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Targeting Synaptic Dysfunction in Alzheimer's Disease Therapy

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Abstract In the past years, major efforts have been made to understand the genetics and molecular pathogenesis of Alzheimer's disease (AD), which has been translated into extensive experimental approaches aimed at slowing down or halting disease progression. Advances in transgenic (Tg) technologies allowed the engineering of different mouse models of AD recapitulating a range of AD-like features. These Tg models provided excellent opportunities to analyze the bases for the temporal evolution of the disease. Several lines of evidence point to synaptic dysfunction as a cause of AD and that synapse loss is a pathological correlate associated with cognitive decline. Therefore, the phenotypic characterization of these animals has included electrophysiological studies to analyze hippocampal synaptic transmission and long-term potentiation, a widely recognized cellular model for learning and memory. Transgenic mice, along with non-Tg models derived mainly from exogenous application of Aβ, have also been useful experimental tools to test the various therapeutic approaches. As a result, numerous pharmacological interventions have been reported to attenuate synaptic dysfunction and improve behavior in the different AD models. To date, however, very few of these findings have resulted in target validation or successful translation into disease-modifying compounds in humans. Here, we will briefly review the synaptic alterations across the different animal models and we will recapitulate the pharmacological strategies aimed at rescuing hippocampal plasticity phenotypes. Finally, we will highlight intrinsic limitations in the use of experimental systems and related challenges in translating preclinical studies into human clinical trials.

Keywords Alzheimer's disease · Amyloid · Peptide · Hippocampus · Synaptic plasticity · Long-term potentiation (LTP) · Pharmacology · Synaptic dysfunction · Neurodegenerative

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Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disease that affects more than 35 million people worldwide. AD is characterized by gradual and progressive memory impairment associated with deterioration of daily living activities and behavioral disturbances throughout the course of the disease.

Although there has been substantial progress in the therapeutic approach to AD in the past years with the use of cholinesterase inhibitors and the glutamate-modulating drug memantine, treatment for AD still remains a challenge for

physicians. In fact, regardless of the therapy prescribed, the current approaches to AD treatment provide only temporary symptomatic relief and do not inhibit and/or reverse the underlying disease mechanisms. This highlights the urgent need for disease-modifying drugs for AD. There are currently approximately 80 compounds at various stages of clinical investigation for the treatment of AD (www.alzforum.org).

From a neuropathological point of view, the AD brain shows senile (neuritic) plaques, neurofibrillary tangles (NFT), and marked atrophy in the brain [1]. The most severe neuropathological changes occur in the hippocampus, followed by the association cortices and subcortical structures, including the amygdala and nucleus basalis of Meynert [2].

In recent years, however, evidence has accumulated demonstrating that synaptic loss, rather than amyloid beta (Aβ) plaques, NFTs, or neuronal loss, is the best pathological correlate of cognitive impairment [1]. Consequently, AD has been suggested to be a form of synaptic plasticity failure [3]. This theory implies that amplification of the plasticity burden at an early stage, leading to a primarily adaptive upregulation of tau phosphorylation and amyloid β precursor protein (AβPP) turnover, may over time contribute to the formation of Aβ and NFTs and eventually precipitate cell death as the final expression of neuroplasticity failure. Consistent with this hypothesis, some brain regions possess more potential for adaptative mechanisms, with neuronal plasticity and synaptic remodeling being particularly elevated in those areas affected early in AD [4]. This indicates that the processes underlying activity-dependent synaptic plasticity in the adult are particularly susceptible to the primary causes of AD.

Of note, impaired synaptic function of the hippocampus appears to be an early event leading to defective hippocampal-dependent memory processing long before the appearance of amyloid plaque burden and neuronal cell death [1, 5]. Therefore, synaptic plasticity is often used to evaluate the phenotype of AD animal models. Accordingly, within the last 20 years, several electrophysiological studies have been performed on several AD experimental models. These models provide important tools to define the temporal evolution of cellular abnormalities in AD brains and to delineate the basic mechanisms that cause synaptic dysfunction. They have also been instrumental in validating drug targets and designing novel pharmacological strategies.

Here we will summarize how hippocampal plasticity is affected across many of these animal models and describe the main pharmacological approaches utilized to rescue synaptic dysfunction.

Experimental Models of AD

There is no existing animal model that resembles all the cognitive, histopathological, biochemical, and behavioral abnormalities observed in AD patients. However, partial reproduction of AD neuropathology and functional deficits has been achieved either with exogenous application of Aβ or through genetically engineered mouse models of AD. A full review of the different experimental AD models is beyond the scope of this work. For more comprehensive reviews, readers may refer to recent reports [6, 7].

Non-transgenic Models

Based on the cholinergic hypothesis, scopolamine-induced amnesia, excitotoxic lesions of the basal forebrain and aged primates have been widely used in the past to evaluate cognitive impairment. Current symptomatic medications for AD were successfully assessed in these models, but their etiological relevance is low [8]. It was originally thought that Aβ plaques, by causing disruption in neural connectivity and function, were responsible for the cognitive decline in AD patients. However, it is now becoming clear that certain of the soluble Aβ species (i.e., monomeric, oligomeric, and protofibrillary Aβ species) seem to be the primary cause for the functional deficits in rodents and probably also contributes to cognitive impairment in AD patients [9]. For these reasons, an alternative approach consisted in the direct in vitro and in vivo application of different synaptotoxic fragments of Aβ. This provided the opportunity to understand how different Aβ-derived diffusible ligands (ADDLs) impact excitatory synaptic transmission and plasticity in the hippocampus.

