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Summary

Synaptic loss is the best correlate of cognitive deficits in Alzheimer's disease (AD). Extensive experimental evidence also indicates alterations of synaptic properties at the early stages of disease progression, before synapse loss and neuronal degeneration. A majority of studies in mouse models of AD have focused on post-synaptic mechanisms, including impairment of long-term plasticity, spine structure and glutamate receptor-mediated transmission. Here we review the literature indicating that the synaptic pathology in AD includes a strong presynaptic component. We describe the evidence indicating presynaptic physiological functions of the major molecular players in AD. These include the amyloid precursor protein (APP) and the two presenilin (PS) paralogs PS1 or PS2, genetically linked to the early-onset form of AD, in addition to tau which accumulates in a pathological form in the AD brain. Three main mechanisms participating in presynaptic functions are highlighted. APP fragments bind to presynaptic receptors (e.g. nAChRs and $GABA_B$ receptors), presenilins control Ca^{2+} homeostasis and Ca^{2+}-sensors, and tau regulates the localization of presynaptic molecules and synaptic vesicles. We then discuss how impairment of these presynaptic physiological functions can explain or forecast the hallmarks of synaptic impairment and associated dysfunction of neuronal circuits in AD. Beyond the physiological roles of the AD-related proteins, studies in AD brains also support preferential presynaptic alteration. This review features presynaptic failure as a strong component of pathological mechanisms in AD.

Introduction

Alzheimer's disease (AD), a neurodegenerative disorder that afflicts over 35 million people throughout the world, is characterized by memory loss and progressive cognitive decline. The characteristic neuropathological hallmarks of AD include amyloid plaques composed of extracellular deposits of Aβ peptides, and neurofibrillary tangles formed by hyper-phosphorylated tau, which progressively worsen over the course of the disease. Most AD cases are sporadic and of unknown etiology; however, in rare familial forms of AD (1-5% of the cases), mutations identified in the genes for the amyloid-precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2) are causal to the disease. Because there is currently no treatment to prevent or reverse the disease, it is essential to continue exploring the diverse possible causes of AD. Among these causes, clinical and neuropathological studies have indicated that synaptic loss correlates strongly with the cognitive deficits seen in AD (DeKosky and Scheff, 1990; Scheff et al., 2007; Selkoe, 2002; Terry et al., 1991).

The implication of synaptic loss or synaptic dysfunction in the etiology of AD has been the subject of intense investigation, mainly using animal models of the disease (Forner et al., 2017; Marchetti and Marie, 2011). Notably, studies exploring the relationship between Aβ peptides, tau, and synaptic deficits and/or loss, have established molecular and physiological mechanisms relevant for memory and cognitive decline characteristic of AD. In addition, both Aβ and tau likely have physiological roles at the synapse. How Aβ oligomers affect synaptic transmission and post-synaptic plasticity (long-term potentiation and long-term depression) has been the subject of recent debates (see (Forner et al., 2017; Spires-Jones and Hyman, 2014)). In physiological conditions, tau is mainly an axonal protein which regulates microtubule stability and thus axonal transport. In AD, tau is hyper-phosphorylated and deposited in intracellular tangles, and pathological tau may lead to synaptic dysfunction by impairing cellular transport of important synaptic molecules at pre- and postsynaptic sides (A. Ittner and L. M. Ittner, 2018).

Altogether, our knowledge of the implication of Aβ peptides and tau in synaptic dysfunction, and the link between these two elements has increased significantly over the past years (A. Ittner and L. M. Ittner, 2018; Marchetti and Marie, 2011; Spires-Jones and Hyman, 2014), but many major questions remain. A majority of the studies have dealt with postsynaptic receptors and dendritic mechanisms, as well as postsynaptic forms of synaptic plasticity. There is however increasing evidence that AD is accompanied with deficits in presynaptic mechanisms and presynaptic forms of plasticity. Impairment of presynaptic mechanisms is expected to greatly influence the activity of neural circuits and can potentially participate in network hyperactivity as observed in mouse models of AD (Busche et al., 2008; Verret et al.,

2012) and in AD patients (Bakker et al., 2012; Vossel et al., 2017), in particular by disrupting the excitatory/inhibitory synaptic balance (Zemin Wang et al., 2017). Although limited as compared to the post-synaptic counterpart, experimental evidence indicates that specifically interfering with presynaptic plasticity *in vivo*, influences memory processes (Monday et al., 2018). For instance, impairment of presynaptic long-term potentiation (LTP) at hippocampal mossy fiber synapses by genetic deletion (e.g in PACAP1, Rim1α, RAB3A, AKAP7 knock-out mice), correlates with memory deficits (Otto et al., 2001; Powell et al., 2004; Ruediger et al., 2011).

Here we will first present studies exploring the physiological function of proteins associated with AD, including APP (and APLP), BACE1, ADAM10 and presenilin which participate in APP processing, the enzymatic cleavage products of APP, and finally the microtubule associated protein tau. We will also review a series of recent findings which demonstrate that synaptic dysfunction in AD pathology comprises a strong presynaptic component.

APP and APP cleavage in presynaptic mechanisms and plasticity

Abundance of APP and APP cleavage machinery in presynaptic terminals and synaptic vesicles

APP and the two paralogs APP-like proteins APLP1 and APLP2, are abundant proteins of the endoplasmic reticulum (ER) and trans-Golgi network (TGN) of neurons (Haass et al., 2012), hence highly expressed at the level of neuronal somata. In addition, the three paralogs are present at the synaptic level (see summary of their locations in Table 1). The synaptic localization of APLP1 is quite specific to the post-synaptic density (PSD), in rat, hamster and human (Kim et al., 1995). APP and APLP2 can be found both at pre- and post-synaptic sites in both the peripheral and central nervous system (Müller et al., 2017), although only a small fraction of APP is found in the PSD (Kim et al., 1995). APP is in fact an abundant protein of presynaptic boutons where it has been estimated to represent close to 1% of presynaptic proteins, with circa 6,000 molecules per "average" bouton (Wilhelm et al., 2014). Moreover, APP is a key protein partner of a multitude of presynaptic proteins of SV machinery as revealed by its brain proteome (Kohli et al., 2012).

Somatic APP is transported to presynaptic compartments via fast anterograde axonal transport (Koo et al., 1990; Sisodia et al., 1993) (Fig. 1A), at a speed slowed down by mutations of PS which are linked to the familial forms of AD (Gunawardena et al., 2013; Lazarov et al., 2007). APP is transported in vesicles associated primarily with kinesin-1C which contain SNARE proteins (such as VAMP2, SNAP25, and syntaxin-1b) and synapsin-I, as well as a subset of components of the active zone (Szodorai et al., 2009). The subcellular

localization of APP within presynaptic compartments is still debated; APP has been either proposed to be enriched within synaptic vesicles (SV) (Groemer et al., 2011; Lundgren et al., 2015), within the active zone (Laßek et al., 2013), or even at the cell surface outside the active zone (Wilhelm et al., 2014). Within presynaptic terminals, APP is detected in only a subgroup of SVs, as revealed by biochemical analysis from purified vesicle fractions, as well as by immunogold electron microscopy (Groemer et al., 2011; Wilhelm et al., 2014). APP is also found in Rab5 positive endosomes distinct from SVs (Ikin et al., 1996) (Fig. 1A). While APP can reach presynaptic terminals as a full-length protein, a large fraction of presynaptic APP exists under N-terminal-truncated forms, i.e. APP-CTFs (Barthet et al., 2018; Buxbaum et al., 1998; Lundgren et al., 2015) (Fig. 1C).

Understanding the physiological role of APP in presynaptic function requires to first identify which of the proteases processing APP and which APP fragments are present in presynaptic compartments. The processing of APP involves several alternative pathways involving distinct proteases located in different subcellular compartments (Haass et al., 2012). APP at the cell surface can undergo a "non-amyloid" sequential processing whereby the alpha-secretase ADAM10 (a desintegrin and metalloprotease 10) cuts within the extracellular juxtamembranous sequence, releasing α-CTF, a 83 amino-acid (a.a.) long transmembrane fragment, and sAPPα, a soluble extracellular fragment (Haass et al., 2012) (Fig. 1B). Alternatively, full-length APP can undergo an amyloidogenic sequential processing, whereby APP endocytosed from the cell surface to Rab5-positive early-endosomes collides with BACE1 (β-secretase-site APP-cleaving enzyme) (Das et al., 2013; Rajendran et al., 2006) (Fig. 1A). APP cleavage by BACE1 consists in the shedding of the ectodomain of APP 28 amino-acids above the membrane, i.e. 99 amino-acids away from the cytosolic C-terminal, releasing the transmembrane β-CTF fragment (Vassar et al., 2014) (Fig. 1B). β-CTF is further cleaved by γ-secretase, a complex intramembrane protease comprising 4 subunits, nicastrin (NCT), APH1, Pen-2 and presenilin (PS), the catalytic subunit of this enzyme (Barthet et al., 2012). The γ-secretase initially performs an endoproteolysis of APP-βCTF at the ε-sites (50 amino-acids away from the cytosolic C-terminal) to release the APP IntraCellular Domain (AICD) in the cytosol and long Aβ peptides which span the membrane (Haass et al., 2012). The γ-secretase completes its action by a carboxy-proteolysis of the long Aβ peptides into shorter ones that are released out of the membrane.

