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Review

Epilepsy and brain inflammation

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ABSTRACT

During the last decade, experimental research has demonstrated a prominent role of glial cells, activated in brain by various injuries, in the mechanisms of seizure precipitation and recurrence. In particular, alterations in the phenotype and function of activated astrocytes and microglial cells have been described in experimental and human epileptic tissue, including modifications in potassium and water channels, alterations of glutamine/glutamate cycle, changes in glutamate receptor expression and transporters, release of neuromodulatory molecules (e.g. gliotransmitters, neurotrophic factors), and induction of molecules involved in inflammatory processes (e.g. cytokines, chemokines, prostaglandins, complement factors, cell adhesion molecules) (Seifert et al., 2006; Vezzani et al., 2011; Wetherington et al., 2008). In particular, brain injury or proconvulsant events can activate microglia and astrocytes to release a number of proinflammatory mediators, thus initiating a cascade of inflammatory processes in brain tissue. Proinflammatory molecules can alter neuronal excitability and affect the physiological functions of glia by paracrine or autocrine actions, thus perturbing the glioneuronal communications. In experimental models, these changes contribute to decreasing the threshold to seizures and may compromise neuronal survival (Riazi et al., 2010; Vezzani et al., 2008). In this context, understanding which are the soluble mediators and the molecular mechanisms crucially involved in glio–neuronal interactions is instrumental to shed light on how brain inflammation may contribute to neuronal hyperexcitability in epilepsy.

This review will report the clinical observations in drug-resistant human epilepsies and the experimental findings in adult and immature rodents linking brain inflammation to the epileptic process in a causal and reciprocal manner. By confronting the clinical evidence with the experimental findings, we will discuss the role of specific soluble inflammatory mediators in the etiopathogenesis of seizures, reporting evidence for both their acute and long term effects on seizure threshold. The possible contribution of these mediators to co-morbidities often described in epilepsy patients will be also discussed. Finally, we will report on the anti-inflammatory treatments with anticonvulsant actions in experimental models highlighting possible therapeutic options for treating drug-resistant seizures and for prevention of epileptogenesis.

Contents

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Introduction

Brain inflammation in human epilepsy

Accumulating clinical evidence strongly supports the relevance of inflammation in the pathophysiology of human epilepsy (Vezzani et al., 2011a, 2011b). Different common infectious or autoimmune diseases can cause recurrent seizures (Bien et al., 2007; Choi and Koh, 2008). The prototype of inflammatory epileptic encephalopathy is represented by the Rasmussen's encephalitis, a severe epileptic encephalopathy of childhood, characterized by intractable focal seizures, hemiparesis and progressive deterioration of cognitive function (Bauer and Bien, 2009; Bien et al., 2002; Pardo et al., 2004). Neuropathological evaluation of tissue of individuals affected by Rasmussen's encephalitis provides evidence of a progressive immune-mediated process of neuronal damage, involving both glial and lymphocytic responses (Pardo et al., 2004). Recent studies suggest as key pathogenetic mechanism a cytotoxic CD8 T cells-mediated attack on both neurons and astrocytes (Bauer et al., 2007; Schwab et al., 2009). The autoimmune nature of Rasmussen's encephalitis is supported by the discovery of antibodies against glutamate-receptor subunit 3 (GluR3) (Rogers et al., 1994). However, GluR3 antibodies are not present in all cases (Watson et al., 2004) and have been also detected in other epilepsy patients with severe intractable seizures (Mantegazza et al., 2002). In addition, autoantibodies against the presynaptic protein Munc18-1 have been identified in a subgroup of these patients (Alvarez-Baron et al., 2008).

A growing number of specific antibodies are being detected in patients with new onset epilepsy and immuno-mediated seizure disorders (Vincent et al., 2010). These antibodies are directed to intracellular targets (glutamic acid decarboxylase), or to cell-surface membrane proteins, such as voltage-gated potassium channels (VGKC-complex proteins) or N-methyl-D-aspartate receptors (Irani et al., 2010; Vincent et al., 2010). Increasing evidence shows that these antibodies are biomarkers for underlying immunopathology of limbic encephalitis which represents a precipitating event in adult-onset temporal lobe epilepsy with hippocampal sclerosis (TLE-MTS) (Bien et al., 2007; Niehusmann et al., 2009).

Clinical and neuropathological evidence suggest that inflammation could play also a central role in seizure disorders without infectious or immune-mediated etiology. Several clinical studies demonstrated increased levels of inflammatory mediators (e.g. cytokines such as Interleukin (IL)-6, Tumor Necrosis Factor (TNF)-α and IL-1β and the IL-1 receptor antagonist(ra)) in serum or CSF (Aronica and Crino, 2011). The activation of the cytokine network in patients with refractory epilepsy (e.g. cell types contributing to inflammation, extent of inflammation in brain tissue) may vary not only depending on seizure severity or duration but also on the epilepsy syndromes (Alapirtti et al., 2009; Bauer et al., 2009). Currently there are no inflammatory biomarkers, detectable in CSF and/or serum, with proven clinical utility for patients with chronic refractory focal epilepsy. A major challenge for the future is to define specific biomarkers which would allow the recognition of appropriate patient populations who might benefit from antiinflammatory or immunomodulatory therapies.

Neuroimaging approaches represent another interesting challenge to study the inflammatory processes in chronic epilepsy. Iron oxide contrast-enhanced MRI has been used to visualize cellular inflammation in patients with multiple sclerosis and stroke (Stoll and Bendszus, 2009). However, the possible application of this approach in patients with focal epilepsy and more subtle inflammatory processes deserves further investigation. Positron emission tomography (PET) with ^{11}C-PK11195 has been also used to show activated astrocytes and microglia in epileptic patients with encephalitis (Banati, 2002; Kumar et al., 2008) or focal cortical dysplasia (Butler et al., 2011). However, this tracer may be not sensitive enough to detect inflammatory changes associated with microglia activation in patients with TLE-MTS (Banati, 2002; Butler et al., 2009). Recently, new promising, more sensitive, PET tracers have been developed to visualize activated glial cells in the epileptogenic zone of MTS patients (Hirvonen et al., 2010). Additional studies are, however, needed to correlate imaging with the neuropathological finding in patients undergoing epilepsy surgery.

