Life Science Informatics Publications

Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences

Journal Home page http://www.rjlbpcs.com/

RJLBPCS

ISSN 2454-6348

Original Review Article **DOI - 10.26479/2018.0402.03**

RISK FACTORS AND CURRENT UNDERSTANDING OF ALZHEIMER'S DISEASE

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ABSTRACT: Alzheimer's is the most common form of dementia, a general term for memory loss and other cognitive abilities serious enough to interfere with daily life. Alzheimer's disease accounts for 60 to 80 percent of dementia cases. About 25 million people are affected worldwide, and the incidence is expected to quadruple by 2050 to approximately 80 million cases owing mainly to increasing life expectancy. AD is the predominant form of senile dementia and is characterized by the presence of extracellular amyloid plaques and intracellular neurofibrillary tangles. The AD brain is marked by severe neurodegeneration such as synaptic loss, atrophy, neuronal loss and depletion of neurotransmitter systems in the hippocampus and cerebral cortex. These facts underline the role of AD as a major health burden and emphasize the need for identification of risk factors and targets for diagnosis, prevention, and treatment. While the neuropathological features of Alzheimer's disease are recognized but the intricacies of the mechanism have not been clearly understood. This lack of understanding regarding the pathogenic process may be the likely reason for the non-availability of effective treatment which can prevent onset and progression of the disease. In this review, authors will discuss the different aspects of pathophysiological mechanisms behind Alzheimer's disease.

KEYWORDS: Alzheimer's disease, neuropathology, oxidative stress, inflammation, risk factors.

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1.INTRODUCTION

Alzheimer disease (AD), a leading cause of dementia, is a neurodegenerative disorder in elderly population (Bird TD, 2005). It is characterized by progressive cognitive decline usually begins with impairment in the ability to form recent memories, but inevitably impaired all intellectual functions and leading to complete dependence for basic functions of daily life (Brookmeyer et al., 2007). The pathological manifestations of AD include extracellular amyloid plaques and intracellular neurofibrillary tangles accompanied by reactive microgliosis, dystrophic neurites, loss of neurons and synapses (Serrano-Pozo et al., 2011). Senile dementia was first described by the German psychiatrist Alois Alzheimer in 1906, however the knowledge about senile dementia is considerably older. Hippocrates (father of Medicine) [460–377 B.C.] represents an early attempt to explain age-related mental dysfunction. But he did not consider it an abnormality, but rather, an unfortunate and inevitable consequence of aging. Cicero, a Roman philosopher, [2nd century B.C.] was clear-sighted in observing that senile debility is a characteristic, not for all old population, but only those who are weak in will (Black, 1991). He also advocated that an active mental life could prevent or at least postpone mental failure (Inouye et al., 1993, Seeman and Albert, 1995, Mahendra, 1987). Furthermore, during the Greco-Roman period, Galen also recognized dementia in the advanced age as a mental disease (Berchtold and Cotman, 1998). Alois Alzheimer provided clinical descriptions of AD when he studied a clinical case of 51-year-old woman named Auguste D admitted to the state asylum in Frankfurt. She was suffering from cognitive and language deficits, auditory hallucinations, delusions, paranoia and aggressive behavior. In 1906, Alzheimer presented Auguste's case at a psychiatry meeting, and his talk was published in 1907. According to Alzheimer’s words in a 1907 paper, “she showed rapidly increasing memory impairments; she was disoriented carrying objects to and fro in her flat and hid them. Sometimes she felt that someone wanted to kill her and began to scream loudly” (Maurer et al., 1997). In 1910, Kraepelin coined the term 'Alzheimer's disease' – a term still used to refer to the most common cause of senile dementia (Ramirez-Bermudez, 2012). The prevalence rate of AD is exponentially accelerating with age, increasing noticeably after 65 years. There is almost a 15-fold enhancement in the prevalence of dementia, predominately in AD, between the ages of 60 and 85 years (Evans et al., 1989). Global prevalence of dementia for 2010 was predicted to be 4.7% in persons 60+ years old with a regional prevalence of 2.6% in Africa, 4.0% in Asia, 6.2% in Europe and 6.5% in North America.

