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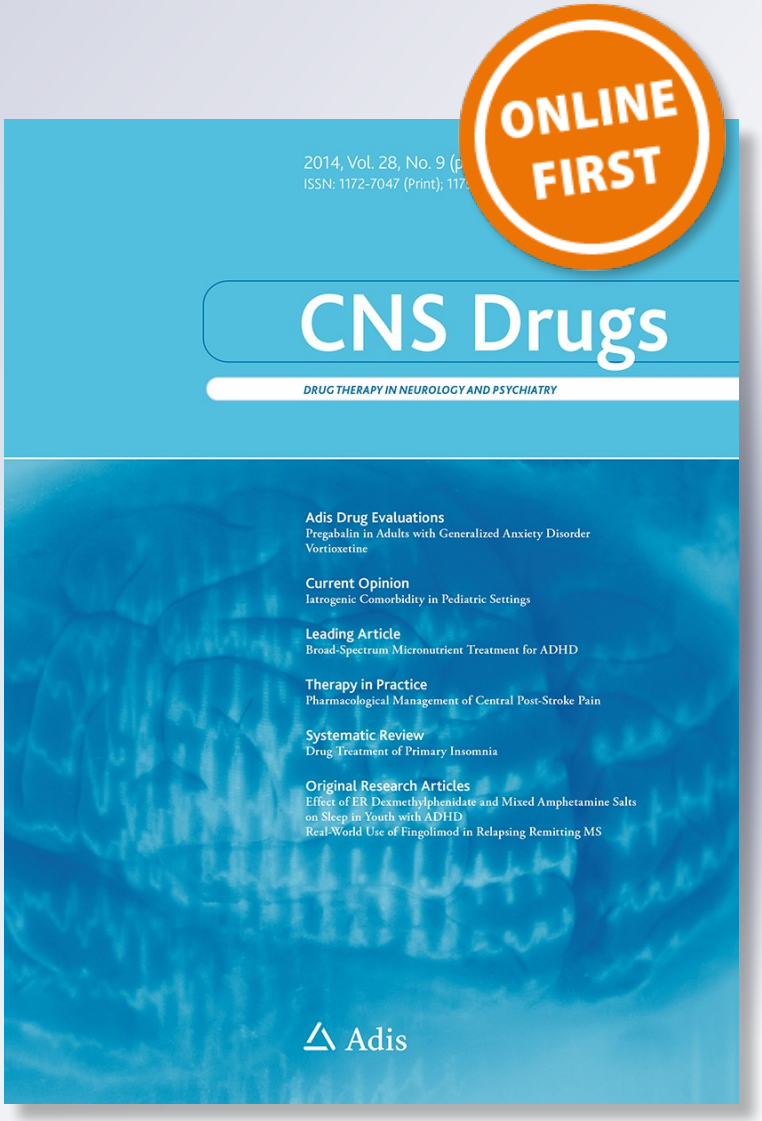

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LEADING ARTICLE

Targeting Brain α7 Nicotinic Acetylcholine Receptors in Alzheimer's Disease: Rationale and Current Status

Ana Sofía Vallés · María Virginia Borroni · Francisco J. Barrantes

Abstract Alzheimer's disease (AD) is the most common form of dementia among older persons. Pathognomonic hallmarks of the disease include the development of amyloid senile plaques and deposits of neurofibrillary tangles. These changes occur in the brain long before the clinical manifestations of AD (cognitive impairment in particular) become apparent. Nicotinic acetylcholine receptors (AChRs), particularly the α7 subtype, are highly expressed in brain regions relevant to cognitive and memory functions and involved in the processing of sensory information. There is strong evidence that implicates the participation of AChRs in AD. This review briefly introduces current strategies addressing the pathophysiologic findings (amyloid-β-peptide plaques, neurofibrillary tangles) and then focuses on more recent efforts of pharmacologic intervention in AD, specifically targeted to the α7 AChR. Whereas cholinesterase inhibitors such as donepezil, galantamine, or rivastigmine, together with the non-competitive *N*-methyl-D-aspartate receptor antagonist memantine are at the forefront of present-day clinical intervention for AD, new insights into AChR molecular pharmacology are bringing other drugs, directed at AChRs, to center stage. Among these are the positive allosteric modulators that selectively target α7 AChRs and are aimed at unleashing the factors that hinder agonist-mediated, α7 AChR channel activation. This calls for more detailed knowledge of the distribution, functional properties, and involvement of AChRs in various signaling cascades—together with the corresponding abnormalities in all these properties—to be able to engineer strategies in drug design and evaluate the therapeutic possibilities of new compounds targeting this class of neurotransmitter receptors.

Key points

Alzheimer's disease (AD) is the prevalent form of dementia in older persons.

A wealth of evidence supports the notion that the neuronal nicotinic acetylcholine receptor is involved in the pathophysiology of AD.

