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A Paradigm Shift: Does Herpes Simplex Virus Type 1 Play a Causal Role in the Progression of Late-Onset Alzheimer's Disease?

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BACKGROUND INFORMATION

The neurological disorder AD is characterized by a gradual deterioration of the major neural networks that coordinate to give rise to our memory, cognition, and sense of identity. This devastating disease currently impacts 36 million patients around the world, costing global healthcare systems $604 billion annually [1]. The incidence of AD is expected to triple by 2050, placing even greater financial and emotional burdens on the affected patients, families, and societies [1]. There are two major forms of AD, early-onset and late-onset. Early-onset AD represents only a minority (1-5%) of cases and is caused by mutations in the amyloid precursor protein (APP), β-, and γ-secretase genes, which cause disruptions in APP processing, resulting in the formation of toxic amyloid-beta (Aβ) plaques [2]. The normal function of APP is involved in the construction and repair of synapses, which when disrupted, contributes to AD neurodegeneration involving significant deterioration of synaptic connections [2]. Late-onset AD, on the other hand, makes up over 95% of cases, with the cause still remaining elusive. The late-onset form is thought to involve multifactorial interactions between genetics, epigenetics, and the environment [2].

Recently studies employing pre- and post-natal mouse lipopolysaccharide stimulation models, led to the proposal of a novel inflammation hypothesis as a possible cause of late-onset AD [3]. The hypothesis claims that chronic systemic inflammation is capable of inducing a state of chronic neuroinflammation, which can promote the hyperphosphorylation of tau (p-tau) (an early pathological feature of late-onset AD) and the deposition of Aβ plaques [4]. It proposes that high levels of proinflammatory cytokines in the CNS cause hyperactivation of microglial cells, disrupting their

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normal phagocytic function which is thought to be involved in the clearance of Aβ peptide accumulations [3]. Over the last decade several *in vitro* and *in* vivo studies of neural HSV1 infection have demonstrated HSV1's ability to induce several of these same pathological features, and thus may serve as an important driver of the inflammation hypothesis. Several comorbidities have been implicated as risk factors for late-onset AD including: cerebrovascular disease, hypertension, type-2 diabetes, obesity, traumatic brain injury, depression, aging, and the *APOE ε4* allele [3]. It is intriguing to note that several of these risk factors involve chronic systemic inflammation, with increased levels of circulating proinflammatory cytokines. These elevated levels can drive increased transport of the pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, directly across the blood brain barrier resulting in chronic neuroinflammation [5].

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HSV1 is a known neural resident, latently infecting peripheral nervous systems (PNS) of 65-90% of global adult populations [6]. The primary site of HSV1 latent PNS infection is the trigeminal ganglion (TG) [6]. In rare cases this infectious agent can cause herpes simplex encephalitis (HSE), an infection of the brain which results in rapid neurodegeneration, often leaving those inflicted with permanent neurological dysfunction [7]. Early studies revealed gross pathological similarities between HSE and AD, with both showing significant atrophy of the temporal, frontal, and hippocampal lobes [8]. Case studies have shown that HSV1 can recurrently reactivate in previous HSE patients, producing symptoms of transient memory loss [9]. These findings led to a hypothesis proposing that mild recurrently reactivating latent CNS HSV1 infections contribute to the characteristic neurodegenerative cascade seen in late-onset AD [6]. Over the last decade several lines of evidence have established positive correlations between latent CNS HSV1 infections and the incidence of late-onset AD. The most noteworthy result stemming from an epidemiological study implicating the combination of CNS HSV1 and APOE ε4 in up to 60% of AD cases [10]. The following article seeks to further probe the pathological interplay between persistently reactivating latent CNS HSV1 infections and late-onset AD.

RESEARCH QUESTIONS

Determining the complex molecular interactions that give rise to this debilitating and emotionally devastating disease has been, and will continue to be a pressing issue in the 21st century, as its immense burden on global health care systems continues to increase exponentially [2]. Fully elucidating HSV1's role in AD progression could lead to anti-viral therapies, being administered in combination with an already developing arsenal of therapeutic options that may slow the onset of AD neurodegeneration. The successful implementation of AD targeted anti-viral therapies, resulting in curative, or preventative outcomes against AD, would result in numerous societal benefits and would surely be a Nobel Prize worthy discovery. Further exploration in this field could have far reaching implications, providing model systems for uncovering the potential viral basis of several other widespread neurological diseases such as schizophrenia.

