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Authors

Pham, Andrew Q

Dore, Kim

Publication Date

2023-04-01

DOI

10.1016/j.semcdb.2022.03.032

HHS Public Access

Author manuscript

Semin Cell Dev Biol. Author manuscript; available in PMC 2023 May 17.

Published in final edited form as:

Semin Cell Dev Biol. 2023 April ; 139: 84–92. doi:10.1016/j.semcdb.2022.03.032.

Novel approaches to increase synaptic resilience as potential treatments for Alzheimer's disease

Andrew Q. Pham,

Kim Dore*

Department of Neurosciences, Center for Neural Circuits and Behavior, UCSD, La Jolla 92093, United States

Abstract

A significant proportion of brains with Alzheimer's disease pathology are obtained from patients that were cognitively normal, suggesting that differences within the brains of these individuals made them resilient to the disease. Here, we describe recent approaches that specifically increase synaptic resilience, as loss of synapses is considered to be the first change in the brains of Alzheimer's patients. We start by discussing studies showing benefit from increased expression of neurotrophic factors and protective genes. Methods that effectively make dendritic spines stronger, specifically by acting through actin network proteins, scaffolding proteins and inhibition of phosphatases are described next. Importantly, the therapeutic strategies presented in this review tackle Alzheimer's disease not by targeting plaques and tangles, but instead by making synapses resilient to the pathology associated with Alzheimer's disease, which has tremendous potential.

Keywords

Neuroprotection; Therapeutic strategies; AD model mice; APP/PS1; PSD-95; phosphatases; cofilin; calcineurin; BDNF; APOE2; Klotho

1. Introduction

In the last few decades, therapeutic strategies against Alzheimer's disease (AD) have been largely focused on reducing brain levels of amyloid-beta (Aβ) and phosphorylated tau. While these disease-modifying approaches are certainly worthy of pursuit, they do not take into account the fact that 30–50% of individuals with Aβ plaques and phosphorylated tau (AD pathology) are cognitively normal [1,2]. Importantly, a recent study showed that the density of dendritic spines in individuals with AD pathology but normal cognition was similar to that of control individuals without AD pathology [3]. In contrast, spine density correlates well with disease severity and is significantly reduced in AD patients [3] (Fig. 1A). This observation is consistent with several other studies demonstrating that loss of synaptic markers appears to be a better predictor for memory deficits and disease

*Corresponding author. kdore@health.ucsd.edu (K. Dore).

Conflicts of interest

We declare no conflicts of interest.

progression in AD patients [4–7]. Therefore, something must be different in the brains of cognitively normal patients, specifically their dendritic spines, which make them resilient against the surrounding AD pathology.

Cognitive reserve, which is related to higher levels of education and intellectual activity throughout a lifetime, has been shown to be correlated with reduced AD risk in humans [8–10]. Environmental enrichment has been used to mimic cognitive reserve in mice and has been found to be beneficial to AD model mice [11,12]. Interestingly, this improvement in memory-related behavioral tests in mice was associated with higher plaque load and Aβ species [11]. This is consistent with observations that synaptic activity increases Aβ production [13]. Such findings clearly demonstrate the powerful impact of cognitive reserve as a neuroprotective mechanism. Moreover, physical activity, especially aerobic exercise, greatly reduces AD risk in humans [14–16]. These lifestyle-based approaches are indeed very interesting ways to prevent or slow the progression of AD.

Here, we describe recent studies investigating synaptic resilience against AD, particularly focusing on approaches aimed at protecting dendritic spines in AD model mice; such approaches could lead to novel therapeutics strategies that could possibly defeat AD. More generally, we examine studies that promote brain reserve, which relate to structural differences that may increase tolerance to AD pathology [8]. A substantial body of evidence suggests that physical activity increases secretion of neurotrophic factors [17–22], which are important for neurogenesis and survival [23]. Indeed, neurotrophic factors increase synapse density in AD model mice [24–27] and, thus, have great potential as AD therapeutics. Because of recent advances in gene therapy, the first single-dose gene therapy for spinal muscular atrophy has recently been approved [28], genetic factors promoting synaptic resilience to AD are also promising novel therapeutic approaches. We will next discuss several genes that have a positive impact on dendritic spines in patients with AD, such as APOE [29–31], klotho [32–34] and TREM2 [35–37], and describe related gene therapy treatment methods if they exist. The synaptic plasticity field has generated a lot of information about the strength and stability of dendritic spines. For example, the size of dendritic spines dramatically increases during long-term synaptic potentiation [38,39] and it is generally accepted that larger dendritic spines are more stable [40–43]. The structural changes associated with synaptic plasticity depend on regulation of actin polymerization [44,45] and several studies have suggested that actin polymerization is affected in AD [46–48]. Consequently, numerous laboratories have developed strategies, based on actin network proteins, to promote spine stability in the face of AD pathology [47–51]. Large and stable dendritic spines contain more PSD-95, a very abundant scaffolding synaptic protein that is selectively reduced in AD [52,53]. Increasing synaptic PSD-95 was shown to protect synapses from Aβ [54] and to rescue memory deficits in AD model mice [55]. Protective effects were also observed with similar scaffolding synaptic proteins like SAP-97 and PSD-93 [56], suggesting that making dendritic spines stronger structurally is beneficial against AD. Furthermore, protein phosphatases are important signaling mole-cules that are required for long-term depression of synaptic transmission and are also implicated in Aβ-induced depression [57]; we will thus conclude with a discussion of therapeutic approaches based on phosphatase inhibition [58,59]. Altogether, these novel approaches to increase

synaptic resilience against AD are reshaping our understanding of the disease and could lead to therapies that have the potential to defeat AD.

