Inflammation and Epilepsy

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In recent years, increasing evidence has indicated that immune and inflammatory reactions occur in brain in various central nervous system (CNS) diseases. Furthermore, inflammatory processes, such as the production of proinflammatory cytokines and related molecules, have been described in brain after seizures induced in experimental models and in clinical cases of epilepsy. Although little is known about the role of inflammation in epilepsy, it has been hypothesized that activation of the innate immune system and associated inflammatory reactions in brain may mediate some of the molecular and structural changes occurring during and after seizure activity. Whether the innate immune response that takes place in epileptic tissue is beneficial or noxious to the CNS is still an open and intriguing question that should be addressed by further investigations.

Several proinflammatory signals, such as cytokines, chemokines, prostaglandins, toll-like receptors, signal-transduction pathways that recruit nuclear factor-κB (NF-κB), complement factors, and cell-adhesion molecules, are rapidly induced in rodent brain during epileptic activity. This observation shows that immune-like mechanisms can be triggered in CNS by seizures, thus challenging neuroscience research to investigate in more detail the mechanisms underlying this activation and its functional consequences. Key, open questions include whether these proinflammatory signals represent a mere epiphenomenon or if they are significantly involved in the etiopathogenesis of seizures and, possibly, contribute to epileptogenesis.

In the attempt to address these crucial questions, basic science first focused on the characterization of the time-course profile of specific proinflammatory events occurring after induction of seizures in otherwise normal rodent brain. Furthermore, much effort has been devoted to study the brain's regional distribution and cell-specific expression of proinflammatory molecules and their signaling, as compared with patterns of seizure spread and the associated neuronal cell loss. Although clear evidence indicates that proinflammatory cytokines can affect the occurrence of seizures (1–6), neuronal viability and their survival after injury (7), induce glial proliferation, enhance blood–brain barrier permeability (8), and inhibit neurogenesis (9,10), scarce information is available so far on the functional consequences of brain inflammatory reactions on epileptogenesis.

Proinflammatory Signaling in CNS

During systemic infections (i.e., mimicked in rodents by administration of lipopolysaccharide [LPS], a component of the gram-negative bacterial wall), the brain triggers an inflammatory response that is mounted to protect the host against infectious microorganisms. This phenomenon comprises an early inflammatory response (innate immunity) which can eventually progress to an adaptive immune response, mediated by activated lymphocytes recruited from the blood (11). The CNS shows a well-organized innate immune reaction in response, not only to systemic or intracerebral bacterial infection, but also to a variety of brain injuries. In particular, proinflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and IL-6, although expressed at very low levels in healthy brain tissue, are rapidly induced after ischemic, traumatic, and excitotoxic damage (7).

Most recently, seizure activity, induced in experimental models of status epilepticus or after intracerebral application of kainic acid, has been reported to increase rapidly the production of proinflammatory cytokines as well as various markers of the innate immunity (e.g., the NF-κB system, prostaglandins and their pathway enzymes, Toll-like receptors, monocyte chemoattractant protein-1, or complement system), both in glia and in neurons (12,13). The increase in messenger RNA (mRNA) expression and protein levels of proinflammatory cytokines after induction of seizures is rapid ($\leq$30 min) and reversible, except for IL-1β, which is still upregulated 60 days after induction of status epilepticus in brain of rats developing spontaneous seizures; cytokines increase specifically in brain regions involved in seizure onset and spread (1,14,15). Evidence of increased production of inflammatory molecules in brain also has been reported in genetic models of audiogenic seizures and in kindling (16,17). Microglia and astrocytes are the first cells to produce cytokines during seizures, and in general, they represent the main sources of proinflammatory molecules in brain. Cytokine receptors, however, are localized in both glia and neurons in normal brain, suggesting that proinflammatory cytokines are

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soluble mediators that can establish functional communication between microglia, astrocytes, and neurons (18–20). In this respect, electrophysiologic findings support a neuromodulatory role of glia-borne cytokines, showing that these molecules affect ionic conductance in neurons and synaptic plasticity (e.g., long-term potentiation) (21–23).

Thus similar patterns of proinflammatory molecules and their signaling pathways are activated after systemic infection or seizures; however, clear differences are found in the duration of these events and in the cell-specific distribution of these changes, as is further discussed later. The general thinking is that the consequences of an increase in brain cytokines and related molecules on brain function depend on the extent and duration of these changes, on the subtype of cytokine receptors recruited, and on the preexisting functional status of the cells exposed to cytokines.

