Chapter 9

Emerging Therapeutic Strategies in Alzheimer's Disease

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Additional information is available at the end of the chapter

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1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia in mid- to late-life. It currently affects about 10% of individuals older than 65 years old, counting for more than 25 million people in the world (Chiba et al., 2007; Huang and Mucke, 2012; Mattson, 2004). A century has passed since the famous neurologist Alois Alzheimer first described about a 51-year-old female patient with severe progressive memory deficit, brain atrophy, senile plaques (SPs, or neuritic plaques), and neurofibrillary tangles (NFTs) in 1906 (1987). SPs and NFTs are abnormal protein aggregates consisting of extracellular amyloid β protein (Aβ) and intracellular hyperphosphorylated microtubule associated protein tau (Braak and Braak, 1991; Perrin et al., 2009). The worst affected areas in AD brains are the olfactory bulb, the cerebral neocortex, and the hippocampus. SPs and NFTs are spatially and temporally disjointed: SPs occur in the cerebral neocortex, preceding the occurrence of NFTs, which is predominant in the entorhinal cortex, by about 10 years (Fig. 1). The onset of mild dementia, or currently described as mild cognitive impairment (MCI), is better correlated with significant synaptic and neuronal loss, which is about 10-15 years behind the occurrence of NFTs.

Knowledge of AD has considerably expanded in the last two decades with the progress in molecular biology and genetics although curative therapy for AD is not yet available. Most AD cases occur sporadically (sporadic AD or SAD), while about 1% of AD cases are inherited in an autosomal dominant manner (familial AD, FAD). In 1984, Glenner and Wong first purified and sequenced Aβ (Glenner and Wong, 1984), which was followed by the identification of amyloid precursor protein (APP) as a source of Aβ (Kang et al., 1987). Genetic analysis of FAD then revealed that mutations in APP co-segregate with FAD (Chartier-Harlin et al., 1991; Goate et al., 1991). Consequently, drug candidates have been developed for AD based on a putative pathogenic hypothesis that increase in Aβ production and aggregation, which can be accelerated by the mutations in genes related to FAD, results in tau hyperphosphorylation and neuronal death. This is termed the "amyloid cascade" hypothesis (Hardy and

Higgins, 1992; Reitz, 2012). In this review, therapeutic strategies for AD will be discussed from a viewpoint of neuronal death and neuroprotection.

2. Molecular pathogenesis of Alzheimer's Disease (AD)

In this section, the overview of molecular pathogenesis of AD will be discussed. This is important to elaborate therapeutic strategies for AD. The current knowledge of pathogenic mechanisms for AD can be classified into two major categories, namely the "amyloid cascade" hypothesis and the alternative hypotheses. Recently, pathogenic roles of signal transducer and activator of transcription 3 (Stat3) and related intracellular signaling pathways in neurons has been described, which is attracting attention of AD researchers (Chiba et al., 2009a; Chiba et al., 2009b; Nicolas et al., 2012). In addition, genome-wide association studies (GWAS) have been carried out rigorously to seek for novel genes and loci related AD. These unbiased global genetic studies are now providing novel insights into both canonical and alternative pathogenic mechanisms for AD.

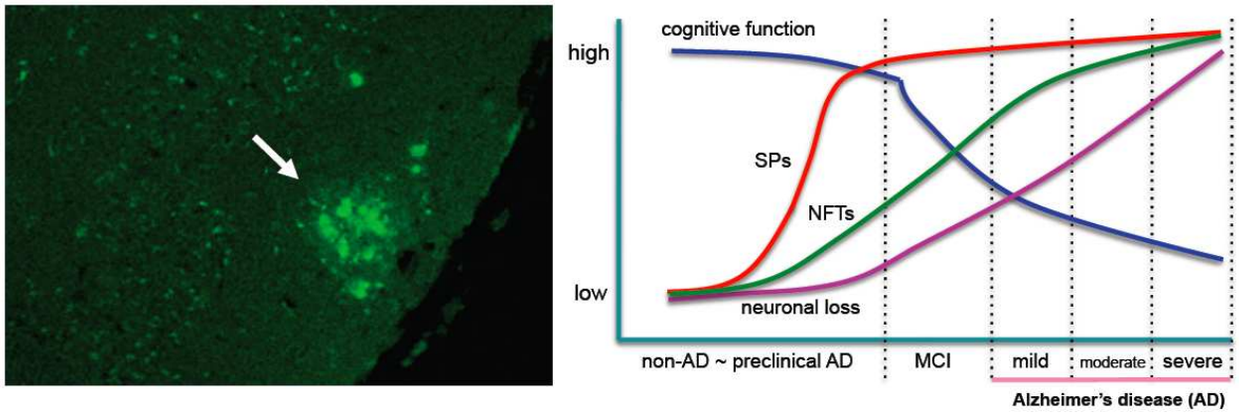

Figure 1. Pathological and clinical features of Alzheimer's disease (AD). (left) Senile plaques (SPs) in the cerebral cortex of an AD model mouse at the age of 12 monthes were stained with Thioflavin T. (right) Clinical process of AD and its relationship with pathological hallmarks of AD (mild cognitive impairment, MCI; cognitive function [blue]; SPs [red]; neurofibrillary tangles, NFTs [green]; neuronal loss [purple]). SP formation precedes NFT formation, which is followed by neuronal loss. Cognitive decline occurs as a result of neuronal loss.

2.1. The "amyloid cascade" hypothesis

2.1.1. Causative genes for FAD and their roles

FAD, which accounts for up to 1% of total AD cases, usually occurs between the age of 40-65 years (early-onset AD, EOAD) and is inherited in an autosomal dominant manner (Bertram et al., 2010; Schellenberg and Montine, 2012). Genetic analysis has identified so far three causative genes for FAD: *amyloid precursor protein (APP)* on chromosome 21, *presenilin 1 (PSEN1)* on chromosome 14 (Sherrington et al., 1995), and *presenilin 2 (PSEN2)* on chromosome 1 (Rogaev et al., 1995).

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APP is ubiquitously expressed type-I single transmembrane glycoprotein (Kang et al., 1987). From its primary structure, it is likely to be a cell surface receptor (Fig. 2A). APP undergoes sequential processing by three proteases: α-, β- and γ-secretase. β- and γ-cleavage generates Aβ, secretory APPβ (sAPPβ), and APP intracellular domain (AICD), whereas α- and γ-cleavage generates secretory APPα (sAPPα), AICD, and p3 fragment (De Strooper and Annaert, 2000; Kawasumi et al., 2002). Since β- and γ-cleavage generates Aβ, it is believed that initial cleavage by β-secretase is pathogenic and one by α-secreatese is non-pathogenic on the other hands. Val 642 Ile (V642I, numbering by a neuron-specific APP695 form) mutation within the transmembrane domain of APP was identified as the first FAD-linked mutation and is called as London-type mutation (Fig. 2B) (Chartier-Harlin et al., 1991; Goate et al., 1991). Then, several other types of mutations in APP, including K595N/M596L (Swedish type mutant or NL mutant), were identified (pathological impact of these mutations will be discussed later, see 2.1.3). It is notable that E618Q (Dutch type, numbering by APP695) mutation within Aβ sequence does not cause FAD but causes cerebral amyloid angiopathy called as hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D) (Fernandez-Madrid et al., 1991), while E618G (Arctic type, numbering by APP695) mutation at the same position causes FAD without severe cerebral amyloid angiopathy (Nilsberth et al., 2001). Recently, a rare recessive (A598V, numbering by APP695; A673V, numbering by a ubiquitous APP770 form) and a disease-resistant mutation (A598T, by APP695; A672T, by APP770) have been identified in APP at Ala 598, the second amino acid in Aβ (Di Fede et al., 2009; Jonsson et al., 2012).

PSEN1 and PSEN2 are highly homologous proteins consisting of 467 and 448 amino acid residues respectively with 8 or 9 transmembrane domains (Laudon et al., 2005; Marjaux et al., 2004) (Fig. 2C). They are ubiquitously expressed and localized in the endoplasmic reticulum (ER) and golgi apparatus. Mutations in the *PSEN1* gene are the most frequently involved in FAD accounting for about 10-20% of all FAD cases. More than one hundred mutations throughout entire *PSEN1* gene have been reported while about ten mutations have been reported in *PSEN2* (Bertram et al., 2010; Schellenberg and Montine, 2012). *PSEN1* and *PSEN2* are now regarded as the active core of the γ-secretase which cleaves the hydrophobic integral membrane domain of APP to generate Aβ. It is now widely recognized that γ-secretase, at least, involves four different proteins: PSEN, nicastrin, Aph-1, and Pen-2 (De Strooper, 2003; Takasugi et al., 2003). It should be noted that FAD-linked mutations in *PSEN1* and *PSEN2* induce neuronal death or enhance neuronal vulnerability to several toxic insults independent of the γ-secretase activity (Guo et al., 1996; Hashimoto et al., 2002a; Hashimoto et al., 2002b; Zhang et al., 1998).

