Neurobiological Mechanisms Involved in the Pathogenesis of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is one of the many neurodegenerative disorders which is characterized by progressive loss of neurons due to the extracellular accumulation of misprocessed and aggregated amyloid beta (Aβ)-plaques and appearance of intracellular neurofibrillary tangles containing hyperphosphorylated tau protein which ultimately leads to loss of synapses and cognitive decline. Aggregation of amyloid beta (Aβ)-plaques is the hallmark of AD. Aβ is the proteolytic cleavage product of amyloid precursor protein (APP) which is cleaved by β- and γ-secretase enzymes into $A\beta_{1-42}$ and $A\beta_{1-40}$ isoforms where the former readily aggregate more rapidly than the latter. Tau protein, the major component of neurofibrillary tangles, is a microtubule-associated protein which is usually soluble but becomes insoluble as it forms tangles of oligomers which is thought to be initiated by toxic concentrations of Aβ-plaques. Recent studies have shown that some genetic mutations, genomic instability and other factors like head injuries, depression, imbalanced diet and age progression all contribute to the development and progression of AD. The most important gene, for which a role in ageing-related late-onset AD has been established since a decade, is APOE where different variants of the gene differently predispose the individuals to the development of AD. In this chapter, we will be highlighting well-established molecular and cellular mechanisms behind the development and progression of AD, the regions in the brain that are affected and the known genetic basis behind the onset and pathophysiology of AD. In the later section, we will address some of

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the current and prospective therapeutic interventions based on our current understanding of neurobiological mechanisms underlying AD.

Keywords
Alzheimer's disease · Aβ-plaques · Neurodegeneration · Cytotoxicity · Neuroinflammation tau protein · Axonal transport

13.1 Introduction

Alzheimer's disease is a type of progressive neurodegenerative disorder characterized by dementia, which constitutes a group of symptoms including problems in learning and memory, defects in language, speech and other cognitive functions that affect individual's ability to carry out his/her routine activities (Fig. 13.1) (Association, A.s 2018). AD was first described almost a century ago by Dr. Alois Alzheimer (German psychiatrist) at a conference of Bavarian Psychiatrists, where Dr. Alois Alzheimer presented an intriguing case of a patient named Auguste D, a lady in mid-50s, suffering from dementia, paranoia and many other psychological changes. Dr. Alois, based on autopsy reports, explained that there were lesions in and around some specific nerve cells of her brain. With the advent of an electron microscope, which allowed the scientists to magnify the neuronal cells up to a

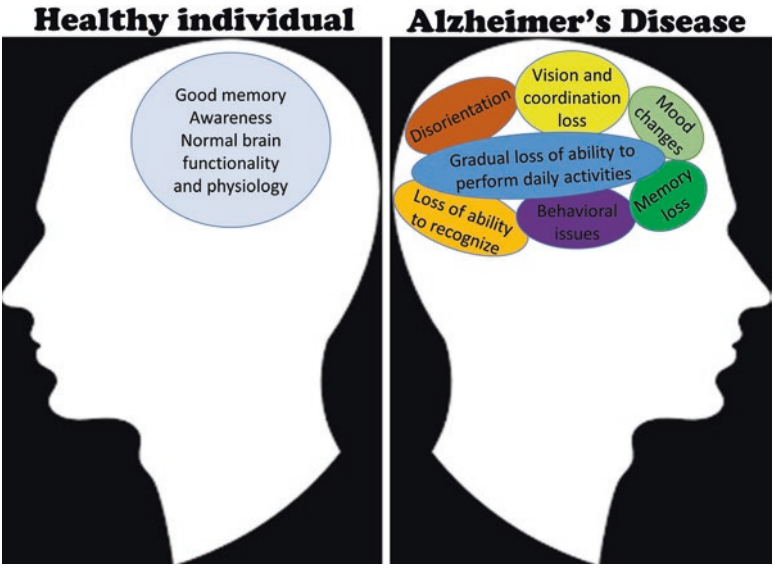

Fig. 13.1 Comparison of brain functionality and physiology of healthy and Alzheimer's disease individual. Alzheimer's disease is characterized by progressive loss of neurons affecting normal brain physiology. Alzheimer's patients suffer from disorientation, memory and behavioural loss and impairments in coordination and suffer an inability to perform day-to-day activity

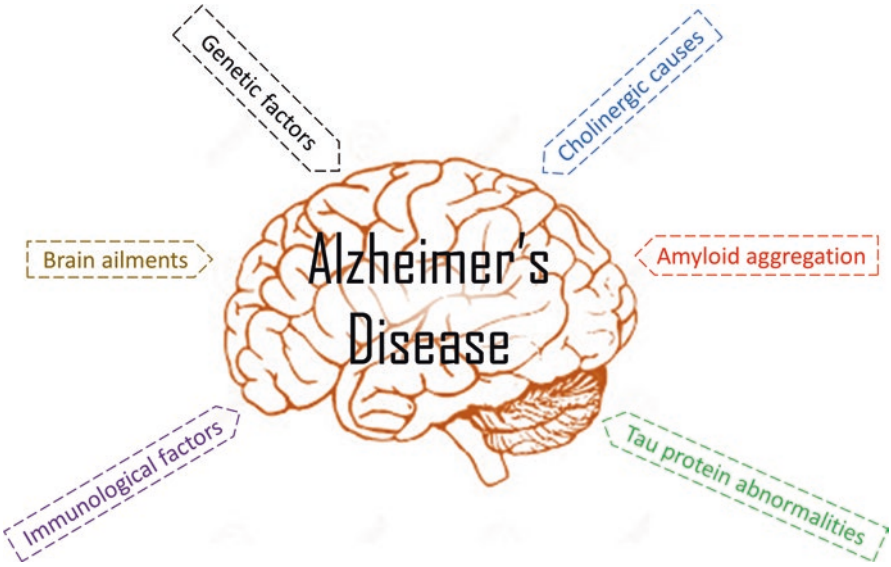

Fig. 13.2 Pathophysiological causes in Alzheimer's disease. Alzheimer's disease could be caused due to a number of underlying biological factors. While aggregation of amyloid beta protein and tau protein abnormalities are believed to be the major contributing factors, other factors involving gene mutations, inflammatory responses and decline in neurotransmitters levels such as acetylcholine may also contribute to the disease onset and progression

million times, further paved the way for understanding the deeper aspects of Alzheimer's disease. By the 1980s protein components of senile plaques and neurofibrillary tangles, which are the hallmarks of Alzheimer's disease, were identified along with the identification and characterization of β-amyloid and microtubule-associated tau proteins (Sisodia and Tanzi 2007).

Current understandings suggest that the causative agents behind Alzheimer's disease vary from brain ailments, cholinergic factors to cellular as well as molecular causes such as genetic susceptibility, protein aggregation/dysfunction and inflammatory factors (Fig. 13.2). In the USA alone, it is estimated that 5.7 million people suffer from Alzheimer's disease, and the number is projected to grow to around 13.8 million by the year 2050. Data recorded from official death certificates in the year 2015 showed that 110,561 Americans had died due to Alzheimer's disease making it the sixth leading cause of deaths in the USA (Association, A.s 2018). Several reports suggest that there is a correlation between Alzheimer's disease and age-specific occurrences which in the last three decades have significantly decreased (Prince et al. 2016; Satizabal et al. 2016; Matthews et al. 2013). Moreover, some studies have found that there is a higher rate of prevalence and incidence of Alzheimer's-related dementia in African-American minorities as compared to European-Americans (Steenland et al. 2016). Thus, an understanding of the genetic, cellular and molecular causes and risk factors of Alzheimer's disease would prolong the life of the patients suffering from it and would pave the way for its early detection so that it can be treated at early stages.

Alzheimer disease is a central nervous system pathology but its consequences and manifestations extend beyond the brain. Alzheimer's pathology affects many brain regions involved in higher brain functions like speech, cognition, decision-making, etc. Moreover, various types of neurons especially acetyl-cholinergic and glutamatergic are affected in the pathophysiology of AD. There is widespread neuronal degeneration in AD which is caused by senile plaques of aggregated amyloid β-protein and neurofibrillary tangles (NFTs) mainly composed of hyperphosphorylated microtubule-associated tau protein, the two histopathological hallmarks of the disease (Sisodia and Tanzi 2007) which finally causes the loss of synapses and neurons leading to gross atrophy of the patient's brain. Although these two hallmarks of AD differentially yet significantly contribute to the development of AD, neurobiologists are divided in their opinion on whether beta-amyloid cascade initiates AD (beta-amyloid hypothesis) or it is the tau protein which gets aggregated due to hyperphosphorylation and misfolding thereby initiating the disease (Mudher and Lovestone 2002). Nevertheless, amyloid beta (Aβ)-protein aggregation and senile plaque formation is still considered to be the distinct and early pathological hallmark in early-onset AD which further induces the activation of sequential events of cell death by hyperphosphorylated tau protein in the form of NFTs (Sun et al. 2015a). In the amyloidogenic pathway, amyloid plaques are formed due to excessive production and aggregation of Aβ-peptide due to proteolysis of the amyloid precursor protein (APP) by α-secretase and β-secretase enzymes respectively. Mutations in the APP gene have been found as the prominent causes responsible for the development of familial AD (Ohshima et al. 2018). Moreover, mutations in other genes encoding for enzymes of APP processing complex like presenilins (PS-I/II), α-secretase and β-secretases cause the impairments in APP processing leading to deleterious accumulation of toxic Aβ-peptides which ultimately cluster into soluble oligomers initiating cell toxicity (Chow et al. 2010; Kelleher and Shen 2017). Moreover, microtubule-associated protein tau when hyperphosphorylated aggregates into NFTs leading to cellular degeneration because of impairments in cell signalling and axonal transport processes causing brain atrophy. Various cell signalling pathways like Wnt/β-catenin and MAPK pathways act downstream of Aβ and tau-mediated effects finally modulating cellular physiology and initiating apoptosis, thereby augmenting neurodegeneration.

