Trends in Pharmacological Sciences

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Review

Neuro-regeneration Therapeutic for Alzheimer's Dementia: Perspectives on Neurotrophic Activity

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Alzheimer's disease (AD), the leading disorder of memory impairment in our aging population, is increasing at an alarming rate. AD is currently identified by three 'gold standard criteria': (i) dementia in life, (ii) amyloid plaques at autopsy, and (iii) neurofibrillary tangles at autopsy. Several autopsy studies have indicated that dementia in life is a consequence of lost synaptic networks in the brain, while many clinical trials targeting neurotoxic amyloid beta (Aβ) have consistently failed to produce therapeutic effects on memory function in AD patients. Restoring cognitive function(s) by activating endogenous repairing/regenerating mechanisms that are synaptogenic and antiapoptotic (preventing neuronal death), however, is emerging as a necessary disease-modifying therapeutic strategy against AD and possibly for other degenerative dementias, such as Parkinson's disease and multi-infarct dementia.

Highlights

Synaptic deficits occur early in Alzheimer's disease (AD) and reflect a decline in synaptic remodeling/repairing capacity, probably due to diminished neurotrophic signaling pathways, such as the protein kinase C-brain-derived neurotrophic factor signaling pathway, of the cognitive networks in the brains.

The synaptic deficiency hypothesis is proposed and discussed, updating the popular amyloid cascade hypothesis and their validities, based on the results of a large number of clinical trials completed so far.

Nonpharmacological interventions and pharmacological agents (although some are more promising and others, less so) that target synaptic functions and improve cognitive functions against AD-related memory impairment tend to exhibit pharmacological profiles that include proneurotrophic, antioxidant, anti-inflammatory, antiamyloid, and antitauopathy activity.

Restoring synaptic functions should be considered as one major therapeutic goal in the treatment of AD patients. Effective therapy appears to be achievable through a sustained normalization of neurotrophic activity in the AD brains.

Alzheimer's Disease

Alzheimer's disease (AD) (see Glossary), a chronic disorder of neurodegeneration, is characterized by memory impairment, formation of senile plaques and neurofibrillary tangles (NFTs), and the loss of synaptic networks. The majority (>95%) of AD cases occur sporadically, without a specific family link, but with age as the single greatest risk factor. After decades of extensive research, there is still no cure for AD, as demonstrated by consistently failed efficacy in clinical trials [1,2]. The four FDA approved AD drugs currently available (donepezil, galantamine, rivastigmine, and memantine) provide symptomatic short-term benefit at best [2]. A recent analysis of data from 2242 individuals, clinically diagnosed with MCI-AD (mild cognitive impairment due to AD) or with mild ADdem (mild AD dementia), available from the National Alzheimer's Coordinating Center's Uniform Data Set, reveals that in the patients who used cholinesterase inhibitors (e.g., Aricept) to treat their cognitive impairment, their cognitive decline became greater after the treatment initiation in both groups [3].

Several different pathologies have been proposed as the underlying cause(s) in AD, including cholinergic deficits, formation/accumulation of neurotoxic substances, oxidative/vascular stress, neuroinflammation, and mitochondrial dysfunction. Amyloid beta (Aβ) accumulation, especially the soluble neurotoxic oligomers, is commonly viewed as the initiator, inducing tau hyperphosphorylation, neuroinflammation, oxidative stress, and mitochondrial dysfunction through its downstream molecular cascades. Aβ and NFTs can activate microglia and induce oxidants and inflammatory factors, which in turn promote further Aβ and NFT formation. The vicious cascade cycle includes interactions between neurotoxic substances and neuroinflammation: toxic Aβ promoting inflammation, which promotes more toxic Aβ (i.e., inflammasome activation is connected to seeding and spreading of Aβ in AD patients) [4,5]. This popular amyloid hypothesis (Figure 1) has, however, two main problems that are not consistent with its validity. First, the

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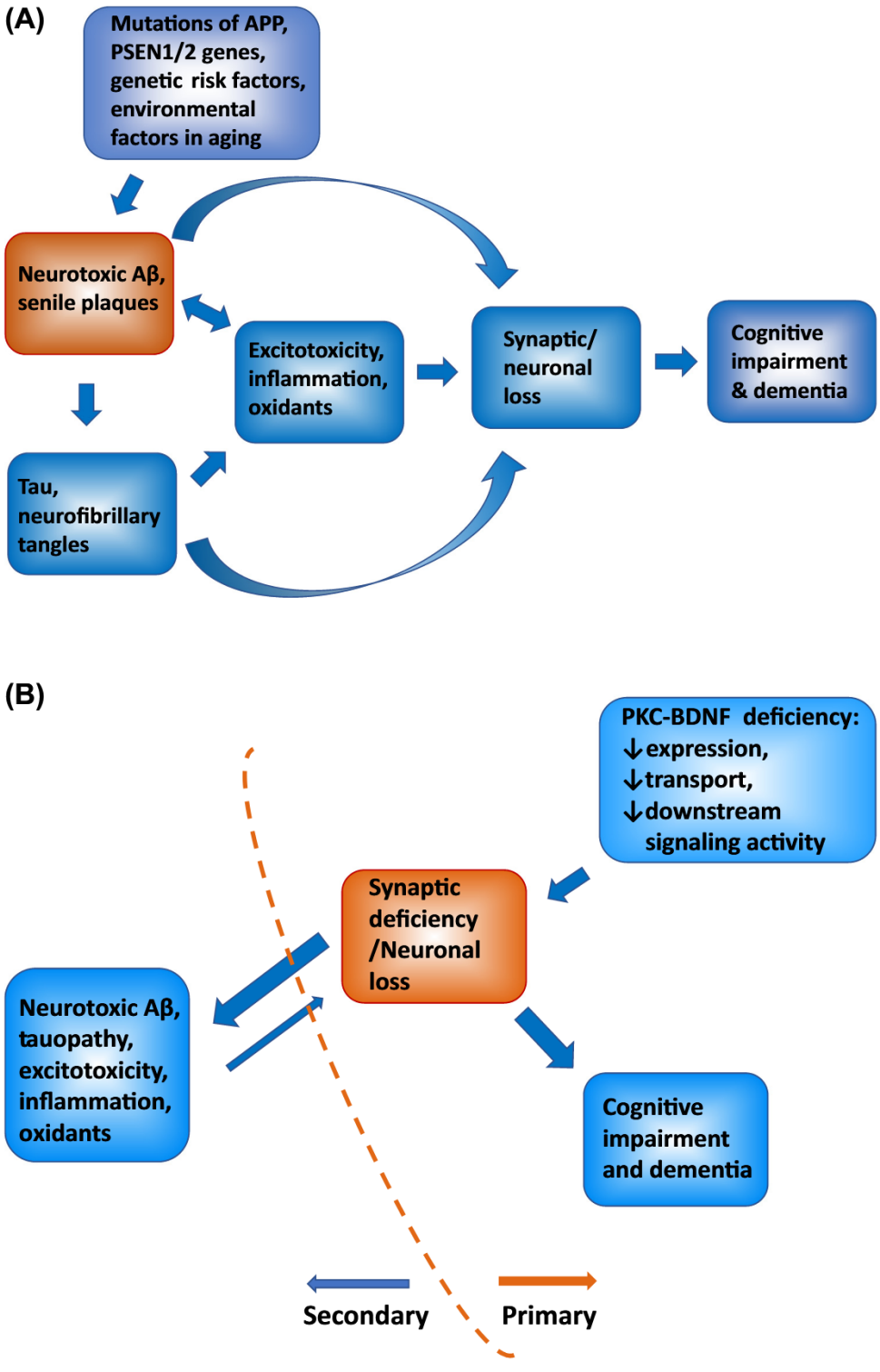

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Glossary

Alzheimer's disease (AD): a chronic disease dominated by a slow progression of memory impairment and dementia, without obvious other pathological causes, such as head trauma or vascular hypoperfusion. Memory, thinking, judgment, language, problem-solving, personality, and movement are all impaired during the disease progression. The disorder is characterized by amyloid accumulation and tauopathy in brains.

Brain-derived neurotrophic factor (BDNF): serves diverse functions in the brain, ranging from promoting neuronal survival, differentiation, to synaptic modulations (maturation and maintenance) and neurogenesis.

Cognition: a mental process, through which subjects acquire knowledge and comprehend through experiencing, thinking, and reasoning. Learning and memory are core features of the process.

Growth associated protein 43 (GAP-43): the growth associated protein 43, a PKC substrate, is a crucial component in neuronal growth/ development, synaptic regeneration, and learning-associated neural plasticity.