2.1.2. Tau-hyperphosphorylation in AD

NFTs are comprised of paired helical filaments (PHFs), which is resulted from hyperphosphorylation of tau at Ser/Thr residues. NFT formation is one of the hallmarks of AD although tau dysfunction is not limited to AD but is widely observed in neurological disorders (usually termed as tauopathy) (Goedert et al., 1998; Johnson and Stoothoff, 2004). It is reported that the number of NFT correlates well with neuronal loss in AD brain and severity of dementia than that of SPs (Braak and Braak, 1991; Perrin et al., 2009). It is also notable that putative tau kinases

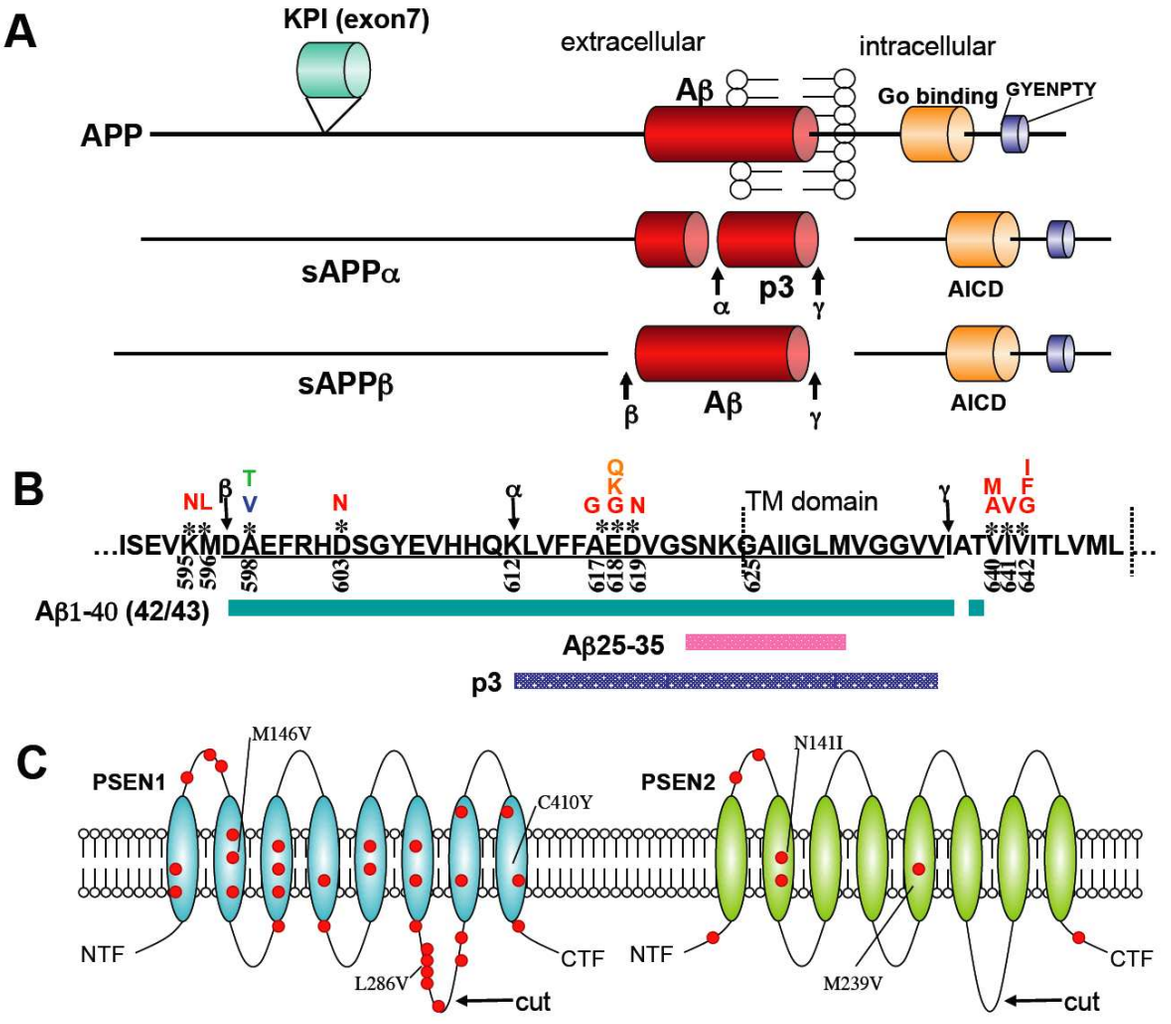

Figure 2. Familial AD (FAD) causative genes. (A) Proteolytic processing of APP. APP is consisting of extracellular, transmembrane and intracellular domains. There are several isoforms of APP with or without a Kunitz protease inhibitor (KPI) domain. Intracellular domain has signal transducing domains such as a G protein-binding motif (Go-binding domain) and an NPXY motif (GYENPTY) recognized by phosphotyrosine-binding domains. Sequential cleavage by α-/γ- or β-/γ-secretases produces soluble APP (sAPPα or sAPPβ, respectively), APP intracellular domain (AICD) and small peptides (Aβ or p3 fragment, respectively). (B) APP mutations were indicated in the Aβ coding region (amino acids). FAD mutations are indicated in red characters (numbering by a neuronal isoform of APP [APP695]); Swedish (K595N/M596N, NL mutation), London (V642I), Flemish (A617G, AD with strokes), Arctic (A618G), Iowa (A619N), German (V640A), French (V640M), Florida (I641V) and Indiana (V642F). Dutch type mutation (E618Q) is related to hereditary cerebral hemorrhage with amyloidosis, Dutch type (HCHWA-D, [orange]). E618K is also related to cerebral hemorrhage with amyloidosis. A598V [blue] is a rare recessive mutation and A598T [green] has been identified as a disease-resistant mutation. (C) Presenilin 1 (PSEN1) and 2 (PSEN2) were also schematically indicated with mutations (red dots). Autocatalytic cleavage of PSENs (arrow) into N- and C-terminal fragments is required for the activation of the γ-secretase.

including glycogen synthase kinase 3β (GSK3β), cyclin dependent kinase 5 (cdk5), c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (p38-MAPK) and Calcium/calmodulin-dependent kinase II (CaMKII) are reported to be upregulated in AD (Ferrer et al., 2002; Ferrer et al., 2001; Sato et al., 2002; Takashima et al., 2001). These data suggest that the mechanism of NFT formation plays an important role in neuronal loss in AD brain. Genetic mutations in tau, however, cause frontotemporal dementia with parkinsonism linked to

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chromosome 17 (FTDP-17) rather than AD (Hutton et al., 1998; Lewis et al., 2000). Recently, however, several observations supporting the relation between tau and AD have been reported, which led to the "amyloid cascade" hypothesis for AD (Fig. 3).

2.1.3. Basis of the "amyloid cascade" hypothesis

The "amyloid cascade hypothesis" postulates that excessive formation of insoluble fibrillar Aβ, with consequent formation of SPs, is the initial event in AD pathogenesis (Hardy and Higgins, 1992; Reitz, 2012). Then, a neurotoxic cascade, including NFT formation, secondarily occurs, leading to synaptic and neuronal loss. The hypothesis is originally based on the two key observations: the detection of Aβ as a main constituent of SPs, and identification of the FAD-causative mutations in the Aβ precursor (*APP*) and γ-secretase genes (*PSEN1* and *PSEN2*) (Bertram et al., 2010; Chiba et al., 2007; Schellenberg and Montine, 2012). Aβ can vary in length at the c-terminus; Aβ1-40 (Aβ40, 40 amino acids) is the most prevalent, followed by Aβ1-42 (Aβ42). The latter has hydrophobic properties and aggregates more readily than Aβ40, which leads to the notion that Aβ42 is the toxic Aβ property. Mutations of all three FAD genes generally increase the ratio of Aβ42 to Aβ40 (Aβ42/Aβ40) and promote Aβ oligomerization and aggregation, followed by the synaptic and neuronal loss.

As already mentioned, SPs and NFTs are distributed independently of each other. Researchers, however, have postulated that NFT formation lies downstream from SP formation to integrate NFTs into the "amyloid cascade", based on the experimental observations showing the relationship between Aβ and NFT formation: (i) APP or PSEN1 transgene enhanced NFT formation in tau transgenic mice (Gotz et al., 2001; Lewis et al., 2001; Oddo et al., 2003), (ii) fetal rat hippocampal neurons and human cortical neurons treated with fibrillar Aβ display an increased degree of tau phosphorylation (Busciglio et al., 1995; Rapoport et al., 2002), (iii) reduction of endogenous levels of tau can ameliorate some of the behavioral and other dificits mediated by Aβ (Roberson et al., 2007), and (iv) mutations in the tau gene cause FTDP-17 with a tau pathology similar to that in AD without SP formation (Hutton et al., 1998; Lewis et al., 2000).

There are several objections to the "amyloid cascade" hypothesis. There is only a weak correlation between cerebral SPs and the severity of dementia. SPs and NFTs may be reactive products resulting from neurodegeneration in AD rather than being its cause. It remains unclear whether and how the deposition of Aβ leads to the formation of NFTs. These should be addressed in the future investigations.

2.2. Stat3 inactivation in the "amyloid casdade"

Signal transducer and activator of transcription 3 (Stat3) is an important mediator of cellular physiological functions such as cell proliferation, differentiation, and survival, mainly upon cytokine receptor stimulation (Chiba et al., 2009a; Stephanou and Latchman, 2005). Immunohistochemical analysis using a specific antibody against phosphorylated (p-) or activated form of Stat3 revealed that p-Stat3 levels were significantly reduced in hippocampal neurons of clinically and pathologically diagnosed AD patients and several lines of AD model mice as

compared with age-matched controls (Chiba et al., 2009b). Animal experiments further showed that (i) i.c.v. injection of toxic Aβ peptide reduces p-Stat3 in hippocampal neurons to induce memory impairment (a toxic Aβ gain of function effect) and that (ii) Aβ passive immunotherapy reduces cerebral Aβ burden and recovers cognitive function of Tg2576 mice in parallel with Stat3 activation in hippocampal neurons (a toxic Aβ loss of function effect). These data suggest that cerebral Aβ levels are inversely correlated with p-STAT3 levels in hippocampal neurons *in vivo* (Chiba et al., 2009b).

Aging, one of the most common risk factor for AD, seems to be one of the other factors responsible for the AD-related neuronal inactivation of Stat3 because p-Stat3 immunoreactivity in hippocampal neurons of young subjects was substantially higher than that of elder cognitively normal subjects in both humans and rodents (Chiba et al., 2009b). Aging-dependent reduction of p-Stat3 levels may be due to age-dependent decrease in endogenous neurotrophic factors, which play a role in sustaining neuronal p-Stat3 levels. In support of this idea, it is reported that endogenous levels of insulin-like growth factor I (IGF-I), which activates Stat3, decrease with aging and that this decrease may be linked to the pathogenesis of AD (Rollero et al., 1998).

Relationship between Stat3 and tau is yet to be elucidated. Stat3 binds to and inhibits stathmin, which depolymerizes microtubules, while tau binds to and stabilizes microtubules (Ng et al., 2006). Involvement of STAT3-mediated stathmin regulation in tau phosphorylation should be addressed in the future research. There are some reports describing Stat3 inactivation and cell death; i.e. Stat3 deletion sensitizes cells to oxidative stress (Barry et al., 2009; Sarafian et al.). Combined with the fact that Aβ induces neuronal death by inducing oxidative stress *in vitro* and *in vivo* (Butterfield et al., 2002; De Felice et al., 2007; Guglielmotto et al., 2009), Stat3 may sensitize neurons to Aβ neurotoxicity through oxidative stress.

