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Synaptic Function and Dysfunction in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a multifactorial neurodegenerative disease, primarily affecting the elderly. Pathophysiological mechanisms have been elucidated in the past decades. First of all, AD is progressive leading to cognitive deficits till dementia. Pathologically, AD features synaptic dysfunction with changes of neuronal circuitry, progressive accumulation of protein aggregates such as the beta amyloid and tau. Herein we critically review neurobiological processes and factors involved in AD, in light of recent results on synaptic dysfunction and impairment of neuronal activity.

Keywords: Synaptic transmission; Synaptic plasticity; Neuronal activity; Beta amyloid; Tau

Introduction

Alzheimer's disease (AD) is a neurodegenerative progressive disease of the elderly leading to dementia. The world Alzheimer report (Alzheimer's disease International, global impact of dementia) of 2015 indicated that 46.8 million people worldwide are living with dementia; this number is expected to double every 20 years [1]. There are two forms of AD.

1. Early onset Familial Alzheimer Disease (eFAD). Abnormalities of the amyloid precursor protein (APP) that render it more amyloidogenic, or defects of processing normal APP cause genetic forms of AD. The literature estimates that eFAD accounts for approximately 2% of all people with dementia (approximately 3-5% of all Alzheimer cases) [1,2]. In these patients, autosomal dominant AD usually develops before age 65 due to mutations of the *APP* gene on chromosome 21 or the presenilin 1 and 2 genes (PSEN1 and PSEN2) on chromosomes 14 and 1, respectively.

2. Sporadic AD (SAD, late-onset). SAD is very common in the elderly (approximately 70% of patients with dementia are attributed to SAD [1]). The cause of SAD is unknown. The vast majority of SAD is not genetically inherited although some genes such as the *APOE* may act as a major risk factor [3].

Vascular diseases such as hypertension and brain ischemia [4,5], diabetes [6,7] and obesity [8], traumatic brain injury [9], mood disorders [10] represent risk factors for SAD.

The neuropathological changes of AD brain include classical hallmarks such as the senile plaques and neurofibrillary tangles, and dystrophic neurites containing hyperphosphorylated tau [11-13]. Additional changes are represented by astrogliosis [14], microglial cell activation [14,15] and inflammatory reaction [16]. Senile plaques with amyloid cores in the brain of AD patients are often described in close proximity to microvessels with amyloid angiopathy [17].

Whereas considerable heterogeneity exists in the degree to which cognitive functions are affected in patients with AD, learning/memory impairment is almost invariably reported in AD [18,19]; typically, declarative memory is impaired and this quite often represents the initial cognitive deficit in AD. Indeed, the initial brain areas involved in the neurodegenerative progression of AD are the entorhinal cortex, hippocampus and temporal cortex [20,21], i.e., crucial areas for learning/memory. The hypothesis has been advanced that impairment of the entorhinal cortex initiates cortical-hippocampal dysfunction in AD [22]. The olfactory bulb, anterior olfactory nucleus, orbitofrontal cortex and parahippocampal cortices receiving olfactory input are all also affected early in AD [23]. Thus, odor recognition performance, in particular the ability to identify familiar odors, in association with episodic memory is impaired early in AD [24].

In addition to eFAD and SAD there are patients with cognitive decline unusual for their age that does not affect daily living (for example difficulty in remembering names of individuals, misplacing keys and spectacles or difficulty in remembering phone numbers, messages and appointments, therefore mostly verbal episodic memory deficit). This clinical state is called mild cognitive impairment (MCI). Some MCI patients progress to AD (roughly 15%/year; [25]), others progress to vascular dementia, but others remain stable or revert to normal, indicating that MCI has diverse causes and represents a heterogeneous group of patients. MCI patients can be further subdivided in: MCI patients with an amnestic profile [26] (impaired episodic memory retention and retrieval) and MCI patients with an anamnestic profile susceptible to be converted in AD.

