Invited Review

The role of cytokines in the pathophysiology of epilepsy

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Recent findings in experimental models and in the clinical setting highlight the possibility that inflammatory processes in the brain contribute to the etiopathogenesis of seizures and to the establishment of a chronic epileptic focus. Prototypical inflammatory cytokines such as IL-1β, TNF-α and IL-6 have been shown to be overexpressed in experimental models of seizures in brain areas of seizure generation and propagation, prominently by glia and to a lesser extent by neurons. Cytokines receptors are also upregulated, and the related intracellular signalling is activated, in both cell populations highlighting autocrine and paracrine actions of cytokines in the brain. Cytokines have been shown to profoundly affect seizures in rodents; in particular, IL-1β is endowed of proconvulsant activity in a large variety of seizure models. The recent demonstration of functional interactions between cytokines and classical neurotransmitters such as glutamate and GABA, suggest the possibility that these interactions underlie the cytokine-mediated changes in neuronal excitability, thus promoting seizure phenomena and the associated neuropathology. These findings point out at novel glio-neuronal communications in diseased conditions and highlight potential new targets for therapeutic intervention.

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1. Introduction

Epilepsy comprises a group of neurological disorders characterized by the periodic occurrence of spontaneous seizures and affecting about 1% of the population worldwide. About 30% of epileptic patients are defined pharmacoresistant since they do not adequately respond to therapies and in these patients the surgical removal of the epileptic focus is often the only therapeutic option to achieve seizure control (Kwan and Brodie, 2006). Pathologic brain specimens from patients with drug resistant epilepsy demonstrated the occurrence of marked reactive gliosis in epileptogenic tissue. Recent studies have implicated glial cells in novel physiological roles in the CNS including modulation of synaptic transmission; therefore, it is plausible that glial cells may have a functional role in the hyperexcitability phenomena which underlie seizures in epilepsy. Alterations in distinct astrocyte membrane channels, receptors and transporters (Seifert et al., 2006) and phenotypic changes in activated microglial cells have been described in chronic epileptic tissue (Boer et al., 2006;Ravizza et al., 2008) and they are possibly associated with the epileptic state characterized by recurrent spontaneous seizures.

Several inflammatory mediators are expressed in activated glial cells in epileptogenic tissue raising the key question of whether this inflammatory process is a mere epiphenomenon of seizure activity and the associated neuronal injury, or if it may contribute to the pathology and if so, then how. Inflammation has been implicated in the progressive nature of neurodegenerative diseases (Griffin, 2006) and inflammatory processes are now considered key contributors to acute and chronic neurodegenerative disorders, such as ischemic stroke and Alzheimer's disease (Allan et al., 2005). Most recently, experimental and clinical findings support a crucial role of inflammatory processes in epilepsy (Vezzani and Granata, 2005) in particular, in the mechanisms underlying the generation of seizures (ictogenesis) and the transformation of a normal neuronal network into a seizure-generating one (i.e. epileptogenesis, Pitkanen and Sutula, 2002). Insight into the role of the cytokines, especially of interleukin-1β (IL-1β), in the evolution of epilepsy has been gained by molecular and pharmacological studies in in vivo models and the use of genetically engineered mice with perturbed cytokine signalling. These approaches are leading to a radically modified view of the role of cytokines in epilepsy which may be germane to other neurological diseases.

