Neurobiology of Aging 34 (2013) 2525–2537

Contents lists available at SciVerse ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Review

Amyloid β precursor protein as a molecular target for amyloid β–induced neuronal degeneration in Alzheimer's disease

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ARTICLE INFO

Article history:
Received 20 February 2013
Received in revised form 17 April 2013
Accepted 20 April 2013
Available online 25 May 2013

Keywords:
APP
Alzheimer's disease
Aβ
Neuritic dystrophy
Synaptic degeneration
Dying-back degeneration

ABSTRACT

A role of amyloid β (Aβ) peptide aggregation and deposition in Alzheimer's disease (AD) pathogenesis is widely accepted. Significantly, abnormalities induced by aggregated Aβ have been linked to synaptic and neuritic degeneration, consistent with the "dying-back" pattern of degeneration that characterizes neurons affected in AD. However, molecular mechanisms underlying the toxic effect of aggregated Aβ remain elusive. In the last 2 decades, a variety of aggregated Aβ species have been identified and their toxic properties demonstrated in diverse experimental systems. Concurrently, specific Aβ assemblies have been shown to interact and misregulate a growing number of molecular effectors with diverse physiological functions. Such pleiotropic effects of aggregated Aβ posit a mayor challenge for the identification of the most cardinal Aβ effectors relevant to AD pathology. In this review, we discuss recent experimental evidence implicating amyloid β precursor protein (APP) as a molecular target for toxic Aβ assemblies. Based on a significant body of pathologic observations and experimental evidence, we propose a novel pathologic feed-forward mechanism linking Aβ aggregation to abnormalities in APP processing and function, which in turn would trigger the progressive loss of neuronal connectivity observed early in AD.

1. Introduction

Alzheimer's disease (AD) is a highly prevalent cause of dementia in elderly people. It is estimated that >30 million people worldwide suffer this disease, and epidemiologic studies predict that this number will exponentially grow in the next decades because of the sustained aging of human population. AD is characterized by progressive mental deterioration associated with degeneration and loss of neurons located in brain regions relevant to superior cognitive functions. The confirmatory AD diagnosis is based on 2 major histopathologic hallmarks: senile plaques, which are extracellular deposits of amyloid β (Aβ) peptide, and neurofibrillary tangles, which are somatic inclusions of the microtubule-associated protein tau. Early in the course of disease, AD is characterized by loss of synaptic function and neuritic dystrophy, characteristic features of neurons undergoing a "dying-back" pattern of degeneration (Kanaan et al., 2012). Increasing pathologic evidence suggests that the cognitive decline observed in the early stages of AD results from deficits in neuronal connectivity, whereas neuronal loss becomes more relevant in the later stages of the disease (Kanaan et al., 2012).

2. Aβ and neurodegeneration in AD

The most accepted mechanistic hypothesis for AD posits that abnormal aggregation and accumulation of Aβ in the brain trigger a cascade of pathologic events leading to progressive neuronal dysfunction (Hardy, 2009; Hardy and Selkoe, 2002; Huang and Mucke, 2012; Karran et al., 2011). Although the physiological role of monomeric, soluble Aβ remains a matter of debate, several lines of evidence indicate that this form of Aβ modulates synaptic function (Abramov et al., 2009; Hsieh et al., 2006; Puzzo e al., 2008; Russell et al., 2012). Therefore, an enormous effort has been dedicated to elucidate mechanisms underlying Aβ aggregation and neurotoxicity. Consistent with the natural propensity of Aβ to self-aggregate, diverse Aβ assemblies displaying various toxic properties have been generated from synthetic peptides (Lambert et al., 1998; Lorenzo and Yankner, 1994; Pike et al., 1991) and/or isolated from human AD brain (Walsh et al., 2002). Aβ assemblies

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http://dx.doi.org/10.1016/j.neurobiolaging.2013.04.021

identified to date include insoluble fibrils found in neuritic plaques, soluble protofibrils, oligomers, and even trimers and dimers, all of which may exist in a dynamic equilibrium in AD brains (Roychaudhuri et al., 2009).

The mechanisms by which Aβ assemblies cause neuronal toxicity remain elusive. However, the identification of several molecular mediators of Aβ toxicity (Table 1) suggests that Aβ elicits a unique mechanism of toxicity, where the property of specific assemblies to recruit multiple molecular effectors would interfere with the normal functionality of various metabolic pathways and intracellular signaling cascades. Accordingly, diverse cellular and systemic functions are affected by Aβ aggregates including ionic plasmalemma conductance, Ca^{2+} homeostasis, mitochondrial function, energy metabolism, cytoskeletal organization, intracellular transport, kinase activation, synaptic transmission, vascular permeability, and inflammatory processes, all of which may ultimately contribute to neuronal degeneration in AD (reviewed by Chen and Yan, 2010; Götz et al., 2011; Mattson, 2004; Reddy and Beal., 2008; Yankner and Lu, 2009). Results from quantitative proteomic experiments using artificial

