Pathophysiological basis of synaptic dysfunction in Alzheimer's disease: A systematic review

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Keywords: synaptic dysfunction, Alzheimer's disease, amyloidosis, tauopathy.

ABSTRACT

Background: Alzheimer's disease (AD) is a neurodegenerative condition that impairs cognition and functionality. The neuropathological hallmarks of AD are neuritic plaques of amyloid beta (AB) and neurofibrillary tangles of hyperphosphorylated tau protein (NFTs). Nevertheless, synaptic dysfunction (SD) has gained attention as an early pathophysiological event that triggers neuronal apoptosis and early cognitive dysfunction. In this study we aim to consolidate the current information regarding synaptic dysfunction in AD.
Methods: A systematic review of literature was carried out in which 875 articles were considered from PubMed, Embase, Cochrane and Bireme. 27 duplicates were excluded as well as 817 references due to wrong study design, wrong publication type, background article, wrong outcome, or wrong population.
Results: 31 references were included out of which 23 analyzed mechanisms related to amyloidosis, 6 to tauopathy and 2 inflammatory responses in AD. Regarding the study design, 18 (58%) were in vitro studies, 4 (13%) were in vivo studies and 9 (29%) in vivo/in vitro studies.
Conclusion: SD in AD is the result of impairment at different molecular and cellular levels. This phenomenon occurs early in the disease course and is mainly related with soluble forms of Aβ and tau protein.

Introduction

Alzheimer's disease (AD) is a neurodegenerative condition that impairs cognition and functionality. Given that there are no treatments to prevent or reverse AD, efforts have been focused on better understanding the causes of the disease (1). Traditionally, the neuropathological characteristics of AD are the presence of beta amyloid (Aβ) aggregation, Tau-induced neurofibrillary tangles, and neuronal loss. A key observation is that these pathological changes during AD begin many years prior to the onset of dementia (2).

Keeping in mind that AD is conceptualized as a clinical continuum, the initial pathological event in AD is amyloidosis and can be found many years before clinical manifestation. Nevertheless, Aβ accumulation is not enough to produce symptoms, thus additional factors contribute to neurodegeneration during the disease course (2). Synaptic dysfunction (SD) has gained attention as the major pathophysiological event and the trigger of both neuronal death and early cognitive dysfunction. Synapses and dendritic spines are dynamic structures, thus molecular changes may cause changes in synaptic connections and plasticity mechanisms (2).
SD in AD is thought to be caused by intermediate peptides, such as soluble AB oligomers (Aβo) and tau oligomers, and it is mainly characterized by impairment in synaptic plasticity mechanisms namely long-term potentiation (LTP) and long-term depression (LTD) in the hippocampus (4). Nevertheless, the pathophysiological pathways by which SD occurs in AD are not completely understood. In this study we consolidate the current information regarding synaptic dysfunction in AD.

Methods

1. Search strategy and selection criteria

An exhaustive search was carried out in the databases "Medline", "Embase", "Bireme Lilacs", Cochrane and Gray Literature. The main objective was to perform a systematic review of the literature on the mechanisms that trigger synaptic dysfunction from the pathophysiological process of Alzheimer's disease.

The inclusion and exclusion criteria were as follows:

Inclusion criteria:

- Methodological design involving the relationship of some pathophysiological processes (amyloidosis, tauopathy, inflammation, oxidative stress) of AD with synaptic dysfunction.
- In vitro or in vivo models.

Exclusion criteria:

- Narrative review type studies, systematic review, clinical trials.
- Studies involving pharmacological intervention
- Post-mortem studies

The search strategy was as follows in each database:

MEDLINE

((Alzheimer Disease[Mesh] OR Alzheimer Disease[tiab]) AND (synaptic dysfunction[tiab])) AND ((((((((((Amyloidosis[Mesh] OR Amyloidosis[tiab]) OR ("beta amyloid production"[tiab])) OR ("beta amyloid aggregation"[tiab])) OR (neurodegeneration[tiab])) OR ("neuronal death"[tiab])) OR (Inflammation[Mesh] OR Inflammation[tiab])) OR (neuroinflammation[tiab])) OR (Tauopathies[Mesh] OR Tauopathies[tiab])) OR ("Tau production"[tiab])) OR ("Tau aggregation"[tiab]))

EMBASE

(('alzheimer disease'/exp OR 'alzheimer disease') AND ('synaptic dysfunction'/exp OR 'synaptic dysfunction') AND (('amyloidosis'/exp OR amyloidosis) OR 'beta amyloid production' OR 'beta amyloid aggregation' OR ('neurodegeneration'/exp OR neurodegeneration) OR 'neuronal death' OR ('inflammation'/exp OR 'inflammation') OR ('neuroinflammation'/exp OR neuroinflammation) OR ('tauopathy'/exp OR 'tauopathy') OR 'tau production' OR 'tau aggregation')) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

BIREME-LILACS

(English and Spanish):

("Alzheimer Disease") AND ("synaptic dysfunction") AND (amyloidosis OR "beta amyloid production" OR "beta amyloid aggregation" OR neurodegeneration OR "neuronal death" OR inflammation OR neuroinflammation OR tauopathies OR "Tau production" OR "Tau aggregation") AND (db:("IBECS" OR "LILACS"))

("Enfermedad de Alzheimer") AND ("Disfunción sináptica") AND (amiloidosis OR "Producción de beta amiloide" OR "Agregación de beta amiloide" OR neurodegeneración OR "muerte neuronal" OR inflamación OR neuroinflamación OR taupatía OR "Producción de tau" OR "Agregación de tau")

COCHRANE

("Alzheimer Disease" and "synaptic dysfunction" and (Amyloidosis or "beta amyloid production" or "beta amyloid aggregation" or neurodegeneration or "neuronal death" or Inflammation or neuroinflammation or Tauopathies or "Tau production" or "Tau aggregation")).

