

## Evidence for a role of nicotinic acetylcholine receptors in schizophrenia

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## 1. ABSTRACT

Schizophrenia is a debilitating, complex and costly illness affecting roughly 1% of the world's inhabitants. The excessive degree of cigarette smoking exhibited by schizophrenic patients suggests that they might be self-medicating to ameliorate certain aspects of the characteristic positive, negative and cognitive symptoms associated with the disease. Morphological examinations found alterations in nicotinic receptors in postmortem tissue from schizophrenic individuals compared to controls, especially in the  $\alpha 7$  and  $\alpha 4\beta 2$  subtypes. These data were consistent with molecular biology studies which demonstrated associations between polymorphisms in gene coding for these receptors and schizophrenia. In studies of nicotinic receptor stimulation in schizophrenia patients, improvement in sensory inhibition and cognitive deficits were observed following treatment, though the effects were transient. These results have spurred the development of new pharmaceuticals specifically designed to modulate nicotinic receptor function. The initial results from clinical trials of these new drugs appear promising, potentially opening new avenues of treatment for this devastating disease.

## 2. INTRODUCTION

### 2.1. Incidence of schizophrenia

Schizophrenia is a complex illness affecting roughly 1% of the world's inhabitants (1-4), although higher incidences (2 – 3%) of the disorder have been observed in more insular populations (5-7). On the whole, the risk of developing schizophrenia is comparable in men and women (8, 9), but gender differences do exist in the initial age of onset of the disease (8, 10-12). First hospital admissions peak in the early twenties in young men, but not until the late twenties in young women, although women exhibit a second smaller peak in initial admissions after age 45. The age of onset of schizophrenia appears to correlate with the severity of symptoms and with a poorer course of the disease in younger men and older women (8, 11, 13).

### 2.2. Cost for diagnosis of schizophrenia

Schizophrenia is a very costly disease. Treatment of psychotic disorders worldwide accounted for 1.5 – 3.0% of national health expenditures from the 1980s to 2002 (United Kingdom - 1.5 – 3.0%, Germany - 1.3%, the Netherlands and France - 2.0%, United States - 2.5%) (14, 15). In 2002, the excess cost of schizophrenia (the cost

above that required for treating individuals without schizophrenia) was estimated to be \$62.7 billion in the United States alone (16). Total direct health care costs (drugs, outpatient care, professional fees, hospital inpatient care, long-term care) accounted for \$22.7 billion of the overall cost, non-health care costs (law enforcement, research and training, homeless shelters) accounted for \$9.3 billion of the overall cost, while the remainder (\$32.4 billion) was due to indirect costs (unemployment, reduced productivity, premature mortality due to suicide, loss of caregiver productivity) (16). In addition to the economic cost, schizophrenia also exacts a high price from the families of schizophrenic patients, resulting in increased stress, strong emotional reaction to the disease, disruption of household routines, restriction of social activities and societal stigma (15). A greater understanding of the etiology of schizophrenia is, therefore, not only important from an individual standpoint, but also important for society as a whole.

### 2.3. Etiology of schizophrenia

Studies examining the relative concordance rate for schizophrenia between monozygotic and dizygotic twins estimate that schizophrenia has a heritability of 80-85% (2). Schizophrenia is not transmitted in a Mendelian fashion, but is thought to result from modest abnormalities in many so-called "risk" genes acting in combination with environmental factors (17). A number of candidate genes for schizophrenia have been identified during recent years. These candidate genes have been linked either to schizophrenia itself or to endophenotypes (traits) associated with schizophrenia (2). A few of the candidate genes include NRG1 (neuregulin 1), DTNBP1 (dysbindin), DAAO (D-aminoacid oxidase), RGS4 (regulator of G-protein signaling-4), COMT (catechol-O-methyltransferase), PRODH (proline dehydrogenase), CAPON (carboxy-terminal PDZ ligand of neuronal nitric oxide synthase), CCK (cholecystokinin) and CHRNA7 (alpha 7 nicotinic acetylcholine receptor).

A variety of environmental factors have been suggested to play a role in the etiology of schizophrenia. Increased vulnerability to schizophrenia has been found following maternal exposure to influenza (18, 19). Obstetric complications are also associated with a higher risk for developing schizophrenia (20), including problems during pregnancy (preeclampsia, diabetes, rhesus incompatibility and bleeding) and during delivery (atonic uterus, asphyxia and emergency caesarian section). Individuals born during winter months also exhibit a higher incidence of schizophrenia (21). Additional environmental risk factors for schizophrenia include cannabis use (22), immigration status (23, 24), urban background (12, 25) and stress (26, 27).

### 2.4. Symptoms of schizophrenia

Schizophrenia is characterized by three general types of symptoms: positive symptoms (psychosis), negative symptoms and cognitive symptoms. Not all schizophrenic patients exhibit each of the symptoms, nor are the symptoms exclusive to schizophrenia (3, 4, 28, 29). Positive symptoms refer to a loss of contact with reality and

consist of hallucinations, delusions, bizarre behavior and positive formal thought disorders. Negative symptoms refer to a diminution in or absence of normal behaviors and include flattening of affect, alogia, avolition and anhedonia. Cognitive symptoms manifest as deficits in attention, learning, memory, concentration and executive functions (abstract thinking, problem solving). Cognitive impairment appears to be present premorbidly in individuals that later develop schizophrenia (30, 31), increases slightly just prior to the onset of psychotic symptoms (30) and may show minimal further deterioration over the course of the disease, or may continue to worsen (30, 32, 33). Of the three symptom categories, degree of cognitive dysfunction appears to be the best predictor of functional outcome in schizophrenic patients (34) and may, with appropriate cognitive assessment tools, serve as a vulnerability marker for schizophrenia (34-36).