In addition to the role of Stat3 in neuronal death, roles of Jak2/Stat3 pathway in synaptic plasticity have been reported. Activation of the Jak2/Stat3 pathway induces presynaptic transcriptional upregulation of cholinergic genes including choline acetyletransferase (ChAT) and vesicular acetylcholine transporter (VAChT) and postsynaptic sensitization of m_1-type muscarinic acetylcholine receptor (m_1-mAChR) to support cholinergic neurotransmission (Chiba et al., 2009b). The Jak2/Stat3 pathway also plays an essential role in the induction of NMDA-receptor dependent long-term depression (NMDAR-LTD) in the hippocampus (Nicolas et al., 2012).

2.3. Emerging genetic risk factors for AD

AD can be classified into early onset (EOAD, <65 years) and late onset (LOAD, >65 years) form. According to family history, AD can be also classified into FAD and sporadic (SAD) (Alves et al., 2010). Although aforementioned three FAD genes generally result in EOAD, there is a substantial genetic component in LOAD as well (an estimated heritability of 58-79%). Accordingly, *apolipoprotein E (APOE)* gene on chromosome 19 has also been shown to be a genetic risk factor for LOAD in the early 1990s (Bertram et al., 2010; Schellenberg and Montine, 2012). *APOE* contains three major alleles: ε2, ε3, and ε4. Inherited ε4 allele is reported to worsen the loss of neuronal function in AD patients and decrease the age of onset (Huang and Mucke, 2012;

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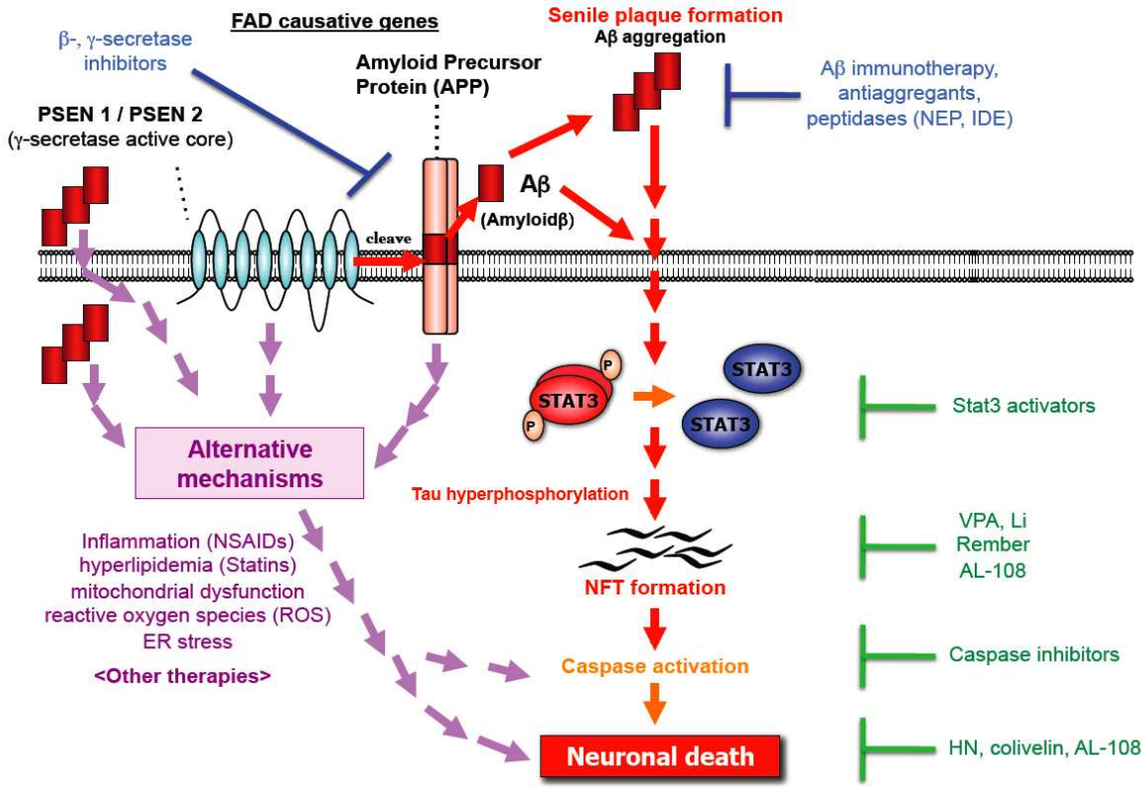

Figure 3. A schematic overview of the "amyloid cascade" hypothesis and therapeutic strategies. (Red arrows) The "amyloid cascade" begins with the proteolytic cleavage of APP by the γ-secretase. Aβ forms toxic oligomers or aggregates, inducing neuronal Stat3 inactivation, NFT formation, caspase activation and neuronal death. Therapies targeting the canonical "amyloid cascade" such as secretase inhibitors and immunotherapy are indicated in blue characters. Therapies targeting on the downstream pathways of the "amyloid cascade" are indicated in green characters. Alternative pathological mechanisms, which can be caused by intracellular Aβ, extracellular Aβ, or FAD mutants themselves, are also targeted (purple). (NEP, neprilysin; IDE, insulin degrading enzyme; VPA, valproic acid; HN, humanin).

Poirier, 2005). One copy of *APOE* ε4 increases the risk for AD fourfold and two copies further raise the risk tenfold. *APOE* is not a causative gene, i.e. *APOE* ε4 is neither necessary nor sufficient for LOAD. In addition to *APOE* itself, a variable-length poly-T (deoxythymidine homopolymer) polymorphism in the *TOMM40* gene, located in a region of strong linkage disequilibrium next to *APOE*, was reported to be associated with the age of onset of LOAD (Lutz et al., 2010; Roses et al.).

Genetic association studies on LOAD susceptibility loci and small nucleotide polymorphisms (SNPs) revealed two genes: *ubiquilin 1 (UBQLN1)* on chromosome 9 (Bertram et al., 2005) and *sortilin-related receptor (SORL1)* (Rogaeva et al., 2007). Identification of *UBQLN1* is intriguing since it not only interacts with PSEN1, PSEN2 and APP but also may play a role in the proteasome degradation of them (Mah et al., 2000; Massey et al., 2004). SORL1 is involved in both trafficking of APP from the cell surface into recycling pathways and processing of APP by γ-secretase. A recent meta-analysis of genetic data and GWAS supported that mutations in *SORL1* may play a role in LOAD although the effect on the AD risk is moderate (Schellenberg and Montine, 2012). On the other hand, no evidence for *UBQLN1* has been provided from GWAS.

Since 2009, several GWAS results have been published (Alves et al., 2010; Bertram, 2011; Eisenstein, 2011; Reitz, 2012; Schellenberg and Montine, 2012). In GWAS, researchers analyze millions of SNPs in affected and healthy individuals. There is a criticism that two many comparisons at the same time will just lead to a number of false positive associations, which cannot be reproduced by other studies. This is partially true. GWAS, however, have identified nine novel loci reproducibly associated with LOAD: (i) *clusterin (CLU)*, (ii) *phosphatidylinositol-binding clathrin assembly protein (PICALM)*, (iii) *complement receptor 1 (CR1)*, (iv) *bridging integrator 1 (BIN1)*, (v) *ATP-binding cassette, subfamily A, member 7 (ABCA7)*, (vi) *membrane-spanning 4-domains, subfamily A, members 4 and 6E (MS4A4/MS4A6E, MS4A cluster)*, (vii) *CD2-associated protein (CD2AP)*, (viii) *CD33 molecule (CD33)* and (ix) *EPH receptor A1 (EPHA1)* (Bertram, 2011). These genes significantly increase risk for LOAD although they rather have small effects on susceptibility to AD (within 1.5 times increase or decrease in odds ratio).

One of the important aims of GWAS is to identify novel pathogenic pathways for AD. Although Morgan, for example, classified risk genes identified from GWAS into three new pathogenic pathways (Morgan): immune system function (*CLU, CR1, ABCA7, MS4A cluster, CD33 and EPHA1*), cholesterol metabolism (*APOE, CLU and ABCA7*) and synaptic dysfunction (*PICALM, BIN1, CD33, CD2AP and EPHA1*). Others assume that most of risk genes are related to the "amyloid cascade", providing a solid support for the "amyloid cascade" hypothesis. This discrepancy is due to multiple functions of each risk gene. E.g. *CLU*, which is also known as *apolipoprotein-J (APOJ)*, helps *APOE* in cholesterol trafficking in the central nervous system and is also involved in Aβ aggregation and clearance. *CR1* is an important component of the innate immune response against infection and is also involved in the clearance of circulating Aβ. In summary, *APOE* is still the biggest risk gene for LOAD and detailed functional analyses are necessary for other novel risk genes to discuss novel or relevant pathogenic mechanisms for AD.

3. Clinically available drugs for AD

In this section, currently available drugs in AD clinics, such as cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists will be discussed (Lleo et al., 2006; Mangialasche et al., 2010). More than 15 years have passed since the first ChEI, donepezil (Aricept®), was approved as a clinical drug for AD in the United States. Many clinical trials and follow-up surveys have revealed marginal to moderate effects of ChEIs and NMDA antagonists in AD patients (Riordan et al., 2011). They show only symptomatic effects although potential neuroprotective effects have been postulated.

3.1. Cholinesterase inhibitors (ChEIs)

Deteriorated cholinergic function such as loss of basal forebrain cholinergic neurons is one of the pathological features of AD (Bartus et al., 1982; Farrimond et al., 2012; Van der Zee et al.). Acetylcholine (ACh), which is one of neurotransmitters functioning in both central and peripheral nervous system, is synthesized from choline and acetyl coenzyme A (acetyl-CoA)

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by an enzyme ChAT in certain neurons. There are two major classes of ACh receptors (AChRs); i.e. ionotropic nicotinic AChR (nAChR) and metabotropic muscarinic AChR (mAChR). ACh in the synaptic cleft is rapidly degraded into two inactive metabolites choline and acetate by an enzyme, ChE. Thus, cholinergic neurotransmission can be improved with ChEIs via prevention of ACh degradation.

