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Evaluating the role of the alpha-7 nicotinic acetylcholine receptor in the pathophysiology and treatment of schizophrenia

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Abstract

The group of schizophrenia disorders affects approximately 1% of the population and has both genetic and environmental etiologies. Sufferers report various behavioral abnormalities including hallucinations and delusions (positive symptoms), reduced joy and amotivation (negative symptoms), plus inattention and poor learning (cognitive deficits). Despite the heterogeneous symptoms experienced, most patients smoke. The self-medication hypothesis posits that patients smoke to alleviate symptoms, consistent with evidence for nicotine-induced enhancement of cognition. While nicotine acts on multiple nicotinic acetylcholine receptors (nAChRs), the primary target of research is often the homomeric α7 nAChR. Given genetic linkages between schizophrenia and this receptor, its association with P50 sensory gating deficits, and its reduced expression in post-mortem brains, many have attempted to develop α7 nAChR ligands for treating schizophrenia. Recent evidence that ligands can be orthosteric agonists or positive allosteric modulators (PAMs) has revitalized the hope for treatment discovery. Herein, we present evidence regarding: 1) Pathophysiological alterations of α7 nAChRs that might occur in patients; 2) Mechanistic evidence for the normal action of α7 nAChRs; 3) Preclinical studies using α7 nAChR orthosteric agonists and type I/II PAMs; and 4) Where successful translational testing has occurred for particular compounds, detailing what is still required. We report that the accumulating evidence is positive, but that greater work is required using positron emission tomography to understand current alterations in α7 nAChR expression and their relationship to symptoms. Finally, cross-species behavioral tasks should be used more regularly to determine the predictive efficacy of treatments.

1. Introduction

Schizophrenia was first described in 1896 [1] and labeled as *dementia praecox*. Although cognitive dysfunction was initially the core component, in the 1950s more traditional diagnoses of schizophrenia became based on positive and negative symptoms [2, 3]. Positive symptoms include behaviors not normally present but appear due to the disorder. These symptoms include hallucinations, delusions, and bizarre behavior. Negative symptoms are behaviors that are normally present but are reduced due to the disease process, including alogia, affective flattening, anhedonia, and avolition [4]. More recently, the cognitive

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symptoms of these patients have again been recognized as core to the disorder since they correlate most closely with functional outcome [5, 6]. Currently approved treatments are primarily efficacious at treating positive symptoms and do not adequately improve cognition or negative symptoms in patients [7–10]. Recent focus has been to develop treatments to enhance cognition in patients on the premise that their functional outcome will also be improved.

The lack of approved treatment for cognition in schizophrenia has made developing such treatments more difficult because there are no positive controls with which to compare a test compound [11]. Research has focused therefore, on identifying aspects of schizophrenia that differ from healthy subjects in order to provide targets to develop treatments. Epidemiological evidence consistently report a higher proportion of smoking in patients with schizophrenia (40–90%) compared with the general population (15–25%) [12–14]. Furthermore, patients with schizophrenia also smoke more cigarettes per day. The primary psychoactive ingredient in cigarette smoke is nicotine and patients with schizophrenia also select cigarettes with higher nicotine content and extract more nicotine per cigarette than healthy controls. The increased smoking rate of patients may reflect self-medication [15–18]. Such an hypothesis is supported by evidence that nicotine improves cognitive functioning in patients, as well as healthy subjects. For example, nicotine-induced improvement in vigilance has been observed using the continuous performance test (CPT) in both healthy volunteers [19–21] and patients with schizophrenia [22], which may exert downstream beneficial effects on other cognitive domains [23] (see also a review by [24]). Nicotine may also have neuroprotective effects. For example, in 50,000 Swedish conscripts, smoking rates were inversely correlated with progression to schizophrenia [25], while smoking has also been associated with later onset [26]. An alternative hypothesis is however, that patients smoke to alleviate some of the negative side-effects of their antipsychotic medication. Because patients not taking antipsychotic medications also smoke at high rates however, it is unlikely patients smoke to alleviate medication side-effects [27]. Moreover, high smoking rates occur before a patient's first episode, prior to treatment [28]. One final hypothesis is that there is shared susceptibility toward smoking and the development of schizophrenia, hence its comorbidity [29]. Given the evidence of nicotine-induced improvements in cognition even in non-smoking patients however, the interest in its beneficial qualities remains high. Since the negative effects of nicotine, such as nausea and addiction, make it an undesirable therapeutic [30, 31], focus has been placed on determining the mechanism underlying its beneficial cognitive action.

1.1. Diverse mechanisms of action of nicotine

Nicotine is the prototypical ligand of the nicotinic acetylcholine receptors (nAChRs). nAChRs are ligand-gated ion channels, existing as combinations from a family of similar but distinct subunits α1-α10, β1–4, γ, δ, and ε [32, 33]. The most predominant receptor in the mammalian brain is the α4β2 nAChR, while there is also high expression of the α7 nAChR [34]. Both receptors are widely expressed in areas of the brain important to cognition, such as the hippocampus, thalamus, frontal, cingulate, occipital cortices [35, 36]. Nicotine binds to heteromeric receptors such as the α4β2 nAChR at higher affinities compared with the homomeric receptors such as the α7 nAChR [37]. Studies support that the α4β2 nAChR is required for the initiation of smoking addiction [38], hence treatments targeted at the α7 nAChR receptor would be less likely to be addictive [39, 40]. Adler et al., [41] proposed that the significantly higher levels of smoking seen in patients with schizophrenia may be due to an implicit desire to activate the α7 nAChR. Certainly, reduced α7 nAChR function can increase an animal's work rate to obtain nicotine once preference is acquired [42]. Geerts [43] has suggested however, that smoking levels may not be high enough to affect α7 nAChRs. Certainly, half a cigarette saturates the α4β2 nAChRs [44] and

so it is unclear why patients smoke so much, commonly chain smoking one cigarette after another. Collectively, the evidence supports that the α7 nAChR receptor is likely important for the degree to which patients smoke, particularly given the work of Brunzell and McIntosh, [42] and the evidence of reduced α7 nAChR expression in patients with schizophrenia ([45], also see section 2.). This mini-review will focus on: 1) Pathophysiological alterations of the α7 nAChR that might occur in patients; 2) Mechanistic evidence for the normal action of α7 nAChR effects; 3) Preclinical studies using α7 nAChR orthosteric agonists as well as type I and II PAMs; and 4) Where successful translational testing has occurred for particular compounds and what is still required.

