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Bioinformatics Review of the Role of HSV-1 in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease characterized by the progressive loss of cognitive functions in affected individuals. Brain tissue pathology is associated with the formation of senile plaques which result from the over-production of amyloid β (Aβ), due to the cleavage of a membrane bound glycoprotein. It is unclear what causes AD and its associated pathologies, but age and genetic predisposition play an import role in the likelihood of disease development. Studies have shown that the reactivation of latent herpes simplex virus 1 (HSV-1) infection can lead to the neuropathy of acute herpes simplex encephalitis (HSE), which causes similar symptoms to AD. HSV-1 infection is a known risk factor for the development of AD, but no study has determined a definitive causal relationship. Using the Qiagen Ingenuity Pathway Analysis (IPA) tool, the inhibitory relationship between therapeutics for AD and HSV-1 were explored. Thirteen drugs developed to decrease Aβ buildup in AD and 32 drugs that act as HSV antivirals were retrieved from the data in the Qiagen Knowledge Base. These drugs were analyzed displayed as two separate networks. While many promising Aβ aggregation-targeting drugs have been discontinued due to lack of efficacy, HSV drugs could serve as potential therapeutics for those with AD. This review aims to describe new insights on how HSV-1 relates to the development of AD and highlight the mechanism of action of Aβ-related drugs and HSV drugs in the context of AD. With HSV-1 being a likely candidate for the causation of AD, there is a need to study the effects of HSV antiviral drugs on those who have AD.

Keywords

Alzheimer's Disease, Amyloid β, Herpes Simplex Virus-1

1. Introduction

Dementia is described as the overall decline in the ability to cognitively function due to a disease or debilitating condition. Clinical characterization of dementia involves the identification of decline in any two of the following cognitive domains: behavior, executive function, language, memory, personality, and visuospatial function [1]. Alzheimer's disease (AD) is the leading cause of dementia and it is estimated that 60% - 80% of the 45 million individuals diagnosed with dementia have AD [2].

This neurodegenerative decline is characterized by a widespread shrinkage of brain mass due to the loss of neurons and their respective dendritic connections. Diagnosis of AD can be accomplished by: 1) the injection and detection of radiolabeled amyloid β (Aβ) biomarkers through a positron emission tomography (PET) scan, or 2) screening the blood or cerebrospinal fluid (CSF) for Aβ_{42}, hyperphosphorylated tau (p-tau) proteins or total tau proteins [3] [4].

There is no cure or prophylactic measure to prevent AD; however, there are currently drug therapies that alleviate some of the cognitive dysfunction or mitigate its severity. There are only two FDA-approved classes of AD drugs, which are cholinesterase inhibitors and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine. AD cholinesterase inhibitors function by inhibiting the breakdown of acetylcholine by acetylcholine esterase in the neuronal synapse. By blocking acetylcholine esterase, there is an increase of acetylcholine and thus an increase in the communication between neurons. It was found that the cholinesterase inhibitors delay the loss of memory in individuals with mild to moderate AD [5]. FDA approved cholinesterase inhibitors include donepezil, galantamine, and rivastigmine; all target acetylcholine esterase, but rivastigmine additionally targets butyrylcholinesterase [6]. NMDA receptors are ionotropic glutamate receptors in neurons and regulate the flow of cations between the extracellular and intracellular space of neurons. NMDA receptors are important in neuron synaptic plasticity and memory function [7]. In AD, the overstimulation of NMDA receptors and excessive Ca^{2+} into neurons result in excitotoxicity which can lead to neurodegeneration [8]. Memantine is a noncompetitive antagonist of the NMDA receptor that functionally blocks the flow of ions and in AD can slightly improve memory and cognitive function.

Overall, AD therapeutics are lacking in the context of significant impact on the disease pathology and progression. By exploring the molecular pathology and potential cause(s) of AD, a better appreciation and thorough understanding of this disease are attainable, resulting in the path forward to more impactful drug therapies.