Table 1
Molecular targets reported for various Aβ assemblies

Molecular target	Aβ assembly	Pathologic effect	Reference
p75NTR	Oligomers	Neuronal degeneration	Yaar et al. (1997)
		Neuritic dystrophy	Perini et al. (2002) and Sotthibundhu et al. (2008)
			Knowles et al. (2009)
NR1 (NMDA receptor)	Oligomers	Synaptic toxicity	Lacor et al. (2004)
		Oxidative stress	De Felice et al. (2007)
NR1/NR2B (NMDA receptor)	Oligomers	Synaptic toxicity	Lacor et al. (2007)
mGluR5 (metabotropic glutamate receptor)	Oligomers	Synaptic toxicity	Renner et al. (2010)
		Altered Ca^{2+} signaling	
EphB2	Oligomers	Synaptic toxicity	Cissé et al. (2011)
α7 nAChRs (acetylcholine receptor)	Oligomers	Synaptic toxicity	Wang et al. (2000)
			Dineley et al. (2001)
			Nagele et al. (2002)
			Fodero et al. (2004)
			Snyder et al. (2005)
RAGE	Fibrils	Oxidative stress	Yan et al. (1996)
	Aβ from AD brain	Activation of microglia and astrocytes	Yan et al. (1997)
	Oligomers	Inflammation	Origlia et al. (2010)
		Synaptic toxicity	Fang et al. (2010)
Class A scavenger receptors	Fibrils	Oxidative stress	El Khoury et al. (1996)
		Activation of microglia	Paresce et al. (1996)
			Paresce et al. (1997)
CD36 (class B scavenger receptor) and CD47	Fibrils	Oxidative stress	Bamberger et al. (2003)
		Inflammation	Coraci et al. (2002)
		Activation of microglia and monocytes	Moore et al. (2002)
Heparan sulfate proteoglycans	Fibrils	Nucleation and Aβ aggregation	Narindrasorasak et al. (1991) and McLaurin
		Inhibition of Aβ degradation	et al. (1999)
		Aβ uptake in neurons	Gupta-Bansal et al. (1995)
			Kanekiyo et al. (2011)
Gangliosides	Fibrils and oligomers	Nucleation and Aβ aggregation	McLaurin and Chakrabartty (1996)
		Membrane disruption and neurotoxicity	Williams et al. (2011)
			Choo-Smith et al. (1997)
			Kakio et al. (2001)
PrPc	Oligomers	Synaptic toxicity	Laurén et al. (2009)
			Gimbel et al. (2010)
			Barry et al. (2011)
			Kessels et al. (2010)
			Cissé et al. (2011)
			Bate and Willians (2011)
			Um et al. (2012)
Neuroligin-1	Oligomers	Nucleation and Aβ aggregation	Dinamarca et al. (2011)
		Synaptic toxicity	
Acetylcholinesterase	Fibrils	Nucleation and Aβ aggregation	Inestrosa et al. (1996)
		Synaptic toxicity	Alvarez et al. (1997)
			Alvarez et al. (1998)
α6β1, α2β1, and αVβ1 integrins	Fibrils and oligomers	Aβ uptake in microglia	Koenigsknecht and Landreth (2004)
		Neuronal toxicity	Wright et al. (2007)
		Synaptic toxicity	Wang et al. (2008)
APP	Fibrils	Neurotoxicity	Lorenzo et al. (2000)
			Van Nostrand et al. (2002)
			Shaked et al. (2006)
			Galvan et al. (2006)
			Sola Vigo et al. (2009)
			Kedikian et al. (2010)
Frizzled (Fz5-CRD)	Oligomers	Inhibition of Wnt signaling pathway	Magdesian et al. (2008)
Insulin receptor (IR)	Oligomers	Synaptic toxicity	Zhao et al. (2008)
			De Felice et al. (2009)
ABAD	Intracellular Aβ	Mitochondrial damage	Yan et al. (1997); Lustbader et al. (2004)
Cyclophilin D	Intracellular Aβ	Mitochondrial damage	Du et al. (2008)
VDAC1	Oligomers	Mitochondrial damage	Manczak and Reddy (2012)

Key: Aβ, amyloid β; AD, Alzheimer's disease; APP, amyloid β precursor protein; NMDA, N-methyl-D-aspartate.

exogenous proteins with intrinsic propensity to form amyloid-like aggregates support this notion. Specifically, it was found that the toxic effects of these artificial proteins correlated with abnormal protein interactions in their aggregated form (Olzscha et al., 2011). Aberrant interactions with these proteins would then trigger alterations in multiple cellular functions (Olzscha et al., 2011). Such pleiotropic mechanism of toxicity poises a challenge for the design of therapeutic interventions for AD and calls for the identification of cardinal Aβ effectors relevant to AD pathogenesis. In this review, we focus on amyloid precursor protein (APP), a protein unequivocally linked to AD pathogenesis. APP is the unique source of Aβ, and genetic alterations in *App*, including gene duplication or missense mutations, lead to early-onset familiar forms of AD (FAD) (see Alzheimer's Disease and Frontotemporal Dementia Mutation Database: http://www.molgen.vib-ua.be/ADMutations). Because pathogenic *App* mutations cluster around or within the Aβ sequence and typically predispose to Aβ aggregation and/or deposition (Tanzi, 2012), it is generally accepted that the pathogenic role of APP in AD is mainly restricted to be the source of Aβ. However, recent data from various independent groups suggest that Aβ aggregates interact with APP, triggering abnormalities in its function and processing that would promote neuronal dysfunction. These observations represent a major focus of this review. First, we briefly summarize various physiological functions proposed for APP and the protein fragments derived from its metabolic processing. Then, we discuss various published reports providing evidence that APP mediates the toxic properties of Aβ assemblies. Finally, we propose a mechanistic model where abnormal APP/Aβ interactions play an important role in the development of early and critical pathogenic events of AD, including synaptic dysfunction and neuritic degeneration.

3. APP: protein structure and metabolic processing

APP was discovered in 1987 as the only source of Aβ (Kang et al., 1987), and the gene encoding this protein (*App*) was mapped to chromosome 21 (Goldgaber et al., 1987; Tanzi et al., 1987). The *App* gene encodes a transmembrane type I protein belonging to a family of conserved proteins that in mammals also include APLP1 and APLP2 (Wasco et al., 1993). Whereas all 3 APP family members are predominantly expressed in the brain, APP and APLP2 are also ubiquitously expressed in other tissues. APP family members display a high degree of homology in the extracellular E1 and E2 domains and in the intracellular C-terminal portion (Fig. 1). Reduced homology exists in the transmembrane and juxtamembrane domains where only APP, but not APLP1 or APLP2, contains the sequence encoding the Aβ peptide. This observation, together with the discovery that >20 mutations in *App* gene are linked to early-onset FAD (see Alzheimer's Disease and Frontotemporal Dementia Mutation Database: http://www.molgen.vib-ua.be/ADMutations), motivated interest of the AD scientific community for understanding the basic biology of APP and its relation to AD pathogenesis (Tanzi, 2012).

Several APP isoforms resulting from alternative splicing have been described, the most abundant being a 695-amino acid–long isoform mainly found in neurons (Mattson, 1997). Also, 770- and 751-amino acid–long isoforms containing a Kunitz protease inhibitor domain are expressed in non-neuronal cells, including glia and endothelial cells (Mattson, 1997). However, the functional relevance of cell type–specific expression of APP splicing variants remains poorly understood.

