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POTENTIAL BIOMARKER FOR EPILEPSY: HIGH-MOBILITY GROUP BOX 1 PROTEIN (HMGB1)

Sultonova Dilbar Azamat qizi
PhD student, assistant of Tashkent Medical Academy

Azizova R. B.
Assosiate professor of Tashkent Medical Academy

Abstract

High mobility group box protein 1 (HMGB1) is a ubiquitous nuclear protein that is generated by glia and neurons in response to inflammasome activation, activating the target cells' RAGE and TLR4 receptors for advanced glycation end products.One of the main triggers of neuroinflammation is the HMGB1/TLR4 axis. Due to its role in traumatic brain injury (TBI), neuroinflammatory diseases, epileptogenesis, and cognitive deficits, HMGB1 has received increased attention recently and has emerged as a novel target for those diseases. But HMGB1 has not been portrayed as a typical predictive biomarker for these illnesses that are mediated by HMGB1.

Keywords: High mobility group box prtein1, neuroinflammation, epileptogenesis, biomarker.

INTRODUCTION

High-mobility group box 1 protein (HMGB1) is a highly conserved nuclear protein with an unexpected extracellular function. In addition to binding DNA, which improves access to transcription factors, it also draws cells across endothelial barriers and encourages the local production of tumor necrosis factor (TNF), interleukin-6 (IL-6), and interferon. □ □ □ □ □ □ HMGB1 is released by necrotic cells and secreted by activated macrophages, natural killer cells, and mature dendritic cells; however, neutrophils do not produce it. As a "leaderless" cytokine, HMGB1 needs special equipment to enter the immunological synapse or to be secreted.In contrast, HMGB1 is locked away in the nucleus following DNA damage brought on by platination, ultraviolet light exposure, or apoptotic cell death. HMGB1 release happens much later during sepsis than the macrophage secretion of the traditional early pro-inflammatory mediators TNF and IL-1.HMGB1 release occurs much later in sepsis than macrophage secretion of the classical early pro-inflammatory mediators TNF and IL-1. RAGE (receptor for advanced glycation end-products), Toll-like receptor 2 (TLR2), TLR4, and potentially other as-yet-unknown receptors are receptors for HMGB1. During sepsis, HMGB1 release occurs considerably later than macrophage secretion of the classical early pro-inflammatory mediators TNF and IL-1.Receptors for HMGB1 include RAGE (receptor for advanced glycation end-products), Toll-like receptor 2 (TLR2), TLR4, and possibly other as-yet-unknown receptors.RAGE is encoded in the MHC class III region and is expressed as both a transmembrane and a soluble molecule, interacting directly with extracellular signal-regulated kinase 1 (ERK1) and/or ERK2 and driving activation of the mitogen-activated protein kinase p38 and nuclear factor-B. RAGE that is soluble blocks RAGE ligands like HMGB1 and S100 proteins. RAGE expression by activated endothelial cells promotes leukocyte recruitment via interaction with myeloid cells expressing the 2-integrin MAC1, which is augmented in the presence of S100 proteins. When activated, macrophages also express HMGB1 at the cell surface, facilitating recruitment via interaction with RAGE expressed by endothelial cells and allowing translocation across endothelial barriers.Controlling HMGB1 activity and release is an approach that is

being developed as an experimental therapy for patients with epilepsy,sepsis, arthritis, cancer, and other disorders.

NEUROINFLAMMATION AS A PRIME DRIVER

Epilepsy is a detrimental neurological illness characterized by spontaneous and recurring seizures that affects people of all ages (Liu et al., 2018). A third of patients are resistant to current anti-epileptic medications (AEDs), which merely provide symptomatic relief rather than affecting the disease process (Ravizza et al., 2017; Walker et al., 2017). In addition, epilepsy complicates the lives of patients and their families in a variety of additional ways. The variety of comorbidities, such as cognitive deficits, anxiety, and depression,all add to the burden.

