GENERAL REVIEW

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The central nervous system is not immunoprivileged: inflammation and epileptogenesis

Centralni nervni sistem nije imunoprivilegovan: inflamacija i epileptogeneza

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Introduction

Epilepsy is a chronic neurological disorder characterized by seizures which are the result of excitation/inhibition disbalance of neurotransmitters in the central nervous system (CNS) [1]. The main substrate in the occurrence of seizures is a transient, sudden, paroxysmal and hypersynchronous activity of the brain neurons, behaviorally manifested by rapid and repetitive skeletal muscle contractions and relaxations [2]. A process of gradual epilepsy development in previously healthy brain is known as epileptogenesis [3].

Approximately 0.5%–1% (about 65 million) of adults and 0.5% of children suffer from epilepsy in the world, while 2 out of 25 people in the general world population had at least one seizure in their lifetime [4]. These facts reflect the impact of epilepsy on the social, economic and emotional aspects of life of these patients as well as treatment costs of this neurological disorder with multiple sociomedical consequences. It is estimated that 6 million people suffer from epilepsy in Europe and 50 thousand people in Serbia nowadays. More than 65% of patients experienced a first seizure attack in childhood (the highest incidence is in the first years of life). Finally, there is another important fact: about 40% of patients with epilepsy are resistant to current antiepileptic therapy [5].

The central nervous suptur (CNS) homeostasis is dependent on the balance of two opposite processes in the brain, e.g., excitation and inhibition. Thus, even minimal disequilibrium between these two processes (i.e., increase of the excitation, decrease of the inhibition, or both) will lead to hyperexcitability and will cause seizures [6]. Molecular pathways of epileptogenesis are still an enigma, and it is consequently difficult to establish the precise classification of epileptic disorders and prevent seizures completely (despite significant progress in the new antiepileptic drugs development).

Epilepsy, as a chronic disorder, is characterized by spontaneous and recurrent seizures caused by certain pathogenic processes that disrupt neuronal and glial cells structure and/or function. Factors that cause epilepsy and provoke individual, isolated convulsions are numerous and very diverse. The most common among them are: fever in children, tricyclic antidepressants, theophylline, drugs intoxications and drugs abuse, acute neurological disorders and infections (meningitis, encephalitis, stroke, head injury, brain abscess, etc.), alcoholism, metabolic disorders (hypo/hyperglycemia, hypocalcaemia) [7], derivative of phencyclidine-metaphit [8], scabicides-lindane [9, 10], sleep disturbances [11–13], hyperhomocysteinemia [14], visual stimuli [15], stress [16], the menstrual cycle [17], a specific diet regimes [18, 19], vascular abnormalities, stroke sequelae and subarachnoid hemorrhage [20]. Experimental models of epilepsy are significant for resolving the mechanisms of epileptogenesis and play very important role in new antiepileptic drugs development. Extensive review of all models of epilepsy goes beyond 50 entries [21].

Some antibiotics, like imipenem/cilastatin [22, 23] and penicillin [24] induce seizures which is also a paradoxical phenomenon clearly demonstrated in experimental and clinical studies.

Inflammation, engaging the immune cells, the molecular mediators and blood vessels, is a complex biological, protective response to the pathogenic factors [25]. In conditions of excessive activity and/or organism immunity collapse, in-

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flammation seems to be potentially harmful and unuseful. Neuroinflammation could be caused by numerous factors and is characterized by activation of glial cells, known as the CNS resident immune cells [26]. Blood-brain barrier (BBB) is built up of astrocytes and endothelial cells and acts as an important isolator of the CNS. Therefore, the CNS is also partially isolated from the peripheral inflammatory cells [27]. Peripheral inflammation is an inflammatory process which occurs outside the CNS and is characterized by the activation of macrophages (peripheral immune cells) [28]. When the BBB is disrupted or its function compromised, peripheral immune cells could migrate into the CNS and induce neuroinflmamation [29].

Inflammatory processes and epileptogenesis

Numerous epidemiological studies have demonstrated that patients with epilepsy are more prone to different inflammatory disorders, i.e., inflammatory diseases are frequent comorbidities in epilepsy [30].