HDAC: histone deacetylase, a class of enzymes that remove the acetyl group from an ε-*N*-acetyl lysine amino acid on histone proteins of DNA, so that the histones wrap the DNA more tightly, making the DNA less accessible to transcription factors.

Protein kinase C (PKC): a family of protein kinase enzymes, 15 isoforms in humans, involved in controlling the function of other proteins through the phosphorylation of their hydroxyl groups of serine and threonine amino acid residues. Some isoforms have been found to play an important role in regulation of neuronal survival, differentiation, maturation, cognitive processes, and maintenance of synaptic/neuronal integrity.

amyloid plaque load does not correlate well with cognitive impairment in AD patients [6], although the plaque load may not accurately reflect the exact level of neurotoxic Aβ in the brain. Second, reducing the neurotoxic amyloid accumulation or its vicious cycle component(s) does not produce the expected therapeutic outcomes in AD patients (see below).

Early amyloid accumulation starts intracellularly and leads to tauopathy, which is more proximal to the disease progression. In a single 3D human neural cell culture system, inhibition of Aβ generation with β- or γ-secretase inhibitors was reported to not only decrease Aβ pathology, but also attenuate tauopathy [7]. $Aβ_{42}$ induces cultured human stem cells to lose plasticity, a deficit that can be rescued with interleukin (IL)-4 [8]. However, problems with multiple clinical trials of amyloid-targeting therapeutics, including an effective removal of neurotoxic Aβ species, and licensed AD therapeutic drugs are their lack of effectiveness in targeting the pathophysiological core underlying the dementia: functional deficits/loss of synapses and neurons beyond the brain's ability to repair. Synapses permit a neuron to pass a signal, chemical or electric, to another cell and are adaptive in operation and structure according to functional demands. Both acquisition of memory and its consolidation/reconsolidation involve restructuring of synapses and their operations [9]. For all the unsettled issues in AD, one finding is clear: the synaptic deficit/loss, revealed among many other pathologies, is highly correlated with the levels of dementia in AD patients [10–12] (Box 1). Within 2–4 years of AD onset, brain biopsies are reported to have a decrease in the number of synapses by 25–30% in the frontal and temporal cortexes [13], most severe (by 44–55%) in the hippocampus [11,14], both in the degenerated and surviving neurons (about 38% loss [12,13]). These correlations strongly indicate that removal of the uncorrelated/weakly correlated pathological factors for a disorder, such as the Aβ for AD or Lewy bodies for Parkinson's disease, is unlikely to produce dramatic therapeutic impacts on **cognition**. Nilvadipine, an antihypertensive drug that has demonstrated antiamyloid, anti-inflammatory, and antitauopathy activity, for example, failed to show therapeutic benefit for mild-to-moderate AD patients in a recent Phase III clinical trial [15]. Verubecestat, an oral β-secretase-1 inhibitor, produced near-maximal reduction of the soluble Aβ in cerebrospinal fluid (by up to 94%) but did not reduce cognitive decline in patients with mild-to-moderate AD [16], and instead worsened cognition in a 2-year, double-blind, placebo-controlled trial of 1454 prodromal AD subjects with a positive amyloid positron emission tomography (PET) scan at baseline [17]. The failed efficacy also includes recent Phase III clinical trials with Aducanumab, a human monoclonal antibody to Aβ oligomers in early AD patients. While tauopathy correlates more closely than amyloid pathology with neuron loss and cognitive decline in AD, obvious tauopathy throughout the

Figure 1. Pathogenesis of Alzheimer's Disease (AD): Amyloid Hypothesis (A) and Synaptic Deficiency Hypothesis (B). (A) The amyloid cascade hypothesis: the deposition of amyloid beta (Aβ) initiates pathological events in the brain: formation of senile plaques and neurofibrillary tangles, oxidant stress, inflammation, synaptic and neuronal injuries, and loss with functional consequences of cognitive impairment and dementia. Toxic Aβ can directly induce synaptic/neuronal damage and produce damages through other mediators, such as hyperphosphorylated tau, excitotoxicity, oxidants, and inflammation. For instance, Aβ oligomers/soluble Aβ bind to glutamate receptors and other components, resulting in influx of extracellular Ca^{2+}, calcium homeostatic disruption, actin depolymerization, actin dynamic disruption through impairing the PI3K/Akt/mTOR pathway, and oxidative stress with the consequence of synaptic failure. The hypothesis predicts that: (i) the pathological cascade can be blocked or arrested by effective removal of Aβ or blocking its formation; and (ii) such effective therapeutics (drugs, antibodies, etc.) would be disease-modifying. (B) The synaptic deficiency hypothesis is consistent with the evidence that formation of Aβ and tau is mainly reactive (secondary) to cell injuries and roles of neurotrophins in synaptic and neuronal survival. In development, the neurons that fail to receive a sufficient level of retrogradely transported neurotrophins from the targeted cells are eliminated through a rapid degeneration mechanism, while similar mechanisms operate in the adult brains but with a rather chronic and slow process, a degeneration process, especially when widespread (primary). The hypothesis predicts that: (i) antiamyloid treatment(s) can only produce very limited therapeutic effects in AD, and (ii) maintaining synaptic efficacy would be AD disease-modifying. Abbreviations: BDNF, brain-derived neurotrophic factor; PKC, protein kinase C.

Box 1. Synaptic Loss in Alzheimer's Disease

Synaptic loss and abnormality occur early in AD and are very highly correlated with severity of the cognitive deficits in AD patients [6]. The synapses in both the degenerated and surviving neurons are affected. The correlations between the cognitive functions in AD patients and plaques and tangles are rather weak [6]. Figure I shows correlated alternations in the number of synapses and neuropil volume in the hippocampal CA1 regions of AD patients with the levels of cognitive deficits: decreases in subjects with mild cognitive impairment and further decreases in mild AD subjects (postmortem human brains [11]).

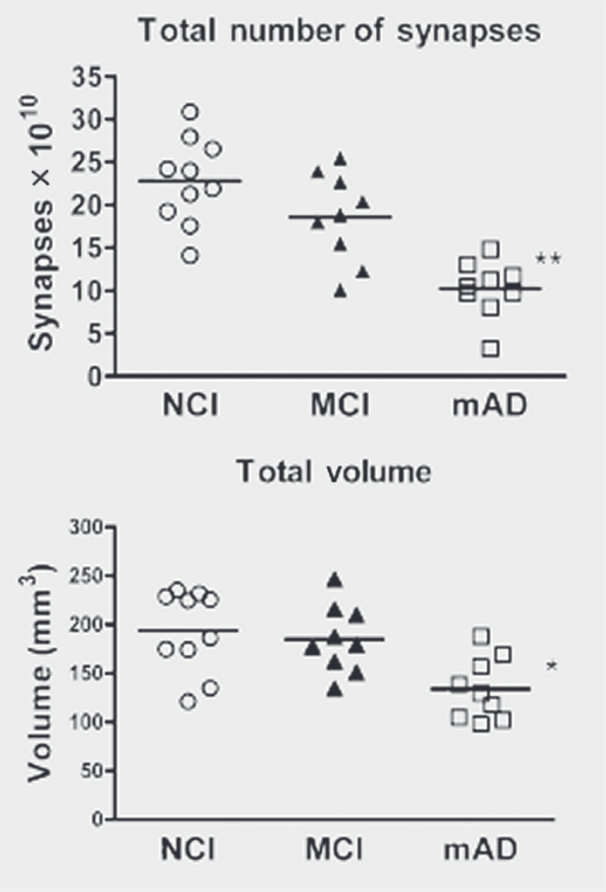

Figure I. The Total Number of Synapses (A) and Neuropil Volume (B) in the Stratum Radiatum Subregion of the Hippocampal CA1 of Three Different Diagnostic Groups of Human Subjects Examined. Figure reproduced and adapted with permission from Wolters Kluwer Health, Inc. [11]. Abbreviations: mAD, Mild Alzheimer's disease; MCI, mild cognitive impairment; NCI, no cognitive impairment.

brain is present only at later AD stages. Most of the initial antitau therapies have been discontinued because of toxicity and/or lack of efficacy [18], in addition to the observation that the existence of NFTs does not necessarily impair neuronal function [2]. However, the existing endogenous neural regeneration/repair mechanisms in adult mammalian brains (see below), though insufficient by itself, raises hopes that AD may be eventually cured through restoring the brains' capacity for neural regeneration. In this short review, we shall discuss the roles of neural and synaptic regeneration in cognition, in cognitive impairments of AD, and as an essential AD therapeutic target.