Neuropathological examination of surgical epilepsy specimens provided evidence of a complex and sustained inflammatory phenomenon, and the associated production of proinflammatory molecules. In patients with TLE-MTS, besides astrogliosis, which is a major histopathological feature of hippocampal sclerosis, prominent activation of cells of the microglia/macrophages lineage has been shown in the hippocampus (Aronica and Gorter, 2007; Ravizza et al., 2008a); in contrast, only few cells of adaptive immunity (CD3/CD8 positive T-lymphocytes) are observed in these specimens, mainly associated with microvessels (Marchi et al., 2010; Ravizza et al., 2008a, 2008b).

The activation of both astrocytes and microglial cells is associated with the induction of major proinflammatory pathways in TLE-MTS (Vezzani et al., 2011a, 2011b), and gene expression profile analysis studies confirmed the prominent upregulation of genes associated with the immune/inflammatory pathways, including several chemokines and pro-inflammatory cytokines (Aronica and Gorter, 2007). Activation the IL-1β system in glial as well as neuronal cells (expressing both IL-1β and its receptor, IL-1R1), has been shown in TLE-MTS specimens, confirming the findings reported in chronic epileptic rats (Ravizza and Vezzani, 2006; Ravizza et al., 2008a). Both the complement pathway and the plasminogen system are also activated within the sclerotic hippocampus in TLE patients (Aronica et al., 2007; Iyer et al., 2010a, 2010b). Since IL-1β, complement components and plasminogen activators can affect the permeability properties of the blood brain barrier (BBB) (Ballabh et al., 2004; Lucas et al., 2006), we can speculate the existence of a reinforcing feedback loop between these pathways, which may contribute the BBB breakdown observed in hippocampal sclerosis (Ravizza et al., 2008a; van Vliet et al., 2007).

Recent studies support the activation of Toll-like receptor (TLR) signaling pathways in epilepsy (Maroso et al., 2010; Riazi et al., 2010). This prototypical inflammatory pathway is activated in response either to pathogens or endogenous ligands released by damaged or stressor-activated cells, named danger signals (*see later for more details*). Interestingly, overexpression of TLR4 in neurons and astrocytes, and its endogenous ligand high mobility group box 1 (HMGB1) has been demonstrated in microglia and astrocytes in

TLE-MTS and focal cortical dysplasia (FCD), confirming the findings reported in chronic epileptic mice (Maroso et al., 2010; Zurolo et al., 2011). Since microglia and astrocytes respond to HMGB1 stimulation with the production of several inflammatory mediators (Andersson et al., 2008; Pedrazzi et al., 2007), and IL-1β can induce the release of HMGB1 in human (Zurolo et al., 2011) and rat (Hayakawa et al., 2010) cultured astrocytes, these cells are likely to play a crucial role in perpetuating the inflammatory response in epilepsy.

Attention has been recently focused on the role of microRNAs (miRNA) in the regulation of the innate and adaptive immune responses. In particular, miR-146a, which can be induced by different pro-inflammatory stimuli such as IL-1β and TNF-α, has been shown to critically modulate innate immunity through regulation of TLR signaling and cytokine responses (Sheedy and O'Neill, 2008; Taganov et al., 2006). Interestingly, this miRNA is upregulated in TLE as well as in experimental models of epilepsy (Aronica et al., 2010; Song et al., 2011). These observations suggest miRNA as potential targets to modulate inflammatory pathways.

Activation of cells of the microglia/macrophage lineage and astrocytes, and concomitant induction of various inflammatory pathways, have been also observed in cortical tubers of patients with tuberous sclerosis complex (TSC) and in FCD, which represent major causes of pediatric epilepsy (Blumcke et al., 2010). Both the innate and the adaptive immune responses are activated in these lesions (Boer et al., 2010; Choi et al., 2009; Iyer et al., 2010a, 2010b; Ravizza et al., 2006a). Activation of plasminogen and focal BBB damage were also observed (Boer et al., 2008; Iyer et al., 2010a, 2010b) as in TLE.

In a cohort of patients with FCD type II, the density of activated Human Leukocyte Antigen (DR)-positive microglial cells and the endogenous levels of IL-1β and its receptor IL-1R1 correlated with the duration of epilepsy, as well as with the frequency of seizures prior to surgical resection (Boer et al., 2006; Ravizza et al., 2006a). The number of HLA-DR-positive microglial cells is significantly higher in FCD type II than in specimens from patients with FCD type I, despite of lack of significant differences in seizure frequency and duration (Iyer et al., 2010a). In both FCD and TSC, CD3/CD8 positive T-cells are detected in close apposition with malformed cells (Boer et al., 2008; Iyer et al., 2010a, 2010b); moreover, the number of T lymphocytes is greater in FCD type II specimens than in FCD type I (Iyer et al., 2010a). More prominent activation of complement, IL-1β and chemokines signaling pathways is also observed in FCD type II (Iyer et al., 2010a, 2010b). These observations suggest that both the recurrent seizures and the underlying neuropathology are important determinants of the extent and the type of inflammatory molecules and cells in epileptic tissue. It could be speculated that the activation of the mammalian target of rapamycin (mTOR) pathway observed in TSC and within the cellular components of FCD type II (but not in FCD type I) could contribute to the inflammatory response. Accordingly, the mTOR pathway has been shown to influence both innate and adaptive immune responses (Schmitz et al., 2008; Weichhart and Saemann, 2009).

Whether the presence of a prominent population of inflammatory cells may contribute to progressive cognitive dysfunction in patients with malformations of cortical development, and more in general in epilepsy, deserves further investigation.

