NEURAL REGENERATION RESEARCH
www.nrronline.org

Review

Interleukin 1β receptor and synaptic dysfunction in recurrent brain infection with Herpes simplex virus type-1

Roberto Piacentini[1, 2, *], Claudio Grassi[1, 2]

https://doi.org/10.4103/NRR.NRR-D-23-01690

Date of submission: October 11, 2023

Date of decision: February 21, 2024

Date of acceptance: March 21, 2024

Date of web publication: April 16, 2024

From the Contents

Abstract

Several experimental evidence suggests a link between brain Herpes simplex virus type-1 infection and the occurrence of Alzheimer's disease. However, the molecular mechanisms underlying this association are not completely understood. Among the molecular mediators of synaptic and cognitive dysfunction occurring after Herpes simplex virus type-1 infection and reactivation in the brain neuroinflammatory cytokines seem to occupy a central role. Here, we specifically reviewed literature reports dealing with the impact of neuroinflammation on synaptic dysfunction observed after recurrent Herpes simplex virus type-1 reactivation in the brain, highlighting the role of interleukins and, in particular, interleukin 1β as a possible target against Herpes simplex virus type-1-induced neuronal dysfunctions.

Key Words: herpes simplex virus type 1; interleukin 1β; microglia; neuroinflammation; synaptic dysfunction

Introduction

There is a growing body of evidence that clearly indicates the potential link between Herpes simplex virus type 1 (HSV-1) infection reaching the brain and the occurrence of neural damage reminiscent of that observed in Alzheimer's disease (AD) patients, especially at early stages of the pathology (see Marcocci et al., 2020; Protto et al., 2022 and references therein). In particular, these molecular and functional alterations take place when HSV-1 reactivation repeatedly occurs within the central nervous system (CNS) after primary infection (De Chiara et al., 2019; Li Puma et al., 2019, 2023). However, the process of HSV-1 reactivation within the brain is not completely understood yet. HSV-1 is known to primarily infect the oral mucosa (e.g., labial epithelial cells) or the eyes, leading to the development of blisters, ulcers, and "cold sores" that are characteristic signs of peripheral HSV-1 infection. After the primary infection, traveling backward along the axons of sensory neurons, the virus reaches the trigeminal ganglia where it becomes latent. Various stressful stimuli can reactivate the virus from latency, and the newly formed virions can be transported back to the site of the primary infection, resulting in the recurrence of typical signs and symptoms of peripheral infection. However, some viral particles, by traveling anterogradely through the ponto-Gasserian tract can reach the brainstem and subsequently spread to the brain via the thalamus, causing a CNS infection (Doll et al., 2019). It is currently unknown whether HSV-1 enters a latent state within the CNS to subsequently reactivate in response to specific stimuli or if virus reactivation within the trigeminal ganglion causes the delivery of new viral particles to the CNS. Nonetheless, following HSV-1 reactivation, viral particles have been detected within the brain (De Chiara et al., 2019, Li Puma et al., 2019). Brain HSV-1 infections may result in highly variable clinical pictures, ranging from encephalitis to completely asymptomatic cases (Matthews et al., 2022). However, the latter may contribute to late-onset neurological disorders, particularly in the elderly. The existence of asymptomatic HSV-1 brain infection makes it challenging to determine the prevalence of CNS HSV-1 infection in the normal population. Postmortem studies conducted several years ago suggested that HSV-1 was present in 65%–75% of the brains of neurologically asymptomatic individuals who were seropositive for HSV-1 (Baringer and Pisani, 1994). Importantly, HSV-1 DNA was found in a higher percentage of

[1]Department of Neuroscience, Università Cattolica del Sacro Cuore, Rome, Italy; [2]Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy
***Correspondence to:** Roberto Piacentini, PhD, roberto.piacentini@unicatt.it.
https://orcid.org/0000-0003-4215-1643 (Roberto Piacentini)

Funding: *This work was supported by Università Cattolica (D1 intramural funds to RP) and by Italian Ministry of University and Research (PRIN 2022ZYLB7B and P2022YW7BP funds to CG).*

How to cite this article: *Piacentini R, Grassi C (2025) Interleukin 1β receptor and synaptic dysfunction in recurrent brain infection with Herpes simplex virus type-1. Neural Regen Res 20(2):416-423.*

brains from AD patients, as demonstrated by Wozniak and Ithzaki, after analyzing a small group of AD patients (6 AD *vs*. 5 controls), revealed HSV-1 DNA in 90% of amyloid plaques (Wozniak and Itzhaki, 2009). HSV-1 reactivation can result in recurrent, often asymptomatic, brain infections leading to AD-like neurological dysfunctions caused by a complex interaction among viral-induced, glial-dependent factors (e.g., neuroinflammation and gliosis) and accumulation of amyloid-β protein and hyperphosphorylated tau at later stages (Harris and Harris, 2015; Itzhaki et al., 2016; Duarte et al., 2019; Marcocci et al., 2020; Laval and Enquist, 2021). However, very recently we reported that in HSV-1-infected, non-encephalitic mice subjected to two virus reactivation synaptic dysfunction was observed also in the absence of frank accumulation of molecular AD hallmarks (Li Puma et al., 2023) and seemed to depend on increased levels of the pro-inflammatory cytokine interleukin 1β (IL-1β).

Here, we specifically reviewed literature reports dealing with the impact of neuroinflammation on synaptic dysfunction observed after virus reactivation in the brain, highlighting the role of interleukins and, in particular, interleukin 1β as a possible target against AD-like, HSV-1-induced neuronal dysfunctions.

Search Strategy

Studied cited in this work were searched on the PubMed database, using the key words "neuroinflammation, synaptic dysfunction, LTP, interleukin, cytokines, viral infections, microglia."

