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Alzheimer's Disease: Current Status of Etiopathogenesis and Therapeutic Strategies

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Abstract: Alzheimer's Disease (AD) is one of the most common age-related neurodegenerative diseases. It is the most prevalent form of dementia, a general term for memory loss. It is characterized by progressive cognitive dysfunction, various behavioral and neuro-psychiatric disturbances that seriously interfere with daily life. Scientists have identified factors that appear to play a role in the development of AD but no definitive causes have been found for this complex disorder. The pathogenesis of Alzheimer's disease is highly complex. While several pathologies characterize this disease, amyloid plaques and neurofibrillary tangles are hallmark neuropathological lesions in AD brain. Current AD therapies are merely palliative and only temporarily slow cognitive decline and treatments that address the underlying pathologic mechanisms of AD are still lacking. In this review, we focus on the current aspects of AD ranging from the key risk factors for AD, the underlying pathogenic events and the novel medications including disease-modifying properties.

Key words: AD therapies, pathologies characterize, risk factors , pathogenic events

INTRODUCTION

Alzheimer's disease was first described in 1906, almost 100 years ago by Alois Alzheimer, a Bavarian psychiatrist. It is the most common cause of dementia, accounting for about 50-60% of all age-related dementia that affects individuals over 65 years of age (Kar *et al*., 2004).The disease accelerates the end of life and AD with its complications represents the fourth leading cause of death (Klein, 2006).While much has been accomplished in Alzheimer disease research in the last 20 years, a great deal remains to be done to improve its diagnosis and treatment. There is increasing evidence that early diagnosis of Alzheimer disease will be key to maximize treatment benefits. But too often, patients are diagnosed in later stages of the disease, when disabling symptoms and neuropathologic changes have become well established (Salloway and Correia, 2009). Advances in understanding the pathogenesis of AD provide a framework for early detection and development of new therapeutic strategies with better beneficial outcome.

RISK FACTORS OF AD

Age: The single greatest risk of developing AD is age. Approximately 8 to 10% of Americans between the ages of 65 and 74 and almost half of those 85 years and older are estimated to have AD (Kar *et al*., 2004).

Genetics of AD: AD can be inherited in an autosomal dominant pattern. Inherited forms of AD account for 5% to 10% of cases (Selkoe, 2001). Mutations on chromosomes 21, 14 and 1 could develop familial AD through increasing the production of Aβ peptide (Saunders, 2001). A gene called Apolipoprotein E (ApoE) appears to be risk factor for late-onset form of Alzheimer's. There are three forms of this gene: ApoE2, ApoE3 and ApoE4. While inheritance of ApoE4 increases the risk of developing the disease, ApoE2 substantially protects against it (Heinzen *et al*., 2010). The mutations in APP gene are the first genetic cause of Alzheimer's disease. The mutations in APP gene are located before β-secretase cleavage site, after α-secretase site, or immediately after γ-secretase cleavage site. Cleavage site selectively increase production of Aβ42 (Da Cruz e Silva and da Cruz e Silva, 2003).

Genetic mutations within presenilin 1 gene (PSEN1, 14 chromosome) and presenilin 2 gene (PSEN2, 1 chromosome) in several early-onset familial AD have been reported (Pleckaityte, 2010). PSEN1 and PSEN2 encode 467 and 448-amino acid transmembrane proteins, respectively. Both presenilins (PS) are expressed in the brain and many tissue cells of the human body. It was shown that PSEN1 and PSEN2 are subunits of γ-secretase, which cleaves APP within its transmembrane domain. γ-secretase generates a spectrum of peptides (varies in length, ≥Aβ42 and ≤Aβ40), termed Aβ, which accumulates in the brains of AD patients (Vetrivel *et al*., 2006; Wakabayashi and De Strooper, 2008). It was suggested that PS mutations selectively elevate the levels of highly amyloidogenic A42 peptides by likely shifting the cleavage site in APP (Vetrivel *et al*., 2006).

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Inflammation: It has been reported that inflammatory mechanisms may play an important role in the pathogenesis of AD. C-Reactive Protein (CRP), marker and mediator of inflammation has been detected in lesions typical for the affected areas of AD brain (Zaciragic *et al*., 2007).

Although the relative roles of Aβ and other potential initiators of inflammation remain unclear, Aβ aggregates and products derived from dead cells can trigger microglia and astrocytes and lead to local inflammation that may further amplify neuronal death. The activation of caspases and signal-dependent transcription factors such as NF-κB and AP-1 results in production of numerous amplifiers (e.g., IL-1β, TNF-α, IL-6) of inflammation. These proinflammatory cytokines, might act directly on neurons to induce apoptosis (McCoy and Tansey, 2008; Simi *et al*., 2007). Furthermore, factors such as TNF-α and IL-1β released by microglia can activate astrocytes, whereas factors released from astrocytes may lead to further activation of microglia (Saijo *et al*., 2009). In addition, APP, presenilin (a component of γ-secretase) and BACE1 (β-secretase) have NF-κB sites in their promoters, and proinflammatory cytokines are known to upregulated their expression in neurons (Sastre *et al*., 2008). Inflammatory mediators acting on neurons might contribute to more production of Aβ, further activating microglia-mediated inflammation. Thus, communication between neurons and glia may amplify the production of neurotoxic factors that contribute to AD pathology (Glass *et al*., 2010).

Environmental factors: Many environmental factors including traumatic injury, systemic infection and diet may influence inflammatory responses that contribute to AD pathology (Migliore and Coppede, 2009). Traumatic injury activates both microglia and astrocytes and could potentially induce self-sustaining inflammatory responses in the brain. Activation of the systemic innate immune system by infection may be involved in the early stages of AD pathogenesis (Van Den Heuvel *et al*., 2007; Perry *et al*., 2007).

Low educational level: The association between low educational level and the risk of AD is consistent with findings from several retrospective and prospective studies (Lindsay *et al*., 2002).

Medical factors: Longitudinal data have implicated vascular factors such as hypertension and atherosclerosis as risk factors for AD. On the other hand, certain immunological histories such as allergic conditions, thyroid disease and viral infections are not associated with AD (Tyas *et al*., 2001).

Life style factors: Lindsay *et al*. (2002) highlighted the potential protective effect of regular physical activity on the risk of AD and its importance because it represents a modifiable lifestyle habit. More recently, this is again reported by Smith *et al*. (2010) who confirmed the protective effect of regular exercise against cognitive impairment as well as all types of dementia, including AD.

CLINICAL PICTURE

The pathologic changes of Alzheimer's disease typically begin many years before its clinical signs are apparent. Most patients pass through a predementia phase called mild cognitive impairment, with early memory loss but with relatively well preserved activities of daily living (Salloway and Correia, 2009). Memory loss is commonly the presenting complaint in AD. Initially the patient has primarily short-term memory loss, manifested by difficulty with recall of new information. Disorientation to time and place, misplacing things, changes in mood or behavior are associated with the memory loss. Remote memory, declines as the disease progresses. In the later stages, there is language impairment as well as previously well-imprinted information, is forgotten (Yaari and Corey-Bloom, 2007). Involvement of other areas of cognition as visuospatial dysfunction, apraxia, agnosia is also common. Disorientation, confusion and problems with reasoning appear as the disease progresses and impair function in activities of daily living (Salloway and Correia, 2009).

In addition, some common behavioral disturbances that include agitation, psychosis, depression, anxiety and insomnia; are apparent (Yaari and Corey-Bloom, 2007).

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

AD is a neurodegenerative disease with complex neuropathology that includes brain inflammation, shrinkage of hippocampus, degeneration of specific neuronal populations (Klein, 2006; Selkoe, 2001). The brain of a patient with AD often shows marked atrophy, with widened sulci and shrinkage of the gyri. The cortical ribbon may be thinned and ventricular dilatation apparent, especially in the temporal horn, due to atrophy of the amygdala and hippocampus (Yaari and Corey-Bloom, 2007).

Microscopically, there is significant loss of neurons in addition to shrinkage of large cortical neurons. The pathological hallmarks of AD include extracellular amyloid beta peptide accumulation, intraneuronal neurofibrillary tangles made of hyper-phosphorylated tau, high levels of oxidative stress and mitochondrial dysfunction. Other features accompanying AD disease include profound loss

of basal forebrain cholinergic neurons that innervate the hippocampus and the neocortex, loss of synapses, neuritic degeneration and gliosis. This pathology culminates in clinical signs predominantly associated with impaired cognitive processes (Galindo *et al*., 2010).

Extracellular neuritic plaques: Neuritic plaques are extracellular lesions composed of a central core of aggregated amyloid-β peptide (Aβ) surrounded by dystrophic neuritis, activated microglia and reactive astrocytes (Klafki *et al*., 2006). Aβ is a natural protein present in the brains and cerebrospinal fluid of healthy humans (Walsh and Selkoe, 2007). This peptide is produced at cholesterol-rich regions of neuronal membranes and secreted into the extracellular space. Aβ peptide can vary in length. The 40-residue peptide Aβ (1-40) represents the most abundant Aβ species in normal and AD brains, followed by the 42-residue peptide Aβ (1-42) (Finder and Glockshuber, 2007). Aβ peptides, recognized as the subunit of the amyloid plaque by Oakley *et al*. (2006) are derived by proteolytic cleavage of APP, a single transmembrane glycoprotein with a long N-terminal extracellular region and a short C-terminal cytoplasmic tail (Kar *et al*., 2004). During the secretory pathway, APP undergoes proteolytic cleavages. The target of α-secretase is distant by 12 amino acids from N- terminal of the APP transmembrane domain. This cleavage results in the release of large soluble fragment (α-APP) into the extracellular space and retention of an 83-residue C-terminal fragment in the membrane (C83). The APP molecules not subjected to α-secretase cleavage can be cleaved by β-secretase, the cleavage site of which is distant by 16 amino acids and a smaller domain (β-APP) is released retaining 99 residues (C99) in the membrane (Pleckaityte, 2010). Three major isoforms of 695, 751 and 770 amino acids are detected, occurring after an alternative splicing of APP. Moreover, the isoforms undergo the posttranslational modifications (glycation, sulfation and phosphorylation). In the nervous system, APP695 is expressed predominantly in neurons, whereas APP770 and APP751 are found in neuronal as well as non-neuronal cells (Kar *et al*., 2004).

