Chapter 2
Potential Animal Models of Alzheimer Disease and Their Importance in Investigating the Pathogenesis of Alzheimer Disease

2.1 Introduction

As stated in Chap. 1, AD is a progressive and irreversible neurodegenerative disease characterized by progressive loss of memory and cognitive function. Risk factors for AD include old age, positive family history, unhealthy life style, consumption of high fat diet, and exposure to toxic environment (Farooqui 2015). Clinically, AD is characterized by deterioration of memory and cognitive function, progressive impairment of activities of daily living, and several neuropsychiatric symptoms. Neuropathologically, AD is characterized by the accumulation of beta-amyloid (Aβ) protein that forms plaques and tau protein phosphorylation that promote the formation and deposition neurofibrillary tangles (NFT) (Farooqui 2010). Many biochemical mechanisms have been proposed to explain the pathogenesis of AD including production of reactive oxygen species, disruption of calcium homeostasis, activation of Wnt pathway, excitotoxicity, activation of apoptotic pathways, neuronal degeneration, and neurotransmitter deficits, the precise role of abnormal protein aggregates in the pathogenesis of AD remains to be clarified (Huang and Jiang 2009; Welsh-Bohmer and White 2009; Querfurth and LaFerla 2010). Human autopsies and animal models studies have indicated that both senile plaques and NFT are co-localized with activated glial cells, supporting the view that reactive gliosis may be closely associated with the pathogenetic role of AD (Craft et al. 2006; Farooqui 2013). Increased generation of Aβ peptides not promotes neuroinflammation through the upregulation of different cytokines, and pro-inflammatory mediators (Tuppo and Arias 2005). It is well known that astrocytes play an important role in the controlling the cerebral homeostasis. Accumulation of Aβ and activation of astrocytes in AD initially (for a short time) is a neuroprotective response aimed at removing injurious stimuli. However, uncontrolled and prolonged activation of astrocytes produces detrimental effects that override the beneficial effects due to upregulation of different cytokines and proinflammatory mediators leading to neurodegeneration directly as well as in an autocrine/paracrine manner expanding the

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neuropathological damage in AD (Mrak and Griffin 2001; Pekny et al. 2014). Among above mentioned hypothesis, Aβ hypothesis has a big support among researchers. According to Aβ hypothesis the accumulation of senile plaques and neurofibrillary tangles is accompanied by neuronal atrophy and progressive synaptic failure, which initially appears in the entorhinal region and the temporal lobe, before progressing to the limbic system and subsequently to major areas of the neocortex, severely damaging the brain (Braak and Braak 1995). Aβ is a peptide (4 kDa) generated by proteolytic processing of the amyloid precursor protein (APP), a transmembrane glycoprotein βAPP (~770 amino acids), which has been implicated in the regulation of neuronal cytoarchitecture, synaptic plasticity, axon guidance, and cell–cell interactions in the brain (Hardy and Selkoe 2002; Zhang et al. 2007, 2011; Haass and Selkoe 2007). To explain neurodegeneration in AD, amyloid cascade hypothesis has been proposed (Tanzi and Bertram 2005). According to this hypothesis, amyloid precursor protein (APP) is processed either by the non-amyloidogenic pathway, or the amyloidogenic pathway (Fig. 2.1) (Chow et al. 2010; Zhang et al. 2012a). In the non-amyloidogenic pathway, α-secretase cleaves APP in the ectodomain within the Aβ region of the APP protein, which precludes the generation of the Aβ peptide (Chow et al. 2010; Zhang et al. 2012a). In the amyloidogenic pathway, APP is processed by the β-site APP-cleaving enzyme (BACE), releasing a soluble APP fragment (sAPPβ), which is secreted outside the cell, leaving behind a membrane-associated C-terminal fragment of 99 or 89 amino acids [C99 or C89 (CTFβ)]. The CTFβ is then broken down by γ-secretase, generating the Aβ peptide and a cytoplasmic APP intracellular domain (AICD) (Chow et al. 2010; Zhang et al. 2012b). Aβ42 peptide oligomerizes, and readily forms aggregates that accumulate in the brain to form plaques whose recognition by brain cell microglial cells instigate a pro-inflammatory microglial response and the release of ROS and pro-inflammatory cytokines (Small et al. 2001; Fu et al. 2014). In addition, neurodegenerative process in AD is associated with alterations in neurogenesis leading to memory dysfunction (Donovan et al. 2006). Aβ accumulation is the consequence of an altered balance between protein synthesis, aggregation rate, and clearance. Accumulation of Aβ plaques contributes not only to the alterations in cellular activities, but also to disrupted communication in the brain, leading to neurotoxic inflammation and neuronal death. NMDA receptors play an important role in the production of Aβ42. Activation of synaptic NMDA receptors promotes the non-amyloidogenic pathway, which not only reduces the generation of Aβ42, but also upregulates extracellular signal-regulated kinase (ERK) and Ca^{2+}/calmodulin-dependent protein kinase (CAMK) pathways. These processes promote cyclic AMP (cAMP) signaling pathway, which is closely associated with the formation of long-term memory (Lonze and Ginty 2002). The cAMP-dependent protein kinase A (PKA), when allosterically activated by cAMP, can phosphorylate cAMP response element binding protein (CREB), a basic leucine zipper transcription factor at serine 133 (Gonzalez and Montminy 1989). Phosphorylated CREB then interacts with the transcription coactivator CREB-binding protein to initiate the transcription and translation of CREB target genes, which are required for the synaptic plasticity mediating long-term memory formation. Recent studies have demonstrated that CREB enhances

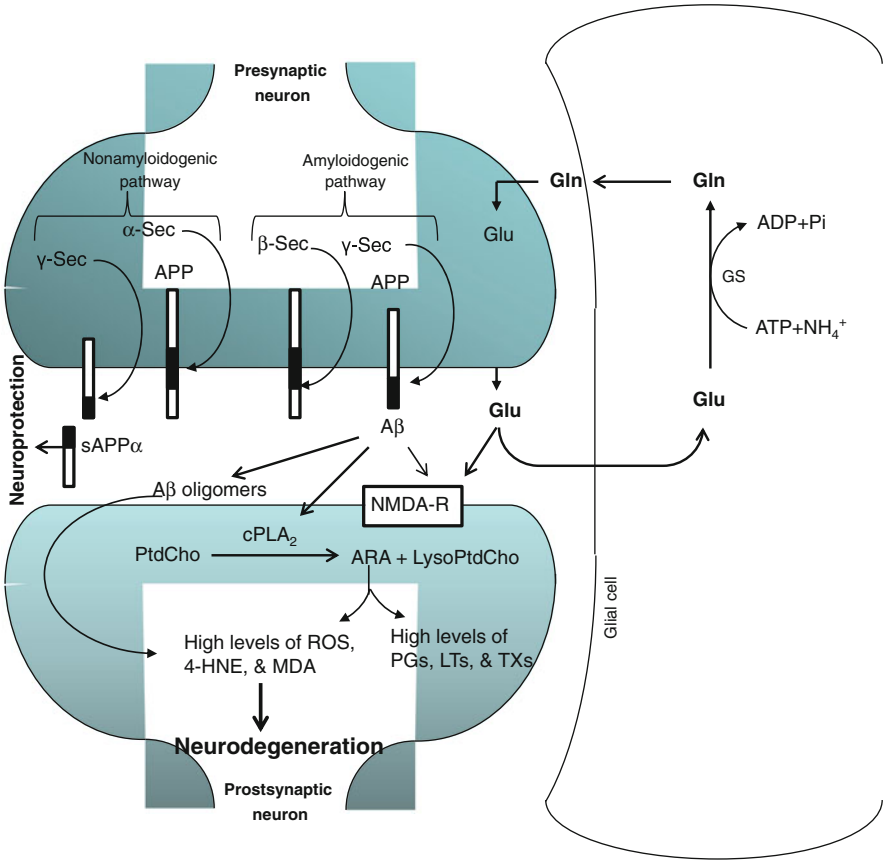

Fig. 2.1 Diagram showing β-Amyloid hypothesis and related molecular events associated with the pathogenesis of Alzheimer disease. Glutamate (*Glu*); glutamine (*Gln*); NMDA receptor (*NMDA-R*); phosphatidylcholine (*PtdCho*); lyso-phosphatidylcholine (*lyso-PtdCho*); cytosolic phospholipase A_2 (*cPLA*$_2$); arachidonic acid (*ARA*); α-secretase (*α-Sec*); β-secretase (*β-Sec*); γ-secretase (*γ-Sec*); amyloid precursor protein (*APP*); β-Amyloid (*Aβ*); Prostaglandins (*PGs*); leukotrienes (*LTs*); thromboxanes (*TXs*); 4-hydroxynonenal (*4-HNE*); and malondialdehyde (*MDA*)

short-term memory by up-regulating brain-derived neurotrophic factor (BDNF), suggesting that CREB signaling is involved in the formation of both short- and long-term memory (Suzuki et al. 2011). CREB-mediated gene expression is impaired in the brains of both AD mouse models and patients (Gong et al. 2004; Phillips et al. 1991), as well as in cultured neurons insulted with Aβ (Tong et al. 2001). Conversely, activation of extrasynaptic NMDA receptors promotes the amyloidogenic pathway leading to increased production of Aβ42 and loss of Ca^{2+} homeostasis. Increased production of Aβ42 not only downregulates the phosphorylation of CREB and enhances LTD, but also induces mitochondrial dysfunction leading to apoptotic cell death (Fig. 2.2) (Hardingham et al. 2002; Bordji et al. 2010). Subsequent activation of downstream signal transduction pathways (such as

