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Review Article

A Study on the Approaches for the Treatment Strategy of Alzheimer's Disease

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Abstract: Numerous medications are now approved to treat and relieve symptoms related to Alzheimer's Disease (A.D.). Most of these drugs regulate the neurotransmitters, thereby modulating the transmission of messages between neurons. However, these drugs are helpful in the reduction of A.D. symptoms associated with particular behavioral problems but are unable to change the underlying pathophysiological process accounting for the disease. In addition, their effectiveness is limited for a small group of people and thus may be helpful for a limited period. Therefore, the scientists are investigating the possible strategies for the symptomatic treatment and finding out the ways to hold back or prevent the disease. Drug development and assessment for newer and better drugs as well as treatment methodologies are caring out by the scientists in ongoing clinical trials. This study has been carried out to accumulate the different treatment strategies, including drug therapies intended for various targets such as loss of specific neurotransmitters & synapses, cerebrovascular function, neurofibrillary tangles & beta-amyloid plaques, as well as other nondrug approaches.

Keywords: Alzheimer's Disease, Therapy, Pharmacological interventions, Prevalence.

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INTRODUCTION

Alzheimer's Disease

Alzheimer's disease (A.D.) is a progressively developing neurodegenerative disorder of the brain in older people with the symptoms of memory loss, cognition, and behavioral abnormalities [1]. The Pathophysiology of A.D. is complex and involves any cellular, molecular and physiological factors, but the development of senile plaques consisting of Amyloid-beta (Aβ) protein & neurofibrillary tangles of microtubule-associated protein tau as well as extensive loss of cholinergic neurons are the pathological hallmarks of A.D. [2-4]. Specifically, there are no highly effective drugs for the treatment A.D., although tremendous progress has been achieved in the comprehension of pathogenesis and etiology of A.D. Currently, in the pathogenesis of A.D.' oxidative stress and cholinergic dysfunction [5] have been concerned as the major causative factors [6].

Prevalence

The number of people worldwide having dementia is around 50 million, along with 10 million new cases per year. One of the most predominant forms of dementia is A.D. It is estimated to contribute about 60–70% of cases. It is anticipated that in 2030 the number of people with dementia will reach 82 million in 2030 which will be 152 in 2050 [7].

Dementia, in particular, Alzheimer's disease, is primarily found in Western Europe with a proximity with North America, and in Sub-Saharan Africa, it is least common. It has been estimated that, by the year 2050, 30% of the population in Western Europe will be over the age of 65 years, and up to 10% will have A.D. [8, 9].

TREATMENT STRATEGIES

The treatment of Alzheimer's disease is aimed to treat the symptoms and improve the quality of life since there is no effective treatment for its relief. Different pathophysiology-based tactics have been devised for the treatment of Alzheimer's disease.

These approaches include modification of the disease, protection of neurons, and nonpharmacologic interventions [10].

Treatment strategy based on pharmacological interventions

A. Cholinergics

A close relationship has been found between cognitive function and the damage of cholinergics [11]. Several therapeutic agents have been investigated over the last two decades. These include anticholinesterases such as Acetylcholinesterase inhibitors (AChEI), namely Tacrine, Donepezil, Rivastigmine, and Galantamine got approval from FDA for the treatment of mild-moderate A.D. It is anticipated that they decline the amyloid-β protein precursor (AβPP) level, thereby decreasing the generation of Aβ and amyloidogenic and ultimately hinder the progression of the disease [12, 13]. In addition, pre and postsynaptic cholinergic stimulation with nicotinic agonists and muscarinic agonists, respectively, have also been investigated [14]. Currently, the brain butyrylcholinesterase inhibitors (BuChEI) are being explored for new drug targets in the A.D. treatment.