AD pathogenesis: Amyloid-dependent mechanisms and synaptic dysfunction

The pathogenesis of AD is characterized by formation of senile plaques and neurofibrillary tangles considered as hallmarks of AD. Aggregates of β-amyloid protein (Aβ) are the principal component of senile plaques [27]. Electron microscopy studies revealed that dense-core plaques comprise aggregates of Aβ, extracelullar filaments (dystrophic neuritis) as well as abnormal mitochondria and dense bodies of probable mitochondrial and lysosomal origin [27-29].

Aβ peptides start to be generated in considerable amounts by

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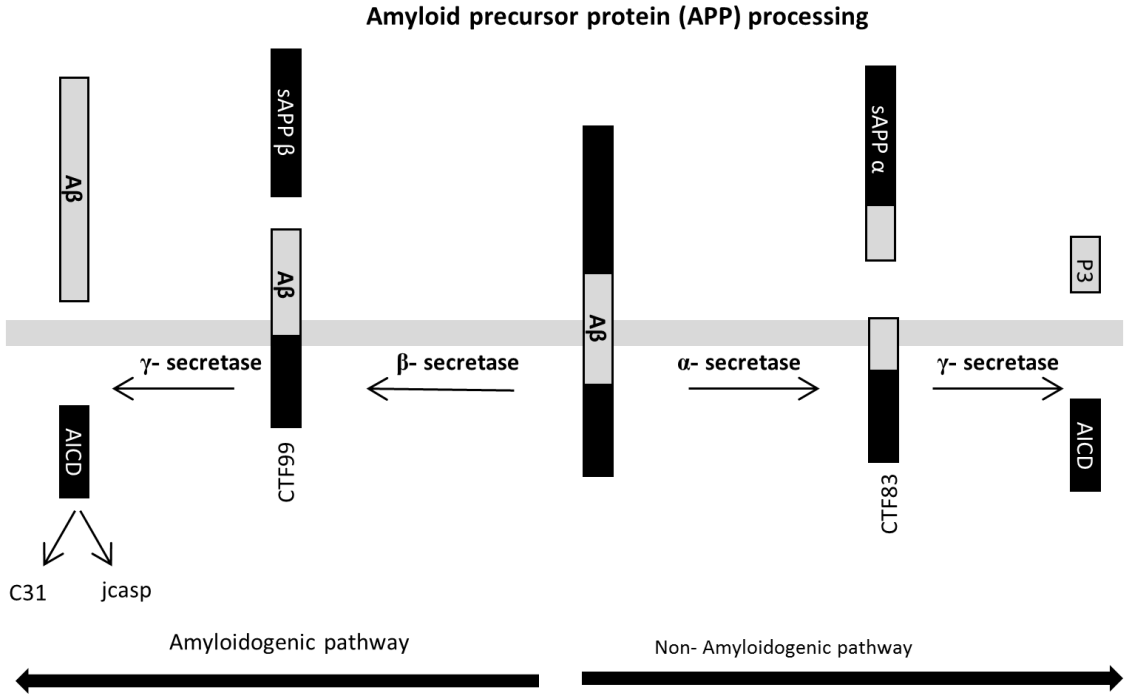

Figure 1: The APP processing. The amyloidogenic processing of APP is due to the sequential activation of β- and presenilin catalytic site of γ-secretases; the four peptides deriving from this pathway, i.e., sAPPβ, Aβ, Jcasp and C31, have been shown to mediate neurite retraction, synaptic inhibition and programmed cell death [31]; the two peptides derived from the non-amyloidogenic processing of APP, sAPPα and P3, mediate neurite extension and inhibit Aβ production and programmed cell death (sAPP=Soluble Amyloid Precursor Protein; AICD=APP Intra-Cellular Domain; CTF=Carboxy-Terminal Fragment).