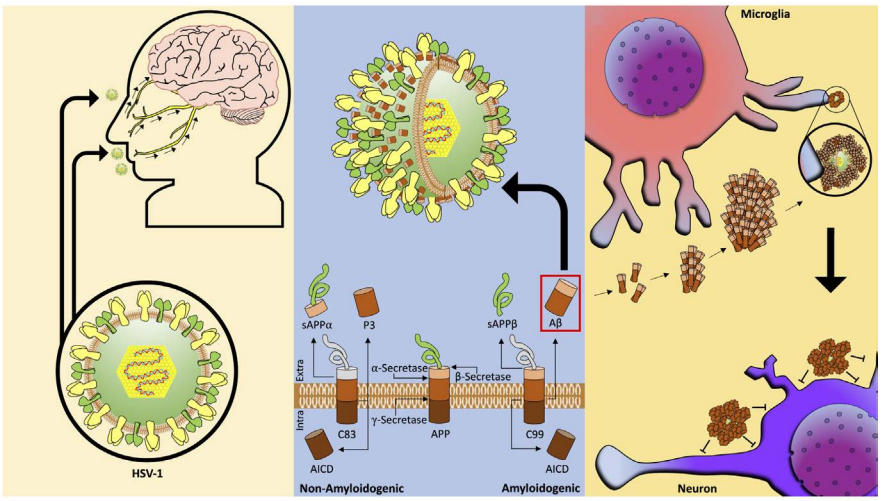
1.1. Microscopic Pathologies of Alzheimer's Disease

The two microscopic pathological hallmarks of an AD brain are the formation of senile plaques (SP) and intracellular neurofibrillary tangles (NFT) within neurons. SPs are large deposits of extracellular protein aggregates that result from

the amyloidosis of the Aβ production pathway in the hippocampal region of the brain from neurons and astrocytes [9]. Aβ is a product of cleavage from the, type I transmembrane glycoprotein, Aβ precursor protein (APP) [10]. Proteolytic cleavage of APP can result in either the amyloidogenic pathway or the non-amyloidogenic pathway (**Figure 1(b)**).

In the non-amyloidogenic pathway, APP is cleaved by the secretase extracellularly to form a soluble APPα and a membranous 83 amino acid C-terminal (C83) [11]. C83 is then cleaved by the γ-secretase complex to form a soluble A$\beta_{17\text{-}40/42}$ (P3) and the APP intracellular domain (AICD) [11]. The γ-secretase complex is composed of four proteins: anterior pharynx-defective 1, nicastrin, presenilin, and presenilin enhancer 2 [12].

Alternatively, with the amyloidogenic pathway, APP is cleaved by β-secretase (otherwise known as BACE1) to form a sAPPβ and a membranous 99 amino acid C-terminal fragment (C99) [11]. C99 is subsequently cleaved by γ-secretase complex to form AICD and the notorious 38 - 42 amino acid long peptide Aβ [11]. Of the Aβ species produced by this cleavage event, A$\beta_{1\text{-}40}$ is predominantly produced (90%) and A$\beta_{1\text{-}42}$ as the minority (10%) [13]. Of the two Aβ species produced, A$\beta_{1\text{-}42}$ is responsible for the Aβ aggregation in AD patients [14]. After the formation of Aβ peptides, further aggregation results in oligomers, fibrils and eventually plaques.



(a) (b) (c)

Figure 1. Hypothesized mechanism of Herpes Simplex Virus-1 (HSV-1) Formation of Senile Plaques in Alzheimer's Disease (AD); (a) HSV-1 infection of eyes, nose, mouth and subsaquent retrograde axonal transport into the brain by means of the cranial nerves; (b) HSV-1 infection of the brain results in the production of an immune response which utilizes the amyloidogenic pathway of amyloid β (Aβ) production as an antimicrobial peptide to sequester the pathogen. Additionally, HSV-1 size and structure allow it to fuctnion as a nanoparticle and attract Aβ to its surface to form a protein corona; (c) Aβ accumulation in the extracellular space forms larger protein fibrils and eventually plaques. Aβ plaques are not cleared by microglia and the accumulation of multiple plaques results in the inhibition of normal neuron function and leads to the cognitive decline in the brain.

NFTs result from the accumulation of p-tau proteins within neurons which functionally impede internal neuronal transport along microtubules and subsequent cell-cell communication [15]. Tau is a protein that is found in abundance inside of neuronal axons [16]. Normally, tau stabilizes the tubulin monomers of microtubules, which allows for vesicle trafficking inside of the cell [17]. In AD, tau is misfolded and in the p-tau conformation, resulting in its aggregation and the formation of paired helical filaments or NFTs which prevents normal functionality [18] [19].

Measurable levels of these APP cleavage products are thought to play an important role in brain homeostasis. Aβ has been found in individuals with and without diagnosed AD, but in noticeably different concentrations. There is 50% less A$\beta_{1\text{-}42}$ in the CSF of individuals with AD compared to those without AD [20]. This is representative of the inverse relationship demonstrated by the high deposition of Aβ in AD brains compared to the relatively low concentrations found in the CSF [21]. Although Aβ has a neurotoxic gain of function in AD brains, a growing amount of evidence supports its numerous homeostatic functions including antimicrobial activity, tumor suppression, blood-brain barrier repair, brain injury recovery, and synapse regulation [22] [23] [24] [25] [26].