Glial-Mediated Neuroinflammation and Viral Infection

Glial cells, in particular astrocytes and microglia, play a key role in CNS physiological function. Astrocytes have been reported to be essential for the well-being of neurons and their network activity. Indeed, besides providing a metabolic support to neurons by lactate secretion after glutamate uploading (the astrocyte-neuron lactate shuttle hypothesis) (Beard et al., 2022), they also modulate communication among neurons (i.e., synaptic transmission) and regulate the molecular mechanisms underlying memory formation (long-term synaptic plasticity), especially in the hippocampus (de Ceglia et al., 2023; Puliatti et al., 2023). Astrocytes also regulate blood flow at the neuro-vascular unit, as well as the extracellular concentration of neuroactive molecules and ions (Lia et al., 2023; Purushotham and Buskila, 2023) thus influencing neuronal functions. Microglia, on the contrary, are the resident macrophages of the CNS and act as the surveillance system against foreign agents (Dadwal and Heneka, 2024). Moreover, they have the important physiological role of maintaining the number of active synapses on neurons during development and adulthood by exerting spine pruning and refinement (Sakai, 2020; Ball et al., 2022). However, when insults or homeostatic challenges occur to the brain, either from outside (bacteria and viruses) or inside the CNS (neurotoxic proteins such as α-synuclein, amyloid-β or tau), both cell types, astrocytes, and microglia, become "reactive" and respond to the noxious stimuli by changing their morphology and mediating neuroinflammatory processes. This occurs through the release of specific neuroinflammation-related molecules such as cytokines, e.g., tumor necrosis factor α (TNF-α), IL-6, and IL-1β, reactive oxygen species, and excitotoxins, including glutamate (Wang et al., 2015; Rauf et al., 2022), that activate several intracellular signals whose final goal is to counteract the adverse agents. Nevertheless, the role of glial cells in neuroinflammation is quite more puzzled. Indeed, the innate immune responses are considered the first line of defense, being protective against pathogens by promoting immunosuppression and tissue repair (e.g., thrombospondins and interleukins such as IL-4, IL-10, and transforming growth factor), but sustained inflammation or chronic activation of glial cells can lead to irreversible CNS damage exacerbating inflammatory reactions and tissue damage by neuroinflammation-related cytokine-dependent (IL-1, and TNF-α) and NO-dependent intracellular signaling pathways potentially lethal for neurons (Colombo and Farina, 2016; Rauf et al., 2022). This double action of glial cells was associated with two different activation states of these cells, i.e., neurotoxic A1/M1 (astrocytes/microglia, respectively) phenotype and neuroprotective A2/M2 phenotype, even if this rigid classification does not reflect all the phenotypes of microglia and astrocytes present in the CNS (Kwon and Koh, 2020; Garland et al., 2022). An extensive review of the molecular pathways underlying glial-mediated neuroinflammation is beyond the scope of this review, and we refer to literature reports specifically dealing with this subject (see for example Giovannoni and Quintana, 2020; Kwon and Koh, 2020; Ding et al., 2021; Patani et al., 2023; Si et al., 2023).

To work as sentinels for innate immunity in the CNS, glial cells express pattern recognition receptors (PRRs). PRRs include classes of membrane-bound receptors (i.e., Toll-like receptors, TLRs), but also intracellular receptors able to detect pathogen nucleic acids (DNAs and RNAs) in the cytoplasm (Takeuchi and Akira, 2010) as well as C-type lectin receptors, cytoplasmic proteins such as the Retinoic acid-inducible gene-I-like receptors (RLRs), and NOD-like receptors (NLRs), operating for detecting pathogens at the cell surface and in intracellular compartments (Li et al., 2021; Li and Wu, 2021). PRRs can be therefore activated by the so-called "pathogen-associated molecular patterns" (PAMPs) or "danger-associated molecular patterns" (DAMPs), that trigger pro-inflammatory cascades and the formation of the nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3 (NLRP3) inflammasome, a protein complex mediating the release of several cytokines including TNF-α, IL-1β and IL-6 (Kwon and Koh, 2020). Brain invasion by herpesviruses can induce both innate and adaptive immune system activation along with glial cell response (Paludan et al., 2013; Verzosa et al., 2021). For example, in mice, HSV (both 1 and 2) are recognized by TLR2 and TLR9, along with RLRs and DNA receptors to control infection (Gonzalez-Dosal et al., 2011). Innate immune system actors such as type I interferons (IFNs) and natural killer cells, activated after PRR-mediated detection of PAMPs, play key roles in the containment of infection (Paludan et al., 2013). Among herpesviruses, CNS invasion by HSV-1 produces PAMPs

such as viral proteins, DNA, and RNA, as well as DAMPs, that activate the host's PRRs and initiate innate immune responses (Mielcarska et al., 2021; Zhao et al., 2021). In particular, HSV-1, which is a DNA virus, can be sensed by several intracellular DNA sensing systems such as DNA-dependent activator of IFN-regulatory factors, absent in melanoma 2 (AIM2), RNA polymerase III, leucine-rich repeat Flightless-interacting protein 1 and IFNγ-inducible protein 16 (Paludan et al., 2013). All TLRs and intracellular nucleic acid sensors, but AIM2, induce intracellular signaling pathways leading to the expression of genes with pro-inflammatory and microbicidal activities, including cytokines and type I IFNs (α and β subtypes). On the contrary, AIM2 leads to inflammasome activation followed by the cleavage of the pro-IL-1β and pro-IL-18 with the subsequent release of the mature and bioactive forms of the cytokines critical for protection from HSV-1 (Karaba et al., 2020). HSV-1 brain infection also induces marked astrogliosis and increased GFAP expression (De Chiara et al., 2019), which can contribute to the increased level of astrocyte-derived cytokines. We also demonstrated that, in a co-culture of murine hippocampal neurons and astrocytes, HSV-1 infects astrocytes earlier than neurons (Li Puma et al., 2021). Indeed, to infect neurons, the virus requires ATP released from astrocytes after HSV-1 binds to their plasma membrane, in order to trigger the molecular cascade leading to viral entry into neurons. This conclusion was supported by data showing that: (i) HSV-1 differently binds neurons and glial cells (Vahlne et al., 1978 and 1980); (ii) cultured astrocytes express higher levels of Heparan Sulfate Proteoglycans than neurons (Li Puma et al., 2021). These proteoglycans are extracellular receptors acting as hooks for the attachment of viral particles to the cell membrane (Shukla and Spear, 2001), thus making cells more susceptible to HSV-1 infection (Potokar et al., 2023). Moreover, it was also demonstrated that murine astrocytes express TRL3 receptors that, when activated by HSV-1, induce an upregulation of TNF-α and IL-6 via the nuclear factor kappa-light-chain-enhancer of activated B cells (also known as nuclear factor kappa B) modulation (Liu et al., 2013). Collectively, these data indicate that astrocytes are the first CNS cells involved in brain invasion by HSV-1, promptly and actively participating in its defensive response as well as the following neuroinflammation.

Cytokine-Dependent Synaptic Modulation

In a recent work, Zipp et al. (2023) elegantly reviewed data demonstrating that immune system activation-derived cytokines (such as members of interleukins family, TNF-α, interferons, and chemokines), that are classically considered the main responsible of peripheral inflammatory processes after presentation of specific stimuli activating either PAMPs or DAMPs, also act as key players in neuronal network function. Indeed, they can modulate synapse development, synaptic transmission, and plasticity, and finally, memory formation and cognition as CNS cells (i.e., neurons, astrocytes, and microglia) express cytokine receptors on their cell membrane (Mousa and Bakhiet, 2013).