Synaptogenesis and Remodeling

Mammalian brains operate on an efficiency principal of keeping the number of synapses modest for a particular function, since signal transfer through synapses is rather expensive in energy cost

[19]. Powered through plasticity, the brain, however, can remodel its structure and operation of synapses/network for new challenges. The downside of this efficiency, the lack of abundance in neural connections, is its vulnerability to injury/damage, especially when this remodeling/regeneration ability is compromised.

Cognitive functions are guarded constantly through active repairing/regeneration against any injury/damage to the synapses/networks. Neural regeneration, or neuro-regeneration, refers to an action or process of regenerating/restoring neuronal structures [19], such as synapses or neurons, from injury/damage, to its preinjury state. A successful neuro-regeneration can be achieved through endogenously or exogenously (neuronal replacement) methods. The endogenous process involves increasing the expression of genes and activity of proteins, such as neurotrophins, **growth associated protein 43** (**GAP-43)**, and many other signaling molecules.

Neurotrophins are a family of proteins, including **brain-derived neurotrophic factor (BDNF)**, nerve growth factor (NGF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4/5), in mammals. NGF, NT3, and NT4 are secreted mainly through constitutive pathways. BDNF, a synaptogenic neurotrophin, is unique for its activity-dependent activation and high level of expression in the brains. In cultured neurons, transient tropomyosin receptor kinase B (TrkB; a BDNF receptor) activation promotes dendritic growth and spine morphogenesis, while sustained TrkB activation facilitates neuronal dendritic arborization and spinogenesis. BDNF plays essential roles in cell proliferation [20], neurogenesis [19,21,22], cognition, and synaptic integrity, including regulation of synaptic transmission, synaptic plasticity, and synaptic growth in developing and adult brains. Activity-dependent BDNF activation in the brain is required for maintenance of mature spine phenotype [23] and involves activity-driven Ca^{2+} signals [24], as well as demethylation of the *BDNF* promotor IV in postmitotic neurons. This demethylation is sufficient to activate BDNF expression [25].

The BDNF signaling pathways in the brains are regulated by specific **protein kinase C** (**PKC**) isoforms. The PKC-BDNF signaling pathways play essential roles in maintaining synaptic functions and structures and a variety of memory tasks. PKCε activation, with bryostatin-1 or other specific agents, promotes BDNF expression and secretion, synaptogenesis, and neurogenesis in the hippocampus and related cortexes and provides protective effects against a variety of neurotoxic events/factors, such as amyloidosis, tauopathy, apoptosis, neuroinflammation, and oxidants (Figure 2). Common pathways, for example, the mammalian target of rapamycin (mTOR) signaling pathway, operate during developmental axon regrowth and axonal regeneration [26]. mTOR, a serine/threonine kinase for cell survival and growth, integrates messages to regulate transcription, translation, and other cellular functions [27] and may also serve as one of the therapeutic targets.

Impaired Neuro-regeneration in AD

Cognition depends on integrity and operational efficacy of synapses, both structural and functional, and both are vulnerable to injuries and disorders. Increasing evidence indicates that synaptic deficiency is a key pathophysiological hallmark in AD. Deficits in BDNF mRNA and spine pathology (synaptic degeneration) are the earliest pathologies in AD [28,29], before any neuronal loss and perhaps prior to Aβ deposition [30,31]. Pathological damage and injury to the brain result in often irreversible dysfunction of the brain, mainly due to the insufficient ability of the brain to regenerate or repair [32]. Thus, a key pathogenic mechanism underlying AD progression is long-term deficits in neurotrophic signaling, deficits observed in preclinical AD [33]: reduction in the PKC-BDNF levels, BDNF transport [34],

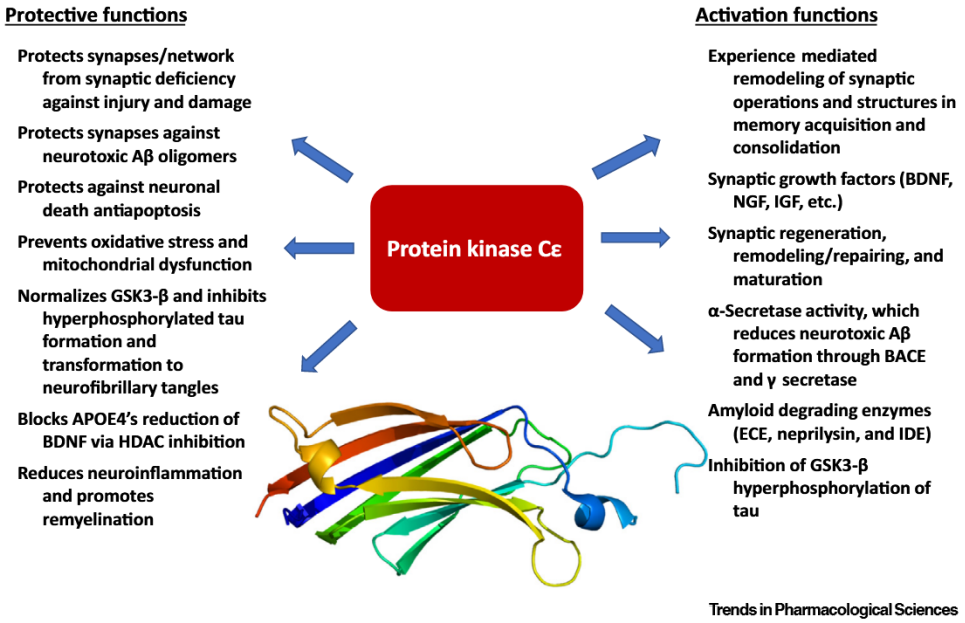

Figure 2. Effects of Protein Kinase Cε (PKCε). PKCε is a key signaling enzyme that correlates synaptic growth and neuronal revitalization and also blocks formation of amyloid beta (Aβ) and abnormal tau. The isoform can be selectively activated by bryostatin-1 or other agents. Through a dynamic regulation of neurotrophin activity and other signaling molecules, such as GAP-43, extracellular-signal-regulated kinases (ERK), and myristoylated alanine-rich C-kinase substrate (MARCKS), the PKC-BDNF (brain-derived neurotrophic factor) signaling pathways play essential roles in maintaining synaptic functions and structures and a variety of memory tasks, such as Pavlovian conditioning of the nudibranch mollusk *Hermissenda*, spatial learning and memory in rats, recognition memory, learning, and memory of eye-blink conditioning in rabbits, olfactory discrimination learning, conditioned avoidance, contextual fear memory, and substance-associated reward memory in other mammalian animal models. Appropriate levels of PKCε activity in the brains maintain synaptic integrity and capacity and reduces prevalence and effects of neurotoxic forms of Aβ and tauopathy. Structure of PKCε based on PyMOL rendering of Protein Data Bank 1gmi and adapted from https://commons.wikimedia.org/w/index.php?curid=8821044. Abbreviations: BACE, β-site APP-cleaving enzyme1; BDNF, brain-derived neurotrophic factor; HDAC, Histone deacetylase; NGF, nerve growth factor.

and/or deficits of BDNF downstream receptors and signaling pathways in the hippocampal and related cortexes.

Mammalian brains have a certain capacity to regenerate/remodel synapses/neural networks when facing injury, disorders, and cognitive challenges. Cognitive impairment becomes evident only when injury/damage/cognitive demands reach a threshold by which the brain can no longer initiate and sustain the required responses. This threshold is lower with neurotrophic hypoactivity.

The brain's responses to injury also involve reactions from its immune system, mainly through microglia, the immune cells of the nervous system. Inflammation can be chronic and systemic in the absence of overt infection. Evidence suggests that microglia might be the mediator of synaptic loss [35]. Upon injury, the immune system in the brain responds quickly, resulting in activation and proliferation of microglia [36–38], inducing the release of associated inflammatory factors, as well as attracting additional immune cells from the blood. Microglia release BDNF and have a strong pro-regenerative role in the nervous system, as in other organs/tissues [39], but also promote activity-dependent synaptic pruning and inflammation (see below). In AD, microglia exert a neuroprotective role through phagocytosis of debris and

toxins, including Aβ, at least initially. However, Aβ affects glial function, leading to neurotoxic consequences, especially when the reaction becomes a chronic and more damaging proinflammatory state [40]. During development, microglia-mediated synapse removal is an important process for proper brain maturation during development. Active microglia promote phagocytosis of neuronal, in particular, synaptic structures [41]. Microglia can also release soluble synaptotoxic factors, such as tumor necrosis factor-α, nitric oxide, and IL-6, promoting synapse loss. Microglia and complement (C1q, the initiating protein of the classical complement cascade, and C3, the microglial complement 3), might be involved in early synaptic loss in AD models [35]. In mammalian brains, microglia are the dominant source of C1q [42]. Diffusible Aβ increases C1q, which promotes activation of C3 [12], which in turn opsonizes subsets of synapses for elimination in developing brains. Activated microglia can also induce astrocytes to become neurotoxic [43]. The neurotoxic astrocytes lose the ability to promote neuronal survival, outgrowth, and synaptogenesis, but rather induce the death of neurons and oligodendrocytes [43]. By using a colony stimulating factor 1 receptor inhibitor PLX5622, which specifically depleted microglia, a recent study indicated that microglia were not essential in retinal ganglion cell degeneration or axonal regeneration after central nervous system (CNS) injury [44], although the removal of death-labeled retinal ganglion cells was impaired after microglia depletion.