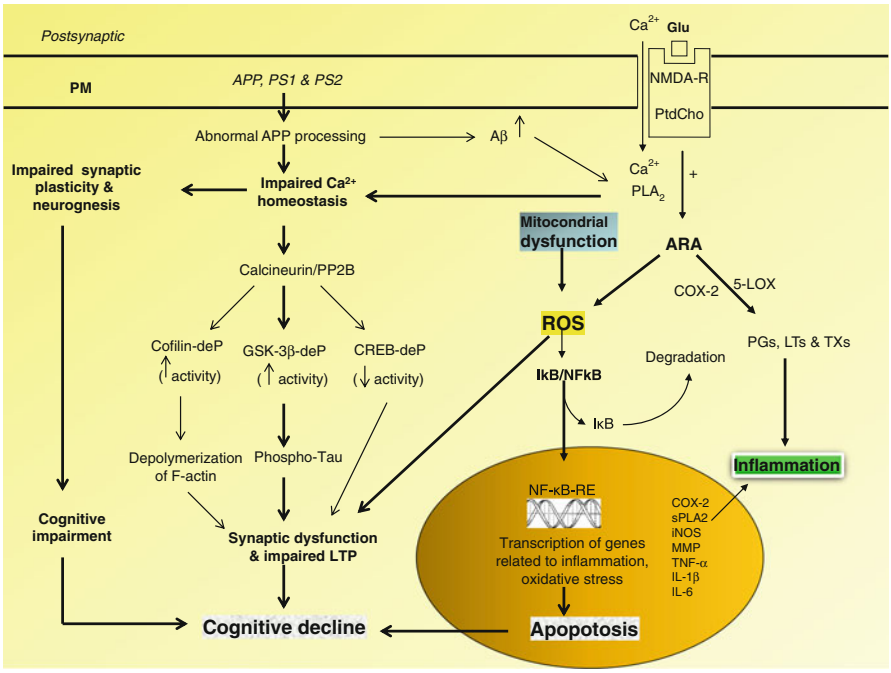

Fig. 2.2 Involvement of NMDA receptor and abnormal APP processing in apoptotic cell death and cognitive decline in Alzheimer disease. Amyloid precursor protein (*APP*); β-amyloid (*Aβ*); glutamate (*Glu*); NMDA receptor (*NMDA-R*); phosphatidylcholine (*PtdCho*); phospholipase A_2 (PLA_2); cyclooxygenase-2 (*COX-2*); 5-lipoxygenase (*5-LOX*); arachidonic acid (*ARA*); prostaglandins (*PGs*); leukotrienes (*LTs*); thromboxanes (*TXs*); reactive oxygen species (*ROS*); nuclear factor-κB (*NF-κB*); nuclear factor-κB-response element (*NF-κB-RE*); inhibitory subunit of NF-κB (*I-κB*); tumor necrosis factor-α (*TNF-α*); interleukin-1β (*IL-1β*); interleukin-6 (*IL-6*); inducible nitric oxide synthase (*iNOS*); secretory phospholipase A_2 ($sPLA_2$); death domain (*DD*); nitric oxide (*NO*); long term potentiation (*LTP*); genes for APP, PS1, and PS2 (*APP; PS1, and PS2*, respectively); Ca^{2+}/calmodulin-dependent protein phosphatase (*calcineurin*); protein phosphatase II (*PP2B*); cofilin (actin binding and modulating proteins); glycogen synthase kinase 3 beta (*GSK-3β*); and cAMP response element-binding protein (*CREB*)

dephosphorylation and activation of the actin filament severing protein cofilin by calcineurin) induce a cascade of pathological events causing synaptic disruption and neuronal loss through mitochondrial dysfunction, induction of oxidative stress, neuroinflammation and alterations in bioenergetic, leading to dysregulation of synaptic neurotransmission and abnormal neuronal network activity (Fig. 2.2) (De Felice et al. 2007; Selkoe 2008; Palop and Mucke 2010; Sakono and Zako 2010; Tomiyama et al. 2010; Farooqui 2010).

Despite of many criticisms against the amyloid cascade hypothesis, it is becoming increasingly evident that this hypothesis can explain not all, but many molecular and cellular aspects of AD including Aβ and Tau pathology. As stated in Chap. 1, most AD cases (more than 95 %) are sporadic with over 65 years old and only less

than 5 % cases are of genetic (familial, FAD) origin-that is, related to a genetic predisposition with mutations in the amyloid precursor protein, presenilin 1, and presenilin 2 genes. Apolipoprotein E (APOE) polymorphisms, sometimes referred to as familial late-onset AD, are not mutations per se, but are a significant predisposing factor (Adalbert et al. 2007). In particular, the *APOE* gene has three isoforms (ε2, ε3 and ε4), with the ε4 isoform being the strongest predisposing allele (Bu 2009). APOE ε3/ε4 heterozygotes have two- to threefold higher risk of developing AD compared with ε3/ε3 homozygotes, and ε4/ε4 homozygotes have more than twofold the risk of the ε3/ε4 genotype, while the presence of ε2 is somewhat protective (Aggarwal et al. 2005). Though sporadic and FAD forms of AD reflect similar pathologies, the underlying causes of pathogenic may vary considerably. As stated above, FAD is linked to specific mutations in APP or PS1 or PS2, located at chromosomes 21, 14, and 1, respectively leading to accumulation of toxic Aβ species in the brain by mid-life. Sporadic AD manifests later in life (over the age of 65 years), and is triggered by more complex neurochemical mechanisms along with genetic components and lifestyle factors (e.g. diet, exercise, and sleep). The histopathological similarity between sporadic and early familial cases has been taken as evidence for a common etiology of the disease. Because in vitro and in vivo data indicated that early onset FAD mutations give rise to the generation of more Aβ peptides and their accumulation has been proposed to be involved in the pathogenesis of FAD. In contrast, the pathogenesis of sporadic AD is very complex and multifactorial involving complex interactions among multiple genetic, epigenetic, and environmental factors. Clinical and epidemiological studies indicate that aging, stress, long term consumption of high calorie diet, aluminum, and viral infections may contribute to the risk of AD (Grant et al. 2002). At the neurochemical level pathogenesis of sporadic AD not only involves the accumulation of Aβ and hyperphosphorylated Tau, but also excitotoxicity, disruption of intracellular calcium homeostasis, oxidative stress, neuroinflammation, loss of memory formation along with reduction in the expression of trophic factors, impairments of axonal transport, and mitochondrial dysfunction (Leuner et al. 2007; Farooqui 2010).

2.2 Potential Animal Models and Alzheimer Disease

Animal models of AD are needed to study the signal transduction mechanisms underlying AD pathogenesis and learning about the effect of genetic and environmental risk factors involved in the pathogenesis of AD. In addition, animal models are also used for developing diagnostic tests and investigating the therapeutic effects of drugs on neuropathology and cognitive function in AD. Animal models are needed for the establishment of pharmacodynamics and pharmacokinetic parameters, the toxicity analysis of new drugs for the treatment of AD. Collective evidence suggests that animal models of AD are not only a cornerstone for studying the pathogenesis of AD, but also for developing and studying pharmacokinetics of drugs.

2.2.1 *Invertebrate Models of Alzheimer Disease*

Invertebrate models have several advantages over vertebrate models (Link 2005; Wu and Luo 2005). The genes and pathways of invertebrate organisms are well-suited to the study of human disease because both pharmacological and genetic manipulations can be performed easily to understand the function of their orthologs in vivo (Table 2.1). Invertebrate models also have other advantages. They are inexpensive, easy to work with, have short lifespans, and often have very well-characterized in terms of stereotypical development and behavior. Two invertebrate model organisms: roundworm *(Caenorhabditis elegan)* and fruit fly *(Drosophila melanogaster)* (Saraceno et al. 2013) qualify for the above criteria. These models are useful tools for studying human AD not only because genes contributing to human AD are homologues in invertebrates, but also because many signaling pathways are conserved and display similar activities (Li and Le 2013). *C. elegans* has been used a fundamental tool for dissecting the pathways that link lifespan to AD. Specifically, one of the major pathways that regulate lifespan is the insulin/IGF-1 signaling (IIS) pathway—a pathway that has been validated in nematodes, flies and mice and strongly implicated in humans (Kenyon et al. 1993; Holzenberger et al. 2003). In *C. elegans* model of AD, knockdown of the insulin/IGF-1 receptor DAF-2 results not only in longevity, but also retardation of Aβ toxicity by delaying the onset of paralysis, supporting the view that there may be a link between the mechanisms of aging and proteotoxicity (Cohen et al. 2006). Modulation of lifespan by

Table 2.1 Listing of invertebrate orthogenes and vertebrate genes contributing to the pathogenesis of AD

