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Review

Targeting the nicotinic alpha7 acetylcholine receptor to enhance cognition in disease

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ABSTRACT

A promising drug target currently under investigation to improve cognitive deficits in neuropsychiatric and neurological disorders is the neuronal nicotinic alpha7 acetylcholine receptor (α7nAChR). Improving cognitive impairments in diseases such as Alzheimer's (AD) and schizophrenia remains a large unmet medical need, and the α7nAChR has many properties that make it an attractive therapeutic target. The α7nAChR is a ligand gated ion channel that has particularly high permeability to Ca^{2+} and is expressed in key brain regions involved in cognitive processes (e.g., hippocampus). The α7nAChRs are localized both pre-synaptically, where they can regulate neurotransmitter release, and post-synaptically where they can activate intracellular signaling cascades and influence downstream processes involved in learning and memory. In particular, activation of the α7nAChR with small molecule agonists enhances long-term potentiation, an *in vitro* model of synaptic plasticity, and improves performance across multiple cognitive domains in rodents, monkeys, and humans. Positive allosteric modulation of the α7nAChR offers an alternate approach to direct agonism that could prove to be particularly beneficial in certain disease populations where smoking nicotine is prevalent (e.g., schizophrenia) and could interfere with an orthosteric agonist approach. The current review focuses on the neurobiology of the α7nAChR, its role in cognition and the development status of some of the most promising molecules advancing for the treatment of cognitive dysfunction in disease.

Contents

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1. Introduction

Cognitive impairments are prevalent in many neurological (e.g., Alzheimer's) and psychiatric (e.g., schizophrenia) diseases, as well as with general aging, and disappointingly there are limited treatment options currently available. Thus, research and development of novel therapies to improve cognitive function continues to warrant investigation and, rightfully so, receives much attention. Cognition itself, is a highly complex CNS function that includes many domains (e.g., memory, attention, executive processes), of which, one or many processes may be compromised in a disease state. The cholinergic system is intimately associated with cognitive function; and, targeted degeneration of these neurons in Alzheimer's disease (AD) underlies the pathology of these patients.

Traditionally, drugs to improve cognition have focused on enhancing cholinergic neurotransmission by inhibiting the hydrolysis of the acetylcholinesterase enzyme (i.e., acetylcholinesterase inhibitors; AChEIs). Acetylcholine (ACh) acts on both nicotinic and muscarinic receptor classes distributed throughout the brain and periphery. More recently, modulating glutamatergic tone with memantine, a drug that antagonize the N-methyl-D-aspartate (NMDA) receptor, has been introduced. Both AChEI and NMDA receptor antagonist approaches are modestly effective at treating memory impairments in Alzheimer's disease (AD), with even more limited success at treating cognitive impairments in schizophrenia (CIAS) and other disorders [1–3]. Thus, the need to improve our fundamental understanding of cognitive processes and to translate those findings into novel therapies remains paramount.

2. Nicotinic acetylcholine receptors (nAChRs)

Nicotine has long been recognized for its ability to improve attention, learning and memory across many species, including rodents, monkeys and humans [4]. Nicotine's actions are mediated through nAChRs located throughout the brain and periphery. In particular, the neuronal nAChR system is responsible for the pro-cognitive properties of nicotine, and has been implicated in diseases in which cognitive deficits are a core feature (e.g., AD, schizophrenia, attention hyperactivity disorder [ADHD]). Moreover, the therapeutic potential of nAChR agonists has been supported by studies in which transdermal administration of nicotine improved attentional performance in patients with the aforementioned diseases/disorders [5]

Nicotinic receptors are members of a superfamily of ligand-gated ion channels that include $GABA_A$, glycine and serotonin-3 ($5\text{-}HT_3$) receptors [6,7]. The nAChRs are pentameric structures comprised of five types of subunits, α (2–10), β (2–4), δ, γ (fetal) and ε (adult) that assemble in a heterologous or homologous manner around a central cationic pore. Orthosteric ligand binding domains are located at the interface of the subunits, and can range from two to five sites depending on the composition of the subunits [8]. In addition, modulation of nAChRs can occur by allosteric binding domains that are distant from the primary active binding sites [9].

The two most predominant nAChRs in the brain are the α4β2 and α7 containing receptors that are classified not only by subunit composition, but also by their binding potency for nicotine or the endogenous ligand, ACh, with the α4β2nAChR having high affinity (nM) and α7nAChR having low affinity for ACh (μM) [10]. Both the α4β2 and the α7 nAChRs have received a great deal of attention as important drug targets for cognitive enhancement each having its own strengths and weaknesses. The focus of this review will be on the investigation of the α7nAChR for cognitive enhancing therapy.

3. α7 Nicotinic acetylcholine receptors (α7nAChRs)

3.1. Structure and localization

The α7nAChR is predominantly considered a homomeric receptor containing five α7 subunits and an equal number of binding sites, with both ACh and choline acting as endogenous ligands for this nAChR subtype. In addition, recent reports have demonstrated that the α7 subunit can co-assemble with the β2 subunit *in vitro*, and evidence of an α7β2nAChR localized on basal forebrain cholinergic neurons has been reported *in vivo* [11,12]. The presence of the heterologous α7β2nAChR in the cholinergic basal forebrain and its sensitivity to beta-amyloid (Aβ) suggest that this nAChR subtype may have relevance to AD in particular.

Localization of the α7nAChR in the rat brain using radiolabeled binding of the selective α7nAChR antagonist, [^{125}I]-α-bugarotoxin (α-BTX), indicates high expression in brain regions recognized as biological substrates for cognitive function, including the hippocampus (CA1, CA3 and dentate gyrus subfields) and cortex (layers I and VI). *In situ* hybridization of mRNA in rat brain has largely paralleled the α7nAChR neuronal expression patterns from the autoradiography studies [6,13–15]. In addition, α7nAChR expression is also present in some subcortical limbic regions and brainstem nuclei (e.g., ventral tegmentum, substantia nigra).

Overall, human α7nAChR localization within the brain is similar to lower species, although some important differences have been reported in brain regions associated with cognition and sensory processing. Whereas little [^{125}I]-αBTX binding has been identified in the thalamic nuclei of the rat, besides lateral and medial geniculate areas, α7nAChRs have been identified in reticular nuclei of the thalamus in cynomolgus macaques [16], and in human brain obtained by postmortem analysis [17,18]. The reticular nucleus of the thalamus receives excitatory input from the cortex and the thalamus, and sends inhibitory projections to dorsal thalamic nuclei [19]. In particular, the reticular nucleus is important in mediating attention and sensory gating, two cognitive processes that are disrupted in schizophrenia, and suggests that the expression of α7nAChRs in this brain region may aid in modulating these processes.