Among cytokines demonstrated to modulate synaptic functions, for example synaptic transmission, synaptic structure (e.g., dendritic spine density), or synaptic plasticity (e.g., long-term potentiation [LTP]; and long-term depression), there are TNF-α, and interleukins such as IL-1β and IL-6 (Khairova et al., 2009; Levin and Godukhin, 2017; Bourgognon and Cavanagh, 2020; Zipp et al., 2023). The former was reported to regulate α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid glutamate receptors (AMPARs), and to enhance the transcription of voltage-gated sodium channels Nav1.3 and Nav1.8 thus increasing central and peripheral neuronal excitability (He et al., 2010; Zipp et al., 2023). At the same time, it has been reported that TNF-α activates TNF receptor 1 in astrocytes, which then increases neuronal presynaptic activity signal via glutamate release and N-methyl-D-aspartate (NMDA) receptor activation (Prieto and Cotman, 2017). Moreover, TNF-α-targeted modulation of astrocyte-neuron crosstalk was reported to contribute to memory impairment via astrocyte signaling in experimental models of neurodegeneration (Habbas et al., 2015; Prieto et al., 2017). On the contrary, contrasting results have been obtained about the effects of interleukin receptor activation and, in particular, those of IL-1β on neuronal excitability (Nemeth and Quan, 2021). In fact, after being released, inflammasoma-derived IL-1β binds its proper receptor IL-1R(1), eliciting the binding of the co-receptor IL-1R Accessory Protein to the previous complex and activating downstream intracellular signaling (Zipp et al., 2023). IL-1R1 is expressed by excitatory glutamatergic neurons at the hippocampal level (whose network is associated with memory formation), where it works together with the glutamate NMDA receptor, subunit NR2B. So, IL-1R1/NR2B association after IL-1β binding triggers NMDA-dependent Ca^{2+} flux through the NMDA receptors thus increasing glutamatergic synaptic transmission. While some studies indicate that the IL-1R binding enhances neuronal excitability, other ones suggest opposite effects mainly mediated by the inhibition of voltage-gated ion (Na^{+} and Ca^{2+}) channels (Zipp et al., 2023). Probably, whether IL-1β and IL-1R activation enhance or dampen neuronal glutamate-mediated excitability depends on its concentration/activation (Nemeth and Quan, 2021). Other than synaptic transmission/excitability, neuroinflammatory molecules released by glial cells (microglia and astrocytes) have been reported to modulate also synaptic structure (i.e., dendritic spine morphology and density). Indeed, it is known the physiological action of microglia in maintaining synaptic spine number by a complex pruning activity. The fractalkine receptor CX3CR1, a G-protein-coupled chemokine receptor highly expressed in microglia, is involved in synapse shaping at the hippocampal level (Paolicelli et al., 2011; Zipp et al., 2023). Activation of microglial CX3CR1 by fractalkine, however, also induces the release of adenosine which, by activating A2A purinergic receptors, determines the release of D-serine which potentiates NMDA-mediated excitatory postsynaptic potentials on neurons. Also, the innate immune receptor "triggering receptor expressed on myeloid cells 2" (TREM2), highly expressed on myeloid cells including CNS microglia, is involved in synapse refinement. Indeed, the lack of TREM2 resulted in impaired synapse elimination from microglia, enhanced excitatory neurotransmission, and reduced long-range neuronal network (Filipello et al., 2018). Interestingly, TREM2 regulates the secretion of pro-inflammatory factors as its absence significantly increases

the levels of pro-inflammatory cytokines and aggravates cognitive defects (Wang et al., 2020). In turn, the above-mentioned anti-inflammatory cytokines IL-4 and IL-10 can upregulate TREM2 expression (Yi et al., 2020). On the contrary, TREM2 expression was reduced under conditions of lipopolysaccharide pro-inflammatory stimulation (Liu et al., 2020). Finally, local hippocampal administration of the proinflammatory IL-1β induces a reduction in the total density of CA1 hippocampal dendritic spines, particularly the mature ones, in mice (Herrera et al., 2019). Consistently with these results, Tong and collaborators reported that IL-1β disrupts brain-derived neurotrophic factor signaling cascades thus impairing the formation of F-actin in dendritic spines (Tong et al., 2012). Different results were instead observed with IL-33, an IL-1-like cytokine secreted by astrocytes that exerts its biological effects via the IL-1 receptor ST2 by activating nuclear factor kappa B (Schmitz et al., 2005). Indeed, this cytokine enhances excitatory synapse formation in CA1 pyramidal neurons in mice (Wang et al., 2021).

Finally, cytokines, and in particular IL-1β, also modulate synaptic plasticity underlying memory formation (i.e., LTP and long-term depression), with different effects depending on their concentration. Indeed, in murine hippocampus elevated levels of IL-1β (obtained after NLRP3 inflammasome-mediated cleavage of its precursor after caspase-1 activation) have been reported to impair LTP and memory in mice, whereas lower levels seem to improve them (Ross et al., 2003; Goshen et al., 2007; Prieto and Cotman, 2017). These effects, however, seem to depend also on the age of mice, being greater in young than in old mice (Takemiya et al., 2017). Even if other neuroinflammatory-related molecules and cytokines (TNF-α, IL-6, IL-18, IFNγ, etc.) have been proven to be involved in LTP and memory impairment (Rizzo et al., 2018), IL-1β seems to be the final common effector (Prieto and Cotman, 2017). Indeed, mice lacking IL-1R show attenuated synaptic deficit upon neuroinflammation (Avital et al., 2003), and antagonists of IL-1R block the suppression of LTP and memory in similar experimental conditions (Schmid et al., 2009). Moreover, enhanced levels of IL-1β are associated with increased expression of the epigenetic repressor MeCP2 known to negatively impact synaptic genes and determine alteration of synaptic function underlying memory (Pozzi et al., 2018). In fact, pharmacological inhibition of IL-1R activity normalizes both MeCP2 expression and IL-1-dependent cognitive deficits (Tomasoni et al., 2017; Li Puma et al., 2023).

Herpes Simplex Virus Type 1 Infection, Interleukin 1β and Synaptic Dysfunction

We recently demonstrated that HSV-1 infection and recurrent reactivations into murine CNS cause neuroinflammation characterized by important gliosis and overproduction of interleukins, such as IL-6 and IL-1β, followed by deficits in brain plasticity and memory (De Chiara et al., 2019; Li Puma et al., 2019, 2023). In particular, in the hippocampi of HSV-1-infected and twice reactivated mice, we observed an IL-1β production that was sensibly greater than that found in mock-infected mice. This increase was, however, transient and IL-1β levels returned to normal values after 1 week from stress-inducing viral reactivation (Li Puma et al., 2023). Under this experimental paradigm, the NR2B subunit of the NMDA receptor was found strongly downregulated in infected mice, thus suggesting a reduced neuronal activity. In agreement with this result, we also found impaired LTP at the hippocampal CA3-CA1 synapse, along with decreased expression of some key synaptic plasticity-related genes and other synaptic proteins involved in synaptic transmission such as synapsin-1 and synaptophysin (Li Puma et al., 2023). All these effects were paralleled by decreased neurogenesis (Li Puma et al., 2019) and cognitive alterations, given that HSV-1-infected mice also showed loss of hippocampal-dependent memory, in terms of recognition, spatial working, and associative memory, after two thermal stress-inducing HSV-1 reactivation to the brain (Li Puma et al., 2023). Even if the mouse model of HSV-1 infection and recurrent reactivation can be considered an experimental model of sporadic AD, this phenotype occurs only after several cycles of virus reactivation, e.g., ≥ 6 (De Chiara et al., 2019), and just after two thermal stress accumulation of Aβ and pTau was limited and unlikely responsible for the synaptic deficits we observed. On the contrary, this picture is compatible with the altered cell management of cytokines, and IL-1β in particular, we observed. Indeed, it is known that IL-1 drives the production of substrates necessary for the formation of neuropathological hallmarks of AD (Griffin et al., 2006); and that increased levels of IL-1β affect hippocampal neurogenesis (Ryan et al., 2013) and synaptic function as mentioned above. Moreover, the dependence of the HSV-1-dependent, synaptic-related deficits on IL-1 overproduction was clearly demonstrated by mouse treatment with the pharmacological IL-1R antagonist Anakinra, a hydrophilic non-glycosylated protein of 153 amino acids able to cross the blood-brain barrier, already used to treat inflammatory diseases (Cvetkovic and Keating, 2002). We indeed found that intraperitoneal administration of this drug across reactivations (i.e., one day before, during, and one day after thermal stresses causing brain HSV-1 reactivation), i.e. when the levels of IL-1 are transiently elevated, almost completely prevented all the functional, molecular and structural detrimental synaptic deficits observed in this mouse model of virus-induced neuroinflammation (Li Puma et al., 2023).

