Review

DOI: 10.5582/ddt.2012.v6.6.285

Review of drugs for Alzheimer's disease

Xiaoting Sun[1], Lan Jin[2,*], Peixue Ling[1,3]

[1] *Institute of Biochemical and Biotechnological Drugs, School of Pharmaceutical Science, Shandong University, Ji'nan, Shandong, China;*
[2] *National Glycoengineering Research Center, Shandong University, Ji'nan, Shandong, China;*
[3] *Institute of Biopharmaceuticals of Shandong Province, Ji'nan, Shandong, China.*

ABSTRACT: Alzheimer's disease (AD) is the most common form of dementia in the elderly. The number of people affected by AD is rapidly increasing. AD is characterized by cerebral atrophy, cerebral senile plaques, intraneuronal neurofibrillary tangles, and neuronal cell loss. Medical treatment of AD has a long history and differing results. We will review the effectiveness and limitations of the drugs used to treat AD.

Keywords: Alzheimer's disease, treatment, drugs

1. Introduction

Many age-related neurodegenerative diseases such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and Parkinson's disease represent a huge challenge for patients and caregivers (*1*). Of these, AD is the most common form of dementia in the elderly (*2*). AD is a progressive disorder (*3*) that affects 2% of the population in industrialized countries. More than 10% of the population over the age of 65 and 50% of the population over the age of 85 are suffering from AD (*4*). As the population ages, this number will double every twenty years, likely increasing to more than 80 million cases by the year 2040 (*5*).

AD is characterized by a series of neuropathologic changes, including cerebral atrophy, cerebral senile plaques containing extracellular deposits of β-amyloid peptide (Aβ), intraneuronal neurofibrillary tangles (NFTs) containing hyperphosphorylated tau protein, and neuronal cell loss (*6,7*). These result in patients suffering from memory loss, confusion, impaired judgment, disorientation, and trouble expressing themselves. The symptoms worsen over time and the disease is fatal. It disrupts the normal lives of patients and poses a substantial economic burden to family and society (*8*). Therefore, AD has garnered increasing attention in terms of its diagnosis, pathological mechanism, and therapeutic agents. The current article reviews the pathological mechanism of AD and drugs used to treat AD and it discusses the effectiveness and limitations of these drugs.

**Address correspondence to:*
Dr. Lan Jin, National Glycoengineering Research Center, Shandong University, No 44, West Wenhua Road, Ji'nan 250012, Shandong, China.
E-mail: lanjin@sdu.edu.cn

2. The neuropathology of Alzheimer's disease

The neuropathology of AD is very complex and has yet to be completely understood. There are several hypotheses that try to explain the pathological mechanism of the disease.

2.1. *Cholinergic dysfunction of the central nervous system*

Early studies showing loss of cholinergic activity in central nervous system (CNS) as AD progresses have been corroborated by numerous studies thus far. The brains of AD patients have very low levels of acetylcholine (ACh) (*9*). According to some pathophysiology research, the loss of cholinergic neurons usually occurs in brain areas associated with memory and learning, such as the hippocampus, nucleus basalis of Meynert, and cortex. A reduction in cholinergic activity is thus thought to be associated with cognitive deficits (*10*). This reduced activity affects synaptic transmission and initiates inflammatory processes. Some reactive oxygen species will be produced, resulting in cell death. Furthermore, Aβ can inhibit cholinergic neurons from absorbing choline and halt the action of cholinergic acetyltransferase (chAT), which inhibit the generation of ACh (*11*). However, whether the decrease in ACh is the cause of AD needs to be studied further.

2.2. *The amyloid cascade hypothesis*

2.2.1. *Amyloid precursor protein (APP) processing*

In humans, *APP* gene is located on chromosome 21. It has 3 major forms: APP695, APP751, and APP770.

The APP protein consists of 695-770 amino acids. It is a transmembrane glycoprotein that exists widely in human histiocytosis. It is widely expressed in the brain and functions as a membrane receptor (*12*). It undergoes cleavage by three types of enzymes: α-secretase, β-secretase, and γ-secretase (Figure 1). The sequential cleavage of APP by α-secretase and γ-secretase produces two soluble peptides, referred to as P3 and sAPPα. The sequential cleavage of APP by β-secretase and γ-secretase generates sAPPβ and insoluble Aβ, respectively. Under normal conditions, APP is cleaved *via* the first pathway. In contrast to Aβ, sAPPα has an important role in maintaining the activity of neurons. It can protect neurons against excitotoxicity and regulate neural stem cell proliferation (*13*).

