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Review article

Chemokines as new inflammatory players in the pathogenesis of epilepsy

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ABSTRACT

A large series of clinical and experimental studies supports a link between inflammation and epilepsy, indicating that inflammatory processes within the brain are important contributors to seizure recurrence and precipitation. Systemic inflammation can precipitate seizures in children suffering from epileptic encephalopathies, and hallmarks of a chronic inflammatory state have been found in patients with temporal lobe epilepsy. Research performed on animal models of epilepsy further corroborates the idea that seizures upregulate inflammatory mediators, which in turn may enhance brain excitability and neuronal degeneration. Several inflammatory molecules and their signaling pathways have been implicated in epilepsy. Among these, the chemokine pathway has increasingly gained attention. Chemokines are small cytokines secreted by blood cells, which act as chemoattractants for leukocyte migration. Recent studies indicate that chemokines and their receptors are also produced by brain cells, and are involved in various neurological disorders including epilepsy. In this review, we will focus on a subset of pro-inflammatory chemokines (namely CCL2, CCL3, CCL5, CX3CL1) and their receptors, and their increasingly recognized role in seizure control.

1. Introduction

Epilepsy is a chronic neurological disorder that affects approximately 65 million people of all ages in the world (Shakirullah et al., 2014). The hallmark of epilepsy is the repeated occurrence of two or more unprovoked seizures, whose clinical manifestation consists of sudden and transitory abnormal episodes of motor, sensory, autonomic, or psychic origin (Shakirullah et al., 2014). Seizure episodes are a result of excessive electrical discharges in a group of neurons in the brain and the behavioral outcome depends on the brain regions where synchronous firing of a neuronal cell group occurs. From a therapeutic point of view, conventional antiepileptic drugs (AEDs) are employed in epilepsy with the aim to reduce this abnormal neural activity. However, about 30% of epileptic patients appear to be resistant to current therapies (Scott Perry and Duchowny, 2013). Mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis is a typical example of drug-resistant epilepsy. For many MTLE patients, the surgical removal of the epileptic focus remains the only option to achieve an acceptable seizure control (Kwan et al., 2011; Lee, 2014). Thus, it is urgent to find alternative and less invasive approaches for drug-resistant epilepsy treatment. Understanding the functional, cellular and molecular mechanisms involved in the pathogenesis of epilepsy should favor the development of novel drugs that interfere with seizure generation.

A rapidly growing body of evidence indicates that inflammatory processes within the brain contribute to seizure recurrence and precipitation. In both epileptic patients and animal models, seizures upregulate or induce inflammatory mediators, which in turn may enhance brain excitability and neuronal degeneration (Vezzani et al., 2011). In this review we will first provide an overview of the involvement of inflammation in epilepsy, we will then focus on a subfamily of pro-inflammatory molecules, called chemokines, and their increasingly recognized role in seizure control.

2. Inflammation and epilepsy

It is now well accepted that inflammatory pathways are implicated in the pathogenesis of several neurodegenerative disorders, such as multiple sclerosis (MS) and Alzheimer disease (AD), and are known to be activated following neurologic infection, ischemic stroke, and traumatic brain injury (Glass et al., 2010). The major players of the

Abbreviations: Aβ, amyloid β; AD, Alzheimer's disease; AEDs, antiepileptic drugs; BBB, blood-brain barrier; CNS, central nervous system; COX, cyclooxygenase; CSF, cerebrospinal fluid; EAE, experimental autoimmune encephalomyelitis; GABA, γ-aminobutyric acid; HAD, HIV associated dementia; HMGB1, high mobility group box 1; IL, interleukin; KA, kainic acid; LPS, lipopolysaccharide; MS, multiple sclerosis; MTLE, mesial temporal lobe epilepsy; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells; PGs, prostaglandins; SE, status epilepticus; SRS, spontaneous recurrent seizures; TLR, Toll-like receptor; TNF, tumor necrosis factor