Protein	Caenorhabditis elegans	Drosophila	Zebrafish	Mouse
APP	Apl-1	appl	Appa, appb	APP
ADAM10	Sup-17	kuzbanian	No α-secretase	ADAM 10 gene present
ADAM17	Adm-4	dBACE	Absent	ADAM 10
β-Secretase	Absent	Absent	Absent	β-secretase
γ-Secretase complex	γ-Secretase complex	γ-Secretase complex	Incomplete γ-Secretase complex	Complete γ-secretase
Tau	Ptl-1	dtau	Mapta/maptb	Tau
APOE	Absent	Absent	Present	APOE
Presenilins	Absent	Absent	Psen1 and psen2	PS1 and PS2
APLP2	Absent	Absent	Absent	Present
MAPT	Absent	Absent	Absent	Present
PSEN1	Absent	Absent	Absent	Present

Most of the proteins associated with AD are evolutionarily conserved in *Drosophila* and *Caenorhabditis elegans* making these organisms attractive model systems for understand the conserved molecular functions of these genes linked to AD. zebrafish (*Danio rerio*) is a promising model organism for studying molecular events in AD (Saraceno et al. 2013)

DAF-2 is highly dependent on HSF-1 and DAF-16, two transcription factors, which have been reported to drive the expression of longevity genes (Hsu et al. 2003). Both transcription factors block proteotoxicity, but they did so through opposing effects. HFS-1 promotes disaggregation, while DAF-16 enhances aggregation forward, possibly as a means of sequestering the amyloidogenic protein from the cellular milieu (Cohen et al. 2006). *C. elegans* model of AD also expresses the tau homologue Ptl-1. Similarly, in *Drosophila*, the expression of human wild-type and mutant forms of Tau and Aβ has provided useful information on the role of Tau and Aβ proteins under physiological and pathological conditions (Wittmann et al. 2001). Collective evidence suggests that invertebrate animal models provide an in vivo system useful for dissecting the molecular mechanisms underlying neurodegeneration in AD. Significantly important information has been obtained on molecular and neurochemical aspects of AD using *Caenorhabditis elegans* and *Drosophila melanogaster* models (Saraceno et al. 2013; Li and Le 2013). Despite of above mentioned advantages invertebrate models, transgenic approaches in *Caenorhabditis elegans* and *Drosophila melanogaster* models suffers from several unphysiological features, such as (a) high protein levels due to the integration of multiple transgene copies into the genome, (b) alterations in brain area specificity and subcellular expression pattern of the transgene compared with the endogenous gene because of the use of an exogenous promoter, and (c) disruption of endogenous gene expression due to the insertion of transgene into the host genome (Baker and Götz 2015). Consequently, alternative strategies such as knock-in approach (P301L mutation of tau into the murine *MAPT* locus) and development od senescence-accelerated SAMP (senescence-accelerated mouse-prone) strain.

2.2.2 Vertebrate Models for Alzheimer Disease

Use of mice (*Mus musculus*) for the development of animal models offer several advantages over invertebrate models. Mice are vertebrates, which more closely related to humans than invertebrate models such as yeast, worms, or flies (Saraceno et al. 2013). Whole genome of mouse has been mapped (Waterston et al. 2002). The proportion of mouse genes with a single identifiable ortholog in the human genome is ~80 %. This makes the mouse an ideal model for investigating environmental and genetic manipulations, which are not feasible in higher primates and humans. The small size and short gestation and life span makes mice amenable animals for rapid breeding in large and, consequently, the feasibility of many studies in a relatively short period. In addition, preclinical experiments with mice model of human diseases can thus be performed in relative short time periods, enabling the chronic study on the effects of drugs in these models. A valid mice model for AD should not only exhibit progressive AD-like neuropathology and cognitive deficits, but like humans it should manifest some memory loss and cognitive deficits with advancing age.

Studies on transgenic (Tg) mice have provided useful information into the chronology of events leading to the pathogenesis of AD. For example, double-Tg mice,

which over-express human mutant APP and tau (Tg line APP^{sw}-tau^{vlw}) mimic several characteristics of the AD phenotype such as deposition of Aβ, hyperphosphorylation of Tau, formation of NFT, glial cell proliferation, and significant neuronal loss in the entorhinal cortex (EC) and CA1 subfield of the hippocampus (Perez et al. 2005; Ribe et al. 2005). All the above phenotypic traits of AD develop in these mice in an age-dependent manner and are accompanied by progressive hippocampus-dependent memory impairment. However, neurodegeneration in these mice predates overt deposition of Aβ, supporting the view that extracellular fibrillar amyloid may not be causing neuronal death. Furthermore, the extent of neurodegeneration in these mice does not correlate well with total immunostained amyloid plaque burden (Ribe et al. 2005). Thus, studies on mice models of AD have provided us an excellent opportunity to track the natural history of oligomeric Aβ (also known as ADDLs) accumulation in their brains and to study the relationships of these Aβ species to AD-related neuropathological changes and cognition (Perez et al. 2005; Ribe et al. 2005). Oligomeric forms of Aβ have been reported to instigate memory loss through their ability to target synapses and disrupt synaptic plasticity (Wang et al. 2002), including inhibition of long-term potentiation (Walsh et al. 2002; Townsend et al. 2006) and prolonged maintenance of long-term depression (Wang et al. 2002). This suggests that soluble oligomeric forms, not fibrillar deposits of Aβ are pathologically important for the synaptic dysfunction of AD (Li et al. 2009a; Koffie et al. 2009). Using microdialysis technique on interstitial fluid (ISF) samples from Alzheimer model APP/PS1 Tg mice at 3 different age stages of AD-like amyloid plaque development, it is shown that high molecular weight (HMW) and low-molecular-weight (LMW) Aβ oligomers are present in brain ISF samples and that levels of ISF Aβ oligomers become elevated with age in the brain of APP/PS1 Tg mice (Takeda et al. 2013). The clearance of HMW Aβ oligomers is slower than LMW Aβ after acute inhibition of γ-secretase activity to stop Aβ synthesis supporting the view that the rate of clearance of various Aβ oligomers from the brain is different from each other (Takeda et al. 2013). As stated in Chap. 1, Aβ oligomers interact with a number of postsynaptic receptors including ionotropic and metabotropic glutamate receptors, the cellular prion protein (PrP^{C}), neuroligin, the Wnt receptor, and insulin receptors (Krafft and Klein 2010; Ferreira and Klein 2011; Viola and Klein 2015). Many neurotoxic effects have been described as resulting from the interaction of Aβ oligomers with several receptors or co-receptors (Velasco et al. 2012).

Extensive investigations on mice models of AD have indicated that unlike the human AD neuropathology, which displays massive neurodegeneration, only very few transgenic animal models show neuronal death and on a scale that does not compare to what is seen on postmortem human brains (Elder et al. 2010). In addition, the way the genetic manipulation translates into the histological and clinical recapitulation of the AD highly depends on the promoter used to insert the transgene and on the genetic background of the recipient animal (Elder et al. 2010). This actually makes any comparison between transgenic mouse models difficult. Furthermore, many mice models do not show cognitive dysfunction despite overexpression of APP (Masliah et al. 2001). The formation of neurofibrillary tangles (NFT) is not observed in most of the APP overexpressing models (Ribeiro et al.

2013). Studies on generation of AD transgenic mice models using Tau protein have revealed that only minor motor impairments with little Tau protein accumulation (mostly in brain and spinal cord), however classic NFT are not observed (Eriksen and Janus 2007; Wiedlocha et al. 2012). Another important issue is that many different mice strains or hybrid strains have been used for developing transgenic mice models (Joseph et al. 2001). The strain heterogeneity makes it difficult to compare transgenic models, as there are strain specific differences in the performance of behavioral tasks have been observed (Joseph et al. 2001). Hybrid mouse strains can also have vision problems that confound any results obtained from behavioral testing (Joseph et al. 2001; Brown 2007). Another aspect of AD pathology, such as the location of Aβ plaques and neurofibrillary tangles, vary depending on the promoter region used for the incorporation of transgene into the animal's genome (Braidy et al. 2012; Lecanu and Papadopoulos 2013). Therefore, different models using similar genetic mutations can produce very different brain pathologies and cognitive deficits. Collective evidence suggests that presently available mice models do not fulfill above mentioned criteria. Thus, at the present time an ideal animal model for AD is not available (Cuadrado-Tejedor and García-Osta 2014). It is worth noting that almost all transgenic models only related to the familial early onset form of AD, which represents a mere 5 % of AD cases. The remaining 95 % are sporadic late-onset forms, the causes and pathogenesis of this form remain elusive. Converging evidence thus suggest that at present mouse models display some neurochemical, neuropathological, and behavioral alterations of AD. However, they do not recapitulate all aspects of human AD. Furthermore, failure of AD immunotherapy in mouse models indicates that there is a need for developing superior models of the AD pathology with cognitive dysfunction.

