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Amyloid Hypothesis and Alzheimer's Disease

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1. Introduction

This chapter reviews the major hypotheses in Alzheimer's disease (AD) research with the focus on amyloid hypothsis. Since amyloid hypothesis of AD pathology was proposed, extracellular amyloid β (Aβ) toxicity and its role of inducing synaptic plasticity and memory function has been studying intensively. Accumulating evidence indicates that Aβ also exists inside the neurons in AD. Intracellular Aβ has great impact on a variety of cellular events from protein degradation, axonal transport, neuronal firing, autophagy to apoptosis, suggesting an important role of Aβ in AD development, especially in the early stage. This chapter overviews the studies on the presence, production, metabolism and toxicity of extracellular and intracellular Aβ. Therapeutics targeting Aβ could be a new and effective treatment for early AD.

2. Overview of Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by age-related impairment in cognition and memory. The first AD case was reported in 1907 in Germany by Dr. Alois Alzheimer of a middle-aged woman who developed memory deficits and progressive loss of cognitive abilities. Many AD patients show clinical symptoms of severe memory loss and progressive cognitive difficulty in their 60's or 70's except the familial AD (FAD) patients who usually show clinical symptoms in their 40's (Price and Sisodia, 1998). These clinical symptoms include abnormalities of learning, memory, problem solving, speaking, calculation, judgment and planning (McKhann et al., 1984). The development of AD is progressive and can sometimes last for over decades. The development of AD can be divided into three stages according to clinical symptoms (Boller et al., 2002). In the mild stage of AD, patients first lose their short-term memory. They tend to forget the recent events, while they still remember the events that happened many years ago. Simple calculation and daily organization become more and more difficult. They become more and more passive for social activities and some of them develop depression and anxiety. In this stage, most of the patients can still maintain normal daily activities. The mild stage usually lasts for 2-3 years (Boller et al., 2002). The second stage of AD is the moderate stage. In this stage, patients cannot recognize family members. They are not able to communicate well with others since they lose thought flow or words during speaking. The daily self-care and housekeeping events of patients require more and more help from

others. Since the daily activities, such as feeding, cooking, dressing and bathing become more and more difficult, the patients are depressed and paranoid more easily (Boller et al., 2002). In the late stage of AD, patients completely lose the abilities to speak, solve problems and make decisions. Daily activities can be affected greatly and everyday life of patients totally depends on caregivers (Price and Sisodia, 1998; Boller et al., 2002).

3. AD pathological hallmarks

AD affects neurons in the neocortex, including the frontal lobe and the temporal lobe (Mann et al., 1985; Mesulam and Geula, 1988; Gomez-Isla et al., 1997), the entorhinal cortex and the hippocampus (Samuel et al., 1994; West et al., 1994; Gomez-Isla et al., 1997). Subcortical limbic areas such as the cholinergic neurons in the basal forebrain (Struble et al., 1986) and the neurons in the amygdala, the anterior nucleus of the thalamus, the raphe, and the locus coeruleus (Price and Sisodia, 1998), are also affected. It is suggested that the first area affected in the brain is the entorhinal cortex and then neurodegeneration progresses to the hippocampus and then to the cortex (Price and Sisodia, 1998).

3.1 Senile plaques

Senile plaques (SPs) are the extracellular proteinacous deposits found in AD patient brains. Deteriorated neurons are often seen near the SP area in the brain (McKhann et al., 1984; Morris et al., 1991; Defigueiredo et al., 1995; Price and Sisodia, 1998; Tseng et al., 1999; Urbanc et al., 1999; Alorainy, 2000). In the SPs, there are dystrophic neuritis. Astrocytes and microglia are often associating with the amyloid deposits (Defigueiredo et al., 1995; Tseng et al., 1999; Urbanc et al., 1999; Alorainy, 2000). The primary proteinacous material of SPs is amyloid β peptide (Aβ), a fibrillar peptide containing 40 to 42 amino acids derived from amyloid precursor protein (APP) (Glenner and Wong, 1984; Masters et al., 1985; Mori et al., 1992; Roher et al., 1993). There are four types of SPs often found in AD brains according to morphology (Defigueiredo et al., 1995; Gearing et al., 1995; Tseng et al., 1999; Urbanc et al., 1999; Alorainy, 2000): (1) Diffuse plaques are usually 10-200 μm in diameter with irregular shapes, in which Aβ is not aggregated into fibrils or deposits. Near these plaques, there are less NFTs and dystrophic neurites. The diffuse plaques are not detectable by Congo red or silver staining, but can be stained by Aβ antibodies. The diffuse plaques are close to neuronal cell bodies, that raises the possibility that the diffuse plaques may originate within the cell body as intracellular Aβ peptides (D'Andrea et al., 2001). The diffuse plaques appear in the DS patients, younger AD patients and other head injury patients (Defigueiredo et al., 1995; Gearing et al., 1995; Tseng et al., 1999; Urbanc et al., 1999; Alorainy, 2000; D'Andrea et al., 2001). All the above evidence suggests that diffuse plaques might be the earliest amyloid aggregates appearing in AD development and the origin of these diffuse plaques might be intracellular amyloid. (2) Primitive plaques are 20-60 μm in diameter, in which Aβ starts to form fibrils and NFTs that are detectable near these plaques. The primitive plaques associate less with the neuronal cell bodies, but more with astrocytes and glial cells. The primitive plaques appear in the older AD patients (Defigueiredo et al., 1995; Gearing et al., 1995; Tseng et al., 1999; Urbanc et al., 1999; Alorainy, 2000). (3) Classic plaques are the most significant type of plaques in AD brains. These plaques are also 20-60 μm in diameter and Aβ peptides form clearly visible aggregates and deposits of fibrils. These aggregates often induce a central dense core

structure surrounded by dystrophic neurites and a large amount of glial cells. The classic plaques are located throughout the hippocampus and the neocortex in advanced and older AD patient brains (Defigueiredo et al., 1995; Gearing et al., 1995; Tseng et al., 1999; Urbanc et al., 1999; Alorainy, 2000). (4) Compact plaques are similar to the classic plaques, with 5-15 μm in diameter, but lack the surrounding dystrophic neurites (Defigueiredo et al., 1995; Gearing et al., 1995; Tseng et al., 1999; Urbanc et al., 1999; Alorainy, 2000). Congo red and silver staining are the common cytochemical detectors for SPs. The Congo red dye forms non-polar hydrogen bonds with amyloid fibrils (Braak et al., 1989). The red to green birefringence occurs when viewed by polarized light due to parallel alignment of the dye molecules on the linearly arranged amyloid fibrils (Braak et al., 1989). Silver staining, on the other hand, detects pre-plaques or presumed early SPs, which cannot be stained by the conventional Congo red staining (Braak et al., 1989).

In addition to human, extracellular SPs are also found in other long-lived mammals, such as some non-human primates like Cheirogelidae, Callitricadae, Cebidae and Pogidae (Struble et al., 1984; Gearing et al., 1995; Gearing et al., 1997), domestic dogs (Cummings et al., 1996; Tekirian et al., 1996), cats (Cummings et al., 1996) and polar bears (Cork et al., 1988; Tekirian et al., 1996). However, common laboratory rats and mice do not have natural accumulation of amyloid with age (Jucker et al., 1994). SPs are often found in the amygdala, the hippocampus and the neocortex (Gearing et al., 1995).

