Synapses and Alzheimer's Disease

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Alzheimer's disease (AD) is a major cause of dementia in the elderly. Pathologically, AD is characterized by the accumulation of insoluble aggregates of Aβ-peptides that are proteolytic cleavage products of the amyloid-β precursor protein ("plaques") and by insoluble filaments composed of hyperphosphorylated tau protein ("tangles"). Familial forms of AD often display increased production of Aβ peptides and/or altered activity of presenilins, the catalytic subunits of γ-secretase that produce Aβ peptides. Although the pathogenesis of AD remains unclear, recent studies have highlighted two major themes that are likely important. First, oligomeric Aβ species have strong detrimental effects on synapse function and structure, particularly on the postsynaptic side. Second, decreased presenilin function impairs synaptic transmission and promotes neurodegeneration. The mechanisms underlying these processes are beginning to be elucidated, and, although their relevance to AD remains debated, understanding these processes will likely allow new therapeutic avenues to AD.

Alzheimer's disease (AD) is a common neurodegenerative disease of the elderly, first described by the physician-pathologist Alois Alzheimer in 1907 (Maurer and Maurer 2003). Clinically, AD is characterized by progressive impairment of memory (particularly short-term memory in early stages) and other cognitive disabilities, personality changes, and ultimately, complete dependence on others. The most prevalent cause of dementia worldwide, AD afflicts >5 million people in the United States and >25 million globally (Alzheimer's Association, http://www.alz.org). Age is the most important risk factor, with the prevalence of AD rising exponentially after 65 (Blennow et al. 2006). However, many cases of so-called AD above 80 yr of age may result from a combination of pathological dementia processes (Fotuhi et al. 2009). The apolipoprotein E (ApoE) gene is the most important genetic susceptibility factor for AD, with the relatively common ApoE4 allele (prevalence ~16%) increasing the risk for AD threefold to fourfold in heterozygous dose (Kim et al. 2009).

The histopathological hallmarks of AD are amyloid plaques (extracellular deposits consisting largely of aggregated amyloid beta [Aβ] peptide that are typically surrounded by neurons with

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dystrophic neurites) and neurofibrillary tangles (NFTs, intracellular filamentous aggregates of hyperphosphorylated tau, a microtubule-binding protein) (Blennow et al. 2006). The development of amyloid plaques typically precedes clinically significant symptoms by at least 10–15 yr. Amyloid plaques are found in a minority of nondemented elderly patients, who may represent a "presymptomatic" AD population. As AD progresses, cognitive function worsens, synapse loss and neuronal cell death become prominent, and there is substantial reduction in brain volume, especially in the entorhinal cortex and hippocampus. The best correlation between dementia and histopathological changes is observed with neurofibrillary tangles, whereas the relationship between the density of amyloid plaques and loss of cognition is weaker (Braak and Braak 1990; Nagy et al. 1995). In addition to amyloid plaques and neurofibrillary tangles, many AD cases exhibit widespread Lewy body pathology. (Lewy bodies are intracellular inclusion bodies that contain aggregates of α-synuclein and other proteins.) Particularly in very old patients, considerable overlap between AD, frontotemporal dementia, Lewy body dementia, and vascular disease is observed, and pure AD may be rare (Fotuhi et al. 2009).

THE ROLE OF Aβ IN AD PATHOGENESIS

Strong, though not yet conclusive, evidence indicates that AD is caused by the toxicity of Aβ peptide, either in the form of a microaggregate or an amyloid deposit. Multiple forms of Aβ are derived by proteolytic cleavage from the type I cell-surface protein APP (amyloid precursor protein), with Aβ40 and Aβ42 being the dominant species (Kang et al. 1987). The term "amyloid hypothesis" broadly posits that excessive amounts of Aβ peptide in the brain—particularly Aβ42—are responsible for AD-related pathology, including amyloid plaques, neurofibrillary tangles, synapse loss, and eventual neuronal cell death (Hardy and Selkoe 2002; Tanzi and Bertram 2005; Blennow et al. 2006). The precise meaning of the amyloid hypothesis changed over the years, and differs among scientists. Originally, it was thought that the actual

amyloid is pathogenic—hence the term "amyloid hypothesis." The more current version of this hypothesis posits that Aβ (especially Aβ42) microaggregates—also termed "soluble Aβ oligomers" or "Aβ-derived diffusible ligands" (ADDLs)—constitute the neurotoxic species that causes AD (Haass and Selkoe 2007; Krafft and Klein 2010).

In addition to the fact that β-amyloid in the brain is a pervasive (and now, defining) feature of AD, two major findings support the amyloid hypothesis in its broader sense: the overproduction of Aβ42 in nearly all familial forms of AD, and the neurotoxic effects of Aβ.

Aβ peptides are derived by proteolytic cleavage from the transmembrane protein APP by the action of integral membrane proteases termed secretases (see Fig. 1). APP is cleaved sequentially: first by α-secretase or β-secretase, then by γ-secretase. In most cell types, the initial cleavage of APP is mediated by α-secretase rather than β-secretase, followed in both cases by cleavage by γ-secretase (Haass and Selkoe 2007). α-Secretase and β-secretase cleave at single sites in the extracellular domain of APP, whereas γ-secretase performs a sequential series of intramembranous cuts on the product of the α-cleavage or β-cleavage, giving rise to Aβ peptides and intracellular fragments (termed "AICDs" for "APP intracellular domains") of varying length (Fig. 1). Aβ42 is more prone to aggregation and believed to be more neurotoxic than Aβ40 and other Aβ variants. In mammals, APP is a member of a gene family that includes APLP1 and APLP2 (APP-like protein1 and 2), which are also cleaved by α-, β-, and γ-secretases. Together, the actions of these proteases acting on APP and APLPs produce a large number of protein fragments and peptides, of which only Aβ42 and Aβ40 peptides from APP appear to aggregate in vivo, and to have pathogenic effects. Although APP is highly conserved evolutionarily, the sequence of Aβ is not, and Aβ derived from non-primates does not appear to aggregate or to cause neurotoxicity.