2. Genetic and pathophysiological linkage between the α7 nAChR and schizophrenia

The epidemiological, genetic, and pathophysiological evidence linking schizophrenia to the α7 nAChR is summarized in table 1. Schizophrenia carries a lifetime risk of 1% [46]. In monozygotic twins however, that risk is ~40%, [47, 48], indicative of a strong genetic contribution to schizophrenia. While numerous genetic studies have implicated diverse risk genes for schizophrenia [49], here we will focus on α7 nAChRs. Wallace and Bertrand provide a good schematic describing the genetic linkage of the α7 nAChR and schizophrenia [50]. Genome-wide association studies have associated copy number variations of a locus containing the α7 nAChR with high risk for schizophrenia [51]. Moreover, α7 nAChR mRNA expression may be regulated by neuregulin-1 genetic variation [52], an established genetic risk factor for schizophrenia [53–56]. More directly, Freedman et al., [57] identified a link between deficient gating of the P50 auditory event-related potential and a locus on chromosome 15q14, at a polymorphic marker <120 kb from the α7 nAChR gene with a LOD score of 5.3, $\Theta = 0.039$, which was replicated in later studies [58, 59], although not all [60]. P50 gating refers to a paradigm in which 2 acoustic clicks are presented about 500 msec apart, resulting in a reduced (i.e. gated) P50 response to the second stimulus. Originally conceptualized as a measure of short-term habituation, P50 gating has been shown to be reduced in patients with schizophrenia and is affected by nicotine [61]. In rodents, the hippocampal P20/N40 potential is considered to provide a putative analog of human P50 gating [62]. Accordingly, the gating of the P20/N40 in various mouse strains correlated with their hippocampal α7 nAChR expression [63]. After administration of nicotine or other α7 nAChR agonists the P20/N40 gating of each strain was improved [63–66], providing converging support for the α7 nAChR as a viable therapeutic target in schizophrenia [43, 67, 68].

Further support for specifically targeting the α7 nAChR in treating schizophrenia comes from post-mortem studies examining the brains of patients. Reduced α7 nAChR protein levels have been observed in post-mortem brains of patients with schizophrenia in the dentate gyrus and CA3 region – though not CA1 [69]. Importantly, this reduced α7 nAChR expression has been linked to the degree of global cognitive dysfunction in these patients [69]. In other studies, Marutle et al., [45] observed reduced α7 nAChR binding in the cingulate cortex of patients, but not the orbitofrontal cortex, with no difference in the dorsolateral prefrontal cortex (PFC). Overall therefore, decreased α7 nAChR binding in post-mortem brains of patients have been noted in the reticular nucleus of the thalamus, the hippocampus, the cingulate cortex, and the frontal lobe regions [45, 70–72], although not all studies have replicated these findings [73]. The brains examined in patients are mostly from chronically ill patients whom have undergone chronic antipsychotic treatment, many with multiple concurrent treatments. Thus, the impact of antipsychotic medication or even smoking status on α7 nAChR binding levels cannot always be accounted for. The effect of chronic antipsychotic treatment can be examined at least using rodent studies. Terry et al., [74] demonstrated that 90-day chlorpromazine, risperidone, and olanzapine treatment

significantly reduced α7 nAChR binding levels of rats in the posterior cortex and amygdala, while haloperidol did not affect binding levels. After 180 days, only risperidone treatment still significantly reduced α7 nAChR binding [74]. Furthermore, the negative association between age and α7 nAChR binding levels in the perirhinal cortex of humans [73] supports the need for further examination of α7 nAChR binding levels in patients across ages. These studies demonstrate the need to understand impact of the disease process on α7 nAChR expression that is untainted by treatment, age, or smoking effects.

One mechanism by which α7 nAChR expression could be examined in patients with fewer confounds than examining post-mortem brain tissue would be to use positron emission tomography (PET) or single-photon emission computed tomography (SPECT). The development of novel α7 nAChR ligands suitable for PET imaging will be a key step forward in understanding altered neurochemistry in patients with schizophrenia. With PET or SPECT studies, α7 nAChR levels could be examined in: a) subjects with a high-risk of psychosis; b) first-episode patients; c) never-medicated patients; d) non-smoking patients; e) chronically ill patients on various antipsychotic medications; and f) smoking vs. non-smoking patients. Furthermore, it would be extremely useful to assess the link between current binding levels in patients and their positive and negative symptoms, functional outcome, and cognitive performance specifically in cognitive domains identified by the National Institute of Mental Health funded initiatives Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS; [75, 76]) and Cognitive Neuroscience Treatment to Improve Cognition in Schizophrenia (CNTRICS; [77]). Unfortunately however, to date no PET or SPECT studies have been conducted examining α7 nAChR binding levels in patients. There are numerous complexities when developing PET or SPECT ligands. Toyohara et al., [78] detailed some complexities regarding the development of α7 nAChR radioligands for PET and SPECT imaging. Up until that point, there were limited options because of a scarcity of high-affinity ligands. By 2013, Horti and colleagues [79] described two novel radioligands [(11)C]A-833834 (5-(6-(5-[(11)C]methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-1H-indole) and [(11)C]A-752274 (2-(6-[(11)C]methyl-3,6-diazabicyclo[3.2.0]heptan-3-yl)-7-(6-methyl-3,6-diazabicyclo[3.2.0]heptan-3-yl)-9H-fluoren-9-one), designed to image functioning α7 nAChR levels in the brain. While these molecules may have high-affinity binding, their low blood-brain barrier (BBB) permeability limits their use in humans [79]. Thus, in terms of α7 nAChR expression, post-mortem brain analysis supports reduced expression in key areas related to cognition and symptoms, but these analyses may be confounded by extraneous factors.