3.2. Neuronal expression and neurotransmission

Neuronal α7nAChRs have been detected at pre-synaptic, post-synaptic and peri-synaptic loci [20], and are implicated in

mediating fast synaptic transmission, neurotransmitter release and synaptic plasticity upon activation. The occurrence of α7nAChRs on presynaptic terminals in brain regions such as the prefrontal cortex [21] and ventral tegmental area [20] suggest that activation of the receptor can directly control excitatory amino acid release independent of membrane depolarization. Data from *in vitro* synaptosome preparations of cortical neurons show that stimulation of the α7nAChR, either with depolarizing current or with the direct agonists (e.g., choline, compound A, AR-R17779) enhances excitatory amino acid release as measured by the glutamate surrogate [^{3}H]-D-aspartate [21–23].

In addition, the presence of α7nAChRs on cholinergic and dopaminergic nerve terminals in the prefrontal cortex [24] suggests that α7nAChR expression is important in mediating additional neurotransmitter systems involved in cognitive function. Consistent with this view, *in vivo* microdialysis studies in rat show acute administration of the α7nAChR agonists, SSR180711 or A-582941 elevates ACh concentration in the prefrontal cortex [25,26]. Similarly, both choline and compound A have been reported to elevate dopamine concentrations in the prefrontal cortex [27], and GTS-21 was shown to significantly increase both dopamine and norepinephrine in the frontoparietal cortex of the rat [28].

3.3. Ca^{2+} permeability

One of the unique characteristics of the ionotropic neuronal α7nAChR is its preference for Ca^{2+} over other cations. This feature is also one of the most interesting with regard to its potential for cognitive enhancement in that Ca^{2+} has well recognized involvement in mediating intracellular signaling cascades and synaptic plasticity [29]. The α7nAChR has a calcium to sodium permeability (P_{Ca}^{2+}:P_{Na}^{+}) ratio of approximately 20 as demonstrated in *Xenopus* oocytes expressing the α7nAChR, which is greater than any of the other nAChRs and the NMDA receptor which shows a P_{Ca}^{2+}:P_{Na}^{+} ratio of approximately 5 [14]. The α7nAChR-mediated Ca^{2+} current is regulated by activation of Ca^{2+}-induced Ca^{2+} release from internal stores, and is different than other nAChRs which are coupled to voltage-operated Ca^{2+} channels [30].

3.4. Synaptic plasticity

α7nAChR expression measured through immunolabeling, [^{125}I]-αBTX binding, and electrophysiology is abundant postsynaptically on GABAergic interneurons in the hippocampus and cortex of both rat and human, where it has been shown to modulate the neuronal circuitry involved in cognitive function by providing inhibitory/disinhibitory tone onto glutamatergic neurons [31–33]. In addition, the high Ca^{2+} permeability of the α7nAChR as well as the localization of these receptors on glutamatergic axon terminals suggest that activating these receptors can lead to enhanced synaptic plasticity [34].

Long term potentiation (LTP), an *in vitro* model of learning and memory [35], is enhanced in the dentate gyrus region of the hippocampus following nicotine administration and this effect is mediated through the α7nAChR in that it can be abolished with the selective α7nAChR antagonist α-methyllycaconitine (MLA) [36]. In addition, selective α7nAChR agonists such as choline, GTS-21/DMBX [37] and SSR180711 [26] amongst others, improve LTP in hippocampal slice preparations from rodent. Moreover, mice that have a genetic deletion of the α7nAChR show deficits in LTP following nicotine administration [36].

3.5. Intracellular signaling

Underlying the enhanced synaptic plasticity observed in hippocampus following nAChR agonist, Bitner et al. [39] have shown that intracellular signaling cascades with recognized importance in mediating cognitive function are triggered following stimulation of the α7nAChR. Using the selective α7nAChR agonist, A-582941, increased extracellular-signal regulated kinase 1/2 (ERK1/2) phosphorylation in the PC12 cell line. In addition, acute administration of A-582941 to mice increased both ERK1/2 and cAMP response element binding (CREB) phosphorylation in cingulate cortex and hippocampus. Both ERK1/2 and CREB are important post-synaptic mediators of synaptic plasticity, and long-term memory processes in multiple species (e.g., *Drosophila*, *Aplysia*, mice), and may underlie the pro-cognitive properties of the α7nAChR selective agonists [39,40].

Following acute administration of A-58291 the neuronal activity marker, c-fos, and the cytoskeletal protein Arc showed a dose-dependent increase in mRNA expression in the medial prefrontal cortex, as well as an increase in the ventral-lateral orbitofrontal cortex. Both findings were identified in juvenile rats, but not in adults and were blocked by the α7nAChR selective antagonist MLA. These data suggest α7nAChR activation leads to increased neuronal activity in brain regions involved in attention and working memory [41].

3.6. Receptor desensitization

The α7nAChR is characterized by its rapid (<100 ms) desensitization following agonist binding [42]. Desensitization renders the receptor temporarily inactive to subsequent agonist activity with recovery rates from desensitization being agonist specific (e.g., choline, acetylcholine) [43]. Although rapid desensitization has been a challenge for studying the α7nAChR involvement in CNS function, it is a sophisticated system that has evolved to control cholinergic signaling, shape synaptic plasticity and possibly prevent excitotoxic cell death mediated through calcium signaling [44]. Identifying molecules that can influence receptor kinetics (activation, recovery rates from inactivation) may therefore be important properties to consider when identifying lead molecules for therapeutic purposes.

A consistent property that has been recognized with the α7nAChR agonists, but also with nicotine and other nAChR subtype agonists, is the presence of U shaped dose response curves following administration [45]. The rapid desensitization of the α7nAChR following agonist administration may underlie the dose limiting loss of effect observed with agonists to this receptor subtype. These effects have been noted and published in electrophysiological, neurochemical and behavioral studies of α7nAChR agonists across species (e.g., [38,46], and have the potential to challenge effective dose selection when entering into a clinical setting.

Whereas activation of the α7nAChR is the predominant hypothesis underlying the cognitive enhancing properties of nicotinic agonists, others have postulated that inactivation of the α7nAChR may be the desired effect for cognitive enhancement [47]. Generally, the α7nAChR antagonists, mecamylamine and MLA are reported to impair cognition (e.g., spatial memory, working memory, long-term memory) across animal models (e.g., water maze, radial arm maze, novel object recognition) and species (e.g., mice, rats, monkeys); however, this provocative hypothesis is based on studies showing that low doses of some nAChR antagonists can have similar effects to agonists (i.e., cognitive enhancement). For example, the α7nAChR antagonist, MLA has been shown to increase LTP in the CA1 region of the hippocampus similar to nicotine [48]. Behaviorally, low doses (μg/kg) of mecamylamine have been shown to improve working memory in a non-human primate model of delayed-match-to-sample, improve spatial navigation in initial trials of a water maze task and a delayed stimulus discrimination task, both in rodents and

monkeys [49]. One potential explanation is that mecamylamine binds to α7nAChRs on GABAergic interneurons in the hippocampus and decreases GABA output, functionally disinhibiting glutamatergic neurons, enhancing excitatory neurotransmission and improving learning and memory. Because of the rapid desensitization properties of the α7nAChR, functional inactivation of these receptors occurs following agonist binding (i.e., similar to low dose antagonist effects), which is proposed to underlie the pro-cognitive effects [47].

