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Targeting of α7 Nicotinic Acetylcholine Receptors in the Treatment of Schizophrenia and the Use of Auditory Sensory Gating as a Translational Biomarker

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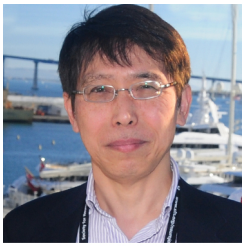

Kenji Hashimoto

Abstract: Accumulating evidence suggests that the α7 subtype of nicotinic acetylcholine receptors (nAChRs) plays a key role in inflammatory processes, thought to be involved in the pathophysiology of neuropsychiatric diseases, such as schizophrenia and Alzheimer's disease. Preclinical and clinical studies showed that the diminished suppression of P50 auditory evoked potentials in patients with schizophrenia may be associated with a decreased density of α7 nAChRs in the brain. This points to a role for auditory sensory gating (P50) as a translational biomarker. A number of agonists and positive allosteric modulators (PAMs) for α7 nAChR promoted beneficial effects in animal models with sensory gating and cognitive deficits. Additionally, several clinical studies showed that α7 nAChR agonists could improve suppression in auditory P50 evoked potentials, as well as cognitive deficits, and negative symptoms in patients with schizophrenia. Taken together, α7 nAChR presents as an extremely attractive therapeutic target for schizophrenia. In this article, the author discusses recent findings on α7 nAChR agonists such as DMXB-A, RG3487, TC-5619, tropisetron, EVP-6124 (encenicline), ABT-126, AQW051 and α7 nAChR PAMs such as JNJ-39393406, PNU-120596 and AVL-3288 (also known as UCI-4083), and their potential as therapeutic drugs for neuropsychiatric diseases, such as schizophrenia.

Keywords: α7 nicotinic acetylcholine receptors, schizophrenia, auditory sensory gating, agonists, allosteric positive modulators, biomarker.

INTRODUCTION

Epidemiological studies showed that patients with psychiatric diseases, including schizophrenia, smoke more heavily than the general population, thereby increasing their morbidity and mortality from smoking-related illnesses [1-5]. This elevated smoking rate in schizophrenia is thought to be a form of self-medication [6, 7]. There are various interpretations of the high smoking rates in schizophrenia, including the ideas that smoking reduces the side effects of antipsychotics [8] and that it alleviates symptoms, including those of depression, anxiety, anhedonia and amotivation [9-11].

Nicotine, the main psychoactive ingredient in tobacco smoke, binds to nicotinic acetylcholine receptors (nAChRs). The main subtypes of nAChRs in the central nervous system (CNS) are the α4β2 and α7 subtypes [12]. Multiple lines of evidence suggest that α7 nAChR plays a key role of the pathophysiology of neuropsychiatric diseases, including schizophrenia, making this receptor subtype one of the most attractive therapeutic targets for these diseases [13-23]. In this article, I will review the recent findings that highlight α7 nAChR as a potential therapeutic target for schizophrenia.

P50 SENSORY GATING AS A DISEASE BIOMARKER

The P50 auditory evoked potential is a positive electroencephalography waveform that occurs 50 milliseconds (msec) after presentation of an auditory stimulus. When pairs of auditory stimuli are presented, with a 500 msec interstimulus interval, normal subjects show significantly reduced responses to the second stimulus. However, patients with schizophrenia fail to adequately inhibit their P50 response to the second stimulus (Fig. **1**). This disability is deemed to be an underlying mechanism of cognitive impairment in schizophrenics, particularly attention deficits and lack of attention sustainment. A number of studies revealed abnormal suppression of P50, not only in schizophrenia patients [24-28], but also their unaffected relatives [29-32]. Recent meta-analyses support the findings of abnormal P50 suppression in patients with schizophrenia [33-36]. The P50 evoked potential has the highest effect size and is the most powerful and reliable neuroscience biomarker in schizophrenia [33]. Interestingly, diminished suppression of P50 was demonstrated in high-risk subjects and first-episode schizophrenic patients [37], although this finding was not replicated in other reports [38, 39]. Further detailed studies using large sample sizes will be needed to confirm the usefulness of auditory sensory gating P50 as an early biomarker for psychosis.