the cleavage of amyloid precursor protein (APP) due to sequential activation of β- and presenilin catalytic site of γ-secretases (Figure 1) for causes that are still unknown in SAD. The four peptides derived from the amyloidogenic processing of APP, i.e., sAPPβ, Aβ, Jcasp and C31, have been shown to mediate neurite retraction, synaptic inhibition and programmed cell death [30]. APP cleavage by α and β-secretases generates soluble secreted fragments (sAPPα and sAPPβ) and membrane-associated carboxy-terminal fragments (CTF), which preclude Aβ generation; the two peptides derived from the non-amyloidogenic processing of APP, sAPPα and CTF, mediate neurite extension, and inhibit Aβ production and programmed cell death [31]. Aβ can be found in different compositions of monomers, oligomers or fibrils [32]; in particular, increasing Aβ level tends to form monomers, which aggregate into oligomers, prefibrillar assemblies (protofibrils) and amyloid fibrils in a concentration-dependent manner. Toxic Aβ peptides are formed by 36-43 amino acids; the 42 amino acid peptide (Aβ42) is one of the most neurotoxic amyloidogenic fragments [33,34] and represents the chief component of senile plaques.

Studies in AD animal models and patients have highlighted a dichotomy between behavioral deficits and neuropathologic findings. Impaired memory and synaptic loss occur before extensive deposition of amyloid in the brains of AD-type murine models and AD patients [35-37].

These observations suggest that early in AD, when levels of amyloid are low, mechanisms amplifying and focusing the effects of amyloid on cellular targets contribute to neuronal dysfunction. It is known that soluble synthetic or naturally produced oligomeric or oligomeric Aβ extracts from cerebral cortex of AD patients are capable of inhibiting hippocampal long-term potentiation (LTP) [38-42], a form of long-term synaptic plasticity thought to underlie learning and memory in the hippocampus and parahippocampal cortices [43]. Furthermore synthetic Aβ formed by dimers and trimers [44] in the low concentration of nanomolar range was capable of inhibiting LTP in the entorhinal cortex (EC) [45]. The EC represents a crucial site for memory formation as it integrates spatial information processed from the medial EC neurons with non-spatial information processed from the lateral EC neurons [46-48]. The involvement of the EC in cognitive processes is relevant for neurodegenerative disorders such as the AD, as it is one of the earliest affected brain regions [49]. This might be the consequence of a particular vulnerability of the superficial layer II neurons, that are susceptible to the deleterious consequences of aging and AD [50]. Interestingly, increasing synthetic Aβ42 concentration induces activation of microglial cells with pro-inflammatory cytokines that progressively affects synaptic transmission, AMPA current and long term depression (LTD, a second form of long term synaptic plasticity), in addition to LTP [51]. Indeed, an increasing level of Aβ42 has been shown to induce synaptic transmission impairment by regulating glutamate receptors trafficking [52,53]. Interestingly, an increase in endogenous Aβ level induced by inhibition of extracellular Aβ degradation causes pre-synaptic enhancement increasing glutamate release [54]. Thus, progression of synaptic dysfunction as well as cognitive decline by accumulation of extracellular Aβ is likely to result in alterations of pre- and post-synaptic proteins [55]. Activation of receptors such as the receptor for advanced glycation end products (RAGE) by Aβ [56] accounts for progress of synaptic dysfunction, development of inflammatory and, possibly, oxidative processes, leading cells to degenerate [51]. Concerning the receptor signaling pathways mediating synaptic dysfunction, it has been reported that Aβ impairs LTP in the hippocampus through JNK, cyclin-dependent

kinase 5 (CDC5), p38 mitogen-activated protein kinase (MAPK) [41]. In particular, low level of synthetic oligomeric Aβ42 inhibits LTP in hippocampus and entorhinal cortex through phosphorylation of p38 MAPK in neurons [45,57,58]. Increasing Aβ induces specific phosphorylation of p38 MAPK and JNK in neuronal and non-neuronal cells along with the induction of pro-inflammatory cytokines, such as the IL-β; as above reported in this condition basal synaptic transmission and long-term synaptic plasticity are affected [51].

