Role of High Mobility Group Box-1 in Status Epilepticus, From Pathophysiology to Biomarker and Therapeutic Potential

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ABSTRACT

Status epilepticus (SE) is a neurological emergency that require prompt diagnostic and treatment measures due to its associated mortality and morbidity. The role of neuro-inflammation in status epilepticus has been studied extensively and many potential molecules have been proposed as a promising biomarkers and therapeutic targets for the condition. Inside the nucleus, HMGB1 is a DNA-binding protein with many housekeeping functions. Under certain conditions, HMGB1 will be translocated to the extracellular space promoting a strong pro-inflammatory reaction with activation of many downstream inflammatory pathways related to seizure onset and progression. In this review the potential role of HMGB1 in the pathogenesis of SE was highlighted stressing on the promising implications of this molecule as a therapeutic target for SE.

Keywords: anti-HMGB1 , HMGB1 , Status epilepticus , neuro-inflammation .

دور HMGB1 في نشوء وتطور الحالة الصرعية وامكانية استخدامه كمؤشر للتشخيص والعلاج

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الخلاصة

الحالة الصرعية هي حالة عصبية طارئة تتطلب إجراءات تشخيصية وعلاجية سريعة بسبب نسب المضاعفات و الوفيات المرتبطة بها. تمت دراسة دور الالتهاب العصبي في حالة الصرع على نطاق واسع وتم اقتراح العديد من الجزيئات المحتملة كعلامات حيوية واعدة وأهداف علاجية لهذه الحالة. داخل النواة ، HMGB1 هو بروتين مرتبط بالحمض النووي له العديد من الوظائف. في ظل ظروف معينة ، ينتقل HMGB1 إلى خارج الخلية مما يسبب تفاعل مناعي قوي مؤيد للالتهابات مصاحب بتنشيط العديد من مسارات الالتهاب المتعلقة ببدء نوبة الصرع وتطورها. في هذه المراجعة ، تم تسليط الضوء على الدور المحتمل لـ HMGB1 في التسبب في SE مع التركيز على الآثار الواعدة لهذا الجزيء كهدف علاجي لـ SE.

الكلمات المفتاحية : الحالة الصرعية ، الالتهاب العصبي، بروتين.HMGB1 .

INTRODUCTION

Status Epilepticus (SE) is a serious, life-threatening emergency in which an intense disruption to normal brain activity is manifested clinically as abnormally prolonged or repetitive seizures without complete recovery in between [1].

Any brain pathology can be manifested as SE, however, stroke, infection, trauma and epilepsy were among the commonest causes of SE in adult age group [2,3].

Clinically, SE can be either convulsive or non-convulsive depending on the presence or absence of seizure manifestations. SE can also be

classified into responsive, refractory or super-refractory based on the treatment response [4]. The main factors determining the outcome in terms of both morbidity and mortality are the duration of SE and its response to treatment [5,6].

Once established, SE requires an urgent and prompt medical intervention to control seizure, improve outcome and to prevent long term adverse effects [7]. Current clinical guidelines indicate the use of benzodiazepines (BDZ) as a first line treatment in SE. In a study conducted recently, BDZ controlled the seizure activity in only 30% of cases and more than 50% of patients required a second line anti-seizure drug (phenytoin, sodium valproate or levetiracetam) to control the SE [8]. If no improvement is noted, the last resource is by giving intravenous anesthesia to suppress seizure activity [8,9]. This variable response to medications in patients with SE is mainly due to dosing errors and delay in initiation of treatment. However, one of the most important factors that hinder the efficacy of these drugs is that these drugs are only seizure suppressant and they don't have any effect on the underlying pathology of the condition.

Recent years have witnessed an improvement in the understandings of both the molecular and cellular bases of seizure initiation and progression in SE especially those related to receptor trafficking, deregulation of expression of ion channels and the role of neuro-inflammation. However, research gaps still need to be filled in regard to the exact pathogenesis of SE, diagnostic biomarkers for non-convulsive SE, prognostic biomarkers and treatment option for refractory and super-refractory cases.