There is now substantial evidence that ADDLs of synthetic human Aβ inhibit the maintenance of hippocampal long-term potentiation (LTP) if applied in vitro [10, 11] or following intracerebroventricular (i.c.v.) administration [12–14]. Besides synthetic Aβ, also soluble oligomers of cell-derived naturally secreted human Aβ impair LTP at concentrations similar to those found in human cerebrospinal fluid (CSF). This effect has been observed following in vivo infusion in living rats [15] or by direct application to hippocampal slices [16]. In addition, it was demonstrated that mouse slices perfused with Aβ oligomers extracted from the cerebral cortex of AD patients showed reduced LTP and enhanced long-term depression. These effects were specifically attributable to Aβ dimers [17].

Taken together, these results provide evidence that decreased hippocampal LTP can be directly attributed to biochemically defined assemblies of human Aβ (with low-n soluble oligomers possibly ranging from dimers to dodecamers), in absence of amyloid fibrils or protofibrils. Nonetheless, the exact mechanism(s) by which soluble oligomers interact with plasma membranes and bind to receptor and/or channel proteins thereby affecting signaling pathways required for synaptic plasticity still remains poorly understood. One limiting factor derived from these studies is the

inability of exogenously applied Aβ to cross the plasmalemma [18], thus not addressing the potentially relevant role of elevated intracellular Aβ.

Transgenic Models

Transgenic (Tg) mouse models that recapitulate the major hallmarks of AD have been utilized since the early 1990s to explore in detail mechanisms underlying disease pathology. Most Tg models of AD have been engineered by inserting mutated human genes in the mouse genome, first identified in early-onset familial cases of AD (FAD). Hereafter, we summarize electrophysiological studies addressing hippocampal synaptic plasticity in the main Tg models.

AβPP-Derived Models

A first effort to create Tg models consisted in overexpressing the entire sequence of the human AβPP gene [19, 20]. Although AβPP transgene was clearly expressed in the brain, it did not lead to significant plaque deposition or any AD-like neuropathological features. Besides AβPP overexpression, the insertion of human AD mutations provided Tg models with elevated levels of $A\beta_{42}$ [21, 22]. The single mutations inserted in the AβPP gene represent FAD-linked mutations, which are named the Swedish (swe), the Indiana (ind), the London (Ld), and the Arctic (arc) mutations.

These models display age-dependent plaque deposition, hyperphosphorylated tau, neuroinflammation, oxidative stress, and hippocampal-dependent memory deficits resembling human AD. However, they do not exhibit NFTs, cholinergic deficits, nor neuronal loss [7].

Unfortunately, electrophysiological analysis of hippocampal synaptic transmission and plasticity on AβPP-based models has generated inconsistent results. For example, in one study, APP_{SWE} mice exhibit normal basal transmission but impaired LTP [23], while in another study synaptic transmission was impaired but LTP was normal [24]. The reason for this inconsistency is not known but could perhaps be related to differences in the housing conditions, experimental variables, or prior experience of the animals. In line with this, we have recently demonstrated that the plasticity phenotype can be strongly influenced by the cognitive history of the animal. Thus, while LTP was normal at naïve synapses, it was impaired following training of a spatial task in the AβPP23 model [25].

PS1-Derived Models

Presenilin 1 (PS1) is implicated in the proteolysis of AβPP as part of the γ-secretase complex [26]. Tg mice expressing either a wild-type or mutated presenilin gene fail to develop significant AD-like phenotypes, despite the presence of elevated Aβ [27–30]. In the context of synaptic plasticity, PS1-derived models show a biphasic phenotype with increased LTP in young mice and reduced LTP at later stages [31, 32].

Double Transgenic Mice

When mutant PS1 mice were crossed to mutant AβPP mice, formation of Aβ plaques was greatly accelerated [33], indicating that there is a synergistic interaction between both genes. In these models, plaques are composed of the $A\beta_{40}$ and $A\beta_{42}$ fragments and are localized in cortical and hippocampal areas [34, 35]. Behavioral deficits in spatial and recognition memory have been found in double Tg mice [35–37], whereas inconsistency between the electrophysiological findings was observed also for this model (reviewed in [38]). In fact, LTP was either reduced [38] or normal [39], possibly depending on the type of PS1 mutation harbored by the mice.

Triple Transgenic Mice

One of the important limitations of the Tg mice described so far is the lack of NFTs despite the presence of hyperphosphorylated tau protein. Oddo et al. [40] generated the first triple transgenic model (3xTg-AD), harboring PS1 (M146V), $A\beta PP_{SWE}$, and microtubule-associated protein tau (MAPT, P301L) transgenes. This model accumulates intraneuronal Aβ and subsequently forms amyloid plaques and MAPT lesions in an age-dependent fashion. Over time these mice also develop synaptic dysfunction, including synaptic transmission and LTP deficits that well correlate with the levels of intraneuronal Aβ [41]. Most recently, new triple Tg lines carrying AβPP, PS2, and tau mutations have been created [42, 43].

Pharmacological Strategies to Rescue Synaptic Dysfunction in Experimental AD

Although the exact pathogenesis of AD remains to be fully defined, several pharmacological approaches for the treatment of AD are under active investigation. In this section we will describe the classes of drugs proven effective to rescue synaptic dysfunction in the different preclinical models of AD (summarized in Table 1). It is beyond the scope of this review to include the rescue achieved by genetic approaches. This has been addressed by a recent review [44].

