Main hypotheses, concepts and theories in the study of Alzheimer's disease

Yuhui An*, Chao Zhang, Siyu He, Chunxia Yao, Limei Zhang, Qian Zhang

Department of Biochemistry and Molecular Biology, Basic Medical College, Zhengzhou University, Zhengzhou, Henan 450052*, China*

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Abstract

The incidence of Alzheimer's disease (AD) is 25 millions worldwide in 2000 and it is expected to increase to 63 and 114 millions in 2030 and 2050, respectively. Nowadays, such aging disease has caused enormous medical and financial burden to the community, which effective prevention and treatment are urgently needed. In this study, we have reviewed different hypotheses, concepts and theories of AD. These include hypothesis related to the loss of cholinergic neuron, calcium, oxidative imbalance, microtubule instability and amyloid cascade; the concepts about mild cognitive impairment and the regulation and interference of original molecule; and the theories of nitric oxide and glutamate neurotoxicity. Although genetic tests have existed for the research of AD, they are considered useful only for the small number of families with a history of early-onset illness. Because AD is a genetically heterogeneous disorder, it is classified as familial and sporadic. We hope this review can briefly provide a summary of the general knowledge about sporadic AD, and help to promote the research on AD or related prevention and treatment. [Life Science Journal. 2008; 5(4): 1 – 5] (ISSN: 1097 – 8135).

Keywords: Alzheimer's disease; cognitive impairment; memory loss; hypothesis; conception; theory

1 Introduction

According to a report of world heath organization (WHO)[1], the incidence of Alzheimer's disease (AD), a feature of memory dysfunction with a progressive loss of learning and memory, is drastically increasing along with human aging. The population of AD will be related to 60% of over-60-year-old population worldwide. In 2000, the incidence of AD is 25 millions. It is estimated that it will reach 63 and 114 millions in year 2030 and 2050, respectively. It is clearly a pressing problem and burden in both the medical and financial view of the society. In this review, different hypotheses, concepts and theories of AD have been summerized. These include hypotheses related to cholinergy, calcium, oxidative imbalance, microtubule instability and amyloid cascade; the concepts about mild cognitive impairment and the regulation and interference of original molecule; and the theories of nitric oxide and glutamate neurotoxicity. Although genetic tests have existed for the research of Alzheimer disease, they are considered useful only for the small number of families with a history of early-onset illness. Because AD is a genetically heterogeneous disorder, it is classified as familial and sporadic[2]. We hope this review can briefly provide a summary of the general knowledge about sporadic AD, and help to promote the research on AD or related prevention and treatment to the next level.

2 The Cholinergic Hypothesis

The cholinergic hypothesis was firstly proposed by Sims *et al* in 1981. They postulated that the synthesis of acetylcholine, a neurotransmitter, was low in the neocortex of the brain in AD patients[3,4]. In supporting this notion, the level of choline acetyltransferase was clearly found downregulated in the hippocampus and frontal cortex, and cholinergic neuron counts in the nucleus basalis was generally lowered in AD condition[5]. For the above reasons, the "cholinergic hypothesis" was suggested to

*Corresponding author. Email: yuhuian@zzu.edu.cn

describe the low level of acetylcholine in the brain of AD patients[3]. Based on this hypothesis some drugs were put under investigations for that they could generally increase the cerebral level of acetylcholine[6].These include the acetylcholinesterase inhibitor, the cholinergic neuron agonist, the acetylcholine releasing agent and the cholinergic neuron proliferation agents etc[7]. Tacrine was the first drug that had launched into the market for treating the loss of memory and intellectual decline in AD patients[8]. However, its side effect such as hepatic toxicity and the lack of ability to delay the progression of disease had resulted in poor outcome and popularity[9,10]. To date, nerve growth factor (NGF) is being studied on its protective characteristic on neurons for AD patients. It is a neuron proliferation agent that can elevate cholinergic neuron counts and protect neurons, particularly cholinergic neuron, from degeneration. Since it is a big molecule which cannot pass through the blood brain barrier, research is ongoing which aims to improve the drug delivery strategy for NGF. So it might become one effective agents used in gene therapy for treating AD[11,12].