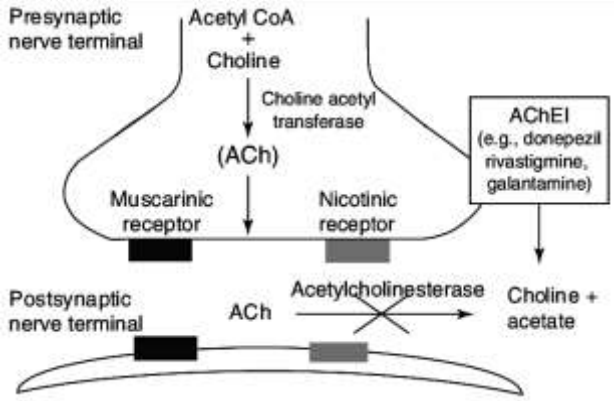

Fig: Mechanism of AchEI [15]

B. N-Methyl-D-aspartate (NMDA) receptor antagonist

In patients with A.D., oxidation of the enzyme glutamine synthetase leads to excess glutamate. Being excitatory neurotransmitters, glutamate causes excessive activation of NMDA receptors. This, in turn causes the death of apoptotic cells and blemishes in cognition and memory [16]. An NMDA receptor antagonist, Memantine blocks exorbitant receptor activation, thereby blocking the pathological activation of this channel. FDA approves this drug, and it is meant for the treatment of moderate to severe A.D. for the preservation of physiological activation in advanced stages of A.D. [17-19].

C. Drugs under experiments

For the treatment A.D. there are many productive therapeutic agents recently under study. Some important ones from them are outlined below.

Therapy based on amyloid hypothesis

The formation β-amyloid (Aβ) plaques are believed to be one of the main contributors in the genetic forms of A.D.; thus the medication concerning the change in the metabolism of amyloid so as to decrease the plaque formation is being evaluated [20].

Hindering the production of Aβ

Shifting of APP processing away from the amyloidogenic b-secretase (also called the b-site APP-cleaving enzyme 1 or BACE1) toward the nonamyloidogenic a-secretase pathway can be achieved by blocking BACE1. Inhibiting this enzyme directly may be problematic because it also cleaves numerous other substrates, including one involved in myelination, but an early candidate has completed a phase I trial.

Antipsychotics

Although frequently used to treat behavioral symptoms, the antipsychotics are not approved by the U.S. FDA for A.D. treatment. Evidence based suggestions demonstatated reduction of psychosis in patients with Alzheimer's disease with risperidone (Risperdal) and olanzapine (Zyprexa [21].

Therapies with Conflicting Evidence

Testosterone

The beneficial effect of testosterone in patients with A.D. is conflicting. Two randomized, double-blind, placebo-controlled studies demonstrated benefit in visuospatial cognition, but it is unclear if this effect is clinically meaningful [22, 23].

D. Antioxidants

Multiple lines of evidence indicate that oxidative stress is an important pathogenic process associated with aging and A.D., while markers of oxidative stress have been shown to precede pathological lesions in A.D., including senile plaques and NFT [24-26]. Antioxidants may thus blunt the cognitive decline in A.D. or slow disease progression [27-29]. The Alzheimer's Disease Cooperative Study compared selegiline, a-tocopherol, or both with placebo [30]. Given the delay in progression to adverse outcome in the treatment groups, and American Academy of Neurology practice parameter states that vitamin E likely delays time to clinical worsening. Vitamin E in combination with vitamin C is also associated with a decrease in the prevalence and incidence of A.D. [31].

E. Statins

Cerebral Aβ levels are decreased in vivo with simvastatin [32] and result in the specific neuropathologic change in statin use of reduced NFT burden at autopsy [33]. The Adult Changes in Thought (ACT) Study also showed a significant protective effect of statins against dementia; however, a later analysis of a larger sample from ACT suggested a protective effect in subjects who began statin use before age 80 [34, 35]. In line with these results, numerous early epidemiologic studies indicated that the use of statins significantly reduces the risk of A.D. [36-38]. However, other extensive prospective cohort studies and two large randomized placebo-controlled trials of statins for

coronary heart disease prevention failed to provide evidence of a protective effect against cognitive decline [39-42]. The pattern of results obtained thus far suggests that statins may slow the progression of the neurodegenerative process but may not be able to reverse neuronal degeneration once it has occurred.

F. Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs can downregulate pro-inflammatory signals, astrocytes & microglia, thus reducing the production of Aβ1–42, thereby diminishing the risks associated with A.D. [43]. The Baltimore Longitudinal Study of Aging outlined a reduced risk for A.D. with NSAID use proportional to the duration of use [44]. Case-control studies of individuals taking NSAIDs for arthritis, a small clinical trial of indomethacin, and many familial studies also indicated protection from the development of A.D. or progression of the disease [45, 46]. Various NSAIDs didn't demonstrate the potential impact on the reduction of cognitive function in patients with dementia or the rate of conversion to A.D. in patients with MCI when used in randomized controlled trials [47-49]. Moreover, a randomized controlled primary prevention trial of NSAIDs in A.D., the A.D. Anti-inflammatory Prevention Trial (ADAPT), was terminated in 2004 secondary to concerns regarding cardiovascular risk [50].

G. Hormone replacement therapy

Estrogen enhances cerebral blood flow, prevents atrophy of cholinergic neurons, reduces oxidative stress, and modulates the effects of nerve growth factors [51]. It may also minimize neuronal injury by decreasing the formation of Aβ. Three prospective, population-based epidemiologic studies suggested that postmenopausal estrogen replacement therapy (HRT) may delay the onset of A.D. One randomized clinical trial and a meta-analysis showed some improvement in cognitive function [52-56]. However, other randomized trials showed an increase in the development of dementia in healthy individuals and no improvement in cognitive or functional outcomes [57-59]. As such, further work is clearly needed to explore the use of HRT in A.D. and whether any effects are direct or indirect [60-61].

H. The Aβ vaccine trials

Removal of excess Aβ from the brain occurs by a reactive T cell response. In 1999, active immunization of transgenic mice producing human Aβ was shown to produce a significant reduction of Aβ plaques [62]. Immunization of the young animals prevented the development of Aβ plaque formation, neuritic dystrophy and astrogliosis. Treatment of the older animals reduced the extent and progression of these neuropathologies [62]. There is evidence for many mechanisms of plaque removal: 1) solubilization by binding of the antibody to Aβ; 2) phagocytosis of opsonized Aβ by microglial cells; and 3) the "sink" hypothesis in which Aβ antibodies remain in the plasma and extract Aβ from the brain by altering equilibrium across the blood-brain barrier [63] to regain functional effects following immunization [53-54]. Following these animal trials, clinical trials of the immunogen AN-1792 [$A\beta_{1-42}$ with adjuvant (QS-21)] were performed by Elan Pharmaceuticals/Wyeth. Phase IIa clinical trials were suspended when 6% of patients in the active treatment group developed meningoencephalitis characterized by subacute neurologic deterioration, lymphocytic pleocytosis, and white matter abnormalities on imaging [64]. Five patients receiving the trial drug died, with one death (secondary to cerebral infarction) considered to be related to study treatment [65].

CONCLUSION

Alzheimer's disease is the world's leading cause of dementia, but no new approved single therapy for the treatment and prevention of A.D. has been devised for greater than a century. The threat of A.D. affecting public health will grow as the life expectancy of the people increases, resulting in a growing population of patients with A.D. Therefore, new, improved strategies are required to prevent and treat A.D. Clinical trials suggest that single-agent therapies cannot hinder the progression of diseases or subsequent symptoms. Thus, the application of combination treatments instead of monotherapy could be a successful approach for A.D. treatment.