AD is a complex disease with multiple factors influencing its pathophysiology; multiple mechanisms may thus contribute to synaptic loss and resilience. Glutamate toxicity is one contributor to synaptic loss: Aβ-related impairment of glutamate reuptake can cause synaptic depression, hyperactivity, and synaptotoxicity [60–62]. Clinical cases of resilience against Aβ accumulation may be attributed to structural differences in Aβ fibril populations [63] and in the relative ratio of different Aβ structural isoforms [64]. Synaptic resilience may also stem from differences in neuroinflammatory responses amongst individuals. Greater microglial activity can help preserve synaptic density and improve cognitive performance [65]. While these mechanisms are promising targets in the treatment of AD, this review will focus on methods that target synaptic resilience more directly.

2. Neurotrophic factors

Healthy lifestyle practices have been part of the clinical recommendations for AD patients for a long time, because these significantly reduce the probability of developing AD [14–16]. Importantly, physical exercise increases levels of brain-derived neurotrophic factor (BDNF), both in humans [18,20,21] and in rodents [17,19,22,68]. One study has shown that treadmill exercise increased BDNF and reduced dendritic spine elimination in mice, leading to greater cognitive performance [68]. Because of the role of BDNF in promoting neuronal survival, and because BDNF expression is reduced early in AD patients [69,70], several studies have aimed to increase BDNF levels to promote synaptic resilience against AD.

A very convincing demonstration of the impact of BNDF on dendritic spines in AD model mice came from experiments where AD model mice (5xFAD) were crossed with mice expressing BDNF under the GFAP promoter, thereby restricting BDNF production to astrocytes. The reduced spine density found in both the prefrontal cortex and hippocampus of 5xFAD mice was rescued following astrocytic expression of BDNF (Fig. 1B) [24]. In parallel, synaptic markers (PSD-95 and synaptophysin) were decreased in 5xFAD mice but were restored to normal levels in AD mice expressing BDNF. Memory deficits observed in 5xFAD mice in novel object recognition, Y-maze and passive avoidance tests were also rescued by expressing BDNF in astrocytes [24], demonstrating that BDNF expression in astrocytes protects synapses and rescues memory impairments. Upregulation of BDNF signaling in an AD rat model, by treatment with the neuropeptide apelin-13, also rescued loss of synaptophysin and memory deficits, providing additional evidence that BDNF is beneficial in AD [25].

The Tuszynski laboratory has been investigating the protective effects of neurotrophins for more than 30 years [71] and has published several papers demonstrating that delivery of BDNF via gene therapy has neuroprotective effects in AD mice, aged rats and non-human primates [26,27]. In J20 AD model mice, injections of lentivirus expressing BDNF into the entorhinal cortex increased BDNF levels in this region as well as in the hippocampus. This resulted in a rescue of synaptophysin levels in both of these brain regions and significantly improved hippocampal-dependent learning (contextual fear conditioning and Morris Water

Maze) [26,27]. Lentiviral expression of BDNF in aged rats also improved improved their performance in the Morris Water Maze test and viral injection in aged monkeys improved visuospatial learning [27]. A clinical trial is now underway to test the therapeutic efficacy of this approach in humans with early signs of AD (ClinicalTrials.gov Identifier: NCT05040217), demonstrating the great potential of this neuroprotective approach.

3. Protective genes

While genetics plays a major role in the incidence of AD, only 1–10% of AD cases are familial cases that are directly linked to gene mutations. Mutations in three specific genes (amyloid precursor protein (APP) and presenilins (PSEN1, PSEN2)) lead to early-onset AD [72,73]. Interestingly, out of approximately 100 disease-causing mutations found in these genes [74], one rare protective mutation was found in the APP gene of an elderly Icelandic population [75]. Perhaps this protective mutation could be developed for gene therapy in the future [76]. In the past few decades, much effort has been devoted to identifying other genes associated with AD heritability [72,74,77]. A variant of apolipoprotein E (APOE), the APOE4 allele, was the first gene to be associated with late-onset AD, which is the most common form of the disease [78]. Another variant of the same gene, APOE2, was later identified to protect subjects from AD [79]. APOE is a protein that is implicated in lipid transport and also binds Aβ [80]. Because of its high AD risk, APOE4 has been the focus of many therapeutic approaches [81]. However, the neuroprotective role of APOE2 may also allow development of therapies that improve synaptic resilience [66,67] (Fig. 1B). Viral expression of the APOE2,3,4 variants had diverse effects in APP/PS1 AD model mice [30]. While expression of APOE4 increased Aβ accumulation, expression of APOE2 reduced Aβ levels. By immunostaining for PSD-95 and synapsin, they found that mice expressing APOE2 lost less synapses near plaques compared to the APOE4 group, further demonstrating how APOE2 helps to protect synapses [30]. Similarly, reductions in spine density observed in two different AD mouse models were rescued in double-transgenic mice expressing human APOE2 [29]. Another study found that inducing expression of APOE2 imparts a neuroprotective effect even in APOE4 knock-in mice [31]. The approach of expressing APOE2 in APOE4 homozygotes, via development of the AAVrh.10hA-POE2 vector that causes CNS-specific APOE2 expression, has reached Phase I clinical trials ([82], ClinicalTrials.gov Identifier: NCT03634007). An interesting case study of a patient with a disease-causing mutation in the PSEN1 gene, which normally would induces AD at an early age (forties), found that the patient was remarkably resistant to the clinical manifestations of AD [83]. This patient was homozygous for the rare Christchurch mutant form of APOE3, which reduces APOE interactions with heparin and lipoprotein receptors [83]. An antibody binding to the mutated APOE region reduced heparin binding in the same way, suggesting that this Christchurch mutation in APOE3 might lead to promising antibody-based therapeutic approaches [83]. The merit of APOE-based approaches will be closely examined in the coming years and promises to improve the cognitive trajectory of AD patients.