4. Targeting the α7nAChR for cognitive enhancement

4.1. Agonists

Development of selective agonists directed to the orthosteric site of the α7nAChR has received a great deal of attention and has resulted in the most advanced drug candidates for this target to date; although positive modulators of the allosteric site have an increasing presence and are discussed more in Section 4.2. Both full (e.g., AR-R17779, SSR180711) and partial (e.g., A-582941, AZD0328) agonists have been investigated with a majority of compounds designed to exhibit partial agonist properties in relation to ACh and/or nicotine. The similarity in sequence homology between the nAChRs and other ligand-gated ion channels such as the 5-HT_3R has proven to be challenging in developing selective α7nAChR agonists, and several α7nAChR agonists also exhibit potent 5-HT_3R antagonist properties (e.g., RG3487, EVP-6124).

4.1.1. Episodic memory

Memory formation that involves recording the contextual details (time, place, emotion) of an event is episodic, and requires the medial temporal lobe of the brain, of which, the hippocampus is an integral structure. Patients in which memory impairments are prominent (e.g., AD) are postulated to benefit from treatments that improve the episodic memory domain. To this end, α7nAChR agonists have consistently enhanced performance in episodic memory tasks preclinically (Table 1). Both object and social recognition models with a temporal deficit provide a reliable method for assessing drug induced cognitive effects in healthy animals. α7nAChR agonist administration either prior to training (e.g., EVP-6124, RG3487), immediately after training (e.g., EVP-6124, RG3487), or prior to testing (e.g., EVP-6124) improves recognition memory. These data suggest that activation of the α7nAChR is involved in acquisition, consolidation and retrieval of the memory. Possibly by enhancing neurotransmission (e.g., glutamate), as well as activating intracellular signaling pathways (ERK1/2), including phosphorylation of transcription factors such as CREB as discussed above (Section 3.5), may contribute to the cognitive enhancing episodic memory effects following α7nAChR activation.

In addition to effects on healthy animals, the full α7nAChR agonist, SEN12333, reversed scopolamine and MK-801 induced cognitive deficits in the object recognition task in rodents suggesting that stimulating the α7nAChR could compensate for deficits in both cholinergic and glutamatergic signaling [51]. Repeated administration of many of the α7nAChR agonists (e.g., RG3487, SSR180711) has demonstrated no loss of efficacy in recognition memory (i.e., no tachyphylaxis), a potentially important attribute for a novel therapeutic agent that would be administered chronically in patients.The improvements in episodic memory by α7nAChR agonists can be blocked with the selective α7nAChR antagonist, MLA, and are absent in α7nAChR knockout mice indicating that the activation of the α7nAChR is critical in mediating the cognitive enhancing effects [38,50,51,52]. Blockade of the pro-cognitive properties of compounds such as RG3487, EVP-6124 and ABBF with α7nAChR antagonists is important as these compounds also act as potent antagonists at the 5-HT_3R. Whereas 5-HT_3R antagonists have shown cognitive enhancing properties in hypo-cholinergic rat models, their pro-cognitive effects have not been demonstrated consistently [53,54].

In AD, the hippocampus is particularly vulnerable to neurodegeneration and memory impairment. Improvements in hippocampally mediated spatial navigation tasks in aged rodents administered α7nAChR agonists (e.g., GTS-21, S24795, RG3487) suggests therapeutic potential in a disease relevant animal model (e.g., AD) [38,55,56]. Similarly, animals with lesions of the nucleus basalis of Meynert (NBM) are used as a model for reduced cholinergic function and memory impairment. Treatment with GTS-21 improved both water maze and inhibitory avoidance behaviors in NBM lesioned animals as compared to vehicle treated control rats [57].

The α7nAChR full agonist SSR180711 was tested extensively for its ability to improve episodic recognition memory following NMDA receptor antagonism, which is used to model aspects of the hypoglutamatergic state in schizophrenia [50]. Acute administration of SSR180711 prior to training improved recognition memory in rat and mouse following a 24 h or 48 h time delay, respectively, an effect that was absent in α7nAChR knockout mice and was blocked in rat by pretreatment with MLA. Following administration of MK-801, SSR180711 reversed both object recognition and spatial working memory deficits by acting at the α7nAChR. In addition, in animals previously administered repeated doses of phencyclidine (PCP) as neonates and tested as adults, or in animals sensitized to PCP as adults and tested following a 10-day washout period, SSR180711 improved recognition memory as compared to the PCP alone groups. These data suggest that α7nAChR agonism may improve cognitive deficits in schizophrenia. Interestingly, using the latent inhibition model, SSR180711 further demonstrated its potential as a cognitive enhancing agent and as an antipsychotic, following treatment of rats with MK-801 or amphetamine [58].

4.1.2. Working memory

Working memory is the ability to hold information temporarily online in order to successfully complete a task, and is one of the most sensitive cognitive functions to decline with aging, stress and disease. Dysfunction of the working memory domain has been described to underlie the cognitive and negative symptoms of schizophrenia, as well as the behavioral disorganization of the disease [59]. Thus, treatments that improve working memory function may have beneficial effects on many facets of a heterogeneous disorder like schizophrenia.

The prefrontal cortex is a primary neural substrate for mediating working memory functions, and the cholinergic and dopaminergic systems have been implicated in shaping this cognitive domain. Evidence of α7nAChR involvement, in particular, has been reported by several labs. Systemic administration of the selective full agonist, AR-R17779 improves working memory performance in rats [60]; conversely, infusion of the α7nAChR antagonist, MLA, into the dorsal or ventral hippocampus impairs working memory performance as assessed in the radial arm maze [61–63] (Table 1). Similarly, α7nAChR KO mice also showed increased latencies to reach an escape platform using spatial cues in a delayed match-to-place water maze paradigm that assesses working and episodic memory [64]. Several pharmacological studies using both young and aged non-human primates have demonstrated working memory improvements following acute administration of α7nAChR agonists (e.g., GTS-21, ABT-107; RG3487) [65–67]. This is important since the prefrontal cortex of the monkey is more phylogenetically similar to the human and performance in tasks mediated by this brain region may better

Table 1
Preclinical cognitive effect of α7nAChR agonists and positive allosteric modulators.