Nicotinic acetylcholine receptors constitute an important pharmacologic target for therapeutic and possibly prophylactic intervention in AD.

1 Introduction

Alzheimer's disease (AD) is a chronic disease with a very long asymptomatic period characterized by progressive and extensive brain atrophy. Typical neuropathologic findings in postmortem brains of AD patients are the senile amyloid plaques, mainly composed of deposits of the 39–42 amino acid amyloid β-peptide (Aβ), and neurofibrillary tangles, composed of hyper-phosphorylated tau protein. The former

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result from cleavage of the amyloid precursor protein (APP), a type I transmembrane protein coded by a single multiexonic gene located in chromosome 21, by the enzymes β and γ secretases. Interestingly, of the total Aβ pool in the brain, there seems to be a misbalance between the ratio of two predominant polypeptides of human Aβ, Aβ40 and Aβ42, in patients with AD. In these patients, Aβ42 levels are much higher than in healthy individuals, leading to highly fibrillogenic and toxic effects on neurons [1]. Although Aβ42 differs from Aβ40 by only two residues, Aβ42 is much more prone to aggregation and more toxic to neurons than Aβ40. Transgenic rat and mouse animal models present deficits in synaptic transmission and plasticity even before amyloid plaque accumulation is detected [2–4], suggesting that tau hyper-phosphorylation and its deposition as neurofibrillary tangles are downstream events to aberrant processing of APP. In brief, the two pathognomonic markers of AD, namely Aβ-peptide deposits and neurofibrillary tangles, are the consequence of neuronal death, preceded, in turn, by deterioration of synaptic transmission and plasticity.

Nicotinic acetylcholine receptors (AChRs) are members of the superfamily of ligand-gated ion channels (LGICs), a collection of neurotransmitter receptors that also includes GABA-$_A$, GABA-$_C$, glycine, 5-HT$_3$, and glutamate receptors and ATP-gated channels. The natural ligand of all AChRs is acetylcholine (ACh), a small-molecular-weight neurotransmitter that triggers the opening of the channel upon binding to the receptor. AChRs are composed of five polypeptide subunits organized pseudo-symmetrically around a central pore [5, 6]. Each subunit contains an extracellular domain, four hydrophobic transmembrane segments arranged in the form of three concentric rings around the pore [7], and a short extracellular carboxy-terminal domain [5, 6].

Historically, the availability of high amounts of AChR protein from the electric organ of the *Torpedo* species [8] and the isolation and characterization of the competitive cholinergic antagonist α-bungarotoxin from the snake *Bungarus multicinctus* [9, 10] are considered to be the landmark findings that contributed to making the AChR the prototype for the LGIC superfamily. In more recent times, the cryoelectron microscopy elucidation of the *Torpedo* AChR structure at 4 Å resolution [11] and the crystal structure of the receptor homolog, the molluscan ACh-binding protein by X-ray diffraction techniques [12, 13], have also had an important impact on our understanding of LGIC structure. These structural findings, in turn, have provided a useful framework to understand and in some cases reinterpret the mechanisms of ligand binding, gating, and blockage of the AChR in molecular detail [14].

Muscle-type AChRs are expressed in the peripheral nervous system (PNS) and neuronal-type AChRs in both the PNS and the central nervous system (CNS), as well as in other non-neural tissues such as immune cells, lymphocytes, lung epithelium, and others [15–17]. In the CNS, the AChR is present in two principal forms: the heteropentameric receptor formed by α4 and β2 subunits and the homopentameric receptor formed exclusively by α7 subunits [15].

The α7 AChR exhibits certain functional properties that distinguish it from other nicotinic receptors: (a) fast desensitizing kinetics, (b) unusually high Ca^{2+} permeability, and (c) high affinity for binding α-bungarotoxin [18, 19]. The α7 AChR is found presynaptically, where it modulates neurotransmitter release, and postsynaptically, where it generates postsynaptic currents [20, 21]. In addition, the perisynaptic presence of the receptor has also been demonstrated, where it modulates neuronal activity, presumably by an unconventional mechanism involving diffusion of the natural neurotransmitter and binding to non-synaptic sites [22]. The α7 AChR is highly expressed in the hippocampus, a region particularly affected in AD [15]. It is involved in cognition and has been associated with pathologic states other than AD, such as schizophrenia [23–29]. Furthermore, and most relevant to this review, it has been reported to interact with amyloid β-peptide (Aβ). Immunocytochemical studies on human sporadic AD brains have shown that α7 AChR is present in amyloid plaques and binds with high affinity to Aβ [30]. Methods based on immunocytochemical techniques have their shortcomings and flaws and should be interpreted with extreme caution, because not all antibodies have been carefully characterized in terms of receptor selectivity [31]. Nevertheless, the link between Aβ and α7 AChR is beyond doubt, as established by multiple studies [32, 33]. However, the consequences of this interaction are still a matter of debate, varying from activation to inhibition of α7 AChR, according to the type, concentration, state of aggregation of the Aβ, and the experimental system employed [32, 33]. Indeed, in postmortem human AD brain, the interaction between α7 AChR and fibrillar Aβ exerts neurotoxic effects mediated partly through a blockade of α7 AChRs, whereas the interaction with oligomeric Aβ may in fact activate α7 AChR [34]. In addition, it was reported that Aβ oligomers acting through α7 AChR induce tau phosphorylation [35]. Because Aβ levels and the state of aggregation of the amyloid peptide change as AD progresses, it is possible that α7 AChR plays different roles in AD pathology depending on the phase of development of the disease.