BACE1 shows a remarkable accumulation in the hippocampal mossy fiber bundle (Hitt et al., 2012; Laird et al., 2005), as well as in the axon terminals of olfactory sensory neurons (OSN) within the olfactory bulb glomeruli (Cao et al., 2012; Rajapaksha et al., 2011). At the ultrastructural level, BACE1 immunoreactivity is high in the large presynaptic mossy fiber

terminals within CA3, possibly present in vesicles or endosomes (Cao et al., 2012; Rajapaksha et al., 2011) (Fig. 1A), some in close proximity of synaptic active zones (Kandalepas et al., 2013). Beyond the strikingly high immunolabeling of BACE1 in hippocampal mossy fibers, BACE1 is also expressed throughout the hippocampus and the brain (Laird et al., 2005), where it colocalizes with the presynaptic marker synaptophysin, but not with the postsynaptic marker MAP2 in CA3 and in CA1. This is in line with the high enrichment of BACE1 in purified synaptic vesicles from rat brain (Lundgren et al., 2015). Overall, these experiments all indicate that a large proportion of BACE1 in the brain is localized within presynaptic terminals.

BACE1 substrates not only include APP, APLP1 and APLP2, but also a large variety of transmembrane proteins (Vassar et al., 2014). BACE1 localization in axons and axon terminals is consistent with the fact that molecules involved in axon guidance, neurite outgrowth, and synapse formation are BACE1 substrates (Vassar et al., 2014). Axon guidance of hippocampal mossy fibers and OSN axons is impaired in BACE1 deficient mice (Cao et al., 2012; Hitt et al., 2012; Rajapaksha et al., 2011). The processing of the axon guidance molecule CHL1, leading to the release of a soluble CHL1 ectodomain may have an important signaling role in axon guidance (Hitt et al., 2012).

In contrast to BACE1, ADAM10 predominantly displays postsynaptic expression (Lundgren et al., 2015; Malinverno et al., 2010; Marcello et al., 2007; Prox et al., 2013; Suzuki et al., 2012). The list of identified ADAM10 substrate candidates however comprises a variety of adhesion molecules which can be present in presynaptic/axonal compartments such as Neurexin or L1 (Kuhn et al., 2016), in addition to APP.

PS1 and PS2, which form the catalytic subunit of γ-secretase (Fig. 2A), are expressed throughout the brain (Kovacs et al., 1996; M. K. Lee et al., 1996), and the proteins have been detected using both immunolabeling (Kovacs et al., 1996; M. K. Lee et al., 1996), and *in situ* detection of radiolabeled selective ligands (Yan et al., 2004). Both approaches show widespread distribution of PS in the brain and provide evidence for expression in presynaptic terminals, in the cerebellum, in hippocampal mossy fiber terminals and olfactory bulb. Interestingly, while PS1 and PS2 exhibit redundant proteolytic functions, they remarkably differ in their subcellular distribution. Indeed, PS2 is mostly expressed in late endosomes and lysosomes while PS1 has a more ubiquitous distribution pattern and is the only isoform to be present at the cell surface (Meckler and Checler, 2016; Sannerud et al., 2016). This pattern may explain why only PS1 is able to cleave N-cadherin, a cell surface adhesion protein (Barthet et al., 2011). The presynaptic localization of PS1 close to the active zone, has been demonstrated by immunolabelling at the ultrastructural level (Kuzuya et al., 2016; Ribaut-Barassin et al., 2000). Super-resolution microscopy (STED and STORM imaging), and a

probe that binds selectively to γ-secretase further confirmed that the active enzyme is present in both the pre- and postsynaptic compartments in primary cultured neurons (Schedin-Weiss et al., 2016). Finally, PS1 interacts with synaptotagmin 1 (Syt1), a Ca^{2+} sensor essential for synaptic vesicle (SV) exocytosis (Kuzuya et al., 2016).

Role of APP and proteolytic fragments in synaptic release and presynaptic plasticity

Insights into the physiological functions of APP and the related APLP proteins (recently reviewed in (Müller et al., 2017)) mainly arise from engineered mouse mutants, including constitutive and conditional single knockout (ko) and double ko mice, and from several knock-in mouse lines. When analyzing synaptic function in mature circuits, these approaches are arguably challenged by developmental consequences linked to the absence of APP during the establishment of synaptic connectivity and during synaptogenesis. Most importantly, single gene-ko approaches of APP, APLP1 and APLP2 have often failed to reveal major phenotypes *in vivo* because of partially overlapping functions and functional compensation, necessitating to systematically knock out APP and the APLPs (Müller et al., 2017). Here we focus on the evidence for a role of APP, APLP proteins and their proteolytic fragments in presynaptic function and plasticity (see summary of their functions in Table 1).

APLP1-ko mice display lower basal synaptic transmission, likely resulting from a reduced spine density (Schilling et al., 2017) in line with a well documented function of APLP1 in synaptic adhesion (Mayer et al., 2017; Schilling et al., 2017). Besides, no specific involvement in presynaptic mechanisms has been reported to date. A role of APP and APLP2 has been clearly identified at the neuromuscular junction (NMJ) (P Wang, 2005; Zilai Wang et al., 2009). $APP^{-/-}$, $APLP2^{-/-}$ and $APP^{-/-}/APLP1^{-/-}$ mice are viable, whereas $APP^{-/-}/APLP2^{-/-}$ and $APLP1^{-/-}/APLP2^{-/-}$ mice die shortly after birth likely due to major NMJ deficits (Heber et al., 2000; P Wang, 2005). The NMJs in APP-ko/APLP2-ko mice exhibit abnormal apposition of presynaptic proteins with postsynaptic AChR clusters and a dramatically reduced number of synaptic vesicles at presynaptic terminals (P Wang, 2005). Consistently, the frequency but not the amplitude of miniature end-plate potentials was markedly decreased (P Wang, 2005). It was proposed that dysregulation of the localization and activity of the high-affinity choline transporter is the primary cause for the NMJ defect in APP-ko/APLP2-ko mice, as well as at cholinergic synapses in the CNS (Baiping Wang et al., 2007). Interestingly, the NMJ phenotype can be observed by selective deletion of APP (on the APLP2-ko background) in either the postsynaptic muscle cells or the presynaptic motoneurons (Zilai Wang et al., 2009). This lends support to the notion that APP acts as a synaptic adhesion molecule, through trans-dimerization of APP family proteins (Soba et al., 2005). This role of APP as an adhesion molecule is important both during synaptogenesis and in the adult to ensure proper synaptic transmission.

In the central nervous system, localization and proteomic studies support a presynaptic role for APP (Kim et al., 1995; Kohli et al., 2012; Del Prete et al., 2014; Wilhelm et al., 2014). Yet, the analysis of constitutive APP-ko (or APLP2-ko) mice at hippocampal excitatory synapses has not provided any evidence for a change in presynaptic parameters which could account for a direct role of APP in glutamate release (Fanutza et al., 2015; Müller et al., 2017). However, mice with conditional deletion of both APP and APLP2 in excitatory forebrain neurons generated using NexCre mice, showed a robust decrease in paired-pulse facilitation at CA3-CA1 connections using short inter-stimulus intervals (Hick et al., 2015), indicative of a presynaptic defect. Short-term synaptic facilitation at CA3-CA1 synapses is also impaired in juvenile APP-ko/APLP2-ko (Fanutza et al., 2015). These data strongly suggest that APP and APLP2 regulate excitatory synaptic transmission at a presynaptic level (Fanutza et al., 2015; Hick et al., 2015) and that APLP2 can compensate for the loss of presynaptic APP function in APP-ko mice. Consistent with a presynaptic function of APP at GABAergic synapses, paired-pulse inhibition of IPSPs is attenuated in CA1 pyramidal neurons in mature APP-ko mice (Seabrook et al., 1999) and in cultured neurons (L. Yang et al., 2009). Interestingly, APP-ko mice show increased levels and activity of L-type Ca^{2+} channels ($Ca_v1.2$), and defects in paired-pulse inhibition are normalized by the pharmacological blockade of L-type Ca^{2+} channels (L. Yang et al., 2009). Although APP interacts with $Ca_v1.2$. in cellular expression systems, the mechanisms by which APP controls presynaptic levels of L-type Ca^{2+} channels is currently unknown. GABAergic synaptic transmission has not yet been analyzed in APP-ko/APLP2-ko mice. Altogether there is solid evidence for a role of APP and APLP2 in the regulation of neurotransmitter release, but additional experiments are needed to understand the precise molecular mechanisms by which APP and APLP2 fine tune release probability and presynaptic short-term plasticity at excitatory synapses. For example, a question which needs to be answered is whether APP (and APLP2) directly control the initial release probability and/or whether they play a role in presynaptic plasticity triggered by repetitive stimulations.

When studying APP function, the complex APP metabolism may be a confounding factor, since APP may act as a full-length protein, but also may act through the fragments released following the cleavage by ADAM10, BACE1 γ-secretases (Müller et al., 2017). The best characterized APP fragments which have been studied for their role in presynaptic mechanisms are the soluble ectodomains (sAPPα or sAPPβ), the APP-CTFs and the Aβ peptides.