2.2.2. *The structure of Aβ*

Aβ is an approximately 40-residue-long peptide. Its molecular weight is ~4,000. There are two main forms of Aβ, $Aβ_{40}$ and $Aβ_{42}$. $Aβ_{42}$ is more hydrophobic and more prone to aggregate and is considered to be the most neurotoxic form. The forms differ in their terminal carbon structures (Figure 2). $Aβ_{42}$ is the major component of senile plaques (SP) (*14*). In a normal brain, the majority of Aβ produced is $Aβ_{40}$, while patients with AD have a high ratio of $Aβ_{42}/Aβ_{40}$. In the brain, Aβ exists in soluble and fibril forms. Formation of Aβ fibrils is a multi-step process that requires a conformational change from an α-helical to β-pleated sheet structure. Many studies have confirmed that the neurotoxicity of Aβ is largely dependent on its ability to form β-sheet structures (*15*).

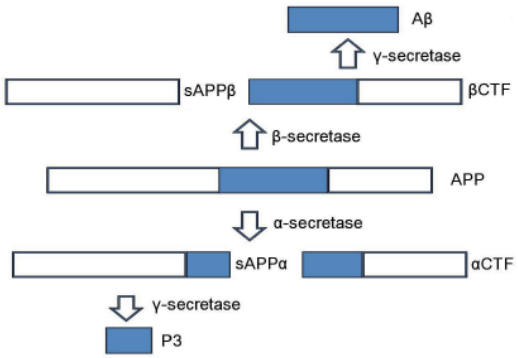


Figure 1. Diagram of APP processing.

2.2.3. *Aβ function*

Many studies have found that overproduction of Aβ results in a neurotoxic effect on neurons. It leads to synaptic dysfunction (*16*) and formation of intraneuronal fibrillary tangles (*17*) and eventually to neuron loss. Soluble Aβ can stimulate neurite growth in a short amount of time, which can increase neurons' survival rate. However, deposited Aβ has the opposite effect on neurons. It can cause the shrinkage of neurites and denaturing of neurons (*18*). Although the overproduction of Aβ has a negative effect on nerve cells, low levels of Aβ can increase hippocampal long-term potentiation and enhance memory.

2.2.4. *The mechanism of Aβ neurotoxicity*

Ca^{2+} is a second messenger in organisms. The extracellular concentration of Ca^{2+} is higher than that of intracellular Ca^{2+}. Aβ can disrupt the calcium channels in the cell membrane, enhancing Ca^{2+} influx and leading to the disequilibrium of calcium. An intracellular Ca^{2+} overload will impair the ability of mitochondria to buffer or cycle Ca^{2+}, resulting in cell toxicity and eventual cell death. The disruption in calcium homeostasis may in turn cause a variety of secondary effects such as lipid peroxidation and generation of free radicals. Over time, these related actions of Aβ will reduce synaptic integrity (*19,20*).

$Aβ_{42}$:

Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala

$Aβ_{40}$:

Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val

Figure 2. The structures of $Aβ_{42}$ and $Aβ_{40}$. $Aβ_{40}$ has two fewer amino acids than $Aβ_{42}$ at the C-terminal end.

2.3. *Neuroinflammation in AD*

Inflammation is one of the secondary effects of Aβ deposition. In the brain, it is characterized by activation of glial cells and expression of key inflammatory mediators. This inflammation is chronic. The cells participating in the action are mainly microglia and astrocytes. They participate in initiation and progression of neurological disorders by releasing cytotoxic molecules such as proinflammatory cytokines, reactive oxygen intermediates, proteinases, and complement proteins. In one form of attack, the activated glial cells kill neurons nearby by releasing reactive oxygen species (ROS), NO, and proteinase that cause neurotoxicity (*21*). In a second form of attack, an inflammatory reaction can stimulate the regeneration of Aβ, aggravating the inflammation and forming a vicious cycle (*22*).