2. Glia as a source of cytokines in epileptic tissue

Experimental evidence in rodent models has demonstrated 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 in glia is triggered by seizures induced by chemoconvulsants or by electrical stimulation (De Simoni et al., 2000;Eriksson et al., 1999; Gorter et al., 2006;Plata-Salaman et al., 2000;Ravizza and Vezzani,
This response consists of an increase in prototypic inflammatory cytokines such as interleukin (IL)-1β, IL-6 and TNF-α in microglia and astrocytes, which is accompanied, and often followed, by a cascade of downstream inflammatory events (i.e. activation of TLR, NFκB, complement system, chemokines, acute phase proteins) (Jankowsky and Patterson, 2001; Turrin and Rivest, 2004; Vezzani and Granata, 2005). Seizure-induced inflammation can also recruit neurons, and in some instances mediates the penetration into the brain parenchyma of cells of the adaptive immune system (Nguyen et al., 2002; Vezzani and Granata, 2005; Boer et al., 2008). It seems therefore that seizures can activate innate immune/inflammatory mechanisms in brain which overlap in many respects with those induced by systemic administration of lipopolysaccharide (LPS), a component of gram negative bacteria mimicking systemic infection (Giovaninni and Weiss, 2007). Notable differences are however, the time-course of these events which are readily reversible after LPS challenge but not so after seizures (see later) and involve predominantly periventricular organs and microvasculature after LPS rather than glia and neurons like in seizures. The use of rat models of epileptogenesis induced by electrical or pilocarpine-induced status epilepticus (Ravizza et al., 2008) has been instrumental for understanding the temporal evolution of inflammatory changes and the cell types and brain regions involved. These models mimic a clinical situation characteristic of the symptomatic types of epilepsy (Pitkanen and Sutula, 2002) in which an initial brain injury, for ex. a prolonged episode of seizures (i.e. status epilepticus), triggers epileptogenesis (i.e. a latency phase lasting > 1 week, devoid of seizure activity but prodromic to the onset of epilepsy) then resulting in the occurrence of chronic spontaneous seizures (i.e. epilepsy) (Dichter, 2006). Immunohistochemical analysis of the temporal and cellular patterns of inflammatory changes in the rat forebrain (Ravizza and Vezzani, 2006; Ravizza et al., 2008), detected a fast increase of IL-1 β in activated microglia and astrocytes during the acute seizures which did not return to the basal level of expression after seizure subsided, but it was still observed during epileptogenesis and in chronic epileptic tissue, thus in rats developing spontaneous seizures. TNF-α and IL-6 also increased in glial cells similarly to IL-1 β, but their upregulation was transient (De Simoni et al., 2000). It appears therefore that the increase in IL-1 β outlasts the acute inciting event while the increase in the other cytokines is time-locked to ongoing epileptiform activity. The chronic expression of IL-1β during epileptogenesis highlights the possibility that this cytokine may contribute to the mechanisms underlying the onset of spontaneous seizures. Interestingly, IL-1β is upregulated during epileptogenesis in astrocytes but not in microglia suggesting a predominant role of astrocytes in sustaining chronic inflammation before the onset of spontaneous seizures (Ravizza et al., 2008). In chronic epileptic tissue both cell populations express high levels of IL-1β, and microglia is especially recruited in rats with frequent spontaneous seizures. During acute seizures, epileptogenesis and chronic seizures, IL-1β-expressing astrocytes outnumber by about 10-fold IL-1β-immunopositive microglia, and this feature is confirmed in human temporal lobe epilepsy (TLE) tissue (Ravizza et al., 2008).

Another interesting feature of the response of the IL-1β system to seizures, is the induction of IL-1 receptor antagonist (ra), a naturally-occurring antagonist of IL-1 receptor type 1 (R1), which acts by limiting IL-1β-mediated actions (Dinarello, 1996). During peripheral inflammatory reactions, IL-1ra is generally produced together with IL-1 and > 100-fold in excess to IL-1 (Dinarello, 1996). Differently, IL-1ra is induced by seizures several hours after IL-1β and never in excess to IL-1 (De Simoni et al., 2000; Eriksson et al., 1999), indicating that the brain is lacking an efficient mechanism to terminate rapidly the effects of IL-1β upon its production.