The Klotho protein (encoded by the KL gene) is associated with slowing down of aging processes and has therefore garnered much interest in relation to multiple age-related diseases [84–86]. Klotho levels are decreased in the cerebrospinal fluid of AD patients

[87] and in the hippocampus of AD mice [32]. Dubal and colleagues asked whether increased klotho levels could ameliorate AD-related impairments by crossing transgenic mice overexpressing klotho [84] with J20 AD model mice [32]. They found that these double-transgenic mice (J20xKL) had a higher density of spines compared to the J20 AD mice (Fig. 1B). Interestingly, klotho overexpression increased synaptic resilience without affecting levels of disease-causing proteins [32]. The synaptic benefits of klotho overexpression in AD mice are paralleled by improvements in memory-related behavioral tests, such as the Morris Water Maze and novel object recognition task [32]. Other studies using lentiviral-mediated overexpression of klotho have shown similar synaptic and cognitive benefits, and additionally found that klotho overexpression improved Aβ clearance [33,34]. These studies demonstrate that klotho overexpression ameliorates AD deficits. Therefore, multiple approaches to increase klotho levels in the brain are being developed, including direct application of protein [88], pharmaceutical upregulation [89], and even gene-editing approaches [90]. Considering this progress as well as the synapto-protective effects of klotho overexpression, it is plausible that these approaches will develop into neuroprotective therapies for AD.

Loss-of-function variants of the microglia-expressed triggering receptor gene (TREM2) are associated with increased AD risk and earlier onset of brain pathology, as well as other physiological anomalies [91, 92]. Ruganzu and colleagues have found that increasing soluble TREM2 levels in APP/PS1 mice through viral expression had beneficial effects in APP/PS1 mice, reducing Aβ accumulation, rescuing synaptic loss and improving performance in the Morris Water Maze test [35]. Elevating TREM2 levels by injecting recombinant TREM2 protein into the hippocampus produced similar ameliorating effects in 5xFAD mice [36]. This approach of increasing TREM2 in AD patients has already reached the clinical testing phase. The TREM2 agonistic antibody AL002 has been shown to activate TREM2, which led to the proliferation of microglia and reduction of Aβ accumulation in AD model mice [37]. Phase I clinical trials have demonstrated that this treatment is well tolerated [37] and Phase II trials (ClinicalTrials.gov Identifier: NCT04592874) are now underway to assess the efficacy of AL002.

Interestingly, using a machine learning approach, a novel protective mutation was recently found in ABHD17a, an enzyme mediating the synaptic removal of PSD-95 (see section on scaffolding proteins below) [93]. Notably, AD patients with the ABHD17a mutation received their AD diagnosis at a significantly older age than those without it [93]. This suggests that this mutation is protective against AD, maybe because it reduces ABHD17a activity towards PSD-95, which would lead to increased synaptic PSD-95. The different approaches presented in this section have significant therapeutic potential; studies in AD mice demonstrated that APOE2 [29–31], klotho [32–34] and TREM2 [35,36] expression led to drastic improvements in synaptic resilience. Importantly, clinical trials testing these strategies in humans are ongoing for APOE2 [82] and TREM2 [37].

4. Actin network proteins

Filamentous actin (F-actin), formed by the polymerization of globular actin, play major roles in providing structural integrity and facilitating dynamic restructuring in response

to learning [44,45]. Importantly, reduced F-actin levels and loss of dendritic spines were observed in 1-month old APP/PS1 mice [46], suggesting that this phenomenon occurs very early in AD. In humans, loss of synaptic F-actin correlated with higher Braak stage, Aβ and Tau pathology and worse global cognition [46]. Moreover, injections of Jasplakinolide, an actin-polymerizing agent, rescued impairments in fear conditioning behavioral tests in 2-months old APP/PS1 mice [46]. In contrast, latrunculin, which blocks actin polymerization, caused reductions in synaptic F-actin as well as poorer fear conditioning performance [46]. Because the degradation of actin architecture has such a big impact in AD, multiple therapeutic approaches have aimed at preserving this support system to make spines more resilient to AD pathology.

Cofilin is one of the most important actin-binding proteins and regulates the actin cytoskeleton in neurons, mainly by mediating F-actin cleavage [94]. Cofilin ability to bind actin and thus its activity, is controlled by phosphorylation, as phosphorylated cofilin cannot bind actin and is considered inactive [94]. Interestingly, application of Aβ oligomers reduced cofilin phosphorylation, increasing its activity [47, 48]. Moreover, cofilin phosphorylation was reduced in AD mice [46,48] and in the frontal cortex of AD patients [47]. However, recent reviews on the role of cofilin in AD specified that different laboratories have come to opposing conclusions on cofilin phosphorylation and its influence on AD pathophysiology, indicating that this is still not completely understood [95,96].

Early findings demonstrated that expression of constitutively inactive cofilin increased spine density as well as spine resilience against the application of Aβ oligomers, indicating the therapeutic potential of cofilin inactivation [97]. The Kang lab at the University of South Florida has produced a series of papers demonstrating the role of cofilin in synaptic degeneration. Reducing cofilin expression or activation through the upstream regulators RanBP9 and SSH1 rescued Aβ-induced reductions in synaptic markers such as F-actin, PSD-95, and debrin (an actin binding protein), suggesting that reduced levels of cofilin improved synaptic resilience [49,50]. This approach also rescued deficits in long-term potentiation (LTP) as well as contextual fear conditioning behavioral experiments [49,50]. Furthermore, expression of constitutively inactive cofilin in a tauopathy model, Tau-P301S mice, prevented LTP deficits, synaptophysin reduction and improved contextual fear conditioning performance [98]. In contrast, expression of constitutively active cofilin mimicked the effects of tau pathology and disrupted the cytoskeleton [98]. Building off these findings, recent approaches have looked at more easily applicable pharmaceutical methods to reduce cofilin activity. Injection of a peptide blocking phosphatases mediating cofilin dephosphorylation in AD mice led to increased cofilin phosphorylation and restoration of glutamatergic receptors levels [48]. Moreover, this approach also improved performance on memory behavioral tests such as the T-maze and novel object recognition [48]. The Shatz lab demonstrated that cofilin phosphorylation is regulated upstream by the Aβ receptor LilrB2 or its murine homologue PirB, as Aβ binding to this receptor causes cofilin dephosphorylation [47]. In contrast with WT mice, application of Aβ oligomers did not affect PSD-95 levels in PirB knockout mice. Moreover, LTP induction and maintenance were improved in these mice as well as performance in the novel object recognition task [47]. More recently, chemical LilrB2 inhibitors were developed and effectively prevented cofilin dephosphorylation [99,100]. They found that application of LilrB2 inhibitors