Five essential questions must be addressed to explore the prospective involvement of recurrently reactivating latent CNS HSV1 infections in AD pathogenesis. When assessing if an infectious agent is potentially implicated in the progression of a chronic disease, it is critical to first demonstrate whether a significantly increased rate of infection in the affected populations is present. Thus, it was important to first assess whether HSV1 CNS infection occurs in patients with AD. Following the determination of a clear association between HSV1 CNS infection and AD, another key question soon arises: how does HSV1 actually establish latent CNS infection? As mentioned above, the combination of CNS HSV1 infection and the *APOE ε4* allele increase the risk for AD. Therefore, exploring interactions between these two factors will prove key to understanding HSV1 driven AD. Furthermore, characterizing the molecular mechanisms of neural HSV1 infection and its impact on current models of AD pathogenesis may provide future AD treatment strategies. Recent evidence has indicated that recurrently reactivating latent CNS HSV1 infections could contribute to the AD degenerative cascade by exacerbating the molecular events outlined in the inflammation hypothesis.

PROJECT NARRATIVE

Does HSV1 CNS infection occur in patients with AD? Accurate quantification is critical when measuring the role of latent CNS HSV1 infections and their co-occurrence with AD. A land mark paper by Itzhaki *et al*. provided the first accurate PCR based demonstration of HSV1 DNA in the brains of individuals with and without AD, revealing that HSV1 infection manifested in the hippocampal, temporal, and frontal lobes of AD patients [10]. Analysis of this cohort led to the discovery that HSV1 infection alone was not a risk factor for AD, but rather the combination of both HSV1 and the *APOE ε4* allele resulted in elevated AD incidence. Another major player in this field, Wozniak *et al*., recently employed HSV1 DNA *in situ* PCR and Aβ immunohistochemistry to assess their rate of co-localization in AD patients [11]. They found 72% of AD Aβ plaques co-localized with HSV1 DNA compared to only 24% of plaques in aged normal controls, providing more evidence for a role of HSV1 infection in AD [11]. Though these findings illustrate that HSV1 infection occurs at increased rates in the brain of AD patients, understanding the cause of HSV1 latent reactivations in the brain will require the mechanisms of initiation of CNS latency must be elucidated.

How does HSV1 establish latent CNS infection? Primary HSV1 infection of the oral mucosa is established early in life causing recurrent cold sores in 20-40% of infected individuals [6]. Once the immune system has successfully stymied HSV1's lytic cycle in the oral mucosa, the virus is then able to establish a persistent secondary infection in the PNS [6]. In order to initiate the latent phase of infection, viral-host cell membrane fusion is induced through viral glycoprotein B and heparin sulphate proteoglycan (HSPG) interactions to gain entrance into trigeminal cranial nerve terminals (Fig. 1) [6]. Viral capsids then migrate along neural microtubule highways eventually reaching HSV1's main site of PNS latency, the TG, a cluster of neural cell bodies located in close proximity to the CNS [6]. From the TG the virus is then able to reactivate and infiltrate the CNS by unknown mechanisms, establishing latent infections in the

