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Review

The Role of HMGB1 in Infection-Related Cognitive Deficits

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Abstract

Infectious diseases caused by fungi, viruses, or bacteria can have a profound impact on human cognition. This can be due to either direct spread to the central nervous system (CNS) or indirect neuroinflammation. Ultimately causing neuronal damage and even neurodegeneration. Deteriorations in cognition, such as poor encoding and attention deficits, have been reported secondary to infectious diseases. Preclinical studies have identified the underlying mechanisms of these infection-related cognitive effects, such as through blood-brain barrier (BBB) disruption and M1 microglial polarization. These mechanisms are spearheaded by inflammatory markers that are released/initiated by the pathogens over the course of the infection. Among them, the high mobility group box 1 (HMGB1) protein is a common biomarker implicated across several infection-related cognitive deficits. Understanding these effects and mechanisms is crucial for the development of strategies to prevent and treat infection-related cognitive impairment. This review will thus consolidate and elucidate the current knowledge on the potential role of HMGB1 as a therapeutic target for infection-related cognitive impairments. This review will not only advance scientific understanding but also have significant clinical and public health implications, especially considering recent global health challenges. Based on the selected articles, extracellular HMGB1, as opposed to intracellular HMGB1, acts as damage-associated molecular patterns (DAMPs) or alarmins when released in the peripheries secondary to inflammasome activation. Due to their low molecular weight, they then enter the CNS through routes such as retrograde transport along the afferent nerves, or simple diffusion across the impaired BBB. This results in further disruption of the brain microenvironment due to the dysregulation of other regulatory pathways. The outcome is structural neuronal changes and cognitive impairment. Given its key role in neuroinflammation, HMGB1 holds promise as both a biomarker for diagnostic detection and a potential therapeutic target candidate for preventing infection-related cognitive impairment.

Keywords: high mobility group box-1; TLR4 receptor; infectious diseases; cognition

1. Introduction

Infectious diseases are a major cause of morbidity and mortality worldwide. According to the annual estimates by the World Health Organization (WHO), there are globally 229 million cases of malaria, 48.9 million cases of sepsis, 37.7 million cases of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) and 10 million people infected with tuberculosis [1]. In terms of mortality, globally every third death is caused by an infection. The twenty-first century witnessed a series of severe infectious disease outbreaks. The most prominent being the coronavirus (COVID)-19 pandemic, which had a devastating impact on lives and livelihoods around the globe [2]. In fact, lower respiratory tract infections remain the world's deadliest communicable disease with 2.6 million lives claimed in 2019 by COVID-19 alone [1]. In addition, infectious diseases also pose disabling long-term consequences to a patient leading to poor quality of life. These include prolonged fatigue, cardiovascular complications and may even affect one's neuropsychiatry and cognition.

Increasing evidence suggests that inflammation triggered by infections may be the driving force towards cognitive decline in later life, whether through direct infiltration by the infectious agents of the central nervous system (CNS) or indirectly through the release of inflammatory cytokines into the brain by systemic infections. Several infectious diseases have been associated with memory impairments such as sepsis, encephalitis, meningitis, acquired immunodeficiency syndrome (AIDS), pneumonia, and cerebral malaria [3–5]. Even COVID-19, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), brought about neurological symptoms, including headache, altered cognition and anosmia. Psychological alterations such as anxiety, depression, and stress have also been reported in these patients [6].

Infections can either cause short-term cognitive impairments that may be reversible upon acute treatment of the disease or permanent cognitive decline that may develop in susceptible individuals gradually. These susceptible individuals could either have an impaired immune system or an already elevated baseline inflammation, which hypothetically could make them more prone to cognitive decline upon further systemic inflammation, similar to the inflamm-aging hypothesis [7]. This implies that infections act as a stimulus to bring about certain, possibly permanent, changes by disrupting homeostasis in the brain. For example, the body's immune system, responsible for detecting such stress via receptors such as inflammasomes, dispatch molecules known as alarmins or damage-associated molecular pattern molecules (DAMPs), for such encounters [8]. These molecules share the common goal of stimulating inflammation upon release in response to noxious stimuli.

The high-mobility group box 1 (HMGB1) protein is one such DAMP that is released passively during cell injury/damage and secreted actively upon inflammatory stimuli [9]. However, excessive release of extracellular HMGB1 has been noted in the pathogenesis of tissue injury and organ dysfunction in several diseases both sterile and infectious in origin [10]. Studies on bacterial infections such as bacterial meningitis, meningoencephalitis, encephalitis and neuroborreliosis, have shown translocation of nucleus HMGB1 from damaged/necrotic tissue into the cytoplasm, which activates inflammasomes [11–13]. In viral infections, HMGB1 was either passively released through cell necrosis or actively released through immune cell activation in diseases like aseptic meningitis, influenza encephalopathy and flavivirus encephalopathy, but not all virus-related infections [10,14]. Interestingly, HMGB1's profile in fungal infections has been rarely reported. However, a prominent fungal CNS infection, known as Cryptococcus neoformans, was shown not lead to an immediate release of HMGB1 but instead a gradual release from cell necrosis alike certain viral infections [15]. The consequences of this HMGB1 release such as functional changes in the context of cognition are yet to be explored.