ameliorated neurite growth, a process compromised by Aβ, suggesting a neuroprotective effect [100]. Along with previous studies showing the synapto-protective effect of cofilin inhibition [47–50,98], these therapeutic approaches are very likely increasing synaptic resilience through reducing cofilin activity by regulating its phosphorylation. Taken together, these findings suggest that cofilin inhibition is a promising therapeutic avenue for providing synaptic resilience in AD (see Fig. 2A).

In opposition to this view, other research groups have found that cofilin inactivation provided artificial actin-stabilizing conditions that allowed for aberrant overgrowth of vulnerable spines [101,102]. Accordingly, cofilin knockout models have shown increased synaptic density, but to the detriment of learning and memory [103]. The Buisson research group provided strong evidence for improving synaptic resilience by upregulating cofilin activity [104]. Looking at PSD-fractions, cofilin was more phosphorylated in spines of three-month-old APP/PS1 mice compared to WT controls. Cofilin phosphorylation was similarly increased in the frontal cortex in humans with AD. However, the average age of control individuals was 49 years and the one of AD cases was 84 years, raising doubt on these results [104]. Confocal imaging also indicated greater cofilin localization to spines in APP/PS1 mice. In order to see if blocking cofilin inactivation could protect synapses, the group used the Rho-kinase (ROCK1) inhibitor Fasudil, which is already used safely in other clinical contexts [105]. Aβ can activate ROCK1 through RhoA [51] and inhibiting ROCK1 affects cofilin by preventing the activation of LIM kinase, which would normally phosphorylate cofilin [51]. Fasudil treatment prevented Aβ-induced cofilin phosphorylation and actin stabilization. Moreover, Fasudil treated neurons had greater synaptic density after a 24-hour Aβ application than control neurons [104]. Similarly, others have shown that Aβ increased phosphorylated cofilin in rat hippocampal neurons and that a peptide blocking LIM kinase activation, consequently activating cofilin, rescued Aβ effects on dendrites [106]. Interestingly, LIM kinase inhibition was also shown to rescue thin spines density, which were specifically affected in AD mice [51]. This finding is in line with another study described below in the scaffolding proteins section [54] and suggests that bigger dendritic spines are protected in AD. These studies provide strong evidence that cofilin activation is also promising as an AD therapy (see Fig. 2B). However, the conflicting findings greatly dampen enthusiasm.

A few other interesting approaches to increase synaptic resilience rely on two actin network proteins, drebin and Rac1. Drebin is an actin-binding protein that is reduced in individuals with AD [107] and in an age dependent manner in APP/PS1 AD mice [108]. Injections of drebin expressing AAV significantly improved performance in the Morris Water Maze test [108]. Rac1 is part of the RhoGTPases family and is implicated in regulating the balance between F-actin and globular actin [109]. Rac1 amounts were reduced in plasma samples from AD patients [110] while in AD mice, two independent groups saw reductions in active Rac1 [110, 111]. Interestingly, a chemical Rac1 inhibitor rescued LTP deficits as well as impairments in the Morris Water Maze test [111]. In contrast, Rac1 expression rescued spine density in the cortex of 7-months old AD mice [110]. Nonetheless, all these studies strongly suggest that actin network proteins are very important in the pathophysiology of AD and that therapeutic approaches acting on these proteins are promising new drug targets.

5. Scaffolding proteins

One of the earliest pathological changes in the brains of patients with Alzheimer's disease (AD) is the loss of synapses [5,6]. However, the molecular pathways preceding synaptic loss are still unclear. Mounting evidence suggests that loss of PSD-95, a major scaffolding protein at the synapse, is one of the first events leading to synaptic loss as it is significantly depleted in the brains AD patients [52,53] as well as in neurons exposed to Aβ [112]. Indeed, PSD-95 is reduced in individuals with mild cognitive impairment [113] suggesting that PSD-95 reduction is an early event in disease progression. Low levels of PSD-95 may thus be a molecular signature of synaptic vulnerability to AD.

A recent study showed that overexpression of PSD-95 could rescue synaptic depression caused by Aβ [54]. This effect appears to be mediated by a blockade of the NMDA receptor ion-flux independent function as PSD-95 expression prevented ion-flux independent long-term depression (LTD) [114] as well as an Aβ-induced conformational movement in the NMDA receptor c-terminal domain [54]. Interestingly, the authors demonstrated that endogenously expressed PSD-95 could also be protective, as larger dendritic spines were not affected by Aβ. Furthermore, as PSD-95 palmitoylation is required for its synaptic clustering [115], palmitoylation resistant PSD-95 was unable to protect synapses from Aβ [54]. Palmostatin B, a drug that inhibits PSD-95 depalmitoylating enzyme (ABHD17) and consequently increases PSD-95 palmitoylation and synaptic amounts, completely reversed synaptic effects of Aβ in hippocampal neurons, including synaptic depression and reduced spine density [54]. This approach could thus lead to a pharmacological therapy against AD. A related study used epigenetic elditing to manipulate PSD-95 gene expression [55]. This approach increased PSD-95 mRNA levels by more than 2-fold in hippocampal neurons and effectively increased the density and size of mushroom type spines without affecting overall spine density in 8-months old mice [55]. Moreover, in 12-months old AD model mice, the authors saw a significant reduction of PSD-95 in synaptic membranes, which was restored to levels comparable to those found in age-matched wild-type mice by their epigenetic editing approach. Increased PSD-95 expression in old AD mice rescued impairments in the novel object recognition task and in a modified version of the Morris Maze test [55]. These two studies suggest that increasing PSD-95, either by blocking its removal from synaptic membranes or by manipulating its expression, is a promising therapeutic avenue against AD.