The mere presence of Aβ does not cause neurodegeneration. Aβ becomes a pathogenic substance when an ordered self-association of Aβ molecules into insoluble fibrils of 6-10 nm in diameter occurs (Pleckaityte, 2010). Accumulation of fibrillar Aβ in plaques in the brain initiates a cascade of events that ultimately leads to neuronal dysfunction, neurodegeneration and dementia (Klafki *et al*., 2006). This underlies the dominant theory for AD, named the "amyloid cascade hypothesis," generated in 1992 by (Herrup, 2010). However, recent experimental studies reported that not only the amyloid fibrils are neurotoxins and that Aβ (1-40) and Aβ (1-42) are also able to adopt to another differently shaped aggregates which are nonfibrillar termed as Aβ "oligomers" (Haass and Selkoe, 2007; Glabe, 2008). These oligomers could target synapses and induce their degeneration (Kar *et al*., 2004).

Neurofibrillary tangles: AD is characterized by the formation of intracellular neurofibrillary tangles (NFTs) which are composed of Paired Helical Filaments (PHF) and occasional single straight filaments, mainly containing an abnormal hyperphosphorylated form of the microtubule associated protein, tau. Hyperphosphorylation of tau in the AD brain is potentially promoted by several kinases, including glycogen synthase kinase-3β, cyclin-dependent kinase-5 and microtubule-affinity regulation kinase (Meraz-Ríos *et al*., 2010).

In healthy neurons, tau proteins are proteins that bind and stabilize microtubules, which make up the cytoskeleton of the cell, by reversible enzymatically mediated phosphorylation and dephosphorylation processes. If the phosphorylated tau is not dephosphorylated, it is unable to bind other microtubules. These results in polymerization of the phosphorylated tau into straight filaments which are then cross-linked by glycosylation to form PHF-tau. Intraneuronal PHF-tau aggregates are often found in conjugation with ubiquitin. Neurofibrillary tangles in the brain of an individual with AD are particularly abundant in the entorhinal cortex, hippocampus, amygdala, association cortices of the frontal, temporal and parietal lobes and certain subcortical nuclei that project to these regions (Kar *et al*., 2004).

Formation of PHF-tau reduces the ability of tau to stabilize microtubules, leading to disruption of neuronal transport and eventually to the death of affected neurons. The extent of neurofibrillary pathology and particularly the number of cortical neurofibrillary tangles, correlates positively with the severity of dementia (Kar *et al*., 2004).

Mitochondrial dysfunction: Mitochondria are involved in multitude of cellular processes that are essential to both survival and death (Benard *et al*., 2007). Metabolic alterations and oxidative stress are key, early contributors in the pathogenesis of Alzheimer Disease (AD). Since damaged mitochondria are less efficient producers of ATP and more efficient producers of reactive oxygen species, it is no wonder that substantial evidence supports a fundamental involvement of mitochondrial dysfunction in the disease process (Zhou *et al*., 2007).

Neuronal activity is extremely energy dependent, as such; neurons are particularly sensitive to mitochondrial functional changes. Neuronal activities such as synaptic transmission, axonal/dendritic transport, ion channels and ion pump activity are energy taxing processes (Kann and Kovacs, 2007). Additionally, the maintenance of calcium homeostasis is critical for neuronal synaptic function and controlled by mitochondria at the synapse (Rusakov, 2006; Hollenbeck, 2005). Notably, in animal models, mitochondrial dysfunction and energy metabolism deficiencies are recognized as one of the early events and correlate with impairments of cognitive abilities in AD (Hauptmann *et al*., 2009). Growing evidence suggests that Aβ has deleterious effects on mitochondrial function and contributes to energy failure, production of Reactive Oxygen Species (ROS) in AD brain and neuronal apoptosis (Chen and Yan, 2007).

Disrupted mitochondrial energy: The disrupted mitochondrial energy production is due to three mechanisms: diminished activity of respiratory enzymes, second impairment of mitochondrial calcium homeostasis which leads to decrease ATP production and lastly altered mitochondrial dynamics.

As the "power houses" of eukaryotic cells, mitochondria contain both citric acid cycle enzymes and respiratory chain components in their matrix and inner membrane. Several studies have demonstrated aberrations in the electron transport chain and Krebs cycle in AD brains. Reduced activity of the enzyme complexes cytochrome oxidase, pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (α-KGDH) have been demonstrated in the frontal, temporal and parietal cortex of AD brains (Chen and Yan, 2007; Galindo *et al*., 2010). It has also been reported that Aβ progressively accumulates in the mitochondrial matrix and that this was associated with diminished enzymatic activity of respiratory chain complexes III and IV, as well as a reduction in the rate of oxygen consumption (Chen and Yan, 2007).

Additional insults to disrupted mitochondrial energy production in AD are altered Ca^{2+} homeostasis. It is believed to be of fundamental importance in the development of AD pathology. Substantial evidence indicates that accumulation of Ca^{2+} within the mitochondria, rather than cytosolic Ca^{2+}, is the most important determinant of cytotoxicity. Impaired mitochondrial Ca^{2+} uptake alters the spatiotemporal characteristics of cellular Ca^{2+} signaling and down regulates mitochondrial metabolism. Mitochondrial Ca^{2+} accumulation contribute to early induction of molecular cell death cascades in several different paradigms (Galindo *et al*., 2010). Non-regulated increases of Ca^{2+} can cause a loss of the mitochondrial transmembrane potential and a consequent reduction in the production of ATP. Ruining the function of ATPase and the biological membranes by Aβ is one of several mechanisms proposed to account for the toxicity of this peptide on biological membranes (Gu *et al*., 2004). In addition to impairing calcium homeostasis, mitochondrial dysfunction reduces the availability of energy for cellular functions such as glutamate uptake; this explains the increased sensitivity to amino acid-mediated excitotoxicity in cells treated with Aâ. It has been suggested that Aâ has the ability to bind directly to NMDA receptors in a way that enhances the ability of Ca^{2+} to enter post-synaptic neurons (De Felice *et al*., 2007); this might cause the chronic opening of NMDA receptor Ca^{2+} channels and leading to constant influx of Ca^{2+} ions with subsequent neuronal excitotoxicity in AD (Galindo *et al*., 2010).

It has been reported that there is neuronal selectivity in mitochondrial dysfunction in AD. This is related to the complex architecture of neurons and inherited dynamics of the mitochondria and their ability to constantly divide and fuse with each other. Depending on physiological conditions, mitochondria can form giant tubule networks within a cell and allow rapid exchange of mitochondrial contents or divide into individual rod-like mitochondrion and allow deep penetration into side short-diameter neuritis (Chan, 2006). This highly dynamic balance of mitochondrial fission and fusion controls mitochondrial morphology, length, size and number and can also regulate mitochondrial function and distribution. Significant changes in mitochondrial size and number occurred in vulnerable neurons in AD suggesting that a potential change in mitochondrial dynamics may be involved (Hirai *et al*., 2001). Such a notion is further supported by the finding that fibroblasts from AD patients demonstrated abnormal mitochondrial dynamics compared to normal healthy fibroblasts from age-matched control patients (Wang *et al*., 2008).

Increased mitochondrial ROS production: Along with the abnormalities in oxidative energy metabolism, there is also evidence of oxidative stress in AD brain. This is manifested by increased protein oxidation, lipid peroxidation, nucleic acid oxidation and glycooxidation (Butterfield *et al*., 2006).

A direct effect of Aβ on mitochondrial properties is suggested by *in vitro* experiments in which cultured cells or isolated mitochondria were exposed to Aβ. In the micromolar concentration range, Aβ induced dose-dependent generation of ROS and ATP depletion associated with depolarization of the mitochondrial

membrane, decreased oxygen consumption and inhibition of respiratory chain enzymes in PC12 cells (Wallace, 2005).

Oxidative stress and Aβ production are proportionally linked to each other because Aβ induces oxidative stress *in vitro* and *in vivo* and lipid peroxidation fosters intracellular Aβ accumulation, creating a vicious positive feedback loop culminating in neurodegeneration (Paola *et al*., 2000; Tamagno *et al*., 2008). Massaad and his coworkers found that mitochondrial ROS affect Aβ processing perhaps at the level of accumulation of fibrillar Aβ into plaques (Massaad *et al*., 2009).

β-secretase (β-site amyloid precursor protein-cleaving enzyme 1) (BACE1), a prerequisite for Aβ genesis, is upregulated in experimental conditions likely associated with energy insufficiency and/or oxidative stress. It is unclear whether the accumulation of ROS is a precursor or a consequence of other cellular dysfunctions. The sources of ROS-mediated damage appear to be multi-faceted in AD, with interactions between abnormal mitochondria, redox transition metals and other factors (Galindo *et al*., 2010).