Numerous clinical and experimental studies have shown that inflammation disrupts the excitation/inhibition balance within the CNS and initiates the process of epileptogenesis. However, unclear relationship exists among the convulsions, inflammation and epilepsy [31–36]. These three factors generate positive feedback loop (*circulus vitiosus*) in which one process is facilitated by another one (Figure 1). Head injuries, tumors and infections of the CNS are characterized by neuroinflammation in its pathological basis. On the other hand, neuroinflammation could be a result of these pathological processes. Also, it is important to notice that seizure could be followed by inflammatory response in the entire CNS [37]. The CNS is not imunoprivileged site in the human body.

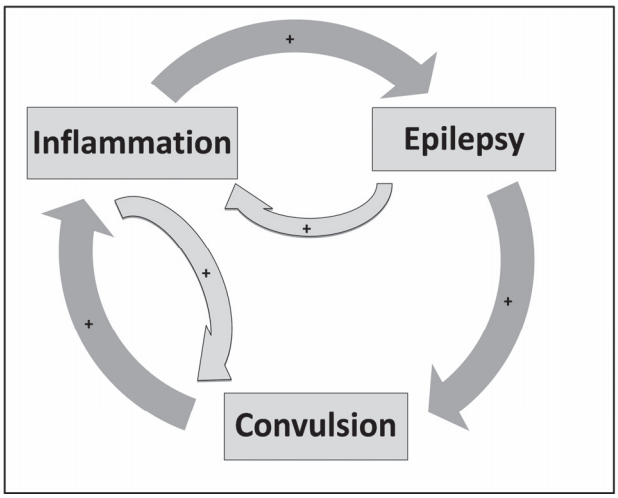

Fig. 1 – The relationship between epilepsy, convulsions and inflammation.
Neuroinflammation and peripheral inflammation could be a etiopathogenic substrate of epileptogenesis and development of epilepsy as a chronic neurological disorder accompanied by convulsive seizures. On the other hand, inflammation could also destroy the excitation/inhibition balance in the central nervous system (CNS) and provoke only isolated convulsions. On the other hand, isolated convulsive seizure could provoke neuroinflammation. Thus, positive feedback loop exists among these factors.

The process of epileptogenesis should not be viewed only through the prism of neural networks disarrangement. Namely, the pathogenesis of epilepsy involves also disarray of non-neural structures such as glial cells, endothelial cells in the CNS, the peripheral leukocytes and BBB injury [38]. Also, the role of extracellular matrix (ECM), as a very important brain substrate consisting of various molecules [e.g., hyaluronan, chondroitin sulfate proteoglycans (CSPGs), glycoprotein tenascin-R and other] derived from both neurons and glial cells [39] has to be addressed in these considerations, having in mind a critical role of cell-ECM interactions. Namely, there is a bidirectional relationship between epileptogenesis and ECM as well as evidences showing that biophysical and biochemical ECM properties modulate immune cell behavior including inflammatory cell migration. Excessive neuronal activity-mediated remodeling of ECM and mutations in ECM molecules (like leucine-rich, glioma-inactivated gene (LGI1), hyaluronan, tissue plasminogen activator (tPA) etc.) and extracellular proteinases [i.e. matrix metalloproteinase-9 (MMP-9)] are potent triggers for epileptogenesis by still unclear mechanisms which include disbalances in GABAergic and glutamatergic activity, mossy fiber sprouting, granule cell dispersion and gliosis (further details could be find in recent focused reviews [39–41]). During inflammation, ECM is altered by several cytokines upregulated at sites of inflammation [like tumor necrosis factor (TNF) and interferon gamma (IFNγ)] as well as by the secretion and/or activation of proteases, like MMPs [42]. On the other hand, neuroinflammation leads to degradation of ECM into immunoreactive fragments (mainly hyaluronan, sulfated proteoglycans and newly expressed tenascin-C), which are considered as damage-associated molecular patterns (DAMPs) capable to activate inflammatory cells via pattern recognition receptors (PRRs) [43]. Hence, progression of neuroinflammation, in turn, leads to further degradation of ECM by positive feedback loop. Therefore, ECM protects neuronal cell rearrangement and excitatory network formation by its nonpermissive function, and any change in neural ECM induced by inflammation, brings a receptive environment for epileptogenesis.