13.2 Brain Areas Affected in AD

The human brain contains around a hundred billion nerve cells which collect, process and transmit the information through electrical and chemical communications. The central nervous system (CNS) in higher vertebrates is divided into four distinct parts which include the cerebrum, cerebellum, diencephalon and brainstem. The average weight of an adult human brain is approximately 1300–1400 grams and is composed mainly of neurons and glial cells. Furthermore, different glial cells such as astrocytes, oligodendrocytes and microglia carry out specialized functions like support, nutrition and immune functions within the CNS. Different brain regions have

diverse functions and are affected differently in various CNS pathophysiologies as suggested by studies utilizing functional magnetic resonance imaging (fMRI), nuclear magnetic resonance (NMR) imaging and post-mortem autopsy reports.

Some brain regions have been found to be more susceptible to the pathophysiological and metabolic features specific to the AD (Liang et al. 2008). The major brain areas where changes in gene expression, metabolic alterations as well as Aβ-plaque formation have been found include the hippocampus, entorhinal cortex, superior frontal gyrus, middle temporal gyrus, posterior cingulate cortex and primary visual cortex, among others (Liang et al. 2008; Valla et al. 2001; Vogt et al. 1992; Li et al. 2012; Cui et al. 2007). Although AD pathology does not affect multiple brain areas simultaneously, gene expression analysis and brain imaging studies have revealed that AD progressively affects the regions one after the other (Thal et al. 2002). AD has its various stages of progression like stage 1 with no impairment, stage 2 with very mild impairment, stage 3 with a mild decline of cognition, stage 4 and 5 with the moderate decline with difficulty in arithmetic calculations to short-term memory loss and significant confusions. In the final stages of 6 and 7, there is severe to the very severe decline of cognitive abilities with reduced ability to respond to the environment and nearing death.

Convincing reports came out in the late 1990s that neuronal atrophy in selective brain regions was highly correlated with the cognitive deficits characteristic of AD. One of the brain regions called the medial temporal lobe (MTL) show the highest density of histopathological markers akin to AD including Aβ-amyloid plaques and neurofibrillary tangles of tau protein (Smith 2002; Jobst et al. 1992). In longitudinal studies of Alzheimer's patients, it was found by various imaging techniques and autopsies that their fluid-filled brain ventricles were enlarged as the brain tissues are progressively lost along with enhanced neuropsychological deterioration in these patients (Luxenberg et al. 1987). Significantly higher loss of tissues from MTL was reported by various CT studies done in AD patients with a rate of 15% of MTL tissue loss per year, therefore, shrinking the MTL rapidly thereby confirming the higher susceptibility of MTL to such catastrophic histopathological events of AD pathology (Jobst et al. 1994). Moreover, in normal healthy subjects, MTL shrunk only minutely (1/10th of the rate as in AD) thereby pointing towards a conclusion that AD cannot be solely occurring due to the rigorous or accelerated ageing but it must be the consequences of a disease process and associated pathology (Smith 2002). Furthermore, reports of serial MRI scans of AD patients suggest that regional atrophy from MTL nucleus spreads progressively to other brain areas in a highly specific manner engulfing most of the brain (Scahill et al. 2002).

As the hippocampus, which is the most important brain area involved in learning and storing memory, is a part of MTL, it is imperative that neuronal atrophy and synapse loss from these important brain areas involved in higher cognitive functions result in cognitive dysfunctions in AD patients. Hippocampal subfields like CA1, CA3, CA2 and dentate gyrus have been differently implicated in AD pathogenesis by various studies so far. High-resolution MRI imaging of AD patients at 3 teslas (magnetic flux density) have shown that CA1 anterior-dorsal region of the hippocampus is severely affected by Alzheimer's-associated atrophy but not in the normal

ageing process (Smith 2002). Some studies have suggested that a specific part of the hippocampus called cornu ammonis (CA), of a normal elderly human, occupies about 1.5 ml volume and harbours about nine million neurons, which shrinks by 66% of the normal volume and the number of neurons in this area of hippocampus significantly drops by 84% in the terminal stage of AD (Bobinski et al. 1996).

Another important brain area which is severely affected in the early stages of AD is the brainstem nucleus locus coeruleus (LC). In the past decades, various studies provided strong evidence by analysing post-mortem autopsy reports of brain samples obtained from AD patients, concluding that in Alzheimer's disease, there is a predominant neuronal loss within LC (German et al. 1992). Moreover, reports suggest that LC is the brain region where the early formation of neurofibrillary tangles occurs in young adults and aged people which serves as the platform for further propagation of the disease (Braak and Del Tredici 2011; Grudzien et al. 2007). Interestingly, reports suggest that in Alzheimer's pathological condition, LC neurons show ectopic expression of cell cycle-regulating proteins like proliferating cell nuclear antigen (PCNA), cyclin-dependent kinase-4 (CDK-4), cyclin D and cyclin B1 reminiscent of cell death by atrophy (Busser et al. 1998). Additionally, one study reports that LC neurons are lost more extensively than cholinergic cells from nucleus basalis of Meynert and corroborated better with the duration of the Alzheimer's disease (Zarow et al. 2003), pointing to the sensitivity of LC neurons to the pathological insults than other brain regions. In addition, LC-NE (norepinephrine) suppresses neuroinflammation via modulation of microglia. Microglia are key players in neuroinflammation-mediated neurodegeneration in AD by suppressing Aβ-42-induced cytokine and chemokine release and NE-activated microglia phagocytose Aβ, thereby preventing their accumulation (Heneka et al. 2010). Therefore, neuronal loss from LC declines the NE content in the brain which might interfere in Aβ-42 clearance by activated microglia leading to its accumulation up to the toxic levels (Chalermpalanupap et al. 2013). LC degeneration-induced NE reductions in the brain promote pro-inflammatory responses while subjugating the anti-inflammatory responses and reducing the clearance of Aβ-42 poses a triple threat in the development of AD (Chalermpalanupap et al. 2013). However, it is not known whether neuronal loss and a concomitant decline in NE in the brain precedes AD pathology or is followed by the onset of AD pathology.

Amygdala, which is a part of the limbic system located in the temporal lobe of the brain, is mainly responsible for emotional and fearful information processing and regulates the fear-based responses, memory and survival instincts. Regression analysis studies have shown that in mild cognitive impairment early stage of AD, amygdala atrophy was severe and comparable to that of the hippocampus (Poulin et al. 2011). Moreover, in various post-mortem reports of AD patients, it has been well documented that β-amyloid senile plaques, as well as neurofibrillary tangles, were significantly present in amygdala along with the prominent loss of amygdalar neurons (Herzog and Kemper 1980; Scott et al. 1991, 1992). However, the comparative studies of neuronal loss and atrophy between amygdala and hippocampus are to some extent inconsistent, but nevertheless, amygdalar atrophy in AD contributes to the progression of neuropsychiatric and emotional disturbances in AD patients.

Recent advances in medical science especially live imaging techniques like fMRI and positron emission tomography (PET) have helped the doctors to locate the brain regions having atrophy in living patients unlike in the past where after death the autopsy reports were main confirmatory evidence of AD. Moreover, in some typical cases of rare AD forms, the atrophy may not begin from hippocampus and memory is not affected in the early stages. One form of atypical AD displays posterior cortical atrophy where early signs of atrophy appear in occipital and parietal lobes which affects the visual and spatial awareness abilities of the patient. Patients usually find it difficult to read or identify objects even if their eyes are healthy. It is still not understood as to why and how the origin of atrophy in the brain differs among individual patients and why the course of progression pattern varies. Future research about coordinated brain areas and their functions could provide us with clues about these unresolved mysteries.

13.3 Cellular Mechanism of Amyloid Beta (Aβ)-Plaque Formation

The cellular, as well as genetic factors contributing to the pathophysiology of AD, have been rigorously investigated, but the molecular mechanisms underlying the progression and epistemology of the symptoms of the disease remained a haunting mystery for scientists so far. As per the reports and research conducted so far in in vitro as well as on various animal models of AD and human autopsies, β-amyloid plaques are said to be the central players involved in the pathogenesis of AD (Fig. 13.3). The amyloid cascade hypothesis was first time proposed by Hardy and Allsop in 1991, and it is still the best explanatory hypothesis supported by a large number of experiments (Carrillo-Mora et al. 2014). According to this hypothesis, the starting events which drive the progression of neural damage in AD include the production and excessive accumulation/aggregation of Aβ-peptides in intracellular as well as in extracellular spaces (Hardy and Allsop 1991; Eckman and Eckman 2007). Since amyloid precursor protein (APP) is the integral membrane receptor glycoprotein of unknown function present on neurons and from which β-amyloid peptides are formed after proteolysis by β-site APP cleaving enzyme-1 (BACE-1) and γ-secretase enzymes, it has remained a prominent target for AD-related research. Amyloid-β (Aβ) peptides formed after proteolysis of APP are mostly short peptides containing 38–43 amino acids. APP, the transmembrane protein, belongs to an evolutionarily conserved protein family which also include APP-like protein-1 (APLP-1) and APLP-2 proteins (Wasco et al. 1993).