The large ectodomain sAPPα binds to APP and/or to surface receptors which have begun to be identified. Transgenic overexpression of sAPPα rescues much of the cognitive and synaptic plasticity deficits observed in APP or APP/APLP2-ko mice (Hick et al., 2015; Richter

et al., 2018); exogenous application of sAPPα increases LTP and NMDAR currents *in vivo* in rats, improves memory and rescues LTP in aged rats (Müller et al., 2017; Weyer et al., 2011). These effects on synaptic plasticity appear to be specific for sAPPα, as incubation of sAPPβ does not rescue LTP in APP/APLP2-ko mice (Hick et al., 2015; Richter et al., 2018). This specificity likely relies on the extreme Cterminal sequence of sAPPα, a sequence absent in sAPPβ and which binds to nicotinic receptors (Richter et al., 2018). Interestingly, sAPPsα, but not sAPPβ, efficiently rescues deficits in short-term facilitation in APP/APLP2-ko mice (Richter et al., 2018), providing evidence that sAPPα exerts some of its specific enhancing effect on synaptic plasticity through presynaptic mechanisms.

APP interacts with the γ-aminobutyric acid type B receptor subunit 1a ($GABA_BR1a$), a receptor which presynaptically regulates both excitatory and inhibitory neurotransmitter release (Schwenk et al., 2015). Detailed interactome analysis has revealed that APP associates with the sushi domains of $GABA_BR1a$ subunit of the $GABA_B$ heterodimers (Schwenk et al., 2015). On the APP side, deletion mapping analysis revealed that the acidic region of the linker domain between the extracellular domain E1 and E2 is the interacting region with $GABA_BR1a$ (Dinamarca et al., 2019). APP regulates $GABA_BR1$ axonal abundance through control of its trafficking as revealed by the moderate reduction in $GABA_B$ mediated inhibition of presynaptic release observed in APP-ko mice (Dinamarca et al., 2019).

Since sAPP shares the same amino-acid sequence than the Nter region of full-length APP, it can potentially bind the same protein partners. As expected, both sAPPα and sAPPβ have been shown to interact with $GABA_B$ receptors (Rice et al., 2019). Exogenous application of both sAPPα and sAPPβ (at nanomolar concentrations) decreases the frequency of mEPSCs and of mIPSCs in mouse hippocampal cultures suggesting a presynaptic mechanisms of action (Rice et al., 2019). In line with such an action on presynaptic $GABA_B$ receptors, exogenous application of sAPP decreases the probably of release, as revealed by the enhancement of short-term plasticity at Sc-CA1 synapses (Rice et al., 2019). The interaction between sAPP and $GABA_BR1a$ receptors could in principle explain in part the effects of sAPPα on LTP, because it can lead to enhanced synaptic activation during the induction protocol. Nevertheless, in this case, it would not account for the selectivity of the effect of sAPPα vs sAPPβ. Besides, the demonstration is based on exogenous application of sAPP at nanomolar concentrations, therefore the physiological conditions under which this interaction can occur to control GABAergic and glutamatergic transmission remain to be investigated.

The impact of soluble Aβ and Aβ oligomers on synaptic transmission has been the subject of numerous studies, and the conclusions appears to depend on the concentration of the peptide in the extracellular space. Picomolar concentrations of exogenous soluble Aβ, which

are thought to reflect physiological concentrations of the peptide (Cirrito et al., 2005) positively modulate long-term potentiation at Sc-CA1 synapses, and also enhance post-tetanic potentiation (Puzzo et al., 2008) providing a first indication of an increase in neurotransmitter release by physiological concentrations of Aβ during a train of stimulation. When the degradation of endogenously released Aβ is prevented by acute inhibition of the Aβ-degrading enzyme neprilysin, the release probability is increased at individual synapses in hippocampal cultured neurons, as assessed by imaging of the activity-dependent synaptic marker FM-43, and presynaptic short-term facilitation is enhanced in a manner which follows a bell-shaped curve as a function of Aβ concentration (Abramov et al., 2009). Hence, Aβ acts as a positive regulator of release probability at hippocampal excitatory synapses (Abramov et al., 2009). This should be taken into consideration when using therapeutic agents which decrease extracellular Aβ concentration. More work is needed to clearly delineate the potential role of Aβ in regulating GABAergic transmission and to explore how APP controls excitation/inhibition balance, hence the activity of neuronal circuits.

Various mechanisms can account for the positive effects of picomolar Aβ. Pharmacological inhibition or genetic invalidation of the alpha7 subunit of nicotinic receptors which is a target of Aβ in presynaptic terminals (Lazarevic et al., 2017; Puzzo et al., 2008; 2011) prevent enhanced synaptic release by Aβ (Dougherty et al., 2003). Homodimerization of APP in the presynaptic plasma membrane, as revealed by FRET imaging, also appears to be required for the enhancement of release probability by Aβ40 monomers and dimers (Fogel et al., 2014). In cultured hippocampal neurons, Aβ40 binds to APP, increases the proportion of APP homodimers, and mediates presynaptic enhancement through activation of a Gi/o signaling pathway which tentatively boosts presynaptic Ca^{2+} transients driven by action potentials and synaptic release (Fogel et al., 2014). It is not clear whether the positive modulatory effects of Aβ participate in the physiological control of local neural circuits activity, or whether they contribute to early synaptic deficit which may eventually lead to the hyperactivity of neural networks as observed in mouse models of AD (Busche et al., 2008; Verret et al., 2012) and in AD patients (Bakker et al., 2012) (Vossel et al., 2017). Along these lines, Aβ-containing brain extracts from AD patients enhance glutamate release probability, although at the same time decrease inhibitory presynaptic release probabilities, hence disrupt the excitatory/inhibitory balance (Zemin Wang et al., 2017).

It is generally accepted that elevated Aβ concentrations (in the nanomolar to micromolar range) and aggregated Aβ species consistently inhibit synaptic transmission and long-term potentiation, albeit these studies have generated heterogeneous and contradictory results. Impairment of synaptic transmission is thought to be mediated by post-synaptic mechanisms,

involving for instance NMDA receptors (reviewed in Sheng et al., 2012). However, incubation of hippocampal cultures with Aβ40 in the nanomolar range (50-500 nM) induces a transient increase in intracellular Ca^{2+} and miniature currents, indicating an early enhancement in vesicular transmitter release, followed by a delayed reduction of the frequency of mEPSCs and of the synaptic pool of vesicles (Parodi et al., 2010). Consistently, the overexpression of APP which leads to high levels of Aβ (Quon et al., 1991), alters synaptic vesicle recycling monitored by FM destaining during extended trains of stimulation (Ting et al., 2007). Another evidence for a negative regulation of presynaptic mechanisms in hippocampal cultures comes from the use of a highly stable oligomeric Aβ complex called "Aβ 1– 42 globulomer" (at a concentration <10 nM) which suppresses both GABAergic and glutamatergic synaptic activity by reduction of vesicular release (Nimmrich et al., 2008).

Paired-pulse facilitation, taken as an index of presynaptic properties, is however not changed at Sc-CA1 synapses upon application in hippocampal slices of soluble Aβ oligomers from several sources (synthetic, cell culture, human brain extracts) (Li et al., 2009). Similarly, early changes in paired-pulse facilitation or in mEPSC frequency are not consistently observed in hippocampal slices of APP-based models of AD (Marchetti and Marie, 2011), which are thought to lead to extracellular accumulation of Aβ. In apparent contradiction, release probability was found to be decreased at Sc-CA1 synapses at an early stage in the APP/PS1 model (but see (Viana da Silva et al., 2016; 2019)), and following application of synthetic Aβ 1-42 oligomers (but not Aβ 1-42 fibrils) at high nanomolar concentration (He et al., 2019). The mechanisms underlying the pathological downregulation of neurotransmitter release is currently still rather elusive. Currently proposed mechanisms include the selective inhibition of presynaptic P/Q channels by the Aβ 1–42 globulomer (Nimmrich et al., 2008), or the impairment of SNARE complex formation and SNARE-mediated exocytosis following the interaction of intracellular Aβ oligomers with syntaxin 1A (Y. Yang et al., 2015). Recently, the mGluR5-PIP2 pathway was found to be a main target of Aβ 1-42 oligomers responsible for the diminution of Pr in hippocampal slices (He et al., 2019). Notably, inhibiting Aβ-induced depletion of PIP2 in CA3 neurons rescued Pr in APP/PS1 mice (He et al., 2019).

Overall, Aβ oligomers exert a biphasic effect on presynaptic mechanisms, with a physiological potentiation of synaptic transmission observed at low concentration (pM to low nM), and a decrease in Pr at high nanomolar concentrations of Aβ oligomers which may be pathological (Lazarevic et al., 2017). Beyond this rather simple rule, various Aβ peptide species, various assemblies of Aβ peptides, their actual concentration in the extracellular space, specific targets at different synapses may all explain the heterogeneity of results obtained. The available data may not yet be sufficient to make accurate predictions about

how changes in presynaptic parameters and plasticity will change the activity of identified neuronal networks at the different stages of the disease. A clear missing piece is an evaluation of pathological forms of Aβ peptides on the excitation/inhibition balance.

Role of PS1 and PS2 in synaptic release and presynaptic plasticity.