ChEIs, such as donepezil (Aricept®), galantamine (Razadyne®) and rivastigmine (Exelon®) are approved by the Food and Drug Administration (FDA) for the treatment of AD (Farrimond et al., 2012; Pettenati et al., 2003). Donepezil is a reversible ChEI with high specificity with few side effects and can be used for all stages of AD. Galantamine, which is approved for mild-to-moderate AD, has multiple functions such as inhibition of ChE, induction of ACh release and allosteric stimulation of nAChR. Rivastigmine, which is also for mild-to-moderate AD, suppresses both acetyl- and butyryl-ChE. Some placebo-controlled, double-blind trials have demonstrated that ChEI therapy results in significant improvement in cognitive performance of AD patients. Unfortunately, however, a long-term rondamized trial named 'AD2000' failed to prove therapeutic benefits of Donepezil (Courtney et al., 2004; Tariot et al., 2001; Winblad et al., 2006). Although ChEIs may slow worsening of AD symptoms to some extent, it should be noted that the effectiveness of ChEIs and how long they work, would vary from person to person. In addition, direct activation of acetylcholine receptors, such as m_1-mAChR and $\alpha 7$ nAChR, is currently under development.

3.2. N-methyl-D-aspartate (NMDA) receptor antagonists

Excitotoxicity by excess amount of glutamatergic neurotransmission is also implicated in the pathogenesis of AD. Memantine (Namenda®) is a non-competitive, voltage-dependent and of moderate affinity N-methyl-D-aspartate (NMDA) receptor antagonist, preventing neuronal cells from excitotoxic death caused by a glutamate-induced excessive income of calcium ions. Memantine was approved by the FDA in 2003 for the treatment of moderate-to-severe AD since it improved cognitive function of AD patients who were receiving stable doses of a ChEI (Tariot et al., 2004). Serious side effects have not been reported to occur at high frequency. In addition to the NMDA antagonism, memantine is reported to decrease Aβ production (Alley et al., 2009; Ray et al., 2009), suppress synaptic dysfunction (Klyubin et al., 2009) and induce protein phosphatase-2A (PP2A)-mediated reduction of tau hyperphosphorylation (Chohan et al., 2006; Martinez-Coria et al., 2010).

3.3. Other supporting drugs

AD patients also suffer from neuropsychiatric symptoms such as apathy, depression, anxiety, psychosis, aggression and sleep disturbances, which are generally called as behavioral and psychological symptoms in dementia (BPSD) (Alves et al., 2010). When BPSD are severe and persist despite the use of ChEIs and memantine, pharmacological treatment will be started. For severe depression, antidepressive drugs such as sertraline, which is one of the selective serotonin reuptake inhibitors (SSRIs) used to treat major depression. Neuroleptic drugs such as risperidone, which is a dopamine antagonist and mainly used to treat schizophrenia, are used to treat aggression, agitation and psychosis. Anxiolytics such as loracepam and oxacepam

(benzodiazepines) are also used to ameliorate anxiety and verbal problems. For sleeping disturbances, non-pharmacological interventions are common because sleeping drugs or sedative-hypnotic medications have only a limited efficacy and significant adverse effects (David et al., 2010; Shub et al., 2009). In addition, melatonin, which is an endogenous regulator of circadian rhythms and is used as a chronobiotic or soporific, showed no benefits in a multicenter, placebo-controlled trial for sleep disturbance in AD (Singer et al., 2003). These drugs are used to reduce BPSD and to improve patients' activities of daily living and quality of life.

4. Emerging therapeutic strategies

Finally, emerging therapeutic strategies will be discussed. For better understanding, strategies are first classified into two major categories: AD-specific and AD-non-specific disease modifying treatments (Table 1). As to AD-specific disease-modifying treatments, the amyloidogenic processes and their regulatory mechanisms are defined as the canonical "amyloid cascade". Strategies based on other findings related to the downstream pathways of the "amyloid cascade" are summarized in the other drugs based on alternative pathways. Drugs related to the downstream mechanisms from the amyloidogenesis including tau phosphorylation and Stat3 inactivation are classified into the alternative pathways here because the connection between the canonical "amyloid cascade" and the downstream mechanisms is still elusive. As to AD-non-specific treatments, regenerative therapy may be realized in the near future with an enormous progress in the field of stem cell biology.

4.1. AD-specific drugs targeting the canonical "amyloid cascade"

In the last 10 years, most pharmaceutical companies were trying hard to develop secretase inhibitors such as α-, β- and γ-secretase inhibitors to suppress amyloid beta production, the initial step of the "amyloid cascade" (Ghosh et al., 2012; Wolfe, 2012). A number of clinical trials of β-secretase inhibitors and γ-secretase inhibitors have been carried out or are ongoing.

Another major attempt has been the development of Aβ immunotherapy to remove amyloid deposits, which is also targeting the initial step of the cascade (Delrieu et al., 2012). Both active and passive immunization have been developed by utilizing Aβ peptide and its antigenic epitopes, or anti-Aβ antibodies.

4.1.1. Aβ immunotherapy to remove brain Aβ

Initial findings from a clinical trial of active Aβ immunotherapy

Aβ immunotherapy is an approach to remove accumulated Aβ in AD brains immunologically: Aβ vaccination therapy and passive immunization with anti-Aβ antibody. Schenk *et al.* reported that the Aβ vaccine named AN-1792, which contains Aβ42 peptide and adjuvants, significantly reduced amyloid plaques in brain of PD-APP mice (Schenk et al., 1999). With the evidence in transgenic mice, clinical trial was started in 2001. Phase II studies performed in

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Europe and USA, however, were suspended since 6% of the subjects gave a sign of meningoencephalitis such as fever, vomiting, headache, loss of consciousness, and so on after the second vaccination (Orgogozo et al., 2003). Patients who received AN-1792 have been reported to show elevated levels of antibodies against Aβ (Hock et al., 2002) and some immunized patients resulted in reduction of amyloid deposits without significant decrease in both NFT formation and neuronal cell death (Nicoll et al., 2003).

As reported, there is a potential risk in the Aβ immunothrerapy that antibodies against APP induce neuronal cell death, which may lead to meningoencephalitis (Rohn et al., 2000; Sudo et al., 2000). Although it is reported that antibodies elevated in patients mainly recognize SPs, there is still a certain possibility that small fraction of elevated antibodies binds to APP and induces neuronal death. Another potential risk is that cytotoxic T cells, which might cause cellular toxicity on neurons, are also activated by active immunization. In agreement, there were a number of lymphocytic infiltration in brains of immunized AD patients (Nicoll et al., 2003).

Improvement of Aβ immunotherapy

Recently, however, several alternatives of Aβ immunotherapy have been proposed. Passive immunization with anti-Aβ monoclonal antibodies is first one (Dodart et al., 2002; Kotilinek et al., 2002). In this approach, it seems easier to control side-effects by using monoclonal antibody than non-specific activation of immune system by active immunization. Active immunization can be safer by specific targeting of immunogen to T-helper cells. Other types of immunization have been also developed. Hara *et al.* developed an oral vaccine using recombinant adeno-associated virus (AAV) vector encoding Aβ cDNA (Hara et al., 2004) and Okura *et al.* developed nonviral Aβ DNA vaccine (Okura et al., 2006). With these vaccines, serum antibodies against Aβ were elevated by ectopic Aβ expression without T cell proliferative response. Safety of these vaccines, however, should be carefully tested.

Improved active Aβ immunotherapy

New vaccines that selectively target B-cell epitopes (N-terminus of Aβ peptide) have been developed. CAD-106, consisting of Aβ1-6 peptide coupled to virus-like carrier particle Qβ (a T-helper cell epitope) could efficiently induce Aβ antibodies without induction of Aβ-specific T-cells (Wiessner et al., 2011). Similar strategy is employed in other vaccines: ACC-01 (Aβ1-6 donjugated to the mutated diphtheria toxin protein CRM19), V-950 (Aβ N-terminus with an aluminium-containing adjuvant with or without ISCOMATRIX), ACI-24 (Aβ1-15 closely apposed to the surface of the liposome), UB-311 (Aβ1-14 associated with the UBITh peptide, a T-helper cell epitope) (Mangialasche et al., 2010; Reitz, 2012). Another active immunization strategy is based on Affitopes, short peptides mimicking parts of native Aβ42 without its sequence identity. AD-01 and AD-02 mimick the N-terminal Aβ fragments. These vaccines are generally reported to be safe and well-tolerated in phase I studies. Results of phase II and III studies are awaited.

Passive Aβ immunotherapy

Passive immunotherapy is based on the administration of antibodies against Aβ. This can be achieved by both monoclonal antibodies and polyclonal immunoglobulins. In animal models,

anti-Aβ antibodies are reported to prevent oligomer formation with reduced brain Aβ load. Several monoclonal antibodies are currently tested in clinical trials: bapineuzumab (AAB-001), solanezumab (LY-2062430), ponezumab (PF-04360365), GSK-933776, R-1450 (RO-4909832), and MABT-5102A (Mangialasche et al., 2010). A phase II study of bapineuzumab in patients with mild to moderate AD did not attain statistical significance on the primary efficacy endpoints in the overall study population (Salloway et al., 2009). They only found some statistically significant benefits in limited subpopulations without the APOE e4 allele. A phase III study of bapineuzumab finally again failed recently (Aug. 6, 2012: www.pfizer.com). Solanezumab, which mobilized brain Aβ in a phase II study (Farlow et al., 2012), also failed to slow cognitive decline in phase III clinical trials including more than 2,050 AD patients (Aug. 24, 2012: www.lilly.com). Ponezumab is a humanized monoclonal IgG2 antibody binding to the C-terminus of Aβ40 and a phase I trial showed that the antibody is well tolerated in AD patients (Freeman et al., 2012). Other antibodies are also currently tested in phase I and II studies.