Targeting Aβ

Currently, the amyloid cascade hypothesis is the most important theory of AD postulating that accumulation of Aβ into plaques is the causative pathological event [45]. Based on this hypothesis, interventions that reduce Aβ load in the

Table 1 Pharmacotherapeutic strategies for the treatment of Alzheimer's disease

Pharmacological strategies	Drugs	Trials/status
Targeting Aβ		
Aβ fibrillogenesis inhibitors	RS-0406, RS-0466	
γ-Secretase inhibitor	DAPM, MK560, CHF5074	II (CHF5074)
Immunotherapy		
	Monoclonal antibody (6E10)	
	Monoclonal antibody (4G8)	
	Monoclonal anti-PrP antibody (6D11)	
	Antigen-binding antibody fragment (D13)	
Tau kinase inhibitors		
GSK-3 inhibitors	AR-A014418	
	Lithium	II
	Kenpaullone	
	CT-99021	
Pan caspase inhibitor	Z-VAD-FMK	
Cdk-5 inhibitors	Butyrolactone	
	Roscovitine	
Phosphatase inhibitors		
Calcineurin (PP2B) inhibitors	FK506	
	Cyclosporin A	
PP1 inhibitors	Tautomycin	
Drugs acting on cholinergic transmission		
α4β2 antagonist	Diihydro-beta-erythroidine	
α7 nAChR antagonist	Methyllycaconitine	
α7 nAChR agonist	Dimethoxynebzylidine	
Acetylcholinesterase inhibitor (AChEI)	Donepezil	IV
nAChR	Nicotine	
Drugs acting on glutamate receptors		
Uncompetitive inhibitor of NMDARs	Memantine	IV
Selective NR2B antagonist	Ifenprodil	
	Ro 25-6981	
mGluR5 NAM	MPEP	
Anti-inflammatory drugs		
TNFα inhibitors	Infliximab	II
	TNF peptide antagonist	II
Inhibitor of TNFα production	Thalidomide	II/III
Interleukin 1 receptor antagonist	IL-1ra	
Selective COX-2 inhibitors	MF tricyclic	
	Ns-398	
Antioxidants		
ROS scavengers	EUK134	
	MitoQ	
	SkQR1	
Insulin and insulin-sensitizing drugs		
Insulin receptor	Insulin	II
Insulin-like growth factor 1 receptor	IGF-1	
Glucagon-like peptide 1 receptor	GLP-1	
GIP		
Insulin-sensitizing drugs/agonists of the PPAR-γ	Thiazolidinediones	II/IV
	Rosiglitazone	II/IV

Table 1 (continued)

Pharmacological strategies	Drugs	Trials/status
Neurotrophins		
trkB-acting neurotrophins	NT4	
Isoleucine derivative	LM11A-31	
Targeting the CREB–CBP pathway		
PDE4 inhibitor	Rolipram	
β2 adrenoceptor agonist	Terbutaline	
Activator of adenylate cyclase	Forskolin	
NO donor	DEA/NO	
sGC stimulator	BAY41-2272	

brain would be likely to attenuate both the neuropathological changes and functional deficits characterizing AD. Indeed, several different Aβ-lowering strategies have been developed over the past years.

Among these, Aβ fibrillogenesis represents a major target for the therapeutic intervention in AD and related human β-amyloidoses [46]. Certain small-molecule inhibitors of synthetic Aβ fibrillogenesis (RS-0406 and RS-0466) inhibit formation of cell-derived, secreted oligomers of Aβ and prevent the impairment of LTP induced by Aβ [47, 48]. Importantly, this protective effect was achieved only under conditions in which they prevented new oligomer formation [49]. In fact, in order to be effective, inhibitors of fibrillogenesis need to be used at the initial stages of oligomerization thus avoiding a paradoxical enhanced neurotoxicity which may derive from active pre-fibrillar assemblies such as low-n oligomers released following inhibition of fibril formation. For these reasons, a promising strategy consisted in preventing the formation of Aβ by enhancing α-secretase activity or inhibiting either β-secretase or γ-secretase activity.

The first attempt to test the potential effects of targeting γ-secretase was conducted by Walsh et al. [15]. In an intriguing study, these authors showed that the cell penetrant γ-secretase inhibitor DAPM was able to restore LTP disruption after i.c.v. infusion of oligomers of human Aβ in rats. A related study showed that 3 days of oral dosing with the γ-secretase inhibitor MK-560 was sufficient to reverse LTP deficit in 6-month-old Tg2576 mice, at a stage when mice show synaptic dysfunction and behavioral changes before significant plaque deposition [50]. This study also highlights the ability of some γ-secretase inhibitors to cross the blood–brain barrier (BBB). Although inhibition of γ-secretase represents a rational pharmacological approach, serious concerns about their toxicity have been raised due to the fact that γ-secretase can cleave several other membrane proteins, the most relevant of which is the Notch protein. The discovery that some NSAIDs behave as γ-secretase modulators, thereby preventing $A\beta_{42}$ production by binding to AβPP rather than to γ-secretase, suggested a way to avoid Notch toxicity. In line with this, we have recently demonstrated that oral administration of the novel γ-secretase modulator CHF5074 was able to restore synaptic plasticity in 5-month-old Tg2576 mice, and this effect was associated with reduced hyperphosphorylated tau and intraneuronal Aβ [51]. Notably, CHF5074 is currently undergoing phase II clinical trial evaluation. Beyond targeting γ-secretase, also the pharmacological inhibition of AβPP cleavage by β-secretase rescued synaptic deficits in a mouse modeling familial Danish dementia [52].

Immunotherapy

One of the most promising disease-modifying therapies for AD is immunization against Aβ. Intracerebroventricular injection of naturally secreted human Aβ inhibited LTP in rat hippocampus in vivo, but a monoclonal antibody (6E10) to Aβ completely prevented LTP impairment even when injected after Aβ. Partial protection against the block of LTP was also present in rats that were successfully actively immunized with pre-aggregated Aβ [53]. A later report showed that also a single intraperitoneal (i.p.) injection of the antibody 6E10 was able to rescue LTP deficit observed in Tg Arc mice [54]. More recently, it was suggested that systemic passive immunization achieved with intracardiac injection of the monoclonal anti-Aβ antibody 4G8 was able to prevent the disruption of synaptic plasticity by Aβ dimer-containing human CSF in vivo [55].

These findings provide important evidence that antibodies directed to Aβ can rapidly neutralize the synaptic plasticity-disrupting effects of low-n oligomers of Aβ in the brain. Recently, passive immunization with anti-tau antibodies has been shown to reduce tau pathology and slow down disease progression in two Tg models of tauopathy [56]. However no studies addressed so far have demonstrated whether this treatment could also rescue synaptic dysfunction in preclinical models of AD.