## 3. SMOKING AND SCHIZOPHRENIA

The incidence of smoking among the mentally ill is disproportionately high compared to the population in general, but the rate in the schizophrenic population even exceeds that seen in other mental illnesses (37, 38). This excessively high rate has long been recognized, but was commonly attributed to institutionalization or social issues as opposed to a biological source (39-41). In fact, cigarettes were often used as a reward for good behavior on psychiatric wards (42, 43), further encouraging smoking in this population. When the health risks of smoking and exposure to second-hand smoke became widely recognized, smoking on wards was curtailed. However, patients began complaining not only of nicotine withdrawal symptoms, but also exhibited an exacerbation of their schizophrenia symptoms (44). This was the first indication that schizophrenia patients might be deriving some psychotropic benefit from smoking.

Even with the recognition of the health risks associated with smoking, the incidence rate among schizophrenia patients remains substantially above that of individuals with other mental illnesses and the population as a whole. Various studies have reported smoking incidence among schizophrenia patients of 50 - 90% (39, 41, 45, 46), among the non-schizophrenic mentally ill population of around 25% (47) and among the general population of between 12 - 22% (39, 47). Even though schizophrenia patients appear to understand the risks associated with smoking and may voice a desire to quit (48, 49), the successful quitting rate is very low (39, 50, 51). Schizophrenia patients tend to be heavy smokers (42, 43, 52, 53), even smoking discarded butts and filters which are highly concentrated with nicotine (41). Schizophrenics also extract higher levels of nicotine from the cigarettes they smoke (53, 54).

### 3.1. Why do schizophrenics smoke?

There are two main theories as to why schizophrenia patients smoke so heavily and in such high numbers. The first states that there is a common neurobiological substrate which underlies both the need to smoke and the vulnerability to schizophrenia (39, 55). The

second is the “self medication” hypothesis in which schizophrenics are thought to smoke to alleviate anhedonic effects of their antipsychotic medication or to relieve symptoms not addressed by their antipsychotic medication.

### 3.1.1. Common neurobiological substrate theory

This theory proposes that the excessive smoking observed in schizophrenic populations occurs because both the need to smoke and the vulnerability to schizophrenia arise from a common neurobiological substrate (39, 55). Support for this viewpoint is provided by reports showing that the initiation of smoking often precedes the onset of schizophrenia symptoms (56-58). Further support is derived from studies suggesting that schizophrenia is a neurodevelopmental disorder (59, 60), with observable deficits in infancy (61) and at school age (62). Although these data provide a plausible foundation for the theory of a common neurobiological substrate, they do not as yet provide insight into the nature of this common substrate. An additional limitation is that direct testing of the theory may prove difficult.

### 3.1.2. Self-medication theory

The self medication theory has two aspects. The first is that smoking alleviates the anhedonia and some of the Parkinson's-like symptoms induced by typical antipsychotic medications. The second is that certain symptoms of schizophrenia are not addressed by antipsychotics and smoking relieves these symptoms.

Nicotine has been demonstrated to increase the release of dopamine, particularly in the mesocorticolimbic and nigrostriatal pathways (63). The nicotine-induced increase in dopaminergic tone supports the notion that smoking may alleviate anhedonia and Parkinson's like symptoms produced by dopaminergic blockade, a component of the typical and many of the atypical antipsychotics (64). Additionally, the increased dopamine release may serve to offset the sedation often observed with antipsychotic medications (65). However, it has been noted that smoking behavior and schizophrenia are associated independently of antipsychotic treatment (56) and the initiation of smoking behavior often precedes the initiation of treatment with antipsychotics (43).

Alternately, the nicotine in cigarette smoke may relieve symptoms unaddressed by antipsychotic medications, such as cognitive impairments or sensory processing deficits. Cognitive issues are now a recognized component of the schizophrenia symptom constellation (see above) and are receiving as much attention as positive and negative symptoms (32, 66). Improvement in cognition in schizophrenia patients has been positively correlated with improved functional outcomes (34). Several studies have demonstrated that stimulation of nicotinic acetylcholine receptors (nAChR) either by nicotine (67-69) or through cholinomimetics such as physostigmine (70) produces improvement in cognitive function in schizophrenia patients. Cognitive deficits are addressed somewhat by atypical antipsychotics, but very poorly by the typical antipsychotics (34, 71). The improvement with atypical antipsychotics is thought to occur as a function of an

increase in acetylcholine release in the prefrontal cortex (72) and the hippocampus (73), thereby increasing stimulation of cholinergic receptors. Thus, unmedicated patients and those on typical antipsychotics may be seeking improvement in their cognitive functioning through smoking cigarettes.

Sensory processing deficits are common among schizophrenia patients and are poorly treated by typical antipsychotics, although some atypical antipsychotics have proven to be more efficacious. Deficits in sensory processing are quantifiable with several different paradigms, including prepulse startle inhibition (PPI) (for review see (74-77), smooth pursuit eye movements (SPEM) (for review see (78-80) and P50 sensory inhibition. In P50 sensory inhibition, repeated stimuli induce activity in an inhibitory circuit in normal individuals such that the evoked response to the repetitive information is suppressed (81-86). This inhibition of response protects the brain from information overload. In schizophrenia patients, this inhibitory circuit does not function normally and these individuals often become overwhelmed or “flooded” by incoming sensory information. This “flooding” phenomenon is thought to lead to personality decompensation (87, 88). Deficits in this P50 sensory processing circuit correlate with cognitive deficits (86, 89), and may be related to impaired attentional indices (89). It is possible to measure the activity in the inhibitory circuit by assessing the EEG evoked responses to closely-paired, identical auditory stimuli. Normal individuals show a significant reduction in response to the second stimulus (ratio second stimulus amplitude/first stimulus amplitude of <0.04) while schizophrenia patients and many first degree relatives show responses of similar magnitude to both stimuli (81, 83, 85), indicating a deficit in normal inhibitory mechanisms in the latter groups. Typical antipsychotics do not improve the deficit (90, 91), while certain of the atypicals, particularly clozapine, show improvement (92, 93). Improvement with olanzapine is more variable (94-96). However, transient improvement in deficient P50 sensory inhibition was observed in controlled studies of nicotine use, either through smoking cigarettes or chewing nicotine gum (97, 98). As it is generally agreed that the active component of cigarette smoke is nicotine (39, 57, 86, 99), these data strongly imply that schizophrenic patients smoke excessively, at least in part, in an attempt to influence nicotinic receptor function.