Brain expression and role of inflammatory molecules in adult rodent models of seizures

Expression studies

The link between brain inflammation and epilepsy, which is supported by the clinical evidence discussed above, fostered experimental studies aimed at elucidating the major sources and inducers of inflammatory molecules in the brain, and the functional consequences of the activation of specific proinflammatory signals. These studies demonstrated several crucial aspects of the inflammatory process (*reviewed in* Vezzani et al., 2011a, 2011b): 1. Inflammation is induced by recurrent seizures; 2. Neuronal cell loss which can be caused by seizures is not a prerequisite for inflammation to occur; rather, the release of proinflammatory cytokines can contribute to cell loss (Allan and Rothwell, 2001), and dying cells may perpetuate inflammation; 3. Seizure-induced brain inflammation is long-lasting and can persist for days after the termination of seizures (De Simoni et al., 2000; Dhote et al., 2007; Ravizza et al., 2008a; Voutsinos-Porche et al., 2004), denoting a failure of endogenous anti-inflammatory control mechanisms. Indeed, measurements of endogenous anti-inflammatory molecules such as IL-1ra demonstrated an inefficient control of the inflammatory response to seizures (De Simoni et al., 2000; Eriksson et al., 2000); 4. In models of epilepsy induced by status epilepticus, traumatic brain injury or prolonged febrile seizures, inflammation precedes the onset of spontaneous seizures suggesting that uncontrolled inflammation may contribute to the development of the epileptic process (De Simoni et al., 2000; Marcon et al., 2009; Ravizza et al., 2008a; Ravizza et al., 2011). Indeed, microarray studies of altered gene transcription in rodent models of TLE, showed that the inflammatory response is among the biological processes mostly upregulated during the epileptogenesis phase (i.e. occurring between the initial brain injury and the onset of epilepsy) (Gorter et al., 2006; Lukasiuk et al., 2006; Majores et al., 2004); 5. Pharmacological blockade of specific pro-inflammatory pathways (e.g. IL-1R/TLR signaling, COX-2) reduces experimental seizures, and transgenic mouse models with altered inflammatory molecules (e.g. cytokines and their receptors or inflammasome components) show changes in seizure threshold (*reviewed in* Ravizza et al., 2011; Riazi et al., 2010; Vezzani et al., 2008). This evidence indicates that brain inflammation contributes to seizures, therefore it should not be considered a mere epiphenomenon of the pathology.

Immunohistochemical studies in experimental models of epilepsy showed that various inflammatory molecules are rapidly induced by seizures, or by brain injury, in locally activated astrocytes and microglia, thus demonstrating that the first wave of inflammation induced by a brain damaging event, occurs in parenchymal brain cells (*reviewed in* Vezzani et al., 2008, 2011a, 2011b). Inflammatory mediators are also induced in endothelial cells of the BBB, indicating that inflammation propagates from glial cells to the brain microvasculature. Moreover, inflammatory mediators could be also released by macrophages and granulocytes entering the brain from the blood during the epileptogenesis phase (Fabene et al., 2008; Ravizza et al., 2008a, 2008b; Zattoni et al., 2011). The interaction of inflammatory molecules produced by perivascular glia, and the extravasation of leukocytes may cause BBB damage and the subsequent leakage of serum proteins into the brain (Oby and Janigro, 2006; Shlosberg et al., 2010; Vezzani et al., 2011a, 2011b). Serum protein extravasation appears to contribute to neuronal network hyperexcitability (*see later*). Inflammatory mediators are also measured in regions of seizure generalization. Notably, these molecules are over-expressed not only after the acute pro-epileptogenic injury and during the epileptogenesis phase, but also in chronic epileptic tissue in the cell populations where they are detected in human TLE specimens (*reviewed in* Vezzani et al., 2011a, 2011b).

Recently, increased IL-1β has been measured in the somatosensory cortex of Genetic Absence Epilepsy Rat from Strasbourg (GAERS), a rat model of absence seizures (Akin et al., 2011), indicating that brain inflammation can be triggered by different types of recurrent seizure activity.

Functional studies

The presence of brain inflammation in epilepsy raised the crucial question about the functional consequences of this phenomenon, thus prompting pharmacological studies in seizure models, and investigations on seizure susceptibility in transgenic mice with altered inflammatory pathways. The initial studies showed that blockade of IL-1β signaling in the brain using IL-1ra drastically reduced seizures in various animal models (De Simoni et al., 2000; Vezzani et al.,

2000, 2002); moreover, mice overexpressing the soluble form of human IL-1ra in astrocytes were intrinsically resistant to seizures (Vezzani et al., 2000). These findings, and the evidence that IL-1β is increased in brain after a pro-convulsant challenge (De Simoni et al., 2000; Minami et al., 1990; Vezzani et al., 1999), indicate that this cytokine contributes to the precipitation and recurrence of seizures. Subsequent studies showed that blockade of IL-1β biosynthesis using specific Interleukin Converting Enzyme (ICE)/Caspase-1 inhibitors (Maroso et al., 2011a, 2011b; Ravizza et al., 2006b, 2008b) caused powerful anticonvulsant effects on acute and chronic seizures. Additional investigations showed the role of other cytokines, specific prostaglandins and complement factors in seizures (*reviewed in* Kulkarni and Dhir, 2009; Riazi et al., 2010; Vezzani et al., 2011a, 2011b). More recently, HMGB1 a *danger signal* with pro-inflammatory properties (Bianchi and Manfredi, 2007) which is released from activated or damaged neurons and glia, was identified as a molecular event crucial for lowering the threshold to seizures (Maroso et al., 2010), in association with IL-1β (Maroso et al., 2011a, 2011b). HMGB1 effects were mediated by the activation of TLR4 overexpressed by neurons undergoing hyperexcitability induced by proconvulsant drugs (Maroso et al., 2010, 2011a, 2011b). In line with these pharmacological data, mice lacking the ICE/Caspase-1 gene, thus unable to produce and release IL-1β, or lacking the IL-1R1 gene thus being unable to activate the IL-1β signaling cascade, or with a defective TLR4 signaling due to a spontaneous loss-of-function receptor mutation, showed a significant delay in the onset of seizures and were intrinsically resistant to seizure activity (Maroso et al., 2010; Ravizza et al., 2006b; Vezzani et al., 2000). Notably, both the IL-1β and TLR signaling are pivotal for the activation of innate immunity and inflammation following pathogen recognition, thus highlighting convergent molecular pathways possibly underlying the proposed causal link between CNS infection and epilepsy (Singh et al., 2008).