Emerging data highlight how the cellular prion protein PrPC can serve as a receptor for Aβ oligomers. Aβ oligomers suppress LTP in murine hippocampal slices but synaptic activity remains preserved in PrPC null mice [57] and following pretreatment with the anti-PrPC antibody 6D11 [58]. LTP was also prevented when AβPP/PS1 mice were intraperitoneally injected with 6D11 [58]. A further study reported that i.c.v. administration of antigen-binding antibody fragment D13, targeting an unknown Aβ-binding site on PrPC, restored LTP deficit induced by AD brain-derived Aβ [59]. While these findings indicate the potential usefulness of immunotherapeutically targeting the binding of synaptotoxic Aβ assemblies to PrPC, two studies [60, 61] and experiments performed in our laboratory (unpublished data) have generated conflicting results.

Tau Kinase Inhibitors

Microtubule-associated protein tau is abnormally hyperphosphorylated in AD. This is likely the result of an imbalance in kinase and phosphatases activities leading to destabilization of microtubules, damage of neuronal cytoskeletal architecture, compromised neuronal transport, dystrophy, and eventually neuronal death [62]. Primary kinases involved in the phosphorylation of tau include glycogen synthase kinase (GSK-3) and cyclin-dependent protein kinase 5 (Cdk-5), thus representing important targets for pharmacological intervention in AD [63]. Several studies, for example, have demonstrated that inhibition of GSK-3 reverses synaptic dysfunction in different models of AD. Accordingly, the selective GSK-3 inhibitor AR-A014418 prevented LTP impairment by human $A\beta_{42}$ in wild-type slices [64] and either lithium or kenpaullone, two structurally distinct GSK-3 antagonists, rescued LTP deficit in slices from Tg2576 mice [65]. The latter study also provided evidence that upregulation of mTOR signaling mediates this neuroprotective effect, supporting the idea that mTOR pathway is compromised in this Tg model. Similar results were obtained with the more specific GSK-3 inhibitor CT-99021; this was able to prevent $A\beta_{42}$-induced impairment of LTP both in organotypic hippocampal cultures and in acute slices from 4- to 5-week-old rats [66]. Additionally it was found that $A\beta_{42}$-induced impairment of LTP was absent in caspase 3 KO mice and that it was inhibited in neurons in organotypic slices that had been transfected with a mutant form of Akt1 that was resistant to cleavage by this caspase [66]. This led to the hypothesis that activation of caspase 3 leads to cleavage of Akt1, thereby removing a tonic inhibition of GSK-3. Besides GSK-3, the pharmacological blockade of Cdk-5 with either butyrolactone or roscovitine also prevented the Aβ-mediated inhibition of LTP [67], confirming previous studies showing that Cdk inhibitors successfully prevent Aβ-induced neurotoxicity [68].

In addition, therapies that stabilize microtubules by compensating for the loss of tau function are nowadays under investigation. Indeed, the reduction in microtubule integrity has been proposed to be an important factor in synaptic dysfunction [69]. Accordingly, taxol was able to protect against synaptic loss in response to lysosomal stress [69]. However, to date, no studies addressing their protective potential in the context of synaptic function have been conducted.

Phosphatase Inhibitors

A growing body of evidence suggests that phosphatases and kinases antagonistically regulate the balance of synaptic strength, thereby serving as a gate for LTP and memory storage [70]. In support of this general model, Aβ-induced LTP deficits could be the consequence of increased phosphatases activity that may shift the gating balance of synaptic plasticity.

Accordingly, it has been shown that blockade of the calcineurin (PP2B) activity with FK506 or cyclosporin A completely prevented Aβ-induced LTP deficits in the hippocampal dentate gyrus [71]. Furthermore the pharmacological inhibition of PP1 with tautomycin was able to reverse the defect in synaptic plasticity in acute hippocampal slices from Tg Arc mice and AβPP/PS1 model [54]. Notably, also genetic inactivation of the striatal-enriched protein tyrosine phosphatase (STEP) reverses cognitive and cellular deficits observed in the triple Tg mouse model [72]. Taken together, these results support an important role for phosphatases in the mechanisms of Aβ oligomer-mediated toxicity, highlighting these proteins as promising targets for the development of potential therapeutic approaches in AD.

Drugs Acting on Cholinergic Transmission

Different strategies have been undertaken to improve cholinergic neurotransmission. These include the increasing of acetylcholine synthesis, facilitation of presynaptic acetylcholine release, stimulation of cholinergic muscarinic and nicotinic receptors, and inhibition of acetylcholine metabolism with cholinesterase inhibitors. A growing body of evidence suggests that Aβ peptide impairs nicotinic acetylcholine receptor (nAChR) function, even though the mechanism remains poorly understood. On the other hand, $A\beta_{42}$ was found to have a beneficial effect on synaptic plasticity at picomolar concentrations (as found in healthy brains) via the activation of presynaptic α7 nAChRs [73].

Experimental evidence suggests that α4β2 and α7 seem to be required for the Aβ-induced suppression of LTP. Accordingly, diihydro-beta-erythroidine, a selective α4β2 antagonist and methyllycaconitine (MLA), a selective α7

nAChR antagonist, have both proven effective in attenuating $A\beta_{31–35}$-mediated LTP impairment [74, 75]. Conversely, another study failed to observe any protective effect of MLA, although a different fragment ($A\beta_{42}$) was used [67]. A further report suggested a protective effect of the α7 agonist dimethoxybenzylidine against Aβ-induced loss of LTP [76]. The different findings may be due to concentration-dependent actions of Aβ, as low levels activate and high levels desensitize α7 [77] and/or interact with other nAChRs subtypes [78]. These data further suggest that the effect of Aβ could be independent from a direct interaction between Aβ and nAChRs.