Innate Immunity: Endotoxemia versus Seizures

The inflammatory response observed after pilocarpine-induced seizures in mice is different in many aspects from that described after systemic injection of bacterial LPS (24,25). Thus proinflammatory molecules are predominantly and first expressed after endotoxemia in circumventricular organs, the choroid plexus, the leptomeninges, and along brain microvessels; the involvement of parenchymal microglia is delayed and more restricted. Neurons do not typically express inflammatory markers after endotoxemia. However, seizures induce a massive inflammatory response in parenchymal cells, involving both microglia and neurons (i.e., NF-κB and cyclo-oxygenase [COX]-2 are significantly expressed by neurons after seizures but not after LPS). Moreover, changes induced by endotoxemia are relatively short when compared with those observed after seizures. These observations suggest that inflammation induced by seizures results from complex neurophysiologic events specific to brain tissue and differs from classical immune reactions triggered by bacterial/viral infections both in the duration and in the cell populations involved.

The lasting stimulation of the innate immune response and related inflammatory reactions observed after seizures may eventually promote infiltration of lymphocytes and the establishment of acquired immunity in the CNS. Whether this transfer actually occurs is still controversial. Indications exist of a late wave of CD-45–positive monocyte penetration into the brain parenchyma after seizures. However, Turrin and Rivest (25) recently reported that markers of adaptive immunity, such as production of IL-12 and interferon-γ (IFN-γ) by activated T cells, are undetectable across the brain of pilocarpine-treated mice at least up to 72 hours after seizure induction. Accordingly, immunostaining for T cells, B cells, and natural killer cells was negative in the brain of kainic acid–treated rats, although granulocytes, macrophages/monocytes, and microglia cells were all detected (26). Thus the innate immune response in experimental models of seizures does not appear to be associated with adaptive immunity and B- or T-cell infiltration and differentiation within a restricted time window after induction of seizures.

In summary, the transient induction of innate immunity processes after infection is an adaptive, beneficial endogenous response. In contrast, inappropriate control of this system, as possibly occurs after seizures, may have deleterious consequences because of the sustained production of specific proinflammatory molecules in brain parenchymal cells.

Functional Studies: Effect of Proinflammatory Molecules on Seizures

Evidence that seizures could trigger lasting inflammatory reactions opened the door to additional questions of whether a protracted proinflammatory state in the CNS may enhance the predisposition of brain tissue to develop seizures and brain damage. This hypothesis has been addressed by using transgenic mice overexpressing proinflammatory cytokines in glia and by increasing the endogenous concentration of proinflammatory molecules, either by their intracerebral application or by using inflammatory stimuli. In addition, if proinflammatory processes are significantly involved in epileptic brain pathology, then antiinflammatory drugs should have a potential benefit.

With models of hippocampal seizures or status epilepticus in rodents, studies have shown that the IL-1β system significantly exacerbates seizure activity. Thus preapplication of this cytokine, with concentrations in the range of those endogenously produced during seizures, prolongs the duration of electrographic and behavioral kainate-induced seizures (2). Subsequent studies have shown that the intracerebral application of IL-1–receptor antagonist (IL-1ra), a naturally occurring molecule that antagonizes the effect of endogenous IL-1β, has powerful anticonvulsant activity (3). Accordingly, IL-1ra–overexpressing mice display a reduced susceptibility to seizures (4). These findings suggest that an endogenous increase in IL-1β has proconvulsant effects. It appears that IL-1β prolongs seizures by increasing glutamatergic neurotransmission (2). In this respect, functional interactions at the molecular level have been reported between IL-1β receptors and N-methyl-D-aspartate receptors, which are coexpressed by hippocampal neurons (29). Other actions may account for the excitatory effects of IL-1β: this cytokine can inhibit glutamate uptake by astrocytes (27) and decreases the peak magnitude of γ-aminobutyric acid (GABA)-mediated currents in cultured hippocampal neurons (21,22).

In contrast, the effect of TNF-α on seizures is still controversial. Recent data, obtained by using in vivo

pharmacologic approaches in wild-type and TNF-α knockout mice, show that TNF-α reduces seizure activity by interacting with TNF-α type II (p75) receptors. Tiansgenic mice expressing moderate increases of TNF-α in glia show a decreased sensitivity to kainate-induced seizures (Vezanni, unpublished data, 2004). However, seizures and brain damage in a rat model of bacterial meningitis were attenuated by large-spectrum inhibitors of both matrix metalloproteinases and TNF-α–converting enzyme, which reduce the soluble form of TNF-α (28). Once again, these apparent discrepancies can be reconciled by taking into account either the differences in TNF-α concentrations or the receptor subtypes predominantly involved in the various experimental models. In accordance with this view, relatively high concentrations of TNF-α exert suppressive effects on *Shigella dysenteriae*-induced seizures, whereas lower concentrations were proconvulsive (5).