Nearly 100 mutations in presenilin-1 and presenilin-2 (PS1 and PS2, the catalytic subunits of γ-secretase) cause familial AD. Familial early-onset AD also results from multiple point mutations in APP that are clustered in and
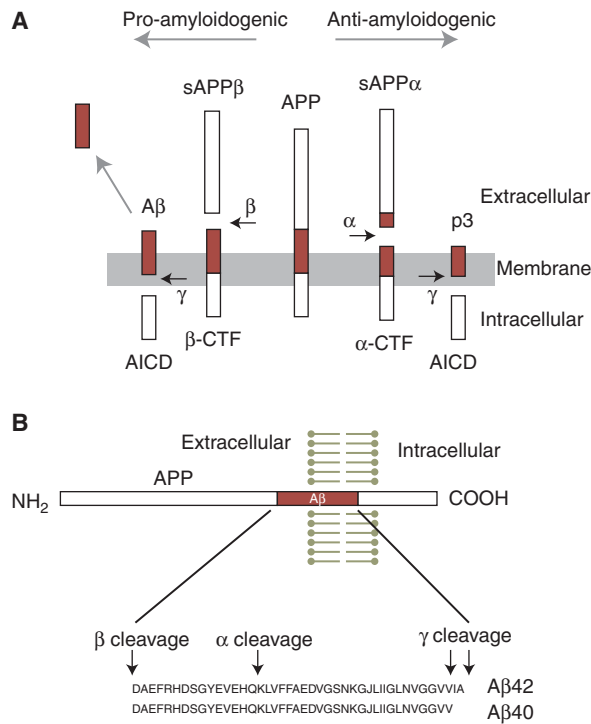
Figure 1. APP processing and the formation of Aβ peptide. (*A, middle*) The full-length human amyloid precursor protein (APP), a single transmembrane protein with an intracellular carboxyl terminus. (Horizontal arrows) Specific protease cleavage sites. In the amyloidogenic pathway (to the *left*), sequential cleavage of APP by β-secretase and γ-secretase releases the soluble extracellular domain of APP (sAPPβ), Aβ peptide, and the intracellular carboxy-terminal domain of APP (AICD). Cleavage by α-secretase prevents formation of Aβ, instead producing sAPPα and p3 peptide. (CTF) Carboxy-terminal fragment of APP, before cleavage by γ-secretase. (*B*) Diagram of the APP polypeptide and sequence of Aβ40 and Aβ42 peptides, with secretase cleavage sites indicated.

around the Aβ sequence. Strikingly, most of these AD-related mutations seem to increase either overall Aβ production or the Aβ42/Aβ40 ratio (Tanzi and Bertram 2005; Blennow et al. 2006; Bettens et al. 2010). Moreover, mutations at the β-secretase cleavage site of APP (such as the Swedish mutation of APP) increase Aβ production by improving APP as a substrate for β-secretase (encoded by BACE1). Several mutations surrounding the γ-secretase cleavage site of APP are believed to favor the production of the more amyloidogenic Aβ42 over Aβ40. Finally, mutations in the middle of the Aβ peptide enhance or alter Aβ aggregation properties. For example, four different point mutations in a single residue (E693) were observed that have distinct effects on the biophysical properties of

Aβ42 and on the clinical phenotype (e.g., see Tomiyama et al. 2008), strongly supporting the pathogenic significance of the Aβ peptides.

Duplications of the APP gene can also lead to familial early-onset AD, presumably by increasing Aβ production (Rovelet-Lecrux et al. 2006). APP lies on chromosome 21 in a region that is duplicated in Down's syndrome, and the presence of an extra copy of APP may contribute to the early-onset Alzheimer's-like pathology that characterizes Down's syndrome. Viewed together, the fact that most mutations causing familial AD either increase Aβ production or shift the Aβ42/40 ratio toward Aβ42 provides strong evidence for a causal role of Aβ peptides in familial AD pathogenesis, although their role in sporadic AD remains less certain. However, there

are some puzzling exceptions to the correlation of pathogenic mutations in presenilins with excess Aβ42 production, and at least some pathogenic mutations of presenilin cause nearly complete inactivation of γ-secretase activity toward APP (Heilig et al. 2010; Pimplikar et al. 2010).

The most recent version of the amyloid hypothesis (or Aβ hypothesis) suggests that AD arises from synaptic toxicity mediated by soluble microaggregates (also termed oligomers) of Aβ, leading to synaptic dysfunction and synapse loss ("synapse failure") (Lambert et al. 1998; Selkoe 2002; Kamenetz et al. 2003; Cleary et al. 2005; Lesne et al. 2006; Haass and Selkoe 2007; Shankar et al. 2007; Krafft and Klein 2010). Aβ has been shown to be neurotoxic in mouse brain in mainly two different experimental paradigms: in transgenic mice that express human mutant APP and overproduce human Aβ40/42, and in slices from wild-type mice that are acutely exposed to various preparations of Aβ microaggregates. Many studies using these approaches are available; for example, as of spring 2011, the transgenic mouse line Tg2576 overexpressing mutant human APP alone was used in more than 600 papers. Despite the fact that both experimental paradigms increase Aβ concentrations, the pathological effects are substantially different between these paradigms, and it remains unclear how they are related to each other and to human AD. In the following, we briefly review the results obtained with these two experimental paradigms and then discuss the implications of these results for understanding AD. Note that because thousands of papers have been published using these paradigms, only selected studies are reviewed here.

TRANSGENIC APPROACHES TO PROBING Aβ NEUROTOXICITY

Mouse models of AD using transgenic expression of mutant human APP (sometimes together with mutant presenilins) have been intensely studied. These models produce high concentrations of Aβ in the brain and develop amyloid plaques with aging (Games et al. 1995; Hsiao et al. 1996) but exhibit either minimal or modest (5%–25%) degrees of neuronal loss, even at

stages when amyloid plaque deposition is plentiful (Bondolfi et al. 2002). Loss of dendritic spines and synapses (or reduced expression of synaptic markers such as synaptophysin) are reported in the brains of transgenic APP or APP/PS mutant mice, but the loss is relatively small and not necessarily correlated with plaque deposition (Hsia et al. 1999; Mucke et al. 2000; Lanz et al. 2003; Boncristiano et al. 2005; Spires et al. 2005; Jacobsen et al. 2006). Although this seemingly argues against Aβ/amyloid being a major causative agent of neuronal death and synapse loss, it should be born in mind that even in human AD, extensive amyloid burden can exist for a decade or more before significant neurodegeneration and clinical cognitive dysfunction occur. (One argument would be that the slow course of disease exceeds the observation period available in AD transgenic mice, which incidentally also have a shortened life span relative to wild type.)