APP is subject to a highly dynamic distribution and intracellular trafficking within cells (Allinquant et al., 1994; Simons et al., 1995; Yamazaki et al., 1995; reviewed by Brunholz et al., 2011). Initially, immature APP traffics through the endoplasmic reticulum and the Golgi apparatus where it undergoes a series of post-translational modifications, including *N*- and *O*-glycosylation and phosphorylation. The modified, mature APP protein is then transported in secretory vesicles to the plasma membrane via axonal transport mechanisms involving conventional kinesin, a major microtubule-dependent molecular motor (Brunholz et al., 2011; Szodorai et al., 2009). After insertion in the plasma membrane, APP can be reinternalized to endosomes from where it can be either recycled back to the cell surface, targeted to lysosomes for degradation, or redistributed to distant cellular compartments through transcytosis (Back et al., 2007; Golde et al., 1992; Haass et al., 1992; Tienari et al., 1996; reviewed by Haass et al., 2012). In addition, APP and its proteolytic fragments (including Aβ) have been observed in mitochondria (Devi et al., 2006; Lustbader et al., 2004; Manczak et al., 2006; Yamaguchi et al., 1992). In neurons, most APP is initially targeted from the trans-Golgi network to the axonal membrane and then to endosomes, from where it can also be redirected to the dendritic compartment via transcytosis (Tienari et al., 1996; Yamazaki et al., 1995). Most APP is found within intracellular compartments, and only 10%–20% is present in the plasma membrane (Thinakaran and Koo, 2008). During development, APP is enriched at the growth cones of developing neurites. In more mature neurons, APP localizes to focal adhesion sites and within pre- and postsynaptic structures of the central and peripheral nervous tissue, suggesting a functional role in neuritic growth and

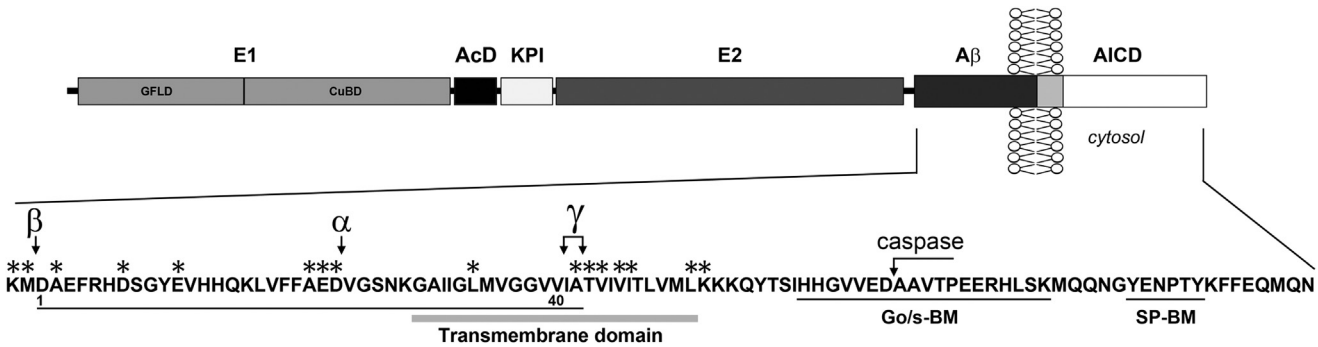

Fig. 1. Scheme depicting the domain structure of amyloid β precursor protein (APP). The E1 domain consisting of the growth factor like domain (GFLD) and the copper-binding domain (CuBD). The acidic domain (AcD) and the Kunitz-type inhibitory domain (Kunitz protease inhibitor [KPI], not present in neurons) bridge the E1 and E2 domains. The E2 domain consists of 2 coiled-coil substructures connected through a continuous helix. The amino acid sequence of amyloid β (Aβ)/transmembrane/intracellular (intracytoplasmic domain of APP [AICD]) domains is shown in the lower part of the figure. Asterisks denote amino acids substituted in familiar forms of AD and APP variants. Arrows indicate cleavage sites for both secretases and caspases. Binding motifs for heterotrimeric Go/s proteins (Go/s-BM) and scaffolding proteins (SP-BM; e.g., Fe65, Mint/X11-family proteins, Dab1, c-Jun N-terminal kinase) are underlined. The Aβ sequence is also underlined.

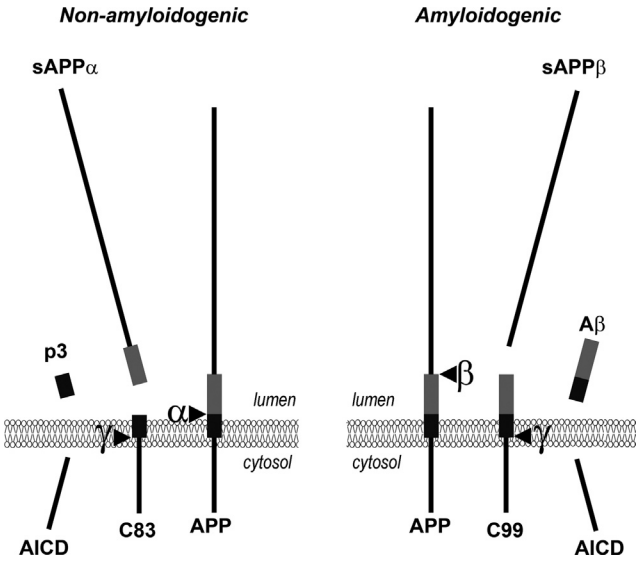

Fig. 2. Pathways for metabolic processing of amyloid β precursor protein (APP). The 2 most prominent metabolic routes and APP proteolytic derivatives are illustrated. APP is substrate for either α- or β-secretase. Therefore, the nonamyloidogenic and the amyloidogenic pathways are mutually exclusive. Whereas several metalloproteinases display α-secretase activity (reviewed by Allison et al., 2003), β-site APP-cleaving enzyme 1 (BACE1) is the only known aspartylprotease with β-secretase activity (reviewed by Kandalepas and Vassar, 2012). Membrane-tethered APP stubs, C83 and C99 (also known as α- and β-carboxy-terminal fragment), are substrates for γ-secretase, a protein complex that includes at least 4 different proteins: anterior pharynx defective 1, nicastrin, presenilin 1 or presenilin 2, and preselinin enhancer-2 (reviewed by Wolfe, 2012).

synaptic plasticity (Ashley et al., 2005; Sabo et al., 2003; Yamazaki et al., 1997).

