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REVIEW OPEN ACCESS

The Role of Synaptopathy in Alzheimer's Disease: A Review of Key Transgenic Mouse Models

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Abstract

Introduction: Long-term potentiation (LTP) and its counterpart, long-term depression (LTD), are considered the cellular basis underpinning learning and memory. Impairments in these processes are associated with neurodegenerative diseases such as Alzheimer's disease (AD). These impairments are emergent during the onset of AD, suggesting a critical role in the pathophysiology of AD. Popular transgenic AD models, such as 5xFAD, 3xTg, Tau MAPT P301L, and APPswe/PSEN1dE9 demonstrate changes in synaptic plasticity early during their lifespan. This systematic review aims to investigate localization and onset of synaptopathy associated with AD.

Methods: A comprehensive literature search was conducted using PubMed (Medline) to identify common features across models associated with synaptic plasticity. Papers were screened through two stages. The first stage involved establishing a set of criteria, including search terms. The second stage centered on ensuring chosen studies focused on synaptopathy and utilized the models selected.

Results: Eight studies were selected across the four transgenic mouse models that established onset and localization of synaptopathy in AD pathophysiology. In the majority of studies, impairments in synaptic plasticity were first found in the CA1 region of the hippocampus. Moreover, onset of these impairments developed prior to onset of neuropathology and behavioral or cognitive deficits. Impairments in synaptic plasticity included inhibition of glutamate release, decreased cell excitability, dendritic atrophy and impaired receptor signaling.

Discussion: The results of this review suggest localization of synaptic plasticity impairments to the CA1 region preceding development of neuropathologies such as amyloid or tau aggregation and cognitive deficits. This indicates an early and critical role of synaptopathy at the CA1 region, implicating it as a potential causal factor in the pathophysiology of AD.

Conclusion: While the FAD models evaluated in this review implicate changes in synaptic plasticity within AD, they are not representative of late onset AD (LOAD), the prevalent form of the disease in the population. Currently research using LOAD models is limited, causing reliance on FAD models for the study of AD. As prevalence of AD increases in the population, it is essential that new models of LOAD are developed and studied to further current understandings of AD pathophysiology.

Keywords: Alzheimer's disease; synaptic plasticity; synaptopathy; FAD; LTP; LTD; CA1; ADAD; LOAD

Introduction

Alzheimer's Disease (AD) is a neurodegenerative disease characterized by severe declines in cognitive performance, particularly in working and long-term declarative memory [1, 2]. Early research on the disease primarily focused on amyloid plaque formation and accumulation of tau tangles [3, 4]. Other neurological changes, such as impairments in synaptic plasticity and neuroinflammation, have also been linked to the disease's pathophysiology [5, 6]. Impairments in synaptic plasticity are believed to play a causal role in the onset and development of AD [5, 6].

Synaptic plasticity is a neurophysiological process that underlies lasting changes in memory and learning [7]. Synapses can strengthen and weaken their connections in response to changing demands, with these processes being referred to as long-term potentiation (LTP) and long-term depression (LTD), respectively [7, 8]. The hippocampus (HPC) is implicated in synaptic plasticity, with current research on LTP relying heavily on examination of the HPC, specifically the CA1 region [7, 9]. The CA1 area is a critical output structure involved in the formation and consolidation of contextual and spatial memory [10, 11]. The CA1 region is mainly composed of pyramidal neurons which are a primary site of excitatory neurotransmission [12]. These cells have complex dendritic structures that allow for LTP through response from the glutamate receptors, including N-methyl-D-aspartate (NMDA) receptors [12]. Since this cell type is largely localized to the CA1 region of the HPC, most LTP occurs in the CA1 [7, 9-12].

