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Article *in* Sub-cellular Biochemistry · December 2012

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Chapter 14
Alzheimer's Disease

Vanessa J. De-Paula, Marcia Radanovic, Breno S. Diniz and Orestes V. Forlenza

Abstract Alzheimer's disease (AD) is a chronic neurodegenerative disease with well-defined pathophysiological mechanisms, mostly affecting medial temporal lobe and associative neocortical structures. Neuritic plaques and neurofibrillary tangles represent the pathological hallmarks of AD, and are respectively related to the accumulation of the amyloid-beta peptide (Aβ) in brain tissues, and to cytoskeletal changes that arise from the hyperphosphorylation of microtubule-associated Tau protein in neurons. According to the amyloid hypothesis of AD, the overproduction of Aβ is a consequence of the disruption of homeostatic processes that regulate the proteolytic cleavage of the amyloid precursor protein (APP). Genetic, age-related and environmental factors contribute to a metabolic shift favoring the amyloidogenic processing of APP in detriment of the physiological, secretory pathway. Aβ peptides are generated by the successive cleavage of APP by beta-secretase (BACE-1) and gamma-secretase, which has been recently characterized as part of the presenilin complex. Among several beta-amyloid isoforms that bear subtle differences depending on the number of C-terminal amino acids, Aβ_{1-42} plays a pivotal role in the pathogenesis of AD. The neurotoxic potential of the Aβ peptide results from its biochemical properties that favor aggregation into insoluble oligomers and protofibrils. These further originate fibrillary Aβ species that accumulate into senile and neuritic plaques. These processes, along with a reduction of Aβ clearance from the brain, leads to the extracellular accumulation of Aβ, and the subsequent activation of neurotoxic cascades that ultimately lead to cytoskeletal changes, neuronal dysfunction and cellular death. Intracerebral amyloidosis develops in AD patients in an age-dependent manner, but recent evidence indicate that it may be observed in some

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J. R. Harris (ed.), *Protein Aggregation and Fibrillogenesis in Cerebral and Systemic Amyloid Disease,* Subcellular Biochemistry 65,
DOI 10.1007/978-94-007-5416-4_14,

subjects as early as in the third or fourth decades of life, with increasing magnitude in late middle age, and highest estimates in old age. According to recent propositions, three clinical phases of Alzheimer's disease may be defined: (i) pre-symptomatic (or pre-clinical) AD, which may last for several years or decades until the overproduction and accumulation of Aβ in the brain reaches a critical level that triggers the amyloid cascade; (ii) pre-dementia phase of AD (compatible with the definition of progressive, amnestic mild cognitive impairment), in which early-stage pathology is present, ranging from mild neuronal dystrophy to early-stage Braak pathology, and may last for several years according to individual resilience and brain reserve; (iii) clinically defined dementia phase of AD, in which cognitive and functional impairment is severe enough to surmount the dementia threshold; at this stage there is significant accumulation of neuritic plaques and neurofibrillary tangles in affected brain areas, bearing relationship with the magnitude of global impairment. New technologies based on structural and functional neuroimaging, and on the biochemical analysis of cerebrospinal fluid may depict correlates of intracerebral amyloidosis in individuals with mild, pre-dementia symptoms. These methods are commonly referred to as AD-related biomarkers, and the combination of clinical and biological information yields good diagnostic accuracy to identify individuals at high risk of AD. In other words, the characterization of pathogenic Aβ by means of biochemical analysis of biological fluids or by molecular neuroimaging are presented as diagnostic tools to help identify AD cases at the earliest stages of the disease process. The relevance of this early diagnosis of AD relies on the hypothesis that pharmacological interventions with disease-modifying compounds are more likely to produce clinically relevant benefits if started early enough in the continuum towards dementia. Therapies targeting the modification of amyloid-related cascades may be viewed as promising strategies to attenuate or even to prevent dementia. Therefore, the cumulative knowledge on the pathogenesis of AD derived from basic science models will hopefully be translated into clinical practice in the forthcoming years.

Keywords Protein · Neuritic plaques · Neurofibrillary tangles · Alzheimer's disease amyloid precursor

Abbreviations

APP	*Amyloid Precursor Protein*
AD	Alzheimer's Disease
APOE	Apolipoprotein E
Aβ	Amyloid-β Peptide
CaMK-ll	Calcium calmodulin-kinase ll
CDK5	Cyclin-Dependent Kinases 5
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CNS	Central Nervous System
CSF	Cerebrospinal fluid
ER	Endoplasmic Reticulum
GSK3β	Glycogen Synthase Kinase-3β

IDE	Insulin-Degrading Enzyme
MAPK	Microtubule Associated Protein Kinases
MCI	Mild Cognitive Impairment
NFT	Neurofibrillary Tangle
NIA	National Institute of Aging
PHF	Paired Helicoidal Filaments
PKA	Protein Kinase A
PKC	Protein Kinase C
PP	Phosphatases Protein
P-Tau	Phosphorylated Tau
sAPPα	Soluble N-terminal Fragment
TGN	Trans-Golgi Network
T-Tau	Total Tau

14.1 Key Players in the Pathophysiology of Alzheimer's Disease (AD)

14.1.1 Amyloid Precursor Protein (APP)

APP is a transmembrane, type-1, integral glycoprotein of 110–130 kDa (Roberts et al. 1994), and represents one of the most abundant proteins in the central nervous system (CNS). It is ubiquitously expressed in human tissues and is located in the plasma membrane as well as in several organelles, such as endoplasmic reticulum (ER), Golgi apparatus, and mitochondria (Rhein and Eckert 2007). There are several amyloid-β species that vary according to the number and sequence of amino acids; those with 40 and 42 amino acids (Aβ_{40} and Aβ_{42}) are the most abundant in the brain (Recuero et al. 2004). Studies in cell biology have demonstrated that Aβ is generated in the Golgi, ER and endosomal/lysosomal system. Truncated Aβ peptides (Aβ_{x-42}, "x" generally ranging from 1 to 11) are preferentially generated within the ER, whereas full-length Aβ peptides (A$\beta_{1-40/42}$) are predominantly originated in the Golgi/trans-Golgi network (TGN) and packaged into post-TGN secretory vesicles (Kulandaivelu and Gopal 2006; Anandatheerthavarada et al. 2003). N-terminal truncation extends to a maximum length around amino acid 11, which renders Aβ even more insoluble, and therefore, represent non-secreted forms (Peskind et al. 2006).