When examining nAChR binding levels using [^{3}H]-nicotine and [^{3}H]-epibatidine that target predominantly high-affinity nAChRs, Breese et al., [80] found that smoking up-regulated binding in control subjects, while this increase was not seen in the hippocampus or thalamus of patients. In contrast, another study observed increased [^{3}H]-cytisine and [^{3}H]-epibatidine binding in patients [45], though smoking status was not identified for all subjects. Importantly, SPECT ligands are available for high-affinity nAChRs and commonly used in smoking studies [81, 82]. When high-affinity nAChRs were examined using SPECT imaging with [^{123}I]5-A-85380, decreased availability was observed in 1-week smoking abstinent patients in the frontal and parietal cortices as well as the thalamus in smoking patients compared with controls [83]. Because this study was conducted in living patients, it was established that their current high-affinity nAChR levels correlated inversely with negative symptom severity. These patients were currently being treated with a variety of antipsychotic medications that could impact nAChR expression. Administering a variety of antipsychotic treatments over 180 days to rats did not alter high-affinity nAChR expression however [84]. Although it was not established whether the medication interfered with chronic nicotine-induced up-regulation, these studies provide support that the lower up-

regulation in smoking patients compared with controls is likely a result of changes germane to the disorder itself. The same control studies including patients at different stages of the disease described above for α7 nAChR radioligands would also be required for high-affinity nAChRs however.

2.1. The putative impact of reduced α7 nAChR expression

Recent reviews by Thomsen et al., [68] and Bencherif et al., [85] have identified meaningful connections between areas of α7 nAChR expression, their effect on other neurotransmitters, and how these changes might relate to the dopamine and glutamate hypotheses of schizophrenia. These connections reveal the impact reduced expression of the α7 nAChR might have on mechanisms likely to be important in the manifestation of schizophrenia. Key to these connections is that α7 nAChRs are ideally located to modulate neurotransmitter release in key regions related to the dopamine and glutamate hypotheses. For example, α7 nAChRs are located on midbrain dopamine cell bodies of the ventral tegmental area (VTA), subthalamic nuclei, presynaptically on dopamine terminal regions in the striatum, nucleus accumbens, and frontal cortex, as well as on glutamate and GABA neurons that project into dopamine regions and terminals [86–89]. Activation of α7 nAChRs can increase dopamine release in the striatum, VTA, nucleus accumbens, and PFC areas [90–92]. Evidence for the nAChR selectivity of agonist effects comes from knockout studies whereby α7 nAChR knockout mice do not exhibit choline-induced striatal dopamine release in mice [93]. Specific targeting of presynaptic α7 nAChRs can enhance AMPA-mediated excitatory postsynaptic currents in VTA [94, 95] and PFC [96] dopaminergic neurons, as well as facilitate glutamatergic synaptic currents in hippocampal neurons [97, 98] and pyramidal neurons in the auditory cortex [99]. α7 nAChR activation releases GABA from GABAergic interneurons [100, 101]. GABA acts on GABAB receptors leading to decreased striatal glutamate release, which may in turn result in the increased dopamine release [85]. Using an enzyme-based microelectrode *in vivo*, Kondardsson-Geuken and colleagues [102] demonstrated that the α7 nAChR modulates glutamate release in the PFC of rats. Interestingly, choline-induced stimulation of glutamate release was blocked by both α-bungarotoxin and kynurenine [102], a precursor of kynurenic acid. The importance of kynurenic acid relates to it being: 1) a negative modulator of α7 nAChR function; 2) elevated in patients with schizophrenia [103, 104]; and 3) disruptive to prepulse inhibition (PPI; [105], a measure of sensorimotor gating disrupted in patients with schizophrenia [106–108]) when elevated. *In vitro* stimulation of the septal cholinergic input induces CA1 hippocampal and VTA long term potentiation (LTP) via α7 nAChRs [94, 109], enhancing hippocampal LTP [110]. Moreover, LTP is reduced in mice with no α7 nAChR expression [111] as well as in patients with schizophrenia [112]. Because striatal dopaminergic neurons are involved in LTP, which may underlie aspects of learning [113], α7 nAChR-induced striatal dopamine release and LTP induction may be linked. Thus, α7 nAChRs can stimulate dopamine release and induce LTP. Such mechanisms can be important for ameliorating impaired cognition and behavioral abnormalities in patients with schizophrenia.