Compound	Agonist/PAM	Cognitive domain	Model	Species/treatment	Result	Reference
A-582941	Agonist	Episodic memory	Social recognition (short delay)	Rat	Improvement	[39]
		Episodic memory	Inhibitory avoidance	Mouse	Improvement	[39]
		Episodic memory	Inhibitory avoidance (short delay)	Spontaneously hypertensive rat	Improvement	[25]
		Working memory	Delayed match to sample	Young and aged NHP	Improvement	[39,144]
		Working memory	Modified Y maze	Mouse/scopolamine deficit	Improvement	[145]
		Sensory gating	Auditory evoked potential	Rat/MLA deficit	Improvement	[39]
		Sensory gating	Auditory evoked potential	DBA/2 mouse	Improvement	[39]
ABBF	Agonist	Episodic memory	Novel object recognition	Mouse	Improvement	[146]
		Episodic memory	Social recognition	Rat	Improvement	[146]
		Working memory	Water maze	Aged rat	Improvement	[146]
ABT-107	Agonist	Episodic memory	Social recognition	Rat	Improvement	[66]
		Episodic memory	Inhibitory avoidance	Mouse	Improvement	[66]
		Working memory	Delayed match to sample	NHP	Improvement	[66]
AR-R17779	Agonist	Episodic memory	Social recognition (24 h delay)	Rat	Improvement	[147]
		Episodic memory	Eyeblink conditioning	Young and aged rabbit	Improvement	[148]
		Working memory	Social recognition (15 min delay)	Rat/scopolamine deficit	Improvement	[147]
		Working memory	Radial arm maze	Rat (normal and fornix lesion)	Improvement	[60]
		Attention	5-Choice serial reaction time	Rat	No effect	[74]
		Attention	5-Choice serial reaction time	Aged rat	No effect	[73]
		Attention	5-Choice serial reaction time	Rat	No effect	[72]
		Sensory gating	Prepulse inhibition of startle	DBA/2 mouse and rat	No effect	[83]
		Sensory gating	Prepulse inhibition of startle	DBA/2 mouse	No effect	[79]
AZD0328	Agonist	Working memory	Novel object recognition (15 min delay)	Mouse	Improvement	[149]
		Working memory	Spatial delayed response	NHP	Improvement	[68]
Compound 23	Agonist	Sensory gating	Auditory evoked potential	Rat/MK801 deficit	Improvement	[150]
Compound 25	Agonist	Working memory	Radial arm maze	Rat/scopolamine deficit	Improvement	[150]
		Sensory gating	Auditory evoked potential	Rat/MK801 deficit	Improvement	[150]
EVP-6124	Agonist	Episodic memory	Novel object recognition (short delay)	Rat/scopolamine deficit	Improvement	[52]
		Episodic memory	Novel object recognition (long delay)	Rat	Improvement	[52]
		Episodic memory	Water maze	Rat	Improvement	[52]
GTS-21	Agonist	Episodic memory	Eyeblink conditioning	Aged rabbit/mecamylamine	Improvement	[151–153]
		Episodic memory	Conditioned avoidance	Aged rat	Improvement	[55]
		Episodic memory	Radial arm maze	Aged rat	Improvement	[55]
		Episodic memory	Water maze	Rat	No effect	[57]
		Episodic memory	Water maze	Rat (NBM lesion)	Improvement	[57]
		Episodic memory	Inhibitory avoidance	Mouse	No effect	[154]
		Episodic memory	Inhibitory avoidance	Rat (NBM lesion)	Improvement	[57]
		Working memory	Lashley maze	Aged rat	Improvement	[55]
		Working memory	Delayed match to sample	Aged NHP	Improvement	[65]
		Working memory	Radial arm maze	Aged rat	Improvement	[55]
		Working memory	Delayed match to sample	Aged NHP/ketamine deficit	Improvement	[47]
		Sensory gating	Prepulse inhibition of startle	DBA/2 mouse and rat	No effect	[83]
		Sensory gating	Prepulse inhibition of startle	DBA/2 mouse	No effect	[79]
		Sensory gating	Auditory evoked potential	DBA/2 mouse	Improvement	[80,155]
		Sensory gating	Auditory evoked potential	DBA/2 mouse/cocaine deficit	Improvement	[156]
		Sensory gating	Auditory evoked potential	Rat/isolation reared	Improvement	[82]
JN403	Agonist	Episodic memory	Social recognition (long delay)	Mouse	Improvement	[157]
		Sensory gating	Auditory evoked potential	DBA/2 mice	Improvement	[157]
PHA543613	Agonist	Episodic memory	Novel object recognition (long delay)	Rat	Improvement	[158]
		Sensory gating	Auditory evoked potential	Rat/amphetamine deficit	Improvement	[158]
PHA568487	Agonist	Sensory gating	Auditory evoked potential	Rat/amphetamine deficit	Improvement	[159]
PHA709829	Agonist	Sensory gating	Auditory evoked potential	Rat/amphetamine deficit	Improvement	[160]
PNU-282987	agonist	Working memory	Modified Y maze	Mouse/scopolamine deficit	Improvement	[145]
		Working memory	Radial arm maze	Rat/frontal cortical infusion	Improvement	[161]
		Sensory gating	Auditory evoked potential	Rat/amphetamine deficit	Improvement	[78,162]
RG3487	Agonist	Episodic memory	Novel object recognition	Rat	Improvement	[38]
		Episodic memory	Morris water maze	Aged rat and mouse	Improvement	[38]
		Attention	Visual signal detection	Rat	Improvement	[71]
		Attention	Object retrieval	NHP	Improvement	[67]
		Working memory	Delayed match to sample	NHP	Improvement	[67]
		Sensory gating	Prepulse inhibition of startle	Rat/apomorphine deficit	Improvement	[38]
		Executive function	Attentional set shifting	Rat/PCP deficit	Improvement	[38]
S 24795	Agonist	Episodic memory	Radial arm maze	Aged mouse	Improvement	[56]
		Episodic memory	Serial discrimination	Aged mouse	Improvement	[163]

Table 1 (*Continued*)