APP is metabolized by two distinct and mutually exclusive pathways: the secretory pathway (or non-amyloidogenic) and the amyloidogenic pathway (Fig. 14.1). In the former, APP is first cleaved by α-secretase, releasing a soluble N-terminal fragment (sAPPα) and a C-terminal fragment (C83), which is further cleaved by the γ-secretase to originate a smaller C-terminal fragment of 3 kDa (C3). The-secretory cleavage of APP is mediated by a group of membrane-bound proteases, which are members of the ADAM (a disintegrin and metalloprotease) family, and α-secretase activity has been attributed to ADAM-10 and ADAM-17 (Buxbaum et al. 1998; Lammich et al. 1999).

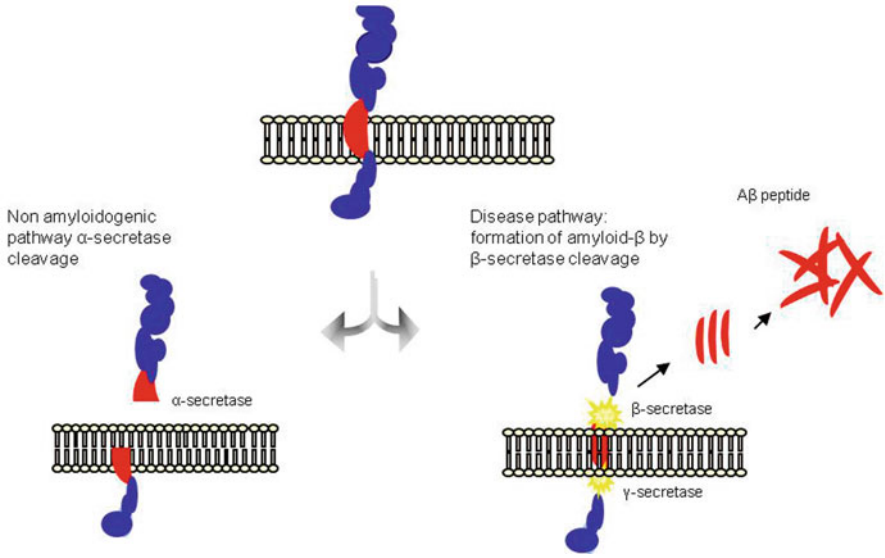

Fig. 14.1 The amyloid precursor protein (APP) is a transmembrane protein cleaved by secretase enzymes. In the secretory (non-amyloidogenic) pathway, APP is initially cleaved by α-secretase, which occurs in the moiety of the amyloid domain (*in red*) and therefore precludes the formation of Aβ. Alternatively, APP is sequentially cleaved by β- and γ-secretases to originate neurotoxic Aβ monomers (amyloidogenic pathway), which polymerize into oligomers and aggregate into amyloid fibrils

The cleavage of APP by α-secretase occurs within the sequence of amino acids that pertain to the Aβ peptide, and therefore precludes the formation of amyloid peptides (Braak and Braak 1998). In the amyloidogenic pathway, APP is alternatively cleaved by β-secretase, releasing a smaller N-terminal fragment (sAPPβ) and a longer C-terminal fragment (C99) that contains the full amyloidogenic sequence of amino acids. A further cleavage of APP by γ-secretase yields the amyloid-β peptides (Aβ).

The Aβ species are released as monomers that progressively aggregate into dimmers, trimers, oligomers, protofibrils and fibrils, to finally deposit and originate the amyloid plaques. Despite their similarities, Aβ_{42} is more prone to aggregation and fibrilization, being the most neurotoxic Aβ peptide. Therefore, Aβ_{42} plays a pivotal in the pathogenesis of AD (Recuero et al. 2004).

Aβ oligomers are considered the most toxic forms of the amyloid derivates (Roberts et al. 1994). They interact with neurons and glial cells leading to the activation of pro-inflammatory cascades, mitochondrial dysfunction and increased oxidative stress (Sanz-Blasco et al. 2008), impairment of intracellular signaling pathways and synaptic plasticity, increased Tau phosphorylation, increased GSK-3β activity, deregulation of calcium metabolism, induction of neuronal apoptosis and cell death (Roberts et al. 1994). These mechanisms altogether give rise to a self-perpetuating, positive feedback loop in which the production of Aβ peptides leads to deleterious events to the neuronal cells, which in turn leads to dysfunction of the

APP metabolism and more production of Aβ peptides. Aβ fibrils deposit in neuritic plaques in a sequential pattern: diffuse neuritic plaques, mature neuritic plaques, senile plaques and phantoms of senile plaques in more advanced stages of the disease. The plaque formation has also deleterious impact to the neurons also leading to their dysfunction and, ultimately, their death (Rhein and Eckert 2007).

Under physiological conditions, the APP is preferentially metabolized in the secretory pathway and there is equilibrium between Aβ peptide production and clearance from the brain (Roberts et al. 1994). Currently, two proteins are deemed as intimately involved in the clearance of Aβ peptides from the brain: apolipoprotein E (APOE) and the insulin-degrading enzyme (IDE). The exact mechanism or mechanisms by which Aβ peptides are cleared from the brain has not been totally elucidated, but a dominant hypothesis is that these proteins bind to the Aβ peptide, inhibiting its aggregation and promoting its clearance from the brain (Recuero et al. 2004). Disadvantageous genetic polymorphisms (such as the ε4 allele of APOE) and pathological conditions related to abnormal IDE homeostasis (e.g., diabetes mellitus) that may favor the amyloidogenic cleavage of APP and/or decrease the Aβ clearance from the brain will therefore facilitate the accumulation of Aβ in the neural tissues and downstream effects of the amyloid cascade (Schmitt 2006).