PS1 and PS2 have multiple substrates and functions beyond serving as a γ-secretase for the final processing of APP (Hass: 2010; Stiller: 2014) (Fig. 2A). The analysis of the function of PS1 and PS2 has mainly relied on cell type-specific conditional knockout approaches, which circumvent the lethality of constitutive knock-out mice due to misprocessing of Notch, and which control for possible compensatory mechanisms between the two orthologs (Shen, 2014). These studies have highlighted the importance of PS in the adult brain, in synaptic function and plasticity. Presynaptic, but not postsynaptic genetic inactivation of PS1 and PS2 alters short-term plasticity and synaptic facilitation at CA1-CA3 connections (Zhang et al., 2009). Similar impairments in short-term plasticity were also observed in knock-in mice with a mutation of PS1 linked to FAD (L435F) on a PS2-ko background (Xia et al., 2015), providing evidence that these FAD mutations of PS1 may act by a loss of function. Presynaptic forms of plasticity are also markedly impaired in two different mouse models with inactivation of PS1 and PS2 at mossy fiber synapses between DG cells and CA3 pyramidal cells (Barthet et al., 2018; S. H. Lee et al., 2017). The giant hippocampal mossy fiber synapses are characterized by low release probability at basal stimulation frequency, a large number of synaptic release sites and a wide dynamic range of presynaptic forms of plasticity; these include low frequency facilitation (up to 3-5Hz), train facilitation, post-tetanic potentiation and long-term potentiation (Rebola et al., 2017). Whereas the basic synaptic release properties are not affected by inactivation of PS at low frequency of stimulation, the extent of both train facilitation and PTP is markedly decreased (Barthet et al., 2018; S. H. Lee et al., 2017). Further electrophysiological analysis points to an impairment in the rate of replenishment of synaptic vesicles to the active zone (Barthet et al., 2018). Notably, inactivation of nicastrin, an indispensable component of the γ-secretase complex, also leads to deficits in presynaptic short-term plasticity including paired-pulse facilitation and train facilitation at Sc-CA1 synapses (S. H. Lee et al., 2014). These experiments performed at two distinct synaptic inputs indicate an essential role of presenilin in the regulation of transmitter release underlying short-term plasticity and indicate that γ-secretase activity is required for this presynaptic function.

There are however conflicting results with regards to the proposed mechanisms by which presenilins impact presynaptic mechanisms and plasticity, which may result from differences in experimental conditions or identity of synapses examined. At Sc-CA1 synapses, depletion

of endoplasmic reticulum Ca^{2+} stores by thapsigargin, or blockade of Ca^{2+} release from these stores by ryanodine receptor (RyR) inhibitors, mimics and occludes the effects of presynaptic presenilin inactivation (Zhang et al., 2009). In parallel, blockade of Ca^{2+} release from endoplasmic reticulum inhibits depolarization-induced Ca^{2+} elevation in the soma of hippocampal neurons (Zhang et al., 2009), suggesting that Ca^{2+} release may also be downregulated in presynaptic terminals upon inactivation of presenilins (Fig. 2A). In addition, in the absence of presenilin, the levels of RyR proteins are reduced in the hippocampus, and RyR-mediated function is impaired as indicated by the reduced Ca^{2+} release from the ER induced by RyR agonists (Wu et al., 2013). Altogether, these findings indicate that PS regulates ER Ca^{2+} homeostasis and suggest that the presynaptic role of presenilin is explained by its regulation of RyRs at Sc-CA1 synapses.

Distinct mechanisms are at play at hippocampal mossy fiber synapses, for which short-term presynaptic plasticity, including paired-pulse facilitation (PPF), does not depend on Ca^{2+} induced Ca^{2+} release (Carter et al., 2002). In the soma of dentate granule cells, the presynaptic neurons to mossy fibers, inactivation of presenilin disrupts Ca^{2+} signals evoked by depolarization (S. H. Lee et al., 2017). Moreover, inhibition of Ca^{2+} release from somatic mitochondria mimics and occludes the decreased somatic Ca^{2+} signal observed in the absence of presenilin, providing an indirect suggestion that dysregulation of Ca^{2+} signaling by mitochondria in presynaptic mossy fiber boutons may contribute to the impairment of presynaptic plasticity in the absence of presenilin (S. H. Lee et al., 2017). More direct evidence for a different mechanism which involves a loss of presynaptic Syt7 has been recently provided (Barthet et al., 2018). Genetic deletion of presynaptic presenilin markedly and selectively decreases the expression of the Ca^{2+} sensor synaptotagmin-7 (Syt7) in mossy fiber synaptic terminals (Barthet et al., 2018); Syt7 is essential for presynaptic facilitation (Jackman et al., 2016) and re-expression of Syt7 in presenilin deficient synapses rescues synaptic facilitation and replenishment of release-competent synaptic vesicles (Barthet et al., 2018). The molecular mechanism involves APP-βCTF, which interacts with Syt7 and accumulates in synaptic terminals under conditions of pharmacological or genetic inhibition of γ-secretase (Barthet et al., 2018) (Fig. 2B). Hence, presenilin plays a major role in presynaptic plasticity at excitatory synapses in the hippocampus, and it would be interesting to extend these investigations to other brain regions and to inhibitory synapses, and test whether presynaptic dysfunction in the absence of presenilin affects excitatory/inhibitory balance and the activity of neuronal circuits.

BACE1 and ADAM10

A role for BACE1 in the regulation of transmitter release and in presynaptic plasticity has been reported. A consistent decrease in the probability of release in BACE1-ko mice, inferred from an increased paired-pulse facilitation has been documented by various labs (Laird et al., 2005, Wang et al., 2008, 2014; Hartmann et al., 2018). In BACE1-ko mice, PPF is increased at Sc-CA1 synapses (Laird et al., 2005) and at mossy fiber synapses onto CA3 pyramidal cells (Hui Wang et al., 2014; 2008). In addition presynaptic mossy fiber LTP is abolished in BACE1-ko mice; this defect can be rescued by simply increasing extracellular Ca^{2+} concentration during LTP induction (Hui Wang et al., 2008), suggesting that presynaptic Ca^{2+} regulation contributes to the loss of presynaptic LTP, although it is not clear whether this is involved in the control of release probability or of presynaptic plasticity mechanisms. Brief activation of α7 nicotinic receptors by nicotine restores PPF ratio and mossy fiber LTP to wild-type levels at mossy fiber synapses in BACE1-ko mice, but does not increase basal synaptic transmission (Hui Wang et al., 2010). This contradicts however the notion that an increase in paired-pulse facilitation in BACE1-ko mice is linked to a decreased Pr, and rather correlates with a role of BACE1 in short-term plasticity in response to repetitive stimulation. This presynaptic function of BACE1 may be related to the proteolysis of APP and/or APLP2, as no major protein of the presynaptic release machinery has yet been identified as a BACE1 substrate (Dislich et al., 2015). Whether these presynaptic consequences of the inactivation of BACE1 can be explained by the expected reduction in Aβ levels on glutamate release remains to be determined.

BACE1 may also have a number of additional interactors in presynaptic terminals. For instance, BACE1 regulates the cAMP/PKA pathway, which is essential for presynaptic LTP at hippocampal mossy fiber synapses (Monday et al., 2018), independently of APP processing (Chen et al., 2012). Rather unexpectedly, BACE1 exerts physiologically significant effects in the regulation of voltage-gated sodium and potassium channels through either enzymatic or non-enzymatic activity (Lehnert et al., 2016). At the presynaptic level, BACE1 directly interacts with a K^+ channel (Kv3.4) involved in the repolarization of presynaptic action potentials at mossy fiber synapses (Hartmann et al., 2018). Through this physical interaction rather than enzymatic activity, BACE-1 promotes the expression of Kv3.4 channels at synaptic terminals, and consequently may participate in the control of action potential-evoked release of glutamate at this synapse (Hartmann et al., 2018). Thus, the regulation of ion channels and of neuronal excitability needs to be taken into consideration when interpreting potential presynaptic effects of BACE1 inhibition or genetic deletion.

In agreement with a predominant post-synaptic expression of ADAM10, its postnatal disruption in the brain does not lead to any distinct presynaptic phenotype at Sc-CA1

synapses, although severe defects in synaptic plasticity and behaviour are observed (Prox et al., 2013). ADAM10 may however play a role as a presynaptic protein at a stage of synaptogenesis and synaptic maturation by interacting with neurexin (Kuhn et al., 2016).

Tau in presynaptic mechanisms and plasticity

Tau in relation to synaptic dysfunction

Neurofibrillary tangles (NFTs), which constitute one of the neuropathological hallmark of AD, are composed of intracellular filamentous aggregates of hyperphosphorylated tau (Grundke-Iqbal et al., 1986). In physiological conditions, tau, a microtubule-binding protein (Fig. 3), is primarily an axonal protein that regulates microtubule stability and axonal transport (Yipeng Wang and Mandelkow, 2015). It has been reported that synaptic dysfunction and abnormalities in axonal transport precede the formation of NFTs and neuronal death in tauopathies (Polydoro et al., 2014). Soluble tau, rather than the aggregated tau forming the neurofibrillary tangles, is thought to be the main toxic element that is able to induce early synaptic deficits preceding synapse and neuronal loss (Sheng et al., 2012; Yipeng Wang and Mandelkow, 2015). Pathological tau is detected in isolated synaptosomes from AD patient brains where it colocalizes with both pre- and post-synaptic markers (Fein et al., 2008; Sokolow et al., 2015; Tai et al., 2014). Pathological hyperphosphorylated tau, present at presynaptic terminals of AD patient brains but not of healthy controls (Zhou et al., 2017) binds to synaptic vesicles (McInnes et al., 2018).