Whereas overall neuron loss is much less prominent in APP and APP/PS models of AD than in human postmortem specimens, careful studies of mouse models have detected significant reduction of neuron numbers in some specific regions of the brain, as well as decreased spine density in specific subdomains of neurons (e.g., see Perez-Cruz et al. 2011; Rupp et al. 2011 and references therein). Moreover, dysmorphic neuronal features, including spine/synapse loss, are particularly concentrated in the neighborhood of amyloid plaques (Spires et al. 2005; Meyer-Luehmann et al. 2008). In mutant APP/PS1 double transgenic mice, in vivo imaging revealed that plaques can form rapidly over ~24 h, followed by recruitment of activated microglia 1–2 d later and development of dysmorphic neurites in the vicinity of the plaque over the subsequent days to weeks (Meyer-Luehmann et al. 2008). Despite the absence of overt neurodegeneration, transgenic mice expressing mutant APP generally display robust deficits in behavioral tasks, particularly of learning and memory (Fig. 2) (e.g., see Hsiao et al. 1996; Saura et al. 2005), suggesting that they are useful models of AD, and in particular, the amyloidosis aspect of AD (Ashe and Zahs 2010; Crews and Masliah 2010).

Synaptic function and plasticity have been extensively studied in APP and APP/PS transgenic mouse models of AD, with focus on CA1 and dentate gyrus subfields of the hippocampus. A comprehensive review of this topic is beyond the scope of this chapter (see also Lüscher and Malenka 2012). A variety of AD transgenic mice show abnormal synaptic transmission and impaired LTP, often well in advance of plaque formation (e.g., Chapman et al. 1999; Hsia et al. 1999; Roberson et al. 2011). However, the electrophysiological findings have been sometimes inconsistent and variable between different mouse models, regions of the hippocampus, and experimental conditions (Chong et al. 2011; Marchetti and Marie 2011).

Many pharmacological treatments, such as inhibition of calcineurin, have been reported to reverse the memory deficits or neuropathology of APP transgenic mice (Dineley et al. 2007; Taglialatela et al. 2009; Wu et al. 2010; Rozkalne et al. 2011). Moreover, a large number of genetic manipulations that ameliorate or aggravate the

pathology observed in APP transgenic mice have been described, although some of the observed effects are likely indirect. Some of the results at first appear to be difficult to understand; for example, expression of EphB2 in the dentate gyrus of APP transgenic mice reversed the memory deficit in these mice (Cisse et al. 2011), even though this brain region is not generally thought to be required for the memory task used. Nevertheless, the genetic approach overall has led to important insights, especially when focused on genes known to interact with APP or otherwise implicated in human AD. Specifically, studies on the effect of the ApoE2, E3, and E4 variants of apolipoprotein ApoE have yielded major observations on the role of ApoE in Aβ clearance and plaque development (Kim et al. 2009; Castellano et al. 2011). Similarly, deletion of Mint/X11 proteins that bind to the cytoplasmic tail of APP significantly ameliorates the plaque load in transgenic mice expressing mutant APP (Ho et al. 2008). Furthermore, a recent study showed that the activity of caspase-3—the main executioner caspase in apoptosis—is elevated in the dendritic spines of hippocampal neurons of 3-month-old APP transgenic mice (line Tg2576) before the appearance of amyloid plaques and in the absence of cell death (D'Amelio et al. 2011). The elevation of caspase-3 activity correlated temporally with memory impairment, reduced spine density and size, altered excitatory synaptic transmission, and enhanced LTD. Remarkably, pharmacological inhibition of caspase-3 ameliorated the synaptic transmission, spine size, and memory deficits in these AD transgenic mice (D'Amelio et al. 2011). Increased caspase-3 activity is also reported in the human AD brain, and elevated levels of caspase-3 were observed in the postsynaptic density fraction of AD brain (Gervais et al. 1999; Stadelmann et al. 1999; Louneva et al. 2008). Moreover, suppression of LTP by Aβ (see below) is prevented by pharmacological inhibition or genetic knockout of caspase-3 (Jo et al. 2011). Thus, caspase-3—sublethally activated—may contribute to synapse dysfunction and loss in AD (Li et al. 2010c; D'Amelio et al. 2011). Importantly, antibodies to Aβ, which are at the
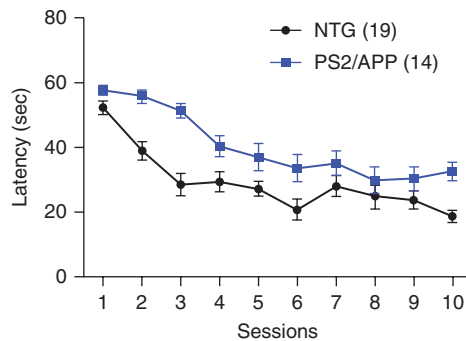

Figure 2. Impaired spatial learning and memory in a transgenic mouse model of Alzheimer's disease. Transgenic mice overexpressing human mutant APP and human mutant presenilin2 (PS2/APP mice) were tested in the acquisition of spatial memory in the Morris water maze at 6 mo of age. PS2/APP mice ($n = 14$) take significantly longer to reach a hidden platform during the 5 d of training (two sessions/day) than nontransgenic controls (NTG, $n = 19$). Repeated-measures ANOVA found a significant genotype ($p < 0.001$) and genotype × session interaction ($p < 0.05$). (Data kindly provided by William Meilandt, Tiffany Wu, and Kimberly Scearce-Levie [Genentech, Inc.].)

forefront of potential AD therapies in clinical trials, can prevent the memory deficits in transgenic mouse models of AD (Dodart et al. 2002; Hartman et al. 2005; Klyubin et al. 2005).