14.1.2 Tau Protein

Tau is a microtubule-associated protein found in most tissues and highly expressed in the peripheral nervous system. In neurons, it is an important component of the cytoskeleton (Kosik 1993). It interacts with α- and β-tubulin, and the phosphorylation state of Tau is critical to stabilize the polymers of tubulin (Fig. 14.2). In neurons, the microtubules are essential for the maintenance of neuronal structure, axonal transport, and neuronal plasticity (Lindwall and Cole 1984).

Tau is widely expressed in the central and peripheral nervous system, and therefore may be regarded as a neuronal phosphoprotein. In addition to the involvement of Tau in the maintenance of neuronal structure and in synaptic plasticity, microtubules are essential for axonal transport of organelles (mitochondria, ER, lysosomes) and vesicles containing proteins and neurotransmitters, which are displaced from the cell body (soma) to distal synapses. The neuronal polarity also depends on the properties of microtubules present in axons and dendrites. In axons, microtubules are uniformly oriented on account of the role of Tau protein (Kosik 1993; Shahani and Brandt 2002).

There is a phosphorylation gradient along the axon and in different brain regions, the distal axon being less phosphorylated, particularly in the white matter (Buée et al. 2000; Hernández and Avila 2007). Changes in the phosphorylation state of Tau occur in the process of remodeling of the cytoskeleton, in which the regulatory mechanisms of Tau phosphorylation become critical to promote synaptic plasticity. The abnormal phosphorylation of Tau negatively affects its ability to bind to tubulin, unsettling the structure of microtubules. In addition, hyperphosphorylated Tau impairs axonal

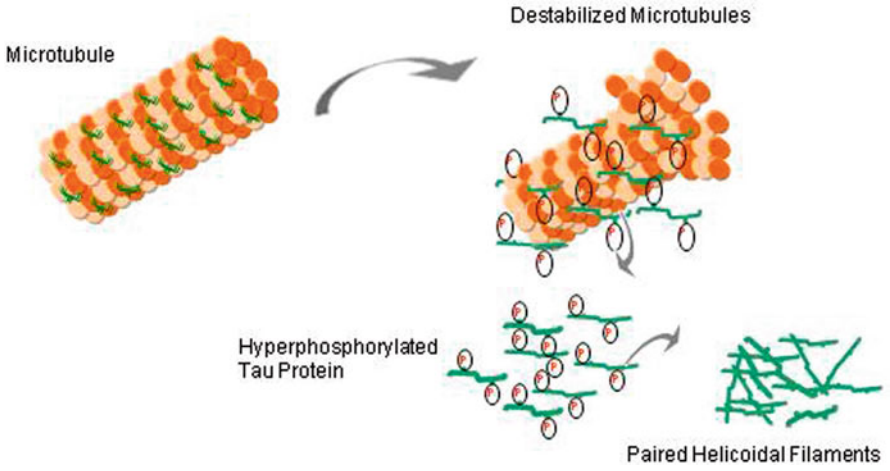

Fig. 14.2 In AD there is a reduction in ability the ability of Tau to bind to tubulin and promote microtubule assembly. Hyperphosphorylated Tau contributes to the destabilization of microtubules, impaired axonal transport, and ultimately the formation of neurofibrillary tangle (NFT) and neuronal death

transport and synaptic metabolism, causing dysfunctions that result in loss of cell viability and ultimately lead to the collapse of microtubular cytoskeleton and neuronal death. The phosphorylation and dephosphorylation of Tau at serine and threonine phosphoepitopes are critical regulatory events in neuronal homeostasis. At these sites, the substrates of phosphatases include ion channels and G protein receptors, where the synaptic traffic and are regulated by reversible phosphorylation of proteins (Wang et al. 2007).

Tau may be found in soluble and insoluble forms, the latter being identified in paired helicoidal filaments (PHF), which are the main component of neurofibrillary tangles (NFT). PHF-Tau complexes have six to eight phosphate groups per molecule of Tau protein, which is much higher than the usual degree of phosphorylation of Tau protein in the healthy brain (i.e., two phosphate groups per molecule).

Six Tau isoforms have been described in mammals. The main differences between these isoforms rely on the existence of three or four tubulin-binding domains, and some minor differences at the N-terminus of the protein (Cleveland and Hoffman 1991; Lovestone and Anderton 1992; Trojanowski et al. 1994; Shahani and Brandt 2002) The interaction between Tau and tubulin is a dynamic process in which Tau promotes its own polymerization and inhibits the fast depolymerization of tubulin (Johnson and Stoothoff 2004). Again, this process is regulated by the balance between phosphorylation and dephosphorylation of its phosphoepitopes. Tau protein has approximately 79 phosphorylation sites at serine and threonine residues (Shahani and Brandt 2002). Phosphorylation and dephosphorylation of these epitopes promote conformational changes that influence the ability of Tau to interact with α- and β-tubulin and stabilize microtubules (Drechsel et al. 1992; Hernández and Avila

2007). Among several protein kinases and proteases are involved in Tau phosphorylation, glycogen synthase kinase-3β (GSK3β) the most important Tau kinase in neurons (Iqbal et al. 2005).

The expression of phosphatases protein (PP) PP1, PP2A and PP5 was found to be reduced in cerebral tissues of patients with AD (Buée et al. 2000; Wang et al. 2007). The majority of serine and threonine phosphoepitopes in fetal and in PHF-Tau is followed by proline residues, suggesting that Tau kinases belong to the family of proline-directed kinases (Wang et al. 2007), namely cyclin-dependent kinases (CDK5), MAP kinases (MAPK) and GSK (Lovestone et al. 1997). Such enzymes are capable to phosphorylate Tau *in vitro* and have been detected in the AD brain. Other proline-directed kinases such as protein kinase C (PKC), casein-kinases l and lI (Drechsel et al. 1992), calcium calmodulin-kinase ll (CaMPK-ll) (Lovestone et al. 1997; Johnson and Stoothoff 2004), and protein kinase A (PKA) have also been identified in neurofibrillary tangles and are involved in the regulation of the activity of the former.

