Nicotinic Acetylcholine Receptors Are Potential Therapeutic Targets of Schizophrenia

Kechun Yang
Department of Neuroscience, Perelman School of Medicine, University of Pennsylvania, 3620 Hamilton Walk, Philadelphia, PA 19104, USA
Email: yangkch2000@gmail.com

Abstract
Schizophrenia is a chronic, severe, and disabling mental illness affecting approximately 2.5 million Americans. Despite enormous efforts made by scientists, the precise etiology of schizophrenia remains largely unknown to date. Interestingly, many lines of evidence over many years have revealed a high prevalence of smoking in patients with psychiatric illnesses, especially schizophrenia. Preclinical and clinical studies indicate that both α7- nicotinic acetylcholine receptors (α7-nAChRs) and β2*-nAChRs play a role in the pathogenesis of schizophrenia. This review emphasizes–evidence of linkage between nAChRs and schizophrenia and potential therapeutic applications of α7-nAChR agonists and β2*-nAChR agonists in the treatment of schizophrenia.

Keywords: α7-nAChRs, β2*-nAChRs, schizophrenia, smoking

Introduction

Schizophrenia was first described as "dementia praecox", which is an adolescent form of schizophrenia characterized by rapid cognitive disintegration, by German psychiatrist Emil Kraepelin in 1887. Then, "dementia praecox" was renamed by Eugen Bleuler, a Swiss psychiatrist, as schizophrenia in 1911. It has been well accepted that schizophrenia is a chronic, devastating mental disorder with a constellation of symptoms including positive (exaggerations of normal thinking and behavior patterns, i.e. delusions, hallucinations, and thought disorder), negative (absence of normal traits/abilities, i.e. apathy, anhedonia, and social withdrawal), and cognitive (memory problems, difficulties with attention and executive function) symptoms (Wishka et al., 2006; Yang et al., 2007; Hauser et al., 2009; Chapleau et al., 2013; Citrome, 2014). Accumulating evidence from pharmacological, biological, and neuroimaging studies have helped form several theories emphasizing that dysregulation of brain neurotransmitter function, in particular, aberrant dopaminergic, serotoninergic, glutamatergic, and noradrenergic systems, may be involved (Yamamoto and Hornykiewicz, 2004; Meltzer and Massey, 2011; Gross et al., 2012; Meltzer et al., 2012; Miyake et al., 2012; Miyamoto et al., 2012; Palaniyappan et al., 2012). Although, the exact etiology underlying schizophrenia is unanswered, several clues, based on early pharmacological interventions, became the basis for our current understanding. The development of antipsychotic drugs for the treatment of schizophrenia began in the latter part of the 19th century (Shen, 1999) and history has demonstrated that it is a challenge for researchers to develop effective drugs for the chronic psychiatric disorders due to the complexity of interactions among neurotransmitters and normal brain function. To date, there are mainly two types of antipsychotic medications. Most of the 1st –generation or (typical) antipsychotics, which were developed in the 1950s, are dopamine D2 receptor antagonists, e.g. chlorpromazine, fluphenazine, haloperidol, and thioridazine. The 2nd –generation or (atypical) antipsychotics, which were first emerged in the 1980s, are antagonism of D2 receptors and serotonin type 2A receptors, e.g. clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, asenapine,

iloperidone, paliperiodine, and lurasidone. (Schultz et al., 2007; Balaraman and Gandhi, 2010; Rado and Janicak, 2010; Miyake et al., 2012; Miyamoto et al., 2012). Unfortunately, the available antipsychotics for the treatment of schizophrenia are often more effective for the positive symptoms and exert little beneficial action on the negative symptoms and the cognitive deficits. In addition, it has been widely observed that long-term administration of these antipsychotics can lead to debilitating extrapyramidal symptoms (e.g. akinesia, akathisia, and other movement disorders), increased risk of cardiovascular disease, and other adverse effects (Drici and Priori, 2007; Li et al., 2011; Gopal et al., 2013; Hill et al., 2013).