REFERENCE

1. What is Alzheimer's disease? Nih.gov. Available from: https://www.nia.nih.gov/health/what-alzheimers-disease Page last accessed on September 17, 2021
2. Masters, C. L., & Selkoe, D. J. (2012). Biochemistry of amyloid β-protein and amyloid deposits in Alzheimer disease. *Cold Spring Harbor perspectives in medicine*, *2*(6), a006262.
3. Iqbal, K., Wang, X., Blanchard, J., Liu, F., Gong, C. X., & Grundke-Iqbal, I. (2010). Alzheimer's disease neurofibrillary degeneration: pivotal and multifactorial. *Biochemical Society transactions*, *38*(4), 962-966.
4. Terry, A. V., & Buccafusco, J. J. (2003). The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: recent challenges and their implications for novel drug development. *Journal of Pharmacology and Experimental Therapeutics*, *306*(3), 821-827.
5. Farlow, M. R., & Evans, R. M. (1998). Pharmacologic treatment of cognition in Alzheimer's dementia. *Neurology*, *51*(1 Suppl 1), S36-S44.
6. Berchtold, N. C., & Cotman, C. W. (1998). Evolution in the conceptualization of dementia and Alzheimer's disease: Greco-Roman period to the 1960s. *Neurobiology of aging*, *19*(3), 173-189.
7. Dementia; Who.int. Available from: https://www.who.int/news-room/fact-