Passive immunization can also be achieved by intravenous infusion of immunoglobins (IVIg), from healthy donors, which are assumed to include naturally occurring polyclonal antibodies against pathogenic Aβ (Britschgi et al., 2009; Dodel et al., 2002; Dodel et al., 2004; Fillit et al., 2009). IVIg is already approved for immune deficiency, meaning that it is safe and well tolerated. Preliminary data from a phase II study showed a positive effect on cognition (Relkin et al., 2009).

Active versus passive Aβ immunotherapy

Active immunotherapy will keep high antibody titers for a long period, enabling few follow-up observations and reduced costs. The control of the antibody concentrations and adverse effects are limited, however. Passive immunotherapy offers a good and rapid control of antibody properties and concentrations. In addition, passive immunotherapy could be more effective in elderly population with reduced immune responses. However, administration of antibodies is time- and money-consuming. The effects of active and passive Aβ immunotherapy are not so much different and unfortunately both immunotherapy are not successful so far.

4.1.2. γ-secretase and β-secretase inhibitors for reduction of Aβ production

Secretases have become the targets to control Aβ production and prevent the progress of AD since Aβ is generated from APP via sequential cleavage by β- and γ-secretases (Chiba et al., 2007; De Strooper and Annaert, 2000). This is the initial step in the canonical "amyloid cascade". Considering that most of the mutant *APP* and *PSEN1* result in increased Aβ42/Aβ40 ratio, abnormal γ-secretase function seems to be closely related to the pathogenesis of AD. In addition, the choice of the first cleavage by α- or β-secretase decides the generation of Aβ, which gives us the notion that β-cleavage inhibition and α-cleavage activation greatly reduce Aβ production.

β-secretase inhibitors

In 1999, β-site APP cleaving enzyme (BACE1), a membrane-anchored aspartyl protease, was reported to have β-secretase activity (John et al., 2003; Vassar et al., 1999). The BACE1 knock out mice studies showed that Aβ levels in brain was drastically reduced, and they remain healthy without any anomaly in clear contrast to that of PSEN knockout mice (Cai et al., 2001; Luo et al.,

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2001). Consequently, it is assumed that β-secretase inhibitors are safer than γ-secretase inhibitors. Recently, however, BACE1/2 double knockout mice was generated and resulted in lethal phenotype, presumably because BACE1/2 have many substrates (including neuregulin-1, which is involved in myelination) required in the development (Dominguez et al., 2005).

Pioglitazone and rosiglitazone are thiazolidinediones, which control blood sugar by stimulating the nuclear peroxisome proliferator-activated receptor γ (PPARγ), clinically used for type II diabetes mellitus (DM). They turned out to be good BACE1 inhibitors: i.e. PPARγ activation by the thiazolidinediones suppresses BACE1 and APP expression (Mangialasche et al., 2010). In addition, pioglitazone and rosiglitazone promote Aβ degradation, which is competitively inhibited by insulin, by reducing insulin concentrations. Results from clinical studies are, however, disappointing (Miller et al., 2011). Neither pioglitazone nor rosiglitazone showed any efficacy on cognition in AD patients.

γ-secretase inhibitors

Development of γ-secretase inhibitors, which suppress the final step in amyloidgenesis, is one of the major issues in AD research. Transition state analogs of γ-secretase, such as L-685458 (Merk), inhibit the γ-secretase activity and decreases production of Aβ40 and Aβ42 (Shearman et al., 2000). Chemical compunds including pepstatin A, sulfonamide derivatives and benzodiazepines are also shown to inhibit the γ-secretase activity in mechanisms other than competitive inhibition (Tian et al., 2002). Since γ-secretase is also involved in processing of other membrane proteins including Notch, γ-secretase inhibitors may induce severe side effects. In agreement, the chronic administration of a γ-secretase inhibitor triggered abnormal blood cell differentiation and damage on digestive tracts (Searfoss et al., 2003). APP-specific γ-secretase inhibitors or γ-secretase modulators may resolve this problem.

Several γ-secretase inhibitors are currently tested in clinical studies: semagacestat (LY450139), begacestat (GSI-953), avagacestat (BMS-708163), PF-3084014, MK-0752, E-2012 and NIC5-15 (Mangialasche et al., 2010). Phase III trials for semagacestat, which inhibits Notch cleavage as well as APP cleavage, not only failed but also worsened clinical measures of cognition and activity of daily living with increased incidence of skin cancer (Cummings, 2010). Other Notch-sparing γ-secretase inhibitors (second-generation inhibitors) such as begacestat and avagacestat are now in phase I or II studies and they show reduction of plasma and/or cerebrospinal fluid (CSF) Aβ levels. PF-3084014, a γ-secretase inhibitor with high selectivity for APP, and NIC5-15, a Notch-sparing γ-secretase inhibitor with insulin sensitizing activity, showed some positive effects with good tolerance and now proceeded into phase II studies (Mangialasche et al., 2010). Effects of a γ-secretase modulator, tarenflurbil, will be discussed later (see 4.3.2.).

***α*-secretase activators**

Upregulation of *α*-cleavage, which results in non-amyloidogenic cleavage of APP, can competitively inhibit β-cleavage, leading to downregulation of Aβ production and reciprocal upregulation of neuroprotective soluble APP*α* (sAPP*α*) secretion (Vingtdeux and Marambaud, 2012). *α*-Secretase is a member of the ADAM (a disintegrin and metalloprotease) family of proteases including ADAM10, ADAM17/TACE (TNF*α* converting enzyme), or ADAM9. There is a number of ways to activate *α*-secretase (Mangialasche et al., 2010): (i) activation of

neurotransmitter receptors such as muscarinic, glutamate, γ-aminobutyric acid (GABA) (e.g. etazolate [SQ-20009, EHT-0202]) and serotonin receptors (e.g. SB-742457, PRX-03140, AVN-322 and RQ-00000009), (ii) steroid hormones such as estrogens and testosterones, and (iii) protein kinase C (PKC) activation (e.g. bryostatin-1). No conclusive results are published yet from clinical trials.

4.1.3. Drugs preventing Aβ aggregation, destabilizing Aβ oligomers and inducing Aβ clearance

Neurotoxic activity of Aβ is likely to be mediated by certain types of soluble oligomers (Di Carlo, 2010; Lesne et al., 2006; Schilling et al., 2008). Oligomerization and aggregation of Aβ further promote SP formation or accumulation of brain Aβ load. Therefore, compounds preventing Aβ aggregation or destabilizing Aβ oligomers seem to be promising drug candidates for AD. Compounds binding to Aβ monomers may prevent oligomerization and promote Aβ degradation, while compounds recognizing Aβ oligomers may neurtralize the neurotoxicity and facilitate Aβ clearance.

Tramiprosate (homotaurine, 3APS), which is one of the non-peptidic anti-aggregants binding to Aβ monomers, failed to show clinical efficacy in a phase III study (the Alphase study) (Aisen et al., 2011). An antifungal and antiprotozoal drug clioquinol (PBT1) (Tabira, 2001), which disrupts interactions between Aβ, copper and zinc, showed positive results in phase II studies, but further studies were halted due to manufacturing toxicity issues (Ritchie et al., 2003; Sampson et al., 2008). PBT2, a second-generation inhibitor without toxicity, also showed promising results in a phase II study (Lannfelt et al., 2008). Scyllo-inositol (ELND-005), an orally administered stereoisomer of inositol, binds to Aβ, inhibits Aβ aggregation and promotes dissociation of aggregates. Phase II studies, however, revealed serious adverse events among patients with high-dose treatments (Salloway et al., 2011). Epigallocatechin-3-gallate (EGCg), a polyphenol from green tea, preventing Aβ aggregation by binding to unfolded Aβ, is currently tested in phase II/III studies (Mandel et al., 2008; Rezai-Zadeh et al., 2005).

Aβ clearance itself is also a target of novel therapeutics, which is based on the fact that Aβ clearance from brains is impaired in AD patients, especially in those with *APOE* ε4. Aβ clearance can be achieved by local Aβ uptake and degradation in the CNS (Aβ degradation will be discussed in 4.1.4), or pumping out of Aβ through the blood-brain-barrier (BBB) from the brain to the plasma. Aβ clearance is facilitated by APOE, the transcription or expression levels of which are regulated by PPARγ and heterodimeric receptors consisting of liver X receptors (LXRs) and retinoid X receptors (RXRs) (Cramer et al., 2012; Huang and Mucke, 2012). Agonists of these receptors could be used to reduce Aβ load in AD brains. Aβ translocation through BBB is regulated by lipoprotein receptor related protein-1 (LRP-1), which is a receptor for APOE and α2-macroglobulin, and the receptor for advanced glycation endproducts (RAGE) (Deane et al., 2003; Deane et al., 2008). LRP-1 pumps Aβ out of the CNS across the BBB, while RAGE supports Aβ influx into the CNS. The soluble form of RAGE (sRAGE) competes with the membrane-linked RAGE, promoting removal of circulating Aβ. A phase II study on a RAGE inhibitor (TTP-488) is ongoing (Mangialasche et al., 2010). Lactoferrin, a globular glycoprotein found in various secretory fluids such as milk, saliva and tears, is known to stimulate LRP-1 (Ito et al., 2007). LRP-1 agonists are also candidates for AD therapy.

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4.1.4. Drugs inducing Aβ degradation

An endopeptidase named neprilysin (NEP) was identified to degrade Aβ aggregates and regulate Aβ metabolism *in vivo* (Iwata et al., 2001; Iwata et al., 2000). It is a type II transmembranous ectoenzyme, and cleaves peptide bond of N-terminal hydrophobic amino acid residue in lower than 5kDa peptide. In knock out mice study, Aβ levels in brain elevated to twice as that in the control mice (Iwata et al., 2001), and NEP gets lower in old wild type mice brain (Iwata et al., 2002). Furthermore, the expression levels of NEP were decreased to the half levels in sporadic AD patients' brain as compared with healthy controls' (Yasojima et al., 2001a; Yasojima et al., 2001b). The cleavege of Aβ by NEP, however, is not so potent that NEP itself may be difficult to be clinically effective. Recently, Saito *et al.* have reported that somatostatin regulates brain Aβ42 through modulating proteolytic degradation catalyzed by NEP (Saito et al., 2005). Somatostatin and its receptor could also be utilized in the Aβ degradation therapy for AD.