The dynamic distribution of APP at different subcellular compartments is accompanied by a complex metabolic processing that includes 2 basic metabolic routes: one precluding and other promoting the generation of Aβ peptides. Accordingly, these routes are designated as the nonamyloidogenic and amyloidogenic pathways, respectively (Fig. 2). A detailed analysis of APP processing is beyond the scope of this review but has been extensively revised elsewhere (Brunholz et al., 2011; Haass et al., 2012). Within the context of this review, suffices to say that in the nonamyloidogenic pathway, APP is first cleaved by α-secretase within the Aβ sequence to generate 2 proteolytic fragments: sAPPα (a secreted protein that encompasses most of the APP ectodomain) and C83 (a protein stub that remains tethered to the plasma membrane for further proteolytic processing). In the amyloidogenic pathway, APP is cleaved by β-secretase at the N-terminus of the Aβ sequence, thus generating a secreted protein (sAPPβ) and a membrane-associated fragment known as C99 comprising the entire Aβ sequence. Both C99 and C83 stubs can be cleaved by γ-secretase within the transmembrane domain, resulting in the release of Aβ or p3 peptides, respectively, and the intracytoplasmic domain of APP (AICD). Because cleavage by γ-secretase is heterogeneous, Aβ peptides from various lengths can be generated, with Aβ1–40 being the most abundant and soluble and the Aβ1–42 the most prone to aggregation (Jarret et al., 1993; McGowan et al., 2006).

It is noteworthy that APP represents only 1 of several secretase substrates. Indeed, several cell surface receptors and proteins including Notch 1, ERBB4, Robo, N-cadherins, neuregulins, P75NTR, LRP1, APLP1, and APLP2, among others, are also cleaved by secretases. Secretase-mediated cleavage of these proteins results in the production of extracellular and intracellular fragments with unique physiological functions (De Strooper et al., 1999; Ni et al., 2001; Reiss et al., 2005; Scheinfeld et al., 2002; reviewed by Bai and Pfaff, 2011). The similarity of APP structure and processing with many of these receptors suggests that APP might also act as a cell surface receptor with specialized functions; however, natural physiological ligands for APP remain elusive.

4. Physiological functions of APP

Various cellular functions have been proposed for APP, but the actual physiological role(s) of this protein remains a matter of debate. *App*-knockout mice are viable and fertile, indicating that loss of APP is not essential for embryonic development and/or the control of vital functions (Li et al., 1996; Zheng et al., 1995). Nevertheless, $APP^{-/-}$ mice display some discrete phenotypic abnormalities including reduced body weight, decreased locomotor activity and forelimb grip strength, defective long-term potentiation, and impairments in learning and memory (Ring et al., 2007; Zheng et al., 1995). Increased reactive gliosis was also reported in these animals, but no obvious evidence of neuronal degeneration was observed (Zheng et al., 1995). Reports of early lethality in $APP^{-/-}$/$APLP1^{-/-}$/$APLP2^{-/-}$ triple knockout, $APP^{-/-}$/$APLP2^{-/-}$, or $APLP1^{-/-}$/$APLP2^{-/-}$ double knockout mice raised the possibility that compensatory mechanisms may mask the functional relevance of APP in $APP^{-/-}$ mice (Heber et al., 2000). Surprisingly, $APP^{-/-}$/$APLP1^{-/-}$ animals are viable, suggesting that APLP2 plays some particular function that cannot be compensated by other APP family members (Heber et al., 2000). Additionally, no apparent abnormalities were reported in $APLP2^{-/-}$ mice (von Koch et al., 1997), further suggesting a functional redundancy among APP family members (for a comprehensive review, see Müller and Zheng, 2012). These in vivo observations strongly suggest that AD-like pathology does not result from loss of APP function alone. A brief description of experimental data suggesting discrete functional roles for APP and APP metabolites is provided subsequently.

5. Roles of APP on cell adhesion, neuritogenesis, and synaptic plasticity

APP family members have been proposed to play a role in cell-to-cell and cell-substratum interactions. For example, membrane-associated forms of APP, APLP1, and APLP2 promote cell-cell adhesion through homo- and heterodimerization (Baumkötter et al., 2012; Soba et al., 2005). Also, Förster resonance energy transfer experiments using quantum dots also revealed a ligand/receptor interaction between the proteolytic APP fragment sAPP and holo-APP in the plasma membrane (Gralle et al., 2009), suggesting a link between the functional activities of sAPP and holo-APP. In addition, holo-APP can form antiparallel dimers through interactions involving the E2 domain (Wang and Ha, 2004), and both the E1 domain and the GAIIG motif within the transmembrane region also play a role in APP dimerization (Kaden et al., 2008; Munter et al., 2007). Moreover, binding of heparin to E1–E2 domains also promotes APP dimerization (Dahms et al., 2010; Gralle et al., 2006). Providing a physiological consequence for these interactions, APP dimerization was shown to affect its processing by secretases (Kaden et al., 2008; Lefort et al., 2012; Munter et al., 2007; Scheuermann et al., 2001).

Because the extracellular portion of APP contains various structural domains, it is not surprising that several putative physiological ligands have been identified for APP. Interestingly, many of these ligands are extracellular matrix components and cell adhesion–related proteins including heparan sulfate proteoglycans, laminin, collagen type I, F-spondin, Nogo-66 receptor, reelin, netrin, and integrin α3β1 (Beher et al., 1996; Clarris et al., 1997; Ho and Südhof, 2004; Hoe et al., 2009; Kibbey et al., 1993; Park et al., 2006). Importantly, binding of APP to each of these molecules

differentially affects its cellular distribution and/or metabolic processing by secretases, indicating that these interactions are functionally relevant. For example, binding of F-spondin to the central E2 domain of APP prevents its cleavage by secretases (Ho and Südhof, 2004). Also, reelin binding to the E1 domain enhances the nonamyloidogenic processing of APP (Hoe et al., 2006, 2009). Finally, netrin reportedly interacts with APP within the Aβ domain, and this interaction results in reduced Aβ generation (Lourenço et al., 2009).