PSD-95 is a member of a family of proteins collectively known as membrane-associated guanylate kinases (MAGUKs) and the PSD-95–like subfamily of neuronal MAGUKs (PSD-MAGUKs) includes PSD-93, SAP102, and SAP97 [116]. Interestingly, not only PSD-95 is associated with AD and other disorders of the nervous system [117]. PSD-93, which is similar to PSD-95 in terms of amino-acid sequence and function, is reduced in the hippocampus of 6-months old APP/PS1 mice [56]. Interestingly, lentivirus-mediated overexpression of PSD-93 rescued deficits observed during Morris Water Maze and fear conditioning behavioral tests in these AD mice [56]. Loss of SAP-102 was observed in the inferior temporal cortex of AD patients and levels of SAP-102 were correlated with disease severity [118]. Moreover, SAP-97 was shown to promote alpha-secretase mediated cleavage of APP [119], which results in the production of non-toxic peptides and could thus be beneficial against AD. Overall, these different studies show that PSD-MAGUKs levels

are reduced during AD and that increasing the amount of these proteins at the synapse could be a general neuroprotection mechanism against AD (see Fig. 3).

6. Inhibition of phosphatases

Phosphatases play important roles in synaptic plasticity, mostly mediating the mechanisms of long-term depression, which is essential for learning and memory [120–122]. However, the dysregulation of these pathways in AD contribute to synaptic degeneration and cognitive decline [57]. This has led to the investigation of phosphatase inhibition approaches for the treatment of AD.

The calcium-dependent phosphatase calcineurin (PP2B) is critical to many of the mechanisms contributing to AD pathology. Calcineurin is required for the internalization of AMPA receptors and is implicated in the synaptic uptake of Aβ as well [123]. Calcineurin inhibition in Aβ-overproducing mice prevented cognitive deficits, suggesting that calcineurin is mediating Aβ-induced memory deficits [124,125]. The calcineurin pathway is critical to synaptic loss seen in AD, as its activation is necessary for synaptic depression [126,127]. The Hyman lab investigated the potential of calcineurin inhibition as a method for improving synaptic resilience. In one of their studies, they focused heavily on dendritic morphology when studying the effects of Aβ-induced activation of calcineurin [58]. They found that AD model mice had less dendritic complexity and spine density, and this phenotype was mimicked by the overexpression of constitutively active calcineurin even in the absence of Aβ. Inhibition of calcineurin through the expression of AKAP79 made synapses resilient to these Aβ-induced effects [58]. The protection of synapses is further indicated by improvements observed in fear conditioning behavioral experiments in AD model mice treated with the calcineurin inhibitor FK506 [124,125]. This inhibitor has been used by numerous research laboratories for a long time, and its clinical form Tacrolimus has been in use for decades to prevent organ transplant rejection [128]. Recently, Tacrolimus has entered Phase II clinical trials for use in AD patients (A ClinicalTrials.gov Identifier: NCT04263519). Hopefully, this trial will add to the body of research supporting the synapto-protective effect of calcineurin inhibition.

Striatal-enriched protein tyrosine phosphatase (STEP) is another phosphatase that is implicated in regulating synaptic plasticity [129]. In humans with AD and two different AD model mice, levels of STEP were increased [130,131]. STEP is activated by calcineurin, active STEP then mediates the internalization of NMDA receptors by dephosphorylating the GluN2B subunit [59]. The Lambroso lab, recently found that STEP inhibition imparts a synapto-protective effect [59]. By using the active site STEP inhibitor TC-2153 on neurons treated with Aβ, dendritic complexity and spine density was preserved. Furthermore, STEP inhibition prevented Aβ-induced reduction of synapsin/PSD-95 colocalization [59]. Dendritic spine density was rescued in AD mice given TC-2153, indicating improvements in synaptic resilience [59]. Older studies on pharmacological and genetic inhibition of STEP in AD model mice have shown to improve memory performance on tasks such as the Morris water maze, Y-maze, and novel object recognition task [131–133]. These cognitive changes occurred in the absence of any change in Aβ accumulation in AD model mice [132]. Taken with the Lambroso lab's findings of STEP inhibition protecting synaptic density, it

demonstrates the capacity of STEP inhibition to improve synaptic resilience against Aβ. Like with other protein tyrosine phosphatase inhibitors, development of STEP inhibitors has been hindered by challenges to cell-permeability and specificity [134]. Recent progress has been made on developing better techniques for identifying STEP and protein tyrosine phosphatase inhibitors with better accuracy [135]. This progress and the capacity of STEP inhibition to improve synaptic resilience, make it a promising candidate for AD treatment in the future.

Other phosphatases, such as PP1 and PP2A, appear to be upregulated in AD [136]. Also, there has not been as much progress or perhaps interest in recent years into therapeutic approaches involving these other phosphatases. Nonetheless, the inhibition calcineurin and STEP are already showing a lot of potential as a novel AD treatment approach (see Fig. 3).

