HHS Public Access

Author manuscript

J Alzheimers Dis Parkinsonism. Author manuscript; available in PMC 2019 October 04.

Published in final edited form as:

J Alzheimers Dis Parkinsonism. 2019 ; 9(5): . doi:10.4172/2161-0460.1000477.

Alzheimer's Disease and Its Potential Alternative Therapeutics

Brent Kisby[#], **Juliet T Jarrell**[#], **M Enes Agar**[#], **David S Cohen**[#], **Eric R Rosin**, **Catherine M Cahill**, **Jack T Rogers**[*], **Xudong Huang**[*]

Neurochemistry Laboratory, Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA

Abstract

Alzheimer's Disease (AD) is a chronic neurodegenerative disease that affects over 5 million individuals in the United States alone. Currently, there are only two kinds of pharmacological interventions available for symptomatic relief of AD; Acetyl Cholinesterase Inhibitors (AChEI) and N-methyl-D-aspartic Acid (NMDA) receptor antagonists and these drugs do not slow down or stop the progression of the disease. Several molecular targets have been implicated in the pathophysiology of AD, such as the tau (τ) protein, Amyloid-beta (Aβ), the Amyloid Precursor Protein (APP) and more and several responses have also been observed in the advancement of the disease, such as reduced neurogenesis, neuroinflammation, oxidative stress and iron overload. In this review, we discuss general features of AD and several small molecules across different experimental AD drug classes that have been studied for their effects in the context of the molecular targets and responses associated with the AD progression. These drugs include: Paroxetine, Desferrioxamine (DFO), N-acetylcysteine (NAC), Posiphen/-(−)Phenserine, JTR-009, Carvedilol, LY450139, Intravenous immunoglobulin G 10%, Indomethacin and Lithium Carbonate (Li_2CO_3).

Keywords

Alzheimer's disease; Neurogenesis; Amyloid precursor protein; Amyloid-beta; Tau protein; Alternative AD therapeutics

Introduction

Alzheimer's Disease (AD) is a chronic neurodegenerative disease that typically occurs in those aged 65 years and older [1]. It presents with a broadly related pathophysiology as Frontotemporal Dementia (FTD) and Amyotrophic Lateral Sclerosis (ALS), also known as

[*]**Corresponding authors:** Jack T. Rogers, Neurochemistry Laboratory, Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, 149 13th Street, Charlestown, MA 02129, USA, Tel: +1-617-726-8838; Fax: +1-617-726-4078; jack.rogers@mgh.harvard.edu; Xudong Huang, Neurochemistry Laboratory, Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, 149 13th Street, Charlestown, MA 02129, USA, Tel: +1-617-724-9778; Fax: +1-617-726-4078; huang.xudong@mgh.harvard.edu.

[#]These authors contribute equally to the manuscript

Conflict of Interest

The authors declare that they do not have any conflicts of interest.

Lou Gehrig's disease. AD is a senile dementia with its pathology occurring up to 18 years before its definitive diagnosis [2]. In 2017, the Alzheimer's association published a 2017 Facts and Figures report indicating that approximately 5.5 million people in America have Alzheimer's and of those 5.5 million, 5.3 million are 65 years of age or older. Additionally, by 2050, the number of people that have Alzheimer's may triple. The report also shows that, between 2000 and 2014, the death rate of Alzheimer's has increased by 89%, by contrast, other public health conditions such as stroke and HIV have observed a 14% and 54% death rate decline, respectively.

AD and other types of dementia are characterized by a loss of ability to solve problems or maintain emotional control. Individuals with dementia experience personality changes and behavioral problems such as agitation and impaired intellectual functioning that interfere with normal activities and relationships. Dementia also generates hallucinations and delusions.

There are currently only a few FDA-approved treatments for AD, which belong to two classes of drugs: Acetyl cholinesterase Inhibitors (AChEI) and N-methyl-D-aspartic Acid (NMDA) antagonists. These treatments have been used for treating the symptoms of cognitive decline and language deficits and do not slow down or stop the progression of the disease. A drug that cures or at least slows down the disease is necessary, as Alzheimer's is becoming pandemic.

Here we review select aspects of the AD pathogenesis, focusing on iron homeostasis and oxidative stress, dysregulation of the APP translation and processing, Amyloid-beta (Aβ) deposition, the proinflammatory cytokine Interleukin-1 beta (IL-1β), tau protein hyperphosphorylation and reduced neurogenesis. Moreover, we address a few compounds that provide alternatives to the current FDA approved drugs and target many different components and pathways of AD.

General Features of AD

Risk factors attributed to AD

There are many environmental and biological risk factors attributed to the pathogenesis of AD, which include, but are not limited to: chronic alcoholism, age, neuroinflammation, Apolipoprotein E fibrillation, iron dysregulation, cerebral ischemia, stress, lack of sleep, genetic mutations, mitochondrial dysfunction, iron overload and oxidative stress and metal dyshomeostasis (i.e., copper, aluminum, iron, manganese)[3–18].

Pathogenesis of AD

AD is a highly complex disease with numerous features. A common generalization is that AD results from insoluble Aβ plaque formation in hippocampal neurons and neuro-fibrillations of tau protein created *via* tau hyperphosphorylation [19–21]. Eventually, these plaques and neuro-fibrillations cause neuronal apoptosis and neurodegeneration [20,21]. Although Aβ plaques and tau neuro-fibrillations are critically important features of AD, there are many other components of the disease as well, some still unknown that should be considered equally in the search for a cure.

Iron and oxidative stress: Iron (Fe) is one of the redox-active transition metals and Fe, along with other metals, has been shown to promote the formation of Aβ plaques and engender neuronal oxidative stress [18]. The ability of Fe to induce oxidative stress is attributed to the valence state of iron (Fe) being reduced from Fe (III) to Fe(II) and this reduction is coupled with hydroxyl radical formations in the brain through the Fenton reaction [15,18]. As shown in multiple studies, the radical formations reduce the proliferation of Neural Stem Cells (NSCs) and neurogenesis in an AD brain [22–24]. Furthermore, oxidative stress has been known to cause tau neurofibrils, neurogenesis deterioration and increased ferritin levels that have been correlated with cognitive decline [25–28].

Amyloid precursor protein: The Amyloid Precursor Protein (APP), which can generate Amyloid-beta (Aβ) through proteolysis, plays a vital role in synaptic formation, iron regulation, neural plasticity and neurogenesis [9,29–33]. The 5' UTR region of the APP plays a role in APP expression and the formation of Aβ and it remains a possibility that these processes are accelerated in the presence of iron through a 5'-Untranslated Region (UTR) iron response element (IRE) in the APP transcript [34,35]. The 5' UTR specific IRE RNA stem loop was first reported in 2002 and has since proven to present a target for chelators and other drugs that inhibit APP translation, such as desferrioxamine, clioquinol, VK-28, piperazine-1, phenserine, tetrathiomolybdate, dimercaptopropanol, paroxetine, azithromycin and a high throughput benzimidazole 5'UTR translation blocker designated as JTR-009 [35–39]. JTR-004, JTR-009, JTR-0013 were among the most potent compounds tested in the high throughput study that inhibit the 5' UTR APP translation, with JTR-009 being the most potent blocker, whereas other endogenous compounds or hormones and amyloid expression such as glucocorticoids have been implicated in increasing APP translation [40].

β-amyloid plaques: Beta-amyloid plaques are one of the two most distinguishing features of AD. There are two types of Aβ subtypes which have been implicated in causing AD progression, these mutations are $A\beta_{1/40}$ and $A\beta_{1/42}$. In the context of AD, Aβ has been known to cause insoluble plaques and inhibit neurogenesis by suppressing proliferation of NSCs, this suppression eventually leads to neuronal apoptosis *in vivo* [41–43]. The build-up of these plaques can create inflammation and oxidative stress [44,45]. A vast amount of research regarding the role of Aβ in Alzheimer's already exists and this research is ongoing.

Tau and tauopathy: The second distinguishing feature of AD other than beta-amyloid plaques is the appearance of tau neurofibrillary tangles. Tau is highly soluble microtubules associated protein that is part of a superclass of Microtubule Associated Proteins (MAP) which regulates neuronal microtubule within axons and are localized in dendrites in AD neuropathology [46]. AD is classified as a tauopathy, tauopathies are a group of neurodegenerative diseases that involve tau tangles. Some other tauopathies include ALS, FTD and Pick's Disease [47–49].

Research about tau is ongoing; a recent report shows that tau protein causes a decline in neurogenesis. In this 12 month study, as tau levels increased, the level of neurogenesis in the hippocampus and Subventricular Zone (SVZ) decreased [50]. Furthermore, prion proteins

(PrP^C), which prevent cells from oxidative stress, interact with tau, but the mechanism and effects of these proteins are unclear, some evidence shows that these proteins stabilize tau and Aβ production, while other evidence suggests that the proteins can arrest APP translation and tau production [51,52]. Tau is regulated by 2 factors: Glycogen Synthase Kinase-3 (GSK-3β) and Cyclin-Dependent Kinase 5 (CDK5). GSK-3β and CDK5 regulate the activation of tau phosphorylation and this phosphorylation leads to tauopathy [53–55]. Researchers studying the inverse effects of GSK-3β have determined that GSK-3β inhibitors, such as Lithium Carbonate (Li_2CO_3), can inhibit the tauopathy in AD [56].