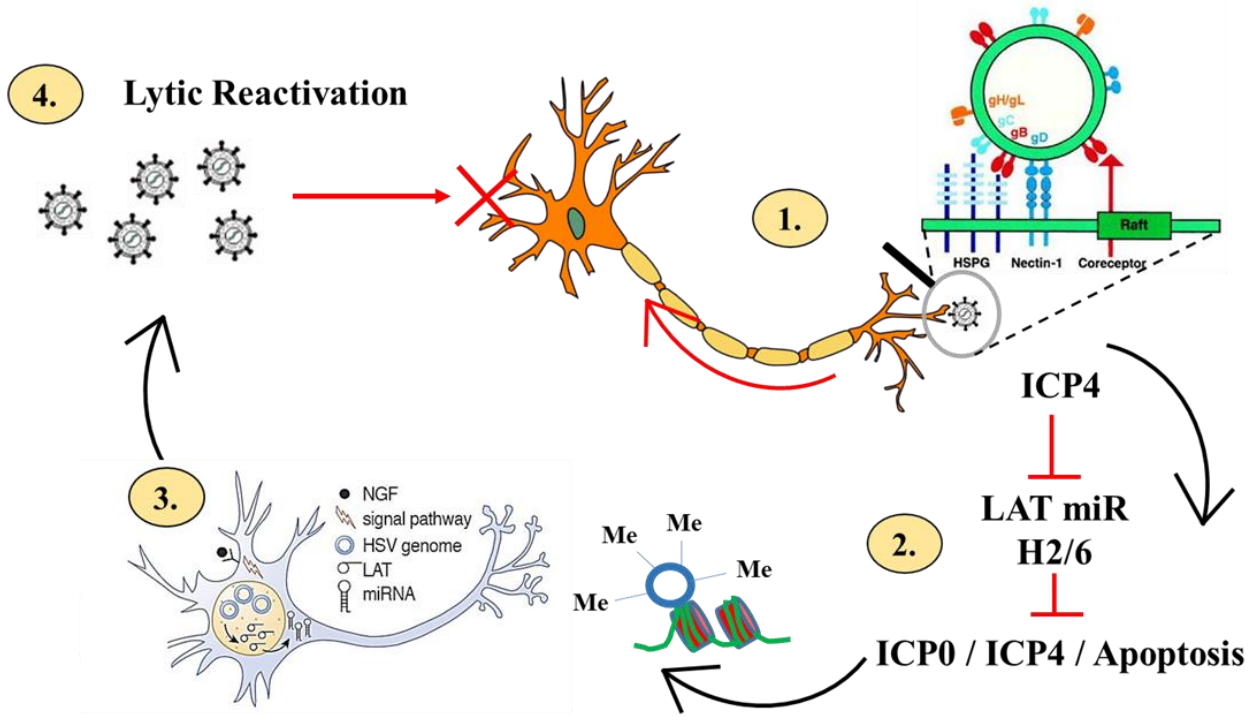

FIG 1 Establishing latent CNS HSV1 infection: 1. HSV1 first migrates along the trigeminal cranial nerve axons to the TG where it migrates into the CNS, entering neurons of the frontal and temporal lobes. **2.** Dynamic interactions between viral LAT derived miRNA and viral master regulators of lytic infection regulate key aspects of the induction of latency. **3.** Viral genomes of infected cells destined for latency undergo hypermethylation for stabilization and gene regulation. **4.** Chronic neuroinflammation can induce lytic reactivation by poorly defined mechanisms.

temporal, frontal, and hippocampal lobes [6]. Latent CNS HSV1 infection has been shown to occur at significantly higher rates in elderly populations [10], suggesting that the gradual deterioration of the immune and neurovascular systems observed throughout normal aging may contribute to the increased rates of HSV1 CNS infiltration [10].

A key knowledge gap in the understanding of HSV1's replication cycle is a precise description of the cellular factors that favour the induction of HSV1 latency. In order for latency to be initiated the viral genome must be hypermethylated for stabilization and suppression of the classical immediate early, early, and late *herpesviridae* gene expression cascade (Fig. 1) [6]. Once stabilized, a single latency associated transcript (LAT) is expressed resulting in the production of several viral miRNAs including miR-H2/6 (Fig. 1) [12]. These miRNA's possess significant complementarity with the mRNA transcript of the master regulator of HSV1 lytic activation, viral protein infected cell polypeptide (ICP) 0, functioning to help maintain latency by repressing ICP 0 expression (Fig. 1) [12]. On the other hand, viral protein ICP 4 is capable of suppressing LAT gene expression by binding to specific regulatory motifs located in the LAT gene sequence, thus performing an opposing function in the regulation of viral latency (Fig. 1) [13]. Though interactions between these factors play an important role in regulating the HSV1 replication cycle, the systemic factors influencing HSV1 latency must also be addressed in the following discussions.

How does the *APOE ε4* allele increase the risk for HSV1 mediated AD?

As previously mentioned, the combination of the *APOE ε4* allele and HSV1 CNS infection are associated with at least 60% of AD cases [10]. The same study also noted that the prevalence of the *APOE ε4* genotype was 40% greater in HSV1 positive AD patients compared to HSV1 negative AD patients, signifying an interdependent relationship between these two factors [10]. Apolipoproteins (APO) make up the outer shell of lipoproteins, functioning to regulate the distribution of lipids throughout the body [6]. APOE coated lipoproteins facilitate the neural delivery of cholesterol through interactions with HSPG, directly competing with HSV1 glycoproteins for cellular entry (Fig. 2) [6]. It's been hypothesized that *APOE ε4* possesses the weakest allelic affinity for HSPG, thus giving HSV1 a competitive advantage by increasing receptor availability, which in turn, increases the rate of cellular entry (Fig. 2) [14]. Furthermore, the type 4 allele is also associated with the highest levels of neuronal