The immune response is proven to be responsible for the initiation and propagation of epilepsy [37, 44, 45]. Neuroinflammation increases the excitability of neurons because it changes the permeability of neurilemmal ion channels, affects the release and reuptake of neurotransmitters and the permeability of the BBB. All these factors decrease the threshold for the occurrence of epileptic discharges [46–48].

Oxidative stress and neuroinflammation: unresolved relationship

Neuroinflammation occurs by activation of glial cells (astrocytes, ependymal and endothelial cells in the first row) with the increased production of proinflammatory cytokines [like interleukin-1 β (IL-1β); tumor necrosis factor-α (TNF-α); prostaglandins, etc.] at the same time. It is also followed by an increased activity of cyclooxygenase-2 (COX-2) [37]. IL-1 receptor /toll-like receptor (IL-1R/TLR) and COX-2-medi-

ated signaling pathways act on neurons via N-methyl-D-aspartate receptor (NMDA), principally via the NMDA receptor subtype 2B (NR2B). It is also followed up by glial dysfunction. All these events may result in increased expression of adhesion molecules on the BBB and dysfunctions of the barrier itself. In this case, serum with albumins as well as activated peripheral leukocytes can "leak" in the brain. This is regarded as a trigger of the process of epileptogenesis and increased concentrations of the excitatory neurotransmitter glutamate and ion channels modulation [1, 38].

Oxidative stress, preponderance of production over the degradation of reactive oxygen species (ROS), manifests its numerous deleterious effects throughout the human body [49, 50] as well as in the brain. Actually, elevated levels of lipid peroxidation, like oxidative stress markers and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase which produces ROS, accompanied with low levels of antioxidants [51, 52] were proved in the blood and the surgically removed brain tissue of patients with epilepsy. Moreover, decreased ability of the brain to defense against oxidative stress led to increased severity of experimentally induced seizures by pentylenetetrazole and kainic acid [53]. We have shown that lipid peroxidation is involved in the etiopathogenesis of the experimental model of seizures caused by lindane [54]. The brain damage, as a consequence of oxidative stress during seizures, was reduced by treatment with antioxidants such as vitamin E [55] and vitamin C [56]. In addition, we have shown that reinforcing the antioxidant capacity of the organism by physical activity reduces the animal susceptibility for development of experimental epileptic activity induced by homocysteine [57].

Although it can be clearly concluded that pathogenesis of epilepsy encompasses both neuroinflammation and oxidative stress, the mutual relationships between these two factors are largely unclear. In addition, it is unclear whether neuroinflammation leads to the generation of epileptic discharges in the brain exclusively via oxidative stress. It is also unclear whether neuroinflammation is a result of the oxidative stress initiated by some third factor (Figure 2).

The role of peripheral inflammation

Peripheral inflammation is associated with a fever, reduction of locomotor activity as well as the excitation/inhibition imbalance in the CNS [58]. It has been concluded that peripheral inflammation could exacerbate seizures and many other neurological disorders [1, 59].

It has been shown that peripheral inflammation decreases the threshold for the occurrence of epileptic seizures in experimental models of peripheral inflammation evoked by administration of bacterial lipopolysaccharide (LPS) [60], a suspension of degraded bacteria, into the peritoneal cavity [61, 62] as well as in experimental models of inflammatory bowel disease [63, 64] and arthritis [63].

Although previous studies did not elucidate exactly how the peripheral inflammation affects the brain, the participation of various cytokines [63] endogenous opioids [60, 64], prostaglandins [60] as well as the signaling pathways mediated by nitric oxide (NO) in this process could be assumed with certainty [60, 62]. According to our results, neurotransmission mediated by NO is an important mechanism in the initiation and propagation of epileptogenesis [9, 65]. Moreover, the activation of the brain glial cells, which are equivalent to the periphery inflammatory cells, increases the production of cytokines in the CNS. Thus, these cells are considered to be an important element of neuroinflammation [35, 36].