Also the effect of nicotine has been evaluated in different experimental models of AD. Both acute and chronic nicotine treatments were found to enhance LTP via α7 receptors [79]. Accordingly, recent work showed a protective effect of chronic nicotine treatment in a rat model of AD [80, 81], although a paradoxical depressive effect of nicotine on the impairment of LTP caused by i.c.v. injection of $A\beta_{40}$ was previously found [82]. Besides nicotine, also donepezil, a widely used drug for the treatment of AD, had neuroprotective effects on synaptic plasticity following $A\beta_{42}$ [83].

Aβ also exerts effects on the cholinergic system by interacting with G protein-coupled muscarinic acetylcholine receptors (mAChRs). It is widely believed that M2 receptors are reduced in the brains of AD patients [84]. Notably, perfusion of medial septum slices with $A\beta_{40}$ reduced excitatory transmission and this effect was blocked by calcicludine (a selective L-type Ca^{2+} channel antagonist) and by pirenzepine, an mAChR antagonist [85]. Interestingly, AβPP/PS1 mice display synaptic dysfunction, which was associated with a decrease in the ability of endogenous mAChR activation to reduce basal glutamatergic transmission in the CA1 area of the hippocampus [86], suggesting that muscarinic receptor dysfunction is among the causes of functional impairment.

Drugs Acting on Glutamate Receptors

There is a growing body of evidence that Aβ soluble oligomers can cause perturbation of glutamatergic signaling, affecting in particular *N*-methyl-D-aspartate (NMDA) and also metabotropic glutamate receptors (mGluRs). Support for a role of NMDA receptors (NMDARs) in the cognitive deficits of AD is also provided by the current use of memantine in clinical practice. Memantine acts as an uncompetitive inhibitor of NMDARs at therapeutic concentrations [87, 88]. Accordingly, if bath applied at a therapeutically relevant concentration, it has been found to reverse LTP deficiency against the rapid disruptive effects of soluble $A\beta_{42}$ both in the CA1 [89] and in the DG [90] of the hippocampus.

$A\beta_{42}$ has been shown to co-immunoprecipitate with the GluN1 and GluN2A subunits of the NMDA receptor [91], and its oligomers bind to excitatory synapses expressing NR1 and NR2B receptors [92]. Moreover, a previous study demonstrated that Aβ activates STEP, which dephosphorylates a regulatory tyrosine site (tyr1472) on the GluN2B subunit, leading to internalization of NMDA receptors [93].

The notion that soluble Aβ-induced impairment of LTP in the CA1 region of hippocampus requires GluN2B-containing NMDARs has been supported by the rescuing effects afforded by the two selective NR2B antagonist ifenprodil and Ro 25-6981 [74, 89]. In an effort to characterize the potential therapeutic value of other allosteric sites on glutamate receptors as alternative targets in the treatment of AD, also MPEP, a specific negative allosteric modulator (NAM) against mGlu5 receptors [94], has been successfully tested [67]. In fact, MPEP can reverse the $A\beta_{42}$ oligomer-induced inhibition of LTP at nanomolar concentrations [89].

Anti-inflammatory Drugs

Converging lines of evidence suggest that neuroinflammatory processes play important roles in the pathogenesis of neurodegenerative diseases. Accordingly, postmortem examination of AD brain shows extensive evidence of inflammation, including activation and proliferation of glia and elevated concentrations of inflammatory mediators. However, it is not clear how early in the disease process brain inflammation occurs or its relative contribution to disease progression and clinical symptoms [95].

Tumor necrosis factor α (TNFα) is a key cytokine that has been involved in several brain functions, as well as in mediating pro-inflammatory processes in neurodegenerative diseases including AD [96]. Considering that TNFα is increased in the brain of AD patients [97] and that it can directly modulate hippocampal synaptic plasticity [98], the question of whether this cytokine could also mediate the detrimental effects of Aβ on LTP was also addressed. Indeed, the suppression of LTP by Aβ was absent in mutant mice null for TNF receptor type 1 and was prevented by the monoclonal antibody infliximab, the TNF peptide antagonist, and thalidomide, the inhibitor of TNFα production [99].

Besides TNFα, the pro-inflammatory cytokine interleukin 1β (IL-1β) has also been reported to mediate the toxic effects of Aβ peptide [100]. Indeed, i.c.v. administration of interleukin 1 receptor antagonist (IL-1ra) rescued post-tetanic potentiation impairment following injection of $A\beta_{40}$ [101].

Several studies in transgenic AβPP mice have documented the effects of nonsteroidal anti-inflammatory agents (NSAIDs) on amyloid load and inflammation [102], but only one study so far has addressed the effects of NSAIDs on Aβ-mediated disruption of synaptic plasticity and memory. It was

found that both MF tricyclic and Ns-398, two selective COX-2 inhibitors, were effective in preventing the disruption of LTP by synthetic soluble $A\beta_{42}$. Of note, the same effect was not achieved with the COX-1 inhibitor piroxicam [103].

Antioxidants

Strong evidence has been accumulated to link reactive oxygen species (ROS) with neurodegenerative diseases [104]. In fact, ROS-mediated oxidative stress is used as a valuable AD biomarker and antioxidants offer new hope to patients suffering from AD [105]. However, current clinical trials with antioxidants resulted in mild or no effects to attenuate disease progression and cognitive dysfunction in AD.