The ideal transgenic model should mimic multiple aspects of the disease including its etiology and a time dependent progression of the pathology, involving similar structures and cells similar to the human pathology. Identifying and targeting the cognitive deficits that occur early in the course of the human AD are critical for producing the maximum impact of treatment on cognitive function and quality of life in AD patients. Earliest neuropathological changes in human AD occur in hippocampus and entorhinal cortex, followed by changes in the medial temporal lobe. In human AD the earliest detectable deficits in cognition are seen in medial temporal lobe-dependent episodic memory (Schmitt et al. 2000; Smith et al. 2007). These early deficits in episodic memory are followed closely by deficits in semantic memory, and both are developed before other deficits in cognitive domains such as attention, visuospatial memory, or executive function (Bondi et al. 2008). These observations support the view that cognitive functions such as episodic and semantic memory that depend heavily on the neural circuitry of the medial and lateral temporal lobes may be impaired earlier than cognitive abilities depending on the circuitry of other brain regions. The development of cognitive deficits in mouse models of AD shows similar, but not identical patterns of progression suggesting that mouse transgenic models do not fully recapitulate the inevitable neuronal loss. Some transgenic mice fail to even demonstrate the phenotypic alterations associated with the modeled diseases, providing further evidence that humans and primates can be more vulnerable than

rodents to the same triggers inducing neurodegeneration, a phenomenon also observed in pharmacological models (Przedborski et al. 2001).

Rats offer numerous advantages over mice for the development of animal models. The rats are physiologically, genetically and morphologically closer to humans than mice (Jacob and Kwitek 2002). Their larger body and brain size facilitates intrathecal administration of drugs, microdialysis, multiple sampling of cerebrospinal fluid, in vivo electrophysiology, as well as neurosurgical and neuroimaging procedures (Tesson et al. 2005). Like humans, the rat contains 6 isoforms of Tau (Hanes et al. 2009; Tran et al. 2013), although the ratio of 4R/3R Tau isoforms is different (9:1 in rats; 1:1 in humans). In addition, rats not only share a good homology with humans in apoE amino acid sequences (73.5 % with human apoE3, 73.9 % with apoE4), but also show finer and more accurate motor coordination than mice and exhibit a richer behavioral display (McLean et al. 1983). Based on these advantages, it is suggested that rats can be used for developing better animal models of AD than mice (Carmo and Claudio Cuello 2013).

The earliest transgenic rat models of AD show accumulation of intracellular Aβ but no senile plaques. Lack of senile plaques may be due to inadequate Aβ levels, since higher concentrations are required to initiate the Aβ deposition. Some of these models also show synaptic dysfunction supporting the view that cognitive deficits are independent of plaque formation but correlate better with Aβ oligomers and other Aβ species (Millington et al. 2014). In contrast, UKUR25 and UKUR28 transgenic rat strains show an accumulation of intracellular Aβ-immunoreactive material in pyramidal neurons of the neocortex and in CA2 and CA3 regions of the hippocampus. These rat models not only support the role of Aβ in the amyloid cascade at the early and pre-plaque phase of the amyloid pathology, but also show dysregulation of ERK2 activation in the brain (Echeverria et al. 2004a) (Table 2.2). Furthermore, it is also reported that accumulation of Aβ is sufficient to trigger the initial steps of the tau-phosphorylation cascade, which may be responsible for impairments in learning and alterations in the MWM task (Echeverria et al. 2004a). Collective evidence suggests that rat models of AD in rats show significant changes in synaptic proteins and memory formation (Vercauteren et al. 2004).

Table 2.2 Animal models of AD in rat that have been used for obtaining information on AD pathogenesis

Name of animal models	Reference
McGill-R-Thy1-APP	Leon et al. (2010)
UKUR25	Echeverria et al. (2004b)
UKUR28	Echeverria et al. (2004b)
Tg6590	Kloskowska et al. (2010)
Tg478	Flood et al. (2009)
Tg1116	Flood et al. (2009)
Tg11587	Liu et al. (2008)
APP21	Agca et al. (2008)
APP31	Agca et al. (2008)

Several transgenic mouse models expressing mutated forms of human Tau containing neurofibrillary degeneration have also been developed (Mocanu et al. 2008; Ramsden et al. 2005). Transgenic mouse model only show minor motor impairments and tau protein accumulation (mostly in brain and spinal cord), however classic NFT are not observed. Behavior analysis of mice and rat models has indicated that rats not only show more progressive cognitive decline in spatial navigation, but also display disturbances in sensorimotor and reflex responses (Hrnkova et al. 2007) than mice. These impairments correlate with the progressive accumulation of argyrophilic NFTs, mature sarcosyl-insoluble Tau complexes, and extensive axonal damage in the brain stem and spinal cord. Although, hyperphosphorylated Tau is present in cortex and hippocampus, but no neuronal loss or occurrence of neurofibrillary tangles has been observed in the brain (Hrnkova et al. 2007). These rats also show a decrease in lifespan (Zilka et al. 2006; Koson et al. 2008).

Infusion of low doses of LPS into rat brain ventricular system results in an animal model with neuroinflammation. This animal model has several parallels characteristics of human AD, including increase in microglial cell activation, onset of astrogliosis, and elevation in tissue levels of IL-1β and TNF-α, elevation in levels of APP (Hauss-Wegrzyniak et al. 1998; Wenk, et al. 2000), along with deficit in the working memory (Hauss-Wegrzyniak et al. 1998, 1999a, b). Above mentioned neurochemical and immunochemical changes have been quantified by Magnetic Resonance Imaging (MRI) in the animal model and AD patients (Bobinski et al. 1999; Forloni et al. 1992). It is also reported that like human AD, the chronic LPS infusion into the ventral forebrain in animal model also results in chronic IL-1β or TNF-α increase and selectively degeneration of cholinergic cells in a time- but not dose-dependent manner (Wenk and Willard 1998; Willard et al. 1999). In the LPS infusion animal model, behavioral, biochemical, and pathological deficits induced by chronic LPS infusion are reversible with chronic administration of either an NSAID (Hauss-Wegrzyniak et al. 1999a, b) or an IL-1RA (Bluthe et al. 1992).

It should be noted that NSAID-mediated beneficial effect is observed only in young rats, with no significant attenuation of the deficits in old rats (Hauss-Wegrzyniak et al. 1999b). NSAID therapy does not have any effect in human AD patients.

There are fundamental differences gene expression, neural circuitry, brain size, proportions of gray and white matters, and neurochemical responses between rodent and human brains. Nonhuman primates (great apes, baboons, macaques, and marmosets) due to genetic lineages share many structural and functional features with humans. So they may provide better animal model for AD than rodents (Finch and Austad 2012). It is realized that the management and care of nonhuman primates are more complicated and the related costs are much higher. Despite of these complications, use of nonhuman primate animal models may provide information on higher intellectual functions such as planning of complex cognitive behaviors, personality expression, decision-making and moderating social behavior (Sutcliffe and Hutcheson 2012).

2.3 Neurotoxin-Based Animal Models for Alzheimer Disease

Neurotoxin-based models involve the disruption of multiple neurotransmitter systems, which partially contribute to the pathophysiology of neurochemical, cognitive, and behavioral disturbances associated with AD. The majority of animal models within this category are based Aon the cholinergic hypothesis of AD (Craig et al. 2011), which states that loss of cholinergic function in the brain contributes significantly to the cognitive decline associated with advanced age and AD (Bartus 2000). Degeneration of cholinergic neurons in the nucleus basalis of Meynert, situated in the basal forebrain and primarily projecting to the neocortex, occurs early in the course of AD (Whitehouse et al. 1982; Dournaud et al. 1995). Intraparenchymal or intracerebroventricular microinjections of glutamate analogs (quinolic, kainic, N-methyl-D-aspartic, ibotenic and quisqualic acids) and the cholinotoxin (AF64A) have been used to generate animal models for AD (Fig. 2.3) (Toledana and Álvarez 2010). Glutamate analogs induce degeneration of glutamatergic neurons, where as AF64A preferentially triggers degeneration of cholinergic neurotransmission (Stephens et al. 1987; Nakahara et al. 1988).

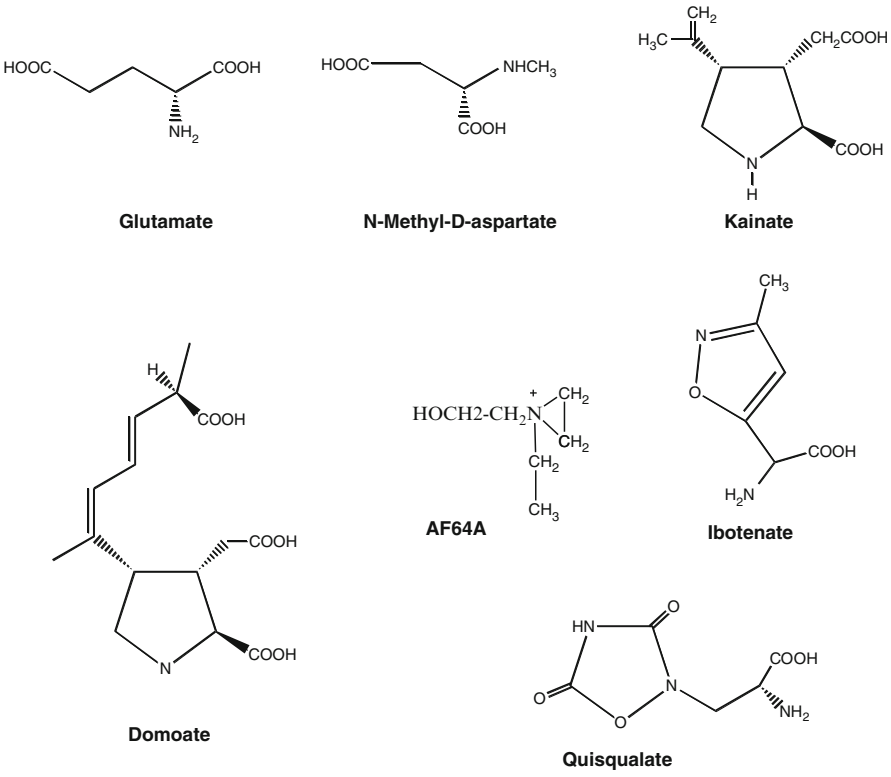

Fig. 2.3 Chemical structures of neurotoxins used for developing animal models of Alzheimer disease