Physiologically, cellular APP processing takes place through two major pathways known as amyloidogenic and non-amyloidogenic. Non-amyloidogenic pathway results in the formation of soluble extracellular fragment known as sAPPα after the extracellular domain of APP is cleaved. The extracellular domain of APP is cleaved by α-secretase enzymes in association with disintegrin and metalloproteinases (ADAM, which also includes ADAM 9, ADAM 10 and ADAM 17) all of which exhibit neuroprotective and neurotrophic activities within the CNS (Pietri et al. 2013;

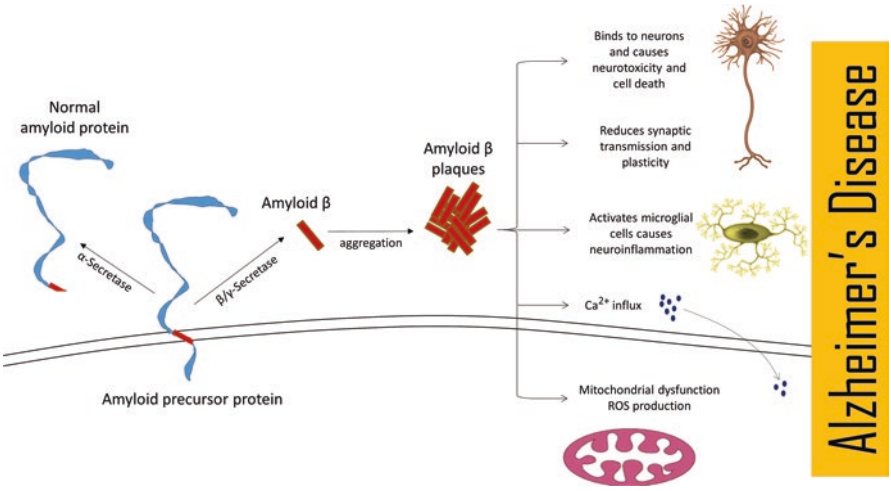

Fig. 13.3 Amyloid beta protein aggregation leads to Alzheimer's disease. According to the most popular hypothesis, amyloid beta aggregation is the major underlying factor behind Alzheimer's disease. Amyloid beta arises by the proteolysis of amyloid precursor membrane protein at β site. Amyloid beta peptides then self-aggregate by direct interaction forming plaques causing cytotoxicity. Generation of these amyloid beta plaques then triggers a number of pathophysiological responses that lead to the development of Alzheimer's disease

Edwards et al. 2008). Next, γ-secretase enzymes residing at the cytosolic side of plasma membrane act on APP resulting in the formation of an intracellular fragment known as APP intracellular C-terminal domain (AICD) (Chang and Suh 2010). However, in the amyloidogenic pathway which is central to the pathogenesis of AD, APP is cleaved by β-secretase enzyme usually called BACE-1, which upon cleavage generates two fragments sAPP-β (N-terminal) and CT99 (Zhang et al. 2012; de Paula et al. 2009). Aβ-peptide is ultimately found to be the main constituent of the senile plaques which are formed by the proteolytic cleavage of APP (Wilquet and De Strooper 2004). Among Aβ-peptides produced after the cleavage of APP, the peptides whose carboxyl terminals end with 40th and 42nd amino acid of APP are designated as Aβ 1–40 and Aβ 1–42, respectively, and these are main constituents of senile plaques responsible for neuronal cell death and are the highest markers in the brain of AD patients (Roher et al. 1993; Miller et al. 1993). Further, CT99 fragment is again cleaved by γ-secretase enzyme complex which also includes nicastrin, presenilin 1 and 2, anterior pharynx defective-1 and presenilin enhancer-2, all of which are located in the plasma membrane as a complex of protein-cleaving enzymes called intra-membrane-cleaving proteases (I-CLiPs). The enzyme, β-secretase or BACE-1, acts on specific β-sites of APP containing aspartic acid-1 and glutamic acid-11 creating C-terminal membrane-embedded fragment of C89 or C99 (Vassar et al. 1999; Gouras et al. 1998). Elevated activity of β/γ-secretase produces enhanced levels of sAPP-β and C99 which are further processed by γ-secretase, ultimately resulting into the formation of Aβ 1–40/Aβ 1–40 and AICD which consequently leads to plaque

formation and apoptosis via activation of caspase-6 enzymes (de Paula et al. 2009; Gupta and Goyal 2016). Because of two additional amino acids alanine and isoleucine present in Aβ 1–42, these peptides become more hydrophobic and vigorously aggregate than Aβ 1–40 peptides (Grimm and Hartmann 2012). All the four components of an intra-membrane complex of γ-secretase mentioned above are vital for processing of APP, but the major contribution to AD pathology comes from presenilins as more than 150 point mutations of autosomal type within these presenilin genes have been linked to familial early-onset AD (Duering et al. 2005; St George-Hyslop and Petit 2005). Furthermore, these point mutations in presenilin genes, especially PS-1, have been found to accelerate the generation of Aβ 1–42 type of peptides by the gain of deleterious functions (Kowalska 2004; Duff et al. 1996).

All these proteolytic activities by intra-membranous γ-secretase complex acting on APP are shown to occur at special membrane microdomains called lipid rafts which are cholesterol and sphingolipid-enriched membrane patches where γ-secretase subunits reside as well. Apart from this, these lipid rafts also serve as a platform for various signal transduction pathways as well as cell adhesion and protein trafficking (Grimm and Hartmann 2012; Vetrivel et al. 2004, 2005). Production of Aβ-peptides is a normal physiological process within the CNS, and in AD, the balance between the rate of Aβ-peptide production and clearance is disturbed which results in aggregation of amyloid plaques due to excessive accumulation of Aβ 1–40 and Aβ 1–42 peptides which ultimately leads to neurotoxicity, oxidative stress, microglial activation and alteration of protein kinase/phosphatase activity which eventually leads to cellular degeneration (Fig. 13.3) (Wildsmith et al. 2013; Selkoe and Hardy 2016; Sun et al. 2015b). The exact mechanisms behind the excessive production or lower rate of clearance of Aβ-peptides and how do these senile plaques induce neuronal cytotoxicity still remains to be elucidated. However, recent reports have provided important clues about the nature of these Aβ-peptides and their interaction with other biomolecules within the cells.

13.3.1 Aβ-Induced Cellular Cytotoxicity

As mentioned earlier, the functions of Aβ-peptides under normal physiological conditions are not well understood and these peptides seem to be present even in healthy individuals and are produced throughout life as normal metabolic or cellular by-products. However, some of the animal model studies fail to assign any particular loss of physiological function to the absence of Aβ-peptides (Sadigh-Eteghad et al. 2014; Luo et al. 2003). Interestingly, exogenously applied Aβ 1–40 peptides to cell cultures at picomolar ranges have displayed neurotrophic and neuroprotective roles (Yankner et al. 1990; Plant et al. 2003). Nevertheless, it is beyond doubt that aggregated Aβ-peptides mainly constituting peptides below 50 amino acid residues forming the amyloid senile plaques are the major hallmarks of the AD pathophysiology impairing synaptic plasticity and memory (Shankar et al. 2008; Kayed et al. 2003). As the disease progresses, the ratio of Aβ 1–42/Aβ 1–40 increases in the brain mainly due to either higher rate of Aβ 1–42 formation or reduced levels of Aβ 1–40 and other

soluble oligomers of Aβ-peptides which results in the formation of senile plaques as Aβ 1–42 are more toxic because of the higher rate of aggregation (Glabe 2005; Walsh and Selkoe 2007). Additionally, Aβ-plaques also interact with some of the cell membrane receptors and other proteins inducing programmed cell death and hence immensely contribute to the neurodegeneration processes (Fig. 13.3) (Zhu et al. 2015; Small et al. 2001). Looking at the molecular levels, oligomerization of Aβ-peptides caused by misfolding of APP-derived peptides could generate cellular ionic imbalances leading to various aspects of pathophysiological outcomes of AD (Lal et al. 2007). This effect is likely mediated by either reactive oxygen species (ROS) generated by Aβ-peptide aggregation or the interaction of these plaques with cellular membranes and associated receptors/ion channels (Fig. 13.3) (Lal et al. 2007).

Interestingly, Aβ-peptides behave as a double-edged sword because on one side, they display neurotrophic and neuroprotective effects and antagonistically they cause diverse toxic effects (Atwood et al. 2003). These differential effects of Aβ-peptides within CNS might be determined by the relative ratio of Aβ 1–40/Aβ 1–42, and it is not well understood how these peptides switch their functionality from being neurotrophic like increasing neurogenesis in the hippocampus and enhancing memory consolidation to being toxic, depressing Long-term potentiation (LTP) and initiating apoptosis (Lopez-Toledano and Shelanski 2004). Some studies have suggested that it is the imbalance between its excessive production and a lower rate of clearance from CNS which makes Aβ-peptides the most toxic by-products impairing other vital cellular signalling processes, altering membrane permeability, inducing excitotoxicity via interaction with many neurotransmitter receptors and creating a flux of ROS with protein oxidation (Carrillo-Mora et al. 2014; Lin et al. 2001; Canevari et al. 1999; Rosales-Corral et al. 2004a; Butterfield et al. 2007). Moreover, human beings are consistently exposed to trace amounts of various metals like aluminium, copper, iron, zinc, etc., and for decades, these metals are suspected to play rather a blurred role as a risk factor in the progression of AD. Interestingly enough, Aβ-peptides are efficient ion chelators, and it has been found that zinc-chelated Aβ-oligomers are more toxic to brain tissues. Further evidence for their role in AD came from various ex vivo studies where it has been shown that zinc-Aβ-oligomers potentially inhibit LTP in the hippocampus via activation of microglia (Lee et al. 2018). Moreover, the size and shape of Aβ-oligomers are correlated with their intensity of toxicity with reports suggesting that an increase in the size of Aβ-oligomer assembly decreases the intensity of deleterious effects (Sengupta et al. 2016). Aβ dimmers have been found to be more toxic than other assemblies and they provide building blocks for the formation of other intermediate Aβ-oligomers (O'Nuallain et al. 2010; Mc Donald et al. 2015).

13.3.2 Aβ-Plaques and Oxidative Stress

Pathophysiology induced by Aβ-senile plaques is mediated by several different mechanisms like defective axonal transport, apoptosis, oxidative stress, calcium

dyshomeostasis, neuroinflammation and mitochondrial malfunctioning (Rosales-Corral et al. 2004b; Moreira 2018). The main source of free radicals (molecular species with one or more unpaired electrons in their outer shell) is the reduction of molecular oxygen in water molecules yielding superoxide radicals which finally produces hydrogen peroxide (H_2O_2) by accepting an electron. Further, H_2O_2 is further reduced to highly reactive hydroxyl radicals called reactive oxygen species (ROS) reacting with biomolecules including proteins, DNA/RNA as well as lipids and damaging them by oxidation-reduction reactions. Enhanced oxidative stress results from an imbalance between the levels of anti-oxidants and oxidants in favour of the later. Recently, there has been a rising interest in the role played by oxidative stress in various neurodegenerative disorders like AD, Parkinson's disease, cerebral ischaemia-reperfusion and Down's syndrome. Elevated oxidative stress is another hallmark of AD, and the recently held notion is that methionine amino acid residue present at the 35th position of Aβ-peptide is crucial for the neurotoxicity induced by Aβ-oligomers by generating oxidative stress (Butterfield et al. 2013). Various lines of evidence indicate that oxidative stress load develops from the cellular lipid bilayers where Aβ 1–42 peptide inserts itself as oligomers initiating lipid peroxidation thereby serving as the source of ROS generation (Markesbery 1997; Mark et al. 1997; Butterfield et al. 2001).