In physiological conditions, tau plays a role as a microtubule stabilizer and does not directly participate in presynaptic mechanisms (Yipeng Wang and Mandelkow, 2015). Accordingly no apparent presynaptic deficit is observed in MAPT-ko mice at CA3-CA1 synapses, albeit contradictory results were reported with regards to long-term synaptic plasticity (Kimura et al., 2013) (Ahmed et al., 2014). It should be noted however that the lack of a synaptic phenotype in MAPT-ko mice might be explained by compensatory mechanisms involving other microtubule-associated proteins (Ma et al., 2014). Tau undergoes post-translational changes, such as phosphorylation, which can lead to the detachment of tau from microtubules and accumulation in cellular compartments such as dendrites and presynaptic terminals in pathological conditions (Yipeng Wang and Mandelkow, 2015). In a transgenic mouse model in which pro-aggregant tau (tau mutation ΔK280) is overexpressed, hippocampal mossy fiber synapses display morphological and functional presynaptic deficits, including a marked impairment in short-term frequency facilitation, and post-tetanic potentiation as well as in presynaptic long-term depression and potentiation in middle-aged mice (this was not observed in 2 month-old mice) (J. M. Decker et al., 2015; Sydow et al., 2011). Notably,

morphometric and ultrastructural analysis of mossy fiber boutons in transgenic mice expressing pro-aggregant tau demonstrated an increase in bouton diameter (by +42%), and a severe reduction of synaptic vesicle density (J. M. Decker et al., 2015). In these mice, presynaptic deficits appear to correspond to a progressive neurodegenerative process which leads to presynaptic dysfunction, rather that demonstrating a direct effect of tau mutants on presynaptic mechanisms. In rTgtauΔC transgenic mice, in which P301L mutant human tau is overexpressed primarily in the entorhinal cortex, presynaptic deficit indicative of changes in the probability of neurotransmitter release are observed at perforant-path synapses to DG cells, at an age prior to the development of neurofibrillary tangles (Polydoro et al., 2014). In addition to the pathological impact of the insoluble forms of tau, it is important to note that soluble tau may also participate in the pathology by decreasing synapse number and depleting synaptic vesicles when being abnormally present in the extracellular space (Bolos et al., 2017). A recent studies has demonstrated that pathological tau binds to synaptic vesicles via its N-terminal domain *in vitro* and *in vivo* in both drosophila and rodents (Zhou et al., 2017). Expression of pathogenic tau mutants significantly impairs vesicle release during sustained high frequency stimulation, leading to a smaller pool of active vesicles and to decreased synaptic transmission compared to controls or animals expressing wild type tau (Zhou et al., 2017). The binding of tau to the transmembrane vesicle protein synaptogyrin-3 (Liu et al., 2016) is the molecular interaction necessary for the association of tau with synaptic vesicles (McInnes et al., 2018) (Fig. 3). Reduction of synaptogyrin-3 rescues presynaptic dysfunction induced by pathological tau at the neuromuscular junction in drosophila and in mouse hippocampal neurons (McInnes et al., 2018). It is proposed that pathological tau, when it is present presynaptically, binds to vesicles through synaptogyrin-3 and polymerizes presynaptic actin using its proline-rich and microtubule-binding domains, thereby impeding the mobilization of synaptic vesicles during repetitive stimulations (Zhou et al., 2017).

In addition to the roles at the presynaptic terminals described above, tau regulates presynaptic plasticity through a more distal presynaptic location. Indeed, a role of tau in the regulation of axon initial segment (AIS) length and plasticity has been recently reported (Sohn et al., 2019). A pathogenic mutant of tau (V337M) shortens the AIS and prevents the activity-dependent remodeling of its cytoskeleton. The mechanism involves the accumulation of the microtubule plus-end tracking protein EBP3 (end-binding protein 3) in the AIS and leads to hyperactivity in response to chronic depolarization.

Tau and APP as regulators of axonal transport to presynaptic terminals

The observation that APP and tau, two main molecular actors of AD, are presynaptic proteins raises questions about their possible functional interaction. APP undergoes fast

anterograde transport along axonal microtubules (Koo et al., 1990; Sisodia et al., 1993), a process which is altered in the context of AD pathology (Stokin et al., 2005). The stabilization of microtubules by tau indicates a theoretical regulation of APP transport by tau, at least indirectly. An early study reported that viral overexpression of tau in N2a cells inhibits APP transport leading to the accumulation of some immobile APP-containing vesicles in the soma (Stamer et al., 2002). tau exists under different splicing isoforms; the variants containing 3 or 4 repeats of microtubule binding domains (3R- or 4R-tau) being the most abundant in the adult brain (Yipeng Wang and Mandelkow, 2015). The modification of the relative abundance of the 3R/4R splice variants impairs both anterograde and retrograde APP transport leading to an increase proportion of immobilized APP-positive vesicles (Lacovich et al., 2017). The functional interaction between tau and APP in relation to axonal transport is also exemplified by the report that FAD APP mutant (K670N/M671L plus V717F) reverses the effect of tau P301L on anterograde transport. Indeed, while tau P301L enhances the anterograde transport of mitochondria (Fig. 3), its co-expression with APP K670N/M671L; V717F reduces it (Adalbert et al., 2018). Conversely, the expression of WT tau but not R406W mutant tau rescues the reduction of axonal transport assessed by MRI in APP-KO mice (Smith et al., 2010). Overall, these data not only indicate that tau regulates APP transport but also that tau and APP influence each other's role in axonal transport. Whether the proteolysis of APP is involved in this mutual influence remains to be examined. Along these lines, it has been reported that the absence of PS combined with the expression of human tau in mice impairs axonal transport and exaggerates tau pathology (Peethumnongsin et al., 2010). Moreover, alteration of APP metabolism through APP mutations or pharmacological inhibition of γ-secretase enhances the amount of tau (Moore et al., 2015).

Presynaptic Ca^{2+} handling in relation to AD

The regulation of presynaptic Ca^{2+} is an essential component of presynaptic release mechanisms and of presynaptic forms of synaptic plasticity (Regehr, 2012). Dysregulated Ca^{2+} handling is considered a contributing factor to AD, with a particular role for the regulation of cytosolic Ca^{2+} by the smooth ER (Stutzmann and Mattson, 2011). Beyond the well-known link between increased cellular Ca^{2+} levels and neurodegenerative processes (LaFerla, 2002), impaired Ca^{2+} regulation also impacts on synaptic function and plasticity, especially at a presynaptic level. There is now strong evidence that Ca^{2+} uptake into presynaptic ER driven by neuronal activity is critical for synaptic function and that this controls release probability (de Juan-Sanz et al., 2017). In several cellular models, mutant presenilin was shown to affect ER Ca^{2+} signaling (Stutzmann and Mattson, 2011; Wu et al., 2013; Zhang et al., 2009). These experiments suggest that dysregulation of Ca^{2+} homeostasis may lead to presynaptic dysfunction in AD. A role of PS on presynaptic Ca^{2+}

handling in animal models of AD is further exemplified in the neocortex in vivo (Lerdkrai et al., 2018). The hyperactivity of cortical neurons in APP/PS1 and in PS1(P45) mutant mice can be explained by a dysfunction of intracellular Ca^{2+} stores within presynaptic boutons, likely mediating heightened neurotransmitter release (Lerdkrai et al., 2018).

Mitochondria, dynamic organelles that generate ATP are also key players in intracellular Ca^{2+} homeostasis (Giorgi et al., 2018). Deficits in Ca^{2+} handling by presynaptic mitochondria may partly explain impaired presynaptic plasticity in the context of AD (Devine and Kittler, 2018). Accumulation of wild-type or arctic form Aβ1-42 expressed in a small group of neurons in the adult fly induces an initial depletion of presynaptic mitochondria, independently of axonal transport, and increases neurotransmission failure (Zhao et al., 2010). At hippocampal mossy fiber synapses, mitochondria contribute to the build-up of residual Ca^{2+} in the giant mossy fiber boutons, and participate in a post-tetanic potentiation (PTP), a form of presynaptic plasticity triggered by high frequency bursts of stimulation (D. Lee et al., 2007). Indirect evidence suggest that Ca^{2+} handling by presynaptic mitochondria may be impaired in the absence of PS (S. H. Lee et al., 2017). However, quantitative EM analysis did not reveal any structural changes in presynaptic mitochondria between control and PSKO mossy fiber synapses (S. H. Lee et al., 2017). Whether and how PS controls the activity of presynaptic mitochondria remains to be established. The localization of mitochondria to presynaptic compartments, through anterograde transport from the soma is under the influence of tau (Fig. 3). Overexpression of tau alters fast axonal transport resulting in impaired anterograde trafficking of mitochondria, among other organelles, to axons in cultured neurons (Stoothoff et al., 2009), as well as in a mouse model of AD (Kopeikina et al., 2011). A marked decrease in axonal trafficking of dense-core vesicles and mitochondria, is also observed in neuronal cultures by live imaging of fluorescent protein-tagged organelles in the presence of high amounts of soluble oligomers of the Aβ peptide (H. Decker et al., 2010). The link between altered trafficking of mitochondria to axon terminals and presynaptic dysfunction in AD needs to be further investigated.