The adhesive properties of APP have also been linked to a tetrapeptide sequence RHDS within the N-terminus of the Aβ peptide, which promotes cell adhesion in an integrin-like manner (Ghiso et al., 1992). In fact, APP colocalizes and interacts with integrin α3β1 at focal adhesion sites and within synapses. Additionally, reelin binds to the E1 extracellular domain of APP, increasing the levels of holo-APP at the cell surface, the secretion of sAPP, and the elongation of neurites by a mechanism dependent on α3β1 integrin (Hoe et al., 2009). Results from experiments using APP messenger RNA (mRNA) antisense and $APP^{-/-}$ mice also support a role of cellular APP in the control of neuritic outgrowth and further demonstrate that the growth-promoting effect of sAPP requires both membrane-associated holo-APP and integrins (Allinquant et al., 1995; Perez et al., 1997). Additionally, in utero electroporation experiments revealed that APP is required for proper migration of neuronal precursors to the cortical plate, a process dependent on cell-cell and cell-substratum adhesions (Young-Pearse et al., 2007). Significantly, these migration defects were fully rescued by human APP, APLP1, or APLP2, suggesting functional compensation among APP family members (Young-Pearse et al., 2008).

The role of APP and its proteolytic fragments on the regulation of synaptic plasticity has been extensively documented. For example, initial reports found increased number of synapses in cortical areas of transgenic mice overexpressing wild-type human APP (Mucke et al., 1994). More recently, it was shown that APP regulates the presynaptic expression and activity of the high-affinity choline transporter at neuromuscular junctions (Wang et al., 2007). Using $APLP2^{-/-}$ mice that also allow the conditional depletion of APP in either motoneurons or muscle, it was determined that the proper formation and function of neuromuscular synapses require APP expression in both pre- and postsynaptic membranes (Wang et al., 2009). Moreover, expression of APP in HEK cells cocultured with primary neurons induced hemisynapse formation (Wang et al., 2009). Based on these observations, APP was proposed to represent a novel class of synaptic adhesion molecule with biochemical properties similar to those reported for neurexins/neuroligins, SynCAMs, and leucine-rich repeat transmembrane neuronal proteins (Baumkötter et al., 2012; Müller and Zheng, 2012; Wang et al., 2009). Collectively, these observations mentioned previously suggest that the neuritogenic and synaptogenic activities of APP involve the modulation of cell-cell and cell-substratum interactions and also the homo- and heterodimerization properties of this molecule. By modulating APP dimerization and processing by secretases, diverse extracellular components and membrane proteins would further regulate APP function.

6. Role of APP on trophic support

Initial experiments in cultured fibroblasts showed that sAPP modulates cell division through the RERMS sequence located in the middle portion of the APP ectodomain (Ninomiya et al., 1993; Saitoh et al., 1989). Additionally, trophic effects of sAPP were widely documented in neuronal cells. For example, application of sAPP to cultured primary neurons promoted long-term survival, enhanced neurite outgrowth, increased synaptic formation, and protected cultured neurons against various toxic stimuli (Mattson, 1997). Extending these observations, intracranial infusion of sAPP-specific antibodies impaired memory, whereas application of sAPP has a memory-enhancing effect (Doyle et al., 1990; Meziane et al., 1998). Together, these findings indicated that sAPP modulates cellular activities involved in cognitive processes, including the functionality and maintenance of synapses and neurites. Interestingly, sAPP binds to and regulates holo-APP dimerization at the plasma membrane, an event required for the neuroprotective effect of sAPP against starvation-induced cell death (Gralle et al., 2009). Whereas sAPP appears to have a beneficial effect to neurons, in vitro overexpression of C99 (a membrane-tethered APP fragment generated after β-secretase cleavage) promotes neuronal degeneration (Yankner et al., 1989; Yoshikawa et al., 1992). The contrasting effect of these APP fragments suggests that neuronal cells depend on an appropriate balance of membrane-tethered APP and sAPP.

It is noteworthy that cultured human Down syndrome (DS) neurons display poor survival rates and defective APP secretion, despite having increased APP expression levels because of chromosome 21 trisomy (Busciglio and Yankner, 1995). The reduced in vitro survival of DS neurons likely results from pathogenic effects originated from multigenic imbalance. Nevertheless, APP appears to play a cardinal role because addition of exogenous sAPP at physiological levels restores long-term viability of cultured DS neurons (Busciglio and Yankner, 1995; Busciglio et al., 2002). Because reduced levels of sAPP have been observed in both DS and AD (Busciglio et al., 2002; Lannfelt et al., 1995; Van Nostrand et al., 1992), it is reasonable to speculate that alterations in APP metabolism and/or function play a role in AD pathogenesis beyond its participation as a source for Aβ. Abnormal *App* dosage also appears to play a significant role in neuronal dysfunction in TS65Dn mice, an animal DS model bearing 3 copies of the *App* gene. For example, a reduction in the number of cholinergic neurons was observed in the entorhinal cortex of TS65Dn mice, but removal of the extra *App* copy was sufficient to prevent this defect (Salehi et al., 2006). Also, altered intracellular Ca^{2+} homeostasis and defective cholinergic function were both described in neuronal cell lines derived from Ts16 mice, but normalizing APP expression through APP-specific mRNA antisense abrogated these deficits (Opazo et al., 2006; Rojas et al., 2008). It remains unclear how alterations in APP levels relate to the AD-like pathology seen in individuals with genetic overexpression of APP, such as DS or FAD because of *App* gene locus duplication (Rovelet-Lecrux et al., 2006) or mutations in the *App* gene-promoter region (Theuns et al., 2006). However, the collective evidence suggests that a delicate balance between APP expression and secretion modulates important neuronal activities including trophic support, synaptic and neuritic plasticity, and survival.

7. Regulation of intracellular signaling pathways by APP

The highest degree of homology among APP family members is found within their intracellular domain, suggesting that this region plays a critical functional role. Indeed, the cytoplasmic domain of all APP family members contain a GYENPTY motif, which mediates their interaction with a number of adaptor proteins including Fe65, Mint/X11-family proteins, Dab1, c-Jun N-terminal kinase, Shc, and Grd2, among others (Matsuda et al., 2001; McLoughlin and Miller, 2008; Russo et al., 2005; Saito et al., 2011). Moreover, the interaction of APP with these proteins modulates the generation of the AICD fragment by secretases. The significance of this modulation relies on reports that AICD, Fe65, and Tip60 can form a tripartite transcriptional complex that controls the expression of several genes, including *KAI1*, *neprilysin*, *LRP1*, and *EGF* receptor (Baek et al., 2002; Cao and Südhof, 2004; Liu et al., 2007; Pardossi-Piquard et al.,

2005; Zhang et al., 2007). The similarity of APP and Notch 1 processing by secretases and the regulation of gene transcription by proteolytic fragments derived from these proteins appear consistent with a role of APP as a cell surface receptor.