2.4. *Other pathogeneses*

An increasing risk factor for AD is ApoE, which is a 34 kDa glycoprotein. It facilitates neuronal repair, it has anti-inflammatory properties, and it facilitates dendritic growth. In humans, there are three major forms of ApoE: ApoE2, ApoE3, and ApoE4. ApoE4 is reported to be associated with AD (*23*). It can promote amyloid deposition, neurotoxicity, oxidative stress, neurofibrillary tangle formation, and increasing brain inflammation. Previous studies have shown that ApoE4 causes mitochondrial damage, microvascular generation, and neural injury (*24*).

In addition, hypercholesterolemia is considered to be a risk factor for AD (*25*). People with a rare mutation in the *APP*, presenilin-1 (*PSEN1*), and presenilin-2 (*PSEN2*) genes are usually at greater risk for developing hypercholesterolemia (*26*). Additionally, several environmental agents, including metals (Al^{3+} (*27*), Hg^{2+} (*28*)), pesticides, dietary factors, and brain injuries, have been suggested as possible risk factors for AD.

3. Drugs used to improve cholinergic function

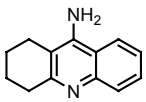
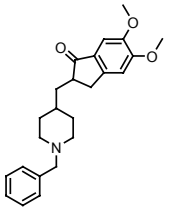
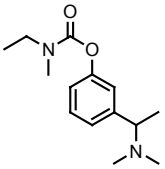
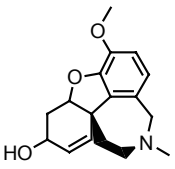
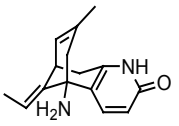
Many drugs have been approved for AD treatment in different stages of the disease, although they all have limited efficacy. The AD process has an apparent linear relationship to the pathological changes in the human brain, indicating that the disease can be halted by medication that interferes with the different stages. Many drugs have been used to improve cholinergic function in patients.

3.1. *Acetylcholinesterase inhibitors*

Acetylcholinesterase inhibitors were the first drugs approved by the FDA to treat AD, representing obvious progress in treatment of the disease. Tacrine, approved by the FDA in 1993, is the first drug used in AD treatment as an acetylcholinesterase inhibitor. The mechanism by which tacrine causes damage is not completely understood and it consistently causes a number of adverse reactions. Tacrine is now rarely used in AD treatment (*29*) due to its hepatotoxicity.

Donepezil is another acetylcholinesterase inhibitor. It is readily absorbed after oral administration. Compared to tacrine, its effects last longer (Table 1). It is better tolerated

Table 1. Comparison of pharmacological characteristics of 5 acetylcholinesterase inhibitors

	Tacrine	Donepezil	Rivastigmine	Galantamine	Huperzine A
Structure					
Target enzymes	AChE and BuChE	AChE	AChE and BuChE	AChE	AChE
Recommended dosage	160 mg/day (four times daily)	10 mg/day (once daily)	9.5 mg/24 h patch (once daily) 12 mg/day (twice daily)	24 mg/day (twice daily)	0.4 mg/day (twice daily)
Plasma half-life	2-4 h	About 70 h	About 3 h (patch) About 1 h (capsule)	About 7 h	About 60 h
Period of disease treatment	—	All stages of Alzheimer's disease	Mild to moderate Alzheimer's disease	Mild to moderate Alzheimer's disease	Mild to moderate Alzheimer's disease
AChE IC_{50} (nM)	190	22	48,000	800	47
BuChE IC_{50} (nM)	47	4.1	54,000	73,000	30
Adverse reactions	Hepatotoxicity	Diarrhea, nausea	Diarrhea, nausea	Nausea, weight loss	Nausea

by patients and causes fewer adverse reactions. Adverse reactions to the drug are primarily nausea, dizziness, diarrhea, and anorexia. All of these are dose-dependent (*30*). A number of clinical trials suggest that it can effectively improve cognitive performance and stabilize the functional ability of patients. It is used to treat mild to moderate AD (*31*).

Rivastigmine is a carbamate derivative. It can reversibly inhibit both acetyl- and butyryl-cholinesterase (AChE and BuChE, respectively). After oral administration, it reaches its peak plasmatic concentration in one hour (*32*). It is the only drug in which cytochrome P450 isoenzymes are not involved in its metabolism, so it can minimize drug-drug interactions. Many clinical trials suggest that rivastigmine has a significant effect on memory and the praxis domains of cognition. Unlike rivastigmine capsules, rivastigmine patches have a significant effect on the language domain. These patches can be used to treat patients with mild to moderate AD (*33*).