Among the most common psychological and clinical observations in AD are the loss of attention and episodic memory impairment [36–38]. As previously stated, several lines of evidence link brain nicotinic AChRs, the α7 in particular, to the development of AD [30, 39–41]. The greater the magnitude of depletion of cholinergic neurons

and associated cholinergic pathways in cognitive-associated brain areas such as the neocortex and hippocampus the more severe the associated dementia, suggesting a relationship between the clinical manifestations and the level of cholinergic decline [42–44]. Because cholinergic pathways are associated with learning and memory, nicotinic agonists and cholinomimetics in general provide symptomatic improvements in cognitive impairment [45, 46] and this constitutes the basis of therapeutic approaches aiming at α7 AChR activation with selective agonists.

2 Therapeutic Targets in Alzheimer's Disease

Several pharmacologic compounds that target Aβ-peptide metabolism have been studied in clinical trials, although the results to date have not been auspicious. Most of the compounds effectively reduce cerebrospinal Aβ-peptide levels and amyloid senile plaques but the expected clinical outcome, cognitive improvement, is not observed [47–49]. These results are consistent with observations based on neuropathologic studies and in vivo imaging of Aβ plaques by positron emission tomography showing that brain amyloid plaque levels do not necessarily correlate with cognitive status [50–52]. Moreover, Aβ-peptide oligomerization and deposition is a slow process and may take up to two decades or more to achieve pathologic levels. In addition, it has been suggested that soluble oligomers are the relevant toxic form of Aβ, showing a better correlation with synaptic dysfunction than senile plaques [52]. Thus, targeting Aβ-peptide deposition and/or removal may prove to be too simplistic and not the ideal therapeutic approach, at least with patients with mild-to-moderate AD. Whether this strategy could be beneficial at earlier asymptomatic stages of the disease remains to be determined. Nonetheless, these results raise the fundamental question of whether increased Aβ-peptide is a primary cause in AD, or whether AD is more likely to be associated with or a consequence of other pathologic processes [53].

Because neurofibrillary tangles are indeed correlated with cognitive status, other possibilities emerge for targeting the tau pathway. In this regard, several inhibitors of tau deposition or aggregation are currently being developed, though only limited clinical trials have so far been undertaken. Inhibiting tau phosphorylation with lithium chloride or sodium valproate effectively reduces cerebrospinal fluid phospho-tau, but is apparently not accompanied by an improvement in cognition in patients with mild-to-moderate AD [54–57]. It therefore appears that when the disease is clinically established, it is unlikely to be reverted by these two means, suggesting that neuronal circuits damaged as a result of neuronal loss are not restored simply by reducing toxic levels of tau. However, neurodegeneration may be slowed down if anti-Aβ or anti phospho-tau therapy is applied at pre-symptomatic stages [53, 58]. Although biomarkers for AD are available and imaging technology is able to detect some of the signs of asymptomatic stages, these are not routinely included in clinical practice, probably owing to the lack of disease-modifying therapies [59]. However, this is most likely to change in the near future because cerebrospinal fluid and imaging