It is generally assumed that receptors coupled to heterotrimeric G proteins, including Go and Gs, must have a 7 transmembrane domain structure. However, increasing evidence indicates that single transmembrane domain proteins including epidermal growth factor receptor, insulin receptor, insulin-like growth factor receptor, fibroblast growth factor receptor, and natriuretic peptide receptor C-type can also interact and signal through G proteins (Patel, 2004). Significantly, a consensus sequence for Go protein binding was identified in the intracellular juxtamembrane domain of APP (Nishimoto et al., 1993). In vitro experiments confirmed this interaction, further revealing histidines at positions 657–658 (APP695 numbering) as critical residues for this interaction (Brouillet et al., 1999; Nishimoto et al., 1993; Okamoto et al., 1995). More recently, it was also observed that a RHLSK motif within the intracellular domain of APP mediates an interaction with Gs (Deyts et al., 2012). Extending these observations, it was observed that APPL, the Drosophila homolog of the mammalian APP, colocalizes with Go in migrating neurons (Swanson et al., 2005) and regulates synaptic structure and number in a manner that requires both the putative Go protein binding site and the GYENPTY motif (Torroja et al., 1999). Furthermore, APP was shown to promote axonal and dendritic outgrowth in mammalian neurons through a mechanism involving Gs-dependent activation (Deyts et al., 2012). Therefore, through interactions between its intracellular domain and various binding partners, including G proteins, membrane-associated APP modulates the activation of various intracellular signaling cascades.

8. Role of APP on AD pathogenesis

The involvement of APP in AD pathology is indisputable because Aβ is only generated from APP metabolic processing, and genetic alterations in *App* suffice to cause early-onset FAD. In addition, a growing body of evidence indicates that APP plays a role in neuronal degeneration in both genetic and sporadic AD. Specifically, APP appears to act as a molecular target for pathologic Aβ assemblies. Such interaction might promote neuronal degeneration though various mechanisms involving both loss and gain of APP function. Experimental evidence supporting this possibility is provided subsequently.

9. APP as a molecular target for toxic, AD-related Aβ assemblies

A direct interaction between Aβ fibrils and the ectodomain of APP has been demonstrated using a variety of experimental conditions (Lorenzo et al., 2000; Melchor et al., 2000; Wagner et al., 2000). In contrast with fibrillar Aβ, monomeric Aβ peptide does not bind APP (Lorenzo et al., 2000; Melchor and Van Nostrand, 2000; Wagner et al., 2000), suggesting that conversion of monomeric Aβ into toxic amyloid fibrils is required for binding to APP. The potential pathologic relevance of these observations is suggested by reports showing accumulation of APP at the proximity of fibrillar neuritic Aβ plaques in AD brains and in congophilic blood vessels of brains affected by hereditary cerebral hemorrhage with amyloidosis—Dutch type, an AD-related pathology (Rijal Upadhaya et al., 2012; Rozemuller et al., 1993). However, experimental work is required to evaluate whether an interaction with Aβ promotes the pathologic accumulation of APP in degenerating neurons in vivo.

Two sequences have been identified on APP that mediate its binding to Aβ fibrils. One is located within the N-terminus of APP and encompasses amino acids 18–119, with His110, Val112, and Ile113 being critical for this binding (Van Nostrand et al., 2002). This 18–119 sequence appears to be relevant for binding of Aβ fibrils to sAPP, rather than holo-APP (Kedikian et al., 2010; White et al., 2003). Consistent with this possibility, it was found that sAPP is sequestered by Aβ fibrils from the media of cultured cells (Heredia et al., 2004), an event that might interfere with the normal trophic functions of sAPP and/or its modulatory role in holo-APP dimerization. A second sequence was mapped to the extracellular juxtamembrane Aβ domain (Shaked et al., 2006; Sola Vigo et al., 2009), which mainly mediates binding of membrane-anchored holo-APP to Aβ fibrils (Kedikian et al., 2010). Interestingly, no sequence homology exists between the 2 Aβ-binding sequences of APP mentioned previously. Interestingly, synthetic peptides corresponding to these sequences aggregate and form fibrils in vitro (Hilbich et al., 1993; Rochet and Landsbury, 2000), suggesting that the binding of APP to Aβ fibrils is conformation dependent and not sequence dependent. Further supporting this notion, it was found that both holo-APP and sAPP interact with fibrils formed by amyloidogenic peptides other than Aβ, including amylin and prion peptides (Lorenzo et al., 2000; White et al., 2003). Therefore, it is likely that toxic Aβ assemblies other than fibrils could also bind APP including dimers, oligomers, or protofibrils. Additional experiments are required to elucidate the structural mechanisms underlying the interaction of APP with toxic Aβ assemblies.