7. Conclusions

In this review, we described several novel approaches that are effectively increasing synaptic resilience against AD. These methods are acting through very different proteins and signaling pathways but are all aimed to make synapses more resilient to AD pathology. The rationale behind these methods is based on the important finding indicating that 30–50% of brains with AD pathology have normal synapses and were from individuals that were cognitively normal [3]. It is possible that these individuals were more physically active, as physical activity is linked to better cardiovascular health, which is affecting AD risk [109]. Moreover, physical activity increases BDNF amounts in the brain [17–22] and approaches to increase BDNF were shown to promote synaptic resilience in AD mice [24–27]. Another global factor influencing AD risk is genetics, however, the majority of findings are related to genes linked to AD risk and very few genes are associated with protection against AD [72,74]. Nevertheless, a few protective genes having positive impact on synapses were found. Expression of APOE2, restored synapses in AD mice [29–31] and a Phase II clinical trial is now testing the efficacy of this approach in AD patients. Methods increasing klotho expression [32–34], a protein promoting healthy aging, are also very promising. TREM2, a receptor expressed in microglia, has gotten a lot of attention recently because several loss of function variants are linked to a considerably increased AD risk [91,92]. Consequently, strategies to increase TREM2 were developed and were found to increase synaptic resilience in AD mice [35–37].

Furthermore, it was demonstrated that individuals with higher lifetime cognitive activity (cognitive reserve) have reduced incidence of AD [109]. Moreover, older memories are maintained better in patients with AD [137–139]. Cognitive activity could thus drive synaptic potentiation and older memories might be represented by larger, more stable spines. Accordingly, therapeutic strategies that stabilize dendritic spines should be beneficial against AD. Several approaches acting on actin network proteins were discussed here [47–51] and are summarized in Fig. 2. Overall, there is a lot of potential but a discrepancy regarding whether cofilin is activated or inactivated in AD reduces the impact of these methods. The amount of scaffolding proteins located at the post-synaptic density (PSD-95, PSD-93 and SAP-102) is directly correlated with the stability of dendritic spines and these proteins are specifically reduced in AD [52,53,56,118]. Therapeutic strategies that can increase

the synaptic concentration of PSD-95 [55,114], PSD-93 [118] and SAP-102 are thus very promising. Phosphatases are implicated in the mechanisms un-derlying synaptic weakening, which ultimately lead to synaptic loss. Hence, pharmaceutical inhibition of calcineurin and STEP, two important phosphatases, were shown to rescue synaptic deficits in AD mice [58,59,124,125,132]. In conclusion, it is clear from the studies discussed in this review that therapeutic strategies aiming to increase synaptic resilience against AD have tremendous potential.

However, since the approaches presented here do not aim to prevent mechanisms contributing to synaptic damage, therapeutic strategies that are protecting synapses are not likely to be efficient at all stages of AD. Interestingly, cognitive reserve seems to significantly delay disease onset but at the cost of a steeper decline afterwards [8]. This would suggest that therapies promoting synaptic resilience might be most efficient at delaying AD onset and that the progression of pathology would become too severe at some point and succeed in destroying synapses and neurons. Consequently, multi-approach treatments combining therapies that protect synapses with ones that target disease-causing proteins could be especially useful in the fight against AD.

Acknowledgements

This publication was supported by the National Institutes of Health, National Institute on Aging, grant RF1 AG067049.

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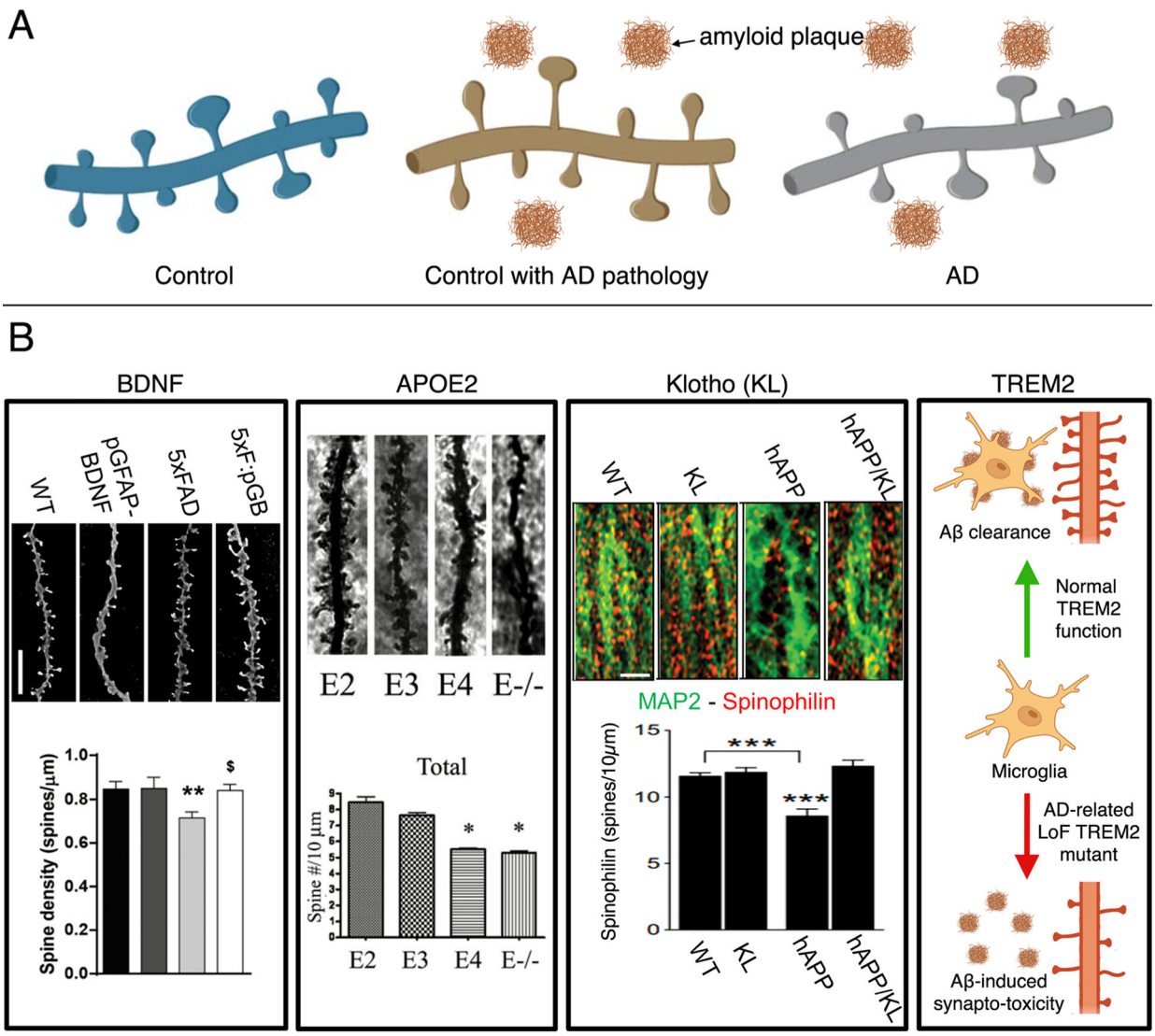