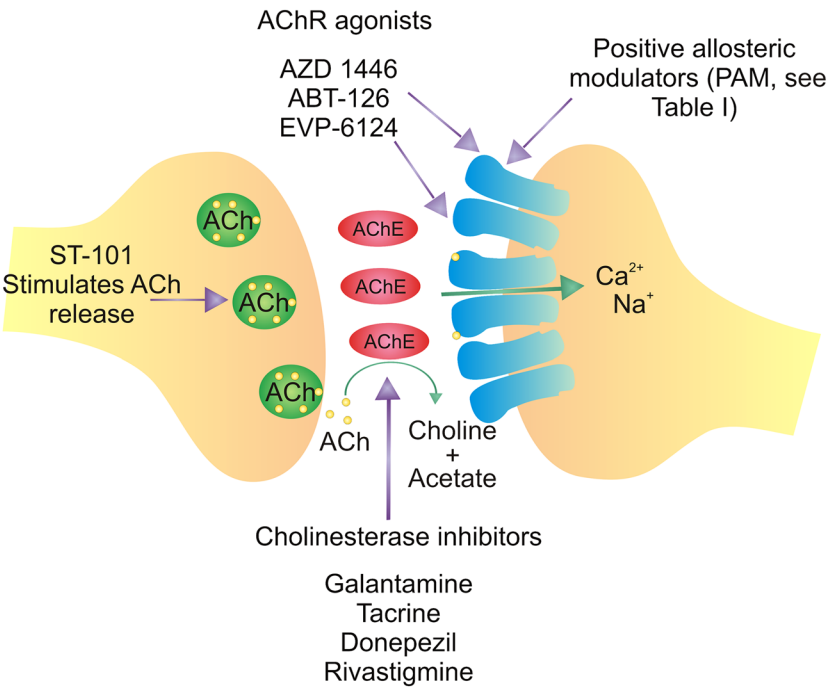

Fig. 1 The cholinergic synapse as a therapeutic target of drugs in Alzheimer's disease. Pharmacologic treatments target different stages of cholinergic transmission, usually with a view to gain of function, i.e., enhancing the efficacy of transmission. Thus, ST-101 stimulates release of the natural neurotransmitter, acetylcholine; cholinesterase inhibitors increase the effective concentration of ACh at the synaptic cleft; orthosteric agonists activate AChR ion channel and downstream signaling, and PAMs potentiate AChR responses. *ACh* acetylcholine, *AChE* acetylcholinesterase, *AChR* acetylcholine receptor, *PAM* positive allosteric modulator

biomarkers are currently being incorporated into revised diagnostic guidelines for AD [60–64].

The third accepted player in AD is the process of cholinergic synaptic transmission proper. This is rooted in the fact that cholinergic system dysfunction is an early and salient feature of AD. Thus, enhancing cholinergic signaling emerges as a primary strategy for improving cognition. Cholinergic dysfunction can be overcome by different means (Fig. 1). Based on the general philosophy of improving AChR synaptic efficacy, the therapeutic strategies vary from increasing the synaptic ACh level to improving agonist-mediated AChR transduction, or attempting to decrease the agonist-mediated desensitization phenomenon. However, the development of therapeutic compounds that can act selectively on different subtypes of AChRs in different brain locations is an extremely complex goal. In simple terms, the theoretically ideal case in drug design terms would be the production of a drug that interacts with a specific receptor subtype, in a selective manner, and with the same potency and timing as the endogenous agonist. The sections that follow discuss possible therapeutic targets aimed at improving cholinergic signaling.

3 Cholinesterase Inhibitors

The pharmacologic repertoire currently approved for AD treatment comprises the *N*-methyl-D-aspartate (NMDA) receptor agonist, memantine, and the cholinesterase inhibitors (galantamine, tacrine, donepezil, and rivastigmine). Therapeutic approaches acting on NMDA receptors are beyond the scope of this review and will not be dealt with here. By prolonging the time spent by ACh at the synapse, cholinesterase inhibitors procure to alleviate the deficit of AChRs at postsynaptic neurons that preclude or hamper cholinergic transmission in AD [65]. However, cholinesterase activity not only modulates cholinergic transmission by hydrolyzing ACh, but also stimulates amyloid plaque formation. Thus, inhibiting the latter increases ACh availability and reduces Aβ deposition [66].

At present, three acetylcholinesterase (AChE) inhibitors are available for the treatment of AD, namely donepezil, rivastigmine, and galantamine. Rivastigmine is an inhibitor of AChE and butyrylcholinesterase with a pseudo-irreversible mode of action [67]. Furthermore, it is the only cholinesterase inhibitor that produces sustained inhibition without increasing the expression of the target enzyme [68]. Galantamine is a selective, rapidly reversible, competitive AChE inhibitor and it can also act as a positive allosteric modulator (PAM) of the AChR (see below) [68, 69]. In fact, donepezil and galantamine have been shown to increase the density of AChRs, as measured by nicotine binding in old rat brains [70]. More importantly, whereas rivastigmine produces an increase in nicotine binding in patients with mild AD, galantamine does not, although both drugs inhibit cholinesterase activity and improve attentional tasks [71, 72]. Thus, AChE inhibition may not be the only mechanism operative in the observed pharmacologic effects.

Phenserine and huperzine A are among the cholinesterase inhibitors under study. Phenserine is a reversible and selective AChE inhibitor in phase III trials. However, there are no data to date on AChE expression and inhibition available for phenserine in the cerebrospinal fluid of patients with AD. Huperzine A is a quinolizidine-type alkaloid isolated from *Huperzia serrata* (Thunb) Trev, a traditional plant used in China for the treatment of swelling, strains, schizophrenia, myasthenia gravis, and organophosphate poisoning [73, 74]. Huperzine A has been described as a reversible and selective AChE inhibitor with oral bioavailability that can cross the blood–brain barrier and exhibits a prolonged half-life [75]. Studies have also demonstrated that this compound has a more potent effect in increasing cortical ACh levels than either donepezil or rivastigmine. Furthermore, huperzine A has been shown to display higher AChE inhibition in vivo [76]. Controversially, phase IV clinical trials conducted in China produced different results from phase II clinical trials conducted in the USA. In the former case, huperzine A caused significant improvements in memory shortages in older persons with benign senescent lack of memory and in patients with AD, with minimal adverse effects and toxicity [77, 78]. In contrast, in the American studies huperzine A showed no beneficial cognitive effect in patients with mild-to-moderate AD [79]. Further study is therefore required to resolve the controversy over the efficacy of this compound.