10. A pathogenic feedback loop triggered by APP-Aβ interactions

The first evidence suggesting a pathogenic loop between aggregated Aβ and APP came from the observation that treatment of cultured human leptomeningeal smooth muscle cells with synthetic Aβ fibrils promotes cellular APP accumulation and enhanced Aβ secretion (Davis-Salinas et al., 1995). Additionally, it was also found that exogenously added fibrillar Aβ42 promotes APP accumulation and the formation of insoluble newly synthesized Aβ42 in HEK cells (Yang et al., 1999). More recently, it was shown that Aβ oligomers enhance the amyloidogenic processing of APP in primary neurons (Marsden et al., 2011). Interestingly, it was recently shown that cross-linking of APP with anti-APP antibody 22C11 (which recognizes an epitope at the N-terminus of APP) is sufficient to raise the levels of Aβ in viable neurons with a concomitant increase in the levels of the β-secretase BACE1 (Lefort et al., 2012). The mechanism appears to involve a sorting defect that stems from the caspase-3–mediated inactivation of a key sorting adaptor protein, namely GGA3, which prevents the lysosomal degradation of BACE1 (Lefort et al., 2012). Likely, the aforementioned mechanism is triggered by Aβ fibrils that also promote APP multimerization (Heredia et al., 2004; Lu et al., 2003; Melchor and Van Nostrand, 2000) and raise BACE1 levels (Zhao et al., 2007). Collectively, these observations suggest a pathologic, APP-dependent feed-forward process for Aβ deposition (Fig. 3). Considering that Aβ is mainly produced at synapses (Brody et al., 2008; Cirrito et al., 2005; Kamenetz et al., 2003; Lazarov et al., 2002) and its accumulation first takes place at this compartment (Capetillo-Zarate et al., 2011), the potential of APP to bind Aβ assemblies and to undergo transcytosis might help to explain the transynaptic spreading of Aβ deposition in transgenic mice and in AD (Harris et al., 2010a; Lazarov et al., 2002; Sheng et al., 2002; Thal et al., 2002). An understanding of molecular mechanisms underlying the feed-forward process between aggregated Aβ and APP will prove essential for the development of rational therapeutic interventions aimed to halt the spreading of Aβ pathology in AD.

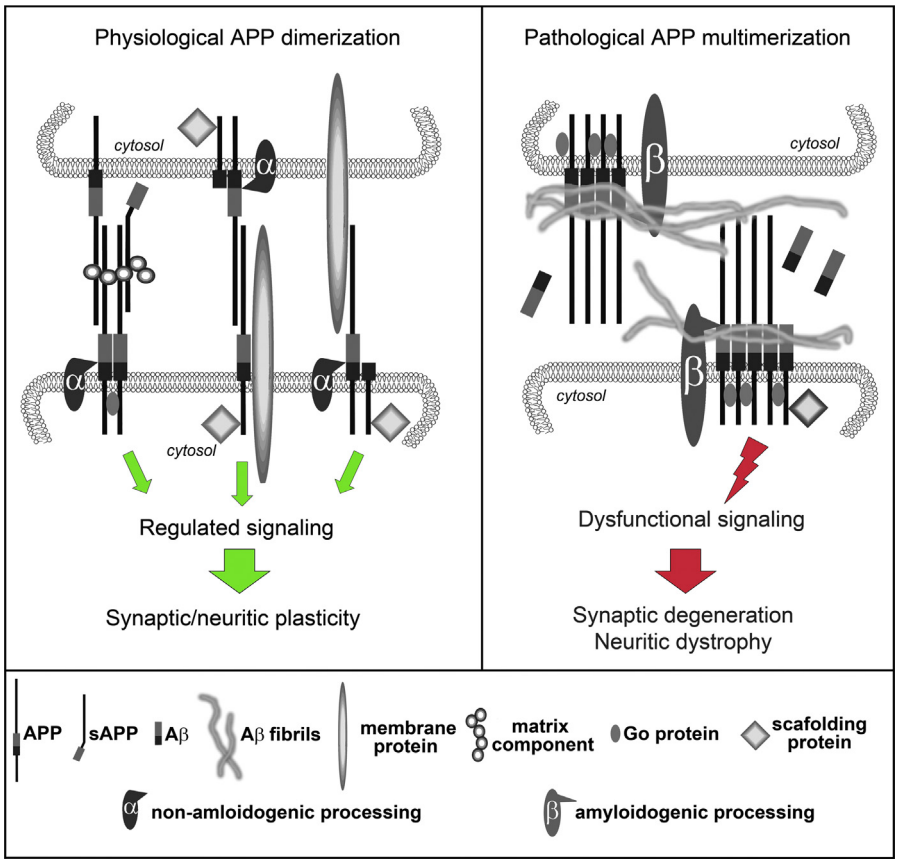

Fig. 3. Scheme representing physiological and maladaptive regulation of amyloid β precursor protein (APP) signaling and processing. In physiological conditions, the formation of *cis* and *trans* homo- and heterodimers of APP is modulated by interactions with transmembrane proteins (e.g., integrins, APLP1), extracellular secreted proteins (e.g., sAPP), or matrix components (e.g., heparan sulfate proteoglycans). These events regulate metabolic processing of APP (preferentially through the nonamyloidogenic pathway) and trigger signaling cascades that functionally modulate synaptic and neuritic plasticity. Binding of amyloid β (Aβ) fibrils to APP abrogates the interaction of APP with physiological ligands and promotes aberrant APP multimerization. These events shift the metabolic processing of APP to the amyloidogenic pathway, spreading Aβ deposition, and trigger dysfunctional signaling cascades leading to synaptic and neuritic degeneration.

11. Pathogenic pathways triggered by Aβ/APP interactions

The interaction between Aβ fibrils and APP might have pathologic relevance for neuronal degeneration. Fibrillar, but not monomeric Aβ, promotes accumulation and multimerization of holo-APP at the cell surface of diverse cell types including neurons, astrocytes, and human cerebrovascular smooth muscle cells (Lu et al., 2003; Melchor et al., 2000; Tsuruma et al., 2012; White et al., 2003). Interestingly, toxic Aβ-induced APP multimerization has been linked to pathogenic events consistent with the early loss of neuronal connectivity characteristic of AD. For example, in cultured hippocampal neurons, Aβ fibrils induced holo-APP accumulation at aberrant focal adhesion sites of dystrophic neurites (Grace and Busciglio, 2003; Grace et al., 2002; Heredia et al., 2004; Pike et al., 1992). This observation was extended to human AD brains, and brains of transgenic AD mouse models, with APP reportedly accumulating in dystrophic neurites close to fibrillar Aβ plaques (Borchelt et al., 1997; Cras et al., 1991; Ohgami et al., 1992; Phinney et al., 1999). Cultured neurons from APP-knockout mice were partially resistant to Aβ-induced toxicity (Lorenzo et al., 2000). Also, APP overexpression enhanced Aβ toxicity in cultured hippocampal neurons (Shaked et al., 2006; Sola Vigo et al., 2009), and deletion of the Aβ-binding sequences on APP abrogated both Aβ-induced APP multimerization and toxicity (Kedikian et al., 2010; Shaked et al., 2006; Sola Vigo et al., 2009). These observations strongly suggest that Aβ-induced APP multimerization promotes neuronal degeneration, consistent with the dying-back pattern of neuronal degeneration observed early in the course of AD (Kanaan et al., 2012).