Fig. 1.

Global factors promoting synaptic resilience against AD, A) Synaptic density in cognitively normal patients with AD pathology (middle) is similar than in control individuals (left), whereas AD patients with symptoms of dementia have reduced spine density (right). From [3], license number from Wiley and sons: 5236170936380, B) Multiple strategies to protect synapses by targeting elements with widespread physiological and CNS effects have been explored. Mice expressing the neurotrophic factor BDNF in astrocytes (pGFAP-BDNF) crossed with AD model mice (5xFAD); 5xF:pGB have normal spine density (left, BDNF label) [24]. Expression of APOE4, a variant associated with increased AD risk, significantly reduced spine density (middle-left, APOE2 label) [67]. Similarly, transgenic mice expressing klotho had higher spine density, even if crossed with mice expressing human APP (middle-right, Klotho label) [32]. Normal TREM2 function helps microglia clear Aβ, while AD related lost of function (LoF) mutants are impacting spine density (left, TREM2 label; figure design with BioRender license: VP23HWXE3T).

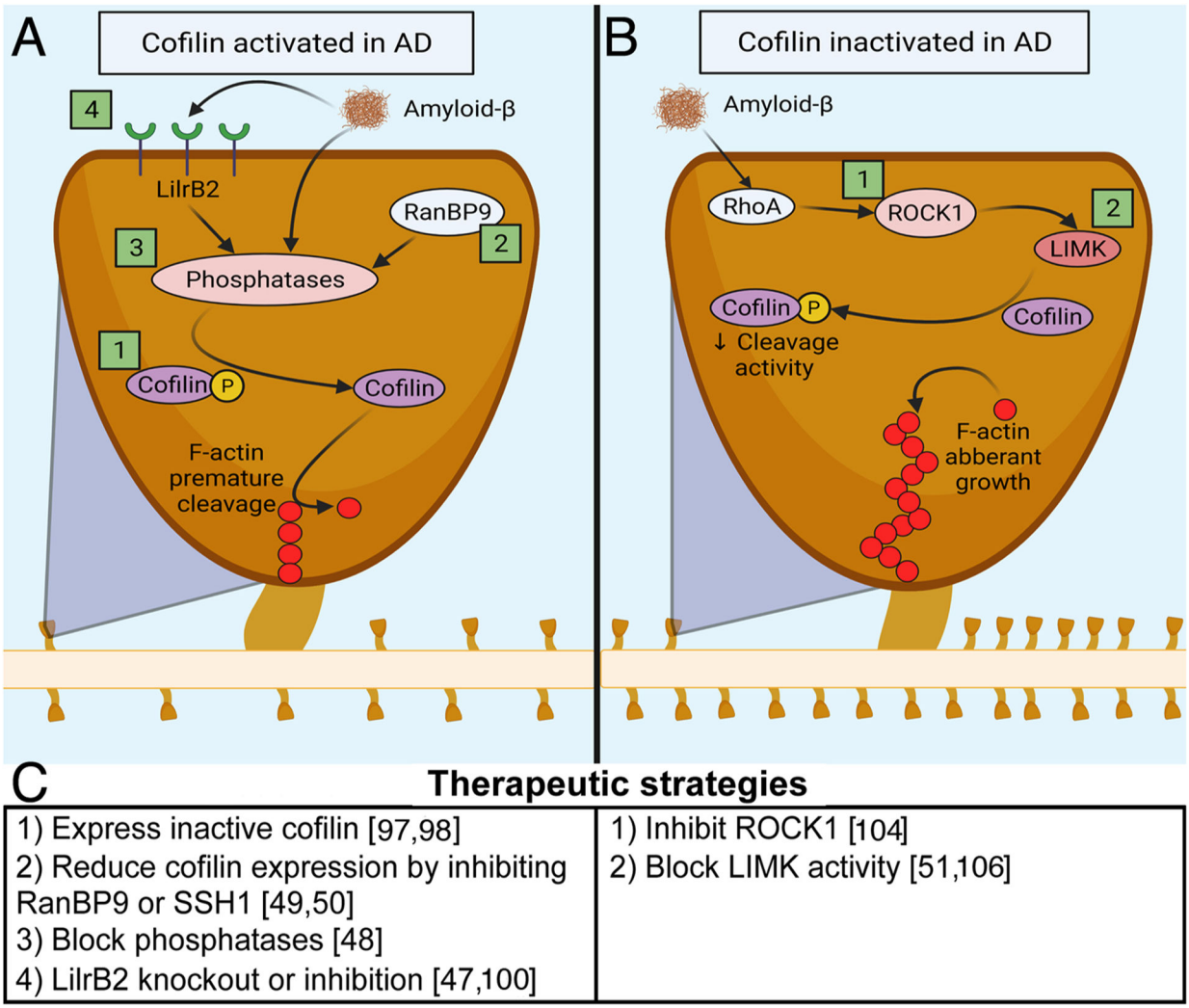

Fig. 2.