In this paper we will review several evidences related to the role of HMGB1 in the pathogenesis of SE and its biomarker and therapeutic potential

High Mobility Group Box-1 (HMGB1):

HMGB1 is a highly conserved intra-nuclear protein that was first identified in 1973 [10]. Within the nucleus, HMGB1 is loosely bound to the DNA to allow the protein to regulate many nuclear events such as DNA repair, recombination, replication and transcription [11,12]. In 1979, the translocation of HMGB1 into the cytoplasm and extracellular space in response to different stimuli (such as tissue injury, infection and trauma) was first identified suggesting an important extra-nuclear function of this protein [13]. HMGB1 localization within the nucleus or cytosol has been found to be linked to its posttranscriptional modification status where acetylated or phosphorylated forms of HMGB1 are destined for extranuclear or extracellular secretion [14–16].

The extracellular release of HMGB1 can be rapid and passive from necrotic and dying cells or slow, active and more controlled in severely stressed cells [15,17]. Upon its release, HMGB1 will mediate a potent inflammatory response through binding with specific cellular receptors known as pattern recognition receptors like interlukin-1-beta (IL1β) and Toll-like receptors (TLR) and receptor for advanced glycation end-products (RAGE), thus, it is now considered as a prototype of a group of molecules known as Damage associated molecular patterns (DAMPs) [18].

In the central nervous system, the post-stress, active secretion of HMGB1 was detected in many cell types (immune cells, neurons and glial cells), after different stimuli (trauma, ischemia, hemorrhage and epileptogenesis) and in both human and animal studies [19–21]. Moreover, HMGB1 induced inflammatory response has been identified in many neurological conditions where inflammation is a paramount feature such as epilepsy [21], Parkinson's disease [22], Multiple Sclerosis [23] and others . Targeting HMGB1 has been reported to be successful in controlling neuro-inflammation in these conditions [24,25].

Experimental Evidences of HMGB1 Role in the Pathogenesis of SE:

An increased expression of extranuclear HMGB1 have been reported in animal models of SE and epilepsy. Electrical or chemical induction of SE in immature and adult rodents remains the main method to evaluate how the brain will respond to different convulsive stimuli. HMGB1 translocation to perinuclear region of astrocytes and hippocampal pyramidal neurons and then to the extracellular space was observed within one and 4 hours after establishment of SE respectively [20]. A parallel increase in the level of downstream receptors (TLR4) of hippocampal neurons and astrocytes [21,24] was also observed. Cytoplasmic localization of HMGB1 was found to be time-dependent with the maximum level of cytoplasmic HMGB1 noted 3 hours after SE onset [24]. Furthermore, in an animal model of refractory SE, a rapid translocation of HMGB1 into the extracellular space was noted during the refractory SE period. This is detected in the peripheral circulation as an increased plasma level of HMGB1 [20].

To confirm its effect, an intracerebroventricular administration of exogenous HMGB1 was investigated. A reduced time to SE after K.A injection was reported and caused a significantly more severe, refractory seizures were detected in a dose-dependent pattern with more disruption and increased leakage of the blood brain barrier [20,24].

Mechanistic Role of HMGB1 in Seizure Generation and Propagation:

Many researchers have investigated the mechanisms by which the extracellular HMGB1 aids the generation and propagation of seizures. Being a strong pro-inflammatory molecule, binding of extracellular HMGB1 to RAGE/TLR leads to activation of tissue inflammatory pathways that involve many other downstream mediators such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and tumor necrosis factor-α (TNF-α). This will induce a strong inflammatory response causing marked neuronal hyperexcitability [26]. A study on primary neuronal cell culture indicated that the neurotoxicity of exogenous HMGB1 is comparable to K.A administration leading to decreased neuronal viability and mitochondrial activity in addition to decreasing the activity of glutamate metabolism enzymes [27]. Moreover, HMGB1 release into the extracellular space and its interaction with TLR-4 increased Ca^{+2} influx to neuronal cell body by NMDA receptors in a dose-dependent manner thus enhancing neuroexcitability and seizure susceptibility [28]. Additionally, the early release of HMGB1 into the extracellular space following SE and the resultant activation of TLR4/RAGE system have shown to be associated with glial cell dependent neurodegeneration and dendrite loss [29,30].