2. Types Of Alzheimer’s Disease

AD is a progressive form of mental deterioration in aged population. There are two types of AD: familial (early onset) and sporadic (late onset). The familial Alzheimer’s disease (FAD) is a consequence of mutations in three major genes, which includes amyloid precursor protein (APP), presenilin1 (PSEN1) and presenilin 2 (PSEN2) genes (Hardy, 1997). It has been reported that prevalence of FAD is relatively rare, consider as less than 5% of the total number of cases of AD

(Acosta-Baena et al., 2011, Alzheimer's, 2012). There are approximately 160 highly penetrant but rare mutations have been described in three genes (APP, PSEN1, and PSEN 2) that cause familial AD (Tanzi et al., 1987, Hardy, 1997). Presenilin is the sub-component of γ-secretase that is responsible for the cleavage of APP (a precursor of amyloid beta). Amyloid beta peptides (Aβ) in the brain of AD patient is a key pathogenic event, are derived from APP through an initial β-secretase cleavage followed by an intramembraneous γ-secretase (Hardy, 1997). Thus, the Aβ production has been increased in familial AD due to mutation in these genes. In contrast to familial AD, many genetic and environmental factors may contribute to the incidence of sporadic AD. However, the mechanisms underlying the pathology of sporadic AD remain mostly unclear. The apolipoprotein E gene (APOE4) has been associated with substantially increased risk for sporadic AD (Roses and Saunders, 1994), since in addition to its role in transportation of lipoproteins, fat-soluble vitamins, cholesterol, it is also involved in the Aβ clearance mechanism (Zannis and Breslow, 1982). A large number of additional polymorphisms of APOE have been associated with risk for sporadic AD (Roses, 1996), which is located in genes that regulate inflammation, oxidative stress, vascular biology, and protease function (Saunders, 2001). Various reports documented that obesity, diabetes, cardiovascular disease, and related factors, as well as cerebral and systemic inflammation increase the risk for sporadic AD (Hoyer et al., 2002, Brouwers et al., 2008). It is remarkable that both sporadic AD and familial AD are characterized by same clinical and neuropathological features including Aβ plaques, accumulation of intracellular neurofibrillary tangles, and pronounced neuronal cell loss.

3. Symptoms Of Alzheimer's Disease

Dementia of the AD type is characterized by a progressive deterioration of memory and cognition. Clinically, AD is characterized by a progressive loss of cognitive function, particularly regarding episodic memory, executive function, and language and visuospatial abilities (Albert, 2011, Holtzman et al., 2011). Impaired episodic memory is one of the most prominent features of AD related to the learning and retention of new information, such as day-to-day activities or the ability to remember current events (Albert, 2011). Moreover, performance in some verbal tasks of episodic memory can even differentiate patients in very early stages of AD from healthy aged controls (Butler and Zeman, 2011). Impairment in both recognition and free recall tasks, suggesting that ineffective consolidation or storage of new information underlies the episodic memory deficits in AD (Butler and Zeman, 2011). Executive function refers to a set of cognitive processes that include planning, working memory, attention, multi-tasking, mental flexibility, and initiation and monitoring of actions (Manes et al., 2011). Executive dysfunction in AD typically manifests first as decreased attention and problem-solving or working memory skills but is also associated with impairments in decision-making (Gleichgerrcht et al., 2010). Episodic memory relies on the hippocampus, executive functions are indicative of frontal cortical function (Dickerson and Eichenbaum, 2010).

Thus, even though the hippocampus is particularly vulnerable in AD, cortical areas and function are also affected even in the early stages of disease. Furthermore, visuospatial deficits (an abilities which related to understanding the visual representations and spatial relationships in learning and performing a task) may also be related to the reduced effectiveness of information processing in the cortical and hippocampal regions thought to underlie visuospatial function (Iachini et al., 2009, Weintraub et al., 2012). Thus, it is considerable that alterations in memory associated with early AD are substantially different from those associated with age-related changes in memory. Intermittent occurrences of the neuropsychiatric symptoms are depression and anxiety, as estimated to be 20% and 50% respectively (Lyketsos et al., 2003). Apathy can appear in all stages of the disease, and it advances with severity of disease. Apathy shows to be an independent syndrome (Steinberg et al., 2008). In early AD, 42% of patients showed apathy, increasing to 90% in severe AD (Mega et al., 1996). This progression reflects the frontal-subcortical dysfunction and the impairment in communication between the anterior cingulate cortex and other cortical areas that accompanies the progression of AD (Robert et al., 2009). Agitation may exist in combination with many different symptoms. Senanarong and their co-workers found significant association between agitation and all other neuropsychiatric inventory (NPI) subscale scores, with substantial correlations presenting with irritability, disinhibition, delusions, and aberrant motor activity (Senanarong et al., 2004). An Asian study found a prevalence of irritability/aggression greater than 70% (Youn et al., 2011). Some studies suggests that alteration in glucose metabolism (measured by positron emission tomography) has also been associated with anxiety, apathy, agitation, and disinhibition in AD (Dillon et al., 2013). Hyperactivity including aberrant motor behavior (wandering, pacing, rummaging, purposeless hyperactivity) is considerable in more than one-quarter of patients with dementia and also constitutes agitation, disinhibition and irritability (Aalten et al., 2007). Agitation along with aggression is the most critical situation as well as along with depression and psychosis, are leading to institutionalization of patient (Gaugler et al., 2009) . Irritability is common and can be annoying; it occurs with a prevalence of ∼40% of patients with mild and moderate AD, increasing to ∼50% of patients in the more severe stages of the disease (Robert et al., 2002). Delusions and hallucinations can be influence 27–45% of AD patients (Leroi et al., 2003), and has been combined with progressive cognitive decline, earlier institutionalization, and caregiver burnout (Lesser and Hughes, 2006). Sleep problems which are estimated to be present in 25–54% of AD patients (Moran et al., 2005), can impact significantly the quality of sleep of caregivers. Sleep disturbance was related to increased institutionalization and the accompanying caregiver stress (Vitiello and Borson, 2001). Personality changes following the onset of AD may be completely opposite of the premorbid personality including irritability, happiness, energy, enthusiasm, contact with reality, maturity, kindness, being reasonable and stable (Strauss et al., 1993). In particular, talkative/quiet, self-reliant/relies on others, down to earth/out of touch, mature/childish, reasonable/unreasonable