One example of the importance of striatal dopamine release is for reward-associative learning. Dopamine plays a key role in the reward-prediction error hypothesis [114–116], firing in response to an unpredicted but not predicted reward [117, 118]. Hence, dopamine strengthens the synaptic connection between reward and action, providing a mechanism for Thorndike's Law of Effect. Patients with schizophrenia exhibit deficits in reward-related learning [119–121], likely associated with reduced brain activation following reward-predicting stimuli as seen in unmedicated patients [122]. Poor reward-related learning in patients may be impacted by lower motivational levels [123], but given the lack of associations with negative symptoms, this deficit is likely specific to reward-associative learning [119, 120, 124]. Interestingly, striatal DRD1 receptors are linked to the direct

pathway that stimulates the thalamus and cortex [125, 126] and is important for the dopamine reward-prediction hypothesis [127]. DRD1 stimulation likely strengthens synaptic connections, promoting LTP [128]. Similarly, DRD1 knockout mice exhibit altered LTP and impaired associative learning [129–131]. In addition to impaired LTP, α7 nAChR knockout mice also exhibit impaired learning from reward-associative cues, from learning complex cognitive tasks such as the 5-choice serial reaction-time task ([132] as well as poor baseline performance), the odor span task [133], and radial arm maze [134] [135] to simple constitutive learning [134]. These mice exhibit normal learning when aversive motivators are used however, such as context fear conditioning or Barnes maze learning [134, 136]. Hence, it has been proposed that the α7 nAChR is key for learning using reward-associative cues [134]. Interestingly, mice with 50% reduced expression of the α7 nAChR exhibit a learning and attentional phenotype between that of knockout and wildtype mice [132, 134]. Given the putatively reduced α7 nAChR expression in patients with schizophrenia, it may be useful to assess the susceptibility of these mice to environmental factors linked with schizophrenia, such as vitamin D deficiency [137, 138] or maternal immune activation during prenatal development [139].

3. Ligands, their targets, and putative effects in preclinical studies

Our knowledge regarding the complexity of the α7 nAChR and its relationship to schizophrenia has increased year after year, consistent with the steady rise in publications on this nAChR, with only 9 in 1996, rising to 45 in 1997, to 268 in 2012 (Figure 1). Knowledge of presynaptic localization of α7 nAChRs have altered viewpoints on doses to be used. For example, presynaptic α7 nAChRs enables low concentrations of a drug to act specifically on this receptor while higher doses may block nAChRs [140, 141]. These findings support the putative U-shaped dose-response function of α7 nAChR treatments and highlight the need to test lower doses. Werkheiser and colleagues [142] discovered that low exposure to the α7 nAChR partial agonist AZD0328 and SSR180711 improved short-term memory (9 minute delay) novel object recognition task (NORT) performance in mice. A molecular mechanism of this effect was proposed whereby low doses of these treatments increased α7 nAChR binding in rats in the frontal cortex and hippocampus, while higher doses decreased binding and did not improve cognition [142]. Thus, dosing may critically relate to the site of action of treatment supporting the assessment of a wide dose range in studies.

The discovery of positive allosteric modulators (PAMs) of α7 nAChR [143] has further opened treatment possibilities [144]. PAMs only function in the presence of the endogenous ligand, preserving the temporal and spatial integrity of neurotransmission. PAMs are also less prone to cause prolonged desensitization of the α7-nAChRs that reduces function, as may occur after chronic administration of orthosteric agonists [145, 146]. In terms of reward-associative learning, this difference could be important given that saliency should only be placed on those stimuli predicting reward, not on any stimuli encountered. Traditional agonists of α7 nAChR act at the extracellular orthosteric binding site located at the interface between two subunits, providing 4 binding sites per receptor. PAMs bind at a different site leading to the potentiation of effects of endogenous ligands. Interestingly, two types of PAM have been discovered that likely have different binding sites (Figure 2). Type I PAMs predominantly affect the peak current response, while type II PAMs increase the duration of the channel opening and are not accompanied by a profound retardation of the kinetics of desensitization [147]. The lack of desensitization in type II PAMs could mediate the lack of repeated treatment-induced up-regulation of α7 nAChRs that is seen in orthosteric modulators and type I PAMs [148]. Type I PAMs have been developed and include CCMI [144], and NS1738 [149]. Type II PAMs include PNU-120596 [150], TQS [147], A-867744 [151], and JNJ-1930942 [152]. Comparing and contrasting the effects of these PAMs by type will be useful for identifying their potential use as treatments by class.