HMGB1 and SE in Clinical Research:

Despite many researches explored HMGB1 role in the animal models of SE, none to our knowledge, have inspected how it behave in patients during or after SE. Further research is needed to study plasma and cerebrospinal fluid (CSF) level of HMGB1 during SE. This is important as it can act as a diagnostic biomarker to confirm the diagnosis of non-convulsive status epilepticus and a prognostic biomarker to indicate mortality and morbidity rates, seizure severity and drug responsiveness. Nevertheless, most reports studied tissue and plasma level of HMGB1 and its downstream receptors in patients suffering from chronic drug resistant epilepsy and found an increased expression of HMGB1 and TLR-4 in plasma of these patients compared to controls and to drug responsive patients [31,32].

Therapeutic Potential of Anti-HMGB1 Monoclonal Antibodies:

The first study to use neutralizing monoclonal antibodies (mAb) to block the pro-inflammatory effect of HMGB1 was performed in 1999. An increased survival rates of mice exposed to endotoxins was reported after administering the anti-HMGB1 mAb [33]. Several studies have been conducted thereafter to determine the beneficial effect of these mAb in reducing the neuro-inflammatory state associated with SE. the first report about the protective effect of antagonizing HMGB1 in a rat model of SE was in 2013. An anti-HMGB1 injected intra-cerebroventricularly after K.A induced SE exerted a neuroprotective effect with reduced neuronal loss and gliosis in these rats in addition to down regulation of IL-1β and TNF-α [30].

In 2017, Zhao *et al* investigated the effect of anti-HMGB1 mAb on different seizure parameters in a model of acute seizure. A dose dependent attenuation of seizures and reduced seizure frequency was noted in addition to less impairment in the cognitive function of the treated rats was reported with minimal side effects. This effect was mainly due to inhibition of translocation of HMGB1 out of the nucleus thus reducing the activation of TLR/RAGE pathway [34]. Studying the effect of anti HMGB1 mAb on the permeability of the blood-brain barrier after SE showed a dose-dependent protective effect.

The role of anti-HMGB1 mAb in refractory SE have gained focus only recently. The co-administration of anti-HMGB1 with diazepam had a significant effect on increasing the seizure free period after intrahippocampal K.A injection with a subsequent significant reduction in the EEG power and duration of SE [24].

Taken together, the increased circulatory level of HMGB1 and the effect of anti-HMGB1 mAb indicate the potential role of this molecule as a diagnostic and prognostic biomarker in SE patients and it promising role as a novel therapeutic target in drug refractory cases.

Conflict of Interest:

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

REFERENCES

1. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus - Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia [Internet]. 2015 Oct [cited 2019 Apr 7];56(10):1515–23. Available from: http://doi.wiley.com/10.1111/epi.13121
2. Leppik IE. Status epilepticus in the elderly. Epilepsia [Internet]. 2018 Oct [cited 2019 May 28];59:140–3. Available from: http://doi.wiley.com/10.1111/epi.14497
3. Trinka E, Höfler J, Zerbs A. Causes of status epilepticus [Internet]. Vol. 53, Epilepsia. Epilepsia; 2012 [cited 2019 May 28]. p. 127–38. Available from: https://pubmed.ncbi.nlm.nih.gov/22946730/
4. Sánchez Fernández I, Abend NS, Agadi S, An S, Arya R, Carpenter JL, et al. Gaps and opportunities in refractory status epilepticus research in children: A multi-center approach by the Pediatric Status Epilepticus Research Group (pSERG). Seizure [Internet]. 2014 Feb 1 [cited 2019 Apr 1];23(2):87–97. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1059131113002811
5. Horváth L, Fekete I, Molnár M, Válóczy R, Márton S, Fekete K. The outcome of status epilepticus and long-term follow-up. Front Neurol [Internet]. 2019 Apr 26 [cited 2019 May 28];10(APR):427. Available from: https://pubmed.ncbi.nlm.nih.gov/31105639
6. Trinka E, Höfler J, Leitinger M, Brigo F. Pharmacotherapy for Status Epilepticus. Vol. 75, Drugs. 2015. p. 1499–521.
7. Crawshaw AA, Cock HR. Medical management of status epilepticus: Emergency room to intensive care unit. Seizure [Internet]. 2020;75:145–52. Available from: http://www.sciencedirect.com/science/article/pii/S1059131119302043
8. Sairanen JJ, Kantanen AM, Hyppölä HT, Kälviäinen RK. Status epilepticus: Practice variation and adherence to treatment guideline in a large community hospital. J Neurol Sci. 2021 Aug 15;427:117542.
9. Neligan , Aidan, Rajakulendran S, Walker MC. Advances in the management of generalized convulsive status epilepticus: what have we learned? Brain [Internet]. 2021 Jun 22 [cited 2021 Nov 6];144(5):1336–41. Available from: https://academic.oup.com/brain/article/144/5/1336/6199170
10. Goodwin GH, Sanders C, Johns EW. A New Group of Chromatin-Associated Proteins with a High Content of Acidic and Basic Amino Acids. Eur J Biochem [Internet]. 1973 Sep 1;38(1):14–9. Available from: https://doi.org/10.1111/j.1432-1033.1973.tb03026.x
11. Stros M. HMGB proteins: interactions with DNA and chromatin. Biochim Biophys Acta. 2010;1799(1–2):101–13.
12. Agresti A, Bianchi ME. HMGB proteins and gene expression. Vol. 13, Current Opinion in Genetics and Development. Elsevier Ltd; 2003. p. 170–8.
13. Bustin M, Neihart NK. Antibodies against chromosomal HMG proteins stain the cytoplasm of mammalian cells. Cell [Internet]. 1979 [cited 2021 Jun 11];16(1):181–9. Available from: https://pubmed.ncbi.nlm.nih.gov/369705/
14. Kaneko Y, Pappas C, Malapira T, Vale FĹ, Tajiri N, Borlongan C V. Extracellular HMGB1 Modulates Glutamate Metabolism Associated with Kainic Acid-Induced Epilepsy-Like Hyperactivity in Primary Rat Neural Cells. Cell Physiol Biochem [Internet]. 2017;41(3):947–59. Available from: https://www.karger.com/DOI/10.1159/000460513
15. Gardella S, Andrei C, Ferrera D, Lotti L V, Torrisi MR, Bianchi ME, et al. The nuclear protein HMGB1 is secreted by monocytes via a non-classical, vesicle-mediated secretory pathway. EMBO Rep [Internet]. 2002/09/13. 2002 Oct;3(10):995–1001. Available from: https://pubmed.ncbi.nlm.nih.gov/12231511
16. Dimov SI, Alexandrova EA, Beltchev BG. Differences between some properties of acetylated and nonacetylated forms of HMG1 protein. Biochem Biophys Res Commun. 1990 Jan 30;166(2):819–26.
17. Scaffidi P, Misteli T, Bianchi ME. Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. Nature. 2002 Jul 11;418(6894):191–5.
18. Vénéreau E, Ceriotti C, Bianchi ME. DAMPs from cell death to new life. Vol. 6, Frontiers in Immunology. Frontiers Media S.A.; 2015.
19. Parker TM, Nguyen AH, Rabang JR, Patil AA, Agrawal DK. The danger zone: Systematic review of the role of HMGB1 danger signalling in traumatic brain injury [Internet]. Vol. 31, Brain Injury. Taylor and Francis Ltd; 2017 [cited 2021 Jun 7]. p. 2–8. Available from: https://pubmed.ncbi.nlm.nih.gov/27819487/
20. Fu L, Liu K, Wake H, Teshigawara K, Yoshino T, Takahashi H, et al. Therapeutic effects of anti-HMGB1 monoclonal antibody on pilocarpine-induced status epilepticus in mice. Sci Rep [Internet]. 2017 Apr 1 [cited 2021 Jun 1];7(1):1179. Available from: https://doi.org/10.1038/s41598-017-01325-y
21. Maroso M, Balosso S, Ravizza T, Liu J, Aronica E, Iyer AM, et al. Toll-like receptor 4 and high-mobility group box-1 are involved in ictogenesis

and can be targeted to reduce seizures. Nat Med [Internet]. 2010 Apr [cited 2021 Jun 7];16(4):413–9. Available from: https://doi.org/10.1038/nm.2127