Recent studies suggest that despite overall impairment of excitatory synaptic function, there may be aberrant hyperactivity in some brain circuits in APP transgenic mice and perhaps (more controversially) in human AD brains. J20 APP transgenic mice, and double transgenic mice expressing both APP and the tyrosine kinase FYN, exhibit spontaneous non-convulsive seizure activity in cortex and hippocampus and increased seizure severity after inhibition of GABA$_A$ receptors (Palop et al. 2007). This is associated with increased sprouting of inhibitory axons in the dentate gyrus, which may serve as a compensatory mechanism against excitotoxicity (Palop et al. 2007). In vivo Ca^{2+} imaging studies corroborate the idea that different subsets of neurons in AD transgenic mice can be hypoactive or hyperactive. The "hyperactive" neurons were found exclusively near amyloid plaques and appeared to result from a relative decrease in synaptic inhibition (Busche et al. 2008). In vivo imaging of aged APP transgenic mouse brain shows elevated intracellular Ca^{2+} and aberrant Ca^{2+} homeostasis in a subset of neurites in the close proximity of amyloid plaques (Kuchibhotla et al. 2008). The abnormal Ca^{2+} handling of neurons affected by amyloid-β was associated with loss of dendritic spines and neuritic dystrophy, mediated in part by the Ca^{2+}-dependent protein phosphatase calcineurin (Wu et al. 2010). It is notable that calcineurin is also required for apoptosis and LTD, as well as for Aβ-induced spine loss and endocytosis of NMDA and AMPA receptors (Snyder et al. 2005; Hsieh et al. 2006; Shankar et al. 2007; Li et al. 2010c).

PROBING Aβ NEUROTOXICITY BY ACUTE EXPOSURE OF NEURONS TO Aβ OLIGOMERS

Synaptotoxic effects have been observed with soluble Aβ oligomers prepared from multiple sources such as synthetic Aβ peptides, APP-transfected cell culture supernatants, APP transgenic mouse brain, and even human AD brain

tissue (Shankar et al. 2008). However, whether toxic soluble Aβ species represent the main toxic entity in AD, whether amyloid plaques are harmful, or whether both act synergistically remains a major question. Amyloid plaques could act as "reservoirs" that release soluble oligomeric Aβ. Indeed, synapse loss seems to be maximal very close to plaques and diminishes with distance from the plaque (Spires et al. 2005; Koffie et al. 2009). Thus, plaques, which are likely surrounded by a high concentration of soluble oligomeric Aβ, can still be central players in the damage to neurons and synapses in AD, even if they are not directly injurious per se.

At nanomolar to low micromolar concentrations, soluble Aβ oligomers impair excitatory synaptic transmission, inhibit long-term potentiation (LTP, a form of synaptic plasticity that is believed to be the cellular correlate of learning and memory), induce loss of dendritic spines, and impair rodent spatial memory (Selkoe 2002; Haass and Selkoe 2007; Crews and Masliah 2010). In addition to synaptic effects, soluble Aβ oligomers can elicit other features of AD, such as tau hyperphosphorylation, production of reactive oxygen species, and neuronal death (albeit weakly) (Lambert et al. 1998; Ashe and Zahs 2010). Given the acute toxic effects of exogenous Aβ microaggregates, it is striking that transgenic mice overproducing Aβ42 for many months exhibit relatively little neuronal cell death, suggesting that the Aβ peptides are rapidly neutralized in these mice, or other compensatory mechanisms exist in vivo.

Aβ acutely alters synaptic plasticity in vitro: One of the most reproducible and widely studied effects is the inhibition of LTP in hippocampal slices (see Fig. 3) (Cullen et al. 1997; Lambert et al. 1998; Chapman et al. 1999; Freir et al. 2001; Walsh et al. 2002; Cleary et al. 2005; Townsend et al. 2006; Krafft and Klein 2010; Jo et al. 2011). In contrast to suppression of LTP, long-term depression (LTD) is unaffected or even enhanced by Aβ (Wang et al. 2002; Hsieh et al. 2006; Shankar et al. 2007, 2008). Thus, in terms of synaptic plasticity, exposure to Aβ seems to favor the weakening, and oppose the strengthening, of synapses. Consistent with its functional effects on LTP and LTD, prolonged exposure to Aβ
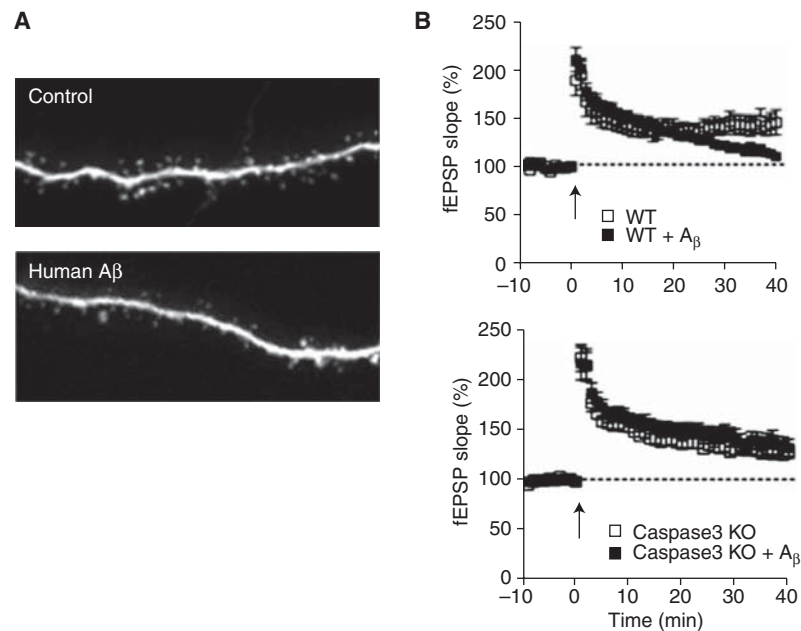
Figure 3. Effects of exogenous Aβ on dendritic spines and long-term potentiation in hippocampal slices. (*A*) Loss of dendritic spines induced by exposure to Aβ oligomers isolated from human AD brains. (*Top*) Image of an apical dendrite of a control CA1 hippocampal pyramidal neuron in an organotypic slice culture, showing the normal high density of dendritic spines. (*Bottom*) A similar neuron in a slice that has been exposed to ∼1 nM soluble Aβ oligomers derived from postmortem human AD brain. Prolonged exposure to Aβ oligomers from a variety of sources leads to loss of ∼50% of dendritic spines and of functional glutamatergic synapses. These images were acquired during the study described by Shankar et al. (2008) and are reprinted with permission from one of the authors. (*B, top*) Sustained long-term potentiation (LTP) is readily inducible by tetanic stimulation in untreated wild-type (WT) acute hippocampal slices (open symbols), but is blocked by exposure of the slice to soluble Aβ oligomers, especially at later time points (filled symbols). (*Bottom*) LTP is also inducible in caspase-3 knockout slices, but it is not suppressed by Aβ oligomers, indicating that caspase-3 is required for Aβ suppression of LTP. (These data were acquired by Kimberly Moore Olsen during the study described by Jo et al. [2011].)

leads to morphological loss of synapses (Fig. 3) (Hsieh et al. 2006; Lacor et al. 2007; Shankar et al. 2007, 2008; Wei et al. 2010). Aβ42, which is more prone to aggregation and more toxic than Aβ40, is also more effective at impairing LTP and reducing spine density (Kessels et al. 2010).