Interleukin-1 beta (IL-1β): Proinflammatory cytokines have been implicated in AD pathogenesis. The most common of the cytokines with respect to AD pathology is Interleukin 1 beta (IL-1β). IL-1β is in the supergroup of Interleukin-1 (IL-1), which includes a plethora of other proinflammatory and anti-inflammatory cytokines. IL-1β is regulated by several factors including, but not limited to, caspase-1, IRAK1/2, transcriptional and translational level regulation and procaspase-1. Limited data indicates IL-1β's role in iron regulation, but one study showed an increase in ferritin protein expression levels due to increased levels of IL-1β in the mitochondria [57]. IL-1β also has a connection to oxidative stress, it is spliced by caspase-1, which is downstream of the cellular oxidative stress pathway [58]. Further review of IL-1β's biochemical properties can be found in Dinarello CA 2011[59].

IL-1β in the brain is localized within microglial cells, astrocytes and B and T cells within the periphery [60–63]. IL-1β has toxic effects because it serially increases APP translation and increases tau phosphorylation [64,65]. Aβ has also been classified as a proinflammatory peptide because it enhances production of pro IL-1β into mature IL-1β and this mature form can create microglial toxicity [66]. Recently, one study showed that a drug called Edaravone can alleviate this microglial toxicity and stop the release of proinflammatory cytokines such as IL-1β [67].

IL-1β can even trigger a positive, inflammatory feedback loop in some vertebrae cells [68]. It is not known whether increased IL-1β and microglial toxicity as a result of this positive feedback loop might precede Aβ production and plaque formation over the time span of AD pathogenesis and more research should be conducted about the relationship between IL-1β and AD, as IL-1β could be an AD drug target, IL-1β is already a drug target for autoimmune disorders [69].

Moreover, a groundbreaking study by Monje et al. showed that inhibiting inflammatory cytokines increases neurogenesis in hippocampal neurons and a more recent review suggests that IL-1β negatively affects neurogenesis, this research further implicates IL-1β's role in neurogenesis and, ultimately, AD [70,71].

Pathology of AD Effects on Neurogenesis

Neurogenesis in humans is found in the the Subventricular Zone (SVZ), the Dentate Gyrus (DG) of the hippocampus and the Olfactory Bulb (OLFB) [72,73]. Neurogenesis is the process of producing adult neurons from Neural Stem Cells (NSCs) [38]. Many studies

suggest that neurogenesis is decreased in AD [73–76]. There are several biological factors that inhibit neurogenesis, such as IL-1β, serotonin depletion, mutations in presenilin-1 and normal aging and shortening of telomeres [19,43,77,78]. It has been hypothesized that since neurogenesis in humans is in the OLFB, early signs of AD progression can manifest in neurogenesis decline, where decreased smell correlates with AD advancement, thus, smell could be helpful in early detection of AD [79]. Moreover, tau presence in the OLFB also correlates with early stage AD [80]. Thus, further understanding of the molecular pathology and the decline of neurogenesis should advance our knowledge about the early signs of clinical AD.

Current Small Molecule Treatments for AD

There are currently two classes of drugs that are used to treat the symptoms of AD: Acetylcholinesterase Inhibitors (AChEI) and N-Methyl-D-Aspartate (NMDA) receptor antagonists [81]. Acetylcholinesterase (AChE) is an enzyme which degrades acetylcholine (ACh) in the synapse [82]. The drugs that belong to the AChEI class are donepezil, rivastigmine and galantamine.

Decreased ACh in the AD brain has been well documented and evidence suggests that an AD-associated lowering of ACh activity in the basal forebrain leads to compromise of executive functions, ACh plays a role in certain cognitive abilities such as attention [83–86]. Studies also show a decrease in AChE activity in AD patients and that AChEI's can reduce IL-1β and increase interleukin-4 (IL-4) [87,88]. There are several reviews on how AChE inhibitors work by arresting the activity of AChE, thus leading to increases in Ach [89–91].

By comparison, NMDA receptor antagonists are used to treat the toxic increases in Glutamate (Glu) within the brain [92]. Glu excitotoxicity has been hypothesized to play a pivotal role in AD pathology because excess Glu in synapses leads to neuronal apoptosis [93]. Memantine, at the time of this review, is the only NMDA antagonist available on the market. Memantine has been shown to be neuroprotective as well as increase LTP in CA1 hippocampal neurons [94–96]. Both NMDA antagonists and AChEI's have been shown to have neurotrophic effects [97,98].

Drawbacks to current AD treatments

Both AChEI's and the NMDA antagonist memantine have a few benefits for AD patients, such as displaying mild neuroprotective properties inhibiting cognitive decline for severe AD patients and facilitating neurogenesis [87,99–103]. However, these drugs do not slow down or stop the progression of the disease, they simply try to relieve symptoms and they become less effective over time [86,104]. Because the current drugs are not curative, many new drugs are in development. According to a September 2017 report, at that time there were 150 drugs in the AD treatment development pipeline, in various clinical stages [105].

Alternative Treatments for AD

There are many benefits and drawbacks to the following alternative treatments. These therapies are possible alternatives to AChEI's and the NMDA antagonist memantine and

have multiple implications for efficacy and improvement of cognition in AD patients. The main goal of these alternative therapeutic compounds is to manage the symptoms of AD and improve a patient's quality of life, while also improving the underlying AD pathology *via* their molecular and biochemical properties. The issue is that definitive conclusions cannot be made about these drugs due to lack of research and/or conflicting research. However, the results from the research that has been done should shed light on more individualized therapies that can assist in AD pathology reversal and enhance hippocampal neurogenesis and memory.

We present several different novel treatment options entering the pipeline that have somewhat been or will be considered for AD or that have not been extensively studied, but have positive effects on different AD targets discussed in the first section of this review.

Paroxetine and various selective serotonin reuptake inhibitors

Paroxetine (Paxil) is a Selective Serotonin Reuptake Inhibitor (SSRI) and is FDA approved for treating depression, mood disorders and anxiety disorders [106,107]. The drug works by inhibiting the reuptake of serotonin (5-HT) on the presynaptic neuron, which then increases 5-HT within the synapse. Paroxetine has been shown to enhance iron homeostasis and act as an inhibitor of the 5'-UTR for APP to generate anti amyloid efficacy [108]. Tucker et al. employed western blotting experiments to demonstrate a consistent 20% reduction in the steady-state levels of APP holoprotein in the brain cortex of paroxetine treated mice [109]. Likewise, according to Payton et al. paroxetine decreased intracellular APP translation [110].

Recent studies have looked at the implications of SSRI's for enhancing cognitive abilities in the context of AD. SSRI's have been shown to be beneficial to hippocampal function with chronic use because they increase NSCs both *in vivo* and *in vitro* through up-regulating phosphorylation of GSK-3β, which in turn modulates the 5-HT_{1A} receptor [111–113]. Fluoxetine and imipramine, two other SSRI's, can reverse the loss of NSCs, so Paroxetine may have this capability as well [114]. Furthermore, Paroxetine has been shown to increase neurogenesis in human stem cells and in rats and improve memory after cerebral ischemia in a rat model [115–118]. Along with Paroxetine, other anti-depressants like amitriptyline, which is a tricyclic antidepressant, have been shown to increase levels of a non-toxic Aβ peptide and neurogenesis [119]. However, one study showed that Paroxetine does not increase total granular neurons or spatial memory [120]. More research needs to be done to determine the effects of Paroxetine and other antidepressant drugs on neurogenesis in AD patients specifically. A 2017 study has shown that Paroxetine can increase ROS, mitochondrial dysfunction and astrocyte apoptosis, so more research about the downsides of Paroxetine is also required [121].

Desferrioxamine (DFO)

Desferrioxamine (DFO) is an FDA approved drug for treatment of iron overload from blood transfusions and it is a potent iron and aluminum chelator. DFO works by binding to metals to create iron displacement and this displacement ultimately prevents the Fenton reaction [122]. DFO has had several benefits for AD patients. First, daily doses of intramuscular (IM)

DFO slowed the progression of AD by decreasing tau and either reduced inflammation or free radical production [49,57]. Second, DFO inhibited the tau protein from hyperphosphorylation *via* GSK-3β [123]. Third, the drug slowed cognitive decline in transgenic APP/PS1 mice and nontransgenic mice and increased memory in an AD rat model [124–126]. Finally, DFO has been proven to inhibit Aβ deposits and apoptosis in the brain of APP/PS1 double transgenic mice [127]. Iron chelators such as DFO are attractive agents that merit further investigation for use in AD. A recent study has shown that iron-chelating nanogels containing DFO components may be more effective for treating iron overload than DFO itself and more research about these nanogels is required [128,129].

N-acetylcysteine (NAC)

NAC is currently an FDA approved antioxidant and it has been shown to suppress the inflammatory nuclear factor-kappa B (NF-kB), which has been implicated in AD [130,131]. NAC works by reducing reactive oxygen species and apoptosis and by modulating glutathione levels [132–134]. Another benefit of NAC is that it enables neuritogenesis and differentiation of stem cells [135]. One recent study showed that NAC reverses oxidative stress due to anxiety in a zebrafish model [136]. There are very few studies on the efficacy of NAC for treating AD and one concern about NAC is its low membrane permeability, but more information on the subject is needed [137].