## 4. NICOTINIC RECEPTORS

Neuronal nAChR are pentameric protein structures forming a membrane channel which fluxes calcium when activated (100-103). To date, 11 genes coding for nicotinic cholinergic subunits have been identified in the mammalian genome. These include  $\alpha 2$ - $\alpha 7$ ,  $\alpha 9$ ,  $\alpha 10$  and  $\beta 2$ - $\beta 4$  (for review see (104-107).  $\alpha 7$  and  $\alpha 9$  subunits form functional homomeric receptors, while the remaining  $\alpha$  subunits combine with  $\beta$  subunits in a 2:3 ratio to form heteromeric structures of various combinations (106, 108-110). Neuronal nicotinic receptors are widely distributed in the central nervous system (CNS). The most common receptor type is the  $\alpha 4\beta 2$ , a high affinity

receptor with a relatively slow desensitization rate (106, 111, 112).  $\alpha 7$  receptors, a low affinity rapidly desensitizing subtype, are also well distributed in the brain (106, 111, 112) while the distributions of other subtypes are more limited in the CNS (111).

### 4.1. Nicotinic Receptors In Schizophrenia

As stated previously, excessive smoking by schizophrenic patients could be a response to abnormal nicotinic receptor function in this disease. Indirect evidence for nicotinic receptor malfunction in schizophrenia was provided by Mukherjee *et al.* (113) who reported significantly higher serum levels of antibodies to nicotinic receptors in schizophrenics compared to controls. Nicotinic receptors are activated by the neurotransmitter acetylcholine. Cholinergic innervation of the forebrain appears to be essentially normal in postmortem schizophrenic brain. The number of cholinergic neurons in the nucleus basalis of Meynert, the source of acetylcholine projections to the forebrain (114) is comparable in schizophrenics and controls (115). In addition, choline acetyltransferase and acetylcholinesterase, two markers for the cholinergic system, exhibit similar levels in the forebrain of schizophrenics and controls (116, 117), although a negative correlation was found between the activity of forebrain choline acetyltransferase and the degree of cognitive impairment in schizophrenic patients (117). In contrast, brainstem cholinergic systems may be compromised in schizophrenia, as abnormalities in pedunculopontine (118) and mesopontine (119) cholinergic neurons have been found in postmortem schizophrenic tissue. These data indicate that if central nicotinic receptors are abnormal in schizophrenia, the abnormalities do not appear to result primarily from changes in cholinergic innervation, except perhaps in the brainstem.

Direct examination of postmortem tissue from schizophrenic patients has generally revealed a decreased density in the low affinity nicotinic receptor subtype – the  $\alpha 7$  receptor. Freedman *et al.* (120) examined binding of  $^{1125}$ - $\alpha$ -bungarotoxin ( $\alpha$ -BTX), an antagonist at the  $\alpha 7$  receptor, to sections of hippocampus from schizophrenics and controls. Tissue from schizophrenic individuals was characterized by fewer  $\alpha$ -BTX-labeled cells as well as by less labeling/cell in the dentate gyrus and hippocampal area CA3. No difference in  $\alpha$ -BTX binding was observed between the two groups in hippocampal area CA1. Binding of  $^{1125}$ - $\alpha$ -BTX to sections of reticular thalamic nucleus (RTN) from schizophrenics was reduced by 25% compared to binding in control RTN sections (121). The RTN was the only thalamic nucleus to exhibit a disparity in  $\alpha 7$  receptor levels between the two cohorts. Schizophrenia-associated decreases in  $\alpha 7$  receptor density have also been observed in several cortical areas. Marutle *et al.* (122) examined  $^{1125}$ - $\alpha$ -BTX binding to sections of three cortical regions from schizophrenic and control brains. The density of  $\alpha$ -BTX binding in the control tissue was highest in the cingulate cortex, intermediate in the orbitofrontal cortex and lowest in the temporal cortex.  $\alpha$ -BTX binding density was reversed in tissue from schizophrenic individuals, i.e. temporal cortex > orbitofrontal cortex > cingulate cortex.