2.3.1 *Cholinergic and Glutamatergic Signaling Animal Models of Alzheimer Disease*

It is well known that both cholinergic and glutamatergic neurons are located in the hippocampus and in the frontal, temporal and parietal cortex are severely affected in AD, whereas similar neurons in the motor and sensory cortex are relatively spared (Francis 2003). Since the hippocampus and cortex are essential for learning and memory, it is possible that degeneration of cholinergic and glutamatergic neurons may be an early event in the pathogenesis of AD (Kar et al. 2004; Morris 2002). Studies on animal models of AD have indicated that upregulation of cholinergic presynaptic boutons occurs before the involvement of glutamatergic terminals, thus raising the possibility that a compromised cholinergic system may affect the functioning/survival of glutamatergic neurons in the brain (Bell and Cuello 2006). Indeed, pyramidal neurons of the cortex that use glutamate as their primary transmitter are known to possess both cholinergic and glutamatergic receptors and receive inputs from the basal forebrain cholinergic neurons (Francis 2003).

Neurochemical investigations on tissues from biopsy and autopsy of the brains of individuals with AD have indicated that a profound reduction in the activity of the ACh-synthesizing enzyme, choline acetyltransferase (ChAT), in the neocortex, which correlates positively with the severity of dementia (Geula and Mesulam 1994; Lander and Lee 1998; Davies and Maloney 1976). Reduced choline uptake, ACh release and loss of cholinergic neurons from the basal forebrain region further indicate a selective presynaptic cholinergic deficit in the hippocampus and neocortex of brains of individuals with AD. ACh exerts effects on the central nervous system by interacting with G-protein-coupled muscarinic and ligand-gated cation channel nicotinic receptors. It is generally believed that M2 receptors, most of which are located on presynaptic cholinergic terminals, are reduced in the brains of individuals with AD (Lander and Lee 1998; Nordberg, et al. 1992). The density of postsynaptic M1 receptors remains unaltered, but there is some evidence for disruption of the coupling between the receptors, their G-proteins and second messengers (Nordberg et al. 1992; Warpman et al. 1993). Administration of acetylcholine agonists (pilocarpine and nicotine) increases learning and memory levels, but acetylcholine antagonists (scopolamine and succinylcholine) decreases learning and memory. Some studies have shown that during learning, the level of acetylcholine is increased in the amygdala, which plays an important role in memory consolidation (McGaugh 2004). It appears that the cholinergic system is involved in mediating this process (McGaugh 2004). The perfect performance of central cholinergic systems (nicotinic and muscarinic systems) is important for consolidation with shuttle box. Administration of acetylcholine agonist and antagonist via ICV affects the consolidation, in a dose-dependent manner (Eidi et al. 2006).

Stimulation of glutamate receptor results in breakdown of neural membrane phospholipids (phosphatidylcholine and plasmalogen) by the stimulation of cytosolic phospholipase A_2 ($cPLA_2$) and plasmalogen-selective phospholipase A_2 (PlsEtn-PLA_2). Stimulation of $cPLA_2$ increases the levels of arachidonate-derived

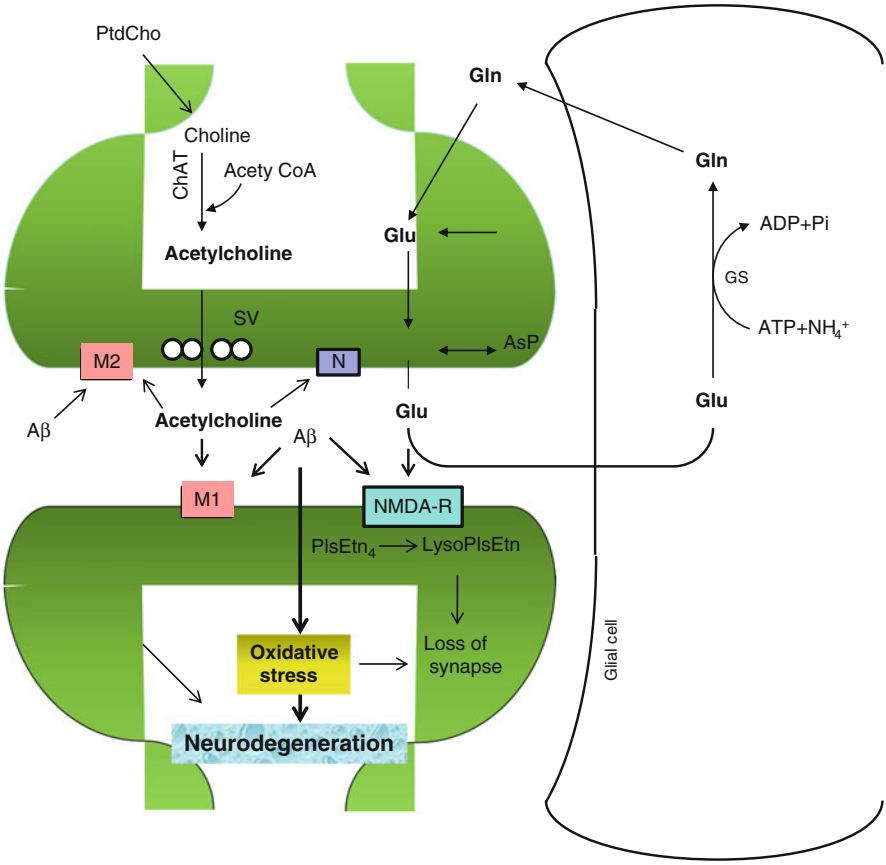

Fig. 2.4 Activities of cholinergic and glutamatergic neurons in the pathogenesis of Alzheimer disease. Amyloid precursor protein (*APP*); β-amyloid (*Aβ*); glutamate (*Glu*); glutamine (*Gln*); NMDA receptor (*NMDA-R*); plasmalogen (*PlsEtn*); 4 (plasmalogen-selective phospholipase A_2); lyso- plasmalogen (*lyso-PlsEtn*); neural membrane phosphatidylcholine (*PtdCho*); muscarinic M1 receptor (*M1*); muscarinic M2 receptor (*M2*); synaptic vesicles (*SV*); and presynaptic nicotinic receptor (*N*)

enzymic and non-enzymic lipid mediators (eicosanoids and 4-HNE, malonaldehyde, respectively), whereas activation of PlsEtn-PLA_2 catabolizes plasmalogen, which are major component of synaptic plasma membrane leading to the loss of synapse (Figs. 2.1 and 2.4). These observations support the view that there is a neurochemical basis of interactions between cholinergic and glutamatergic systems and their potential implications in triggering pathological abnormalities in Alzheimer disease (Revett et al. 2013).

Overstimulation of NMDA receptors for longer time period (i.e., more than 24 h) increases amyloidogenic APP processing and formation of high levels of Aβ (Bordji et al. 2010; Lesné et al. 2005). In AD, the accumulation of Aβ not only enhances neuronal sensitivity to glutamate, but also increases the activity of synaptic networks,

resulting in excitatory potentials and Ca^{2+} influx (Brorson et al. 1995). Aβ-mediates its toxic effect either by facilitating Ca^{2+} influx into neurons leading to the activation of Ca^{2+}-dependent enzymes or by forming an oligomeric pore in the membrane. These processes may stimulate more glutamate release from glutamatergic axon terminals and/or increase intracellular calcium concentration in dendrites, thus rendering neurons vulnerable to excitotoxicity (Bobich et al. 2004; Bezprozvanny and Mattson 2008). Aβ oligomers can also promote the generation of ROS, which may trigger membrane-associated oxidative stress leading to impairment in the functions of ion-motive ATPases and glutamate and glucose transporters rendering neurons vulnerable to excitotoxicity (Camandola and Mattson 2011). Overstimulation of glutamate receptors may not only result in the collapse of mitochondrial potential and deregulation of calcium homeostasis, but also production of high levels of ROS, 4-hydroxynonenal (4-HNE), and other arachidonic acid-derived lipid mediators (Farooqui and Horrocks 2006). 4-HNE forms adducts with membrane proteins including those crucial for maintaining ATP levels, resting membrane potential and extracellular glutamate levels (Esterbauer et al. 1991; Farooqui 2011).