3. Cytokine receptors in seizures

Investigation of the pattern of expression of cytokine receptors in seizures is important to give clues of the cell populations targeted by the cytokines. IL-1R1, which mediates the biological responses to IL-1β, is barely detectable in normal brain tissue but it is rapidly increased (< 2 h) in hippocampal neurons after seizures, and a later wave of expression is observed during epileptogenesis also in astrocytes (Ravizza and Vezzani, 2006; Ravizza et al., 2008), thus indicating both paracrine and autocrine actions of IL-1β acting as a soluble mediator of glio-neuronal communications in epileptogenic tissue. Strong IL-1β and IL-1R1 immunoreactivity was found during epileptogenesis also in perivascular astrocytic endfoot impinging on blood vessels and in endothelial cells of the microvasculature. These changes were associated with tissue extravasation of serum albumin (Ravizza et al., 2008) possibly linking inflammation to changes in blood–brain barrier (BBB) permeability. IL-1β can affect the permeability properties of the BBB (Ferrari et al., 2004) via disruption of the tight-junction organization or production of nitric oxide and activation of matrix metalloproteinases in endothelial cells (for review see Allan et al., 2005). These changes may have relevant functional consequences since alterations in the BBB permeability can result in chronic neuronal hyperexcitability (Oby and Janigro, 2006; Seiffert et al., 2004; Ivens et al., 2007). Moreover, alterations in BBB permeability may favor the entry into the brain of cells of the adaptive and innate immune system and this phenomenon may contribute to perpetuate inflammation (Nguyen et al., 2002). Noteworthy, the extent of BBB leakage positively correlates with the frequency of spontaneous seizures in rats (van Vliet et al., 2006).

IL-6 receptor mRNA is not detected in normal brain but it is increased after seizures in rat forebrain and in the meninges together with Gp130, its signalling transducer protein (Lehtimaki et al., 2003); granule cells in the hippocampus and astrocytes appear to be predominantly involved in these changes (Choi et al., 2003). No information is available on the tissue or cellular expression of TNF-alpha receptors after seizures.

4. Chronic inflammation and seizure susceptibility

Experimental evidence in rodents shows that a large variety of brain insults (i.e. neurotrauma, stroke, infection, perinatal injury, febrile seizures, etc.) can induce inflammation in the brain (Vezzani and Granata, 2005). These injuries in humans represent risk factors for the development of epilepsy, suggesting that an inciting 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 set the basis for the late onset of epilepsy. 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 and neuronal cell loss. Thus, transgenic mice overexpressing IL-6 in astrocytes showed an increased sensitivity to seizures induced by glutamatergic agonists and a constitutive loss of γ-aminobutyric acid (GABA)- and parvalbumin-positive neurons in the hippocampus, which may be implicated in their propensity to develop seizures (Samland et al., 2003). High overexpression of brain TNF-α and IL-6 in transgenic mice was associated with the occurrence of age-dependent neurodegenerative changes and sporadic spontaneous seizures (Akassoglou et al., 1997; Campbell et al., 1993). These findings therefore indicate a pro-epileptogenic potential of chronically elevated levels of cytokines in the brain. Enhanced seizure susceptibility was also demonstrated in rodents after systemic administration of LPS, and this effect was blocked by antiinflammatory drugs (Sayyah et al., 2003). Moreover, a first exposure to seizures in 15-day old rats
was associated with chronic brain inflammation and the development of a lower threshold for seizure induction in adulthood (Somera-Molina et al., 2007).

The experimental studies in models of endotoxemia or seizures suggest that a transient and strictly controlled inflammation in the brain represents a homeostatic response aimed at protecting the brain from noxious events whereas if inflammation is chronic or inappropriately controlled, then it can become detrimental to neurons, thus representing a maladaptive change which may contribute to the CNS pathology.

5. Clinical studies

The first clinical insight into a possible role of inflammation in epilepsy is the evidence that selected anti-inflammatory drugs, including steroids, display anticonvulsant activity and may control seizures which are otherwise refractory to classical antiepileptic drugs (Vezzani and Granata, 2005).

Subsequently, several reports showed increased cytokines in serum and CSF in patients with epilepsy. For example, recent tonic-clonic seizures induce higher IL-6 levels and lower IL-1Ra-to-IL-1β ratio (Peltola et al., 2000). Because the IL-6 concentration in CSF is much higher than in plasma, the most likely origin of CSF cytokines appears to be the brain.

