



Modulation of neuronal excitability by immune mediators in epilepsy

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A complex set of inflammatory molecules and their receptors has been described in epileptogenic foci in different forms of pharmacoresistant 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-1beta and TNF-alpha) 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.

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Current Opinion in Pharmacology 2016, **26**:118–123

This review comes from a themed issue on **Neurosciences**

Edited by **Diana Amantea**

For a complete overview see the [Issue](#) and the [Editorial](#)

Available online 26th November 2015

<http://dx.doi.org/10.1016/j.coph.2015.11.002>

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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 [3,4^{*},5^{*}]. Proinflammatory cytokines, such as interleukin (IL)-1beta and tumor necrosis factor (TNF)-alpha, 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 [7,8,9^{*},10^{*}].

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, among others) 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, for example, *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*,25,26]. 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 Ca^{2+} 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 fore-brain 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

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