Activation of mitochondrial-mediated apoptotic pathway: Mitochondria play a pivotal role in life and death of cells and likely contribute importantly to the initiation or progression of AD (Picklo and Montine, 2007). Extensive studies have suggested that increased permeabilization of the mitochondrial membrane with subsequent release of cytochrome c is a key initiative step in the apoptotic process (Gogvadze *et al*., 2006). Mitochondrial Membrane Permeabilization (MMP) is induced by a variety of pathologically relevant second messengers, including ROS, Ca^{2+}, stress kinases and pro-apoptotic members of the Bcl-2 family. Two mechanisms have been proposed to explain the MMP: the formation of a mitochondrial Permeability Transition Pore (mPTP) and the insertion of Bcl-2 family members at the mitochondrial membrane (Galindo *et al*., 2010)

As regard the first mechanism, it has been observed that the mPTP is composed of 3 main components. These include voltage-dependent anion channel in the outer membrane, adenine nucleotide translocase protein in the inner membrane and cyclophilin D (cypD) protein in the matrix (Halestrap *et al*., 2002; Zamzami *et al*., 2005; Benardi *et al*., 2006). Interestingly Aβ has been demonstrated to bind to and associate with cypD, thus providing a mechanistic link to Aβ, mitochondrial dysfunction, and neurodegeneration (Serrano and Klann, 2004) and the absence of cypD has similarly been shown to protect neurons from Aβ-induced death (Du *et al*., 2008). In addition, it has been reported that Aβ can exacerbate calcium-dependent formation of the mPTP, resulting in decreased mitochondrial transmembrane potential, decreased capacity to accumulate calcium and uncoupling of respiration (Moreira *et al*., 2001, 2002).

Second mechanism related to the Bcl-2 family of proteins, is still under investigations. The full manner in which it modulates the changes in membrane permeability remains unknown. The activity of these proteins is related to the release of proapoptotic factors (formerly sequestered within the mitochondria) into the cytoplasm, probably through the formation of ion and/or protein transport channels (Galindo *et al*., 2010).

Loss of basal forebrain cholinergic neurons and synaptic loss: Li and Shen (2000) reported that one of the major characteristics of AD is the degeneration of basal forehead cholinergic neurons. Clinical evidence obtained from AD patients has shown a specific reduction in choline acetyltransferase, acetylcholine esterase activities in biopsied brain tissue and a loss of cholinergic neurons indicating the involvement of the forebrain cholinergic system in AD (Klafki *et al*., 2006). Numerous experimental studies have demonstrated that lesions of the basal forebrain cholinergic system result in significant learning and memory impairment thus indicate the important role of the cholinergic system in learning and memory processing (Li and Shen, 2000; Schaeffer *et al*., 2009). There are two major cholinergic systems existing in the basal forebrain: One derives from the nucleus basalis magnocellularis which projects primarily to the cerebral cortex, the other derives from the medial septum which projects primarily to the hippocampus. Lesions in these two pathways have been shown to produce significant memory deficits (Li and Shen, 2000).

Aβ accumulation may trigger or contribute to the process of neurodegeneration. However, the mechanisms whereby Aβ induces basal forebrain cholinergic cell loss and cognitive impairment remain obscure. Physiologically relevant concentrations of Aβ-related peptides have acute, negative effects on multiple aspects of acetylcholine synthesis and release, without inducing toxicity. Synaptic loss is the most robust correlate of AD associated with cognitive deficits (Lambert *et al*., 2007). Pleckaityte (2010) reported the existence of fibrillar intermediates called protofibrils (PFs). PFs are the structural intermediates to fully fledged fibrils and they are neurologically active. Aβ derived diffusible ligands (ADDL)-like oligomeric assemblies have also been isolated from the brain of AD patients and their presence correlated with memory loss (Gong *et al*., 2003). It is suggested that not only PFs and ADDLs are neurologically active but small oligomeric forms

(dimeric and trimeric oligomers) occurring *in vivo* have also been detected in human brain (Lesné *et al*., 2006). These monomeric and oligomeric Aβ and ADDLs target synapses and induce their degeneration (Coleman *et al*., 2004; Lacor *et al*., 2004).

TREATMENT

Current available medications that have passed FDA approval for the treatment of AD include acetylcholine esterase inhibitors for mild to moderate cases and Memantine, an N-methyl-D- aspartate receptor antagonist for the treatment of moderate to severe Alzheimer dementia. All these drugs produce only modest symptomatic improvements in some of the patients. None of the available medications, however, appears to be able to cure Alzheimer's dementia or to stop disease progression. Therefore, there is a great need for development of therapeutic strategies with disease modifying effects based on the underlying pathogenetic cascade of events that characterize AD (Salloway and Correia, 2009; Klafki *et al*., 2006). In this review, we will discuss both symptomatic and disease modifying approaches looking forward for complete cure of AD.

Symptomatic approaches

Treatment for cognitive deterioration

Choline esterase inhibitors: The "Cholinergic hypothesis" of AD posits the degeneration of the cholinergic neurons in the basal forebrain and the loss of cholinergic transmission in the cerebral cortex and other areas as the principal cause of cognitive dysfunction in patients with AD (Kar *et al*., 2004). The hypothesis is supported by evidence that drugs that potentiate central cholinergic function have some value in symptomatic treatment during early stages of the disease (Trinh *et al*., 2003). M_1 muscarinic acetylcholine-receptor agonists were suggested to be potentially useful not only for symptomatic treatment of AD but to a limited extent also for causal therapy (Fisher, 2000; Fisher *et al*., 2000).

In the last decade, the Food and Drug Administration in the United States approved four drugs for the treatment of AD: tacrine, donepezil, rivastigmine and most recently, galantamine. All four drugs inhibit acetylcholinesterase, the degradative enzyme for acetylcholine, thereby increasing the duration of action of acetylcholine. These medications are associated with modest, symptomatic improvement for some patients with AD (Doody *et al*., 2001). They tend to stabilize memory during the first year of treatment and make the subsequent decline more gradual (Salloway and Correia, 2009). However, it has been reported that, although the cholinesterase inhibitors improve cognitive and global function in many patients, but their efficacy wanes over time (Saunders, 2001; Walker *et al*., 2005). Recently, Malek *et al*. (2009) showed for the first time that central administration of GH ameliorates impairment of spatial learning and memory in aged rats with AD-like cognitive deficiency. GH and in some extents IGF-1 affects most of the major neurotransmitters differently in several brain regions, including the noradrenergic, dopaminergic, glutaminergic (at least at the receptor level), opioidergic and cholinergic systems. GH may be useful in the treatment of men. Surely, this usefulness needs more and deep human studies.

N-methyl-D-aspartate (NMDA) receptor antagonist: Memantine is a non-competitive NMDA-receptor antagonist with moderate affinity that appears to be able to protect neurons while leaving physiological NMDA-receptor activation unaffected (Sonkusare *et al*., 2005). It interacts with the NMDA receptor at therapeutic concentrations (Rogawski and Wenk, 2003; Klafki *et al*., 2006). Memantine, currently the only symptomatic treatment approved for moderate to severe AD, protects against the neurodegenerative effects of the excitatory neurotransmitter glutamate (Jacobsen *et al*., 2005). It has also been reported that it may provide symptomatic improvement through effects on the functions of hippocampal neurons (Reisberg *et al*., 2003). A combination therapy over 6 months with memantine plus donepezil (choline esterase inhibitor) in patients with moderate to severe AD significantly improved cognition, activities of daily living and behavior compared with placebo (Tariot *et al*., 2004). The durability of clinical improvements associated with memantine treatment is not known.

Treatment for behavioral disturbances: Neuropsychiatric symptoms, known to be very common among patients with AD, have been reported in more than 80% of subjects in most studies (Yaari and Corey-Bloom, 2007). Behavioral problems are often the most disturbing symptoms in dementia, often leading to higher levels of care. Apathy is the most common behavioral symptom in Alzheimer disease, increasing with disease severity. There is no approved treatment for these apathetic symptoms till now. Depression and irritability are common and may respond well to low doses of serotonin reuptake inhibitors (Salloway and Correia, 2009). Agitation and psychosis are distressing and are likely to overwhelm the caregiver's ability to cope. Recent studies have raised concern about the safety and efficacy of atypical neuroleptics in patients with dementia and suggest that these drugs be used with careful monitoring (Schneider *et al*., 2006).

Disease-modifying approaches

Amyloid - based therapies: Although the exact mechanism is still unclear, it is widely believed that dysfunctional Aβ metabolism is the underlying cause for the neurodegeneration and dementia observed in AD. Therefore, a leading strategy for the development of AD pharmacotherapies is modulation of Aβ production, aggregation and/or clearance. It is assumed that altering these processes will stop and/or reverse the pathological neuronal loss and the clinical cognitive decline (Biran *et al*., 2009).

Inhibitors and/or modulators of the secretases: Following their discovery and characterization, the APP secretases became attractive targets for development of anti-amyloid disease modifying treatments. The logic behind modulating the APP secretases is twofold: stimulating α-secretase cleavage in order to direct APP processing towards the non-amyloidogenic pathway or suppressing β- and/or γ-secretase cleavage in order to reduce the amount of Aβ produced. It has been shown that muscarinic AChE-receptor agonists can foster α-secretase processing of APP to subsequently result in a reduction in Aβ levels (Wolf *et al*., 1995; Fisher, 2000; Fisher *et al*., 2000). Numerous β- and γ-secretase inhibitors and/or modulators have also been designed. However, the majority of these agents are not specific for the secretase cleavage of APP. This, in turn, may prevent the cleavage and processing of additional substrates, which could result in various adverse effects (Evin *et al*., 2006; Tschape and Hartmann, 2006).

One concern about the γ-secretases is that they are involved in the cleavage of the Notch transmembrane receptors. It has been reported that Notch-deficient knock-out mice exhibit reduced hippocampal neuroplasticity, neurodegeneration and impaired memory (Saura *et al*., 2004; Wang *et al*., 2004). Another concern is that chronic inhibition, in animal models, is associated with effects in the gastrointestinal system, thymus and spleen (Neugroschl and Sano, 2010).