Role of cofilin in AD pathology and therapeutic strategies. There are opposing findings on cofilin activity in AD. A) One proposed model is that Aβ promote the activation of phosphatases, which will dephosphorylate and activate cofilin. Increased cofilin activity will cause premature cleavage of F-actin, inhibiting the development of dendritic spines. B) Another proposed model is that Aβ accumulation causes the activation of kinases, which phosphorylate and inactivate cofilin. The inhibition F-actin cleavage may cause aberrant dendritic spine growth. C) Therapeutic strategies based on both cofilin activation and inactivation have shown potential to ameliorate AD related impairments. Figure design with BioRender license: VP23HWXE3T.

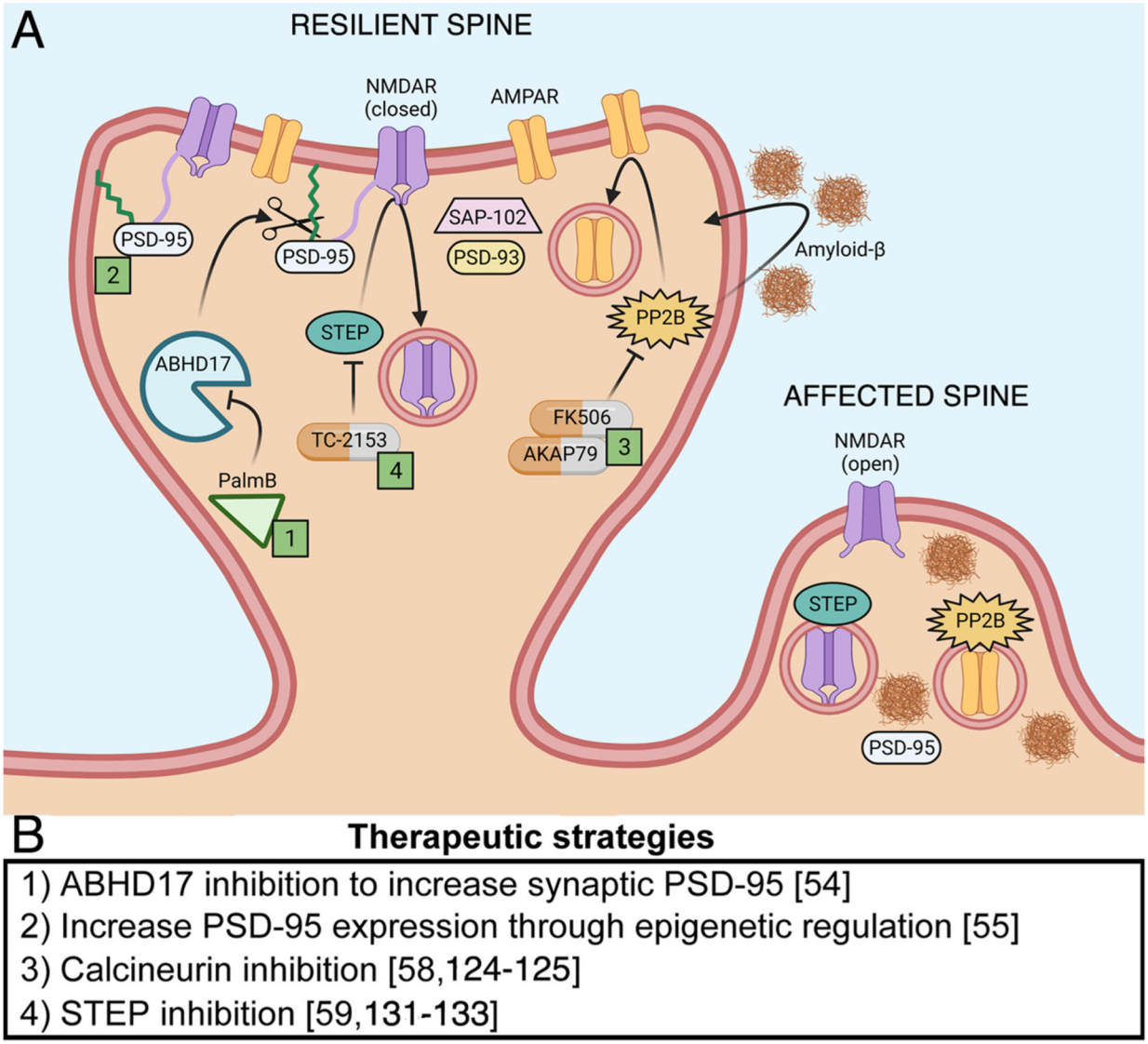

Fig. 3.

Increasing synaptic scaffolding proteins or inhibiting phosphatases to promote synaptic resilience against AD, A) Mechanisms contributing to synaptic degeneration during AD. Depalmitoylation of PSD-95 by ABHD17 disrupts the anchoring of glutamatergic receptors to the postsynaptic membrane. PP2B/calcineurin causes Aβ plaque internalization and AMPA receptor endocytosis. Activation of STEP leads to NMDA receptor endocytosis. Receptor internalization contributes to the shrinking of dendritic spines (right). In addition, decreased levels of PSD-MAGUKS such as PSD-95, PSD-93 and SAP-102 are characteristic of AD. Green numbered boxes highlight the B) therapeutic strategies that have proven effective in ameliorating the effects of AD. Figure design with BioRender license: VP23HWXE3T.