Aβ-dependent toxicity is also mediated by internalization of Aβ peptides into neuronal cells, which contributes to disrupt neuronal functions [59,60]. One important question concerns the mechanism underlying Aβ transport from the extracellular to intracellular space. It has been reported that RAGE expressed in brain endothelial cells mediates Aβ transport across the blood brain barrier [61]. More recently, Takuma et al. [62] reported that RAGE represents at least a co-factor contributing to translocation across cell membrane of Aβ driving its transport and delivery to different subcellular spaces including mitochondria. Mitochondrial dysfunction with resultant neuronal perturbation and cognitive impairment [29,63] is considered a key feature in AD neuropathology and synapto-toxicity. Recent studies have shown that Aβ-binding alcohol dehydrogenase (ABAD), an enzyme present in neuronal mitochondria, exacerbates Aβ-induced mitochondrial and neuronal dysfunction; indeed, inhibition of the ABAD-Aβ interaction protects mitochondrial function and improves learning/memory [64]. Thus, Aβ-dependent synaptic dysfunction is mediated by several factors and mechanisms and its outcome depends on: level/accumulation of Aβ peptides, their aggregation state (monomers, oligomers, protofibrils, fibrils and plaques), signaling pathways activated in different neural cells, translocation across cell membrane and transport of Aβ peptide.

Actually, Aβ can be considered a product of APP metabolism. Indeed, Aβ level is detectable even in young healthy people but at a very low level. This result is in accordance with a supposed trophic role of low Aβ level [65]; remarkably, Puzzo et al. [66,67] showed that a very low level of exogenously applied Aβ42 (picomolar range) enhances synaptic plasticity and memory by acting through α7 nicotinic receptor and confirmed that endogenous low Aβ is necessary for synaptic plasticity and memory. Thus, the accumulation (enhanced formation and/or defective clearance) of Aβ in specific areas of the brain (parahippocampal cortices, hippocampus and neocortical areas) for unknown cause(s) can be considered as an early pathologic event in AD leading to synaptic dysfunction. An alternative intriguing possibility is that mechanisms triggering the initial conversion of Aβ soluble protein into filamentous fibrillar species, with prion-like domains, are at the origin of AD pathogenesis [68]. However, several studies suggest that pre-fibrillar species, such as the Aβ oligomers in AD, may be more detrimental than fibrillar species [42], at least during an early stage in AD. During the progression of AD, misfolded Aβ and, possibly, tau filamentous species, might be involved in the propagation from one neuron to the next and from one brain region to another [68]. Interestingly, there is a relationship between the pathogenic amyloid β-peptide species and tau pathology; for example, intracerebral administration of Aβ1-42 fibrils into a mutant tau transgenic mouse induced tau hyperphosphorylation and local neurofibrillary tangles [69].