There are a number of BACE (β-site amyloid precursor protein-cleaving enzyme) inhibitors that have been described in animal models but have not yet progressed to clinical trials. A number of approaches, including the creation of novel antibodies to target the BACE cleavage site of APP, have been taken (Neugroschl and Sano, 2010). BACE inhibition, in theory, should not be associated with the same toxicity risk as γ-secretase inhibition (Luo *et al*., 2003).

Aggregation inhibitors: The amyloid hypothesis posits that aggregated Aβ is particularly toxic to cells and thus blocking aggregation and ultimately preventing plaques from forming could change the course of the illness (Neugroschl and Sano, 2010). Tramiprosate is a glycosaminoglycan (GAG) mimetic that is in clinical trial testing. Sulfated glycosaminoglycans bind to soluble Aβ, facilitating macrofibrillar aggregation and deposition of amyloid plaques. GAG-mimetics compete for GAG binding sites, block fibril formation and reduce deposition of Aβ in the brain (Gervais *et al*., 2001; Garceau *et al*., 2002). Tramiprosate reduces plaque burden and decreases CSF concentrations of Aβ in transgenic mice (Geerts, 2004). Unfortunately, results of the use of this drug in Phase II clinical showed that the only significant effect of tramiprosate treatment was a dose-dependent reduction in CSF $A\beta_{1-42}$, but had no significant impact on CSF $A\beta_{1-40}$ and tau, or on psychometric scores (Aisen *et al*., 2006). Despite these disappointing results, the investigational drug progressed into a phase III trial in Northern America, which was recently declared by the FDA to have failed.

Immunotherapy: A novel and controversial approach to treat AD is based on vaccine therapy. Transgenic mouse models of AD actively immunized with Aβ (Buttini *et al*., 2005; Morgan *et al*., 2000) or passively immunized with humanized anti-Aβ antibodies (Biran *et al*., 2009; Lombardo *et al*., 2003) showed reduced Aβ, tau-pathology, neutralized soluble Aβ oligomers. Such Aβ-based immunotherapy protects against synaptic degeneration and improved synaptic plasticity. All these changes were accompanied by improved learning. Immunization against Aβ thus appeared to be the much-anticipated breakthrough in the development of AD therapeutics, in addition to being the primary test of the amyloid cascade hypothesis. However, the long-term clinical follow-up of 80 patients demonstrated that, despite a varied degree of Aβ plaque removal, there was no prevention of progressive neurodegeneration and no evidence for improved survival (Holmes *et al*., 2008). This failed trial has led researchers to develop more selective and advanced immunotherapies (White *et al*., 2006).

Statins: Epidemiologic evidence suggests that statins may reduce the risk of developing AD (Jick *et al*., 2000; Wolozin *et al*., 2000). The mechanism of this putative protective effect is not completely understood, but may be related to the relationship between elevated cholesterol and amyloid deposition (Golde, 2003). The involvement of apolipoprotein E, an established AD risk factor, in cholesterol metabolism provides support for this hypothesis (Silvestrelli *et al*., 2006). Alternatively, the statins could influence APP metabolism through a cholesterol-independent mechanism in which α-secretase

activity is increased. The statins appear to upregulate α-secretase activity by inhibiting Rho-associated protein kinase 1, an enzyme that modulates α-secretase activity. By enhancing the activity of α-secretase, which cleaves APP into soluble products, production of $A\beta_{42}$ is precluded (Pedrini *et al*., 2005).

Advanced glycation end products: Advanced Glycation End products (AGEs) are formed endogenously during glycation and can also be ingested in a variety of foods (Vlassara *et al*., 2002). These AGEs have been implicated in aging through a variety of mechanisms, including increased protein cross linking and increased free radical formation and as proinflammatory mediators. Receptor for AGEs is an immunoglobulin supergene family expressed on the cell surface of multiple cell types throughout the brain and on the blood brain barrier. In AD, this receptor is up-regulated on cells in the hippocampus, such as astrocytes and microglia (Sasaki *et al*., 2001). Amyloid is known to bind to this receptor. This may be one way in which the inflammatory cascade is stimulated and thus may lead to cell death. Preclinical studies have suggested that blocking this receptor against amyloid binding protects the cell by decreasing plaque formation and inflammation and it may have an effect on memory functioning (Chen *et al*., 2007). Clinical studies are still ongoing.

Peroxisome proliferator-activated receptor-gamma agonists: The peroxisome proliferator-activated receptor-gamma agonists, rosiglitazone and pioglitazone, have been assessed as potential anti-amyloid disease-modifying treatments in recently reported phase II trials of patients with AD. Evidence of reductions in Aβ levels, plaque deposition and microglial-mediated inflammation in animal models provides mechanistic support for these studies (Heneka *et al*., 2005). Clinical trials in diabetic and non-diabetic patients with AD are still under investigations.

Erythropoeitin derivatives: Erythropoeitin (EPO), a well-established hematopoietic factor, possesses generalized neuroprotective and neurotrophic properties. *In vivo*, EPO protects neurons from cerebral ischemia and traumatic brain injury (Kassem and Yassin, 2010; Evans and Persinger, 2010). Increased expression of EPO receptors in the brains of AD patients support a role for EPO derivatives in this prototype of neurodegenerative disorders. Protection by EPO derivatives against beta amyloid toxicity in cultured neurons have also been documented. However, no data on the effects of EPO derivatives in animal models of AD are available thus far. Slight improvements in functional outcome indeed have been reported in models of Parkinson disease and amyotrophic lateral sclerosis (Siren *et al*., 2009).

Tau- based therapies: Several investigational drugs that target Aβ have failed to show strong correlation between a reduction in amyloid burden and improvements in cognitive decline in large-scale clinical trials. Therefore, another potential therapeutic avenue has been directed towards the alternate hypothesis regarding the pathophysiology of AD which is the hyperphosphorylation of Tau proteins. Other neuroprotective strategies could also be targeted towards varieties of secondary mechanisms such as oxidative injury and lipid peroxidation of cell membranes (Yaari and Corey-Bloom, 2007), inflammation (Metcalfe and Figueiredo-Pereira, 2010) and alteration of metal ion homeostasis (Crouch *et al*., 2007).

Therapeutic approaches directed against tau protein include

Inhibitors of tau kinases (Sun *et al*., 2002): Major kinases are reported to be up-regulated in AD and other taupathies (Ferrer *et al*., 2005; Biran *et al*., 2009). These kinases are involved in the phosphorylation of Tau protein. They include: glycogen synthase kinase 3, cyclin-dependent protein kinase-5, casein kinase-1, protein kinase A, protein kinase C, calcium and calmodulin-dependent protein kinase-II, microtubule-affinity regulation kinase and mitogen activated protein kinase family members (Biran *et al*., 2009). These proteins have been suggested as therapeutic targets for AD. However, this approach is hindered due to the ubiquitous expression of these kinases, their pleiotropic activities in countless cellular functions and the low selectivity of inhibitors for specific kinases (Churcher, 2006; Stoothoff and Johnson, 2005).

Tau protein aggregation inhibitors: The pathological aggregation of Tau correlates closely with the progression of AD (Meraz-Ríos *et al*., 2010). Therefore, the development of Tau aggregation inhibitors that would also be able to disaggregate filaments could provide an alternative to existing pharmaceutics strategies (Bulic *et al*., 2007). The inhibitory effect of those compounds could take place on different levels, for example, interference with a particular Tau conformation, association of dimers or oligomers, elongation of filaments and so on. In particular, this compound could interfere with the initial generation of nuclei or with the further elongation of fibrils. This could be achieved by tight binding of the compound to the protein monomer or

oligomer. Other therapeutic includes the steric obstruction of the protein-protein interaction by the compound or interference with the polyanion inducers of aggregation (Pickhart *et al.*, 2007).

Neuroprotective approaches targeting secondary mechanisms

Antioxidants: Antioxidant molecules are capable of neutralizing free or incorrectly bound metals, thereby interfering with the 'down-stream' generation of ROS and other radicals. Therefore, antioxidants may be used mainly as a preventive approach (Behl and Moosmann, 2002). Numerous molecules with antioxidant properties include: oestrogen, Soy meal, melatonin, Vitamin C and E (L-ascorbate and α-topopherol, respectively), ginkgo bilboa extract, curcumin and flavonoids. It has been shown that these antioxidant molecules have neuroprotective effects against Aβ-induced toxicity in cell-based experiments (Zatta *et al*., 2003; Shishodia *et al*., 2005) and animal models (Sarkaki *et al*., 2008;Yang *et al*., 2005; Defeudis, 2002) but have had conflicting results in clinical settings (Zandi *et al*., 2004; Schneider *et al*., 2005).

Anti-inflammatory drugs: Markers of neuroinflanmation including activated microglia and astrocytes, complement components and inflammatory cytokines are typically observed in association with AD neuropathology (Tuppo and Arias, 2005). Observational retrospective and prospective studies indicated that the long-term use of non steroidal anti-inflammatory (NSAIDs) may have a preventive effect against the development of AD suggesting that neuroinflammation may contribute to the neurodegeneration (Szekely *et al*., 2004). Some NSAIDs including ibuprofen can modify γ-secretase activity in such a way that, specifically, the production of $A\beta_{42}$ peptides is decreased (Weggen *et al*., 2001). In APP-transgenic mice, ibuprofen reduced amyloid load and microglial activation (Lim *et al*., 2000) suggesting an effect at an early stage of plaque pathology.

