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Smoking, Genetics and Schizophrenia: Evidence for Self Medication

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Abstract

Schizophrenia is a common mental illness with a high prevalence of smoking. More than 80% of schizophrenics smoke compared to 25% of the general population. Both schizophrenia and tobacco use have strong genetic components, which may overlap. It has been suggested that smoking in schizophrenia may be a form of self-medication in an attempt to treat an underlying biological pathology. Smoking normalizes auditory evoked potential and eye tracking deficits in schizophrenia, as well as improving cognitive function. Nicotine acts through a family of nicotinic receptors with either high or low affinity for nicotine. The loci for several of these receptors have been genetically linked to both smoking and to schizophrenia. Smoking changes gene expression for more than 200 genes in human hippocampus, and differentially normalizes aberrant gene expression in schizophrenia. The $\alpha 7^*$ nicotinic receptor, linked to schizophrenia and smoking, has been implicated in sensory processing deficits and is important for cognition and protection from neurotoxicity. Nicotine, however, has multiple health risks and desensitizes the receptor. A Phase I trial of DMXB-A, an $\alpha 7^*$ agonist, shows improvement in both P50 gating and in cognition, suggesting that further development of nicotinic cholinergic drugs is a promising direction in schizophrenia research.

Schizophrenia and smoking are closely connected. The prevalence of tobacco use in schizophrenia is inordinately high. Only 25% of the general population now smokes, but more than 80% of schizophrenics use tobacco products (de Leon and Diaz, 2005; Diwan et al., 1998; George and Krystal, 2000; Hakko et al., 2006; Leonard et al., 2000; CDC, 2005). Schizophrenics smoke high-tar cigarettes and extract more nicotine per cigarette than do control smokers (Olinicy et al., 1997; Strand and Nyback, 2005). Smoking in schizophrenia may begin in the prodromal phase of the disorder (Weiser et al., 2003). Although many aspects of nicotine addiction in schizophrenia are similar to those of non-mentally ill smokers (Mansvelder et al., 2006; Ziedonis et al., 1994), it has been proposed that smoking in schizophrenia may also be a form of self-medication, as an attempt to correct underlying neuropathologies (Adler et al., 1990; Adler et al., 1993; Adler et al., 1998; Leonard et al., 2001; Kumari and Postma, 2005; Sacco et al., 2004). Growing evidence supports this hypothesis.

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Nicotinic receptors are genetically linked to smoking and schizophrenia

Nicotine acts through a family of nicotinic acetylcholine receptors found in the brain and periphery (Leonard and Bertrand, 2001; Gotti et al., 2006). The neuronal nicotinic receptor gene family, as expressed in mammalian tissues, consists of 11 genes ($\alpha 2$ - $\alpha 7$, $\alpha 9$, $\alpha 10$; $\beta 2$ - $\beta 4$). The receptor assembles as a pentamer (Cooper et al., 1991). Upon ligand binding, the channel opens and fluxes Na^+ and Ca^{++} (Vijayaraghavan et al., 1992). Receptors are of two classes, those consisting of both α and β subunits and homomers of $\alpha 7$ subunits. Nicotinic receptors are further characterized by those that bind nicotine with high affinity (principally $\alpha 4\beta 2^*$) and the low affinity $\alpha 7^*$ receptor (McGehee and Role, 1995; Leonard and Bertrand, 2001).

Both tobacco use (Heath and Martin, 1993; Bergen and Caporaso, 1999; Carmelli et al., 1992; Bierut et al., 2007; Saccone et al., 2007) and schizophrenia (Owen et al., 2004; Tsuang and Faraone, 1994; Badner and Gershon, 2002; Lewis et al., 2003; Harrison and Weinberger, 2005) have strong genetic components. Several nicotinic receptor genes have recently been associated with nicotine dependence (Saccone et al., 2007). Additionally, genetic linkage studies of smoking in schizophrenia show that these linkage sites coincide with replicated sites of linkage in schizophrenia as a disease (Faraone et al., 2004), suggesting a genetic overlap between smoking and schizophrenia. Faraone et al. found linkage of smoking in schizophrenia to the $\alpha 2$ (8p21), $\beta 2$ (1q21), and $\alpha 7$ (15q14) nicotinic receptor subunits. The locus of the $\alpha 7$ subunit, 15q14, has also been linked to the P50 deficit in schizophrenia with a LOD score of 5.3 (Freedman et al., 1997). Linkage of this site to schizophrenia has been replicated in multiple studies (Freedman et al., 2001a; Freedman et al., 2001b; Leonard et al., 1998; Xu et al., 2001; Liu et al., 2001; Tsuang et al., 2001; Kaufmann et al., 1998; Stober et al., 2000; Riley et al., 2000). A linkage of smoking in schizophrenia to a dinucleotide repeat in intron 2 of the $\alpha 7$ gene, *CHRNA7*, was recently reported (De Luca et al., 2004), further supporting a role for the $\alpha 7^*$ receptor in smoking in schizophrenia.