3.2 Neurofibrillary tangles

In AD brains, besides SPs, another striking pathological feature is intracellular neurofibrillary tangles (NFTs). The affected neurons often show intracellular accumulations of single straight filaments and paired helical filaments and neuropil threads (Arnold et al., 1991; Braak and Braak, 1994; Gold, 2002). The major component of these poorly soluble filaments is hyperphosphorylated tau, a 68 kDa microtubule-associated protein (Lee et al., 1991; Gomez-Isla et al., 1996; Hardy, 2003; Roder, 2003). The diseases with tau-based neurofibrillary pathology include: AD, Down's syndrome (DS), amyotrophic lateral sclerosis/parkinsonism-dementia complex, Creutzfeldt-Jakob disease, frontotemporal dementia, Pick's disease and argyrophilic grain dementia. Among these diseases, amyotrophic lateral sclerosis and frontotemporal dementia have the most significant neurofibrillary pathology (Michaelis et al., 2002; Hardy, 2003; Roder, 2003). Furthermore, besides human, tau immunoreactivity and deposition-like structures are also found in rhesus monkeys (Garver et al., 1994; Hartig et al., 2000). NFTs can be detected by anti-tau antibody or silver staining. In AD, NFTs are found in the hippocampus, the entorhinal cortex, the association cortex and some other subcortical areas, such as the nucleus basalis of Meynert, the amygdala and the dorsal raphe (Arnold et al., 1991; Braak and Braak, 1994).

In vitro exposure of non-phosphorylated recombinant tau to high concentrations of sulfated glycosaminoglycans leads to the formation of paired helical filaments and single-strand filaments (Goedert et al., 1996). These results suggest that tau phosphorylation as well as the interaction of tau and glycosaminoglycans may play a role in abnormal filament formation *in vivo*. Phosphorylated tau has reduced ability to bind microtubules, which changes the stability of microtubules. In addition, phosphorylated tau may also affect intracellular transportation, cellular geometry and neuronal viability (Lassmann et al., 1995; Smale et al., 1995; Troncoso et al., 1996).

3.3 Synaptic and neuronal loss
3.3.1 Synaptic loss

In AD, a significant synaptic loss ranging from 20% to 50% is reported. Biochemistry, electron microscopy and immunocytochemistry have shown a decrease in synaptic density, presynaptic terminals, synaptic vesicle and synaptic protein markers in AD brains compared with the normal aged controls (Terry et al., 1991; Geula, 1998; Larson et al., 1999; Yao et al., 1999; Ashe, 2000; Baloyannis et al., 2000; Terry, 2000; Masliah, 2001; Masliah et al., 2001b; Price et al., 2001; Scheff and Price, 2001; Scheff et al., 2001; Stephan et al., 2001; Callahan et al., 2002; Chan et al., 2002; Dodd, 2002). Although synaptic loss is remarkable in AD, it is not specific to AD. Reduction in synaptic density is also found in Pick's disease, Huntington's disease, Parkinson's disease as well as in vascular dementia (Geula, 1998; Larson et al., 1999; Yao et al., 1999; Ashe, 2000; Baloyannis et al., 2000; Terry, 2000; Masliah, 2001; Masliah et al., 2001b; Price et al., 2001; Scheff and Price, 2001; Scheff et al., 2001; Stephan et al., 2001; Callahan et al., 2002; Chan et al., 2002; Dodd, 2002).

Since one of the most important physiological functions of synapses is to release and accept neurotransmitters, the changes of activity of these neurotransmitters in neurodegenerative diseases have also been intensively studied (Terry, 2000). In AD, most significant lesions happen in the cholinergic, adrenergic and serotoninergic systems (Davies and Maloney, 1976; Geula, 1998; Larson et al., 1999; Yao et al., 1999; Ashe, 2000; Baloyannis et al., 2000; Terry, 2000; Masliah, 2001; Masliah et al., 2001b; Price et al., 2001; Scheff and Price, 2001; Scheff et al., 2001; Stephan et al., 2001; Callahan et al., 2002; Chan et al., 2002; Dodd, 2002). Some other peptidergic neurotransmitters also decrease in AD, such as somatostatin, neuropeptide Y and substance P (Terry, 2000).

Synaptic loss might be one of the first events in AD development (Terry et al., 1991; Terry, 2000; Selkoe, 2002). Decrease in presynaptic terminals, synaptic vesicle and synaptic protein markers occur in very early stage of AD (Ashe, 2000; Terry, 2000; Masliah et al., 2001b; Price et al., 2001; Scheff et al., 2001; Callahan et al., 2002; Chan et al., 2002; Dodd, 2002). In the transgenic mice with FAD mutations, synaptophysin, marker for presynaptic protein, decreases before the appearance of Aβ deposits and formation of plaques (Hamos et al., 1989; Masliah et al., 1989; Selkoe, 2002). Most importantly, the decline of function of synaptic transmission occurs even before synaptic structural changes (Masliah, 2001; Scheff and Price, 2001; Chan et al., 2002; Selkoe, 2002). Long-term potentiation (LTP) is commonly accepted as a measurement for capacity of synaptic plasticity, which is the basis of learning, memory and complex information processing. The incidence and duration of LTP formation are used as an indication for formation and maintenance of working memory. Several lines of FAD mutant transgenic mice show a decline in the formation of LTP and synaptic excitation before the appearance of synaptic loss, plaques and other AD pathology (Geula, 1998; Ashe, 2000; Masliah, 2001; Masliah et al., 2001b; Scheff and Price, 2001; Callahan et al., 2002; Chan et al., 2002; Selkoe, 2002). In summary, synaptic loss seems to appear earlier than all other pathological markers and the functional loss of synapses may be responsible for the initiation of cognitive decline in AD patients.

3.3.2 Neuronal loss

Synaptic loss and degeneration induce neuronal dysfunction and cell body loss. Neuronal loss in the cerebral cortex and the hippocampus is a hallmark feature of AD. Some of AD

patients at late stage of the disease can have a severe decrease in brain volume and weight due to either neuronal loss or atrophy (Smale et al., 1995; Cotman and Su, 1996; Gomez-Isla et al., 1996; Gomez-Isla et al., 1997; Li et al., 1997; Su et al., 1997; Gomez-Isla et al., 1999). Assumption-based and design-based unbiased stereological cell counting shows decreased density of neurons in the cerebral cortex, the entorhinal cortex, the association cortex, the basal nucleus of Meynert, the locus coeruleus and the dorsal raphe of AD brains (Bondareff et al., 1982; Lippa et al., 1992; Gomez-Isla et al., 1996; Gomez-Isla et al., 1997; Gomez-Isla et al., 1999; Colle et al., 2000). Profound neuronal loss is especially observed in the entorhinal cortex in the mild AD brains (Gomez-Isla et al., 1996; Gomez-Isla et al., 1997; Gomez-Isla et al., 1999). Besides AD, significant neuronal loss is also observed in the entorhinal cortex in very mild cognitive impairment patient brains (Gomez-Isla et al., 1996; Gomez-Isla et al., 1997; Gomez-Isla et al., 1999). These data suggest that neuronal loss may be one of the early events before formation of SPs and NFTs in AD development.

The loss of cholinergic neurons in AD is widely studied. The hippocampus and cortex receive major cholinergic input from the basal forebrain nuclei (Hohmann et al., 1987). Decrease of choline acetyltransferase activity and acetylcholine synthesis correlate well with the degree of cognitive impairment in AD patients (Mesulam, 1986; Hohmann et al., 1987; Pearson and Powell, 1987). Cholinergic neuronal lesion can be detected in the patients that have showed clinical memory loss symptoms for less than one year (Whitehouse et al., 1981; Whitehouse et al., 1982; Francis et al., 1993; Weinstock, 1997). However, markers for dopamine, γ-aminobutyric acid (GABA), or somatostatin are not altered (Whitehouse et al., 1981; Whitehouse et al., 1982; Francis et al., 1993). These results suggest that cholinergic neuronal loss is probably one of the early events in AD.

