Pathophysiological Features of Alzheimers Disease: A Review

Prabhjot Kaur

University Institute of Pharma Sciences, Chandigarh University, Gharuan, Mohali, Punjab-140413, E-mail: prabhrozia28@gmail.com

Address for correspondence: Ms. Prabhjot Kaur, Assistant Professor, University Institute of Pharma Sciences, Chandigarh University, Gharuan, Mohali, Punjab-140413. *E-mail: prabhrozia28@gmail.com*

Abstract

Alzheimer's disease (AD) was depicted firstly by Alois Alzheimer in 1906 and was renamed later by Emil Kraepelin (Moller *et al*., 1998). It is characterized by progressive deterioration of memory. Many factors contribute to pathophysiology of Alzheimers disese which have been described using several hypotheses. This review gives a brief outline on the hypotheses involved behind the pathophysiology of the disease.

Introduction

AD is a neurodegenerative disorder characterised by progressive degeneration of the hippocampal and cortical neurons that leads to impairment of memory and cognitive ability (Albert *et al*., 2011). Histopathological changes existing in AD comprise of deposition of amyloid-β (Aβ) peptides extracellularly forming senile plaques (SP) and neurofibrillary tangles (NFT) of hyperphosphorylated tau formation intracellularly in the brain which are commonly regarded as the pathological features of the disease (Dong *et al*., 2003). Central to the degenerative process is the development of plaques and neurofibrillary tangles, although many other abnormalities also occur during the progression of AD. The different hypothesis that describe pathogenesis of AD includes β- amyloid hypothesis, Tau protein neurofibrillary tangles hypothesis, oxidative stress hypothesis, cholinergic hypothesis, nitric oxide theory, glutamate hypothesis, chronic inflammation hypothesis, cholesterol hypothesis and other neurotransmitter deficiency.

Amyloid Cascade hypothesis

Evidences indicate that in the amyloid cascade hypothesis gradual aberrant accumulation of Aβ initiates a complex, multistep cascade of neuropathological events that leads to development of both forms of AD i.e. familial AD and sporadic AD (Hardy *et al*., 2002). Aβ is a 4 kDa protein in which micro heterogeneity in amino acid sequence occurs in many biophysical states. Under physiological condition, most of Aβ peptide is in the form of Aβ1-40 residues while less than 5% of the newly generated Aβ ends at residue 42, forming long form of Aβ1-42 peptide which is more prone to aggregation than Aβ1-40 form and is initiating formation of pathological oligomers, fibrils and plaques (Gandy, 2005). Oligomers and fibrils appear to be the most potent neurotoxins while the end stage senile plaques are relatively inert. Previously, it was proposed that extracellular Aβ aggregates in the form of senile plaques are the main pathogenic species but recently it has been recognized that intraneuronal accumulation of the oligomeric non-fibrillar Aβ form precedes and contributes to the extracellular pathology (Gimenez *et al*., 2007). Aβ is generated from mature APP which is a membrane spanning glycoprotein expressed in brain and CNS and is encoded by APP located on chromosome 21 (Shahani *et al*., 2014). APP is metabolized by two pathways in a competitive manner, α-secretase pathway resulting in non-toxic products, and β-secretase leading to products which may be substrate for γ-secretase generating Aβ1-40/42 (Gandy, 2005). In physiological condition, the production and clearance of Aβ are balanced however in pathological case of increased production of total Aβ or increased Aβ1-42/Aβ1-40 ratio or in case of decreased Aβ degradation/clearance, Aβ1-42 levels are elevated. The production of highly aggregatable Aβ1-42 form can be enhanced by mutations happening in three different genes, APP, PS1 and PS2 that cause familial AD whereas reduced Aβ clearance can appear due to decreased expression of enzyme responsible for its removal, the insulin degrading enzyme (IDE), as found in sporadic AD (Gandy, 2005). In spite of the primary cause and clinical form of AD, the amyloid cascade hypothesis proposes that both conditions lead to accumulation of Aβ1-42, oligomerization and plaque formation, which further initiates a whole range of pathological cascade effects; microgliosis and astrocytosis, inflammatory response, oxidative stress, neuronal/neuritic dysfunction, cell death, neurotransmitter deficits, and finally, memory loss. (Gimenez *et al*., 2007)