Although the contribution of brain inflammation to seizure activity has been demonstrated in various experimental settings, its involvement in epileptogenesis is still hypothetical, although long-term effect of brain inflammation on neuronal excitability have been reported (Riazi et al., 2010). In favor of such pro-epileptogenic role there is evidence that CNS injuries such as trauma, stroke, viral infection, febrile seizures, status epilepticus occurring either in infancy or during a lifetime are considered common risk factors for developing epilepsy, and long lasting CNS inflammation develops rapidly after these events. Moreover, astrocytic overexpression of cytokines such as TNF-α or IL-6 results in age-dependent development of neurological dysfunctions, including increased seizure susceptibility and spontaneous seizures (Akassoglou et al., 1997; Stalder et al., 1998). Pharmacological attempts to interfere with brain inflammation induced by status epilepticus or by kindling using COX-2 inhibitors (Jung et al., 2006), antibodies against endothelial cell adhesion molecules (Fabene et al., 2008), mTOR pathway inhibitor (Zeng et al., 2009) and immunosuppressant drugs (*reviewed* Ravizza et al., 2011), provided some support to the involvement of inflammation in the development of epileptogenesis. These studies indeed reported a reduction of the frequency of spontaneous seizures in post-SE models (Fabene et al., 2008; Jung et al., 2006; Zeng et al., 2009) or a delay in kindling epileptogenesis in the absence of afterdischarge modifications (*reviewed* in Ravizza et al., 2011).

Molecular mechanisms by which inflammation contributes to seizures

The mechanisms underlying the proconvulsant effects of IL-1β and HMGB1 include rapid post-translational changes in N-methyl-D-aspartate (NMDA) receptor phosphorylation leading to increased receptor function (Balosso et al., 2008; Maroso et al., 2010; Viviani et al., 2003). Namely, the activation of IL-1R1/TLR4 axis by their endogenous ligands induces Src kinase-dependent phosphorylation of the NR2B subunit of the NMDA receptors (Balosso et al., 2008; Maroso et al., 2010), a pathway responsible for potentiation of NMDA-dependent Ca^{2+} influx (Viviani et al., 2003). Pharmacological blockade of this molecular chain of events in vivo precludes the proconvulsant activity of these pro-inflammatory molecules (Balosso et al., 2008; Maroso et al., 2010). A contribution of brain inflammation to some of the acquired channelopathies described in epilepsy should also be considered (Viviani et al., 2007).

The activation of the IL-1R1/TLR4 signaling may also trigger transcriptional changes which could promote chronic inflammation via NFkB-dependent transcription of inflammatory genes. Moreover, transcriptional events induced by inflammatory mediators may contribute to a lasting decrease in seizure threshold by inducing the expression of genes involved in neurogenesis, cell death, and molecular and synaptic plasticity (O'Neill and Bowie, 2007; Vezzani et al., 2011a; Wetherington et al., 2008), which are processes developing during epileptogenesis, and possibly contributing to it (Pitkanen, 2010). Inflammatory molecules can also contribute to hyperexcitability by inhibiting the astrocytic glutamate reuptake (Hu et al., 2000) and by inducing changes in glutamate receptor subunit expression, thus leading to increased glutamatergic neurotransmission (Balosso et al., 2009; Seifert et al., 2006; Stellwagen et al., 2005). A reduction in GABA-mediated inhibition in inflamed brain tissue can be anticipated by the ability of IL-1β and TNF-α to reduce GABA-mediated chloride currents or GABA-A receptor expression at neuronal membranes, respectively (*reviewed in* Vezzani et al., 2011a, 2011b; Viviani et al., 2007).

Finally, brain inflammation may contribute to BBB breakdown and to the consequent parenchymal accumulation of serum albumin and IgG. Albumin has been shown to induce long lasting hyperexcitability by impairing astrocyte capacity to buffer extracellular potassium and glutamate via activation of the Transforming Growth Factor (TGF)-β pathway which results in down-regulation of Kir4.1 and glutamate transporter (Cacheaux et al., 2009; Friedman et al., 2009; Shlosberg et al., 2010).

The multifaceted mechanisms triggered by brain inflammation and the time frame in which these individual mechanisms are evolving might explain the latency phase that typically occurs between the inflammatory challenge and the onset of epilepsy.

Inflammation and the immature brain

Inflammation in the developing brain is unique compared to the adult brain for several reasons: 1) inflammatory mediators play a role in normal development; 2) developmental timelines affect how an immature brain will respond; 3) infants may exhibit unique seizures that require unique models.

Pro-inflammatory molecules are also a part of normal developmental processes in the immature brain (Boulanger, 2009; Carpentier and Palmer, 2009; Fourgeaud and Boulanger, 2010) in that they regulate neurogenesis and modulate synapse formation. These molecules include TLRs (Okun et al., 2011), major histocompatibility complex class I proteins (Goddard et al., 2007), complement proteins (*reviewed in* Veerhuis et al., 2011) and cytokines (Duchowny et al., 2000; Giulian et al., 1988; Golan et al., 2004; Spulber et al., 2011). It is likely that excess signaling by these molecules, either in response to a seizure, or resulting from some infectious process, has the potential to interfere with normal developmental processes. In this regard, it is interesting that many of the epilepsy and seizure disorders in pediatric epilepsy are thought to be related to aberrant neuronal connections and malformations of cortical development (Duchowny et al., 2000; Nelson and Ellenberg, 1976).