Compound	Agonist/PAM	Cognitive domain	Model	Species/treatment	Result	Reference
		Working memory	Radial arm maze	Aged mouse	Improvement	[56]
SEN12333	Agonist	Episodic memory	Novel object recognition (24 h delay)	Rat	Improvement	[51]
		Episodic memory	Novel object recognition (1–4 h delay)	Rat/scopolamine or MK801 deficit	Improvement	[51]
		Episodic memory	Inhibitory avoidance (24 h delay)	Rat/scopolamine deficit	Improvement	[51]
		Sensory gating	Prepulse inhibition of startle	Rat/apomorphine deficit	Improvement	[51]
SSR180711	Agonist	Episodic memory	Novel object recognition (24–48 h delay)	Rat, mouse	Improvement	[50]
		Episodic memory	Novel object recognition (1 h delay)	Rat/MK801 deficit w/and w/o MLA	Improvement	[50]
		Episodic memory	Novel object recognition (48 h delay)	α7nAChR knockout mouse	No effect	[50]
		Episodic memory	Novel object recognition	Mouse/PCP deficit	Improvement	[164]
		Episodic memory	Latent inhibition	Rat/MK801 or amphetamine deficit	Improvement	[58]
		Episodic memory	Latent inhibiton	Rat/NOS inhibitor as neonates	Improvement	[58]
		Working memory	Water maze	Rat/MK801 deficit	Improvement	[50]
		Working memory	Modified Y maze	Mouse/scopolamine or PCP deficit	Improvement	[145,165]
		Working memory	Linear maze	Rat/PCP deficit	Improvement	[50]
		Attention	Social novelty discrimination	Rat/PCP as neonates	Improvement	[50]
TC-5619	Agonist	Episodic memory	Novel object recognition (0.5–18 h delay)	Rat	Improvement	[166]
		Sensory gating	Prepulse inhibition of startle	Mice	No effect	[166]
		Sensory gating	Prepulse inhibition of startle	WT and th(*tk*-)/th(*tk*-) mice	Improvement	[166]
		Sensory gating	Prepulse inhibition of startle	Rat/apomorphine deficit	Improvement	[166]
A-867744	PAM	Sensory gating	Auditory evoked potential	DBA/2 mouse	Improvement	[167]
Compound A	PAM	Sensory gating	Prepulse inhibition of startle	Rat/isolation rearing	Improvement	[168]
JNJ-1930942	PAM	Sensory gating	Auditory evoked potential	DBA/2 mouse	Improvement	[89]
NS1738	PAM	Episodic memory	Water maze	Rat/scopolamine deficit	Improvement	[91]
		Episodic memory	Social recognition (2 h delay)	Rat	Improvement	[91]
PNU-120596	PAM	Sensory gating	Auditory evoked potential	Rat/amphetamine deficit	Improvement	[87]
SB-206553	PAM	Sensory gating	Prepulse inhibition of startle	Rat/MK801 deficit	Improvement	[90]
XY 4083/Compound 6	PAM	Working memory	Radial arm maze	Rat	Improvement	[88]
	PAM	Sensory gating	Auditory evoked potential	DBA/2 mouse	Improvement	[88]

NHP: non-human primate; MLA: methyllycaconitine; PCP: phencyclidine; NOS: nitric oxide synthase; NBM: nucleus basalis of Meynert.

represent the performance of human behavior. Interestingly, the partial α7nAChR agonist, AZD0328, administered at very low doses (ng/kg) either acutely or chronically improved working memory performance in a non-human primate species that persisted for up to 1 month after treatment [68].

4.1.3. Attention

Attention is mediated by the prefrontal cortex and is one of the most consistently reported cognitive functions assessed when investigating nicotinic systems. As attention underlies many cognitive functions, improvement in this domain could have wide-spread effects in diseases such as schizophrenia and ADHD, in which attentional deficits are prominent, Cholinergic systems are critically involved in the neuronal circuitry mediating attentional processes in the forebrain and lesioning this system results in impaired performance. Moreover, drugs that increase cholinergic neurotransmission or stimulate nAChRs enhance attentional processes. Mice with targeted deletions of the α7nAChR show impaired attentional processing in 5-choice serial reaction time (5-CSRT) and odor span tasks [69]. Moreover, the deficit in the 5-CSRT task in knockout mice was not improved following systemic administration of nicotine underscoring the importance of α7nAChR in attention [70]. However, the effects of α7nAChR agonists on tasks that measure sustained attention have produced mixed results. RG3487 has been reported to improve attentional performance in a visual signal detection model of sustained attention in rat [71], and improves accuracy in the object retrieval attentional model in non-human primates [67]. Interestingly, RG3487 also was reported to improve performance in attentional set shifting model in rat following sub-chronic PCP administration [38]. However, several pharmacological studies using the full agonist AR-R17779 have not improved performance in the 5-choice serial reaction time task [72–74] (Table 1). In addition, systemic administration of MLA had no effect on the nicotine-induced increase in anticipatory responding and decreased reaction time in a sustained attention in rats suggesting that the α7nAChR may not be involved in mediating nicotine's effects in this model [75]. Differences in task demand, pharmacological and neurochemical properties between RG3487 and AR-R17779 may explain the differing results obtained in these attentional tasks.

One consideration in developing potential new therapies for cognitive impairing diseases is to recognize the possible concomitant medications of the target patient population and to model the effects of these combined therapies. For an AD population, background cholinesterase inhibitors are the current standard of care. Since these drugs increase ACh, the endogenous ligand of the α7nAChR, it is possible that interaction of these compounds at the neurochemical level may influence the efficacy necessitating alterations in dose selection. Whereas administration of RG3487 and donepezil at sub-threshold doses produced a significant improvement in accuracy in a non-human primate model of attention, the combination of effective doses of both compounds shifted the dose response curve to the left as compared to RG3487 treatment alone [46]. However, in a separate study, continual infusion of ABT-107 and donepezil at clinically relevant concentrations continued to show improvements in short term memory [66].

4.1.4. Sensory gating

Deficits in sensory gating have been documented extensively in schizophrenia and may represent an endophenotype of the

disease. Sensory gating is a measure of pre-attentive cognitive processes and can be assessed directly by recording electroencephalography responses to auditory evoked potentials (AEP) or behaviorally by startle responses following an auditory cue (pre-pulse inhibition of startle; PPI) [76]. In AEP, a conditioning stimulus precedes a test stimulus and a ratio of test-to-conditioning, which represents the level of gating (e.g., a high ratio means impaired gating), can be calculated. Similarly, in PPI, a weak pre-pulse stimulus precedes a strong startle inducing stimulus, and a ratio of the behavioral responses in both conditions can be assessed.

The α7nAChRs, more so than other cholinergic receptors, are central to the function of auditory sensory gating, in which schizophrenic patients show marked deficits [77]. Activation of α7nAChRs has been shown to increase GABAergic neurotransmission, which is hypothesized to restore sensory gating deficits associated with schizophrenia [78]. In DBA/2 mice, a naturally occurring reduction in α7nAChRs is observed along with deficits in sensorimotor gating, which has made this an appropriate schizophrenia-like model for studying the effects of potential α7nAChR therapies [79]. GTS-21, as well as several other α7nAChR agonists, normalize the sensory gating deficits in DBA/2 mice, an effect that is blocked with the α7nAChR antagonist, α-BTX, but not with the non-selective nAChR antagonist mecamylamine [80] (Table 1). Consistent with these data, administration of α-BTX alone impairs AEPs [81].

Gating responses can be disrupted experimentally by dopaminergic receptor agonists (e.g., apomorphine) and glutamatergic NMDA receptor antagonists (e.g., MK-801) and these methods are used to induce schizophrenia-like symptoms in animals. Typical and atypical antipsychotic drugs (e.g., haloperidol) can reverse these deficits. Similarly, many of the α7nAChR agonists tested (e.g., SEN12333, RG3487, PNU282987, A-582941) can reverse pharmacological induced deficits in AEPs and/or PPI [25,38,51,78]. GTS-21 has shown a mixed effect in that it reversed AEP deficits in DBA/2 mice and in isolation reared rats [80,82], but had no effect in DBA/2 mice or normally reared rats when tested in the PPI model [83]. AR-R17779 also failed to improve auditory gating deficits in PPI [79,83]. Although AEP and PPI share many similar features (e.g., pharmacology, neurobiology) and are both impaired in schizophrenia, a lack of correlation between the two models has been reported and suggests that both models are useful to assess pre-attentive processing [84].

