Review Article

An update on the pathophysiology and pharmacology of Alzheimer' disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease. Plaques and tangles are described as the characteristics features of AD, which are neurotoxic entities, deposited in the diseased patients. There are very few drugs available for the treatment of AD. Those available options are primarily the approaches to overcome cholinergic hypofunction, through the inhibition of acetylcholinesterase enzyme. Other disease modifying candidates are strongly needed to overcome the progressive dementia in AD. These new drugs will serve as a great hope for the AD patients and families of the AD patients.

Introduction

Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of dementia which was explained by a German psychiatrist Dr. Alois Alzheimer (1864-1915) for the first time in 1906. This disease is known by the name of Dr. Alzheimer as "Alzheimer's disease" and this name was given by Kraeplin (Blennow et al., 2006). Dr. Alzheimer came across a patient during his experience and later he described his first case, representing as a true picture of AD with plaques and fibrils bundled as neurofibrillary tangles (Selkoe, 2001, Blennow et al., 2006, Avramopoulos, 2009). These plaques and tangles are neurotoxic in nature (Ahmed et al., 2011). Today it has been understood that the AD is a chronic progressive neurodegenerative disease and it is the most common form of dementia, accounting for 50–60 % of all cases (Blennow et al., 2006). There is a profound cholinergic hypofucntion in AD, which results in decline in the cognitive functions (Ahmed and Gilani, 2009, Ahmed et al., 2010). Clinical symptoms in AD can be sub-divided into three groups such as; (i) cognitive dysfunction (memory loss, language difficulties and intellectual function), (ii) psychiatric symptoms which include agitation, depression, delusion, hallucination, insomnia and wandering (Burns et al., 1990, Lahiri. et al., 2002, Burns and Iliffe, 2009) and collectively these are grouped as non-cognitive symptoms and (iii) group of symptoms represented by the AD patients, such as difficulties in performing activities of daily life, including shopping, eating, dressing and driving (Lahiri. et al., 2002, Burns and Iliffe, 2009). AD progresses from memory loss to the substantial dementia and death within eight years of the age (Avramopoulos, 2009).

Epidemiology and Risk Factors

Prevalence

AD has been established to be one of the most common forms of dementia. It is estimated that half of the people over the age of 85 are affected with AD (Suh and Checler, 2002), affecting about 10 % population of the world (Vagnucci and Li, 2003). The prevalence of the dementia below 60-64 years of the aged population is 1 %, but increases exponentially with increasing age and at the age of 85 years and older, prevalence is found to be 25–33 % in western countries (Ferri et al., 2005, Blennow et al., 2006). AD represents as the sixth leading cause of deaths and these figures are rising. In 2001, 24 million people were reported suffering from dementia and this figure is going to be doubled every 20 years, with expected number of around 81 million cases in 2040 (Ferri et al., 2005). Representing data from the developing countries is sparse but estimates show that 60 % of the AD patients are expected to live developing countries (Blennow et al., 2006). There is limited data available regarding the prevalence of AD in Pakistan because of the limited reports from Pakistani population, but the figures from China (neighbour country) indicate high prevalence like western countries (Zhang et al., 2005). According to a recent estimate, over 5.3 million people in USA alone have AD, with 5.1 million people over the age of 65 years and 0.2 million below 65 years of age. In terms of its economic impact, estimated direct and indirect cost of AD is USD 148 billion annually.

Risk factors

Aging represents as the most established risk factor (Lahiri. et al., 2002, Ferri et al., 2005). Epidemiological studies have also established association of several risk factors with AD. Low educational and occupational level, low mental ability during early life and reduced activity in late life to be associated with AD (Mayeux, 2003, Mortimer et al., 2003). Several studies have shown as head injury to be one of the risk factor in AD (Kalaria, 2001, Marx, 2001, Lahiri. et al., 2002, Jellinger, 2004). There has also been evidence for the role of cardiovascular health in AD (Mayeux, 2003).