In the embryonic stages of development, neuronal Tau is predominantly in hyperphosphorylated state. This is due the great demand for neuroplastic changes in neurons and synapses at early developmental stages of the CNS (Lovestone et al. 1997). In the mature CNS, Tau phosphoepitopes are maintained in a predominantly dephosphorylated state, which confers the necessary stability of the cytoskeleton to maintain neuronal homeostasis (Johnson and Stoothoff 2004). Nevertheless, dynamic changes in Tau phosphorylation are important for neuronal responses, including neurite outgrowth and synaptic plasticity (Iqbal et al. 2005). Under pathological conditions such as AD, Tau can be abnormally hyperphosphorylated. This abnormality impairs its capacity to bind to tubulin, destabilizing the microtubular structure. In addition, it impairs axonal transport and synaptic metabolism, leading to cytoskeleton collapse, loss of cellular viability and neuronal death (Drechsel et al. 1992).

14.1.3 The Amyloid Cascade

The amyloid hypothesis of AD was described in the early 1990's (Hardy and Higgins 1992). According to it, the accumulation of Aβ peptides into senile and neuritic plaques in the brain, either due to an increased production or decreased clearance, is the core feature in the pathogenesis of AD. Therefore, Aβ triggers several deleterious events that disrupt neuronal homeostasis, e.g., mitochondrial dysfunction, activation of oxidative stress and inflammatory cascades (Selkoe 1991), impaired neurotrophic support and response to injury, decreased neuroplasticity and neurogenesis, hyperphosphorylation of Tau protein, apoptosis, and abnormalities in calcium metabolism. These events are subject to positive feedback, amplifying Aβ-related neurotoxicity, and culminating with neuronal death (Kulandaivelu and Gopal 2006). Recent evidence indicated that not only the Aβ peptides *per se* may act as a trigger to the amyloid cascade, but rather the oligomeric and fibrillary forms, which are currently regard the most toxic forms of Aβ (Vieira et al. 2007).

The amyloid cascade hypothesis was based mostly on findings from *in vitro* and *in vivo* studies, and was further strengthened by the discovery of genetic mutations associated with early-onset, familial AD. These are severe forms of the disease, in which massive intracerebral amyloidogenesis occur prematurely as a consequence of mutations affecting APP metabolism (i.e., mutations in the APP gene in chromosome 21, and in presenilin 1 and 2 genes in chromosomes 14 and 1 respectively). The genetic manipulation of these AD-related mutations was the most important asset for the development of genetically modified animal models of AD (Kulandaivelu and Gopal 2006).

There are several caveats regarding the amyloid hypothesis of AD. First, neuropathological studies did not find a significant correlation between amyloid plaque density in the brain and the severity of dementia. The senile plaques are extracellular deposits consisting of a central core of Aβ peptide surrounded by activated microglia and reactive astrocytes, which are associated with neuronal degeneration. AD is the only neurodegenerative disease in which the Aβ peptide is the considered the pathological cornerstone; in contrast, a significant number of non-demented elderly subjects have amyloid plaques in the brain in *post-mortem* examination; in some cases, plaque counts in non-demented individuals are comparable to those found in AD patients (Lippa and Morris 2006). Also, most of anti-amyloid based therapeutic strategies failed to show clinically relevant results either in improving cognitive performance or in halting the clinical progression of dementia (Lippa and Morris 2006; Cummings 2006). Finally, the cellular and animal models of AD are based mostly on the genetic mutation associated with the early-onset AD. Nevertheless, early-onset AD accounts for the minority of the cases of dementia, whereas late-onset AD is far more common and is not associated with the aforementioned mutations. As opposed to that, sporadic AD has a multifactorial etiology, involving multiple genetic polymorphisms with minor risk-effects and other pathological mechanisms, in addition to the amyloidogenesis *per se* (Holmes et al. 2008)

14.1.4 Tau-related Hypotheses

One of the neuropathological hallmarks of AD is the presence of intra-neuronal lesions called neurofibrillary tangles (Swerdlow 2007b). The main components of NFTs are the paired helicoidal filaments, which are constituted fundamentally of hyperphosphorylated Tau. At least 25 abnormal phosphorylation sites were described in PHF-Tau in AD (Braak and Tredici 2004), and the abnormal phosphorylation of Tau protein is a marker of neuronal degeneration in this disorder (Mazanetz and Fischer 2007). The phosphorylation of the serine/threonine residues near the binding region of Tau to tubulin favors Tau disaggregation and their reassembly into PHf (Iqbal et al. 2005). Due to the importance of Tau in maintaining the neuronal stability and homeostasis, its abnormal phosphorylation leads to a cascade of neuronal events that ultimately cause the neuronal dysfunction and death.

There are several lines of evidence that support the notion that the disruption of Tau homeostasis is a primary event in AD. Besides AD, Tau abnormalities are also found in other neurodegenerative disorders, such as frontotemporal dementia, cortico-basal degeneration, multiple system atrophy, and motor neuron disease (Iqbal et al. 2005). For these reason, these conditions are referred to as *tauopathies*. Neuropathological studies have demonstrated that the evolution of the distribution of NFT in the brain correlates with the clinical progression of cognitive deficits in AD. Moreover, intra-neuronal hyperphosphorylated Tau can be found in the brain of subjects with very mild dementia, unaccompanied by Aβ pathology (Braak and Tredici 2004). Therefore, the hyperphosphorylation of Tau may be the initial step in the physiopathology of AD; other pathological events, including abnormal APP metabolism leading to excessive Aβ production, may be secondary to the former disruption of neuronal homeostasis (Rhein and Eckert 2007). Nevertheless, the larger body of evidence relating the amyloid pathology in AD and the lack of no genetic mutations in Tau gene associated to early or late-onset AD weaken the hypothesis that Tau pathology is the earliest event in AD (Oide et al. 2006).