Normalization of sensory processing and cognitive deficits by smoking in schizophrenia

Schizophrenics suffer from multiple sensory processing deficits including auditory sensory processing (P50 deficits) (Adler et al., 1991), eye-tracking deficits (Iacono et al., 1992; Ross et al., 1998; Holzman et al., 1973), pre-pulse inhibition (PPI) abnormalities (Braff et al., 2001; Meincke et al., 2004), and cognitive deficiencies (Barch et al., 2003; Cornblatt and Malhotra, 2001; Leger et al., 2000). Smoking has been found to improve all of these deficits in schizophrenic patients.

The P50 response is measured by electroencephalography as a wave that occurs with a 50 msec latency after an auditory stimulus. When a second stimulus is given 0.5 sec later, the response is inhibited or gated (Adler et al., 1991). Schizophrenics, however, fail to gate out the second response, suggesting that an inhibitory mechanism is aberrant in these patients (Adler et al., 1982; Freedman et al., 2000). The P50 deficit is inherited; approximately 50% of first degree relatives of schizophrenics also have the deficit (Waldo et al., 2000). Smoking transiently normalizes the P50 deficit, in both schizophrenic patients (Adler et al., 1993; Griffith et al., 1998), and their first-degree relatives (Adler et al., 1992).

Pre-pulse inhibition (PPI) is somewhat similar to effects seen in the P50 response. PPI measures the effects of a weak stimulus given prior to a strong stimulus on the response to the strong stimulus. A normal performance is a reduction in the amplitude of the second response (Graham, 1975), again implying an inhibitory mechanism. PPI is abnormal in schizophrenic subjects; the first stimulus does not inhibit the second response (Braff et al., 2001). As with the P50 deficit, PPI appears to be inherited (Anokhin et al., 2003). These two endophenotypes

may have some causal factors in common, but they are inherited independently (Kumari et al., 2000) and, unlike the P50, PPI involves a motor response. Smoking has a positive effect on PPI deficits in schizophrenia (Kumari et al., 2001). PPI is impaired by smoking abstinence in schizophrenia and improved by acute smoking reinstatement, mediated by stimulation of nicotinic receptors (George et al., 2006).

Eye-tracking deficits are also inherited (Holzman et al., 1984) and improved by smoking in schizophrenia (Olincy et al., 1998;Larrison-Faucher et al., 2004;Avila et al., 2003). The eye-tracking abnormalities most often studied include smooth-pursuit (SPEM) and antisaccade responses. The first measures accuracy of eye movement following a moving target, and the latter measures an inhibitory response in which the subject is asked to generate an eye movement in opposite orientation to the target. Both SPEM and antisaccade performance were improved in schizophrenic patients on nicotine (Olincy et al., 2003;Klein and Andresen, 1991;Depatie et al., 2002;Avila et al., 2003). It has also been recently shown in an fMRI study that eye-tracking performance is improved through cholinergic stimulation of the hippocampus and cingulate gyrus (Tanabe et al., 2006).

Nicotine is known to improve cognitive function in animal studies (Levin and Simon, 1998;Levin et al., 2006). Cognitive deficits are common in schizophrenia including decreased attention and working memory (Barch et al., 2003;Cornblatt and Malhotra, 2001;Leger et al., 2000;Sharma and Antonova, 2003). Both attention (Lohr and Flynn, 1992) and working memory (Jacobsen et al., 2004;Myers et al., 2004;Sacco et al., 2005) are improved in schizophrenic patients by smoking. Withdrawal of schizophrenic smokers worsened a visuospatial working memory task (George et al., 2002).

These results are summarized in Table 1 and are consistent with a self-medication hypothesis. Schizophrenics may be attempting to treat these underlying endophenotypic deficits by smoking.