Because different parts of the brain develop with different temporal trajectories (Dobbing and Sands, 1973), inflammation may affect neuronal excitability differently at different maturational points (Ben-Ari and Holmes, 2006). This concept becomes even more relevant when one is inducing seizures in rodents (Scantlebury et al., 2007) where

brain development is on a very different time line than in humans (Clancy et al., 2007). In young rodents, major transmitter systems undergo important changes in the first 2 weeks of life; for example, GABA switches from excitatory to inhibitory in nature (Ben-Ari, 2006).

Seizures in infancy take many forms and the role of inflammation has, until recently, received little investigation. However, in Rasmussen's encephalitis, which occurs generally under the age of 15, there is considerable evidence for brain inflammation. That is, in children with Rasmussen's encephalitis and several types of intractable epilepsy, there is evidence of microglial activation and upregulated pro-inflammatory cytokines in surgical resections (Choi et al., 2009). Infantile spasms have been modeled (Scantlebury et al., 2010; Stafstrom, 2009), but the pathological mechanisms, including inflammation, are not well understood (Brunson et al., 2002; Karvelas et al., 2009). In contrast, febrile seizures have been extensively studied in experimental models and a role for inflammation in their etiology has been intensively explored. Thus the following section will be largely devoted to a discussion of the involvement of inflammatory processes in febrile seizures.

As febrile seizures in humans are the most common seizures of infancy, increasing attention has been directed at understanding their underlying mechanisms, determining if they lead to adult TLE and revealing predictive biomarkers of epileptogenesis. While some clinical findings have emerged (McClelland et al., 2011), most of the data implicating inflammation in febrile seizures has been obtained from animal models. There have been a number of different approaches to modeling febrile seizures. Possibly the most common has been the use of externally applied heat to produce a hyperthermic seizure to mimic the hyperthermia of 'fever' (Baram and Shinnar, 2002; Holtzman et al., 1981). While this model does not necessarily replicate a true infectious fever (i.e. defined as a 'hyperthermic' seizure, rather than a febrile seizure), and may implicate respiratory alkalosis as one of the underlying mechanism (Schuchmann et al., 2008), much useful information has been obtained using this approach (Dubé et al., 2006a). Hyperthermic seizures have also been imposed upon genetic models that display increased seizure susceptibility (Oakley et al., 2009). Another model incorporates fever induced by the bacterial product, lipopolysaccharide (LPS) (i.e. defined as a 'febrile' seizure), but seizure precipitation requires a concurrent pharmacological stimulus (Heida et al., 2004). Furthermore, it should be noted that the profile of changes activated within the brain by LPS may not necessarily replicate exactly that of a true bacterial infection (Schwarz and Bilbo, 2011). Recently authors have utilized LPS concurrently with hyperthermia (Auvin et al., 2009), cortical injury (Gibbs et al., 2008; Scantlebury et al., 2005) or other convulsant stimuli (Auvin et al., 2010a, 2010b). Independently of the model, there is now increasing evidence that both the induction of the seizure and its neurological sequelae in the immature brain involve inflammatory processes.

Inflammation and febrile seizures

During bacterial or viral infections, immune cells synthesize a number of pro- and anti-inflammatory cytokines (Blatteis, 2007) and also generate a mirror inflammatory process within the brain (Heida et al., 2009; Turrin et al., 2001). Thus, it is interesting that monocytes from children with febrile seizures show enhanced LPS- or viral-stimulated synthesis of IL-1β in vitro (Helminen and Vesikari, 1990; Matsuo et al., 2006). However, there have been divergent findings on whether children with febrile seizures have increased plasma levels of pro-and anti-inflammatory cytokines (Lahat et al., 1997; Tomoum et al., 2007; Virta et al., 2002a, 2002b). While most studies have not reported increased levels in CSF samples from children with febrile seizures (Asano et al., 2010; Ichiyama et al., 1998; Tomoum et al., 2007), it is unlikely that lumbar CSF levels accurately reflect parenchymal brain levels of cytokines. Additional evidence implicating cytokines is that genetic susceptibility to febrile seizures is associated with polymorphisms of the IL-1β (Kanemoto et al., 2003; Kira et al., 2005, 2010; Virta et al., 2002a, 2002b) and IL-1ra (Serdaroglu et al., 2009) gene promoters.

There is compelling evidence for a role of cytokines and inflammation in experimental febrile seizures. Hyperthermic seizures elicited in juvenile mice deficient in IL-1 receptors occurred at higher threshold temperatures, whereas intracerebroventricular (icv) infusion of IL-1β into wild type mice not only lowered the temperature threshold to seizures but also generated seizures on its own (Dubé et al., 2005). Interestingly, temperature thresholds for hyperthermic seizures in postnatal (P)11–16 rats were not altered by systemic LPS (Auvin et al., 2009). The numbers of febrile seizures in P14 rats were also increased by icv IL-1β and reduced by icv IL-1ra (Heida and Pittman, 2005); furthermore, rats with febrile seizures displayed increased hippocampal IL-1β at the onset of the seizure, whereas levels of IL-1ra did not change. IL-1β expression is also elevated in activated astrocytes after hyperthermic seizures (Dubé et al., 2010). These observations indicate that an excess IL-1β/IL-1ra ratio favors seizure generation.

It is likely that CNS inflammation and cytokines play a role in other postnatal seizures. Inflammation induced by a low dose of LPS reduced the electrically induced afterdischarge threshold in the hippocampus and increased the rate of acquisition of kindling induced seizures (Auvin et al., 2010a, 2010b). In related studies, seizure induced hippocampal injury due to lithium/pilocarpine-induced status epilepticus was enhanced in the presence of LPS (Sankar et al., 2007). Kainic acid-induced seizures in immature rodents also elicit increases in CNS cytokines and brain inflammation (Somera-Molina et al., 2007), but only if induced at about 2 weeks of age and in older animals. Moreover, in this model brain inflammation precedes the development of cell loss in the hippocampus suggesting it may play a role in seizure-induced neurodegeneration (Rizzi et al., 2003). Since P4 rats respond to peripheral infection with robust CNS inflammation (Bilbo et al., 2005), this age-dependent seizure-induced inflammation may be ascribed to uncoupling between seizures and activation of transcriptional factors promoting inflammation such as AP-1 or NFkB (Rizzi et al., 2003).