The selective cyclooxygenase (COX)-2 inhibitor rofecoxib and the non-selective NSAID, naproxen, were also tested in a clinical randomized control trial for the treatment of mild to moderate AD. However, neither drug was able to slow the rate of cognitive decline as compared with the placebo control group (Aisen *et al*., 2003). Mocellin (2006) reported that (COX)-2 inhibitor possesses an antitumour activity that may be attributed to inhibition of angiogenesis mediated by PG and VEGF. Later on, El Sayed *et al.* (2009) reported that a combination therapy of both (COX)-2 inhibitor and angiotensin converting enzyme inhibitor protected the AD brain against cerebrovascular angiopathy and deposition of amyloid plaques with marked improvement of cognitive impairment and attenuation of inflammatory cytokines.

Therapeutic approaches targeting alteration of metal ion homeostasis: Other than the amyloid cascade hypothesis of AD, alteration of metal ion homeostasis plays also a critical role in AD pathogenesis. Cerebral concentrations of Zinc (Zn), Copper (Cu) and iron (Fe) ions are significantly elevated in AD, compared to age-matched controls (Adlard and Bush, 2006). It was found that NFTs may in some way be involved in, or regulated by, metal metabolism. Zinc ions (Zn^{2+}) (Suh *et al*., 2000) and the iron regulatory protein-2 (Biran *et al*., 2009), for example, have been found to co-localize with NFT-containing neurons. Addition of Zn^{2+} to mouse and human neuroblastoma cells induces tau-hyperphosphorylation (Björkdahl *et al*., 2005). Ferric ions (Fe^{3+}) and cupric ions (Cu^{2+}) can bind to various 'repeat' motifs on tau, thus altering the protein's conformation, promoting its phosphorylation (Malm *et al*., 2007) and inducing its aggregation (Ma *et al*., 2005; Zhou *et al*., 2007). In addition, interactions between metals, APP and Aβ that may influence Aβ aggregation and Aβ-associated toxicity have also been suggested (Biran *et al*., 2009). Bush and Tanzi (2008) proposed" the metal theory of AD" which states that the age-related endogenous metal dyshomeostasis in the brain allows binding of redox-active metal ions (Cu^{2+} and Fe^{3+}) to Aβ. This can lead to neurotoxicity as Cu^{2+} stabilizes the neurotoxic, oligomeric Aβ species (Yoshiike *et al*., 2001; Garai *et al*., 2007) and promotes the generation of Metallated-Aβ (Atwood *et al*., 2004). The latter has an increased affinity for the phospholipid heads of the membrane bilayer (Lau *et al*., 2006; Ciccotosto *et al*., 2004) which acts as a reductant in the production of Reactive Oxygen Species (ROS). The resulting radicals induce oxidative stress damage of lipids, proteins and DNA, ultimately leading to synaptic and neuronal loss (Bush, 2000, 2003; Barnham *et al*., 2004; Sayre *et al*., 2000). Accordingly, modulation of metal ions has been proposed as a disease-modifying therapeutic strategy for AD (Crouch *et al*., 2007; Bush, 2002). Antioxidants and metal-modulators such as metal chelators, metal complexes, metal-protein attenuating compounds, represent such therapeutic strategies. These pharmacotherapeutics aim to restore metal homeostasis, inhibit Aβ-metal interactions and/or inhibit metallated Aβ-catalysed oxidation (Biran *et al*., 2009).

Neuronal regeneration approaches: There are no effective interventions till now that significantly forestall or reverse neurodegeneration and cognitive decline in

AD. In the past decade, the generation of new neurons has been recognized to continue throughout adult life in the brain's neurogenic zones. A major challenge has been to find ways to harness the potential of the brain's own neural stem cells to repair or replace injured and dying neurons. In the past five years it has become evident that Bone Marrow (BM) houses more 'primitive', multipotent stem cells that are capable of giving rise to tissues of all embryonic germ layers. BM-derived cells have been shown by independent investigators to give rise to neural cells *in vitro*. In addition, *in vivo* studies showed that BM cells migrate into the brain where they appear to differentiate into neurons and glia. The mechanism for transdifferentiation of BM to neural cells is not clear and may reflect the capacity of BM-derived cells to fuse with injured neurons (Wu *et al*., 2007).

The administration of Hematopoietic Growth Factors (HGF) or cytokines has been shown to promote brain repair by a number of mechanisms, including increased neurogenesis, anti-apoptosis and increased mobilization of bone marrow-derived microglia into brain. In this light, cytokine treatments may provide a new therapeutic approach for many brain disorders, including neurodegenerative diseases like AD. In addition, neuronal hematopoietic growth factor receptors provide novel targets for the discovery of peptide-mimetic drugs that can forestall or reverse the pathological progression of AD (Sanchez-Ramos *et al*., 2008). The application of HGF for the treatment of AD has not yet been undertaken but there is a strong rationale for initiating clinical studies.

CONCLUSION

In this review we tried to cover briefly the different aspects of AD, its cause, pathophysiological changes, clinical picture and treatment. AD is an irreversible progressive neurodegenerative disease that slowly destroys memory and thinking skills. Many risk factors are associated with the development of the disease; the accuracy of its diagnosis is a problem inherent to all studies of this disease. The disease is characterized by elevated amyloidogenesis through activation of β- and γ-secretases accompanied with inhibition of α-secretase leading to elevated $A\beta_{1-42}$ level. This co-elevated inflammation and amyloidogenesis resulted in neuronal cell death and thus memory impairment. Different classes of potentially disease-modifying treatments that interrupt early pathological events include immunotherapies; secretase inhibitors; selective $A\beta_{42}$-lowering agents; statins; anti-Aβ aggregation agents; peroxisome proliferator-activated receptor-gamma agonists; and others. There is hope that in the coming future, improved treatments and diagnostic methods will soon be available and will be of great help to minimize the occurrence of the disease and treat its patients.

REFERENCES

Adlard, P.A. and A.I. Bush, 2006. Metals and Alzheimer's disease. J. Alzheimers. Dis., 10: 145-163.

Aisen, P.S., K.A. Schafer, M. Grundman, E. Pfeiffer and M. Sano *et al*., 2003. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: A randomized controlled trial. J. Am. Med. Assoc., 289: 2819-2826.

Aisen, P.S., D. Saumier, R. Briand, J. Laurin, F. Gervais, P. Tremblay and D. Garceau, 2006. A phase II study targeting amyloid-beta with 3APS in mild-to-moderate Alzheimer disease. Neurol., 67: 1757-1763.

Atwood, C.S., G. Perry, H. Zeng, Y. Kato and W.D. Jones *et al*., 2004. Copper mediates dityrosine cross-linking of Alzheimer's amyloid-ß. Biochemistry, 43: 560-568.

Barnham, K.J., C.L. Masters and A.I. Bush, 2004. Neurodegenerative diseases and oxidative stress. Nat. Rev. Drug Discov., 3: 205-214.

Behl, C. and B. Moosmann, 2002. Antioxidant neuroprotection in Alzheimers disease as preventive and therapeutic approach. Free Radic. Biol. Med., 33: 182-191.

Benard, G., N. Bellance, D. James, P. Parrone, H. Fernandez, T. Letellier and R. Rossignol, 2007. Mitochondrial bioenergetics and structural network organization. J. Cell. Sci., 120: 838-848.

Benardi, P., A. Krauskopf, E. Basso, V. Petronilli, E. Blalahy-Dysan, F. Di Lisa and M.A. Forte, 2006. The mitochondrial permeability transition from *in vitro* artifact to disease target. FEBS J., 273: 2077-2099.

Biran, Y., C.L. Masters, K.J. Barnham, A.I. Bush and P.A. Adlard, 2009. Pharmacotherapeutic targets in Alzheimers disease. J. Cell Mol. Med., 13: 61-86.

Bjorkdahl, C., M.J. Sjogren, B. Winblad and J.J. Pei, 2005. Zinc induces neurofilament phosphorylation independent of p70 S6 kinase in N2a cells. Neuroreport, 16: 591-595.

Bulic, B., M. Pickhart, I. Khlistunova, J. Biernat, E.M. Mandelkow, E. Mandelkow and H. Waldmann, 2007. Rhodanine-based tau aggregation inhibitors in cell models of tauopathy. Angew. Chem. Int. Ed., 46: 9215-9219.

Bush, A.I. and R.E. Tanzi, 2008. Therapeutics for Alzheimers disease based on the metal hypothesis. Neurotherapeutics, 5: 421-432.

Bush, A.I., 2000. Metals and neuroscience. Curr. Opin. Chem. Biol., 4: 184-191.

Bush, A.I., 2002. Metal complexing agents as therapies for Alzheimers disease. Neurobiol. Aging, 23: 1031-1038.

Bush, A.I., 2003. The metallobiology of Alzheimers disease. Trends Neurosci., 26: 207-214.

Butterfield, D.A., M. Perluigi and R. Sultana, 2006. Oxidative stress in Alzheimers disease brain: New insights from redox proteomics. Eur. J. Pharmacol., 545: 39-50.

Buttini, M., E. Masliah, R. Barbour, H. Grajeda and R. Motter *et al.*, 2005. ß-Amyloid immunotherapy prevents synaptic degeneration in a mouse model of Alzheimers disease. J. Neurosci., 25: 9096-9101.

Chan, D.C., 2006. Mitochondrial fusion and fission in mammals. Annu. Rev. Cell. Dev. Biol., 22: 79-99.

Chen, J.X. and S.D. Yan, 2007. Amyloid-β-induced mitochondrial dysfunction. J. Alzheimers Dis., 12: 177-184.