Neuronal nicotinic acetylcholine receptors (nAChRs) belong to the superfamily of ligand-gated ion channels. A wide variety of subtypes (α2-α7 and β2-β4) of nAChRs have been identified in the central nervous system. nAChRs have varied roles in modulating a wide range of brain functions via various nAChRs expressed presynapticaly , postsynaptically, and extrasynaptically in the brain (Dani and Bertrand, 2007; Yang et al., 2009b). Both α7- and β2*-nAChRs are widely expressed in the throughout the brain and are especially prevalent in the mesocorticolimbic dopamine pathway, the medial habenula, the interpeduncular nucleus, and the hippocampus, and have critical physiological roles in regulating neuronal signaling, nicotine and ethanol addiction, learning and memory, and some cognitive behavioral actions (Song et al., 2005; Lopez-Hernandez et al., 2009; Rollema et al., 2009; Yang et al., 2009a; Gao et al., 2010; Gu and Yakel, 2011; Jin et al., 2011; Yang et al., 2011; Hendrickson et al., 2013). Functional changes in nAChRs have been implicated in various dysfunction including addiction and schizophrenia (Dani and Bertrand, 2007). For example, recent studies have shown that nAChRs, in particular homomeric α7-nAChRs (Fig 1A), could be a potential drug target for schizophrenia especially for the treatment of impaired cognitive function (Wishka et al., 2006; Hauser et al., 2009; Hajos and Rogers, 2010; Toyohara and Hashimoto, 2010; Buchanan and Schwarcz, 2011; Ishikawa and Hashimoto, 2011; Tregellas et al., 2011; Zhang et al., 2012a; Wallace and Bertrand, 2013). However, new evidence also indicates that β2*-nAChRs (* indicates other nAChR subunits may be present in the receptor, e.g. heteromeric α4β2-nAChRs shown in figure 1B are formed by α4 and β2 subunits) might play an important role in mediating negative symptoms of schizophrenia (D'Souza et al., 2012).. The present review focuses primarily on the recent advances in our understanding of the potential therapeutic roles for nAChRs as a drug target in future clinical treatment of schizophrenia.

High smoking rates in schizophrenic patients

Epidemiological studies conducted in different countries demonstrated that smoking occurs at much higher rates among schizophrenic patients when compared with the normal population(Kelly, 2000; de Leon and Diaz, 2005; Zhang et al., 2012b; Jiang et al., 2013) and patients with other severe psychiatric illnesses (e.g., mania, organic mental disorders, mood disorders, major depressive disorder, and anxiety disorder) (Hughes et al., 1986; A et al., 2003; de Leon and Diaz, 2005). Furthermore, smokers with schizophrenia smoked more cigarettes and had relatively lower smoking cessation rates when compared with smokers in the control population (Kelly, 2000; Zhang et al., 2012b). To date, it is still unclear why there is such a high smoking prevalence rate in people with schizophrenia. Multiple lines of evidence demonstrated that tobacco consumption might alleviate some schizophrenia symptoms. Most of these studies have shown that smoking significantly improves negative symptoms (Smith et al., 2002; Zhang et al., 2007; Olincy and Freedman, 2012; Jiang et al., 2013) but only has minor or no effect on positive symptoms, anxiety, and depression (Smith et al., 2002; Barnes et al., 2006). The possible mechanisms are thought to be due to the activation of nAChRs by nicotine, which results in increasing

brain dopamine (DA) levels plus partially restoring abnormality in the P50 sensory gating in schizophrenics (Sanchez-Morla et al., 2008). Accumulating evidence indicates that patients with schizophrenia often have deficit in P50 sensory gating, which can be measured by recording event-related potentials induced by paired auditory stimuli with various intervals (e.g. 0.5, 1.0, or 2.0 sec) between the unconditioned (1st) stimulus and the conditioned (2nd) stimulus. The positive electroencephalographic P50 waveform can be recorded 50 ms right after an auditory stimulus (Fig. 2). When paired auditory stimuli with a 0.5 sec interstimulus interval are applied, the conditioned response (Fig. 2A Red) is greatly smaller than the unconditioned response (Fig. 2A Black) in healthy controls, which means the P50 response is dramatically suppressed by the unconditioned stimulus. Whereas patients with schizophrenia (Fig. 2B) show significantly less P50 suppression than healthy subjects do under the same experimental conditions (Fig. 2A) suggesting that the brains of schizophrenic patients have impaired ability to filter out unnecessary sensory information (Sanchez-Morla et al., 2008; Daskalakis and George, 2009). Thus, the P50 sensory gating deficit is a sensitive neurobiological marker observed in schizophrenic patients (Sanchez-Morla et al., 2008). In fact a number of psychopharmacological and genetic studies demonstrate that a decrease in α7-nAChR function or even a −2 bp deletion in the nAChR α7 subunit gene may increase risk factor for developing the P50 sensory gating deficit (Raux et al., 2002; Toyohara and Hashimoto, 2010).