Therefore, there is a clinical need for innovative biomarkers that can predict and evaluate the illness status and patient response to epilepsy therapy. There is also an urgent need to explore new therapies for epilepsy that not only delay seizure onset but also minimise associated comorbidities. In this regard, HMGB1 has emerged as a new frontier and an increasing number of preclinical studies targeting HMGB1 have been successful in various neurological diseases induced by inflammatory responses (Wang et al., 2017; Zhao et al., 2017; Andersson et al., 2018).High mobility group box 1 proteins are a family of DAMPs (Lotze and Tracey, 2005), which are highly conserved non-histone nuclear proteins that contribute to the architecture of chromatin DNA (Baxevanis and Landsman, 1995). HMGB1 acts as an inflammatory cytokine in response to epileptogenic insults (Kaneko et al., 2017). HMGB1 acts as a pathogenic inflammatory response to mediate a number of conditions such as epilepsy (Maroso et al., 2010), septic shock (Wang et al., 1999), ischaemia (Kim et al., 2006; Wang et al., 2015), TBI (Okuma et al., 2012), PD (Sasaki et al., 2016), AD (Fujita et al., 2016) and MS (Andersson et al., 2008). Structural evaluation of HMGB1 suggests that it has two domains for DNA binding, known as box A and box B, and a C-terminal acidic tail consisting of repeated glutamic and aspartic acid residues (Venereau et al., 2016; Aucott et al., 2018b). DAMPs can affect synaptic function in brain regions such as the hippocampus, which is implicated in hyperexcitability and cognitive decline in epilepsy (Ravizza et al., 2017). It has been reported that immediately after neuronal injury there is a passive release of significant amounts of HMGB1 from the nucleus into the extracellular space (Scaffidi et al., 2002).High mobility group box 1 has several extracellular receptors such as RAGE, TLR9, TLR4, TLR2, integrin, a-synuclein filaments, proteoglycans, T-cell immunoglobulin and mucin domain (TIM-3), triggering receptor expressed on myeloid cells-1 (TREM1), cluster of differentiation 24 (CD24), C-X-C CXCR4, N-methyl-D-aspartate receptor (NMDAR) (Kang et al., 2014). Among these receptors, RAGE and TLR4 are the only ones that have been extensively studied and reported without doubt (Andersson et al., 2018). HMGB1 initiates several cell responses, including inflammation, and mediates the activation of the inflammatory process by binding to RAGE and TLR4 (Bianchi and Manfredi, 2007; Iori et al., 2013). In neuroinflammatory conditions, HMGB1 is actively released by neurons and glial cells upon inflammasome activation and in turn activates at least two PRRs, namely TLR4 and RAGE on target cells (Ravizza et al., 2017). Although clinical studies have not yet been reported, treatments based on HMGB1 antagonists that target extracellular HMGB1 have produced intriguing outcomes in a variety of animal settings. Previous research identified HMGB1 translocation as the primary cause of TBI (Li Y. et al., 2017). Since it has a connection to epilepsy, HMGB1 has recently drawn more attention (Zhao et al., 2017). Though the precise mechanism is still unknown, it has been hypothesized that HMGB1 may play a role in epileptogenesis, particularly through the disruption of the BBB and the induction of inflammatory processes. The role of HMGB1 in the pathogenesis of epilepsy has been investigated in a number of studies in the past (Fu et al., 2017). HMGB1 is important in cognitive decline because it is thought to disrupt the BBB, resulting in cognitive deficits in aged rats (Heet al., 2012). HMGB1 plays a critical role as an initiator and amplifier of neuroinflammation as well as in neuronal excitation, which is interesting given the mounting evidence that neuroinflammation is strongly associated with epilepsy and cognitive dysfunction following TBI (Frank et al., 2015). According to Annegers and Coan (2000), epilepsy is highly likely to develop after a traumatic brain injury (TBI), and it is linked to neurological comorbidities like cognitive dysfunction (Pascente et al., 2016; Ravizza et al., 2017). Inflammatory mediators have been implicated as the cause of both seizures and epileptogenesis in a number of