1.2. Genetic Influencers of Alzheimer's Disease Susceptibility

It is known that certain genes have a role in the development of early-onset AD (EOAD) or late-onset AD (LOAD). Only a select number of relevant EOAD genes will be discussed in relation to this review. EOAD, also called familial AD, is characterized by the development of AD before the age of 65 [27]. LOAD, also called sporadic AD, is characterized by the development of AD after the age of 65. EOAD susceptibility occurs from having the genetic predisposition to predominantly produce the more aggregation prone A$\beta_{1\text{-}42}$ species as opposed to the A$\beta_{1\text{-}40}$ species. The genes included in this category are APP, PSEN1 and PSEN2.

APP encodes for APP, which is the transmembrane protein responsible for the formation of Aβ. Mutations in APP result in APP which favors the A$\beta_{1\text{-}42}$ cleavage product over the A$\beta_{1\text{-}40}$ [28]. Intimately related to APP is the γ-secretase complex which controls A$\beta_{1\text{-}42}$ production. PSEN1 and PSEN2 encode the presenilin, which is the catalytic component of the γ-secretase complex [29]. Mutations in PSEN1 and PSEN*2* cause the γ-secretase complex to produce a higher proportion of the A$\beta_{1\text{-}42}$, which results in the formation of Aβ aggregates [30].

ApoE is a gene that encodes for the apolipoprotein E (ApoE), which affects mostly LOAD. ApoE functions in lipid homeostasis and the packaging of cholesterol in the body. There are three major ApoE isoforms, ApoE2, ApoE3 and ApoE4, which are differentiated by two amino acid substitutions at positions 112 and 158 [31]. ApoE3 is the major isoform and has no effect on AD pathology, while ApoE2 is found to reduce AD risk and ApoE4 is found to increase AD risk [32]. Specific to the CNS, ApoE is produced by astrocytes and is involved in the lipid distribution to regenerated neuronal axons and Schwann cell remyelination [33]. In relation to brain homeostasis, ApoE binds and subsequently cleaves Aβ

in the extracellular space, which increases Aβ clearance. ApoE4 is the least efficient at Aβ clearance, and results in a higher proportion of the aggregating A$\beta_{1\text{-}42}$ [33]. ApoE4 also plays a role in neurotoxicity, the phosphorylation of the tau protein and NFT formation [34] [35] [36].

1.3. Antimicrobial Properties of Amyloid β

The genetic sequence of Aβ is >95% identical to its homologous mammalian counterparts [37]. APP knockout studies have shown that there is detrimental effects on neuronal dendrite and axon growth in cell culture, which corroborates similar findings in APP deficient mouse models [38] [39]. Thus, it is thought that its genetic conservation is in part due to its beneficial properties. Aβ can act as an antimicrobial compound against bacteria, fungi and viruses and a bioflocculant against naturally occurring biological byproducts and toxic agents in the extracellular fluid [9]. Experimental evidence showed that Aβ can functionally inhibit the growth of different bacteria and fungi in vitro [40] [41]. The Aβ antimicrobial mechanism of action is thought to be derived from its ability to form fibrils which can insert into the phospholipid bilayers of microorganisms and cause the unrestricted flow of extracellular contents into their internal compartments [42]. Additionally, the aggregation of Aβ can immobilize microorganisms in the extracellular space which prevents them from antagonizing the cells of the brain [9] [41]. Deposits of Aβ have been associated with the recruitment of microglia, which are likely essential for the clearance of accumulated proteins and the ensnared microorganisms through phagocytosis or opsonization [43] [44]. The antimicrobial properties of Aβ are illustrated in the upper half of **Figure 1(b)**.

1.4. The Pathogen Hypothesis of Alzheimer's Disease

In the case of AD, there is evidence that herpes simplex virus 1 (HSV-1) infection might be the initial cause of senile plaque formation in LOAD. Using in situ polymerase chain reaction and immunohistochemistry, HSV-1 DNA was found to localize within senile plaques of AD patients [45]. HSV-1 localization within plaques is shown in **Figure 1(c)**. An earlier study by Wozniak *et al.* shows that culturing HSV-1 with neuronal and glial cells leads to an increase in intracellular A$\beta_{1\text{-}40/42}$ and in mice HSV-1 infection leads to A$\beta_{1\text{-}42}$ deposits in the brain [46]. These findings support the Pathogen Hypothesis of AD, which posits that a pathogen, like HSV-1, is likely the cause or is exacerbating AD pathogenesis. HSV-1 causes a similar associated encephalopathy to AD called herpes simplex encephalitis (HSE). HSE diagnosed individuals show similar cognitive dysfunction to those who suffer from AD [47]. Interestingly, HSV-1 is prevalent in the brains of elderly individuals and considered a risk factor for the development of AD in ApoE-ε4 carriers [48].