Considering the hypothesis that HMGB1 mediates cognitive decline in sepsis survivors, previous studies suggest that tumor necrosis factor (TNF), interleukin (IL)-1 along with HMGB1 play critical roles in modulating neuronal activity associated with cognition and behavior [16]. TNF regulates the expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and N-methyl-D-aspartate receptors (NMDARs) on neurons, which are essential for learning and memory. Similarly, IL-1β and HMGB1 also modulate NMDARs, leading to functional changes that can impact memory. Administration of anti-TNF antibody and anti-IL-1 antibody in acute murine injury and infection models has been shown to significantly improve cognitive abnormalities [17]. However, there have been limited studies with regards to HMGB1 and cognition in the infection setting, thus speculating if anti-HMGB1 could also improve cognitive impairments post-infection. If so, HMGB1 may be a promising therapeutic target for infection initiated cognitive decline. Therefore, this review aims to elucidate the potential role of HMGB1 as a therapeutic target for post-infection related cognitive decline. The objectives of this review are first to consolidate the role of HMGB1 in post-infection cognitive deficits based on current literature and the second is to explore the potential role of HMGB1 as a therapeutic target for post-infection cognitive deficits based on identified mechanism of action in the pathology. A robust literature search was performed to identify existing articles related to HMGB1 and infection-related cognition, using three databases; PubMed, Ovid Medline and Scopus. We selected the relevant articles based on the following inclusion criteria: full-text English articles, and articles that investigate HMGB1 in relation to infection, and exclusion criteria: articles that did not investigate cognitive effects in relation to infection. Although this is a narrative review, we have summarized and critically appraised the relevant selected literature for an updated view of this topic.

2. Literature Overview On HMGB1's Role In Infection-Related Cognitive Deficits

The literature search and selection, based on the inclusion and exclusion criteria, yielded a total of 15 studies related to the topic at hand. Among these articles, there were 3 clinical studies that evaluated viral-origins: HIV-associated cognitive disorders (HAND), 1 preclinical study that investigated bacterial-related origins: necrotizing enterocolitis (NEC)-associated cognitive impairment, and the rest were 11 preclinical studies on non-specific bacterial or viral origins: sepsis associated encephalopathy (SAE)-associated cognitive deficits. Unfortunately, there were no papers on HMGB1 in fungal infection-related cognitive impairment. The studies are presented in Table 1 (Ref. [18–20]) and Table 2 (Ref. [21–32]). Table 1 consists of the 3 clinical studies and Table 2 consists of the 12 preclinical studies.

With regards to the 3 selected clinical studies, all participants were adults with 2 studies having a female predominance and 1 having a male participant predominance. In all 3 studies, the cases and the controls were divided into neuropsychologically impaired persons (NPI) versus neuropsychologically normal persons (NPN) [18–20]. The remainder were 12 pre-clinical studies with a mixture of models, out of which the only study that focused on necrotizing enterocolitis (NEC) used 7 to 12 weeks old male and female C57BL/6 and Cx3cr1cre-ERT2 strains of mice [21]. The rest were studies that assessed sepsis induced cognitive deficits, largely in the C57BL/6 strain of mice. The other models used include BALB/c, CD-1, wild type and Wistar rats. In terms of gender, most studies employed male mice.

Table 1. Summary of the selected clinical articles on the role of HMGB1 in infection-related cognitive deficits.

Disease modality	Sample characteristics	HMGB1 findings	Cognitive results	Relationship between HMGB1 & Cognition	References
HAND	60 frozen plasma samples 38 F, 22 M all with HIV infection NPI = 40, NPN = 20 Mean age: 46.1 to 47.8 years	HMGB1 was elevated in NPI compared to NPN participants with men driving the increase.	GDS test score was significantly higher in NPI versus NPN participants.	↑ in HMGB1 levels = ↑ in cognitive impairment	[18]
HAND	35 Plasma NDE samples. 34 M, 1F Cases group; NPI = 1 and NPN = 12 Control group; NPI = 3 and NPN = 9 Mean age: 52.1 to 58.0 years	In both cases and controls NDE from NPI participants had significantly higher HMGB1 protein levels compared with NPN individuals, regardless of underlying infection. NDE HMGB1 protein levels significantly decreased with age.	Domains tested were attention working memory, information processing speed, executive function, verbal learning, and memory. NPI participants from both groups scored lower than the NPN participants.	↑ in HMGB1 levels = ↑ in cognitive impairment	[19]
HAND	80 plasma samples 29 M and 51F 4 groups, 20/group; HIV-negative NPN, HIV-positive NPN, HIV-positive ANI and HIV-positive MND Mean ages: 46.1 to 49.7 years	HMGB1, was increased in NDE from impaired men but not women regardless of underlying infection.	Participants in ANI and MND groups showed more severe neuropsychological impairment as shown by GDS.	↑ in HMGB1 levels = ↑ in cognitive impairment	[20]

↑: increase. HMGB1, high-mobility group box 1; HAND, HIV-associated cognitive disorders; HIV, human immunodeficiency virus; NPI, neuropsychologically impaired persons; NPN, neuropsychologically normal; NDE, neuron derived exosome; ANI, Asymptomatic Neurocognitive Impairment; MND, mild neurocognitive disorder; GDS, global deficit score.

Table 2. Summary of the selected preclinical studies on the role of HMGB1 in infection-related cognitive deficits.