3.4 Correlation of AD pathology to dementia levels

Besides the main pathology discussed above, some other pathologies of AD include granulovacuolar degeneration, cerebral amyloid angiopathy, blood-brain barrier disorder, white matter lesions, neuropil thread and gliosis (Jellinger, 2002a; Jellinger, 2002b, c; Jellinger and Attems, 2003). Because of a lack of diagnostic markers for live AD patients, the definite diagnosis of AD depends on cognitive tests and a quantitative assessment of numbers of SPs and NFTs in the postmortem brain tissues. However, studies of the relationship of the major AD pathological markers with clinical dementia levels suggest that the best correlation with dementia is neither SPs nor NFTs. The extent of neuronal and synaptic loss correlates better with the severity of clinical disease than the neuropathological lesions, SPs and NFTs (De Kosky and Scheff, 1990; Terry et al., 1991), suggesting that neuronal loss has a closer and more direct relationship to clinical dementia.

4. Aβ and Aβ hypothesis in AD

4.1 Production of Aβ
4.1.1 APP

One of the most remarkable pathological features of AD is extracellular deposition of SPs containing Aβ peptide aggregates derived from amyloid precursor protein (APP). APP, cloned in 1987 (Kang et al., 1987), is a type-1 transmembrane glycoprotein with ten isoforms generated by alternative mRNA splicing. APP is encoded by a single gene at human

chromosome 21 containing 18 exons (Kang et al., 1987; Goate et al., 1991). APP has a signal peptide, a large extracellular N terminal domain and a small intracellular C terminal domain, a single transmembrane domain and an endocytosis signal at the C terminal (Golde et al., 1992; Haass et al., 1992a; Haass et al., 1992b; Haass et al., 1994; Lai et al., 1995) (Figure 1A). Among ten isoforms of APP ranging from 563 to 770 amino acids, the major ones are APP_{770}, APP_{751} and APP_{695}. Isoforms APP_{751} and APP_{770} are expressed in both peripheral neural and non-neural tissues and have a protease inhibitor domain in the extracellular regions (Kitaguchi et al., 1988; Ponte et al., 1988). Isoform APP_{695}, which lacks the KPI domain, is expressed at high levels in the brain (Yamada et al., 1989; Kang and Muller-Hill, 1990; LeBlanc et al., 1991). Since the CNS neurons are mostly affected in AD, intensive efforts have been made to focus on the APP_{695} isoform (Sinha and Lieberburg, 1999).

Under physiological conditions, newly synthesized APP matures in the endoplasmic reticulum and the Golgi, acquiring N- and O-linked glycosylation and phosphorylation. The function of APP phosphorylation is not known yet. APP is located in the neuronal cell bodies as well as axons. Cellular APP is transported by the fast anterograde system (Koo et al., 1990; Sisodia et al., 1993), therefore, it is suggested that APP may play a role in neurite
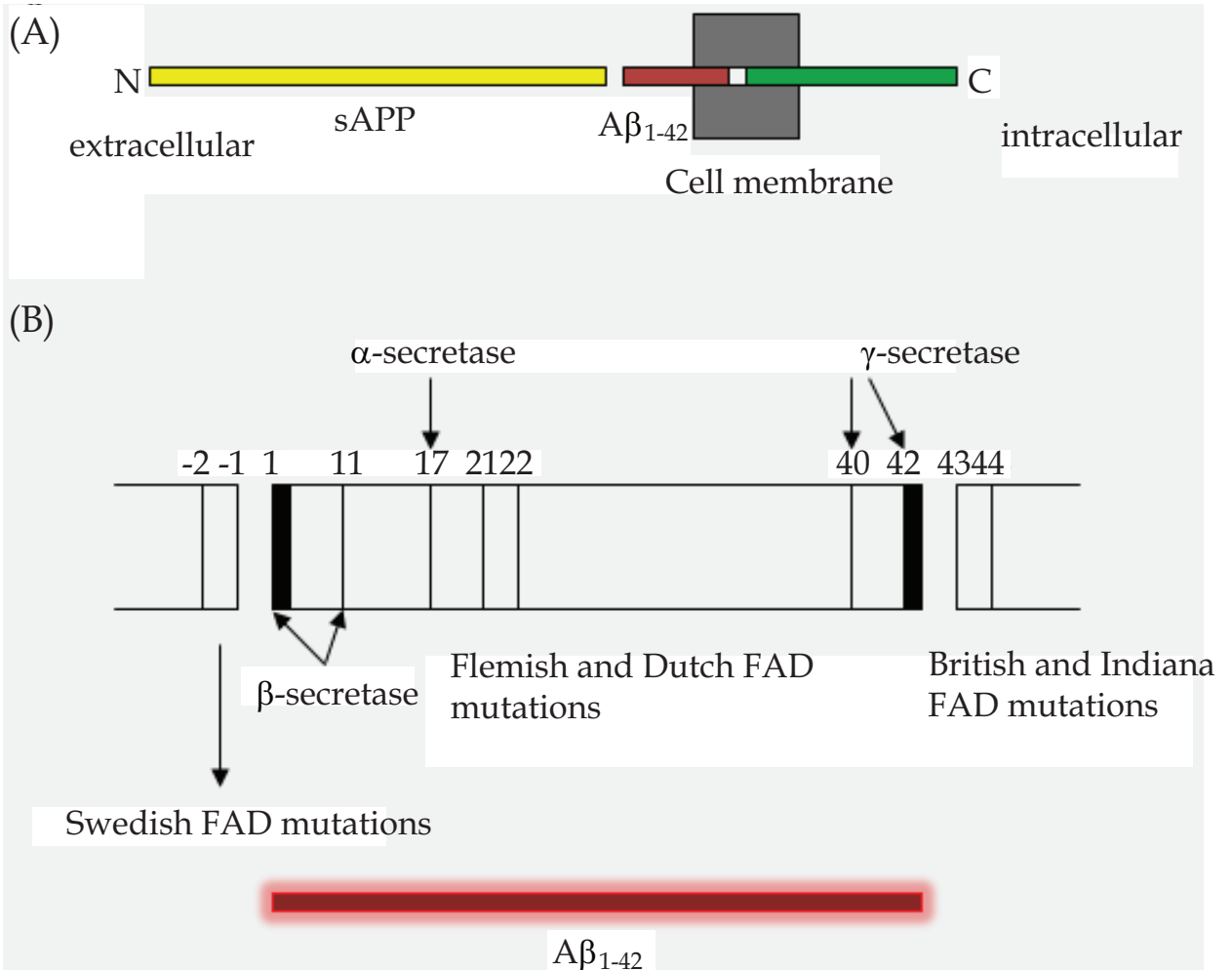

Fig. 1. Schematic diagram of APP and its cleavage. (A) Full-length APP is located in the cell membrane. (B) APP can be cleaved at α-, or β- and γ-secretase sites. FAD mutations are often at cleavage sites

outgrowth and extension, and probably in synaptic transmission and maintenance of axons (Yamaguchi et al., 1990; Yamaguchi et al., 1994). In addition, APP has been suggested to have neuroprotective function or neurotrophic roles (Mattson et al., 1993b). APP knockouts are fertile (Zheng et al., 1996). Neuroanatomical studies of APP knockout mouse brains show no significant differences relative to the wild-type control brains (Zheng et al., 1996). APP can be cleaved at the C terminal by α-secretase near the cell surface to generate a secreted fragment (Sinha and Lieberburg, 1999) (Figure 1B). The exact location of α-secretase activity is still unknown, although some data suggest that α-cleavage occurs mainly at trans-Golgi or plasma membrane (Kuentzel et al., 1993). One possible explanation for the uncertainty about the localization of α-secretase is that there may be more than one enzyme with the α-secretase activity. The candidates for α-secretase are two members of the family of disintegrin and metalloprotease ADAM: tumour necrosis factor-converting enzyme (TACE or ADAM-17) and ADAM-10. TACE can process pro-TNF, creating the extracellular TNF in a similar way to APP. The blockage or knockout of TACE can decrease the release of sAPP (Buxbaum et al., 1998). However, cells lacking TACE still retain part of α-secretase activity (Buxbaum et al., 1998). In addition to TACE, overexpression of ADAM-10 increases α-cleavage of APP (Lammich et al., 1999). A dominant negative form of ADAM-10 inhibits α-secretase activity, but does not totally abolish sAPP production (Lammich et al., 1999). ADAM-10 is inactive in the Golgi, while becomes activated at the plasma membrane (Lammich et al., 1999). Therefore, TACE and ADAM-10 may both contribute to α-cleavage.