seemed more sensitive to the severity of dementia than the other personality traits (Archer et al., 2007). These traits may be useful to understand personality changes in people with dementia.

4. Neuropathology of Alzheimer's disease

AD is promptly becoming one of the most common clinical manifestations which affect the elder population. The molecular and pathological substrate of people diagnosed with AD is not fully understood. It has been difficult to directly establish the sequence of pathogenic events in disease because brain tissue from AD patient can only be studied after death (McKhann et al., 1984). A multifactorial pathogenesis of AD involved genetic mutations and risk factors, abnormal processing of Aβ and microtubule-associated protein tau, inflammatory mechanisms, deficits of neurotrophic factors, oxidative stress and excitotoxicity, metabolic dysfunctions and alterations in several neurotransmitters (acetylcholine, noradrenaline, serotonin, glutamate) (Mattson and Magnus, 2006). The interplay of these pathogenic factors gives rise to the typical neuropathology of AD with senile plaques, neurofibrillary tangles, synaptic loss and neuronal apoptosis/degeneration, leading to brain atrophy and cognitive impairment.

4.1. Hypothesis of Genetic mutation

Rare mutations in three genes have been firmly implicated in familial early-onset disease: amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2) (Goate et al., 1991, Levy-Lahad et al., 1995). These mutations have high penetrance, are mostly inherited in an autosomal dominant pattern and leads to enhanced Aβ42 peptide levels, aggregation and an early onset of disease, typically beginning in the fourth or fifth decade of life. APP mutations account for a very small fraction of AD incidence (less than 1% of all AD patients). So far, 20 pathogenic mutations in the APP gene, 124 mutations in the PS1 gene and 8 mutations in the PS2 gene have been explained in AD (Kowalska, 2004) and the mutations have a direct effect on Aβ fibril formation. Both APP and PS mutations affect the activity of secretases (α, β, and γ) during APP processing leading to overproduction of amyloidogenic Aβ42 (Borchelt et al., 1996). A significant up-regulation in the concentration of Aβ42/Aβ40 ratio is found in the majority of familial cases induced by these mutations. Mutations in the PS gene might be disrupting function of γ-secretase through subtle conformational alterations, which is responsible for the processing of the APP (Steiner and Haass, 2000). It also decreased the intracellular signaling pathway that control transcription of chaperones, which regulates the improper folding of proteins (Steiner and Haass, 2000). Although mutations in these three genes represent rare causes of AD, their discovery greatly supported a pivotal role for Aβ in the pathogenesis of AD. So far, no evidence of an altered Aβ generation has been reported in sporadic late-onset AD, which commences after age of approximately 65 years. Thus, it is considerable to assume that Aβ aggregation in sporadic AD may be induced by some unknown post-translational modifications of Aβ and/or by a perturbed mechanism of Aβ clearance (Rolyan et al., 2011). Some biological studies confirm that changes in cholesterol metabolism in neurons may