Most recently, the analysis of human brain specimens from drug-refractory epileptic patients showed strong activation of the IL-1β/IL-1R1 system in brain resident cells, such as in glia and neurons, similar to that described in brain tissue from chronic epileptic rats (Vezzani and Vezzani, 2006; Vezzani et al., 2008). Cells of adaptive immunity were detected in some but not all types of epilepsy: for example, a notable absence of adaptive immunity in brain tissue was described in TLE clearly differentiating this type of epilepsy from Rasmussen's encephalitis or epilepsies associated with malformations of cortical development where adaptive immunity may play a critical role in the neuropathology (Vezzani and Granata, 2005; Boer et al., 2008). Noteworthy, in epilepsy associated with malformations of cortical development, a positive correlation was found between the percentage of IL-1β-positive cells and the frequency of seizures prior to surgical resection (Ravizza et al., 2006a). Moreover, the finding that ongoing inflammatory events occur during epileptogenesis in experimental models suggests that the activation of the IL-1β system observed in human chronic epileptic tissue may precede the onset of epilepsy possibly playing an etiopathogenetic role.

6. Functional and pharmacological studies in experimental models

The role of cytokines in seizures and epileptogenesis has been investigated using genetically-modified mice with a perturbed cytokine system or by pharmacological means using receptor antagonists or cytokine synthesis inhibitors, or by intracerebral injection of the cytokines themselves. In this respect, most of the data so far available concern IL-1β and TNF-α. The preapplication of IL-1β in rodent brain, by using concentrations within the range of those endogenously produced by seizures, prolongs the duration of seizures induced by intracerebral injection of chemokonvulsant drugs, such as the glutamate analog kainic acid or the GABAβ antagonist bicuculline (Vezzani et al., 1999, 2000). Importantly, the intracerebral injection of IL-1ra mediates powerful anticonvulsant effects (Vezzani et al., 2002), and transgenic mice over-expressing IL-1ra in astrocytes have a reduced susceptibility to seizures (Vezzani et al., 2000). Because the only action of IL-1ra is to inhibit the effects of IL-1β, these data demonstrate that an endogenous increase in brain IL-1β contributes to seizures in these models. Accordingly, selective blockade, or gene deletion, of interleukin-converting enzyme (ICE or caspase-1), the enzyme which cleaves pro-IL-1β producing the mature and biologically active form of IL-1β, reduces seizures significantly (Ravizza et al., 2006b).

One report showed that IL-1β can delay epileptogenesis in the kindling model but this study used daily intraventricular injections of IL-1β at doses 100 times lower than those shown to exacerbate seizures (Sayyah et al., 2005). This evidence is in accordance with the inhibition by low doses of IL-1β of long-term potentiation (Cunningham et al., 1996), a form of neuronal plasticity that shares common mechanisms with kindling. Thus, the extent of a raise of IL-1β in brain tissue appears to be a crucial factor which determines the consequences on neuronal excitability, and detrimental effects are likely to be induced by relatively high levels of this cytokine. In this respect, another important aspect is the pattern of expression of cytokine receptors in the target tissue. A typical example is represented by TNF-α whose effects on seizures depend both on its brain levels and on the receptor subtypes predominantly activated by this cytokine. In particular, nanomolar amounts of mouse recombinant TNF-α injected into the mouse hippocampus reduce seizures, and this action is mediated by p75 receptors expressed by neurons (Balosso et al., 2005). Importantly, transgenic mice with low to moderate overexpression of TNF-α in astrocytes also show decreased susceptibility to seizures (Balosso et al., 2005), whereas mice with high overexpression of TNF-α in astrocytes or neurons develop signs of neurologic dysfunction (Aksosoglou et al., 1997; Probert et al., 1995). A protective role of TNF-α on seizures has also been recently described using mice with a genetic deletion of the p55 receptor; these mice were more susceptible to seizures and displayed enhanced seizure-associated neurodegeneration and glia activation as compared to wild-type mice (Lu et al., 2008).

TNF-α type 1 (p55) receptors contain an intracellular “death domain,” and they appear to contribute predominantly to cell damage (MacEwan, 2002). Seizures promote the formation of a complex between the “death domain” of this receptor and activating factors that result in the induction of proapoptotic signals. Neutralizing antibodies to TNF-α reduced the number of DNA-damaged cells in the hippocampus after kainate seizures (Shinoda et al., 2003), suggesting that p55 receptors mediate the pro-neurotoxic effects of TNF-α.