In addition to α-secretase pathway, APP can also be cleaved by putative β- and γ-secretases to generate Aβ fragments containing 39-43 amino acids (Figure 1B). The majority of Aβ peptides is the 40 amino acid long $A\beta_{1-40}$, only 10% of the species are the 42 amino acid peptide $A\beta_{1-42}$. β-site APP cleaving enzyme (BACE or Asp2) has been suggested to be responsible for β-secretase activity. BACE is a member of pepsin family of aspartyl proteases (Vassar et al., 1999). BACE cleaves full-length APP at Asp1 (Vassar et al., 1999). The Swedish FAD mutation, which is known to enhance β-secretase cleavage, also promotes cleavage of APP at Asp1 by BACE (Vassar et al., 1999). BACE is co-localized with APP in many regions, especially in neurons. BACE also has a subcellular distribution similar to β-secretase (Vassar et al., 1999).

Recent studies suggest that γ-secretase may not be a single protein but rather mediated by a complex of a number of proteins. γ-secretase activity happens when APP is cleaved within the complex containing presenilin, APP binding proteins Nicastrin, Aph-1 and Pen-2 (Yu et al., 2000; Chen et al., 2001; Chung and Struhl, 2001; Satoh and Kuroda, 2001; Hu et al., 2002). There are two proposed β- and γ-secretase pathways. One is called the endosomal/lysosomal pathway. Secreted APP is endocytosed and delivered to endosomes and lysosomes where β- and γ-secretase cleavages occur. The other pathway suggests that Aβ generation occurs in the endoplasmic reticulum and Golgi-derived vesicles (Chyung et al., 1997; Sinha and Lieberburg, 1999). The γ-cleavage and the role of presenilins in this cleavage are discussed in details in the following section about presenilins.

Mutations in the APP gene identified 25 families of FAD worldwide (Chartier-Harlin et al., 1991a; Chartier-Harlin et al., 1991b) (Figure 1B). All these APP mutations are missense mutations. Double mutation Lys670Asn/Met671Leu ("Swedish" mutation), Ala693Gly ("Flemish" mutation), Glu693Gln ("Dutch" mutation) and Ile716Val (Czech et al., 2000) increase Aβ production, especially the generation of $A\beta_{1-42}$. The "Dutch" mutation is a point

mutation within the Aβ peptide sequence and leads to a conformational change of Aβ, which increases the aggregation of Aβ peptides and forms fibrils (Levy et al., 1990; Wisniewski et al., 1997). The "Flemish" mutation is also located within Aβ sequence and alters γ-secretase activity leading to increased production of $Aβ_{1-42}$ (Haass et al., 1994). The "Arctic" mutation Glu693Gly does not increase Aβ production, but the amount of protofibrils of Aβ increases (Nilsberth et al., 2001). Besides the APP mutations leading to obligate AD phenotype, other evidence that APP is associated with AD comes from DS patients. DS patients have 3 copies of chromosome 21 leading to overexpression of APP. Almost all DS patients develop AD in their 30-40's (reviewed by (Lott and Head, 2001)). Two "APP-like" genes APLP1 amd APLP2 have been localized to human chromosome 19 and suggested to be a strong candidate for late onset FAD (Wasco et al., 1992).

4.1.2 Presenilin

Besides the APP gene, FAD is also associated with mutations in the presenilin (PS) genes (Deng et al., 1996a; Busciglio et al., 1997; Hartmann et al., 1997; Price and Sisodia, 1998; Grace et al., 2002; Grace and Busciglio, 2003). PSs are transmembrane proteins with 8 transmembrane domains, located mainly in the endoplasmic reticulum, Golgi, endoplasmic reticulum-Golgi intermediate structures, and synaptic terminals as detected by electron microscopy (Cook et al., 1996; Takashima et al., 1996; Culvenor et al., 1997; Huynh et al., 1997; Lah et al., 1997; McGeer et al., 1998; Tanimukai et al., 1999; Culvenor et al., 2000; Siman et al., 2001). The PS1 gene is located on human chromosome 14 and the PS2 gene is on chromosome 1 (Sherrington et al., 1996). In humans, both PS1 and PS2 are encoded by 12 exons (Hutton et al., 1996). PSs are highly expressed in human brain, especially in neurons, and in most peripheral tissues (Deng et al., 1996b; Sherrington et al., 1996). There is a strong sequence homology between PS1 and PS2 (Sherrington et al., 1996). PSs are highly conserved from Drosophila to human (Hong and Koo, 1997; Berezovska et al., 1999). While no PS homologues are found in yeast, a PS homologue is found in *Arabidopsis thaliana*, (Czech et al., 2000). PSs are not glycosylated, sulfated or acylated (De Strooper et al., 1997).

The physiological functions of PSs are widely studied. PS knockout studies show that PS1 is important for axial skeleton development. PS1 knockouts have severe defects in their bone and skeleton systems. Interestingly, the phenotype of PS1 knockouts is very similar to the Notch-1 knockouts, which indicates that PSs may play an important role in the Notch signaling pathway (Wong et al., 1997). In addition, the interaction between PSs and Notch is suggested by co-immunoprecipitation of endogenous Notch and PSs in cultured *Drosophila* cells (Ray et al., 1999). Notch is processed in the secretory pathway and cleaved at the Golgi. The two truncated subunits of Notch form a protein complex in the plasma membrane and act as a receptor. When Notch ligand binds to this receptor, one of the two subunits gets cleaved at the extracellular site near the membrane. Then, the intracellular fragment of the cleaved subunit is released into the cytosol. This fragment then translocates into the nucleus and acts as a part of a transcriptional factor complex. This complex can regulate, at the transcriptional level, Notch target genes (De Strooper et al., 1999). The studies of the PS knockouts and Notch function suggest that PSs may be the proteases responsible for Notch cleavage and regulating the trafficking of cleaved Notch to the cytosol (De Strooper et al., 1999). A similar scenario has been proposed for APP processing by PS (De Strooper et al., 1999).

The link between PS1 or PS2 with AD was found through genetic studies of FAD cases. PS1 mutation families have early onset of AD at around 50 years old, whereas PS2 mutation families develop AD symptoms between 40-80 years old (Rogaev et al., 1995). The majority of these PS mutations are missense mutations leading to amino acid change in the protein sequence. If an individual carries a PS mutation, the probability of developing early onset AD is higher than 95% (Annaert et al., 1999). PS mutations are likely to be a "gain of toxic function" resulting in the abnormal APP processing, probably as part of the "γ-secretase" complex that generates Aβ fragments. PS mutations increase Aβ, especially $Aβ_{1-42}$ production (Busciglio et al., 1997; Hartmann et al., 1997). PSs can interact with APP directly. This is supported by the fact that APP and PSs can be co-immunoprecipitated in transfected cells and interact in a yeast two-hybrid system (Waragai et al., 1997; Weidemann et al., 1997; Xia et al., 1998). Whether PSs act directly as the γ-secretase and how PSs cleave APP inside its transmembrane domain are still not clear yet. One model proposes that PSs regulate APP intracellular trafficking and lead APP to the subcellular compartments, most possibly, the endoplasmic reticulum, where γ-secretase cleavage happens (Davis et al., 1998). Two aspartic acid sites (D257, D385) on PS1 are likely to be critical for γ-secretase cleavage because mutations of these two sites significantly decrease γ-secretase cleavage (Tandon and Fraser, 2002). Since γ-secretase cleavage happens inside of the transmembrane domain of APP, it is suggested that the γ-secretase complex (PSs, Nicastrin, Aph-1 and Pen-2) form a pore structure on the membrane. APP is then located and stabilized in the middle of the pore by Nicastrin or Pen-2 (Yu et al., 2000; Chen et al., 2001; Chung and Struhl, 2001; Satoh and Kuroda, 2001; Hu et al., 2002).