The use of translational biomarkers to validate animal models is a necessary process in the development of novel therapeutic drugs. Deficits in sensory information processing in schizophrenia are typically assessed in animal models using rodents. The hippocampal P20-N40 auditory evoked potential in rodents is thought to be analogous to the human P50 potential. Stevens *et al*. [40] reported a correlation between inhibitory gating (P20-N40) of the hippocampal auditory evoked response and hippocampal α7 nAChR density in inbred mouse strains. The auditory sensory gating deficits of DBA/2 mice with low density α7 nAChR have been utilized in an animal model of schizophrenia [41, 42]. The auditory sensory gating deficits of DBA/2 mice are improved by clozapine treatment and this effect is blocked by the α7 nAChR antagonist, α-bungarotoxin, implicating an α7 nAChR mediated mechanism in auditory sensory gating deficits [43].

Clozapine is reported to normalize P50 suppression in patients with schizophrenia unlike other antipsychotics [25, 44, 45], and this normalization corresponds with an improvement in clinical symptoms [44]. It is likely that clozapine blockade of 5-hydroxytryptamine-3 (5-HT_3) receptors results in the release of acetylcholine from presynaptic terminals, which in turn stimulates α7 nAChR in the brain [46].

Postmortem studies of schizophrenia patients show decreased density of α7 nAChR in the dentate gyrus of the hippocampus, as well as area CA3, the reticular thalamic nucleus and the frontal and cingulate gyri [47-50]. Interestingly, this reduced expression of α7

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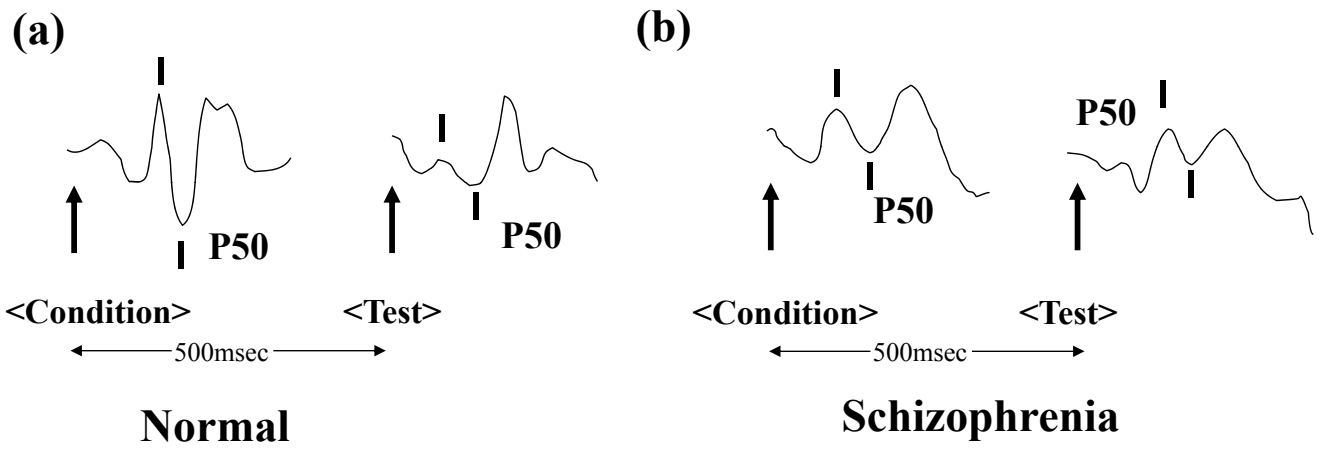


Fig. (1). P50 auditory evoked potentials as a biomarker for schizophrenia. Arrows show the onset of auditory stimuli. While normal healthy subjects show a lower response to the second stimulus (test), patients with schizophrenia fail to show this suppression.

nAChR has been linked to the degree of global cognitive deficits in patients with schizophrenia [51]. These results indicate that the P20-N40 auditory evoked potential in rodents and the P50 auditory evoked potential in humans could represent a translational biomarker from rodents to humans. This would make auditory evoked potentials an invaluable translational biomarker in the development of novel therapeutic drugs for schizophrenia [52].

NICOTINE AND AUDITORY P50 DEFICITS

Nicotine is known to restore P50 deficits in schizophrenic patients [53] and their first degree relatives [54]. However, there is no improvement in sensory gating deficits when mecamylamine, an α4β2 nAChR antagonist is administered in DBA/2 mice [55]. This led to the proposal that α7 nAChR, and not α4β2 nAChR, may be the major cholinergic receptor responsible for auditory P50 gating [56, 57].

AUDITORY P50 GATING AND THE *CHRNA7* GENE

A genome-wide linkage analysis of nine multiplex families with schizophrenia revealed maximal linkage of the P50 deficit to chromosome 15q14, at a polymorphic marker, less than 120 kb from the α7 nAChR gene (*CHRNA7*), with a logarithm of odds (LOD) score of 5.3, Θ = 0.039 [58]. This linkage has been replicated in families from the National Institute of Mental Health (NIMH) Schizophrenia Genetics Initiative [59], but is not supported by all studies [60, 61]. A single nucleotide polymorphism in the 5' core promoter region of the *CHRNA7* gene is significantly associated with P50 suppression deficits [62, 63].