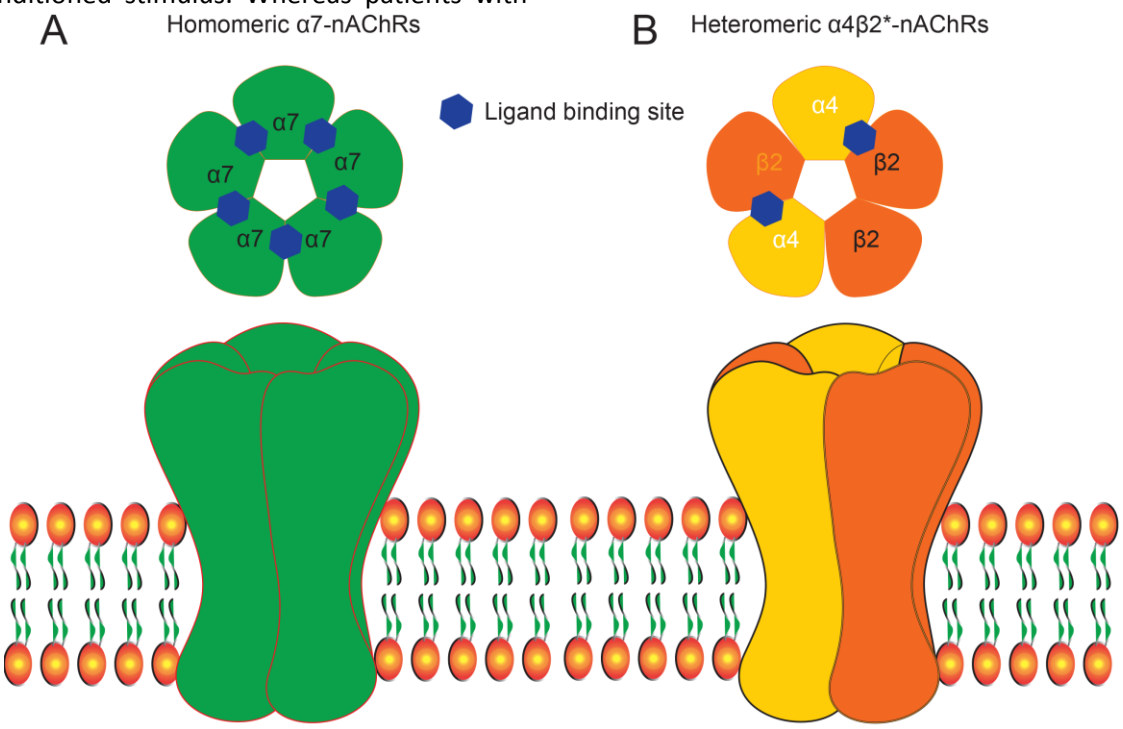

Figure 1. Structure of nAChRs. Neuronal nAChRs are formed by five subunits. Homomeric α7-nAChRs are usually formed by five α7 subunits (A). While, all heteromeric nAChRs are composed of five nAChR subunits, which can be at least one type of α subunit plus one type of β subunit, for example α4β2-nAChRs contain two α4 and three β2 subunits (B).