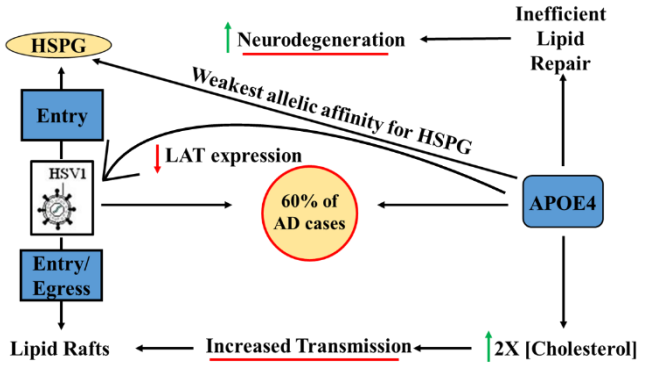

FIG 2 Deciphering interplay between HSV1 and APOE4: Network diagram depicting some of the mechanisms in which presence of the *APOE ε4* allele enhances the rate of HSV1 lytic reactivation and the extent of viral mediated neurodegeneration. Highlighting how the *APOE ε4* allele enables increased rates of HSV1 cellular entry/egress, low levels of LAT expression, & ineffective lipid repair processes.

membrane cholesterol, enhancing lipid raft mediated viral transmission [6] (Fig. 2). An *in vivo* study comparing CNS HSV1 infection in mice homozygous for either *APOE ε3* or *ε4* provided additional evidence for APOE4 mediated increases in viral transmission, as *APOE* ε4 mice challenged with CNS HSV1 displayed a 13-fold greater viral load compared to mice bearing the *APOE ε3* allele [15]. Additional studies evaluating these transgenic mice indicated that CNS HSV1 migration levels were dependent on APOE gene dose, with the greatest migration occurring in *APOE ε4* mice [16].

The *APOE ε4* allele can also contribute mechanistically to the neurodegeneration observed in HSV1 mediated AD [6]. APOE4 has been shown to be associated with the lowest levels of LAT expression and highest levels of immediate early gene expression, suggestive of a connection between APOE status and increased risk for latent viral reactivation (Fig. 2) [17]. These studies showed that APOE4 expressing mice exhibited a prolonged lytic phase of infection, contributing to greater levels of HSV1 mediated neural cell death [17]. Additionally, APOE is known to interact with oligomeric forms of Aβ peptides, with type 4 exhibiting the greatest allelic affinity to these peptides, suggestive of a potential role in their formation [18]. In fact, APOE4 expression is correlated with the highest Aβ plaque burden in humans [18]. APOE is also known to be involved in the cellular export of Aβ peptides, with APOE4 displaying the least efficient peptide export mechanism [19]. This lower efficiency may also explain the elevated presence of Aβ plaques in *APOE ε4* mice challenged with HSV1 [19]. When considering the