4.2. Positive allosteric modulators

An alternative approach to directly activating the orthosteric α7nAChR site is to design molecules that target and positively modulate the allosteric receptor site. An α7nAChR positive allosteric modulator (PAM) may offer several advantages over the direct agonist approach: (1) activation of the α7nAChR occurs exclusively in the presence of the endogenous agonist, ACh, and is therefore temporally managed (i.e., phasic stimulation); (2) may be less prone to cause prolonged desensitization of the α7nAChR following stimulation, and hence avoid loss of function as may occur with protracted agonist exposure; 3) avoids direct competitive interactions at the orthosteric binding site with nicotine in a smoking population. This latter issue may be of concern for a disease such as schizophrenia wherein over 65% of the population is estimated to smoke [85,86].

PNU-120596 is one of the most extensively characterized PAMs and was the first α7nAChR PAMs to show *in vivo* efficacy in an amphetamine-induced auditory gating deficit paradigm in anesthetized rats [87] (Table 1). However, the significant retardation of the desensitization kinetics by this compound and the potential for excitoxicity through excessive Ca^{2+} entry has limited the advancement of this compound.

The α7nAChR PAM, Compound 6, potentiated α7nAChR agonist signals and preserved the native ion channel kinetics. Compound 6 did not induce toxicity in a SH-α7 cell line, whereas PNU-120596 was toxic, presumably through high intracellular Ca^{2+} levels [88]. In addition, Compound 6 improved sensory gating in DBA/2 mice.

A recently described selective α7nAChR PAM, JNJ-1930942 is reported to potentiate α7nAChR agonist effects as measured in an electrophysiological assessment in the GH4C1 cell lines expressing α7nAChRs. Interestingly, the potentiation by JNJ-1930942 was primarily caused by alteration in the receptor desensitization characteristics, while activation/deactivation kinetics and recovery from desensitization were essentially intact [89]. Moreover, JNJ-1930942 improves sensory gating in the DBA/2 mice that have been described previously to have naturally occurring gating deficits and decreased α7nAChR expression.

In an interesting re-evaluation of the pharmacological properties of SB-206553, which was originally characterized as a serotonin 2B/2C antagonist, it was recently described to also have α7nAChR PAM properties, and reversed MK-801 deficits in the rat PPI model [90].

Most α7nAChR PAMs to date have reported *in vivo* effects on sensory gating models. NS1738, a selective α7nAChR PAM has demonstrated improvements in acquisition of a water maze task in scopolamine treated animals [91]. These data suggest that the PAMs may be useful in conditions of altered cholinergic tone (e.g., AD). NS1738 also improved short term social recognition, a test of episodic memory.

Several groups have α7nAChR PAMs in various stages of preclinical and early clinical development. Xytis, with XY-4083, is the first company reporting a Phase I-ready α7nAChR PAM. As a potential advantage of the PAM approach may be to avoid competitive interaction at the orthosteric site with nicotine in a smoking population, it will be interesting to evaluate whether this benefit exists in human populations with any novel α7nAChR PAM.

5. α7nAChRs in Alzheimer's disease

5.1. Pathology

AD is a devastating neurodegenerative disorder that is defined by a progressive decline in cognitive processes that can include an inability to remember new information, difficulty in completing familiar tasks, impairments in spatial reasoning and general confusion. In addition, patients can suffer from behavioral abnormalities associated with the disease including agitation, aggression and social withdrawal that have an enormous impact on the caregivers of these patients. Pathologically, AD is characterized by the deposition of beta amyloid (Aβ) containing plaques in the brain, neurofibrillary tangles, neuroinflammation and neuronal loss. The prevalence of AD is estimated at 26.6 million in 2006 and is expected to increase to over 100 million by 2050 [92].

Involvement of the α7nAChR in the progression of AD has been suggested, in part, because of its high expression in brain regions that are involved in cognitive processes [93], and are particularly vulnerable in AD pathology (i.e., hippocampus and cortex) [94–97]. Consistent with this idea, significant reductions in α7nAChR protein levels have been observed in postmortem brains of Alzheimer's patients [98,99], and correlations between cognitive decline associated with disease progression and the loss of α7 (and other) nAChRs in the cortex has been reported using ^{11}C-nicotine binding PET imaging in patients diagnosed with probable AD [99]. However, not all studies have reported decreased α7nAChR expression in the brains of AD patients, which may reflect high variability in the receptor expression in these patients [100].

5.2. Neuroprotection

An accumulating body of evidence suggests that α7nAChRs may be involved in the pathogenesis of AD. Some [101,102], but not all [103–105] studies have reported that Aβ peptides bind with high affinity to α7nAChR, [106,107]; exerting an inhibitory effect [103]. Consistent with this hypothesis, knocking out the α7nAChR in a transgenic mouse model of AD conferred a benefit in learning and memory and preserved synaptic integrity compared to transgenic controls [108]. However, activation of the α7nAChR may exhibit beneficial effects in that administration of nicotine and nAChR agonists have shown to be neuroprotective against Aβ peptide-mediated neurotoxicity *in vitro* and *in vivo*. These effects were mediated by α7nAChR activation of the pro-survival pathway (phosphatidylinositol 3-kinase (PI3K)-Akt kinase-Bcl2), as neuroprotection was prevented by selective α7nAChR antagonists and PI3K inhibitors [109–114].

GTS-21 (DMXB) administration to rats for 3 months attenuated the loss of parietal neurons following bilateral NBM lesions providing *in vivo* evidence of neuroprotection by activating the α7nAChR [112]. In addition, 10-day administration of GTS-21 to mice following intracerebrovascular infusion of the toxic Aβ (25–35) peptide reduced cognitive deficits in the water maze test [113]. Similarly, neuroprotective effects of α7nAChR agonists have been identified *in vivo* with SEN12333 [51]. In this study, quisqualate injections into the nucleus basalis of Meynert produced significant cholinergic cell death (74% reduction) as measured by choline acetyltransferace (ChAT) immunoreactivity in this brain region of the rat. Subchronic administration of SEN12333 for 7 days significantly reversed the quisqualate induced cholinergic cell loss.

Recently, Bitner et al. [66] demonstrated disease modifying effects with the selective α7nAChR agonist ABT-107. Continuous infusion of ABT-107 for 10 days in an AD transgenic mouse model (tau/APP transgenic mice) reduced tau hyperphosphorylation immunoreactivity in spinal sections. Previously, this same group had reported activation of α7nAChR modulates glycogen synthase kinase-3-beta through a PI3K-Akt pathway to reduce tau hyperphosphorylation [114].