The Consortium on the Genetics of Schizophrenia (COGS), a 7-site study designed to eliminate site to site recording method differences, examined P50 suppression in 181 probands with schizophrenia, 429 of their first degree relatives, and 333 community comparison control subjects [64]. The results of this study led to the suggestion that auditory P50 deficits may be a possible schizophrenia endophenotype [64]. A recent analysis of 94 candidate genes and 12 endophenotypes for schizophrenia, obtained from COGS showed that the *CHRNA7* gene is associated with schizophrenia [65].

It is reported that the *CHRNA7* gene, located at chromosome 15q13.3 is partially duplicated [66]. The *CHRFAM7A* gene formed from the partial duplication of CHRNA7, acts as a dominant negative modulator of CNRNA7 function and is critical for receptor regulation in humans [67]. Furthermore, a 2-base pair deletion polymorphism in the partial duplication of *CHRFAM7A* shows association with schizophrenia [68].

α7 nAChR agonists

A number of α7 nAChR agonists have been developed as therapeutic drugs for the treatment of schizophrenia [13-23]. Agonists such as PHA-543613, N-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]furo[2, 3-c]pyridine-5-carboxamide hydrochloride [69], PHA-568487, *N*-(3*R*)-1-azabicyclo[2.2.2]oct-3-yl-2, 3-dihydro-1, 4-benzodioxin-6-carboxamide fumarate [70], ABT-107, 5-(6-[(3*R*)-1-azabicyclo [2.2.2]oct-3-yloxy] pyridazin-3-yl)-1H-indole [71-73], SSR180711, 1, 4-diazabicyclo[3.2.2]nonane-4-carboxylic acid, 4-bromophenyl ester [74-76], CP-810123, 4-(5-methyloxazolo[4, 5-b]pyridin-2-yl)-1, 4-diazabicyclo[3.2.2]nonane [77], and AZD0328, (2′*R*)-spiro-[1-azabicyclo[2.2.2]octane-3, 2′(3′H)-furo[2, 3-b]pyridine [78, 79] (Fig. **2**) were all discontinued after Phase I clinical trials, due to various adverse effects [80]. Next, I will discuss the drugs currently undergoing investigation in clinical trials.

DMXB-A

DMXB-A (formally called GTS-21), 3-(2, 4-dimethoxybenzylidene)-anabaseine (Fig. **3**), is an analogue of anabaseine, a marine worm toxin, with a structure related to nicotine. DMXB-A is a partial agonist at the α7 nAChR and an antagonist at α4β2 nAChR. In addition, its major metabolite, 4-OH DMXB-A may be an α7 nAChR antagonist [22]. Reports suggest that DMXB-A improves the deficits in auditory sensory gating of DBA/2 mice [81-83] and isolation-reared rats [84].

A clinical study in healthy subjects showed positive effects for DMXB-A in attention, working memory and episodic memory [85]. A proof-of-concept study for DMXB-A in patients with schizophrenia demonstrated normalization of P50 deficits and cognitive improvement [86]. Although the Phase II study did not show improvements in the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery, high doses (150 mg/day, b.i.d., 4-weeks) of DMXB-A improved negative symptoms [87].

A randomized, double-blind crossover study showed that DMXB-A administered at 150 mg/day, twice daily, for 4 weeks diminished hippocampal activity during pursuit eye movements [88]. These findings are consistent with the established function of α7 nAChR on inhibitory interneurons in the hippocampus [88]. A subsequent study showed that DMXB-A (75 and 150 mg/day) induced several alterations in the default network activity in schizophrenia, including a reduction in activity within the posterior cingulate, inferior parietal cortex, and medial frontal gyrus and an in-