1.5. Amyloid β and Apolipo Protein E Protein Coronas

Nanoparticles have the potential to serve as vectors that can antagonize cells or

microscopic structures. Peptides and protein fragments have the ability to adhere to nanoparticles, which endow said particle with a new range of effector abilities, in what is termed a protein corona [49]. The surface of nanoparticles has high free energy, which is lowered by the presence of biomolecules. A corona of biomolecules is produced on the surface as a result of dispersion [50]. Viruses, being non-living infectious agents, have been shown to share some biophysical functionality with nanoparticles, and thus are subject to the recruitment of an external protein corona layer in the extracellular milieu. Incubation of respiratory syncytial virus (RSV) with different biological fluids resulted in a diverse range of protein coronas when compared between and within the fluids, and in some cases, increased RSV infectivity [51]. In the same study by Ezzat *et al*., RSVs with protein coronae increase amyloid formation and specifically HSV-1 with coronae increase Aβ_{42} aggregation kinetics. Additionally, Ezzat *et al*. found that the HSV-1 protein corona was enriched in Aβ_{42}, ApoE and to a lesser extent Aβ_{40}, which is illustrated in the upper half of **Figure 1(b)**. This specific study gives additional support to the pathogen hypothesis and possibly supplies the mechanism for HSV-1 and its presumptive causation of LOAD. Prior studies have shown that the ApoE-ε4 is a genetic risk factor for oral herpes labialis and the development of oral herpetic lesions at a higher rate than individuals with one of the other alleles [52] [53].

1.6. Herpes Simplex Virus-1: General Virology & Route of Infection

HSV-1 is classified as part of the family *Herpesviridae*, within the subfamily *Alphaherpesvirinae*, as the genus *Simplexvirus* and is formally known as *Human Herpesvirus* 1. HSV-1 is organized with nonchromatinized viral dsDNA packed in a toroidal structure as its innermost layer [54]. Encapsulating the genome is the protein capsid, which has icosahedral symmetry and contains 162 capsomer subunits [55]. The genome, together with the capsid is called the nucleocapsid. Surrounding the nucleocapsid is unstructured proteinaceous tegument layer. The host cell-derived envelope is the outermost structure and is studded with a number of viral glycoproteins which are used by the mature virus to gain entry into receptive cells [56].

HSV-1 *in-vivo* cell tropism consists of epidermal keratinocytes, mucosal epithelial cells, corneal epithelial cells and neurons [57] [58]. Viral entry into epithelial cells is mediated by either membrane fusion or pH-dependent endocytosis [59]. HSV-1 utilizes 5 glycoproteins gB, gC, gD, gH, and gL in the viral entry process [60]. Initially, gC and gB are used to anchor HSV-1 to host-cell glycosaminoglycans, so gD can interact with one of its three receptors: nectins, 3-O-sulfated heparan sulfate or herpesvirus entry mediator [61]. It is postulated that gD binding its receptor causes gH/gL conformational change and subsequent or concurrent change in gB to allow for viral fusion [62]. After viral entry into the host-cell, the tegument layer is exposed and its interaction with dynein motor proteins allows for viral translocation to the nucleus by way of microtubules [63]. Once inside of

the nucleus, HSV-1 can perform transcription, replication and assembly. As the assembled virus is released from the nucleus, it buds into a vesicle released from the *trans*-Golgi network and acquires an outer envelope [64]. HSV-1 vesicles are subsequently exocytosed by the infected cell [65]. This complicated process of viral egress from epithelial cells can result in progeny positioned for neuronal or latent infection.

As epithelial cells release viruses by either budding or cell lysis, they can find their way to the receptive surface of the axon of a peripheral neuron. Here, HSV-1 undergoes retrograde axonal transport to make its way to the soma of the neuron [66]. Once inside the neuronal nuclei, HSV-1 takes a latent episomal form, where it remains dormant, but not integrated, in chromatin. Latent HSV-1 down regulates its lytic cycle and significant viral activity returns with neuronal damage or activation, where progeny virus are produced and travel by anterograde transport and are released from the axon terminal to infect epithelial cells, a process called reactivation [67].

