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Increased nicotine and cotinine levels in smokers with schizophrenia and schizoaffective disorder is not a metabolic effect

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Abstract

It has been hypothesized that smokers with schizophrenia take in more nicotine per cigarette than smokers without this disorder. This study examines this phenomenon by comparing the serum nicotine and cotinine levels in smokers with either schizophrenia or schizoaffective disorder compared to control smokers without mental illness. Serum cotinine and nicotine levels of smokers with schizophrenia or schizoaffective disorder were 1.3 times higher than control smokers (cotinine 291 versus 227 ng/mL; $p=0.0115$; nicotine 28 versus 21 ng/mL; $p<0.001$) despite smoking a similar number of cigarettes per day. Similar serum 3′-hydroxycotinine (3HC) to cotinine ratios in both groups indicate that this difference was not due to differences in the rate of metabolism of nicotine or cotinine. By examining serum nicotine and 3HC/cotinine ratios in addition to cotinine, this study expands upon previous research that relied on cotinine as an indirect indicator for nicotine intake. Our data support the hypothesis that the increased serum nicotine and cotinine levels observed are attributable to an increased nicotine intake per cigarette in smokers with schizophrenia as compared to those without mental illness.

Keywords: Schizophrenia; Nicotine; Smoking; Cotinine

1. Introduction

People with schizophrenia are nearly three times as likely to smoke as the general population, with most studies finding prevalence rates of 70–90% (Hughes et al., 1986; de Leon et al., 1995; Ziedonis et al., 1994). Even using a conservative smoking prevalence rate of 70%, we can estimate that there are more than 2,000,000 smokers with schizophrenia in the U.S. presently, based on a 1% population estimate for schizophrenia. International studies have also typically found increased rates of smoking among persons with schizophrenia (de Leon et al., 2002; Liao et al., 2002;

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Kelly and McCreadie, 1999; Beratis et al., 2001). Smokers with schizophrenia have mortality rates that exceed that of the general population. Smoking-related fatal diseases are more prevalent in individuals with schizophrenia, with 2.2 times the risk of cardiovascular mortality and 3.2 times the risk of respiratory disease, both of which are highly linked to smoking (Curkendall et al., 2004; Brown et al., 2000; Joukamaa et al., 2001).

Heavy smoking (defined as more than 20 cigarettes per day), is common both in schizophrenia (Hughes et al., 1986; de Leon et al., 1995; Kelly and McCreadie, 1999; Vanable et al., 2003) and bipolar disorder (Gonzalez-Pinto et al., 1998) and is linked to the presence and severity of psychotic symptoms among bipolar patients (Corvin et al., 2001). Smokers with schizophrenia are highly nicotine dependent and enter tobacco treatment smoking an average of 25 cigarettes per day, with Fagerstrom measures of nicotine dependence in the moderate to severe range (George et al., 2002a; Williams et al., 2004; Steinberg et al., 2004).

It has been proposed that smokers with schizophrenia are more efficient smokers, who take in more nicotine per cigarette than smokers without this disorder. There is evidence both supporting and contradicting this claim. The first discovery by Olincy et al. (1997) showed that concentrations of cotinine, the major proximate metabolite of nicotine, were higher in the urine of 20 smokers with schizophrenia when compared to normal controls who smoked the same number of cigarettes per day. This study was valuable, but limited by its small sample size, lack of SCID diagnoses for schizophrenia, lack of measurement of blood nicotine concentration and use of an enzyme-linked immunoassay technology, rather than gas or liquid chromatography, which have greater specificity and sensitivity (Dhar, 2004). Another group has recently demonstrated a similar finding of increased saliva cotinine in smokers with schizophrenia compared to controls who smoked the same amount of cigarettes per day (Strand and Nyback, 2005). Cotinine has a half-life averaging 16 h (Benowitz et al., 1983), making it easy to measure in body fluids with an exposure detection range of 3–5 days. This measure is also much less dependent on the time to last cigarette than is nicotine, which has a half-life of 2 h.

A report of 13 smokers with schizophrenia who underwent functional magnetic resonance imaging (fMRI) had higher plasma nicotine and cotinine levels than control smokers although the procedures did not standardize the time since last cigarette (Jacobsen et al., 2004). A study on the effects of smoking abstinence on working memory showed higher plasma cotinine levels in schizophrenic versus control smokers but the difference was not statistically significant (George et al., 2002b). One group recently failed to find higher urinary cotinine levels in smokers with schizophrenia, although this study did not control for amount of cigarettes per day (Bozikas et al., 2005).

Studies of smoking topography would be useful to demonstrate that smokers with schizophrenia differ in their cigarette puffing behavior but to date, none have been published. A preliminary report of smoking topography showed that smokers with psychotic disorders smoke differently than controls with out psychiatric illness taking more puffs per cigarette, with a shorter inter-puff interval, and a greater total puff duration compared to controls, suggesting greater intake of nicotine (Caskey et al., 2003). Limitations of this study include small sample sizes and lack of blood sampling for nicotine in all subjects.

One objective of this study was to measure serum nicotine and cotinine levels in 100 smokers with schizophrenia or schizoaffective disorder and compare these to control smokers without mental illness. Because we were concerned about possible metabolic differences in smokers with schizophrenia that could affect nicotine and cotinine levels we also measured levels of the cotinine metabolite, 3′-hydroxycotinine (3HC). The metabolism of nicotine to its proximate metabolite cotinine is metabolized primarily by the liver enzyme CYP2A6 (Hukkanen et al., 2005). The metabolism of cotinine to its main metabolite 3HC is also mediated primarily or exclusively by CYP2A6. Individuals with no CYP2A6 activity due to gene deletion for little or no 3HC, confirming the specificity of the enzyme (Dempsey et al., 2004). The ratio of 3HC/cotinine (i.e. the metabolic product/parent compound) has been used as a marker of CYP2A6 activity. (Dempsey et al., 2004). The ratio, measured in plasma or saliva, has been shown to be highly correlated with the clearance of nicotine administered orally. Our second objective was to compare the 3HC to cotinine ratios in schizophrenics and controls to examine the possibility of differences in the rate of