Changes in Tau metabolism are also related with NMDA receptor function. Tau has a dendritic function in postsynaptic targeting of the Src kinase Fyn, which phosphorylates the NMDA receptor (Suzuki and Okumura-Noji 1995). Missorting of Tau in transgenic mice expressing truncated Tau or absence of Tau in Tau knockout mice disrupt postsynaptic targeting of Fyn. Reduced expression of Tau uncouples NMDA-mediated excitotoxicity and mitigates Aβ toxicity (Ittner et al. 2010). Reducing endogenous Tau levels prevent behavioral deficits in transgenic mice expressing human APP, and protect both transgenic and nontransgenic mice against excitotoxicity (Roberson et al. 2007). Collective evidence suggests that chronic neuronal excitotoxicity may contribute to AD via promoting abnormal hyperphosphorylation of tau (Liang et al. 2009).

2.3.2 Aluminum in the Development of Animal Models of Alzheimer Disease

Aluminum is the most common metal and the third most abundant element in the earth's crust (Exley 2012). Humans get exposed to toxic levels of aluminum via common products such as antiperspirants, antacids, food, water, aluminum-based household products, cosmatics, and vaccines. In vitro and in vivo studies have indicated that aluminum produces oxidative stress though it is devoid of redox capacity in biological systems (Sharma et al. 2013; Satoh et al. 2005). Aluminum produces apoptotic cell death through the involvement of mitochondrial and endoplastic reticulum-mediated oxidative stress processes associated with caspase 9, caspase 12, and caspase 3 activation (Rizvi et al. 2014).

Levels of aluminum are significantly increased in brains of patients with AD. The molecular mechanisms associated with neurotoxic action of aluminum in AD are not fully understood. However, in vitro studies indicate that at low levels aluminum

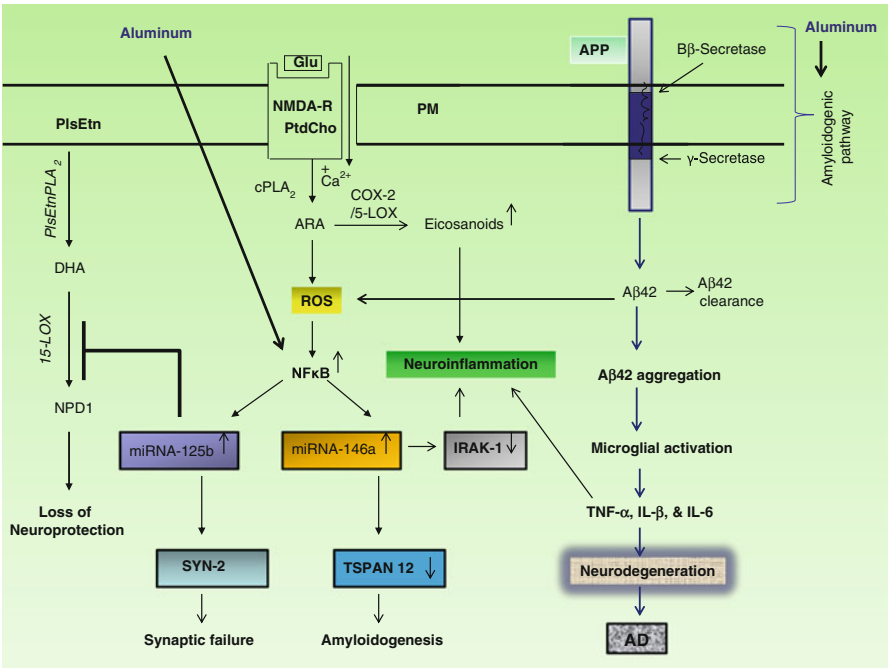

Fig. 2.5 Contribution of aluminum in the pathogenesis of Alzheimer disease. Amyloid precursor protein (*APP*); β-amyloid (*Aβ*); glutamate (*Glu*); NMDA receptor (*NMDA-R*); phosphatidylcholine (*PtdCho*); cytosolic phospholipase A_2 (*cPLA*$_2$); cyclooxygenase-2 (*COX-2*); lipoxygenase (*LOX*); arachidonic acid (*ARA*); docosahexaenoic acid (*DHA*); eicosanoids (prostaglandins, leukotrienes, and thromboxanes); neuroprotectin D1 (*NPD1*); reactive oxygen species (*ROS*); nuclear factor-κB (*NF-κB*); tumor necrosis factor-α (*TNF-α*); interleukin-1β (*IL-1β*); interleukin-6 (*IL-6*); interleukin-1 receptor-associated kinase (*IRAK*); synapsin-2 (*SYN-2*), and tetraspanin-12 (*TSPAN12*)

induces Tau aggregation (Mizoroki et al. 2007). Aluminum may also modulate Aβ aggregation, oligomerization, and ROS-mediated neurotoxicity (Fig. 2.5) (Bharathi et al. 2008; Rondeau et al. 2009a, b; Rodella et al. 2008; Walton and Wang 2009; Yumoto et al. 2009). Aluminum not only alters normal processing of Aβ precursor protein (Drago et al. 2008), but also stimulates amyloidogenesis. In addition, aluminum inhibits the proteolytic degradation of Aβ peptide via cathepsin D, triggering the intracellular accumulation of Aβ peptide (Sakamoto et al. 2006). Therefore, many primary therapeutic goals are targeted at reducing the metal-induced Aβ aggregation into toxic components. One of the therapeutic strategies is development of the agents that can chelate metal ions (Zatta et al. 2009) and to prevent the metal ions from the interaction with Aβ peptide as well as to attenuate the metal-induced redox activity and neurotoxicity of the peptides (Rodríguez-Rodríguez et al. 2009).

Chronic intragastric (i.g.) administration of aluminium gluconate (Al^{3+} 200 mg/kg per day) not only results in significant increase of hippocampal metal ion levels (Al, Fe, Mn, Cu and Zn), but also causes learning and memory function disorders in rats (Yu et al. 2014). Aluminium gluconate administration-mediated chronic brain

damage in rats can be prevented by meloxicam, a COX-2 inhibitor (Su et al. 2009) suggesting that the over-expression of COX-2 may play an important role in the neurodegeneration, and the inhibitors of COX-2 may prevent the acute and chronic brain damages mediated by aluminium gluconate. In addition, aluminum stimulates NF-κB, which is involved in IL-1 receptor-associated kinase (IRAK)-mediated neuroinflammation (Zhao et al. 2014). Aluminum has also been reported to inhibit brain carbohydrate metabolizing enzymes and utilization of carbohydrates. This may be one potential mechanism by which aluminum may act as a neurotoxicant (Lai and Blass 1984). Contribution of aluminum in the pathogenesis of AD is supported by several recently described observations: (a) aluminum promotes inflammatory signaling through the activation of NF-κB (Bondy 2013; Walton 2013) and (b) aluminum induces strikingly similar messenger RNA (mRNAs) and micro RNAs (miRNAs) to those found to be increased in AD. These miRNAs (miRNA-9, miRNA-34a, miRNA-125b, miRNA-146a, and miRNA-155) are under transcriptional control by the pro-inflammatory transcription factor NF-κB. Among these miRNAs subfamily, miRNA-125b occurs abundantly in human brain. Bioinformatics analysis has demonstrated that an up-regulated miRNA-125b may potentially target the 3′ untranslated region (3′-UTR) of the messenger RNA (mRNA) encoding (a) a 15-lipoxygenase (15-LOX) (Zhao et al. 2014), the enzyme that oxidizes and facilitates the conversion of docosahexaneoic acid into neuroprotectin D1 (NPD1), a docosanoid, which is closely associated with neuroprotective effects of docosahexaenoic acid (Farooqui 2009, 2011). In addition, dietary aluminum enhances lipid peroxidation, oxidative stress, apoptosis, and gene expression deficits in transgenic animal models of AD (Praticò et al. 2002; Bharathi et al. 2008; Zhang et al. 2012b). Finally, like human AD, the administration of aluminum in animal models contributes to alterations in chromatin, impairment in ATP production and utilization (Lukiw and Pogue 2007; Pogue et al. 2012; Bhattacharjee et al. 2013). Furthermore, in aged rats, aluminum treatment alters levels of copper, zinc, and manganese in certain brain regions and results in an enlargement of hippocampal mossy fibers (Fattoretti et al. 2004). In rat brain, aluminum -induced damages to the brain include neuropathological, neurochemical, neurophysiological, and neurobehavioral alterations. Among the alterations, the most notable are poor learning and behavioral functions, which involve changes in acetylcholinesterase, an enzyme, which is closely associated with deterioration of the learning ability of rats (Kawahara and Kato-Negishi 2011). The animal models show that subcutaneous injections of aluminum hydroxide induce apoptotic neuronal death, decrease in motor function, and increase in anxiety in mice (Shaw et al. 2013). Rabbits have been reported to very sensitive to aluminum exposure, with intracerebral and intravenous infusions reproducing some of the pathological features consistent with AD (Savory et al. 2006). However, oral administration of aluminum has proven less successful in inducing pathological features of AD. AD models mentioned above have been used to gain knowledge not only on molecular mechanism of action of neurotoxins, but also on the neural mechanisms underlying memory dysfunction caused by neurotoxins. This has resulted in better understanding of cholinergic innervations in the aetiology and treatment of AD. The suitability of neurotoxin models has been questioned

because conflicting and controversial results due to the chemical nature of lesion-inducing neurotoxins, concentration of neurotoxin used, and even the morphological, histochemical, biochemical and cognitive methods used to produce phenotypes in the model (Toledana and Álvarez 2010). Neurotoxin-based models produce neurodegeneration in hippocampus and cortical areas in animal, but neurotoxin models have failed to replicate the classic pathological hallmarks and the insidious and progressive nature of the human AD (Toledana and Álvarez 2010).