underlie the pathological processes in AD (Castellano et al., 2011). The APOE-4 allele of apolipoprotein E gene encoding a protein directly involved in the regulation of lipid metabolism is a major risk factor in sporadic late-onset AD (Castellano et al., 2011). APOE-4 related risk in population has been estimated at 20% (Slooter et al., 1998). But mechanism is still not fully understood how APOE-4 increases risk of AD. Several evidences suggest that APOE-4 modulates the distribution and metabolism of cholesterol in neuronal membranes in an allele-dependent manner. Moreover, it has been suggested that Aβ begins to accumulate in the brain through its binding to a glycolipid molecule, GM1 ganglioside (Yanagisawa et al., 1995). The GM1 ganglioside may be considered as a molecular chaperone for conversion of Aβ. Based on the unique molecular characteristics of GM1 ganglioside-bound Aβ, including its extremely high aggregation potential and altered immunoreactivity, it was hypothesized that Aβ adopts an altered conformation after binding to GM1 and accelerates aggregation of soluble Aβ by acting as a seed (Yanagisawa and Ihara, 1998). It has been found that the binding of Aβ to GM1 is significantly accelerated in cholesterol-rich domains. There are several reports indicating that Aβ initially accumulates in the fractions with the lipid composition similar to that of lipid rafts (Tun et al., 2002, Ehehalt et al., 2003). Therefore, it is very likely that APOE-4 is associated with impairment in membrane lipids, including cholesterol and gangliosides, are highly involved in the aggregation of soluble Aβ in AD brains.

4.2. Amyloid beta hypothesis

Amyloid beta (Aβ) plaques are a certified lesion of people having a clinical diagnosis with AD. The dispersion of Aβ deposits changes with time and reflects the expansion of Aβ deposition in the diseased brain (Thal et al., 2000). First, senile plaques occur as a diffuse and "fleecy" form throughout the neocortex which extends to other brain regions. In a second stage, Aβ plaques appear in allocortical areas (e.g. entorhinal cortex and subiculum/ CA1 region). In the third stage, plaques found to be in the basal ganglia, thalamus, and in hypothalamus. In the fourth stage, amyloid plaque reaches the midbrain and medulla oblongata. At last in a fifth stage, senile plaques appear in the pons and cerebellum (Thal et al., 2006). Amyloid cascade hypothesis was formulated to give a framework for resolving the biochemical mechanisms underlying the neurodegenerative processes occurring in Alzheimer's disease and for the design of potential therapeutics (Hardy and Higgins, 1992). The hypothesis stated Aβ (40–42 amino acids) as a center stage in the cell death process, derived by abnormal proteolytic processing of the membrane glycoprotein APP. In addition to being a precursor of amyloid β-peptide, APP is considered ubiquitously as a type I membrane glycoprotein and has specific biochemical and pathological roles in other tissues. For example, as a primary androgen target gene that promotes prostate cancer growth which is significantly elevated in colon and pancreatic tumors suggesting its role in cell growth, differentiation and carcinogenesis (Takayama et al., 2009, Venkataramani et al., 2010). There are two conflicting pathways of APP

metabolism occurring naturally, of which the amyloidogenic pathway is initiated by β-secretase (a membrane-bound aspartic proteinases) which was further cleaved by the γ-secretase resulting in production of Aβ peptides (O'Brien and Wong, 2011, Zhang et al., 2012). This pathway produced not only Aβ but a number of other physiologically active metabolites including the cleaved intracellular domain (AICD), which could contribute to the pathological processes leading to AD. Normal proteolytic process was involving the initial cleavage of APP by a zinc metalloproteinase, α secretase followed by γ- secretase. Since α secretase cleaves APP within the Aβ peptide region, it inhibits the Aβ formation and activates the pathway which is potentially neuroprotective (O'Brien and Wong, 2011, Beckett et al., 2012). The accumulation of Aβ peptides mediates neuronal cytotoxicity by inducing a cascade of neuropathogenic events leading to brain deterioration (Hardy and Selkoe, 2002, Glenner and Wong, 2012). Several mechanisms have been suggested to be involved in this process including direct cytotoxicity, production of reactive oxygen species, up-regulated intracellular response to excitatory amino acids, and disruption of calcium homeostasis (Smith et al., 1996). The strong cytotoxicity of the pre-fibrillar amyloid accumulation may be a direct consequence of their interactions with cell membranes causing membrane damage through the formation of non-specific ion channels (Lin et al., 2001). This could disrupt cellular homeostasis, impairing fundamental cellular processes by oxidative stress and increasing free [Ca2+]i that eventually cause apoptotic cell death (Stefani and Dobson, 2003). Furthermore, Aβ binds directly to glutamate receptors (including NMDA receptors) resulting in reduced signaling, disrupting the structure of the synapse and depleting synaptic vesicles (Scheff and Price, 2003, Shankar et al., 2007, Parodi et al., 2010). Aβ oligomers have also been proposed to impair LTP by binding to the prion protein which leads to increased Fyn activity and NR2B phosphorylation in neuritis (Lauren et al., 2009). Fyn is a member of Src family of tyrosine kinases which regulates the cell-cell adhesion and receptor clustering. Overproduction of Aβ in neuronal cells increases the level of GSK3 (glycogen synthase kinase 3) which are involved in cell cycle regulation by phosphorylating cyclin-dependent protein kinase 5 (Cdk5) (Asuni et al., 2006). Increased level of GSK3 induced the hyperphosphorylation of tau protein resulting in formation of neurofibrillary tangles (Lucas et al., 2001).