3 The Conception of Mild Cognitive Impairment

In clinical research of AD, Petersen *et al* suggested "the conception of mild cognitive impairment (MCI)"[13]. It postulated a state between normal aging and AD[14]. At the state, patients with MCI are yet to reach the pathological standard of AD, but they are people of higher risk to develop AD. About 15% of MCI sufferers will finally develop AD every year[15]. Research has shown that MCI represents an early point of decline on the continuum of AD that is different from normal aging of various aspects. These include reduction of learning ability, rapid loss of short-term memory, elevation of intrusion errors, and poor recognition discriminability[16]. The proposed adjustments and additions (neuropsychological instruments and the incorporation of depressive symptoms) in the diagnostic flowchart of Petersen may serve as useful tools for clinicians when making a diagnosis of MCI[17].

4 The Hypothesis of Oxidative Stress and Oxidative Imbalance

In recent years, studies have revealed a close association between increased oxidative stress and AD[18]. It is well recognized that oxidative imbalance and stress can play a crucial role in the pathogenesis of neuron degeneration and death[19,20]. Increasing evidence have also supported a role of oxidative imbalance, characterized by impaired antioxidant enzymatic activity and increased reactive oxygen species (ROS) production in AD. Those ROS include the free radicals (e.g. superoxide and hydroxyl radicals), nonradical oxygen species (e.g. hydrogen peroxide and peroxynitrite), and reactive lipids and carbohydrates (e.g. ketoaldehydes, hydroxynonene). In general, oxidative damage to DNA can occur via various pathways such as the oxidative modification of the nucleotide bases, sugars, or simply by forming crosslinks. Such modifications can lead to mutations, pathologies, cellular aging and death. Moreover, oxidation of protein appears to play a causative role in many chronic aging diseases including cataractogenesis[21], rheumatoid arthritis[22], and various neurodegenerative diseases including AD[23].

5 Nitric Oxide Theory

Nitric oxide (NO) theory is another hypothesis in molecular etiology of AD[24]. NO and other reactive nitrogen species appear to play several crucial roles in the brain. These include physiological processes such as neuromodulation, neurotransmission and synaptic plasticity, and pathological processes such as neurodegeneration and neuroinflammation[25]. NO is synthesized by the nitric oxide synthase (NOS), which is present in the mammalian brain in three different isoforms, two constitutive enzymes (i.e. neuronal, nNOS, and endothelial eNOS) and one inducible enzyme (iNOS). Nitric oxide synthase neurons are abundant in the human cortex, and their distribution differs between different cortical regions, and there are differences between normal aging and Alzheimer patients in the frontal cortex and the hippocampus[26]. All three isoforms are aberrantly expressed in Alzheimer's disease giving rise to elevated levels of nitric oxide apparently involved in the pathogenesis of this disease by various different mechanisms including oxidative stress and activation of intracellular signalling mechanisms[27]. In AD cases, aberrant expression of eNOS (NOS-3) in cortical pyramidal cells was highly co-localized with nitrotyrosine. Furthermore, iNOS (NOS-2) and eNOS were highly expressed in astrocytes in AD[28]. eNOS (NOS-3) overexpression can result in apoptosis accompanied by increased levels of p53, p21/Waf1, Bax, and CD95[29]. However, iNOS has been found to be a major contributor to initiation/exacerbation of the central nervous system (CNS) inflammatory/degenerative conditions through the production of excessive NO which generates reactive nitrogen species (RNSs)[30]. The up-regulation of NOS expression, suggesting overproduction of NO, can causes a decrease in cerebral blood flow, involving microvasculopathy with impaired NO release,

which in turn results in regional metabolic dysfunction[31]. NO is thermodynamically unstable and tends to react with other molecules, resulting in the oxidation, nitrosylation or nitration of proteins, with the concomitant effects on many cellular mechanisms. NO intracellular signaling involves the activation of guanylate cyclase but it also interacts with MAPKs, apoptosis-related proteins, and mitochondrial respiratory chain or anti-proliferative molecules[32]. NO can be scavenged in a rapid reaction with superoxide (O^2-) to generate peroxynitrite (ONOO-), with a half-life less than 1 second. ONOO- is a potent oxidant and the primary component of nitroxidative stress. At high concentrations (> 100 nM), ONOO- can undergo homolytic or heterolytic cleavage to produce NO_2^+, NO_2, and OH·, highly reactive oxidative species and secondary components of nitroxidative stress. The high nitroxidative stress can initiate a cascade of redox reactions which can trigger apoptosis and evoke cytotoxic effects on neurons and endothelial cells[33]. NO also induces tau hyperphosphorylation at Ser396/404 and Ser262 in HEK293/tau441 cells with a simultaneous activation of glycogen synthase kinase-3beta (GSK-3beta)[34].