3.1. Orthosteric agonists at the α7 nAChR

Early studies examining the cognitive effects of orthosteric agonists at α7 nAChRs in rat attention measured by the 5-choice serial reaction-time task were not positive [153–155], and could relate to the use of acute dosing or the poor BBB permeability of these compounds [156, 157]. This agonist, AR-R 17779, did improve long-term social recognition in rats at similar doses however [158]. More positive findings came from the partial agonist GTS-21 (DMXBA) which improved P20/N40 auditory gating in mouse strains with poor gating [64] and in isolation-reared rats [159]. More potent full agonist compounds with good BBB permeability have proven more efficacious. For example, the full orthosteric agonist 5-(6-[(3R)-1-azabicyclo[2.2.2]oct-3-yloxy] pyridazin-3-yl)-1H-indole (ABT-107) improved delay-dependent working memory in monkeys and social recognition in rats [160]. Such findings are particularly interesting given that ABT-107 is tolerable and crosses the BBB in healthy humans [161]. Tropisetron is an anti-emetic used during chemotherapy [162] and in addition to being a 5-HT3 antagonist, it is a partial orthosteric agonist at α7 nAChRs. Repeated treatment (14 days) with tropisetron improved NORT performance in mice [163], subjected to the sub-chronic phencyclidine (PCP) induced cognitive deficit model of schizophrenia [164, 165]. Kohnomi and colleagues [166] demonstrated that tropisetron blocked apomorphine-induced disruption of prepulse inhibition of startle (PPI) – a reliable model of antipsychotic efficacy [167]. This effect was blocked by the selective α7 nAChR antagonist methylycaconicitine (MLA), supporting an α7 nAChR not 5-HT_3 receptor mechanism of action. Importantly, tropisetron attenuated apomorphine-induced increase in c-fos positive cells in the VTA, but not the nucleus accumbens or the dorsolateral striatum [166]. These data support α7 nAChR-induced changes that are mediated via the indirect dopamine release in the VTA. Moreover, these data would suggest tropisetron might improve positive and cognitive symptoms of patients with schizophrenia. Another orthosteric partial agonist with 5-HT_3 receptor antagonist affinity is R3487 (otherwise known as MEM3454), which improved sustained attention task performance in female rats, driven primarily by responses to target stimuli [168]. Another full orthosteric agonist is compound A (R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide), the administration of which leads to dopamine release in the PFC [169] and improved non-spatial working memory as measured by the odor span task [170]. TC-5619 is a full orthosteric agonist at α7 nAChR and improved PPI and social approach in the th(tk−)/th(tk −) mouse model of schizophrenia, while improving NORT (24 hour delay) in rats [171]. Moreover, TC-5619 improved apomorphine-induced disruption in PPI, a test for antipsychotic efficacy [108]. These findings support the putative utility of TC-5619 at treating positive, negative, and cognitive symptoms of patients with schizophrenia. Low doses of the orthosteric α7 nAChR agonist AZD0328 increased dopamine release in mice [90] and monkeys [92]. Moreover, low doses of AZD0328 improved delay-dependent working memory in monkeys, delay-dependent memory in mice using the NORT [142], and delayed reinforcement learning in rats [90]. Higher doses tended to disrupt performance however [142], supporting the U-shaped dose response of α7 nAChR treatments. Direct PFC-induced administration of the orthosteric full agonist PNU 282987 improved radial arm maze learning in rats [172]. Systemic administration of PNU 282987 also reversed PCP-induced disruption of NORT in rats [173], although similar doses did not improve attentional functioning in normal or scopolamine-induced inattention in mice, unlike nicotine [174]. The orthosteric partial agonist EVP-6124 [(R)-7-chloro-N-quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide] improved long-term (24 hour) NORT performance, perhaps by potentiating the actions of acetylcholine [175]. Since this effect was blocked by MLA, it was hypothesized that EVP-6124 could improve cognition in patients with memory disorders, such as schizophrenia. Finally, the orthosteric full agonist CP-810123 was noted to have high BBB permeability and bioavailability, and reversed amphetamine-induced disruption in sensory gating as well as scopolamine-induced disruption of 30-min delayed

NORT in rats [176]. Thus, there is increasing preclinical evidence of novel orthosteric ligands that may improve some of the behavioral abnormalities associated with schizophrenia.

3.2. Positive allosteric modulators of the α7 nAChR

α7 nAChR orthosteric agonists and PAMs can exert similar effects, e.g. the orthosteric partial agonist SSR180711 enhanced LTP [177] as did the type II PAM JNJ-1930942 [152]. Direct comparisons between orthosteric agonists (partial or full), type I, or II PAMs have rarely been conducted in preclinical tests. Thomsen and colleagues [148] demonstrated that repeated administration of the full orthosteric agonist A-582941 increased α7 nAChR binding and improved long-term memory (24 hr) for social discrimination in rats, an effect not seen after single administration. Similarly, the α7 nAChR type I PAM AVL-3288 – but not the type II PAM PNU-120596 – improved long-term memory for social discrimination in rats only after a 7-day repeated administration. Such evidence could relate to the α7 nAChR up-regulation that occurs with orthosteric agonists and type I PAMs but not type II PAMs [178]. Other preclinical tests have supported the use of acute dosing of orthosteric agonists (described in 3.1.), type I, and II PAMs. The type I PAM CCMI improved the working memory performance of rats in the radial maze [144]. Another type I PAM, NS 1738, reversed scopolamine-induced deficits in water maze learning and social recognition memory in rats [149]. In another animal model of schizophrenia, kynurenic acid impaired set-shifting deficits in rats which was reversed by systemic or intra-PFC administration of the type I PAM galantamine [179], likely via enhanced PFC glutamate release [102]. Evidence supporting that these effects were α7 nAChR PAM-related and not from the acetylcholinesterase inhibition action of galantamine came from a lack of donepizil-induced (another acetylcholinesterase inhibitor) reversal of the same deficits [180]. In contrast, the type II PAM PNU-120596 improved long-term (48 hour) object recognition memory in rats only when co-administered with the acetylcholinesterase inhibitor donepezil, an affect blocked by the α7 nAChR antagonist MLA [181]. PNU-120596 also only improved water maze learning in age-induced cognitively impaired rats and delayed-matched to sample in monkeys over longer delays when co-administered with donepezil [181]. PNU-120596 treatment alone was successful in an animal model of schizophrenia, reversing the effects of PCP-induced set-shifting and NORT deficits of rats [182]. The mechanism underlying this acute type II PAM effect is unclear and while improvements have been observed in manipulation-induced deficits, donepezil improved performance alone in the same rats. Another type II PAM JNJ-1930942, improved P20/N40 sensory gating measured in DBA/2 mice, an effect blocked by α-bungarotoxin [152]. These type II PAMs therefore require further investigation and clinical trials (see 3.3 and table 2).

In summary, α7 nAChR treatments have come a long way from their early development, with numerous groups and companies involved in developing novel α7 nAChR agonists. The focus on good BBB permeability has enhanced treatments available with which to test hypotheses and potential clinical efficacy. The focus on ensuring safety and tolerability has likewise improved the likelihood of testing the translational validity of early preclinical findings. Making these treatments available for independent testing in other domains would greatly improve the likelihood of identifying specific cognitive and behavioral domains that are relevant for testing in the clinic.