Chen, X., D.G. Walker, A.M. Schmidt, O. Arancio, L.F. Lue and S.D. Yan, 2007. RAGE: A potential target for Abeta-mediated cellular perturbation in Alzheimers disease. Curr. Mol. Med., 7: 735-742.

Churcher, I., 2006. Tau therapeutic strategies for the treatment of Alzheimers disease. Curr. Top. Med. Chem., 6: 579-595.

Ciccotosto, G.D., D. Tew, C.C. Curtain, D. Smith and D. Carrington *et al.*, 2004. Enhanced toxicity and cellular binding of a modified amyloid ß peptide with a methionine to valine substitution. J. Biol. Chem., 279: 42528-42534.

Coleman, P., H. Federoff and R. Kurlan, 2004. A focus on the synapse for neuroprotection in Alzheimer disease and other dementias. Neurology, 63: 1155-1162.

Crouch, P.J., A.R. White and A.I. Bush, 2007. The modulation of metal bio-availability as a therapeutic strategy for the treatment of Alzheimers disease. FEBS J., 274: 3775-3783.

Da Cruz e Silva, E.F. and O.A. da Cruz e Silva, 2003. Protein phosphorylation and APP metabolism. Neurochem. Res., 28: 1553-1561.

De Felice, F.G., P.T. Velasco, M.P. Lambert, K. Viola, S.J. Fernandez, S.T. Ferreira and W.L. Klein, 2007. Abeta oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor-dependent mechanism that is blocked by the Alzheimer drug memantine. J. Biol. Chem., 282: 11590-11601.

Defeudis, F.V., 2002. Bilobalide and neuroprotection. Pharmacol. Res., 46: 565-568.

Doody, R.S., J.C. Stevens, C. Beck, R.M. Dubinsky and J.A. Kaye *et al.*, 2001. Practice parameter: Management of dementia (an evidence-based review). Report of the quality standards subcommittee of the American academy of neurology. Neurology, 56: 1154-1166.

Du, H., L. Guo, F. Fang, D. Chen and A.A. Sosunov *et al.*, 2008. Cyclophilin D deficiency attenuates mitochondrial and neuronal perturbation and ameliorates learning and memory in Alzheimers disease. Nat. Med., 14: 1097-1105.

El-Sayed, N.S., L.A. Kassem and O.A. Heikal, 2009. Promising therapy for Alzheimers disease targeting angiotensin converting enzyme and the cyclooxygense-2 isoform. Drug Discov. Ther., 3: 307-315.

Evans, P. and M.A. Persinger, 2010. Erythropoietin and mild traumatic brain injury: Neuroprotective potential and dangerous side-effects. J. Biol. Sci., 10: 739-746.

Evin, G., M.F. Sernee and C.L. Masters, 2006. Inhibition of gamma-secretase as a therapeutic intervention for Alzheimers disease: Prospects, limitations and strategies. CNS Drugs, 20: 351-372.

Ferrer, I., T. Gomez-Isla, B. Puig, M. Freixes, E. Ribe, E. Dalfo and J. Avila, 2005. Current advances on different kinases involved in tau phosphorylation and implications in Alzheimers disease and tauopathies. Curr. Alzheimer Res., 2: 3-18.

Finder, V.H. and R. Glockshuber, 2007. Amyloid-beta aggregation. Neurodegener. Dis., 4: 13-27.

Fisher, A., 2000. Therapeutic strategies in Alzheimers disease: M1 muscarinic agonists. Japan J. Pharmacol., 84: 101-112.

Fisher, A., D.M. Michaelson, R. Brandeis, R. Haring, S. Chapman and Z. Pittel, 2000. M1 muscarinic agonists as potential disease-modifying agents in Alzheimers disease: Rationale and perspectives. Ann. N. Y. Acad. Sci., 920: 315-320.

Galindo, M.F., I. Ikuta, X. Zhu, G. Casadesus and J. Jordan, 2010. Mitochondrial biology in Alzheimers disease pathogenesis. J. Neurochem., 114: 933-945.

Garai, K., B. Sahoo, S.K. Kaushalya, R. Desai and S. Maiti, 2007. Zinc lowers amyloid-ß toxicity by selectively precipitating aggregation intermediates. Biochemistry, 46: 10655-10663.

Garceau, D., C. Gurbindo and J. Laurin, 2002. Safety, tolerability and pharmacokinetic profile of Alzhemed, An anti-amyloid agent for Alzheimer's disease, in healthy subjects. Proceedings of the 7th International Geneva/Springfield Symposium on Advances in Alzheimer Therapy, April 3-6, 2002, Geneva, Switzerland.

Geerts, H., 2004. NC-531 Neurochem. Curr. Opin. Investig. Drugs, 5: 95-100.

Gervais, F., R. Chalifour, D. Garceau, X. Kong and J. Laurin *et al.*, 2001. Glycosaminoglycan mimetics: A therapeutic approach to cerebral amyloid angiopathy. Amyloid, 8: 28-35.

Glabe, C.G., 2008. Structural classification of toxic amyloid oligomers. J. Biol. Chem., 283: 29639-29643.

Glass, C.K., K. Saijo, B. Winner, M.C. Marchetto and F.H. Gage, 2010. Mechanisms underlying inflammation in neurodegeneration. Cell, 140: 918-934.

Gogvadze, V., S. Orrenius and B. Zhivotovsky, 2006. Multiple pathways of cytochrome c release from mitochondria in apoptosis. Biochim. Biophys. Acta Bioenergetics, 1757: 639-647.

Golde, T.E., 2003. Alzheimer disease therapy: Can the amyloid cascade be halted? J. Clin. Invest., 111: 11-18.

Gong, Y., L. Chang, K.L. Viola, P.N. Lacor and M.P. Lambert *et al.*, 2003. Alzheimers disease-affected brain: presence of oligomeric Aß ligands (ADDLs) suggests a molecular basis for reversible memory loss. Proc. Natl. Acad. Sci. USA., 100: 10417-10422.

Gu, Q.B., J.X. Zhao, J. Fei and W. Schwarz, 2004. Modulation of Na(+),K(+) pumping and neurotransmitter uptake by beta-amyloid. Neuroscience, 126: 61-67.

Haass, C. and D.J. Selkoe, 2007. Soluble protein oligomers in neurodegeneration: Lessons from the Alzheimers amyloid ß-peptide. Nat. Rev. Mol. Cell. Biol., 8: 101-112.

Halestrap, A.P., G.P. McStay and S.J. Clarke, 2002. The permeability transition pore complex: Another view. Biochimie, 84: 153-166.

Hauptmann, S., I. Scherping, S. Drose, U. Brandt and W.E. Muller *et al.*, 2009. Mitochondrial dysfunction: An early event in Alzheimer pathology accumulates with age in AD transgenic mice. Neurobiol. Aging, 30: 1574-1586.

Heinzen, E.L., A.C. Need, K.M. Hayden, O. Chiba-Falek and A.D. Roses *et al.*, 2010. Genome-wide scan of copy number variation in late-onset Alzheimers disease. J. Alzheimers. Dis., 19: 69-77.

Heneka, M.T., M. Sastre, L. Dumitrescu-Ozimek, A. Hanke and I. Dewachter *et al.*, 2005. Acute treatment with the PPARgamma agonist pioglitazone and ibuprofen reduces glial inflammation and Abeta1-42 levels in APPV7171 transgenic mice. Brain, 128: 1442-1453.

Herrup, K., 2010. Reimagining Alzheimer's disease-An age-based hypothesis. J. Neurosci., 30: 16755-16762.

Hirai, K., G. Aliev, A. Nunomura, H. Fujioka and R.L Russell *et al.*, 2001. Mitochondrial abnormalities in Alzheimers disease. J. Neurosci., 21: 3017-3023.

Hollenbeck, P.J., 2005. Mitochondria and neurotransmission: Evacuating the synapse. Neuron, 47: 331-333.

Holmes, C., D. Boche, D. Wilkinson, G. Yadegarfar and V. Hopkins *et al.*, 2008. Long-term effects of Abeta42 immunisation in Alzheimers disease: Follow- up of a randomised, placebo-controlled phase I trial. Lancet, 372: 216-223.

Jacobsen, J.S., P. Reinhart and M.N. Pangalos, 2005. Current concepts in therapeutic strategies targeting cognitive decline and disease modification in Alzheimers disease. NeuroRx., 2: 612-626.

Jick. H., G.L. Zornberg, S.S. Jick, S. Seshardi and D.A. Drachman, 2000. Statins and the risk of dementia. Lancet, 356: 1627-1631.

Kann, O. and R. Kovacs, 2007. Mitochondria and neuronal activity. Am. J. Physiol. Cell. Physiol., 292: C641-C657.

Kar, S., S.P. Slowikowski, D. Westaway and H.T. Mount, 2004. Interactions between ß-amyloid and central cholinergic neurons: Implications for Alzheimers disease. J. Psychiatry Neurosci., 29: 427-441.

Kassem, L.A. and N.A. Yassin, 2010. Role of erythropoeitin in prevention of chemotherapy-induced peripheral neuropathy. Pak. J. Biol. Sci., 13: 577-587.

Klafki, H.W., M. Staufenbiel, J. Kornhuber and J. Wiltfang, 2006. Therapeutic approaches to Alzheimers disease. Brain, 129: 2840-2855.

Klein, W.L., 2006. Cytotoxic Intermediates in the Fibrillation Pathway: Aβ Oligomers in Alzheimers Disease as a Case Study. In: Protein Misfolding, Aggregation and Conformational Diseases, Uvertsky, V.N. and A.L. Fink (Eds.). Springer, New York, pp: 61-75.