Posiphen/phenserine/JTR selective APP inhibitors

Phenserine both inhibits the 5'UTR of APP and also has AChEI properties, furthermore, it reduces APP expression in response to IL-1β and it inhibits translation of APP [138,139]. Posiphen is an enantiomer of phenserine and it is not an AChEI. Both posiphen and phenserine metabolites exhibit neuroprotective behaviors [140]. Furthermore, a recent study explored the relationship between phenserine and its inhibition of Pre-Programmed Cell Death (PPCD), which is a feature of Alzheimer's and this study serves as a starting model for further research [141]. However, how phenserine promotes neuroprotection or acts as an APP translation blockade is unknown. Despite the biological benefits, there have been statistical controversies over the efficacy of posiphen and phenserine, based on their clinical trials [142]. More information is required concerning posiphen and phenserine.

Along with posiphen/phenserine, another preclinical compound mentioned previously in this review, designated as JTR-009, more effectively blocks APP translation *via* the 5' UTR than phenserine and posiphen. JTR-009 inhibited the APP 5'UTR to directly limit Aβ [39,108]. JTR-009 has an IC_{50}=100 nM inhibition value for the 5' UTR region of APP, while posiphen has an IC_{50}=5μM inhibition value [39,143]. JTR-009 is an interesting compound and more current research about its properties is required.

Carvedilol

Carvedilol is an FDA approved agent which blocks the beta adrenergic receptor and is mainly prescribed for high blood pressure [144]. Carvedilol protects against Aluminum toxicity and a recent study has shown that aluminum oxide particles inhibit spatial learning and memory [145,146]. However, it is unclear if this drug affects iron homeostasis [145]. Carvedilol has also been shown to decrease IL-1β levels, so it could possibly promote

neurogenesis because IL-1β has been shown to decrease neurogenesis [147]. Furthermore, in one study, carvedilol prevented toxicity *via* Aβ, reduced ROS levels and decreased apoptosis signaling in mice Neuro 2a (N2a) cells [148]. Carvedilol is the only screened compound of its kind for its effects on various components of AD and whether or not other beta blocker drugs such as propranolol or metoprolol could produce similar effects is unknown.

LY450139

Pharmacologically, γ-secretase inhibitors like LY450139 (also known as Semagcestat) could potentially prevent APP progression into Aβ, previous studies have shown that γ-secretase inhibitors reduce Aβ peptides *in vitro* and one study has shown that LY450139 reduces Aβ *in vivo* [149–151]. A few studies in particular have demonstrated the positive effects of LY450139. In one study, the drug was shown to target Aβ and PS-1 by increasing the $Aβ_{40}$/$Aβ_{42}$ ratio [152]. Another study showed that it reduced newly synthesized Aβ peptides and yet another showed that it improved cognition in patients that had medium to high levels of Aβ [153,154].

However, there are several issues with LY450139 1) it worsened cognitive abilities in AD patients in some research settings, 2) it showed an increase in skin cancer and 3) it is neurotoxic (decreases dendritic spine density) [149,155,156]. In summary, this drug is a promising compound for the reduction of Aβ, nevertheless, like other drugs that showed initial promise, LY450139 has not been well tolerated in clinical trials, it has been terminated at phase 3 and other γ-secretase inhibitors have also been unsuccessful thus far [157–159]. Perhaps a formula that combines LY450139 with a less problematic drug would be more successful, as LY450139 does have some positive molecular capabilities but seems to be harmful to patients. One study suggests that the drug has failed in clinical trials because modulators of activity surrounding γ-secretase can aid in the progression of Alzheimer's and that moderate inhibition of γ-secretase does not have beneficial effects, LY450139 may only be moderately inhibiting γ-secretase and this may be the reason that it has been unsuccessful [160]. Furthermore, an intriguing study complicates the discussion about this drug, as it states that Semagcestat is not actually a γ-secretase inhibitor and the results of this study warrant further investigation as to the true role of LY450139 [161]. LY450139 has some promising molecular capabilities despite its flaws, so its potential for AD should continue to be explored.

IVIG 10%

IVIG (intravenous immunoglobulin) is an FDA approved biologic for the treatment of autoimmune diseases like Kawasaki disease [162]. A recent phase 3 clinical trial of IVIG for Alzheimer's patients showed that the drug did not measurably improve cognition or function in a time span of 18 months, however, an older study showed that it increased Mini-Mental State Examination (MMSE) results over a 6 month period [163,164]. Moreover, many studies have indicated that IVIG treatment has many benefits for the AD brain, such as: 1) protecting against Aβ toxicity, 2) protecting against oxidative stress, 3) inhibiting levels of IL-1β and 4) promoting beneficial synaptic function [164–168]. One study has shown that IVIG treatment increased neurogenesis [10]. Studies have yet to be conducted about whether IVIG treatments may mediate or even block activation of the APP 5' UTR specific IL-1

responsive acute box element when APP translation is induced in a pro-amyloidogenic pathway. These studies could reveal another mechanism by which immune suppressing antibodies may carry out beneficial effects for AD patients.

Indomethacin and other NSAIDS

Neuroinflammation has been strongly implicated in AD pathology and non-steroidal anti-inflammatory drugs (NSAIDs) like Indomethacin may reduce the expression and signaling of neuroinflammatory cytokines IL-1β and IL-6 [70,169]. This reduction may help to slow the progression of AD at early stages. Indomethacin and other NSAIDs have also been shown to prevent the Aβ plaques found in AD by indirectly inhibiting the effects of Aβ aggregation *via* IL-1β and Indomethacin has been proven to reduce oxidative stress in the rat brain [170,171].

Furthermore, NSAIDS affect neurogenesis, a recent study showed that Indomethacin helped to improve decreased neurogenesis due to alcohol exposure, while another from 2017 showed that it elevated numbers of new hippocampal neurons [172,173]. A recent review discusses relevant research surrounding NSAIDS and Alzheimer's, particularly in the context of the allegedbutsofarunclearneuroprotective role of NSAIDS and proposes that low concentrations of NSAIDS may be neuroprotective because of their inhibition of mitochondrial calcium overload [174,175]. Although indomethacin and other NSAIDS have some promising capabilities, the drugs have produced mixed effects in AD clinical trials and their precise mechanism of action on AD is still unclear, therefore, more research is required [176,177].

Lithium carbonate (Li_2CO_3)

Lithium Carbonate (Li2CO3) is an FDA approved agent used to treat Bipolar disorder and other behavioral disorders. Research has shown that Lithium Carbonate can inhibit GSK-3β and GSK-3β is known to increase tau neurofibrils *via* tau phosphorylation [178,179]. In addition, an increase in GSK-3 was implicated in Aβ-induced neurodegeneration [180]. Additionally, Li_2CO_3 protects newly proliferated neurons and other hippocampal neurons and increases neural precursors, but it is unknown if the compound is neurogenic or if it simply increases fetal progenitors [181–183]. However, Lithium Carbonate can cause serious side effects in AD patients and a 2017 study proposed that ionic co-crystal of Lithium Salicylate and 1-Proline (LISPRO) is a more effective form of Lithium (Li) treatment for Alzheimer's because it creates higher and more stable levels of Li, is safer for patients and significantly reduced Aβ and tau-phosphorylation [184]. More research about this alternate form of Li is needed.

Furthermore, Li is also of interest to the APP 5' UTR translation model. It is an alkali metal that may impart anti-amyloid therapy by competing with iron to bind to the IRE RNA stem loop in APP mRNA. Therefore, it is critical to test the anti-amyloid efficacy of lithium *via* the IRP/APP IRE interaction in the 5' UTR of APP transcript while noting that Li, at the same time, may enhance neurogenesis.

Conclusion

AD is an extremely complex, polygenic and multifactorial disease that incorporates several biochemical proteins such as Tau, APP, Aβ, etc. Since AD is so complex, the development of new pharmaceuticals is necessary to combat such a detrimental disease. There are currently only four FDA approved medications that treat AD symptoms: donepezil, galantamine, rivastigmine and memantine. They work by either inhibiting AChE or antagonizing NMDA receptors, however, they present issues. The treatments only slow the cognitive decline by increasing ACh or attempting to prevent neural damage by Glu neurotoxicity and no current treatment can fully stop or slow down the progression of the disease. The discussed experimental treatments in this review show great promise for arresting AD pathology. However, there are also several downsides to these treatments. While many of the drugs discussed have relevant molecular properties, some have not worked well in clinical trials. In addition, there is still a lack of research about these experimental treatments. The treatments listed in this review are not the only drugs currently being tested and more research needs to be done about the effectiveness of these drugs and others in the context of AD.

Furthermore, neurogenesis in AD patients is severely reduced and most of the discussed treatments have had a positive effect on neurogenesis in some studies, however, it is not entirely known how these drugs actually affect neurogenesis. It is also unclear how these drugs affect the anatomy of the brain. Further insights into the way neurogenic processes can establish new neurons and new connections between neurons and the way that alternative drug treatments for AD affects these processes are necessary, because neurons in the brain can become so vulnerable to AD.

Acknowledgments

Funding

This work was supported in part by the Psychiatry Department of Massachusetts General Hospital (MGH). JTR was supported by the Zenith Fellows award from the Alzheimer's Association and a grant from the Michael J. Fox Foundation. XH is supported by a NIH grant-R01AG056614.