Genetics of Alzheimer's disease

Like the classical case represented by the Alois Alzheimer,

Corresponding Author: Touqeer Ahmed NUST Publishing, © (2012), ISSN: 2072-4659

the onset of this devastating disorder is relatively not in very old age population, mean age is below 65 years of the age (given the name of pre-senile dementia). This lead scientists to distinguish this from senile dementia and soon led to the discovery of genes involved in familial, autosomal dominant AD (FAD). First mutation to be identified was in amyloid precursor protein (APP) located on chromosome 21 (Goate et al., 1991). Moreover, additional mutation were found in presenilin 1 (*PSEN1* located on chromosome 14) and presenilin 2 (*PSEN2* located on chromosome 1) which account for most of the cases of familial AD (Levy-Lahad et al., 1995a, Levy-Lahad et al., 1995b, Sherrington et al., 1995). Especially, when it comes to the late onset of the disease the genetics are much more complicated (Avramopoulos, 2009) and *APOE* (located on chromosome 19) was found to be associated with AD (Corder et al., 1993, Poirier et al., 1993), where, it poses as a risk factor in late AD (Strittmatter et al., 1993, Burns and Iliffe, 2009). APOE has three isoforms and APOE ϵ4 is responsible for modifying the onset of AD (Poirier et al., 1993) with increasing risk several times in APOE ϵ4 allele homozygotes (Farrer et al., 1997). Each allele copy lowering the age by almost 10 years (Corder et al., 1993) and accounts for most of the sporadic cases (Raber et al., 2004). Until now several mutations have been identified and show association, whose details could be found at "www.alzgene.org".

Pathogenesis of Alzheimer's disease

AD is characterized by the deposition of the amyloid plaques (also known as senile plaques which are composed of the amyloid peptides (Aβ)) located extracellularly and neurofibrillary tangles (intracellular). Neurofibrillary tangles are composed of hyperphoshorylated tau proteins (Selkoe, 2001, Palmer, 2002) that has detrimental effect on synapses and neurons, resulting in the degenerative changes, by the activation of inflammatory pathways, oxidative stress and mitochondrial dysfunction (Kroemer et al., 2007). Amyloid plaques originate from amyloid precursor protein (APP) which is type I transmembrane glycoprotein (Suh and Checler, 2002), processed by various proteases generating Aβ fragment. APP is processed either through amyloidogenic or non-amyloidogenic pathway.

Under the normal conditions when Aβ peptide is produced, it is cleared by the process of degradation through various peptidases, such as, insulin degrading enzyme, neprilysin, and by endothelin converting enzyme (Carson and Turner, 2002). The famous amyloid cascade hypothesis explains that in AD, balance between the production and effective clearance is lost with dominating production, thus resulting in the deposition of Aβ peptide and leading to the development of the dementia (Hardy and Selkoe, 2002).

On the other hand tangles in the brain are composed of hyperphosphorylated tau protein (Grundke-Iqbal et al., 1986). Tau is a key protein that binds microtubules through its microtubules binding domain and provides the basis of microtubules functional assembly into the elongated structure in the axons. In the normal state tau is phosphorylated (by GSK-3β, CDK5) and dephosphorylated (by PP-1 and PP-2A) and there is balance between these two processes (Iqbal et al., 2005). But in AD this balance is towards the hyperphosphorylation of the tau proteins, thus microtubules subunits loose assembly and fall apart, disrupting axonal structure as well as the normal transport, this event results in severely compromised synaptic function (Iqbal et al., 2005).

In addition to these pathologies there is an initial selected loss of the cholinergic neurons in basal forebrain whose axons project into cortex and hippocampus (Fisher, 2000). As a result of this loss, there is decrease in intellectual function specially defect in memory. Cholinergic hypothesis provided the basis for the development of therapy in AD which provides symptomatic treatment.