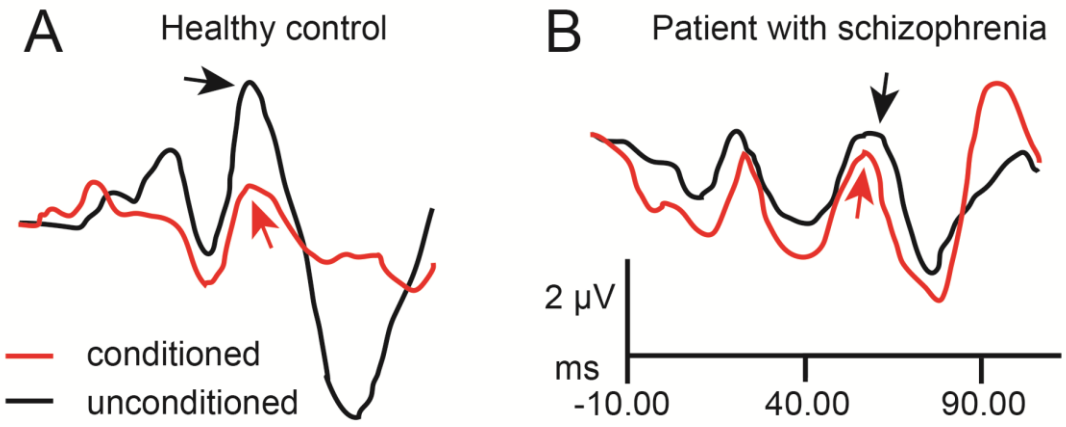

Figure 2. P50 suppression in (A) a healthy subject and (B) a patient with schizophrenia. Waveforms represent event-related potential recordings in response to paired auditory clicks presented 0.5 sec apart. The difference represents an index of P50 suppression, or sensory gating. In A (the healthy subject), there is an attenuation of the P50 waveform response, representing significant P50 suppression. In B (the patient with schizophrenia), there is minimal demonstrable difference between the conditioned P50 waveform response and the unconditioned response, representing a relative lack of P50 suppression. Arrows indicate P50 waveforms. Adapted from Daskalakis and George (2009) with permission.

A recent study, however, reported that smoking also improves positive symptoms. For example, Zhang *et al*. (Zhang et al., 2007) recently reported that smokers with schizophrenia have fewer positive symptoms, evidenced as lower symptom subscales of the Positive and Negative Syndrome Scale, than non-smoker patients with schizophrenia. In addition, nicotine nasal spray can modestly improve performance on attention and visual-spatial memory in patients of schizophrenia (Smith et al., 2006). Furthermore, cigarette smoking might significantly alleviate cognitive impairments and decrease medication side effects such as parkinsonism and tardive dyskinesia caused by antipsychotic treatment (Goff et al., 1992; Sagud et al., 2009). A more recent study demonstrated that smokers with schizophrenia have significantly greater TCQ-SF (Tobacco Craving Questionnaire-Short Form) scores than smokers without a psychiatric disorder 15 min post-smoking suggesting higher tobacco craving might at least partially contribute to such higher smoking rates in patients of schizophrenia (Lo et al., 2011).

Evidence of linkage between decreased function of α7-nAChRs and schizophrenia

Studies in both heterologous and native cells have demonstrated that nAChRs composed of α7 subunits (α7-nAChRs) have the highest calcium/sodium permeability ratio (P_{Ca}/P_{Na}) (Albuquerque et al., 2009; Uteshev, 2010). Thus, activation of α7-nAChRs can dramatically increase intracellular calcium concentration, which has important roles in modulating Ca^{2+}-dependent mechanisms including controlling neurotransmitter release, activation of some second messenger pathways, neuroprotection, and neurotoxicity (Meyer et al., 1998; Suzuki et al., 2006; Liu et al., 2012; Liu et al., 2013). Multiple lines of evidence have also suggested that α7-nAChRs are widely expressed throughout the human central nervous system (CNS) and play a role in a number of disorders

of human CNS including schizophrenia (Woodruff-Pak and Gould, 2002; Mathew et al., 2007; Castner et al., 2011; Ishikawa and Hashimoto, 2011; Tregellas et al., 2011; Olincy and Freedman, 2012; Palma et al., 2012; Bakanidze et al., 2013; Wallace and Bertrand, 2013).

First, evidence from studies in human postmortem brains shows that either α7-nAChR binding or α7-nAChR expression is significantly lower in several brain areas including the frontal cortex, the hippocampus, the reticular nucleus of the thalamus, the cingulate cortex, and the frontal lobe regions of schizophrenic patients compared to non-schizophrenic controls (Court et al., 1999; Guan et al., 1999; Marutle et al., 2001; Mathew et al., 2007; Mexal et al., 2010) suggesting a role for α7-nAChRs in the pathophysiology of schizophrenia.