Despite the strong evidences supporting the primary role of either Aβ peptides or hyperphosphorylated Tau protein in the pathogenesis of AD, neither of these hypotheses fully accounts for the wide spectrum of pathological changes in AD. Therefore, some alternative and complementary hypotheses have been proposed to explain the physiopathology of AD. Most of these hypotheses involve the activity of proteins and enzymes that exert their biological functions upstream in the cascades involved in the regulation of the APP/Aβ and Tau metabolism.

GSK3β is a key enzyme in the regulation cell cycle; in neurons it plays a pivotal role in the regulation of Tau phosphorylation (i.e., overactive GSK3β leads to hyperphosphorylation of Tau). Recent studies have also demonstrated that the deregulation of GSK3β activity is involved in several other pathological events associated with AD, for instance, increased production of the Aβ peptide, induction of apoptosis, and impaired neurogenesis and synaptic plasticity (Lippa and Morris 2006). *In vitro* studies have shown that the pharmacological activation of GSK3β leads to neuronal changes and death in a similar fashion as observed in AD (Cummings 2006; Holmes et al. 2008). On the other hand, *in vitro* and *in vivo* studies have demonstrated that the pharmacological inhibition of GSK3β (e.g., with lithium salts) protected neurons against mechanisms of degeneration induced by Aβ and hyperphosphorylated Tau (Cummings 2006; Swerdlow 2007a).

Few studies have been carried out in humans to determine the activity of GSK3β in AD patients. One interesting study has shown that GSK3β activity is increased in leukocyte of patients with AD and mild cognitive impairment (MCI) (Hye A et al. 2005). According to the GSK3β hypothesis of AD (Braak and Tredici 2004), increased GSK3β activity is an early pathological event in the pathophysiology of AD, by triggering a cascade of events culminating both in increased production of Aβ and Tau hyperphosphorylation. Despite the elegant mechanisms elicited by the GSK3β hypothesis, which encompasses in a broader sense both amyloid- and Tau-related mechanisms, it lacks consistent empirical evidences.

14.2 Clinical-Pathological Aspects

The neuropathology of AD was first described by Alois Alzheimer in two patients showing diffuse cortical atrophy, neurofibrillary tangles (only in the initial patient) and senile plaques (in both cases) distributed throughout the cerebral cortex (Moller and Graeber 1998). Glenner and Wong, in 1984, identified the sequence of the proteinaceous central component of the senile plaques, by isolating the amyloid from meningeal vessels from AD patients. The senile (neuritic) plaques are diffusely distributed in the neocortex and limbic system in patients who have AD (Mesulam 2000). Other forms of Aβ accumulation include diffuse (non-neuritic) plaques and vascular deposition that may lead to cerebral hemorrhage.

The establishment of a correlation between the neuropathological findings in AD patients and in middle-aged subjects with Down's syndrome (who have trisomy of the chromosome 21) has led to the identification of the gene that encodes the β-amyloid protein precursor (APP) in the same chromosome (Kang et al. 1987).

In early-onset familial cases of AD, occurring as an autosomal dominant trait, three distinct mutations are described: the aforementioned APP gene on chromosome 21 (Murrell et al. 1991), the presenilin 1 gene on chromosome 14 (Sherrington et al. 1995), and the presenilin 2 gene on chromosome 1 (Levy-Lahad et al. 1995). The fact that the presenilins are related to the γ-secretase complex strongly favored the amyloid cascade hypothesis in AD pathogenesis (De Strooper 2003).

High levels of Aβ peptide can be found in the brain of individuals without cognitive decline as early as the age of 40 years, preceding the formation of neuritic plaques (Funato et al. 1998). This deposition seems to occur earlier in carriers of the ε4 allele of APOE (Morishima-Kawashima et al. 2000), whose homozygosity constitutes a well-known risk factor for the development of AD.

Although Alzheimer's disease is the only neurodegenerative disorder in which the Aβ peptide is considered by many to be a pathological cornerstone, the question remains open: is the deposition of Aβ protein a central event in the pathophysiology of AD or just a biomarker of an underlying process still to be fully understood?

The several issues regarding the Aβ cascade hypothesis, the most important of all is perhaps the fact that neuropathological studies did not find a strict correlation between neuritic plaque density and number in the brain and the severity of dementia, the latter appearing to correlate more significantly with the density of neurofibrillary tangles (Knopman et al. 2003; Sonnen et al. 2007). It has been thus hypothesized that this poor relationship between neuritic plaque density and severity of dementia might be better understood if preamyloid-like soluble aggregates of Aβ (Aβ oligomers) are the causative agents of neurotoxicity in AD (Lesne and Kotilinek 2005; Eckman and Eckman 2007)

This lack of clinico-pathological correlation has led to a consensus to distinguish the clinical term "Alzheimer disease" from "Alzheimer disease neuropathological alterations". Clinical AD refers to a set of clinical signs and cognitive/behavioral symptoms that are present in patients who have substantial AD neuropathological changes. AD neuropathology describes the presence and extent of pathological changes of AD observed at brain autopsy regardless of the clinical picture exhibited by the patient.

14.2.1 Neuropathological Diagnosis of AD

The proposed National Institute on Aging—Alzheimer's Association guidelines for the neuropathological assessment of AD (NIA—Alzheimer's Association 2011, draft) recommends that the diagnosis should be based on an "ABC" score where A and C stand for amyloid pathology (while "B" stands for neurofibrillary tangles according to Braak and Braak criteria), as follows:

- A. Presence of amyloid plaques (modified from Thal et al. 2002):
  - A0: No Aβ or amyloid plaques
  - A1: Neocortical Aβ or amyloid plaques in sections of frontal, temporal, or parietal lobes
  - A2: A1 plus hippocampal Aβ or amyloid plaques
  - A3: A2 plus neostriatal Aβ or amyloid plaques
- C. Presence of neuritic plaques (modified from the CERAD protocol, which employs a semi-quantitative evaluation of neuritic plaques) (Mirra et al. 1991):
  - C0: No neuritic plaques
  - C1: CERAD score sparse
  - C2: CERAD score moderate
  - C3: CERAD score frequent

Clinico-pathological correlations guidelines were also proposed: for patients without cognitive impairment, it should be considered that AD neuropathological changes may represent a preclinical stage of the disease that may last for years (Sperling et al. 2011, 2003); for individuals with cognitive impairment, the presence of widespread neurofibrillary tangles with varying degrees of Aβ accumulation and neuritic plaques should be interpreted as an adequate cause of cognitive impairment or dementia. However, a low density of neurofibrillary tangles, even when associated with frequent neuritic plaques most likely indicate other diseases leading to cognitive impairment.