Several studies have demonstrated that intraneuronal Aβ is linked to altered mitochondrial function [106]. In fact, Aβ can directly affect mitochondrial function, thus causing oxidative stress [107]. However, the exact mechanisms underlying Aβ-mediated mitochondrial disruption have not yet been fully elucidated. Notably, it recently emerged that Cyclophilin D (CypD), an integral component of the mitochondrial permeability transition pore, can interact with mitochondrial Aβ thereby precipitating neuronal and synaptic stress. In fact, either the genetic removal of this Aβ-binding partner or its pharmacological inhibition with cyclosporin A improved synaptic dysfunction by $A\beta_{42}$ application. In the presence of the ROS-scavenging enzymes SOD plus catalase, LTP was further alleviated [108]. There are two other structurally distinct ROS scavengers, EUK134 and MitoQ, a synthetic SOD and catalase mimetic and a mitochondria-targeted antioxidant, respectively. They were able to attenuate LTP deficit following $A\beta_{42}$ application and in AβPP/PS1 mice [109]. A related study demonstrated that rats treated with i.p. injections of SkQR1, a mitochondria-targeted plastoquinone derivative, exhibit normal hippocampal LTP levels in the presence of $A\beta_{42}$ [110]. This study also highlights the ability of novel antioxidants to cross the BBB.

Insulin and Insulin-Sensitizing Drugs

Several studies show that insulin plays a key role in higher brain functions such as learning and memory [111] and synaptic plasticity [112], whereas impairment of insulin signaling has been linked to neurodegenerative disorders [113]. For example, a clinical study has revealed that the insulin levels in CSF were decreased in patients with sporadic AD [114]. It has also been reported that insulin can protect hippocampal neurons against Aβ-induced cytotoxicity [115], suggesting a potential crosstalk between insulin and Aβ. In a recent work, it was demonstrated that insulin and insulin growth factor 1 (IGF-1) inhibit formation of Aβ oligomers and thus prevent the block of LTP induced by different Aβ fragments [116].

In addition to insulin, also pretreatment with the glucagon-like peptide 1 (GLP-1), which physiologically stimulates insulin release, has been proven effective in reversing LTP following $A\beta_{25-35}$ [117], $A\beta_{40}$ [118], and in aged AβPP/PS1 mice [119]. Similar results were also obtained with the novel glucose-dependent insulinotropic polypeptide (GIP), a peptide hormone targeting pancreatic islets to enhance insulin secretion [117].

Insulin-sensitizing drugs such as the thiazolidinediones act as specific agonists of the peroxisome proliferator-activated receptor gamma (PPAR-γ), thereby sensitizing insulin action in the target sites. Different PPAR-γ agonists attenuated the detrimental effects of $A\beta_{40}$ on LTP [120], and rosiglitazone improved learning and memory deficits in the Tg2576 mouse model [121]. Taken together, these preclinical results raise the possibility that insulin and insulin-sensitizing drugs may serve as therapeutic agents for the treatment of AD.

Neurotrophins

The growing evidence that neurotrophins are essential modulators of synaptic plasticity [122] and that synaptic transmission becomes dysfunctional before the onset of AD raise the question of whether synaptic failure could be ascribed to neurotrophin dysregulation. In line with this notion, a Tg mouse line expressing chronic nerve growth factor (NGF) deprivation displays age-related defects in synaptic plasticity, supporting a "neurotrophic unbalance" hypothesis underlying AD-like neurodegeneration [123]. Accordingly, exogenous supply of neurotrophins was proven effective to restore synaptic alterations in experimental AD. Indeed, it was recently demonstrated that application of neurotrophin 4 (NT4), a neurotrophic factor that signals predominantly through the TrkB receptor tyrosine kinase, prevented LTP deficits induced by Aβ both in the CA1 and DG of rat hippocampal slices [124]. This rescuing effect was associated with enhanced CaMKII autophosphorylation, a signaling event normally stimulated by LTP but suppressed by $A\beta_{42}$.

On the other hand, Aβ can directly bind to p75 neurotrophin receptors ($p75^{NTR}$), which are best known for mediating neuronal death and have been consistently linked to the pathology of AD [125]. Therefore, blocking this receptor with the isoleucine derivative LM11A-31 rescued Aβ-induced LTP impairment without affecting baseline transmission [126]. These results highlight neurotrophins or their analogs as a new class of candidate molecule compounds for AD therapeutics. Intriguingly, encapsulated cell biodelivery of NGF to AD patients is currently undergoing phase I clinical trials.

Targeting the CREB–CBP Pathway

Genetic and pharmacological studies in a variety of organisms have demonstrated that cAMP response element-binding protein (CREB)–CREB binding protein (CBP) is a signaling mechanism regulating LTP and is required for long-term memory formation [127]. For these reasons, the synaptic dysfunction associated with experimental AD could result from impaired CREB–CBP signaling. Indeed, reduced expression of the CREB–CBP pathway was found in conditional double knockout mice both lacking both presenilins [128]. In line with this reasoning, several pharmacological approaches targeting the cAMP/PKA/CREB pathway were proven effective in reversing LTP impairment in Tg and non-Tg models of AD.

Accordingly, the phosphodiesterase (PDE) 4 inhibitor rolipram enhanced LTP in wild-type mice [129] and ameliorated LTP deficit either in AβPP/PS1 mice [130] or in acute slices exposed to Aβ [131]. Similarly, also the PDE5 inhibitor sildenafil rescued synaptic deficits in the AβPP/PS1 model, re-establishing normal levels of CREB phosphorylation after tetanic stimulation [132]. Other drugs that stimulate the cAMP/PKA signaling pathway, as the activator of adenylate cyclase forskolin [131] or the β2 adrenoceptor agonist terbutaline [133], showed similar neuroprotective effects.

Considering that cAMP/PKA and NO/cGMP/cGK pathways are known to converge onto CREB to maintain synaptic plasticity [134], another study tested whether targeting the NO/cGMP/cGK/CREB system also alleviated Aβ-induced suppression of LTP. Indeed, application of the NO donor DEA/NO, the sGC stimulator BAY41-2272, and the cGMP analogs 8-Br-cGMP and 8-pCPT-cGMP were all effective in rescuing Aβ-induced LTP impairment and in normalizing phospho-CREB activity during synaptic potentiation [135].