4.3.Tangle hypothesis

Neurofibrillary degeneration of the AD type consists of the abnormally hyperphosphorylated tau which obviously involves several different aetiopathogenic mechanisms. In healthy aged individuals, neurofibrillary pathology is identified in the entorhinal cortex. However, neurofibrillary degeneration extends from the entorhinal cortex first to the hippocampus and then to the rest of the neocortex in AD (Gomez-Isla et al., 1996). Apparently neurofibrillary degradation in the neocortex is requisite for dementia; neither β-amyloidosis of the brain nor the presence of neurofibrillary pathology in the entorhinal cortex alone are sufficient for the clinical expression of the disease (Iqbal

et al., 1989). In the diseased brain, all of the six tau isoforms are hyperphosphorylated and accumulated into paired helical filaments (Grundke-Iqbal et al., 1986, Goedert et al., 1992). Although conformational changes and truncation of tau following its hyperphosphorylation have been reported in AD, the most established and compelling cause of neurofibrillary degeneration in AD (Jicha et al., 1999, Delobel et al., 2008) and related tauopathies is the consequence of abnormal hyperphosphorylation of this protein (Alonso et al., 1994). Two major recognized functions of tau are its ability to promote assembly and to maintain structure of microtubules (Weingarten et al., 1975) which are maintained by its degree of phosphorylation (Khatoon et al., 1995). Neurofibrillary degeneration, a histopathological hallmark of AD and related tauopathies, is caused by multiple factors. These multiple causes involve not only mutations in the tau gene, APP gene, PS1 gene and PS2 gene, but also metabolic abnormalities and environmental factors. Tau is a substrate for several protein kinases (Singh et al., 1994, Johnson and Hartigan, 1999) such as GSK3 and Cdk5 (Iqbal et al., 2005, Pei et al., 2008). GSK3, a serine/threonine kinase, is expressed at high levels in neurons where it plays important roles in regulating structural and metabolic plasticity (Soutar et al., 2010). Hyper-activation of GSK3 may facilitate the tau hyperphosphorylation in the neuron, in turn of which, formation of neurofibrillary tangles (Avila et al., 2010). Cdk5 activation through complex formation with p35 is linked with physiological activation of Cdk5, the truncated p25 form aggressively stimulates Cdk5, resulting in abnormal phosphorylation of substrates such as tau (Ahlijanian et al., 2000). Although the hyperactivation of Cdk5/p35/p25 has been linked with the pathogenesis of neurodegenerative diseases such as AD, its physiological properties have been implicated in critical functions such as neuroblast migration and synaptic plasticity (Fischer et al., 2005, Hirota et al., 2007). Since Cdk5 plays a role in synaptic function and neuronal integrity, abnormal activation of this molecule by Aβ might impair the functioning of mature neurons and also contribute to alterations in neurogenesis by impairing cell maturation. The condition of phosphorylation of a protein is a function of the balance between the activities of the protein kinases and the protein phosphatases that regulate its phosphorylation (Gong et al., 2000, Bennecib et al., 2001) and has been strongly implicated as a cause of abnormal hyperphosphorylation of tau (Iqbal et al., 2009). Protein phosphatase activity is governed by two heat-stable proteins, inhibitor-1and inhibitor-2 (Li et al., 1995, Tsujio et al., 2005). The mRNAs and protein expression of both of these inhibitors are up-regulated in AD-affected brain (Tanimukai et al., 2005). Inhibitor-2, a primarily nuclear protein, is selectively cleaved into an N-terminal half (I2NTF) and a C-terminal half (I2CTF), and is translocated from the neuronal nucleus to the cytoplasm and co-exist with NFTs in AD affected brain. Expression of I2CTF in the brain causes abnormal hyperphosphorylation of tau and reference memory impairment in rats, suggesting a novel aetiopathogenic mechanism of neurofibrillary degeneration involving cleavage of I2 PP2A and generation of I2CTF (Tanimukai et al., 2005). Phosphorylation of tau is also maintained by its degree of O-GlcNAcylation which