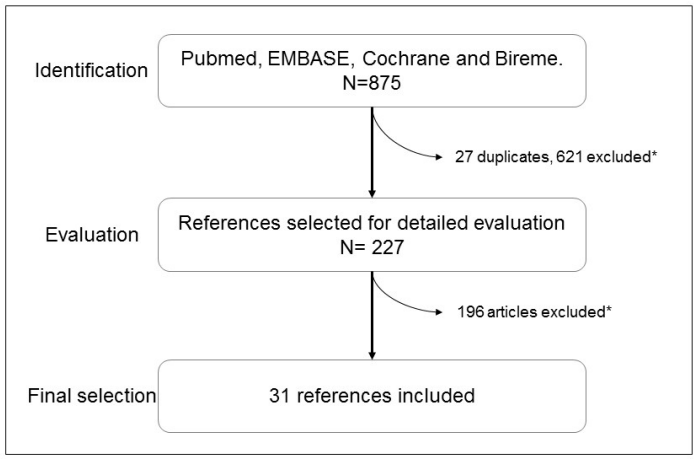
OPENGREY

(Alzheimer disease AND synaptic dysfunction).

No restrictions were placed by language or year of publication. Two independent reviewers (D-A and AGN) carried out the selection of articles; when there were discrepancies, a third reviewer was used.

A total of 875 articles were included. In the first screening, a careful reading of titles and abstracts was performed; 27 duplicate manuscripts were excluded. The criteria used to exclude were: wrong study design (those relating SD and other factors like physical activity, CNS infections), wrong publication type, background article, wrong outcome or wrong population. A total of 621 papers were excluded in this first phase. In the second part, the article was read to define its inclusion in the study. The same criteria were taken into account. Finally, 31 articles were selected. (Figure 1.)

Figure 1. Flow chart of eligibility criteria



*Articles excluded for wrong study design, wrong publication type, background article, wrong outcome or wrong population

2. Data extraction

After the selection process of experiments, 31 papers were included. A detailed reading of the text was performed, and relevant information was collected in a comparative table. (Table 1).

Results

1. Study characteristics

Out of the 31 studies, 23 analyzed mechanisms related to amyloidosis, 6 to tauopathy and 2 inflammatory responses in AD. Regarding the study design, 18 (58%) were in vitro studies, 4 (13%) were in vivo studies and 9 (29%) in vivo/in vitro studies.
Most of the experiments were developed in the United States (14 papers), England (3 papers), Italy (3 papers), France (2 papers), India (2 papers), Belgium (1 paper), China (1 paper), Germany (1 paper), Korea (1 paper), Mexico (1 paper), Portugal (1 paper).

Discussion

1. Amyloidosis and synaptic dysfunction

a. Specific molecules involved in synaptic transmission

AD is thought to be primarily a synaptopathy due to synapse loss and altered connectivity in early stages of the disease. The implication of SD in AD has been subject of investigation, mainly in animal models. Regarding neural structure, the major synaptic change reported is reduction of axons terminals without impairment in dendritic spines. Nevertheless, instability in both axons and dendrites can be found in transgenic mice models, and this is not related to proximity to Aβ plaques (5).

Several molecules have been involved between Aβ and SD. Synaptophysin has been proposed as a major molecule involved in the pathophysiology of synaptic impairment in AD. This molecule is an integral membrane protein localized in synaptic vesicles (SV) and is part of the pore complex, thus involved in neurotransmitter release. One study demonstrated that Aβ interacts with synaptophysin and interferes with the

formation of the complex VAMP2/Synaptophysin, affecting the formation of the SNARE complex during the formation of the fusion pore complex (6).

Similarly, endophilin 1 is a molecule widely spread in the human brain and is a key regulator of SV endocytosis. A study performed with cultured hippocampal cells from rats demonstrated that endophilin 1 expression was higher in neurons exposed to Aβ oligomers (Aβo) prior neuronal death, in comparison with controls. In the same vein, silencing the expression of endophilin 1 in cells treated with Aβo, miniature excitatory postsynaptic currents (mEPSC) increased, suggesting a negative effect of endophilin 1 in neuronal plasticity (4). These findings are supported by a previous study in which increased levels of endophilin 1 in neurons exposed to Aβ was linked to an increase in the activation of the stress kinase c-Jun-N-terminal and subsequent neuronal death (7).

Scaffold proteins in dendritic spines have also been related with SD in AD. To analyze Shank and Homer protein involvement, an experiment with cultured hippocampal cells from rats that underwent exposure to synthetic Aβ1-40, showed that Aβo triggered reduction of Shank and Homer proteins in postsynaptic density by either impairment of protein synthesis or increased degradation. The latter was mediated by glutamate receptor activation (8).

As mentioned before, various molecules have been studied in Aβ-induced SD. In an experiment with cultured hippocampal cells from rats exposed to Aβo, impairment of dynamin 1 was found. They reported decrease in full length and increase in its proteolytic fragment. This results in lost ability to release neurotransmitters successively due to ineffective vesicle recycling, accumulation of synaptic vesicles at the cellular membrane and reduced synaptic vesicle pool (9).