A 50% decrease in  $^{1125}$ - $\alpha$ -BTX binding was detected in the cingulate cortex of schizophrenics in this study, but only in comparison to controls with a history of smoking. Guan *et al.* (123) analyzed the density of  $\alpha 7$  receptors in frontal and parietal cortical homogenates from schizophrenic patients and controls using antibodies to the  $\alpha 7$  receptor. When compared to controls, a 40% decrease in  $\alpha 7$  receptor levels was observed in frontal, but not parietal, regions of schizophrenic cortex. A 20 - 28% reduction in  $\alpha 7$  receptor immunoreactivity, with no change in  $\alpha 7$  receptor mRNA levels, was reported in the dorsal lateral prefrontal cortex (Brodmann area 46) of schizophrenic individuals compared to controls (124). The data from these two studies should be viewed with caution, however, as antibodies to the  $\alpha 7$  receptor have recently been shown to be nonselective (125). A 2.7-fold increase in mRNA for the  $\alpha 7$  receptor was found in stellate neurons of schizophrenic entorhinal cortex by Hemby *et al.* (126), contrary to the results of Martin-Ruiz *et al.* (124). To date, only one study has reported comparable levels of  $\alpha 7$  receptors in postmortem tissue from schizophrenics and controls (127). In this study,  $\alpha 7$  receptor density was measured in homogenates of hippocampus and cortex (area 8/9) using the  $\alpha 7$  receptor antagonist  $^3\text{H}$ -methyllycaconitine (MLA) instead of  $^{1125}$ - $\alpha$ -BTX. The use of this alternate  $\alpha 7$  receptor antagonist may account for the lack of binding differences in the two groups. Taken together, the majority of the data suggest that schizophrenia is characterized by a decrease in  $\alpha 7$  receptor density in circumscribed regions of the brain.

The literature is less consistent with regard to schizophrenia-associated alterations in brain levels of high affinity nicotinic receptors – those containing  $\beta 2$ ,  $\alpha 4$  and/or  $\alpha 3$  subunits. Significant reductions in binding of both  $^3\text{H}$ -cytisine (120) and  $^3\text{H}$ -nicotine (127) to hippocampal homogenates was observed in schizophrenic smokers compared to control smokers, suggesting that high affinity nicotinic receptors are decreased in schizophrenic hippocampus. No change in  $^3\text{H}$ -nicotine binding was observed in sections of postmortem schizophrenic thalamus relative to controls (121) nor in thalamic homogenates (127) from schizophrenic smokers *versus* control smokers, suggesting that high affinity nicotinic receptors are unaltered in schizophrenia in this brain region. In postmortem striatal sections from schizophrenic patients, binding of  $^3\text{H}$ -nicotine was 48 - 78% above control values overall, but only 24 - 49% above the values of controls that smoked (128). These data conflict, however, with reports of a significant reduction in binding of  $^3\text{H}$ -epibatidine to caudate homogenates from schizophrenic smokers compared to control smokers (127) and of a 30% reduction in binding of  $^3\text{H}$ -cytisine to striatal homogenates (129) in schizophrenics relative to controls. Contradictory data has also been reported for high affinity nicotinic receptors in the cerebral cortex. Breese *et al.* (127) found significant decreases in binding of both  $^3\text{H}$ -nicotine and  $^3\text{H}$ -epibatidine in cortical homogenates from schizophrenic smokers compared to control smokers. These data disagree with observations by Marutle *et al.* (122) of increased  $^3\text{H}$ -cytisine binding in orbitofrontal cortex ( $\uparrow$  52 - 59%) and cingulate cortex ( $\uparrow$  15 - 22%) as well as increased  $^3\text{H}$ -

epibatidine binding in temporal cortex ( $\uparrow$  52 – 59%) from schizophrenics relative to controls matched for smoking history. Martin-Ruiz *et al.* (124) also reported two-fold increases in  $^3\text{H}$ -epibatidine binding in homogenates of schizophrenic dorsolateral prefrontal cortex (Brodmann area 46) compared to controls matched for smoking history. Immunoreactivity for  $\alpha_4$ ,  $\alpha_3$  and  $\beta_2$  nicotinic subunits was not changed in this study despite the increase in  $^3\text{H}$ -epibatidine binding. Again, caution should be used in evaluating the immunohistochemistry data, as antibodies to all nicotinic receptor subunits, including the  $\alpha_4$ ,  $\alpha_3$  and  $\beta_2$  subunits, have been shown to be unreliable (130). Therefore, it is currently unclear whether, and in what direction, levels of high affinity nicotinic receptors may be altered in cerebral cortex and striatum from schizophrenic patients. The variability in the binding data could arise from disparities in tissue sampling, from differences in experimental techniques used and/or from differential treatment of the schizophrenic patients, although neuroleptic administration in animals does not appear to affect high affinity nicotinic receptor binding (131, 132). It is possible that significant changes in the levels of nicotinic receptor subtypes occur only in a subpopulation of schizophrenic individuals, while alterations in nAChR function (see below) without changes in receptor density may be a more common feature of the disease.

Support for a schizophrenia-associated alteration in the function of high affinity nicotinic receptors has recently been provided. Cigarette smoking in normal controls is associated with an upregulation of high affinity nicotinic receptors. Breese *et al.* (131) found significant increases in  $^3\text{H}$ -nicotine binding in postmortem hippocampus and thalamus from life-long smoking controls compared to non-smoking controls. The increase in  $^3\text{H}$ -nicotine binding was due to an increase in the number of receptors ( $B_{\text{max}}$ ) with no change in the affinity of the receptors ( $K_d$ ). The extent of increased  $^3\text{H}$ -nicotine binding was dependent upon the number of packs of cigarettes smoked per day, indicating that normal smokers exhibit a dose-dependent increase in  $^3\text{H}$ -nicotine binding sites. Binding of  $^3\text{H}$ -nicotine in tissue from individuals that had stopped smoking for at least two months prior to death was at or below non-smoking control values. When  $^3\text{H}$ -nicotine binding was compared across postmortem tissues from schizophrenic smokers, nonsmokers and smokers who had quit, a marginally significant increase in binding density was seen in schizophrenic smokers relative to nonsmokers only in cerebral cortex (127). Surprisingly, binding of  $^3\text{H}$ -nicotine in hippocampus and thalamus did not differ across the three groups. Binding of  $^3\text{H}$ -epibatidine in cortex again differed significantly between schizophrenic smokers and nonsmokers, but no difference was seen in  $^3\text{H}$ -epibatidine binding in caudate from the three groups. When  $^3\text{H}$ -nicotine binding was correlated with smoking history, an increase in binding was found with increasing smoking in hippocampus and cortex from both schizophrenics and controls. However, the slope of the regression line in schizophrenics was reduced 40% (hippocampus) and 50% (cortex) relative to control smokers. Binding of  $^3\text{H}$ -epibatidine in thalamus and caudate was not correlated with smoking history. Correlation of smoking history with