Disease Modality	Sample characteristics	HMGB1 findings	Cognitive results	Relationship between HMGB1 & Cognition	References
NEC- associated brain injury	Male and female C57Bl/6 and Cx3cr1$^{cre\text{-}ERT2}$ mice 7–12 weeks old	Mice lacking HMGB1 on intestinal epithelium subjected to NEC had significantly lower levels of HMGB1 in circulation.	Impaired spatial working memory and novel object recognition memory in mice subjected to experimental NEC.	↑ in HMGB1 levels = ↑ in microgial activation & cognitive impairment via the TLR4 receptor activation on the intestinal epithelium	[21]
SAE	Male BALB/c mice 6–8 weeks old 2 groups, 20/group; cecal ligation and perforation (CLP) surgery, sham surgery	Serum HMGB1 levels remain elevated in sepsis survivors for weeks and return to baseline after 12 weeks (post CLP) only.	CLP group mice exhibited significantly impaired memory function in the clock maze task at 4 weeks and this lasted for 4 months.	↑ in HMGB1 levels = ↓ in normal cognition by impairing the structure & function of hippocampal neurons	[22]
SAE	Female WT mice 8 weeks old, 20–25 g 4 groups, 20/group; Sham group, sham + H_2 group, CLP group and CLP + H_2 group	In the CLP group, HMGB1 levels were significantly upregulated compared with the sham group. After inhalation of H_2, HMGB1 levels decreased in the CLP + H_2 group compared with the CLP group.	Spatial learning and memory function were significantly impaired in the CLP group. H_2 inhalation ameliorated these deficits in the CLP + H_2 group *vs* CLP group.	↑ in HMGB1 levels = ↑ in BBB impairment, causing barin damage manifesting as cognitive impairment	[23]
SAE	Male adult Wistar 60-day-old Subjected to CLP or sham surgery. 2 groups, 6/group; CLP group and sham surgery group	Serum HMGB1 levels increased 15 and 30 days after CLP Hippocampal and prefrontal cortex HMGB1 levels decreased 15 days after CLP	Sepsis induces a significant impairment in memory retention tasks, and animals treated with RAGE ab administration had performance like control animals.	↑ in HMGB1 levels = ↑ in cognitive impairment by the activation of RAGE in the hippocampus which is important in normal cognition	[24]
SAE	C57BL/6 mice 18–25 g N = 10 in naïve and n = 6 in LPS group at each test time point.	Increased expression of HMGB-1 found in the hippocampus of LPS mice compared to naïve mice.	Sepsis-survivor animals showed decrease in testing startle response and latency in water maze test, which last for at least for 15 days after LPS injection.	↑ in HMGB-1 levels = ↑ in cognitive impairment by binding to TLR-4 and/or RAGE to induce long-term inhibition of autophagy, which in turn accounts for the impaired brain dysfunction	[25]
SAE	Male C57BL6J mice 6–8 weeks old, 20–24 g 4 groups, 20/group; Control, Control + H_2, SAE, SAE + H_2. SAE induced by intraperitoneal injection of human stool suspension	Expression of HMGB1 increased in the SAE group at each time point 6, 12, 24 h after modelling ($p < 0.05$ *vs* control group). H_2 treatment decreased the concentration ($p < 0.05$ *vs* SAE group)	Spatial learning and memory were impaired in SAE group *vs* control. H_2 inhalation reversed these impairments ($p < 0.05$ *vs* SAE group)	↑ in HMGB-1 levels = ↑ in cognitive impairment by damage to endothelial cell function which in turn destroys BBB	[26]

Table 2. Continued.

Disease Modality	Sample characteristics	HMGB1 findings	Cognitive results	Relationship between HMGB1 & Cognition	References
SAE	C57BL/6 mice 8–10 weeks, 20–25 g 5 groups, 15/group; Sham group, CLP group, CLP + siNC group, CLP + siCirc group, CLP + siCirc + antagomir group	CLP treatment triggered the upregulation of HMGB1 ($p < 0.05$ *vs* sham group). In the CLP + siCirc groups this effect was reversed ($p < 0.05$ *vs* CLP group). In the CLP + siCirc + antagomir group, there was upregulation of HMGB1 ($p < 0.05$ *vs* CLP + siCirc group).	Learning and memory functions were impaired in the CLP group compared with the Sham group. Effect on learning was improved in the CLP + siCirc group *vs* CLP group. This therapeutic effect was revered in the CLP + siCirc + antagomir group.	↓ in HMGB-1 levels = ↑ in cognition via the miR-181c-5p-HMGB1 signaling pathway.	[27]
SAE	Male C57BL/6 mice 3–4 months old, 25–32 g 4 groups: Control + vehicle (normal saline) group; Control + LMWH group; LPS + vehicle group; or LPS + LMWH group.	HMGB1 was significantly increased at day 7 after LPS administration and these changes were reversed by LMWH administration.	In the contextual fear conditioning test, LPS treated mice displayed less freezing time compared with those in the control group, which was reversed by treatment of LMWH No significant difference in post tone freezing time in the auditory-cued fear conditioning test among the four groups.	↑ in HMGB-1 levels = ↑ in hippocampal dependent memory impairment by the binding of TLR4 to the intracellular myeloid differentiation factor 88 that activates NF-κB which is responsible for the induction of various inflammatory molecules that affects the learning and memory functions	[28]
SAE	Male CD-1 mice 6–8-week-old Experiment 1, 3 groups: control, sham surgery and sepsis. Experiment 2, 4 groups: sham surgery, sepsis, dexmedetomidine plus sham surgery and dexmedetomidine plus sepsis.	Septic mice had elevated levels of HMGB1 expression compared to the sham surgery and control groups in all experiments. Administration of dexmedetomidine reversed these effects ($p < 0.05$ *vs* sepsis group).	The septic groups displayed impaired spatial learning and memory compared with sham surgery mice and control mice. Administration of dexmedetomidine reversed these effects.	↓ in HMGB-1 levels = ↑ in cognition via the Alpha2A adrenoceptor pathway.	[29]
SAE	Male wild type C57BL/6 mice 6–8 weeks old, 20–22 g 4 groups; sham CLP group (sham-1), CLP group, sham ICV injection group (sham-2), CLP plus ICV injection group (BoxA, 1 µg).	HMGB1 expression in cortex, hippocampus and striatum were all significantly upregulated and elevated in the sepsis group ($p < 0.05$ *vs* Sham group).	The sepsis group compared to the sham group showed significant spatial learning and memory impairment, observed by significantly longer latency times and decreased frequency and duration time in the target zone in MWM respectively. ICV injection attenuated these effects in the CLP + ICV group.	↓ in HMGB-1 levels = ↓ in cognitive impairment due to antagonism of cerebral HMGB1 via intracerebroventricular injection of BoxA.	[30]

Table 2. Continued.

