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Review article

Neurocognitive endophenotypes in schizophrenia: Modulation by nicotinic receptor systems

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ABSTRACT

Cigarette smoking is the leading preventable cause of death in the Western world, with a considerably higher prevalence observed in schizophrenia compared to the general population. Despite the negative health consequences of smoking heavily, it has been proposed that individuals with schizophrenia may maintain smoking behaviors to remediate symptoms associated with the disorder. Neurocognitive deficits are a core feature of schizophrenia and are present in approximately 80% of patients. Further, these deficits constitute an endophenotype of schizophrenia, as they are stable across disease phases, and are heritable. The neurocognitive deficits that are present in schizophrenia are especially debilitating, since they are associated with poor clinical and functional outcomes and community integration. Interestingly, these deficits may also constitute a vulnerability factor towards the initiation and maintenance of tobacco use. Contributing to the potential shared vulnerability between schizophrenia and tobacco dependence is a dysregulation of the nicotinic acetylcholine receptor (nAChR) system. Pre-clinical evidence has shown that nicotine affects several neurotransmitter systems, including dopamine (DA), glutamate, and γ-aminobutyric acid (GABA), and certain neuropsychological deficits associated with these neurotransmitters (reaction time, spatial working memory, sustained attention, and sensory gating) are improved after nicotine administration in patients with schizophrenia. These positive effects on neurocognition appear to be more pronounced in smokers with schizophrenia, and may be an important mechanism that explains the co-morbidity of schizophrenia and tobacco dependence.

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Contents

1. Introduction

Cigarette smoking is the leading preventable cause of death in the Western world (Mokdad et al., 2004), with a considerably higher prevalence seen among those with a psychiatric diagnosis, especially schizophrenia (45–85% versus 17% in the Canadian general population) (Kalman et al., 2005; Lasser et al., 2000). Not only are individuals with schizophrenia more likely to smoke cigarettes, but they smoke more cigarettes per day, are more nicotine dependent, and smoke more intensely (e.g., more puffs per cigarette, greater puff volume, and higher carbon monoxide (CO) boosts) (Tidey et al., 2005). Despite the negative health consequences of smoking heavily, it has been proposed that individuals with schizophrenia may sustain smoking to remediate certain symptoms of the disorder. Specifically, patients with schizophrenia may derive cognitive enhancement by means of cigarette smoking.

Neurocognitive deficits are a core feature of schizophrenia for which there are no satisfactory treatments. Cognitive deficits are present in approximately 80% of patients (Keefe et al., 2005) and affect many domains including attention, social cognition, executive function, and working memory (Heinrichs and Zakzanis, 1998). While positive and negative symptoms of schizophrenia are the most pronounced features of the illness insofar as leading to acute hospitalization and treatment, neurocognitive deficits have been relatively neglected, both in treatment and in research. Cognitive deficits that are present in schizophrenia are especially debilitating, as they lead to poor clinical, social, and functional outcomes. Moreover, these deficits are present throughout the patient's lifetime and are not the result of the positive or negative symptoms of the disorder, or antipsychotic treatment and appear to be stable and heritable features of schizophrenia (Green et al., 2004). As such, neurocognitive deficits are considered an endophenotype associated with this illness (Gottesman and Gould, 2003). These deficits may also constitute a vulnerability factor towards the initiation and maintenance of tobacco use (George, 2007; Sacco et al., 2004; Wing et al., 2012), as several studies have noted transient normalization of several neurophysiological measures of information processing after cigarette smoking or nicotine administration (Adler et al., 1993, 1998; Depatie et al., 2002; George et al., 2006; Olincy et al., 1998; Woznica et al., 2009), as well as further cognitive decline after smoking abstinence (George et al., 2002).

Two overarching theories that may explain the high smoking prevalence that is observed among schizophrenia patients are the self-medication hypothesis (SMH) and the addiction vulnerability hypothesis (AVH). The SMH proposes that individuals with schizophrenia smoke to help ameliorate psychiatric symptomatology associated with the disorder (e.g., positive and negative symptoms, cognitive deficits, anxiety), as well as antipsychotic side effects (Khantzian, 1985; Winterer, 2010). The AVH (Chambers et al., 2001) proposes that there are shared genetic factors and brain abnormalities that underlie both schizophrenia and tobacco addiction (Chambers, 2009; George, 2007). We will focus specifically on nicotinic acetylcholine receptor (nAChR) dysfunction, and how this may contribute both to the cognitive deficits and the high smoking prevalence that is seen in individuals with schizophrenia.