Scatchard analysis of  $^3\text{H}$ -nicotine and  $^3\text{H}$ -epibatidine binding in cortical tissue from schizophrenics and controls revealed a reduced level of receptor binding in tissue from the schizophrenic patients for the same level of cigarette smoking compared to controls. Thus, high affinity nicotinic receptors exhibit abnormal function in schizophrenic patients in that they fail to up-regulate in a normal manner in response to cigarette smoking.

### 4.2. Nicotinic receptor subunit genes in schizophrenia

Nicotinic receptors could be altered in schizophrenia as a result of polymorphisms in the genes encoding the nicotinic receptor subunits. As stated previously, schizophrenia is thought to arise from a combination of multigene abnormalities and environmental factors (17). Data from a number of studies suggest that CHRNA7, the gene encoding the  $\alpha 7$  nicotinic receptor subunit, may be a susceptibility gene for schizophrenia. The deficit in hippocampal auditory (P50) sensory processing characteristic of schizophrenic patients has been genetically linked to a dinucleotide polymorphism at the chromosome 15q13-14 site of the  $\alpha 7$  receptor (133). In addition, linkage of schizophrenia itself to the chromosome 15q13-14 site has been found in the NIMH Genetic Initiative pedigrees (134-137) as well as in several other pedigrees (138-144), although other studies have reported no linkage between CHRNA7 and schizophrenia in their population samples (145-148).

Human CHRNA7 maps to chromosome 15 (15q13-14), has 10 exons, is estimated to be larger than 75 kb and has consensus sites for binding of transcription factors Sp1, AP-2, Egr-1 and CREB (149). A partial duplication (exons 5 – 10) of CHRNA7, along with five novel exons (D, D', C, B, A), maps approximately 1-Mb centromeric to CHRNA7 on chromosome 15. The duplicated sequence (CHRFAM7A), which includes the novel exons, is expressed as mRNA in human brain, but the functional role of the product is unknown (149). Thirty-three molecular variants were identified in the coding region and intron/exon borders of CHRNA7 and its partial duplication by Gault *et al.* (150). Twenty-one of these variants were found in exons, but non-synonymous changes were rare and were not found to cosegregate with either the hippocampal auditory (P50) sensory processing deficit observed in schizophrenia or with schizophrenia itself (150). These data indicate that the  $\alpha 7$  receptor should function normally despite being reduced in density in many areas of schizophrenic brain. Analysis of different alleles of the dinucleotide repeat marker D15S165 in the 15q14 region (136) revealed that two of the alleles showed both familial transmission disequilibrium and population-wide association with schizophrenia. In addition, schizophrenic patients with one allele of the marker exhibited an earlier age of onset, greater numbers of hospitalizations and greater nicotine abuse than did patients with the second allele. Raux *et al.* (151) examined whether a molecular variant of CHRFAM7A, the –2 bp deletion of exon 6, was a risk factor for schizophrenia. They determined that having at least one of these molecular variants did not constitute a risk factor for the disease. However, this polymorphism did appear to be associated with abnormal

P50 sensory processing (ratio >0.05), although most of the effect was in non-schizophrenics.

A number of molecular variants have also been found in the core promoter of CHRNA7 (152, 153). Several of these molecular variants result in decreased  $\alpha 7$  receptor expression in an *in vitro* expression system, suggesting that they might cause the decrease in  $\alpha 7$  receptor density observed in schizophrenic brain. The prevalence of these functional promoter variants was statistically greater in schizophrenic individuals, but they were also found in controls (150). The control subjects could be distributed into three groups (152, 153). The first group had P50 ratios < 0.20, the second group had P50 ratios between 0.20 and 0.50 while the third group had P50 ratios > 0.50. Thus, sensory processing appeared normal in the first two groups while the third group exhibited a deficit in sensory processing. Controls with no promoter variants were found in groups one and two, with the majority in group one. On the other hand, controls with promoter variants were distributed among all three groups, but group three, the group exhibiting abnormal P50 responses, consisted only of controls with a promoter variant. These data suggest a strong relationship between CHRNA7 promoter variants and decreased sensory processing (152, 153), similar to the findings of Raux *et al.* (151) for the CHRFAM7A gene.

The majority of high affinity nicotinic receptors are comprised primarily of  $\alpha 4$  and  $\beta 2$  subunits (154). The gene for the  $\alpha 4$  subunit (CHRNA4) is assigned to human chromosome 20q13.2-13.3 and spans more than 17 kb while the gene for the  $\beta 2$  subunit (CHRNA2) is assigned to human chromosome 1q21 and spans only 14 kb (155). Little is known about the possible role of molecular variants in CHRNA4 and/or CHRNA2 in determining the schizophrenia-associated changes in high affinity nicotinic receptors. An initial investigation of this question was conducted by DeLuca *et al.* (155) who performed allele, haplotype and interaction analysis of the two genes using a family-based association approach in which each family had at least one schizophrenic individual. The data indicated that while molecular variants in one gene alone were not sufficient to confer susceptibility to schizophrenia, an interaction between three CHRNA4 molecular variants and one CHRNA2 molecular variant produced significant risk for schizophrenia.