Mechanism of cell death in Alzheimer's disease

Different mechanisms of neuronal cell death have been manifested in AD. Aβ is a protein fragment which is cleaved product of the APP. Aβ is neurotoxic which deposits in the brain of AD patients. Aβ deposition activates different signaling pathways which are responsible for cell death. Various mechanisms are proposed, which account for the Aβ induced toxicity. It has been reported that Aβ induces toxicity by the enhancement of Ca^{++} channels (Mattson et al., 1992), which results in the rise in intracellular Ca^{++} through voltage dependent Ca^{++} channels (Davidson et al., 1994, Weiss et al., 1994). Ca^{++} has various functions in cell signaling when in physiological concentration. Rise in intracellular Ca^{++} beyond certain limits can be lethal for cells, leading to cytotoxicity. In addition to Ca^{++} influx, Aβ fragments elevate glutamate release (Harkany et al., 2000). Electrophysiological studies in cortical pyramidal neurons indicate that Aβ induces excitatory post synaptic potential and train of action potentials by increasing excitability of glutamatergic projections (Gu et al., 2003), end result of this is again rise in intracellular cations specially Ca^{++}. Intracellular rise in Ca^{++} burden directs cells for apoptosis.

Beta amyloid fragments in the primary hippocampal neurons have shown to induce apoptosis through the mitochondrial pathways (Nilsen et al., 2006), thus translocating Bax to mitochondria resulting in release of the cytochrome C and activating apoptotic pathway.

Currently available treatment options

Drachman and Leavitt reported in 1974 that muscarinic antagonists, such as scopolamine produces cognition impairment similar to memory deficit observed in elderly people (Drachman and Leavitt, 1974). This provided a base that cholinergic system has important physiological role in the cognitive functions. Subsequent reports have shown reduction in cholineacetyltransferase activity in cerebral cortex and nucleus basalis of Meynert of patients affected by AD (Liberini et al., 1996). It is now quite evident that degeneration of the basal forebrain neurons as well as loss of cholinergic projections to various cortical areas is

responsible for deficits in neuropsychology (Liberini et al., 1996).

There are two ways to enhance cholinergic functions; one is to inhibit the enzyme acetylcholinesterase (AChE) , responsible for the breakdown of endogenous acetylcholine (ACh) while the other approach is to directly stimulate muscarinic receptors (using muscarinic agonists).

Acetylcholinesterase inhibitors. ACh is an important physiological neurotransmitter, which is quickly hydrolyzed by endogenous enzyme, AChE. The inhibition of the enzyme results in more ACh available to interact with postsynaptic muscarinic receptors. Currently available medicines for AD therapy are AChE inhibitors (Lopez et al., 2002). AChE inhibitor drugs approved by FDA in USA for the symptomatic treatment of AD are are rivastigmine, galantamine and donepezil (Lahiri. et al., 2002, Blennow et al., 2006), which show multiple side-effects limiting their usefulness in AD. Considering the mechanism of AChE inhibition, these drugs provide effective symptomatic treatment for variable period of time (Courtney et al., 2004, Bullock and Dengiz, 2005, Bullock et al., 2005), but do not change the course of AD (Blennow et al., 2006).

Muscarinic agonists. Selective loss of cholinergic neurons in central nervous system served as a target for the development of medicines which can enhance cholinergic transmission for the AD therapy. Selective muscarinic receptor (M_1) agonist is the suitable candidate (Fisher, 2000). M_1 receptors can be targeted because this is the major subtype of muscarinic receptors found in hippocampus and cortex (Friedman, 2004); this strategy can reduce side-effects associated with the stimulation of other muscarinic receptors. The activation of the muscarinic receptors modifies the APP processing and inhibits Aβ production (Gu et al., 2003). Currently, there is limited availability of M_1 agonists which have limitation either due to narrow selectivity resulting in side effects, poor bioavailability or penetration into blood brain barrier, thus requiring larger doses (Fisher, 2000).

Memantine. Memantine is another drug which is non-competitive NMDA receptor antagonist that has protective effect from increased glutamate levels mediated excitotoxicity, without interfering with physiological activation of NMDA receptors (Wilcock, 2003). Clinical trial suggest modest efficacy of memantine in moderate to severe AD patients (Wilcock, 2003).

Potential treatment options highlighted through epidemiology studies

As the knowledge about disease progresses, different pharmacological treatment options are coming into consideration. Several epidemiological studies have shown protective effects of the different drugs; some of them are summarized here.