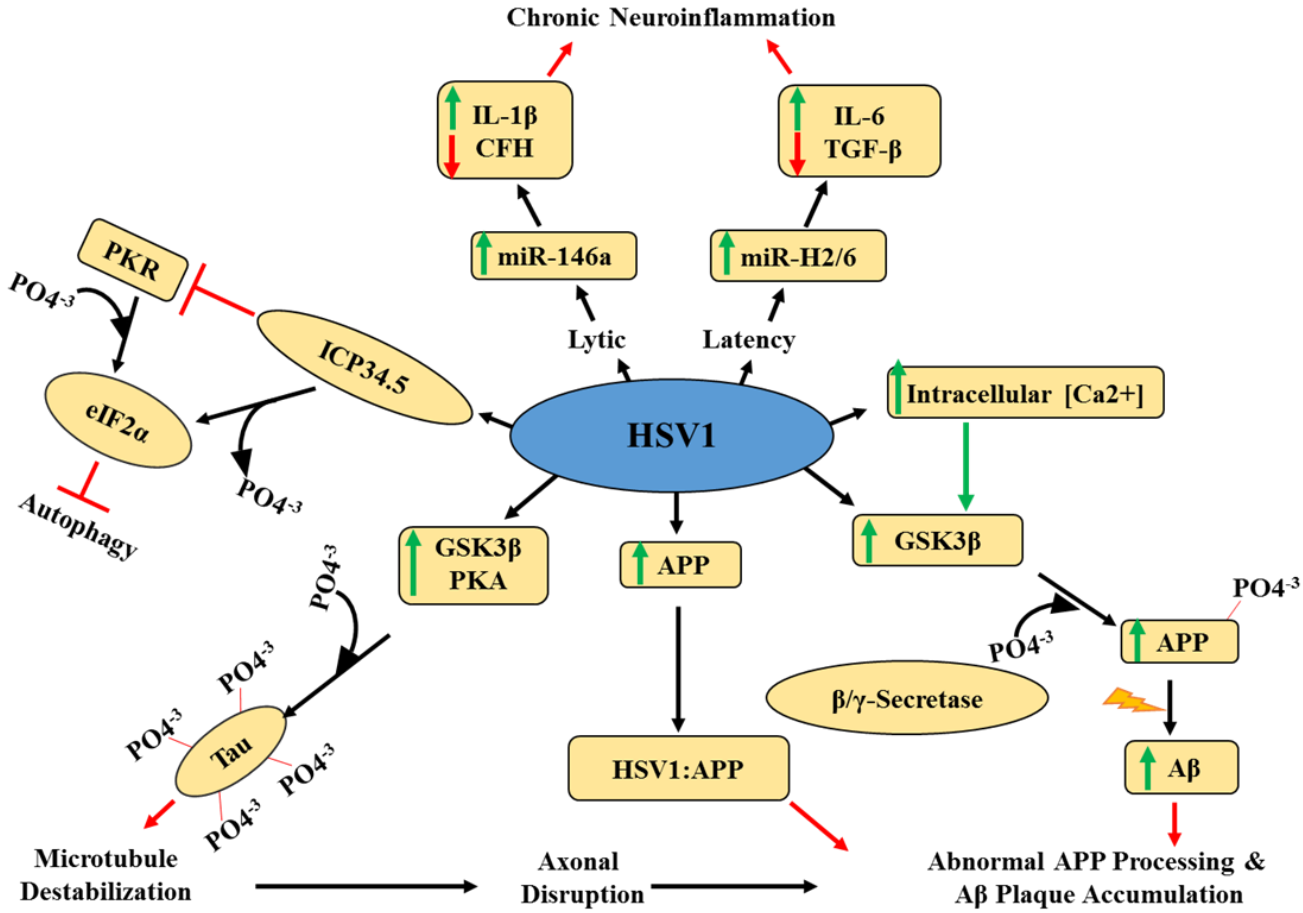

FIG 3 Molecular mechanisms of HSV1 infection driving AD progression: Network diagram demonstrating the mechanisms of HSV1 latent infection and lytic reactivation, and how they contribute to the major hallmarks of AD neurodegeneration, including chronic neuroinflammation, disruption of autophagy and microtubule transport, and abnormal APP processing into Aβ plaques.

multiple layers of APOE4's HSV1 interactions and contributions to AD pathology, the observed increased risk for AD associated neurodegeneration imparted by the combination is intuitive (Fig. 2) [6].

How does HSV1 cause AD neuropathology?

Recurrently reactivating latent CNS HSV1 infection can give rise to several of the major hallmarks of AD neuropathology including chronic neuroinflammation, oxidative stress, impaired autophagy, microtubule dysfunction, and Aβ plaque formation. Host immune responses to both lytic and latent infections can cause upregulation of proinflammatory cytokines interleukin 6 (IL-6) and interleukin 1-beta (IL-1β), and downregulation of immunosuppressive factors transforming growth factor beta (TGF-β) and the negative regulator of complement activation, complement factor H (CFH) (Fig. 3) [20, 21]. HSV1-mediated modulation of the CNS cytokine profile promotes neuroinflammation, triggering lytic reactivation from the latent state [22, 23]. The establishment of HSV1 latency has been shown to be dependent on nerve growth factor (NGF) signalling [22]. HSV1 mediated upregulation of the proinflammatory cytokine IL-6 decreases NGF signalling and increases expression of signal transducers and activators of transcription (STAT) [22]. STAT can bind regulatory sequences on the LAT gene, which may disrupt LAT expression inducing viral reactivation [22]. Oxidative damage is another known early indicator of AD progression, preceding the formation of characteristic pathological features such as NFTs and Aβ plaques [24]. An early response to reactivation of latent HSV1 infection is the production of reactive oxygen species (ROS), which can further modify host inflammatory responses to stimulate additional oxidative damage to nucleic acids, proteins, & lipids [25]. Moreover, latent HSV1 infection alone has