Second, there is a large body of evidence to suggest that the P50 sensory gating (inhibition of a second auditory stimulus evoked response) is impaired in persons with schizophrenia (Martin and Freedman, 2007; Zhang et al., 2012a) and a decrease in α7-nAChR function appears to contribute to the deficits in P50 auditory gating (Toyohara and Hashimoto, 2010). Electrophysiological recordings have been performed to directly measure neuronal responsiveness to auditory stimuli in the hippocampus of chloral hydrate-anesthetized animals (Luntz-Leybman et al., 1992; Stevens et al., 1998). It was found that blockade of α7-nAChRs with selective α7-nAChR antagonist, α-bungarotoxin, is sufficient to disrupt the normal gating of response to repeated auditory stimuli applied at 500 ms interval (Luntz-Leybman et al., 1992). Importantly, selective α7-nAChR partial agonist, GTS-21, dose-dependently normalizes sensory inhibition in DBA/2 mice, which have schizophrenia-like deficits in sensory inhibition. Unsurprisingly, improved sensory inhibition produced by GTS-21 can be blocked by α-bungarotoxin but not by mecamylamine (Stevens et al., 1998). Furthermore, a recent study found that selective α7-nAChR agonist, N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-chlorobenzamide hydrochloride (PNU-282987), significantly increases the frequency of GABAergic synaptic activity, as seen using whole-cell patch clamp recordings in hippocampal slices and further restores amphetamine-induced auditory deficits by employing *in vivo* electrophysiological recordings in chloral hydrate-anesthetized rats (Hajos et al., 2005). These electrophysiological data point to a critical role of α7-nAChRs in modulation of P50 sensory gating function, at least in the hippocampus via enhanced GABAergic neurotransmission.

Third, genetic studies provide further evidence that mutations in α7-nAChR gene may play a causal role in the pathogenesis of schizophrenia although it is highly likely that other gene alterations are causal in the disorder (International Schizophrenia, 2008; Lupski, 2008; Stefansson et al., 2008). In 1997 Freedman *et al*. conducted a genome-wide survey of genetic variations in α7-nAChR gene using the polymorphic marker D15S1360, which is a yeast artificial chromosome containing the α7-nAChR gene. They found that brothers and/or sisters who share abnormal sensor gating (indicated by elevated P50 ratios) have generally also inherited the same D15S1360 allele from at least one parent in 9 families with a high incidence of schizophrenia with 104 members. The study also identified a highly significant linkage between a dinucleotide polymorphism at chromosome 15q13-14 (chromosome 15, band q13-14), the site of α7-nAChRs, and P50 abnormalities and schizophrenia (Freedman et al., 1997). The role of α7-nAChR gene variant in schizophrenia was further confirmed by a study authored by Leonard *et al*. showing significantly greater multiple polymorphisms in the core promotor region of α7-nAChR gene in schizophrenic subjects than in the controls (Leonard et al., 2002). Furthermore, Bakanidze *et al*. found that the T allele was more frequently expressed in single-nucleotide polymorphism (SNP) rs904952 in

schizophrenic patients compared to healthy controls after investigating 5 SNPs of the α7-nAChR gene (Bakanidze et al., 2013). Recent studies published in Nature reported that a deletion of 15q13.3 was detected in patients with schizophrenia by employing genome-wide survey of rare copy number variations in thousands of schizophrenia cases and controls (International Schizophrenia, 2008; Stefansson et al., 2008). In addition to the above direct genetic variants in the α7-nAChR gene, it was also reported that significantly lower levels of α7-nAChR mRNA expression and decreases in [^{125}I] α-bungarotoxin binding in human postmortem dorsolateral prefrontal cortex in individuals carrying risk alleles at two schizophrenia-associated neuregulin 1 (NRG1) SNPs, SNP8NRG221132 and rs6994992, which suggests that NRG1 risk alleles might down-regulate the physiological function of α7-nAChRs though the precise mechanisms are largely unknown (Mathew et al., 2007).

In short, downregulation of α7-nAChR function will likely increase the risk for schizophrenia.

Therapeutic potential of selective molecules targeted to α7-nAChRs in schizophrenia