As the cycle of HSV-1 latency and reactivation continues, infectious virus can make its way to the neurons of the CNS. HSV-1 infection of the eyes, nose or mouth can situate the virus in close proximity to the brain, where it can travel to cranial nerves and into the CNS (**Figure 1(a)**). HSV-1 has been found in the trigeminal, facial and vestibular nerve ganglia [68]. HSV-1 infection of corneal epithelial cells is thought to result in travel along the branches of the trigeminal nerves and into the trigeminal ganglion [69]. In mouse studies, HSV-1 infection was detected in the olfactory bulbs, following ocular infection [70]. Through positioning of the cranial nerves, HSV-1 is primed to infect neurons of brain, with reports of virus being found in the cerebellum, hippocampus, entorhinal cortex and frontal cortex [71] [72]. Of note, both the hippocampus and the entorhinal cortex are known brain regions of atrophy in patients with dementia and AD [73]. It is through these mechanisms, that HSV-1 enters the brain and can cause HSE and potentially AD. The aforementioned CNS pathologies can result in dysphasia, aphasia, ataxia and amnesia [74] [75]. Both AD and HSE are unique, yet similar, due to overlap in symptoms and a relationship or connection to HSV-1.

1.7. Amyloid β Aggregation-Targeting Therapies

To date, there are no approved Aβ aggregation-targeting therapies that improve the cognitive decline resulting from AD. There have been many therapy types that have tried to target the issue of Aβ accumulation including: α-secretase activators, β-secretase inhibitors, γ-secretase inhibitors, γ-secretase modulators, active immunotherapies, Aβ aggregation inhibitors, and passive immunotherapies. These aforementioned therapy types have found no significant clinical impact on treating AD. Since Aβ is an antimicrobial peptide, many promising studies that use Aβ-targeting drugs to ameliorate Aβ brain aggregation found increased infection rates, as a result of Aβ depletion. A meta-analysis of 10 trials involving 5227 patients in total found that γ-secretase inhibitors were associated

with an increased risk of infection [76]. A study of ELND005, an Aβ-targeting drug, found that high doses of the drug resulted in increased infection rates [77].

Using the Qiagen Ingenuity Pathway Analysis (IPA) tool, different Aβ therapeutics for AD were identified and displayed as an interactive network (**Figure 2**). The selection criteria for Aβ therapeutics were based on whether the drugs have shown any ability to affect Aβ aggregation. Thus, each drug that has and is being used to treat AD were kept in the dataset and the group was further filtered to contain only those drugs that decreased AD, reduced Aβ plaque formation, or helped clear Aβ plaques. The different drugs displayed, when hypothetically activated (red), using the Molecule Activity Predictor (MAP) tool show inhibitory effects on different AD conditions (blue) (**Figure 2**). Shown in **Figure 2**, AD, Early-stage AD (EOAD), Familial AD (LOAD) and Mild AD are among the AD conditions associated with inhibitory findings from different studies and trials. The functions of each drug and mechanism of action were tabulated along with the type of AD that they were found to affect and the number of related results corroborating each finding (**Table 1**).

Table 1. Thirteen drugs that target Amyloid β aggregation in relation to their effect on Alzheimer's Disease (AD). Drugs were chosen based on their ability to decrease AD using the Ingenuity Pathway Analysis IPA BioProfiler tool. Brief mechanistic functions of the drugs are detailed. The number of associated findings for each drug is shown and whether the effect on the disease or function is causal or correlated is listed.

Drugs	Molecule Function	Effect on Disease or Function	Disease or Function	Causal or Correlated	Findings
Atabecestat	BACE Inhibitor	decreases	AD	Causal	1
Bapineuzumab	IgG_1 that binds soluble/fibrillar Aβ	decreases	AD	Causal	7
BAN2401	IgG_1 that binds Aβ protofibrils	decreases	Early Stage AD	Causal	1
Crenezumab	IgG_4 that binds Aβ peptides, oligomers, fibrils and has low affinity for monomers	decreases	AD, Mild AD, Prodromal AD	Causal	4
Elenbecestat	BACE inhibitor	decreases	Mild AD	Causal	1
Gantenerumab	IgG_1 that binds Aβ fibrils	decreases	AD, Early Stage AD, Familial AD, Mild AD, Prodromal AD	Causal	6
Lanabecestat	$BACE_1$ inhibitor	decreases	AD	Causal	3
Latrepiridine	Antihistamine that modulates neurotransmitters and block Aβ-mediated toxicity	decreases	AD	Causal	7
Semagacestat	γ-secretase inhibitor	decreases	AD	Causal	3
SK-PC-B70M	Protects against Aβ-mediated toxicity	decreases	AD	Causal	1
Solanezumab	IgG_1 that binds Aβ peptides and monomers	decreases	AD, Familial AD, Prodromal AD	Causal	7
Tarenflurbil	NSAID R-enantiomer that modulates γ-secretase activity to reduce Aβ aggregate formation	decreases	AD	Causal	2
Tramiprosate	Taurine derivative that prevents Aβ β-sheet formation	decreases	AD	Causal	3

a. β-secretase (BACE), Amyloid β (Aβ), Alzheimer's Disease (AD).