Presynaptic failure in AD, evidence from human studies.

What is the evidence, beyond animal studies, for the contribution of a presynaptic failure component in AD pathology? Post-mortem studies have shown that alteration of synaptic markers (Terry et al., 1991) (Hamos et al., 1989) and synaptic loss (DeKosky and Scheff, 1990) correlate strongly with the cognitive deficits seen in AD (Selkoe, 2002). Synaptic pathology in AD represents a spectrum of alterations and pathogenic molecular cascades, spanning from minor functional alterations to irreversible synaptic loss, which can either occur at a pre- or postsynaptic level. There are however several correlative evidence

indicating that presynaptic terminals preferentially deteriorate early during the course of the disease.

A recent meta-analysis has covered more than 400 publications focusing on synapses and synaptic marker loss in postmortem tissues from patients with AD and control subjects (de Wilde et al., 2016). The study indicates that, while deficits in protein abundance is observed at both sides of synapses, the impairment is much more profound at the presynaptic site (de Wilde et al., 2016). In majority, the presynaptic proteins reduced in AD brains belong to the "calcium regulation" and "vesicle organization" categories in agreement with the functional pathways impaired in mouse models (and documented above). Intriguingly, this preference in pre vs postsynaptic alterations are remarkably more pronounced in the hippocampus (de Wilde et al., 2016). An unbiased proteomic analysis of laser-dissected molecular layer of the dentate gyrus in AD patients revealed a selective decrease in the abundance of several presynaptic proteins over postsynaptic proteins (Haytural et al., 2020). The molecular layer of the DG contains synaptic inputs from the entorhinal cortex, a pathway altered early in AD pathology. Among altered presynaptic proteins, Complexins I and II (Cpx I and II) and Synaptogyrin I were particularly affected, confirming a previous report showing that Cpx are dysregulated in AD (Ramos-Miguel et al., 2017). The dysregulation of Cpx I is particularly interesting since its variation correlates with cognitive decline in patients at early Braak stages (Ramos-Miguel et al., 2017). The role of Cpx in vesicle fusion and exocytosis is debated; Cpx appear to be key regulators of the core fusion machinery (López-Murcia et al., 2019; Scholz et al., 2019), although they could also contribute to a clamping mechanism whereby the CpxII C-terminus hinders spontaneous SNARE complex assembly (Makke et al., 2018). It is thus difficult to predict the consequences of a drop of Cpx in human synaptic circuits.

The overall decrease in presynaptic markers observed in brains or synaptic homogenates from AD patients contrasts with reports indicating accumulation of presynaptic proteins like synaptophysin in amyloid plaques or within surrounding dystrophic neurites (Kandalepas et al., 2013). Photo-tagging of amyloid plaques proteins followed by identification and quantification has led to the observation that numerous presynaptic proteins are enriched within plaques (SNAP-25, VAMP2, vATPase) while the plaques appeared to be devoid of uniquely post-synaptic proteins (Hadley et al., 2015). These indications do not necessarily support an overall increase of these proteins in AD brains, but rather highlight accumulation in discrete microscopic regions such as amyloid plaques, in contrast with the general downregulation of presynaptic proteins in brain or synaptic homogenates.

In brains from AD patients, transmission electron microscopy has revealed synapse specific deficits in the number of mitochondria, accompanied with abnormal mitochondrial

morphology in presynaptic but not postsynaptic compartments (Pickett et al., 2018). This supports the notion that axonal transport of mitochondria to synaptic terminals is an important feature to vulnerable cortical regions in AD. In early AD, dysfunctional axonal transport could lead to an early decrease of some presynaptic proteins while others accumulate in dystrophic neurites that surrounds amyloid plaques or even within the plaques, according to the "traffic jam" hypothesis of AD (Stokin et al., 2005). Thus, alteration of the trafficking of key presynaptic proteins may lead to early presynaptic dysfunction and neuronal circuit impairment. In view of the genetic evidence linking APP to AD and because the interactome of APP includes multiple presynaptic proteins, it is tempting to hypothesize that initial alteration of APP trafficking leads in turn to dysfunctional transport of key presynaptic proteins. The presynaptic compartment, and primarily presynaptic APP, may therefore represent a target for early pharmacological intervention before the pathology is too advanced.

Changes in the composition of the presynaptic proteome in AD brains may impact on the relative abundance of presynaptic proteins or peptides present in the cerebrospinal fluid (CSF) or blood plasma of AD patients. Enhanced amounts of tau and reduced amounts of Aβ in the CSF and plasma of AD patient are commonly used as standard biomarkers for the diagnostic of the disease (Fig 4). In addition, different presynaptic proteins including SNAP-25 (Brinkmalm et al., 2014), Syt1 (Öhrfelt et al., 2016), and Growth-associated protein 43 (GAP-43) (Sandelius et al., 2018) are significantly increased in the CSF of AD patients, representing a new class of biomarkers closely reflecting the early mechanism of AD pathology. The increased amount of these proteins in CSF may be a consequence of their dispersion from intracellular compartments to the extracellular space during presynaptic degeneration.

It is moreover striking that APP accumulation is a marker of axonal damage in several pathologies including multiple sclerosis (Kornek et al., 2010; Kuhlmann et al., 2002), myelopathy (Umehara et al., 2000) or upon herpes simplex encephalitis (Mori et al., 2005). The role of APP in these pathologies is unknown, but given the well documented role of APP in synapse formation (Müller et al., 2017), it is tempting to postulate a role for presynaptic APP in synapse repair. Thus, APP may relay protective physiological functions in some pathological contexts and yet be detrimental at high concentrations or in the aging brain. In view of the knowledge reviewed here, these detrimental effects could well be related to the dysregulation of key presynaptic functions.

Conclusions

Here we review accumulating evidence suggesting that key molecules implicated in the physiopathology of AD exert a wide array of presynaptic functions (Table 1). Among this variety of mechanisms, three main mechanisms can be highlighted. Firstly, APP fragments regulate synaptic transmission by binding to presynaptic receptors (e.g. nAChRs and $GABA_B$ receptors). Secondly, presenilins control Ca^{2+} homeostasis and Ca^{2+} sensors involved in presynaptic plasticity. Thirdly, tau regulates the localization and mobility of presynaptic molecules and organelles, including mitochondria and synaptic vesicles. These results clearly underline an important function of AD-related proteins in synaptic transmission and plasticity through the regulation of presynaptic mechanisms.

Alteration of presynaptic mechanisms likely participate in the hyperactivity of cortical circuits observed in the context of AD, through disruption of the excitation/inhibition balance (Zott et al., 2018). Although disruption of presynaptic mechanisms and short-term plasticity directly impacts on the activity of neural circuits in many brain areas, less is known on the role of presynaptic long-term plasticity in behavioral processes and in particular in memory processes (Monday et al., 2018). In contrast, strong evidence indicates that post-synaptic forms of plasticity, which are also impaired in models of AD, are required for memory encoding and recall (Morris, 2006). Nonetheless, it will be interesting to further investigate how impairment of presynaptic plasticity affects memory encoding and consolidation through AD-related mechanism. Most animal studies presented in this review deal with experimental approaches based on the genetic removal, or overexpression of key hallmark molecules in AD, or exogenous application of APP fragments. Although necessary, these approaches represent a notable limitation in understanding the physiopathology of presynaptic dysfunction in the human AD brain. The use of neurons derived from iPSCs and of brain organoids in the context of AD, will open the possibility of validating presynaptic mechanisms as a target for therapeutic intervention in AD progression (Gerakis and Hetz, 2019). Interestingly, recent electrophysiological studies on hiPSC-derived cerebrocortical neuronal cultures and cerebral organoids bearing AD-related mutations, show presynaptic deficits at both inhibitory and excitatory synapses in parallel with aberrant hyperexcitability (Ghatak et al., 2019).

Beyond the physiological role of the AD-related proteins, studies in human tissues from AD patients also support the notion that pathological mechanisms in AD involve a strong presynaptic component. Indeed, synapses appear to be preferentially affected at the presynaptic level in AD brains. These discoveries featuring presynaptic failure in AD could be the ground for new therapeutical strategies targeting presynaptic receptors and mechanisms.

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Figures legends

Figure 1: Presynaptic localization of APP and its proteases BACE1 and PS.

(A) Diagram of a presynapse revealing the transport of APP and subcellular localization of its proteolysis. (1) APP undergoes fast axonal transport. (2) A fraction of APP reaches the cell surface. (3) APP is transported to early endosome or recycling endosomes (RE) and to late endosomes (LE) where it can be cleaved by BACE1 and PS. (4) A fraction of synaptic vesicles (SV) contains both APP under its full-length form and β-CTF. (B) Scheme of APP proteolysis. APP is a type 1 transmembrane protein which can be cleaved sequentially by ectodomain shedding followed by intramembrane proteolysis via PS. The ectodomain shedding can be performed either by ADAM10 (α-secretase; left) or by BACE1 (β-secretase; right) releasing respectively the soluble APP-Nter fragments sAPPα or sAPPβ and the transmembrane stubs αCTF or βCTF. Their intramembrane proteolysis leads to p3 and AICD or Aβ and AICD respectively. (C) Both BACE1 and APP-βCTF are enriched in purified SV fraction (adapted from Lundgren et al., 2015).