sheets/detail/dementia; Page last accessed on December 08, 2020
8. Alzheimer's News Today: Alzheimer's Disease Statistics. Available at https://alzheimersnewstoday.com/alzheimers-disease-statistics/?cn-reloaded=1. Page last accessed on December 08, 2020
9. Evans, D., Ganguli, M., Harris, T., Kawas, C., & Larson, E. B. (1999). Women and Alzheimer disease. *Alzheimer Disease & Associated Disorders*, *13*(4), 187-189.
10. Upadhyaya, P., Seth, V., & Ahmad, M. (2010). Therapy of Alzheimers disease: an update. *African Journal of Pharmacy and Pharmacology*, *4*(6), 408-421.
11. Whitehouse, P. J. (1993). Cholinergic therapy in dementia. *Acta Neurologica Scandinavica*, *88*(S149), 42-45.
12. Giacobini, E., Mori, F., & LAI, C. C. (1996). The Effect of Cholinesterase Inhibitors on the Secretion of APPS from Rat Brain Cortex a. *Annals of the New York Academy of Sciences*, *777*(1), 393-398.
13. Mori, F., Lai, C. C., Fusi, F., & Giacobini, E. (1995). Cholinesterase inhibitors increase secretion of APPs in rat brain cortex. *Neuroreport: An International Journal for the Rapid Communication of Research in Neuroscience*, 6(4), 633-636.
14. Hebert, L. E., Scherr, P. A., Bienias, J. L., Bennett, D. A., & Evans, D. A. (2003). Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Archives of neurology*, *60*(8), 1119-1122.
15. Moghul, S., & Wilkinson, D. (2001). Use of acetylcholinesterase inhibitors in Alzheimer's disease. *Expert Review of Neurotherapeutics*, *1*(1), 61-69.
16. Danysz, W., & Parsons, C. G. (2003). The NMDA receptor antagonist memantine as a symptomatological and neuroprotective treatment for Alzheimer's disease: preclinical evidence. *International journal of geriatric psychiatry*, *18*(S1), S23-S32.
17. Winblad, B., & Poritis, N. (1999). Memantine in severe dementia: results of the 9M-best study (benefit and efficacy in severly demented patients during treatment with memantine). *International journal of geriatric psychiatry*, *14*(2), 135-146.
18. Johnson, J. W., & Kotermanski, S. E. (2006). Mechanism of action of memantine. *Current opinion in pharmacology*, *6*(1), 61-67.
19. Reisberg, B., Doody, R., Stöffler, A., Schmitt, F., Ferris, S., & Möbius, H. J. (2003). Memantine in moderate-to-severe Alzheimer's disease. *New England Journal of Medicine*, *348*(14), 1333-1341.
20. Neugroschl, J., & Sano, M. (2010). Current treatment and recent clinical research in Alzheimer's disease. *Mount Sinai Journal of Medicine: A Journal of Translational and Personalized Medicine: A Journal of Translational and Personalized Medicine*, *77*(1), 3-16.
21. Ballard, C. G., Waite, J., & Birks, J. (2006). Atypical antipsychotics for aggression and psychosis in Alzheimer's disease. *Cochrane Database of Systematic Reviews*, (1), CD003476.
22. Tan, R. S., & Pu, S. J. (2003). A pilot study on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease. *The Aging Male*, *6*(1), 13-17.
23. Cherrier, M. M., Matsumoto, A. M., Amory, J. K., Asthana, S., Bremner, W., Peskind, E. R., ... & Craft, S. (2005). Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment. *Neurology*, *64*(12), 2063-2068.
24. Nunomura, A., Perry, G., Pappolla, M. A., Wade, R., Hirai, K., Chiba, S., & Smith, M. A. (1999). RNA oxidation is a prominent feature of vulnerable neurons in Alzheimer's disease. *Journal of Neuroscience*, *19*(6), 1959-1964.
25. Nunomura, A., Perry, G., Aliev, G., Hirai, K., Takeda, A., Balraj, E. K., ... & Smith, M. A. (2001). Oxidative damage is the earliest event in Alzheimer disease. *Journal of Neuropathology & Experimental Neurology*, *60*(8), 759-767.
26. Sayre, L. M., Zelasko, D. A., Harris, P. L., Perry, G., Salomon, R. G., & Smith, M. A. (1997). 4-Hydroxynonenal-derived advanced lipid peroxidation end products are increased in Alzheimer's disease. *Journal of neurochemistry*, *68*(5), 2092-2097.
27. Jama, J. W., Launer, L. J., Witteman, J. C. M., Den Breeijen, J. H., Breteler, M. M. B., Grobbee, D. E., & Hofman, A. (1996). Dietary antioxidants and cognitive function in a population-based sample of older persons: the Rotterdam Study. *American journal of epidemiology*, *144*(3), 275-280.
28. Perrig, W. J., Perrig, P., & Stähelin, H. B. (1997). The relation between antioxidants and memory performance in the old and very old. *Journal of the American Geriatrics Society*, *45*(6), 718-724.
29. Rottkamp, C. A., Nunomura, A., Hirai, K., Sayre, L. M., & Perry, G. (2000). Will antioxidants fulfill their expectations for the treatment of Alzheimer disease?. *Mechanisms of ageing and development*, *116*(2-3), 169-179.
30. Sano, M., Ernesto, C., Thomas, R. G., Klauber, M. R., Schafer, K., Grundman, M., ... & Thal, L. J. (1997). A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *New England Journal of Medicine*, *336*(17), 1216-1222.
31. Zandi, P. P., Anthony, J. C., Khachaturian, A. S., Stone, S. V., Gustafson, D., Tschanz, J. T., ... & Cache County Study Group. (2004). Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. *Archives of neurology*, *61*(1), 82-88.