References

1. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, et al. (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7: 270–279. [PubMed: 21514249]
2. Rajan KB, Wilson RS, Weuve J, Barnes LL, Evans DA (2015) Cognitive impairment 18 years before clinical diagnosis of Alzheimer disease dementia. Neurology 85: 898–904. [PubMed: 26109713]
3. Anstey KJ, Mack HA, Cherbuin N (2009) Alcohol consumption as a risk factor for dementia and cognitive decline: Meta-analysis of prospective studies. Am J Geriatr Psychiatry 17: 542–555. [PubMed: 19546653]
4. Self RL, Smith KJ, Mulholland PJ, Prendergast MA (2005) Ethanol exposure and withdrawal sensitizes the rat hippocampal CA1 pyramidal cell region to beta-amyloid (25–35)-induced cytotoxicity: NMDA receptor involvement. Alcohol Clin Exp Res 29: 2063–2069. [PubMed: 16340465]

5. Matthews FE, Brayne C, Lowe J, McKeith I, Wharton SB, et al. (2009) Epidemiological pathology of dementia: Attributable-risks at death in the Medical Research Council Cognitive Function and Ageing Study. PLoS Med 6: e1000180. [PubMed: 19901977]
6. Alcolea D, Martinez-Lage P, Sanchez-Juan P, Olazaran J, Antunez C, et al. (2015) Amyloid precursor protein metabolism and inflammation markers in preclinical Alzheimer disease. Neurology 85: 626–633. [PubMed: 26180139]
7. Hori Y, Hashimoto T, Nomoto H, Hyman BT, Iwatsubo T (2018) Role of apolipoprotein E in beta-amyloidogenesis: Isoform-specific effects on protofibril to fibril conversion of Abeta in vitro and brain Abeta deposition in vivo. J Biol Chem 293: 7267. [PubMed: 29752420]
8. Carter DB (2005) The interaction of amyloid-beta with ApoE. Subcell Biochem 38: 255–272. [PubMed: 15709483]
9. Cahill CM, Lahiri DK, Huang X, Rogers JT (2009) Amyloid precursor protein and alpha synuclein translation, implications for iron and inflammation in neurodegenerative diseases. Biochim Biophys Acta 1790: 615–628. [PubMed: 19166904]
10. Heikkinen R, Malm T, Heikkila J, Muona A, Tanila H, et al. (2004) Susceptibility to focal and global brain ischemia of Alzheimer mice displaying abeta deposits: Effect of immunoglobulin. Aging Dis 5: 76–87.
11. Campbell SN, Zhang C, Monte L, Roe AD, Rice KC, et al. (2015) Increased tau phosphorylation and aggregation in the hippocampus of mice overexpressing corticotropin-releasing factor. J Alzheimers Dis 43: 967–976. [PubMed: 25125464]
12. Rothman SM, Mattson MP (2010) Adverse stress, hippocampal networks and Alzheimer's disease. Neuromolecular Med 12: 56–70. [PubMed: 19943124]
13. Boots EA, Schultz SA, Clark LR, Racine AM, Darst BF, et al. (2017) BDNF Val66Met predicts cognitive decline in the Wisconsin Registry for Alzheimer's Prevention. Neurology 88: 2098–2106. [PubMed: 28468845]
14. Ohta S, Ohsawa I (2006) Dysfunction of mitochondria and oxidative stress in the pathogenesis of Alzheimer's disease: On defects in the cytochrome c oxidase complex and aldehyde detoxification. J Alzheimers Dis 9: 155–166.
15. Lei P, Ayton S, Finkelstein DI, Spoerri L, Ciccotosto GD, et al. (2012) Tau deficiency induces parkinsonism with dementia by impairing APP-mediated iron export. Nat Med 18: 291–295. [PubMed: 22286308]
16. Connor JR, Milward EA, Moalem S, Sampietro M, Boyer P, et al. (2001) Is hemochromatosis a risk factor for Alzheimer's disease? J Alzheimers Dis 3: 471–477. [PubMed: 12214033]
17. Ayton S, Lei P, Bush AI (2013) Metallostasis in Alzheimer's disease. Free Radic Biol Med 62: 76–89. [PubMed: 23142767]
18. Huang X, Moir RD, Tanzi RE, Bush AI, Rogers JT (2004) Redox-active metals, oxidative stress, and Alzheimer's disease pathology. Ann N Y Acad Sci 1012: 153–163. [PubMed: 15105262]
19. Glenner GG, Wong CW (1984) Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. Biochem Biophys Res Commun 120: 885–890. [PubMed: 6375662]
20. Ali T, Yoon GH, Shah SA, Lee HY, Kim MO (2015) Osmotin attenuates amyloid beta-induced memory impairment, tau phosphorylation and neurodegeneration in the mouse hippocampus. Sci Rep 5: 11708. [PubMed: 26118757]
21. Lloret A, Fuchsberger T, Giraldo E, Vina J (2015) Molecular mechanisms linking amyloid beta toxicity and Tau hyperphosphorylation in Alzheimers disease. Free Radic Biol Med 83: 186–191. [PubMed: 25746773]
22. Kuhn HG, Dickinson-Anson H, Gage FH (1996) Neurogenesis in the dentate gyrus of the adult rat: Age-related decrease of neuronal progenitor proliferation. J Neurosci 16: 2027–2033. [PubMed: 8604047]
23. Kempermann G, Kuhn HG, Winkler J, Gage FH (1998) New nerve cells for the adult brain. Adult neurogenesis and stem cell concepts in neurologic research. Nervenarzt 69: 851–857. [PubMed: 9834473]

24. Knoth R, Singec I, Ditter M, Pantazis G, Capetian P, et al. (2010) Murine features of neurogenesis in the human hippocampus across the lifespan from 0 to 100 years. PloS one 5: e8809. [PubMed: 20126454]
25. Dubinina EE, Schedrina LV, Neznanov NG, Zalutskaya NM, Zakharchenko DV (2015) Oxidative stress and its effect on cells functional activity of Alzheimer's disease. Biomed Khim 61: 57–69. [PubMed: 25762599]
26. Zhou ZD, Chan CH, Ma QH, Xu XH, Xiao ZC, et al. (2011) The roles of amyloid precursor protein (APP) in neurogenesis: Implications to pathogenesis and therapy of Alzheimer disease. Cell Adh Migr 5: 280–292. [PubMed: 21785276]
27. Hamilton A, Holscher C (2012) The effect of ageing on neurogenesis and oxidative stress in the APP(swe)/PS1(deltaE9) mouse model of alzheimer's disease. Brain Res 1449: 83–93. [PubMed: 22418058]
28. Prasanthi JR, Schrag M, Dasari B, Marwarha G, Dickson A, et al. (2012) Deferiprone reduces amyloid-beta and tau phosphorylation levels but not reactive oxygen species generation in hippocampus of rabbits fed a cholesterol-enriched diet. J Alzheimers Dis 30: 167–182. [PubMed: 22406440]
29. Saburova EA, Vasiliev AN, Kravtsova VV, Ryabova EV, Zefirov AL, et al. (2017) Human APP gene expression alters active zone distribution and spontaneous neurotransmitter release at the drosophila larval neuromuscular junction. Neural Plast 2017: 9202584.
30. Duce JA, Tsatsanis A, Cater MA, James SA, Robb E, et al. (2010) Iron-export ferroxidase activity of beta-amyloid precursor protein is inhibited by zinc in Alzheimer's disease. Cell 142: 857–867. [PubMed: 20817278]
31. Bergstrom P, Agholme L, Nazir FH, Satir TM, Toombs J, et al. (2016) Amyloid precursor protein expression and processing are differentially regulated during cortical neuron differentiation. Sci Rep 6: 29200. [PubMed: 27383650]
32. Borysov SI, Granic A, Padmanabhan J, Walczak CE, Potter H (2011) Alzheimer abeta disrupts the mitotic spindle and directly inhibits mitotic microtubule motors. Cell Cycle 10: 1397–1410. [PubMed: 21566458]
33. Zheng M, Liu J, Ruan Z, Tian S, Ma Y, et al. (2013) Intrahippocampal injection of Abeta1–42 inhibits neurogenesis and down-regulates IFN-gamma and NF-kappa B expression in hippocampus of adult mouse brain. Amyloid 20: 13–20. [PubMed: 23286786]
34. Bandyopadhyay S, Ni J, Ruggiero A, Walshe K, Rogers MS, et al. (2006) A high-throughput drug screen targeted to the 5'untranslated region of Alzheimer amyloid precursor protein mRNA. J Biomol Screen 11: 469–480. [PubMed: 16928984]
35. Rogers JT, Randall JD, Cahill CM, Eder PS, Huang X, et al. (2002) An iron-responsive element type II in the 5'-untranslated region of the Alzheimer's amyloid precursor protein transcript. J Biol Chem 277: 45518–45528. [PubMed: 12198135]
36. Bandyopadhyay S, Huang X, Cho H, Greig NH, Youdim MB, et al. (2006) Metal specificity of an iron-responsive element in Alzheimer's APP mRNA 5'untranslated region, tolerance of SH-SY5Y and H4 neural cells to desferrioxamine, clioquinol, VK-28 and a piperazine chelator. J Neural Transm 71: 237–247.
37. Venti A, Giordano T, Eder P, Bush AI, Lahiri DK, et al. (2004) The integrated role of desferrioxamine and phenserine targeted to an iron-responsive element in the APP-mRNA 5'-untranslated region. Ann N Y Acad Sci 1035: 34–48. [PubMed: 15681799]
38. Morse LJ, Payton SM, Cuny GD, Rogers JT (2004) FDA-preapproved drugs targeted to the translational regulation and processing of the amyloid precursor protein. J Mol Neurosci 24: 129–136. [PubMed: 15314261]
39. Bandyopadhyay S, Cahill C, Balleidier A, Huang C, Lahiri DK, et al. (2013) Novel 5' untranslated region directed blockers of iron-regulatory protein-1 dependent amyloid precursor protein translation: Implications for down syndrome and Alzheimer's disease. PloS one 8: e65978. [PubMed: 23935819]
40. Green KN, Billings LM, Roozendaal B, McGaugh JL, LaFerla FM (2006) Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. J Neurosci 26: 9047–9056. [PubMed: 16943563]