Also, synapsin is a protein that links actin to SV and is critically involved in vesicular trafficking. This protein can be phosphorylated by protein kinase A (PKA) and Ca2+/calmodulin-dependent protein kinase IV (CaMKIV), resulting in disassociation of the actin-SV binding. We found a report that demonstrated in an animal model that soluble Aβ1-42 (sAβ1-42) promotes phosphorylation of synapsin and thus inhibits actin-SV coupling (10). This finding suggests that sAβ1–42 increases the Ca2+-dependent phosphorylation of Ser9 of synapsin through CaMKIV, disrupting SV reallocation and preventing neurons forming new synapses during plasticity.

b. Presynaptic regulation

There is increased evidence of deficits in presynaptic mechanisms and presynaptic forms of plasticity in AD. Disruption of the excitatory/inhibitory synaptic balance and network hyperactivity are greatly influenced by presynaptic dysregulation. Another aspect regarding presynaptic mechanisms is SV regulation and distribution.

We found two studies that aimed to explore how intersynaptic vesicular trafficking might be involved in synaptic dysfunction in AD. One of them, a live-cell imaging technique, was used to monitor SV in hippocampal cultured neurons from embryonic day 18 Sprague-Dawley rat embryos. They performed a chemically induced long term potentiation (LTP) with forskolin, and exposed some of the cultures to sAβ1-42. They found that sAβ1-42 blocked the stimulatory effect of forskolin in synaptogenesis and inhibited chemically induced LTP new synapse formation. Furthermore, the process

of intersynaptic vesicular trafficking, that is critically involved in presynapse formation, was significantly reduced in cells exposed to sAβ-142 (10).

In the same vein, the second report found that sAβ1-42 strongly inhibited activity-dependent synaptogenesis and intersynaptic vesicular trafficking. The latter is critically involved in new synapses formation and synaptic plasticity, and it is explained by the fact that direct recruitment of vesicles promotes synaptic strength, modulates SV pools in presynaptic terminals, without disrupting the integrity of neighboring synapses (10).

c. Mechanisms of neuronal plasticity

Hippocampus is a well-studied part of the vertebrae brain, and it has been recognized for its important role in memory storage. Long term potentiation (LTP) and long-term depression (LTD) serve as electrophysiological correlates of basic cellular mechanisms involved in learning and memory in mammals. Specifically, LTP has been related to conditioned fear memory, conversion of short-term memory into long-term memory, acquisition of information about novel space, among others (11,12).

The CA1 region is a hippocampal section of special interest for its neuronal distribution. A descriptive analysis aimed to evaluate LTP and LTD variations between apical and basal dendrites of the CA1 region, when exposed to Aβo. They found that LTP is impaired in both apical and basal dendrites, specifically homosynaptic LTP. Additionally, LTD was induced in the presence of Aβo in both apical and basal dendritic compartments. This Aβ-facilitated-LTD was completely blocked when a metabotropic glutamate receptor antagonist was added, thus glutamatergic signaling helps regulate synaptic depression (13).

Similarly, one study reported that LTP threshold was increased in pre-fibrillary stages of amyloidosis and this was accompanied by reductions in short-term potentiation, synaptic response to burst stimulation and NMDA receptor-mediated component of excitatory synaptic transmission (14). These findings suggest that synaptic dysfunction happens early in the disease course, before neuritic plaques are detected. Supporting these findings, a different report determined that Aβo produced a reduction of the amounts of potentiation in early and late-phase of LTP. When applying synthetic Aβ in fibrillary form, the reduction was only evident in late-phase LTP without affecting the early phase (15).

In the same vein, a report aimed to analyze how relative levels of pre-fibrillary Aβ in the hippocampus relate to synaptic and genomic changes. A mouse model of increasing Aβ (Transgenic for familial Alzheimer's disease genes APP/PSEN1) was used and electrophysiological measures were performed three times. In the third week of culture, Aβ was detectable just above the limit of detection and Aβ38:Aβ40:Aβ42 ratio was 3:6:2. By two months, the Aβ peptides were detected and the ratio among peptides subtypes was similar but the levels were approximately 50% higher. By 4-month-old, plaques were already detectable, levels of Aβ42 increased approximately 25-fold and Aβ40 by 7-fold, thus Aβ42 levels were similar to Aβ40. These findings suggest that the rate of deposition accelerates when Aβ40:Aβ42 ratio is 1:1, but synaptic changes are not dependent on this. Thus, regarding synaptic function, changes in spontaneous excitatory postsynaptic currents were similar as those seen in the 2nd month, a stage in which no plaques were reported and overall Aβ levels and

ratio Aβ40:Aβ42 was 3-fold lower. This demonstrated that synaptic impairment is an early event in the pathophysiology of AD (16).

Nevertheless, exposure to amyloid requires additional elements in order to become deleterious. It was demonstrated that short exposures to picomolar (pM) concentrations of Aβ facilitate synaptic potentiation both in hippocampal cultures and slices and enhance memory in mice. In contrast, longer exposures lasting for several hours lead to reduction of synaptic plasticity, memory formation and altered expression of molecules involved in synaptic transmission like synaptophysin and synapsin (17).

d. Glutamate neurotransmission

It is well known that neurotoxicity and neuronal cell death in AD might be mediated by augmented release of glutamate. In fact, glutamatergic neurotransmission has been closely involved with synaptic dysfunction. It has been proposed that Aβ1-42 induces N-methyl-D-aspartate receptor (NMDAr) endocytosis and impairs its transport to the cellular membrane (18). The underlying mechanism is thought to be activation of α-7 nicotinic receptor and protein phosphatase 2B (PP2B), resulting in dephosphorylation of tyrosine phosphatase STEP which in turn generates endocytosis of NMDAr (18).