Several other studies report the efficacy of Anakinra in counteracting inflammatory-dependent brain alterations in mice. For example, Anakinra has been shown to attenuate the frequency and duration of seizures observed in anti-NMDA encephalitis and to revert memory deficit, assessed by novel object recognition paradigm, in this mouse model of neuroinflammation (Taraschenko et al., 2021). Anakinra was initially used as a drug for the treatment of Cryopyrin-Associated Periodic Syndromes that are characterized by increased concentrations of IL-1β. Increased serum concentration of IL-1β (similar to that observed in Cryopyrin-Associated Periodic Syndromes) has also been demonstrated in mice harboring mutations in the *NLRP3* gene (Brydges et al., 2009). Even if, more in general, it is widely recognized that NLRP3 inflammasome mediates IL-1β production in several models on inflammation (Brydges et al., 2009; Negash et al., 2013; Cullen et al., 2015; Kang et al., 2017).

This is particularly important for HSV-1 given that it has been demonstrated that this virus can activate NLRP3-mediated IL-1β-dependent pathway (Karaba et al., 2020; Johnson et al., 2013; Hu et al., 2022) thus allowing us to hypothesize that targeting NLRP3 inflammasome can be an efficacious therapeutic strategy for fighting viral infection (Deng et al., 2023). Moreover, by looking at the link between HSV-1-induced neuroinflammation and Alzheimer's disease, several studies demonstrated that NLRP3 inflammasome is a key molecular player in the AD neuroinflammatory pathway, causing caspase-1 activation and the secretion of IL-1β (Feng et al., 2020; Liang et al., 2022). In our case, the blockade of IL-1 receptors prevented molecular, structural, and functional alterations of the synaptic function observed in the HSV-1-infected mice independently of the regulation of viral replication. In fact, Anakinra did not significantly affect HSV-1 titer in the supernatants of infected cultured murine neurons (Li Puma et al., 2023), thus indicating that IL-1β is a major determinant of HSV-1-induced synaptic dysfunction (**Figure 1**).

However, many other viruses initiated IL-1β production through NLRP3 inflammasome (Zheng et al., 2023). Indeed, IL-1β acts downstream of NLRP3 to induce the expression of proinflammatory genes and by recruitment of immune cells against virus infection and the nuclear factor kappa B-dependent inflammation. For these reasons, antagonizing IL-1 receptors might ameliorate the clinical outcomes of several viral infections (Franzetti et al., 2021; Schworer et al., 2023) without exerting any direct antiviral action. Among the virus infections particularly susceptible to IL-1β-mediated signaling are those caused by influenza viruses (e.g., influenza A virus). Indeed, infection by the influenza A virus both *in vitro* (on pulmonary-derived cell lines [Kim et al., 2015]) and *in vivo* (at the pulmonary level [Bawazeer et al., 2021]), induces increased production of proinflammatory cytokines known as "cytokine storm" (also observed after organism invasion by other respiratory viruses such as SARS-CoV-2 [Isacson, 2020]). Kim et al. (2015) and Bawazeer et al. (2021) demonstrated that inhibition of IL-1β by specific blockers or antibodies determines the reduction of the inflammation induced by influenza A infection, as well as the consequences of the infection, thus indicating a key role for this cytokine in the viral illness. Bucher et al. (2017) found that after lung infection with influenza virus H1N1, both IL-1α and IL-1β levels were increased. But, in slight contrast with the previous results, antibody treatment with anti-IL-1β alone was not able to revert cell infiltration (e.g., neutrophils and macrophages). On the contrary, a slightly stronger effect was observed with the blockade of IL-1R1 using a specific antibody, but concomitant inhibition of both IL-1α and IL-1β resulted in a larger effect. Noteworthy, other than pulmonary diseases, infection by influenza viruses induces had been reported to induce cognitive deficit and synaptic remodeling associated with increased pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IFN-α) (Jurgens et al., 2012; Hosseini et al., 2018). These data suggest that approaches aimed at regulating glial cell activity may represent a future strategy to prevent deleterious virus-induced long-term effects on the brain.

Neuroinflammation in Neonatal Herpes Simplex Virus Type 1 Infections

It is known that HSV-1 can determine infection also at genital levels. Virus reactivation during pregnancy or peripartum exposes fetuses or neonates to infection (James et al., 2014; James and Kimberlin, 2015). Given the great ability of these viruses to infect immature cells, especially at CNS level (Li Puma et al., 2019), this event can cause significant diseases