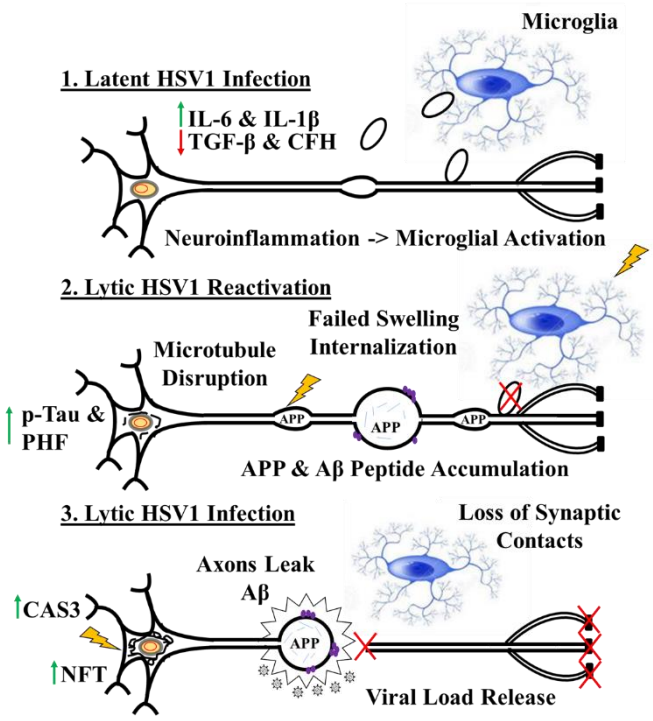

FIG 4 Persistently reactivating latent CNS HSV infections as a driver of the inflammation hypothesis: Cartoon depiction of how HSV1 may contribute to the gradual deterioration of neural networks causing AD. The figure is adapted from Knuesel *et al.*'s review of the inflammation hypothesis to highlight progression of latent infection to the lytic reactivation leading to the formation of Aβ plaques. NFTs, and eventual neural cell death [26].

been shown to promote oxidative damage and persistent inflammation, therefore also contributing to the onset of chronic neuroinflammation [25]. The elevated levels of ROS have even been detected in surrounding uninfected cells, signifying more pervasive effects of HSV1 infection throughout the CNS. It has been shown that ROS can directly increase the levels of p-tau and Aβ peptide aggregates *in vitro*, providing further evidence of HSV1 infection as a driving factor of AD pathogenesis [26].

Another early molecular indicator of AD progression is the disruption of neural microtubule highways, which function to transport neurotransmitters and key growth factors for the maintenance of synaptic connections [27]. Microtubule dysfunction is thought to be initiated by hyperphosphorylation of tau, an important microtubule stabilization factor, which can induce the formation of toxic aggregates called paired helical filaments (PHFs) (Fig. 3) [27]. HSV1 has been shown to increase the levels of p-tau through the activation of glycogen synthase kinase 3 (GSK3β) and protein kinase A (PKA) (Fig. 3) [24, 28]. Activation of GSK3β is induced by HSV1 binding to potassium (K^+) and sodium (Na^{2+}) channels, causing reduced K^+ efflux and enhanced Na^{2+} influx, which results in rapid membrane depolarization of infected neurons [29]. This depolarization causes activation of the inositol 1, 4, 5-triphosphate receptor, which promotes calcium efflux from the endoplasmic reticulum, leading to GSK3β activation [29]. These two kinases can directly phosphorylate tau, causing aggregation into PHFs. These are later cleaved by HSV1 activated Caspase 3 (Cas3), forming toxic NFTs [29, 30].

As previously mentioned a key pathological feature of AD is the formation of toxic Aβ plaques that contribute to the eventual loss of neural synapses and cell death [26]. HSV1 initiates the deposition and formation of Aβ plaques by first upregulating APP expression. APP is then phosphorylated by GSK3β on the Thr668 residue, enhancing its β-secretase-mediated degradation into Aβ peptides, which go on to form the same toxic plaques seen in AD (Fig. 3) [29]. A complementary finding showed that mice brains infected with HSV1 exhibited increased β- and γ-secretase expression, which both contribute to the elevated rates of APP conversion into toxic Aβ peptides (Fig. 3) [31]. Additionally, assembled HSV1 virions have been shown to associate with APP during axonal transport, thus it has been hypothesized that this interaction may disrupt the normal processing of APP, further contributing to the formation of Aβ plaques (Fig. 3) [32]. Another factor contributing to their formation is the inhibition of the innate immune systems autophagy/protein kinase R (PKR) response through the viral protein ICP34.5 [33]. During HSV1 viral replication complementary RNA transcripts are produced from the viral genome. These complementary RNA transcripts can form dsRNA hybrids, triggering the innate immune systems PKR response [33]. PKR phosphorylates the ribosomal elongation initiation factor 2-alpha (eIF2-α), terminating protein synthesis and promoting autophagy [33]. The viral protein ICP34.5 can reverse this response by specifically dephosphorylating eIF2-α, therefore preventing the autophagic response and allowing for further accumulation of Aβ plaques (Fig. 3) [33]. These molecular mechanisms highlight the multitude of similarities between HSV1 infection and AD pathogenesis, providing a comprehensive collection of evidence for a viral role in AD.