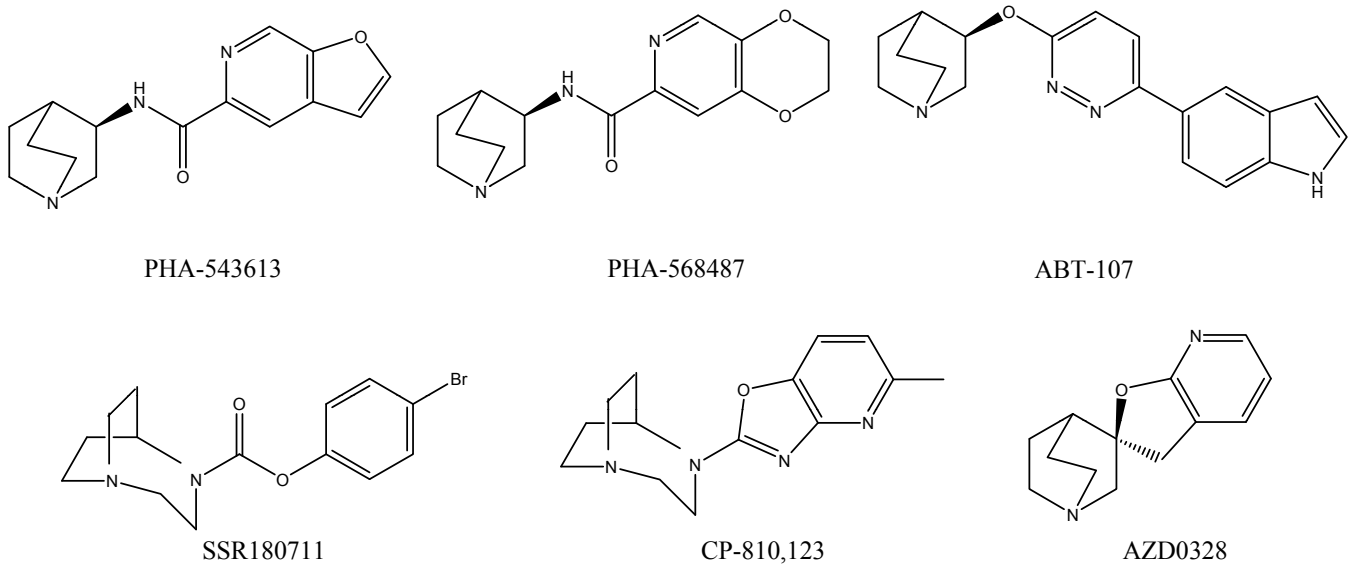


Fig. (2). Chemical structures of α7 nAChR agonists, including PHA-543613, PHA-568487, ABT-107, SSR180711, CP-810, 123, and AZD0328.

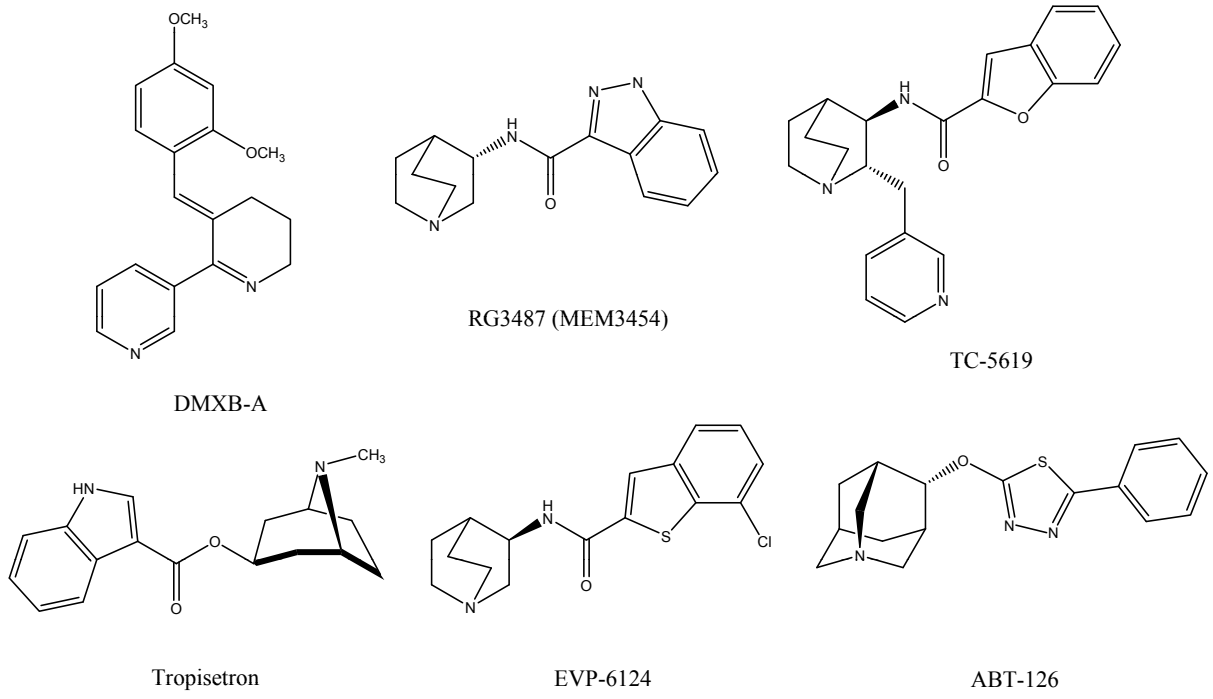


Fig. (3). Chemical structures of α7 nAChR agonists, including DMXB-A, RG3487 (MEM3454), TC-5619, tropisetron, EVP-6124 (encenicline), and ABT-126.