All in all, the use of cholinesterase inhibitors appears to have a beneficial impact on behavioral and psychiatric symptoms; however, there is no proof of superiority of one particular drug over another with respect to cognitive, behavioral, or functional clinical outcomes [80, 81].

4 Nicotinic Receptor Agonists

An additional approach to enhance ACh signaling between neurons is the use of cholinergic agonists to improve performance in learning and memory tasks (for a review, see [82]). Increasing attention is being paid to developing selective AChR agonists, with the capacity to enhance cognition without causing adverse effects associated with pan activation of AChRs (or muscarinic acetylcholine receptors). This line of thought is based on the fact that nicotine, a cholinergic agonist lacking selectivity for most AChRs, has been shown to improve attention, learning, and memory through interaction with neuronal AChRs [83]. Moreover, a recent study reported that nicotine can protect

from both early postsynaptic impairment and late presynaptic damage caused by Aβ oligomers [84]. This protection is apparently effected through the activation of α7AChR and the downstream cascade of the phosphatidylinositol-3-kinase signaling pathway. This pathway, in turn, cross-talks with the *Wnt* signaling pathway and both should be explored as potential therapeutic targets for AD. Furthermore, in a recent work by Lu and collaborators [85] this year, a protein called repressor element 1 silencing transcription factor ("REST"), normally expressed at low levels in the neurons of young healthy human brains, is reported to be markedly reduced in patients with mild cognitive impairment and AD. Interestingly, the authors report that stress can increase *Wnt* signaling, which in turn induces REST expression.

An important disadvantage of the use of agonists in AD is the fact that agonist treatment probably leads to non-physiologic receptor activation. Furthermore, cholinergic agonists bind to extracellular sites, the orthosteric agonist sites, located at the interface between two α subunits [86, 87]. Although the potency of the agonist may not be exactly the same for different AChR subtypes, the prolonged presence of the ligand at the agonist site leads to the desensitized state of the receptor, and this thermodynamically end state driven by the agonist decreases the expected effect of the surrogate agonist [88]. Thus, the resulting compounds do not produce an "either/or" effect: activation and desensitization of AChRs both contribute to pharmacologic behavior, as is dramatically clear in the case in nicotine addiction and mood disorders [88]. However, desensitization may be compensated by the up-regulation of AChRs observed after long-term agonist treatment. Indeed, up-regulation of α7 AChR protein levels in the frontal cortex or hippocampus of mice was observed in vivo with very low doses of AZD0328 and SSR180711, two partial agonists of the receptor. Cognition was correspondingly found to increase in this model system [89]. Up-regulation of different AChR subtypes with nicotine was extensively studied in relation to tobacco addiction [90, 91].

In addition, preclinical studies performed with the selective α7 AChR agonist A-582941 in a mice model of AD have shown that although pathologic findings such as amyloid deposition and neurofibrillary tangles did not change in treated mice, cognition was completely restored to the level of age-matched non-transgenic wild-type mice [92]. Moreover, the α7 AChR partial agonist SSR180711 completely rescued early as well as late LTP impaired by Aβ42 oligomers in hippocampal slices, whereas donepezil, a cholinesterase inhibitor, and TC-1827, an α4β2 AChR agonist, did not [93]. These results highlight the potential of α7 AChR as a therapeutic target in AD.

A few AChR agonists aimed at the treatment of AD are currently in developmental phases II and III. One such compound is ABT-126 (AbbVie spun), a drug that at high doses achieves similar cognitive gains to those reported for donepezil, and the use of which improves scores on memory tests in the Alzheimer Disease Assessment Scale-Cognitive subscale compared with the placebo group. Studies are currently being carried out on ABT-126 (AbbVie spun) to determine whether it provides additional benefits in combination with the drug donepezil (preliminary data can be found in http://www.alzforum.org/).

An additional drug in a phase III study, (*R*)-7-chloro-*N*-quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide (EVP-6124 from EnVivo Pharmaceutical), was characterized as a novel and selective partial agonist of the α7 AChR. Prickaerts and colleagues [94] demonstrated that exposure of α7 AChRs to EVP-6124 at a sub- to low nanomolar range was responsible for its pro-cognitive effects through a co-agonist type of mechanism. The findings have opened up promising therapeutic possibilities in combination with classical acetylcholinesterase inhibitors at lower than typically prescribed doses. The cognitive-enhancing effects observed after EVP-6124 administration appear to occur at concentrations in the brain below those causing desensitization of AChRs. Other agonists such as AQW051, TC-5619 [95], and GTS-21 [96] have entered clinical-phase stages more recently, but no results are available to date.