Neurofibrillary Tangles and Tau Protein

Microtubules are essential components of neuronal cell structure; they deliver nutrients and assist in synaptic transmission along the length of the neuronal axon (Hardy *et al*., 2002). During AD pathogenesis, tau protein becomes hyperphosphorylated and disrupts their bonds to microtubules. Thus microtubule structure collapse and destroy the neuron's transport and communication system leading to neuronal cell death (Spillantini *et al*., 2013). Tau is a protein associated with microtubules that functions to stabilize the microtubules. There are more than 30 distinct mutations or pathogenic nucleotide substitutions in the gene for tau (Goedert *et al*., 2005). These mutations may lead to degeneration of neurons by different mechanisms like alterations in tau splicing, leading to abnormal patterns of tau isoform expression, prevention of tau's ability to bind to and stabilize microtubules and enhanced fibrillation of tau (Iqbal *et al*., 2014). Neurofibrillary tangles result from the neuronal microtubule destruction caused by the modification of tau (Xie *et al*., 2014). It is the distribution within brain and their co-occurrence with plaques that make NFTs a distinctive AD hallmark.

Cholinergic Hypothesis

Acetylcholine is an important neurotransmitter in brain regions involving memory. In AD, acetylcholine abnormalities are the most prominent of neurotransmitter changes, primarily because of the reduced activity of choline acetyltransferase (an enzyme involved in acetylcholine synthesis). By late stage AD, the number of cholinergic neurons is markedly reduced, particularly in the basal forebrain (Tiraboschi *et al*., 2002)

Acetylcholine binds to two postsynaptic receptor subtypes: muscarinic and nicotinic. Presynaptic nicotinic receptors influence the release of neurotransmitters important for mood and memory (i.e. acetylcholine, glutamate, serotonin and norepinephrine (Molas *et al*., 2014) Loss of nicotinic receptor subtypes in the hippocampus and cortex has also been observed in AD (Steven *et al*., 2009).

Glutamatergic and Excitotoxic Hypothesis

Glutamate is the primary excitotoxic ubiquitous neurotransmitter in central nervous system and is involved in essentially all CNS functions (Rogawski *et al*., 2003). Glutamatergic neurotransmission is virtually involved in learning, memory and the shaping of neuronal architecture. AD brains contain fewer NMDA receptors (a type of glutamate receptors) than normal brains (Sze *et al*., 2001). Excessive or unregulated glutamate signalling is also found in AD brains that eventually lead to neurotoxicity (Danysz *et al*., 2000). This is not caused

by excess glutamate production or release, but by postsynaptic receptor defects that result in sustained low level activation (Siegal, 2005). Continuous activation of glutamate NMDA receptors lead to chronic calcium influx that interferes with normal signal transduction and over time, increase production of APP. Increase in APP is associated with higher rate of plaque development, hyperphosphorylation of tau protein and neuronal toxicity (Abramov *et al*., 2004).

Oxidative Stress Hypothesis

Oxidative stress plays a central role in the pathogenesis of AD leading to neuronal dysfunction and cell death (Jomova *et al.,* 2010). The increased level of oxidative stress in the AD brain is reflected by increased protein and DNA oxidation, enhanced lipid peroxidation, decreased level of cytochrome c oxidase and advanced glycosylation end products (Fleming *et al*., 2012). Oxidative stress occurs when there is an imbalance between the production and quenching of free radicals from oxygen species. These reactive oxygen species (ROS) play a role in many chronic diseases including mitochondrial diseases (Enns *et al*., 2012), neurodegenerative diseases (Skulachev *et al*., 2009), renal disease (Madeo *et al*., 2013), arteriosclerosis (Morre *et al*., 2011; Tsai *et al.,* 2011), diabetes (Karunakaran *et al*., 2013) and cancer (Mc carty *et al*., 2010). The process of aging is also associated with increased oxidative stress (Kritchevsky *et al*., 1996). During pathological redox reactions ROS can denature biomolecules such as proteins, lipids and nucleic acids. This can initiate tissue damage via apoptosis and necrosis. Oxidative stress can also influence DNA methylation which regulates gene expression (Fleming *et al*., 2012).