Based on transfection experiments in which APP or βCTF (the APP fragment remaining after β-secretase cleavage) (see Fig. 1) is overexpressed in hippocampal slice cultures, Aβ appears to impair glutamatergic transmission by promoting the internalization of postsynaptic glutamate receptors, which is associated with loss of dendritic spines (Hsieh et al. 2006). In this experimental model, Aβ-induced synaptic depression shows similarity with LTD, which is also mediated by the endocytosis of AMPA receptors and associated with shrinkage and/or loss of dendritic spines (Malenka and Bear 2004; Zhou et al. 2004). Moreover, the synaptic depression induced by APP/Aβ overexpression in neurons requires second-messenger pathways necessary for LTD, such as calcineurin; it can be blocked by overexpression of an AMPA receptor mutant that also prevents LTD (Hsieh et al. 2006). In this context, it is interesting that endocytosis abnormalities are present early in AD (Pimplikar et al. 2010). Moreover, both LTD and AMPA receptor internalization require the activation of caspase-3 via the mitochondrial pathway of apoptosis (Li et al. 2010c), a pathway

that is also implicated in the neurotoxicity of Aβ. Indeed, excessive mitochondrial fission has been implicated in Aβ-induced spine loss and neuronal toxicity (Cho et al. 2009). In general, however, exogenously added Aβ has few immediate effects on basal AMPA receptor-mediated synaptic transmission (Shankar et al. 2007; Jo et al. 2011), suggesting that strong basal synaptic depression might require prolonged Aβ overproduction from transfection of APP or βCTF. Nevertheless, it is conceptually useful to think of Aβ-triggered signaling mechanisms as promoting AMPA receptor internalization, thereby impairing LTP and favoring LTD.

It should be remembered that experiments showing the detrimental effects of Aβ on synapses typically use high concentrations of soluble Aβ oligomers, or overexpression of APP constructs that produce Aβ at high local concentrations; these manipulations may or may not be relevant in vivo or in AD. Moreover, experiments based on APP overexpression cannot exclude the possibility that other non-Aβ products of APP processing are involved in the pathogenesis or modulate the action of Aβ (see below).

The loss of synapses is one of the best anatomical correlates of cognitive deficits in human AD and a better disease predictor than the amyloid plaque load (Terry et al. 1991). Synapse loss is likely a morphological reflection of the synaptic dysfunction that begins early in the disease. Application of Aβ oligomers reduces the density of spines in organotypic hippocampal slice cultures and dissociated cultured neurons (Fig. 3) (Hsieh et al. 2006; Calabrese et al. 2007; Lacor et al. 2007; Shankar et al. 2007; Wei et al. 2010). The reduction in dendritic spine number occurs progressively over 5–15 d of exposure to Aβ in vitro (Shankar et al. 2007), as opposed to the 2-h exposure needed for inhibition of LTP by exogenously applied Aβ oligomers (Jo et al. 2011). Aβ-induced spine loss is associated with a decrease in glutamate receptors and requires the activity of calcineurin, which is a calcium-dependent protein phosphatase also necessary for LTD (Snyder et al. 2005; Hsieh et al. 2006; Shankar et al. 2007; Sun et al. 2009). It is widely believed that the synaptic dysfunction and synapse loss contribute to the cognitive deficits of patients with AD. Consistent with this idea, soluble Aβ can disrupt cognitive function after infusion into the CNS in mice (Cleary et al. 2005; Lesne et al. 2006; Shankar et al. 2008).

What intracellular signaling pathways are activated by Aβ? As discussed above, Aβ may stimulate—directly or indirectly—the mitochondrial pathway of apoptosis, which can culminate in cell death or synaptic depression due to the subapoptotic activation of caspase-3. Aβ is also reported to trigger Ca^{2+} influx, excitotoxicity, and stress-related signaling pathways in neurons, which may exacerbate aging-related increases in oxidative stress, impaired energy metabolism, and defective Ca^{2+} homeostasis (Bezprozvanny and Mattson 2008). Pharmacological data suggest that oligomeric Aβ-induced Ca^{2+} influx occurs through postsynaptic NMDA receptors, and this can lead to excessive formation of reactive oxygen species (De Felice et al. 2007), as well as calpain activation and degradation of critical proteins (Kelly and Ferreira 2006). An excitotoxic action of Aβ via NMDA receptors could explain why memantine, a weak NMDA receptor antagonist, has modest efficacy as a cognition-enhancing drug in AD patients.

The protein kinase glycogen synthase kinase-3 (GSK3; especially the isoform GSK3β) is implicated in Alzheimer's disease because it phosphorylates tau and increases Aβ production and toxicity (Ryder et al. 2003; Bhat et al. 2004). Aβ stimulates GSK3 activity, and GSK3 inhibitors can abrogate the neurotoxicity of Aβ (Fitzjohn et al. 2008; Hu et al. 2009). Interestingly, GSK3 activation promotes NMDA receptor-dependent LTD and inhibits LTP in the hippocampus (Peineau et al. 2007), which is similar to the effects of Aβ.

The interpretation of the acute Aβ administration studies assumes the existence of an "Aβ receptor." Indeed, Aβ oligomers have been reported to bind in a punctate synaptic pattern on excitatory neurons in dissociated culture (Lacor et al. 2004, 2007; Koffie et al. 2009; Lauren et al. 2009), suggesting the presence of such an Aβ receptor at synapses. Numerous Aβ receptor candidates have been proposed, including NMDA receptors (De Felice et al. 2007; Decker

et al. 2010), glutamate transporters (Li et al. 2009), mGluR5 (Renner et al. 2010), α7-nicotinic acetylcholine receptors (Wang et al. 2000; Dineley et al. 2001; Snyder et al. 2005), and cellular prion protein (Lauren et al. 2009). Some of these putative receptors are plausible and could potentially explain the synaptotoxic effects of Aβ. For example, direct Aβ binding may activate NMDA receptors, leading to excitotoxicity that causes the Aβ-induced spine loss and synaptic depression (Kamenetz et al. 2003; Wei et al. 2010). Aβ has also been reported to induce aberrant clustering and activation of mGluR5 receptors, leading to elevated postsynaptic intracellular calcium and synaptic defects that are prevented by mGluR5 antagonists (Renner et al. 2010). Alternatively, Aβ inhibition of glutamate re-uptake mechanisms may indirectly cause nonphysiological activation of extrasynaptic NMDA receptors (Li et al. 2009). Overall, it seems unlikely that there are multiple high-affinity-specific Aβ receptors, and considerable controversy exists about which, if any, of these receptors are functionally important for Aβ toxicity.