2.3.3 Transgenic Models of Alzheimer Disease

Most transgenic mouse models are generated by microinjecting complementary DNA (cDNA), containing a transgene of interest into the pronucleβ of a large number of zygotes (Cho et al. 2009). Resulting embryos are then implanted into pseudopregnant dams for normal gestation. Generating gene targeted mice is a complex process (Cho et al. 2009; Platt et al. 2013). Creating viable mice takes many attempts, and consumes a significant amount of resources. After the initial genetic modification has been introduced, a new mouse line can be crossed into a pre-existing mouse line that already displays one or more other aspects of the disease neuropathology. Hence, given sufficient time, funding, and resources one can build increasingly complex mice models of the AD. Using transgenic mice many AD models have been developed. These mice not only overexpress mutant forms of human APP, presenilins, and/or tau protein in the brain, but also show many neurochemical characteristics. Thus, knockout mice have been designed and developed for alterations in APP, secretases, i.e., BACE, PSEN1 and PSEN2, ADAM10 (Shen et al. 1997; Luo et al. 2001; Lee et al. 2003) as well as for APP and Tau proteins. Examples these models are Tg2576, PDAPP, TgAPP23, Tg-APPswe/PS1dE9, 3xTg-AD, and 5XFAD mice. The list of transgenic AD models is available at the web site of the Alzheimer Research Forum (http://www.alzforum.org/res/com/tra/default.asp). Many of the transgenic AD models show accumulation of Aβ, plaque pathogenesis, gliosis, neuronal loss, Tau pathology, and/or cognitive impairments, but no single transgenic AD model recapitulates all aspects of AD neurochemistry and pathology. Using above mouse transgenic models, most investigators have focused their attention on understanding the molecular mechanism related to suppression of genes that encode proteins that contribute to the pathogenesis AD along with neurobehavioral and pathological changes. The comparative analysis of these AD models suggests that AD models can be classified into two distinct plaque deposition groups. Early plaque depositing models such as APPswe/PS1dE9, 3xTg-AD and 5XFAD, which may be useful to study the biochemical aspects of APP metabolism, whereas late plaque depositing models such as Tg2576, PDAPP, and TgAPP23, which can provide useful information on physiological and environmental aspects of AD pathogenesis, which occur on a longer time scale (Shen et al. 1997; Luo et al. 2001; Lee et al. 2003; Lee and Han 2013). More than 20 autosomal dominant APP mutations linked to AD have been discovered (http://www.molgen.ua.ac.be/ADMutations). These mutations

show enhancement in the aggregation of Aβ by several mechanisms such as Swedish mutation, Arctic mutation, and a mutation near the γ-secretase site. Swedish mutation promotes APP cleavage near the β-secretase site (Mullan et al. 1992) leading to enhancement in overall production of all forms of Aβ. The Arctic mutation (a mutation within Aβ) enhances protofibril formation (Nilsberth et al. 2001). Several mutations near the γ-secretase site increase the relative production of the Aβ42 (Goate et al. 1991; Murrell et al. 2000). The impact of β-secretase deletion in wild-type mice produces subtle changes in anxiety and sensorimotor abilities (Kobayashi et al. 2008) leading to enhancement in long-term depression (Wang et al. 2008). In contrast, β-secretase manipulations in APP overexpression models not only prevent amyloid pathology, neurodegeneration, and astrogliosis, but also restore cognitive deficits (Ohno et al. 2007). Restoration of long-term potentiation and improved cognitive performance are also reported after partial reduction of β-secretase in 5xFAD animals (Kimura et al. 2010). Conversely, human *bace1* (*hbace1*) coexpression in mice carrying human app_{swe} (Mohajeri et al. 2004) or app_{695} (Chiocco et al. 2004) elevates APP processing and the release of toxic Aβ42, sAPPβ, C99, and C89 terminal fragments. These findings support the view that β-secretase is the key enzyme in amyloidosis, and its inhibition can be used as a target for the treatment of AD.

To avoid the complications of transgenic protein overexpression, attempts have also been to generate more physiologically relevant animal models of AD. Thus, AD knock-in models are generated by introducing human *APP* and/or *PSEN1* FAD mutations and humanized Aβ to the endogenous mouse gene (Guo et al. 2012; Flood et al. 2002; Köhler et al. 2005). Knock-in mice with human *APP* have several advantages over the traditional transgenic models. Due to the presence of native promoter control mice containing human *APP* show physiological levels of protein expression without any changes in the temporal and spatial expression patterns. In contrast to transgenic models in which the existence of mouse proteins may complicate the phenotypes, the mouse gene products are replaced with the humanized mutant proteins in knock-in models. In contrast to human AD, Knock-in mice show the expression of human Aβ, but no tau abnormality has been reported. Duplications of the APP gene also lead to the induction of all forms of Aβ (Sleegers et al. 2006). Recently, an autosomal recessive mutation involving the deletion of glutamate at Aβ residue 22 has been discovered in a woman with dementia who apparently lacks amyloid plaques imaged with PiB (Tomiyama et al. 2008). This discovery raises possibility that amyloid plaques may not be required for the onset of neurodegeneration in AD. Studies on the effect of genetic ablation of Nrf2 on APP/Aβ processing and/or aggregation as well as changes in autophagic dysfunction in APP/PS1 mice indicate that there is a significant increase in inflammatory response in APP/PS1 mice lacking Nrf2. These changes are accompanied by increase in intracellular levels of APP, Aβ (1-42), and Aβ (1-40) without a change in the total full-length APP. APP/PS1 mouse with Nrf2 deficiency not only displays a shift in APP and Aβ levels in the insoluble fraction, but also show an increase in poly-ubiquitin conjugated proteins. APP/PS1-mediated autophagic dysfunction is also enhanced in Nrf2-deficient mice. Finally, neurons in the APP/PS1/Nrf2-/- mice display an increase in the accumulation of multivesicular bodies, endosomes, and lysosomes (Joshi et al. 2015).

In vitro and in vivo studies strongly indicate that high level of Aβ peptide is the primary causative agents in the pathogenesis of AD (Tanzi and Bertram 2005). Reduction in Aβ clearance and its deposition is one potential mechanism leading to increased cerebral Aβ levels in AD. However, it is also possible that small increases in Aβ production over time may tip the balance toward Aβ accumulation. *APP* mutant mice show an age-dependent extracellular plaque deposition primarily in neocortex and hippocampus, accompanied by severe gliosis. Most *APP* mutants contain no neurofibrillary tangles. However, they do contain amyloid deposits and hyperphosphorylated Tau but without tangles (Tiraboschi et al. 2004). One exception is the transgenic model expressing *APP, PS1,* and *Mapt* (3xTg-AD) characterized by Aβ plaques and neurofibrillary tangles (Oddo et al. 2003). The number of CA1 neurons is inversely correlated with CA1 plaque load and neuron loss was observed primarily in the vicinity of extracellular plaques. The molecular mechanisms linking Aβ and tau pathologies remain elusive. According to the Aβ cascade hypothesis, excessive amount of Aβ peptides generated by abnormal APP metabolism initiates the pathogenesis of AD, which leads to Aβ plaque formation, tau hyperphosphorylation, and neurodegeneration (Karran et al. 2011). This hypothesis is supported by AD genetics (Golde et al. 2011), but not by mouse AD model studies. In APP transgenic line J20 model the aggressive deposition of Aβ is not accompanied by enhanced Tau phosphorylation (Roberson et al. 2007). Aβ and Tau hyperphosphorylation coexist but in an independent manner in a double transgenic mouse model of human mutant APP (APP23) and wild type tau (ALZ17) (Clavaguera et al. 2013). Thus, more studies are needed on mechanisms linking Aβ and Tau pathologies. Collective evidence suggests that transgenic models have provided some valuable information on the molecular mechanism and understanding of AD progression, but they still do not recapitulate all aspects of human AD (Zheng et al. 1996; Takei et al. 2000).

Presenilin knockout mice have also been reported to display marked neurodegeneration in cerebral cortex along with loss of memory and induction of synaptic dysfunction (Shen et al. 1997; Saura et al. 2004). Thus far, over 200 autosomal dominant mis-sense mutations have been reported in the genes for APP and presenilin (the γ-secretase catalytic subunit). These mutations may contribute to FAD, which are found very near to the β- and γ-secretase cleavage sites. They may not only contribute to increase APP processing, but also mediate the elevation in levels of total Aβ as well as Aβ42. BACE is the exclusive β-secretase, which controls the production of Aβ and has an essential role in the etiology of AD. Knockout mice for β-secretase have also been generated. They do not produce Aβ and are perfectly viable tool for understanding the neurochemical mechanisms of pathogenesis of AD (Luo et al. 2001; Roberds et al. 2001). However, BACE knockout mice show significant decrease in the intensity of myelination and reduction in myelin thickness (Hu et al. 2006; Willem et al. 2006), supporting the view that BACE may play an important role in myelinogenesis and brain development.

