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INFLAMMATORY REACTION IN EPILEPSY

REAÇÃO INFLAMATÓRIA NA EPILEPSIA

REACCIÓN INFLAMATORIA EN LA EPILEPSIA

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ABSTRACT

Epilepsies are the second most common neurological disease. The pathological mechanisms of this disease are not fully understood. Several studies claim that inflammation plays a significant role both in structural and physiological changes that lead to the emergence of seizures. Although in some epilepsies, such as Rasmussen's encephalitis, the inflammation has definite importance, in several other epileptic syndromes, the participation of inflammatory reaction still lacks evidence. In such cases, the experimental models are useful for reveal how cytokines, molecules that modulate the inflammatory response, may affect seizures and how seizures may change the expression of these inflammatory molecules. Even with these works, much remains to be clarified with regard to the influence of inflammation on epileptic syndromes. The purpose of this brief review is to discuss the links between inflammatory processes, the origin of crises, and tissue damages in epilepsy.

Keywords: Epilepsy; Inflammation; Models, animal; Rasmussen Syndrome; Interleukins.

RESUMO

As epilepsias são a segunda doença neurológica mais frequentes. Os mecanismos patológicos dessa doença ainda não são completamente compreendidos. Vários trabalhos alegam que a inflamação tem um papel importante tanto nas alterações estruturais quanto fisiológicas que levam à geração de crises. Embora em alguns tipos de epilepsia, como a encefalite de Rasmussen, a inflamação tenha importância evidente, em várias outras síndromes epilépticas ainda faltam evidências para confirmar a participação da reação inflamatória. Nesses casos, os modelos experimentais são úteis para revelar como as citocinas, moléculas que modulam a resposta inflamatória, podem afetar as crises e como as crises podem alterar a expressão dessas moléculas inflamatórias. Mesmo com esses trabalhos, muito ainda precisa ser esclarecido com relação à influência da inflamação sobre as síndromes epilépticas. O objetivo desta breve revisão foi discutir as ligações entre os processos inflamatórios, a origem das crises e os danos teciduais na epilepsia.

Descritores: *Epilepsia; Inflamação; Modelos animais; Encefalite; Interleucinas.*

RESUMEN

Las epilepsias son la segunda enfermedad neurológica más común. Los mecanismos patológicos de esta enfermedad no se entienden completamente. Varios estudios afirman que la inflamación juega un papel importante tanto en los cambios estructurales como en los fisiológicos que conducen a la generación de las convulsiones. Aunque en algunos tipos de epilepsia, tales como la encefalitis de Rasmussen, la inflamación tiene una importancia evidente, en varios otros síndromes epilépticos todavía carecen de pruebas para confirmar la participación de la reacción inflamatoria. En estos casos, los modelos experimentales son útiles para revelar cómo las citoquinas, moléculas que modulan la respuesta inflamatoria, pueden afectar a las convulsiones y cómo las convulsiones pueden cambiar la expresión de estas moléculas inflamatorias. Incluso con estos trabajos, queda mucho por aclarar con respecto a la influencia de la inflamación en los síndromes epilépticos. El propósito de esta breve revisión es discutir los vínculos entre los procesos inflamatorios, el origen de la crisis y el daño tisular en la epilepsia.

Descriptores: *Epilepsia, Inflamación, Modelos animales, Encefalitis, Interleucinas.*

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INTRODUCTION

Epilepsy is characterized by an enduring cerebral predisposition to seizure generation, which leads neurobiological, cognitive, psychological, and social consequences[1]. World prevalence varies between 1% and 3%, depending on the region[2]. Epilepsy etiologies can be idiopathic, symptomatic or cryptogenic[3,4].

Several pathological changes occur in the brain of epileptic patients Amongst the changes seen are reduced GABAergic neurotransmission, changes in NMDA and AMPA receptors, ionic unbalance and changes in Ca^{2+}-dependent intracellular signal cascades, synaptic reorganization, selective neuron death, and astrogliosis[5]. According to some studies, inflammatory reaction is an important factor for epileptogenesis and seizure generation. In this review, we aim to report the inflammatory reaction in the central nervous system, as well as human and animal model data regarding the role of several inflammatory changes in epileptogenesis, epilepsy, and seizure generation.

Inflammation in the central nervous system

The inflammatory reaction is a characteristic response of vascularized tissues to injuries, aiming to isolate and eliminate the aggressor agent, and also to remodel the insulted tissue. An excessive reaction, however, could lead to pathophysiological changes in the tissue.