41. Tamaoka A, Odaka A, Ishibashi Y, Usami M, Sahara N, et al. (1994) APP717 missense mutation affects the ratio of amyloid beta protein species (A beta 1–42/43 and a beta 1–40) in familial Alzheimer's disease brain. J Biol Chem 269: 32721–32724. [PubMed: 7806491]
42. Haughey NJ, Nath A, Chan SL, Borchard AC, Rao MS, et al. (2002) Disruption of neurogenesis by amyloid beta-peptide and perturbed neural progenitor cell homeostasis, in models of Alzheimer's disease. J Neurochem 83: 1509–1524. [PubMed: 12472904]
43. Liu L, Rando TA (2011) Manifestations and mechanisms of stem cell aging. J Cell Biol 193: 257–266. [PubMed: 21502357]
44. Salminen A, Ojala J, Kauppinen A, Kaarniranta K, Suuronen T (2009) Inflammation in Alzheimer's disease: Amyloid-beta oligomers trigger innate immunity defence via pattern recognition receptors. Prog Neurobiol 87: 181–194. [PubMed: 19388207]
45. Cheignon C, Tomas M, Bonnefont-Rousselot D, Faller P, Hureau C, et al. (2018) Oxidative stress and the amyloid beta peptide in Alzheimer's disease. Redox Biol 14: 450–464. [PubMed: 29080524]
46. Binder LI, Frankfurter A, Rebhun LI (1985) The distribution of tau in the mammalian central nervous system. J Cell Biol 101: 1371–1378. [PubMed: 3930508]
47. Hof PR, Nimchinsky EA, Buee-Scherrer V, Buee L, Nasrallah J, et al. (1994) Amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam: Quantitative neuropathology, immunohistochemical analysis of neuronal vulnerability and comparison with related neurodegenerative disorders. Acta Neuropathol 88: 397–404. [PubMed: 7847067]
48. Hirano A, Malamud N, Kurland LT (1961) Parkinsonism-dementia complex, an endemic disease on the island of Guam. II. Pathological features. Brain J Neurol 84: 662–679.
49. Lieberman AP, Trojanowski JQ, Lee VM, Balin BJ, Ding XS, et al. (1998) Cognitive, neuroimaging and pathological studies in a patient with Pick's disease. Ann Neurol 43: 259–265. [PubMed: 9485069]
50. Komuro Y, Xu G, Bhaskar K, Lamb BT (2015) Human tau expression reduces adult neurogenesis in a mouse model of tauopathy. Neurobiol Aging 36: 2034–2042. [PubMed: 25863528]
51. Schmitz M, Wulf K, Signore SC, Schulz-Schaeffer WJ, Kermer P, et al. (2014) Impact of the cellular prion protein on amyloid-beta and 3PO-tau processing. J Alzheimer's Dis 38: 551–565. [PubMed: 24028865]
52. Younan ND, Chen KF, Rose RS, Crowther DC, Viles JH (2018) Prion protein stabilizes amyloid-beta (Aβ) oligomers and enhances Aβ neurotoxicity in a Drosophila model of Alzheimer disease. J Biol Chem 293: 13090–13099. [PubMed: 29887525]
53. Hong M, Lee VM (1997) Insulin and insulin-like growth factor-1 regulate tau phosphorylation in cultured human neurons. J Biol Chem 272: 19547–19553. [PubMed: 9235959]
54. Muyllaert D, Terwel D, Borghgraef P, Devijver H, Dewachter I, et al. (2006) Transgenic mouse models for Alzheimer's disease: The role of GSK-3B in combined amyloid and tau-pathology. Rev Neurol (Paris) 162: 903–907. [PubMed: 17028556]
55. Sun LH, Ban T, Liu CD, Chen QX, Wang X, et al. (2015) Activation of Cdk5/p25 and tau phosphorylation following chronic brain hypo perfusion in rats involves microRNA-195 down-regulation. J Neurochem 134: 1139–1151. [PubMed: 26118667]
56. Noble W, Planel E, Zehr C, Olm V, Meyerson J, et al. (2005) Inhibition of glycogen synthase kinase-3 by lithium correlates with reduced tauopathy and degeneration in vivo. Proc Natl Acad Sci U S A 102: 6990–6995. [PubMed: 15867159]
57. Yang H, Guan H, Yang M, Liu Z, Takeuchi S, et al. (2015) Upregulation of mitochondrial ferritin by proinflammatory cytokines: Implications for a role in Alzheimer's disease. J Alzheimers Dis 45: 797–811. [PubMed: 25624418]
58. Yan B, Han P, Pan L, Lu W, Xiong J, et al. (2014) IL-1beta and reactive oxygen species differentially regulate neutrophil directional migration and Basal random motility in a zebra fish injury-induced inflammation model. J Immunol 192: 5998–6008. [PubMed: 24835391]
59. Dinarello CA (2011) Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. Blood 117: 3720–3732. [PubMed: 21304099]

60. Pearson VL, Rothwell NJ, Toulmond S (1999) Excitotoxic brain damage in the rat induces interleukin-1beta protein in microglia and astrocytes: Correlation with the progression of cell death. Glia 25: 311–323. [PubMed: 10028914]
61. Scripter JL, Ko J, Kow K, Arimura A, Ide CF (1997) Regulation by interleukin-1beta of formation of a line of delimiting astrocytes following prenatal trauma to the brain of the mouse. Exp Neurol 145: 329–341. [PubMed: 9217070]
62. Wang L, Jiang Q, Chu J, Lin L, Li XG, et al. (2013) Expression of Tau40 induces activation of cultured rat microglial cells. PloS one 8: e76057. [PubMed: 24146816]
63. Ben-Sasson SZ, Hu-Li J, Quiel J, Cauchetaux S, Ratner M, et al. (2009) IL-1 acts directly on CD4 T cells to enhance their antigen-driven expansion and differentiation. Proc Natl Acad Sci U S A 106: 7119–7124. [PubMed: 19359475]
64. Rogers JT, Leiter LM, McPhee J, Cahill CM, Zhan SS, et al. (1999) Translation of the alzheimer amyloid precursor protein mRNA is up-regulated by interleukin-1 through 5'-untranslated region sequences. J Biol Chem 274: 6421–6431. [PubMed: 10037734]
65. Kitazawa M, Oddo S, Yamasaki TR, Green KN, LaFerla FM (2005) Lipopolysaccharide-induced inflammation exacerbates tau pathology by a cyclin-dependent kinase 5-mediated pathway in a transgenic model of Alzheimer's disease. J Neurosci 25: 8843–8853. [PubMed: 16192374]
66. Parajuli B, Sonobe Y, Horiuchi H, Takeuchi H, Mizuno T, et al. (2013) Oligomeric amyloid beta induces IL-1beta processing via production of ROS: Implication in Alzheimer's disease. Cell Death Dis 4: e975. [PubMed: 24357806]
67. Wang HM, Zhang T, Huang JK, Xiang JY, Chen JJ, et al. (2017) Edaravone attenuates the proinflammatory response in amyloid-beta-treated microglia by inhibiting NLRP3 inflammasome-mediated IL-1beta secretion. Cell Physiol Biochem 43: 1113–1125. [PubMed: 28977782]
68. Jimbo K, Park JS, Yokosuka K, Sato K, Nagata K (2005) Positive feedback loop of interleukin-1beta upregulating production of inflammatory mediators in human intervertebral disc cells in vitro. J Neurosurg Spine 2: 589–595. [PubMed: 15945434]
69. Arranz L, Arriero MDM, Villatoro A (2017) Interleukin-1beta as emerging therapeutic target in hematological malignancies and potentially in their complications. Blood Rev 31: 306–317. [PubMed: 28495184]
70. Monje ML, Toda H, Palmer TD (2003) Inflammatory blockade restores adult hippocampal neurogenesis. Sci 302: 1760–1765.
71. O'Leime CS, Cryan JF, Nolan YM (2017) Nuclear deterrents: Intrinsic regulators of IL-1beta-induced effects on hippocampal neurogenesis. Brain Behav Immun 66: 394–412. [PubMed: 28751020]
72. Fiorentini A, Rosi MC, Grossi C, Luccarini I, Casamenti F (2010) Lithium improves hippocampal neurogenesis, neuropathology and cognitive functions in APP mutant mice. PloS one 5: e14382. [PubMed: 21187954]
73. Donovan MH, Yazdani U, Norris RD, Games D, German DC, et al. (2006) Decreased adult hippocampal neurogenesis in the PDAPP mouse model of Alzheimer's disease. J Comp Neurol 495: 70–83. [PubMed: 16432899]
74. Hollands C, Bartolotti N, Lazarov O (2016) Alzheimer's disease and hippocampal adult neurogenesis; exploring shared mechanisms. Front Neurosci 10: 178. [PubMed: 27199641]
75. Demars M, Hu YS, Gadadhar A, Lazarov O (2010) Impaired neurogenesis is an early event in the etiology of familial Alzheimer's disease in transgenic mice. J Neurosci Res 88: 2103–2017. [PubMed: 20209626]
76. Demars MP, Hollands C, Kda TZ, Lazarov O (2013) Soluble amyloid precursor protein-alpha rescues age-linked decline in neural progenitor cell proliferation. Neurobiol Aging 34: 2431–240. [PubMed: 23683827]
77. Brezun JM, Daszuta A (1999) Depletion in serotonin decreases neurogenesis in the dentate gyrus and the subventricular zone of adult rats. Neurosci 89: 999–1002.
78. Kiyota T, Morrison CM, Tu G, Dyavarshetty B, Weir RA, et al. (2015) Presenilin-1 familial Alzheimer's disease mutation alters hippocampal neurogenesis and memory function in CCL2 null mice. Brain Behav Immun 49: 311–321. [PubMed: 26112421]