Animal studies show a link between the $\alpha 7^*$ receptor and sensory processing deficits

In animal studies, blockade of the $\alpha 7^*$ receptor with specific antagonists results in loss of auditory sensory gating, similar to that seen in schizophrenia (Luntz-Leybman et al., 1992). A mouse model of low levels of hippocampal *Chrna7* expression exists in the DBA/2j mouse compared to the C3H strain with high levels of expression (Stevens et al., 1996). Treatment of these mice with 3–2,4 dimethoxybenzylidene anabaseine (DMXB-A), a specific agonist of the $\alpha 7^*$ receptor results in normalization of the sensory gating deficit (Simosky et al., 2001;Stevens et al., 1998).

Nicotinic receptor expression is low in postmortem brain of schizophrenic subjects

The expression of the *CHRNA7* gene is low in schizophrenic postmortem hippocampus (Freedman et al., 1995). This finding has been replicated in cortex (Guan et al., 1999;Marutle et al., 2001) and in the reticular nucleus of the thalamus (Court et al., 1999). The *CHRNA7* gene has been cloned (Peng et al., 1994;Breese et al., 1997a). The gene is partially duplicated; exons 5–10 were duplicated proximal to the full-length *CHRNA7* gene, interrupting a partial duplication of a second gene (Gault et al., 1998). A transcript from the chimeric gene, *CHRFAMA7*, is expressed in the brain and periphery as mRNA. It does not appear to form a functional receptor, nor to interfere with expression of the full-length receptor (Villiger et al., 2002). Function of the duplicated gene remains unknown, but it is present in fewer copies in both schizophrenia and bipolar disorder (Gault et al., 1998;De Luca et al., 2006a;Perl et al.,

2006). A 2bp deletion in the duplicated gene, *CHRFAMA7*, has been associated with risk for the P50 deficit (Raux et al., 2002).

High affinity nicotinic receptors, principally the $\alpha 4\beta 2^*$ receptors, are also decreased in expression in schizophrenic hippocampus, as determined by [^3H]-nicotine binding (Breese et al., 2000). In normal hippocampus, receptors in smokers increase in number by approximately 50% (Breese et al., 1997b). However, in schizophrenic subjects, this increase does not occur. Schizophrenic smokers have only slightly elevated receptor binding (Breese et al., 2000). A recent report shows a genetic interaction between the $\alpha 4$ and $\beta 2$ subunits and schizophrenia (De Luca et al., 2006b), again suggesting a link between nicotinic receptors and the disorder. There is also recent evidence in animal studies that the $\alpha 4\beta 2^*$ receptor may contribute to the effects of nicotine on sensory gating in a mouse model (Radek et al., 2006).

Consequences of decreased levels of nicotinic receptors in schizophrenia

The functions of nicotinic receptors are several. Stimulation of the receptors by acetylcholine, the endogenous ligand, or nicotine opens the channel allowing Ca^{++} influx (Mansvelder and McGehee, 2002; McGehee and Role, 1996; Vijayaraghavan et al., 1992). This results in release of a large number of different neurotransmitters, including dopamine, glutamate, acetylcholine, serotonin, and GABA (Dajas-Bailador and Wonnacott, 2004; Wonnacott, 1997; Rousseau et al., 2005; Guo et al., 1998; Zhu and Chiappinelli, 2002). The $\alpha 7^*$ receptor can also have a post-synaptic localization in or near the NMDA post-synaptic density (PSD) (Conroy et al., 2003; Shoop et al., 1999; Levy and Aoki, 2002) where Ca^{++} influx can have downstream effects on gene expression. It is the modulation of these neurotransmitter systems by chronic nicotine stimulation that likely results in addiction to tobacco products. For schizophrenic smokers, decreased nicotinic receptors can lead to changes in overall neurotransmitter release and also changes in gene expression, compared to control smokers (Leonard, 2003). A microarray study of global gene expression in human hippocampus of control and schizophrenic smokers and non-smokers showed that 277 genes were significantly changed in expression in smokers. The most significantly changed group of genes were those playing a role in the NMDA-PSD. More importantly, in schizophrenic smokers, 77 genes were differentially regulated by smoking (Mexal et al., 2005). The differential regulation fit specific patterns showing that gene expression was abnormal in schizophrenic non-smokers, compared to control subjects (either up- or down-regulated). In schizophrenic smokers, the expression was brought to control levels, or normalized. If the expression of a specific gene was up-regulated in schizophrenic non-smokers, in schizophrenic smokers expression was decreased to control levels. If the expression was decreased in schizophrenic non-smokers, compared with controls, it was increased to control expression values in schizophrenic smokers (Mexal et al., 2005). The microarray results were confirmed by real-time quantitative PCR (qRT-PCR). These results are consistent with a self medication model for smoking in schizophrenia (Table 1); smoking is normalizing gene expression for a large number of genes, several of which lie in the NMDA-PSD, the most prevalent excitatory synapse in brain.