### 4.3. Potential epigenetic modification of nicotinic receptors in schizophrenia

Schizophrenia-associated abnormalities in nicotinic receptors might occur secondary to changes in gene expression that result from alterations in epigenetic regulation. The two most well-studied mechanisms of epigenetic regulation are DNA methylation (covalent modification of cytosine) and post-translational modification of histones (methylation, acetylation, phosphorylation, sumoylation) (156). These mechanisms work together (157, 158) to fine tune gene expression (159). If these, or other epigenetic mechanisms, are abnormal in schizophrenia, they might disrupt normal

expression of many genes, including those encoding nicotinic receptors (159-166).

Evidence is accumulating to suggest that the DNA methylation status of at least some genes is altered in schizophrenia. The promoter of the reelin (RELN) gene was found to be hypermethylated in samples of postmortem cortex from schizophrenics *versus* controls (167, 168). The cytosine-guanine dinucleotide (CpG) island of sex-determining region Y-box containing gene 10 (SOX 10) was also found to be highly methylated in postmortem brain tissue from schizophrenic patients relative to controls (169). In contrast, a trend towards lower levels of methylated deoxycytidine (mC) in DNA from peripheral leukocytes was observed in male schizophrenic patients compared to gender-matched controls (170). To date, nothing is known about the DNA methylation status of nicotinic receptor genes in schizophrenic patients or in controls. However, chronic administration (8 days) of nicotine bitartrate (1.5 mg/kg) had no effect on mRNA expression of DNA-methyltransferase 1 in the frontal cortex of mice (171), suggesting that cigarette smoking by schizophrenic patients may not influence this epigenetic mechanism.

### 4.4. Nicotinic receptor assembly and surface expression in schizophrenia

Nicotinic receptors could be altered in schizophrenia as a result of abnormal assembly processes. Little direct information is available about the assembly of nicotinic receptors in the brain. Nevertheless, insight has been gained by examining assembly of nicotinic receptors at the neuromuscular junction (NMJ). Briefly, the process involves 1) translation of mRNA for the subunits comprising the NMJ nicotinic receptor by ribosomes present on the endoplasmic reticulum (ER), 2) folding and oligomerization of the subunits within the ER with the probable help of a variety of chaperone proteins and 3) exportation of properly assembled receptor pentamers from the ER to the Golgi complex, then to the cell surface. Subunit precursors that fail to properly fold and/or assemble are degraded within the ER (172-174). The assembly of nicotinic receptors is slow and inefficient (174). The slow kinetics of nicotinic receptor assembly may be due, in part, to the slowness of the interaction between the nicotinic receptor subunit precursors and the chaperone proteins (174).

The chaperone protein 14-3-3 $\eta$  has recently been found to interact with the  $\alpha 4$  nicotinic receptor subunit and appears to regulate the surface expression levels of  $\alpha 4\beta 2$  nicotinic receptors (175). The gene encoding 14-3-3 $\eta$  maps to chromosome 22q12, a region implicated in schizophrenia (reviewed in (176)). A significant association between polymorphic variants of the 14-3-3 $\eta$  gene and schizophrenia has been reported in two studies (177, 178), although not in others (179-181) while microarray analysis has revealed differential expression of 14-3-3 $\eta$  between schizophrenics and controls (182, 183). If the function of the 14-3-3 $\eta$  protein is abnormal in schizophrenia, the result could be an alteration in  $\alpha 4\beta 2$

assembly and a decrease in the density of  $\alpha 4\beta 2$  nicotinic receptors in schizophrenic brain.

Data has recently been reported to suggest that nicotine itself can act as a pharmacological chaperone with regard to assembly of  $\alpha 4\beta 2$  nAChRs. Administration of nicotine, other nicotinic agonists and even nicotinic antagonists to cultured cells (184-186) results in an upregulation of  $\alpha 4\beta 2$  nAChRs on the surface of the cells. The upregulation appeared to occur as a result of nicotine stabilizing  $\alpha 4\beta 2$  receptor subunit precursors within the ER that would otherwise be degraded, allowing a greater number of mature receptors to be moved to the cell surface. In contrast, the increased binding of  $^{125}\text{I}$ -epibatidine to surface  $\alpha 4\beta 2$  nAChRs observed by Vallejo *et al.* (187) following nicotine administration to HEK cells did not appear to be due to changes in  $\alpha 4\beta 2$  receptor assembly, trafficking or cell-surface turnover. In fact, these authors found no change in the actual density of surface  $\alpha 4\beta 2$  receptors at all. Instead, the nicotine treatment appeared to alter the functional state of the receptors already on the surface such that they exhibited a slowing in desensitization and an increase in sensitivity when exposed to nicotine.

As stated previously, the majority of schizophrenic patients smoke very heavily. This high level of smoking could be an attempt to alter  $\alpha 4\beta 2$  nAChR function by increasing receptor assembly and transport to the surface, by altering the functional state of receptors already present on the surface or both. The observation that the degree of upregulation of  $\alpha 4\beta 2$  receptors in schizophrenic individuals for a given level of smoking is less than that seen in controls at the same level of smoking (127) clearly suggests that however nicotine is influencing the density of  $\alpha 4\beta 2$  receptors in brain, these mechanisms may be abnormal in schizophrenia.