Recent studies have suggested that lofty levels of oxidative stress occur in brain regions where Aβ 1–42 levels are high compared to the brain regions having lower levels of Aβ 1–42 oligomers (Butterfield and Boyd-Kimball 2018). Furthermore, studies on cortical synaptosomes, cultured hippocampal neurons and primary neuronal/astrocytes cultures indicate that Aβ-peptides of various lengths induces protein oxidation as measured by elevated levels of protein carbonyls (Perluigi et al. 2006a; Varadarajan et al. 1999, 2001). In the presence of many anti-oxidants including vitamin E, Aβ 1–42 oligomers failed to generate ROS in neuronal cultures and protein oxidation was prevented (Yatin et al. 1999). Interestingly, in vivo administration of anti-oxidants like D609 (a tricyclodecanol xanthic acid derivative) and ferulic acid ethyl ester (FAEE) independently abrogated protein carbonyl production (protein oxidation) induced by Aβ 1–42 oligomers (Perluigi et al. 2006b; Ansari et al. 2006). These studies indicate that Aβ-oligomers induce oxidative stress via peroxidation of proteins and lipids rendering them unstable and dysfunctional leading to the progression of AD.

Neuronal membranes are most dynamic in function as they are electrically excitable and any functional or structural alteration of neuronal membranes could lead to disastrous consequences for their survival. Aβ 1–42 oligomers interact with neuronal membranes and jeopardize their functional integrity by various mechanisms including insertion into the membrane and subsequent pore formation leading to changes in membrane permeability (Butterfield and Lashuel 2010). Apart from pore formation, neuronal membranes could be potential targets for ROS resulting in disruption of their function via several mechanisms like lipid peroxidation reactions which have been shown to induce loss of asymmetry in phospholipids in membranes of synaptosome which serves as an early signal for apoptosis. Among the products of lipid peroxidation which are elevated in AD pathology, 4-hydroxynonenal (4HNE) and

acrolein (an unsaturated aldehyde) are highly reactive and both induce apoptosis and disrupt ionic homeostasis of neuronal cells (Castegna et al. 2004). The enzyme amino-phospholipid translocase or flippase, which is ATP dependent, maintains the asymmetry of lipid bilayers, and 4HNE generated by lipid peroxidation oxidizes a cysteine residue in its catalytic domain rendering the flippase enzyme dysfunctional and thereby disrupting the bilayer asymmetry. Furthermore, 4HNE lipid peroxidation product can alter the conformational structure and function of various membrane proteins by conjugating with them and subsequently causing neurotoxicity and neural degeneration in AD (Subramaniam et al. 1997). Another important mechanism by which ROS accelerates the pathophysiology induced by Aβ-peptides is acting via membrane receptor known as low-density lipoprotein receptor-related protein 1 (LRP1) which is also known by other names such as apolipoprotein E receptor (APOER). LRP1, a protein receptor known to play an important role in cellular endocytosis, apolipoprotein metabolism and cell signalling, was recently shown to undergo oxidation by ROS resulting in impaired clearance of Aβ-peptides from the brain (Cheignon et al. 2018). It is well established that LRP-1 is a multifunctional receptor protein that plays an important role in the efflux of toxic Aβ-peptides from CNS to blood via blood-brain barrier, and this activity is significantly reduced under AD pathology (Jeynes and Provias 2008; Sagare et al. 2007; Ito et al. 2007).

As mentioned earlier, Aβ-peptides has metal chelating properties and interact with metals like zinc, copper, and iron which enhances the cytotoxicity of Aβ-peptides via ROS and biomolecular oxidation. It has been suggested that elevated ROS load in AD brain is highly correlated with increased concentrations of iron (Fe) and copper (Cu) in the brain, both of which are responsible for ROS generation via Fenton reaction (Jomova et al. 2010). Recent results obtained from Rutherford backscattering spectrometry and scanning transmission ion microscopy substantiate the facts that toxicity induced by Aβ-peptides is elevated in presence of metal ions as they deposit in and around Aβ-plaques as compared with surrounding tissues resulting in fibril assembly as well as β-sheet formation in Aβ-peptides (Rajendran et al. 2009). As mentioned earlier that Aβ-induced cytotoxicity depends on the conformational structure and length of the Aβ-peptides where non-β sheets are non-fibrillar and β sheets are fibrillar and toxic. Recent studies suggest that the aggregation of Aβ-peptides is also controlled by pH, the concentration of Aβ-peptides as well as levels of metal ions including copper, zinc, and iron (Jomova et al. 2010). In natural healthy state, generation of ROS is followed by elevated levels of anti-oxidant enzymes like haem oxygenase-1, catalase and superoxide dismutase (SOD), and interestingly the mRNA levels of these enzymes are reportedly elevated in a consistent manner under AD pathology (Premkumar et al. 1995), but the activity of these anti-oxidant enzymes is significantly reduced, and the causes for this reduced activity are not clear (Omar et al. 1999). Some studies showed that ribonucleic acid (RNA) is one of the major targets of ROS-induced oxidation in the pathology of AD, whereas mitochondria serve as the main source of ROS generation (Nunomura et al. 2009). However, the exact mechanism behind amyloid plaque deposition and elevated ROS load is not fully understood yet some evidence conclude that

aggregated Aβ-plaques initiate a chronic inflammatory response in AD pathology and enormous free radicals are released from activated microglial cells.

Strong evidence supports the view that the cytotoxicity of Aβ-peptides is not inherent and requires the presence of ROS to induce such toxic cellular effects leading to AD pathology. Indeed, it was shown that in the absence of redox metal ions like copper, zinc or iron, Aβ-peptides did not induce toxic effects as the strong binding capacity of Aβ-peptides to these metals to reduce them subsequently producing hydrogen peroxide as well ROS load (Huang et al. 1999). As mentioned earlier, methionine 35 of Aβ-peptides is strongly implicated in AD pathogenesis as this residue of Aβ-peptide is the most susceptible to oxidation reactions in vivo (Jomova et al. 2010). Reports suggest that methionine-35 gets oxidized to methionine-sulphoxide which significantly reduces the pro-apoptotic and toxic effects of Aβ-peptides on isolated mitochondria (Jomova et al. 2010). Furthermore, lipid peroxidation due to ROS results in the formation of various carbonyl products which can damage DNA and proteins. Various types of advanced glycation end products (AGE) and advanced lipid peroxidation end products (ALE) are produced during ROS reactions. These AGEs and ALEs further interact with receptors like a receptor for AGEs (RAGE) activating downstream signalling pathways which subsequently leads to the production of pro-inflammatory cytokines such as interleukin-6 (Valko et al. 2005). Recent research reports suggest that glyceraldehyde-derived AGEs mediated by ROS reactions elevate the APP and Aβ levels in mice models, and in the presence of AGEs, the toxicity of Aβ-peptides is significantly heightened (Ko et al. 2015). The mechanism behind the role played by AGEs in AD pathology is still debatable, but new reports are emerging which suggest that AGEs up-regulate the expression of the proteins associated with the processing of APP including BACE1 and PS1 and reduce the expression of neuroprotective as well as antioxidative sirtuin-1 via ROS action. AGEs are also reported to up-regulate the expression of GRP78 (an endoplasmic reticulum chaperone protein) and elevate the cell-death signalling pathways including proteins like p53 and pro-apoptotic caspases (Ko et al. 2015). Therefore, ROS generated by Aβ-peptide aggregation alter the chemical nature of vital biomolecules generating secondary toxic products which ultimately leads to neuronal death via different cellular signalling pathways.

Normal ageing has its effects on the functioning of microglia like heightened activation but reduced function and proliferation as a result of cellular senescence (Miller and Streit 2007), and these processes contribute to the age-associated neurodegenerative diseases. In pursuit of phagocytosis of Aβ-plaques, activated microglia release pro-inflammatory chemokines and are clustered around amyloid plaques mounting a sustained inflammatory response which significantly damage neurons (Meda et al. 1995). Furthermore, as mentioned above, ROS load is an important hallmark of AD; microglia activation-induced neuronal damage also involves ROS production in AD, and it is still not clear how Aβ induces ROS generation in microglia, but it likely involves the binding of Aβ-peptides to the cell surface receptors and ion channels on microglia. Recent reports suggest that Aβ-oligomers stimulate microglial cells for ROS production by acting on certain ion channels and one such ion channel has been identified as voltage-gated transient receptor potential ion

channel (TRPV) based on inhibition by drugs which aborted ROS production in stimulated microglia (Schilling and Eder 2011). These cation channels modulating Aβ-induced microglial ROS production could serve as potential therapeutic drug targets for controlling AD pathogenesis. Generation of ROS inside microglia is derived from various sources acted upon by peroxidase enzymes like NADPH oxidase which plays an indispensable role in the generation of oxygen free radicals from molecular oxygen which further takes part in the formation of ROS consequently modulating morphology and pro-inflammatory gene expression in activated microglial cells (Gao et al. 2002; Qin et al. 2004). It is interesting to note that the expression of microglial NADPH oxidase is up-regulated in neurodegenerative diseases like AD and Parkinson's disease (PD) pointing towards the importance of this enzyme in neurodegeneration diseases where it could be targeted for treatment of AD and PD because it is the main ROS-producing enzyme (Wu et al. 2003; Block 2008).

Therefore, an important link between AD pathology and oxidative stress load is through protein oxidation and lipid peroxidation induced by ROS which accelerates AD pathology via secondary effects of these ROS on cells. Finding early markers in AD has been the toughest task for neurobiologists and oxidative stress as an early biomarker in the aetiology of mild cognitive impairment (MCI) stage of AD would provide an important diagnostic methodology for early detection of AD (Butterfield et al. 2006). Interestingly Aβ-peptide itself undergoes oxidative damage in the presence of ROS, and oxidized Aβ-peptide further coordinates metal ions consequently creating more ROS load (Cassagnes et al. 2013) as well as accelerates the aggregation of Aβ-peptide. Hence, the possibility of therapeutic strategies targeting ROS pathways derived from better and deeper insights of mechanisms involved in ROS generation could be a step forward towards treating AD. Moreover, it is known that Aβ-induced-oxidative stress is not global in the brain of AD patients; rather Aβ-poor regions like the cerebellum do not show signs of ROS production in AD pathology pointing to the fact that Aβ-formation is upstream of ROS generation and strategies targeting excess production of Aβ-peptide shall be able to restrict ROS production also (Cheignon et al. 2018). However, it is still unclear whether oxidative stress associated with Aβ inducing neurodegeneration is the primary or secondary to the alternative sources of ROS generation.