Galantamine is an extract of the flowers and bulbs of lilies, daffodils, and related plants. It is a selective acetylcholinesterase inhibitor. It improves cognitive dysfunction and affords neuronal protection, preventing the cytotoxicity caused by aggregation of Aβ (*34*). It is also believed to enhance central neurotransmission. The clinical efficacy of galantamine is almost equivalent to that of donepezil (*35*).

Huperzine A is a plant-based alkaloid from a plant named *Huperzia serrata*. It is an effective AChE inhibitor that can cross the blood-brain barrier (BBB). Huperzine A provides neuroprotection against neuronal damage. It has stronger inhibition and better selectivity than tacrine and galantamine (*36*).

In addition to the aforementioned drugs, many acetylcholinesterase inhibitors are used to treat AD, such as metrifonate and physostigmine and its derivatives. These drugs may provide protection against oxidative stress and Aβ toxicity. Although they increase synaptic transmission, acetylcholinesterase inhibitors also have several limitations. They are expensive and usually provide limited benefits. They may damage the neuronal membrane and more guidance is needed regarding their clinical use.

3.2. *M_1 receptor agonists*

M_1 muscarinic receptors remain mostly intact in the brains of AD patients. Therefore, M_1 receptors are considered to be an attractive therapeutic target for AD treatment. M_1 receptor agonists ameliorate the symptoms of AD and also delay the disease's progression. Several such drugs are used to treat AD, such as xanomeline (*37*) and milameline.

Xanomeline is a function selective muscarinic M_1/M_4-preferring receptor agonist. It can cross the BBB. Many clinical studies have noted significant improvement in the cognitive function of patients with AD. The drug's most common adverse effects are gastrointestinal response and cardiovascular adverse reactions.

4. Anti-Aβ drugs

β-Amyloid peptides are the main contributors to the pathology of AD. Many studies have found that overproduction of Aβ results in a neurotoxic effect on neurons. It leads to synaptic dysfunction, formation of intraneuronal fibrillary tangles (*17*), and eventually neuron loss. The deposited Aβ can cause the shrinkage of neurites and denaturing of neurons. Aβ can disrupt the calcium channels in the cell membrane, enhancing Ca^{2+} influx and leading to the disequilibrium of calcium. Therefore, anti-Aβ drugs may be the most effective drugs for AD treatment.

4.1. *Calcium antagonists*

An overload or insufficiency of calcium in nerve cells affects the production, transmission, and release of neurotransmitters. Drugs widely used in AD treatment as calcium antagonists are nimodipine, flunarizine, verapamil, and tetrandrine.

Nimodipine (*38*) is an L-type calcium channel antagonist. It is highly lipophilic and it can readily cross the BBB and effectively inhibit calcium influx, enhancing blood flow in the brain. It appears to be tolerated well by patients with fewer adverse reactions (*39*).

4.2. *Antioxidants*

Antioxidants can prevent the degeneration of nerve cells by eliminating active oxygen or preventing its generation. Vitamin E is the most commonly used antioxidant. It is a lipophilic vitamin. Many clinical trials have suggested that it can prevent oxidative action. It can decrease cellular death induced by Aβ and attenuate toxicity in neuroblastoma cells (*40*).

There are other common clinical antioxidant drugs, such as selegiline and melatonin. Selegiline is a selective monoamine antioxidant. It does help somewhat to improve the cognition, behavior, and mood of patients. However it does not globally benefit cognition, functional ability, and behavior (*41*). Melatonin functions by regulating circadian rhythms, clearing free radicals (*42*), improving immunity (*43*), and generally inhibiting the oxidation of biomolecules. It also has significant anti-amyloidogenic action. It prevents Aβ fibrillogenesis and aggregation by disrupting the imidazole-carboxylate salt bridge (*44*).

4.3. *Nonsteroidal anti-inflammatory drugs*

Many clinical studies have suggested that nonsteroidal anti-inflammatory drugs (NSAIDs) could be used

to prevent rather than treat AD. The mechanism of NSAIDs might be by inhibiting inflammation associated with the generation of SP (*45*). NSAIDs include indomethacin, tenidap, aspirin, ibuprofen, and naproxen (*46*). However, NSAIDs are known for their liver and kidney toxicity.