Lacor, P.N., M.C. Buniel, L. Chang, S. Fernandez and Y. Gong *et al.*, 2004. Synaptic targeting by Alzheimers-related amyloid beta oligomers. J. Neurosci., 24: 10191-10200.

Lambert, M.P., P.T. Velasco, L. Chang, K.L. Viola and S. Fernandez *et al.*, 2007. Monoclonal antibodies that target pathological assemblies of Abeta. J. Neurochem., 100: 23-35.

Lau, T.L., E.E. Ambroggio, D.J. Tew, R. Cappai and C.L. Masters *et al.*, 2006. Amyloid-β peptide disruption of lipid membranes and the effect of metal ions. J. Mol. Biol., 356: 759-770.

Lesne, S., M.T. Koh, L. Kotilinek, R. Kayed and C.G. Glabe *et al.*, 2006. A specific amyloid-ß protein assembly in the brain impairs memory. Nature, 440: 352-357.

Li, H. and X. Shen, 2000. Selective loss of basal forebrain cholinergic neurons in APP770 transgenic mice. Chin. Med. J., 113: 1040-1042.

Lim, G.P., F. Yang, T. Chu, P. Chen and W. Beech *et al*., 2000. Ibuprofen suppresses plaque pathology and inflammation in a mouse model for Alzheimers disease. J. Neurosci., 20: 5709-5714.

Lindsay, J., D. Laurin, R. Verreault, R. Hebert, B. Helliwell, G. Hill and L. McDowel, 2002. Risk factors for alzheimers disease: A prospective analysis from the canadian study of health and aging. Am. J. Epidemiol., 156: 445-453.

Lombardo, J.A., E.A. Stern, M.E. McLellan, S.T. Kajdasz, G.A. Hickey, B.J. Bacskai and B.T. Hyman, 2003. Amyloid-beta antibody treatment leads to rapid normalization of plaque induced neuritic alterations. J. Neurosci., 23: 10879-10883.

Luo, Y., B. Bolon, M.A. Damore, D. Fitzpatrick and H. Liu *et al*., 2003. BACE1 (beta-secretase) knockout mice do not acquire compensatory gene expression changes or develop neural lesions over time. Neurobiol. Dis., 14: 81-88.

Ma, Q., Y. Li, J. Du, K. Kanazawa, T. Nemoto, H. Nakanishi and Y. Zhao, 2005. Binding of copper (II) ion to an Alzheimer's tau peptide as revealed by MALDI-TOF MS, CD and NMR. Biopolymers, 79: 74-85.

Malek, M., S. Zahedi Asl, A. Sarkaki, Y. Farbood and A.H. Doulah, 2009. The effect of intra-hippocampal injection of growth hormone on spatial learning and memory in animal model of alzheimers disease. Pak. J. Biol. Sci., 12: 1237-1245.

Malm, T.M., H. Livonen, G. Goldsteins, V. Keksa-Goldsteine, T. Ahtonleml *et al*., 2007. Pyrrolidine dithiocarbamate activates Akt and improves spatial learning in APP/PS1 mice without affecting β-amyloid burden. J. Neurosci., 27: 3712-3721.

Massaad, C.A., T.M. Washington, R.G. Pautler and E. Klann, 2009. Overexpression of SOD-2 reduces hippocampal superoxide and prevents memory deficits in a mouse model of Alzheimers disease. Proc. Natl. Acad. Sci. U.S.A., 106: 13576-13581.

McCoy, M.K. and M.G. Tansey, 2008. TNF signaling inhibition in the CNS: Implications for normal brain function and neurodegenerative disease. J. Neuroinflammation., 2: 45-45.

Meraz-Rios, M.A., K.I. Lira-De Leon, V. Campos-Pena, M.A. De Anda-Hernandez and R. Mena-Lopez, 2010. Tau oligomers and aggregation in Alzheimers disease. J. Neurochem., 112: 1353-1367.

Metcalfe, M.J. and M.E. Figueiredo-Pereira, 2010. Relationship between tau pathology and neuroinflammation in Alzheimers disease. Mt. Sinai. J. Med., 77: 50-58.

Migliore, L. and F. Coppede, 2009. Genetics, environmental factors and the emerging role of epigenetics in neurodegenerative diseases. Mutat. Res., 667: 82-97.

Mocellin, S., 2006. Tumor vasculature: The achilles heel of cancer. Int. J. Cancer Res., 2: 176-187.

Moreira, P.I., M.S. Santos, A. Moreno and C. Oliveira, 2001. Amyloid beta-peptide promotes permeability transition pore in brain mitochondria. Biosci. Rep., 21: 789-800.

Moreira, P.I., M.S. Santos, A. Moreno, A.C. Rego and C. Oliveira, 2002. Effect of amyloid beta-peptide on permeability transition pore: A comparative study. J. Neurosci. Res., 69: 257-267.

Morgan, D., D.M. Diamond, P.E. Gottschall, K.E. Ugen and C. Dickey *et al*., 2000. A ß peptide vaccination prevents memory loss in an animal model of Alzheimers disease. Nature, 408: 982-985.

Neugroschl, J. and M. Sano, 2010. Current treatment and recent clinical research in Alzheimers disease. Mount. Sinai J. Med., 77: 3-16.

Oakley, H., S.L. Cole, S. Logan, E. Maus and P. Shao *et al*., 2006. Intraneuronal beta-amyloid aggregates, neurodegeneration and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: Potential factors in amyloid plaque formation. J. Neurosci., 26: 10129-10140.

Paola, D., C. Domenicotti, M. Nitti, A. Vitali and R. Borghi *et al*., 2000. Oxidative stress induces increase in intracellular amyloid beta-protein production and selective activation of betaI and betaII PKCs in NT2 cells. Biochem. Biophys. Res. Commun., 268: 642-646.

Pedrini, S., T.L. Carter, G. Prendergast, S. Petanceska, M.E. Ehrlich and S. Gandy, 2005. Modulation of statin-activated shedding of Alzheimer APP ectodomain by ROCK. PLoS. Med., 2: e18-e18.

Perry, V.H., C. Cunningham and C. Holmes, 2007. Systemic infections and inflammation affect chronic neurodegeneration. Nat. Rev. Immunol., 7: 161-167.

Pickhart, M., G. Larbig, I. Khlistunova, A. Coksezen and B. Meyer *et al*., 2007. Phenylthiazolyl-hydrazide and its derivates are potent inhibitors of Tau aggregation and toxicity *in vitro* and in cells. Biochemistry, 46: 10016-10023.

Picklo, Sr. M.J. and T.J. Montine, 2007. Mitochondrial effects of lipid-derived neurotoxins. J. Alzheimers Dis., 12: 185-193.

Pleckaityte, M., 2010. Alzheimers disease: A molecular mechanism, new hypotheses and therapeutic strategies. Med. (Kaunas), 46: 70-76.

Reisberg, B., R. Doody, A. Stöffler, F. Schmitt, S. Ferris and H.J. Möbius, 2003. Memantine in moderate- to-severe Alzheimers disease. N. Engl. J. Med., 348: 1333-1341.

Rogawski, M.A. and G.L. Wenk, 2003. The neuropharmacological basis for the use of memantine in the treatment of Alzheimer's disease. CNS Drug Rev., 9: 275-308.

Rusakov, D.A., 2006. Ca^{2+} dependent mechanisms of presynaptic control at central synapses. Neuroscientist, 12: 317-326.

Saijo, K., B. Winner, C.T. Carson, J.G. Collier and L. Boyer *et al*., 2009. Nurr1/CoREST pathway in microglia and astrocytes protects dopaminergic neurons from inflammation induced death. Cell, 137: 47-59.

Salloway, S. and S. Correia, 2009. Alzheimer disease: Time to improve its diagnosis and treatment. Cleve. Clin. J. Med., 76: 49-58.

Sanchez-Ramos, J., S. Song, C. Cao and G. Arendash, 2008. The potential of hematopoietic growth factors for treatment of Alzheimers disease: A mini-review. BMC Neurosci., 9: S3-S3.

Sarkaki, A., R. Amani, M. Badavi, A.Z. Moghaddam, H. Aligholi, M. Safahani and M.H. Haghighizadeh, 2008. Pre-treatment effect of different doses of soy isoflavones on spatial learning and memory in an ovariectomized animal model of alzheimer`s disease. Pak. J. Biol. Sci., 11: 1114-1119.

Sasaki, N., S. Toki, H. Chowei, T. Saito and N. Nakano *et al*., 2001. Immunohistochemical distribution of the receptor for advanced glycation end products in neurons and astrocytes in Alzheimers disease. Brain Res., 888: 256-262.

Sastre, M., J. Walter and S.M. Gentleman, 2008. Interactions between APP secretases and inflammatory mediators. J. Neuroinflammation, 5: 25-25.

Saunders, A.M., 2001. Gene identification in Alzheimer's disease. Pharmacogenomics, 2: 239-249.

Saura, C.A., S.Y. Choi, V. Beglopoulos, S. Malkani and D. Zhang *et al*., 2004. Loss of presenilin function causes impairments of memory and synaptic plasticity followed by age-dependent neurodegeneration. Neuron, 42: 23-36.

Sayre, L.M., G. Perry, P.L.R. Harris, Y. Liu, K.A. Schubert and M.A. Smith, 2000. In situ oxidative catalysis by neurofibrillary tangles and senile plaques in Alzheimer's disease a central role for bound transition metals. J. Neurochem., 74: 270-279.

Schaeffer, E.L., B.A. Novaes, E.R. da Silva, H.D. Skaf and A.G. Mendes-Neto, 2009. Strategies to promote differentiation of newborn neurons into mature functional cells in Alzheimer brain. Prog. Neuropsychopharmacol. Biol. Psychiatry, 33: 1087-1102.