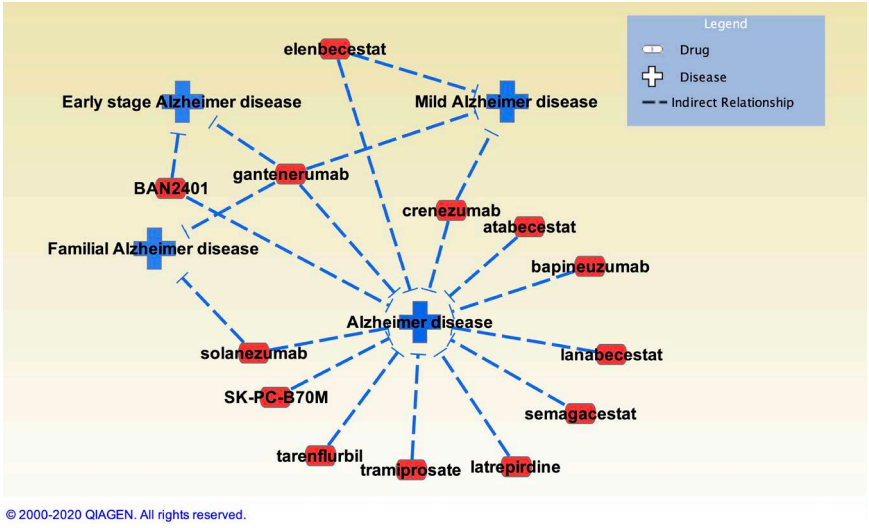


Figure 2. Drugs involved in targeting of Amyloid β (Aβ) Aggregation in Alzheimer's Disease (AD). Thirteen drugs that target Aβ aggregation were retrieved from the Qiagen Knowledge Base using the Ingenuity Pathway Analysis (IPA) software. Drugs are shown as "pills" and when activated have red coloration. Each drug exerts an effect on a particular AD condition, shown as "crosses". The blue coloration of the AD conditions represents predicated inhibition due to the activation of the aforementioned drugs. The network(s) were generated by using the IPA (QIAGEN Inc., https://www.qiagenbioinformatics.com/products/ingenuity-pathway-analysis).

The Aβ-targeting drugs shown in **Figure 2** and **Table 1** do not represent all Aβ-targeting drugs, as the curation of information was limited to the Qiagen Knowledge Base and its findings. Of the 13 representative Aβ-targeting drugs, five were monoclonal antibodies directed at Aβ post-cleavage, three were β-secretase inhibitors, two acted on the γ-secretase complex and the remaining three had unique mechanisms of action (**Table 1**). Of these 13 drugs, only two have not yet failed to show efficacy, being BAN2401 and gantenerumab. In an 18-month Phase 2b clinical trial, BAN2401 treatment with the highest study dose showed a statistically significant slowing of overall AD-related cognitive decline and a reduction in the Aβ in patient brains according to PET scans [78]. In a two-year study, high-dose administration of gantenerumab reduced Aβ to normal levels in half of the 67 tested patients [79].

1.8. Using Herpes Simplex Antivirals for Alzheimer's Disease

While Aβ-targeting drugs have proven to inefficacious, antivirals prescribed for general HSV infections have much higher merit for their respective target. Similarly using IPA, different antivirals for HSV were identified and displayed as an interactive network (**Figure 3**). The selection criteria for the HSV antivirals were based on whether the drugs have shown any effect on HSVs or HSV-1 specifically. Drugs were further filtered to those that inhibited HSV replication or HSV function in related diseases. The different drugs displayed, when hypothetically activated (red), using the MAP tool, showed inhibitory effects on different stages in the HSV replication cycle and different HSV-related pathologies (blue) (**Figure 3**).