Recent studies have provided evidence that Aβ peptide, possibly through the activation of GluN2B, mGlu5, or α7 nicotinic receptor, could downregulate the ERK/MAPK/CREB cascade, thereby negatively regulating synaptic plasticity. On this line, blockade of the p38 MAPK by SB203580 was able to prevent Aβ-mediated suppression of LTP [67, 74], further confirming that pharmacological modulation of these pathways might be beneficial for AD therapeutics.

Emerging data also point out that epigenetic mechanisms are involved in the altered synaptic function and memory associated with AD [136]. In this scenario, Aβ and tau protein have been shown to interact with CREB/CBP signaling, downregulating CBP and in turn reducing histone acetylation in different preclinical models of neurodegeneration [137, 138]. Therefore, histone deacetylase (HDAC) inhibitors, which are currently being used in clinical trials for the treatment of some forms of cancer, are now also being considered as potential memory enhancers.

Experimental evidence shows that HDAC inhibitors enhance LTP in wild-type mice [139] and rescue hippocampal LTP in AβPP/PS1 mice [140]. In this respect, HDAC inhibitors represent novel compounds to effectively counteract disease progression in AD [141].

Other Neuroprotective Strategies

Several other rescuing strategies were evaluated in experimental AD. These include multitarget drugs or compounds acting with unconventional or still unknown mechanism. Among these, over the past years Humanin (HNG) has received much attention. HNG is a novel peptide cloned from a cDNA library of the occipital lobe of an AD brain [142], which has proven effective against all sorts of AD-relevant insults in vitro. The tyrosine kinase pathway mediated the protective action of HNG against Aβ-induced LTP impairment, since genistein abolished this effect [143, 144].

It has been reported that protein kinase C (PKC) plays a leading role in the cellular signaling cascade targeting protein synthesis and thereby LTP formation [145, 146]. In particular, human studies have shown that PKC and its adaptor protein RACK1 (receptor for activated C kinase 1) are both deficient in AD [147]. In this context, phorbol–myristate–acetate, a membrane-permeable PKC agonist, effectively prevented $A\beta_{31-35}$-induced deficits in the early and late components of LTP [144].

Another kinase crucially involved in AD pathogenesis is the c-jun N-terminal kinase (JNK) [148]. Indeed Aβ-induced changes in hippocampal plasticity were shown to be dependent upon IL-1β-triggered activation of JNK [149]. Accordingly, different JNK inhibitors rescued LTP deficit induced by synthetic and cell-derived Aβ [67] and in the TgCRND8 mouse model [150].

Overactivation of proteins known as calpains, which are involved in memory formation, has been also linked to AD [151]. Thus, different calpain inhibitors have been shown to reverse synaptic plasticity impairment in AβPP/PS1 slices [37] and in slices exposed to the soluble human Aβ [74].

Other neuroprotective agents reported to rescue hippocampal LTP suppression by different Aβ fragments include the L-type calcium channel (VDCC) blocker verapamil [152], arginine vasopressin [153], neuregulin 1 [154], and the novel phospholipid-based drug formulation VP025 [155]. Protection against Aβ-induced abnormal synaptic function has also been obtained with some traditional medicinal products such as Ginkgo Biloba extracts [156], curcumin [157], huperzine A [158], and the herb mixture Danggui-Shaoyao-San [159].

Other electrophysiological studies performed in Tg models of AD suggest neuroprotective effects of estradiol [160], picrotoxin [161], and the nonselective adrenergic receptor antagonist carvedilol [162].