6 The Theory of Glutamate Neurotoxicity/Calcium Hypothesis

The theory of glutamate neurotoxicity and the calcium (Ca^{2+}) hypothesis belong to the same theory. Simpson *et al*[35] found that glutamate-containing nerve terminals are severely reduced in AD. Glutamate can increase the intracellular Ca^{2+} activity. This finally leads to a Ca^{2+} influx via NMDA receptor of glutamate, an excitatory amino acid, which can act on the NMDA receptors on spinal cord neurons, channels[36] and results in dysregulation of multiple Ca^{2+}-dependent processes including learning or memory loss. Based on this observation, the calcium hypothesis was suggested[37], and antagonist of NMDA receptor was being investigated for its application as a novel therapeutic approach for AD[38].

7 The Hypothesis of Microtubule Instability

The hypothesis of microtubule instability comes from the observation to the phenomena in which tau protein promotes microtubule assembly and stabilizes microtubules, yet hyperphosphorylated tau did not[39]. Hyperphosphorylated tau-induced disruption of microtubule network results in both axonal and dendritic neurodegeneration seen in AD patients[40]. It is known that the state of tau phosphorylation is mainly regulated by maintaining the balance between tau phosphatase(s) activity and tau kinase(s) activity. Since many studies have shown that hyperphosphorylation of tau in the brain of AD might be due to a decrease of tau phosphatase(s) activity[41,42]. The related enzymes became potential target candidate that might be employed in the treatment of AD.

8 The Amyloid Cascade Hypothesis

Beta-amyloid (Abeta), a 4200-dalton peptide isolated from extraparenchymal meningeal vessels, neuritic plaques, and neurofibrillary tangles, has been revealed as an important pathological factor in the neural system[43]. An investigation which studied the amyloid deposition in the brain and other organs in 105 consecutive autopsy cases, aged 59 to 101 years, had verified a close relationship between Abeta and AD[44]. Nowadays, a pathological cascade was suggested for AD. This started with the Abeta deposition, then leads to tau phosphorylation and tangle formation and finally neuronal death[45]. It is generally believed that a beta fibrils deposited in amyloid plaques will lead to the formation of beta-derived diffusible ligands (ADDL). The ADDL will bind to synaptic spines at or near NMDA receptors which results in synaptic loss, oxidative damage, and AD-type tau hyperphosphorylation[46]. However, some studies in somatostatin cells have revealed an independent status of Abeta deposition and hyperphosphorylation of tau which could not be explained by the amyloid cascade hypothesis[47]. Therefore, such hypothesis is still controversial, yet it is mostly accepted as one of the implications in the pathological aging processes including AD[48].

9 The Conception of Regulation and Interference of Original Molecules

Neurotoxic molecules, which can generate neurotoxicity to nervous cells, can induce AD. We have summarized in the above sessions that ROS, NO, tau protein, Abeta are endogenous neurotoxic molecules. Our genuine question should be about the origin of those molecules. For ROS, it is obvious that they came from oxidative reaction where oxidative enzyme and substrates should count as their origin[18–23]. For NO, there is no doubt that its original substances are L-arginine and nitric oxide synthase[24–34]. Furthermore, tau kinase and tau phosphatase are the original molecule of hyperphosphorylated tau, yet it needs an imbalance of the state to make it pathological[39–42]. For the formation of Abeta, amyloid precursor protein (APP), a membrane protein of 695 amino acids[49], β- and γ-secretase can be regarded as the original molecules. APP involves in the initial of a cascade, in which when hydroly-