5 Positive Allosteric Modulators (PAMs)

Why allosteric modulators? Two compelling reasons are that allosteric ligands offer the potential for greater receptor subtype selectivity, because of higher sequence divergence in allosteric sites across receptor subtypes relative to the conserved orthosteric domain, and, second, because they can selectively modulate orthosteric ligand actions at a given subtype of receptors to the exclusion of others [87]. In the particular case of the AChR, development of positive allosteric modulators (PAMs) shows promise, for instance, in alleviating desensitization associated with prolonged agonist exposure. PAMs bind to distinct non-overlapping allosteric sites that are topologically differently located from the canonical ("orthosteric") agonist binding domains used by the natural neurotransmitter, other conventional agonists such as nicotine or carbamoylcholine, or competitive antagonists. PAM binding causes conformational changes in the receptor that synergize and augment the natural signals elicited by co-bound orthosteric ligands. In the case of the α7 AChR, the orthosteric agonist-recognition sites are located in the extracellular domain, at the interface between two α7 subunits, providing a total of five binding sites per receptor

oligomer [97]. Conventional orthosteric agonists increase receptor activity [87]. Except for a few exceptional cases if the agonist is not bound to the receptor's orthosteric site, PAMs do not produce AChR activation on their own [98, 99], but rather increase the action (affinity and/or efficacy of the orthosteric agonist [87]). Several groups have studied whether PAMs have any effect on the equilibrium binding of radiolabeled high-affinity agonists or antagonists of the α7 AChR in membrane preparations from rodent brain or heterologous expression systems, confirming that PAMs bind at a site different from the canonical agonist binding site [99–105]. Therefore, only in the presence of a full or partial agonist can PAMs facilitate agonist-evoked responses by modifying energy barriers associated with transitions between functional conformations [106]. In this way, in contrast with canonical orthosteric-site agonists, the temporal and spatial integrity of neurotransmission is preserved.

Why are PAMs particularly suitable for targeting α7 AChRs? This type of neuronal receptor exhibits distinctive functional characteristics such as unusually high Ca^{2+} permeability, low probability of channel opening, and rapid desensitization. Williams et al. [106] have pointed out that these properties may limit the therapeutic usefulness of ligands binding exclusively to the orthosteric agonist binding sites. The use of PAMs may therefore prove a stronger therapeutic option than that provided by conventional agonists alone. However, when the integrity of cholinergic neurons is compromised to the point where ACh synthesis is also compromised, PAM treatment may be ineffective; combining with an agonist may increase the efficacy of this therapeutic approach in such cases.

PAMs aimed at the α7 AChR have been divided into two classes, types I and II, based on the modulation exerted on receptor function [107], and a third class grouping those compounds having intermediate effects between those of type I and II drugs. Tables 1 and 2 list a series of PAM compounds that have been studied to date.

Upon application of an α7 agonist, type I PAMs increase receptor sensitivity to the agonist, enhancing current amplitudes and the empiric Hill coefficient, with minor or no effect on the basic onset and decay kinetics or shape of the ionic current response. However, only two compounds (NS-1738 and 5-HI) need the extracellular domain of the α7 AChR to potentiate the response, whereas others (ivermectin and LY-2087101) do not. Ivermectin binds to the transmembrane region of the AChR. Thus, the available experimental data suggest that the potentiation profile of type I PAMs involves more than one mechanism and site of action. Type II PAMs affect cholinergic responses by slowing the decay kinetics; they can even activate α7 AChRs that have been previously desensitized by the agonist [103, 104, 107–109].

Table 1 Acetylcholine receptor (AChR) agonists currently in clinical phase trials

AChR agonist	References
A-582941	[92]
SSR180711	[93]
ABT-126	
EVP-6124	[94]
AQW051	
TC-5619	[95]
GTS-21	[96]

In addition, endogenous molecules acting as PAM have been identified. Secreted mammalian Ly6/urokinase plasminogen activator receptor-related protein-1 is a small protein that acts as an endogenous PAM of the α7 AChR [110]. It increases AChR potency and the Hill coefficient without affecting desensitization kinetics, thus mimicking the type I PAM mode of action [110]. It is expressed in spinal cord neurons, lymphocytes, and keratinocytes; however, little is known about its expression or function in the CNS [111–113].