32. Fassbender, K., Simons, M., Bergmann, C., Stroick, M., Lütjohann, D., Keller, P., ... & Hartmann, T. (2001). Simvastatin strongly reduces levels of Alzheimer's disease β-amyloid peptides Aβ42 and Aβ40 in vitro and in vivo. *Proceedings of the National Academy of Sciences*, *98*(10), 5856-5861.
33. Li, G., Larson, E. B., Sonnen, J. A., Shofer, J. B., Petrie, E. C., Schantz, A., ... & Montine, T. J. (2007). Statin therapy is associated with reduced neuropathologic changes of Alzheimer disease. *Neurology*, *69*(9), 878-885.
34. Li, G., Higdon, R., Kukull, W. A., Peskind, E., Moore, K. V. V., Tsuang, D., ... & Larson, E. B. (2004). Statin therapy and risk of dementia in the elderly: a community-based prospective cohort study. *Neurology*, *63*(9), 1624-1628.
35. Jick, H. Z. G. L., Zornberg, G. L., Jick, S. S., Seshadri, S., & Drachman, D. A. (2000). Statins and the risk of dementia. *The Lancet*, *356*(9242), 1627-1631.
36. Rockwood, K., Kirkland, S., Hogan, D. B., MacKnight, C., Merry, H., Verreault, R., ... & McDowell, I. (2002). Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. *Archives of neurology*, *59*(2), 223-227.
37. Wolozin, B., Kellman, W., Ruosseau, P., Celesia, G. G., & Siegel, G. (2000). Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. *Archives of neurology*, *57*(10), 1439-1443.
38. Yaffe, K., Barrett-Connor, E., Lin, F., & Grady, D. (2002). Serum lipoprotein levels, statin use, and cognitive function in older women. *Archives of neurology*, *59*(3), 378-384.
39. Heart Protection Study Collaborative Group. (2002). MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebocontrolled trial. *The Lancet*, *360*(9326), 7-22.
40. Rea, T. D., Breitner, J. C., Psaty, B. M., Fitzpatrick, A. L., Lopez, O. L., Newman, A. B., ... & Kuller, L. H. (2005). Statin use and the risk of incident dementia: the Cardiovascular Health Study. *Archives of neurology*, *62*(7), 1047-1051.
41. Shepherd, J., Blauw, G. J., Murphy, M. B., Bollen, E. L., Buckley, B. M., Cobbe, S. M., ... & Westendorp, R. G. (2002). Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *The Lancet*, *360*(9346), 1623-1630.
42. Zandi, P. P., Sparks, D. L., Khachaturian, A. S., Tschanz, J., Norton, M., Steinberg, M., ... & Cache County Study investigators. (2005). Do statins reduce risk of incident dementia and Alzheimer disease?: the Cache County Study. *Archives of General Psychiatry*, *62*(2), 217-224.
43. Breitner, J. C. S., Gau, B. A., Welsh, K. A., Plassman, B. L., McDonald, W. M., Helms, M. J., & Anthony, J. C. (1994). Inverse association of anti-inflammatory treatments and Alzheimer's disease: initial results of a co-twin control study. *Neurology*, *44*(2), 227-232.
44. Stewart, W. F., Kawas, C., Corrada, M., & Metter, E. J. (1997). Risk of Alzheimer's disease and duration of NSAID use. *Neurology*, *48*(3), 626-632.
45. Andersen, K., Launer, L. J., Ott, A., Hoes, A. W., Breteler, M. M. B., & Hofman, A. (1995). Do nonsteroidal anti-inflammatory drugs decrease the risk for Alzheimer's disease?: The Rotterdam Study. *Neurology*, *45*(8), 1441-1445.
46. Rogers, J., Kirby, L. C., Hempelman, S. R., Berry, D. L., McGeer, P. L., Kaszniak, A. W., ... & Kogan, F. (1993). Clinical trial of indomethacin in Alzheimer's disease. *Neurology*, *43*(8), 1609-1611.
47. Aisen, P. S., Schafer, K. A., Grundman, M., Pfeiffer, E., Sano, M., Davis, K. L., ... & Thal, L. J. (2003). Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. *Jama*, *289*(21), 2819-2826.
48. Thal, L. J., Ferris, S. H., Kirby, L., Block, G. A., Lines, C. R., Yuen, E., ... & Reines, S. A. (2005). A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. *Neuropsychopharmacology*, *30*(6), 1204-1215.
49. Wyss-Coray, T. (2006). Inflammation in Alzheimer disease: driving force, bystander or beneficial response?. *Nature medicine*, *12*(9), 1005-1015.
50. ADAPT Research Group. (2006). Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT). *PLoS clinical trials*, *1*(7), e33.
51. Goutte, C., Tsunozaki, M., Hale, V. A., & Priess, J. R. (2002). APH-1 is a multipass membrane protein essential for the Notch signaling pathway in Caenorhabditis elegans embryos. *Proceedings of the National Academy of Sciences*, *99*(2), 775-779.
52. Bard, F., Cannon, C., Barbour, R., Burke, R. L., Games, D., Grajeda, H., ... & Yednock, T. (2000). Peripherally administered antibodies against amyloid β-peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease. *Nature medicine*, *6*(8), 916-919.
53. Janus, C., Pearson, J., McLaurin, J., Mathews, P. M., Jiang, Y., Schmidt, S. D., ... & Westaway, D. (2000). Aβ peptide immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease. *Nature*, *408*(6815), 979-982.
54. Morgan, D., Diamond, D. M., Gottschall, P. E., Ugen, K. E., Dickey, C., Hardy, J., ... & Arendash, G. W. (2000). Aβ peptide vaccination prevents memory loss in an animal model of Alzheimer's disease. *Nature*, *408*(6815), 982-985.