crease in precuneus activity [89]. Interestingly, the most robust difference, namely reduced activity in the posterior cingulate is affected by the CHRNA7 genotype. These findings suggest a dysfunction in α7 nAChR and the default network function in schizophrenia.

Because of low bioavailability and low half-life of DMXB-A in humans, a sustained-release DMXB-A-SR system has been developed. This is currently being investigated in a randomized, placebo-controlled study, of sustained-release DMXB-A-SR in patients with schizophrenia [90].

RG3487 (or MEM 3454)

RG3487 (formally called MEM3487), *N*-[(3S)-1-azabicyclo [2.2.2]oct-3-yl]-1*H*-indazole-3-carboxamide hydrochloride (Fig. **3**), is an orally available, partial agonist at α7 nAChR (Ki = 6 nM for human α7 nAChR) and 5-HT_3 antagonist, with no appreciable cross-reactivity with other nicotinic receptor subtypes or CNS targets [91]. RG3487 was effective at improving visual sustained attention, when given acutely in rats [92]. In another study, RG3487 improved object recognition memory in rats after acute or repeated administration. Furthermore, RG3487 improved apomorphine-

induced prepulse inhibition (PPI) deficits and the *N*-methyl-D-aspartate (NMDA) receptor antagonist phencyclidine (PCP)-induced impairments in an attentional set-shifting model [91]. These observations highlight RG3487 as a novel and potent drug capable of improving cognitive performance and sensorimotor gating.

A Phase 2 trial evaluating the safety and efficacy of RG3487 demonstrated statistically significant effects on cognition in patients with schizophrenia and Alzheimer's disease [18, 20, 92]. However, there are currently no licensing plans from Roche for use of this drug in schizophrenia.

TC-5619

TC-5619, (2*S*, 3*R*)-*N*-[2-(pyridin-3-ylmethyl)-1-azabicyclo [2.2.2]oct-3-yl] benzo[b]-furan- 2-carboxamide (Fig. **3**), is a novel partial agonist, with high affinity at α7 nAChR (Ki=1.40 nM for human α7 nAChR)[80, 93]. In the novel object recognition test in animals, TC-5619 improved short-term working memory. It also demonstrated therapeutic efficacy in the social withdrawal model in mice, suggesting an effectiveness in ameliorating the negative symptoms of schizophrenia [93].

A randomized, placebo-controlled study of TC-5619 in the USA and India, demonstrated that this drug improved executive function and negative symptoms in patients with schizophrenia [94]. Furthermore, it showed a statistically significant drug effect on working memory in tobacco users. TC-5619 was generally well tolerated with no clinically noteworthy safety findings. It showed statistically significant benefits on the Groton Maze Learning task of the CogState battery in patients, compared with the placebo group. This study pinpoints potential benefits for the use of TC-5619 in treating cognitive impairment and negative symptoms associated with schizophrenia. A 30-week, multi-center, double-blind, randomized, placebo-controlled study of TC-5619 (5 and 50 mg) in outpatients with schizophrenia is currently underway [95].

Tropisetron

Tropisetron (Fig. **3**) is a potent 5-HT_3 receptor antagonist, marketed outside of the United States for the treatment of patients with chemotherapy induced or postoperative nausea and vomiting [15, 18, 20]. Tropisetron is a partial, high affinity agonist at α7 nAChR, whereas ondansetron, another 5-HT_3 receptor antagonist, shows weak affinity at α 7 nAChR [96, 97]. We previously reported that tropisetron improves deficient auditory inhibition processing in DBA/2 mice, and that this improvement could be antagonized by co-administration of methyllycaconitine (MLA) [98]. We also reported that PCP-induced cognitive deficits could be improved by subsequent subchronic administration of tropisetron, but not ondansetron, and that this improvement was also antagonized by co-administration of MLA [99]. Furthermore, tropisetron was capable of attenuating PPI deficits in rats after PCP or apomorphine dosing, and yet again, this effect was antagonized by MLA [100].