13.4 Role of Tau Protein in the Development of AD

Another important pathological hallmark of AD is the excessive accrual of hyperphosphorylated microtubule-associated protein (MAP) called tau protein which forms the intracellular neurofibrillary tangles (NFTs) inside the neurons leading to a plethora of physiological dysfunctions (Buee et al. 2000). We will now discuss the probable cellular and molecular mechanisms behind the generation and pathology induced by NFTs.

Tau, an unfolded microtubule-associated protein which binds to microtubules of the cytoskeleton, is involved in their assembly as well as stabilization (Grundke-Iqbal et al. 1986). Tau proteins are mostly located in axons and in small quantities

are also found in dendrites of neurons (Ittner et al. 2010). Apart from these two places, tau proteins within the nucleus play a vital role in the regulation of transcriptional activity as well as in genomic maintenance under non-pathological physiological conditions (Violet et al. 2015). Under normal physiological conditions, tau provides stability to microtubules and also regulates the intracellular trafficking of vesicles and other transport processes within neurons which makes it an important player in the axonal transport process and defects therein during AD pathologies (Vershinin et al. 2007; Talmat-Amar et al. 2018). However, during AD, the normal physiological function of tau is disrupted which consequently leads to the development of neurofibrillary tangles (NFT) (Fig. 13.4). The gene which encodes for tau protein is located on chromosome 17 consisting of 16 exons. Alternative splicing of exons including 2, 3 and 10 leads to six possible combinations, for six tau protein isoforms, mainly found in neurons and mostly located in axonal regions. These six isoforms of tau usually contain 352–441 amino acid residues. The three isoforms which do not have exon 10 contain three binding domains with the microtubules (3R) and the other three have four (4R). The latter isoforms having 4R have stronger interaction and better stability (Buee et al. 2000). Alternative splicing of a single gene called microtubule-associative protein tau (MAPT) generates numerous isoforms of tau protein. Primarily, tau plays an important role in maintaining overall

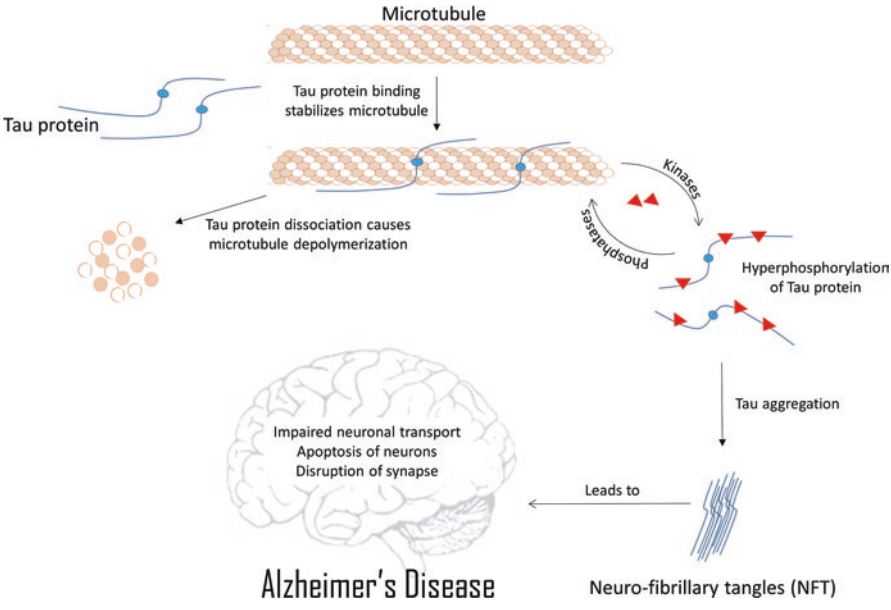

Fig. 13.4 Tau protein-mediated development of Alzheimer's disease. Tau proteins are important for the stability and functionality of microtubules. Hyperphosphorylation of tau protein causes its dissociation from microtubules, which then promotes pairing of hyperphosphorylated tau threads. Many phosphorylated tau threads associate together to generate neurofibrillary tangles (NFT) which could block synaptic junctions thereby causing blockage of axonal transport and neuronal cell deaths

neuronal morphology as it regulates certain vital cellular processes including neurite outgrowth, microtubule assembly as well as stability which are indispensable for cytoskeleton maintenance and axonal transport processes (Wang and Mandelkow 2016).

Additionally, tau is tightly regulated during homeostasis as well as under stress-induced cellular responses by a cascade of post-translational modifications such as glycation, glycosylation, cleavage, nitration, ubiquitination and phosphorylation. Post-translational interferences severely affect tau-microtubule binding and consequently promote its misfolding causing it to aggregate into NFTs. Normal site-specific phosphorylation of the tau protein by various kinases regulates its ability to bind tubulin and promote microtubule assembly (Lindwall and Cole 1984). Optimal levels of tau phosphorylation are required for the proper functioning of tau protein, whereas excessive phosphorylation disrupts optimal functions involving tau protein which also enhance tau-tau protein aggregation resulting in the formation of NFTs (Fig. 13.4). Tau contains 85 putative serine or threonine phosphorylation sites mainly located in the microtubule-binding region (MBR) and the proline-rich domain of the protein (Hanger et al. 2009). Phosphorylation of tau protein is mediated by several types of protein kinases such as the serine/threonine/tyrosine kinases and most of the sites are located on either side of MBR.

Hyperphosphorylation of tau proteins causes the helical and straight filaments to form neurofibrillary tangles. The loss of microtubules-binding capacity provokes cytoskeleton destabilization, affecting neuronal transport processes like synaptic transmission and depriving neurons of trophic factors which eventually causes neurodegeneration and neuronal death (Fig. 13.4) (Montoliu-Gaya and Villegas 2015). The major tau kinases that play an important role in its phosphorylation include GSK3β, cyclin-dependent protein kinase 5 (CDK5), cAMP-dependent protein kinase (PKA), MAPK, calcium-calmodulin-dependent protein kinase II (CaMk II) (Baudier and Cole 1988) and microtubule affinity-regulating kinase (MARK) (Noble et al. 2003). Various in vivo and in vitro studies suggested that GSK-3β plays a vital role in controlling tau phosphorylation at various specific amino acid residue sites including $Ser^{199, 404,396,400}$, Thr^{231} and Ser^{413} residues that are mostly phosphorylated in tau which subsequently aggregates into toxic paired helical filaments (PHF) (Liu et al. 2002). Among various kinases which take part in phosphorylation cascade of tau, GSK-3β plays a major role in phosphorylating tau under in vivo conditions. Furthermore, phosphorylation of GSK-3β kinase at Thr^{231} residue induces a local conformational rearrangement resulting in increased accessibility of GSK-3β or other kinases to excessively phosphorylate tau protein at various sites leading to its hyperphosphorylated state aggregating into PHFs. On the other hand, in vitro studies have found a set of protein phosphatases which play a complementary and opposite role in de-phosphorylation of tau including protein phosphatase 1(PP1), PP2A, PP2B and PP2C that might act as therapeutic targets in near future (Avila et al. 2004). Among these protein phosphatases, PP2A has a stronger role in dephosphorylation of abnormal tau as compared to other phosphatases (Gong et al. 1994). Reports suggest that overall tau protein phosphorylation status is three to four times higher in AD-affected brain samples as compared to samples from a healthy brain.

Strong evidence suggests that dysregulated and high phosphorylation status of tau is central to the AD progression and pathogenesis, however, under normal conditions, all tau proteins are associated and bound to the microtubules. Apart from tau hyperphosphorylation, numerous other neuronal proteins, such as MAP 1B, neurofilaments, β-tubulin, as well as β-catenin, are also hyperphosphorylated under AD pathology in the brain. Therefore, it can be concluded that decreased PP2A phosphatase activity, which removes the phosphate groups from these proteins including tau, might be the underlying cause for abnormal hyperphosphorylation of tau in AD leading to cytotoxicity and progression of the disease.

The histopathological indices of AD patient's brain samples are characterized not only by the presence of intracellular NFTs but also by the presence of Aβ-plaques. These neuritic plaques would further stimulate the production of more NFTs disrupting synaptic topography, consequently reducing the rate of neurotransmission as well as inducing atrophy of tangle-containing neurons ultimately resulting into the behavioural pathophysiological signs including dementia (Hardy and Selkoe 2002). The role played by Aβ-oligomers in inducing hyper-phosphorylation of tau protein through activation of GSK-3β kinase has been identified as connecting link between Aβ-plaques and tau pathologies in AD progression (Stancu et al. 2014). Accumulation of Aβ-oligomers affects downstream Akt-cell survival signalling pathways through inhibition of phosphatidylinositol-3-kinase (PI-3K) as well as by activating GSK-3β, subsequently causing tau hyperphosphorylation (Magrane et al. 2005). Additionally, studies have found that Aβ-peptides up-regulates calcineurin-1 (RCAN1) expression which induces long-term depression at synapses and facilitates increased tau phosphorylation through two different mechanisms. Firstly, RCAN1 hinders the activity of calcineurin, which is a phosphatase and takes part in tau dephosphorylation, and secondly, RCAN1 up-regulates the activity of GSK-3β, a kinase which hyperphopshorylates tau causing PHF-induced toxicity. Therefore, these reports suggest that elevated expression of RCAN1 has a major role in AD progression and it also elevates the pathophysiology of AD by causing mitochondrial dysfunctions which ultimately activate many apoptotic pathways leading to neurodegeneration (Lloret et al. 2011).