involves serine/threonine residues (Arnold et al., 1996). O-GlcNAcylation, including that of tau, is down-regulated in AD-affected brain (Liu et al., 2004). This is probably due to a decrease in brain glucose metabolism caused by a decrease in the level of the glucose transporters Glut1 and Glut3 (Liu et al., 2009); the brain level of Glut3 is also down-regulated in diabetes and in cases of AD with diabetes, providing an elucidation of diabetes as a risk factor and a metabolic cause of AD. Thus, alteration in the phosphorylation state of tau can lead to destabilization of microtubules, causing neuronal dysfunction, ultimately triggering cell death of the neuron (Mi and Johnson, 2006, Farias et al., 2011).

5. Risk factors of Alzheimer's disease

Alzheimer's disease is a heterogeneous and multifactorial disorder. Various factors have been associated with increasing the risk of AD, among those; cerebrovascular disease and its antecedents are most consistently reported. A history of diabetes, hypertension, smoking, obesity, and dyslipidemia have all been found to increase the risk of AD(Yip et al., 2006) (Jin et al., 2008) (Reitz et al., 2008) (Rastas et al., 2010). Aging is considered as a major risk factor of AD (Braak and Braak, 1997). Clinical studies illustrated that distribution of neurofibrillary tangles and Aβ deposits was found to be increased with age (Stoltzner et al., 2000). Aging is associated with reductions in cortical thickness, white matter integrity and neurotransmitter function in the brain regions (Sole-Padulles et al., 2009). Mitochondrial dysfunction is the main culprit of age-related toxicity. An age-dependent impairment of mitochondrial function may be due to decreased electron transfer, disrupt permeability of the inner membrane and decreased ATP production (Li et al., 2004). In consequence of this, increased ROS production affects the replication and transcription of mitochondrial DNA (mtDNA) resulting in a decline mitochondrial function which in turn leads to enhanced ROS production and further damage to mtDNA resulting in diminished energy production (Friel, 2000). In addition, decreased mitochondrial permeability facilitate the intracellular accumulation of Ca2+ which further trigger to the apoptotic pathways (Parihar and Brewer, 2010). Furthermore, the production of inflammatory mediators (inflammatory cytokines, interleukins, neurotrophins), activation of glia and other immune cells disrupted the cell homeostasis along with age. These inflammatory molecules are required for the physiological action of immune processes, which produces direct effects on neural plasticity and neurogenesis (Yirmiya and Goshen, 2011). Further, it also facilitates many forms of neuropathology associated with normal aging as well as AD (Yirmiya and Goshen, 2011). Some studies demonstrated that disruption in communication between neuron and microglia cell in aged brain could be one of the factors that precedes and initiates the increase in chronic inflammatory states underlying age-related impairments of cognition and hippocampal neurogenesis (Gemma et al., 2010). Various studies reported that cognitive impairment with age is the consequence of hypofunction of synaptic transmission due to dysfunctioning of voltage-dependent calcium channels (Tanaka and Ando, 2001). Perturbations in the functional state