In addition, we reported that a single oral dose of tropisetron (10 mg) could improve P50 suppression deficits in non-smoking patients with schizophrenia [101]. In support of these findings, a randomized, placebo-controlled study of tropisetron found that administration of tropisetron (10 mg), but not placebo, significantly improved auditory sensory gating P50 deficits in non-smoking patients with schizophrenia [102]. Interestingly, we found that sustained visual attention in non-smoking patients was also significantly improved by tropisetron treatment [102]. Tropisetron was well tolerated in this trial, and was associated with no untoward effects.

Subsequent short-term treatment with tropisetron at 5, 10, or 20 mg/day for 10-days, showed an overall significant improvement in cognitive deficits in non-smoking patients with schizophrenia, at all doses, with 10 mg showing the greatest improvement in the immediate memory index score and 20 mg in the delayed memory index score on the Repeatable Battery for the Assessment of Neuropsychological Status battery [103]. In addition, sensory gating P50 deficits showed recovery which correlated significantly with cognitive improvement. A recent, placebo-controlled study using tropisetron in conjunction with risperidone, showed that tropisetron (10 mg/day for 8-weeks) promoted greater enhancement in negative symptom scores and general psychopathology in patients with chronic stable schizophrenia [104].

These cumulative findings point towards tropisetron as a potential therapeutic drug for cognitive deficits and negative symptoms in schizophrenia. This drug is already in use worldwide for the treatment of various diseases, and further studies using large cohorts will be needed to confirm the efficacy of tropisetron in schizophrenia. To this end, a randomized, placebo-controlled study of tropisetron (10 mg/day for 12-weeks) plus risperidone (6 mg/day) in Chinese patients (n = 200) with early phase schizophrenia is currently underway [105].

EVP-6124 (Encenicline)

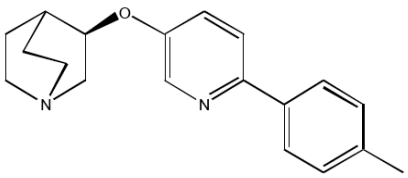
EVP-6124 (encenicline), (*R*)-7-chloro-*N*-quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide (Fig. **3**), is a potent and selective partial agonist at α7 nAChR (Ki = 9.98 nM for [^{3}H]MLA binding, Ki = 4.33 nM for [^{125}I]α-bungarotoxin binding) [106]. At a concentration of 10 μM, EVP-6124 lacked appreciable interaction with more than 60 molecular targets in a selectivity screening panel, which included receptors, ion channels, and amine transporters. Furthermore, EVP-6124 (0.3 mg/kg, orally) significantly restored memory function in scopolamine-treated rats, tested in the object recognition task, and this restorative effect was blocked by MLA [106].

A randomized, placebo-controlled Phase 2b study showed that when taken in combination with second-generation antipsychotics and using CogState battery tests, EVP-6124 exerted a clinically meaningful and statistically significant impact on patients' overall cognition, the trial's primary endpoint [107-109]. Additionally, EVP-6124 showed statistically significant clinical effects in key secondary endpoints, namely, improved clinical function, as assessed by the Schizophrenia Cognition Rating Scale, and reduced negative symptoms. Importantly, EVP-6124 was generally safe and well-tolerated during the three-month dosing period of the trial [110]. Double-blind, placebo-controlled, Phase 3 studies of EVP-6124 in patients with schizophrenia are currently underway [110]. In addition, two Phase III trials of EVP-6124 in patients with mild-to moderate Alzheimer's disease are also underway [111].

ABT-126 and AQW-051

ABT-126 (AbbVie), (4*s*)-4-(5-phenyl-1, 3, 4-thiadiazol-2-yloxy)-1-azatricyclo[3.3.1.1^{3,7}]decane (Fig. **3**), is a novel partial agonist at α7 nAChR (Ki = 12 nM for human α7 nAChR, Ki = 1740 nM for α4β2 nAChR, Ki = 140 nM for 5-HT_3 receptor) [112, 113]. A recent randomized, double-blind, placebo-controlled, multicenter Phase 2 study of ABT-126 in subjects (N=260) with mild-to-moderate Alzheimer's related dementia, was presented at the Alzheimer's Association International Conference [113]. High-dose ABT-126 improved Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) scores in a manner similar to donepezil. This ADAS-cog improvement correlated with ABT-126 plasma levels. Several clinical studies of ABT-126 in patients with schizophrenia are underway [114-116].