Another study wanted to describe the natural course of synaptic dysfunction with cultured hippocampal cells from transgenic mice with Swedish-Indiana APP mutation. The evaluation was performed in the CA1 region and in the dentate gyrus (DG). They observed that in early stages of the disease there was absence of amyloid plaques in both CA1 and DG regions, but interestingly, the CA1 showed a decrease in the ratio NMDAr/AMPAr and reduction of LTP. Electrophysiological experiments exhibited a higher amount of peptides in the CA1 region in comparison to DG in early stages. Throughout the disease, the CA1 region showed reduction of the ratio NMDAr/AMPAr, in the DG this was only evident in late stages. Impairment of LTP and accumulation of Aβ was similar in both regions in the final phase (19).

In order to assess the contribution of AMPAr in LTP impairment, rectification indexes in CA1 and DG regions were performed. No differences in AMPAr currents were found between transgenic (TG) and wild type (WT) groups of neurons. This suggests that AMPAr do not seem to play a major role in LTP impairment. Finally, paired-pulse facilitation was not altered, supporting the view that impairment in LTP in this model is mediated through NMDAr dysfunction postsynaptically in both CA1 and DG regions (19).

e. Cytoskeletal structure, amyloidosis, and synaptic dysfunction

Dendritic spines, among neurites, are the primary site for receiving information and cellular substrates for synaptic plasticity. They can undergo synaptic-activity-dependent modifications such as enlargement or shrinkage during LTP or LTD respectively. F-actin is a protein involved in spine formation and synaptic-activity-dependent structural changes in dendritic spines. One report found that alteration of F-actin equilibrium occurs during initial stages of AD pathogenesis and affects cytoskeletal architecture in postsynaptic neurites. This was due to Aβ1-42-induced-depolymerization of F-actin, affecting total dendritic spines, spine total extent, spine surface area, diameter of the spine head and spine cross-sectional area. The pathophysiological mechanism involved in F-actin conversion to G-actin is thought to

be dephosphorylation of p-cofilin, which leads to decrease in the p-cofilin/cofilin ratio and in consequence F-actin loss (20).

These findings are supported by a report in which alpha-tubulin, another component of cytoskeletal architecture, got altered when exposing hippocampal neurons to Aβ. Additionally, beta-III tubulin was significantly correlated with reduced neurite length and neuronal DNA fragmentation. In the presence of memantine, Aβ-induced decline in beta-III tubulin was not significant, but it did not prevent the toxic effect completely. The latter gives insight into the involvement of NMDA signaling in microtubule disassembling associated with neurite retraction and DNA fragmentation (21).

2. Tau pathology and synaptic dysfunction

Tau is a microtubule binding protein that, in physiological conditions, serves to stabilize microtubules, mediates microtubule assembly, axonal transport and neurite outgrowth. Under pathological conditions, tau gets phosphorylated 3-4 times more than normal conditions, leading to its detachment from microtubules and further accumulation in the somatodendritic compartment (22).
In order to analyze the contribution of tau protein to synaptic dysfunction in AD, one of the studies described the role of synaptogyrin-3 in this process. They reported that tau binds to synaptogyrin-3, a transmembrane SV protein, affecting SV mobility and lowering neurotransmission. Given that synaptogyrin-3 is only present in SVs, these results give insight to the relationship between tau and SD in AD (23). The latter is supported by a previous study, which reported that low levels of tau protein were capable of induce cognitive decline, reduce synapses and proteins related to synaptic formation, neuronal death and inflammatory response mediated by astrocytic activation (24).

As reported in Aβo-induced synaptic dysfunction, it seems that pre-filaments forms of tau may be more cytotoxic than neurofibrillary tangles (NFTs). Indeed, it has been described that cellular death precedes formation of NFTs (25). An in vivo/in vitro experiment performed in mice gave evidence supporting this hypothesis. They found a higher neuronal damage in neurons treated with oligomeric tau versus NFTs. To assess synaptic function, biochemical and histochemical analysis was performed to evaluate synaptophysin, synapsin-1 and septin-11 levels. It was reported that synaptophysin and septin-11 levels decreased in tau oligomers-treated neurons of the CA1 region of the hippocampus (26).

Furthermore, calcium homeostasis has been related to tau pathology in AD. In fact, a study found that oligomeric tau accumulated in astrocytes and in consequence astrocytes exhibited a significant reduction in the amplitude of ATP-induced Ca2+ currents. Also, gliotransmitter release from astrocytes was impaired in neurons treated with oligomeric tau, especially glutamate and serine, through ATP signaling impairment (27). In the same vein, it was demonstrated that tau limited the depolarization-evoked glutamate release, likely acting on regulation of intracellular calcium dynamics. One hypothesis that helps explain this association is that tau might interact with cellular membrane, affecting its viscosity and in consequence partitioning the voltage-gated calcium-channels (28).

3. Inflammatory response, SD and AD

Even though amyloidosis and tauopathy are both related to local inflammatory response, there is not much evidence relating inflammation, SD and AD. The first study found that in mice with the APP/PSEN1 mutation there was a loss of protein translation caused by an increase in reactive oxygen species (ROS). The latter caused impairment in the signaling pathway of AKT1-mTOR (Mammalian target of rapamycin), critically involved in activity-dependent protein translation and in consequence in synaptic plasticity (29).

Previous reports have also described the involvement of prostaglandin E2 (PGE2) in AD. It is thought that PGE2 can stimulate AB production (30). One of the analyzed studies found that PGE2 impairs LTP through activation of the PGE2 receptor 3 (EP3), in the mossy fibers of the hippocampus CA3 region. The previous finding was reported in cultured hippocampal cells from male mice with the APP(Sweden)/PSEN1 mutation (31).

Conclusion

SD in AD is the result of impairment at different molecular and cellular levels. This phenomenon occurs early in the disease course and is mainly related with soluble forms of AB and tau protein.