AD pathogenesis: Tau-dependent mechanisms and synaptic dysfunction

Tau is highly expressed in neurons and is abundant in axons [70]. Tau facilitates assembly and stabilization of microtubule polymers [71,72], modulating microtubule dynamics. Thus, under physiological conditions tau is mainly expressed within neurons. Human tau has been implicated in the pathogenesis of several neurodegenerative diseases, including AD [73]. Mouse models which overexpress forms of human tau have been generated and reproduce synaptic dysfunction, cognitive impairment and neurodegeneration [74-76]. Hyperphosphorylated, insoluble, and filamentous tau proteins were shown to be the main component of neurofibrillary tangles (NFTs), a pathological hallmark of AD and other tauopathies [70]. NFTs accumulate inside the cells, disrupting the intracellular transport system. Cytoskeletal changes are visible as dystrophic neurites, pre-tangles, NFTs in the cell bodies of affected neurons in AD even before plaque formation [77,78]. The neurofibrillary tangles are composed of paired helical filaments (PHF) with hyperphosphorylated forms of tau protein as the main component; the other component is represented by misfolded tau. Bundles of these PHF are also found in neurites [20,79]. Tau hyperphosphorylation can increase abnormal folding, fragmentation, aggregation and/or the development of NFTs leading to activation of intracellular pathways involved in synaptic dysfunction and neuronal toxicity; phosphorylation of tau potentiates MAPK activation similarly to Aβ and tau is one of p38 MAPK substrates [80]. Interestingly, transgenic mouse models suggest that neuronal loss and memory impairment are associated with the presence of soluble tau protein [75] (tau oligomers). Studies on cell viability have shown that misfolding of tau leads to the aggregation of tau and the appearance of toxic tau species in the extracellular space [81,82]. The endogenous intracellular tau may be released as aggregates to the extracellular space upon neuron degeneration [81]. Extracellular tau could be toxic by increasing intracellular calcium into neighboring neurons [82]. The presence of extracellular tau can be due to other causes, for example exocytosis; the N-terminal region of tau seems to be required for its secretion [83]. Neuronal toxicity may be caused by tau aggregates, even small and soluble aggregates in the form of oligomers, which have been identified in AD brain [84]. Tau can be released into the extracellular space, as oligomers [85]. Cells can take up extracellular aggregated tau [86], thus contributing to propagation of tau pathology. Formation of tau oligomers induces synaptic dysfunction and cognitive impairments [87], suggesting that this is the tau involved in early synapto-toxicity and cognitive impairment [88]. Indeed, in AD brains loss of synapses precedes NFTs formation and correlates with cognitive deficits [89,90]. Accordingly, it has been shown that prior to the formation of aggregates; tau can bind to pre-synaptic vesicles via its N-terminal domain inducing synaptic dysfunction [91]. Development of tau pathology closely associates with progressive neuronal loss and cognitive decline. In the brains of AD patients, for instance, tau pathology follows an anatomically defined pattern [20]; tau pathology spreads in the entorhinal cortex and then accumulates within limbic areas, followed by neocortical areas. Accumulation of extracellular tau species could be involved in neuron-to-neuron propagation of neurofibrillary pathology and progression of tau toxicity that spreads throughout defined pattern of brain regions. The oligomers in the extracellular space could be taken-up by healthy neurons inducing further aggregation of tau [86] and propagation of neurofibrillary pathology. Recently, it has been shown that oligomeric extracellular tau is able to interact with cell receptors resulting in synaptic dysfunction and signaling propagation that could contribute to onset of neurodegeneration [92]. Moreover, these observations point to the involvement of extracellular tau species as one of the main agent in the neuron-to-neuron propagation of neurofibrillary pathology and progression of synaptic dysfunction and cognitive impairment in AD.

AD pathogenesis: The neurotrophic factors

Selective vulnerability of basal forebrain cholinergic neurons (BFCNs) contributes to cognitive decline in AD patients [93,94]. BFCNs depend on the neurotrophin nerve growth factor (NGF) [95] for their trophism and survival [96]. Moreover, other neurotrophins, such as the brain-derived neurotrophic factor (BDNF), provide a high level of protection to neurons in brain injury and diseases [97,98]. BDNF together with its receptor TrkB (tropomyosin receptor kinase), is highly expressed in several brain areas where it acts as one of the chief regulator of synaptic plasticity and synaptogenesis [99,100]. The BDNF appears to be reduced in AD brain [101-103]. Thus, the hypothesis can be raised that neurotrophins, particularly NGF and BDNF, and their receptors, are involved in the pathogenesis of neurodegenerative diseases such as the AD. In addition, the possibilities of neurotrophin-based therapeutic approaches should be evaluated. Interestingly, BDNF prevents Aβ-dependent impairment of LTP by reducing p38 MAPK phosphorylation [104]. Similarly, human painless NGF is capable of preventing synaptic plasticity impairment in the EC of the 5xFAD mouse model, either when acutely supplied on slices or following three weeks of intranasal treatment [105].