22. Yang Y, Han C, Guo L, Guan Q. High expression of the HMGB1-TLR4 axis and its downstream signaling factors in patients with Parkinson's disease and the relationship of pathological staging. Brain Behav. 2018 Apr;8(4):e00948.
23. Hassan-Smith GZ, Messahel S, Mazibrada G, Gonzalez AM, Nagaraju S, Carey M, et al. HIGH-MOBILITY GROUP BOX 1 (HMGB1) EXPRESSION IS INCREASED IN THE NORMAL-APPEARING BRAIN TISSUE OF MULTIPLE SCLEROSIS (MS) PATIENTS VS. CONTROLS. J Neurol Neurosurg Psychiatry [Internet]. 2014 Oct 1;85(10):e4.39-e4. Available from: http://jnnp.bmj.com/content/85/10/e4.39.abstract
24. Zhao J, Zheng Y, Liu K, Chen J, Lai N, Fei F, et al. HMGB1 Is a Therapeutic Target and Biomarker in Diazepam-Refractory Status Epilepticus with Wide Time Window. Neurotherapeutics [Internet]. 2019 Dec 1 [cited 2021 Sep 23];17(2):710–21. Available from: https://pubmed.ncbi.nlm.nih.gov/31802434/
25. Wang D, Liu K, Wake H, Teshigawara K, Mori S, Nishibori M. Anti-high mobility group box-1 (HMGB1) antibody inhibits hemorrhage-induced brain injury and improved neurological deficits in rats. Sci Rep [Internet]. 2017 Apr 10 [cited 2020 May 13];7(1):46243. Available from: https://doi.org/10.1038/srep46243
26. Iori V, Maroso M, Rizzi M, Iyer AM, Vertemara R, Carli M, et al. Receptor for Advanced Glycation Endproducts is upregulated in temporal lobe epilepsy and contributes to experimental seizures. Neurobiol Dis. 2013;
27. Kaneko Y, Pappas C, Malapira T, Vale FĹĹ, Tajiri N, Borlongan CV V. Extracellular HMGB1 Modulates Glutamate Metabolism Associated with Kainic Acid-Induced Epilepsy-Like Hyperactivity in Primary Rat Neural Cells. Cell Physiol Biochem [Internet]. 2017 May 1 [cited 2021 Sep 24];41(3):947–59. Available from: https://www.karger.com/DOI/10.1159/000460513
28. Balosso S, Liu J, Bianchi ME, Vezzani A. Disulfide-Containing High Mobility Group Box-1 Promotes N-Methyl-d-Aspartate Receptor Function and Excitotoxicity by Activating Toll-Like Receptor 4-Dependent Signaling in Hippocampal Neurons. Antioxid Redox Signal [Internet]. 2013 Oct 5;21(12):1726–40. Available from: https://doi.org/10.1089/ars.2013.5349
29. Rosciszewski G, Cadena V, Auzmendi J, Cieri MB, Lukin J, Rossi AR, et al. Detrimental Effects of HMGB-1 Require Microglial-Astroglial Interaction: Implications for the Status Epilepticus -Induced Neuroinflammation [Internet]. Frontiers in Cellular Neuroscience Frontiers; Aug 27, 2019 p. 380. Available from: https://www.frontiersin.org/article/10.3389/fncel.2019.00380
30. Li Z, Li B, Zhu X, Yin P, Liu J, Huang S, et al. Neuroprotective effects of anti-high-mobility group box 1 antibody in juvenile rat hippocampus after kainic acid-induced status epilepticus. Neuroreport. 2013;
31. Walker L, Tse K, Ricci E, Thippeswamy T, Sills GJ, White SH, et al. High mobility group box 1 in the inflammatory pathogenesis of epilepsy: profiling circulating levels after experimental and clinical seizures. Lancet [Internet]. 2014 Feb;383:S105. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673614603688
32. Kan M, Song L, Zhang X, Zhang J, Fang P. Circulating high mobility group box-1 and toll-like receptor 4 expressions increase the risk and severity of epilepsy. Brazilian J Med Biol Res = Rev Bras Pesqui medicas e Biol. 2019;52(7):e7374.
33. Wang H, Bloom O, Zhang M, Vishnubhakat JM, Ombrellino M, Che J, et al. HMG-1 as a late mediator of endotoxin lethality in mice. Science. 1999 Jul;285(5425):248–51.
34. Zhao J, Wang Y, Xu C, Liu K, Wang Y, Chen L, et al. Therapeutic potential of an anti-high mobility group box-1 monoclonal antibody in epilepsy. Brain Behav Immun [Internet]. 2017;64:308–19. Available from: http://www.sciencedirect.com/science/article/pii/S0889159117300247