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Table 1. Description of analyzed articles

Title	First author	Year of publication	Country	Study design	Population	Pathophysiological pathway	Target	Methods	Results
Endophilin 1 knockdown prevents synaptic dysfunction induced by oligomeric amyloid β	Yin, Y.	2019	China	In vitro	Hippocampal cell culture of rats and preparation of Aβ derived from human samples	Amyloidosis	Endophilin 1	Hippocampal cell cultures and transfection, Western blotting, fluorescence immunostaining, determination of neuronal survival rate, electrophysiology.	Oligomeric amyloid beta caused synaptic dysfunction and endophilin 1 was highly expressed prior to neuronal death of cultured hippocampal neurons.

Dopaminergic neurotransmission dysfunction induced by amyloid-b transforms cortical long-term potentiation into long-term depression and produces memory impairment	Moreno-Castiilla, P	2016	Mexico	In vivo	Triple transgenic and wild type male mice.	Amyloidosis	Dopamin	Behavioral tasks, free-moving microdialysis, in vivo electrophysiological recordings, pharmacologic manipulations, and histologic and immunohistochemical analyses in the 3Tg-AD model,	Amyloid beta decreased cortical dopamine levels and converted in vivo long-term potentiation (LTP) into long-term depression (LTD).
Aβ mediates F-actin disassembly in dendritic spines leading to cognitive deficits in Alzheimer's disease	Kommaddi, R	2018	India	In vivo / In vitro	Transgenic (TG) APP/PS1 mice for in vivo measurements. Cultured neurons from TG APP/PS1 mice, wild type (WT) mice and C57BL/6 mice neurons exposed to low concentrations of Aβ 42.	Amyloidosis	F-actina	In vivo behavioral and in vitro biochemical experiments were performed in TG and WT mice. Synaptosomal levels of F-actin,G-actin, and total actin were measured in postmortem frontal cortex neurons from NCI, MCI and AD subjects.	TG male mice (APPswe/PS1) at 1 month age showed depolymerization of synaptosomal F-actin accompanied by increased globular-actin (G-actin). At 2 months of age, deficits in recall after fear conditioning was found in TG mice.
A critical role for the PAR-1/MARK-tau axis in mediating the toxic effects of Ab on synapses and dendritic spines	Yu, W.	2012	United States	In vitro	Rat E18 hippocampal neuron primary cultures	Amyloidosis	PAR-1/MAPK	Neuron cultures and exposure to 5 mcg of Aβ42. Immunofluorescence analysis and electrophysiological records were obtained to count the number of dendritic spines, GluR1, synapsin 1 and PSD-95. Recombinant RNA was built to induce overexpression of PAR1 and MARK4.	PAR-1/MAPK family kinases play a critical role in Aβ toxicity on synapses and dendritic spines. Overexpression of MARK4 led to tau hyperphosphorylation and synaptic dysfunction, phenotypes also observed after Aβ exposure.
Amyloid-Beta Peptide 1-42 Causes Microtubule Deregulation through Nmethyl-D-aspartate Receptors in Mature Hippocampal Cultures	Mota, S.	2012	Portugal	In vitro	Wistar fetal rats at embryonic 18-19 day.	Amyloidosis	Beta III-tubulin and polymerized tubulin	Primary hippocampal cell culture, exposure to 500 nM of Aβ and NMDA treatment. Antagonists of rNMDA were added (MK-801, memantine, ifenprodil). Immunocytochemistry analysis and fluorescence microscopy was performed.	Aβ1-42 caused a decrease in total and polymerized levels of beta-III tubulin and polymerized alpha-tubulin, suggesting microtubule disassembly. This finding was significantly correlated with reduced neurite length. Also, Aβ induced DNA fragmentation in both neuronal and non-neuronal cells.

Soluble Aβ Oligomers Impair Dipolar Heterodendritic Plasticity by Activation of mGluR in the Hippocampal CA1 Region	Zhao, J.	2018	United States	In vitro	Mice C57BL/6 and 129 (male and female, 6~8 weeks old)	Amyloidosis	mGluR	Cultured hippocampal cells from mice were exposed to human oligomeric Aβ. A protocol to record postsynaptic potentials in the CA1 region was performed. LTP was induced with 2 consecutive trains of stimuli at 100 Hz separated by 20s, or 10 pulses at 10 Hz separated by 10s in basal and apical dendrites.	oAβ induced LTD in both apical and basal dendrites as well as reduction in neurotransmission. Basal dendrites are more resistant to Aβ-mediated synaptotoxicity.
Longitudinal testing of hippocampal plasticity reveals the onset and maintenance of endogenous human Aβ-induced synaptic dysfunction in individual freely behaving pre-plaque transgenic rats: rapid reversal by anti-Aβ agents	Qi, Y.	2014	Ireland	In vivo, in vitro	Male TG rats expressing APP751 with Swedish and Indiana mutations under the control of the murine Thy1.2 pro-moter (McGill-R-Thy1-APP) and their age-matched WT.	Amyloidosis	N/A	For in vivo measures, a surgery was performed to place electrodes in the CA1 region. Then the brain was removed and hippocampal samples were taken, electrodes were placed in the cultured neurons. Immunohistochemistry and staining was carried out.	Longitudinal in vivo studies revealed an age-dependent inhibition of long-term potentiation without a change in baseline synaptic transmission. In vitro analyses showed reduction in NMDA receptor-mediated synaptic currents.
Disassembly of Shank and Homer Synaptic Clusters Is Driven by Soluble β-Amyloid1-40 through Divergent NMDAR-Dependent Signalling Pathways	Roselli, F.	2009	Germany	In vitro	Primary cell cultures from cortical tissues from 4-day-old Winstar rats.	Amyloidosis	Homer1b and Shank1	Frontal cortex neurons were cultured and analyses were carried out after 10-13 days after culture. Electron microscopic visualization of cells was performed, as well as Western blot and staining techniques. Synthetic Aβ1-40 was used.	Aβ disrupts Homer and Shank scaffold proteins, decreases postsynaptic density and reduces synaptic availability of mGluR1.
Amyloid-β Acts as a Regulator of Neurotransmitter Release Disrupting the Interaction between Synaptophysin and VAMP2	Russell, CL.	2012	England	In vitro	Sprague Dawley E18 rat embryos.	Amyloidosis	Synaptophysin / VAMP2	Primary cultures of CA3-CA1 hippocampal cells were prepared. Immunocytochemistry and FM1-43FX labeling was performed, proteins were extracted and underwent immunoprecipitation. Electrophysiological recordings were taken. Synthetic Aβ peptides were used.	Aβ disrupts the complex formed between synaptophysin and VAMP2, increasing the number of primed vesicles and exocytosis. Aβ impaired synaptic transmission.