79. Lazarov O, Marr RA (2010) Neurogenesis and alzheimer's disease: At the crossroads. Exp Neurol 223: 267–281. [PubMed: 19699201]
80. Attems J, Jellinger KA (2006) Olfactory tau pathology in alzheimer disease and mild cognitive impairment. Clin Neuropathol 25: 265–271. [PubMed: 17140156]
81. Yiannopoulou KG, Papageorgiou SG (2013) Current and future treatments for Alzheimer's disease. Ther Adv Neurol Disord 6: 19–33. [PubMed: 23277790]
82. Pohanka M (2012) Acetylcholinesterase inhibitors: A patent review (2008-present). Expert Opin Ther Pat 22: 871–86. [PubMed: 22768972]
83. Francis PT (2005) The interplay of neurotransmitters in Alzheimer's disease. CNS Spectr 10: 6–9.
84. Zhang Y, Wang J, Wang C, Li Z, Liu X, et al. (2018) Pharmacological basis for the use of evodiamine in alzheimer's disease: Antioxidation and antiapoptosis. Int J Mol Sci 19: 1527.
85. Bullock R, Lane R (2007) Executive dyscontrol in dementia, with emphasis on subcortical pathology and the role of butyrylcholinesterase. Curr Alzheimer Res 4: 277–293. [PubMed: 17627485]
86. de Oliveira FF, Bertolucci PH, Chen ES, Smith MC (2014) Assessment of risk factors for earlier onset of sporadic Alzheimer's disease dementia. Neurol India 62: 625–630. [PubMed: 25591674]
87. Kihara T, Shimohama S (2004) Alzheimer's disease and acetylcholine receptors. Acta Neurobiol Exp 64: 99–105.
88. Gambi F, Reale M, Iarlori C, Salone A, Toma L, et al. (2004) Alzheimer patients treated with an AchE inhibitor show higher IL-4 and lower IL-1 beta levels and expression in peripheral blood mononuclear cells. J Clin Psychopharmacol 24: 314–321. [PubMed: 15118486]
89. Anand P, Singh B (2013) A review on cholinesterase inhibitors for Alzheimer's disease. Arch Pharm Res 36: 375–399. [PubMed: 23435942]
90. Ellis JM (2005) Cholinesterase inhibitors in the treatment of dementia. J Am Osteopath Assoc 105: 145–158. [PubMed: 15863734]
91. Colovic MB, Krstic DZ, Lazarevic-Pasti TD, Bondzic AM, Vasic VM (2013) Acetylcholinesterase inhibitors: Pharmacology and toxicology. Curr Neuropharmacol 11: 315–335. [PubMed: 24179466]
92. Wang R, Reddy PH (2017) Role of glutamate and NMDA receptors in alzheimer's disease. J Alzheimer's Dis 57: 1041–1048. [PubMed: 27662322]
93. Ankarcrona M, Dypbukt JM, Bonfoco E, Zhivotovsky B, Orrenius S, et al. (1995) Glutamate-induced neuronal death: a succession of necrosis or apoptosis depending on mitochondrial function. Neuron 15: 961–973. [PubMed: 7576644]
94. Frankiewicz T, Parsons CG (1999) Memantine restores long term potentiation impaired by tonic N-methyl-D-aspartate (NMDA) receptor activation following reduction of Mg2+ in hippocampal slices. Neuropharmacology 38: 1253–1259. [PubMed: 10471078]
95. Frankiewicz T, Pilc A, Parsons CG (2000) Differential effects of NMDA-receptor antagonists on long-term potentiation and hypoxic/hypoglycaemic excitotoxicity in hippocampal slices. Neuropharmacology 39: 631–642. [PubMed: 10728884]
96. Frankiewicz T, Potier B, Bashir ZI, Collingridge GL, Parsons CG (1996) Effects of memantine and MK-801 on NMDA-induced currents in cultured neurones and on synaptic transmission and LTP in area CA1 of rat hippocampal slices. Br J Pharmacol 117: 689–697. [PubMed: 8646415]
97. Atluri P, Fleck MW, Shen Q, Mah SJ, Stadfelt D, et al. (2001) Functional nicotinic acetylcholine receptor expression in stem and progenitor cells of the early embryonic mouse cerebral cortex. Dev Biol 240: 143–156. [PubMed: 11784052]
98. Bernabeu R, Sharp FR (2000) NMDA and AMPA/kainate glutamate receptors modulate dentate neurogenesis and CA3 synapsin-I in normal and ischemic hippocampus. J Cereb Blood Flow Metab 20: 1669–1680. [PubMed: 11129783]
99. Akaike A (2006) Preclinical evidence of neuroprotection by cholinesterase inhibitors. Alzheimer Dis Assoc Disord 20: S8–11. [PubMed: 16772755]
100. Karolczak D, Sawicka E, Dorszewska J, Radel A, Bodnar M, et al. (2013) Memantine-neuroprotective drug in aging brain. Pol J Pathol 64: 196–203. [PubMed: 24166606]

101. Jin K, Xie L, Mao XO, Greenberg DA (2006) Alzheimer's disease drugs promote neurogenesis. Brain Res 1085: 183–188. [PubMed: 16580645]
102. Kotani S, Yamauchi T, Teramoto T, Ogura H (2008) Donepezil, an acetylcholinesterase inhibitor, enhances adult hippocampal neurogenesis. Chem Biol Interact 175: 227–230. [PubMed: 18501884]
103. Taupin P (2010) A dual activity of ROS and oxidative stress on adult neurogenesis and Alzheimer's disease. Cent Nerv Syst Agents Med Chem 10: 16–21. [PubMed: 20236039]
104. Folch J, Ettcheto M, Petrov D, Abad S, Pedros I, et al. (2018) Review of the advances in treatment for alzheimer disease: Strategies for combating beta-amyloid protein. Neurologia 33: 47–58. [PubMed: 25976937]
105. Cummings J, Lee G, Mortsdorf T, Ritter A, Zhong K (2017) Alzheimer's disease drug development pipeline: 2017. Alzheimers Dement 3: 367–384.
106. Pollack MH, Zaninelli R, Goddard A, McCafferty JP, Bellew KM, et al. (2001) Paroxetine in the treatment of generalized anxiety disorder: Results of a placebo-controlled, flexible-dosage trial. J Clin Psychiatry 62: 350–357. [PubMed: 11411817]
107. Purgato M, Papola D, Gastaldon C, Trespidi C, Magni LR, et al. (2014) Paroxetine versus other anti-depressive agents for depression. Cochrane Database Syst Rev 4: CD006531.
108. Bandyopadhyay S, Rogers JT (2014) Alzheimer's disease therapeutics targeted to the control of amyloid precursor protein translation: maintenance of brain iron homeostasis. Biochem Pharmacol 88: 486–494. [PubMed: 24513321]
109. Tucker S, Ahl M, Cho HH, Bandyopadhyay S, Cuny GD, et al. (2006) RNA therapeutics directed to the non coding regions of APP mRNA, in vivo anti-amyloid efficacy of paroxetine, erythromycin and N-acetyl cysteine. Curr Alzheimer Res 3: 221–227. [PubMed: 16842099]
110. Payton S, Cahill CM, Randall JD, Gullans SR, Rogers JT (2003) Drug discovery targeted to the Alzheimer's APP mRNA 5'-untranslated region: the action of paroxetine and dimercaptopropanol. J Mol Neurosci 20: 267–275. [PubMed: 14501007]
111. Segi-Nishida E (2017) The effect of serotonin-targeting antidepressants on neurogenesis and neuronal maturation of the hippocampus mediated via 5-HT1A and 5-HT4 receptors. Front Cell Neurosci 11: 142. [PubMed: 28559799]
112. Okamoto H, Voleti B, Banasr M, Sarhan M, Duric V, et al. (2010) Wnt2 expression and signaling is increased by different classes of antidepressant treatments. Biol Psychiatry 68: 521–527. [PubMed: 20570247]
113. Meunier CNJ, Cancela JM, Fossier P (2017) Lack of GSK3beta activation and modulation of synaptic plasticity by dopamine in 5-HT1A-receptor KO mice. Neuropharmacology 113: 124–136. [PubMed: 27678414]
114. Hitoshi S, Maruta N, Higashi M, Kumar A, Kato N, et al. (2007) Antidepressant drugs reverse the loss of adult neural stem cells following chronic stress. J Neurosci Res 85: 3574–3585. [PubMed: 17668856]
115. Jahromi M, Razavi S, Amirpour N, Khosravizadeh Z (2016) Paroxetine can enhance neurogenesis during neurogenic differentiation of human adipose-derived stem cells. Avicenna J Med Biotechnol 8: 152–158. [PubMed: 27920882]
116. Vichier-Guerre C, Parker M, Pomerantz Y, Finnell RH, Cabrera RM (2017) Impact of selective serotonin reuptake inhibitors on neural crest stem cell formation. Toxicol Lett 281: 20–25. [PubMed: 28844482]
117. Peng ZW, Xue F, Wang HN, Zhang RG, Chen YC, et al. (2013) Paroxetine up-regulates neurogenesis in hippocampus-derived neural stem cell from fetal rats. Mol Cell Biochem 375: 105–113. [PubMed: 23291919]
118. Naderi Y, Parvardeh S, Zanjani TM, Sabetkasaei M (2018) Neuroprotective effect of paroxetine on memory deficit induced by cerebral ischemia after transient bilateral occlusion of common carotid arteries in rat. Iran J Pharm Res 17: 215–224. [PubMed: 29755553]
119. Chadwick W, Mitchell N, Caroll J, Zhou Y, Park SS, et al. (2011) Amitriptyline-mediated cognitive enhancement in aged 3xTg Alzheimer's disease mice is associated with neurogenesis and neurotrophic activity. PloS One 6: e21660. [PubMed: 21738757]