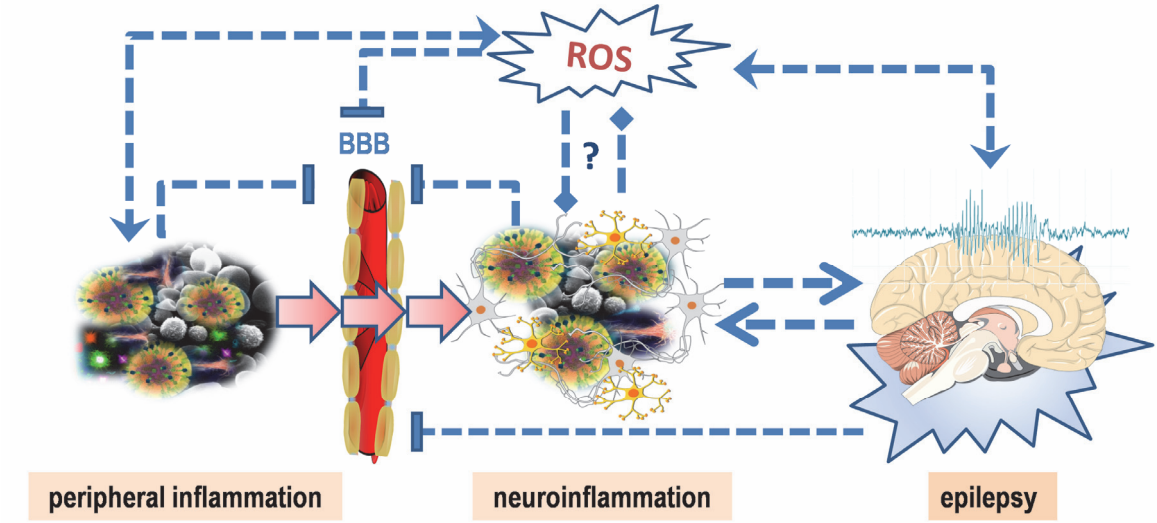

Fig. 2 – The relationship between epilepsy, peripheral inflammation, neuroinflammation and oxidative stress. Peripheral inflammation, after generalization and extension via disrupted blood-brain barrier (BBB) to the central nervous system (CNS) causes neuroinflammation which results in development of epilepsy. Epilepsy followed by convulsions compromised competency of the BBB and enhances neuroinflammatory and oxidative stress response. Oxidative stress [presented as excessive reactive oxygen species (ROS)] and neuroinflammation participate together in the etiopathogenesis of seizures. However, their interrelationship is not clear (denoted with interrogation mark). Oxidative stress, induced by any pathogen may result in development of neuroinflammation, but, on the other hand, neuroinflammation by itself may result in oxidative stress. Arrows denote plus effect, while (I) denote negative effect.

Peripheral inflammation is accompanied by an increased production of proinflammatory cytokines, like IL-1β, IL-6 and TNF-α, which may contribute to the activation of glial cells and induction of neuroinflammation [66–69]. On the other hand, the role of COX-2 was emphasized in the process of neuroinflammation and oxidative stress, both acting to reduce the seizure threshold [70, 71]. The concentration and activity of the COX-2 enzyme sre markedly increased during seizures [72], especially in the hippocampus [73] which has essential role in the epilepsy generalization. Indeed, Ho et al. [70] showed reduction of seizure number in the experimental model of peripheral inflammation accompanied by neuroinflammation and oxidative stress in the hippocampus upon intracerebral administration of a COX-2 inhibitor and ROS scavenger. Also Eun et al. [74] potentiated hyperthermia-induced seizures by administration of LPS, which is a further proof that peripheral inflammation can potentiate seizures.

Conclusion

Many neurological conditions and disorders, in the first raw inflammatory diseases of the CNS (meningitis, encephalitis), CNS injuries, stroke, etc., are associated with inflammation. On the other hand, clinical course of these disorders frequently includes seizures. Inflammation is a common factor that disrupts homeostasis in the CNS neural networks; it acts proepileptogenically and causes seizures.

Taking into account all the above-mentioned facts, it is clear that neuroinflammation, together with its specific relation to ROS and changes in neural ECM, is interconnected with epileptogenesis, being its cause, or a consequence. Neuroinflammation reduces the threshold for initiation of the CNS hyperexcitability and disrupts the competency of the BBB.

It is reasonable to assume that therapeutic treatment of peripheral inflammation alongside with neuroinflammation can provide beneficial effects for patients with epilepsy by reducing the seizure number. Thus, this is a promising alley of future therapeutic modalities in epileptology.

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