In AD, LTP in the CA1 region can become impaired due to elevated levels of amyloid peptide (Aβ-42), which is particularly vulnerable to oligomerization [13, 14]. When Aβ42 aggregates, it leads to formation of amyloid oligomers, affecting both the structure of pyramidal cells and their receptor expression [14]. Amyloid-beta oligomerization also affects LTD through inhibition of glutamate reuptake, causing an imbalance of excitatory and inhibitory NMDA receptor signalling, leading to synaptic depression [7, 15]. These impairments in both LTP and LTD are associated with neuroinflammation, eventual neuronal death, as well as later behavioral and cognitive deficits observed in AD [14]

To further understand the role of LTP on the neurophysiological changes associated with AD, studies using rodent models are employed. Current transgenic models are created through the insertion of mutations from humans into the rodent genome. The most common form of mutations used are familial AD (FAD) mutations. These FAD mutations cause early onset autosomal dominant AD (ADAD) and are typically expressed through the following genes: amyloid precursor protein (APP), presenilin1 (PS1), and presenilin2 (PS2), causing over-production of Aβ42 peptide [13]. In addition, some transgenic models rely on the use of mutations in the microtubule associated protein tau (MAPT) gene. Mutations in the MAPT gene cause abnormal aggregation of tau in neurons such as neurofibrillary tangles seen in AD [16]. As a result, rodents with these mutations can act as a useful AD model of tauopathy.

Current studies examining the various transgenic models of AD focus largely on amyloid beta and tau aggregation. Therefore, there is little research on the role of synaptic plasticity in early development of AD across transgenic models. Moreover, existing studies do not specifically compare the localization or onset of synaptic plasticity impairments across models. In this review, we examine four prominent models of AD, with specific emphasis on changes in synaptic plasticity. By doing this, we aim to highlight similarities in localization and onset of synaptopathy associated with AD and demonstrate the critical role of synaptic plasticity in the pathophysiology of AD.

Methods

Model Selection

Four transgenic models were selected for review based on a six-factor criterion. Chosen models demonstrated the traits described in Table 1.

Table 1. Key Criterion Used for Model Selection

Genetic Validity	Can these models recapitulate human mutations in AD related to synaptic loss?
Pathological Profile	Can these models recapitulate neurophysiological features that implicate synaptic loss?
Electrophysiological Profile	Can these models demonstrate alterations in LTP and LTD, particularly in hippocampal function of synaptic plasticity?
Pathophysiological Profile	Can these models recapitulate age-dependent progression of synaptic loss and neurodegeneration?
Behavioural Phenotypes	Can these models demonstrate behavioural and cognitive deficits related to changes in synaptic plasticity?
Scientific Relevance	Can these models offer reproducible insights into synaptic plasticity impairments in AD?

Search Strategy

Authors conducted a literature search according to PRISMA (2020) guidelines for papers published within the last 10 years. The search engine PubMed (Medline) was used to conduct the search. Papers published in English and including the following terms: in vivo model OR rodent model AND synaptic plasticity OR LTP AND LTD AND Alzheimer's Disease OR APPswe OR PSEN1de9 OR line 85 OR 5xFAD OR 3xTg OR TauP301L were included. A total of 5,150 papers were identified via this initial screening. In the secondary stage of the selection process, authors further sorted articles by model type, titles and abstracts. Papers that primarily targeted synaptic plasticity, through electrophysiological and behavioral data were approved and selected.

Results

This systematic review synthesized current knowledge on synaptic plasticity and behavioural phenotypes in rodent models of AD. During the literature search, a total of 5,150 articles were identified through the database. After a comprehensive screening process, 8 papers were chosen for inclusion in this review. The four models included different genetic mutations or composition of mutations that expressed phenotypes specified in Table 1.

We considered amyloid plaques and hyperphosphorylated tau tangles as primary pathological capitulations with neuroinflammation considered a symptomatic pathology, as opposed to a primary one. A causal role of inflammation on synaptic impairment is not strongly supported in FAD models, though recent literature has implicated a primary role for it in the development of late onset AD (LOAD) [17, 18]. Synaptopathy in the CA1

region was implicated as a common site for both amyloid plaque and tau pathophysiology. Synaptic deficits in the form of inhibited glutamate release, decreased cell excitability, dendritic atrophy and impaired receptor signalling were observed. These impairments were observed in the CA1 region prior to the onset of neuropathological development in the form of amyloid plaques or tau tangles across models.