4.4. *Hypolipidemic drugs*

The expression of ApoE can lead to Aβ deposition and the formation of amyloid plaques. Nowadays, the use of ApoE isomers can effectively reduce the formation of amyloid plaques.

4.5. *Iron chelators*

High levels of iron have been found in both SP and NTFs in the brain. Ions may be involved in free radical formation and neuron degeneration. They may bind tightly to Aβ, possibly causing damage to neurons.

Treatment with iron chelators aims to remove excess iron that causes neurotoxicity in brain tissue. Iron chelators have a high affinity for iron. As an example, desferrioxamine, a natural iron scavenger, is a specific chelator with a high affinity for aluminum, copper, and zinc. Desferrioxamine is widely used in the treatment of AD (*47*). However, it requires continuous dosing due to its short circulating half-life. A drawback, however, is that it can cause serious adverse reactions such as injection site reactions and retinal toxicity (*48*).

5. Vaccines

Immunotherapy may be one of the most promising approaches to preventing the aggregation of Aβ (*49*). Many clinical trials have shown that anti-Aβ antibodies are effective in clearing Aβ deposits. Vaccination therapy for AD was invented by Dale Schenk and his colleagues in 1999 (*50*). They found that amyloid deposits were significantly reduced when they immunized young APP transgenic mice with Aβ and an adjuvant. The first clinical trial vaccine was AN-1792, which consisted of synthetic Aβ and adjuvant QS21. Patients who were suffering mild-to-moderate AD were treated with this vaccine. The trial was halted because 6% of patients developed subacute meningoencephalitis after one to three intramuscular injections of the vaccine. The meningoencephalitis was believed to be caused by a T cell-mediated autoimmune response. Many passive immunization clinical trials using anti-Aβ antibodies are now underway. There are many challenges to developing future Aβ vaccines. For example, a vaccine should help to prevent the disease in the early stages and it should be inexpensive; antigen targets should also be appropriately selected. Moreover, it should be efficacious in patients regardless of their immune status and it should facilitate compliance.

6. Conclusion and perspectives for the future

AD is a nervous system disease that exists in patients for many years. Many efforts are currently underway to explore the pathology of AD and develop appropriate treatments. These strategies focus on slowing disease progression and maintaining patients' quality of life. Nonetheless, there is no treatment that effectively stops the disease's progression. Accurate diagnosis of AD is problematic. Therefore, researchers need to recognize early signs of AD and explore new therapies to combat AD.

Acknowledgements

This project was supported by the Shandong Provincial Natural Science Foundation, China (No. ZR2011CM038).

References

1. Hu WT, Chen-Plotkin A, Arnold SE, Grossman M, Clark CM, Shaw LM, McCluskey L, Elman L, Karlawish J, Hurtig HI, Siderowf A, Lee VM, Soares H, Trojanowski JQ. Biomarker discovery for Alzheimer's disease, frontotemporal lobar degeneration, and Parkinson's disease. Acta Neuropathol. 2010; 120:385-399.
2. Forlenza OV, Diniz BS, Gattaz WF. Diagnosis and biomarkers of predementia in Alzheimer's disease. BMC Med. 2010; 8:89-102.
3. Sabbagh M, Cummings J. Progressive cholinergic decline in Alzheimer's disease: Consideration for treatment with donepezil 23 mg in patients with moderate to severe symptomatology. BMC Neurol. 2011; 11:21-26.
4. Zhang YW, Thompson R, Zhang H, Xu H. APP processing in Alzheimer's disease. Mol Brain. 2011; 4:3-15.
5. Massoud F, Gauthier S. Update on the pharmacological treatment of Alzheimer's disease. Curr Neuropharmacol. 2010; 8:69-80.
6. Amatsubo T, Yanagisawa D, Morikawa S, Taguchi H, Tooyama I. Amyloid imaging using high-field magnetic resonance. Magn Reson Med Sci. 2010; 9:95-99.
7. Wang JM, Sun C. Calcium and neurogenesis in Alzheimer's disease. Front Neurosci. 2010; 4:194-198.
8. Coppede F. One-carbon metabolism and Alzheimer's disease: Focus on epigenetics. Curr Genomics. 2010; 11:246-260.
9. Wollen KA. Alzheimer's disease: The pros and cons of pharmaceutical, nutritional, botanical, and stimulatory therapies, with a discussion of treatment strategies from the perspective of patients and practitioners. Altern Med Rev. 2010; 15:223-244.
10. Mufson EJ, Counts SE, Perez SE, Ginsberg SD. Cholinergic system during the progressing of Alzheimer's disease: Therapeutic implications. Expert Rev Neurother. 2008; 8:1703-1718.
11. Watanabe T, Iwasaki K, Ishikane S, Naitou T, Yoshimitsu Y, Yamagata N, Ozdemir MB, Takasaki K, Egashira N, Mishima K, Fujiwara M. Spatial memory impairment without apoptosis induced by the combination of β-amyloid oligomers and cerebral ischemia is related to decreased acetylcholine release in rats. J Pharmacol Sci. 2008; 106:84-91.
12. Bekris LM, Yu CE, Bird TD, Tsuang DW. Genetics of