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inflammatory response in the brain are resident cellular elements. Microglia and astrocytes are strongly activated in most neurodegenerative diseases and produce a variety of inflammatory mediators. In particular, in the diseased brain microglia rapidly reacts, changes morphology (a process referred to as "priming") and can ultimately acquire a phagocytic function (Minghetti, 2005; Perry and Holmes, 2014). Whether the neuroinflammatory reaction is beneficial or detrimental for disease progression is still a matter of debate. Indeed, molecular and cellular responses can be either neuroprotective or neurotoxic depending on several parameters. The concept of "microglia polarization" provides a good example in this respect. According to the classical view, microglial cells respond to acute brain injury becoming activated and developing M1-like (proinflammatory) or M2-like (anti-inflammatory) phenotypes (Lan et al., 2017). It is, however, important to note that this classification has been recently questioned (Ransohoff, 2016).

In the last decade, clinical observations and experimental findings supported a link between inflammation and epilepsy. This link has been shown in human and experimental acquired epilepsies (de Vries et al., 2012; Devinsky et al., 2013; Fabene et al., 2008; Friedman and Dingledine, 2011; Pernot et al., 2011; Vezzani et al., 2013; Aronica et al., 2017), while evidence for a role of inflammation in genetic epilepsies is just beginning to emerge (Shandra et al., 2017). Complex febrile seizures in childhood have long been associated with the later development of temporal lobe epilepsy and febrile illnesses in people with epilepsy can trigger seizures. In surgically resected brain tissue from patients with drug-resistant epilepsy, all of the hallmarks of a chronic inflammatory state have been found, including reactive gliosis and overexpression of cytokines and chemokines. Research using experimental models further corroborates the idea that inflammatory processes have a crucial role in epilepsy. These investigations have also tried to elucidate some unresolved questions such as how inflammation is generated in the epileptic brain and whether inflammation exacerbates the epileptic phenotype.

2.1. Seizures upregulate inflammatory mediators

In rodent models of epilepsy, pharmacological or electrical stimulation of seizures triggers rapid induction of inflammatory mediators in the brain (Vezzani et al., 2013, 2011) and other areas of the central nervous system (CNS), such as the retina (Ahl et al., 2016). Pro-inflammatory cytokines including interleukin (IL) 1β, tumor necrosis factor (TNF) alpha, IL-6 and high mobility group box 1 (HMGB1) are rapidly released from glial cells (Vezzani et al., 2013, 2011) and cytokine receptor expression is induced or upregulated in neurons as well as in microglia and astrocytes (Balosso et al., 2005; Lehtimäki et al., 2003; Ravizza and Vezzani, 2006; Vezzani and Granata, 2005), following epileptic seizures. In addition to inflammatory cytokines, other inflammatory factors such as prostaglandins (PGs) markedly increase following seizures (Shimada et al., 2014). Consistent with this, the enzyme cyclooxygenase-2 (COX-2), responsible for PGs synthesis, is rapidly induced in the brain following seizures (Yoshikawa et al., 2006). A prominent activation of the classical complement pathway was also found in experimental and human temporal lobe epilepsy (Aronica et al., 2007). In addition to the molecules mentioned above, chemokines and their receptors are also produced during epileptic events (Cerri et al., 2016; Foresti et al., 2009; Manley et al., 2007; Xu et al., 2009).