experimental and clinical studies (Vezzani and Granata, 2005; Shimada et al., 2014). According to Vezzani et al. (2011), brain inflammation plays a role in both the development of individual seizures and cell death, which in turn plays a role in the development of seizures by activating inflammatory pathways. Additionally, research shows that inflammation can both contribute to and result from epilepsy (Vezzani et al., 2011). According to Webster et al. (2017), traumatic brain injury triggers a neuroinflammatory axis in the brain that promotes neurodegeneration and raises the risk of starting epileptogenesis. However, the likelihood of developing epilepsy following a TBI ranges from 4.4% to 53% (Frey, 2003) and increases with higher levels. Inflammatory mediators have been implicated as the cause of both seizures and epileptogenesis in a number of experimental and clinical studies (Vezzani and Granata, 2005; Shimada et al., 2014). According to Vezzani et al. (2011), brain inflammation plays a role in both the development of individual seizures and cell death, which in turn plays a role in the development of seizures by activating inflammatory pathways. Additionally, research shows that inflammation can both contribute to and result from epilepsy (Vezzani et al., 2011). According to Webster et al. (2017), traumatic brain injury triggers a neuroinflammatory axis in the brain that promotes neurodegeneration and raises the risk of starting epileptogenesis. However, the likelihood of developing epilepsy following a TBI ranges from 4.4% to 53% (Frey, 2003) and increases with higher levels.

THE ROLE OF HMGB1 IN EPILEPSY

Epileptogenesis is defined as complex anatomical changes in the brain that transform a healthy brain into a brain that is disabled by recurrent seizure activity (Sloviter and Bumanglag, 2013). Epileptogenesis is aggravated by neurodegeneration (Pitkanen and Lukasiuk, 2009; Reddy, 2013), BBB disruption (Bar-Klein et al., 2017), the glutamatergic system (Aroniadou-Anderjaska et al., 2008), oxidative stress (Ashrafi et al., 2007), and epigenetic DNA modification (Hauser et al., 1993).Current needs include a thorough understanding of disease pathophysiology and the development of novel therapeutic approaches for epilepsy-related hyperexcitability due to the absence of disease-modifying effects in standard AEDs. Much focus has been placed on the potential harmful function of HMGB1 in the formation and recurrence of seizures as researchers look for molecular mediators of epileptogenesis in animal models (Kaneko et al., 2017; Yang et al., 2017). Despite enormous scientific progress, the pathophysiology of epilepsy is still unclear; nonetheless, brain inflammation is thought to be a contributing factor (Riazi et al., 2010). HMGB1 was discovered to function like an inflammatory cytokine in response to epileptogenic stimuli, and there is growing evidence that neuroinflammatory processes play a role in the pathogenesis of seizures and epilepsy (Kaneko et al., 2017). It has been suggested that glial cell activation plays a significant role in the onset of epilepsy, and during seizures, HMGB1 may drive microglial activation via the TLR4/NF-B signaling pathway (Shi et al., 2018). HMGB1 stimulates IL-1R/TLR signaling in neurons and plays a vital role in seizure genesis and recurrence via NMDA-NR2B receptor phosphorylation accelerated by fast sarcoma family kinases. Additionally, HMGB1 plays a crucial role in epileptogenesis by activating microglia and the TLR4-NF-B signaling pathway (Shi et al., 2018). Numerous studies have noted HMGB1's involvement in seizures, however the precise mechanism by which HMGB1 causes seizures to occur has not been fully studied. According to Palleria et al. (2015), mesial temporal lobe epilepsy (MTLE) is one of the most prevalent refractory focal epilepsy syndromes; it is yet unclear what function HMGB1 plays in the pathophysiology of MTLE. A study on experimental MTLE found that the expression of the genes HMGB1 and TLR4 was significantly increased in the rat's hippocampi, and it linked this overexpression of these genes to the pathogenesis of MTLE in young rats. Additionally, it is well known that HMGB1 and its receptors (RAGE and TLR4), as well as the pro-inflammatory cytokine IL-1, have a role in initiating and maintaining seizures. The translocation and release of HMGB1 occurs in the pathogenic epileptogenic foci of several types of epilepsy, according to pharmacological and genetic research on animal and clinical brain specimens (Maroso et al., 2010; Iori et al., 2013). In kainite and bicuculline-induced seizure models, it is important to note that the HMGB1/TLR4 axis not only decreased seizure frequency and duration but also sped up seizure onset, which typically happens within minutes (Maroso et al., 2010). This indicates the critical role of HMGB1 in the precipitation of the first seizure following