Several transgenic or gene-targeted mouse lines expressing human apoE3 or apoE4 have also been developed, without co-expression of mutant hAPP. Transgenic mice expressing apoE4 in neurons on a murine *Apoe* knockout background show age- and female gender-dependent spatial learning and memory deficits, which are not seen in neuron-specific apoE3 mice (Raber et al. 2000). Morphological studies have shown that neuronal apoE3, but not apoE4, retards the age-dependent neuronal death in apoE-null mice (Buttini et al. 1999, 2010). ApoE4 not only impairs synaptogenesis, but also decreases dendritic spine density in vivo in apoE transgenic and gene-targeted mice as well as in primary neuronal cultures (Brodbeck et al. 2011; Dumanis et al. 2009). In addition, neural stem cells in adult mice express apoE and apoE4 impairs adult hippocampal neurogenesis (Li et al. 2009b), which may contribute to apoE4-mediated impairment in learning and memory and cognitive function. Since there is no Aβ accumulation in any of these apoE4 mouse models, which support the view that an Aβ-independent role of apoE4 in inducing neuronal and behavioral deficits in vivo. While many of the above mentioned transgenic mice accumulate Aβ and develop Aβ plaque pathology along with cognitive impairment, they are unable to induce NFT formation. To determine the contribution of tau protein hyperphosphorylation in the pathogenesis of AD, several mouse models have been established that overexpress either wild-type or mutated human tau protein. It is reported that Tau protein mutations are associated with frontotemporal dementia, but not with AD (Duyckaerts et al. 2008). Introduction of human Tau proteins containing FTD mutations result in NFT formation (Gotz et al. 2001; Lewis et al. 2000; Tanemura et al. 2002; Allen et al. 2002). Tau protein containing G272V and P301S mutations produce both NFT formation and severe cognitive deficits (Schindowski et al. 2006). In an effort to model NFT pathology that is relevant to AD rather than FTD, tau knockout mice were crossed with mice expressing human genomic tau protein, resulting in mice expressing human but not murine tau protein (hTau). However, these mice express minimal NFT pathology (Andorfer et al. 2003).

It is becoming increasingly evident that type 2 diabetes mellitus and metabolic syndrome are risk factors for stroke, AD, and depression (Farooqui et al. 2012; Farooqui 2013). Due to improved treatments, type 2 diabetes mellitus patients are living longer, putting them at increased risk for age-related complications along with risk of stroke, AD, and depression. Recent studies have described the generation of a novel mouse model combining the key features of obesity, diabetes, and AD. In these studies, the obese and diabetic *db/db* mouse (Srinivasan and Ramarao 2007) is crossed with the $APP^{\Delta NL/\Delta NL} \times PS1^{P264L/P264L}$ knock-in model of AD (Reaume et al. 1996; Siman et al. 2000; Niedowicz et al. 2014). The resulting mice are called *db/AD*. These mice are morbidly obese, have glucose intolerant, show insulin resistance, and display parenchymal amyloid plaques similar to the parental lines. In addition, these mice show profound cognitive impairment and marked cerebrovascular abnormalities, which are Aβ/tau-independent mechanism. Long term consumption of high-fat diet is known to induce the accumulation of Aβ not only in the brain of wild type rabbits, rodents, and APP Tg mice (Sparks et al. 1994; Refolo

et al. 2000; Ho et al. 2004), but also in humans (Farooqui 2015). The molecular mechanisms associated with high-fat mediated Aβ accumulation in the brain are not fully understood. However, autophagosome-mediated enhancement in amyloidogenic APP processing (Son et al. 2012) or up-regulation of BACE1 (Guglielmotto et al. 2012) may increase high-fat induced Aβ generation by above mentioned mechanisms. Furthermore, soluble Aβ itself is believed to reduce endothelial function and vascular reactivity in mice (Niwa et al. 2000) and humans (Dumas et al. 2012; den Abeelen et al. 2014). Collective evidence suggests that *db/AD* model is a unique. It can be used to study overlap among molecular mechanisms of obesity, type 2 diabetes mellitus, and AD in old animals.

2.4 Animal Models of Alzheimer Disease in Cell Culture

Attempts have been to establish Aβ-pathologies such as production, secretion, oligomerization and aggregation of Aβ peptides utilizing a novel platform to model the pathological processing of mutant human APPswe protein for Aβ genesis, oligomerization and aggregation, the initial events of AD pathogenesis (Ghate et al. 2014). Neurosphere cultures have been prepared from AD transgenic (*APPswe, PSEN1dE9*) mice embryos. These cultures not only show positive expression for both transgenes at the mRNA level and express humanized APP and its proteolytic products including Aβ peptides. Analysis of Tg+ve neurosphere lysates the presence of both monomeric and various oligomeric Aβ peptides similar to an 18-month old Tg+ve mouse brain homogenate. Tg+ve neurosphere cultures secrete a large amount of human Aβ peptides that consist of Aβ40 and Aβ42 with a very high Aβ42/Aβ40 ratio comparable to that of human AD brain homogenates and more than any cellular model of AD. Tg+ve culture supernatants also contain monomeric and various pathogenic Aβ peptide oligomers (ranging from 2-mer to 12-mer; the Aβ star oligomer) (Ghate et al. 2014). In addition, conformation-dependent immunocytochemistry demonstrated the presence of intracellular and extracellular Aβ peptides within neurospheres. The neurosphere culture system has many advantages over existing cellular models. Thus, (a) neurosphere cultures contain both brain stem and progenitor like cells, which can differentiate towards mature brain cells like neurons and astrocytes that are not possible in transformed cell lines, (b) these cultures can synthesize and secrete both Aβ peptides, (c) these cultures show high Aβ42/Aβ40 ratio, (d) produce pathogenic Aβ peptide oligomerization, which is comparable with the animal models of AD and much higher than existing cellular models of AD, including iPSC based models of AD (Israel et al. 2012) and (e) demonstrate intracellular and extracellular aggregation of Aβ peptides. It is proposed that studies with neurosphere cell culture may advance not only our understanding of pathogenesis of AD, but may provide better understanding of therapeutic agents on decreasing the beta amyloid synthesis and aggregation within neural cells (Ghate et al. 2014).

2.5 The Gap Between Mouse Models and Human Patients of Alzheimer Disease

The lack of an ideal animal model and specific biomarkers for AD progression makes it not only difficult to learn molecular mechanism associated with the pathogenesis of AD, but also complicate to discover the drugs that can prevent neurodegeneration in AD. At present mice models of AD mimic only few aspects of the disease, which are neither enough to learn about the molecular mechanism, specific biomarkers, and develop new treatment (Elder et al. 2010). Another possibility is that senile plaques and neurofibrillary tangles are endpoints for different disease-driving mechanisms. Thus, achieving a successful inhibition of Aβ and tau pathologies may not result in the successful for treating AD. AD is a multifactorial disease so its treatment may require a multitarget approach. To generate better animal models for AD, one has to develop better understanding of the molecular neuropathological mechanisms not only associated with neurodegeneration, but also behavioral and memory losses. Another important point is either the lack or low of neurodegeneration in animal models compared to human subjects, who show slow and continuous neurodegeneration with the progression of the disease. This is tempting to speculate that more research breakthroughs in development of animal models are needed for the development of models reflecting the heterogeneity of the disease (Cuadrado-Tejedor and García-Osta 2014). Also, discovery of specific biomakers is necessary not only to identify AD progression in a large population, but also for monitoring clinical trials and responses to medication.

2.6 Conclusion

AD is a multifactorial disease characterized by the accumulation of senile plaques, which are composed of oligomers of Aβ and neurofibrillary tangles and hyperphosphorylated Tau protein. In addition, neurochemical changes in AD include slow excitotoxicity, mitochondrial dysfunction, oxidative stress, and neuroinflammation. Neurotoxin-induce animal models of AD show very little neuropathological changes, but they induce mitochondrial dysfunction, oxidative stress, and neuroinflammation. Animal models for AD have been developed in both invertebrates (fruit flies and roundworms) and vertebrates (mice, rats, and rabbits). Most mice models are based on familial AD mutations of genes involved in the amyloidogenic process, such as the APP, MAPT, PS1, PS2 tau protein and apoE. Some models also incorporate Tau mutations, which are known to cause frontotemporal dementia, a condition, which shares some elements of neuropathology with AD. Transgenic mice develop several lesions similar to those of AD, including diffuse and neuritic amyloid deposits, cerebral amyloid angiopathy, dystrophic neurites and synapses, and amyloid-associated neuroinflammation. However, other features of AD, such as

neurofibrillary tangles, nerve cell loss, and significant memory deficits are not satisfactorily reproduced in these models. This suggests that despite various modifications specific to AD in the genome of animals, investigators have failed to create an ideal animal model, which can be fully characterized by all the pathological and neurochemical changes that can occur in AD. Nevertheless, the role of transgenic animals is undeniable, both in research on AD neuropathology and for testing new therapies, such as immunotherapy. It is well understood that it is difficult to reproduce all anatomical characteristics and cognitive ability of humans in mice because of lower-order of cognition found in mice. In addition, there are substantial anatomical differences between mouse and human brains, particularly that the mouse brain has a higher gray-to-white matter ratio. Still, transgenic mice have provided valuable genetic, neurochemical, and neuropathological information on AD. Better transgenic models of AD are needed for future research in higher animals, which are closer to humans not only in anatomy, but also in cognitive function, behavior and social responses.

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