Studies cited above reveal that hyperphosphorylation of tau is central to the development and progression of AD via NFT-induced cellular toxicity leading to neuronal degeneration. Abnormally hyperphosphorylated tau protein, apart from losing its biological activity by disassociating from microtubules, also promotes its polymerization into PHFs. The soluble abnormal tau and/or its oligomers are in many ways toxic to neurons probably due to the defence mechanisms employed by neurons. Abnormally, hyper-phosphorylated tau via self-aggregation further polymerizes into highly aggregated PHFs/NFTs which finally choke the affected neurons by impairing their axonal transport processes thereby depriving them of neurotrophic factors inducing cell death (Fig. 13.4). A large number of reports have revealed a role for abnormally phosphorylated tau protein in the neuronal cytoskeleton collapse in ageing and neurodegenerative tauopathies in AD. Control of tau phosphorylation by targeting tau kinases such as GSK-3β might be a feasible therapeutic strategy to prevent tau aggregation and its associated pathological effects in

controlling AD progression. However, excessive phosphorylation of tau appears to be a prerequisite but not sufficient alone to induce tau aggregation. Therefore, other tau post-translational modifications might also be involved in tau pathologies. However, tau proteins forming NFTs regardless of its post-translational modifications can also lead to cellular toxicity, and furthermore, it has been shown that suppression of tau pathology also blocks Aβ-induced toxicity and reduces memory deficit in AD animal models. These data provide a future perspective suggesting that reduction of the overall tau phosphorylation status may constitute a neuroprotective strategy to prevent tauopathy-induced AD. However, some studies suggest depleting axonal tau protein would hinder active axonal transport processes, and, as exemplified for cholinergic neurons, reducing axonal transport processes would ultimately deplete neurotrophic growth factors (NFG) and their receptors inducing neuronal degeneration. Moreover, the collapse of the neuronal cytoskeleton may have deleterious outcomes for a number of cellular processes including axonal and dendritic transport systems, affecting the distribution of proteins within a neuron, irregular distribution of signalling molecules and organelles throughout the cell. Maintenance of neuronal morphology, as well as contacts with neighbouring neurons through synaptic connectivity, will also be affected. Deterioration of these indispensable cellular physiological processes ultimately leads to neurodegeneration and cognitive impairments in AD patients. Therefore, amelioration of tau dysfunctions and maintenance of the neuronal cytoskeleton by restoring axonal transport processes could be important therapeutic strategies for the treatment of AD in the near future.

13.5 Axonal Transport Dysfunctions in AD

In AD animal models especially in rodents, it has been found that death of the neurons occurs via multiple pathways involved in atrophy or apoptosis. Long before in 1939, Huxley and Hodgkin using the squid giant axon demonstrated how an action potential is carried along the axons, and consequently, it was found later that these action potentials mediate the release of neurotransmitter vesicles into the synapse for neuronal communication (Hodgkin and Huxley 1939; Vicario-Orri et al. 2015). A large number of studies have provided convincing evidence that structural, as well as functional, defects in axons play a crucial role in the pathophysiology of AD. The intriguing hypothesis is that the main distinctive feature that makes neurons more prone to AD-associated atrophy is their widely extended cellular morphology consisting of about 99% of cellular volume in axonal compartments alone (Morfini et al. 2009). Neurons within the nervous system communicate with each other by sending the information via electric or chemical signal down their axons to their axon terminals which are received by postsynaptic neurons via their dendrites. Proper functioning of axons and their respective terminals depend heavily on the axonal transport processes carrying various proteins, neurotransmitter vesicles, organelles and other macromolecules from the cell body to the axon terminals. Axonal transport is one of the main cellular processes by which neuronal function is maintained and it requires cytoskeleton proteins like motor and adaptor proteins

for trafficking and transportation of cargoes within the neuronal cells. Reports suggest that axonopathy was found to precede other well-established AD-related pathologies by more than a year in mouse models of AD and also in early stages of human AD patients (Stokin et al. 2005). Axonal transport defects involve axonal swelling due to excessive accumulation of vesicles, microtubule-associated and motor proteins and cellular organelles which block the neuronal communication by hindering synaptic transmission due to impaired vesicular transport (Yagishita 1978). Cytoskeleton motor proteins like dyneins, myosins and kinesins carry axonal cargoes from soma to the axonal terminals via tracks made up of microtubules and are therefore vital to understand the role of imbalanced and dysregulated transport processes occurring in axons and its involvement in the pathogenesis of AD and related neurodegenerative diseases (Cash et al. 2003). Microtubules in the axons of neurons have a discrete polarity with the faster growing plus end laid towards the nerve terminals and slower growing minus end pointed towards the soma. Furthermore, various genetic and biochemical studies have shown that the kinesin superfamily of proteins move towards the plus end and carry out fast anterograde (from cell body to the nerve terminals) transport in neurons, whereas most of the retrograde transport (from nerve terminals to the cell body) is carried by dynein proteins (Goldstein and Yang 2000; Hirokawa 1998). A study carried in *Drosophila* genetically disrupted cytoplasmic dynein heavy chain (cDHC) and dynactin subunit p150 (Glued) resulted in a phenotype of the fly similar to that observed when genetic disruption of kinesin-1 subunits was carried which consequently resulted in posterior paralysis of larva and tremendous axonal swellings filled by membranous cargoes in nerves (Martin et al. 1999). Additionally, *roadblock*-a new *Drosophila* mutant of axonal transport having same posterior paralysis and axonal swellings with accumulations of cargoes was employed to identify a new dynein light chain, again supplementing the existing evidence that dynein plays an essential role in retrograde axonal transport system (Bowman et al. 1999).

Axonal transport is classified into two types: slow transport involving slower rates of cargo movements which mainly consist of anterograde movement of cytoplasmic proteins and cytoskeleton elements involved in neuronal morphogenesis and fast anterograde transport (FAT) which is bidirectional in movement (Hirokawa 1998; Brown 2003). Additionally, FAT is involved in the transport of synaptic vesicles and neurotrophic factors which ensure synaptic activity as well as neuronal health simultaneously; therefore, FAT pathways are severely affected in AD pathology. Various primary mutations found in genes encoding proteins for axonal transport machinery play a critical role in an imbalance of FAT and subsequent progress of various neurodegenerative diseases of CNS. For example, in vitro studies have found that mutations in kinesin protein KIF5A resulted in dysfunctional and pathogenic anterograde axonal transport in a neurodegenerative disease called hereditary spastic paraplegia (HSP) which primarily affects motoneurons (Ebbing et al. 2008). Similarly, there are other CNS diseases and pathologies associated or caused by mutations in kinesin superfamily of proteins. Anterograde vesicular transport is rendered dysfunctional in Charcot-Marie-Tooth hereditary neuropathy type-2 (CMT-2) disease by the mutation in another kinesin called KIF1β causing distal muscle

weakness and atrophy (Zhao et al. 2001; Xu et al. 2018). Interestingly, in another neurodegenerative disorder called spinal and bulbar muscular atrophy (SBMA) which is also known as Kennedy's disease, one of the proteins taking part in axonal retrograde transport, namely, dynactin, was found mutated at p150 subunit (Puls et al. 2003). Dynactin-1 mutations are also responsible for other neurodegenerative diseases like Perry syndrome characterized by Parkinsonian-neuronal loss and dementia (Farrer et al. 2009; Newsway et al. 2010). Apart from these primary mutations in axonal transport machinery-related genes, there are various other mutations that cause secondary malfunctioning in the FAT process like mutations of SGP4 encoding spastin protein which is an ATPase-regulating microtubule dynamics and is involved in around 40% of autosomal dominant forms of hereditary spastic paraplegia (HSP) disease (Baas and Qiang 2005). Furthermore, knocking-out of SGP4 gene in mice resulted in the tremendous accumulation of cellular organelles along with cytoskeleton proteins and subsequent swelling of the axons characterizing the impairment of axonal transport machinery in these animal models (Tarrade et al. 2006). Axonal transport also helps the neurons in meeting energy demands by transporting mitochondria in both the directions and mutations in mitofusin-2 gene which encodes an outer mitochondrial membrane GTPase involved in mitochondrial transport along the axon disrupt both anterograde as well as retrograde transport of mitochondria in Charcot-Marie-Tooth disease (CMT) type 2A (Misko et al. 2010; Baloh et al. 2007). Although it is an established fact that axonal transport dysfunctions precede the progression of various neurodegenerative diseases, it is however not well understood how exactly the defects in FAT cause the development of these diseases as their mechanism are yet to be established clearly. However, identification and characterization of primary mutations in proteins involved in axonal transport machinery provides strong evidence that FAT defects play a crucial role in the development of these neurodegenerative diseases.

Unlike above neurodegenerative diseases, there is no particular known mutation in axonal transport machinery that could lead to the progression of AD. However, most of the studies suggest that FAT defects precede some of the pathogenic hallmarks in the progression of AD in human patients as well as in transgenic mice models for AD (Stokin et al. 2005). Most of the proteins taking part in the processing of APP which also leads into the formation of toxic Aβ-peptides undergo axonal transport including APP, BACE1 (β-secretase) and PS1, and all of them have played an important role in the aetiology and progression of AD. In AD, due to dysfunctional axonal transport, neurotrophins have been found to be irregularly distributed and dysregulated leading to decreased survival of neurons (Vicario-Orri et al. 2015). Although the exact functions of APP remains a mystery, some studies have implicated APP in fast axonal transport by acting as a receptor for anterograde motor kinesin (Kamal et al. 2001). Furthermore, tau which is a microtubule-associated protein that binds and stabilizes microtubules is hyperphosphorylated and entangled in AD; therefore, in its absence, microtubules become destabilized, and axonal transport is disrupted in AD pathology indicating exciting possibility to treat AD by the use of microtubule-stabilizing drugs including taxanes, epothilones as well as peloruside as shown by recent reports (Higuchi et al. 2002; Lee et al. 1994). It is a

well-established fact that APP is transported in axons via FAT and this process is dependent on kinesin-1 protein (Kamal et al. 2001; Koo et al. 1990; Ferreira et al. 1993). Furthermore, it has been suggested that APP may be transported by a vesicular complex also containing BACE-1 and presenilins which are critical for processing of APP into amyloidogenic/toxic Aβ-peptides which later aggregate into oligomers (Kamal et al. 2001; Gunawardena and Goldstein 2001). These studies altogether suggest that misregulation of APP directly by mutations like in familial AD or indirectly via proteins interacting with APP during its processing and transport could lead to defects in FAT and deprive the neurons of critical components essential for survival thereby initiating neurodegeneration (Gunawardena and Goldstein 2004).