4.2 Aβ involvement and Aβ hypothesis in AD

To date, the cause of AD is still not clear. Major pathological features of AD are intracellular NFTs composed of hyperphosphorylated tau, extracellular SPs containing Aβ peptides, and massive synaptic and neuronal loss. Accordingly, there are tau, Aβ and synaptic-neuronal loss hypotheses for the cause of AD. The amyloid hypothesis, on the other hand, emphasizes that increased Aβ production or failure of Aβ clearance induces gradual Aβ accumulation through life, resulting in the formation of amyloid plaques, which induces inflammatory responses and in turn induces synaptic damage, tangles, and then neuronal loss (Podlisny et al., 1987; Hardy and Higgins, 1992). The evidence supporting the amyloid hypothesis comes from studies showing that most of FAD mutations increase Aβ production (Czech et al., 2000). As mentioned in the Aβ section above, both extracellular and intracellular Aβ are toxic to cells. In addition, co-expression of mutant APP and mutant tau increase NFTs, but not SPs, suggesting that Aβ production and accumulation may be upstream to tau to induce tangle formation (Lewis et al., 2001). In addition, the evidence from Down's syndrome patients suggests that SP formation precedes NFT (Mann et al., 1989; Lemere et al., 1996). Furthermore, in a FAD mutation carrier who died from other disease unrelated to AD in middle life, autopsy showed that the load of amyloid deposition and SPs but not NFT (Smith et al., 2001), suggesting that SP formation may happen before NFT formation. However, tau mutants can cause fontotemporal dementia where lots of tangles, but not amyloid deposits, are found in the brain, suggesting that NFT and SP formation may be independent (Hutton et al., 1998; Poorkaj et al., 1998; Spillantini and Goedert, 1998). Therefore, from this point of view, it seems that Aβ accumulation is either preceding or independent of NFT formation. The Aβ deposition in the neural parenchyma occurs early in

plaque formation, and this peptide species is the major component in the mature plaque (Price and Sisodia, 1998). Aβ production increases in the cells expressing FAD mutations (Price and Sisodia, 1998). These Aβ deposits may also act as a backbone for the subsequent deposits of other proteins, such as α_1-antichymotrypsin, apolipoprotein E (apoE) and J (Rogers et al., 1988).

The aggregations of Aβ are toxic to neurons and are thought to contribute to neuronal loss in AD development (Yankner, 1996). Since extracellular Aβ deposition is a major pathological hallmark of AD, considerable attention has been devoted to the Aβ cytotoxicity hypothesis, which argues that the extracellular Aβ (eAβ), especially $eA\beta_{1-42}$, induces neuronal death, therefore, is one of the primary causes of AD (Yankner et al., 1990; Roses, 1996; Scheuner et al., 1996; Sinha and Lieberburg, 1999; De Strooper and Annaert, 2000; Wang et al., 2001). The eAβ toxicity hypothesis is supported by the fact that fibrillar eAβ is toxic to various systems, including cell lines and primary cells in cultures (Yankner et al., 1990; Kowall et al., 1991; Pike et al., 1991; Busciglio et al., 1992, Busciglio, 1993 #189; Behl et al., 1994; Hoyer, 1994; Lorenzo and Yankner, 1994b; Price et al., 1995; Lorenzo and Yankner, 1996; Roher et al., 1996). Furthermore, levels of Aβ, especially $A\beta_{1-42}$, increase in the AD brains and in the serum or fibroblasts from the AD patients (reviewed by (Price and Sisodia, 1998)). Although the mechanism of eAβ cytotoxicity is still not fully understood, proposed eAβ toxicity mechanisms include: increasing vulnerability of cells to a secondary insult (Mattson et al., 1993a; Behl et al., 1994), changes in calcium influx (Ho et al., 2001), increasing oxidative stress (Behl et al., 1994), activation of inflammation and microglia (Eikelenboom et al., 2002; Gasic-Milenkovic et al., 2003), changes in tau phosphorylation (Ghribi et al., 2003), induction of apoptosis (Colurso et al., 2003; Hashimoto et al., 2003; Monsonego et al., 2003), induction of lysosomal protease activity and damaging membrane (Bahr and Bendiske, 2002; Bendiske and Bahr, 2003). Also, eAβ can interacts with receptors on the cell membrane, such as the p75 neurotrophin receptors, APP, receptors for advanced glycation endproducts (RAGE) (Loo et al., 1993; Yan et al., 1997; Yarr et al., 1997; Yaar et al., 2002).

Like many other amyloidogenous proteins, Aβ undergoes oligomerization and fibrillation under physiological situations (Zerovnik et al., 2011). The mechanisms of amyloid fibril formation have been suggested as "templating and nucleation models", "linear colloid-like assembly of spherical oligomers", and "domain-swapping" (Zerovnik et al., 2011). Recent studies have demonstrated that soluble Aβ oligomers have toxic role (Haass and Selkoe, 2007; Walsh and Selkoe, 2007). Aβ oligomers have been shown to induce cognitive defects when transferred into wild type murine brains (Podlisny et al., 1998; Walsh et al., 2000; Walsh et al., 2002b; Walsh et al., 2002a; Walsh et al., 2005b; Walsh et al., 2005a; Lesne et al., 2006; Townsend et al., 2006; Shankar et al., 2009). Soluble oligomers form trimers and tetramers that disrupt normal synaptic function (Salminen et al., 2008), precede synapse loss (Salminen et al., 2008). Aβ oligomers induce inhibited LTP and enhanced long-term depression (Malchiodi-Albedi et al., 2011). The mechanisms of Aβ oligomer toxicity have been suggested to be associated with calcium dysregulation (Malchiodi-Albedi et al., 2011), inflammation activation (Salminen et al., 2008), potassium efflux activation (Salminen et al., 2008) and interaction with membrane lipid rafts (Simons and Gerl, 2010) and microglia (Malchiodi-Albedi et al., 2011).

Several lines of evidence suggest that eAβ may not be the sole contributor to AD pathology. First, in AD patients, the severity of Aβ deposition correlates poorly with clinical dementia

levels (Barcikowska et al., 1992). Second, in some AD animal models, Aβ accumulates and forms SPs in the absence of the other two AD pathological features, neuronal loss and NFTs (Price and Sisodia, 1998; Masliah et al., 2001a). Third, eAβ toxicity generally requires non-physiological micro molar levels of Aβ in the culture medium. Moreover, some groups have reported that eAβ is not toxic even at high micro molar concentration in rat PC12, human IMR32 cells and in monkey cerebral cortex (Busciglio et al., 1992; Podlisny et al., 1993; Gschwind and Huber, 1995). One of the best models to study human age-related diseases, human primary cultured neurons, is resistent to 10 μM of eAβ (Mattson et al., 1992; Paradis et al., 1996). A secondary insult, such as serum deprivation, is required for eAβ to induce cell death in human neurons (Paradis et al., 1996). Fourth, transgenic mice carrying FAD APP^{V717F} mutation show neuronal and synaptic loss before Aβ accumulation (Hsia et al., 1999). In addition, human neuronal cell death induced by serum deprivation increases eAβ production, suggesting that eAβ generation is a consequence instead of a cause of neuronal cell loss (LeBlanc et al., 1999). Interestingly, in human primary neurons, p75 neurotrophin receptors play a protective role against eAβ toxicity. Blocking p75 by anti-sense constructs or antibody significantly promotes eAβ toxicity (Zhang et al., 2003). In addition, in some AD animal models, Aβ accumulates to form SPs in the absence of two other AD pathological features, neuronal loss and NFT (Price and Sisodia, 1998; Masliah et al., 2001a). Furthermore, the number of SPs does not correlate with the degree of cognitive impairment. In some older people without dementia, lots of SPs are found in their brains.