Imbalance in the response of pre and post-synaptic components to amyloidopathy	Stephen, TL.	2019	England	In vivo, in vitro	Adult female of the J20 line (Aβ-overexpressing mice with Swedish and Indiana mutations) and their WT littermates controls.	Amyloidosis	N/A	For in vivo recordings, cranial windows were surgically placed in the somatosensory cortex. Imaging process was performed with a two-photon microscope.	Synaptic turnover is higher in the presence of Aβ and this is accompanied by a reduction in pre but not postsynaptic densities. These findings are independent of plaque proximity.
Fibrillar β-Amyloid Impairs the Late Phase of Long Term Potentiation	Puzzo, D.	2006	United States	In vivo	C57/BL6 male mice.	Amyloidosis	N/A	Electrons were placed in the stratum radiatum of the CA1 region. Fibrillary and oligomeric Aβ was administered.	Aβ impaires the late protein-synthesis dependent phase of LTP.
TRPA1 channels promote astrocytic Ca2+ hyperactivity and synaptic dysfunction mediated by oligomeric forms of amyloid-β peptide	Bosson, A.	2017	France	In vitro	TG mice with the APP/PS1-21 mutation, Swiss mice and WT controls.	Amyloidosis	N/A	Hippocampal cells were cultured. Astrocytes were dyed with Fluo-4 and calcium imaging was performed. Whole-cell recordings were taken and spontaneous excitatory postsynaptic currents were collected. oAβ was applied.	oAβ caused calcium hyperactivity in the astrocytic population. This phenomenon is independent of neuronal activity and is repaired by transient receptor potential A1 (TRPA1) channels blockade. TRPA1 hyperactivity triggers glutamate spontaneuos activity in neurons.
β-amyloid impairs axonal BDNF retrograde trafficking	Poon, WW.	2011	United States	In vitro	Embryos from E18 rat and E16 mice. Mice Tg2576 with the double APP mutation K670N M671L.	Amyloidosis	Brain-derived neurotrophic factor (BDNF)	Hippocampal neurons were cultured in a microfluidic chamber, BDNF-GFP molecules and oAβ were added. Immunocytochemistry analyses and quantification of TrkB, Rab7 y BDNF-GFP were performed.	Aβ affects BDNF-mediated TrkB retrograde trafficking.
Regulation of NMDA receptor trafficking by amyloid-b	Snyder, EM.	2005	United States	In vitro/In vivo	Mice with APP Swedish mutation.	Amyloidosis	N-methyl-D-aspartate receptor (NMDAr)	Hippocampal neurons from the CA1 region were extracted and cultured. NMDA currents were induced with glycine infusion. Patch-clamp recordings and biotinylation procedures were carried out.	Aβ reduced expression of NMDAr by increased endocytosis. This was mediated by activation of the a-7 nicotinic receptor, protein phosphatase 2B (PP2B) and the tyrosine phosphatase STEP. Reducing Aβ by treating neurons with gamma-secretase inhibitor restored surface expression of NMDAr.

Region- and age-dependent reductions of hippocampal long-term potentiation and NMDA to AMPA ratio in a genetic model of Alzheimer's disease	Tozzi, A.	2015	Italy	In vitro	TG mice expressing the Swedish and/or Indiana APP mutation and age-matched WT.	Amyloidosis	rNMDA/rAMPA	Hippocampus was extracted and electrodes were placed in the CA1 region and in the dentate gyrus (DG). Excitatory postsynaptic potentials were induced with different amplitude stimuli.	Presence of oAβ was seen in 2-month old mice in the CA1 region but not in the DG. In 6-month-old mice, the presence of oAβ and plaques was evident and LTP was reduced in CA1 and DG regions. Loss of LTP was linked to reduced NMDA/AMPA ratio. LTP was rescued in the presence of neostigmine in the CA1 region at early stages, memantine restored LTP selectively in DG at later stages.
β-Amyloid-induced Dynamin 1 Degradation Is Mediated by N-Methyl-D-Aspartate Receptors in Hippocampal Neurons	Kelly, BL.	2006	United States	In vitro	Embryonic day 18 rat embryos.	Amyloidosis	Dynamin 1	Primary cultures of hippocampal neurons were performed. Then pre-fibrillary Aβ was added to the culture medium. Cultures were transferred to Inmobilon for immunodetection. Immunocytochemistry and calcium imaging techniques were carried out.	oAβ induced sustained calcium influx, calpain activation, and dynamin 1 degradation.
Time-dependent reversal of synaptic plasticity induced by physiological concentrations of oligomeric Aβ42: an early index of Alzheimer's disease	Koppensteiner, P.	2016	United States	In vivo/ In vitro	C5BLJ/6J mice at postnatal day 0-1.	Amyloidosis	N/A	Primary hippocampal cell cultures were prepared, an infusion of Aβ was added and electrophysiological measures were recorded. In vivo procedures consisted of Aβ infusion and fear conditioning tasks.	Short exposures to Aβ enhanced synaptic plasticity and longer exposures impaired it. The latter was concomitant with an increase in the basal frequency of spontaneous neurotransmitter release, a higher basal number of functional presynaptic release sites, and a redistribution of synaptic proteins including the vesicle-associated proteins synapsin I, synaptophysin, and the postsynaptic glutamate receptor I. These findings were in line with in vivo reports.
First effects of rising amyloid-b in transgenic mouse brain: synaptic transmission and gene expression	Cummings, DM.	2014	England	In vivo	TG mice with APP/PSEN1 mutation and WT controls.	Amyloidosis	N/A	Acute brain slices were prepared and immersed in synthetic LCR, patch-clamp recordings were made and histological evaluation of hippocampal cells was performed. Data was obtained from 3	In the third postnatal week, Aβ peptides were not detectable. At 2 months levels increased 50% and the first changes in synaptic currents were detected. At 4 months, Aβ42:Aβ40 ratio increased and plaques appeared.