Microglia-mediated cellular damage and synaptic loss are mainly secondary, further worsening the sustained low repairing/regeneration ability in AD brains. Associated with the early stage of AD is a reduced signal pathway (the PKC-BDNF-TrkB signaling pathway), PKCε activity, and neurotrophic activity in the brain [34,45], which may account for the alterations in the memory deficits, neuronal cell death, and synaptic deficiency in AD [46].

Neuro-regeneration Targeting Interventions for Memory Impairment

Memory impairment and dementia are the consequences of synaptic/neuronal deficits. The intrinsic neuro-regeneration capacity in the mammalian brain has been shown to be very limited, even after eliminating multiple known inhibitory signals [47]. In the adult mouse brain, most axons cannot regenerate sufficiently, even with precise laser-mediated lesions that produce minor scarring [48]. This low endogenous capacity for neuro-regeneration in mammalian brains does not mean, however, that this capacity cannot be enhanced to achieve dramatic outcomes. Spines are highly dynamic and capable of remodeling and restoring their original structure, location, and function [49], when triggered with appropriate therapeutics, such as neurotrophic activators (see below). Therapeutic strategies aimed at the reactivation of these pathways in injured CNS neurons might be successful in enhancing our capacity to revitalize neurons and regenerate synapses.

Nonpharmacological Intervention

A wide range of nonpharmacological approaches have been tried to treat AD models and AD patients. Some have been reported to promote neurotrophic activity and neuro-regeneration and exhibit therapeutic value against cognitive impairments, but their clinical utility is still preliminary. Readers are referred to a recent review for their utility and limitations [50].

Environmental Enrichment and Exercise

Increasing evidence suggests that manipulating neuronal activity [51] might be an approach for enhancing intrinsic neuronal growth ability. Calcium influx into the axoplasm is one of the first signals caused by injury, a back-propagating signal required to activate endogenous protein synthesis for sealing the membranes, assembly of growth cone, and enzymatic histone acetylation [52]. Environmental enrichment and physical exercise are the least invasive

approaches that enhance endogenous neuro-regeneration, although they are mild and limited [53], they produce impacts better than social enrichment for reducing memory deficits in AD rats [54].

Brain Stimulation

Brain stimulation has generated some hope for symptomatic relief in AD. Transcranial current stimulation, a noninvasive technique, induces BDNF expression and secretion and enhances passive avoidance learning, an effect blocked by TrkB inhibitor [55]. Deep brain stimulation, an invasive neurosurgical procedure, involves driving a small burr hole into the skull and inserting thin electrodes deep into specific brain targets to stimulate the tissue electrically. Thus, brain activity accessible under surgery can also be directly measured. In a recent clinical trial with mild AD cases, a fornix deep brain stimulation increased glucose metabolism but produced no differences in cognitive outcomes [56]. A direct electric pulse may cause an acute depolarization and a disruption in memory formation and recall [57]. Brain stimulation thus has risks of interfering with memory functions, resulting in adverse reaction in cognition [58].

Neural Stem Cells

Loss of neurons could be significant, especially at the late AD stage. Repopulation of the lost neuronal circuity with stem cells and regeneration of the lost structures/synapses are rational strategies in therapy for patients with late-stage AD. Several exogenous sources are available [59]. The therapeutic effects of stem cells rely on two developments: an incorporation of the cells into the neural network and an increased secretion of neurotrophins, which promote endogenous neuro-regeneration [60]. Alternatively, the endogenous source can also be activated through neurogenesis and/or through direct reprogramming [61]. In preclinical studies, most hippocampus transplanted neonatal mouse subventricular zone-derived neural stem cells are reported to differentiate into neurons [62], resulting in cognitive improvements in animal models ([63], but see [64]). The mesenchymal stem cells (MSCs), for instance, have been reported to produce neurotherapeutic effects in animal models [65,66], but not in AD patients [59] (i.e., they caused no slowing of cognitive decline and AD pathology over the 24 months of follow-up). While still not precisely defined, the therapeutic mechanism(s) may include inducing neurorepairing activity through BDNF in addition to a potential integration into the existing brain network of the host. In a recent study, BDNF was used to modify human umbilical cord MSCs and transplantation of these cells to the hippocampal area of Aβ-impaired rats significantly improved their spatial learning and memory abilities, enhanced the activation of astrocytes and microglia, reduced the expression of Aβ and recombinant human β-site APP-cleaving enzyme1 (BACE1), inhibited neuronal apoptosis, and promoted neurogenesis [60]. An enhanced BDNF activity may underlie the improved outcome [60]. The future of such cell therapy in AD patients, of course, depends on its cognitive efficacy and long-term safety. This is particularly true since there have been few demonstrations that exogenously introduced stem cells form functioning synaptic networks that are capable of meaningful information processing.

Pharmacological Interventions

As mentioned above, whilst adult mammalian brains have capacity for synaptic/neuronal repair and remodeling, this regenerative capacity is insufficient for replacing the number of synapses/neurons lost due to injury or neurodegenerative disorders, even after enhancement through physical exercise or environmental enrichment. The question is thus how to address the insufficient neural regeneration through synaptic/neuronal pharmacology. Several compounds, such as bryostatin-1 and DCP-LA (see below and Figure 3), show promising therapeutic potential against AD. These agents, including those promising and less so, tend to possess a similar pattern of