Recently, findings implicating intracellular Aβ (iAβ) accumulation and toxicity in AD are attracting more and more attention. The accumulation of iAβ has been observed. First, iAβ$_{1-42}$ significantly accumulates in the pyramidal neurons of the hippocampus and the entorhinal cortex in mild cognitive impairment and AD patient brains (Chui et al., 1999; Gouras et al., 2000; D'Andrea et al., 2001; D'Andrea et al., 2002; Nagele et al., 2002; Tabira et al., 2002; Takahashi et al., 2002; Wang et al., 2002). Similar accumulations of Aβ$_{1-42}$ also occur in neurons of DS (Busciglio et al., 2002; Takahashi et al., 2002) and muscle cells of IBM individuals (Askanas et al., 1992; Sugarman et al., 2002), two degenerative disorders other than AD associated with amyloid deposition. Second, this iAβ$_{1-42}$ accumulation appears earlier than amyloid plaque formation (Gouras et al., 2000; D'Andrea et al., 2001; Tabira et al., 2002; Takahashi et al., 2002; Wang et al., 2002). Third, in the cell culture system, accumulation of iAβ$_{1-42}$ was reported (Yang et al., 1998; Greenfield et al., 1999). Fourth, in the transgenic animal models, iAβ accumulation precedes NFT formation in APP/PS1 double mutant mice (Wirths et al., 2001). In the APP mutant mice where synaptic loss happens before the presence of eAβ, iAβ was also reported (Li et al., 1996; Masliah et al., 1996; Hsia et al., 1999). Furthermore, using neuronal specific promoter NF-L, Aβ$_{1-42}$ expressed intracellularly in the neurons of transgenic mice induces dramatic cell loss (LaFerla et al., 1995). Microinjection of intracellular Aβ$_{1-42}$ into neurons induces dramatic cell death mediated through the activation of p53, Bax and caspase-6 (Zhang et al., 2002; Li et al., 2007). Intracellular Aβ$_{1-42}$ also causes electrophysiological property changes in primary human neurons (Hou et al., 2009). Androgen (Zhang et al., 2004), estrogen (Zhang et al., 2004), galanin (Cui et al., 2010) can protect against such toxicity.

Under physiological conditions, Aβ peptides are normally generated in the endoplasmic reticulum, Golgi or endosomal-lysosomal pathway, and secreted to the extracellular environment (Martin et al., 1995; Chyung et al., 1997; Tienari et al., 1997; Lee et al., 1998;

Greenfield et al., 1999). There are three possible pathways that may generate iAβ. One is that Aβ goes through endoplasmic reticulum-associated degradation (ERAD) pathway. When Aβ is made in the endoplasmic reticulum, the insoluble Aβ could be recognized as a misfolded protein and then reverse translocate from the endoplasmic reticulum to the cytosol. The misfolded proteins are then ubiquitinated and sent to proteasome for degradation (Werner et al., 1996; Greenfield et al., 1999; Friedlander et al., 2000; Ng et al., 2000; VanSlyke and Musil, 2002). It is possible that aging decreases proteasome activity (Merker et al., 2001), which leads to insufficient degradation and clearance of Aβ. The second possible way to generate iAβ is that Aβ fragments can be located in the endosome/lysosome transported from the trans-Golgi or through endocytosis. It has been suggested that Aβ can increase the membrane permeability of lysosome (Yang et al., 1998). Therefore, the Aβ within the endosome/lysosome can break the lysosome membrane and leak out of the vesicles. The third possible way is that there could be leakage happening along any of the secretory pathway. It is even possible that secreted Aβ passively diffuses into the cytosol through the plasma membrane or is actively uptaken by certain receptors on the plasma membrane.

5. Potential AD therapies based on Aβ hypothesis

5.1 Decreasing Aβ production

Aβ is generated from cleavage of APP by β- and γ-secretase (Vassar and Citron, 2000). β-secretase, a membrane-bound aspartic protease, is also called BACE, is most abundant in the brain (Vassar and Citron, 2000). BACE knockout mice apparently lack phenotype, which suggests that maybe inhibition of BACE in adult mice does not have side effect, and can be an excellent drug target for the cure of AD. However, there is a homologue of BACE, BACE2 (Vassar and Citron, 2000), which compensates the function of BACE. So, drugs which inhibit BACE, not BACE2, make sense in decreasing Aβ production. γ-secretase releases Aβ from APP. However, compared to β-secretase, γ-secretase is less understood. It is known that transmembrane proteins PS1 and PS2 (Strooper and Annaert, 2001), and nicastrin (Kopan and Goate, 2002) are required for the activity of γ-secretase. γ-secretase is involved in the cleavage of other integral membrane proteins including Notch (Strooper and Annaert, 2001), CD44 receptor (Okamoto et al., 2001). The mice die early in embryogenesis if γ-secretase is totally inhibited. Therefore, reasonable treatment with γ-secretase is partially inhibit γ-secretase, or inhibits the γ-secretase specifically cleaves APP to yield Aβ (Strooper and Annaert, 2001) (Figure 2).

Non-steroidal anti-inflammatory drugs (NSAIDs) are also candidates for AD drug target, because inflammation in AD is an important inducement for neuronal loss and it causes microglia activation, cytokines and complement components in the vicinity of the plaques (McGeer and McGeer, 1999; Akiyama et al., 2000). Clinic treatment of NSAIDs could specifically slow down the progression of AD (in t' Veld et al., 2001). NSAIDs target cyclooxygenases (COX) 1 and 2, while COX-2 inhibitors have little effects (McGeer, 2000). Recently, the study shows that the protective role of NSAIDs may be independent of their role in inflammation (Weggen et al., 2001). The production of Aβ in NSAIDs treated cells is apparently inhibited (De Strooper and Konig, 2001). But we still don't know how the NSAIDs specifically reduce the production of Aβ (Figure 2).
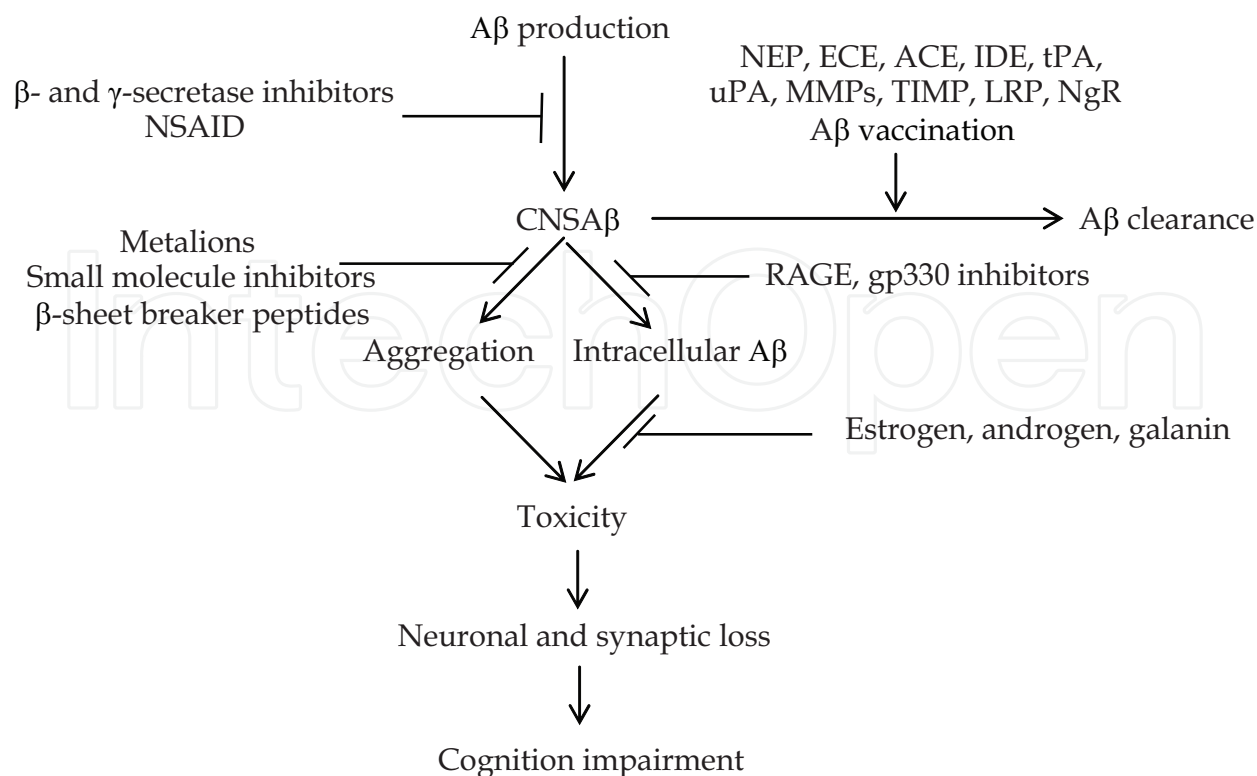
Fig. 2. Schematic diagram of Aβ production, clearance, aggregation and toxicity