Brain inflammation has particularities, and experimental models are useful to investigate the course of inflammatory changes in the brain. Studies with experimental models have clarified the importance of T-cells in tissue protection, the contribution of adhesion molecules, cytokines, and enzymes for the recruitment of macrophages, as well as the modulatory action of glial cells on the inflammatory process[6]. However, several questions on brain inflammatory reaction remain unsolved. For instance, the mechanisms responsible for different patterns of inflammatory response in brain diseases such as multiple sclerosis and viral encephalitis[6]. Besides, only recently a study described the existence of functional lymphatic vessels in the brain [7]. Such unexpected finding indicates a probable doorway for the entrance of immune cells in the central nervous system[7].

Inflammatory changes in epilepsy

In the last decades, the role of inflammation in the physiopathology of human epilepsy has gained attention. Several inflammatory molecules were observed in the brain after epileptic seizures[8,9]. Some syndromes, such as Rasmussen's encephalitis and West syndrome, present an important therapeutic response to steroidal anti-inflammatory drugs. In TLE, experimental models and human studies have described chronic inflammation with microgliosis, astrogliosis, and the expression of several inflammatory molecules in the epileptic focus [8,10-12]. The expression of IL-1β, NFκB and COX-2 after pilocarpine-induced status epilepticus is associated with neuron death and astroglial activation[13] Recent studies from our group have shown increased neuroinflammatory-related molecules in TLE patients[11, 12].

Rasmussen's encephalitis

Rasmussen's encephalitis is a rare epileptic syndrome, characterized by brain inflammation that evolves to atrophy of the affected hemisphere, progressive hemiparesis, cognitive impairment, and continuous epileptic seizures[14]. It affects children in the first ten years of life and seldom starts in the adult period[15]. The main treatment for Rasmussen's encephalitis is hemispherectomy.

Histological evaluation shows chronic cortical inflammation, infiltration of T-cells, neuron loss, microglial nodules, reactive astroglia, and, in some cases, evidences of neuronophagia[16,17]. The specific etiology, however, remains unknown[17] There is evidence pointing out that a viral infection could be the etiology of the autoimmune reaction and chronic inflammation characteristics of Rasmussen's[14]. However, some ultrastructural studies have not found evidence of viral infection, autoimmune reaction or disruption of the blood-brain barrier[16].

Some studies have offered an alternative hypothesis for the development of Rasmussen's encephalitis. One study has proposed that anti-GluR3 autoantibodies would be generated during the humoral response to a pathogen[18]. In an unrelated event or brain injury, opening of the blood-brain barrier would expose GluR3 do autoimmune attack, triggering the autoimmune reaction and Rasmussen's onset[18]. This hypothesis was based on the reduction of seizure and cognitive improvement of children with Rasmussen and serum anti-GluR3 antibodies after plasmapheresis[18]. However, not all Rasmussen cases present with anti-GluR3 antibodies[14]. Another hypothesis proposes that granzyme B release from T-cells would promote the tissue damage[17,19]. With damage, GluR3 antigens would be released, leading to autoantibody production, which, in its turn, would promote seizures by binding glutamate receptors[14]. The presence of large groups of T cells in patients is the primary support for this model[17, 19].

Clinical characteristics of Rasmussen's differs in manifestation, pathological findings, and progression[14]. As an example, two cases with clinical and histological Rasmussen's characteristics, including hemiparesis, had no seizures[20]. It is possible that a careful evaluation and the definition of pathological degrees could improve the prognosis and provide new treatment strategies[21].

Experimental models

Experimental models are extremely useful to evaluate the influence of inflammatory molecules in brain diseases. If maintained for a long time, inflammation can increase the tissue damage, instead of promoting healing and protection. In epilepsy, the effect of inflammatory molecules depends on the type of molecules, on the number of receptors, and on the duration of the exposure[8,22]. The impacts of inflammatory molecules also depend on the animal model, and external factors not directly related to the type of insult[8,22].

Influence of inflammatory molecules on epilepsy models

The influence of inflammatory molecules in neuron death and seizure generation was evaluated with knockout mice, overexpression models, and by inhibitory chemical manipulations. Interleukin-1β receptor type I (IL-1R type I) deficient mice have a delayed onset of bicuculline-induced seizures when compared to wild-type mice[23]. Mice overexpressing IL-1β receptor antagonist (IL-Ra) have a lower number and duration

of seizures[23]. Furthermore, knockout mice for caspase-1, an enzyme needed for IL-1β activation, have delayed seizure onset and reduced number and duration of seizures after treatment with kainic acid (KA)[24]. Inhibition of caspase-1 in Sprague-Dawley rats delays seizure onset, and reduces the number and duration of KA-induced seizures, similar to data from knockout mice[24]. In hippocampal slices, inhibition of caspase-1 promotes a lower production of IL-1β after exposure to lipopolysaccharide (LPS)[24]. IL-1β also seems to me crucial to febrile seizures[8]. Sprague-Dawley rats injected with a combination of IL-1β and AMPA have increased seizure activity than rats treated with AMPA alone[25]. Wistar rats subjected to audiogenic amygdala kindling treated with IL-1β, on the other hand, have reduced after discharges, lower seizure severity and increased threshold to full kindling[26]. In summary, most studies indicate a proconvulsant effect of IL-1β.