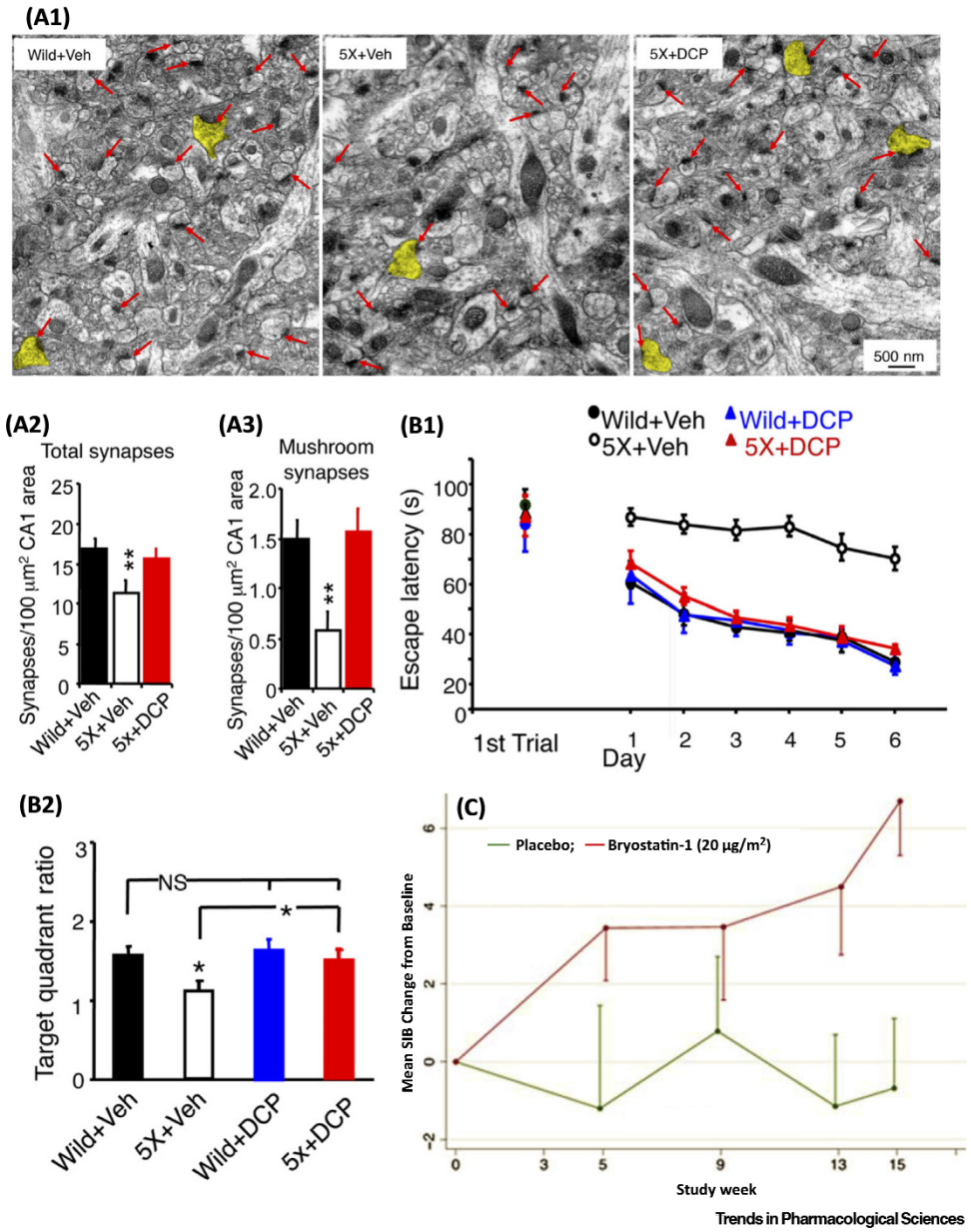

Figure 3. Enhancement of Brain Protein Kinase (PK)Cε-BDNF (Brain-Derived Neurotrophic Factor) Signaling Activity Produces Therapeutic Effects on Learning and Memory in 5xFAD Mice and Advanced Alzheimer's Disease (AD) Patients. (A) DCP-LA, a selective PKCε activator, rescues, through blind-evaluation of synapses with electron microscopy (A1), the ability to maintain the number of synapses (A2) and the capacity in formation mushroom synapses (A3) in the hippocampus of 5xFAD mice. Yellow highlights mushroom spine synapses, and red, synapses. (B) DCP-LA prevents deficits in water-maze spatial learning (B1, shown as means ± SEM (standard error of the mean), using the daily three trials as a block) and memory performance (B2, target quadrant ratios) in 5xFAD mice. Data are shown as means ± SEM; *, $P \leq 0.05$; **, $P \leq 0.01$. Figure reproduced, with permission, from [7]. (C) Bryostatin-1 produces a significant improvement in cognition, evaluated with Severe Impairment Battery (SIB) in advanced AD patients without memantine. The traces show that SIB improves throughout the trial in the bryostatin-1 group and that SIB declines in the placebo group. Figure reproduced, with permission, from [105]. Abbreviations: Bry, bryostatin-1; DCP, DCP-LA; Veh, vehicle; 5x, 5xFAD transgenic mice.

multiple pharmacological profiles, such as antioxidant, anti-inflammatory, pro-BDNF, and pro-synaptic remodeling/regeneration.

Antioxidants

Oxidants may play an important role in AD pathology, synaptic dysfunction, and cognitive impairment [67]. Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene), a polyphenolic compound (in grapes, peanuts, berries, and more than 70 other plant species), can activate Sirtuin 1 (SIRT1, silent information regulator-1), an NAD+-dependent protein deacetylase, and produce pro-BDNF, antioxidative, anti-inflammatory, and antiapoptotic processes, autophagy regulation, and neuroprotection against cognitive impairment [68,69]. *Sirt1* knockout mice exhibited defects in dendritic development and synaptic function [70].

Curcumin, (1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), a component of Indian spice turmeric, can bind directly to Aβ and prevent Aβ aggregation [71], in addition to its antioxidant and anti-inflammatory action [72,73]. Clinical studies of curcumin in mild AD, however, found no significant differences in cognition between placebo and intervention groups [74]. It is not clear whether the failure is due to its poor absorption [75].

Anti-inflammatory Agents

Two types of observations suggest involvement of inflammation in AD. First, early studies reveal the existence of reactive microglia surrounding amyloid plaques in AD brains [76]. Second, the prevalence of AD in patients with rheumatoid arthritis is unexpectedly low [77], probably due to the usage of anti-inflammatory therapy, as in the long-term users of nonsteroidal anti-inflammatory drugs (NSAIDs) [78]. However, it has not been actually well established whether this overt plaque-related inflammatory/immune process is helpful or destructive in the context of AD progression. There is abundant evidence that anti-inflammatory treatments can produce anti-AD impacts in AD models [79]. But, the importance of neuroinflammation in AD pathogenesis and progression has been questioned by an equal number of observations. Donepezil, for instance, can effectively inhibit microglial activation in APP/PS1 mice and produce cognitive improvements [80], but does not appear to modify AD progression. Anti-inflammatory cytokines have also been reported to increase AD plaque burden and worsen cognitive outcomes in AD mice [81,82]. The controversy does urge caution in focusing on the therapeutic strategies through inhibiting microglial activation before we fully understand the role of inflammation in AD. Although there are a large number of failed clinical trials with anti-inflammatory agents in AD patients [43,83,84], including some classical NSAIDs, such as ibuprofen, rofecoxib, celecoxib, and R-flurbiprofen, and other anti-inflammatories, such as pioglitazone (acting on PPAR-γ), steroids, and aspirin, these trials do not necessarily rule out the involvement of neuroinflammation in preclinical AD pathology [85]. The late AD inflammation may just represent a tissue resolution [86], less relevant in AD pathology since it wanes with age [87].

Histone Deacetylase (HDAC) Inhibitors

Histone deacetylation has been implicated in contributing to the AD-like phenotype. A high level of HDAC3 expression is seen in the hippocampus and cortical areas. An increased nuclear translocation of **HDACs** is associated with BDNF downregulation in human neurons, a response that can be evoked by Aβ oligomers or ApoE4 but reversed with PKCε activator bryostatin-1 [88]. HDAC inhibitors have been tested for their therapeutic effects in AD [89]. RGFP-966, a brain-penetrant and selective HDAC3 inhibitor, has been found to increase histone H3 and H4 acetylation and BDNF expression, decrease tauopathy and Aβ1–42 accumulation, and improve spatial learning and memory in 3xTg-AD mice [90].

Enhancing PKC-BDNF Signaling

Several signaling pathways play critical roles in synaptogenesis, synaptic maturation, and synaptic repair, the endogenous mechanisms to maintain synaptic/neuronal integrity against injury/damage/cognitive challenges. Their actions can be modulated through pharmacological treatment and neurotrophic activation.

Synaptic repair and behavioral normalization can be achieved with an enhanced neurotrophic activity without targeting Aβ and tauopathy [91,92]. In a recent study, a combination of BDNF and induced neurogenesis is reported to reduce cognitive impairment in 5xFAD mice [93]. More recently, conditional BDNF delivery from astrocytes through overexpressing BDNF under the GFAP promoter, has been found to rescue memory deficits, spine density, and synaptic properties in 5xFAD mice [94]. The authors concluded that the effects of conditional BDNF did not result from reduction in amyloidosis or neurogenesis improvement, but rather from changes in structural and functional synaptic properties [94]. With a focus on reversing synaptic and neuronal loss in AD, we have developed a therapeutic strategy that has shown a neurorestorative potential (i.e., to restore lost synapses in AD brains in preclinical studies) [9,95], as well as the concomitant potential to prevent apoptosis [9,96–98], reduce Aβ oligomers, lower hyperphosphorylated tau [9,97–100], mRNA stabilization of growth factor mRNAs, and reduce oxidative stress [101]. Activators of PKCε (Figure 2) with bryostatin-1, a relatively selective and powerful PKCε activator with clinical safety profile at appropriate doses [102], and DCP-LA (Figure 3) have been shown to increase synaptic numbers via synaptic growth factors [103,104]. Bryostatin-1, a macrocyclic lactone, enhances BDNF expression/secretion and synaptic remodeling/synaptogenesis in the brain and produces several other anti-AD effects, such as antiapoptosis, anti-inflammation, antiamyloidosis, antitauopathy, and antioxidant, at therapeutic doses [10,105].

Clinical trials using recombinant BDNF are disappointing so far, most likely due to poor delivery and a short half-life of BDNF *in vivo*. Chronic administration of bryostatin-1, however, has been shown to improve cognitive functions in advanced AD patients in the absence of memantine (Figure 3) [105]. An optimal prodrug of the BDNF mimetic compound 7,8-dihydroxyflavone (7,8-DHF), a potent small molecular TrkB agonist with poor oral bioavailability, has recently been found to prevent Aβ deposition and synaptic loss in the hippocampus in 5XFAD mice [106]. ROCK (Rho kinase) inhibitors, such as FSD-C10 [107], have also been found to promote BDNF and GDNF activity, reduce Aβ and tauopathy, and improve cognition in APP/PS1 mice [108].