3.3. Translating preclinical evidence to clinical studies

The partial orthosteric agonist GTS-21 (DMXB-A) is probably the most widely tested α7 nAChR compound in patients with schizophrenia. To date, DMXB-A has had mixed results clinically. In a proof-of-concept study, Olincy et al., [183] reported that DMXB-A led to improvements in neurocognitive functioning and gating of P50 auditory evoked potentials in

patients [183], which was consistent with improved P20/N40 in mice. In a larger double-blind follow-up study however, Freedman and colleagues [184] did not see the same cognitive enhancement from DMXB-A in patients as measured by the MATRICS Consensus Cognitive Battery in a crossover trial design. There were significant improvements at the higher dose on the Scale for the Assessment of Negative Symptoms (SANS), however [184]. Other small-scale fMRI studies (n=16) demonstrated that DMXB-A could improve the default network during a smooth pursuit eye-tracking task, which may be more prominent in people with a common vs. minor allele of the single nucleotide polymorphism (SNP), rs3087454 A/C [185]. Future studies will likely examine the impact this SNP has had on data collected to date. This SNP could also underlie the reason why in one study DMXB-A improved cognition, but in the larger sample at a higher dose it improved negative symptoms. Without further analyses however, these possibilities remain speculative.

Interestingly, and consistent with DMXB-A, the partial agonist TC-5619 developed by Targacept also improved negative symptoms as measured by the SANS in patients with schizophrenia (n=185) [186]. TC-5619 also improved maze learning of the CogState battery in a Phase II trial of patients with schizophrenia, possibly potentiated in smokers [186]. Given the success of TC-5619 in a model of positive symptoms [171], it is unfortunate that TC-5619 was only tested in combination with risperidone or quetiapine (chosen due to their common use in treating schizophrenia). Social cognition and memory data in humans were not presented in the Phase II trial [186]. Conducting such studies would have been useful for comparative purposes. In an 8-week double-blind study, the partial agonist tropisetron improved P50 gating and sustained attention of non-smoking patients with schizophrenia when tested in the Cambridge Neuropsychological Test Automated Battery (CANTAB) but did not affect positive or negative symptoms [187]. In a 10-day double-blind trial in nonsmoking patients with schizophrenia, tropisetron did improve immediate and delayed memory, as well as P50 gating in patients [188]. In a more recent 8-week double-blind trial as an add-on to risperidone treatment, tropisetron improved negative, but not positive, symptoms in patients with schizophrenia [189]. These data in part validate some of the preclinical evidence suggesting pro-memory efficacy of tropisetron, but not evidence for antipsychotic efficacy [166]. Studies specifically assessing negative symptom efficacy in animals, NORT-like memory in humans, and generating evidence for tropisetron-induced amelioration of positive symptoms, would provide greater support for cross-species translational validity of tropisetron trials. This latter inconsistency may be in part because as with the TC-5619 study, the patients were already receiving the atypical antipsychotic risperidone however [187]. In an as-yet not peer-reviewed published study, Envivo note that their α7 nAChR orthosteric partial agonist EVP-6124, when tested as an add-on to atypical antipsychotics in 319 patients, improved cognition and negative symptoms of patients with schizophrenia or schizoaffective disorder in a phase II trial as measured by Cogstate examination [190]. Once published, it will be interesting to see if the cognitive improvement is seen in visual memory, as was presented in preclinical studies [175]. Recently, the translational efficacy of JNJ-1930942 was assessed for improving sensory gating in patients as was discovered in DBA/2 mice [152]. Winterer et al., [191] examined whether acute doses of JNJ-1930942 would improve various markers of sensory gating in patients with schizophrenia in a within-subjects design (P50, P300, and mismatch negativity). No positive effect of JNJ-1930942 on any measure was observed however [191]. This lack of effect could relate to the use of patients that smoke as opposed to non-smokers. Given that in some preclinical studies the type II PAM PNU-120596 only improved performance in rodents when co-administered donepezil, further studies should examine the effects of co-treatment with donepezil. Alternatively, because the patients tested were being treated with a variety of antipsychotic treatments, preclinical studies should also be conducted in combination

with antipsychotic treatment [11, 192, 193]. Finally, variations in the aforementioned SNP could preclude any positive effect of JNJ-1930942 in some of the patients.

Several α7 nAChR treatments (the partial and full orthosteric agonists DMXBA and TC-5619 respectively) have now demonstrated reductions in negative symptoms after chronic treatment in separate studies. Unfortunately, few preclinical studies have examined aspects of α7 nAChR contribution to behaviors relevant to negative symptoms. Conceivably however, these findings could relate to the putative action of the α7 nAChR on reward-associative learning, whereby activating the receptor has enhanced general reward-associations, perhaps via its indirect dopamine release and subsequent D1 activation in the striatum [194, 195]. Future studies would benefit from testing the effects of α7 nAChR treatments on reward-associative learning in cross-species tests, such as those described by CNTRICS [196]. Examining the correlation between any changes in reward-associative learning performances observed and negative symptoms would also be very useful. The evidence of preclinical to clinical testing effects for putative treatment compounds is summarized in table 2.

4. Conclusions and recommendations for future directions

The studies presented here are an overview of attempts to develop selective α7 nAChR treatments for the behavioral abnormalities seen in patients with schizophrenia. While many of these studies have been discussed elsewhere (in particular, see Geerts or Thomsen and colleagues [43, 68] for useful tables), this review has attempted to bring together: 1) Pathophysiological alterations that might occur in patients; 2) Mechanistic evidence for the normal action of α7 nAChR effects; 3) Preclinical studies using α7 nAChR orthosteric agonists as well as type I and II PAMs; and 4) Where successful translational testing has occurred for particular compounds and what is still required. It is clear that further assessments differentiating the role of partial and full agonists vs. type I or II PAMs are required in tests with translational validity for those used in humans. Presynaptic localization of α7 nAChR also supports assessing a wide dose range of α7 nAChR and may explain U-shaped dose responses observed in orthosteric agonist studies (see section 3.1). Wide dose response ranges may be needed given that higher doses of orthosteric agonists can be deleterious to rodent performance. These deleterious effects could result in adherence issues in clinical trials, although it is unclear whether chronic treatment – as will be used in clinical trials - will have the same deleterious effects. Chronic treatment results in receptor up-regulation, which may also underlie some of the beneficial effects of orthosteric agonists. Using PET or SPECT to determine α7 nAChR expression in patients in various states (see above) will also be critical given the putative importance of treatment-induced receptor up-regulation as well as the modeling of symptom domains relevant to schizophrenia. Moreover, demonstrating an α7 nAChR agonist-induced dopamine release in humans as is seen in rodents could be a vital biomarker for proof of consistency of action across species. Importantly, other nAChRs can increase dopamine release in the VTA, e.g. via α6β2 nAChR activation [197]. Nicotinic treatments may also need to be tested as more than simple add-ons to antipsychotic treatment to improve cognition alone, but possibly also as augmentation treatments to cognitive training therapies [198, 199]. In fact, given the putative role of the α7 nAChR in reward-associative learning and the use of positive feedback during such cognitive training, treatments targeted at this receptor may be ideal for augmenting cognitive training [192]