A new facet of the Aβ hypothesis emerged with the discovery that Aβ amyloid pathology can spread during the time course of months in mouse brain after infusion of Alzheimer's brain extracts (Kane et al. 2000). More recent studies revealed that even when Aβ is first introduced into the peritoneum, it can "seed" amyloid deposition in the brain (Eisele et al. 2010). These new observations suggest that Aβ neurotoxicity may spread from cell to cell via a "prion-like" mechanism in which a disease-related Aβ conformation is capable of nucleating the conformational transformation of endogenous normal Aβ.

NORMAL FUNCTIONS OF APP AND APP PROCESSING

Despite strong evidence that APP processing and Aβ production are involved in the pathogenesis of AD—or at least in familial early-onset AD—the normal functions of APP remain elusive. Adding to the mystery is the fact that APP is widely expressed in non-neural tissues and gives rise to measurable levels of Aβ outside of the CNS, including in plasma. Most confounding,

however, is the fact that, as described above, APP is a member of a gene family that includes APLP1 and APLP2, which are all processed by α-, β-, and γ-secretases. There is considerable evidence for functional redundancy among these three genes, but only APP is implicated in AD. Genetic studies revealed that double knockout of either APP and APLP2, or of APLP1 and APLP2, causes lethality, whereas double knockout of APP and APLP1 (which is expressed at lowest levels) does not (Heber et al. 2000). Among various phenotypes, these mice exhibit deficits in neuromuscular junction formation and changes in gene expression (Li et al. 2010a). Strikingly, the lethality or the neuromuscular junction phenotype of APP/APLP2 double-KO mice cannot be rescued by APP knockin mice in which only the extracellular sAPP β-secretase cleavage product of APP is produced (Li et al. 2010a), or in which the cytoplasmic tail of APP is truncated (Li et al. 2010b). Although the soluble sAPPβ fragment was unable to rescue the lethality of the double-KO mice, it did rescue some of the gene expression changes, providing evidence for a biological function of the extracellular sAPP fragment (Fig. 1) (Li et al. 2010a). One important implication of the mouse genetic analysis of APP is that the essential functions of APP and APLPs are likely mediated by conserved sequences among them, thus arguing against a normal function of the Aβ peptide.

A possible clue to the physiological function of APP is the activity-dependent regulation of Aβ production and/or secretion. Aβ secretion is enhanced by neural activity in vitro and in vivo (Kamenetz et al. 2003; Cirrito et al. 2005; Ting et al. 2007; Wei et al. 2010). In human brain, regions with high resting "default mode" activity by functional MRI imaging show a higher Aβ plaque load (Buckner et al. 2005). These findings suggest that synaptic activity regulates APP processing, although it is unclear whether the regulation occurs at the level of α/β- or γ-secretase. Given the fact that the resulting cleavage products derived from APP, APLP1, and APLP2 show high homologies in the sequences corresponding to the sAPP and the intracellular AICD fragment of APP, but none in the sequences corresponding to the Aβ peptides, it seems likely

that the functional importance of the activity-dependent cleavage of APP and its homologs resides in the conserved sequences, with Aβ being perhaps an incidental side-product.

Holtzman and colleagues (Kang et al. 2009) used microdialysis to measure the amount of Aβ in vivo in the extracellular interstitial fluid of hippocampus. Extracellular Aβ varied with a diurnal rhythm, correlating with wakefulness in both wild-type and mutant APP transgenic mice. Sleep deprivation acutely elevated extracellular Aβ, apparently via enhanced orexin signaling (a neuropeptide system that promotes wakefulness). Remarkably, chronic sleep restriction significantly increased, and an orexin receptor antagonist decreased, amyloid plaque load in AD transgenic mice (Kang et al. 2009). Because wakefulness is associated with a net increase in brain synaptic activity, the control of Aβ by the sleep–wake cycle is consistent with the idea that neuronal activity is a key regulator of APP processing.

Finally, the cytoplasmic fragment of APP (APP intracellular domain, AICD) (see Fig. 1), which is released by γ-secretase cleavage, can translocate to the nucleus, regulate gene transcription, and affect calcium signaling, synaptic plasticity, and memory (Cao and Sudhof 2001; Gao and Pimplikar 2001; Ma et al. 2007). As a transcriptional regulator, AICD was proposed not to be a transcription factor like the Notch intracellular domain NICD, but to affect chromatin remodeling via binding to the histone acetyltransferase Tip60 (Cao and Sudhof 2001, 2004). Interestingly, transgenic mice overexpressing the AICD by itself exhibit AD-like features, including hyperphosphorylation and aggregation of tau, neurodegeneration, and memory deficits (Ghosal et al. 2009). These studies underscore the importance of considering the non-Aβ products of APP in the pathogenesis of AD.

PRESENILIN, APOE4, AND SYNAPTIC FUNCTION

As the catalytic component of γ-secretase and a common site of mutations underlying familial AD, presenilins have generally been thought of in the context of APP processing and Aβ production. However, presenilins have a multitude of substrates and functions beyond serving as γ-secretase for APP; thus, they can act independent of APP processing to affect synapse function and neurodegeneration (Shen and Kelleher 2007; Lee et al. 2010; Pimplikar et al. 2010).

Conditional knockout of presenilins in the mouse forebrain results in impaired NMDA receptor function, defective LTP, defective learning and memory, and age-related neurodegeneration (Saura et al. 2004; Zhang et al. 2009). By genetically disrupting presenilins specifically in presynaptic (CA3) or postsynaptic (CA1) neurons in hippocampus, Zhang et al. (2009) showed that presynaptic but not postsynaptic presenilin is required to support normal LTP as well as short-term plasticity and synaptic facilitation. Presynaptic disruption of presenilins reduced the probability of glutamate release during stimulus trains, most likely via effects on intracellular Ca^{2+} release from ER stores in presynaptic terminals (Zhang et al. 2009). Familial AD mutations in presenilins have been linked to abnormal Ca^{2+} handling in neurons, and presenilins may regulate Ca^{2+} leak from the ER (Zhang et al. 2010). These findings raise the possibility that presynaptic dysfunction might be an early component of synaptic dysfunction in Alzheimer's disease, and that presenilins can affect synapses via a loss-of-function mechanism, as opposed to the gain-of-function increase in the Aβ42/Aβ40 ratio that is typically assumed under the amyloid hypothesis (Fig. 4). Nevertheless, conditional genetic inactivation of PS1 can rescue learning deficits in the context of APP transgenic mice, at least in young APP transgenic mice (Saura et al. 2005).