We propose that there is value in treating cognitive deficits and co-morbid tobacco addiction simultaneously in people with schizophrenia. This review will present the most current information about the effects of nAChR dysregulation, as well as exogenous nicotinic agents, on neurocognitive deficits seen in schizophrenia. To this end, a comprehensive picture will be presented, examining different aspects of cognition, as well as including studies from multiple disciplines. Finally, a critical review will be presented to assess the present state of the field, where the gaps are, and to suggest future directions in the way of improving treatment options for those with schizophrenia and co-morbid tobacco dependence.

2. Neurobiology of nicotinic acetylcholine receptors (nAChRs)

An emerging area of research is the potential shared vulnerability between schizophrenia and tobacco dependence, based on putative dysregulation of the nicotinic acetylcholine receptor (nAChR) systems. Nicotine, the main psychoactive constituent in tobacco smoke, acts at the $\alpha4\beta2$ nAChR subtype; This receptor is also activated by the endogenous neurotransmitter acetylcholine. nAChRs in the central nervous system (CNS) are pentameric ion channel complexes (Dani et al., 2011) comprised of two α and three β subunits. There are seven α subunits designated $\alpha2$–$\alpha9$ and three β subunits designated $\beta2$–$\beta4$. Thus, there is considerable diversity in subunit combinations, which may explain some of the region-specific and functional selectivity of the effects of nicotinic agents throughout the CNS. Further, the subunits that comprise nAChRs determine whether they are high-affinity or low-affinity: those that contain the β subunits belong to the high-affinity family while those that contain only α subunits belong to the low-affinity family. These pentameric receptors are either homomerically or heteromerically arranged (e.g., $(\alpha7)_5$ or $(\alpha4)_3(\beta2)_2$). Activation of nAChRs leads to Na^+/Ca^{2+} ion channel fluxes and neuronal firing. Chronic exposure to nicotine results in receptor desensitization (Pidoplichko et al., 1997), inactivation, and upregulation (Gentry and Lukas, 2002). This increase in receptor number is dose-dependent but also reversible in smokers who quit smoking (Breese et al., 1997). Due to their wide distribution throughout the CNS, nAChRs are situated on several different neurotransmitter secreting neuron types. Of importance for nicotine addiction are the nAChRs situated on mesolimbic dopamine (DA) neurons that project from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc). Activation of nAChRs on mesolimbic DA neurons leads to DA release in the NAcc, which helps to facilitate the addictive process involved in chronic tobacco use.

At low concentrations of nicotine, $\alpha4\beta2$ nAChR stimulation of afferent GABAergic projections onto mesoaccumbal DA neurons predominates, leading to reduced mesolimbic DA neuron firing and DA release. At higher nicotine concentrations, $\alpha4\beta2$ nAChRs desensitize and activation of $\alpha7$ nAChRs on glutamatergic projections predominates, leading to increased mesolimbic DA neuron firing and DA secretion. Subsequently, nAChRs desensitize within several milliseconds of activation by nicotine. nAChRs then resensitize after overnight abstinence, which presumably explains why most smokers report that the first cigarette in the morning is the most satisfying.

Evidence suggests that individuals with schizophrenia, specifically smokers, show reduced upregulation of high-affinity nAChRs (Breese et al., 2000). Work by D'Souza et al. (2012) have demonstrated that smokers with schizophrenia have reduced $\beta2$ availability, which also correlated with greater severity of negative symptoms. Further, those with schizophrenia also have fewer α-bungarotoxin (α-BTX) binding sites in the hippocampus, which is indicative of a reduction in $\alpha7$ nAChRs (Adler et al., 1998; Freedman et al., 1995; Leonard et al., 1996). This subunit has been genetically linked to schizophrenia, specifically P50 sensory gating deficits, an index of information processing (Freedman et al., 1997), as well as functional polymorphisms of the low-affinity nAChRs that alter sensory physiology (Leonard et al., 2000).

Neuroimaging techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fRMI) could possibly be used to study the effects that nicotine has on neurocognition. Recent functional neuroimaging studies (Brody et al., 2006; Esterlis et al., 2010) have shown that, after smoking to satiety, nAChR saturation levels are similar to the saturation levels seen after smoking just a few puffs. Therefore, while binding to central nAChRs is an important first step in the effects of nicotine, it is not a complete explanation for continued smoking behaviors. Further, given that nicotine administration improves cognition in patients with schizophrenia, and that smoking just a few puffs from a cigarette results in nAChR saturation, it can be concluded that nAChRs are critical to cognitive function in schizophrenia.