AQW051, (*R*)-3-(6-*p*-tolyl-pyridin-3-yloxy)-1-aza-bicyclo (2.2.2.)octane (Fig. **4**), displayed high affinity for the human α7 nAChR with high selectivity towards other nAchRs [117]. AQW051 showed good oral bioavailability and rapid penetration into the rodent brain. Furthermore, AQW051 was effective in the animal models of object recognition, social recognition, and water maze [117]. Phase I study showed that AQW051 was well tolerated



AQW051

Fig. (4). Chemical structures of α7 nAChR agonist AQW051.

in healthy young and elderly subjects. No serious adverse effects were shown [117]. Two such clinical studies in patients with chronic stable schizophrenia have been completed [118], while a subsequent, randomized, double-blind, placebo-controlled study of AQW051 (10 mg/day for 12-weeks) in patients with stable schizophrenia is underway [119].

α7 nAChR PAMs

Although many α7 nAChR full agonists protect against the deterioration of cognitive functions, the rapid desensitization of α7 nAChR, a process that occurs in milliseconds, raises concerns about the long-term administration of this class of compounds [120]. Nevertheless, PAMs of α7 nAChR have been the subject of much attention [18, 20, 121-123]. Based on electrophysiological characterization, at least two types of PAMs have been suggested: type I and type II. Both types increase the potency and efficacy of agonist-induced responses, which are observed as increases in peak agonist-evoked current responses, but type II has the additional ability to modify the desensitization profile of agonist responses [123].

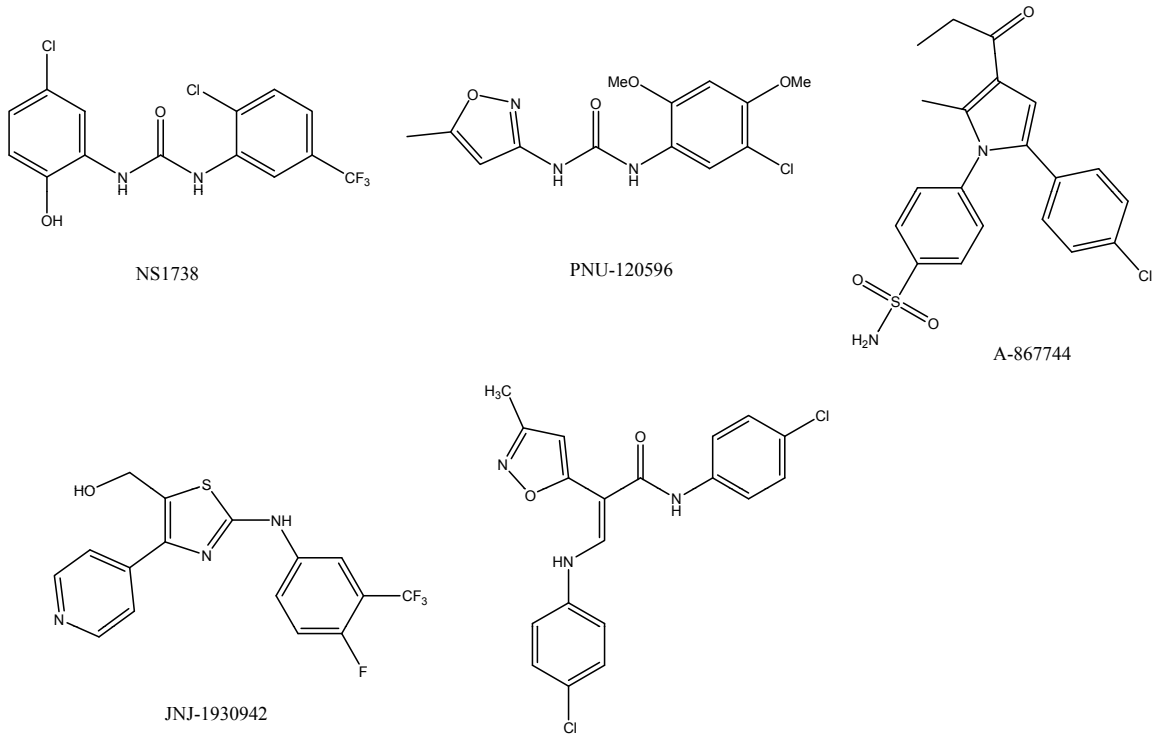
A number of new α7 nAChR PAMs, such as NS-1738, 1-(5-chloro-2-hydroxy-phenyl)-3-(2-chloro-5-trifluoromethyl-phenyl)-urea [124, 125], PNU-120596, 1-(5-chloro-2, 4-dimethoxy-phenyl)-3-(5-methyl-isoxazol-3-yl)-urea [126-129], A-867744, 4-(5-(4-chlorophenyl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide [130, 131], and JNJ-1930942, 2-[[4-fluoro-3-(trifluoromethyl)phenyl]amino]-4-(4-pyridinyl)-5-thiazolemethanol, [132], have been developed (Fig. **5**). Below is a discussion of PAMs currently being tested in clinical trials.