Disease Modality	Sample characteristics	HMGB1 findings	Cognitive results	Relationship between HMGB1 & Cognition	References
SAE	Male C57BL/6 mice 6–8 weeks old, 20–25 g 4 groups; sham group, the sham + H_2 group, the CLP group, and the CLP + H_2 group.	In the CLP group, hippocampal HMGB1 levels were significantly increased compared with the sham group. After H_2 treatment, its expression was decreased in CLP + H_2 group ($p < 0.05$ *vs* CLP group)	The CLP group compared to the sham group showed significant spatial learning and memory impairment, observed by significantly longer escape times and decreased time in target platform crossing in MWM respectively. Hydrogen gas inhalation reversed these effects in the CLP + H_2 group.	↓ in HMGB-1 levels via DNA methylation catalyzed by DNMT1 & DNMT3a- mediated BDNF promoter IV methylation = ↑ in cognitive functioning	[31]
SAE	Male C57BL/6J mice 6–8 weeks, 20–25 g 4 groups; Sham group, Sham + H_2 group, CLP group and CLP + H_2 group.	Hippocampal HMGB1 levels were increased ($p < 0.05$ *vs* sham group) Hydrogen gas inhalation reversed this by increasing the levels of anti-inflammatory cytokines IL-10 and TGF-beta in the CLP + H_2 group ($p < 0.05$ *vs* CLP group)	The CLP group compared to the sham group showed significant spatial learning and memory impairment, observed by significantly longer escape times and decreased probe trial times in MWM respectively. Hydrogen gas inhalation reversed these effects in the CLP + H_2 group.	↓ in HMGB-1 levels = ↑ in cognition via microglial polarization mediated by the mTOR-autophagy signaling pathway.	[32]

↑: increase. HAND, HIV-associated neurocognitive disorders; HIV, human immunodeficiency virus; NPI, neuropsychologically impaired; NPN, neuropsychologically normal; GDS, global deficit score; nEV, neuronal extracellular vesicle; NDEs, neuron derived exosomes; ANI, asymptomatic neurocognitive impairment; MND, mild neurocognitive disorder; NEC, necrotizing enterocolitis; TLR4, toll-like receptor 4; SAE, sepsis-associated encephalopathy; CLP, cecal ligation and puncture; RAGE, receptor for glycation end products; WT, wild type; H_2, Hydrogen gas; BBB, blood brain barrier; RAGEab, RAGE antibodies; LPS, lipopolysaccharide; siNC, circPTK2 control siRNA; siCirc, circPTK2 siRNA; BDNF, brain derived neurotrophic factor; DNMT1, DNA methyltransferase 1; DNMT3a, DNA methyltransferase 3a; promotor IV, promotor 4; LMWH, low molecular weight heparin; ICV, intracerebroventricular; IL-10, interluekin-10; TGF-beta, transforming growth factor beta; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; MWM, Morris water maze.

The youngest mice used were 60 days old and the oldest were 3 to 4 months old, with the average being 6 to 8 weeks old [22–32].

In terms of significant findings, in the three studies that evaluated HAND, HMGB1 levels were elevated in all neuropsychologically impaired participants regardless of their HIV-seropositivity status [18–20]. In the study based on NEC, HMGB1 levels in circulation were elevated in NEC-model wild type mice compared to mice that had HMGB1 free intestines generated (HMGB1ΔIEC). Furthermore, induction of experimental NEC led to impaired neurocognitive function in the intervention mice group, with significantly impaired spatial working memory and novel object recognition memory [21]. Lastly, among the studies that assessed sepsis-related cognitive deficits, HMGB1 levels were significantly raised in the intervention groups subjected to experimental sepsis when compared with the controls. The groups subjected to septic challenge also developed impaired cognitive function, which was observed in their performance during the cognitive tests such the Morris water maze [22–32].

3. HIV-Associated Neurocognitive Disorders (HAND)

HAND is a spectrum of cognitive impairments that occurs in individuals living with HIV. HAND is categorized into three main subtypes, each differing in severity and impact on daily life. The mildest form of HAND is asymptomatic neurocognitive impairment (ANI). Patients with ANI exhibit subtle cognitive deficits, detectable only through specialized neuropsychological testing. Despite the subtility of the symptoms, ANI is concerning because it indicates some degree of underlying neurocognitive decline. ANI is the most prevalent subtype of HAND, affecting an estimated 33–50% of HIV-positive individuals [33]. Next, is the mild neurocognitive disorder (MND) type representing a more advanced stage of cognitive impairment. Individuals with MND experience noticeable difficulties with cognitive tasks such as memory, attention, and executive functioning. MND is less common than ANI, with a prevalence of about 12–20% among HIV-positive individuals [34]. This subtype reflects more significant neurocognitive challenges but does not reach the severity of dementia [33,34]. The most severe form of HAND is HIV-Associated Dementia (HAD). HAD involves profound cognitive, motor, and behavioral impairments that significantly disrupt daily life. Patients with HAD may struggle with memory loss, concentration difficulties, motor coordination problems, and changes in behavior or personality. Unlike the previous two types of HAND, HAD type can be debilitating, requiring substantial care and support. Although the prevalence of HAD has decreased in recent times, affecting approximately 2–8% of HIV-positive individuals, it remains a serious concern, particularly for those who are untreated or have advanced HIV [33–36]. Several key factors contribute to the development of HAND, including high HIV viral loads, low CD4+ T-cell counts, and the effectiveness of anti-retroviral therapy (ART). While ART has reduced the incidence of severe forms like HAD, cognitive impairments can still occur, possibly due to persistent inflammation.