6 Type I PAMs as Therapeutic Options

Among type I PAMs, we find compounds such as AVL-3288, (*N*-4-chlorophenyl)-α-[[(4-chloro-phenyl) amino]methylene]-3-methyl-5-isoxazoleacet-amide), also known as XY-4083 and originally referred to as Compound 6 (CCMI), a PAM used for the treatment of cognitive deficits in CNS disorders such as schizophrenia and potentially AD and attention-deficity hyperactivity disorder [114], currently in human phase I trials. In rats, repeated treatment with AVL-3288 showed improved social discrimination after 24 h, although no effects were apparent in animals after a single administration [115]. AVL-3288 also improved the performance of a radial arm maze task in rats and normalized sensory-gating deficits in the DBA/2 mouse [104]. However, this compound also acts as a $GABA_A$ receptor PAM, thus indicating its lack of selectivity [104].

As previously indicated, galantamine is a well-known acetylcholinesterase inhibitor [116] used in clinical practice for the treatment of AD. It has also been reported to act as an α7 AChR PAM, the latter effect being responsible, at least in part, for its clinical efficacy [117, 118]. However, galantamine lacks selectivity, because it can also modulate other AChRs and even NMDA receptors [118, 119]. This compound is charged under physiologic pH and some authors suggest that this property could provide a unique binding site near the AChR orthosteric agonist site [120].

5-Hydroxyindole (5-HI) is a serotonin metabolite [117] that has low potency and low selectivity for AChRs,

Table 2 Positive allosteric modulators (PAMs) potentiate the agonist-evoked response by binding to a site distinct from the agonist binding site. PAMs lack intrinsic agonist activity

Type I without affecting decay kinetics	Type II affecting receptor desensitization kinetics	Type I/type II intermediate
AVL-3288	PNU 120596	SB-206553
NS-1738	TQS	JNJ-1930942
Galantamine	A-867744	
5-HI		
Compound 2087101		
Genistein		
Ivermectin		

because it also potentiates 5-hydroxytryptamine 3 ($5HT_3$) receptors [121, 122]. Interestingly, although nicotine and epibatidine were unable to elicit glutamate release, [123, 124] the presence of 5-hydroxyindole reverts this phenomenon through α7 nicotinic AChR activation in rat hippocampal and cortical synaptosomes [123]. However, this compound is active at high micromolar to millimolar concentrations, thus precluding its clinical applicability [125].

Compound 2087101 ((2-amino-5-keto) thiazole) can potentiate responses and the efficacy of an agonist when acting on several AChR subtypes (α2β4, α4β2, α4β4, and α7 AChRs) [126] in a concentration-dependent manner. This potentiation is non-competitive and independent of agonist concentration and may thus be operative in situations with low ACh release [126].

Genistein is a non-selective kinase inhibitor [127] that has been shown to increase α7 AChR responses [107, 128, 129]. Although the mechanism of action of this drug could involve tyrosine kinase inhibition, direct allosteric modulation is not discarded because it is the only compound among other kinase inhibitors studied (staurosporine, herbimycin A, PP2, or SU6656) that is able to increase α7 AChR-mediated ionic currents at concentrations showing effective kinase inhibition [130, 131]. Furthermore, treatments with tyrosine kinases inhibitors are not able to abolish or attenuate the modulatory effect of genistein [107].

NS-1738 (1-(5-chloro-2-hydroxy-phenyl)-3-(2-chloro-5-trifluoromethyl-phenyl)-urea is an α7 AChR PAM that has also been shown to inhibit the response of α3β4 and α4β2 AChRs, the former receptor being involved in the control of bladder and cardiac function and the latter in the reinforcing effects of nicotine related to addiction (see review by [132]). NS-1738 reversed scopolamine-induced water maze learning and a social recognition memory task [105] but has yet to be tested clinically.

Ivermectin is an antiparasitic (antihelminthic) agent that enhances ACh-induced α7 AChR responses [133], and can thus be classified as an α7 PAM. It exerts a range of actions on diverse members of the Cys-loop receptor family and on some other members of the LGICs. These targets include both excitatory and inhibitory neurotransmitter receptors, making this compound non-selective for α7 AChRs [134–137].

BNC375 is a novel type I PAM acting on the α7 AChR that has proved effective across a wide range of agonist concentrations and has demonstrated efficacy in animal models of episodic and working memory with a broad therapeutic window. BNC375 matches the performance of donepezil and is Bionomics' and Merck clinical candidate for AD [138].

7 Type II PAMs as a Therapeutic Alternative

Type II PAMs include PNU-120596 (1-(5-chloro-2,4-dimethoxy-phenyl)-3-(5-methyl-isoxazol-3-yl)-urea), which modulates the α7 AchR-desensitized state [109, 139]; it has no effect on ion selectivity and minor effects on channel conductance [109], stabilizing the intrinsic states of the channel. This drug has not been tested clinically. However, PNU-120596 was shown to improve the auditory gating deficit induced by amphetamine in rats [109] and has been able to reverse scopolamine-induced deficits in fear conditioning as well as in novel object recognition tests in rats. Consistently, these effects were reversed by the α7 AChR antagonist methyl-*N*-aconitine, indicating α7 AChR selectivity. In this study, sub-threshold doses of PNU-120596 were shown to enhance the fear conditioning effects of a low dose of nicotine, but active doses of PNU 120596 and nicotine retained the pro-cognitive effects [140]. In a more recent study, PNU-120596 was shown to attenuate the deficits induced by sub-chronic phencyclidine treatment in the extra-dimensional shift phase of an attentional set-shifting task [98, 115, 141].