Figure 2: Various presynaptic functions of PS.

(A) (1) PS is the catalytic subunit of γ-secretase intramembrane protease. It cleaves various substrates including presynaptic proteins like neurexin. (2) APP-βCTF is the direct substrate of PS. It interacts with synaptotagmin 7 (Syt7). By controlling APP-βCTF amount, PS controls the availability of Syt7 to dynamically regulate the pool of releasable synaptic vesicles (SV). (3) PS also regulates Ca^{2+} homeostasis via endoplasmic reticulum ryanodine receptor (RyR). This regulates presynaptic short-term plasticity at Schaffer collaterals. (B) Pharmacological inhibition of PS proteolytic function leads to the accumulation of APP-βCTF observed in homogenates. A parallel decrease of the amount of Syt7 is observed. (C) Presynaptic genetic invalidation of PS also leads to the accumulation of APP-βCTF in presynaptic compartments. This leads to a remarkable decrease in the amount of Syt7. (B) and (C) are adapted from Barthet et al., 2018.

Figure 3: Role of Tau in axonal transport and regulation of synaptic vesicles.

(1) Tau is a microtubule associated protein involved in their stabilization. (2) As a consequence, Tau regulates the axonal transport of various molecules and organelles including APP and mitochondria. (3) Tau also associates with synaptogyrin-3, an integral synaptic vesicle (SV) protein leading to a decreased mobility of SV which in turns impact synaptic transmission.

Figure 4: Presynaptic failure in AD pathology.

(1) Tau aggregates intracellularly under the form of fibrils. (1') Its increased concentration in both cerebrospinal fluid (CSF) and plasma is used as a biomarker. (2) BACE1 strongly accumulates in dystrophic neurites. (3) This may participate in dysregulated Aβ production. (3') The decreased concentration of circulating Aβ in CSF and plasma is used as a standard biomarker in AD. (4) The level of some key presynaptic proteins like synaptogyrin-1 and complexin is decreased in AD. (5) Strikingly, the amount of some other presynaptic proteins (including synaptotagmin-1/4, synaptophysin, SNAP-25, VAMP2, vATPase...) increases in situ and/or (5') in the extracellular fluids.

Figure 1

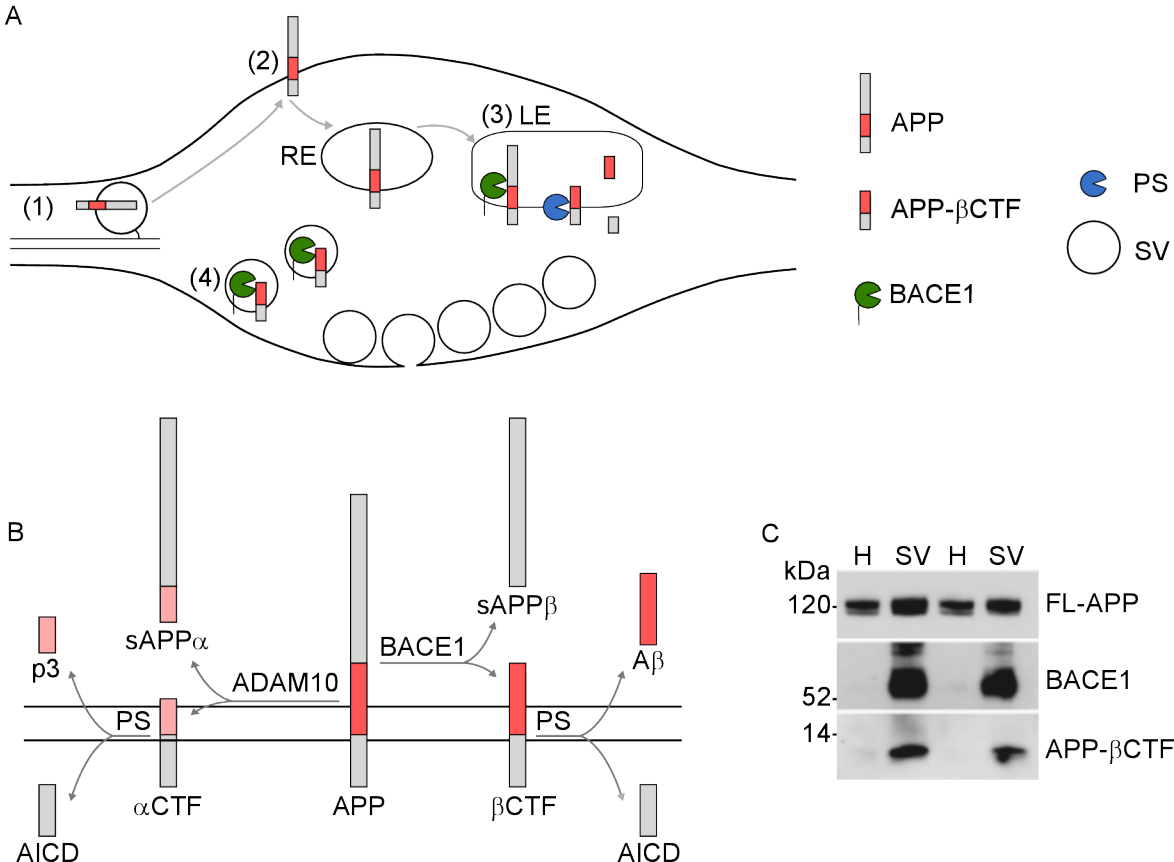
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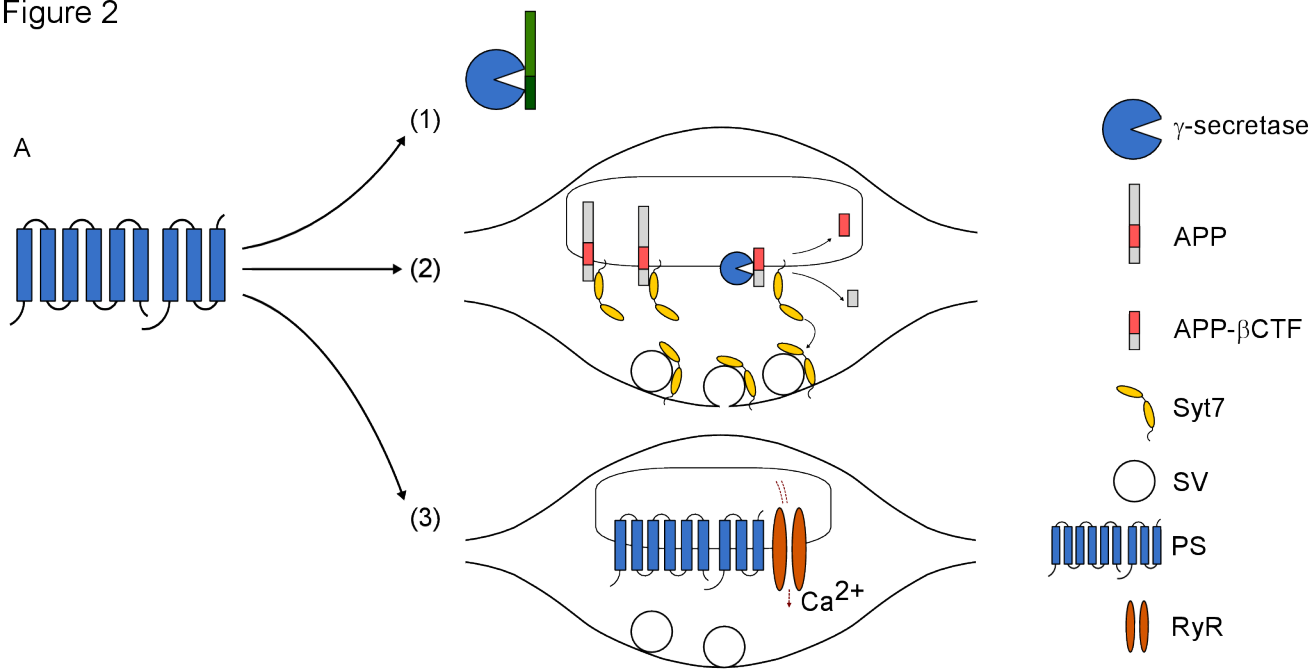
Figure 2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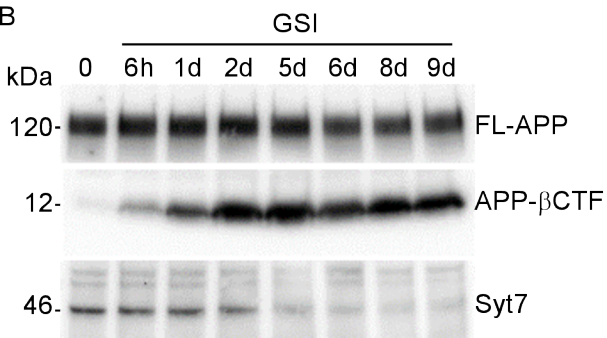
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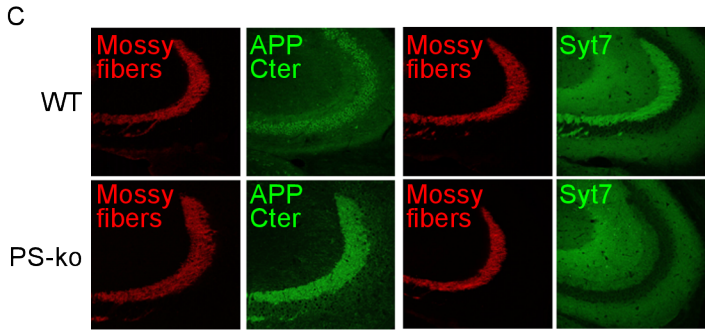
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Figure 3