Compared to ART, combination anti-retroviral therapy (cART) has definitely revolutionized the treatment of HIV, leading to significant reductions in mortality, opportunistic infections, and severe HIV-related conditions like HAD, transforming HIV into a chronic, manageable condition with improved life expectancy. However, challenges still remain, including managing long-term side effects, ensuring adherence, and addressing residual health issues like neurocognitive impairments that persist in some individuals despite effective treatment [35]. This suggest that whether ART or cART, both has a limitation towards reversing or preserving the cognitive effects of the infection. Thus, clinical practice currently seeks for predictive biomarkers to aid in the early diagnosis of ANI and MND. This is because these individuals have a propensity to transition to consequent severe stage. For instance, in the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study, participants with ANI at baseline were 2 to 6 times more likely to develop symptomatic HAND during follow-up than the control group with no neurocognitive impairment [31]. This implies that the CNS is a vital reservoir for HIV and certain individuals have early onset cognitive involvement following infection in the absence of any symptoms. Therefore, a biomarker that either detects HAND in its preclinical phase or predicts cognitive deterioration (likely in 23% of ANI patients), can lead to prompt intervention, leading to the preservation of cognitive function [30].

The three studies included in this review had the common goal of determining such a biomarker that accurately reflects the functional status of neurons in chronic HIV patients undergoing antiretroviral therapy (Table 1). Among the alarmins involved in the neuropathogenesis of HAND, HMGB1 is of particular interest. Significant levels of this protein along with its antibodies were identified in the plasma and cerebrospinal fluid (CSF) of patients with HAND [9]. Pulliam L *et al.* [18], and Sun B *et al.* [19], measured HMGB1 levels contained in exosomes, which were isolated from the plasma of participants with and without chronic HIV infection. Exosomes are involved in cell-cell communication in normal homeostasis and at the same time are carriers of toxic proteins released during degenerative processes. The exosomes of interest in all three studies, were specifically of neuronal origin (NDEs). They were extracted through a precipitation/immunoaffinity approach using antibodies against the neuronal adhesion molecule, L1 cell adhesion molecule (L1CAM) and the contents queried for HIV associated neurological disorders (HAND). Consequently, in both cases and controls, the HMGB1 levels were elevated in the partic-

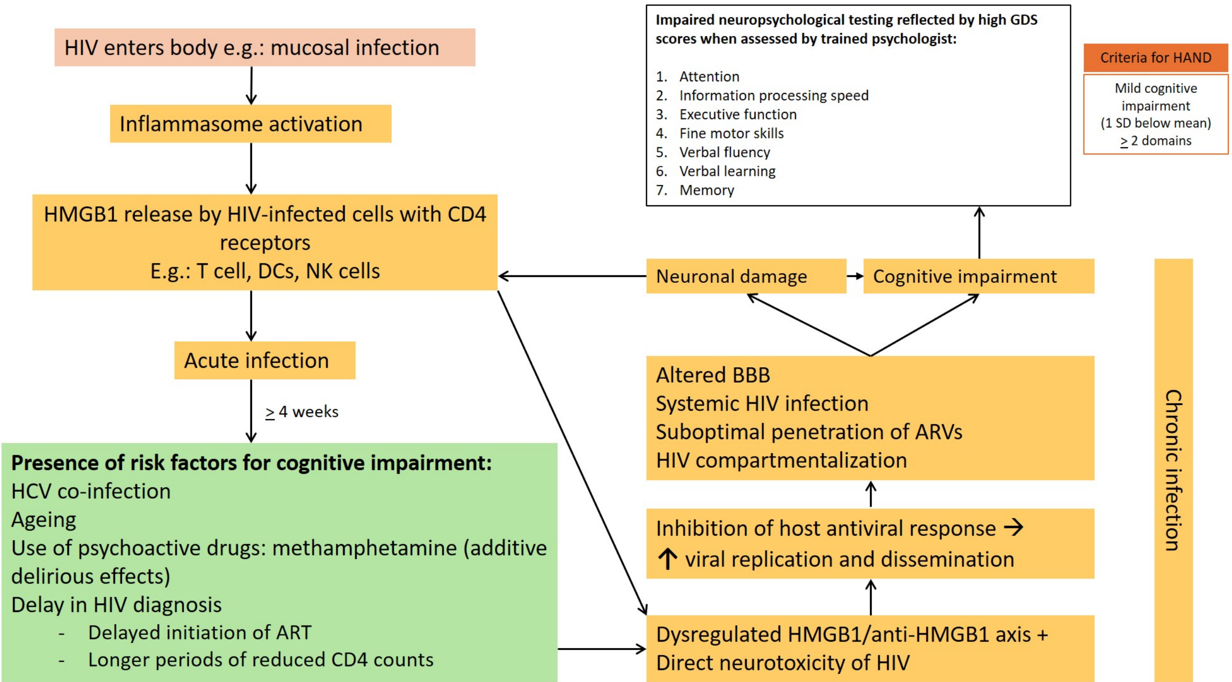

Fig. 1. Pathological mechanism in HAND and the role of HMGB1. ART, anti-retroviral therapy; CD4, cluster of differentiation 4; DCs, dendritic cells; NK, natural killer; HCV, Hepatitis C virus; ARVs; anti-retrovirals; SD, standard deviation.

ipants categorized as NPI in comparison to those who were NPN [8–10]. This implies underlying neuronal damage in the former and hence the subsequent release of toxic products via exosomes. Furthermore, all the neuropsychologically impaired participants in both the cases and the control groups in Sun B *et al.*'s study [19,20], had raised HMGB1 levels. This suggests their specificity to neurodegenerative processes regardless of underlying HIV status.

In persons living with HIV, the mechanisms by which the peripheral HMGB1 proteins reach the CNS to precipitate structural and functional changes is brought about by three pathways. These are (1) transport of the virus into brain by infected cells such as macrophages; (2) direct passage of the virus itself across the blood brain barrier (BBB); and (3) release of the virus by infected endothelial cells. This paves the way for subsequent entry of proinflammatory cytokines such as HMGB1 [30]. Furthermore, risk factors for development of cognitive impairment, which include hepatitis-C coinfection, concurrent substance use e.g.: methamphetamine and problems associated with delayed diagnosis of HIV such as delayed ART initiation has been identified. Therefore, it can be concluded that the compartmentalization of the CNS by the HIV is a complex interplay of several factors [36]. Fig. 1 summarizes the important mechanisms.