Since proinflammatory cytokines, including IL-1β, act as pyrogens after their central or systemic administration, recent studies have addressed the possibility that the increase in brain IL-1β during fever may evoke seizures in immature rodent brain (Dubé et al., 2005; Heida and Pittman, 2005). Investigations of this aspect are clinically relevant since fever as a systemic response to infection, inflammation or stress, can evoke febrile seizures in infants and children, and prolonged febrile seizures are closely linked to the development of temporal lobe epilepsy (Dubé et al., 2006). Intracerebral application of IL-1β reduced the threshold to seizures in two models of febrile convulsions caused by hyperthermia (Dubé et al., 2005) or by LPS-induced fever in immature rodents (Heida and Pittman, 2005). Moreover, mice with a deletion of the IL-1R1 gene were resistant to induction of hyperthermia-induced seizure, thus suggesting that IL-1β signalling contributes critically to hyperexcitability and the consequent seizure activity. The active involvement of IL-1β in the mechanism of febrile convulsions is suggested by the experiment (Heida and Pittman, 2005) showing that the immature rats experiencing seizures at the onset of LPS-induced fever in response to a subconvulsant dose of kainate are only those (~50%) showing upregulation of IL-1β in their hippocampi. Importantly, both seizing and not seizing rats displayed the same raise in brain temperature and a similar increase in IL-1β in the hypothalamus.

Finally, IL-1β and TNF-α have been implicated in the increased susceptibility to seizures caused by systemic infection induced...
by Shigella dysenteriae in mice (Yuhas et al., 1999) or in spontaneous seizures ensuing in a neonatal rat model of pneumococcal meningitis (Meli et al., 2004).

The role of IL-6 in seizures has been addressed in a few reports using mice with a genetic deletion of the IL-6 gene, or assessing seizures after systemic administration of this cytokine in normal rodents. Mice lacking the IL-6 gene showed an increased seizure susceptibility to various chemoconvulsants, in particular to glutamate receptor agonists (De Sarro et al., 2004), and an enhanced propensity to develop audiogenic seizures (De Luca et al., 2004). IL-6 was also shown, upon its intranasal application to neonatal rats, to delay the onset of hyperthermia-induced convulsions and reduce their severity (Fukuda et al., 2007). These findings therefore support an anticonvulsant role of this cytokine; however a proconvulsant action of IL-6 was also described against generalized seizures induced by the GABA receptor antagonist pentylenetetrazole (Kaloueff et al., 2004), suggesting that the action of IL-6 depends on the mechanism recruited in the initiation and propagation of seizures.

There is still limited information on the role of other cytokines in seizure phenomena; a detailed information has been reported in previous reviews (Jankowsky and Patterson, 2001; Vezzani and Granata, 2005).

7. The role of cytokines in neuronal excitability

7.1. IL-1β

Recent evidence demonstrated that IL-1R1 colocalizes on hippocampal pyramidal neurons with the N-methyl-D-aspartate (NMDA) receptor, a subtype of glutamate receptors crucially involved in the onset and spread of seizures. IL-1β via activation of neuronal IL-1R1 induces Src kinase-mediated tyrosine phosphorylation of the NR2B subunit of the NMDA receptor. As a consequence of this action, NMDA receptor-mediated Ca2+ influx into neurons is enhanced by IL-1β and this effect plays a role in promoting excitotoxicity (Viviani et al., 2003) and possibly in seizure generation (Vezzani and Baram, 2007). Furthermore, the phosphorylation of the NR2B subunit appears to stabilize receptor localization within the membrane compartment by preventing endocytosis and protecting this subunit from calpain degradation (Viviani et al., 2007). IL-1β can also inhibit the astrocytic reuptake of glutamate (Hu et al., 2000) and increase its glial release possibly via TNF-α production (Bezzi et al., 2001), thus 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 (Fellin et al., 2006; Tian et al., 2005). Moreover, IL-1β can increase neuronal glutamate release also via the activation of inducible nitric oxide synthase in astrocytes (Casamenti et al., 1999). These neuronal and astrocytic effects of IL-1β may underlie its proconvulsant activity via an increase in glutamatergic transmission. IL-1β can also inhibit GABA-mediated Cl− fluxes, thus possibly reducing inhibitory transmission (Wang et al., 2000).