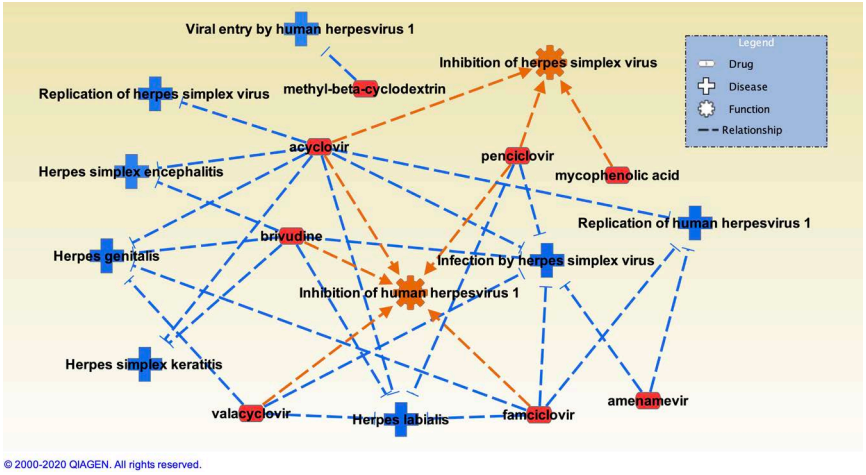


Figure 3. Chemical drugs that inhibit Herpes Simplex Virus (HSV). The top eight HSV antiviral compounds, with the most literature findings, retrieved from the Qiagen knowledge base using the Ingenuity Pathway Analysis (IPA) software. Findings were filtered for chemical drugs that have antiviral effects on the HSV genus or specifically HSV-1. Drugs are shown as "pills" and when activated have red coloration. Each drug exerts an effect on a particular stage of the HSV replication cycle/related HSV pathology or HSV function, shown as "crosses" or "gears" respectively. The blue coloration of the HSV stage or disease pathology represents predicated inhibition due to the activation of the aforementioned drugs. The orange coloration of the HSV function represents predicated activation due to the activation of the connected drugs. The network(s) were generated by using the IPA (QIAGEN Inc., https://www.qiagenbioinformatics.com/products/ingenuity-pathway-analysis).

In **Figure 3**, there were HSV antivirals targeting infection by and replication of HSV, replication of HSV-1 and viral entry by HSV-1, HSE, herpes genitalis, herpes labialis and herpes simplex keratitis. Additionally, some HSV antivirals targeted and activated the function of the virus, shown as orange "gears" (**Figure 3**). The mechanism of action of each HSV drug was tabulated along with the target of inhibition that they were found to affect, and the number of related results associated with each finding (**Table 2**).

Again, the HSV shown in **Figure 3** and **Table 2** do not represent the full spectrum of HSV antivirals. Of the 32 representative HSV antivirals, nine were nucleoside analogs, five were immune modulators and 18 had unique or unknown functionality (**Table 2**). Among the nucleoside analogs, 6 were FDA approved for usage as antivirals, 2 are no longer licensed and 1 is approved for use only in select European countries. A study using Vero cells showed that HSV-1 induces Aβ aggregation and p-tau, but when the antivirals acyclovir, penciclovir and foscarnet were independently applied, there was a significant reduction in both Aβ and p-tau and significant or at least reduced levels of HSV-1 [80]. A nationwide Taiwanese study found that the risk of developing senile dementia in those infected with HSV was 2.542-fold higher than that of the control group and the results for the development of AD were similar [81]. In the same study looking at those treated with antiherpetics and those who were not, over the course of 10 years, it was found that there was an 80% reduction in the incidence

Table 2. Thirty-two chemical drugs that inhibit Herpes Simplex Virus (HSV) or its realted pathologies. Drugs were chosen, using the ingenuity pathway analysis BioProfiler tool, based on their ability to decrease HSV, HSV-1 or related pathologies. Brief descriptions of the drug mechanisms of action are provided. The number of associated findings is shown and whether the drug effect on disease is caused or correlated is listed.