Alzheimer disease. J Geriatr Psychiatry Neurol. 2010; 23:213-227.
13. Pagani L, Eckert A. Amyloid-β interaction with mitochondria. Int J Alzheimers Dis. 2011; 10:1-11.
14. Li T, Zhao ZX. β-Amyloid and Alzheimer disease: Recent progress. Acad J Second Mil Med Univ. 2010; 31:1133-1137.
15. He H, Dong W, Huang F. Anti-amyloidogenic and anti-apoptotic role of melatonin in Alzheimer disease. Curr Neuropharmacol. 2010; 8:211-217.
16. Ondrejcak T, Klyubin I, Hu NW, Barry AE, Cullen WK, Rowan MJ. Alzheimer's disease amyloid β-protein and synaptic function. Neuromolecular Med. 2010; 12:13-26.
17. Giaccone G, Pedrotti B, Miqheli A, *et al*. βPP and Tau interaction. A possible link between amyloid and neurofibrillary tangles in Alzheimer's disease. Am J Pathol. 1996; 148:79-87.
18. Armstrong RA. The pathogenesis of Alzheimer's disease: A reevaluation of the "amyloid cascade hypothesis". Int J Alzheimers Dis. 2011; 10:1-6.
19. Supnet C, Bezprozvanny I. Neuronal calcium signaling, mitochondrial dysfunction, and Alzheimer's disease. J Alzheimers Dis. 2010; 20:487-498.
20. Itkin A, Dupres B, Dufrene YF, Bechinger B, Ruysschaert JM, Raussens V. Calcium ions promote formation of amyloid β-peptide (1-40) oligomers causally implicated in neuronal toxicity of Alzheimer's disease. PLoS One. 2011; 6:1-10.
21. Ramberg V, Tracy LM, Samuelsson M, Nilsson LN, Iverfeldt K. The CCAAT/enhancer binding protein (C/EBP) δ is differently regulated by fibrillar and oligomeric forms of the Alzheimer amyloid-β peptide. J Neuroinflammation. 2011; 8:34-60.
22. Lei LW, Wang Y. Progress of pathogenesy and inflammation in Alzheimer's disease. Med Recap. 2008; 14:3041-3043.
23. Nishitsuji K, Hosono T, Nakamura T, Bu G, Michikawa M. Apolipoprotein E regulates the integrity of tight junctions in an isoform-dependent manner in an *in vitro* blood-brain-barrier model. J Biol Chem. 2011; 286:17536-17542.
24. Altman R, Rutledge JC. The vascular contribution to Alzheimer's disease. Clin Sci. 2010; 119:407-421.
25. Bates KA, Sohrabi HR, Rodrigues M, *et al*. Association of cardiovascular factors and Alzheimer's disease plasma amyloid-β protein in subjective memory complainers. J Alzheimers Dis. 2009; 17:305-318.
26. Zhuang Y, Chen J. Research process on causes and mechanism of Alzheimer's Disease. J Jilin Med Col. 2008; 29:101-104.
27. Kawahara M, Kato-Negishi M. Link between aluminum and the pathogenesis of Alzheimer's disease: The integration of the aluminum and amyloid cascade hypotheses. Int J Alzheimers Dis. 2011; 10:1-17.
28. Mutter J, Curth A, Naumann J, Deth R, Walach H. Does inorganic mercury play a role in Alzheimer's disease? A systematic review and an integrated molecular mechanism. J Alzheimers Dis. 2010; 22:357-374.
29. Wu TY, Chen CP, Jinn TR. Alzheimer's disease: Aging, insomnia and epigenetics. Taiwan J Obstet Gynecol. 2010; 49:468-472.
30. Aranda-Abreu GE, Hernandez-Aquilar ME, Denes JM, Garcia Hernandez LI, Rivero MH. Rehabilitating a brain with Alzheumer's: A proposal. Clin Interv Aging. 2011; 6:53-59.