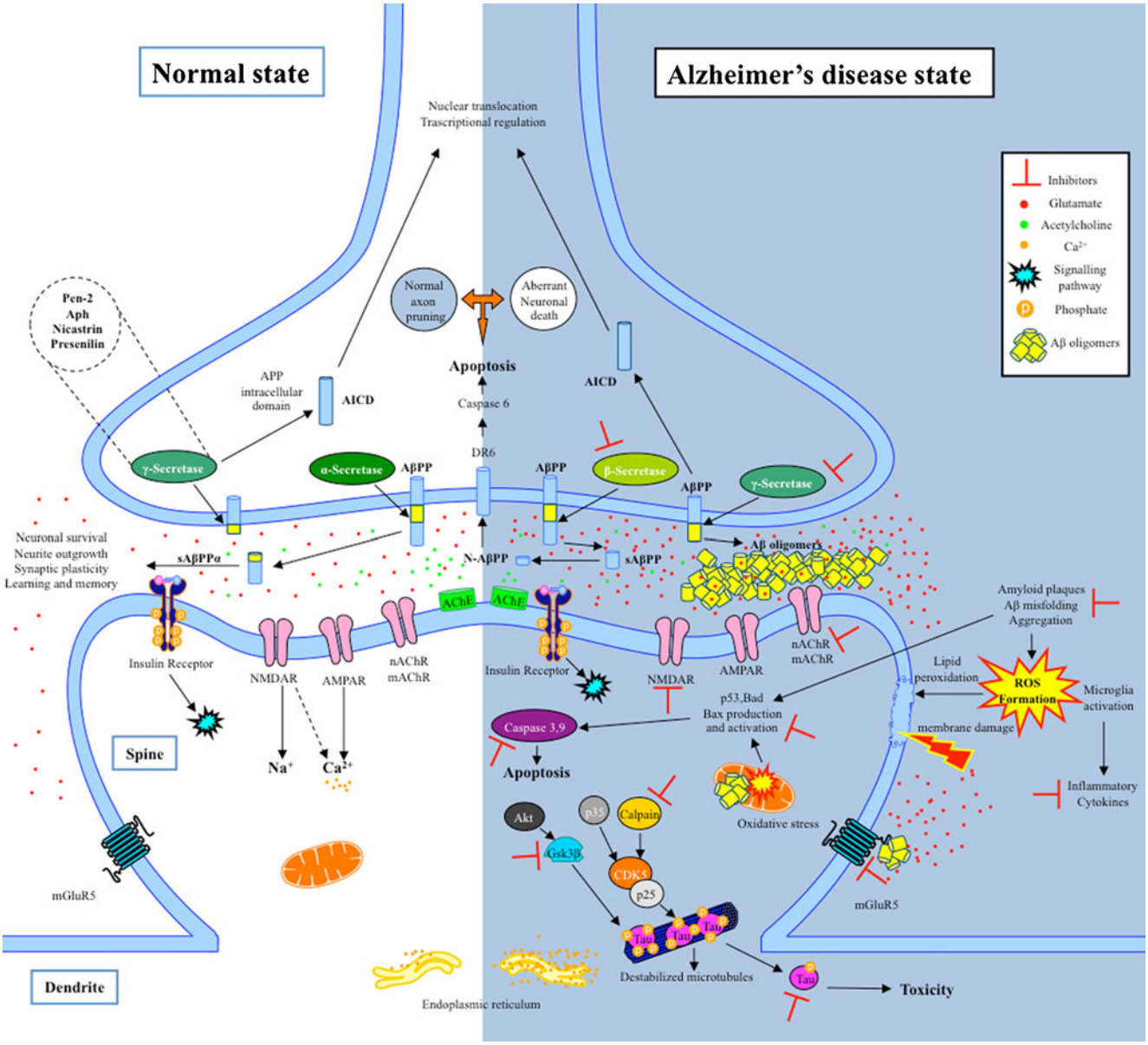

Fig. 1 Proposed molecular mechanisms behind the experimental treatment approaches to Alzheimer's disease. Crucial to AD is the differential processing of the integral membrane protein amyloid β precursor protein (*AβPP*) in the normal versus diseased state. In the normal state, cleavage of APP by α-secretase generates soluble amino-terminal ectodomain of AβPP (*sAβPPα*) and C83 C-terminal stub. The physiological role of sAβPPα is associated with neuronal survival, neurite outgrowth, synaptic plasticity, and learning and memory. In the disease state, AβPP is sequentially cleaved by β-secretase and γ-secretase to form soluble AβPP (*sAβPP*). Aβ is secreted into the extracellular spaces and accumulates to form oligomers, fibrils and eventually senile plaques. $Aβ_{40/42}$ oligomers bind to several surface receptors, disrupt membrane integrity, perturb calcium homeostasis, trigger inflammatory state and mitochondrial oxidative stress, ultimately leading to neuronal cell death. The microtubule-associated protein tau is abnormally hyperphosphorylated in AD and accumulates in neurons forming neurofibrillary tangle. The major sites for pharmacological intervention are also highlighted (see text for details)

Limitations of Preclinical Models and Future Challenges

This review has documented how a large variety of pharmacological interventions can rescue synaptic dysfunction in experimental AD, yet this success in rodents has not been translated into successful therapies for humans. There are a number of reasons why preclinical studies may have failed to predict the outcome of clinical studies.

First, the consideration that Tg mice carry FAD mutations, accounting for only 1–10 % of all AD cases in humans, rather than the prevalent sporadic (SAD) form. Also, while these models develop specific hallmarks of AD, they do not recapitulate every aspect of the complex human disease. An important issue that needs to be considered is whether the similar temporal profile of disease progression in AD patients is also conserved in Tg mice. For

example, while in Tg mice cognitive deficits precede plaque load, in human patients the latter is more likely to happen first. Second, the weakness with Tg mice is that there is almost no neuronal cell death, differently from the substantial neurodegeneration occurring in the human AD brain.

In general, it can be assumed that animal models of AD are more useful as models of specific disease targets and pathways. For this reason, they serve as tools for testing the efficacy of candidate molecules on drug targets that may be involved in AD pathogenesis. This target-driven approach in animal models has translated over the past years to several therapeutic studies in humans (see Table 1).

Besides the intrinsic limitations of animal models, experimental studies are also susceptible to experimental bias. The most frequently underestimated issues are related to gender- and litter-dependent differences, variances in transgene expression across generations, and diverse genetic background between drug- and placebo-treated groups. Other intrinsic limitations to be considered in translation are differences between mouse/human species including diversities in cerebrovascular anatomy, neuronal network physiology, disease susceptibility, and perhaps most importantly dynamics of drug-target interactions. For these reasons, therapeutic studies carried out in vivo should include a complete pharmacokinetics/pharmacodynamics profile to maintain appropriate dosing and timing of treatment. Toxicological studies should be addressed in order to minimize putative off-target influence on the results. Ideally, positive results should be re-evaluated in multiple lines of mice, preferably in several laboratories, and negative results should also be published in the scientific literature. Certainly, raising the quality of preclinical research can make the translation to human clinical trials more efficient and reliable.

Conclusions

Looking ahead, prevalence of AD will overtake cardiovascular diseases and AIDS in its prevalence (World Health Organization). Therefore, continuous efforts are geared towards the discovery of new anti-AD agents. The plastic nature of synapses and their early involvement in the cognitive decline associated with AD models provide new potential targets for pharmacological intervention. It is becoming clear that therapeutic approaches cannot be directed to single targets, but to a combination of targets which should be considered for effective therapies (summarized in Fig. 1). Certainly, to ensure a successful outcome, therapy should start at the very early stage. In addition, highly sensitive and specific biomarkers for diagnosing AD need to be identified in order to recognize AD patients at the onset of the disease. Besides diagnosis, markers would also be essential to follow-up disease progression, to monitor the efficacy of treatments during preclinical studies, and to predict potential therapeutic effects in humans.

In spite of their limitations, experimental models of AD still remain the most important scientific tool to understand the basic mechanisms underlying AD. Indeed, a more careful design of preclinical studies will provide important contributions to the development of the first approved disease-modifying drug for AD.

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