Anti-inflammatory drugs: AD is also considered as a chronic inflammatory disease (Ahmed and Gilani, 2011). There are several studies supporting the use of anti-inflammatory drugs, with some beneficial effects in AD. Retrospective studies, that compared the frequency of nonsteroidal anti-inflammatory drugs (NSAIDs) use and AD progression, suggested slowing down the onset of AD (Li et al., 1992, Breitner et al., 1994). Ibuprofen, a well known NSAID, exerts beneficial effects by reducing Aβ amyloid deposition and senile plaque formation (Lim et al., 2000). In addition, studies on animals provide consolidation of this concept, that NSAIDs may protect against AD by suppressing inflammatory process (Netland et al., 1998, Lim et al., 2000).

Antioxidants: It has been widely supported in the literature that Aβ fragments produce oxidative radicals (Behl et al., 1994, Butterfield et al., 1994), which play an important role in AD pathogenesis. Therefore, therapeutic interventions to reduce oxidative damage induced injury, may retard and slow down the onset of disease. In-vivo studies as well as cell culture system have shown that Aβ-induced neurotoxicity is attenuated with vitamin E (Behl et al., 1992, Yamada et al., 1999, Huang et al., 2000). Antioxidant, such as Vitamin E intake can reduce the risk of AD (Sano et al., 1997, Engelhart et al., 2002, Morris et al., 2002).

Calcium channel blockers. Ca^{++} channel blockers (CCB) produce their beneficial effects by inhibiting pathological rise in intracellular Ca^{++}, which is the result of different events taking place in AD. In-vitro, Aβ has been shown to form Ca^{++} channels in membranes (Lin et al., 1999), thus, resulting in potentiation of toxicity (Rovira et al., 2002). Nimodipine, a CCB showed attenuation of Aβ-induced toxicity in cell culture (Weiss et al., 1994). In a recent report, CCBs have been shown to have beneficial effects in AD (Vagnucci and Li, 2003). Elderly patients who were treated with CCBs, showed decline in dementia (Forette et al., 1998).

Cholesterol lowering drugs. A few studies have shown to reduce the incidence of disease with usage of cholesterol lowering drugs, such as, statins (Jick et al., 2000, Wolozin et al., 2000), however; evidence becomes weak where some reports either do not show protective effect (Rea et al., 2005, Zandi et al., 2005) or marginal effect (Sparks et al., 2005) with cholesterol lowering drugs.

Future drug targets in Alzheimer's disease with disease modifying potential

The precise cause of the AD is not clear yet. There are series of questions which are still to be answered, such as; plaques come first or the initial selective cholinergic hypofunction; targeting disease by inhibiting plaques and tangles formation or to inhibit the secretase enzyme, or to clear Aβ using vaccines as pharmacological tool.

There are a limited number of medicines available for the treatment of AD, main drugs are AChE inhibitors, and there is a wide room available for newer drugs. AChE inhibitors partly overcome memory deficit in disease providing symptomatic treatment, but do not delay the time course of the disease. Hence, there is a need to combat this

disease by discovering candidates with disease modifying potential. Moreover, targeting through multiple pathways, which are activated as a result of cascades that are responsible to damage neurons need to be targeted. Drugs targeting α, β and γ secretase (enzymes responsible for the processing of APP) activity are being widely explored as target in AD with different degrees of success (Luo et al., 2001, Petit et al., 2001, Chang et al., 2004, Etcheberrigaray et al., 2004, Siemers et al., 2005). In addition, an approach to develop Aβ vaccine is also being investigated (Schenk et al., 1999, Bard et al., 2000). There is also some developing interest to have drugs chelating metal ions, which induce Aβ aggregations and show toxic effects (Cherny et al., 2001, Ritchie et al., 2003)