55. Mucke, L., Masliah, E., Yu, G. Q., Mallory, M., Rockenstein, E. M., Tatsuno, G., ... & McConlogue, L. (2000). High-level neuronal expression of Aβ1–42 in wild-type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation. *Journal of Neuroscience*, *20*(11), 4050-4058.
56. Nicoll, J. A., Wilkinson, D., Holmes, C., Steart, P., Markham, H., & Weller, R. O. (2003). Neuropathology of human Alzheimer disease after immunization with amyloid-β peptide: a case report. *Nature medicine*, *9*(4), 448-452.
57. Becher, B., Prat, A., & Antel, J. P. (2000). Brain-immune connection: immuno-regulatory properties of CNS-resident cells. *Glia*, *29*(4), 293-304.
58. Francis, R., McGrath, G., Zhang, J., Ruddy, D. A., Sym, M., Apfeld, J., ... & Curtis, D. (2002). aph-1 and pen-2 are required for Notch pathway signaling, γ-secretase cleavage of βAPP, and presenilin protein accumulation. *Developmental cell*, *3*(1), 85-97.
59. Monsonego, A., Zota, V., Karni, A., Krieger, J. I., Bar-Or, A., Bitan, G., ... & Weiner, H. L. (2003). Increased T cell reactivity to amyloid β protein in older humans and patients with Alzheimer disease. *The Journal of clinical investigation*, *112*(3), 415-422.
60. Casadesus, G., Milliken, E. L., Webber, K. M., Bowen, R. L., Lei, Z., Rao, C. V., ... & Smith, M. A. (2007). Increases in luteinizing hormone are associated with declines in cognitive performance. *Molecular and cellular endocrinology*, *269*(1-2), 107-111.
61. Webber, K. M., Casadesus, G., Marlatt, M. W., Perry, G., Hamlin, C. R., Atwood, C. S., ... & Smith, M. A. (2005). Estrogen bows to a new master: the role of gonadotropins in Alzheimer pathogenesis. *Annals of the New York Academy of Sciences*, *1052*(1), 201-209..
62. Schenk, D., Barbour, R., Dunn, W., Gordon, G., Grajeda, H., Guido, T., ... & Seubert, P. (1999). Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature*, *400*(6740), 173-177.
63. Nicoll, J. A., Barton, E., Boche, D., Neal, J. W., Ferrer, I., Thompson, P., ... & Holmes, C. (2006). Aβ species removal after Aβ42 immunization. *Journal of Neuropathology & Experimental Neurology*, *65*(11), 1040-1048.
64. Orgogozo, J. M., Gilman, S., Dartigues, J. F., Laurent, B., Puel, M., Kirby, L. C., ... & Hock, C. (2003). Subacute meningoencephalitis in a subset of patients with AD after Aβ42 immunization. *Neurology*, *61*(1), 46-54.
65. Gilman, S., Koller, M., Black, R. S., Jenkins, L., Griffith, S. G., Fox, N. C., ... & Orgogozo, J. M. (2005). Clinical effects of Aβ immunization (AN1792) in patients with AD in an interrupted trial. *Neurology*, *64*(9), 1553-1562.