								weeks-old, 2 months and 4 months-old mice.	
Caspase Activation and Caspase-Mediated Cleavage of APP Is Associated with Amyloid b-Protein-Induced Synapse Loss in Alzheimer's Disease	Park, G.	2020	United States	In vitro	TG mice with the D664A mutation in APP.	Amyloidosis	Caspase	Hippocampal cell culture, dendritic spines analysis, treatment with gamma-secretase and caspase inhibitors, immunohistological assessment to evaluate caspase activity.	The caspase inhibition model, reduction of Aβ-induced synaptic injury was reported, as well as attenuation of reduction in dendritic spines.
Amyloid-β Induces a Caspase-Mediated Cleavage of P2X4 to Promote Purinotoxicity	Varma, R.	2009	United States	In vitro	Embryonic day 18 Sprague-Dawley rat embryos.	Amyloidosis	Purinergic receptor P2X4	Cell cultures, immunoblot analysis, immunofluorescence microscopy. Neurons were exposed to a lentivirus to induce expression of P2X4, quantification of cell survival was performed, as well as measurements of intracellular calcium, caspase activity and electrophysiological recordings.	Aβ1-42 promoted accumulation of the calcium permeable purinergic P2X4 in neurons. Additionally, it induced a caspase-3 mediated cleavage of the receptor that slowed channel closure times.
Triple-Transgenic Model of Alzheimer's Disease with Plaques and Tangles: Intracellular Aβ and Synaptic Dysfunction	Oddo, S.	2003	United States	In vivo	Triple transgenic mice (Swedish APP mutation, human tau p301L y PS1 m146v) and WT controls.	Amyloidosis	NA	Human APP cDNA harboring the Swedish double mutation was subcloned into exon 3 of the Thy1.2 expression cassette. ELISAs, immunoblot, immunohistochemistry and electrophysiological measures.	Synaptic dysfunction, including LTP impairment, manifests in an age-dependent manner, but before plaques and tangle formation.
Impaired AMPA signaling and cytoskeletal alterations induce early synaptic dysfunction in a mouse model of Alzheimer's disease	Baglietto-Vargas, D.	2018	United States	In vitro	Triple transgenic mice (APP, tau y PS1) and WT controls, of 3 months and 7-8 months old.	Amyloidosis	AMPAr	Cell cultures, immunotherapy, electrophysiological measures, Immunohistochemistry analysis and electron microscopy visualization.	AMPA signaling is impaired early in the disease course in an AD. It is associated with changes in dendritic spine structure and is correlated with the presence of soluble Aβ and tau.

Activation of CaMKIV by soluble amyloid-β 1-42 impedes trafficking of axonal vesicles and impairs activity-dependent synaptogenesis	Park, D.	2017	Korea	In vitro	Embryonic day 18 Sprague-Dawley rat embryos.	Amyloidosis	Ca2+/calmodulin-dependent protein kinase IV (CaMKIV)	Plasmid construction for synapsin 1a and CaMKIV, antibodies selection (phospho-Ser9 –synapsin, synapsin I, phosphoThr196–CaMKIV, CaMKIV, mCherry, b-tubulin , 6E10 , Aβ1–42-1 or Aβ1–42-2, synaptophysin, actin, and glutathione S-transferase), synthetic Aβ1-42 preparation, hippocampal cells cultures, transfection, treatment with gamma-secretase inhibitor, LTP chemically induced, immunocytochemistry measures and microtubule staining, calcium measurements.	Exposure to low concentrations of Aβ1-42 impaired Ca2+ clearance from presynaptic terminals and increased the basal Ca2+ concentration. This caused an increase in the phosphorylation of CaMKIV and its substrate synapsin, which markedly inhibited SV trafficking along axons between synapses. The latter was prevented by an inhibitor of CaMK kinase, by antibodies against Aβ1-42, or by expression of a phosphodeficient synapsin mutant.
Synaptogyrin-3 Mediates Presynaptic Dysfunction Induced by Tau	McInnes J	2018	Belgium	In vitro, In vivo	PS19 mice expressing human TauP301S(1N 4R isoform) under control of the mouse prion promoter, neuromuscular junction experiments in larvae of Drosophila melanogaster, hippocampal human neurons.	Tauopathy	Synaptogyrin-3	Isolation of synaptic vesicles (SV) from human brain tissue and Drosophila brain, purification of human recombinant Tau protein, in vitro essays to evaluate binding of SV-Tau, mass spectrometry to identify SV-related proteins. Then immunofluorescence and electrophysiological recordings were performed in the neuromuscular junction of Drosophila and in hippocampal neurons of mice.	Tau binds to presynaptic vesicles through synaptogyrin-3. In fly and mouse models of Tauopathy, reduction of Synaptogyrin-3 prevents the association of presynaptic Tau with vesicles, alleviates Tau-induced defects in vesicle mobility, and restores neurotransmitter release.
Abnormal tau induces cognitive impairment through two different mechanisms: synaptic dysfunction and neuronal loss	Di J	2016	United States	In vitro, In vivo	Murine model with expression of phospho-tau, cellular culture from neuroblastoma cells of mouse.	Tauopathy	NA	Mouse neuroblastoma cells were cultured and transfected to induce phosphorylation of Tau. Then immunochemistry and immunofluorescence was performed to evaluate neuronal death and synaptic dysfunction. Electron microscopy was used	Low phosphorylated tau levels resulted in significant cognitive deficits, decrease in the number of synapses, and reduction of synaptic proteins. Induction tau triggered neuronal death, astrocytosis, and loss of the processes in CA1.