REFERENCES

1. Alzheimer's Association 2009. pp 1-12.
2. Ahmed T, Enam SA, Gilani AH. 2012. Curcuminoids enhance memory in an amyloid-infused rat model of Alzheimer's disease. Neuroscience, 169:1296-1306.
3. Ahmed T, Gilani AH. 2009. Inhibitory effect of curcuminoids on acetylcholinesterase activity and attenuation of scopolamine-induced amnesia may explain medicinal use of turmeric in Alzheimer's disease. Pharmacol Biochem Behav, 91:554-559.
4. Ahmed T, Gilani AH. 2011. A comparative study of curcuminoids to measure their effect on inflammatory and apoptotic gene expression in an Abeta plus ibotenic acid-infused rat model of Alzheimer's disease. Brain Res, 1400:1-18.
5. Ahmed T, Gilani AH, Hosseinmardi N, Semnanian S, Enam SA, Fathollahi Y. 2011. Curcuminoids rescue long-term potentiation impaired by amyloid peptide in rat hippocampal slices. Synapse, 65:572-582.
6. Avramopoulos D. 2009. Genetics of Alzheimer's disease: recent advances. Genome Med, 1:34.
7. Bard F, Cannon C, Barbour R, Burke RL, Games D, Grajeda H, Guido T, Hu K, Huang J, Johnson-Wood K, Khan K, Kholodenko D, Lee M, Lieberburg I, Motter R, Nguyen M, Soriano F, Vasquez N, Weiss K, Welch B, Seubert P, Schenk D, Yednock T. 2000. Peripherally administered antibodies against amyloid beta-peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease. Nat Med, 6:916-919.
8. Behl C, Davis J, Cole GM, Schubert D. 1992. Vitamin E protects nerve cells from amyloid beta protein toxicity. Biochem Biophys Res Commun, 186:944-950.
9. Behl C, Davis JB, Lesley R, Schubert D. 1994. Hydrogen peroxide mediates amyloid beta protein toxicity. Cell, 77:817-827.
10. Blennow K, de Leon MJ, Zetterberg H. 2006. Alzheimer's disease. Lancet, 368:387-403.
11. Breitner JC, Gau BA, Welsh KA, Plassman BL, McDonald WM, Helms MJ, Anthony JC. 1994. Inverse association of anti-inflammatory treatments and Alzheimer's disease: initial results of a co-twin control study. Neurology, 44:227-232.
12. Bullock R, Dengiz A. 2005. Cognitive performance in patients with Alzheimer's disease receiving cholinesterase inhibitors for up to 5 years. Int J Clin Pract, 59:817-822.
13. Bullock R, Touchon J, Bergman H, Gambina G, He Y, Rapatz G, Nagel J, Lane R. 2005. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. Curr Med Res Opin, 21:1317-1327.
14. Burns A, Iliffe S. 2009b. Alzheimer's disease. Bmj, 338:158.
15. Burns A, Jacoby R, Levy R. 1990. Psychiatric phenomena in Alzheimer's disease. IV: Disorders of behaviour. Br J Psychiatry, 157:86-94.
16. Butterfield DA, Hensley K, Harris M, Mattson M, Carney J. 1994. beta-Amyloid peptide free radical fragments initiate synaptosomal lipoperoxidation in a sequence-specific fashion: implications to Alzheimer's disease. Biochem Biophys Res Commun, 200:710-715.
17. Carson JA, Turner AJ. 2002. Beta-amyloid catabolism: roles for neprilysin (NEP) and other metallopeptidases? J Neurochem, 81:1-8.
18. Chang WP, Koelsch G, Wong S, Downs D, Da H, Weerasena V, Gordon B, Devasamudram T, Bilcer G, Ghosh AK, Tang J. 2004. In vivo inhibition of Abeta production by memapsin 2 (beta-secretase) inhibitors. J Neurochem, 89:1409-1416.
19. Cherny RA, Atwood CS, Xilinas ME, Gray DN, Jones WD, McLean CA, Barnham KJ, Volitakis I, Fraser FW, Kim Y, Huang X, Goldstein LE, Moir RD, Lim JT, Beyreuther K, Zheng H, Tanzi RE, Masters CL, Bush AI. 2001. Treatment with a copper-zinc chelator markedly and rapidly inhibits beta-amyloid accumulation in Alzheimer's disease transgenic mice. Neuron, 30:665-676.
20. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science, 261:921-923.
21. Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, Edwards S, Hardyman W, Raftery J, Crome P, Lendon C, Shaw H, Bentham P. 2004. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet, 363:2105-2115.
22. Davidson RM, Shajenko L, Donta TS. 1994. Amyloid beta-peptide (A beta P) potentiates a nimodipine-sensitive L-type barium conductance in N1E-115 neuroblastoma cells. Brain Res, 643:324-327.
23. Drachman DA, Leavitt J. 1974. Human memory and the cholinergic system. A relationship to aging? Arch Neurol, 30:113-121.
24. Engelhart MJ, Geerlings MI, Ruitenberg A, van Swieten JC, Hofman A, Witteman JC, Breteler MM. 2002. Dietary intake of antioxidants and risk of Alzheimer disease. Jama, 287:3223-3229.
25. Etcheberrigaray R, Tan M, Dewachter I, Kuiperi C, Van der Auwera I, Wera S, Qiao L, Bank B, Nelson TJ, Kozikowski AP, Van Leuven F, Alkon DL. 2004. Therapeutic effects of PKC activators in Alzheimer's