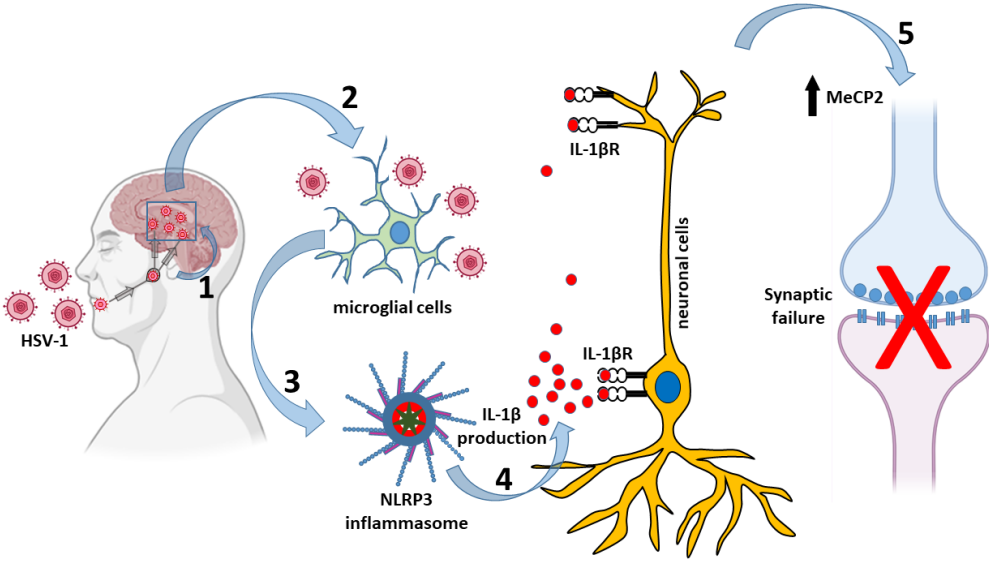

Figure 1 | **After primary infection of mouth and labia, HSV-1 goes in latency in the trigeminal ganglia.**
Following some stressful stimuli virus can be reactivated and vial particles may spread to the brain (1). Here it is recognized by microglial cells (2) thus determining activation of the NLRP3 inflammasome (3) and secretion of the cytokine IL-1β (4). Increased levels of IL-1β activate the epigenetic repressor MeCP2 (5) known to negatively regulate synaptic genes and determine synaptic failure. Created with Microsoft PowerPoint 365. HSV-1: Herpes simplex virus type 1; IL-1β: interleukin 1β; IL-1βR: interleukin 1β receptor; MeCP2: methyl CpG binding protein 2; NLRP3: nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3.

leading to neurodevelopmental disorders and even death in infants. Neonates develop three main types of infection: localized skin, eyes, or mouth infection; CNS infection; and disseminated infection, which involves several organs including the brain (Kimberlin et al., 2004). To date, therapy for neonatal HSV-1 infection is based on antiviral (e.g., acyclovir) administration (Samies and James, 2020; Melvin et al., 2022) even if, despite rapid diagnosis and improved management, high morbidity and mortality are still present among infected infants. Based on the previously discussed results, it is not yet clearly established to what extent these effects depend on neuroinflammation secondary to the infection. It was first found that neonates with disseminated HSV infection exhibited higher serum levels of IL-6 and sTNF-R1 (the natural homeostatic regulator of the action of TNF-α) with respect to healthy neonates, and these levels correlated with HSV load (Kawada et al., 2004). Consistently with these results, a study carried out in 2020 indicates that HSV-1 infection of cerebral organoids induces microglial and astrocytic activation (increases in IBA-1 and GFAP expression levels, respectively) that is accompanied by increased mRNA expressions of pro-inflammatory (TNF-α and IL-6) and anti-inflammatory (IL-10, and IL-4) cytokines (Qiao et al., 2020). In addition, a more recent study conducted on human fetal organotypic brain slice cultures (an experimental model resembling developing brain tissue) infected with HSV-1 and HSV-2 demonstrated the induction of an inflammatory phenotype in astrocytes along with a significant increase of *IFNB1*, *IL6*, and *TNFA* mRNA expression (Rashidi et al., 2024).

Conclusions

In conclusion, here we critically reviewed some literature reports showing the role of neuroinflammatory cytokines, especially IL-1β, in synaptic dysfunction, at both structural and functional levels, in terms of altered synaptic transmission, synaptic plasticity, and memory formation in the hippocampus. By highlighting the increased production of IL-1β, likely mediated by PAMPs and NLRP3 inflammasome, in our experimental mouse model of sporadic AD induced by HSV-1 infection and recurrent reactivation, our research has demonstrated the remarkable ability of Anakinra to revert the synaptic dysfunction observed in this model, especially when AD hallmarks are not yet accumulated. These findings support the hypothesis that counteracting the IL-1 receptor might be a therapeutic strategy for fighting the onset of AD-like synaptic dysfunction, at least when it is triggered by microbial agents. By bridging the gap between neuroinflammation, IL-1β signaling, and synaptic plasticity, we would propose the development of IL-1 receptor-targeted therapies for ameliorating synaptic dysfunctions and/or potentially preventing or delaying the onset of AD-related cognitive impairments.

In general, these findings are important for developing a strategy aimed at treating downstream effects of HSV infection. Indeed, although the inflammatory response is essential for the host defense mechanisms, its modulation or inhibition could represent an effective therapeutic intervention. Thus, the combination of antiviral and anti-inflammatory therapies may improve the health of individuals infected with HSV-1.

Author contributions: *Manuscript was written and revised by RP and CG. Both authors approved the final version of the manuscript.*
Conflicts of interest: *The authors declare no conflicts of interest.*
Data availability statement: *Not applicable.*

References

Avital A, Goshen I, Kamsler A, Segal M, Iverfeldt K, Richter-Levin G, Yirmiya R (2003) Impaired interleukin-1 signaling is associated with deficits in hippocampal memory processes and neural plasticity. Hippocampus 13:826-834.

Ball JB, Green-Fulgham SM, Watkins LR (2022) Mechanisms of microglia-mediated synapse turnover and synaptogenesis. Prog Neurobiol 218:102336.

Baringer JR, Pisani P (1994) Herpes simplex virus genomes in human nervous system tissue analyzed by polymerase chain reaction. Ann Neurol 36:823-829.

Bawazeer AO, Rosli S, Harpur CM, Docherty CA, Mansell A, Tate MD (2021) Interleukin-1β exacerbates disease and is a potential therapeutic target to reduce pulmonary inflammation during severe influenza A virus infection. Immunol Cell Biol 99:737-748.

Beard E, Lengacher S, Dias S, Magistretti PJ, Finsterwald C (2022) Astrocytes as key regulators of brain energy metabolism: new therapeutic perspectives. Front Physiol 12:825816.

Bourgognon JM, Cavanagh J (2020) The role of cytokines in modulating learning and memory and brain plasticity. Brain Neurosci Adv 4:2398212820979802.

Brydges SD, Mueller JL, McGeough MD, Pena CA, Misaghi A, Gandhi C, Putnam CD, Boyle DL, Firestein GS, Horner AA, Soroosh P, Watford WT, O'Shea JJ, Kastner DL, Hoffman HM (2009) Inflammasome-mediated disease animal models reveal roles for innate but not adaptive immunity. Immunity 30:875-887.

Bucher H, Mang S, Keck M, Przibilla M, Lamb DJ, Schiele F, Wittenbrink M, Fuchs K, Jung B, Erb KJ, Peter D (2017) Neutralization of both IL-1α/IL-1β plays a major role in suppressing combined cigarette smoke/virus-induced pulmonary inflammation in mice. Pulm Pharmacol Ther 44:96-105.

Colombo E, Farina C (2016) Astrocytes: key regulators of neuroinflammation. Trends Immunol 37:608-620.

Cullen SP, Kearney CJ, Clancy DM, Martin SJ (2015) Diverse activators of the NLRP3 inflammasome promote IL-1β secretion by triggering necrosis. Cell Rep 11:1535-1548.

Cvetkovic RS, Keating G (2002) Anakinra. BioDrugs 16:303-311.

