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The Association Between Herpes Simplex Virus Type 1 Reactivation and Alzheimer's Disease

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Abstract

This review will focus on the interaction of herpes simplex virus type 1 (HSV-1) and its causative role in pathogenesis of Alzheimer's disease (AD) noting specifically, the epidemiological relevance of addressing this problem, as well as the molecular pathways associated. HSV-1 reactivation tends to be one of the primary causative events that is responsible for many of the pathologies associated with AD, such as: amyloid beta (Aβ) accumulation caused by malfunctioning cleavage of amyloid precursor protein (APP) as well as tau hyperphosphorylation. HSV-1 reactivation is a primary causative event in downstream dysfunction and is also shown to be directed by the c-Jun N-terminal kinase (JNK) stress pathway; however, the glycogen synthase kinase type-3 (GSK-3) pathway is most important for Aβ accumulation and is also associated with tau hyperphosphorylation: the two proteins responsible for AD. The purpose of discussing these molecular pathways associated with the connection between HSV-1 and AD is to prove that proactive treatment is a necessity, while also advocating for a more detailed understanding of the causative affects of HSV-1 on AD. This review is important to increase awareness of the association between this highly prevalent virus and an extremely debilitating disease, with the goal of increased understanding and treatment for both HSV-1 and Alzheimer's disease.

Keywords

Herpes simplex virus type 1; Alzheimer's disease; GSK-3; JNK, amyloid beta

Introduction

Alzheimer's disease (AD) is a progressive and neurodegenerative disorder characterized by the decline of cognitive functions such as: memory, reasoning, language, etc. (Selkoe, 2011). This disease's etiology is rooted in normally soluble proteins: amyloid β-protein (Aβ) and tau (Selkoe, 2011). Aβ plaques are produced in nets that surround neurons and have become a hallmark of AD diagnosis (Selkoe, 2011). AD alone is the "sixth leading cause of death in the United States" (McQuillan & Paulose-Ram, 2018) and in 2010, out of all states and the District of Columbia, the CDC found that 31 of those states showed "death rates from Alzheimer's disease that were above the national rate" (McQuillan & Paulose-Ram, 2018). Though there are numerous risk factors associated with AD, infectious agents may be key players in understanding AD pathogenesis. Specifically, epidemiological and experimental evidence is beginning to demonstrate a link between Herpes Simplex Virus type 1 (HSV-1) reactivation and AD pathogenesis (Lövheim, Gilthorpe, Adolfsson, Nilsson, & Elgh, 2015). HSV-1 was found to have a prevalence of 47.8% in 2015 and the prevalence was found to increase with age (Tejada-Vera, 2013). HSV-1 reactivation is the primary event that induces cellular cascades, that eventually lead to Aβ accumulation (Piacentini et al., 2015). C-Jun N-terminal kinase (JNK) have been found to be a critical component in HSV-1 reactivation, as well as histone demethylase activity (Cliffe et al., 2015). The link between HSV-1 and AD is being explored through mechanisms related to the production of Aβ protein aggregates, looking specifically at how these aggregates are formed, namely through amyloid precursor protein (APP) cleavage pathways (Chang et al., 2006; Kimberly, 2005; Kimura, Hata, & Suzuki, 2016; Piacentini et al., 2015). It is now known that phosphorylation of threonine residue at position 668 (Thr668) is a critical step in the downstream production of Aβ (Chang et al., 2006; Piacentini et al., 2015), and is then dependent upon glycogen synthase kinase (GSK)-3, JNK, and Cyclin-dependent kinase 5; though there is some debate surrounding which pathway is most important, some recent experiments report compelling evidence for the GSK-3 mediation of APP phosphorylation, and the subsequent Aβ production (Piacentini et al., 2015). This literature suggests that HSV-1 reactivation pathways could be playing a critical role in Aβ production, and subsequently, the development of AD; however, there is still debate surrounding what cellular pathways lead to the subsequent accumulation of Aβ, as well as, what function this performs for the cell, be it protective, or

purely detrimental. The purpose of this paper is to review the current literature available on cellular pathways related specifically to Aβ production, while aiming to understand what this means for neural function and how this relates to Alzheimer's disease.

Alzheimer's Disease

Epidemiology of Alzheimer's Disease

Posing a significant threat to the aging population across the globe, treatment and understanding of AD is still lacking. Newfound focus has been placed on the amyloid hypothesis, showing that amyloid β plaques play a critical role in inducing AD pathology. One important set of structures observed in the brain of those with Alzheimer's include, "senile plaques, and neurofibrillary tangles (NFTs)". Senile plaques are extracellular protein aggregates composed of Aβ, a protein formed via the cleavage of a neural cell integral membrane protein, amyloid precursor protein (APP) (Harris & Harris, 2018). NFT's are intracellular deposits of "abnormally hyperphosphorylated tau proteins" (Harris & Harris, 2018). Though some debate surrounds which protein (amyloid or tau) is more important in understanding AD pathogenesis, Lewis et al., 2001 demonstrated through analysis of transgenic mice overexpressing both mutant human APP, and tau protein, that said mice undergo an increased genesis of tau-positive tangles with Aβ plaques being unaltered in both structure, and number (Lewis et al., 2001). Compared to mice that overexpressed tau protein alone, this finding demonstrates that altered APP processing occurs *before* tau alterations occur downstream in the AD pathogenic cascade. Other studies have supported this previous finding, concluding that AB toxicity was dependent on tau through the examination of mice hippocampal cultures. This information suggests that tau proteins do play a significant role in AD pathology; however, tau proteins are a downstream byproduct that is produced due to alterations in Aβ anabolism or clearance pathways.