sis of β- and γ-secretase occurs, the neurotoxic molecule Abeta will be induced[50,51]. Therefore, we are suggesting here that if the formation of the original molecules are regulated in an purpose to reduce their generation of neurotoxic molecules, the condition of AD might be curable or slowed down in progression. Based on this, we have previously suggested a conception of "regulation and interference of original molecules" (RIOM)[52]. Thereafter, several studies have positively evaluated this concept. For example, an inhibitor of cysteine protease and secretase was found to reduce Abeta production[53]. The regulatory effects of acidic peptide on the levels of N-methyl-D-aspartate receptor, the NGF and the Abeta peptide have evidence to interfere with original molecule[54], and lead to an effective therapy to AD[55]. Furthermore, okadaic acid was also found to reduce mint-1, mint-2, and APP overexpressionin neurons[56]. The plasma concentration of NO in the AD patients was also found to be decreased with an artificial increase of homocysteine[57]. Similarly, NADPH oxidase was down-regulated by an introduction of heme oxygenase-1 *in vivo*, that resulted in a decrease in oxidative stress[58]. All of the above demonstrated either regulation or interference on the original molecules, via an interaction with enzymatic activity and gene expression. It is a valuable platform for further investigation which would be carried out to reveal if any of the interferences might be helpful in reducing the occurrence of AD. Those reagents or substances which successfully cause the interferences might as well serve as a novel therapeutic strategy in treating aging diseases in the near future.

References

1. Loncarevic N, Mehmedika-Sulic E, Alajibegovic, *et al*. The neurologist role in diagnostics and therapy of the Alzheimer's disease. Med Arc 2005; 59(2): 106 – 9.
2. Schutte DL. Alzheimer disease and genetics: anticipating the questions. Am J Nurs 2006; 106(12): 40 – 7.
3. Sims NR, Bowen DM, Davison AN. [14]acetylcholine synthesis and [14]carbon dioxide production from [U-14]glucose by tissue prisms human neocortex. Biochem J 1981; 196(3): 867 – 76.
4. Greenwald BS, Davis KI. Experimental pharmacology of Alzheimer's disease. Adv Neurol 1983; 38: 87 – 102.
5. Terry AV Jr, Buclatusco JJ. The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: recent challenges and their implication for novel drug development. J Pharmacol Exp Ther 2003; 306(3): 821 – 7.
6. Weinstock M. The pharmacotherapy of Alzheimer's disease based on the cholinergic hypothesis: an update. Neurodegeneration 1995; 4(4): 349 – 56.
7. Freo U, Pizzolato G, Dam M, *et al*. A short review of cognitive and functional neuroimaging studies of cholinergic drugs: implications for therapeutic potentials. J Neural Transm 2002; 109(5 – 6): 857 – 70.
8. Alfirevic A, Mills T, Carr D, Barratt BJ, *et al*. Tacrine-induced liver damage: an analysis of 19 candidate genes. Pharmacogenet Genomics 2007; 17(12): 1091 – 100.
9. Ori CJ, Monette J, Sourial N, *et al*. The use of a cholinesterase inhibitor review committee in long-term care. J Am Med Dir Assoc 2007; 8(4): 243 – 7.
10. Golder TF. Disease modifying therapy for AD? J Neurochem 2006; 99(3): 689 – 707.
11. Castellanos-Ortega MR, Cruz-Aguado R, Martinez L, *et al*. Nerve growth factor: possibilities and limitations of its clinical application. Rev Neurol 1999; 29(5): 439 – 47.
12. Tuszynski MH. Nerve growth factor gene therapy in Alzheimer disease. Alzheimer Dis Assoc Disord 2007; 21(2): 179 – 89.