Seizure susceptibility also was assessed in transgenic mice overexpressing IL-6 in glia, showing that they have a profound increase in sensitivity to glutamatergic (but not to cholinergic) agonists (6). Interestingly, IL-6–overexpressing mice showed neuronal loss of GABA- and parvalbumin-positive neurons in the hippocampus. In different studies, TNF-α and IL-6 transgenic mice develop neurodegenerative changes and behavioral seizures, in an age-dependent manner, when overexpressing these cytokines in high amounts in glia, but not in neurons (30,31).

The experiments carried out in transgenic mice suggest that a preexisting chronic, proinflammatory state in the brain can predispose to seizures and promote neurologic dysfunctions. In this respect, systemic administration of LPS to mice was reported to decrease their threshold to pentylenetetrazole-induced seizures, and this effect was blocked by antiinflammatory drugs (32). Finally, sequential infusion of individual proteins of the membrane attack complex (MAC) of the complement system into the rat hippocampus induced both behavioral and electrographic seizures and cytotoxicity (33). This finding implies that deposition of the complement MAC in brain tissue may contribute to epileptic seizures and cell death in diverse CNS diseases (e.g., Rasmussen encephalitis).

Antiinflammatory Drugs and Seizures in Experimental Models

Various pharmacologic studies report inhibition of seizures by using nonsteroidal antiinflammatory drugs. An early report shows attenuation of penicillin-induced electrocorticographic and motor seizures in rats, by using ibuprofen, paracetamol, and indomethacin (34). Aspirin also was reported to protect mice from pentylenetetrazole- and maximal-electroshock–induced seizures and to potentiate the anticonvulsant action of diazepam (DZP) and sodium valproate (VPA) (35). Interestingly, both VPA and carbamazepine (CBZ) inhibit the production of inflammatory mediators in the in vitro preparations. In particular, among the commonly used antiepileptic drugs, VPA inhibits LPS-induced activation of NF-κB as well as the production of TNF-α and IL-6 in monocytes and glioma cells; and CBZ was shown to decrease LPS-induced production of prostaglandins and activity of phospholipase A in rat glial cells (36,37).

Conflicting data are available on the effect of prostaglandins on seizures. Several studies have demonstrated increased synthesis of cerebral prostaglandins after convulsions; however, it appears that they can either reduce or promote seizures, depending on the type of prostaglandins produced. For example, Paoletti et al. (38) demonstrated that tacrine-induced seizures in rats, and the consequent hippocampal damage, can be abolished by inhibiting prostaglandin E_2 (PGE_2) production, by using COX-2 inhibitors (38). Similarly, a COX/lipoxygenase inhibitor reduced the severity of seizures and protected from irreversible brain lesions induced by kainic acid in rats (39).

Inflammation and Seizure-induced Long-term Sequelae

Inflammatory processes have been implicated in both acute and chronic neurodegenerative conditions. Accumulating evidence has shown that brain injury per se, in the absence of seizure activity, is accompanied by a marked inflammatory reaction, which is characterized by increased expression of various proinflammatory molecules, activation of microglia, and infiltration of monocytes/macrophages (7).

Indirect evidence supports the involvement of proinflammatory molecules in seizure-induced cell damage, and this hypothesis relies mainly on the temporal and regional pattern of expression of these molecules as compared with the onset and occurrence of neuronal damage. Although increases in cytokines and other markers of inflammation have been observed before significant neuronal death, it is difficult to distinguish between the cytokine response to injury and the early expression that might contribute to cell death. When administered individually, cytokines tend not to evoke cell death directly, but they have synergistic effects that can result in neurotoxicity (e.g., IL-1β plus TNF-α). Intracerebral injections of TNF-α or IL-1β exacerbate excitotoxic injury in vivo, whereas IL-1ra reduces excitotoxic, traumatic, and ischemic brain damage. Evidence also exists of the involvement of cytokines in apoptotic mechanisms (7).

In addition, an elegant study by Dinkel et al. (26) showed that the extent of damage after an excitotoxic insult in the hippocampus correlates significantly with the antecedent inflammatory cell infiltration (granulocyte and macrophages) and with activation of microglia, suggesting that neuronal damage, at

least in part, was caused by the preceding inflammation. It is important to underline that cytokines also can have neurotrophic actions on neurons, which are possibly mediated by their ability to increase the production of neurotrophins (12,40). Thus glial cells (in particular, astrocytes) are a principal source of neurotrophins and growth factors, which are induced by cytokines and exert neuroprotective actions.

The final outcome of an increase in brain cytokines on cell survival is likely to be determined by the extent of their production (neurotoxic effects are usually mediated by relatively high doses), the length of time the brain tissue is exposed to that specific cytokine, and the balance between neurotrophic and inflammatory factors produced in tissue by the competent cells.

