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Review

The Role of High Mobility Group Box-1 in Epileptogenesis

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High mobility group box-1 (HMGB1) is a non-histone, DNA-binding nuclear protein belonging to the family of damage-associated molecular patterns (DAMPs). HMGB1 has been reported to play an important role during epileptogenesis although the mechanisms of its actions are still not clear. Many hypotheses have been suggested especially about the relationship between HMGB1 and inflammation responses and blood-brain barrier disruption during epileptogenesis. In this review, we will mainly discuss the role of HMGB1 in epileptogenesis.

Key words: HMGB1, epileptogenesis, inflammation, blood-brain barrier

Epilepsy is a severe neurological disorder characterized by spontaneous and recurrent seizures, affecting about 1% of the general population of all ages and races in the world. However, the mechanisms of epileptogenesis remain unknown. Epilepsy is often refractory to pharmacological treatment [1]. For example, about one third of patients are resistant to anti-epileptic drugs (AEDs) [2,3]. Additionally, current AEDs relieve symptoms rather than interfere with the causal mechanisms of the disease, and therefore do not cure the disorder. Thus, the development of a novel anti-epileptic therapeutic is crucial. Usually, most patients do not realize that they have epilepsy until they start experiencing seizures. Clinical trial designs for novel therapeutics against epileptogenesis are hampered by the lack of non-invasive biomarkers that allow for the early identification of patients at high risk of developing epilepsy.

Relationship between Central Nervous System (CNS) Disorders and Inflammation

In recent years, it has been suggested that neuroinflammatory processes play an important role in CNS disorders. Thus, the selective targeting of CNS inflammation might be a viable strategy for interfering with the progression of neurodegenerative disorders [4]. Translational and clinical evidence support the possibility that neuroinflammatory mediators are implicated in seizures and epileptogenesis [5,6], putting forth the hypothesis that inflammation in the brain contributes to the generation of seizures as well as to cell damage and death. In turn, these inflammatory processes trigger further seizures via the activation of inflammatory pathways [7]. Thus, inflammation can have a causative role as well as a consequential one in regards to epileptogenesis [7].

High-mobility group box 1 (HMGB1) protein is a non-histone, DNA-binding nuclear protein belonging to the family of damage-associated molecular patterns (DAMPs) [8]. Under normal conditions, HMGB1 plays important roles in the regulation of gene expression and DNA repair, and contributes to the architecture of chromatin DNA [9]. Mice and rats share 100% of the amino-acid sequence for HMGB1, while rodents and humans have a 99% homology for the protein [10]. HMGB1 has two domains for DNA binding, known as

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box A and box B, as well as a C-terminus acidic tail comprised of repeating glutamate and aspartic acid residues [11, 12]. A member of the DAMP family, HMGB1 is able to influence synaptic function in brain regions such as the hippocampus, which is itself involved in hyperexcitability and cognitive decline during epileptogenesis [2].

HMGB1 has received increasing attention in regard to its role in epilepsy [13]. Its involvement with epileptogenesis is hypothesised to pertain to its role in the induction of inflammatory processes in the peripheral environment, and in the disruption of the blood-brain barrier (BBB) during the initiation and development of epileptic conditions.

The Role of HMGB1 in Neuroinflammation in Epileptogenesis

HMGB1 acts as a pathogenic inflammatory response mediator in a range of conditions. Evidence for its role in many CNS disorders and insults like stroke, trauma, epilepsy and even Alzheimer's Disease has been reported. HMGB1 also acts as an initiator and amplifier of neuroinflammation in brain injury types that are highly associated with epilepsy and cognitive dysfunction ascribed to neuronal excitation [14-16]. HMGB1 can be passively released by glia and neurons upon inflammasome activation, and activates the receptor for advanced glycation end products (RAGE) and toll-like receptor (TLR) 4. Furthermore, it is released from apoptotic and necrotic cells, and actively translocated from the nucleus to the cytoplasm during pyroptosis and inflammasome activation. HMGB1 also contributes to increased inflammatory responses in the peripheral environment [3, 13, 15-23]. Extracellularly-released HMGB1 can be partially oxidized via the formation of a disulfide bond between cysteine 23 (C23) and cysteine 45 (C45). This disulfide HMGB1 isoform enhances neuronal excitability and proinflammatory activity through the activation of TLR4. Also, HMGB1 activity leads to neuronal cell loss, neuroinflammation, epilepsy and cognitive dysfunction via the activation of its receptors, RAGE and TLR4 [24]. Moreover, HMGB1 has been shown to suppress long-term potentiation (LTP) and cause memory deficits in mice in a TLR4- and RAGE-dependent manner. These effects are associated with increased activation of JNK and NF-κB [25, 26]. The HMGB1/TLR4 axis is speculated to be a key initiator of neuroinflammatory factors in epileptogenesis, and has consequently gained interest in the field.