13. Petersen RC, Parisil JE, Dickson DW, *et al*. Neuropathologic features of amnestic mild cognitive impairment. Arch Neurol 2006; 63(5): 645 – 6.
14. Mariani E, Monastero R, Meocci P. Mild cognitive impairment: a systematic review. J Alzheimers Dis 2007; 12(1): 23 – 35.
15. Apostolova LG, Steiner CA, Akopyan GG, *et al*. Three-dimensional gray matter atrophy mapping in mild cognitive impairment and mild Alzheimer disease. Arch Neurol 2007; 64(10): 1489 – 95.
16. Greenaway MC, Lacritz LH, Binergar D, *et al*. Patterns of verbal memory performance in mild cognitive impairment, Alzheimer disease and normal aging. Cogn Behav Neurol 2006; 19(2): 79 – 84.
17. Dierckx E, Engelborghs S, De Raedt R, *et al*. Mild cognitive impairment: what's in a name? Gerontology 2007; 53(1): 28 – 35.
18. Shibata N, Kobayashi M. The role for oxidative stress in neurodegenerative diseases. Brain Nerve 2008; 60(2): 157 – 70.
19. Markesbery WR. Oxidative stress hypothesis in Alzheimer's disease . Free Radic Biol Med 1997; 23(1): 134 – 47.
20. Guidi I, Galimberti D, Lonati S, *et al*. Oxidative imbalance in patients with mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 2006; 27(2): 262 – 9.
21. Moreira PI, Santos MS, Oliveria CR, *et al*. Alzheimer disease and the role of free radicals in the pathogenesis of the disease. CNS Neurol Disord Drug Targets 2008; 7(1): 3 – 10.
22. Cedergren J, Forslund T, Sundqvist T, *et al*. Intracellular oxidative activation in synovial fluid neutrophils from patients with rheumatoid arthritis but not from other arthritis patients. J Rheumatol 2007; 34(11): 2162 – 70.
23. Gracy RW, Talent JM, Kong Y, *et al*. Reactive oxygen species: the unavoidable environmental insult? Mutat Res 1999; 428(1 – 2): 17 – 22.
24. McCann SM, Mastronardi C, de Laurentiis A, *et al*. The nitric oxide theory of aging revisited. Ann N Y Acad Sci 2005; 1057: 64 – 84.
25. Aliyev A, Seyidova D, Rzayev N, *et al*. Is nitric oxide a key target in the pathogenesis of brain lesions during the development of Alzheimer's disease? Neurol Res 2004; 26(5): 547 – 53.
26. Calabress V, Bates TE, Stella AM. NO synthase and NO-dependent signal pathways in brain aging and neurodegenerative disorders: the role of oxidant/antioxidant balance. Neurochem Res 2000; 25(9–10): 1315 – 41.
27. Yew DT, Wong HW, Li WP, *et al*. Nitric oxide synthase neurons in different areas of normal aged and Alzheimer's brains. Neuroscience 1999; 89(3): 675 – 86.
28. Luth HJ, Holzer M, Gartner U, *et al*. Expression of endothelial and inducible NOS-isoforms is increased in Alzheimer's disease, in APP23 transgenic mice and after experimental brain lesion in rat: evidence for an induction by amyloid pathology. Brain Res 2001; 913(1): 57 – 67.
29. Luth HJ, Munch G, Arendt T. Aberrant expression of NOS isoforms in Alzheimer's disease is structurally related to nitrotyrosine formation. Brain Res 2002; 953(1–2): 135 – 43.
30. de La Monte SM, Chiche J, von dem Bussche A, *et al*. Nitric oxide synthase-3 overexpression causes apoptosis and impairs neuronal mitochondrial function: relevance to Alzheimer's-type neurodegeneration. Lab Invest 2003; 83(2): 287 – 98.
31. Pannu R, Singh I. Pharmacological strategies for the regulation of inducible nitric oxide synthase: neurodegenerative versus neuroprotective mechanisms. Neurochem Int 2006; 49(2): 170 – 82.
32. Togo T, Katsuse O, Iseki E. Nitric oxide pathways in Alzheimer's disease and other neurodegenerative dementias. Neurol Res 2004; 26(5):