7.2. TNF-α

This cytokine has been shown to increase the mean frequency of AMPA-dependent miniature excitatory postsynaptic currents in hippocampal neurons and to decrease GABA-A-mediated inhibitory synaptic strength. These effects are likely to be mediated by TNF-α ability to activate the recruitment of AMPA receptors lacking the GluR2 subunit at neuronal membranes, thus in a molecular conformation which favors Ca2+ influx into neurons, and to induce endocytosis of GABA-A receptors (Beattie et al., 2002; Stellwagen et al., 2005).

These fast post-translational effects of inflammatory cytokines represent novel pathways by which inflammatory molecules produced in diseased tissue can affect neurotransmission and contribute to hyperexcitability and the associated neuropathology.

8. The role of cytokines in seizure-associated neuronal damage

In the mature rodent brain, status epilepticus leads to a loss of neurons in the hippocampal formation and in other forebrain areas involved in the epileptic activity (Majores et al., 2007). Cytokines and other inflammatory mediators have been shown to contribute to both excitotoxic and apoptotic neuronal death (Allan et al., 2005), highlighting the possibility that the production and release of cytokines during seizures by glia and/or by cells of the adaptive immune system may contribute to seizure-mediated neuronal damage. This hypothesis is supported by the following evidence: (1) the increase in brain cytokines induced by seizures precedes by several hours the onset of neuronal cell damage in the same tissue; (2) there is a strict temporal association between the age-dependent onset of seizure-induced cell loss and the seizure-induced production of cytokines during postnatal development. Thus, both phenomena occur in rats to a significant extent only after the second postnatal week, although rats can experience severe seizures (but no cell loss or inflammation) within the first and second postnatal week of life (Rizzi et al., 2003). The deleterious effects of cytokines on neuronal survival may involve the production of various neurotoxic compounds via autocrine or paracrine mechanisms (Allan et al., 2005). Additionally, cytokines can enhance NMDA- and AMPA-mediated Ca2+ influx into neurons (see previous paragraph) therefore contributing to cell damage via increased neuronal excitability (Vezzani and Baram, 2007).

Importantly, although cytokines can promote neurodegeneration, their effects on the threshold, frequency and duration of seizures are independent on cell death. Thus, cytokines affect the threshold to seizures in models of febrile convulsions where no cell loss occurs (Vezzani and Baram, 2007), and they increase seizure activity also in non-lesional models of seizures, such as in bicuculline-treated rats and mice (Vezzani et al., 1999, 2000) where epileptic activity is not associated with neurodegenerative effects. Moreover, the effects of cytokines on seizure activity have a very rapid onset which is not compatible with the long-term sequelae of neurodegenerative events triggered by seizures.

Additionally, injection of LPS to 15-day old rats exposed to pilocarpine increased status epilepticus induced damage (Auvin et al., 2007) without altering the duration of the acute epileptic activity, thus clearly dissociating the effects of cytokines on cell survival from those on neuronal excitability.

Finally, notable examples exist of a dual role of cytokines on neuronal survival in diseased tissue (Allan et al., 2005). In particular, neuroprotective actions of IL-1β have been reported (Bernardino et al., 2005) likely mediated by the ability of this cytokine to induce the synthesis of growth factors from astrocytes, then promoting cell repair mechanisms. Other potential mechanisms of neuroprotection induced by cytokines include stimulation of antioxidant pathways, induction of manganese superoxide dismutase or calbindin which counteracts the elevation of intracellular Ca2+ induced by cell injuries (Allan et al., 2005). In this respect, IL-1β and TNF-α can either reduce or exacerbate glutamate receptor-mediated excitotoxicity in organotypic slice cultures, depending on their extracellular concentrations, the length of time the tissue is exposed to these cytokines during the injury, and the receptor types activated by these cytokines (Bernardino et al., 2005).