disease transgenic mice. Proc Natl Acad Sci U S A, 101:11141-11146.
26. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM. 1997. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. Jama, 278:1349-1356.
27. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M. 2000. Global prevalence of dementia: a Delphi consensus study. Lancet, 366:2112-2117.
28. Fisher A. 2000. Therapeutic strategies in Alzheimer's disease: M1 muscarinic agonists. Jpn J Pharmacol, 84:101-112.
29. Forette F, Seux ML, Staessen JA, Thijs L, Birkenhager WH, Babarskiene MR, Babeanu S, Bossini A, Gil-Extremera B, Girerd X, Laks T, Lilov E, Moisseyev V, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Fagard R. 1998. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet, 352:1347-1351.
30. Friedman JI.2004. Cholinergic targets for cognitive enhancement in schizophrenia: focus on cholinesterase inhibitors and muscarinic agonists. Psychopharmacology (Berl), 174:45-53.
31. Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, Giuffra L, Haynes A, Irving N, James L, et al. 1991. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature, 349:704-706.
32. Grundke-Iqbal I, Iqbal K, Tung YC, Quinlan M, Wisniewski HM, Binder LI. 1986. Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. Proc Natl Acad Sci U S A, 83:4913-4917.
33. Gu Z, Zhong P, Yan Z. 2003. Activation of muscarinic receptors inhibits beta-amyloid peptide-induced signaling in cortical slices. J Biol Chem, 278:17546-17556.
34. Hardy J, Selkoe DJ. 2002. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science, 297:353-356.
35. Harkany T, Abraham I, Timmerman W, Laskay G, Toth B, Sasvari M, Konya C, Sebens JB, Korf J, Nyakas C, Zarandi M, Soos K, Penke B, Luiten PG. 2000. beta-amyloid neurotoxicity is mediated by a glutamate-triggered excitotoxic cascade in rat nucleus basalis. Eur J Neurosci, 12:2735-2745.
36. Huang HM, Ou HC, Hsieh SJ. 2000. Antioxidants prevent amyloid peptide-induced apoptosis and alteration of calcium homeostasis in cultured cortical neurons. Life Sci, 66:1879-1892.
37. Iqbal K, Alonso Adel C, Chen S, Chohan MO, El-Akkad E, Gong CX, Khatoon S, Li B, Liu F, Rahman A, Tanimukai H, Grundke-Iqbal I. 2005. Tau pathology in Alzheimer disease and other tauopathies. Biochim Biophys Acta, 1739:198-210.
38. Jellinger KA. 2004. Head injury and dementia. Curr Opin Neurol, 17:719-723.
39. Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. 2000. Statins and the risk of dementia. Lancet, 356:1627-1631.
40. Kalaria RN. 2001. Advances in molecular genetics and pathology of cerebrovascular disorders. Trends Neurosci, 24:392-400.
41. Kroemer G, Galluzzi L, Brenner C. 2007. Mitochondrial membrane permeabilization in cell death. Physiol Rev, 87:99-163.
42. Lahiri. DK, Farlow. MR, Greig. NH, Sambamurti. K. 2002. Current drug targets for Alzheimer's disease treatment. Drug Development Research, 56:267-281.
43. Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, Pettingell WH, Yu CE, Jondro PD, Schmidt SD, Wang K, et al. 1995a. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. Science, 269:973-977.
44. Levy-Lahad E, Wijsman EM, Nemens E, Anderson L, Goddard KA, Weber JL, Bird TD, Schellenberg GD. 1995b. A familial Alzheimer's disease locus on chromosome 1. Science, 269:970-973.
45. Li G, Shen YC, Li YT, Chen CH, Zhau YW, Silverman JM.1992. A case-control study of Alzheimer's disease in China. Neurology, 42:1481-1488.
46. Liberini P, Valerio A, Memo M, Spano PF. 1996. Lewy-body dementia and responsiveness to cholinesterase inhibitors: a paradigm for heterogeneity of Alzheimer's disease? Trends Pharmacol Sci, 17:155-160.
47. Lim GP, Yang F, Chu T, Chen P, Beech W, Teter B, Tran T, Ubeda O, Ashe KH, Frautschy SA, Cole GM. 2000. Ibuprofen suppresses plaque pathology and inflammation in a mouse model for Alzheimer's disease. J Neurosci, 20:5709-5714.
48. Lin H, Zhu YJ, Lal R. 1999. Amyloid beta protein (1-40) forms calcium-permeable, Zn2+-sensitive channel in reconstituted lipid vesicles. Biochemistry, 38:11189-11196.
49. Lopez S, Bastida J, Viladomat F, Codina C. 2002. Acetylcholinesterase inhibitory activity of some Amaryllidaceae alkaloids and Narcissus extracts. Life Sci, 71:2521-2529.
50. Luo Y, Bolon B, Kahn S, Bennett BD, Babu-Khan S, Denis P, Fan W, Kha H, Zhang J, Gong Y, Martin L, Louis JC, Yan Q, Richards WG, Citron M, Vassar R. 2001. Mice deficient in BACE1, the Alzheimer's beta-secretase, have normal phenotype and abolished beta-amyloid generation. Nat Neurosci, 4:231-232.
51. Marx J. 2001. Alzheimer's disease. Bad for the heart, bad for the mind? Science, 294:508-509.
52. Mattson MP, Cheng B, Davis D, Bryant K, Lieberburg I, Rydel RE. 1992. beta-Amyloid peptides destabilize calcium homeostasis and render human cortical neurons vulnerable to excitotoxicity. J Neurosci, 12:376-389.
53. Mayeux R. 2003. Epidemiology of neurodegeneration. Annu Rev Neurosci, 26:81-104.

54. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N, Wilson RS, Scherr PA. 2002. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. Jama, 287:3230-3237.
55. Mortimer JA, Snowdon DA, Markesbery WR. 2003. Head circumference, education and risk of dementia: findings from the Nun Study. J Clin Exp Neuropsychol, 25:671-679.
56. Netland EE, Newton JL, Majocha RE, Tate BA. 1998. Indomethacin reverses the microglial response to amyloid beta-protein. Neurobiol Aging, 19:201-204.
57. Nilsen J, Chen S, Irwin RW, Iwamoto S, Brinton RD. 2006. Estrogen protects neuronal cells from amyloid beta-induced apoptosis via regulation of mitochondrial proteins and function. BMC Neurosci, 7:74.
58. Palmer AM. 2002. Pharmacotherapy for Alzheimer's disease: progress and prospects. Trends Pharmacol Sci, 23:426-433.
59. Petit A, Bihel F, Alves da Costa C, Pourquie O, Checler F, Kraus JL. 2001. New protease inhibitors prevent gamma-secretase-mediated production of Abeta40/42 without affecting Notch cleavage. Nat Cell Biol, 3:507-511.
60. Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S. 1993. Apolipoprotein E polymorphism and Alzheimer's disease. Lancet, 342:697-699.
61. Raber J, Huang Y, Ashford JW. 2004. ApoE genotype accounts for the vast majority of AD risk and AD pathology. Neurobiol Aging, 25:641-650.
62. Rea TD, Breitner JC, Psaty BM, Fitzpatrick AL, Lopez OL, Newman AB, Hazzard WR, Zandi PP, Burke GL, Lyketsos CG, Bernick C, Kuller LH. 2005. Statin use and the risk of incident dementia: the Cardiovascular Health Study. Arch Neurol, 62:1047-1051.
63. Ritchie CW, Bush AI, Mackinnon A, Macfarlane S, Mastwyk M, MacGregor L, Kiers L, Cherny R, Li QX, Tammer A, Carrington D, Mavros C, Volitakis I, Xilinas M, Ames D, Davis S, Beyreuther K, Tanzi RE, Masters CL. 2003. Metal-protein attenuation with iodochlorhydroxyquin (clioquinol) targeting Abeta amyloid deposition and toxicity in Alzheimer disease: a pilot phase 2 clinical trial. Arch Neurol, 60:1685-1691.
64. Rovira C, Arbez N, Mariani J. 2002. Abeta(25-35) and Abeta(1-40) act on different calcium channels in CA1 hippocampal neurons. Biochem Biophys Res Commun, 296:1317-1321.
65. Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, Woodbury P, Growdon J, Cotman CW, Pfeiffer E, Schneider LS, Thal LJ. 1997. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med, 336:1216-1222.
66. Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, Guido T, Hu K, Huang J, Johnson-Wood K, Khan K, Kholodenko D, Lee M, Liao Z, Lieberburg I, Motter R, Mutter L, Soriano F, Shopp G, Vasquez N, Vandevert C, Walker S, Wogulis M, Yednock T, Games D, Seubert P. 1999. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. Nature, 400:173-177.
67. Selkoe DJ. 2001. Alzheimer's disease: genes, proteins, and therapy. Physiol Rev, 81:741-766.
68. Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, Chi H, Lin C, Li G, Holman K, et al. 1995. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature, 375:754-760.
69. Siemers E, Skinner M, Dean RA, Gonzales C, Satterwhite J, Farlow M, Ness D, May PC. 2005. Safety, tolerability, and changes in amyloid beta concentrations after administration of a gamma-secretase inhibitor in volunteers. Clin Neuropharmacol, 28:126-132.
70. Sparks DL, Sabbagh MN, Connor DJ, Lopez J, Launer LJ, Browne P, Wasser D, Johnson-Traver S, Lochhead J, Ziolwolski C. 2005. Atorvastatin for the treatment of mild to moderate Alzheimer disease: preliminary results. Arch Neurol, 62:753-757.
71. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD. 1993. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci U S A, 90:1977-1981.
72. Suh YH, Checler F. 2002. Amyloid precursor protein, presenilins, and alpha-synuclein: molecular pathogenesis and pharmacological applications in Alzheimer's disease. Pharmacol Rev, 54:469-525.
73. Vagnucci AH, Jr., Li WW. 2003. Alzheimer's disease and angiogenesis. Lancet, 361:605-608.
74. Weiss JH, Pike CJ, Cotman CW. 1994. Ca2+ channel blockers attenuate beta-amyloid peptide toxicity to cortical neurons in culture. J Neurochem, 62:372-375.
75. Wilcock GK. 2003. Memantine for the treatment of dementia. Lancet Neurol, 2:503-505.
76. Wolozin B, Kellman W, Ruosseau P, Celesia GG, Siegel G. 2000. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. Arch Neurol, 57:1439-1443.
77. Yamada K, Tanaka T, Han D, Senzaki K, Kameyama T, Nabeshima T. 1999. Protective effects of idebenone and alpha-tocopherol on beta-amyloid-(1-42)-induced learning and memory deficits in rats: implication of oxidative stress in beta-amyloid-induced neurotoxicity in vivo. Eur J Neurosci, 11:83-90.
78. Zandi PP, Sparks DL, Khachaturian AS, Tschanz J, Norton M, Steinberg M, Welsh-Bohmer KA, Breitner JC. 2005. Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County Study. Arch Gen Psychiatry, 62:217-224.
79. Zhang ZX, Zahner GE, Roman GC, Liu J, Hong Z, Qu QM, Liu XH, Zhang XJ, Zhou B, Wu CB, Tang MN, Hong X, Li H. 2005. Dementia subtypes in China: prevalence in Beijing, Xian, Shanghai, and Chengdu. Arch Neurol, 62:447-453.