It has been proposed that seizures induce inflammation first in brain endothelial cells (upregulating adhesion molecules and other factors; Fabene et al., 2008; Librizzi et al., 2007), then in perivascular glia, which produces and releases cytokines and PGs (Vezzani et al., 2011). Cytokines bind their receptors and activate signaling cascades that result in the synthesis of chemokines, cytokines, enzymes (e.g., COX-2) and receptors, which further sustain the inflammatory response. For example, IL-1β and HMGB1 respectively bind IL receptor 1 (IL-1R1) and Toll-like receptor 4 (TLR4); their binding activates intracellular pathways converging on the nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB). The transcription factor NFkB is common to many pathways activated by inflammatory ligands, and modulates the expression of many genes involved in inflammation, cell death/survival, and synaptic plasticity (O'Neill and Kaltschmidt, 1997; Vezzani et al., 2011). Seizure-induced brain inflammation may trigger the recruitment of peripheral inflammatory cells. In particular, chemokines act as chemoattractants for blood cells (Ley et al., 2007; Shi and Pamer, 2014) and are responsible for leucocyte recruitment in epileptic brains (Fabene et al., 2010, 2008; Ravizza et al., 2008; Zattoni et al., 2011; Varvel et al., 2016).

It is important to mention that in epileptic brain local inflammatory responses have been observed in conjunction with seizure-promoted blood-brain barrier (BBB) disruption (Fabene et al., 2008; Marchi et al., 2007; Zattoni et al., 2011).

2.2. Inflammation promotes seizures

Brain inflammatory pathways play a key role in seizure generation and exacerbation (Balosso et al., 2005; Maroso et al., 2010; Vezzani et al., 2000; Xiong et al., 2003). For example, IL-1β causes potent proconvulsant effects by mediating enhanced calcium influx through NMDA receptors (Vezzani et al., 2013). Peripheral inflammation can also impact on seizure propensity and this is already evident from the above outlined clinical observation that fever can cause seizures (Cross, 2012). Many experimental evidences further corroborate the notion that systemic infection can trigger or sustain seizures (de Vries et al., 2012; Friedman and Dingledine, 2011; Galic et al., 2008; Györffy et al., 2014; Marchi et al., 2014; Riazi et al., 2008; Sayyah et al., 2003; Zattoni et al., 2011). Systemic inflammation reduces the threshold for pharmacologically induced acute seizures in animals (Sayyah et al., 2003; Riazi et al., 2008), and this has been linked to upregulation of proinflammatory cytokines (Riazi et al., 2008). A systemic inflammatory challenge during a critical period in early development leaves a lasting impact on brain excitability and seizure susceptibility later in life (Galic et al., 2008). Interestingly, pilocarpine, one of the most widely used proconvulsant agents, does not require access to the brain to induce status epilepticus (SE, defined as a seizure lasting > 30 min), apparently acting as a peripheral proinflammatory agent that triggers seizures (Marchi et al., 2014).

The proconvulsant effect of systemic inflammation is well described in several studies that used lipopolysaccharide (LPS) as inducer of peripheral infection (Cerri et al., 2016; Galic et al., 2008; Györffy et al., 2014; Sayyah et al., 2003). LPS administration produces convulsions in rats treated with a subconvulsant dose of kainic acid (KA) (Heida et al., 2005). Systemic LPS also enhances baseline hippocampal excitability and increases progression of rapid kindling, an effect that is counteracted by neutralization of IL-1β (Auvin et al., 2010). Our recent work showed, for the first time, that LPS challenge is able to increase the frequency of spontaneous recurrent seizures (SRS) in a murine model of MTLE based on intrahippocampal injection of KA (Cerri et al., 2016). These data add a novel mechanistic insight since peripheral inflammation appears to target specifically the mechanisms responsible for seizure onset without affecting seizure termination. Indeed, LPS increased frequency of ictal events with no effect on seizure duration (Cerri et al., 2016). The effects of systemic infection on seizures may be explained considering that i) a peripheral inflammatory stimulus triggers a local brain inflammatory "mirror" reaction (i.e., cytokine and chemokine production) similar to the response elicited in the periphery (Perry and Holmes, 2014); ii) the diseased brain, such as the epileptic brain, can display an amplified, exaggerated response to a systemic inflammatory challenge as a result of microglia priming (Perry and Holmes, 2014).

Understanding the complex role of inflammation in the generation and exacerbation of epilepsy is crucial for the identification of new molecular targets for therapeutic intervention. Some strategies able to