5.2 Increasing Aβ clearance
5.2.1 Neprilysin (NEP)

Neprilysin, also called neutral endopeptidease (NEP), enkephalinase, CD10, or common acute lymphoblastic leukemia antigen (CALLA), is a zinc metallopeptidase with a zinc-binding motif (Turner and Tanzawa, 1997). NEP is a type II integral membrane protein with a short amino-terminal and localized at the cell membrane. NEP binds to many extracellular proteins or peptides, such as enkephalins, substance P, atrial natriuretic peptide, somatostatin, endothelin and insulin B chain. The physiological role of NEP is not fully understood yet. Studies suggest its possible implications in the regulation of natriuretic and vasodilator peptides in the kidney, the modulation of inflammatory response by neutrophils and the inactivation of mitogenic signaling in various cells (Turner et al., 2001). NEP is highly localized at the synapses (Schwartz et al., 1980) and colocalized with SP and Aβ (Sato et al., 1991). NEP can hydrolyze synthetic $A\beta_{1-40}$ *in vitro* (Howell et al., 1995) and synthetic $A\beta_{1-42}$ injected into rat hippocampus *in vivo* (Iwata et al., 2000). Mice with disrupted NEP gene show decreased ability of degrading exogenous $A\beta_{1-42}$ and endogenous $A\beta_{40/42}$ (Iwata et al., 2001). Endogenous Aβ accumulates in the hippocampus of this animal model which correlates with the severity of AD pathology (Iwata et al., 2001). Also, in human AD brain samples, NEP mRNA levels are low in the vulnerable areas, such as the hippocampus and the temporal cortex (Yasojima et al., 2001) (Figure 2).

Besides NEP, two other proteases related to NEP were also found to degrade Aβ. Endothelin-converting enzyme (ECE) hydrolyzes endogenous and synthetic Aβ in neuroblastoma cells and transfected CHO cells (Eckman et al., 2001). ECE can also degrade $A\beta_{1-40}$ and $A\beta_{1-42}$ into $A\beta_{1-16}$, $A\beta_{1-17}$ and $A\beta_{1-19}$ *in vitro* (Eckman et al., 2001). An intronic polymorphism of angiotensin

converting enzyme (ACE) is found to be a possible susceptibility genetic factor (Narain et al., 2000). Purified ACE from human seminal fluid is able to degrade $A\beta_{1-40}$ and reduce $A\beta$ fibrillogenesis and cytotoxicity (Hu et al., 2001) (Figure 2).

5.2.2 Insulin-degrading enzyme (IDE)

Insulin-degrading enzyme (IDE), also called insulysin and insulinase, is a neutral thiol metalloendopeptidase with an inverted zinc-binding site. IDE can hydrolyze multiple peptides, including amylin, and the APP intracellular domain in addition to $A\beta$ (Duckworth et al., 1998; Selkoe, 2001). Purified nondenatured IDE migrates from 300kDa to 110kDa after denaturation, which indicates that native IDE exists as a mixture of dimers and tetramers (Authier et al., 1996; Duckworth et al., 1998). IDE is significantly activated in neutral pH and dimmers formation (Mirsky et al., 1949; Kurochkin, 2001; Song et al., 2003). IDE was found to be located to the ^{125}I-labeled synthetic $A\beta$ in cytosol fractions from rat brain and liver (Kurochkin and Goto, 1994). Purified IDE effectively degrades $A\beta$ *in vivo* and *in vitro* (McDermott and Gibson, 1997; Perez et al., 2000), proved by the transgenic APP mouse as well (Farris et al., 2003; Farris et al., 2004) (Figure 2).

5.2.3 Plasmin, tissue plasminogen activator (tPA), urokinase-type plaminogen activator (uPA), matrix metalloproteinases and endosomal/lysosomal proteases

Plasmin, a serin protease, can degrade many extracellular matrix components (Werb, 1997). Plasmin, tissue plasminogen activator (tPA), and urokinase-type plaminogen activator (uPA) all belong to the plasimin system (Henkin et al., 1991). Plasmin, the active serine protease, is generated from tPA expressed in neurons and uPA expressed in neurons and microglial cells by cleavage of plasminogen (Madani et al., 2003). It is reported that plasmin significantly decreases the neurotoxicity of $A\beta$ aggregation by degrading $A\beta$, which has been proved by cell culture (Ledesma et al., 2000; Ledesma et al., 2003) (Figure 2).

Matrix metalloproteinases (MMPs) is a large family which can degrade and remodel extracellular matrix. MMPs have common propeptide and N-terminal catalytic domains (Yong et al., 1998). MMPs are activated by a proteolytic processing, regulated by tissue inhibitors of matrix metalloproteinases (TIMP), which can bind to the active or the inactive form of the MMPs (Brew et al., 2000). TIMP is found to co-localize with neuritic plaques and neurofibrillary tangles. Incubation of MMP-9 and synthetic $A\beta$1-40 can produce several products of degradation (Backstrom et al., 1996). The other MMPs can also performe this kind of cleavage (Figure 2).

Endosomal and lysosomal proteases can protect neuron cells by internalization of extracellular $A\beta$ though a number of receptors such as lipoprotein receptor-related protein (LRP), receptor for advanced glycation and products (RAGE), gp330/megalin and P-glycoproein as indicated in the following text. In AD models, alterations occur to lysosomal, including the accumulation of lysosomes and lysosomal hydrolases, next to $A\beta$ deposits (Ii et al., 1993; Cataldo et al., 1994). Cathepsin D protein level and activity are increased in aging brain, and the CSF of AD patients (Cataldo et al., 1995; Hoffman et al., 1998). It is reported that cathepsin D gene is associated with sporadic AD (Papassotiropoulos et al., 1999) (Figure 2).

5.2.4 Aβ vaccination

The active and passive immunizations have been examined in *in vitro* models and proven effective against $A\beta$ pathology, cellular alterations and cognitive impairment in AD animal

models (Schenk et al., 1999; Bard et al., 2000; Janus et al., 2000; Morgan et al., 2000; DeMattos et al., 2001; Lemere et al., 2001; DeMattos et al., 2002a; DeMattos et al., 2002b; Dodart et al., 2002; Matsuoka et al., 2003; Lemere et al., 2004; Hartman et al., 2005; Selkoe, 2007; Vasilevko et al., 2007; Yamada et al., 2009). After vaccination of Aβ, a transgenic mouse over expressing a mutant form of human APP is protected against amyloid plaque formation (Schenk et al., 1999). This vaccination not only protects Aβ aggregation, but also clears the amyloids in the brain of adult mice (Weiner et al., 2000). For vaccination, the antibody is directly injected by intraperitoneal immunization (Bard et al., 2000; DeMattos et al., 2001). The antibodies go across the blood-brain barrier, and probably trigger microglia to phagocytose Aβ. There is an alternative working mechanism: the antibodies make Aβ trapped in the plasma, which in turn reduce the extracellular concentration of Aβ (Janus et al., 2000; Morgan et al., 2000). Although the concentration of Aβ decreased after the vaccination, the cognitive function in these models is not apparently affected, which may due to the metabolism of Aβ; another problem for the vaccination is the clinical signs of inflammation in the CNS of several patients. According to Aβ vaccination, lower toxicity and higher immunogenicity (Nicolau et al., 2002) should be mainly considered (Figure 2).