5XFAD (C57BL6)

The 5xFAD model is one of the most commonly used in AD research, comprising around 10% of AD mouse studies [19]. 5xFAD was originally created by Oakley et. al to study the impacts of very high cerebral Aβ42 levels (cerebral amyloidosis) [13]. The model expresses neuron-specific transgenes with five FAD mutations, three mutations in APP and two in PS1 [13]. Within the APP gene this model carries the K670N/M671L, V717l, and I716V mutations; and within the PS1 gene it contains the M146L and L286V mutations [13]. The combination of these mutations results in very high levels of Aβ42, causing amyloid aggregation to occur early and aggressively during development [13, 20]. Aggregation of amyloid proteins can be observed in 5xFAD mice as early as 2 months (restricted to the cortex and subiculum), with significant aggregation presenting in the spinal cord at 4 months, and finally the hippocampus, thalamus, olfactory bulbs, and basal brain regions at 6 months [21]. 5xFAD mice also exhibit neuroinflammation as early as 2 months, with progressive inflammation at 4 and 12 months corresponding to Aβ aggregation [22]. Behavioral tasks show age related impairments in 5xFAD mice at 4, 8, 12, and 18 months on spatial memory and motor performance [23]. The selected papers on 5xFAD mice describe decreased LTP as early as 10 weeks with significant impairments in LTP induction in the CA1 region of the hippocampus observed at 4-6 months, worsening with age across 8 and 12 months [23, 24].

APPswe/PSEN1dE9 (Line 85)

Similarly to the 5xFAD model, the APPswe/PSEN1dE9 mouse model is used for the study of cerebral amyloidosis and includes mutations of the APP and PSEN1 genes. The model was created through two mutations in chromosome 9: Mo/HuAPP (K670N/M671L) and hPSEN1 ΔE9 [21]. The first of the two mutations is in the APP gene, containing the Swedish mutation, K670N/M671L [21, 25]. The second is in the PS1 gene with the insertion of human PSEN1 and a deletion of exon 9 [21, 25]. These genetic alterations lead to aggregation of amyloid proteins in the cortex and hippocampus around 5-6 months [21].

Line 85 mice demonstrate decreases in LTP in the prefrontal cortex [26]. However, loss of synaptic plasticity in the CA1 region of the hippocampus and amygdala is debated, as studies have yielded varying results [21, 26]. The synaptic loss and changes in LTP associated with the APPswe/PS1dE9 model have been implicated in mood and memory dysfunction as well as general cognitive impairments, suggesting a causal role in AD development [21, 25].

3xTG

In addition to mutations in the APP gene, the 3xTG model also contains a mutation in MAPT (P301L) [21]. P301L is a common variant of the MAPT gene, associated with behavioural and cognitive impairments of frontotemporal dementia [16, 27]. P301L occurs within exon 10 and affects 4-repeat tau isoforms, leading to selective aggregation of 4R tau [28]. As a result of mutations in both the APP and MAPT genes, 3xTG transgenic mice present with amyloid plaque development at about 6 months and tau tangles at roughly 12-15 months [29]. Amyloid plaque formation is first observed at 6 months in the CA1 and subiculum regions of the HPC and spread to the entorhinal cortex at about 12 months. Cognitive decline is observed starting at 6 months [29].

Synaptic plasticity deficits become apparent in 3xTG mice around 3-4 months, with decreased levels of LTP induction observed in the CA1 due to NMDA receptor abnormalities [30, 31]. These changes in synaptic plasticity have been attributed to abnormal intracellular immunoreactivity and lead to cognitive impairments such as issues with memory retention, memory retrieval, and spatial memory [30, 31].

Tau P301L

Tau P301L also expresses MAPT P301L, however, in contrast to the other models described, this model does not contain any mutations in other genes [32]. In Tau P301L, this mutation is associated with abnormal tau aggregation resembling tangles in the brain stem, spinal cord, midbrain and to a lesser extent in the cerebral cortex [32]. Tau aggregation in these regions of the central nervous system is observed around 8 months [32].