### 4.5. Calcium regulation of nicotinic receptors in schizophrenia

Intracellular calcium levels can modulate voltage- and ligand-gated ion channels via calcium binding and calcium sensor proteins (188-190). The calcium sensor protein visinin-like protein-1 (VILIP-1) has recently been found to interact with  $\alpha 4\beta 2$  nicotinic receptors (191). Coexpression of VILIP-1 with recombinant  $\alpha 4\beta 2$  receptors resulted in an upregulation (~2-fold) in the density of surface  $\alpha 4\beta 2$  receptors and an increase (~3-fold) in the sensitivity of the receptors to acetylcholine. The VILIP-1-induced changes in  $\alpha 4\beta 2$  receptor characteristics were hypothesized to result from an alteration in receptor turnover combined with stabilization of the receptor in a state with higher agonist sensitivity (191). Bernstein *et al.* (192) observed a differential pattern of VILIP-1 immunoreactivity in postmortem hippocampus from schizophrenic patients compared to controls, suggesting that the function of this calcium sensing protein is altered in schizophrenia. Disruption in the modulatory role of VILIP-1 could account to some extent for the altered function in  $\alpha 4\beta 2$  nicotinic receptors documented in schizophrenia.

## 5. POTENTIAL NEW THERAPIES

There are several approaches to improving nicotinic receptor-associated deficits in schizophrenia. The first method, smoking cigarettes, was found by the schizophrenia patients themselves. However, this method, as well as nicotine substitute approaches like the nicotine patch, suffer from the desensitization problem. They are effective transiently, but rapidly decrease in efficacy due to receptor desensitization which severely limits their usefulness. Nicotine substitutes that can be administered intermittently, such as the inhaler or nicotine lozenges or gum, offer a somewhat better approach in that the plasma levels of nicotine can be allowed to drop off, permitting receptor resensitization before the next administration. Although the nicotine substitutes do not subject the patient to the 200+ additional chemicals found in cigarette smoke, they still have the significant disadvantage of incurring nicotine dependence just like cigarettes (106). However, the nicotine substitute approaches are only minimally effective in reducing cigarette smoking in schizophrenic individuals (51, 193-197). The nominal effectiveness of nicotine transdermal patches and nasal spray on smoking cessation was not due to an inability of the patients to tolerate the treatments. Instead, these nicotine substitution approaches may not provide high enough doses of nicotine when used as normally prescribed.

Animal models of schizophrenia have provided useful insights for elaborating new treatment strategies. The nicotinic receptor subtypes associated with P50 sensory inhibition have been identified in rodent models of this paradigm. Quantification of P50 sensory inhibition requires measurement of two evoked responses, the response to the first stimulus, called the conditioned response and the response to the second stimulus, called the test response. Studies in rodents have identified the  $\alpha 4\beta 2$  subtype as mediating the conditioned response (198). Increased activity at these receptors increases the amplitude of the conditioned response suggesting increased hippocampal excitability. The test response is mediated by  $\alpha 7$  nicotinic receptors (199) that reside, at least in part, on inhibitory hippocampal interneurons (200, 201). Cholinergic activation of interneuron  $\alpha 7$  receptors by input from septal neurons (202) leads to GABA release (203, 204). Subsequent binding of GABA to GABA<sub>B</sub> receptors present on pyramidal neurons (205) results in inhibition of a subpopulation of the pyramidal cells and a reduction in the amplitude of the test response (see (206) for circuit diagram). Thus, normal processing of sensory input by the hippocampus appears to require optimal levels of both  $\alpha 7$  and GABA<sub>B</sub> receptors. A 50% reduction in  $\alpha 7$  receptor density has been found in postmortem hippocampus from schizophrenic patients compared to controls (120). In addition, a recent study (207) reported that GABA<sub>B</sub> receptor immunolabeling of hippocampal pyramidal cells was markedly reduced in postmortem tissue from schizophrenics relative to controls. Therefore, schizophrenia-associated deficits in hippocampal sensory processing may result from a decrease in  $\alpha 7$  receptors, in GABA<sub>B</sub> receptors or both.

Data from animal models of the sensory processing deficit observed in schizophrenia suggest that reduced levels of hippocampal  $\alpha 7$  receptors may be the critical factor. DBA/2 mice exhibit a deficit in sensory inhibition as well as reduced numbers of hippocampal  $\alpha 7$  receptors (208). Stimulation of the  $\alpha 7$  receptors by exogenous agonists such as nicotine or DMXB-A, an agonist at the  $\alpha 7$  receptor (209-211), corrects the sensory processing abnormality present in this mouse strain (86, 212, 213). Correction of the sensory processing deficit observed in DBA/2 mice by administration of nicotinic agonists is reminiscent of the normalization of P50 response seen in schizophrenic patients after they are given nicotine gum or are allowed to smoke. The nicotine-mediated increase in  $\alpha 7$  receptor stimulation is hypothesized to produce increased GABA release, increased activation of GABA<sub>B</sub> receptors and enhanced inhibition of response to repetitive sensory stimulation. Thus, development of drugs that selectively target the  $\alpha 7$  receptor might prove useful in ameliorating the sensory flooding commonly experienced by schizophrenic patients.

The improvement seen in rodent models with the selective  $\alpha 7$  agonist DMXB-A (213-215) led to the first clinical study of this drug (216). In the recently published Phase I clinical study, DMXB-A was administered acutely to non-smoking schizophrenia patients and both P50 sensory inhibition and cognitive functioning were assessed. Other than nicotine, this is the first study of direct nicotinic agonist effects on P50 sensory inhibition and cognition in humans to be published. This work showed that selective stimulation of  $\alpha 7$  nicotinic receptors produced concurrent improvements in both neurocognitive measures and P50 sensory inhibition in a population of non-smoking schizophrenia patients who were stable on their antipsychotic medication (216). These data suggest that stimulation of nicotinic receptors, specifically the  $\alpha 7$  subtype, produces improvement in two deficits that are not well treated, even in patients that are stably maintained on antipsychotic medication. It is noteworthy that none of the patients in this study were taking clozapine, an atypical antipsychotic, which has been shown to produce improvements in both of these measures without additional nicotinic receptor stimulation (34, 92, 93). The results of the initial DMXB-A study lend credence to the "smoking as self-medication for unaddressed symptom" theory. In this light, it is interesting to note that schizophrenia patients are exceptionally poor at smoking cessation (39, 49-51), but patients on clozapine, which increases release of acetylcholine, spontaneously decrease their smoking behavior (93).