Concluding Remarks

It has been well established that pathological changes in the AD brain occur early, many years before any clinical symptoms. Aβ could accumulate in the brains for 15–20 years before any AD clinical symptoms [109,110]. Evidence supports the notion that cognitive deficits occur only when synapses/neural network cannot be appropriately maintained through neuronal/synaptic repair and synaptogenesis/neuro-regeneration to meet cognitive demands, indicating that synaptic deficiency should be the focused therapeutic target. The synaptic deficiency hypothesis (Figure 1), consistent with enormous evidence that an early failed maintenance in synaptic integrity triggers neurodegeneration in the brain and cognitive decline, does not rule out the pathological contribution of neurotoxic Aβ and tauopathy to synaptic/cognitive deficits in AD and potential therapeutic benefits of anti-Aβ and antitauopathy. Along this line is also the evidence that oral *Porphyromonas gingivalis* infection results in accumulation of neurotoxic gingipains in AD brains and amyloidosis [111]. Gingipain inhibitors could be valuable for treating *P. gingivalis* and stopping neurodegeneration in AD. The possibility also exists that Aβ and tau synergize to impair the functional integrity of neural circuits [112]. However, evidence is abundant that formation of amyloid and

Outstanding Questions

What are the determinants that dictate the progression rate in Alzheimer's dementia?

Would the degree of synaptic deficiency be both essential and sufficient?

Would a co-antitauopathy treatment make a dramatic difference in therapeutic outcomes?

What circumstances/conditions establish the major switch towards the opposite reactions of triggering or inhibiting neuro-regeneration/synaptic repairing in the AD brain?

How can a sustained normalization of brain neurotrophic activity be achieved clinically?

Would such a treatment require a lifetime adjustment?

hyperphosphorylated tau is reactive (secondary; [60,113,114,119]) to brain injury, hypoactive BDNF [102], and deficient BDNF-associated degenerative processes, as are microglia and neurotoxic astrocytes. Amyloid accumulation and tauopathy can reduce BDNF levels and secretion [115], probably contributing to a further (secondary) reduction in neurotrophic activity in the brain (Figure 1B).

Accumulating evidence, to date, suggests that structural and functional deficits of synapses are at the core of the underlying pathophysiology in AD (see Outstanding Questions). In clinical trials, AD therapeutics that target synaptic loss and dysfunction (i.e., to slow, halt, or reverse progression of the disorders at the level of synapses), via synaptogenic molecular cascades such as the PKC-BDNF signaling pathway, show promising results [105]. This differs from the failure of 300–400 AD drug candidates in recent years [116]. The key to effective neurotrophic therapy in AD appears to require a sustained and appropriate PKC-BDNF activity in the brain, guiding against the aging/disease-related neurodegenerative process. A too-high level of PKC-BDNF activity can also be neurotoxic [117,118]. Overcoming the self-repair limitation in the mammalian brain would transform how AD patients, and others with memory disorders, are treated clinically.

Disclaimer Statement

The authors declare no competing financial interests. Neurotrope, Inc., the current employer of the authors, however, sponsors clinical trials for AD therapeutics, including bryostatin-1.

References

1. Robinson, S.R. *et al.* (2004) Lessons from the AN 1792 Alzheimer vaccine: lest we forget. *Neurobiol. Aging* 25, 609–615
2. Huang, Y. and Mucke, L. (2012) Alzheimer mechanisms and therapeutic strategies. *Cell* 148, 1204–1222
3. Han, J.Y. *et al.* (2019) Cholinesterase inhibitors may not benefit mild cognitive impairment and mild Alzheimer disease dementia. *Alzheimer Dis. Assoc. Disord.* 33, 87–94
4. Venegas, C. *et al.* (2017) Microglia-derived ASC specks cross-seed amyloid-β in Alzheimer's disease. *Nature* 552, 355–361
5. Kinney, J.W. *et al.* (2018) Inflammation as a central mechanism in Alzheimer's disease. *Alzheimers Dement. (NY)* 4, 575–590
6. Terry, R.D. *et al.* (1991) Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Ann. Neurol.* 30, 572–580
7. Choi, S.H. *et al.* (2014) A three-dimensional human neural cell culture model of Alzheimer's disease. *Nature* 515, 274–278
8. Papadimitriou, C. *et al.* (2018) 3D culture method for Alzheimer's disease modeling reveals interleukin-4 rescues Aβ42-induced loss of human neural stem cell plasticity. *Dev. Cell* 46, 85–101
9. Hongpaisan, J. and Alkon, D.L. (2007) A structural basis for enhancement of long-term associative memory in single dendritic spines regulated by PKC. *Proc. Natl. Acad. Sci. U. S. A.* 104, 19571–19576
10. Hongpaisan, J. *et al.* (2011) PKCε activation prevents synaptic loss, Aβ elevation, and cognitive deficits in Alzheimer's disease transgenic mice. *J. Neurosci.* 31, 630–643
11. Scheff, S.W. *et al.* (2007) Synaptic alterations in CA1 in mild Alzheimer disease and mild cognitive impairment. *Neurology* 68, 1501–1508
12. Masliah, E. *et al.* (2001) Altered expression of synaptic proteins occurs early during progression of Alzheimer's disease. *Neurology* 56, 127–129
13. Davies, C.A. *et al.* (1987) A quantitative morphometric analysis of the neuronal and synaptic content of the frontal and temporal cortex in patients with Alzheimer's disease. *J. Neurol. Sci.* 78, 151–164
14. Coleman, P.D. and Yao, P.J. (2003) Synaptic slaughter in Alzheimer's disease. *Neurobiol. Aging* 24, 1023–1027
15. Lawlor, B. *et al.* (2019) Nilvadipine in mild to moderate Alzheimer disease: a randomised controlled trial. *PLoS Med.* 15, e1002660
16. Egan, M.F. *et al.* (2018) Randomized trial of verubecestat for mild-to-moderate Alzheimer's disease. *N. Engl. J. Med.* 378, 1691–1703
17. Cummings, J. (2018) APECS trial of the BACE1 inhibitor verubecestat for prodromal Alzheimer's disease. *J. Prev. Alzheimers Dis.* 5, S1
18. Congdon, E.E. and Sigurdsson, E.M. (2018) Tau- targeting therapies for Alzheimer disease. *Nat. Rev. Neurol.* 14, 399–415
19. Sun, M.K. (2018) Roles of neural regeneration in memory pharmacology. *Neural Regen. Res.* 13, 406–407
20. Wu, B.W. *et al.* (2018) Effects of microRNA-10a on synapse remodeling in hippocampal neurons and neuronal cell proliferation and apoptosis through the BDNF-TrkB signaling pathway in a rat model of Alzheimer's disease. *J. Cell. Physiol.* 233, 5281–5292
21. Lev-Vachnish, Y. *et al.* (2019) L-Lactate promotes adult hippocampal neurogenesis. *Front. Neurosci.* 13, 403
22. Cheng, L. *et al.* (2019) 3β,23,28-Trihydroxy-12-oleanene 3β-caffeate from desmodium sambuense-induced neurogenesis in PC12 cells mediated by ER stress and BDNF-TrkB signaling pathways. *Mol. Pharmacol.* 16, 1423–1432
23. Kellner, Y. *et al.* (2014) The BDNF effects on dendritic spines of mature hippocampal neurons depend on neuronal activity. *Front. Synaptic Neurosci.* 6, 5
24. Tabuchi, A. *et al.* (2000) Differential activation of brain-derived neurotrophic factor gene promoters I and III by Ca^{2+} signals evoked via L-type voltage-dependent and N-methyl-D-aspartate receptor Ca^{2+} channels. *J. Biol. Chem.* 275, 17269–17275
25. Liu, X.S. *et al.* (2016) Editing DNA methylation in the mammalian genome. *Cell* 167, 233–247
26. Mar, F.M. *et al.* (2014) Cell intrinsic control of axon regeneration. *EMBO Rep.* 15, 254–263
27. Switon, K. *et al.* (2017) Molecular neurobiology of mTOR. *Neuroscience* 341, 112–153
28. Iulita, M.F. *et al.* (2017) Differential deregulation of NGF and BDNF neurotrophins in a transgenic rat model of Alzheimer's disease. *Neurobiol. Dis.* 108, 307–323
29. Kaminari, A. *et al.* (2017) Overexpression of matrix metalloproteinase-9 (MMP-9) rescues insulin-mediated impairment in the 5XFAD model of Alzheimer's disease. *Sci. Rep.* 7, 683