A study by Muller-Thomsen et al. found that P301L mutated mice had impaired synaptic function at the CA1 before significant tau aggregation could be observed [33]. These impairments were specific to CA1 pyramidal cells leading to decreased transmission and excitability of CA1 neurons and a consequent reduction in CA1 LTP [34, 35]. Additionally, Tau P301L mice do not display cognitive impairments until 18-21 months, well after LTP disruption [36].

Table 2. Summary of Studies that Investigated Synaptic Impairments

Paper	Model	Sample Size	Methodology	Findings
Lysikova et al., 2023	APPswe/PS1dE9	*n= 300* Transgenic: n=52.4% Wildtype: n=47.6%	Aβ aggregation was assessed using immunofluorescence staining. Rodents were assessed at 5.5 and 10 months.	Aβ aggregation was progressively observed in transgenic mice at both 5.5 and 10 months. No amyloid aggregation was found in control mice.
Chen et al., 2022	5xFAD	*n=31* Transgenic: n=16 Wildtype: n=15	APP levels were assessed using immunofluorescence staining in the PFC and V1. Electrophysiological measures included examining changes in LTP which were assessed using field excitatory postsynaptic potentials at 6-8 weeks.	Transgenic mice demonstrated increased immunoreactivity in the L5 of the PFC during early post-weaning age (around 21-28 days). APP signals increased with age in transgenic mice. No signal was observed in control mice.
Lopes et. al., 2023	APP/PS1	Sample size not reported. Authors reported 4-8 mice used in the Morris water maze and 5-13 in the open field test.	Behavioral measures included a Morris Water Maze test and open field test. Electrophysiological measures included examining changes in LTP which were assessed using field excitatory postsynaptic potentials.	Transgenic mice took significantly longer to reach the platform in the Morris Water Maze test than controls. Transgenic mice also showed increased anxiety-like behavior in the open field test and reduced LTP in the PFC.
Müller-Thomsen et. al., 2021	Tau P301L	*n=81* Transgenic: n=16 Wildtype: n=15	Electrophysiological measures included examining changes in LTP which were assessed using extracellular field potential recordings and single cell recordings. Morphological measures include spine density, volume.	Transgenic mice CA1 cells atrophied in the form of decreased dendritic length and volume. This atrophy was correlated with decreased LTP induction and in the CA1 leading to decreased cell excitability.
Clark et. al., 2015	3xTg-AD	*n= 46* Transgenic: n=23 Wildtype: n=22	Behavioral measures included a radial arm maze test at 2.5 months and 7.5 months age. Electrophysiological measures included examining changes in LTP which were assessed using extracellular field potential recordings from the CA1.	Transgenic mice were impaired in the behavioral task at both 3 and 8 months of age suggesting deficits in spatial and working memory. NDMA receptor mechanisms in LTP were impaired in 3xTg mice at 3 and 8 months of age, with less total LTP observed specifically at 8 months.
Hunsberger et. al., 2014	TauP301L	*n=42* Transgenic: n=14 Wildtype: n=23	Behavioral measures included a Barnes maze task. Tau pathology was assessed using a panel of antibodies via immunohistochemistry.	Transgenic mice displayed impaired memory compared to controls during the Barnes maze task around 5 months. Immunohistochemistry results indicated abnormal tau conformation in transgenic mice.

Paper	Model	Sample Size	Methodology	Findings
Hatch et. al., 2017	P301L – rTg4510/pR5	*n=37* Transgenic: n=23 Wildtype: n=14	Electrophysiological measures included examining changes in LTP which were assessed using whole-cell patch-clamp for neuronal excitability in the CA1.	Transgenic mice displayed decreased firing of CA1 neurons and depolarized action potential, with the onset of hyperphosphorylated tau before serious neurodegeneration.
Javonillo et. al., 2022	3xTg-AD	*n=60* Transgenic: n=30 Wildtype: n=30	Aβ and tau levels were assessed using immunofluorescence staining. Electrophysiological measures included examining changes in LTP which were assessed using field excitatory postsynaptic potentials.	At 18 months, transgenic mice displayed significant increases in both Aβ40 and Aβ42 in the HPC and cortex. Increased tau levels were also observed in these brain regions in the transgenic mice between 4 and 12 months. Finally, decreased LTP was found at 4 months in the HPC in 3xTg-AD mice.