Do reactivating HSV1 infections enhance the AD degenerative cascade?

This final question attempts to address how the reactivation of latent CNS HSV1 infections could be driving the inflammation hypothesis, by presenting the previously described mechanisms as a sequential cascade of events contributing to AD progression. A recent study has shown that the presence of anti-HSV1 immunoglobulin M (IgM) in serum is a strong risk factor for AD [34]. IgM is a short lived antibody, therefore its presence provides evidence of recent latent HSV1 reactivation. As previously discussed, when HSV1 first establishes latent infection in the CNS, the immune system is activated by the increased production of proinflammatory cytokines and ROS, promoting a state of chronic neuroinflammation. CNS neural HSV1 reactivation results in proinflammatory cytokine and viral induced increases in p-tau leading to PHF formation and axonal microtubular destabilization (Fig. 4). Microtubule dysfunction can impair normal axonal protein extrusion mechanisms, resulting in the formation of local swellings along axons, a known early pathological feature of AD (Fig. 4) [35]. These local swellings may disrupt the microtubular transport of phosphorylated APP (p-APP) inhibiting its ability to engage in its normal function maintaining synaptic connections. However, normal p-APP transport may also be disrupted by direct association with assembled HSV1 virions resulting in abnormal p-APP accumulation within axonal swellings, a microenvironment favourable for its eventual pathologic processing into plaque forming Aβ peptides (Fig. 4).

The inflammation hypothesis posits that chronic neuroinflammation can cause microglial hyperactivation [27]. One of the normal functions of microglia involves clearing axonal debris, which may serve as a neuroprotective mechanism to counter age-associated accumulation of misfolded or damaged proteins [3]. Microglial hyperactivation can inhibit the phagocytosis of p-APP and Aβ peptide-filled swellings which form due to HSV1-mediated microtubule dysfunction [27]. Without microglial support the Aβ peptide-filled swellings expand to the point at which they can become leaky, resulting in the gradual deposition of Aβ plaques (Fig. 4) [27]. Disrupted axonal transport inhibits the delivery of important neural factors required for the formation and repair of synapses, including APP, causing the characteristic loss of synaptic connections observed in AD (Fig. 4) [27]. As the axonal swellings continue to expand and eventually burst, they release excitotoxic and proinflammatory molecules. This results in a vicious cycle further driving AD progression (Fig. 4) [27]. Persistent reactivations continuing over several years may gradually lead to neural cell death, driven by HSV1 Cas3 activation, and caspase-mediated cleavage of p-tau and PHFs into fragments. These fragments aggregate into NFTs, which destroy neural cell membranes (Fig. 4). The interconnectivity observed between the pathological progressions of both persistently reactivating latent CNS HSV1 infection and chronic neuroinflammation described in the inflammation hypothesis, make a strong case for the involvement of HSV1 in the late onset form of AD.

SUMMARY AND CONCLUSION

Over the last few decades several studies from over 37 different research groups have provided consistent evidence for a role of HSV1 in AD, with very few contradictory findings. Despite these advances, the concept of a viral role in AD is still considered controversial by researchers in the field. This is not surprising though, as resistance to the idea of viral involvement in chronic diseases is prevalent in the medical sciences: for instance, the discovery of the first oncovirus was highly contentious [36]. When considering the mounting support for HSV1's role in AD, it is important to consider a potential anti-viral therapy for combating AD. The current gold standard treatment for HSE is the FDA approved guanosine nucleoside analogue, acyclovir, which is normally administered as the prodrug, valacyclovir (VCV), due to its enhanced bio-availability [37]. VCV has repeatedly been proven to be highly effective and extremely safe for HSE treatment [37], which had led to *in vitro* and *in* vivo studies exploring whether VCV could disrupt the deleterious effects of persistent HSV1 reactivations in the CNS. *In vitro* treatment of HSV1-infected neural cells with VCV resulted in diminished p-tau levels and reduced Aβ peptide levels to normal levels [38]. Another important study, performed by Kumar *et al.* on rabbits latently infected with HSV1, involved treatment with high doses of VCV followed by subsequent monitoring of viral DNA tear burden. This study revealed significant reductions in viral DNA copy number in rabbits treated with VCV [39]. Given the strong evidence supporting a causal role for persistent CNS HSV1 infection in driving AD progression, the next step would be to perform clinical trials assessing the efficacy of VCV in preventing or delaying the onset of AD. Despite VCV's known long term effectiveness and tolerability there have still been no clinical trials of antiviral treatment for AD patients. Granting

organizations and pharmaceutical companies have refused to provide funding, this may be the fault of VCV already being off patent [37, 40].