30. Arendt, T. (2009) Synaptic degeneration in Alzheimer's disease. *Acta Neuropathol.* 118, 167–179
31. Selkoe, D.J. (2002) Alzheimer's disease is a synaptic failure. *Science* 298, 789–791
32. Silver, J. and Miller, J.H. (2004) Regeneration beyond the glial scar. *Nat. Rev. Neurosci.* 5, 146–156
33. Ginsberg, S.D. *et al.* (2010) Microarray analysis of hippocampal CA1 neurons implicates early endosomal dysfunction during Alzheimer's disease progression. *Biol. Psychiatry* 68, 885–893
34. Khan, T.K. *et al.* (2015) PKCε deficits in Alzheimer's disease brains and skin fibroblasts. *J. Alzheimers Dis.* 43, 491–509
35. Hong, S. *et al.* (2016) Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science* 352, 712–716
36. Henstridge, C.M. *et al.* (2019) Beyond the neuron-cellular interactions early in Alzheimer's disease pathogenesis. *Nat. Rev. Neurosci.* 20, 94–108
37. Eikelenboom, P. *et al.* (2002) Neuroinflammation in Alzheimer's disease and prion disease. *Glia* 40, 232–239
38. Felsky, D. *et al.* (2019) Neuropathological correlates and genetic architecture of microglial activation in elderly human brain. *Nat. Commun.* 10, 409
39. Adams, K. and Gallo, V. (2018) The diversity and disparity of the glial scar. *Nat. Neurosci.* 21, 9–15
40. Heneka, M.T. *et al.* (2015) Neuroinflammation in Alzheimer's disease. *Lancet Neurol.* 14, 388–405
41. Rajendran, L. and Paolicelli, R.C. (2018) Microglia-mediated synapse loss in Alzheimer's disease. *J. Neurosci.* 38, 2911–2919
42. Fonseca, M.I. *et al.* (2017) Cell-specific deletion of C1qa identifies microglia as the dominant source of C1q in mouse brain. *J. Neuroinflammation* 14, 48
43. Liddelow, S.A. *et al.* (2017) Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* 541, 481–487
44. Hilla, A.M. *et al.* (2019) Microglia are irrelevant for neuronal degeneration and axon regeneration after acute injury. *J. Neurosci.* 37, 6113–6124
45. Forlenza, O.V. *et al.* (2015) Decreased neurotrophic support is associated with cognitive decline in non-demented subjects. *J. Alzheimers Dis.* 46, 423–429
46. von Bohlen Und Halbach, O. and von Bohlen Und Halbach, V. (2018) BDNF effects on dendritic spine morphology and hippocampal function. *Cell Tissue Res.* 373, 729–741
47. Yiu, G. and He, Z. (2006) Glial inhibition of CNS axon regeneration. *Nat. Rev. Neurosci.* 7, 617–627
48. Barini, E. *et al.* (2016) Metformin promotes tau aggregation and exacerbates abnormal behavior in a mouse model of tauopathy. *Mol. Neurodegener.* 11, 16
49. Tseng, C.Y. and Firestein, B.L. (2011) The role of PSD-95 and cypin in morphological changes in dendrites following sublethal NMDA exposure. *J. Neurosci.* 31, 15468–15480
50. Zucchella, C. *et al.* (2018) The multidisciplinary approach to Alzheimer's disease and dementia. A narrative review of non-pharmacological treatment. *Front. Neurol.* 9, 1058
51. Morris, G.P. *et al.* (2014) Inconsistencies and controversies surrounding the amyloid hypothesis of Alzheimer's disease. *Acta Neuropathol. Commun.* 2, 135
52. Lozano, A.M. *et al.* (2016) A phase II study of fornix deep brain stimulation in mild Alzheimer's disease. *J. Alzheimers Dis.* 54, 777–787
53. Gates, N. *et al.* (2013) The effect of exercise training on cognitive function in older adults with mild cognitive impairment: a meta-analysis of randomized controlled trials. *Am. J. Geriatr. Psychiatry* 21, 1086–1097
54. Prado Lima, M.G. *et al.* (2018) Environmental enrichment and exercise are better than social enrichment to reduce memory deficits in amyloid beta neurotoxicity. *Proc. Natl. Acad. Sci. U. S. A.* 115, E2403–E2409
55. Yu, T-H. *et al.* (2019) Transcranial direct current stimulation induces hippocampal metaplasticity mediated by brain-derived neurotrophic factor. *Neuropharmacology* 144, 358–367
56. Mao, Z.Q. *et al.* (2018) Partial improvement in performance of patients with severe Alzheimer's disease at an early stage of fornix deep brain stimulation. *Neural Regen. Res.* 13, 2164–2172
57. Hescham, S. *et al.* (2013) Deep brain stimulation in dementia-related disorders. *Neurosci. Biobehav. Rev.* 37, 2666–2675
58. Puy, L. *et al.* (2018) Acute dementia after deep brain stimulation in Parkinson disease. *World Neurosurg.* 119, 63–65
59. Duncan, T. and Valenzuela, M. (2017) Alzheimer's disease, dementia, and stem cell therapy. *Stem Cell Res. Ther.* 8, 111
60. Hu, W. *et al.* (2019) Brain-derived neurotrophic factor modified human umbilical cord mesenchymal stem cells-derived cholinergic-like neurons improve spatial learning and memory ability in Alzheimer's disease rats. *Brain Res.* 1710, 61–73
61. Barker, R.A. *et al.* (2018) New approaches for brain repair – from rescue to reprogramming. *Nature* 557, 329–334
62. Zhang, W. *et al.* (2017) NSCs promote hippocampal neurogenesis, metabolic changes and synaptogenesis in APP/PS1 transgenic mice. *Hippocampus* 27, 1250–1263
63. Ager, R.R. *et al.* (2015) Human neural stem cells improve cognition and promote synaptic growth in two complementary transgenic models of Alzheimer's disease and neuronal loss. *Hippocampus* 25, 813–826
64. Marsh, S.E. *et al.* (2017) HuCNS-SC human NSCs fail to differentiate, form ectopic clusters, and provide no cognitive benefits in a transgenic model of Alzheimer's disease. *Stem Cell Rep.* 8, 235–248
65. Yang, H. *et al.* (2013) Human umbilical cord mesenchymal stem cell-derived neuron-like cells rescue memory deficits and reduce amyloid-beta deposition in an AβPP/PS1 transgenic mouse model. *Stem Cell Res. Ther.* 4, 1
66. Kim, K-S. *et al.* (2013) Long-term immunomodulatory effect of amniotic stem cells in an Alzheimer's disease model. *Neurobiol. Aging* 34, 2408–2420
67. Kamat, P.K. *et al.* (2016) Mechanism of oxidative stress and synapse dysfunction in the pathogenesis of Alzheimer's disease: understanding the therapeutics strategies. *Mol. Neurobiol.* 53, 648–661
68. Cao, W. *et al.* (2018) Resveratrol boosts cognitive function by targeting SIRT1. *Neurochem. Res.* 43, 1705–1713
69. Sun, A.Y. *et al.* (2010) Resveratrol as a therapeutic agent for neurodegenerative diseases. *Mol. Neurobiol.* 41, 375–383
70. Ng, F. *et al.* (2015) SIRT1 in the brain-connections with aging-associated disorders and lifespan. *Front. Cell. Neurosci.* 9, 64
71. Kozmon, S. and Tvaroška, I. (2015) Molecular dynamic studies of amyloid-beta interactions with curcumin and Cu^{2+} ions. *Chem. Papers* 69, 1262–1276
72. Chen, M. *et al.* (2019) Use of curcumin in diagnosis, prevention, and treatment of Alzheimer's disease. *Neural. Regen. Res.* 13, 742–752
73. Hu, S. *et al.* (2015) Clinical development of curcumin in neurodegenerative disease. *Expert. Rev. Neurother.* 15, 629–637
74. Baum, L. *et al.* (2008) Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease. *J. Clin. Psychopharmacol.* 28, 110–113
75. Reddy, P.H. *et al.* (2018) Protective effects of Indian spice curcumin against amyloid-β in Alzheimer's disease. *J. Alzheimers Dis.* 61, 843–866
76. McGeer, P.L. *et al.* (1987) Reactive microglia in patients with senile dementia of the Alzheimer type are positive for the histocompatibility glycoprotein HLA-DR. *Neurosci. Lett.* 79, 195–200
77. McGeer, P.L. *et al.* (1990) Anti-inflammatory drugs and Alzheimer disease. *Lancet* 335, 1037
78. Wang, J. *et al.* (2015) Anti-inflammatory drugs and risk of Alzheimer's disease: an updated systematic review and meta-analysis. *J. Alzheimers Dis.* 44, 385–396
79. Cavanagh, C. and Wong, T.P. (2018) Preventing synaptic deficits in Alzheimer's disease by inhibiting tumor necrosis factor alpha signaling. *IBRO Rep.* 4, 18–21
80. Guo, H.B. *et al.* (2015) Donepezil improves learning and memory deficits in APP/PS1 mice by inhibition of microglial activation. *Neuroscience* 290C, 530–542
81. Chakrabarty, P. *et al.* (2015) IL-10 alters immunoproteostasis in APP mice, increasing plaque burden and worsening cognitive behavior. *Neuron* 85, 519–533
82. Guillot-Sestier, M.V. *et al.* (2015) Il10 deficiency rebalances innate immunity to mitigate Alzheimer-like pathology. *Neuron* 85, 534–548