The ApoE4 allele of ApoE—a major brain apolipoprotein—is a strong genetic risk factor for AD, but little is known about how it affects neuronal or synaptic function (Kim et al. 2009). Not only are human ApoE4 carriers more likely to get AD, but they also show earlier accumulation of amyloid plaque and a younger age of onset of dementia. This problem seems to arise because the ApoE4 isoform is associated with less efficient clearing of Aβ from the brain, rather than increased production of Aβ (Castellano et al. 2011). The ApoE receptors ApoER2 and VLDLR,
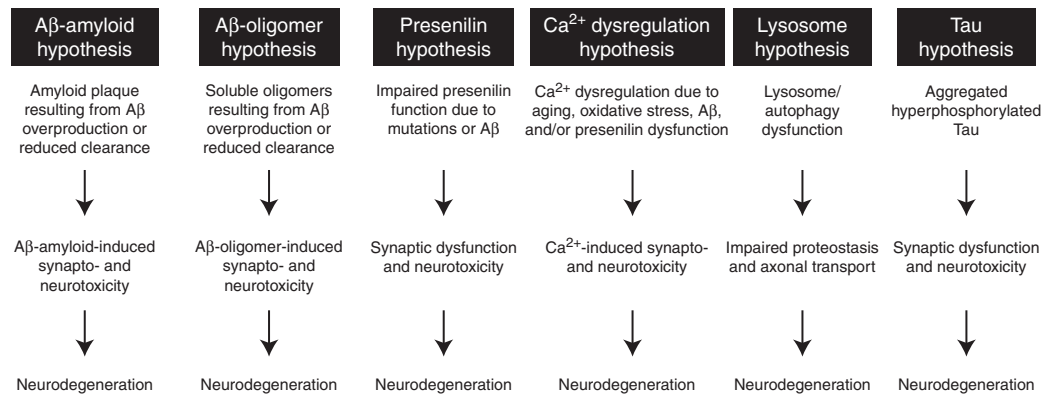
Aβ-amyloid hypothesis	Aβ-oligomer hypothesis	Presenilin hypothesis	Ca²⁺ dysregulation hypothesis	Lysosome hypothesis	Tau hypothesis
Amyloid plaque resulting from Aβ overproduction or reduced clearance	Soluble oligomers resulting from Aβ overproduction or reduced clearance	Impaired presenilin function due to mutations or Aβ	Ca^{2+} dysregulation due to aging, oxidative stress, Aβ, and/or presenilin dysfunction	Lysosome/ autophagy dysfunction	Aggregated hyperphosphorylated Tau
↓	↓	↓	↓	↓	↓
Aβ-amyloid-induced synapto- and neurotoxicity	Aβ-oligomer-induced synapto- and neurotoxicity	Synaptic dysfunction and neurotoxicity	Ca^{2+}-induced synapto- and neurotoxicity	Impaired proteostasis and axonal transport	Synaptic dysfunction and neurotoxicity
↓	↓	↓	↓	↓	↓
Neurodegeneration	Neurodegeneration	Neurodegeneration	Neurodegeneration	Neurodegeneration	Neurodegeneration

Figure 4. Pathogenic hypotheses for synaptic and neuronal toxicity in Alzheimer's disease. The specific hypotheses shown are not mutually exclusive, and, moreover, they likely "cross-talk" with each other. For instance, Aβ may induce tau hyperphosphorylation and aggregation, and presenilin mutations may cause lysosome and autophagy dysfunction (Pimplikar et al. 2010; Nixon and Yang 2011). Not all possible mechanisms of synaptic and neural toxicity are shown here (see text for additional examples).

which are expressed on neurons, aid in the transport of cholesterol from astrocytes to neurons, but also function as signaling receptors for Reelin, an extracellular protein that regulates neuronal migration in early development as well as synaptic function in the adult brain (Herz and Chen 2006). Reelin induces phosphorylation of NMDA receptor GluN2 subunits and enhances NMDA receptor activity and LTP, thereby countering the inhibitory effects of soluble Aβ on synaptic plasticity (Durakoglugil et al. 2009). ApoE4 is more effective than other ApoE isoforms in depleting ApoER2 as well as NMDA receptors and AMPA receptors from the neuronal surface; in this way, ApoE4 could exacerbate the synaptic impairment of AD by inhibiting the ability of Reelin to stimulate NMDA receptor function and LTP (Durakoglugil et al. 2009).

Aβ MAY NOT BE THE WHOLE STORY: WHAT CAUSES AD?

The cumulative evidence outlined above, on balance, supports the amyloid (or better, the Aβ) hypothesis, but leaves some space for doubt. Four main observations give rise to concerns about the amyloid hypothesis. First, as described above, not all AD-related mutations in APP and presenilins fit the concept of Aβ42 overproduction. Especially the presence of loss-of-function

presenilin mutations that appear to decrease Aβ42 production is puzzling (Shen and Kelleher 2007). Second, no treatment targeting Aβ has yet shown convincing efficacy in phase III human clinical trials, although we all hope this will change soon given the large number of ongoing trials. It should be acknowledged, however, that some of the clinical trials lack pharmacodynamic evidence of adequately hitting the drug target. Moreover, an argument can be made that by the time AD patients are treated in those clinical trials published so far, the neuronal damage done by Aβ has already occurred and cannot be reversed simply by reducing Aβ. Third, Aβ accumulation or levels do not correlate with dementia in patients more than 80 yr of age; even in younger patients, neurofibrillary tangles are much better predictors of cognitive performance than Aβ plaques (e.g., see Bancher et al. 1993). Fourth, the inability of mouse models in which human Aβ42 is overproduced to recapitulate the neurodegeneration observed in human AD patients is concerning. However, it should be pointed out that even in human AD, there is a time lag of more than a decade between amyloid plaque deposition and clinical dementia.