Insulin degrading enzyme (IDE) is another enzyme degrading Aβ (Qiu et al., 1998). Overexpression of IDE in AD mouse models retarded or even completely prevented SP formation, while IDE knockout mice showed increased levels of Aβ and insulin (Farris et al., 2003; Leissring et al., 2003). Cabrol *et al.* performed high-throughput compound screening for small-molecule activator of IDE and found promising compound activating IDE by binding to its putative ATP-binding domain (Cabrol et al., 2009). Current investigations have further suggested that Aβ degradation is also mediated by multiple types of proteases including presequence peptidase, endothelin converting enzyme (ECE), angiotensin-converting enzyme (ACE), the uPA/tPA-plasmin system, transthyretin (TTR, gelsolin, α2-macroglobulin and matrix metalloproteinases (MMP-2 and 9) (Nalivaeva et al., 2012).

4.2. AD-specific drugs based on the alternative pathways

Drugs targeting the downstream pathways of the "amyloid cascade" have been also developed. These include tau inhibitors and neuronal death inhibitors. Tau inhibitors are either based on suppression of tau phosphorylation or inhibition of tau aggregation. Glycogen-synthase-kinase-3β (GSK3β) inhibitors are shown to reduce tau phosphorylation and methylene blue inhibits tau aggretation. Neuronal death can be suppressed by endogenous soluble factors such as leptin, AL-108 (NAP) and humanin (HN) as well as artificially modified small peptides such as colivelin (CLN) (Chiba et al., 2009a). Some of them activate Stat3, which is specifically inactivated in AD patients. AL-108 shows anti-Aβ activity and anti-tau activity at the same time.

Alternative therapeutic targets are also emerging. One of the major targets is related to the metabolic syndrome. Several lines of evidence supported that the metabolic syndrome increases the relative risk of AD (Misiak et al., 2012). Especially, there seems to be a link between type 2 diabetes mellitus (DM) and AD. Thiazolidinediones, commonly used for type 2 DM such as piaglitazone and rosiglitazone, are already mentioned focusing on their BACE1 inhibiting activity. In addition, there is epidemiological evidence that drugs used for high cholesterol (hypercholesterolemia) and high blood pressure also lower the risk of AD (Burgos et al., 2012; Davies et al., 2011).

Symptomatic treatments (= currently available)	
Treatments for AD-related dementia	Treatments for BPSD
1. **Cholinesterase inhibitors (ChEIs):** donepezil (Aricept®), galantamine (Razadyne®), rivastigmine (Exelon®) 2. **NMDA receptor antagonist:** memantine (Namenda®)	1. Anti-depresseive drugs: sertraline (SSRI) etc. 2. Neuroleptic: risperidone (atypical antipsychotics) etc. 3. Anxiolytics: loracepam, oxacepam (benzodiazepines) etc. 4. Sleep disturbance: non-pharmacological interventions
AD-specific Disease-modifying treatments	
Drugs targeting the canonical "amyloid cascade"	Drugs based on the alternative pathways
1. **Aβ immunotherapy (IT):** active IT: AN-1792 (f), CAD-106, ACC-01, V-950 etc. passive IT: bapineurzumab (f), solanezumab (f), IVIg etc. 2. **Secretase inhibitors:** suppression of Aβ production β-inhibitors: pioglitazone (f), rosiglitazone (f). γ-inhibitors: semagacestat (f), begacestat, avagacestat etc. α-activators: etazolate, SB-742457, bryostatin-1 etc. 3. **Aβ aggregation inhibitor:** tramiprosate (f), PBT2 etc. 4. **Aβ degradation:** Aβ degradase (NEP, IDE) activator	1. Drugs based on tau pathology: VPA (f), Li (f), Rember 2. Neuronal death inhibitors: caspase inhibitors (Q-VD-OPh), neuroprotective peptides (HN, colivelin, AL-108 etc.) 3. Stat3 activation therapy: cytokines, PTP inhibitors etc. 4. Prion hypothesis for AD 5. Drugs based on epidemiological findings in AD 5-1. NSAIDs: Flurizan (f) 5-2. Statins: atorvastatin (f), simvastatin (f) 5-3. Dimebon (f)
AD-non-specific Disease-modifying treatments	
Memory enhancing treatments	Regenerative treatments
1. Antioxidants: vitamin E (f), natural polyphenols 2. Neurotrophic factors: NGF, BDNF, bFGF, VEGF, HGF etc. 3. Other drugs: PDE9A inhibitor, DHA (f) etc.	1. Implantation of NSCs, NPCs, neurons 2. Activation of endogenous neurogenesis: BDNF etc.

Table 1. Therapeutic strategy for AD. Drugs which failed in clinical trials are indicated with "(f)".

4.2.1. Drugs based on tau pathology

In AD, abnormally hyperphosphorylated tau forms aggregates called NFT. This pathway can be inhibited by preventing either hyperphosphorylation or aggregation. Tau phosphorylation is regulated by the equilibrium between tau kinases (e.g. cdk5, JNK and GSK3β) and tau phosphatases (e.g. protein phosphatase 2A [PP2A]). Aggregated tau shows β-sheet structure similar to Aβ aggregates although tau locates only in the cytoplasm.

Valproate (valproic acid, VPA) is reported to suppress tau phosphorylation via inhibiting cdk5 and GSK3β (Hu et al., 2011). This is so far the only compound, which reached phase III studies, in this category. Unfortunately, VPA showed no efficacy on cognition (Mangialasche et al., 2010; Tariot and Aisen, 2009). Lithium (Li), as well as VPA, is a well-known drug for psychiatric disorder, inhibiting GSK3β. A small clinical study with Li, however, did not show any cognitive benefit or any change in biomarkers (Hampel et al., 2009). Regardless of these failures, several GSK3 inhibitors are under development. NP-031112 (NP-12) is one of those GSK3 inhibitors and is currently tested in a phase II study, the result of which have not been reported.

Methylene blue (Rember®), which is used as a redox indicator in analytical chemistry and as a dye for nuclear staining in histology, is recently attracting attention as an anti-aggregant for

tau (Schirmer et al., 2011). Rember also has antioxidant activity and supports mitochondrial function. A phase II study showed slower disease progression in patients receiving a middle-dose (60 mg) although the highest-dose (100 mg) failed to show its efficacy presumably due to drug formulation defects (Mangialasche et al., 2010). A phase III study is now on-going.

4.2.2. Neuronal death inhibitors

Neuronal death is directly implicated in the pathogenesis of AD (Rohn and Head, 2009). Neuronal loss, but not SPs, correlates with the cognitive impairment in AD. Consequently, it is supposed that neuronal death suppression will result in potent therapeutic effect or even a curative one. Neuronal death could be caused by not only toxic Aβ oligomers but also death signals activated by mutations in the FAD genes. Notably, the death signals can differ depending on the types of FAD genes and the types of mutations (Chiba et al., 2007; Kawasumi et al., 2002). Apoptosis is implicated in the neuronal loss related to AD: terminal deoxyuridine triphosphate nick endlabeling (TUNEL)-staining and caspase activation are observed in neurons of patients' brains.

Complicated mechanisms of neuronal loss

It was a milestone in AD research that Yamatsuji *et al.* first showed that expression of FAD-associated mutants of *APP* (V642I/F/G) induce apoptosis via a mechanism independent of Aβ because it suggested not only that there might be neurotoxic insults other than Aβ underlying AD pathogenesis but also that APP might have physiological function besides its role as a precursor of Aβ (Yamatsuji et al., 1996). Actually, multiple groups have confirmed that overexpression of FAD mutants of *APP* induces neuronal cell death by triggering intracellular death signaling cascades (Hashimoto et al., 2000; Zhao et al., 1997). In addition, a number of observations support the idea that APP might function as a cell-surface receptor inducing cell death signals. Given that APP-dimerization activates the intracellular death signals identical to that induced by FAD mutants of APP without ligand stimulation, it is likely that there is a natural ligand for APP to trigger intracellular death signals. In accordance with the idea, transforming growth factor β2 (TGFβ2) and death receptor 6 (DR6) are reported to be physiological ligands for APP triggering the fore-mentioned death signals (Hashimoto et al., 2005; Nikolaev et al., 2009).

FAD-linked mutants of *PSEN1* and *PSEN2* also enhance cell death in several cell lines and primary neurons. Mechanisms of death induced by mutants of *PSEN1* is likely to be distinct from that by *PSEN2*. *PSEN1* mutants induce calcium-dependent oxidative stress (Guo et al., 1996), destabilization of β-catenin (Zhang et al., 1998), down-regulation of Akt (Weihl et al., 1999), ER stress (Mattson et al., 1998), and activation of nitric oxide synthase (NOS)-mediated caspase-independent death signals (Hashimoto et al., 2002a), while PSEN2 mutants induce downregulation of Bcl-X(L) (Passer et al., 1999) and Bcl-2 (Araki et al., 2001), activation of NADPH oxidase and xanthine oxidase (XO) (Hashimoto et al., 2002b).

Activated caspases may serve as positive feedback regulators of death. APP is reported to be a substrate for caspase-3, which may contribute to Aβ formation and synaptic loss (Gervais et

al., 1999). Tau is also a substrate for caspases and truncation of tau by caspases may lead to the formation of paired helical filaments (PHFs) and further NFTs (Gamblin et al., 2003).

Caspase inhibitors for AD

Evidence supports a role for executioner caspases including caspases-3, -6 and -7 in the pathogenesis of AD. Caspase activation can be prevented by peptide-based inhibitors such as Z-VAD-fmk and Z-DEVD-fmk (more specific to caspase-3). Although these inhibitors are potent and efficient *in vitro*, establishment of a proper drug delivery system and formulation is necessary for *in vivo* treatment of AD patients (Rohn and Head, 2009). An alternative small molecule, the quinolyl-valyl-O-methylaspartyl-[-2, 6-difluorophenoxy]-methyl ketone (Q-VD-OPh), has been developed to substitute Z-VAD-fmk (Caserta et al., 2003). Q-VD-OPh is not toxic to cells at high concentrations and is systemically active, demonstrating efficacy in animal models of Parkinson's disease (PD), Huntington's disease (HD) and stroke (Renolleau et al., 2007; Yang et al., 2004).