								to assess synapses length and postsynaptic density. Mice of 15–24 months were subjected to memory and learning tasks.	
Reduced gliotransmitter release from astrocytes mediates tau-induced synaptic dysfunction in cultured hippocampal neurons	Piacentini R	2017	Italy	In vitro	WT E18 C57/bl6 mice	Tauopathy	Gliotransmitters	Primary cultures of hippocampal neurons and astrocytes, recombinant tau protein and human AD tau preparation and oligomerization, assessment of tau uploading, confocal calcium imaging, high performance liquid chromatography (HPLC) measurements, whole cell patch-clamp recordings, immunocytochemistry and western blot.	Extracellular tau oligomers are abundantly and rapidly accumulated in astrocytes where they disrupt intracellular Ca2+ signaling and release of gliotransmitters, especially ATP. Consequently, synaptic vesicle release, the expression of pre- and post-synaptic proteins, and miniature excitatory postsynaptic currents frequency and amplitude were reduced in neighboring neurons. Tau uploading from astrocytes required APP.
Tau oligomers impair memory and induce synaptic and mitochondrial dysfunction in wild-type mice	Lasagna-Reeves CA	2011	United States	In vitro, In vivo	C57BL/6 mice	Tauopathy	Synaptophysin, septin-11, mitochondrial complex.	Tau subcortical stereotaxic injection was performed in mice and then object recognition tasks were performed. Hippocampal neurons samples were isolated and western blot was carried out to identify proteins related to synaptic and mitochondrial function. To assess neuronal damage and neurodegeneration immunohistochemical and microscopic analysis was completed.	Tau oligomers impaired memory consolidation, whereas tau fibrils and monomers did not. Additionally, tau oligomers induced synaptic dysfunction by reducing the levels of synaptic vesicle-associated proteins synaptophysin and septin-11. Tau oligomers produced mitochondrial dysfunction and activated caspase-9,
Extracellular truncated tau causes early presynaptic dysfunction associated with Alzheimer's disease and other tauopathies	Florenzano F	2017	Italy	In vitro	Wistar rats	Tauopathy	NA	Preparation of tau peptides, purification of synaptosomes from rats, intracellular calcium imaging, immunofluorescence, western blot and densitometry analysis.	Low levels of tau protein accumulate at presynaptic terminals and affect glutamate transmission. Neuritic dystrophy, microtubules breakdown, deregulation in presynaptic proteins and loss of mitochondria was only seen

									with prolonged exposures to tau protein.
Phosphorylation in two discrete tau domains regulates a stepwise process leading to postsynaptic dysfunction	Teracski s PJ	2021	United States	In vitro	Sprague Dawley rats	Tauopathy	NA	Primary hippocampal neuron culture, transfection with human tau. Electrophysiological measurements of excitatory postsynaptic currents, microscopic imaging to evaluate dendritic spines and immunocytochemistry analysis.	Tau phosphorylation in the C-terminal domains results in mislocalization to dendritic spines. When phosphorylated in the N-terminal domain, reduction of functional AMPA receptors was reported.
Reactive Oxygen Species-Mediated Loss of Synaptic Akt1 Signaling Leads to Deficient Activity-Dependent Protein Translation Early in Alzheimer's Disease	Ahmad, F.	2017	India	In vivo, in vitro	Mice with the APP/PSEN1mutation divided in three groups by age: 1-1.5, 3-4, 9-12 months old and WT controls.	Inflammation	Akt1	Primary antibodies against pAkt1 y Akt1 were prepared. Synaptoneurosomes were prepared tissue from mice and postmortem human brains, then immunoblotting and immunoprecipitation of Akt1 was performed. Then primary neuronal cultures were established and assays to evaluate ROS and Akt1 expression were performed.	It was demonstrated that ROS-mediated oxidative modification of Akt1 contributes to synaptic dysfunction in AD, seen as loss of activity-dependent protein translation, a process essential for synaptic plasticity.
PGE2-EP3 signaling pathway impairs hippocampal presynaptic long-term plasticity in a mouse model of Alzheimer's disease	Maingret, V.	2017	France	In vitro	Male mice with the APP(Swe)/PS1 mutation and paired controls.	Inflammation	PGE2-EP3	Acute hippocampal slices were transferred into a recording chamber to record electrophysiological variables. Then RNA isolation, reverse transcription, and quantitative PCR was performed, as well as immunohistochemistry analyses.	PGE2 had no effect on either basal transmission or short-term plasticity. But it strongly impaired presynaptic Mf-CA3 long-term potentiation (LTP) by acting on PGE2 receptor 3 (EP3) receptors.