Discussion

Main Findings

In this review, we examined four prevalent AD models to demonstrate the role of synaptic plasticity in the pathophysiology of the disease. Specifically, we chose to focus on the localization and onset of synaptopathy. Our findings as summarized in Table 2 indicate localization of synaptic plasticity impairments to the CA1 region of the HPC. Additionally, these impairments appear to precede development of neuropathologies such as amyloid or tau aggregation and cognitive deficits. This is in line with the role of the CA1 in learning and memory, as the primary site of LTP, suggesting synaptic impairments in this region lead to behavioral and cognitive deficits [7]. These results suggest an early and causal role of synaptopathy in the pathophysiology of AD.

Limitations

While current transgenic models are valuable for studying Alzheimer's disease (AD), their reliance on FAD mutations presents a challenge. FAD cases of AD account for only about 5% of all AD cases, making LOAD the prevalent disease form in the population [37]. Although these models accurately reflect the pathophysiology of early-onset AD, their relevance to LOAD is unclear [38]. LOAD emphasizes the interaction of genetic and environmental factors in disease penetrance in contrast to the emphasis of pathological aggregation in ADAD [39, 40]. Currently, few LOAD models are viable, and the existing ones fail to accurately represent all the symptoms and pathologies associated with the disease. Consequently, much of the literature to date focuses on FAD models of AD.

Future Research

Current development of LOAD models largely relies on the gene APOE. This gene has three main variations: ε2, ε3, and ε4. Different combinations of APOE alleles can increase risk for LOAD development, with homozygous cases of APOE ε4 being the strongest genetic predictor of AD [41]. Research has demonstrated that carriers of APOE ε4 are at higher risk for aggregation of amyloid-beta and age-related cognitive decline [41]. To date, the APOE4 knock-in model is the most prevalent LOAD iteration, demonstrating impairments in synaptic plasticity independent of classical neuropathology [42-45]. The most recent LOAD model, developed by Kortredes and colleagues, is the LOAD2 model which relies on both genetic and environmental factors [46]. In addition to containing a triple mutation line of APOE4, TREM2 and humanized Aβ, Kortredes and colleagues subjugated LOAD2 mice to a high fat and sugar diet [46]. Subsequently, they demonstrated early neuronal loss, and impaired synaptic functioning, providing evidence for synaptic impairment in LOAD. As more representative models of LOAD are developed, future research should continue to rely on the interaction of genetic and environmental factors to study synaptopathy in AD.

Conclusions

This review evaluated the common and critical features of synaptopathy in relevant AD mouse models. The CA1 region was identified as a common site for synaptopathy prior to amyloid plaque and tau pathology in early-stage ADAD. The papers reviewed here focused on FAD models, which provide a valuable tool for studying various features of AD. However, the clinical insights using these models

are limited due to prevalence of LOAD in comparison to ADAD in the population [37]. Early studies using LOAD models, provide evidence of synaptopathy as a causal factor of AD, independent of amyloid and tau pathology [42-47].

These preliminary insights provide an important benchmark for targeting synaptic plasticity in future AD research. Given the rise of AD in the population, further LOAD studies are needed to deepen current understanding of the disease and refine therapeutic approaches.

List of Abbreviations
AD: Alzheimer's disease
ADAD: autosomal dominant Alzheimer's disease
APP: amyloid precursor protein
FAD: familial Alzheimer's disease
HPC: hippocampus
LOAD: late onset Alzheimer's disease
LTD: long-term depression
LTP: long-term potentiation
MAPT: microtubule associated protein tau
NMDA: N-methyl D-aspartate
PSEN1: presenilin1
PSEN2: presenilin2

Conflicts of Interest
The authors declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent
This paper was a literature review that only evaluated pre-existing studies, and therefore did not require ethics approval nor participant consent.

Authors' Contributions
ES: Collection and analysis of literature, drafting and revision of the manuscript and gave final approval of the version for submission.
HA: Collection and analysis of literature, drafting and revision of the manuscript and gave final approval of the version for submission.
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