a pro-convulsant administration. According to research on PRNCs, abnormal extracellular HMGB1 may play a role in the pathophysiology of epilepsy-related hyperexcitability. This research established HMGB1 as a major pathophysiological contributor to the onset of epilepsy-related hyperexcitability (Kaneko et al., 2017).A crucial mechanism of seizure initiation involves HMGB1 proteins activating TLR4 in neurons and astrocytes, and inhibiting TLR4 signaling with an antagonist may lessen the severity of epilepsy (Iori et al., 2013). According to research on post-surgery patients with intractable epilepsy, the brains of these patients had higher levels of HMGB1, TLR4, RAGE, NF-B, p65, inducible nitric oxide synthase (iNOS), as well as IL-1, IL-6, TNF-, TGF-, and IL-10 (Shi et al., 2018). In recent years, epilepsy treatment focusing on HMGB1/TLR4/RAGE signaling has received significant atraction. HMGB1 expression and inhibition of the TLR4/NF-B signaling pathway by microRNA-129-5p prevented the onset of autoimmune encephalomyelitis (AE)-related epilepsy (Liu et al., 2017). In addition to showing increased expression of HMGB1 and TLR4 in human epileptogenic tissue, which is similar to a mouse model of chronic seizures and suggests a role for the HMGB1- TLR4 axis in human epilepsy (Maroso et al., 2010), HMGB1 and TLR4 antagonists also slowed seizure precipitation, prevented acute and chronic seizure recurrence in C57BL/6 mice. Therefore, HMGB1/RAGE/TLR4 signaling may have a role in the initiation and maintenance of seizures in people, and it can be successfully targeted to provide anticonvulsant effects in epilepsies that are drug-resistant. In a KA-induced model of SE, the expression of the HMGB1 protein was shown to be greatly increased in the hippocampus and cortex after 24 hours, indicating that the HMGB1 protein plays a significant role in epilepsy. HMGB1 contributes to the development of febrile seizures and intensifies hypothermia-induced seizures. It is yet unknown how exactly HMGB1 causes febrile seizures. There is a dearth of information available for the evaluation of the therapeutic advantages of HMGB1 inhibitors in animal models of epilepsy. Glycyrrhizin, however, exhibits neuroprotection against lithium/pilocarpine-induced SE in rats and also lessens pilocarpine-induced oxidative injury and inflammatory responses by reducing IL-1 and TNF-, but it does not exhibit anti-epileptic effect. Glycyrrhizin exerts neuroprotective but not anti-epileptic effects by suppressing both acute and delayed HMGB1 inductions in the the hippocampal cornu ammonis (CA)1 and CA3 region as well as its accumulation in serum. Dynamic changes in HMGB1 expression in the hippocampus of the mouse brain were reported after KA administration. As HMGB1 is prevented from being translocated from nuclei after a seizure, anti-HMGB1 mAb has an anti-seizure effect as evidenced by the absence of disruption in the physical EEG rhythm and fundamental physical functions. A deeper understanding of the typical biologic processes, pathogenic processes, or reactions to an exposure or intervention, including therapeutic interventions with broad applications that are clinically able to stop disease progression or to improve its clinical course, will eventually be possible thanks to HMGB1 as a biomarker of epileptogenesis. Furthermore, a thorough knowledge of the molecular process by which HMGB1 triggers seizures via inflammatory signaling will be crucial in developing novel medicines that focus on inflammatory pathways to reduce seizures. However, more research is required to determine whether HMGB1 is related to seizures. Overall research results point to the possibility of a novel treatment approach for epilepsy in the form of inhibiting the HMGB1/TLR4/RAGE regulatory axis.

Conclusion:

Neurological disorders such traumatic brain injury (TBI), neuroinflammation, epilepsy, and cognitive dystrophy are all mediated by the nuclear protein HMGB1.

The functional biomarker HMGB1 may be present in TBI, neuroinflammation, epileptogenesis, and cognitive dystrophy.

A potential treatment approach against a number of HMGB1-mediated disorders, including traumatic brain injury (TBI), neuroinflammation, epilepsy, and cognitive dystrophy, may involve inhibiting the HMGB1/RAGE/TLR4 signaling axis.

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