It has been previously suggested that there is a translational disconnect from preclinical to clinical studies, whereby the primary effect of α7 nAChR treatments is to improve attention in rodents, an effect not seen in humans [68]. The majority of studies leading to this critique however, are NORT or P20/N40 studies. Few claim NORT measures attention however,

more likely aspects of short-term memory [200], while the P20/N40 is an analog of the P50 measure of sensory gating and is also not claimed to assess attention (see section 2.0). In fact, several positive preclinical P20/N40 effects of α7 nAChR agonists have often been replicated in human P50 studies (see section 3.3). As described above, for cognitive domains it is rare that clinical tests examine the same domain as have been tested in preclinical models. Tasks are being developed however, to assess similar cognitive domains such as attention in preclinical models as well as in man. For example, the development of cross-species tests of attention such as the mouse/rat/human sustained attention task and 5 choice continuous performance tests will provide a greater opportunity to test the translational validity such treatments. To date, α7 nAChR agonists have exhibited limited efficacy in either task [174], except the partial orthosteric agonist and $5HT_3$ antagonist R3487 [168]. Using such cross-species tests for cognition, and developing models for negative symptoms, may improve the translational capacity of treatment development.

Finally, it is important to note that our interest in nAChR stems from initial epidemiological studies demonstrating the preference of patients with schizophrenia to smoke at higher rates than the general population, followed by observations that smokers outperformed non-smokers in cognitive tasks. Experimental studies demonstrating that nicotine can improve attention/cognition in healthy subjects and patients with schizophrenia support the premise that the mechanism by which a treatment works remains intact in patients with schizophrenia. Hence, treatments aimed at nAChRs remain a viable target for development.

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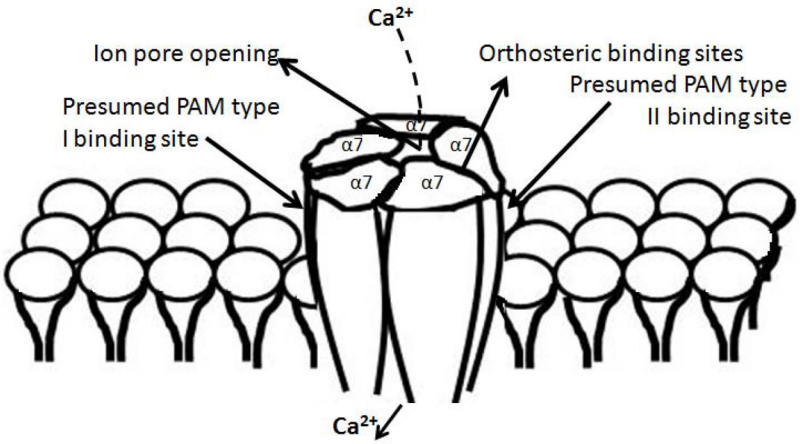

Figure 1. Graphical representation of year-by-year publications involving the α7 nAChR when searched on Pubmed using the terms "alpha7 AND nicotinic"

From few publications early on, maintaining between 0–10 until 1996, there has been a steady increase in publications citing the α7 nAChR. The figures for 2013 are only recorded as far as June 25th, 2013.

