role in the immune response to infections for promoting pathogen removal and tissue healing.

The IL-1 receptor (IL-1R1) and Toll-like receptor (TLR) signaling

The induction of this signaling in immune cells is crucial for activating inflammatory pathways in tissue. This signaling is triggered either by receptor recognition of *pathogen associated molecular patterns* (PAMPS) during infections, or by binding of endogenous molecules released from injured cells, e.g., *danger associated molecular patterns* or danger signals (DAMPS) during “sterile inflammation”, to alert the microenvironment of imminent or ongoing tissue damage [23]. Recent findings provide a pathophysiological link between the activation of these receptors and rapid changes in neuronal excitability. The IL-1R1 and TLR4, and their respective cognate endogenous ligands IL-1beta and HMGB1, are induced in glia and neurons in human epilepsy and in the related experimental models [4,12,24–26]. IL-1beta and HMGB1 are strictly interconnected, as shown by the involvement of NALP3 inflammasome/caspase-1 in their biosynthesis and release, and the common molecular pathways they activate in neurons and in glia (NFkB-dependent gene transcription) [27,28]. The contribution of this signaling to seizures was shown on the one hand by the dramatic decrease in seizure frequency provoked by pharmacological interventions which prevent or reverse signaling activation in brain, and on the other hand by the exacerbation of seizures induced by brain application of either IL-1beta or HMGB1 [4,24,29]. Accordingly, decreased intrinsic seizure susceptibility was reported in transgenic mice with impaired signaling activation [30–32]. Moreover, cortical application of lipopolysaccharide (LPS), a TLR4 activator, in rats rapidly increases the excitability of local neurons as assessed by measuring amplitudes of sensory evoked field potentials and spontaneous activity [33]. A ten-fold higher LPS concentration could even evoke epileptiform activity which involved IL-1beta release from activated microglia [33].

We recently showed that the redox state of the extracellular *milieu* is essential for mediating the proconvulsive activity of HMGB1 [34]. In fact, only the disulfide (oxidized) isoform of this molecule activates TLR4 and promotes seizures but not the reduced form, which has instead chemoattractive properties [35,36].

The involvement of this innate immunity signals in seizures indicates that neuronal excitability is affected by both IL-1beta and HMGB1. Looking into the molecular mechanisms underlying this effect, we found that the activation of IL-1R1 or TLR4 in neurons induces, within minutes, the Src kinase-mediated phosphorylation of the NR2B subunit of the N-methyl-D-aspartate (NMDA) receptor complex, thus leading to the increased neuronal Ca²⁺ influx [32,34,37,38]. This post-translational molecular event underlies the proconvulsive activity of both IL-1beta and HMGB1, as well as their excitotoxic properties. Moreover, a recent paper described that the activation of TLR4 by HMGB1 increased afferent evoked dentate gyrus excitability after concussive brain injury in mice [39], an event that increases the risk of developing epileptic seizures in animal models and in humans. Additional molecular mechanisms that might contribute to hyperexcitability phenomena with relevance for seizures include the downregulation of the hyperpolarization-activated cyclic nucleotide-gated (HCN1) channel, and the associated Ih current, on dendrites of hippocampal pyramidal neurons (*unpublished data*) and the reduction of GABA-A receptor mediated currents [25,40]. Finally, both IL-1beta and HMGB1 have been reported to increase the extracellular glutamate levels either by inhibiting glutamate re-

uptake or promoting its release from glia, or by enhancing NMDA-mediated glutamate release from synaptic terminals, thereby increasing neuronal excitability [reviewed in [10]; 41,42]. The promoting effects of IL-1beta on glutamatergic transmission can also be mediated by PKC phosphorylation of the transient receptor potential vanilloid 1 channel (TRPV1) [43]. TRPV1 also mediates the inhibitory effects of IL-1beta on spontaneous inhibitory post-synaptic potentials [44,45], thus reinforcing the evidence that this cytokine induces defects in GABAergic neurotransmission in forebrain which may be relevant for seizures [25].

TNF-alpha, p55 and p75 receptors

Emerging evidence has demonstrated that, in addition to its effects on cell survival, TNF-alpha has neuromodulatory properties by promoting fast changes in neuronal excitability [46]. In analogy with IL-1beta and HMGB1, TNF-alpha affects seizure susceptibility in animal models as shown by pharmacological interventions that either mimic cytokine's action or block either TNFR1 (p55) or TNFR2 (p75) receptor signaling [29,38,47]. In general, TNFR1 has been reported to mediate the ictogenic effects of TNF-alpha, whereas TNFR2 mediates the neuroprotective actions of this cytokine. Interestingly, a progressive reduction of TNFR2 with a concomitant increase of TNFR1 in forebrain neurons was reported in animal models of seizures [47], therefore shifting the balance towards the excitotoxic effects of this cytokine.

TNF-alpha can induce neuronal channelopathies since it affects both the assembly and the synaptic clustering of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors as well as the membrane expression of GABA-A receptors. In particular, TNF-alpha by activating intracellular kinases induces the expression of extrasynaptic GLUR2-lacking, thus Ca^{2+} permeable, AMPA receptors, a mechanism involved in excitotoxicity and synaptic scaling [48–50]. TNF-alpha promotes the induction of neuronal NMDA-NR1 receptors [51] and the endocytosis of GABA-A receptors, therefore decreasing inhibitory strength and reinforcing excitability [49]. Activation of protein kinases, such as PI3K and PKC, mediates TNF-alpha as well as IL-1beta modifications in the function of both receptor- and voltage-gated ion channels in neurons [5]. TNF-alpha can also induce glutamate release from microglia [52] and astrocytes [53]. In microglia, TNF-alpha evokes glutamate release by increasing the glutaminase conversion of glutamine to glutamate which is released *via* connexin 36 hemi-channels [52]. The astrocytic TNF-alpha evoked release involves COX-2/PGE2 synthesis, thereby resulting in increased intracellular Ca^{2+} mobilization [53].