As already stated, the elderly without dementia or those clinically diagnosed as MCI can harbor AD pathology that may be quite indistinguishable from that of persons with dementia (Rentz et al. 2010). Moreover, neuritic plaques (as well as neurofibrillary tangles) may also be present in "normal aging". Despite this, the correspondence between clinical and pathological diagnosis in AD ranges from 70 to 90 % (Swerdlow 2007a).

There is much less data on about the underlying neuropathology of MCI; some studies have suggested that about one half of persons clinically diagnosed as MCI have sufficient neuropathology to warrant the pathologic diagnosis of AD (Markesbery et al. 2006; Schneider et al. 2009a), and, as a group, they tend to display an intermediate pattern of AD pathology (between subjects no cognitive impairment and those with dementia), which suggests a gradual accumulation of neuropathological changes in the progression from cognitively normal to dementia (Bennett et al. 2005).

One study has showed that up to one third of the subjects considered to cognitively normal when tested a few months prior to death had neuropathological alterations

that were sufficient to render them to be diagnosed as AD patients (although in general these neuropathological alterations tend to be less severe than those found in subjects clinically diagnosed as MCI or AD). Moreover, a lower performance in specific cognitive domains, such as episodic memory, was found in normal subjects presenting neuropathological changes when compared to those who had not such alterations (Bennett et al. 2006).

The fact that it takes many years for AD to develop may explain the presence of varying degrees of pathological alterations before subjects start to present clinical symptoms, especially if we take into account a number of factors that may interfere with the course of the disease. This becomes particularly evident when we observe the overlap of neuropathological alterations in patients who are still regarded as MCI and those with dementia and such observations have given rise to the concept of "cognitive functional reserve". The cognitive reserve may be due to several factors such as high educational level (Roe et al. 2007), the maintenance of intellectual activities across the life span (Wilson et al. 2002), nutrition habits (Petot and Friedland 2004), lifestyle and the coexistence of other medical conditions as systemic arterial hypertension, diabetes, obesity, etc., (Scarmeas and Stern 2003), and genetics (Tupler et al. 2007).

Another source of uncertainty in assessing the exact role of Aβ deposition in the pathogenesis of AD is the fact that over 50 % of dementia cases are of mixed etiology (Schneider et al. 2009a, b), with concomitant neuropathological findings of either vascular or Lewy body's disease. The coexistence of more than one pathology decreases brain reserve and increases the likelihood of developing dementia. Also, the distribution of mixed dementias differs depending on the population studied: in memory clinics, there is a higher frequency of pathologically proven Lewy body's disease and frontotemporal dementia (regardless of the clinical diagnosis), while in community-based studies, pathologically proven AD and AD with vascular disease prevail (Schneider et al. 2009a).

It is worthy of note that most anti-amyloid based therapeutic strategies have failed to show clinically relevant results either in improving cognition or in halting the clinical progression of dementia (Cummings 2006) and, finally, cellular and animal models of AD are based largely on genetic mutations associated with familial, early-onset AD, which accounts for a small proportion of dementia cases. Since late-onset AD represents the vast majority of cases, that it is not determined by a single gene mutation (but rather has a multifactorial nature), and considering that amyloidogenesis in these patients occurs to a lesser extent compared to the early AD, questions have been raised concerning the appropriateness of early-onset AD models to aid understanding of late-onset AD (Swerdlow 2007a).

14.2.2 Clinical Diagnosis of AD

The advances in the understanding of the chain of pathological events that lead to AD and the acknowledgment of its long pre-clinical stages required a significant revision of AD diagnostic criteria. The NINCDS-ADRDA diagnostic criteria for AD

Table 14.1 Revised diagnostic criteria for AD

Clinical stage	Criteria	Biomarkers	Observations
Dermentia of AD type	Probable AD: insidious onset of progressive learning impairment and memory deficit + impairment in other cognitive domains. The initial presentation can also be as non-amnestic impairments (language, visuospacial and executive dysfunction) Possible AD: typical clinical presentation but the patients presents concomitant evidence of significant cerebrovascular disease or feature of other dementing disorders (e.g. Lewy Body Dementia)	*Amyloid-related biomarkers* CSF: ↓ Aβ_{42} Amyloid imaging: high retention of amyloid ligands (e.g. PiB) *Neurodegeneration-related biomarkers* CSF: ↑ T-Tau, ↑ P-Tau MRI: hippocampal atrophy PET: temporoparietal hypoperfusion	The criteria acknowledge the possibility of atypical presentations of AD The clinical diagnosis is strengthened by the presence of one or more positive biomarkers for cerebral amyloidosis
Prodromal AD	Concern regarding cognitive changes over time Lower than expected performance on one or more cognitive domains adjusted for age and educational status Independence in activities of daily living Not demented	*Amyloid-related biomarkers* CSF: ↓ Aβ_{42} Amyloid imaging: high retention of amyloid ligands (e.g. PiB) *Neurodegeneration-related biomarkers* CSF: ↑ T-Tau, ↑ P-Tau MRI: hippocampal atrophy PET: temporoparietal hypoperfusion	The degree of certainty of prodromal AD increases by the presence of positive amyloid-related biomarkers The presence of neurodegeneration-related biomarkers also increases the probability of prodromal AD, but are more specific to the risk of imminent progression to the dementia of AD type The absence of positive amyloid-related biomarkers indicates of low risk of AD
Pre-clinical AD	Normal cognitive performance or very mild cognitive difficulties (still compatible with normal cognition)	*Amyloid-related biomarkers* CSF: ↓ Aβ_{42} Amyloid imaging: high retention of amyloid ligands (e.g. PiB) No changes in *Neurodegeneration-related biomarkers*	Very few controlled studies have been conducted with these diagnostic criteria. Thus, these criteria should be used for research purpose only