5.3. Clinical

It is therefore not surprising, given the promising preclinical data, that α7nAChR agonists are currently pursued in double blind placebo controlled clinical studies for the treatment of AD. RG3487 is the most advanced molecule awaiting the announcement of a global multicenter Phase 2b study in 360 mild-moderate AD patients treated for 24-weeks as adjunctive therapy to donepezil (Table 2). RG3487, an α7nAChR agonist with potent 5-HT_3R antagonist properties has previously reported positive signals of cognitive enhancement in an 80 patient mild-moderate monotherapy AD study in the domains of quality of episodic secondary memory, working memory and speed of memory (manuscript under review) using the computerized test battery CDR. Interestingly, the improvements in cognitive signal in the Phase 2a AD study also exhibited an inverted U shaped curve with doses of 5 and 15 mg being more promising than the 50 mg dose group, which coupled with the preclinical NHP data previously reported [46] and led Roche to explore the lower dose range in the Phase 2b study. Results of this study investigating a more advanced AD population (as defined their MMSE entry criteria) in the add-on setting to donepezil treatment have not yet been reported.

EnVivo Pharmaceuticals also have an α7nAChR partial agonist, EVP-6124, which exhibits 5-H T_3R antagonism and α3β4nAChR antagonist activity in clinical development. EVP-6124 is partnered with Mitsubishi Tanabe Pharma Corporation for development and commercialization in Japan and other Asian markets. EVP-6124 has been investigated in two small AD studies of short duration and been reported to exhibit positive signals using a computerized test battery (Cogstate) in a study involving 48 mild-moderate AD patients when added onto donepezil or rivastigmine treatment for 28 days [115]. No data have been released on the monotherapy study. EVP-6124 has a long half-life (approximately 60 h compared to the 7–9 h half-life for RG3487), and it will be interesting to see if this confers a clinical advantage or whether receptor desensitization caused by prolonged agonist exposure may limit the therapeutic benefit. EVP-6124 is currently in a 300 patient Phase 2b study in mild-moderate AD patients for 24 weeks. According the EnVivo Company web site, results of this study are anticipated early 2012.

Abbott, who have a long history of working on this target also have ABT-126 a selective α7nAChR agonist in Phase 2 development for AD. There is limited clinical data available on this drug which is currently in a four arm, 12-week monotherapy study examining 2 doses of ABT-126 against placebo and 10 mg donepezil as a positive comparator. This study is reported as completed in www.clinicaltrials.gov, (December 2010) but no results have been disclosed as of June 2011.

6. α7nAChRs in schizophrenia

6.1. Cognition

Schizophrenia manifests itself with both positive (delusions, hallucinations) and negative (avolition, affective flattening) symptoms, and cognitive impairments. Therapies for treating the positive symptoms of the disease have been in place since the

Table 2
Clinical development status of α7nAChR agonists and positive allosteric modulators.

Compound	Agonist/ PAM	Indications Pursued	Development Phase	Organization	Comment
ABT-126	Agonist	AD, CIAS	II	Abbott	Results anticipated 2011
EVP-6124; MT-4666	Agonist	AD, CIAS	II	En Vivo Pharmaceuticals/Mitsubishi Tanabe Pharma	Positive results reported for schizophrenia AD results anticipated 2012
GTS-21; DMXB	Agonist	AD, CIAS, ADHD	II	CoMentis	Considered a tool compound
RG3487; R3487; MEM3454	Agonist	AD, CIAS	II	Roche/Memory Pharmaceuticals	AD results anticipated 2011 CIAS terminated
TC-5619	Agonist	AD, CIAS, ADHD	II	Targacept	Positive results reported for schizophrenia AD Results anticipated 2011 ADHD terminated
SSR180711	Agonist	AD	II	Sanofi Aventis	Study terminated
AZD0328	Agonist	AD, CIAS	I, II	AstraZeneca	CIAS study terminated
CP-8101243	Agonist	CIAS	I	Pfizer	Development reported terminated
RG4996; R4996; MEM63908	Agonist	AD	I	Roche/Memory Pharmaceuticals	No further development reported
XY-4083	PAM	Cognitive Disorders	I	Xytis Pharmaceuticals	No further development reported

discovery of chlorpromazine close to 60 years ago. Whereas these treatments have evolved into newer generation antipsychotics with fewer side effects, they are not ideal in that they leave many of the core symptoms of schizophrenia untouched.

It has been estimated that between 75% and 90% of schizophrenic patients show deficits in at least one cognitive domain [116]. Moreover, these cognitive deficits can occur earlier than the onset of psychotic symptoms, as well as in the absence of psychotic symptoms. In addition, many first-degree relatives of schizophrenic patients also show patterns of impaired cognition similar to their schizophrenic relatives [117]. Cognitive impairments in schizophrenia (CIAS) affect multiple domains (e.g., attention, problem solving, learning/memory), and are major predictors of functional outcome and continue to be a large unmet medical need. In the early part of the 2000s, the National Institute of Mental Health (NIMH) initiative, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), was designed as a multi-sector collaboration between government-industry-academia to enable the discovery and development of new treatments for CIAS. In particular, the goals of the MATRICS were to establish (1) how to measure cognition in schizophrenia; (2) promising pharmacological approaches; (3) clinical trial design for putative treatments; and, (4) regulatory approval for new drugs for CIAS.

From the MATRICS initiative, three primary drug mechanisms of interest were identified: cholinergic, dopaminergic and glutamatergic. Of the cholinergic approaches, the α7nAChR was identified as a top target of investigation [118], and the Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) initiative investigated lead cognitive enhancing molecules (e.g., GTS-21/DMXB-A) for efficacy in clinical trials up through proof-of-concept in schizophrenic patients.

6.2. Sensory gating

Inability to filter or gate sensory information in schizophrenia may contribute to the widespread cognitive deficits associated with the disease. In particular, impairments in attention are widely reported for patients with schizophrenia. A recent meta-analysis of tobacco smoking in schizophrenia reported over 65% of patients smoke, which is about 5× higher than the general population [85]. One hypothesis is that these patients are attempting to medicate themselves to improve the symptoms associated with the disease. In particular, the hypothesis is supported by studies showing nicotine reversed antipsychotic induced impairments in cognitive performance (i.e., nicotine reduced response time and increased accuracy) in schizophrenic patients [119]; and, a transient improvement in P50 sensory gating following nicotine administration to schizophrenic patients [120].

A significant decrease in the [^{125}I]-α-BTX binding in the hippocampus of schizophrenic patients has been reported postmortem [121]. P50 gating responses are in part mediated by α7nAChRs in the hippocampus [122], thus a decrease in this receptor expression may underlie the P50 gating deficits. As mentioned earlier, the α7nAChR is also a central mediator of sensory gating, and abnormal P50 suppression (a measure of sensory gating) has been linked to genetic markers near the locus (<120 kb) of the α7nAChR subunit gene on chromosome 15q14 [123]; however,lthough this linkage has not been consistently observed [124]. In addition, the occurrence of single nucleotide polymorphisms in *CHRNA7* core promoter has been significantly associated with deficits in P50 suppression in schizophrenics [125]. Administration of non-selective α7nAChR agonists including tropisetron (also a 5-HT$_3$R antagonist) and nicotine reverse the P50 auditory gating deficit observed in patients [126,127].