5.2.5 Receptor mediated Aβ clearance

LRP and RAGE are both multi-ligand receptors binding to various ligands (Tanzi et al., 2004), trafficking Aβ across the blood-brain barrier (BBB) (Deane et al., 2004; Zlokovic, 2008). LRP1, a member of the low-density lipoprotein (LDL) receptor family, binds to various structurally unrelated ligands, apoE, APP, lactoferrin and Aβ included (Deane and Zlokovic, 2007). LRP1 antagonists (Shibata et al., 2000) or low expression level of LRP1 (Van Uden et al., 2002) apparently increase Aβ load (Deane et al., 2008; Marques et al., 2009). β-secretase cleaves the extracellular domain of LRP to produce soluble LRP, which can binds to free Aβ in the plasma in order to reduce the concentration of extracellular Aβ (Sagare et al., 2007). RAGE is a member of immunoglobulin super family, mediating the reentry of Aβ in to the brain through BBB. RAGE can bind to soluble Aβ at a nanomolar concentration (Deane et al., 2003), and this kind of interaction is indicated in injuries, imflammatory, and AD brains (Yan et al., 1996; Stern et al., 2002; Deane et al., 2003). In addition, Nogo-66 receptor (NgR) (Park and Strittmatter, 2007; Tang and Liou, 2007), gp330/megalin and P-glycoproein (Zlokovic, 1996; Lam et al., 2001) can also contribute to Aβ trafficking, with their respective role in transforming Aβ through BBB unknown (Figure 2).

Besides the clearance pathways mentioned above, one of the AD risk factor apoE ε4 allele can alter Aβ clearance (Castellano et al., 2011). In a mouse model of Aβ-amyloidosis expressing human apoE isoforms (PDAPP/TRE), the concentration and clearance of soluble Aβ in the brain interstitial fluid is reported to depend on the isoform type of apoE, especially in aged PDAPP/TRE mice (Castellano et al., 2011).

5.3 Preventing Aβ aggregation formation

Mental ions like Cu^{2+} and Zn^{2+} are found to reduce the aggregation and toxicity of Aβ (Atwood et al., 1998). Clioruinol, an antibiotic and Cu^{2+}/Zn^{2+} clelator that crosses the blood-brain barrier, can significantly decrease brain Aβ depositon in APP-transgenic mice after 9-week treatment (Cherny et al., 2001). In the progression of Aβ aggregation formation, a number of small molecules can interfere with the Aβ fibril *in vivo* or *in vitro*, such as rifampicin (Tomiyama et al., 1996), Congo red (Lorenzo and Yankner, 1994a), benzofuran

(Howlett et al., 1999), and Nicotine (Salomon et al., 1996) etc., with different principles as follows. Rifampicin prevents Aβ-induced oxidative damage as a free radical scavenger, because the nahpthohydroquinone and naphthoquinone structure protect the neuron cells (Tomiyama et al., 1996). Congo reds may inhibit the aggregation of Aβ through two sulfonate groups at a certain distance, which indicates the specific interaction of the negatively charged sulfonate moieties with Aβ (Pollack et al., 1995; Klunk et al., 1998). Just like a number of tetracyclic and carbazole-type compounds, benzofuran inhibits Aβ fibril formation, as a result of the inhibitory properties of these compounds (Howlett et al., 1999). Nicotine can prevent the conformational transition from α-helix to β-sheet (Salomon et al., 1996), and attenuate the neurotoxicity of Aβ through the nicotine receptor (Zamani et al., 1997). Nicotine also enhances the biosynthesis and secretion of transthyretin, which could bind to Aβ peptide to inhibit the formation of amyloid deposition (Tsuzuki et al., 2000). "β-sheet breaker peptides", another way to prevent Aβ aggregation formation, are two peptides with sequences complementary to Aβ, with additional proline residues, which inhibit the formation of β-sheet structures (Soto et al., 1996; Soto et al., 1998). The sequences of the "β sheet breaker peptides" are RDLPFFDVPID and LPFFD. According to the usage of peptides in the treatment of disease in the central nervous system, rapid proteolytic degradation in the plasma and cerebrospinal fluid, and low permeability across the blood-brain barrier should be taken into account (Poduslo et al., 1999) (Figure 2).

6. List of abbreviations

Aβ: amyloid β; ACE: angiotensin converting enzyme; AD: Alzheimer's disease; apoE: apolipoprotein E; APP: amyloid precursor protein; BACE: β-site APP cleaving enzyme; BBB: blood-brain barrier; CALLA: common acute lymphoblastic leukemia antigen; COX: cyclooxygenases; DS: Down's syndrome; eAβ: extracellular Aβ; ECE: endothelin-converting enzyme; ERAD: endoplasmic reticulum-associated degradation; FAD: familial AD; GABA: γ-aminobutyric acid; iAβ: intracellular Aβ; IDE: insulin-degrading enzyme; LRP: lipoprotein receptor-related protein; LTP: long-term potentiation; MMP: matrix metalloproteinases; NEP: neutral endopeptidease; NFT: neurofibrillary tangles; NgR: Nogo-66 receptor; NSAID: non-steroidal anti-inflammatory drug; PS: presenilin; RAGE: receptor for advanced glycation end products; SP: senile plaques; TACE: tumour necrosis factor-converting enzyme; TIMP: tissue inhibitors of matrix metalloproteinases; tPA: tissue plasminogen activator; uPA: urokinase-type plaminogen activator

7. Conclusions

Amyloid hypothesis stating that Aβ is the primary cause of AD has been proposed and examined in AD research field. However, many controversial issues still exist and further studies are needed to increase our understanding about AD development and progression. The therapeutics, which stem from the knowledge of basic research, may become another effective way to evaluate the theory itself.

8. Disclosure statement

All authors declare no actual or potential conflicts of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the work submitted that could inappropriately influence (bias) their work.

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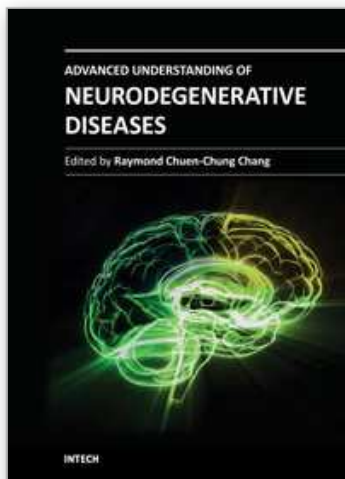
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Advanced Understanding of Neurodegenerative Diseases

Edited by Dr Raymond Chuen-Chung Chang

Advanced Understanding of Neurodegenerative Diseases focuses on different types of diseases, including Alzheimer's disease, frontotemporal dementia, different tauopathies, Parkinson's disease, prion disease, motor neuron diseases such as multiple sclerosis and spinal muscular atrophy. This book provides a clear explanation of different neurodegenerative diseases with new concepts of understand the etiology, pathological mechanisms, drug screening methodology and new therapeutic interventions. Other chapters discuss how hormones and health food supplements affect disease progression of neurodegenerative diseases. From a more technical point of view, some chapters deal with the aggregation of prion proteins in prion diseases. An additional chapter to discuss application of stem cells. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

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