(McKhann et al. 1984) were based mostly in the clinical presentation of dementia and were largely exclusionary, i.e., AD was diagnosed after the exclusion of other possible causes of dementia. Recently, a workgroup launched by the National Institute of Aging (NIA) and the Alzheimer's Association proposed an extensive revision of its diagnostic criteria, including the recognition of its pre-clinical and prodromal stages (Mckhann et al. 2011; Sperling et al. 2011, 2003; Albert et al. 2011). Table 14.1 shows the current diagnostic criteria for clinical AD and its pre-clinical and prodromal stages.

14.3 Alzheimer's Disease Biomarkers

A biomarker is a characteristic that can be measured and evaluated as an indicator of normal or pathological process, or to monitor the effect of therapeutical interventions on specific biological cascades (Wagner 2009). The ideal diagnostic marker for AD should meet at least three basic requirements: (i) reflect core neurobiological changes subsequent to the disease process; (ii) be validated by post-mortem studies, assuming that the neuropathological findings as gold standards; and (iii) be measurable as early as possible in the disease continuum—ideally at pre-symptomatic stages (NIA 2011). Additional requirements include being non-invasive and simple to perform, precise and reliable, and adequate for large-scale screenings. Among many candidate markers of amyloidogenesis, those with the most promising results and potential to clinical application are the amyloid-β_{1-42} ($A\beta_{42}$) peptide in the cerebrospinal fluid (CSF) and the *in vivo*, molecular imaging of $A\beta_{42}$ deposits in the brain with positron emission tomography (PET) (Blennow et al. 2010).

14.3.1 Cerebrospinal Fluid (CSF) Biomarkers

The CSF may be considered the ideal source for biomarkers in AD. It is in intimate contact with the cerebral tissue, and pathological changes in the brain are often reflected in the CSF (Reiber 2001). Among several potential diagnostic biomarkers, the most consistent findings have been obtained with the measurement of CSF concentrations of $A\beta_{42}$, along with total Tau (T-Tau) and phosphorylated Tau (P-Tau) (Blennow 2004). AD patients characteristically display low concentrations of $A\beta_{42}$ (Sunderland et al. 2003). The reduction in the CSF $A\beta_{42}$ is thought to be secondary to a "sinking" effect of this peptide into plaques during the progression of brain amyloidogenesis (Bates et al. 2009). Also, these patients show high concentrations of T-Tau and P-Tau. This pattern of CSF biomarkers is commonly referred to as the "AD signature" in the CSF (Diniz et al. 2008). This biomarker signature reflects core pathophysiological features of the disease (Wiltfang et al. 2005), and has been validated in *post-mortem* studies (Buerger et al. 2006; Clark et al. 2003; Tapiola et al. 2009).

Several studies have been published to support the notion that this AD-positive CSF pattern has good diagnostic accuracy to distinguish between normal ageing and AD (>85 %) and a positive predictive value (>90 %) to determine the dementia outcome in patients with MCI (Blennow and Hampel 2003; Hansson et al. 2006). However, in the differential diagnosis of established dementia syndromes, the sensitivity and specificity profile to differentiate AD from other dementias is significantly lower (Andreasen et al. 2001). Large-scale longitudinal studies of MCI cohorts consistently demonstrated that the presence of the "AD signature" in the CSF has a good diagnostic accuracy (i.e. >80 %) to discriminate patients with MCI who progress to AD ("MCI-converters") from those who remain cognitively stable ("MCI-stable" patients) and healthy controls (Hansson et al. 2006), and also from those MCI patients who progress to non-AD dementias (Riemenschneider et al. 2002; Mattsson et al. 2009). Interestingly, MCI patients with progressive deficits (albeit did not reach the threshold of dementia diagnosis) have a similar CSF biomarker signature as the MCI-converters patients. On the other hand, MCI patients who display non-progressive deficits over time have a CSF biomarker pattern very similar to that found in healthy older adults. These sets of data have been extensively replicated by different research groups worldwide and by meta-analytical studies (Arai et al. 2000; Hampel et al. 2004; Shaw et al. 2009; Forlenza et al. 2010a).

Taken together, there is a large bulk of evidence that the "AD signature" in the CSF is a strong predictor of the dementia outcome. In other words, MCI patients who will convert to AD have a CSF biomarker pattern indistinguishable of that found in patients with dementia of the AD-type. Otherwise, MCI subjects with a non-AD CSF signature have a low probability to develop AD, even upon long-term follow-up.

Yet, methodological limitations need to be overcome before the assessment of CSF biomarkers can be used in the routine clinical assessment of patients with cognitive complaints. Although the determinations of CSF concentrations of these biomarkers using ELISA or multiplex techniques (e.g., xMAP-Luminex) have low coefficients of intra-laboratory variability (5–10 %), the high inter-laboratorial variation (20–30 %) is a major obstacle for the comparison of data generated in different settings (Mattsson et al. 2010). Multiple sources of bias include pre-assay (i.e., lumbar puncture protocol, sample handling and aliquot storing prior to experimentation), intra-assay (different methods and protocols for the determination of the concentrations of biomarkers), and post-assay variations (e.g., definition of norms for patients and controls to guide the interpretation of results) (Mattsson et al. 2010, 2011). This situation is a major limitation for the establishment of multicentric cooperation and the establishment of gold-standard protocols and reference values to be shared by distinct laboratories.