Another potential therapeutic strategy lies on upregulation of anti-apoptotic Bcl-2 protein. Small compounds inhibiting Bcl-2 have been synthesized for the treatment of cancer, while compounds activating Bcl-2 have not been obtained so far. In addition, Bcl-2 should not be activated systemically because of expected severe side effects such as tumorigenesis. Consequently, the delivery of *Bcl-2* gene by viral vectors, such as adenoviruses, AAV and lentiviruses, is considered. Local delivery of *Bcl-2* and its family genes by viral vectors are shown to be efficient in several animal models of neurodegeneration including cerebral ischemia, axotomy and amyotrophic lateral sclerosis (ALS) (Caleo et al., 2002; Kilic et al., 2002; Yamashita et al., 2001).

Another potential drug candidate is minocycline, which is reported to prevent mitochondrial release of cytochrome c and the following caspase-3 activation (Hashimoto, 2011). Minocycline is an orally available second-generation tetracycline, which can cross the BBB. It is reported that minocycline elicited therapeutic effects in animal models of ischemic brain injury, ALS, PD, HD and multiple sclerosis (Berger, 2000; Du et al., 2001; Zhu et al., 2002). Recent studies revealed that minocycline protects neurons and reduces Aβ deposition in AD mice although efficacy of minocycline in AD is yet to be carefully addressed (Choi et al., 2007; Seabrook et al., 2006).

Multi-spectrum neuroprotective factor, humanin and its derivatives

A functional screening for a death-suppressing factor, which antagonizes death induced by overexpression of V642I-APP, was carried out with a cDNA library established from occipital lobes of AD patients, which are relatively preserved regions in AD brains (Hashimoto et al., 2001b). As a result, cDNA encoding a novel 24 amino-acid peptide, termed humanin (HN), was identified (MAPRGFSCLLLLTSEIDLPVKRRA). Notably, HN specifically abolished death induced by AD-related neurotoxicity such as soluble oligomeric Aβ and *PSEN1*/*PSEN2* mutants as well as overexpressed *APP* mutants, but did not suppress neurotoxicity related to PD, HD and prion diseases (Hashimoto et al., 2001a; Hashimoto et al., 2001b). As a result of detailed structural characterization of HN, several types of HN derivatives with higher efficacy, such as S14G-HN (HNG), have been developed (Chiba et al., 2007; Hashimoto et al., 2001a). One of HN derivatives termed colivelin (SALLRSIPA-PAGASRLLLLTGEIDLP, a 26 amino-acid peptide) elicits 10^8-fold more potent effects than authentic HN (Chiba et al., 2005).

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HN derivatives ameliorate cognitive deficits observed in several types of AD model mice, presumably through activating its receptor consisting of the cytokine receptor gp130 and the downstream intracellular signaling pathways including the Jak2/Stat3 pathway (Chiba et al., 2009a; Yamada et al., 2008).

Effects of HN on the metabolic syndrome including DM and atherosclerosis are also reported: (i) HN suppresses pancreatic β-cell death (Hoang et al., 2010), (ii) HN increases peripheral insulin sensitivity (Muzumdar et al., 2009), and (iii) HN protects endothelial cells from LDL-induced oxidative stress (Bachar et al., 2010; Oh et al., 2011). These findings suggest that HN may reduce risks for LOAD through improving glucose and lipid metabolisms.

Activity-dependent neurotrophic factor (ADNF) and NAP

ADNF-9 or SAL (SALLRSIPA, a 9 amino-acid peptide) is an active core domain of ADNF, which antagonizes various types of neurotoxicity, such as tetrodotoxin (TTX), oxidative stress, NMDA, Aβ, ALS and gp120 of human immunodeficiency virus (HIV) (Brenneman and Gozes, 1996; Chiba et al., 2004; Chiba et al., 2007; Chiba et al., 2006; Dibbern et al., 1997). ADNF-9 exerts a neuroprotective effect at extremely low concentrations, such as hundred femtomolar concentrations, while it loses its neuroprotective effect at 1 nM or greater concentrations. Although ADNF receptors have not been identified, ADNF-mediated prosurvival mechanisms have been reported to involve activation of (i) CREB, (ii) NFkB, (iii) CaMKIV, (iv) hsp60, (v) transcriptional up-regulation of IGF-I, and (vi) poly ADP-ribosylation (Chiba et al., 2007).

Through expression screening of proteins recognized by antiserum against ADNF, a gene-encoding, activity-dependent neurotrophic protein (ADNP) was identified (Bassan et al., 1999). An eight-amino-acid sequence termed NAP (NAPVSIPQ, an 8 amino-acid peptide) in ADNP shows homology with ADNF and is recognized by antiserum against ADNF. NAP exhibits ADNF-like neuroprotective activity against various insults. NAP and its relative peptides, such as ADNF-9, D-SAL, and D-NAP have been reported to bind to and stabilize tubulin (Gozes and Divinski, 2004). NAP suppressed zinc-mediated microtubule depolymerization in astrocytes by promoting microtubule assembly and reorganization (Gozes and Divinski, 2007; Vulih-Shultzman et al., 2007). Accordingly, NAP is reported to protect neurons from tau-related neurotoxicity.

AL-108 (Davunetide), an intranasal formulation of NAP, and AL-208, an intravenous formulation of NAP, have been developed for clinical use (Shiryaev et al., 2011). A phase II study was safe and well tolerated and had positive effects on cognition. Currently, a phase III study is on-going.

4.2.3. Stat3 activation therapy for AD

Stat3 activation is another option for AD therapy, which can be achieved by soluble factors activating Stat3 signals; i.e. activation of upstream kinases and suppression of endogenous Stat3 inhibitors or regulators (Chiba et al., 2009a). As mentioned above, HN and its derivatives activate the Jak2/Stat3 signaling pathway. There are also many types of cytokines activating Stat3, such as interleukin-6 (IL-6) family cytokines (IL-6, ciliary neurotrophic factor [CNTF], leukemia inhibitory factor [LIF] and cardiotrophin-1 [CT-1]), erythropoietin (EPO), IL-27,

granulocyte-colony stimulating factor (G-CSF), and leptin. Administration of these soluble factors could be considered although the bioavailability and delivery of these cytokines into the CNS should be addressed. Stat3 is phosphorylated by cellular Tyr kinases such as Jaks and Src family kinases. Synthetic activators such as Src family activator (EPQYEEIPIYL, Src family activator from Santa Cruz Biothechnology, sc-3052) may activate Stat3 to suppress the pathogenesis of AD although it may bring a large risk of carcinogenesis.

There are several endogenous regulator of Stat3: protein Tyr phosphatases (PTPs) like Src homology region 2 domain-containing phosphatase-1 (SHP-1) and SHP-2, suppressor of cytokine signaling 3 (SOCS3) and protein inhibitor of activated Stat3 (PIAS3) (Chiba et al., 2009a; Hendriks et al., 2012; Stephanou and Latchman, 2005). There are a number of PTPs and some of them are involved in the dephosphorylation or inactivation of the Jak2/Stat3 signaling pathway. SOCS3 is transcriptionally induced by activated Stat3 as a negative feedback regulator. SOCS3 binds to and inhibits Jak2 to prevent Stat3 phosphorylation. PIAS3 is a nuclear protein inhibiting activated Stat3 via multiple mechanisms. Expression of PIAS3 seems to be epigenetically regulated. Regulation of PIAS3 may contribute to recover Stat3 phosphorylation in AD.

4.2.4. Drugs based on prion protein

Prion diseases such as Creutzfeldt-Jakob disease are transmitted from patients to others by infectious agents consisting of misfolded proteins. The prion hypothesis for AD, suspected during 1970s and 80s, is re-emerging based on the reports that AD pathology can be transmitted to mice as prions do (Eisele et al., 2009; Eisele et al., 2010). Recent findings support the notion that there is a considerable similarity between Aβ and prion protein: (i) Aβ aggregation has similar structure to prion protein aggregation (Nussbaum et al., 2012), (ii) Aβ oligomer binds to postsynaptic prion protein to impair neuronal function (Um et al., 2012), and (iii) Aβ aggregates infect like prions (Stohr et al., 2012). Accordingly, AD therapy targeting prion proteins or prophylaxis for AD based on the prion hypothesis may be possible.

4.3. AD-specific drugs based on epidemiological findings

Epidemiology, as well as genetics, has pointed out several important aspects of the pathogenesis of AD. Based on the findings, a number of clinical trials have been carried out.

4.3.1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Anti-inflammatory agents have been attracting attentions based on the fact that there is severe astrogliosis in AD brains and that epidemiological study showed that long-term users of nonsteroidal anti-inflammatory drugs (NSAIDs) have the lower risk of AD (Etminan et al., 2003). Considering that there are also several NSAIDs without benefits for AD patients including rofecoxib (a selective cyclooxygenase-2 [COX-2] inhibitor), and naproxen (a mixed COX-1 and 2 inhibitor) (Aisen et al., 2003), there seems to be additional anti-AD mechanisms other than attenuation of inflammatory response in effective NSAIDs including ibuprofen and indomethacin. For example, some NSAIDs may directly modify the γ-secretase activity and reduce Aβ42 levels without any evidence of inhibition of Notch processing, which might

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results in severe side effect (Lim et al., 2000; Lleo et al., 2004; Weggen et al., 2001). Flurizan (Tarenflurbil or R-flurbiprofen) is originally developed as an NSAID and is shown to reduce toxic longer Aβ42 levels as a γ-secretase modifier. In 2008, Myriad Genetics, Inc. announced that an 18-month phase III study of Flurizan in patients with mild AD (the Act-Earil-AD trial), unfortunately failed to achieve significant disease-modifying effect and that they decided to discontinue development of Flurizan (www.myriad.com) (Green et al., 2009). It should be noted that several COX-2 inhibitors may increase the production of the toxic Aβ42 peptide (Kukar et al., 2005). Further basic study about how and which NSAIDs work on AD should be piled up and elaborate clinical trials are essential.