120. Olesen LO, Sivasaravanaparan M, Severino M, Babcock AA, Bouzinova EV, et al. (2017) Neuron and neuroblast numbers and cytogenesis in the dentate gyrus of aged APPswe/PS1dE9 transgenic mice: Effect of long-term treatment with paroxetine. Neurobiol Dis 104: 50–60. [PubMed: 28461249]

121. Then CK, Liu KH, Liao MH, Chung KH, Wang JY, et al. (2017) Antidepressants, sertraline and paroxetine, increase calcium influx and induce mitochondrial damage-mediated apoptosis of astrocytes. Oncotarget 8: 115490–115502. [PubMed: 29383176]

122. Bibi H, Vinokur V, Waisman D, Elenberg Y, Landesberg A, et al. (2014) Zn/Ga-DFO iron-chelating complex attenuates the inflammatory process in a mouse model of asthma. Redox Biol 2: 814–819. [PubMed: 25009783]

123. Guo C, Wang P, Zhong ML, Wang T, Huang XS, et al. (2013) Deferoxamine inhibits iron induced hippocampal tau phosphorylation in the alzheimer transgenic mouse brain. Neurochem Int 62: 165–172. [PubMed: 23262393]

124. Guo C, Wang T, Zheng W, Shan ZY, Teng WP, et al. (2013) Intranasal deferoxamine reverses iron-induced memory deficits and inhibits amyloidogenic APP processing in a transgenic mouse model of Alzheimer's disease. Neurobiol Aging 34: 562–575. [PubMed: 22717236]

125. de Lima MN, Presti-Torres J, Caldana F, Grazziotin MM, Scalco FS, et al. (2007) Desferoxamine reverses neonatal iron-induced recognition memory impairment in rats. Eur J Pharmacol 570: 111–114. [PubMed: 17617402]

126. Fine JM, Forsberg AC, Stroebel BM, Faltesek KA, Verden DR, et al. (2017) Intranasal deferoxamine affects memory loss, oxidation and the insulin pathway in the streptozotocin rat model of alzheimer's disease. J Neurol Sci 380: 164–171. [PubMed: 28870559]

127. Zhang Y, He ML (2017) Deferoxamine enhances alternative activation of microglia and inhibits amyloid beta deposits in APP/PS1 mice. Brain Res 1677: 86–92. [PubMed: 28963052]

128. Liu Z, Qiao J, Nagy T, Xiong MP (2018) ROS-triggered degradable iron-chelating nanogels: Safely improving iron elimination in vivo. J Control Release 283: 84–93. [PubMed: 29792889]

129. Wang Y, Liu Z, Lin TM, Chanana S, Xiong MP (2018) Nanogel-DFO conjugates as a model to investigate pharmacokinetics, biodistribution and iron chelation in vivo. Int J Pharm 538: 79–86. [PubMed: 29341909]

130. Oka S, Kamata H, Kamata K, Yagisawa H, Hirata H (2000) N-acetylcysteine suppresses TNF-induced NF-kappaB activation through inhibition of IkappaB kinases. FEBS Lett 472: 196–202. [PubMed: 10788610]

131. Jones SV, Kounatidis I (2017) Nuclear factor-Kappa B and alzheimer disease, unifying genetic and environmental risk factors from cell to humans. Front Immunol 8: 1805. [PubMed: 29312321]

132. Medved I, Brown MJ, Bjorksten AR, Murphy KT, Petersen AC, et al. (2004) N-acetylcysteine enhances muscle cysteine and glutathione availability and attenuates fatigue during prolonged exercise in endurance-trained individuals. J Appl Physiol 97: 1477–1485. [PubMed: 15194675]

133. Matuszczak Y, Farid M, Jones J, Lansdowne S, Smith MA, et al. (2005) Effects of N-acetyl cysteine on glutathione oxidation and fatigue during handgrip exercise. Muscle Nerve 32: 633–638. [PubMed: 16025522]

134. Jiao Y, Ma S, Wang Y, Li J, Shan L, et al. (2016) N-Acetyl cysteine depletes reactive oxygen species and prevents dental monomer-induced intrinsic mitochondrial apoptosis in vitro in human dental pulp cells. PloS one 11: e0147858. [PubMed: 26808507]

135. Qian HR, Yang Y (2009) Neuron differentiation and neuritogenesis stimulated by N-acetylcysteine (NAC). Acta Pharmacol Sin 30: 907–912. [PubMed: 19574996]

136. Mocelin R, Marcon M, D'Ambros S, Mattos J, Sachett A, et al. (2019) N-Acetylcysteine reverses anxiety and oxidative damage induced by unpredictable chronic stress in zebrafish. Mol Neurobiol 56: 1188–1195. [PubMed: 29876880]

137. Hara Y, McKeehan N, Dacks PA, Fillit HM (2017) Evaluation of the neuroprotective potential of n-acetylcysteine for prevention and treatment of cognitive aging and dementia. The Journal of Prevention of Alzheimer's Disease 4: 201–206.

138. Yu QS, Reale M, Kamal MA, Holloway HW, Luo W, et al. (2013) Synthesis of the alzheimer drug posiphen into its primary metabolic products (+)-N1-norPosiphen, (+)-N8-norPosiphen and (+)-

N1, N8-bisnorPosiphen, their inhibition of amyloid precursor protein, alpha-Synuclein synthesis, interleukin-1beta release and cholinergic action. Antiinflamm Antiallergy Agents Med Chem 12: 117–128. [PubMed: 23360256]

139. Lahiri DK, Chen D, Maloney B, Holloway HW, Yu QS, et al. (2007) The experimental alzheimer's disease drug posiphen [(+)-phenserine] lowers amyloid-beta peptide levels in cell culture and mice. J Pharmacol Exp Ther 320: 386–396. [PubMed: 17003227]
140. Lilja AM, Luo Y, Yu QS, Rojdner J, Li Y, et al. (2013) Neurotrophic and neuroprotective actions of (−)- and (+)-phenserine, candidate drugs for alzheimer's disease. PloS one 8: e54887. [PubMed: 23382994]
141. Becker RE, Greig NH, Lahiri DK, Bledsoe J, Majercik S, et al. (2018) (−)-Phenserine and inhibiting pre-programmed cell death: In pursuit of a novel intervention for alzheimer's disease. Curr Alzheimer Res 15: 883–891. [PubMed: 29318971]
142. Winblad B, Giacobini E, Frolich L, Friedhoff LT, Bruinsma G, et al. (2010) Phenserine efficacy in alzheimer's disease. J Alzheimers Dis 22: 1201–1208. [PubMed: 20930279]
143. Zhou ZD, Tan EK (2017) Iron regulatory protein (IRP)-iron responsive element (IRE) signaling pathway in human neurodegenerative diseases. Mol Neurodegener 12: 75. [PubMed: 29061112]
144. Wong GW, Laugerotte A, Wright JM (2015) Blood pressure lowering efficacy of dual alpha and beta blockers for primary hypertension. Cochrane Database Syst Rev 8: CD007449.
145. Kumar A, Prakash A, Dogra S (2011) Neuroprotective effect of carvedilol against aluminium induced toxicity: Possible behavioral and biochemical alterations in rats. Pharmacol Rep 63: 915–923. [PubMed: 22001979]
146. M'Rad I, Jeljeli M, Rihane N, Hilber P, Sakly M, et al. (2018) Aluminium oxide nanoparticles compromise spatial learning and memory performance in rats. EXCLI J 17: 200–210. [PubMed: 29743858]
147. de Araujo RF, Souza TO, de Medeiros CA, de Souza LB, Freitas Mde L, et al. (2013) Carvedilol decrease IL-1beta and TNF-alpha, inhibits MMP-2, MMP-9, COX-2 and RANKL expression and up-regulates OPG in a rat model of periodontitis. PloS one 8: e66391. [PubMed: 23843954]
148. Liu J, Wang M (2018) Carvedilol protection against endogenous Aβ-induced neurotoxicity in N2a cells. Cell Stress Chaperones 23: 695–702. [PubMed: 29435723]
149. D'Onofrio G, Panza F, Frisardi V, Solfrizzi V, Imbimbo BP, et al. (2012) Advances in the identification of gamma-secretase inhibitors for the treatment of alzheimer's disease. Expert Opin Drug Discov 7: 19–37. [PubMed: 22468891]
150. Panza F, Frisardi V, Imbimbo BP, Capurso C, Logroscino G, et al. (2010) Review: Gamma-Secretase inhibitors for the treatment of alzheimer's disease: The current state. CNS Neurosci Ther 16: 272–284. [PubMed: 20560993]
151. Doody RS, Raman R, Sperling RA, Seimers E, Sethuraman G, et al. (2015) Peripheral and central effects of gamma-secretase inhibition by semagacestat in alzheimer's disease. Alzheimers Res Ther 7: 36. [PubMed: 26064192]
152. Liu Q, Waltz S, Woodruff G, Ouyang J, Israel MA, et al. (2014) Effect of potent gamma-secretase modulator in human neurons derived from multiple presenilin 1-induced pluripotent stem cell mutant carriers. JAMA Neurol 71: 1481–1489. [PubMed: 25285942]
153. Chavez-Gutierrez L, Bammens L, Benilova I, Vandersteen A, Benurwar M, et al. (2012) The mechanism of gamma-secretase dysfunction in familial Alzheimer disease. EMBO J 31: 2261–2274. [PubMed: 22505025]
154. Geerts H, Spiros A, Roberts P (2018) Impact of amyloid-beta changes on cognitive outcomes in Alzheimer's disease: analysis of clinical trials using a quantitative systems pharmacology model. Alzheimers Res Ther 10: 14. [PubMed: 29394903]
155. Rosenberg PB, Lanctot KL, Herrmann N, Mintzer JE, Porsteinsson AP, et al. (2016) Changes in neuropsychiatric inventory associated with semagacestat treatment of Alzheimer's disease. J Alzheimer's Dis 54: 373–381. [PubMed: 27567808]
156. Penninkilampi R, Brothers HM, Eslick GD (2016) Pharmacological agents targeting gamma-secretase increase risk of cancer and cognitive decline in Alzheimer's disease patients: A systematic review and meta-analysis. J Alzheimer's Dis 53: 1395–1404. [PubMed: 27392862]