The findings from the studies also highlighted the role of exosomes as a potential biomarker aid to help understand the extent of neurodegeneration associated with cognitive impairment induced by infection such as HIV (Table 1). In addition, it carries benefits such as being inexpensive and minimally invasive to the patient since HMGB1 levels can be detected via a blood test as opposed to traditional methods of identifying cognitive impairment such as neuroimaging and lumbar punctures for CSF analysis [8–10]. However currently no data is available on the cut-off ranges for HMGB1 levels in the plasma. More studies are needed to investigate HMGB1 plasma test sensitivity and specificity rates, as exosomal HMGB1 levels were raised in all NPI participants regardless of their HIV-seropositivity status, suggesting sensitivity range may be a key diagnostic factor.

4. NEC-Induced Cognitive Impairment

NEC among premature infants has an estimated incidence of 10% worldwide and is the leading cause of mortality in this demographic [21]. Despite the survival rate following NEC being about 50%, it is estimated that half the survivors go on to develop cognitive impairments [37,38]. These impairments are reported to be more debilitating and complicated to manage than non-NEC associated neurocognitive deficits [39–41]. Previous research surrounding perinatal cognitive dysfunction using models of chronic hypoxia or carotid ligation, have demonstrated that microglial activation results in the loss of oligodendrocytes progenitor cells (OPCs). These are glial cells that play a role in myelin regeneration therefore their loss leads to demyelination, which contributes to cognitive deterioration. Studies have shown that the pathophysiology surrounding NEC-induced cognitive impairment also follows the same pattern [21,42].

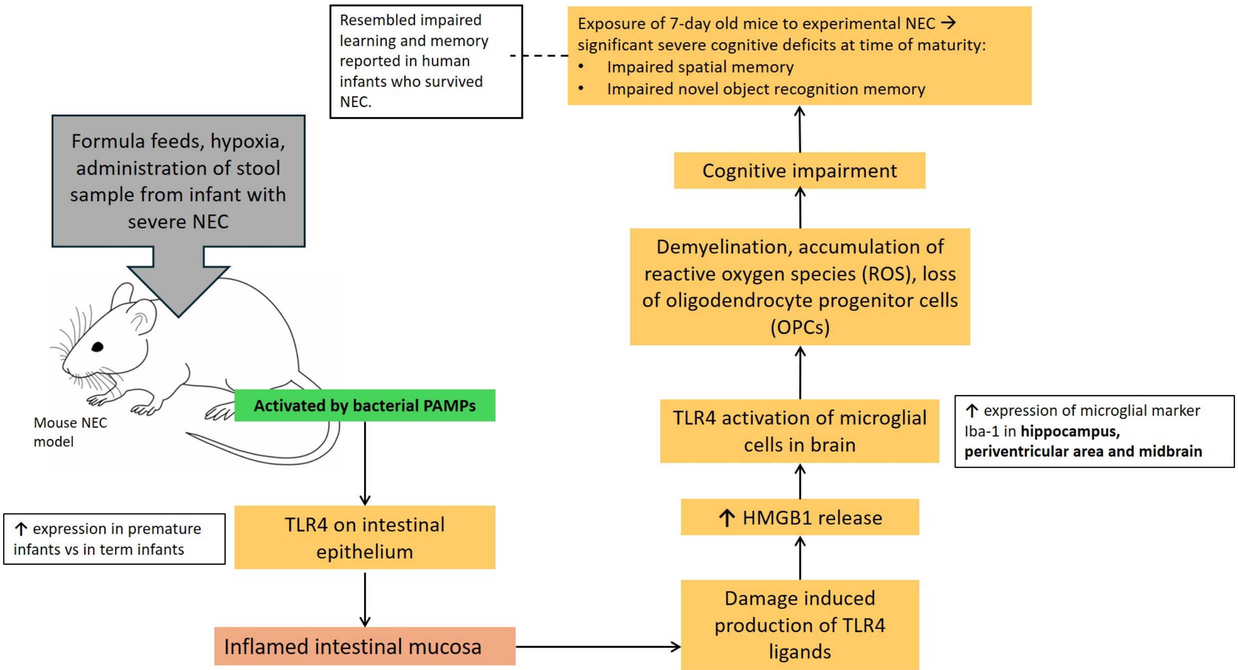

Fig. 2. Pathological mechanism in NEC-induced cognitive deficits and the role of HMGB1. ↑: increase. PAMPs, pathogen-associated molecular patterns; lba-1, ionized calcium binding adaptor molecule 1.

Based on the studies included in this review, the researchers found that the endogenous toll-like receptor 4 (TLR4) ligand, HMGB1 are released from the intestinal epithelium in NEC mice models and activates the TLR4 receptor on microglia. The increased TLR4 activation of microglial cells especially in the hippocampus, periventricular and midbrain regions can lead to significant deteriorations in spatial working memory and novel object recognition memory [21], thus resulting in perinatal cognitive dysfunction. These cognitive deficits could potentially resemble the signs and symptoms of learning and memory decline in human infants who survived NEC. Another factor leading to the increased HMGB1 in the systemic circulation was also the result of the increased expression of TLR4 receptors in the premature intestine compared to that of a term infant. Therefore, interestingly these findings could have implications for current surgical management of NEC [40]. We can now postulate that the incomplete or delayed surgical removal of the necrotic intestinal tissue is the main potentiator of neurotoxic changes in the preterm infant with NEC. Fig. 2 highlights the important mechanisms.

5. Sepsis-Associated Encephalopathy (SAE)

Sepsis is characterized as a syndrome of dysregulated immune function following an infection, which results in damage to the host organs. It continues to be a significant health burden worldwide, but its disease mechanisms are complex and thus inadequately elucidated [43]. Sepsis-associated encephalopathy (SAE) is a complication of sepsis characterized by global cerebral dysfunction in the absence of primary CNS infection, with an incidence as high as 70%. It poses a significant disease burden, even in survivors of SAE whereby cognitive impairment persists for several years [22]. Therefore there is a dire need for therapeutic advancements in this regard as current treatment is largely supportive care [44].