Dadwal S, Heneka MT (2024) Microglia heterogeneity in health and disease. FEBS Open Bio 14:217-229.

de Ceglia R, Ledonne A, Litvin DG, Lind BL, Carriero G, Latagliata EC, Bindocci E, Di Castro MA, Savtchouk I, Vitali I, Ranjak A, Congiu M, Canonica T, Wisden W, Harris K, Mameli M, Mercuri N, Telley L, Volterra A (2023) Specialized astrocytes mediate glutamatergic gliotransmission in the CNS. Nature 622:120-129.

De Chiara G, Piacentini R, Fabiani M, Mastrodonato A, Marcocci ME, Limongi D, Napoletani G, Protto V, Coluccio P, Celestino I, Li Puma DD, Grassi C, Palamara AT (2019) Recurrent herpes simplex virus-1 infection induces hallmarks of neurodegeneration and cognitive deficits in mice. PLoS Pathog 15:e1007617.

Deng CH, Li TQ, Zhang W, Zhao Q, Wang Y (2023) Targeting inflammasome activation in viral infection: a therapeutic solution? Viruses 15:1451.

Ding ZB, Song LJ, Wang Q, Kumar G, Yan YQ, Ma CG (2021) Astrocytes: a double-edged sword in neurodegenerative diseases. Neural Regen Res 16:1702-1710.

Doll JR, Thompson RL, Sawtell NM (2019) Infectious herpes simplex virus in the brain stem is correlated with reactivation in the trigeminal ganglia. J Virol 93:e02209-18.

Duarte LF, Farías MA, Álvarez DM, Bueno SM, Riedel CA, González PA (2019) Herpes simplex virus type 1 infection of the central nervous system: insights into proposed interrelationships with neurodegenerative disorders. Front Cell Neurosci 13:46.

Feng YS, Tan ZX, Wu LY, Dong F, Zhang F (2020) The involvement of NLRP3 inflammasome in the treatment of Alzheimer's disease. Ageing Res Rev 64:101192.

Filipello F, et al. (2020) The microglial innate immune receptor TREM2 is required for synapse elimination and normal brain connectivity. Immunity 48:979-991.

Franzetti M, et al. (2021) IL-1 receptor antagonist anakinra in the treatment of COVID-19 acute respiratory distress syndrome: a retrospective, observational study. J Immunol 206:1569-1575.

Garland EF, Hartnell IJ, Boche D (2022) Microglia and astrocyte function and communication: what do we know in humans? Front Neurosci 16:824888.

Giovannoni F, Quintana FJ (2020) The role of astrocytes in CNS inflammation. Trends Immunol 41:805-819.

Gonzalez-Dosal R, Horan KA, Rahbek SH, Ichijo H, Chen ZJ, Mieyal JJ, Hartmann R, Paludan SR (2011) HSV infection induces production of ROS, which potentiate signaling from pattern recognition receptors: role for S-glutathionylation of TRAF3 and 6. PLoS Pathogens 7:e1002250.

Goshen I, Kreisel T, Ounallah-Saad H, Renbaum P, Zalzstein Y, Ben-Hur T, Levy-Lahad E, Yirmiya R (2007) A dual role for interleukin-1 in hippocampal-dependent memory processes. Psychoneuroendocrinology 32:1106-1115.

Griffin WS, Liu L, Li Y, Mrak RE, Barger SW (2006) Interleukin-1 mediates Alzheimer and Lewy body pathologies. J Neuroinflammation 3:5.

Habbas S, Santello M, Becker D, Stubbe H, Zappia G, Liaudet N, Klaus FR, Kollias G, Fontana A, Pryce CR, Suter T, Volterra A (2015) Neuroinflammatory TNFα impairs memory via astrocyte signaling. Cell 163:1730-1741.

Harris SA, Harris EA (2015) Herpes simplex virus type 1 and other pathogens are key causative factors in sporadic Alzheimer's disease. J Alzheimers Dis 48:319-353.

He XH, Zang Y, Chen X, Pang RP, Xu JT, Zhou X, Wei XH, Li YY, Xin WJ, Qin ZH, Liu XG (2010) TNF-α contributes to up-regulation of Nav1.3 and Nav1.8 in DRG neurons following motor fiber injury. Pain 151:266-279.

Herrera G, Calfa G, Schiöth HB, Lasaga M, Scimonelli T (2019) Memory consolidation impairment induced by interleukin-1β is associated with changes in hippocampal structural plasticity. Behav Brain Res 370:111969.

Hosseini S, Wilk E, Michaelsen-Preusse K, Gerhauser I, Baumgärtner W, Geffers R, Schughart K, Korte M (2018) Long-term neuroinflammation induced by influenza A virus infection and the impact on hippocampal neuron morphology and function. J Neurosci. 38:3060-3080.

Hu X, Zeng Q, Xiao J, Qin S, Wang Y, Shan T, Hu D, Zhu Y, Liu K, Zheng K, Wang Y, Ren Z (2022) Herpes simplex virus 1 induces microglia gasdermin d-dependent pyroptosis through activating the NLR family pyrin domain containing 3 inflammasome. Front Microbiol 13:838808.

Itzhaki RF, et al. (2016) Microbes and Alzheimer's disease. J Alzheimers Dis 51:979-984.

Isacson O (2020) The consequences of coronavirus-induced cytokine storm are associated with neurological diseases, which may be preventable. Front Neurol 11:745.

James SH, Sheffield JS, Kimberlin DW (2014) Mother-to-child transmission of herpes simplex virus. J Pediatric Infect Dis Soc 3:S19-23.

James SH, Kimberlin DW (2015) Neonatal herpes simplex virus infection. Infect Dis Clin North Am 29:391-400.

Johnson KE, Chikoti L, Chandran B (2013) Herpes simplex virus 1 infection induces activation and subsequent inhibition of the IFI16 and NLRP3 inflammasomes. J Virol 87:5005-5018.

Jurgens HA, Amancherla K, Johnson RW (2012) Influenza infection induces neuroinflammation, alters hippocampal neuron morphology, and impairs cognition in adult mice. J Neurosci 32:3958-3968.

Kang MJ, Jo SG, Kim DJ, Park JH (2017) NLRP3 inflammasome mediates interleukin-1β production in immune cells in response to Acinetobacter baumannii and contributes to pulmonary inflammation in mice. Immunology 150:495-505.

Karaba AH, Figueroa A, Massaccesi G, Botto S, DeFilippis VR, Cox AL (2020) Herpes simplex virus type 1 inflammasome activation in proinflammatory human macrophages is dependent on NLRP3, ASC, and caspase-1. PLoS One 15:e0229570.

Kawada J, Kimura H, Ito Y, Ando Y, Tanaka-Kitajima N, Hayakawa M, Nunoi H, Endo F, Morishima T (2004) Evaluation of systemic inflammatory responses in neonates with herpes simplex virus infection. J Infect Dis 190:494-498.