Activation of caspases and neuronal apoptosis has both been proposed to play a role in AD pathology (reviewed by Hyman and Yuan, 2012). Supporting an involvement of aggregated Aβ deposition in this process, it was found that Aβ promotes caspase activation and apoptotic death of cultured neurons in vitro (Harada and Sugimoto, 1999; Ivins et al., 1999; Loo et al., 1993; Nakagawa et al., 2000; Troy et al., 2000). Aβ also promotes caspase-dependent cleavage of APP, and event resulting in the release of C31, an intracellular APP fragment with cytotoxic properties (Galvan et al., 2002; Lu et al., 2000). The toxic mechanism of C31 in cultured cells was initially linked to alterations in the transcriptional activity of AICD (Kinoshita et al., 2002). More recently, it was observed that C31 toxicity requires holo-APP expression and depends on the ability of the peptide to promote holo-APP multimerization by a yet undefined mechanism (Park et al., 2009). The relevance of caspase-mediated APP cleavage in vivo has been addressed using genetically modified mice that express a mutant version of APP (D664A) that precludes caspase-dependent generation of C31 (Galvan et al., 2006). Significantly, neither Aβ pathology nor accumulation of Aβ plaques was affected in transgenic mice expressing D664A APP along with the Swedish and Indiana FAD-APP mutations. However, several pathologic events found in the Swedish and Indiana FAD-APP double-mutant mice were prevented in these triple-mutant mice, including astrogliosis, synapse loss, defective long-term potentiation, and cognitive deficits (Galvan

et al., 2006, 2008; Saganich et al., 2006; Zhang et al., 2009). These observations suggest that pathogenic changes triggered by Aβ aggregation and/or accumulation require caspase-dependent generation of an APP fragment comprising the intracellular cytoplasmic domain. However, a recent work challenged these observations (Harris et al., 2010b), and thus, the toxic effect of C31 in vivo remains on debate (Bredesen et al., 2010).

Several observations suggest that APP modulates G proteindependent intracellular signaling. Overexpression of several FAD-APP mutations (i.e., Val642) promoted constitutively activation of heterotrimeric Go proteins (Okamoto et al., 1996), ultimately inducing apoptotic cell death in neuroblastoma cell lines (Giambarella et al., 1997; Yamatsuji et al., 1996a, 1996b). Experiments in cultured hippocampal neurons extended these results, showing that binding of Aβ fibrils to holo-APP promotes APP multimerization and trigger toxicity through a mechanism involving Go activation (Heredia et al., 2004; Sola Vigo et al., 2009). Together, these evidences suggest that APP-mediated alterations in Go signaling contribute to the toxic effects elicited by Aβ assemblies. Also, it was found that molecules that bind APP and promote its multimerization such as transforming growth factor β2 and APP-specific antibodies (i.e., 22C11) induce toxicity by a Go-dependent mechanism (Hashimoto et al., 2003, 2005; Okamoto et al., 1995; Rohn et al., 2000; Sudo et al., 2000, 2001). Additional evidence suggests that multimerization of holo-APP at the plasma membrane induces additional alterations in intracellular signaling. For example, overexpression of FAD-linked APP in primary neurons promoted apoptosis by a mechanism involving activation of Go, c-Jun N-terminal kinase (Niikura et al., 2004), and p21-activated kinase (PAK) (McPhie et al., 2003). Interestingly, in both AD brains and in FAD-APP transgenic mice, affected neurons display increased accumulation of active PAK in the surroundings of Aβ plaques (Ma et al., 2008; Zhao et al., 2006).

12. Concluding remarks and future directions

Aβ deposition is an early event in AD that precedes neuronal degeneration and cognitive decline by several years or even decades (Bateman et al., 2012; Ingelsson et al., 2004; Thal et al., 2002). Significantly, studies from various independent groups established APP as a molecular target for pathologic Aβ assemblies and a critical mediator of Aβ-induced toxicity. Based on the pathologic and experimental evidence discussed previously, we propose a model of AD pathogenesis where aggregated Aβ-induced multimerization of APP at the cell surface represents a primary pathogenic event that triggers dying-back degeneration of neurons (Fig. 3). In this model, the normal physiological role of APP as a modulator of cell-cell and cell-substratum adhesions in neurites and synapses would be compromised by its interaction with toxic Aβ aggregates. By inducing aberrant APP multimerization, Aβ aggregates would trigger aberrant intracellular signaling cascades promoting synaptic and neuritic abnormalities (Grace and Busciglio, 2003; Heredia et al., 2004; Tsai et al., 2004), cytoskeletal alterations (Busciglio et al., 1995; Heredia et al., 2006), and axonal transport defects (Brunholz et al., 2011; Pigino et al., 2009). Additionally, binding of aggregated Aβ to APP would also promote increased metabolic processing of APP through the amyloidogenic pathway, further contributing to Aβ deposition, neuritic degeneration, and synapse loss in AD.

An understanding of the mechanisms underlying APP interactions with specific Aβ assemblies might lead to the development of novel therapeutic strategies for AD. Such strategies would aim to prevent the selective APP interactions with toxic Aβ assemblies. Several important questions await experimental testing. Among these, it remains unclear whether all toxic Aβ assemblies interact with APP or induce APP multimerization. Structural studies will also be required to determine whether a conformational change in the ectodomain of APP involves binding to aggregated Aβ. This knowledge would be potentially helpful for rational therapeutic drug design. Equally important will be to address how toxic Aβ assemblies enhance the amyloidogenic processing of APP. Finally, mechanisms linking Aβ-induced APP multimerization to neuritic dystrophy, synaptic loss, and tau pathology remain to be defined (Brunholz et al., 2011). Addressing these questions might shed light into the normal physiological function of APP and its potential as a therapeutic target for AD.

Disclosure statement

The authors of this work disclose that there are no conflicts of interest of any type that could inappropriately influence the work.

Acknowledgements

This work was supported by grants from CONICET, SECyT-UNC, and ANPCyT (PICT 2010-1895) to AL and National Institutes of Health NS066942A, ALS/CVS Therapy Alliance, and Brain Research Foundation grants to GM. AL is career members of CONICET.

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