31. Benjamin B, Burns A. Donepezil for Alzheimer's disease. Expert Rev Neurother. 2007; 7:1243-1249.
32. Kurz A, Farlow M, Lefevre G. Pharmacokinetics of a novel transdermal rivastigmine patch for the treatment of Alzheimer's disease: A review. Int J Clin Pract. 2009; 63:799-805.
33. Grossberg GT, Schmitt FA, Meng X, Tekin S, Olin J. Reviews: Effects of transdermal rivastigmine on ADAS-cog items in mild-to-moderate Alzheimer's disease. Am J Alzheimers Dis Other Demen. 2010; 25:627-633.
34. Ago Y, Koda K, Takuma K, Matsuda T. Pharmacological aspects of the acetylcholinesterase inhibitor galantamine. J Pharmacol Sci. 2011; 116:6-17.
35. Seltzer B. Galantamine-ER for the treatment of mild-to-moderate Alzheimer's disease. Clin Interv Aging. 2010; 5:1-6.
36. Zheng R, Su YF. Research progress of clinical use of Huperzine A. Pract Pharm Clin Remedies. 2008; 11:107-108.
37. Jakubik J, Michal P, Machova E, Dolezal V. Importance and prospects for design of selective muscarinic agonists. Physiol Res. 2008; 57(Suppl 3):39-47.
38. Disterhoft JF, Oh MM. Pharmacological and molecular enhancement of learning in aging and Alzheimer's disease. J Physiol Paris. 2006; 99:180-192.
39. Lopez-Arrieta JM, Birks J. Nimodipine for primary degenerative, mixed and vascular dementia. Cochrane Database Syst Rev. 2002; 3:CD000147.
40. Mas E, Dupuy AM, Artero S, Portet F, Cristol JP, Ritchie K, Touchon J. Functional vitamin E deficiency in ApoE4 patients with Alzheimer's disease. Dement Geriatr Cogn Disord. 2006; 21:198-204.
41. DelaGarza VW. Pharmacologic treatment of Alzheimer's disease: An update. Am Fam Physician. 2003; 68:1365-1372.
42. Wang X. The anti-apoptotic activity of melatonin in neurodegenerative diseases. CNS Neurosci Ther. 2009; 15:345-357.
43. Esposito E, Cuzzocrea S. Antiinflammatory activity of melatonin in central nervous system. Curr Neuropharmacol. 2010; 8:228-242.
44. He H, Dong W, Huang F. Anti-amyloidogenic and anti-apoptotic role of melatonin in Alzheimer disease. Curr Neuropharmacol. 2010; 8:211-217.
45. Krause DL, Muller N. Neuroinflammation, microglia and implications for anti-inflammatory treatment in Alzheimer's disease. Int J Alzheimers Dis. 2010; 10:1-9.
46. Davies P, Koppel J. Mechanism-based treatment for Alzheimer's disease. Dialogues Clin Neurosci. 2009; 11:159-169.
47. Liu G, Men P, Perry G, Smith MA. Nanoparticle and iron chelators as a potential novel Alzheimer therapy. Methods Mol Biol. 2010; 610:123-144.
48. Oshiro S, Morioka MS, Kikuchi M. Dysregulation of iron metabolism in Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Adv Pharmacol Sci. 2011; 10:1155-1163.
49. Xing XN, Zhang WG, Sha S, Li Y, Guo R, Wang C, Cao YP. Amyloid β 3-10 DNA vaccination suggests a potential new treatment for Alzheimer's disease in BALB/c mice. Chin Med J (Engl). 2011; 124:2636-2641.
50. Xing XN, Zhang WG, Sha S, Li Y, Guo R, Wang C, Cao YP. Amyloid β3-10 DNA vaccination suggests a potential new treatment for Alzheimer's disease in BALB/c mice. Chin Med J. 2011; 124:2636-2641.

(Received April 5, 2012; Revised October 30, 2012; Accepted December 5, 2012)