Some of the arguments against the Aβ hypothesis can be explained by the notion that many patients with dementia above age 80 who are diagnosed with AD may actually either have a

combination of AD with other types of dementias, especially vascular dementia, or not have AD at all (Fotuhi et al. 2009). If so, the lack of treatment success targeting solely Aβ and the lack of correlation between dementia and Aβ plaque load is not surprising, and future therapies should also consider therapies directed toward other targets or combination therapies or should be directed potentially toward a more defined patient population. An alternative explanation for the problems with the Aβ hypothesis is that the hypothesis is incorrect, and that the underlying pathogenesis is mediated by a different process. For example, it has been shown that presenilin loss of function induces neurodegeneration in mice (Saura et al. 2004), leading to the "presenilin hypothesis" of AD whereby AD pathogenesis is a loss-of-function state of γ-secretase (Fig. 4) (Shen and Kelleher 2007). The presenilin loss-of-function hypothesis explains the presence and nature of presenilin mutations in AD and is supported by mouse genetics. However, the presenilin hypothesis does not readily account for APP mutations in familial AD; in particular, this hypothesis is difficult to reconcile with the propensity of some APP mutations to produce cerebrovascular rather than neuronal lesions.

TAU AND SYNAPTIC FUNCTION

The accumulation within neurons of hyperphosphorylated and aggregated forms of tau as paired neurofilaments is thought to be a key step in AD pathogenesis. The characteristic tau pathology of AD lags behind amyloid plaques (by up to many years), but is more closely correlated with neurodegeneration and cognitive impairment in AD than is plaque pathology (Braak and Braak 1991). In the extended "amyloid cascade hypothesis," tau hyperphosphorylation and cell death are considered to be downstream effects of Aβ accumulation (Hardy and Selkoe 2002). It is unclear how Aβ toxicity leads to tau pathology, and it is controversial whether there is a causal pathway connecting the two. Oligomeric Aβ applied to neurons can induce tau phosphorylation; however, tau can also form aggregates in the absence of Aβ

pathology, as in the so-called tauopathies such as frontotemporal dementia (FTD), where mutations have been identified in the tau gene (*MAPT*) (Ballatore et al. 2007). Mutant tau is clearly toxic to neurons: Transgenic overexpression in the brain of a mutant tau that causes familial tauopathy results in age-dependent formation of NFTs, as well as synaptic impairment, neuronal death, and behavioral impairment. Interestingly, when expression of the mutant tau transgene was later turned off, memory function recovered, and neurodegeneration was halted despite persistence of tau aggregates in the brain, suggesting that the continuous presence of a soluble tau species rather than NFTs themselves is the toxic entity (Santacruz et al. 2005; Sydow et al. 2011).

In APP transgenic mouse models of AD, genetic deficiency of endogenous tau appears to mitigate Aβ synaptotoxicity and to prevent cognitive dysfunction and other behavioral abnormalities without reducing Aβ load, suggesting that tau is required somehow for Aβ-mediated toxicity (Roberson et al. 2007, 2011; Ittner et al. 2010). However, in these AD mouse models, aggregation of hyperphosphorylated tau is not observed, and it is unclear why deletion of tau would be beneficial. In fact, the function of tau in the basic biology of neurons, synaptic transmission, and overall brain function has not been elucidated in detail, and it is uncertain whether tau exerts a direct effect on synapses.

A major problem is that so little is known about the normal function of tau. A microtubule-binding protein, tau was regarded as primarily an axonal protein that regulates microtubule stability and transport (Dixit et al. 2008). However, hyperphosphorylated tau also accumulates in the somatodendritic compartment of neurons in AD (Ballatore et al. 2007; Li et al. 2011), and mislocalization of hyperphosphorylated tau in dendritic spines may disrupt glutamate receptor trafficking and hence synaptic function (Hoover et al. 2010). Provocative studies suggest that in the absence of tau, the postsynaptic targeting of non-receptor tyrosine kinase Fyn is disrupted (Ittner et al. 2010). Fyn—a component of the postsynaptic density of excitatory synapses—phosphorylates

the NMDA receptor subunit GluN2B (also termed NR2B), thereby enhancing NMDA receptor surface expression and function, a process that is antagonized by the tyrosine phosphatase STEP (Braithwaite et al. 2006). Overexpression of Fyn exacerbates, whereas Fyn knockout ameliorates, the neuronal and cognitive deficits in APP transgenic mice, consistent with the idea that Fyn plays a role in AD, potentially in synergy with Aβ-mediated toxicity (Chin et al. 2005). Loss of postsynaptic Fyn could protect from Aβ toxicity by reducing the excitotoxic actions of NMDA receptors. In this respect, it is notable that the GluN2B subtype is particularly implicated in both excitotoxicity and Aβ-mediated toxicity (Liu et al. 2007; Li et al. 2009; Tu et al. 2010). What is puzzling about these findings, however, is that no major effects of tau deletion on synaptic transmission were reported, and none of the many papers in this area examine how synaptic function is changed in any of these conditions. Much more work needs to be done to clarify how tau hyperphosphorylation and aggregation contribute mechanistically to the synaptic deficits and neuronal death in AD.

CONCLUDING REMARKS

AD is a prevalent cause of dementia in the elderly and probably involves major dysfunctions of synapses caused by increased levels of soluble Aβ oligomers and/or decreased levels of presenilin function. Despite a vast amount of data that include descriptions of mutations in APP and presenilin genes causing AD, isoforms of ApoE genes predisposing to AD, mouse models replicating some of these genetic conditions, and biochemical studies of Aβ and APP processing, the pathogenesis of AD remains incompletely understood, and its relation to other forms of dementia continues to be unclear. Given the special vulnerability of axons, nerve terminals, and dendritic spines to injury, an axosynaptic origin of neurodegeneration makes eminent sense, but it is still unknown whether a single pathogenic pathway underlies such synapse-based neurodegeneration, or whether AD neurodegeneration is mediated by a multitude of independent insults that work in combination to eventually annihilate a synapse and kill a neuron (see Fig. 4). Even fundamental biological questions—such as whether a biological receptor for Aβ exists, or what physiological functions presenilins perform independently of their role as catalytic subunits in γ-secretase—remain unanswered. Given these uncertainties, it seems likely that significant progress in understanding late-life neurodegeneration will require a better understanding of the neurobiology of aging and of the molecular regulation of synapses in the mature brain.

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