Alternatives to smoking for schizophrenia

Smoking improves psychiatric symptoms in schizophrenia (Glynn and Sussman, 1990), particularly negative symptoms (Smith et al., 2002; Dalack et al., 1999). However nicotine is obviously not a good drug for schizophrenia. Besides its adverse health risks, nicotine quickly desensitizes its receptors (Alkondon et al., 2000; Benwell et al., 1995; Dani et al., 2000; Grady et al., 1994; Griffith et al., 1998; Marks et al., 1994; Quick and Lester, 2002), abrogating its effects. The $\alpha 7^*$ receptor has been selected as a major target for drug development for cognitive deficits in schizophrenia by the NIMH Committee on Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) (Bromley, 2005; Psychiatric News,

2006). Recently several new agonists have been introduced, including 3–2,4 dimethoxybenzylidene anabaseine (DMXB-A), a derivative of a marine worm toxin (Martin et al., 2004; Kem, 2000). In animal models, DMXB-A was found to normalize aberrant auditory gating (O'Neill et al., 2003; Stevens et al., 1998) and to have effects on cognition (Arendash et al., 1995; Bjugstad et al., 1996; Kem, 2000; Hunter et al., 1994). A Phase I trial of adjunct DMXB-A for schizophrenic non-smokers has been completed. Results show improvements in both the sensory processing P50 deficit and in cognition (Olincy et al., 2006). The major effect on cognition was on attention, as measured by the Repeatable Battery for Assessment of Neuropsychological Status (RBANS). A Phase II trial is underway in which effects in schizophrenic smokers will be assessed. Such drugs may be effective for smoking in schizophrenia as well as for cognitive and sensory therapy. Clozapine, an atypical neuroleptic, results in decreased smoking in schizophrenia (McEvoy et al., 1995; George et al., 1995). Clozapine blocks the 5HT₃ receptor, resulting in release of acetylcholine (Shirazi-Southall et al., 2002). Clozapine also normalizes the P50 deficit in schizophrenia (Nagamoto et al., 1996). Another antagonist of the 5HT₃ receptor, tropisetron, was recently shown to normalize the P50 deficit (Koike et al., 2005). The hypothesis of the action of these drugs is that they act at nicotinic receptors by releasing endogenous acetylcholine.

Summary

While some aspects of nicotine addiction are likely to be similar across all chronic users of tobacco products, both biological and molecular evidence suggests that schizophrenics are smoking, at least partially, to self-medicate underlying neuropathology. Sensory processing deficits are normalized by smoking in schizophrenia. Low levels of nicotinic receptors in schizophrenia may lead to differences in neurotransmitter release and differential changes in gene expression in which abnormal expression is normalized by smoking. The development of drugs targeted to nicotinic receptors, particularly the $\alpha 7^*$ receptor, represents an important research endeavor.

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Table 1

Evidence for self-medication by smoking in schizophrenia

Effect of Nicotine	References
Normalizes P50 deficit	Adler et al., 1993; Griffith et al., 1998
Improves eye-tracking deficits	Klein and Andresen, 1991; Olincy et al., 1998; Depatie et al., 2002; Avila et al., 2003; Larrison-Faucher et al., 2004; Tanabe et al., 2006
Improves pre-pulse inhibition (PPI)	Kumari et al., 2001; George et al., 2006
Improves cognition	Lohr and Flynn, 1992; Smith et al., 2002; Jacobsen et al., 2004; Myers et al., 2004; George et al., 2002; Sacco et al., 2005
Improves psychiatric symptoms	Glynn and Sussman, 1990; Dalack et al., 1999; Smith et al., 2002
Normalizes aberrant gene expression	Mexal et al., 2005