Numerous compounds targeting α7-nAChRs (e.g. Tropisetron, EVP-6124, TC-5619, GTS-21, PNU-282987, PHA-568487, and CP-810123) have been developed and tested in preclinical and clinical trials as potential therapies for pharmacological treatment of schizophrenia particularly targeting at negative symptoms and impaired cognitive function of the disease (Stevens et al., 1998; Hajos et al., 2005; Walker et al., 2006; Wishka et al., 2006; O'Donnell et al., 2010; Zhang et al., 2012a; Wallace and Bertrand, 2013). Some of them show good cognitive benefits in schizophrenic patients. For example, EVP-6124, a novel α7-nAChR partial agonist developed by EnVivo Pharmaceuticals has significant and clinically meaningful effects on cognitive impairment of schizophrenic patients (Preskorn et al., 2014). EnVivo Pharmaceuticals has already started a two randomized, double-blind, placebo-controlled Phase 3 clinical trial to evaluate EVP-6124's effect on improving cognition in patients with cognitive impairment caused by schizophrenia (news from ClinicalTrials.gov). Recently, Zhang *et al*. found that 10 days of treatment with three doses of tropisetron (5, 10, and 20 mg/day) significantly improved both P50 auditory gating deficits and overall cognitive performance in 40 nonsmoking patients with schizophrenia (Zhang et al., 2012a). In order to screen more compounds targeted to α7-nAChRs for new drug development, different animal models of schizophrenia have been used in preclinical studies. Some promising compounds such as 282987, PHA-568487, and CP-810123 have been developed and have been demonstrate to have good *in vivo* efficacy in amphetamine-induced auditory gating deficits and novel object recognition in rats (Walker et al., 2006; Wishka et al., 2006; O'Donnell et al., 2010). Furthermore, these compounds also display good oral bioavailability and rapid brain penetration, which can afford high levels of receptor occupancy (Walker et al., 2006; Wishka et al., 2006; O'Donnell et al., 2010). These encouraging preclinical and clinical observations suggest that the development of compounds targeting α7-nAChRs may hold important clues into the etiology and treatment of schizophrenia.

Potential roles of β2*-nAChRs in schizophrenia

Compared to α7-nAChRs, β2*-nAChRs (i.e. α4β2-nAChRs) are more abundantly expressed in the brain. It is widely accepted that β2*-nAChRs are critical in regulating DA release in the brain and in mediating the reinforcing effects of nicotine (Picciotto et al., 1998). Related studies further indicate that β2*-nAChRs are involved in working memory, attentional performance, and some cognitive behavioral actions (Picciotto et al., 1998; Picciotto et al., 2000; Zhou et al., 2001; Loughead et al., 2010). For example, β2 knock-out animals showed a significant decrease in

hippocampal neurons (in both CA3 and CA1 subareas) using Feulgen and Nissl staining and corresponding impairment in spatial leaning as measured using Morris water maze in aged animals (Zoli et al., 1999). These observations strongly suggest that loss of β2*-nAChRs might have a role in age related cognitive deficits and neurodegenerative disorders observed in physiological ageing of the brain. Compared to control subject researchers found significantly reduced levels of β2*-nAChRs have been detected in postmortem brain tissue samples (i.e. the hippocampus, cortex, and caudate) of smokers with schizophrenia (Breese et al., 2000). Whereas levels of β2*-nAChRs were significantly increased in non-psychotic control subjects (Breese et al., 2000). These observations indicate an overall down-regulation of β2*-nAChRs, which is the normally up-regulated in healthy controls, in brain tissue of smokers with schizophrenia. More evidence supporting lower levels of β2*-nAChRs in smokers with schizophrenia was provided by a recent in vivo study by D'Souza *et al*. In the study the availability of β2*-nAChRs was compared by using single–photon emission computed tomography in smokers with schizophrenia and matched control smokers (D'Souza et al., 2012). They reported that β2*-nAChR availability was significantly lower (21%–26%) in the frontal cortex, the parietal cortex, and the thalamus in smokers with schizophrenia. In addition, they also found a reverse correlation between negative symptoms and β2*-nAChR availability (i.e. patients with higher levels of negative symptoms had lower β2*-nAChR availability) in smokers with schizophrenia (D'Souza et al., 2012). Furthermore, varenicline, a partial agonist for α4β2-nAChRs, has been developed and has been tried in 12 smokers with schizophrenia (Rollema et al., 2009). The clinical study demonstrated that varenicline can significantly improve some cognitive test scores after 9 weeks of treatment (Rollema et al., 2009). Taken together, these findings support an important role of β2*-nAChRs in the pathophysiology of schizophrenia, which suggests that targeting β2*-nAChRs could be a potential direction to develop drugs for the treatment of schizophrenia.

Conclusion

Cigarette smoking is extremely common among patients with schizophrenia. Smoking shows significant effect on alleviating negative symptoms, positive symptoms, and cognitive impairments in the patients, Findings from genetic studies, in vivo clinical studies, and studies in human postmortem brains suggest that both α7 and β2*-nAChRs are involved in at least some of the pathophysiological processes in schizophrenia. Drugs targeting these receptors such as EVP-6124 and varenicline might provide a novel and more comprehensive therapeutic than currently prescribed antipsychotics.

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