In terms of pathophysiology it is established that regardless of the mechanism involved, the development of sepsis and its associated complications can be attributed to heightened neuroinflammation and the subsequent immunosuppression [9]. Current monotherapies such as TNF-α targeted therapies and IL-1 receptor agonist administration have demonstrated minimal clinical success [45,46]. The failure of which has been attributed to the timing of administration. This is because these cytokines are mainly expressed during the “early-phase” of the disease, and hence the treatment might have been initiated late [38]. This implies that targeting a “late-phase” cytokine can potentially be beneficial. Hence, HMGB1, a known delayed mediator of sepsis, is one such therapeutic candidate. The eleven studies that assessed sepsis in this regard, collectively demonstrated that mice models surviving severe sepsis induced by either cecal ligation and puncture (CLP) or lipopolysaccharide (LPS) administration have elevated HMGB1 levels in their serum as well centrally in the prefrontal and hippocampal cortex [21–32]. These mice subsequently went on to develop memory and learning impairments alike the clinical phenomenon seen in real patients.

In terms of underlying mechanisms, the blood brain barrier (BBB) disruption was a common pathology seen

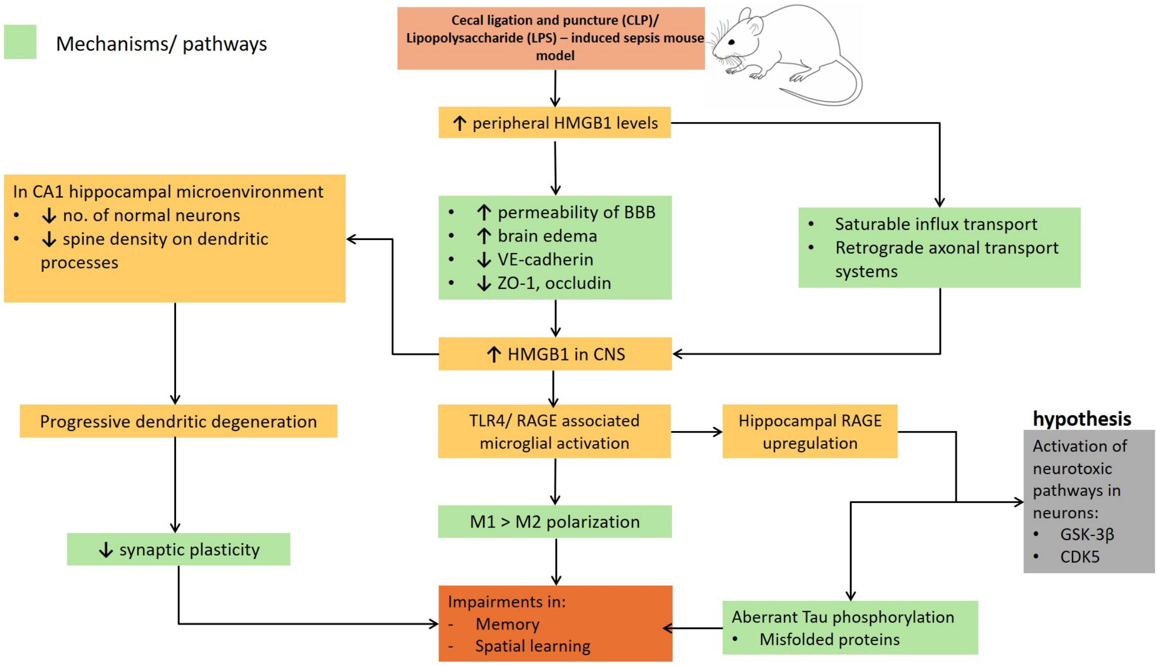

Fig. 3. Pathological mechanism in SAE and the role of HMGB1. ↑: increase; ↓: decrease. CNS, central nervous system; CA1, cornu ammonis region 1; VE-cadherin, vascular endothelial-cadherin; ZO-1, Zonula Occludens-1; GSK-3β, glycogen synthase kinase-3 beta; CDK5, cyclin-dependent kinase 5.

across the studies (Table 2). This was postulated to be due to HMGB1 and other inflammatory cytokines' mediated damage to BBB-tight junction proteins such as vascular endothelial (VE)-cadherin and occludin. This then also brought about the simple diffusion of peripheral HMGB1 across the BBB due to their low molecular weight. The other mechanisms by which circulating HMGB1 reached the brain is hypothesized to be via involvement of an influx transporter located at the BBB and retrograde axonal transport. Subsequently the elevation of central HMGB1 brought about two important changes, which include (1) structural changes to the cornu ammonis region 1 (CA1) hippocampal environment; and (2) TLR4/receptor for glycation end products (RAGE)-associated microglial activation. In the CA1 region, there were reductions in the number of neurons as well as progressive dendritic degeneration contributing to impaired synaptic plasticity. These findings are significant as theory shows that CA1 neurons are involved in encoding and retrieving hippocampal dependent memories [21]. Furthermore, the TLR4/RAGE activation of microglial cells consequently led to two further neurotoxic changes which include (1) M1 microglial polarization exceeding M2 microglial polarization; and (2) hyperphosphorylated tau-proteins. M1-macrophages are known to be proinflammatory while M2-macrophages have anti-inflammatory effects linked with tissue repair [47]. Moreover, the presence of aberrant tau phosphorylation shows an overlap of the neurodegenerative pathology underlying that of Alzheimer's disease. These findings are summarized in Fig. 3.