9. Concluding remarks

The initiation of a pro-epileptogenic inflammatory response within the CNS can be envisaged as a consequence to an intrinsic
“injurious” event, and the experimental studies in models of epileptogenesis following an episode of status epilepticus support this possibility. The initial challenge, however, may also originate within peripheral lymphoid tissues, for example when epilepsy evolves after systemic infectious diseases, encephalitis, or in prolonged seizures associated with fever.

A genetic predisposition to develop sustained inflammatory reactions in response to otherwise ineffective stimuli has been suggested by studies of IL-1β gene polymorphisms in children with febrile seizures and in patients with TLE preceded by prolonged febrile seizures. However, these data are still controversial and this notion has been recently challenged (Tan et al., 2004).

The cytokine response to brain injury induced by a large variety of insults (Vezzani and Granata, 2005) may be a common substrate of epileptogenesis independent on the underlying etiology (Fig. 1). However, brain inflammation has been described also in patients with multiple sclerosis or with chronic neurodegenerative disorders, and the majority of these patients, despite the activation of inflammatory pathways, do not develop seizures. Thus, the role played by inflammation in distinct neuropathologies clearly depends on the tissue microenvironment, the specific brain areas and the neuronal circuitry involved.

Experimental studies show that once seizures develop, they can contribute to perpetuate inflammation in the brain (Fig. 1) although the mechanism(s) underlying seizure-evoked inflammation are still unknown. As far as IL-1β is concerned, it can be postulated that seizure-induced chronic overexpression of this cytokine in brain tissue contributes to enduring alterations in gene expression programs that may underlie the epileptogenic process (Vezzani and Baram, 2007). In particular, IL-1β may trigger the classical cascade of events which includes the activation of the mitogen-activated protein kinases and NF-κB-dependent pathways, thus resulting in the transcription of genes that may contribute to the acquired molecular changes (e.g. modifications in ion channels) associated with the epileptogenic process (Pitkanen

Fig. 1. Induction of brain inflammation in epileptogenic tissue. Various brain injuries, even subclinical, occurring at birth or during a lifetime may trigger brain inflammation chiefly involving the production of cytokines and related downstream inflammatory mediators. This event may lead to changes in brain parenchyma such as leakage of the BBB, neuronal hyperexcitability and cell damage that can contribute to lower the threshold for seizure induction and to trigger epileptogenesis, thus setting the basis for the onset of epilepsy. Activation of innate immune mechanisms during epileptogenesis can recruit inflammatory cells from the periphery thus perpetuating inflammation. The onset of seizures can in turn further promote inflammation via the production of proinflammatory cytokines and downstream inflammatory mediators.

![Diagram](image_url)

Fig. 2. IL-1β signalling in epilepsy. This schema depicts the cascade of events that may underlie the actions of IL-1β after its production and release in the brain following a precipitating event (i.e. a primary brain insult). Activation of IL-1β–IL-1R1 signalling can trigger rapid effects on neuronal excitability mediated by post-translational changes in ion channels coupled to glutamate receptors involving the activation of Src kinase (Viviani et al., 2003) and phosphoinositide 3 kinase (PI3K) (Stellwagen et al., 2005). These actions may underlie the proconvulsive actions of IL-1β and contribute to seizure-associated neuronal death. Long-term effects may also be triggered by IL-1β via transcriptional activation of NF-κB and MAPK-dependent genes involved in structural and functional changes in glia and neuronal networks. These actions, individually or in concert, may contribute to epileptogenesis and ictogenesis. The induction of neuronal cell death does not appear to be a prerequisite for the proepileptogenic actions of IL-1β. Adapted from Vezzani and Baram (2007).
and Sutula, 2002). The recently described fast-onset posttranslational actions of IL-1β and TNF-α on glutamate receptors and transporters may affect neuronal excitability and contribute to increase the susceptibility to seizures. Genomic and rapid effects of IL-1 systemic cytokine mediators may affect both neuronal cell excitability and their survival to noxious stimuli (Fig. 2).

Further investigations into the role of cytokines, and more broadly of inflammatory mediators, in epileptic tissue may add important insights into the mechanisms of ictogenesis and epileptogenesis. This information may allow the development of innovative strategies to block the activation of cytokine-mediated signalling 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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