Electrical stimuli or chemiconvulsants, like kainic acid (KA) or pilocarpine, are used to induce the acute stages of epilepsy in animal models. Researchers observed the translocation of HMGB1 in the brain within 1 h of the onset of seizures, as well as a dramatic increase in plasma concentrations of HMGB1 4 h after seizure induction with pilocarpine [19]. This implies that seizure activity is a trigger for HMGB1 translocation and its subsequent release. Seizures are also associated with the up-regulation of TLR4 and RAGE expression on neurons and astrocytes [16, 27, 28], as well as with the upregulation of several related inflammatory factors in the hippocampus. According to these studies, the neutralisation of HMGB1 might be a novel therapeutic strategy for epileptogenesis.

Previous studies have shown that the neutralisation of HMGB1 with an anti-HMGB1 monoclonal antibody (mAb) can be a potential novel strategy against multiple sclerosis (MS), possibly due to the resulting inhibition of pro-inflammatory cytokine production in the peripheral environment. Further, the mAb therapy reduces CNS pathological injury [29]. Anti-HMGB1 mAb enhances the activity of HMGB1 Box A, a protein fragment with antagonistic activity against HMGB1 [13, 15, 19], and reduces the frequency and severity of seizure events. Zhao *et al.*'s study [13] report similar findings in that an anti-HMGB1 mAb treatment was sufficient in significantly reducing the number of spontaneous seizures in developing animals with induced epileptogenesis [13]. Studies concerned with HMGB1 intervention in established CNS animal models propose that the observed neuroprotective effects are due to a reduction in brain and blood HMGB1 levels [20]. The HMGB1 receptors, TLR4 and RAGE, play crucial roles in the presence of elevated extracellular HMGB1 levels during epileptogenesis in epileptic models [25]. Evidence therefore indicates that the release of endogenous HMGB1 following epileptogenic events is involved in the pathogenesis of seizures, and likewise contributes to the recurrence of seizures. HMGB1 neutralisation therapies have been shown to be beneficial, and confer remarkable neuroprotection in several models of neuroinflammation, further supporting the contention for its use as a novel therapy for epileptogenesis.

The Role of HMGB1 on Blood-brain Barrier (BBB) Disruption in Epileptogenesis

Recent studies suggest the involvement of HMGB1 in epileptogenesis, especially via the disruption of the BBB in contributing to the pathogenesis of epilepsy [19]. HMGB1-related break-down of the BBB is tied to cognitive deficits in aged rats [30]. BBB disruption in the presence of HMGB1 is widely associated with many CNS disorders, such as brain trauma and epilepsy. In these CNS disorders, inflammatory events occur on brain vessels, leading to serum albumin extravasation, which marks BBB dysfunction, thus suggesting the involvement of HMGB1 in the disruption of vascular barriers [31]. In one study, BBB break-down was observed 4 h after pilocarpine treatment, while leakage was significantly decreased after HMGB1 neutralisation with intravenous anti-HMGB1 mAbs, as observed with Evans Blue, a serum albumin marker [19]. The benefits of anti-HMGB1 mAb have been demonstrated in other animal models of epilepsy as well.

Neuroinflammation directly alters BBB permeability via cytokine-mediated activation of metalloproteinases, or via the disruption of tight junctions [32, 33]. This suggests the likely benefit of anti-inflammatory treatment for epileptogenesis. In addition, glial and astrocyte activation is purported to serve an important role in the development of epilepsy in animal models. Since HMGB1 might mediate microglial activation via the TLR4/NF-κB signalling pathway [6], and is also implicated in the break-down of the BBB and secreted in the CNS and peripherally, an anti-inflammatory therapeutic strategy might prove to be beneficial in treating epileptogenesis.

HMGB1: A Biomarker of Epileptogenesis

The translocation and release of HMGB1 occur in different kinds of epilepsy as evidenced in pharmacological studies using animal brains, as well as in clinical specimens [15]. Abnormal extracellular HMGB1 levels contribute to the pathophysiology of epilepsy-related hyperexcitability, which might in turn contribute to seizure onset. Thus, HMGB1 might play a crucial role in contributing to the onset of epilepsy-related hyperexcitability [16]. HMGB1 expression was significantly elevated in the hippocampus and cortex 24 h after KA-induced status epilepticus, and increased in plasma 4 h after pilocarpine treatment, suggesting the potentially crucial role of HMGB1 in epilepsy [34]. Anti-HMGB1 mAb is able to reduce the frequency of seizures and to improve cognitive function, additionally supporting evidence for using HMGB1 as a biomarker of epileptogenesis [19].

Similarly, anti-HMGB1 mAb treatment inhibits BBB leakage and HMGB1 translocation in peripheral sites after pilocarpine induction, suggesting that the inhibition of HMGB1 translocation potentially reduces or affects BBB permeability [19]. The cited studies implicate HMGB1 in the generation of seizures, thus indicating a potentially important target in epileptogenesis. HMGB1 levels in plasma could be a reliable biomarker for epileptogenesis and seizure recurrence, further implying that treatment using anti-HMGB1 antibodies might be a novel therapeutic strategy for epileptogenesis.

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