Nitric oxide hypothesis

NO plays an important role in brain physiological processes like neuromodulation, neurotransmission and synaptic plasticity and the pathological processes such as neurodegeneration and neuroinflammation (Calabrese *et al*., 2004). Synthesis of nitric oxide takes place by the enzyme nitric oxide synthase (NOS) which is present in three isoforms: endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS) (Calabrese *et al*., 2004). In AD, all three isoforms are expressed and involved in pathogenesis by various mechanisms including oxidative stress and activation of intracellular signalling mechanisms (Luth *et al*., 2001). iNos has been proved to be a major contributor for initiation of CNS degenerative conditions by producing excessive NO which generates reactive nitrogen species (RNSs) (Lunderberg *et al*., 2008). NO is not stable thermodynamically and tends to

react with other molecules resulting in oxidation, nitrosylation of proteins which further affects the cellular mechanisms such as activation of guanylate cyclase (Pacher *et al*., 2007). NO can generate peroxynitrite ($ONOO^-$) by reacting with super oxide (O^{2-}) which is a potent oxidant and primary component of nitroxidative stress (Farkas and Luiten., 2001). When peroxynitrite is present in high amount it can undergo hemolytic and heterolytic cleavage to produce highly reactive oxidative species and secondary components of nitroxidative stress (NO_2^+, NO_2 and OH). The resulting nitroxidative stress initiate redox reactions which lead to apoptosis and produce cytotoxic effects on neurons and endothelial cells (Guix *et al*., 2005).

Chronic inflammation hypothesis

Microglias are the predominant immune cells which are primarily involved in inflammatory process in the central nervous system (CNS). In AD not only neurons get affected but microglias also get involved in inflammatory responses to injury and infection (Amor *et al*., 2010). Increased amount of inflammatory mediators has been seen in post-mortem brain of patient suffering from alzheimer's disease (Morimoto *et al*., 2011). Aβ- plaques, NFTs and damaged neurons may stimulate inflammation. It is widely accepted that β amyloid triggers pro-inflammatory reactions of microglia. Microglia gets activated and release cytotoxic molecules such as cytokines, proteinases, reactive oxygen species (Wilcock, 2012). Cytokines then promotes apoptosis of neurons and oligodendrocytes and induce myelin damage, by stimulating inflammatory processes (Ramesh *et al*., 2013). Inflammation in AD can also be observed by increased prostaglandins which are produced by COX-1 and COX-2 (Kotilinek *et al*., 2008).

Cholesterol playing a role in AD

Human brain bears highest amount of cholesterol than any other human body part. Brain comprises of 25% of body's unesterified cholesterol whereas CNS account for only 2% body mass (Dietschy *et al*., 2004). From in vivo and in vitro data it is suggested that with increase and decrease in cholesterol level Aβ production also increase and decrease (Ghribi *et al*., 2006). Any defect in its metabolism is associated with apolipoprotein E (APOE) genetic risk, Aβ production and aggregation and vasculopathy of alzheimer's disease. Cholesterol decreases membrane lipid turnover thus promoting Aβ generation, aggregation and decreasing its clearance from brain (Marwarha *et al*., 2010).

Deficiency of Neurotransmitters

Serotonin is known to be important in affective illness such as depression and anxiety and reduction in serotonin may lead to AD (Messner *et al*., 2008). Study has indicated that alteration in serotonin receptors and transporters leads to declined cognition. Norepinephrine neurons are lost in AD and its level is also seen to be reduced (Heneka *et al*., 2002). In addition to AD, norepinephrine also plays a role in some behavioural symptoms of dementia such as aggregation, agitation and psychosis respectively (Herrmann *et al*., 2004).

Conclusion

Alzheimers disease is the leading cause of deaths worldwide. Understanding the mechanisms behind the disease is imperative to look after the treatment approaches towards it. Many hypotheses have been proposed depending upon the cause of disease. Among all amyloid β deposition and neurofibrillary tangles formation have been proposed as the major pathophysiological mechanism behind the disease. Neurotransmitters deficiencies, oxidative and nitro oxidative stress, cholesterol and neuronal inflammation also contribute to Alzheimers pathology to a remarkable extent.

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