In addition, the role of HMGB1 in three novel pathways in the sepsis models was also brought to light. These were namely miR-181c-5p-HMGB1 signaling pathway, DNA methylation mediated brain derived neurotrophic factor (BDNF) promotor-IV methylation and the alpha2A adrenoreceptor pathways. In studies surrounding neurodegeneration, it was concluded that microRNA-181c down-regulation resulted in the development of Alzheimer's disease (Table 1). It was also discovered that the aberrant expression of this microRNA protected neuronal cells from tumor necrosis factor-alpha medicated microglial apoptosis [23]. Interestingly upregulation of miR-181c in mice models with sepsis-induced cognitive deficits, had similar neuroprotective effects, whereby of significance there was down-regulation of HMGB1 expression. A reduction in the neuroinflammatory changes brought about by microglial activation and preservation of the BBB integrity was also noted. Subsequently the cognitive deficits were reversible. These findings, therefore may have implications for genetic therapy as specific genes can be exploited for early invention in septic patients prone to develop neurocognitive disorders.

In terms of DNA methylation, enzymes known as DNA methyltransferases (DNMTs) such as DNMT1 and DNMT3a catalyze the epigenetic process by adding methyl groups to the DNA molecule. Hypermethylation of the BDNF promotor-IV has been associated with the pathology of several neurological diseases. Therefore, experimenting to silence rodent promotor IV by decreasing the levels of DNMTs through hydrogen inhalation, interestingly enhanced the BDNF expression and overtime antagonized the poor spatial learning and memory among the septic rats. Many studies have postulated that BDNF plays a vital role in the formation and maintenance of memories by promoting changes in the morphology of dendritic spines to stabilize them. It is also a key regulator of plasticity changes in the brain and in this regard, its increased expression was associated with consequent lowered levels of HMGB1 [27]. Finally, the role of HMGB1 in alpha2A adrenoreceptor antagonism, in the locus coeruleus by dexmedetomidine was studied. Dexmedetomidine, a sedative used in intensive care units, has been proven to have better outcomes in septic patients in clinical studies, with reduced rates of neuro-dysfunction compared to benzodiazepines such as lorazepam [44]. However, following the reduction of HMGB1 levels after administration of dexmedetomidine, it can be concluded that it also manifests advantageous anti-inflammatory properties. Therefore, this is a niche for further studies to help highlight its neuroprotective effects in septic patients.

6. Post-Infection Seizures

It is important to highlight that infection, particularly brain infections, has been shown to predispose individuals to epileptic seizures. For example, febrile seizures or febrile infection-related epilepsy (FIRES), which is common in the pediatric age group, is caused by acute CNS infections such as meningitis or encephalitis. In fact, even in adults, meningitis and encephalitis are some of the well-established etiologies of acquired epilepsy [48]. Cognitive deficits have been showcased as a clinical manifestation or a complication of seizures due to the progression of neuroinflammation and neurodegeneration of hyperactive neuronal networks [49]. Moreover, one of the side effects of common antiseizure medications is related to cognition [49]. Over the recent years, several preclinical studies have looked into the molecular mechanisms responsible for epilepsy-related cognitive deficits following an infection. Among them the activation of the HMGB1-TLR4 axis was found to promote neuronal excitability and lower the seizure threshold. Similar to cognition pathology, HMGB1 activates glial-mediated neuroinflammation which results in a pro-neuroinflammatory cascade that leads to calcium influx in the neurons and thereby increasing neuronal activation [50,51]. Therefore, this suggest that HMGB1 also has the potential to be a novel anti-seizure drug that preserves cognition.

7. Conclusions

This review concluded that HMGB1 is a common biomarker involved in HAND, NEC and sepsis associated cognitive impairments. This may also be true for other primary CNS or systemic infections but further studies involving other disease models are required to confirm this extrapolation. Nevertheless, we suggest that HMGB1 could be a potential therapeutic target in infectious diseases, which requires clinical trials for further validation, as most of the available studies involved preclinical models with small sample sizes. Clinical trials are also required to determine the sensitivity range of serum HMGB1 levels for diagnostic and/or therapeutic purposes. Based on the current studies, high levels of HMGB1 were related to TLR4 and NMDAR activation, leading to pro-inflammatory cascade that result in degeneration of neurons/dendrites, thus giving rise to cognitive deficits. Furthermore, whether HMGB1 plays a central role in COVID-19 associated cognitive deficits is a relevant topic for future research, particularly since most of the global population was affected by this infection.

Abbreviations

HAND, HIV-associated neurocognitive disorders; HIV, human immunodeficiency virus; NPI, neuropsychologically impaired, NPN, neuropsychologically normal; GDS, global deficit score; nEV, neuronal extracellular vesicle; NDEs, neuron derived exosomes; ANI, asymptomatic neurocognitive impairment; MND, mild neurocognitive disorder; NEC, necrotizing enterocolitis; TLR4, toll-like receptor 4; SAE, sepsis-associated encephalopathy; CLP, cecal ligation and puncture; RAGE, receptor for glycation end products; WT, wild type; H_2, Hydrogen gas; BBB, blood brain barrier; RAGEab, RAGE antibodies; LPS, lipopolysaccharide; siNC, circPTK2 control siRNA; siCirc, circPTK2 siRNA; BDNF, brain derived neurotrophic factor; DNMT1, DNA methyltransferase 1; DNMT3a, DNA methyltransferase 3a; promotor IV, promotor 4; LMWH, low molecular weight heparin; ICV, intracerebroventricular; IL-10, interluekin-10; TGF-beta, transforming growth factor beta.

Author Contributions

TR, AA and MFS have conceptualized and designed the study. FII, WRW and ETMS performed the literature search. FII and TR collected, assembled the data and drafted the manuscript. FII, TR, AA and MFS analyzed the articles. TR, AA and MFS revised the manuscript critically. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Given the role as the Guest Editor, Mohd. Farooq Shaikh had no involvement in the peer-review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Xudong Huang and Lin-Hua Jiang.

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