Chemical Drugs	Molecule Function	Effect on Disease or Function	Disease or Function	Causal or Correlated	Findings
2-deoxyglucose	Modified glucose that prevents viral and entry and acts as a glycosylation inhibitor	decreases	HSK	Causal	1
3-deazaaristeromycin	Broad acting antiviral that induces significant increase in interferon	decreases	Replication of HSV-1	Causal	1
Acyclovir	Guanosine nucleoside analogue	decreases increases	HG, HL, HSE, HSK, Infection by HSV, Replication of HSV/HSV-1 Inhibition of HSV/HSV-1	Causal	35
Amenamevir	Helicase-primase inhibitor	decreases	Infection by HSV, Replication of HSV-1	Causal	5
Brivudine	Thymidine nucleoside analogue	decreases increases	HL, HG, HSE, HSK, Infection by HSV Inhibition of HSV-1	Causal	7
Celgosivir	α-glucosidase I inhibitor	decreases	Quantity of HSV-1	Causal	1
Cidofavir	Cytidine nucleoside analogue	increases	Inhibition of HSV-1	Causal	2
Dextran Sulfate	Glycosoaminoglycan analogue	decreases	Replication of HSV-1	Causal	1
Docosanol	Aliphatic alcohol that inhibits viral envelope-cell membrane fusion	decreases	HL	Causal	2
Epigallocatechin-gallate	Catechin that likely inhibts viral attachment, entry, and or fusion	increases	Inactivation of HSV-1	Causal	2
Famciclovir	Guanosine nucleoside analogue	decreases increases	HG, HL, Infection by HSV-1, Replication of HSV-1 Inhibition of HSV-1	Causal	19
Foscarnet	Mimics pyrophosphate anion and binds DNA polymerase to inhibit activity	increases	Inhibition of HSV-1	Causal	2
Ganciclovir	Guanosine nucleoside analogue	increases	Inhibition of HSV	Causal	2
Idoxuridine	Thymidine nucleoside analogue	decreases increases	Infection by HSV Inhibition of HSV-1	Causal	1
Imiquimod	Toll-like recpetor 7 agonist	decreases increases	Infection by HSV, Replication of HSV-1 Inhibition of HSV-1	Causal	3
Lipopolysaccharide	May decrease susceptibility to viral infection	decreases	Infection by HSV-1	Causal	1
ME 609	Acyclovir-hydrocortisone combination	decreases	HL	Causal	3
Methyl-β-cyclodextrin	Removes cholesterol from membranes and prevents/reduces viral entry	decreases	Viral Entry by HSV-1	Causal	5
Mycophenolic acid	Depletes GTP levels and enhances nucleoside analgoue activity	increases	Inhibition of HSV	Causal	6
NB001	Nanoemulsion that disrupts viral envelope	decreases	HL	Causal	2

Continued

Nystatin	Sequesters cholesterol and prevents viral attachment, entry and or fusion	decreases	Viral Entry by HSV-1	Causal	1
Penciclovir	Guanosine nucleoside analogue	decreases increases	HL, Infection by HSV Inhibition of HSV/HSV-1	Causal	9
Pentosan Polysulfate	Interferes with viral adsoprtion	decreases	Replication of HSV	Causal	1
Prednisolone Phosphate	Anti-inflammatory	decreases	HSK	Causal	1
PRO 2000	N/A	decreases	HG	Causal	1
Pyrithione	Prevents activation of NF-κB by interfering with proteasome function	increases	Inhibition of HSV-1	Causal	2
Resiquimod	Toll-like recpetor 7 agonist	decreases	Infection by HSV	Causal	1
Trichosanthin	Type I ribosome-inactivating protein	affects increases	Replication of HSV-1 Inhibition of HSV-1	Causal	2
Trifluridine	Thymidine nucleoside analogue	decreases increases	Infection by HSV Inhibition of HSV-1	Causal	2
Valacyclovir	Prodrug of acyclovir	decreases increases	HG, HL, Infection by HSV Inhibition of HSV-1	Causal	20
Vidarabine	Adenosine nucleoside analogue	decreases	Infection by HSV	Causal	1
Zinc Gluconate	Interferes with viral glycoproteins and prevents membrane fusion	decreases	HL	Causal	1

a. Herpes simplex virus (HSV), herpes simplex virus-1 (HSV-1), herpes simplex encephalitis (HSE), herpes simplex keratitis (HSK), herpes genitalis (HG), herpes labialis (HL).

of senile dementia development. These results indicate a causal link between HSV and the development of senile dementia and further show that antiviral intervention can help prevent brain damage that occurs as a result of neurodegeneration [82].

2. Conclusion

AD is a complicated disease due to the number of factors that have been suggested to be a part of the pathology and the notable length of time it takes for symptoms to manifest. As the properties of Aβ have been elucidated, it is clear that it is not solely an indicator of disease and is actually part of normal innate immune function. HSV-1 was initially thought to be unrelated to AD altogether, but evidence for the etiological role of HSV-1 in the causation or development of AD is slowly building. Since Aβ-targeting has proven to not be a viable means of combating AD, new avenues of treatment need to be explored. As more experimental evidence accumulates, the likelihood of a clinical study on the effects of HSV antivirals in relation to AD progression draws closer. Since antivirals for HSV show efficacy in inhibiting viral replication and some have been shown experimentally to decrease Aβ and p-tau concentrations, these antivirals could provide a direction to a novel avenue of AD drug therapy. The evidence presented in this review aims to highlight this elusive relationship between HSV-1 and AD and support the further research and investigation of this topic.

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Conflicts of Interest

The authors declare no conflict of interest.

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