Other actions of cytokines that may be relevant for epilepsy are their reported effects on brain microvasculature (IL-1β can induce neovascularization) and damage to the blood–brain barrier, leading to its increased permeability to normally excluded substances and cells (e.g., upregulation of cell-adhesion molecules, such as intracellular adhesion molecule-1 [ICAM-1] and E-selectin, in endothelial cells are involved in leukocyte infiltration). Most recently, an inhibitory action of inflammatory molecules (e.g., IL-6) on neurogenesis was reported (9). In particular, neuroinflammation, induced by radiation injury or by LPS, inhibits neurogenesis, whereas inflammation blockade with indomethacin or inhibition of microglia activation by minocycline, restores neurogenesis (9,10).

Human Evidence

Molecules of both innate and adaptive immunity have been shown in brain specimens of a variety of neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington disease, multiple sclerosis, amyotrophic lateral sclerosis, as well as epilepsy. Levels of immunoreactive IL-1 were found to be elevated in surgically resected human temporal lobe tissue from patients with intractable epilepsy, as compared with postmortem tissue from neurologically unaffected subjects (41). Immunoreactive cells were 3 times more numerous in epileptic than in control tissue, and these cells had the morphologic characteristics of activated microglia. Inflammatory reactions in human temporal lobe epilepsy with hippocampal sclerosis also have been reported, as a measure of increased expression of NF-κB, both in reactive astrocytes and in surviving hippocampal neurons (42). These results suggest that in epileptic hippocampi with typical sclerosis, inflammatory processes are chronically active or transiently reinduced by recurrent seizures, or both.

Recent genetic studies have shown that a polymorphism in the promoter region at position –511 of the *IL-1*β gene is associated with therapy-resistant epilepsy in subjects with temporal lobe epilepsy and hippocampal sclerosis and in children with febrile seizures (43,44). This polymorphism, when present in homozygotes, appears to be associated with enhanced ability to produce cytokines after a proper stimulus. Thus minor events during development, such as febrile convulsions, could set up in these subjects a cascade of proinflammatory events leading to hippocampal sclerosis. However, one study in white populations did not confirm the evidence reported by Kanemoto (45), raising the issue that some polymorphisms may be related to specific ethnicity.

These genetic observations, together with the experimental evidence that seizures per se increase cytokine levels in brain, led to the study of proinflammatory molecules in cerebral spinal fluid (CSF) and serum from epilepsy patients. In these studies, IL-6 is the cytokine repeatedly identified as being significantly elevated in plasma and CSF of epilepsy patients with recent tonic–clonic seizures. Ambiguous results, instead, are reported for IL-1β in CSF, where either no increase or significant elevation was measured. Analysis of peripheral blood mononuclear cells highlighted in some, but not all (46) instances, enhanced the ability of these cells to produced inflammatory molecules and express markers of inflammation, when harvested from epilepsy patients or children with recent febrile seizures (47,48). Therefore these data are compatible with an inflammatory state in the epileptic brain and, perhaps, in peripheral monocytes from epilepsy patients.

Increased serum or brain levels of proinflammatory cytokines and markers of immune system activation have been described in patients with West syndrome (49) and tuberous sclerosis (50), two neurologic disorders associated with epilepsy. In particular, expression of molecules involved in cytokine signaling (ICAM-1 and NF-κB) and TNF-α has been found in dysplastic neurons and giant cells in tubers. This observation leads to the hypothesis that initiation of an inflammatory response in tubers may be directly related to epileptogenesis in these lesions. Interestingly, the deletion of the *TSCI* gene in mice results in spontaneous seizures by the age of 2 months, suggesting the possibility that proinflammatory components of tubers may reflect downstream effects of the *TSC1* or *TSC2* gene mutations and contribute to epileptogenesis.

Finally, one of the best indications of an involvement of inflammatory and immune reactions in the pathogenesis of human CNS disorders associated with epilepsy comes from studies of Rasmussen encephalitis. Neuropathologic examinations of affected brain tissue revealed both perivascular lymphocytes and scattered microglia nodules in close apposition with neurons. In addition, a dramatic increase in the expression of several inflammation-related genes (e.g., *IL-1*β and *TNF-*α) was described in brain specimens from a patient with chronic focal Rasmussen encephalitis and active seizures (51).

Concluding Remarks

The innate immune response triggered in brain by systemic infection involves proinflammatory signals, which also are recruited by epileptic activity. However, the adaptive response to infection is rapid, reversible, and aimed at eliminating pathogens from the host tissue. Prolonged stimulation of proinflammatory signals, by seizures or a persistent proinflammatory situation in brain, may contribute to the establishment of a pathologic substrate (e.g., neurodegeneration, neuronal hyperexcitability, blood–brain barrier damage), playing a role in epileptogenesis and in the acute manifestation or reinforcement of seizures. The hypothetical involvement of proinflammatory signals in the pathogenesis and sequelae of seizures needs further support from preclinical and clinical investigations. If this relation were proven, it might open new avenues to the treatment of seizures and for retarding epileptogenesis or the progression of the disease.

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