Long term effects of early seizures and inflammation

A recurring question is whether febrile seizures increase the risk of subsequent epilepsy. Retrospective and prospective clinical studies have not given yet a clear picture (McClelland et al., 2011; Reid et al., 2009). However, the possibility that inflammatory markers might be predictive of later epileptogenesis has been considered (Dubé et al., 2010). A DNA microarray study on leukocytes stimulated with a TLR3 ligand indicated that cytokine and chemokine genes were upregulated more in leukocytes from a febrile seizures group of children than from controls. It is not known if there is a correlation between subsequent development of epilepsy and any particular inflammation-related gene.

Both febrile seizures and other seizures in experimental models cause long term increases in brain excitability (Riazi et al., 2010). A febrile seizure in LPS-treated P14 rats lowers electrically induced afterdischarge threshold, but not kindling progression in adult rats as compared to febrile P14 rats that did not have seizures (Heida et al., 2005). Febrile P14 rats with no febrile seizures showed lower levels of inflammation in their hippocampi (Heida and Pittman, 2005). This is important because subsequent studies revealed that brain inflammation alone in P14 rats, whether generated by peripheral LPS (Galic et al., 2008) or by direct stimulation of TLR3 receptors in the brain (Galic et al., 2009) increases brain excitability in adulthood. TNFα and microglial activation in the postnatal period were implicated as precipitating factors. Inflammation arising from hyperthermic seizures and concomitant LPS in P14 rats also increases excitability of the adult rat brain compared to subjects that had only the hypethermic seizures (Auvin et al., 2009). These effects were IL-1β dependent and also contributed to epileptogenesis (Auvin et al.,

2010a, 2010b). Prolonged hyperthermic seizures in postnatal rats have also been reported to lead to adult TLE (Dubé et al., 2006a, 2006b) and this occurred only in animals having chronically elevated IL-1β in the hippocampus (Dubé et al., 2010).

In summary, there is now a strong evidence that inflammation, arising from an immune stimulus or from a seizure, predisposes the immature brain to increased excitability in adulthood. The mechanisms that produce this state of increased excitability are not yet well understood, but may involve alterations in glutamate receptors in forebrain (Harré et al., 2008). There is still much that remains unknown; future studies must explore the immature brain for other inflammatory changes and for possible inflammation-induced alterations in the BBB (Marcon et al., 2009) and leukocyte migration into the brain (Friedman and Dingledine, 2011).

Role of brain inflammation in neuropsychiatric comorbidities of epilepsy

Seizures represent the most dramatic hallmark of epilepsy. At the same time many epilepsy patients develop neurological, psychiatric and somatic comorbidities, with the prevalence substantially exceeding that in the general population. Causes that underlie comorbid conditions in epilepsy are frequently unknown. Observations that even with effective management of seizures, comorbidities may persist, have led to the acknowledgement that these conditions require targeted mechanistic studies which would ultimately lead to the development of their evidence-based therapies (NINDS/NIH, 2007).

Psychiatric co-morbidities are a particularly heavy burden on epilepsy patients: they exacerbate social maladaption and may have higher negative impact on the patient quality of life than the frequency of seizures (Garcia-Morales et al., 2008).

Brain inflammation has been implicated in the pathophysiology of several neuropsychiatric conditions. It is therefore conceivable that inflammatory processes which are triggered in the brain by an epileptogenic insult may, concurrently with seizures, lead to the development of neuropsychiatric abnormalities. Below, we discuss possible role of inflammation in the pathophysiology of three common neuropsychiatric comorbidities of epilepsy: depression, memory impairments, and autism spectrum disorder.

Depression

Between 10% and 60% of epilepsy patients exhibit symptoms of depression (Mendez et al., 1986). Among mechanisms of major depression, the deficiency of serotonergic transmission has been widely accepted, and represents a basis for the treatment with selective serotonin reuptake inhibitors, such as fluoxetine (Dantzer et al., 2011). According to the serotonergic hypothesis, depression evolves as a result of the diminished output of serotonin from raphe nucleus into afferent projections, such as to the neocortex and the hippocampus (Manji et al., 2001). The paucity of central serotonergic transmission may result from the increased autoinhibition of neurotransmitter release, particularly due to the enhanced function of presynaptic serotonin 1A (5-HT1A) receptors (Parsey et al., 2006).

Another commonly acknowledged mechanism of depression is the dysregulation of the hypothalamo-pituitary-adrenocortical (HPA) axis, that is the failure of the feedback autoinhibitory loop via which circulating glucocorticoids normally regulate their own production by inhibiting the release of corticotropin releasing hormone and adrenocorticotropic hormone (Carroll et al., 2007). The dysregulation of the HPA axis may lead to depression by upregulating presynaptic 5-HT1A receptors, and thus by shifting the control of serotonin release from raphe neurons in favor of autoinhibition (Judge et al., 2004).

At the same time, both clinical and experimental evidence point toward inflammation as a possible mechanistic factor in depression. On the one hand, laboratory blood analysis of patients with major depression frequently identifies the presence of inflammatory biomarkers (Bremmer et al., 2008; Dantzer et al., 2011). On the other hand, patients with primarily chronic inflammatory diseases (e.g. rheumatoid arthritis) commonly exhibit mood impairments (Bruce, 2008). Furthermore, chemokine immunotherapy has been reported to induce clinical symptoms of depression (Dantzer and Kelley, 1989). In the experimental setting, LPS induced inflammation in rodents is accompanied by what is known as “LPS sickness” behavior that leads to a set of behavioral impairments, some of which are indicative of depressive state, particularly anhedonia and hopelessness (Dantzer, 2006). Moreover, even depressive impairments not primarily associated with inflammatory stimuli (e.g. depression induced by stress) are amenable to the treatment with anti-inflammatory drugs, such as minocycline and celecoxib (Guo et al., 2009; Molina-Hernandez et al., 2008).