Schneider, L.S., S.T. DeKosky, M.R. Farlow, P.N. Tariot, R. Hoerr and M. Kieser, 2005. A randomized, double-blind, placebo-controlled trial of two doses of ginkgo biloba extract in dementia of the Alzheimers type. Curr. Alzheimer. Res., 2: 541-551.

Schneider, L.S., P.N. Tariot, K.S. Dagerman, S.M. Davi and J.K. Hsiao *et al*., 2006. Effectiveness of atypical antipsychotic drugs in patients with Alzheimers disease. N. Engl. J. Med., 355: 1525-1538.

Selkoe, D.J., 2001. Alzheimers disease: Genes, proteins and therapy. Physiol. Rev., 81: 741-766.

Serrano, F. and E. Klann, 2004. Reactive oxygen species and synaptic plasticity in the aging hippocampus. Ageing Res. Rev., 3: 431-443.

Shishodia, S., G. Sethi and B.B. Aggarwal, 2005. Curcumin: Getting back to the roots. Ann. N. Y. Acad. Sci., 1056: 206-217.

Silvestrelli, G., A. Lanari, L. Parnetti, D. Tomassoni and F. Amenta, 2006. Treatment of Alzheimers disease: From pharmacology to a better understanding of disease pathophysiology. Mech. Ageing. Dev., 127: 148-157.

Simi, A., N. Tsakiri, P. Wang and N.J. Rothwell, 2007. Interleukin-1 and inflammatory neurodegeneration. Biochem. Soc. Trans., 35: 1122-1126.

Siren, A.L., T. Fasshauer, C. Bartels and H. Ehrenreich, 2009. Therapeutic potential of erythropoietin and its structural or functional variants in the nervous system. Neurotherapeutics, 6: 108-127.

Smith, P.J., J.A. Blumenthal, M.A. Babyak, L. Craighead and K.A. Welsh-Bohmer *et al*., 2010. Effects of the dietary approaches to stop hypertension diet, exercise and caloric restriction on neurocognition in overweight adults with high blood pressure. Hypertension, 55: 1331-1338.

Sonkusare, S.K., C.L. Kaul and P. Ramarao, 2005. Dementia of Alzheimers disease and other neurodegenerative disorders- memantine, a new hope. Pharmacol. Res., 51: 1-17.

Stoothoff, W.H. and G.V.W. Johnson, 2005. Tau phosphorylation: Physiological and pathological consequences. Biochim. Biophys. Acta., 1739: 280-297.

Suh, S.W., K.B. Jensen, M.S. Jensen, D.S. Suva, P.J. Kesslak, G. Danscher and C.J. Frederickson, 2000. Histochemically-reactive zinc in amyloid plaques, angiopathy and degenerating neurons of Alzheimers diseased brains. Brain Res., 852: 274-278.

Sun, X., S. Sato, O. Murayama, M. Murayama, J.M. Park, H. Yamaguchi and A. Takashima, 2002. Lithium inhibits amyloid secretion in COS7 cells transfected with amyloid precursor protein C100. Neurosci. Lett., 321: 61-64.

Szekely, C.A., J.E. Thorne, P.P. Zandi, M. Ek, E. Messias, J.C. Breitner and S.N. Goodman, 2004. Nonsteroidal anti-inflammatory drugs for the prevention of Alzheimers disease: A systematic review. Neuroepidemiology, 23: 159-169.

Tamagno, E., M. Guglielmotto, M. Aragno, R. Borghi and R. Autelli *et al*., 2008. Oxidative stress activates a positive feedback between the gamma- and beta-secretase cleavages of the beta-amyloid precursor protein. J. Neurochem., 104: 683-695.

Tariot, P.N., M.R. Farlow, G.T. Grossberg, S.M. Graham, S. McDonald, I. Gergel and Memantine Study Group, 2004. Memantine treatment in patients with moderate to severe Alzheimers disease already receiving donepezil. A randomized controlled trial. JAMA., 291: 317-324.

Trinh, N.H., J. Hoblyn, S. Mohanty and K. Yaffe, 2003. Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: A meta-analysis. J. Am. Med. Assco., 289: 210-216.

Tschape, J.A. and T. Hartmann, 2006. Therapeutic perspectives in Alzheimers disease. Recent Patents. CNS Drug Discov., 1: 119-127.

Tuppo, E.E. and H.R. Arias, 2005. The role of inflammation in Alzheimers disease. Cell. Biol., 37: 289-305.

Tyas, S.L., J. Manfreda, L.A. Strain and P.R. Montgomery, 2001. Risk factors for Alzheimers disease: A population-based, longitudinal study in Manitoba, Canada. Int. J. Epidemiol., 30: 590-597.

Van Den Heuvel, C., E. Thornton and R. Vink, 2007. Traumatic brain injury and Alzheimers disease: A review. Prog. Brain Res., 161: 303-316.

Vetrivel, K.S., Y.W. Zhang, H. Xu and G. Thinakaran, 2006. Pathological and physiological functions of presenilins. Mol. Neurodegener., 1: 4-4.

Vlassara, H., W. Cai, J. Crandall, T. Goldberg and R. Oberstein *et al*., 2002. Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. Proc. Natl. Acad. Sci. USA., 99: 15596-15601.

Wakabayashi, T. and B. De Strooper, 2008. Presenilins: Members of the ?-secretase quartets, but part-time soloists too. Physiology, 23: 194-204.

Walker, L.C., C.C. Ibegbu, C.W. Todd, H.L. Robinson, M. Jucker, H. LeVine and S. Gandy, 2005. Emerging prospects for the disease-modifying treatment of Alzheimers disease. Biochem. Pharmacol., 69: 1001-1008.

Wallace, D.C., 2005. A mitochondrial paradigm of metabolic and degenerative diseases, aging and cancer: A dawn for evolutionary medicine. Annu. Rev. Genet., 39: 359-407.

Walsh, D.M. and D.J. Selkoe, 2007. Aβ oligomers-a decade of discovery. J. Neurochem., 101: 1172-1184.

Wang, Y., S.L. Chan, L. Miele, P.J. Yao, J. Mackes, D.K. Ingram, M.P. Mattson and K. Furukawa, 2004. Involvement of Notch signaling in hippocampal synaptic plasticity. Proc. Natl. Acad. Sci., 101: 9458-9462.

Wang, X., B. Su, H. Fujioka and X. Zhu, 2008. Dynamin-like protein 1 reduction underlies mitochondrial morphology and distribution abnormalities in fibroblasts from sporadic Alzheimers disease patients. Am. J. Pathol., 173: 470-482.

Weggen, S., J.L. Eriksen, P. Das, S.A. Sagi and R. Wang *et al*., 2001. A subset of NSAIDs lower amyloidogenic Abeta42 independently of cyclooxygenase activity. Nature, 414: 212-216.

White, A.R., T. Du, K.M. Laughton, I. Volitakis and R.A. Sharples *et al*., 2006. Degradation of the Alzheimer disease amyloid beta peptide by metal dependent up-regulation of metalloprotease activity. J. Biol. Chem., 281: 17670-17680.

Wolf, B.A., A.M. Wertkin, Y.C. Jolly, R.P. Yasuda and B.B. Wolfe *et al*., 1995. Muscarinic regulation of Alzheimers disease amyloid precursor protein secretion and amyloid beta- protein production in human neuronal NT2N cells. J. Biol. Chem., 270: 4916-4922.

Wolozin, B., W. Kellman, P. Ruosseau, G.G. Celesia and G. Siegel, 2000. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors. Arch. Neurol., 57: 1439-1443.

Wu, Q.Y., J. Li, Z.T. Feng and T.H. Wang, 2007. Bone marrow stromal cells of transgenic mice can improve the cognitive ability of an Alzheimers disease rat model. Neurosci. Lett., 471: 281-285.

Yaari, R. and J. Corey-Bloom, 2007. Alzheimers disease: Pathology and pathophysiology. Semin. Neurol., 27: 32-41.

Yang, F., G.P. Lim, A.N. Begum, O.J. Ubeda, M.R. Simmons *et al*., 2005. Curcumin inhibits formation of amyloid β oligomers and fibrils, binds plaques and reduces amyloid *in vivo*. J. Biol. Chem., 280: 5892-5901.

Yoshiike, Y., K. Tanemura, O. Murayama, T. Akagi and M. Murayama *et al*., 2001. New insights on how metals disrupt amyloid β-aggregation and their effects on amyloid-β cytotoxicity. J. Biol. Chem., 276: 32293-32299.

Zaciragic, A., O. Lepara, A. Valjevac, S. Arslanagic and A. Fajkic *et al*., 2007. Elevated serum C-reactive protein concentration in Bosnian patients with probable Alzheimers disease. J. Alzheimers. Dis., 12: 151-156.

Zamzami, N., N. Larochette and G. Kroemer, 2005. Mitochondrial permeability transition in apoptosis and necrosis. Cell Death Differ., 12: 1478-1480.

Zandi, P.P., J.C. Anthony, A.S. Khachaturian, S.V. Stone and D. Gustafson *et al*., 2004. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: The cache county study. Arch. Neurol., 61: 82-88.

Zatta, P., G. Tognon and P. Carampin, 2003. Melatonin prevents free radical formation due to the interaction between β-amyloid peptides and metal ions [Al(III), Zn(II), Cu(II) Mn(II), Fe(II)]. J. Pineal. Res., 35: 98-103.

Zhou, L.X., J.T. Du, Z.Y. Zeng, W.H. Wu and Y.F. Zhao *et al*., 2007. Copper (II) modulates *in vitro* aggregation of a tau peptide. Peptides, 28: 2229-2234.