As presenilin proteins help in the processing of APP, mutations in presenilin genes have been observed in most cases of early familial AD. Several studies suggest that presenilin interacts with glycogen synthase kinase-3β (GSK3β) and its substrate tau (Takashima et al. 1998). GSK3β play various roles and it phosphorylates kinesin light chains which lead to detachment of motor from the cargo thereby preventing further transport of cargoes (Morfini et al. 2002). Early studies conducted on transgenic mice overexpressing wild-type APP showed that before the appearance of Aβ-plaques, FAT defects, characterized by axonal swellings due to the accumulation of cellular organelles, cytoskeleton proteins and vesicles, were found in the brain which suggested that FAT events may play an important role in AD progression (Stokin et al. 2005). Furthermore, these disruptions in FAT happened in absence of phosphorylated tau protein suggesting that Aβ-peptide is the main trigger of such alterations in axonal transport (Wirths et al. 2006). Additionally, it has been shown in transgenic mice overexpressing mutated form of APP (Tg2576) that the FAT rates of olfactory nerve considerably decrease even before the plaque formation appears (Smith et al. 2007). Further, APP is carried down to axon by FAT through an indirect interaction with JNK interacting protein-1 known as JIP1 (Matsuda et al. 2001; Muresan and Muresan 2005). Scaffolding protein JIP1, in turn, binds to kinesin light chain (KLC) at its C-terminal at a conserved 11 amino acid motif and helps in the bidirectional transport of APP, and knocking out JIP1 produces anterograde and retrograde transport deficits of APP in neurons which further leads to axonopathy (Verhey et al. 2001). Apart from Aβ-induced axonal transport impairments, NFTs equally play an important role in this dysfunction as tau protein binds and stabilizes the microtubules which are indispensable for transport processes like rail tracks of cellular trafficking. Hyperphosphorylated tau destabilizes microtubules shattering off the axonal transport process and depriving neurons of trophic factors needed for its survival. The most deleterious effects of impairments in axonal transport are caused by roadblocks in organelle transport like mitochondria to the axonal terminals where the intense energy demanding processes like vesicular trafficking and exocytosis needs immense ATP generated by mitochondria. Apart from this axonal transport impairments also affect neurotransmission as neurons are unable to move neurotransmitter vesicles inside them causing loss of synapses and apoptosis.

13.5.1 Aβ-Induced Secondary Impairments in Axonal Transport

As Aβ-peptides occur in monomers, dimers, oligomers and fibrillar structures, their toxicity levels are correlated with their size and structures. Both monomeric and fibrillar Aβ-peptides have been shown to affect the axonal transport machinery in general and mitochondrial transport in particular in cultured hippocampal neurons (Rui et al. 2006; Hiruma et al. 2003). The role of soluble oligomers of Aβ in FAT defects has been assessed most because of the strong evidence that these soluble oligomers are most toxic causing profound neurodegeneration. These soluble oligomers of Aβ when applied to squid and murine hippocampal neurons disrupted their FAT machinery probably mediated by NMDA receptor-dependent mechanisms involving GSK3β (Pigino et al. 2009; Decker et al. 2010). Although, Aβ-oligomers have been found to disrupt both the types of transport processes, anterograde and retrograde, recent studies suggest that they affect anterograde transport more significantly than retrograde transport (Rui et al. 2006; Wang et al. 2010) by which synaptic vesicle and mitochondrial anterograde transport is prohibited which subsequently disrupt synaptic activity and ultimately lead to neural degeneration. Furthermore, it is not known how exactly Aβ-oligomers disrupt FAT, but new insights point towards various plausible mechanisms including inhibitory effects of Aβ-oligomers on actin polymerization and aggregation (Hiruma et al. 2003). Studies suggest that both high concentration and low concentration of Aβ-oligomers cause defects in axonal transport and such defects are reversible upon washout of Aβ-oligomers (Hiruma et al. 2003; Tang et al. 2012).

As axonal transport is a fundamental need for the survival and maintenance of neuronal health, its disruption is bound to lead a cascade of pathologies subsequently leading to various types of neuronal degenerative diseases. Many studies have proposed that FAT disruption is one of the main causes behind the progression of AD and it involves both Aβ-soluble oligomers as well as hyperphosphorylated tau proteins. However, the precise mechanism of how FAT leads to the development of diseases like AD remains unknown and additionally it is not well understood if FAT defects are the primary causes of the disease or they are simply the consequences of AD pathology.

13.6 Mitochondrial Dysfunctions in the Pathophysiology of AD

The energy demands of the brain are significantly high and account for around 20% of the energy consumption of the whole body (Magistretti and Allaman 2015). Mitochondria are the key organelle responsible for cellular energy production, and its loss of function may result in moderate to severe fatigue and diminished production of ATP at the cellular level. As neurons exclusively use glucose as the primary energy source unless starved, this depicts their higher dependence on mitochondria for aerobic oxidative phosphorylation for their energetic needs. The energy requirements of neurons are largely driven to maintain the ionic gradients across the plasma

membranes which are critical for the generation of action potentials (nerve impulses) and hence neuronal communication. Therefore, it is not surprising that malfunctioning of mitochondria could lead to plethora of deleterious consequences including generation of free radicals, modulation of mitochondrial permeability transition and secondary excitotoxicity, impaired calcium buffering and oxidative damage which all are well reported in a number of neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's and amyotrophic lateral sclerosis (McInnes 2013).

Since mitochondria are vulnerable to oxidative damage, the interaction between oxidative stress and mitochondrial dysfunction may initiate or accelerate the generation of reactive oxygen species that are critical for the pathogenesis of AD (Wang et al. 2014). Oxidative stress-induced damage involves functional alterations in mitochondria which are early observed events in AD prior to the appearances of Aß-plaques. In AD pathogenesis, the impaired activity of three important enzymes involved in the tricarboxylic acid (TCA) including pyruvate dehydrogenase, isocitrate dehydrogenase and α-ketoglutarate dehydrogenase is observed due to mitochondrial dysfunctioning (Gibson et al. 2012). Reports suggest that impaired ATP generation within a neuron also leads to activation of kinases such as ERK1 and ERK2 which further phosphorylates tau proteins in paired helical filaments, like a state similar in AD pathogenesis. A higher degree of β-amyloid deposition, overexpression of oxidative stress markers, mitochondrial DNA (mtDNA) deletions and mitochondrial structural abnormalities are found in animal models of AD as compared to normal control subjects.

13.6.1 Alterations in Metabolic Functions and mtDNA Defects in AD

As mitochondria are indispensable for providing the energy source to the neurons for their maintenance of ionic gradients across the plasma membrane and constant release of synaptic vesicles whenever action potential is generated, defects in mitochondrial enzymatic machinery have been reported in AD pathology. Studies of transcriptome and genomic analysis revealed that glucose metabolism in cerebral tissues declined in AD which was found to be associated with down-regulation of nuclear genes encoding subunits of the mitochondrial electron transport chain (Godoy et al. 2014). A number of mitochondrial key enzymes like cytochrome oxidase are reported to have reduced expression in the brain under AD pathology. Additionally, elevated levels of oxidative stress likely cause a further decline in enzymatic activities and expression profiles of some of the important metabolic enzymes such as α-ketoglutarate dehydrogenase complex, cytochrome oxidase (COX) and pyruvate dehydrogenase complex (García et al. 2013). Furthermore, utilizing electron micrography, cytochrome oxidase (COX) histochemical staining and mtDNA in situ hybridization techniques, various reports suggest that neurons which displayed ROS-induced damage also had increased mtDNA content and elevated expression of COX in AD biopsy samples (Bonda et al. 2010). Additionally, it has been suggested that in AD, there is enhanced oxidative damage in nuclear and

mtDNA in neurons under oxidative stress indicated by the presence of higher levels of multiple oxidized bases in nuclear and mtDNA from AD patient samples. Since key enzymatic complexes of the citric acid cycle as well as of electron transport chain (ETC) act as oxidizing or reducing mediators/agents, any dysfunctions in these complexes result in the aberrant transfer of electrons consequently generating oxidative free radicals which further lead to mitochondrial stress and initiation of apoptosis. Interestingly, mitochondrial ETC complex-I and complex-IV deregulations have been found tau-toxicity and Aβ-dependent processes respectively (Eckert et al. 2010). Apart from displaying lower expression/activity of α-ketoglutarate in AD pathology, AD brain has significant loss of α-ketoglutarate enriched neurons in cortical layer 2/4 of which is mostly affected in AD.

As neuroscientists are constantly searching for early detectable biomarkers for AD diagnosis at initial stages, indicators like decline in brain glucose metabolism are considered useful measures to consider cognition status and functionality in AD and are useful for early diagnosis and to predict future cognitive decline as reduced glucose metabolism in the diseased brain is one of the significant abnormalities under AD pathogenesis. Deficits in mitochondrial functions and glucose metabolism are well-established pathological hallmarks of AD and brain ageing contributing to neurodegeneration. In fact, in early AD, the brain shows region-specific hypometabolism of glucose and mitochondrial dysfunctions having harmful consequences for neurons by producing large ROS, depleting ATP levels and caspase-3-mediated programmed cell death (Fig. 13.5). Progressive accumulations of Aβ-peptides in mitochondria have been reported to alter mitochondrial dynamics including fission-fusion equilibrium and Aβ-induced activation of NMDAR's along with the excessive release of calcium from the lumen of endoplasmic reticulum

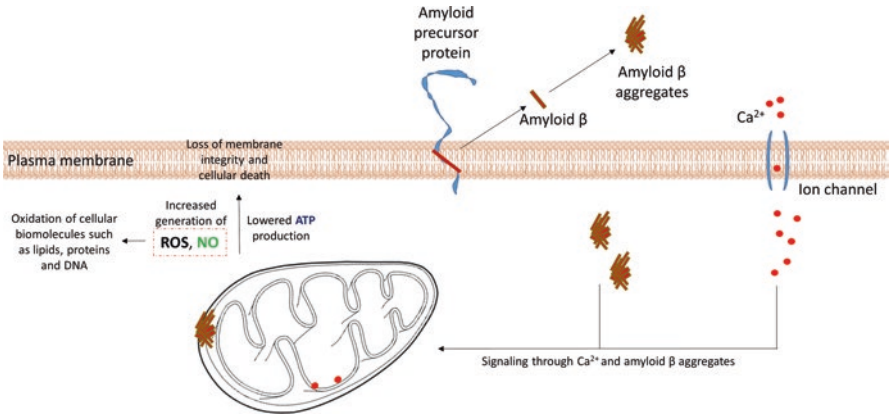

Fig. 13.5 Role of mitochondrial dysfunction in the pathogenesis of Alzheimer's disease. Aggregation of amyloid beta proteins and an increased influx of calcium ions caused a rapid generation of reactive oxygen species and nitric oxide molecules. These increased levels of ROS and NO species then trigger a number of secondary responses such as oxidation of DNA, proteins and lipids, loss of membrane integrity and cellular death, features which are the hallmark of neuronal degradation and development of Alzheimer's disease

causes calcium dyshomeostasis in mitochondria resulting in neuronal injury (Xu et al. 2017). Substantiated by positron emission tomography (PET) imaging, most dementia patients display decreased glucose metabolism in many brain areas, however, severe changes have been reported in parieto-temporal association cortex and in the frontal lobes while brainstem, cerebellum and basal ganglia are not affected. Various reports suggest that Aβ-peptides are inserted and clog many mitochondrial protein importing channels thereby depriving this organelle of various nuclear genome-encoded proteins/enzymes like COX which finally degenerate these organelles and ultimately the whole neurons are killed. Therefore, restoring metabolic defects in mitochondria and rescuing the reduced expression of glycolytic and oxidative phosphorylation enzymes could potentially act as one of the most important therapeutic targets for AD treatment.