Brain IL-1β has been regarded as a key factor in the inflammation-associated depression (Goshen and Yirmiya, 2009). For example, IL-1β induced behavioral (Dunn and Swiergiel, 2005) and neuroendocrine (Parsadaniantz et al., 1997) symptoms of depression in rodents. In the light of the discussed overexpression of both IL-1β and its receptors in the epileptic hippocampus, it is conceivable that such overexpression, along with its contribution in the epileptic process, may concurrently lead to depression. In addition, IL-1β directly suppresses the firing of raphe serotonin neurons, thus reducing the availability of serotonin in raphe afferents (Brambilla et al., 2007).

Animals which develop chronic epilepsy following status epilepticus, exhibit behavioral deficits indicative of depression, particularly anhedonia and despair. These impairments develop as a result of consecutive dysregulation of the HPA axis, enhanced function of presynaptic 5-HT1A receptors and the diminished raphe-hippocampal serotonergic transmission (Mazarati et al., 2008, 2009, 2010; Pineda et al., 2011). Importantly, epilepsy-associated depression is resistant to the treatment with fluoxetine (Mazarati et al., 2008), and persists upon suppression of spontaneous seizures with topiramate (personal unpublished data). Remarkably, despite the resistance to conventional antidepressant and anticonvulsant medications, behavioral, neuroendocrine, biochemical and receptor hallmarks of epilepsy-associated depression are alleviated by intrahippocampal administration of human recombinant IL1-ra (Mazarati et al., 2010). This suggests that depression in epileptic subjects may, at least in part, stem from the overexpression of hippocampal IL-1β with the subsequent involvement of the HPA axis and brain serotonergic transmission.

Memory impairments

Memory and cognitive impairments are common in epilepsy patients (Giovagnoli and Avanzini, 1999) and have been extensively studied using animal epilepsy models. The causes of these impairments have been attributed to neuronal hippocampal cell loss (Holmes et al., 2002), the dysfunction of surviving hippocampal neurons (Karnam et al., 2009), as well as to adverse effects of antiepileptic drugs (Sankar and Holmes, 2004).

Several mediators of inflammation exert detrimental effects on learning and memory. For example, memory deficits represent one of hallmarks of the LPS sickness behavior (Tarr et al., 2011), and also develop as a result of excessive IL-1β signaling (Goshen and Yirmiya, 2009).

Recent studies have been pointing toward the RAGE mediated inflammatory pathway as an important negative regulator of learning and memory. In particular, the increased RAGE signaling has been implicated in mechanisms of memory impairments in Alzheimer's disease (Arancio et al., 2004).

As it has been discussed earlier, HMGB1 is overexpressed in the epileptic tissue and may precipitate ictogenesis primarily via activating TLR4 (Maroso et al., 2010). However, since RAGE also employs HMGB1 as its ligand (Rauvala and Rouhiainen, 2010), it is conceivable that dual stimulation of TLR4 and RAGE by HMGB1 may, along with exacerbating seizures, lead to memory dysfunction. Along these

lines, we examined effects of exogenously administered HMGB1 on memory in wild type, TLR4 knockout (KO) and RAGE KO mice. We opted for the novel object recognition test, which afforded the examination of non-spatial memory, the latter being commonly impaired in Alzheimer's patients (Pike and Savage, 2008), and reportedly, in patients with TLE (Schwarze et al., 2009). Intracerebroventricular administration of HMGB1 in the amount which had been proven to precipitate seizures, disrupted object memory encoding equally in wild type, RAGE KO and TLR4 KO animals. Furthermore, the blockade of TLR4 in RAGE KO mice by means of LPS from *Rhodobacter sphaeroides* (*LPS-RS*) abolished amnestic effects of HMGB1 (Mazarati et al., 2011). Thus, excessive HMGB1 signaling in the epileptic brain may lead to concurrent selective memory deficits via activating both TLR4 and RAGE. In addition, in the light of a possible role of RAGE in Alzheimer's dementia, it is tempting to speculate that the HMGB1-induced overstimulation of RAGE may represent a mechanistic link explaining high incidence of comorbidity between epilepsy and Alzheimer's disease (Noebels, 2011).

Autism spectrum disorder

One third of patients with epilepsy fit criteria for autism diagnosis (Clarke et al., 2005). Mechanisms which underlie autism remain by and large elusive, but undoubtedly include genetic (e.g. fragile X chromosome, oxytocin deficiency) (Patterson, 2011), as well as environmental factors. Among the latter, maternal inflammation has been implicated by a number of clinical and experimental findings (Patterson, 2011). A recent epidemiological study has confirmed that maternal infection represents a major risk factor for autism in the offspring (Atladottir et al., 2010). In the laboratory setting, the exposure of pregnant rodents to either LPS or poly I:C (i.e. the stimulation of TLR4 and TLR3 respectively), leads to the development in the offspring of autistic abnormalities, including impairments in social interaction, communication, and recognition, as well as neophobia (Patterson, 2009, 2011). Electrophysiological studies in these subjects have revealed impaired communication between the hippocampus and prefrontal cortex, which represents a hallmark of autism spectrum disorder (Baharnoori et al., 2009). Among inflammatory cytokines, IL-6 has been strongly associated with autistic impairments. Thus, an injection of IL-6 in pregnant mice induces behavioral autism-like abnormalities in the offspring; conversely, anti-IL-6 antibody prevents the occurrence of autism in pups exposed to poly I:C in utero (Smith et al., 2007).