Guided by the findings highlighted in this paper, clinicians could now perform a longitudinal study, using APOE status, serum anti-HSV1 IgM & CSF proinflammatory cytokine levels as early surveillance biomarkers for AD. High risk individuals could then be placed on a long term daily dosage of VCV, accompanied by periodic monitoring of the participant's blood for viral DNA load. If the VCV treatment regimen proved to inhibit CNS HSV1 latent reactivations, preventing the progression of AD, this would be a Nobel Prize worthy discovery due to the massive emotional and financial burden AD places on society today. The idea of pre-screening for AD risk factors brings up important bioethical considerations, as many individuals may not be inclined to learn of their potential risk. Accordingly, these screening methods would only be provided for interested populations, as these tests could provide certain individuals with peace of mind, and maybe even a chance of preventing or delaying disease onset. If antiviral treatment proved unsuccessful, additional treatment strategies could be pursued, such as small molecule kinase inhibitors, CNS targeted anti-inflammatories to skew microglial hyperactivation, and HSV1 vaccines.

In the last few years several phase III AD clinical trials of drugs targeting the β and γ secretase components of the amyloid cascade have lacked efficacy, casting doubts on the long standing "Amyloid Cascade Hypothesis" that proposes Aβ plaques are the central causative agents of AD neurodegeneration [41, 42]. This has led researchers to explore alternative therapeutic targets, one of which being GSK-3α/β, a key player in pathological progression of HSV1 mediated AD [43]. A host of GSK-3α/β antagonists have been developed, one example being tideglusib, which has recently been shown to improve the cognition of AD patients in a phase II clinical trial [44]. An additional approach worthy of further academic pursuit is the use of anti-inflammatory agents to reduce the chronic neuroinflammation speculated to accelerate disease progression. To date numerous clinical trials implementing a variety of non-steroidal anti-inflammatory drugs have yielded rather disappointing results, but this is likely attributable to a failure to account for the highly context-dependent and stage-dependent nature of microglial activation states [45, 46]. Furthermore, a recent breakthrough in the field of *herpesviridae* vaccinology has demonstrated a novel method for generating a live attenuated HSV2 vaccine, capable of generating sterile immunity and preventing the establishment of viral latency [47]. Applying these same principles for the production of a similar HSV1-specific live attenuated vaccine could provide a source of potent anti-HSV1 antibody dependent cell-mediated immunity that could help slow down the rate of recurrent latent reactivations in the aging brain. Vaccinated elderly populations could be studied to assess any impact on their rates of progression to mild cognitive impairment and AD.

An alternative avenue for future discovery includes undertaking a basic science approach, attempting to enrich our understanding of the precise cellular factors regulating the establishment and maintenance of CNS HSV1 latent infection. Uncovering the complex mechanisms of HSV1 CNS latency could provide an additional route to the Nobel Prize, prompting the pursuit of novel treatment strategies aimed at inhibiting the persistent nature and spread of latent infection in the aging brains of adult populations. Over the next decade, AD researchers must shift their focus onto the early molecular events driving disease progression, such as HSV1 viral reactivations, oxidative stress and chronic neuroinflammation to identify the cause of late-onset AD, which will lead to the development of curative therapies.

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ACRONYMS

Alzheimer's disease (AD), herpes simplex virus type 1 (HSV1), central nervous system (CNS), apolipoprotein E type 4 (*APOE ε*4), amyloid-beta (Aβ), neurofibrillary tangles (NFTs), hyperphosphorylated Tau (p-Tau), peripheral nervous system (PNS), herpes simplex encephalitis (HSE), amyloid precursor protein (APP), trigeminal ganglion (TG), heparin sulphate proteoglycan (HSPG), latency associated transcript (LAT), infected cell polypeptide (ICP) interleukin (IL), transforming growth factor beta (TGF-β), complement factor H (CFH), nerve growth factor (NGF), signal transducers and activators of transcription (STAT), reactive oxygen species (ROS), paired helical filaments (PHFs), glycogen synthase kinase 3 beta (GSK3β), protein kinase A (PKA), Caspase 3 (Cas3), protein kinase R (PKR), valacyclovir (VCV), Immunoglobulin M (IgM), phosphorylated APP (p-APP)