Neuronal Activity in AD

Disrupted neuronal network increases seizure activity in AD, contributing to cognitive decline [106]. Elevated electrical activity in the hippocampus has been observed early in AD in stages preceding the formation of senile plaques [107]. Interestingly, a recent paper suggested that APP molecules may function as surface receptors modulating the Aβ signaling [108]; the Authors showed that neurons in hippocampus became hyperactive at the pre-synaptic site through APP homodimer as pre-synaptic receptor, which binds Aβ40 following a rise in its concentration. If very low Aβ level is essential for the normal day-to-day life in agreement to Puzzo et al. [66,67], thus, we can hypothesize that when the level of Aβ peptides is even slightly increased, it causes neuronal hyperactivity and neuronal functional impairment in several brain areas as also frequently reported in MCI patients [109].

Since neuronal activity increases Aβ production, it is likely that regional differences in neuronal activity may underlie early Aβ aggregation and deposition in specific brain areas such as the hippocampus and additional areas that belong to the default mode network (DMN) [110]. As reported above, the typical hallmarks of AD, such as the presence of amyloid protein and neurofibrillary tangles, are seen primarily in the EC in mild AD and "spread" to the hippocampus and other cortical areas as the disease progresses [20]. Thus, the hypothesis has been raised that neurodegeneration primarily observed in EC neurons may cause trans-synaptic deficits initiating the cortical-hippocampal network dysfunction in mouse models and human patients with AD. Indeed, in an AD mouse model, selective overexpression of mutant amyloid precursor protein (APP) predominantly in layer II/III neurons of the EC caused an aberrant excitatory cortico-hippocampal network activity leading to behavioral abnormalities [22]. Moreover, the time-course of synaptic impairment of the EC layer II in human amyloid precursor protein J20 transgenic mice (mhAPP), has been characterized. Although this murine model of AD displays diffuse amyloid accumulation in the brain, synaptic dysfunction is first observed in the intrinsic circuitry of the EC and then propagates to its main target area (i.e., the hippocampus). This suggests a precise temporal profile and an exact order of involvement of different circuitries during the progression of synaptic dysfunction in mhAPP mice, possibly corresponding to different stages of Aβ accumulation [111].

Concerning tau, its release can be stimulated by enhanced neuronal activity; Wu et al. [112] showed that increasing neuronal activity enhances release and transfer of tau *in vitro* and exacerbate tau pathology in vivo. As neurons within the AD brain can be hyperactive [106], thus enhanced neuronal activity may increase tau pathology. More recently, Fu et al. [113] showed that in a transgenic mouse model expressing mutant human tau predominantly in the EC, the formation of tangles in old mice was associated with excitatory cell loss and cognitive deficits in grid cell function. In addition, the tau pathology in the aged mice was accompanied by spatial memory deficits. These results suggest that in addition to Aβ, the tau protein could contribute to the synaptic alterations in the EC underlying the deterioration of spatial cognition described in AD patients.

Remarkably, later stages in AD progression are generally associated with a greater Aβ load, tau aggregation and hyperphosphorylation that exaggerate impairments in synaptic and cognitive function; AMPA and NMDA current are impaired, glutamate receptors trafficking altered and metabolism reduced. In addition, reduced synaptic activity causes detrimental effects on synapses and memory, favoring the accumulation of intraneuronal Aβ [57]. Independently of amyloid, the progressive impairment of synaptic and cognitive functions in AD is generally thought to result from a reduction in neuronal and synaptic activities in brain areas such as the entorhinal cortex and hippocampus. However, recent studies revealed a more complex picture of the neuronal defects in late stages of AD, showing both hypo- and hyper-activity in several brain regions; interestingly, hyperactive neurons were found in the vicinity of beta amyloid plaques [114].

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