Amyloid Beta's Importance in Alzheimer's Disease

Though it is known that Aβ plays a significant role in AD, it also important to note the vitality of Aβ in its non-pathogenic form, as this can provide possibly explanations as to how

HSV-1 is disrupting these functions. In normal brains, amyloid beta peptides are found at low levels, and may play a critical role in synaptogenesis, antioxidant activity, calcium homeostasis and neurogenesis (Cárdenas-Aguayo et al., 2014). While, in AD brains, or brains rich amyloid fibril plaques, quantifable neuron loss is recorded within mice hippocampus at ages 14-18 months (Selkoe, 2011). AD, though complex, is highly dependent upon Aβ accumulation in the form of senile plaques, and the subsequent NFTs development caused by hyperphosphorylated tau.

Herpes Simplex Virus Type-1

HSV-1: Structure and Prevalence

HSV-1, a high prevalent virus, affects about 3.7 billion (67% of the adult population) people globally and is a neurotropic pathogen that has an increased prevalence with age (World Health Organization, 2017). The virus primarily infects epithelial cells of the oral and nasal mucosa. During lytic replication viral particles may reach sensory neurons, and then via axonal transport travel to the trigeminal ganglion. From the trigeminal ganglion the virus may travel via axonal transport thus reaching the central nervous system (CNS) (Piacentini et al., 2014). Post infection the virus enters a lysogenic lifecycle, lying dormant in the host sensory ganglia allowing for a life-long infection: bypassing and evading the host immune system (Cliffe & Wilson, 2017). When reactivation occurs and the virus enters a productive lifecycle, lytic lesions arise termed: herpes labialis or cold sores (Piacentini et al., 2014). The viral reactivation which induces lesions, occur in episodes. The virus will then return to to a dormant (lysogenic) lifecycle until the next episode. This shows that HSV-1 not only has access to the brain but has a unique lifecycle that forces lytic genes to rely on cellular machinery and activities.

JNK Pathway is Essential for HSV-1 Reactivation

An important pathway to HSV-1 reactivation is the JNK stress pathway. This pathway is dependent upon the inhibition of phosphoinositide 3-kinase (PI3K) signaling (Cliffe & Wilson, 2017). The reason PI3K must be inhibited to initiate lytic mRNA synthesis is because the cell

lacks viral proteins, and thus the reactivation of lytic genes must rely on cellular machinery and activities. In neurons JNK, a common stress-response pathway, is also involved in dendritic arborization and synaptic plasticity (Coffey, 2014). Considering that both functions are affected by AD pathology, this poses a possible mechanistic link between HSV-1 and AD pathology. JNK is also essential for HSV gene expression during reactivation and induces a methyl/phospho switch on histone H3S10, activating viral lytic promoters. Due to this unique mechanism of histone modification, lytic gene expression is able to occur, all while repressive histone modifications (lysine residues) remain (Cliffe et al., 2015). This mechanism shows how "episodes" of transcription occur: a key characteristic of HSV-1. This shows that the JNK pathway is one major reactivation cascade that can allow for lytic gene expression to occur via activation of a normally dormant heterochromatic set of DNA; however, JNK does not appear to be a critical step involved in the accumulation of Aβ.

GSK-3 Mediation of Both Amyloid Beta Accumulation, and Tau Hyperphosphorylation

Piacentini et al. (2015) reports that GSK-3 is the primary kinase involved in phosphorylation of APP at Thr668 in rat cortical neurons *in vitro*. This phosphorylation of APP through calcium-activated GSK-3 is an essential step in the Aβ accumulation process. APP is both a substrate for JNK, and GSK-3, though there is no significant phosphorylation of APP by JNK (Piacentini et al., 2015). This suggests that JNK may only play a role in the reactivation process, and not the subsequent accumulation of Aβ. It has been found that HSV-1 infected cells hyperphosphorylated tau protein at a significantly higher rate (by a factor of four), and that HSV-1 upregulates GSK-3β, which is an enzyme also involved in phosphorylation of tau proteins: not only APP (Harris & Harris, 2018). GSK-3 could be a shared pathway between both Aβ accumulation, and tau hyperphosphorylation, thus serving as a connection between the two proteins that are both key components of neural dysfunction associated with AD. Both amyloid proteins are manipulated by GSK-3, as well as tau proteins, showing a direct mechanistic link between HSV-1 and AD, a disease that is dependent upon both Aβ and tau.