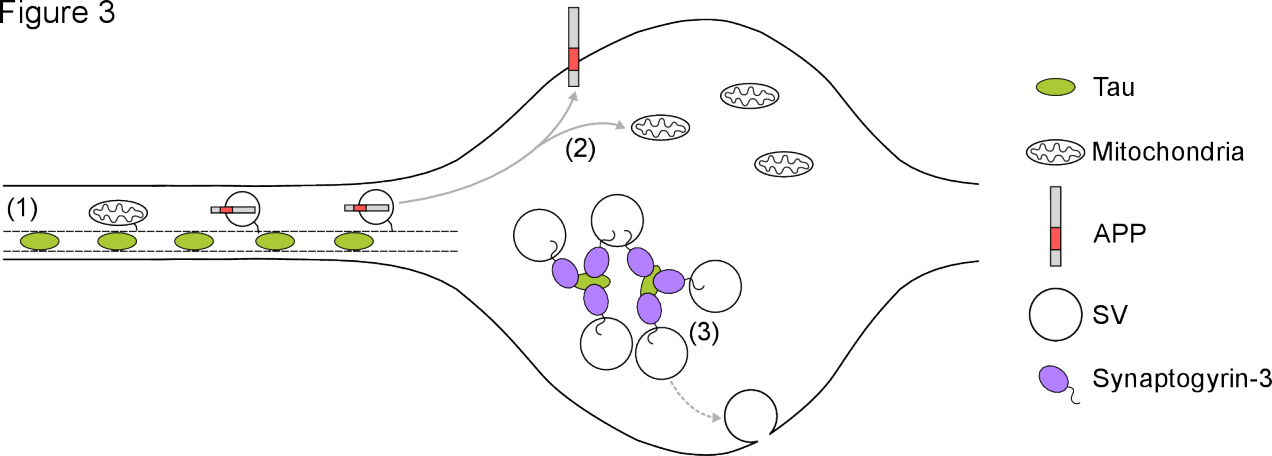
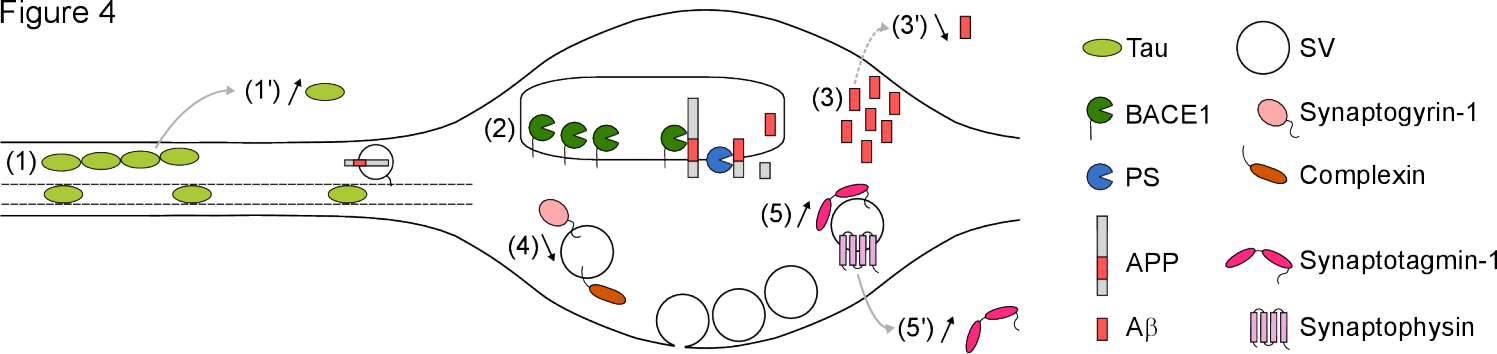


Figure 4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Complexin
APP
Synaptotagmin-1
Aβ
Synaptophysin

Table 1

Gene / Molecule	Subcellular localization	Changes in presynaptic parameters in KO or Tg or in treated conditions	Possible presynaptic mechanisms
ADAM10	Abundant at cell surface, mostly post-synaptic (Malinverno et al., 2010; Marcello et al., 2007; Prox et al., 2013; Suzuki et al., 2012)	No distinctive presynaptic alteration in cKO (Prox et al, 2013)	Not reported
APLP1	Abundant at cell surface (Kaden et al., 2009) and at PSD (Kim et al, 1995).	Lower basal synaptic transmission (reduced spine density) (Schilling et al, 2017)	Not reported
APLP2	Present both at presynapses and PSD (Müller et al, 2017)	Unaffected presynaptic parameters (PPF) in single KO (Midthune et al, 2012), but see APP/APLP2	Not reported probably due to compensation
APP	Mostly intracellular in the soma at steady-state but undergoes fast axonal transport (Koo et al, 1990) and is present at preS (Kim et al, 1995; Kohli et al, 2012; Del Prete et al, 2014; Wilhelm et al, 2014)	Decreased PPI (Seabrook et al, 1999) Unaltered excitatory basal transmission and PPF (Weyer et al, 2014) but see APP/APLP2. Accumulation of APP-βCTF in PSKO leads to altered preS facilitation (Barthet et al, 2018)	Not reported probably due to compensation but accumulation of APP-βCTF impairs Syt7 function (Barthet et al, 2018)
APP/APLP2	See single gene description	Decrease PPF (Hick et al 2015; Richter et al, 2018) Increased PPF (Fanutza et al, 2015)	Modulation of $GABA_B$-R by sAPPα (Schwenk et al, 2015; Rice et al, 2019) Modulation of α7nAchR by Aβ (Dougherty et al, 2003; Lazarevic et al, 2017; Puzzo et al, 2008; 2011) or sAPPα (Richter et al, 2018)
APPoverEx	See single gene description	Absence of change in PPF (Marchetti and Marie, 2011; Viana da Silva et al, 2016; 2019) Decrease in synaptic vesicle recycling (Ting et al, 2007)	Decreased synaptic vesicle recycling could result from Aβ and/or βCTF (prevented by BACE deletion: Ting et al, 2007)
Aβ	Mostly extracellular but intracellular production	Absence of change in PPF (Li et al, 2009) Decrease in PPF (He et al, 2009)	Proposed to regulate probability of release (Abramov et al, 2009).

		Decrease in synaptic vesicle recycling (Nimmrich et al, 2008) Potentiation at pM to low nM concentration, decrease at high nM concentrations which may be pathological (Lazarevic et al, 2017).	Binding of α7nAchR (Dougherty et al, 2003; Lazarevic et al, 2017; Puzzo et al, 2008; 2011)
sAPPα	Extracellular	Unchanged PPF (Moreno et al., 2015)	Modulation of metabotropic (Rice et al, 2019) and Ca^{2+} signaling pathways (Richter et al, 2018)
Bace1	Presynaptic - endosomal (Hitt et al, 2012; Laird et al, 2005; Cao et al, 2012; Rajapaksha et al, 2011)	Increased PPF (Laird et al, 2005, Wang et al, 2008, 2014; Hartmann et al, 2018) Decreased basal transmission (Hartmann et al, 2018)	Possible modulation of presynaptic strength through promoting Aβ (Cai et al 2001) and preventing sAPPα production and by promoting Kv3.4 cell surface expression (Hartmann et al, 2018)
PS	Ubiquitous expression in cell membranes. PS1 enriched in ER and plasma membrane, PS2 in late endosomes and lysosomes (Sannerud et al, 2016; Meckler F et al, 2016)	Decrease short-term plasticity (Zhang et al, 2009; Lee et al, 2017; Barthet et al, 2018)	Ca^{2+} homeostasis (ER stores: Zhang et al, 2009); regulation of Ca^{2+} sensor (Syt7: Barthet et al, 2018)
PS1 G344 Tg mouse	See single gene description	Hyperactivity (neuronal firing assessed with Ca^{2+} indicator: Lerdkrai et al, 2018)	Possibly Ca^{2+}-mediated excitation
Tau	Axonal (Wang and Mandelkow, 2015)	No alteration reported	Regulation of synaptic vesicles availability (revealed by aggregant forms more than deletion, see below)
Tau mutations P301S, V337M, R406W	Impaired subcellular localization (presence in dendrite, accumulation) (Allen et al, 2002)	Decreases neurotransmission during burst stimulations (Zhou et al, 2017, McInnes et al, 2018)	Reduced SV mobility leading to impairment SV recruitment (docking) during burst stimulation
Tau mutation ΔK280	Impaired subcellular localization (presence in dendrite, accumulation) (Mocanu et al, 2008)	Decrease facilitation (Decker et al, 2015)	Reduced SV mobility leading to impairment SV recruitment (docking) during repetitive stimulation

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