157. De-Strooper B (2014) Lessons from a failed gamma-secretase Alzheimer trial. Cell 159: 721–726. [PubMed: 25417150]

158. Doody RS, Raman R, Farlow M, Iwatsubo T, Vellas B, et al. (2013) A phase 3 trial of semagacestat for treatment of Alzheimer's disease. N Engl J Med 369: 341–350. [PubMed: 23883379]

159. Gu K, Li Q, Lin H, Zhu J, Mo J, et al. (2017) Gamma secretase inhibitors: A patent review (2013–2015). Expert Opin Ther Pat 27: 851–866. [PubMed: 28350212]

160. Svedruzic ZM, Popovic K, Sendula-Jengic V (2013) Modulators of gamma-secretase activity can facilitate the toxic side-effects and pathogenesis of Alzheimer's disease. PloS one 8: e50759. [PubMed: 23308095]

161. Tagami S, Yanagida K, Kodama TS, Takami M, Mizuta N, et al. (2017) Semagacestat is a pseudo-inhibitor of gamma-secretase. Cell Rep 21: 259–273. [PubMed: 28978478]

162. Lo MS, Newburger JW (2018) Role of intravenous immunoglobulin in the treatment of Kawasaki disease. Int J Rheum Dis 21: 64–69. [PubMed: 29205910]

163. Relkin NR, Thomas RG, Rissman RA, Brewer JB, Rafii MS, et al. (2017) A phase 3 trial of IV immunoglobulin for Alzheimer disease. Neurology 88: 1768–1775. [PubMed: 28381506]

164. Relkin NR, Szabo P, Adamiak B, Burgut T, Monthe C, et al. (2009) 18-Month study of intravenous immunoglobulin for treatment of mild Alzheimer disease. Neurobiol Aging 30: 1728–1736. [PubMed: 18294736]

165. Magga J, Puli L, Pihlaja R, Kanninen K, Neulamaa S, et al. (2010) Human intravenous immunoglobulin provides protection against Abeta toxicity by multiple mechanisms in a mouse model of Alzheimer's disease. J Neuroinflammation 7: 90. [PubMed: 21138577]

166. Counts SE, Ray B, Mufson EJ, Perez SE, He B, et al. (2014) Intravenous Immunoglobulin (IVIG) treatment exerts antioxidant and neuropreservatory effects in preclinical models of Alzheimer's disease. J Clin Immunol 34: S80–85. [PubMed: 24760109]

167. Inci A, Unal DS, Ozes NO, Erin N, Akcakus M, et al. (2013) The efficacy of intravenous immunoglobulin on lipopolysaccharide-induced fetal brain inflammation in preterm rats. Am J Obstet Gynecol 209: 347 e1–8. [PubMed: 23791686]

168. Sudduth TL, Greenstein A, Wilcock DM (2013) Intracranial injection of Gammagard, a human IVIg, modulates the inflammatory response of the brain and lowers Abeta in APP/PS1 mice along a different time course than anti-Abeta antibodies. J Neurosci 33: 9684–9692. [PubMed: 23739965]

169. Morales I, Guzman-Martinez L, Cerda-Troncoso C, Farias GA, Maccioni RB (2014) Neuroinflammation in the pathogenesis of Alzheimer's disease. A rational framework for the search of novel therapeutic approaches. Front Cell Neurosci 8: 112. [PubMed: 24795567]

170. Morita M, Osoda K, Yamazaki M, Shirai F, Matsuoka N, et al. (2009) Effects of non-steroidal anti-inflammatory drugs on Abeta deposition in Abeta(1–42) transgenic C. elegans. Brain Res 1295: 186–1891. [PubMed: 19666013]

171. Guzman DC, Herrera MO, Brizuela NO, Mejia GB, Garcia EH, et al. (2018) Oseltamivir and indomethacin reduce the oxidative stress in brain and stomach of infected rats. APMIS 126: 128–134. [PubMed: 29271004]

172. Vetreno RP, Lawrimore CJ, Rowsey PJ, Crews FT (2018) Persistent adult neuroimmune activation and loss of hippocampal neurogenesis following adolescent ethanol exposure: blockade by exercise and the anti-inflammatory drug indomethacin. Front Neurosci 12: 200. [PubMed: 29643762]

173. McGuiness JA, Scheinert RB, Asokan A, Stadler VC, Lee CS, et al. (2017) Indomethacin increases neurogenesis across age groups and improves delayed probe trial difference scores in middle-aged rats. Front Aging Neurosci 9: 280. [PubMed: 28928652]

174. Sanz-Blasco S, Calvo-Rodriguez M, Caballero E, Garcia-Durillo M, Nunez L, et al. (2018) Is it All Said for NSAIDs in Alzheimer's Disease? Role of Mitochondrial Calcium Uptake. Curr Alzheimer Res 15: 504–510. [PubMed: 29283047]

175. Calvo-Rodriguez M, Garcia-Durillo M, Villalobos C, Nunez L (2016) Aging enables Ca2+ overload and apoptosis induced by amyloid-beta oligomers in rat hippocampal neurons:

Neuroprotection by non-steroidal anti-inflammatory drugs and r-flurbiprofen in aging neurons. J Alzheimer's Dis 54: 207–221. [PubMed: 27447424]

176. Imbimbo BP, Solfrizzi V, Panza F (2010) Are NSAIDs useful to treat Alzheimer's disease or mild cognitive impairment? Front Aging Neurosci 2: 19. [PubMed: 20725517]
177. Wang J, Tan L, Wang HF, Tan CC, Meng XF, et al. (2015) Anti-inflammatory drugs and risk of Alzheimer's disease: An updated systematic review and meta-analysis. J Alzheimer's Dis 44: 385–396. [PubMed: 25227314]
178. Tian N, Kanno T, Jin Y, Nishizaki T (2014) Lithium potentiates GSK-3beta activity by inhibiting phosphoinositide 3-kinase-mediated Akt phosphorylation. Biochem Biophys Res Commun 450: 746–749. [PubMed: 24950409]
179. Rankin CA, Sun Q, Gamblin TC (2007) Tau phosphorylation by GSK-3beta promotes tangle-like filament morphology. Mol Neurodegener 2: 12. [PubMed: 17598919]
180. Hu S, Begum AN, Jones MR, Oh MS, Beech WK, et al. (2009) GSK3 inhibitors show benefits in an Alzheimer's disease (AD) model of neurodegeneration but adverse effects in control animals. Neurobiol Dis 33: 193–206. [PubMed: 19038340]
181. Vo TM, Perry P, Ellerby M, Bohnert K (2015) Is lithium a neuroprotective agent? Ann Clin Psychiatry 27: 49–54. [PubMed: 25696782]
182. Wexler EM, Geschwind DH, Palmer TD (2008) Lithium regulates adult hippocampal progenitor development through canonical Wnt pathway activation. Mol Psychiatry 13: 285–292. [PubMed: 17968353]
183. Klein PS, Melton DA (1996) A molecular mechanism for the effect of lithium on development. Proc Natl Acad Sci U S A 93: 8455–8459. [PubMed: 8710892]
184. Habib A, Sawmiller D, Li S, Xiang Y, Rongo D, et al. (2017) LISPRO mitigates beta-amyloid and associated pathologies in Alzheimer's mice. Cell Death Dis 8: e2880. [PubMed: 28617434]