14.3.2 Amyloid-β_{42} Molecular Imaging

The possibility to visualise *in vivo* the amyloid pathology in the brain has been a major advance in AD-related biomarker research. Many compounds have been developed

and launched so far, including the "Pittsburgh Coumpound B" (PiB) (Mathis et al. 2003; Klunk et al. 2004), the F-BAY94-9172 (Rowe et al. 2008), the FDDNP, a dual, amyloid and Tau-binding compound (Small et al. 2006), the Florbetapir (Choi et al. 2009), among others.

In AD, there is an increased global cortical and regional retention of PiB and other compounds, particularly in the cingulate, temporal, parietal and frontal cortices (Edison et al. 2007). Studies with amyloid imaging in mild AD have a very high sensitivity (over 90 %), but the specificity is age-dependent, due to the increasing deposition of Aβ overtime in healthy elders. Important studies have shown correlations between intracerebral amyloid content (as shown by PiB scans) and CSF concentrations of $A\beta_{42}$ in patients with mild AD as compared to controls (Fagan et al. 2006; Fagan et al. 2009).

Patients with amnestic MCI also show increased PiB retention as compared to healthy older subjects, but to a lesser extent to those observed in AD patients. Positive PiB scans predict conversion, and PiB retention (global and regional) correlates with cognitive performance (Kemppainen et al. 2007; Forsberg et al. 2008). In a prospective study, PiB-positive MCI patients had a higher conversion rate than PiB-negative patients; in addition, the amyloid load was negatively associated with time to conversion (Okello et al. 2009). PiB retention was also observed in elderly subjects without cognitive complaints or dementia; it is noteworthy that a higher retention at baseline was associated with a worse cognitive performance and predicted a faster decline (Villemagne et al. 2008; Aizenstein et al. 2008; Resnick et al. 2010; Reiman et al. 2009). These findings are largely compatible with the CSF biomarkers as predictors of cognitive deterioration in non-demented older adults (Fagan et al. 2007).

14.3.3 Pre-dementia and Pre-clinical AD: The Role of Amyloid-Related Biomarkers

Recent evidences derived from biomarkers research strengthen the primary role of amyloid pathology in AD. Data from CSF and molecular imaging studies reinforces the notion that the accumulation of $A\beta$ in the AD brain precedes the onset of functional and structural changes characteristic of AD (Fellgiebel et al. 2004; Bouwman et al. 2007; Josephs et al. 2008; Hansson et al. 2009; Jack et al. 2009a). These observations lead to the development of a hypothetical cascade of biological events that begins by the production and accumulation of $A\beta_{42}$ (i.e. reduced CSF $A\beta_{42}$ and increased PiB retention) in the brain that triggers secondary pathological events culminating in synaptic dysfunction and regional hypometabolism (FDG-PET studies), neurodegeneration (i.e. increased CSF Tau and phospho-Tau proteins) and structural changes (hippocampal and other regional atrophy). Finally subjects start experiencing cognitive deficits and functional difficulties, reaching the threshold for dementia diagnosis. (Jack et al. 2009b; Forlenza et al. 2010b).

14.4 Amyloid-Based Disease-Modifying Therapies

Given the relevance of cerebral amyloidogenesis in AD, several drugs and therapeutical strategies have been developed to either reduce the production of amyloid-β or to accelerate its clearance in the brain. The goals are to delay the clinical progression in patients with AD, but most importantly, to prevent new dementia cases in older subjects. The most common mechanisms of action of these drugs are the inhibition of gamma and beta-secretase activity and immunetherapeutical approaches (Citron 2010). Despite the sound preclinical rationale, no therapeutical agent so far has consistently shown a significant/benefit for patients with AD.

The gamma- and beta-secretase inhibitors were the first agents to show promising disease-modifying effect for AD (Panza et al. 2009). These drugs were able to reduce cerebral amyloid burden and improving memory deficits in transgenic mice models of AD (Chang et al. 2004; Lahiri et al. 2007; Imbimbo et al. 2007). Phase I and II clinical trials showed a mild but significant improvement in cognitive deficits in subjects with mild to moderate AD (Fleisher et al. 2008; Siemers et al. 2006). These results encouraged phase III clinical trials with these agents. However, the results were largely negative, with no improvement in cognition or functional status and increased risk of serious adverse events in patients with mild to moderate AD (Green et al. 2009; Carlson et al. 2011).

Immunotherapeutical strategies have been extensively studied for AD since early 2000. Two main approaches have been developed so far: active and passive immunotherapy (Brody and Holtzman 2008). The active immunotherapy (i.e. anti-amyloid vaccine) aims to sensitize the immune system to improve the amyloid clearance by activating microglial cells (Morgan et al. 2000). This would not only reduce the amount of soluble amyloid species but also the amyloid plaques in the brain. Preclinical studies showed a significant improvement of memory deficits along a drastic reduction of amyloid burden in transgenic mice without a significant local neuroinflammatory reaction. However, a phase II clinical trial needed to be prematurely interrupted due to clinically significant neuroinflammatory reaction that led to brain oedema and death in patients who received the amyloid vaccine (Orgogozo et al. 2003; Gilman et al. 2005). Follow-up of patients recruited to this trial showed that vaccine was not associated to significant clinical improvement in patients receiving the vaccine; nonetheless, the neuropathological examination of brains of patients who received the vaccine demonstrated a significant reduction in amyloid plaques in all brain regions but also increased reactive microglia and perivascular oedema (Nicoll et al. 2003).

More recently, passive immunotherapy approaches with anti-amyloid antibodies have been developed. This strategy also aims to improve the clearance of brain amyloid without activating the microglial system and thus reducing the risk of neuroinflammation (Lichtlen and Mohajeri 2008; Geylis and Steinitz 2006; Roher et al. 2011; Serrano-Pozo et al. 2010). Phase II clinical trials had promising results, with patients showing a significant improvement in cognition, without the emergence of serious adverse events (Salloway et al. 2009; Rinne et al. 2010). Currently, phase III clinical trials are underway to establish the clinical efficacy and safety of these agents in mild AD.

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