83. Gupta, P.P. *et al.* (2015) Role of traditional nonsteroidal anti-inflammatory drugs in Alzheimer's disease: a meta-analysis of randomized clinical trials. *Alzheimers Dis. Other Demen.* 30, 178–182
84. Calsolaro, V. and Edison, P. (2016) Neuroinflammation in Alzheimer's disease: current evidence and future directions. *Alzheimers Dement.* 12, 719–732
85. Cuello, A.C. (2017) Early and late CNS inflammation in Alzheimer's disease: two extremes of a continuum? *Trends Pharmacol. Sci.* 38, 956–966
86. Keren-Shaul, H. *et al.* (2017) A unique microglia type associated with restricting development of Alzheimer's disease. *Cell* 169, 1276–1290
87. Hoozemans, J.J.M. *et al.* (2011) Neuroinflammation in Alzheimer's disease wanes with age. *J. Neuroinflammation* 8, 171
88. Sen, A. *et al.* (2015) ApoE4 and Aβ oligomers reduce BDNF expression via HDAC nuclear translocation. *J. Neurosci.* 35, 7538–7551
89. Gräff, J. and Tsai, L-H. (2013) The potential of HDAC inhibitors as cognitive enhancers. *Annu. Rev. Pharmacol. Toxicol.* 53, 311–330
90. Janczura, K.J. *et al.* (2018) Inhibition of HDAC3 reverses Alzheimer's disease-related pathologies *in vitro* and in the 3xTg-AD mouse model. *Proc. Natl. Acad. Sci. U. S. A.* 115, E11148–E11157
91. Nagahara, A.H. *et al.* (2013) Early BDNF treatment ameliorates cell loss in the entorhinal cortex of APP transgenic mice. *J. Neurosci.* 33, 15596–15602
92. Jiao, S-S. *et al.* (2016) Brain-derived neurotrophic factor protects against tau-related neurodegeneration of Alzheimer's disease. *Tranl. Psychiatry* 6, e907
93. Choi, S.H. *et al.* (2018) Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model. *Science* 361, eaan8821
94. de Pins, B. *et al.* (2019) Conditional BDNF delivery from astrocytes rescues memory deficits, spine density and synaptic properties in the 5xFAD mouse model of Alzheimer disease. *J. Neurosci.* 39, 2441–2458
95. Sun, M-K. *et al.* (2015) Towards universal therapeutics for memory disorders. *Trends in Pharmacol. Sci.* 36, 384–394
96. Baazaoui, N. and Iqbal, K. (2018) A novel therapeutic approach to treat Alzheimer's disease by neurotrophic support during the period of synaptic compensation. *J. Alzheimers Dis.* 62, 1211–1218
97. Sun, M.-K. *et al.* (2008) Post-stroke neuronal rescue and synaptogenesis mediated *in vivo* by PKC in adult brains. *Proc. Natl. Acad. Sci. U. S. A.* 105, 13620–13625
98. Nelson, T.J. *et al.* (2009) Reduction of beta-amyloid levels by novel PKC (epsilon) activators. *J. Biol. Chem.* 284, 34514–34521
99. Alkon, D.L. *et al.* (2007) PKC signaling deficits: a mechanistic hypothesis for the origins of Alzheimer's disease. *Trends Pharmacol. Sci.* 28, 51–60
100. Xu, A-H. *et al.* (2018) Exogenous brain-derived neurotrophic factor attenuates cognitive impairment induced by okadaic acid in a rat model of Alzheimer's disease. *Neural Regen. Res.* 13, 2173–2181
101. Sen, A. *et al.* (2018) Loss in PKC epsilon causes downregulation of MnSOD and BDNF expression in neurons of Alzheimer's disease hippocampus. *J. Alzheimers Dis.* 63, 1173–1189
102. Nelson, T.J. *et al.* (2017) Bryostatin effects on cognitive function and PKCε in Alzheimer's phase IIa and expanded access trials. *J. Alzheimers Dis.* 58, 521–535
103. Sun, M.-K. *et al.* (2009) Post-ischemic PKC activation rescues retrograde and anterograde long-term memory. *Proc. Natl. Acad. Sci. U. S. A.* 106, 14676–14680
104. Sen, A. *et al.* (2012) Apolipoprotein E3 (ApoE3) but not ApoE4 protects against synaptic loss through increased expression of protein kinase Cε. *J. Biol. Chem.* 287, 15947–15948
105. Farlow, M.R. *et al.* (2018) A randomized, double-blind, placebo-controlled, phase II study assessing safety, tolerability, and efficacy of bryostatin in the treatment of moderately severe to severe Alzheimer's disease. *J. Alzheimers Dis.* 67, 555–570
106. Chen, C. *et al.* (2018) The prodrug of 7,8-dihydroxyflavone development and therapeutic efficacy for treating Alzheimer's disease. *Proc. Natl. Acad. Sci. U. S. A.* 115, 578–583
107. Li, Y.H. *et al.* (2014) Intranasal delivery of FSD-C10, a novel Rho kinase inhibitor, exhibits therapeutic potential in experimental autoimmune encephalomyelitis. *Immunology* 143, 219–229
108. Gu, Q.F. *et al.* (2018) Therapeutic effect of Rho kinase inhibitor FSD-C10 in a mouse model of Alzheimer's disease. *Exp. Ther. Med.* 16, 3929–3938
109. Lin, P-Y. *et al.* (2018) Genetic dissection of presynaptic and postsynaptic BDNF-TrkB signaling in synaptic efficacy of CA3-CA1 synapses. *Cell Rep.* 24, 1550–1561
110. Hardy, J. and Selkoe, D.J. (2002) The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* 297, 353–356
111. Dominy, S.S. *et al.* (2019) *Porphyromonas gingivalis* in Alzheimer's disease brains: evidence for disease causation and treatment with small-molecule inhibitors. *Sci Adv.* 5, eaau3333
112. Panza, F. *et al.* (2019) Amyloid-β immunotherapy for Alzheimer disease: is it now a long shot? *Ann. Neurol.* 85, 303–315
113. Busche, M.A. *et al.* (2019) Tau impairs neural circuits, dominating amyloid-β effects, in Alzheimer models *in vivo*. *Nat. Neurosci.* 22, 57–64
114. Shokri-Kojori, E. *et al.* (2018) β-Amyloid accumulation in the human brain after one night of sleep deprivation. *Proc. Natl. Acad. Sci. U. S. A.* 115, 4483–4488
115. Atasoy, I.L. *et al.* (2017) Both secreted and the cellular levels of BDNF attenuated due to tau hyperphosphorylation in primary cultures of cortical neurons. *J. Chem. Neuroanat.* 80, 19–26
116. Becker, R.E. and Greig, N.H. (2019) Can we prevent dementia and not prevent neurons from dying? *J. Alzheimers Dis.* 68, 489–492
117. Martínez-Serrano, A. and Björklund, A. (1996) Protection of the neostriatum against excitotoxic damage by neurotrophin-producing, genetically modified neural stem cells. *J. Neurosci.* 16, 4604–4616
118. Kells, A.P. *et al.* (2008) AAV-BDNF mediated attenuation of quinolinic acid-induced neuropathology and motor function impairment. *Gene Ther.* 15, 966–977
119. Giuffrida, M.L. *et al.* (2018) A promising connection between BDNF and Alzheimer's disease. *Aging (Albany NY)* 10, 1791–1792