Furthermore, increased oxidative damage to mtDNA causing mitochondrial dysfunctions to exacerbate the pathology in AD further links the ROS cascade with AD pathology (Fig. 13.5). Elevated levels of sporadic mutations are found in the mitochondrial DNA control regions which are unique to AD. As a result of such mutations, there are reduced levels of protective proteins like histones and other DNA repair machinery proteins; thus the hotspots of ROS attack increase and make mtDNA vulnerable (Xu et al. 2017). Analysis of the oxidized nucleotide levels in mitochondria shows almost three times higher oxidative damage in AD brain which might be the cause of increased mutation. Many of these mutations occur at the important transcription as well as at replication regulatory elements that causes reduced expression of vital mitochondrial proteins subsequently causing deleterious effects on mitochondrial function. Reports suggest that mtDNA deletions are responsible for deficiency of various mitochondrial enzymes like COX which is a well-characterized marker of mitochondrial dysfunction atypical in AD pathology (Moreira 2018). Moreover, recent data on mtDNA rearrangement from post-mortem AD brain tissues of AD patients suggest that there are three kinds of DNA rearrangements including deletions, F-type rearrangements (duplication) and R-type rearrangements, and these rearrangements are 2.7-fold higher in AD pathology which may be the driving force for AD pathology rather than consequences of it (Chen et al. 2016). As the mitochondria are versatile organelle and neurons are highly energy demanding, the continuous DNA replication in mitochondria for distribution to its daughter organelle makes their genome prone to replication errors resulting in the accumulation of a large pool of mutations. Apart from these mutations, mtDNA rearrangements including deletions, tandem duplications as well as insertions subsequently alter the protein-coding function of this organelle DNA which is deleterious for neuronal physiology and ultimately result in cell death.

13.6.2 Mitochondrial Dysfunction and Neuronal Apoptosis in AD

Apoptosis is a programmed cell death that is involved in the selective demise of neurons during early development, toxic insults to cells and various neurodegenerative diseases including AD. Mitochondria are versatile cell organelles which

coordinate many cellular processes like redox signalling, calcium homeostasis, energy production, synaptic plasticity and arbitration of cell survival or death. Mitochondria lie in the centre of the intrinsic apoptotic pathway which predominates in the nervous system and is initiated by receiving cell death signals like DNA damage, depletion of trophic factors and oxidative stress (Mattson et al. 2008). Intrinsic pathway involves activation of various kinases like JNK and other transcription factors like p53 which induce the gene expression and mitochondrial translocation of various pro-apoptotic proteins such as Bax and Bak which belong to Bcl-2 family members, forming a pore in the outer mitochondrial membrane. Cytochrome-c escapes from mitochondria through these membrane pores and once in the cytosol, it binds to apoptosis protease activating factor-1 as well as ATP to form apoptosome which then activates caspase-9 and that in turn cleaves and activates caspase-3 executing programmed cell death (Mattson et al. 2008).

In neurodegenerative pathology such as AD, oxidative stress and malfunctioning of mitochondria inappropriately initiate apoptosis accelerating neurodegeneration. Aβ-peptides affect mitochondrial physiology in many ways, including inhibiting α-subunit of ATP synthase, declining activities of many enzymes of Kreb's cycle, reducing respiratory state and inhibiting the transportation of nuclear proteins to mitochondria thereby rendering the mitochondria dysfunctional. Furthermore, pore formation by Aβ in mt-membrane releases cytochrome-c thereby initiating apoptosis contributing to the neurodegeneration process. Additionally, under AD pathology, cytochrome-c release via mt-membrane pores activates caspase 9, and further it cleaves and activates caspase 3 which has been shown to cleave tau protein at D421 site which assists in nucleation-dependent NFT formation (Rissman et al. 2004). Therefore, one of the main targets in combating mitochondrial dysfunction-induced cell death is to overexpress the anti-apoptotic genes, for example, overexpression of Bcl-2 genes may protect neurons against Aß-induced cell death.

13.7 Conclusion

Advances made in molecular biological tools during the last few decades have essentially contributed to the understanding of cellular as well as molecular mechanisms including cell signalling pathways underlying AD pathogenesis (Fig. 13.6). Present understanding of the underlying complex molecular mechanisms involved in the development of AD involves various hypothesis where a plethora of factors interrelates with each other but none of these hypotheses fully explains the complex dogma of cellular pathology involved in AD pathogenesis thereby demanding further investigations. Less is known about the mechanisms responsible for initial triggering as well as early factors causing AD including abnormal accumulation of Aβ oligomers, oxidative stress and tau pathology remain poorly understood and it remains a challenge as to how these factors contribute to neuronal killing creating memory deficits and other behavioural consequences of AD. Genetic factors drastically contribute to the development and progression of AD but still, the cause of these pathological factors and their interaction with environmental factors is still unknown.

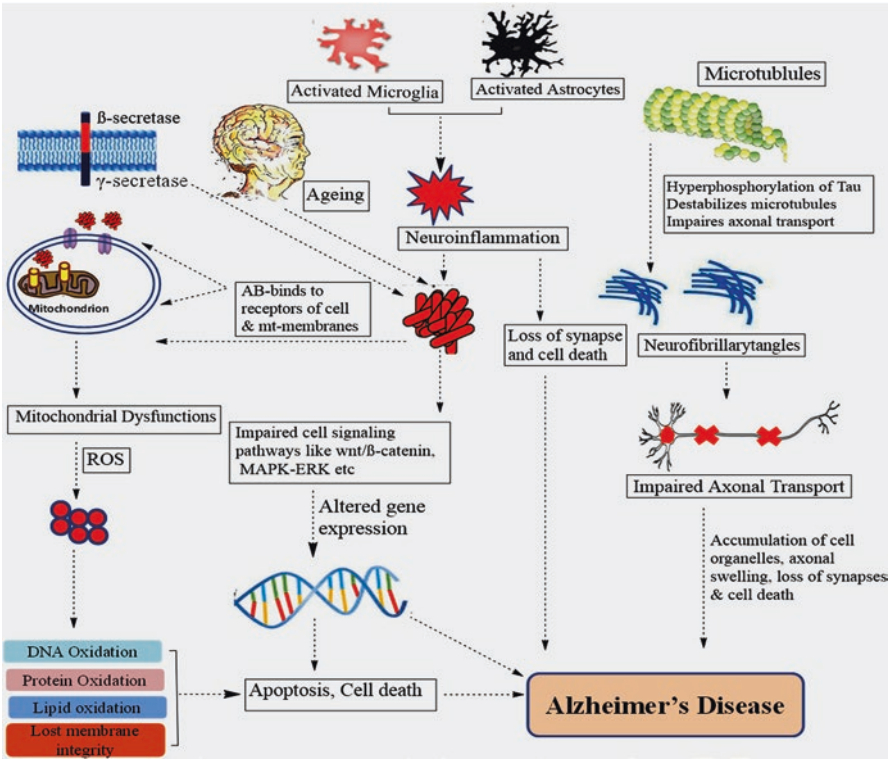

Fig. 13.6 Neurobiological mechanisms involved in the pathogenesis of Alzheimer's disease. A schematic model illustrating diverse neurobiological mechanisms that leads to the onset and development of Alzheimer's disease

A deeper understanding of the imbalances between the rate of Aβ production and its clearance as well as enzymatic activities in tau hyperphosphorylation will provide some clues about the possible treatment strategies for AD. Targeting rate-limiting enzymes for Aβ production such as BACE1 for therapeutic potential has not provided much help; therefore, new molecular targets such as Wnt/β-catenin and MAPK pathways as well as increasing scavenging capacities of biological scavengers to decrease oxidative stress may prove helpful. Oxidative stress has been found to induce tau hyperphosphorylation via enhanced activation of GSKβ-3 enzyme, and furthermore, this shatters off the axonal transport in neurons leading to their apoptosis; therefore, new anti-oxidant compounds shall be screened for scavenging ROS. Mitochondrial dysfunctions significantly contribute to the development and progression of AD and is an early feature in AD pathology. These abnormalities in mitochondria function like oxidative stress, aberrant calcium buffering and inappropriate initiating of the intrinsic pathway of apoptosis together lead to neuronal atrophy in AD brain.

Further, research is required to address the complicated questions and missing links in the pathophysiology of AD. A deeper understanding of the complex factors underlying the majority of AD behavioural symptoms like cognitive decline, mood, and loss of speech as well as for neuronal atrophy may contribute to the development of novel clinical intervention and therapeutics. Current researches are majorly focused on deciphering early detection markers of AD pathology which could provide ample time for therapeutic interventions leading to the cure at the appropriate time before its pathology spreads globally in the brain. In the coming years, we may have new and deeper insights about the complicated mechanisms which lead to these pathophysiological changes in the brain, and treating AD would become more procurable.

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