Synaptic Dysfunction

Presynaptic Protein Downregulation Connected with GSK-3 and HSV-1

Neural dysfunction and reduced synaptic activity can be measured by examining two pre-synaptic proteins. These two synaptic proteins are known as Synapsin-1 and synaptophysin with both being reported in decreased levels of AD brains (Harris & Harris, 2018). Importantly, HSV-1 infected cells also produce marked decreases in both proteins as well. To understand how this occurs, the GSK-3 pathway was studied in relation to both presynaptic proteins. Although, GSK-3 is an important molecular pathway in understanding how amyloid proteins accumulate, there is no evidence showing that GSK-3 has a *direct* involvement in neural dysfunction; rather, an indirect involvement. It has been reported that, even when GSK-3 is inhibited, synapsin-1 and synaptophysin levels do not change; rather, when amyloid precursor proteins are present, both of the presynaptic proteins are both reduced (Piacentini et al., 2015). This means that while GSK-3 is directly involved in the production of APP, it is not directly responsible for reducing synapsin-1 and synaptophysin levels; rather, GSK-3 is an upstream modulator of APP, the ladder producing a decrease in synapsin-1 and synaptophysin.

HSV-1 Affects CREB Via GSK-3 Pathway

GSK-3 activation and Aβ accumulation are both important components in understanding the disease pathology of Alzheimer's. GSK-3, playing a major role in both Aβ and tau protein accumulation, is also important in understanding how this HSV-1 can induce synaptic dysfunction. GSK-3 has been found to be an upstream regulator of the cyclic AMP-response element-binding protein (CREB). CREB is a major indicator of synaptic function and is a target of Aβ (Harris & Harris, 2018). Importantly, GSK-3 has been found to induce upregulation of CREB phosphorylated at ser 129 ($CREB^{ser\ 129}$). $CREB^{ser\ 129}$ is the inhibitory version of the transcription factor: CREB (Piacentini et al., 2015). This indicates that HSV-1, an up-regulatory agent of the GSK-3 pathway, indirectly increases the levels of $CREB^{ser\ 129}$. It is unclear what this means for other downstream events and needs further research to uncover what explicitly this means for the accumulation of Aβ; though, it is clear that the transcription factor (CREB) is

essential in understanding exactly how HSV-1 infection can lead to neural dysfunction: a hallmark of AD.

Antiviral Agents as Proactive Treatment for Alzheimer's Disease

As demonstrated, there is a significant pathological overlap between Alzheimer's disease and herpes simplex virus type-1 (HSV-1) viral reactivation mechanisms, both involved in neural degradation and decreased synaptic potential. Primarily, this dysfunction is a result of the GSK-3 pathway, a kinase that is activated by the large influx of calcium induced by viral reactivation. Not only is there a molecular overlap in pathology between this virus and AD, some studies have explored HSV-1 as an additive agent. In a large matched cohort study performed in Taiwan with information gathered from their National Health Insurance Program, it was found that in comparison to non-HSV-infected subjects, those with HSV infections had an increased risk of any type of dementia, even after controlling for individuals that were diagnosed with dementia within the first 5 years (Tzeng et al. 2018). This research supports the notion that there is a more direct link between not only HSV-1, but HSV-2 as well. Considering that Herpes Simplex Virus (Types 1 and 2) is a prevalent global virus and has a direct link with multiple forms of dementia, treatment and development of new treatments should be pursued. Tzeng et al. 2018 reported that subjects that were treated for herpes infections with anti-herpetic medications, had approximal 3 times reduced risk of Alzheimer's disease, as well as overall dementia. In short: their findings show that if a patient is treated for a herpes simplex infection, then their risk for dementia is similar to that of someone who does not have the virus at all. Medications such as Acyclovir, Valaciclovir, Famciclovir, Ganciclovir, and Valganciclovir are all examples of anti-herpetic medications that can be used for the treatment of herpes simplex type virus (Tzeng et al., 2018). It is important to note that while this research is useful for providing a possible link between AD and HSV, there are confounding variables that the researchers could not control for, as well as all the information for dementia was gathered via insurance claims. Despite these limitations, this study provides a strong framework for further clinical trials utilizing anti-herpetic medications in the proactive treatment of AD.

Conclusion

The neurodegenerative disease: Alzheimer's disease, is a major threat for the aging population, both in the United States, and across the globe. Alzheimer's disease is characterized by the accumulation of amyloid beta plaques, and tau hyperphosphorylation aggregates, that both disrupt neural function. Importantly, the herpes simplex virus type 1 (HSV-1) is known to directly modify the production of amyloid beta proteins and has an indirect influence on tau hyperphosphorylation through the glycogen synthase type 3 pathway (GSK-3). HSV-1 is even more prevalent than Alzheimer's disease with a dramatic prevalence rate across the globe. Herpes simplex virus type 1 normally influences molecular pathways during its reactivation, or the transition from a lysogenic (latent) lifecycle, to a lytic (active) lifecycle. This process has been shown to be mediated by the c-Jun N terminal kinase stress response pathway (JNK); however, the JNK pathway is not directly responsible for abnormal protein accumulation. In this paper I have explored each of these molecular pathways, and how they further the argument that HSV-1 is a causative agent in AD pathogenesis, thus showing that the need for proactive treatment of AD is necessary, in conjunction with increased research into the link between this virus and other types of dementia, including AD.

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