The success of DMXB-A has stimulated interest by pharmaceutical companies to develop additional  $\alpha 7$  agonists as potential therapeutic agents for the treatment of schizophrenia. Rogers and colleagues recently published pre-clinical data on a putative therapeutic for the treatment of cognitive deficits in schizophrenia (217), but no clinical trials have been published. Other companies are in pursuit of similar compounds.

An alternate approach to stimulation of nicotinic receptors with a direct agonist is indirect stimulation of acetylcholine release. Recent studies have utilized 5-HT<sub>3</sub> (serotonin receptor 3) antagonists such as ondansetron and tropisetron in schizophrenia patients and rodent models of P50 sensory inhibition deficits. 5-HT<sub>3</sub> receptors tonically inhibit acetylcholine release (218), thus blockade of these receptors induces increased release of acetylcholine. Ondansetron administration to schizophrenia patients stable on antipsychotic medication produced improvement in P50 sensory inhibition (219) and in some cognitive deficits (220). The 5-HT<sub>3</sub> antagonist tropisetron also acts as a direct  $\alpha 7$  nicotinic agonist (221, 222). When administered to schizophrenia patients (223) or DBA/2 mice (224), improvement in P50 sensory inhibition was observed. Thus, indirect agonists which can increase acetylcholine release are another potential therapeutic approach.

Very recently, positive allosteric modulators (PAMs) of  $\alpha 7$  nicotinic receptors have gained interest as potential therapeutics. These compounds alter the channel open time and/or the desensitization/resensitization dynamics of the  $\alpha 7$  receptor. In a seminal paper in the field, Hurst and colleagues demonstrated that a PAM for  $\alpha 7$  nicotinic receptors could modify cholinergic neurotransmission *in vivo* (225). This compound increased channel open time, increased acetylcholine-evoked GABA release and improved P50 sensory inhibition in a rodent model. This work suggests that PAMs, which do not directly stimulate the receptor but instead increase efficacy of endogenously released acetylcholine, may represent a ripe target for new drug development.

## 6. PERSPECTIVE

The information discussed above indicates that:

- 1) Schizophrenia is a relatively common disease that exacts a prohibitive cost both to the individual and to society. The disease is characterized by positive, negative and cognitive symptoms that are inadequately treated by the currently available typical and atypical antipsychotic drugs. Schizophrenia exhibits a high degree of heritability and is thought to result from small abnormalities in many genes coupled with environmental influences.

- 2) Schizophrenic individuals exhibit excessive levels of cigarette smoking which transiently improves some of the cognitive and sensory processing deficits characteristic of the disease. This extreme smoking behavior suggested that nicotinic receptors might be abnormal in schizophrenics, since nicotine is thought to be the major active component of cigarette smoke.

- 3) Studies evaluating this hypothesis concluded that the  $\alpha 7$  subtype of nicotinic receptor is decreased in many regions of postmortem schizophrenic brain. The data is less clear regarding the density of the  $\alpha 4\beta 2$  subtype, although these receptors exhibit abnormalities in function.



4) The schizophrenia-associated alterations in nicotinic receptor levels and function may arise from abnormalities in the genes encoding the nicotinic receptors, from abnormalities in epigenetic regulation of the genes encoding the nicotinic receptors, from abnormalities in nicotinic receptor assembly, from abnormalities in molecules regulating calcium signaling and/or from abnormalities in mechanism not yet examined.

The discovery of abnormal nicotinic receptor processes in schizophrenia has led to the development of new pharmaceuticals directed at nicotinic receptor subtypes. Importantly, these new drugs appear to reduce not only the sensory processing deficits observed in schizophrenia, but also the cognitive deficits. As the degree of cognitive impairment is a crucial predictor of the overall outcome for schizophrenic patients, these new therapies may herald a significant breakthrough in the treatment of this devastating disease.

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- Abbreviations:** NRG1: neuregulin 1 gene, DTNBP1 – dysbindin gene, DAAO: D-aminoacid oxidase gene, RGS4: regulator of G-protein signaling-4 gene, COMT: catechol-O-methyltransferase gene, PRODH: proline dehydrogenase gene, CAPON: carboxy-terminal PDZ ligand of neuronal nitric oxide synthase gene, CCK – cholecystokinin gene, CHRNA7: alpha 7 nicotinic acetylcholine receptor subunit gene, PPI: prepulse startle inhibition, SPEM: smooth pursuit eye movements,  $\alpha$ -BTX:  $\alpha$ -bungarotoxin, MLA – methyllycaconitine, CHRFA7A: duplicated sequence of the alpha 7 nicotinic acetylcholine receptor gene, CHRNA4 – alpha 4 nicotinic acetylcholine receptor subunit gene, CHRNA2 – beta 2 nicotinic acetylcholine receptor subunit gene, NMJ: neuromuscular junction, ER: endoplasmic reticulum, VILIP-1: visinin-like protein-1, 5-HT – serotonin, DMXB-A: 3-(2,4 dimethoxybenzylidene) anabaseine, PAMs: positive allosteric modulators, CNS: central nervous system, RTN: reticular thalamic nucleus
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