4-(1-napthyl)-3*a*,4,5,9*b*-tetrahydro-3*H*-cyclopenta[*c*]quinoline-8-sulfonamide (TQS) has been shown to significantly increase the apparent peak current response and to reduce the current decay rate of α7 AChR channels

activated by ACh application [107], although the significance of these data remains to be clarified.

A-867744 is a prototypical type II PAM that not only enhances the peak α7 AChR current evoked by nicotinic agonists but also slows down the desensitization of agonist responses. A-867744 was also demonstrated to dramatically enhance Ca^{2+} responses and ERK phosphorylation in a concentration-dependent manner [103, 142]. Interestingly, ERK1/2 phosphorylation in response to α7 AChR agonists has been recently demonstrated in vitro [138–145] and in vivo [146].

8 Type I/Type II Intermediate Compounds

Other α7 AChR PAMs with a structurally different chemotype, i.e., structurally departing from other known PAM compounds, have been characterized (type I/type II intermediate compounds). 3,5-dihydro-5-methyl-*N*-3-pyridinylbenzo[1,2-b:4,5-b']-di pyrrole-1(2H)-carboxamide, SB-206553, was shown by Dunlop and colleagues [101] to potentiate the evoked α7 AChR-mediated calcium signal in the presence of nicotine in GH4C1 cells and also to potentiate ACh-induced currents in CA1 stratum radiatum interneurons in rat hippocampal slices. However, SB-206553 is essentially devoid of AChR subtype selectivity, because it can also inhibit the response of α3β4 AChRs [101] and can even function as an antagonist of 5-HT2B/C [147] and 5-HT_3 receptors [101]. 2-[[4-fluoro-3-(trifluoromethyl)phenyl]amino]-4-(4-pyridinyl)-5-thiazolemethanol, JNJ-1930942, is a compound that enhances both the efficacy and the potency of orthosteric cholinergic agonists without directly activating the α7 AChR. JNJ-1930942 potentiates the choline-evoked rise in intracellular Ca^{2+} levels in the GH4C1 cell line expressing the cloned human α7 AChR and does not act on α4β2, α3β4 AchRs, or the 5-HT_{3A} channel. The mechanism of action of JNJ-1930942 results mainly from affecting receptor desensitization, leaving activation and deactivation kinetics as well as recovery from desensitization relatively unchanged [99]. The reduction of the fast desensitization step is responsible for the enhanced current amplitude [99].

A different approach towards improving cholinergic signaling is to stimulate ACh release. An example of a drug in phase II development for AD that follows this concept is ST-101(spiro[imidazo[1,2-a]pyridine-3,2-indan]-2(3H)-one), also coded as ZSET1446 by Sonexa Therapeutics). This compound is able to cross the blood–brain barrier and activate T-type voltage-gated calcium channels. It has shown effectiveness in restoring the learning and memory capability of cognitively impaired animal models of AD [118, 148]. Interestingly, a recent study suggests that co-application of ZSET1446 and the NMDA receptor antagonist memantine has a positive effect on cognitive functions in mice and rats. An increase in the extracellular levels of ACh in the hippocampus was observed upon application of this compound [149, 150]. It was also demonstrated that α7 AChR has a permissive role in NMDA receptor action in the primate prefrontal cortex, strengthening cognitive functions, thus suggesting a promising combination therapy of these two compounds in clinical settings [151].

9 Conclusions

It is unlikely that targeting a single factor at a time will have sufficient impact on a multifactorial complicated disease such as AD. Reinforcing neurotransmission could be beneficial in attempting to ameliorate symptoms at early stages of treatment, as demonstrated by the long-standing success of cholinesterase inhibitors; however, without removing the harmful potential of excess Aβ and/or tau, synaptic and dendritic damage will progress, eventually leading to neuronal death. In contrast, removal of Aβ and/or tau appears to be a potential brake to neuronal damage, but is most unlikely to lead to the recovery of injured neurons and much less to the replenishment of lost neurons.

Efforts should be aimed at maximizing functional specificity of targets at the molecular, cellular, and tissue levels. It would be desirable to selectively target individual classes of AChRs with drugs active only in particular regions or nuclei of the brain. This is a daunting challenge, perhaps even bordering on the utopian in terms of our current state of knowledge. Identifying prodromic markers of early physiopathologic stages of AD should also be a major goal of current efforts, such that the selective drugs can be aimed at ameliorating dysfunction or at least delaying the onset of disease in genetically predisposed subjects at asymptomatic stages.

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