Khairova RA, Machado-Vieira R, Du J, Manji HK (2009) A potential role for pro-inflammatory cytokines in regulating synaptic plasticity in major depressive disorder. Int J Neuropsychopharmacol 12:561-578.

Kim KS, Jung H, Shin IK, Choi BR, Kim DH (2015) Induction of interleukin-1 beta (IL-1β) is a critical component of lung inflammation during influenza A (H1N1) virus infection. J Med Virol 87:1104-1112.

Kimberlin DW (2004) Neonatal herpes simplex infection. Clin Microbiol Rev 17:1-13.

Kwon HS, Koh SH (2020) Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. Transl Neurodegener 9:42.

Laval K, Enquist LW (2021) The potential role of herpes simplex virus type 1 and neuroinflammation in the pathogenesis of Alzheimer's disease. Front Neurol 12:658695.

Levin SG, Godukhin OV (2017) Modulating effect of cytokines on mechanisms of synaptic plasticity in the brain. Biochemistry (Mosc) 82:264-274.

Li D, Wu M (2021) Pattern recognition receptors in health and diseases. Signal Transduct Target Ther 6:291.

Li L, Acioglu C, Heary RF, Elkabes S (2021) Role of astroglial toll-like receptors (TLRs) in central nervous system infections, injury and neurodegenerative diseases. Brain Behav Immun 91:740-755.

Li Puma DD, Piacentini R, Leone L, Gironi K, Marcocci ME, De Chiara G, Palamara AT, Grassi C (2019) Herpes simplex virus type-1 infection impairs adult hippocampal neurogenesis via amyloid-β protein accumulation. Stem Cells 37:1467-1480.

Li Puma DD, Marcocci ME, Lazzarino G, De Chiara G, Tavazzi B, Palamara AT, Piacentini R, Grassi C (2021) Ca2+-dependent release of ATP from astrocytes affects Herpes simplex virus type 1 infection of neurons. Glia 69:201-215.

Li Puma DD, Colussi C, Bandiera B, Puliatti G, Rinaudo M, Cocco S, Paciello F, Re A, Ripoli C, De Chiara G, Bertozzi A, Palamara AT, Piacentini R, Grassi C (2023) Interleukin 1β triggers synaptic and memory deficits in Herpes simplex virus type-1-infected mice by downregulating the expression of synaptic plasticity-related genes via the epigenetic MeCP2/HDAC4 complex. Cell Mol Life Sci 80:172.

Lia A, Di Spiezio A, Speggiorin M, Zonta M (2023) Two decades of astrocytes in neurovascular coupling. Front Netw Physiol 3:1162757.

Liang T, Zhang Y, Wu S, Chen Q, Wang L (2022) The role of NLRP3 inflammasome in Alzheimer's disease and potential therapeutic targets. Front Pharmacol 13:845185.

Liu W, Taso O, Wang R, Bayram S, Graham AC, Garcia-Reitboeck P, Mallach A, Andrews WD, Piers TM, Botia JA, Pocock JM, Cummings DM, Hardy J, Edwards FA, Salih DA (2020) Trem2 promotes anti-inflammatory responses in microglia and is suppressed under pro-inflammatory conditions. Hum Mol Genet 29:3224-3248.

Liu Z, Guan Y, Sun X, Shi L, Liang R, Lv X, Xin W (2013) HSV-1 activates NF-kappaB in mouse astrocytes and increases TNF-alpha and IL-6 expression via Toll-like receptor 3. Neurol Res 35:755-762.

Marcocci ME, Napoletani G, Protto V, Kolesova O, Piacentini R, Li Puma DD, Lomonte P, Grassi C, Palamara AT, De Chiara G (2020) Herpes simplex virus-1 in the brain: the dark side of a sneaky infection. Trends Microbiol 28:808-820.

Matthews E, Beckham JD, Piquet AL, Tyler KL, Chauhan L, Pastula DM (2022) Herpesvirus-associated encephalitis: an update. Curr Trop Med Rep 9:92-100.

Melvin AJ, Mohan KM, Vora SB, Selke S, Sullivan E, Wald A (2002) Neonatal herpes simplex virus infection: epidemiology and outcomes in the modern era. J Pediatric Infect Dis Soc 11:94-101.

Mielcarska MB, Skowrońska K, Wyżewski Z, Toka FN (2021). Disrupting neurons and glial cells oneness in the brain-the possible causal role of herpes simplex virus type 1 (HSV-1) in Alzheimer's disease. Int J Mol Sci 23:242.

Mousa A, Bakhiet M (2013) Role of cytokine signaling during nervous system development. Int J Mol Sci 14:13931-13957.

Negash AA, Ramos HJ, Crochet N, Lau DT, Doehle B, Papic N, Delker DA, Jo J, Bertoletti A, Hagedorn CH, Gale M Jr. (2013) IL-1β production through the NLRP3 inflammasome by hepatic macrophages links hepatitis C virus infection with liver inflammation and disease. PLoS Pathog 9:e1003330.

Nemeth DP, Quan N (2021) Modulation of neural networks by interleukin-1. Brain Plast 7:17-32.

Paludan SR, Bowie AG, Horan KA, Fitzgerald KA (2011) Recognition of herpesviruses by the innate immune system. Nat Rev Immunol 11:143-54.

Paolicelli RC, Bolasco G, Pagani F, Maggi L, Scianni M, Panzanelli P, Giustetto M, Ferreira TA, Guiducci E, Dumas L, Ragozzino D, Gross CT (2011) Synaptic pruning by microglia is necessary for normal brain development. Science 333:1456-1458.

Patani R, Hardingham GE, Liddelow SA (2023) Functional roles of reactive astrocytes in neuroinflammation and neurodegeneration. Nat Rev Neurol 19:395-409.

Potokar M, Zorec R, Jorgačevski J (2023) Astrocytes are a key target for neurotropic viral infection. Cells 12:2307.

Pozzi D, Menna E, Canzi A, Desiato G, Mantovani C, Matteoli M (2018) The communication between the immune and nervous systems: the role of IL-1β in synaptopathies. Front Mol Neurosci 11:111.

Prieto GA, Cotman CW (2017) Cytokines and cytokine networks target neurons to modulate long-term potentiation. Cytokine Growth Factor Rev 34:27-33.

Protto V, Marcocci ME, Miteva MT, Piacentini R, Li Puma DD, Grassi C, Palamara AT, De Chiara G (2022) Role of HSV-1 in Alzheimer's disease pathogenesis: a challenge for novel preventive/therapeutic strategies. Curr Opin Pharmacol 63:102200.

Puliatti G, Li Puma DD, Aceto G, Lazzarino G, Acquarone E, Mangione R, D'Adamio L, Ripoli C, Arancio O, Piacentini R, Grassi C (2023) Intracellular accumulation of tau oligomers in astrocytes and their synaptotoxic action rely on amyloid precursor protein intracellular domain-dependent expression of glypican-4. Prog Neurobiol 227:102482.