Interleukin-6 (IL-6) seems to have both pro and anticonvulsant effects. For instance, knockout mice for IL-6 have a higher susceptibility to audiogenic-induced seizures, but not to maximal electroshock[27]. Reduced levels of GABA, glycine, glutamate, and glutamine were observed in these knockout mice, as well as increased aspartate levels. IL-6 knockout mice also have a higher susceptibility to KA-induced seizures, increased neuron loss, lower levels of metallothioneins I/II, higher levels of nitric oxide synthase and decreased astrogliosis[28]. Intranasal application of IL-6 increases mortality and severity of pentylenetetrazole (PTZ) induced seizures[29]. The neuromodulatory effect of IL-6 might be related to the influence of this molecule on the expression of metallothioneins, on the expression and function of adenosine receptors type A1, and over GABAergic neurotransmission[28-30].

Mutation in the High-mobility group box 1 protein (HMGB1) binding site in Toll-like receptor 4 (TLR4), a receptor important in pathogen recognition, increases latency to KA-induced seizures, whereas the binding of HMGB1 to wild-type receptors increases seizure frequency and duration[31]. Antagonists of TLR4 increase seizure latency and reduce duration and frequency of KA-induced and bicuculline-induced seizures[31]. The proconvulsant effect of HMG1 in TLR4 seems dependent of GluN2B-containing NMDA receptors since the block of this receptor subtype undo the effects of HMGB1 on KA-induced seizures[31].

Influence of seizures on inflammatory molecules expression

After seizures, several molecules are up or down regulated[32]. Inflammatory mediators and proteins that control reactive oxygen species are increased to minimize tissue damage. Several studies have evaluated the expression of inflammatory molecules after seizures, to establish correlations between seizures and epilepsy.

Wistar rats submitted to PTZ induced seizures have higher levels of IL-1, IL-6, superoxide dismutase and catalase when compared to controls[33]. TLR4 is expressed in astrocytes and neurons in animals submitted to KA or bicuculline-induced status epilepticus. TLR4 is also expressed in hippocampi of TLE patients[31].

KA-induced status epilepticus is associated with increased levels of IL-1β, tumor necrosis factor alpha (TNF-α), IL-6, leukemia inhibitory factor (LIF) and the signal transducer glycoprotein 130 (Gp130)[34]. Studies with Sprague-Dawley rats also found increased IL-1β, TNF-α, IL-6, IL-Ra, as well as astrogliosis, after KA-induced status[35,36].

Some studies have indicated a significant crosstalk between seizures, oxidative stress and inflammation in epilepsy models. A study by inhibition of lipid peroxidation found reduced levels of IL-1β, reduced edema and increased latency to seizures[37]. Another study showed that transgenic mice overexpressing metallothioneins I/II have lower microglial activation, lower neuron loss, lower levels of IL-1, IL-6, IL-12, and TNF-α, and higher levels of IL-10, basic fibroblast growth factor (bFGF), transforming growth factor beta (TGF-β), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell-derived neurotrophic factor (GDNF)[38].

Rats treated with the nerve agent soman, a cholinesterase enzyme inhibitor, present higher levels of oxidative stress, increased neuron death, and higher IL-1β [39,40]. The antidote for soman significantly reduces IL-1β and reduces seizure-induced damage [39, 40]. Another cholinesterase inhibitor, sarin promotes increase in the expression of IL-1β, IL-6, TNF-α, and prostaglandin E2 (PGE2)[41]. Another study with sarin found that IL-1 was increased in seizing rats, but not in non-seizing rats[42].

CONCLUDING REMARKS

Several questions arise from the studies linking epilepsy and inflammation. Not all human epilepsies have a close relation to inflammation, comparing with Rasmussen's encephalitis. Besides, more clinical studies are needed to clarify the importance of inflammatory disease in epilepsies.

One problem to be defined is the pro- and anti-inflammatory actions of several cytokines. For instance, TNF-α is both pro and anti-inflammatory, depending on the concentration and kind of receptor in which it binds[8]. The same occurs with IL-6[27,29]. Thus, a generalization is not possible. Transgenic/knockout mice often present with changes in several pathways not directly linked to the protein of interest, making it difficult to separate the effect of a single protein.

Although not all epilepsies have high inflammatory changes, the presence of gliosis and some inflammatory molecules in the epileptic focus point out that the inflammation can be important in several epilepsies.

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