AVL-3288 (or CCMI, UCI-4083)

N-(4-chlorophenyl)-α-[[(4-chlorophenyl)amino]methylene]-3-methyl-5-isoxazoleacet-amide (AVL-3288, CCMI, or UCI-4083) (Fig. **5**) is a type I PAM. This is designated as the compound 6 in the literature [133]. AVL-3288 evokes robust, positive modulation of agonist-induced currents at α7 nAChR, while preserving the characteristic rapid desensitization kinetics. In addition, it has little to no efficacy at other ligand-gated ion channels. In rodent models, AVL-3288 promoted improvements in sensory gating and MK-801 evoked hyper-locomotion, as well as enhanced performance in the eight-arm radial maze [133]. A new Phase I study to evaluate the safety and pharmacokinetics of oral doses of AVL-3288 in healthy subjects is underway [134].

JNJ-39393406

JNJ-39393406, another α7 nAChR PAM, has been developed and used in clinical trials. Although the chemical structure of JNJ-39393406 has not been disclosed, it is known that it does not act on α4β2 nAChR, or the 5-HT_3 receptor, nor does it interact with a panel of 62 receptors and enzymes [135], indicating a selectivity for 7 nAChR. JNJ-39393406 was shown to be effective in different animal models of cognition, such as the attentional set-shifting test and novel recognition test. In addition, this compound improved



NS1738

PNU-120596

A-867744

JNJ-1930942

AVL-3288 (CCMI or UCI-4083)

Fig. (5). Chemical structure of α7 nAChR PAMs, including NS1738, PNU-120596, A-867744, JNJ-1930942, and AVL-3288 (CCMI or UCI-4083).

sensory gating deficits in DBA2 mice [135]. Unfortunately, a recent multicenter, double-blind, placebo-controlled, randomized study found that JNJ-39393406 showed no potential to reverse auditory sensory P50 deficits in patients with schizophrenia [135]. This finding led to the discontinuation of the trial. Despite this, a clinical study of JNJ-39393406 will be performed for smoking cessation under the National Institute of Health, USA [136].

FUTURE DIRECTIONS

Cognitive deficits as seen in schizophrenia are frequently severe, leading to decreased functional outcome and quality of life. Although there are potential therapeutic drugs to treat the positive symptoms of schizophrenia, few drugs can effectively restore cognitive functions. Given the key role of α7 nAChR in auditory P50 deficits, as well as cognitive deficits, this receptor is an encouraging therapeutic target for schizophrenia, especially for the hard to treat cognitive disabilities.

A recent study showed that α7 nAChR stimulation is essential for excitation of NMDA receptor-mediated working memory [137], implying that α7 nAChR agonists may ameliorate key deficits in schizophrenia. Also, considering the NMDA receptor hypofunction hypothesis in schizophrenia [138-142], it is likely that stimulation by α7 nAChR agonists and PAMs could confer beneficial effects in patients with schizophrenia.

Accumulating evidence suggests a key role for α7 nAChR in inflammation [143-145], a process implicated in the pathophysiology of a number of neuropsychiatric diseases, including schizophrenia, Alzheimer's disease and major depression [146-153]. Therefore, it is also highly likely that α7 nAChR could represent a therapeutic target for inflammation-related neuropsychiatric diseases.

CONFLICT OF INTEREST

Dr. Kenji Hashimoto holds a patent for the use of tropisetron in neuropsychiatric diseases, including schizophrenia and Alzheimer's disease.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

ACh	=	Acetylcholine
ADAS-cog	=	Alzheimer's Disease Assessment Scale-cognitive subscale
CNS	=	Central nervous system
COGS	=	Consortium on the Genetics of Schizophrenia
DMXB-A	=	3-(2, 4-dimethoxybenzylidene)-anabaseine
5-HT_3	=	5-Hydroxytryptamine-3
LOD	=	Logarithm of odds
MATRICS	=	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MLA	=	Methyllycaconitine
nAChR	=	Nicotinic acetylcholine receptor
NIMH	=	National Institute of Mental Health
NMDA	=	*N*-methyl D-aspartate
PAM	=	Positive allosteric modulator
PCP	=	Phencyclidine
PPI	=	Prepulse inhibition

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