Purushotham SS, Buskila Y (2023) Astrocytic modulation of neuronal signalling. Front Netw Physiol 3:1205544.

Qiao H, Guo M, Shang J, Zhao W, Wang Z, Liu N, Li B, Zhou Y, Wu Y, Chen P (2020) Herpes simplex virus type 1 infection leads to neurodevelopmental disorder associated neuropathological changes. PLoS Pathog 16: e1008899.

Rashidi AS, Tran DN, Peelen CR, van Gent M, Ouwendijk WJD, Verjans GMGM (2024) Herpes simplex virus infection induces necroptosis of neurons and astrocytes in human fetal organotypic brain slice cultures. J Neuroinflammation 21:38.

Rauf A, Badoni H, Abu-Izneid T, Olatunde A, Rahman MM, Painuli S, Semwal P, Wilairatana P, Mubarak MS (2022) Neuroinflammatory markers: key indicators in the pathology of neurodegenerative diseases. Molecules 27:3194.

Rizzo FR, Musella A, De Vito F, Fresegna D, Bullitta S, Vanni V, Guadalupi L, Stampanoni Bassi M, Buttari F, Mandolesi G, Centonze D, Gentile A (2018) Tumor necrosis factor and interleukin-1β modulate synaptic plasticity during neuroinflammation. Neural Plast 2018:8430123.

Ross FM, Allan SM, Rothwell NJ, Verkhratsky A (2003) A dual role for interleukin-1 in LTP in mouse hippocampal slices. J Neuroimmunol 144:61-67.

Ryan SM, O'Keeffe GW, O'Connor C, Keeshan K, Nolan YM (2013) Negative regulation of TLX by IL-1β correlates with an inhibition of adult hippocampal neural precursor cell proliferation. Brain Behav Immun 33:7-13.

Sakai J (2020) Core concept: how synaptic pruning shapes neural wiring during development and, possibly, in disease. Proc Natl Acad Sci U S A 117:16096-16099.

Samies NL, James SH (2020) Prevention and treatment of neonatal herpes simplex virus infection. Antiviral Res 176:104721.

Schmid AW, Lynch MA, Herron CE (2009) The effects of IL-1 receptor antagonist on beta amyloid mediated depression of LTP in the rat CA1 in vivo. Hippocampus 19:670-676.

Schworer SA, Chason KD, Chen G, Chen J, Zhou H, Burbank AJ, Kesic MJ, Hernandez ML (2023) IL-1 receptor antagonist attenuates proinflammatory responses to rhinovirus in airway epithelium. J Allergy Clin Immunol 151:1577-1584.

Shukla D, Spear PG (2001) Herpesviruses and heparan sulfate: an intimate relationship in aid of viral entry. J Clin Invest 108:503-510.

Si ZZ, Zou CJ, Mei X, Li XF, Luo H, Shen Y, Hu J, Li XX, Wu L, Liu Y (2023) Targeting neuroinflammation in Alzheimer's disease: from mechanisms to clinical applications. Neural Regen Res 18:708-715.

Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanahan TK, Zurawski G, Moshrefi M, Qin J, Li X, Gorman DM, Bazan JF, Kastelein RA (2005) IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. Immunity 23:479-490.

Takemiya T, Fumizawa K, Yamagata K, Iwakura Y, Kawakami M (2017) Brain interleukin-1 facilitates learning of a water maze spatial memory task in young mice. Front Behav Neurosci 11:202.

Takeuchi O, Akira S (2010) Pattern recognition receptors and inflammation. Cell 140:805-820.

Taraschenko O, Fox HS, Zekeridou A, Pittock SJ, Eldridge E, Farukhuddin F, Al-Saleem F, Devi Kattala C, Dessain SK, Casale G, Willcockson G, Dingledine R (2021) Seizures and memory impairment induced by patient-derived anti-N-methyl-D-aspartate receptor antibodies in mice are attenuated by anakinra, an interleukin-1 receptor antagonist. Epilepsia 62:671-682.

Tomasoni R, Morini R, Lopez-Atalaya JP, Corradini I, Canzi A, Rasile M, Mantovani C, Pozzi D, Garlanda C, Mantovani A, Menna E, Barco A, Matteoli M (2017) Lack of IL-1R8 in neurons causes hyperactivation of IL-1 receptor pathway and induces MECP2-dependent synaptic defects. Elife 6:e21735.

Tong L, Prieto GA, Kramár EA, Smith ED, Cribbs DH, Lynch G, Cotman CW (2012) Brain-derived neurotrophic factor-dependent synaptic plasticity is suppressed by interleukin-1β via p38 mitogen-activated protein kinase. J Neurosci 32:17714-17724.

Vahlne A, Nyström B, Sandberg M, Hamberger A, Lycke E (1978) Attachment of herpes simplex virus to neurons and glial cells. J Gen Virol 40:359-371.

Vahlne A, Svennerholm B, Sandberg M, Hamberger A, Lycke E (1980) Differences in attachment between herpes simplex type 1 and type 2 viruses to neurons and glial cells. Infect Immun 28:675-80.

Verzosa AL, McGeever LA, Bhark SJ, Delgado T, Salazar N, Sanchez EL (2021) Herpes simplex virus 1 infection of neuronal and non-neuronal cells elicits specific innate immune responses and immune evasion mechanisms. Front Immunol 12:644664.

Wang WY, Tan MS, Yu JT, Tan L (2015) Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. Ann Transl Med 3:136.

Wang Y, Fu WY, Cheung K, Hung KW, Chen C, Geng H, Yung WH, Qu JY, Fu AKY, Ip NY (2021) Astrocyte-secreted IL-33 mediates homeostatic synaptic plasticity in the adult hippocampus. Proc Natl Acad Sci U S A 118:e2020810118.

Wang Y, Lin Y, Wang L, Zhan H, Luo X, Zeng Y, Wu W, Zhang X, Wang F (2020) TREM2 ameliorates neuroinflammatory response and cognitive impairment via PI3K/AKT/FoxO3a signaling pathway in Alzheimer's disease mice. Aging (Albany NY) 12:20862-20879.

Wozniak MA, Mee AP, Itzhaki RF (2009) Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques. J Pathol 217:131-138.

Yi S, Jiang X, Tang X, Li Y, Xiao C, Zhang J (2020) IL-4 and IL-10 promotes phagocytic activity of microglia by up-regulation of TREM2. Cytotechnology 72:589-602.

Zheng Q, Hua C, Liang Q, Cheng H (2023) The NLRP3 inflammasome in viral infection (Review). Mol Med Rep 28:160.

Zhao J, Qin C, Liu Y, Rao Y, Feng P (2021) Herpes simplex virus and pattern recognition receptors: an arms race. Front Immunol 11:613799.

Zipp F, Bittner S, Schafer DP (2023) Cytokines as emerging regulators of central nervous system synapses. Immunity 56:914-925.

C-Editors: Zhao M, Liu WJ, Qiu Y; T-Editor: Jia Y