Postnatal inflammation has been associated with autism as well. For example, the increased blood levels of RAGE ligands such as HMGB1 and S100A9 (Boso et al., 2006; Emanuele et al., 2010), as well as the enhanced reactivity of TLR2 and TLR4 expressing monocytes (Enstrom et al., 2010) have been documented in autistic patients.

Direct evidence that brain inflammation may be a causative factor in the epilepsy-associated autistic like behavior is presently lacking; however, the fact that the same inflammatory processes which are present in the epileptic brain, are also involved in mechanisms of autism, opens promising avenues for the research in this direction.

In conclusion, there is compelling evidence that brain inflammation may be either a primary cause, or at least a confounding factor in the development of neuropsychiatric comorbidities of epilepsy. It is conceivable that inflammatory processes triggered in the epileptic brain, may translate into concrete neuropsychiatric syndromes once combined with specific (e.g. genetic) predisposing factors.

Conclusions

Activation of specific pro-inflammatory pathways has been demonstrated in human and experimental epileptic brain tissue. Various convulsant and pro-epileptogenic brain insults (i.e. neurotrauma,

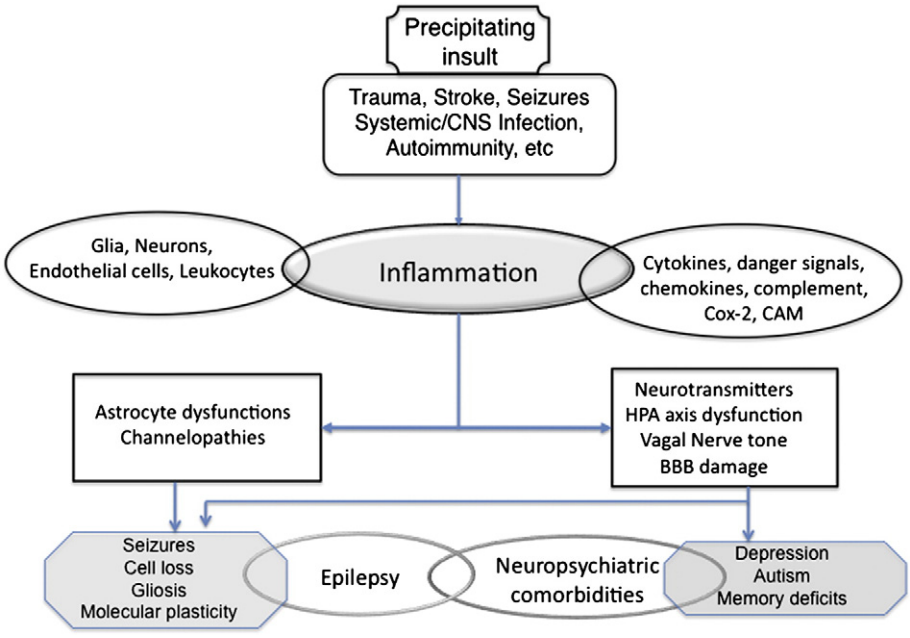

Fig. 1. The cascade of inflammatory events in epilepsy. Pathological events initiated either in the CNS by local injuries, or in the periphery by infections, or in the context of autoimmune disorders, result in the activation of brain parenchymal cells (microglia, astrocytes, neurons), endothelial cells of the BBB and leukocytes. These cells produce and release inflammatory mediators in the brain, eliciting a cascade of downstream events causing a spectrum of physiopathological effects. Specifically, cytokines and danger signals induce inflammatory molecules responsible either for direct activation of glial or neuronal signaling pathways, or for BBB breakdown. Inflammatory mediators can activate specific receptors expressed by glia and neurons, inducing rapid non-transcriptional effects on voltage-gated and receptor-gated ion channels, neurotransmitter release and glutamate receptors leading to increased neuronal excitability. Transcriptional activation of genes can also be triggered by inflammatory molecules such as cytokines which may perpetuate brain inflammation and contribute to long-term molecular plasticity involved in epileptogenesis. IgG/albumin extravasation in brain following BBB breakdown can promote activation of inflammatory signals and impair astrocyte functions. These effects contribute to the generation of individual seizures and cell death which, in turn, activate further inflammation, thus establishing a vicious cycle contributing to the development of epilepsy. Since brain inflammation has been implicated in the pathophysiology of several neuropsychiatric conditions it is conceivable that inflammatory processes and mechanisms which are triggered in the brain by an epileptogenic insult may, concurrently with seizures, lead to the development of some neuropsychiatric abnormalities which are considered to be comorbidities of epilepsy, such as depression, memory impairments, and autism spectrum disorder.

stroke, infection, perinatal injury, febrile seizures, status epilepticus) induce long-lasting inflammation in the brain by activating specific pro-inflammatory pathways inefficiently controlled by endogenous anti-inflammatory mechanisms. The initiation of an inflammatory response in the brain may be a consequence of an intrinsic injury, or the initial challenge may originate within peripheral lymphoid tissues for example when epilepsy evolves after systemic infectious diseases, encephalitis, or prolonged seizures associated with fever. Experimental studies show that once seizures develop, they can contribute to perpetuate inflammation in the brain via mechanisms which may involve transcription of inflammatory genes or post-translational changes in cytokine release machinery. Specific inflammatory mediators contribute to decrease seizure threshold in animal models either by direct effects on neuronal excitability or by activating transcription of genes involved in synaptic and molecular plasticity. Thus, the available evidence suggests that an epileptogenic event, even if subclinical, occurring at birth or during the lifetime may initiate a cascade of inflammatory processes contributing to the onset of epilepsy and to seizure recurrence. The presence of activated inflammatory pathways in epileptic brain may also contribute to co-morbities often associated with epilepsy (Fig. 1).

These findings highlight the possibility to block the activation of inflammatory signalings as potential new targets for therapeutic intervention with disease-modifying effects, particularly for epileptic patients not responding to conventional antiepileptic drugs.

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