4.3.2. Inhibitors for cholesterol synthesis: Statins

High cholesterol level is now recognized as a risk factor for LOAD (Shobab et al., 2005). As already mentioned, *APOE*, which is involved in lipid metabolisms, is reported to be a risk factor for LOAD (Bertram, 2011; Schellenberg and Montine, 2012). In this line, it was reported that long-term taking of HMG-CoA reductase inhibitors (statins) lowered the risk of AD significantly (Jick et al., 2000; Wolozin et al., 2000). In APP transgenic mice, statins improved brain pathology (Refolo et al., 2001). The mechanism in detail is unclear, but one possible mechanism is that statins modulate secretases: activation of α-secretase and inhibition of β-secretase to exert its anti-AD effect (Kojro et al., 2001; Parsons et al., 2006). These facts and clinical safety of chronic use of statins led this therapy to clinical trials. Recently, no significant clinical benefit on cognition or global functioning was, unfortunately, reported for atorvastatin and simvastatin in phase III studies (Feldman et al., 2010; Sano et al., 2011).

4.3.3. Dimebon

Dimebon (latrepirdine) received a huge attention as a potential therapy for AD after a publication in the *Lancet* of a positive phase II study carried out in Russia (Doody et al., 2008; Jones, 2010). Dimebon is an orally available and well-tolerated drug, which used to be approved for clinical use in Russia as a non-selective anti-histamine drug. Dimebon is reported to elicit multiple anti-AD effects such as ChE inhibition, prevention of NMDA-mediated excitotoxicity and inhibition of mitochondrial permeability transition pore opening. The phase III study of dimebon, called the CONNECTION study, unfortunately, showed no clinical benefit on co-primary (cognition and global function) and secondary endpoints. Moreover, an additional phase III study called the CONCERT study again failed to show efficacy of dimebon (announcement from Pfizer and Medivation on Jan 17, 2012, www.medivation.com). Complete discrepancy between the results of phase II and phase III studies has brought researchers a huge confusion. Negative comments about the underlying rationale for the use of dimebon in AD are currently increasing because of the complete failure of dimebon in the phase III studies.

4.4. AD-non-specific drugs for dementia

AD-non-specific drugs are also possible. The therapeutic bases of these drugs lie on protection of neurons from aging-related toxicity such as oxidative stress, promotion of synaptic plasticity and regeneration of neural tissues using stem cell technologies.

4.4.1. Antioxidants

Antioxidants are assumed to trap toxic reactive oxygen species (ROS), which increase as aging. ROS is also present in the damaged neurons containing NFTs or close to SPs. The principal antioxidant strategy involves treatments with vitamin E (α-tocopherol), which resulted in benefit for AD patients in a randomized, placebo-controlled trial (Sano et al., 1997). Vitamin E, however, does not seem to be so effective because it failed to show reproducible efficacy in a double-blind study performed recently (Petersen et al., 2005). Natural polyphenolic compounds such as ginkgo biloba extracts, curcumin, green tea catechins and grape-seed oil extract (resveratrol) are also attracting attention as antioxidants (Aranda-Abreu et al., 2011).

4.4.2. Neurotrophic factors to promote synaptic plasticity

Neurotrophins are well-characterized "trophic" factors, which generally promote neuronal survival and plasticity (Chiba et al., 2007). Each factor has its own relevance in AD. Nerve growth factor (NGF), which is discovered in the 1950s to be the first neurotrophic factor, mainly expressed in the peripheral nervous system, but also plays a key role in stimulation, maintenance, and survival of basal forebrain cholinergic neurons, which are destroyed in AD. Brain-derived neurotrophic factor (BDNF), purified from porcine brain homogenates in 1982, is highly expressed in cortical and hippocampal structures and plays roles in neuronal survival, neurite outgrowth and synaptic plasticity. A SNP in the *BDNF* gene that results in Met substitution of Val 66 in the pro-domain (V66M-BDNF or BDNFMet) causes dysregulation in BDNF secretion, which is linked to memory impairment as well as to altered susceptibility to neuropsychiatric disorders, such as AD, PD, depression, eating disorder, and bipolar disorder (Hong et al., 2011; Nagata et al., 2012).

Basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and hepatocyte growth factor (HGF) are also considered to be neurotrophic or neuroprotective factors whose receptors belong to the tyrosine kinase receptor family. bFGF and HGF exhibit a neuroprotective effect against Aβ neurotoxicity (Hashimoto et al., 2004; Takeuchi et al., 2008). Genetic variations in the VEGF gene modifies risks of AD (Del Bo et al., 2009).

Clinical application of these factors seem to be relatively difficult because proteins are not stable and are not easily delivered through BBB. Clinical studies on NGF, however, are promising. NGF treatments were initially based on intracerebroventricular infusion, which counterbalanced the positive effects with adverse effects. Accordingly, other drug delivery systems are currently tested in clinical trials: gene therapy with AAV or genetically modified fibroblasts producing NGF, encapsulated-cell biodelivery, intranasal delivery and topical application on the ocular surface (Mangialasche et al., 2010; Tuszynski et al., 2005).

4.4.3. Other therapies promoting synaptic plasticity

Phosphodiesterase inhibitors

Phosphodiesterases (PDEs) such as PDE-2, -4, -5 and -9 are expressed in the brain and play a key role in synaptic plasticity (Domek-Lopacinska and Strosznajder, 2010). Cyclic GMP

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(cGMP) positively regulates synaptic plasticity in this scheme, suggesting that PDE should be suppressed to increase cGMP. Consequently, PDE9A inhibitors are reported to promote synaptic plasticity via activation of cGMP signaling pathways (Andreeva et al., 2001). PF-04447943 is a selective PDE9A inhibitor, increasing cGMP concentrations in the CSF of healthy volunteers, and is being tested in a phase II study among mild-to-moderate AD patients (Mangialasche et al., 2010).

Omega-3 polyunsaturated fatty acids (docosahexaenoic acid etc.)

Omega-3 polyunsaturated fatty acids, such as docosahexaenoic acid (DHA), are involved in neurite outgrowth, remodeling of membrane lipid rafts and neurogenesis (Aranda-Abreu et al., 2011). They are also reported to suppress tau hyperphosphorylation and Aβ aggregation. Omega-3 fatty acids may repair damages in neuronal membranes and restore lipid rafts for appropriate trafficking of membrane proteins, leading to promotion of synaptic activity. Some clinical trials have reported beneficial effects of DHA in elderly people with cognitive impairment but other studies resulted in no effects on AD patients (Quinn et al., 2010).

4.4.4. Neuroregenerative therapy

Adult neurogenesis is now generally recognized. In adult brains, neurogenesis occurs mainly in two regions of the CNS including the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of hippocampal dentate gyri (Rodriguez and Verkhratsky, 2011). Multipotent neural stem cells (NSCs), localized in these regions, undergo self-renewal and differentiation into neuronal progenitor cells (NPCs) or glial progenitor cells (GPCs) with a faster cell cycle, which ultimately differentiate into neurons or glia. Impaired neurogenesis is expected for AD patients with massive neuronal loss. There is, however, a prevalent controversy among neurogenesis in AD brains. In a number of animal models for AD, toxic Aβ oligomers seem to enhance neurogenesis (Jin et al., 2004a; Sotthibundhu et al., 2009) although there are still several inconsistent observations that neurogenesis is disturbed in AD models (Feng et al., 2001; Haughey et al., 2002; Rodriguez et al., 2008). In post mortem AD brains, reduction of NPCs in the SVZ (Ziabreva et al., 2006) and an increase in NPCs in the DG (Jin et al., 2004b) are reported inconsistently as well. Accordingly, further clarification is mandatory.

Regardless of the discussion on the neurogenesis in AD brains, neuroregeneration, which can be achieved by either enhancement of endogenous neurogenesis or implantation of neurons or their progenitors (cell therapy), is getting to be considered as a valid therapeutic strategy for AD. This is mainly due to the progress in stem cell biology and a number of successful observations in preclinical studies. NSCs can be cultured and expanded *in vitro*. Moreover, NSCs can be differentiated from embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSs) established from AD patients themselves. Stem cell transplantation experiments have been carried out in animal models with some positive observations (Moghadam et al., 2009; Park et al., 2012; Wu et al., 2008; Yamasaki et al., 2007). These experiments, however, did not show significant regeneration or replacement of neural circuits by transplanted stem cells. Some of them used gene-modified stem cells with NGF or ChAT expression, supporting function of endogenous neurons. Delivery methods for NSCs/NPCs, cell viability and efficiency of engraftment should be considerably improved as well as resolving the safety issues. Endogenous neurogenesis is shown to be upregulated by soluble factors such as

serotonin (5-HT) agonists and BDNF in rodents (Lee et al., 2002; Santarelli et al., 2003). Effects in humans should be carefully addressed.

5. Conclusion

Disease-modifying therapy for AD is not yet available despite vast efforts on drug development and plenty of candidate drugs. As shown in Table 1, failure rate of phase II and III clinical trials for AD are extremely high, meaning not only that current *in vitro* or pre-clinical models of AD can hardly predict the clinical efficacy but also that drugs, which showed only a mild effect in phase II studies, would eventually fail in phase III studies. Consequently, ChEIs and memantine are still in the center of clinical therapies for AD. The "amyloid cascade" hypothesis certainly gave us important insights into AD pathogenesis and provided a number of candidates, most of which are still under assessment in clinical trials. However, the results obtained from completed clinical trials are rather negative for the "amyloid cascade" hypothesis: e.g. Aβ immunotherapy and β-/γ-secretase inhibitors continue to fail in the trials. In addition, there are critical objections to the "amyloid cascade", which has not been properly answered: (i) about one third of the cases of a cognitively normal elder population showed AD-like brain pathology such as SPs and NFTs (Bennett et al., 2006), and (ii) post-mortem pathological analyses of AD brains with immunotherapy revealed that a certain population of patients with Aβ immunotherapy resulted in significant decrease in senile plaques without significant recovery of cognitive function (Gilman et al., 2005; Nicoll et al., 2003). Time might have come to further modify the "amyloid cascade", integrate alternative hypotheses into it, or reconstitute a novel hypothesis for AD, in order to develop clinically effective AD therapies.

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