of aged neurons might influence the neuronal homeostasis, makes more vulnerable to neurodegenerative disease (Dickstein et al., 2007). The presence of type II diabetes could increase the risk of AD by two-fold (Farris et al., 2003, Luchsinger et al., 2004). It has been suggested that diabetes directly influences Aβ accumulation in the brain due to hyperinsulinemia, which disrupts Aβ clearance by competing for the insulin-degrading enzyme (Selkoe, 2000, Farris et al., 2003). Since insulin can cross the blood–brain barrier, therefore peripheral insulin infusion in the aged population increases Aβ-42 levels in the CSF, a surrogate marker of Aβ clearance in the brain (Watson et al., 2003). Insulin receptors were also reported to be impaired in early stage of AD. Peripheral hyperinsulinemia may downregulate insulin transport across the blood–brain barrier due to saturation over physiological levels resulting in reduction of insulin levels in the brain (Park, 2001). Reduced insulin levels mediate the downregulation of insulin-degrading enzyme, which further affects the Aβ clearance (Watson et al., 2003). Adiponectin, leptin, resistin, TNF-α and IL-6 were also found to be associated with insulin resistance and hyperinsulinemia, which may directly or indirectly increases the AD risk (Trujillo and Scherer, 2005, Yu and Ginsberg, 2005). A meta-analysis of cohort studies analyzing type II diabetes and other glucose or insulin related disorders showed enhanced risk of AD (Profenno et al. 2009). Reger et al. (Reger et al., 2008) have been reported that the administration of intranasal insulin ameliorates the cognitive performance in early phases of AD and in patients with amnestic mild cognitive impairment (Watson et al., 2005). Observational studies implicate blood pressure as a possible contributor to late-life dementia suggesting that mid-life hypertension increases the risk of late-life dementia (Yamada et al., 2003, Elias et al., 2004, Whitmer et al., 2005). Blood pressure begins to decrease along with the onset and progression of AD, possibly related to vessel stiffening, weight loss, and alteration in the autonomic regulation of blood flow (Lithell et al., 2004, Peters et al., 2010). Cerebrovascular disease (such as hemorrhagic infarcts, small and large ischemic cortical infarcts, vasculopathies and white matter changes) and AD co-exists with advanced age and various studies indicated vascular disease as a risk factor for AD dementia (Schneider and Bennett, 2010). Pendlebury and Rothwell (Pendlebury and Rothwell, 2009) evaluated data from clinical-based cohorts and estimated recurrence of new-onset dementia to be approximately 7% after first stroke. Cdk5 involved in neuronal maturation, migration and in neuronal plasticity, was found to be significantly increased in rodent models of ischemia and hypoxia owing to hypoperfusion which further induced overexpression of BACE1 (β- site APP cleaving enzymes-1) resulting increases production of Aβ peptides (Wen et al., 2008). In addition, cdk5 may also be involved in the abnormal phosphorylation of tau, contributing to the formation of neurofibrillary tangles (Wen et al., 2007). Aberrant cdk5 activation was also found to be associated with neuronal apoptosis. This kinase might be a key protein linking neurofibrillary tangles pathology to amyloid plaques. Hyperintensities in white matter are frequently recognized by MRI in patients with

dementia, but the mechanisms by which white matter alteration contributes to cognitive decline are unclear (Wright et al., 2008). Thalamic vascular disease shows weak performance on cognitive tasks, particularly those related to the frontal and temporal lobe function, including memory storage and retrieval (Swartz et al., 2008). Several studies found that low body mass index or being underweight were apparent risk factors for dementia and age-related brain dysfunctions such as atrophy (Faxen-Irving et al., 2005). In contrast various prospective studies associated with both low and high body weight, increased the risk of AD (Waldstein and Katzel, 2006, Arbus et al., 2008). The mechanisms by which body weight affects AD are unknown, but may include effects such as insulin resistance or the co-incidence of type II diabetes (Profenno et al., 2010). Several earlier studies initially suggested that smoking lowers the risk of AD, but subsequent prospective studies showed an increased risk or no association with disease (Doll et al., 2000). A statistically significant relationship exists between smoking and AD due to an actual protective effect of nicotine, which may up-regulate the cholinergic nicotinic receptors in brain, thus enhancing the cholinergic metabolism (Whitehouse et al., 1988). Cholinergic dysfunctions are characterized by reduced levels of ACh, acetylcholine transferase and/or nicotinic acetylcholine receptors which were invariably observed in AD brains. Elevated oxidative stress caused by smoking may be opposed to the positive effect of nicotine because oxidative stress has been implicated as a putative pathogenic factor of AD (Rottkamp et al., 2000, Perry et al., 2002). Generation of free radicals caused by smoking may induce the inflammation, which further activates phagocytes that further increases the oxidative damage (Traber et al., 2000). Individuals suffering from traumatic brain injury have a higher risk of dementia as compared to those without a trauma history (Koponen et al., 2004). A meta-analysis that described the risk of dementia is higher among men with a history of traumatic brain injury (Fleminger et al., 2003). Postmortem and experimental studies suggest that after brain injury both Aβ deposition (Hartman et al., 2002, Iwata et al., 2002, Stone et al., 2002) and intraneuronal tau pathology are increased, even in younger patients (Smith et al., 2003). Various studies reported that environmental factors such as aluminum (Al), zinc (Zn), copper (cu), arsenic and iron (Fe) may participate in aging or aging-related diseases (Migliore and Coppede, 2009, Debacq-Chainiaux et al., 2012) including AD (Moulton and Yang, 2012). The involvement of aluminum (Al) neurotoxicity in AD neurodegeneration has been documented in various studies (Crapper et al., 1973). Increased Al levels in drinking water may enhance the risk for AD (McLachlan et al., 1996, Rondeau et al., 2000). It has been reported that Al participates in the formation of NFTs and neuritic plaques (Langui et al., 1990, Mera, 1991), that causes apoptosis in neurons (Bharathi et al., 2008). Another study has been suggested that Zn is a key component of amyloid plaques observed in AD patient (Sensi et al., 2009), and also facilitate the hyperphosphorylation of tau protein (Bjorkdahl et al., 2005). Zn participates in the formation of toxic small oligomer intermediates, associated with the accumulation of Aβ oligomers on the neuronal surface (Lesne et al., 2006, Dukes et al., 2008).