Long term modification in neuronal excitability

In addition to the rapid effects on neuronal excitability above described, which are mediated by post-translational modifications in neuronal channels, a transient raise in IL-1beta and TNF-alpha in microglial cell resident in seizure susceptible brain areas, can induce long-lasting and profound synaptic changes in brain. This results in a chronic decrease in seizure threshold, also evoking behavioral comorbidities such as anxiety, depression, and cognitive dysfunction [21,22,54]. Neuronal cell loss is increased in seizing rats if they are pre-exposed

to LPS 24 h before the convulsive challenge [55], and seizure threshold is reduced in adult rats that have been exposed to LPS during the first two post-natal weeks [22].

In the frame of long-term consequences on neuronal function, there is increasing evidence that injury-induced brain inflammation contributes to the development and extension of brain tissue that generates spontaneous seizures (i.e. epileptogenesis) in animal models of symptomatic epilepsies [56].

Conclusions

Activation of innate immunity and inflammation have been demonstrated in epilepsy also in the absence of infection or autoimmune conditions. In the context of “sterile inflammation” triggered either by recurrent seizures or epileptogenic brain injuries, neurons and glia release endogenous DAMPs such as HMGB1 and proinflammatory cytokines such as IL-1beta and TNF-alpha that, by activating their cognate receptors, trigger NFkB-dependent inflammatory gene cascades in injured tissue and exert direct *neuromodulatory* functions. Signaling activation in neurons increases excitability by inducing both *rapid* and *long-term* changes in receptor- and voltage-gated ion channels, and enhancing glutamate release (Table 1). Notably, these non conventional pathways activated in brain are independent on the classical immune actions mediated by the inflammatory molecules. This chain of event contributes to the generation and establishment of an hyperexcitable neuronal network which contributes to seizure mechanisms, neuropathology and comorbidities in experimental models (Figure 1).

These preclinical findings, together with the presence of inflammation in human epilepsy brain, indicates that antiinflammatory drugs might be considered to complement the symptomatic treatment provided by the available antiepileptic drugs (AEDs), particularly in epilepsies not responding to AEDs. This novel therapeutic approach by resolving the inflammatory processes in the brain would raise hyperexcitability threshold thereby decreasing the likelihood of seizure recurrence, and hopefully may provide a means for disease modifications rather than a mere symptomatic control of seizures [57].

Acknowledgments

Supported by Fondazione Monzino and Epitarget (FP7/2007–2013, grant agreement n°602102) and NIH grant P20NS080185 (AV).

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Highlights

- Inflammatory molecules have neuromodulatory effects distinct from their immune functions
- Inflammatory molecules contribute to neuronal hyperexcitability underlying seizures
- Inhibition of specific inflammatory signals reduces seizures and epileptogenesis

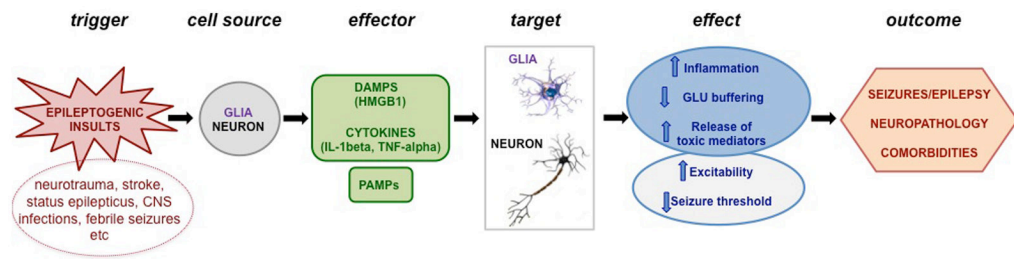


Figure 1. Schematic representation of the molecular events linking activation of innate immunity/inflammation to epilepsy. See conclusion paragraph for details.

Table 1

Summary of cytokine and HMGB1 effects on neuronal excitability and the related molecular mechanisms in seizure and excitotoxicity models

Cytokine/receptor	Molecular target	Cell signaling	Functional readout
<i>IL-1β/IL-1R1</i>	NMDAR-NR2B	Protein kinase Src	Increased Ca ²⁺ influx Hyperexcitability/Excitotoxicity Increased seizure susceptibility
	GABA-A R	Protein kinase C	Decreased GABA current
	TRPV1	Protein kinase C	Increased glutamate release Decreased GABA current
<i>TNFR1(p55)</i>	AMPA-GLUR2	PI3K/Akt	Increased Ca ²⁺ influx Hyperexcitability/Excitotoxicity
	AMPA-GLUR1/2	Protein phosphatase 1	Reduction of glutamatergic drive
	AMPA-GLUR1 NMDAR-NR1	n.d.	Increased seizure susceptibility
	GABA-A R <i>β2/β3 subunits</i>	n.d.	Decreased inhibitory synaptic strength
	CXCR4	COX-2/PGE2	Increased astrocytic glutamate release
	GLUTAMINASE	Glutamine/glutamate conversion	Increased microglial glutamate release
<i>TNFR2 (p75)</i>	AMPA-GLUR2/3		Decreased response to glutamate
	KA-GLUR6/7 NMDAR-NR2	n.d.	Decreased seizure susceptibility
<i>HMGB1/TLR4</i>	NMDAR-NR2B	Protein kinase Src	Increased Ca ²⁺ influx Hyperexcitability/Excitotoxicity
	NMDAR	n.d.	Increased seizure susceptibility Increased Ca ²⁺ influx
	Glial glutamate-aspartate transporter	n.d.	Increased glutamate release from astrocytes