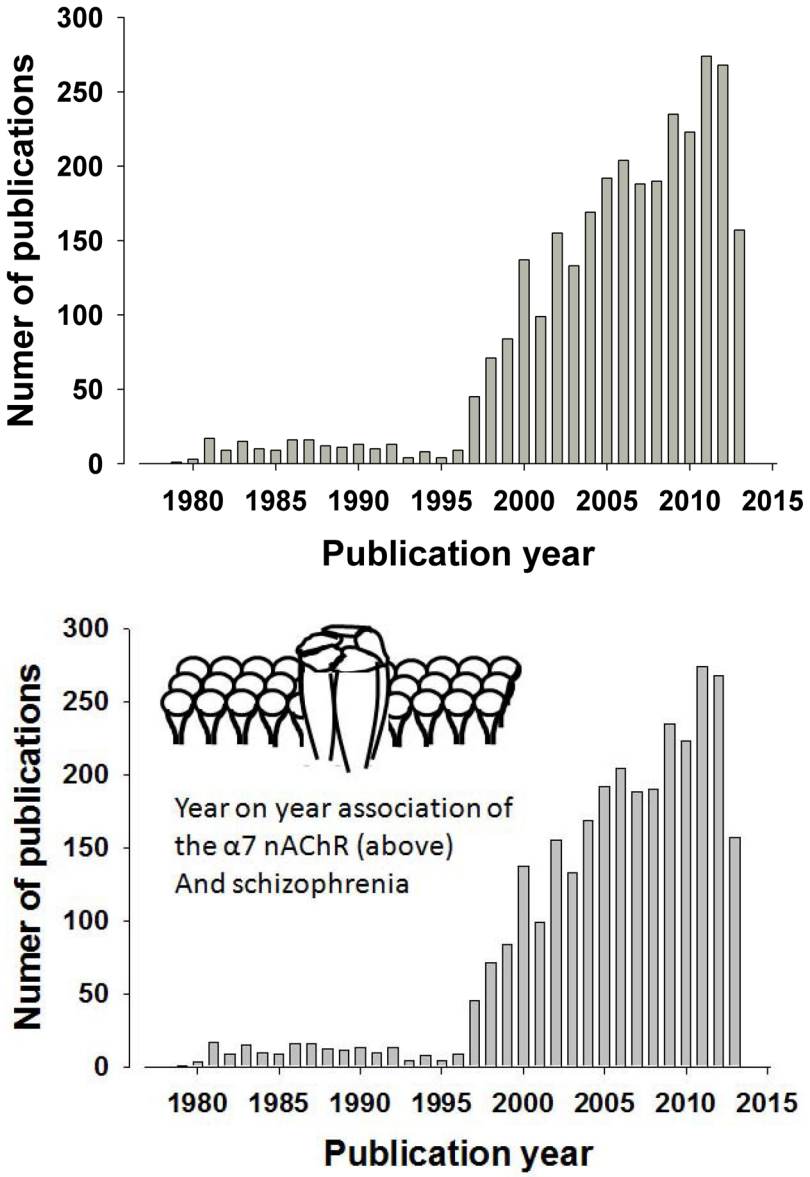

Figure 2. Schematic representation of the α7 nAChR and its associated binding sites

The homomeric α7 nAChR consists of 5 transmembrane spanning α7 subunits. The conjunction of each subunit is a potential binding site (4 in total) for orthosteric agonists, which includes the natural ligands acetylcholine and choline. When the ion channel is opened by an agonist, calcium (Ca^{2+}) can enter the cell (see [68] for further downstream effects). The discovery of type I and II positive allosteric modulators (PAMs) has led to the hypothesis that they bind at different sites since they potentiate or prolong the effects of natural ligands (respectively).

Table 1

Pathophysiological linkage between the α7 nAChR and schizophrenia

Linkage type	Evidence	References
Genetic	P50 deficit linked to chromosome 15q14	[56]
	Genome wide association studies	[50]
Post-Mortem	Reduced binding in dentate gyrus and CA3 region	[69]
	Reduced binding in the cingulate cortex	[46]
	Frontal lobe regions	[70–72]
Epidemiology	High nicotine-seeking behavior	[15–18]
Treatment	Nicotine improves symptoms including cognitive functioning	[19–22]

Table 2

Preclinical to clinical development of α7 nAChR treatments to date

Compound	Preclinical findings	Clinical findings & Comments	Reference
Partial Orthosteric agonists			
DMXBA (GTS-21)	Acutely improved P20/N40 gating in mice and isolation-reared rats	Chronic treatment Improved P50 gating In large sample no cognitive but some negative symptom improvements, effects may be allelic influenced	[64, 154, 183–185]
AZD0328	Improved NORT in mice (9 min delay)	Not yet tested clinically	[162]
SSR180711	Improved NORT in mice (9 min delay)	Not yet tested clinically	[162]
Tropisetron	Repeated dosing improved NORT (24 hr) in normal and PCP-treated mice. Blocked apomorphine-induced PPI deficits	Chronic treatment improved P50 gating, sustained attention, and negative symptoms Did not improve short-term memory	[163–166 and 186–188]
R3487	Improved sustained attention	Not yet tested clinically	[168]
Full Orthosteric agonists			
ABT-107	Improved delay-dependent and social recognition memory	BBB-penetrant in humans, other effects not yet tested	[160 and 161]
AR-R 17779	No effect on sustained attention, improved social recognition (24 hr)	Unsuitable kinetic profile for humans	[153–155, 158]
Compound A	Improved non-spatial working memory span	Not yet tested clinically	[170]
TC-5619	Improved PPI and social approach in th(tk−)/th(tk−) mouse model Improved NORT (24 hour) in rats Blocked apomorphine-induced PPI deficits	Improved maze learning and negative symptoms clinically No change in positive symptoms reported; may be influenced by co- treatment with antipsychotics	[108, 170, 185]
AZD0328	Acutely improved delay-dependent memory in monkeys and NORT (15 min) in mice, improved delayed learning in rats	Disruptive at higher doses in animals Not yet tested clinically	[90 and 142]
PNU 282987	Improved radial arm maze learning in rats Reversed PCP-induced deficits of NORT Did not prevent normal or scopolamine- induced deficits in attention/ vigilance	Unsuitable kinetic profile for humans	[172–174]
A-582941	Repeated treatment improved social discrimination (24 hr) in rats	Effects in animals not seen after single administration, not tested clinically	[148]
Type I Positive Allosteric Modulators			
AVL-3288	Repeated treatment improved social discrimination (24 hr) in rats	Effects in animals not seen after single administration, not tested clinically	[148]
CCMI	Improved working memory span in rats using the radial arm maze	Not yet tested clinically	[144]
NS 1738	Reversed scopolamine-induced water- maze learning and social recognition memory	Not yet tested clinically	[149]
Type II Positive Allosteric Modulators			
PNU-120596	Acute nor chronic treatment affected social discrimination (24 hr) in rats Blocked NORT (24 hr), and age-induced water maze learning deficits Reversed PCP-induced NORT (1 min) and set-shifting deficits	Baseline improvement in rodents only seen with donepezil co-administration Not yet tested clinically	[148, 181, and 182]
JNJ-1930942	Acutely improved P20/N40 sensory gating in mice	Did not improve any clinical sensory gating using acute doses	[152 and 191]

NORT=novel object recognition task; PPI=prepulse inhibition; PCP=phencyclidine