Deshpande et al. (Deshpande et al., 2009) have demonstrated that Zn promotes the binding of Aβ to NR2B, an N-methyl-D-aspartate receptor subunit that is responsible for the induction of excitotoxicity. It is well known that acute exposure to arsenic impairs brain functions (Freeman and Couch, 1978, Lee et al., 1991). Exposure to the arsenic results in a 4-fold increase in tau phosphorylation at many of the sites that are hyperphosphorylated in paired helical filament tau (Giasson et al., 2002). Cu is also thought to be involved in pathogenesis of AD, but still is unknown whether deficiency or overload occurs. Some studies have shown that Cu deficiency is associated with AD (Sparks and Schreurs, 2003) while another study indicated that chronic Cu exposure contributes to AD in humans (Brewer, 2009). Furthermore, some studies reported that Pb is associated with deficits in cognitive functions, has been attributed to over expression and activation of serine/threonine protein phosphatases, suggesting a possible neurotoxicity mechanism of Pb (Rahman et al., 2011). Iron accumulation has been demonstrated in cells associated with neuritic plaques in AD (Ghribi et al., 2006). Iron regulates α-secretase activity to influence APP cleavage resulting in Aβ plaque formation (Bodovitz et al., 1995).

6. Protective Factors That Reduce Risk Of Alzheimer Disease

Clinically, individuals with intellectually enriched lifestyles, such as high educational and/or occupational attainment, have a decreased risk for AD. Various studies emphasized that the education-related factors delay the onset of AD-type dementia, allow individuals to cope up more effectively with brain alteration encountered in normal aging. Having an extensive community network proved to be protective for the onset of dementia (Fratiglioni et al., 1997), and involvement in mental, social, and other productive activities was associated with decreased risk of incidental dementia (Wang et al., 2002). In contrast to the studies above, in which more cognitive reserve was associated with better outcomes, a series of studies of patients with AD reported that those with greater reserve have poorer outcomes (Geerlings et al., 1999). Diet may play a crucial role in the prevention of dementia through effects on blood pressure and other risk factors (Elias et al., 2004). Regulation on risk factors may also prevent further progression of the dementia by high intake of vegetables, legumes, fruits, and cereals; high intake of unsaturated fatty acids; a moderately high intake of fish; a low-to-moderate intake of dairy products; a low intake of meat and poultry; and regular but moderate quantity of ethanol, primarily in the form of wine and generally during meals (Trichopoulou et al., 2003, Schaefer et al., 2006, van Gelder et al., 2007). In a follow-up analysis, adequate nutrition may also be associated with decreased onset of cognitive impairment and its progression from mild to severe cognitive deficits (Scarmeas et al., 2009). Trans-unsaturated fats were associated with a three folds higher risk of developing AD, whereas the more intake of n-6 polyunsaturated fats and monounsaturated fats decreased AD risk (Morris et al., 2003). Exercise can increase learning ability in both young and aged animals (van Praag et al., 1999) through the activation of brain plasticity mechanism, rejuvenate neuronal circuits (Cotman and Berchtold,

2002), promote brain vascularization and accelerate neurogenesis (van Praag et al., 1999). It may also enhance neuronal survival and resistance to brain insults (Carro et al., 2001), reduce inflammation (Reuben et al., 2003), elevated levels of brain derived neurotrophic factor, mobilize gene expression profiles that would be suggestive of ameliorating brain plasticity (Cotman and Berchtold, 2002).

7. CONCLUSION:

There are still no effective treatments to prevent, halt, or reverse Alzheimer's disease. Studies demonstrate that the disease has multiple causes. Interdisciplinary approaches combining biochemistry, molecular and cell biology, and transgenic modeling have revealed some of its molecular mechanisms. Progress in chemistry, radiology, and systems biology is beginning to provide useful biomarkers, and the emergence of personalized medicine is assured to transform pharmaceutical development and clinical trials. However, investigative and drug development efforts should be diversified to fully address the multifactoriality of the disease.

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