563 – 6.
33. Guix FX, Uribesalgo I, Coma M, *et al*. The physiology and pathophysiology of nitric oxide in the brain. Prog Neurobiol 2005; 76(2): 126 – 52.
34. Malinski T. Nitric oxide and nitroxidative stress in Alzheimer's disease. J Alzheimers Dis 2007; 11(2): 207 – 18.
35. Simpson MD, Royston MC, Deakin JF, *et al*. Regional changes in [3H]D-aspartate and [3H]TCP binding sites in Alzheimer's disease brains. Brain Res 1988; 462(1): 76 – 82.
36. MacDermott AB, Mayer ML, Westbrook GL, *et al*. NMDA-receptor activation increases cytoplasmic calcium concentration in cultured spinal cord neurons. Nature 1986; 321(6069): 519 – 22.
37. Thibault O, Gant JC, Landfield PW. Expansion of the calcium hypothesis of brain aging and Alzheimer's disease: minding the store. Aging Cell 2007; 6(3): 307 – 17.
38. Flarlow MR. NMDA receptor antagonists: A new therapeutic approach for Alzheimer's disease. Geriatrics 2004; 59(6): 22 – 7.
39. Strittmatter WJ, Weisgraber KH, Goedert M, *et al*. Hypothesis: microtubule instability and paired helical filament formation in the Alzheimer disease brain are related to apolipoprotein E genotype. Exp Neurol 1994; 125(2): 163 – 71.
40. Li B, Chohan MO, Grundke-Iqbal I, *et al*. Disruption of microtubule network by Alzheimer abnormally hyperphosphorylated tau. Acta Neuropathol 2007; 113(5): 501 – 11.
41. Liu F, Liang Z, Gong CX. Hyperphosphorylation of tau and protein phosphatases in Alzheimer disease. Panminerva Med 2006; 48(2): 97 – 108.
42. Luna-Munoz J, Chuvez-Macias L, Garcia-Sierra F, *et al*. Earliest stages of tau conformational changes are related to the appearance of a sequence of specific phospho-dependent tau epitopes in Alzheimer's disease. J Alzheimers Dis 2007; 12(4): 365 – 75.
43. Pardridge WM, Vinters HV, Yang J, *et al*. Amyloid angiopathy of Alzheimer's disease: amino acid composition and partial sequence of a 4200-dalton peptide isolated from cortical microvessels. J Neurochem 1987; 49(5): 1394 – 401.
44. Yamada M, Tsukagoshi, Otomo E, *et al*. Systemic amyloid deposition in old age and dementia of Alzheimer type: the relationship of brain amyloid to other amyloid. Acta Neuropathol 1988; 77(2): 136 – 41.
45. Hardy J, Allsop D. Amyloid deposition as the central event in the aetiology of Alzheimer's disease. Trends Pharmacol Sci 1991; 12(10): 383 – 8.
46. Viola KL, Velasco PT, Klein WL. Why Alzheimer's is a disease of memory: the attack on synapses by A beta oligomers (ADDLs). J Nutr Health Aging 2008; 12(1): 51S – 7S.
47. Van de Nes JA, Konermann S, Nafe R, *et al*. Beta-protein/A4 deposits are not associated with hyperphosphorylated tau in somatostatin neurons in the hypothalamus of Alzheimer's disease patients. Acta Neuropathol 2006; 111(2): 126 – 38.
48. Hanson AJ, Prasad JE, Nahreini P, *et al*. Overexpression of amyloid precursor protein is associated with degeneration, decreased viability, and increased damage caused by neurotoxins (prostaglandins A1 and E2, hydrogen peroxide, and nitric oxide) in differentiated neuroblastoma cells. J Neurosci Res 2003; 74(1): 148 – 59.
49. Octave JN. Alzheimer disease: cellular and molecular aspects. Bull Mem Acad R Med Gelg 2005; 160(10–12): 445 – 9.
50. Deshpande A, Mina E, Glabe C, *et al*. Different conformations of amyloid beta induce neurotoxicity by distinct mechanism in human cortical neuron. J Neurosci 2006; 26(22): 6011 – 8.
51. Thitavat S, Ortiz D, Rogers E, *et al*. Folate, Vitamin E, and acetyl-L-carnitine provide synthetic protection against oxidative stress resulting from exposure of human neuroblastoma cells to amyloid-beta. Brain Res 2005; 1061(2): 114 – 7.
52. An YH. New progression of senile dementia: regulation and interference of original molecule. Henan Medical Research 2007; 16(1): 84 – 5.
53. Hook G, Hook VY, Kindy M. Cysteine protease inhibitors reduce brain beta-amyloid and beta-secretase activity *in vivo* and are potential Alzheimer's disease therapeutics. Bio Chem 2007; 388(9): 979 – 83.
54. An YH, Zhao HJ, Cai SD, *et al*. Regulatory effects of acidic peptide on the levels of N-methyl-D-aspartate receptor, nerve growth factor and beta-amyloid peptide in the brain of rats with Alzheimer disease. Chinese Clinical Rehabilitation 2006; 10(42): 202 – 4.
55. An YH, Xie XY, Chen ZR, *et al*. Influence of acidic peptide on learning and memory of rats with Alzheimer's disease. Chinese Clinical Rehabilitation 2006; 10(6): 185 – 7.
56. Yonn S, Choi J, Haam J, *et al*. Reduction of mint-1, mint-2, and APP overexpression in okadaic acid-treated neurons. Neuroreport 2007; 18(18): 1879 – 83.
57. Selley ML. Increased concentrations of homocysteine and asymmetric dimethylarginine and decreased concentrations of nitric oxide in the plasma of patients with Alzheimer's disease. Neurobiol Aging 2003; 24(7): 903 – 7.
58. Datla SR, Dusting GJ, Mori TA, *et al*. Induction of heme oxygenase-1 *in vivo* suppresses NADPH oxidase derived oxidative stress. Hypertension 2007; 50(4): 636 – 42.