6.3. Clinical

Administration of the α7nAChR partial agonist, GTS-21, to nonsmoking schizophrenic patients significantly improved cognitive performance in the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) test, and it normalized the P50 auditory evoked potential [128]. However, neither GTS-21 in a small cross over design study, nor RG3487 in a 215 patient double-blind, placebo-controlled adjunctive to antipsychotics study (including smokers), reversed cognitive impairments in schizophrenic patients using the MATRICS scale [129,130] (Table 2). The lead molecule currently in clinical development for CIAS is TC-5619, which was recently announced [131] to have positive results for both negative symptoms and cognition in a 12-week study in both smokers and non-smokers. The negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS) and cognition using the Cogstate schizophrenia battery. Despite these positive findings, AstraZeneca subsequently announced they are declining their option to license TC 5619. EVP-6124 from En Vivo is also in a Phase 2 study in schizophrenia initiated in January 2010 following the positive biomarker data evaluating sensory processing (measuring the evoked responses; P300, P50 and mismatch negativity), and cognitive processing (using Cogstate) in a small 20 patient Phase 1b study. Positive results on the overall cognitive index (Cogstate) have recently been reported with positive trend on the MATRICS for US patients and improvements in negative symptoms and overall clinical function also reported in a press release and the presentation of the data in full is eagerly anticipated. ABT-126 is also in a 210 patient Phase 2 study for CIAS (adjunctive to background antipsychotics), and although MATRICS is the primary outcome measure, Abbott have also included CANTAB for cognitive assessment, as well as scales to assess positive and negative symptoms in the disease. Results are anticipated mid 2011. With the recent announcements by Targacept and EnVivo, α7nAChR agonists may be realizing some of their potential as promising adjunctive treatment paradigms to improve cognitive impairments and negative symptoms in schizophrenia.

7. α7nAChRs in ADHD

Attention deficit hyperactivity disorder (ADHD) is diagnosed by impaired attention, increased impulsivity and hyperactivity [132], associated with cognitive impairments observed in both children and adults. Nicotinic systems have been implicated in ADHD for several reasons: (1) Nicotine improves attention in ADHD adults (as well as smokers and nonsmokers and in animals) [133]: (2) comorbidity of smoking and ADHD is approximately 40% (equivalent to smoking rates in other psychiatric disorders) [134]; (3) ADHD is a major risk factor for early initiation of smoking [135]; (4) maternal smoking increases risk of ADHD [136]. Nicotine may act to improve attention and decrease hyperactivity by increasing prefrontal dopamine concentrations, an effect observed with ADHD therapies (e.g., methylphenidate). Moreover, selective a7nAChR agonists have been shown to elicit dopamine release in the prefrontal cortex and to improve attention [23]. However, no genetic association between the *CHRNA7* microsatellite markers and ADHD have been identified using a linkage disequilibrium method in children [137].

Currently, both GTS-21 and TC-5619 have been tested clinically in adult patients with ADHD in randomized, double-blind, placebo-controlled studies (Table 2). Disappointingly, TC-5619 reportedly did not reach its primary endpoint in this patient population, which was a change from baseline in the Conner's adult ADHD ratings scale. The results from the GTS-21 study have not been reported to date.

8. α7nAChRs in autism

Autism is characterized in the *Diagnostic and Statistical Manual of Mental Disorders* (version IV) by impairments in social interactions, communication deficits and restricted and repetitive behaviors [132]. Cholinergic abnormalities and disruption in cholinergic function is an evolving hypothesis underlying autism spectrum disorders [138,139]. Age-dependent changes in neuronal cell numbers and morphology in the cholinergic nucleus of the diagonal band of Broca of patients diagnosed with autism have been noted. In particular, the neurons are notably abnormally large in children (<13 years old) as compared to controls. With age, these cells become small, pale and decrease in number in adults (>21 years old) [140].α-BTX binding and immunoreactivity studies show no evidence of altered α7nAChR levels in the frontal and parietal cortex of autistic patients [138]; although, α7nAChR binding was significantly increased in the granule cell layer of the cerebellum of autistic patients compared to the control cohort [141].

Alterations in cholinergic signaling and processing may be involved in the pathology and/or symptomatology of autism. A significantly higher concentration of choline was indentified in the prefrontal cortex of patients with Asperger's syndrome that correlated with social impairments as compared to high functioning individuals [142]. In addition, significantly higher ratios of choline to creatine levels have been identified in the left hippocampus-amygdala region and cerebellum of autistic children and this seems to be associated with language impairment as compared to typically developing children.

Dysfunction in inhibitory signaling in autism has been hypothesized to involve the α7nAChR. As mentioned above, sensory gating as regulated by the P50 response is mediated by the α7nAChR. In autistic children, shorter latencies to evoke auditory-induced P50 responses were noted in autistic children although the evoked responses themselves were equivalent in both autistics and the controls. However, in autistic children with learning deficits, impairments in P50 gating responses were identified. Interestingly, when correlating gamma neuronal oscillations, which is a physiological measure indicative of cognitive function, evidence for a disruption in prefrontal cortical function was described. Namely, autistic patients with low IQ showed higher gamma synchronization that was inversely correlated with impaired P50 suppression [143]. Alterations in inhibitory/excitatory neurotransmission may be involved in these dysfunctions. The localization of the α7nAChR on GABAergic interneurons in the hippocampus may be involved. At present, the role of the α7nAChR system in the pathophysiology of autism remains uncertain, but is an area of continued interest [139].

To date, no known clinical trials have been initiated to investigate α7nAChR agonists or PAMs for autism or its associated disorders.

9. Perspectives

Cognitive impairing diseases remain large unmet medical conditions, with conventional therapies (e.g., AChEIs) providing only modest and transient improvements. The investment into discovery and development of novel therapies to treat patients with these disorders clearly is warranted. Selective activation of the α7nAChR presents an exciting opportunity to improve cognition in several disease populations through a unique mechanism of action. Relatively consistent pro-cognitive effects have been reported with α7nAChR agonists across cognitive domains in rodents, non-human primates, healthy volunteers and patients. In addition, evidence of neuroprotective and disease modifying effects following α7nAChR activation make this an important target for an AD population. Furthermore, restricted target distribution primarily in the brain offers the potential of fewer side effects than the existing AChEIs such as donepezil. There are however challenges associated with developing novel therapies directed at the α7nAChR, including effective dose selection considering the widespread "inverted U" shaped dose responses observed preclinically; potential interactions with concomitant medications (e.g., AChEIs, antipsychotics); and, functional consequences of receptor desensitization following chronic use.

It is therefore an exciting time, as several of the most advanced α7nAChR agonists in development are currently in critical proof-of-concept studies for both AD and schizophrenia that will undoubtedly shed light on whether targeting the orthosteric binding site on the receptor will be therapeutically beneficial in these diseases. To that end, following the advancement of the α7nAChR positive allosteric modulators as an alternative approach to directly targeting the α7nAChR will subsequently improve our understanding of the cognitive enhancing potential of this drug target in a clinical setting.

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