

Nicotine Dependence, Symptoms and Oxidative Stress in Male Patients with Schizophrenia

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The high rate of smoking in schizophrenia may reflect patients' attempts to reduce the side effects of antipsychotic medications, and one mechanism for this reduction may be a reduction in oxidative stress and free radical-mediated brain damage that may contribute to schizophrenic symptoms and to complications of its treatment. Symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS), side effects were assessed with the Simpson and Angus Rating Scale (SAS), and malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) activities were measured in plasma. All of these measures were compared in 130 male inpatients with DSM-IV schizophrenia: 104 smokers and 26 non-smokers. The results showed that the positive PANSS symptoms were lower in smokers than non-smokers (14.5 vs 17.5), while the negative symptoms were lower in those who smoked more cigarettes ($r = -0.23$). The SAS showed no differences. The CAT activity was correlated with both GSH-Px and SOD activities. Of the three enzymes only the CAT activity was significantly higher in smokers than non-smokers (2.9 vs 1.6 U/ml), but greater SOD activity correlated more cigarettes smoked ($r = 0.24$). Consistent with some protection against oxidative stress, MDA also was significantly lower in smokers than non-smokers (9.2 vs 14.4 nmol/ml). The fewer positive symptoms in smokers and fewer negative symptoms in those who smoked more cigarettes may be a selection bias, but appears to be associated with decreased oxidative stress and lipid peroxidation in schizophrenics who smoke tobacco.

Neuropsychopharmacology (2007) **32**, 2020–2024; doi:10.1038/sj.npp.1301317; published online 17 January 2007

Keywords: schizophrenia; nicotine; cigarette smoking; oxidative stress; antioxidant enzymes; symptom

INTRODUCTION

Between 40 and 90% of schizophrenic patients smoke, which is substantially higher than a variety of comparison populations (Dalack *et al*, 1998; Kelly and McCreddie, 1999), including those with other severe mental illnesses (LLerena *et al*, 2002). These higher rates in schizophrenia persist across cultures and countries and after correcting for possible confounds, such as marital and socio-economic status, alcohol use, antipsychotic use, or institutionalization (de Leon *et al*, 2002; LLerena *et al*, 2002; Lohr and Flynn,

1992). Smokers with schizophrenia also smoke more, favor stronger cigarettes and extract more nicotine from their cigarettes (Olinicy *et al*, 1997) than normal smokers. The reasons for this widespread smoking in schizophrenia are not well understood, but they may be attempting to reduce the side effects of antipsychotic medications, to alleviate negative symptoms and/or cognitive deficits associated with schizophrenia (Adler *et al*, 1998; Kumari and Postma, 2005).

Nicotine in quantities similar to those in cigarette smoke can induce oxidative stress, as shown *in vitro* and *in vivo* (Solak *et al*, 2005). Increased lipid peroxidation occurs in Chinese hamster ovary cells (Yildiz *et al*, 1998) and pancreatic tissue of rats (Wetscher *et al*, 1995) that are incubated with nicotine. After intraperitoneal nicotine the liver, lung and heart tissues of rats also show lipid peroxidation (Helen *et al*, 2003). Furthermore, the plasma of smokers shows increased products of lipid peroxidation (Kharb and Singh, 2000). The significant cognitive, intellectual and behavioral impairments in the offspring of mothers who smoke during pregnancy may be related to oxidative stress and oxidative cellular injury (Ernst *et al*, 2001).

However, nicotine may also have antioxidant potential and neuroprotective effects. For example, epidemiological

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Received 30 May 2006; revised 29 October 2006; accepted 27 November 2006

data suggest an inverse correlation between nicotine use (in the form of smoking) and the rate of progression of Parkinson's disease (PD) or Alzheimer's disease (AD) (Quik, 2004; Sabbagh *et al*, 2002). As enhanced oxidative stress contributes to both PD and AD, nicotine might reverse this component of these two diseases (Linert *et al*, 1999). Experimental data in animal models of PD have also shown the protective effects of nicotine on nigrostriatal degeneration (Soto-Otero *et al*, 2002).

Recent data suggest that reasonably low dose of nicotine may act as an antioxidant and play an important role for neuroprotective effect, whereas high concentration may induce neurotoxicity and stimulate oxidative stress (Guan *et al*, 2003).

Patients with schizophrenia may have altered antioxidant enzyme activities and increased levels of lipid peroxidation (Lohr and Browning, 1995; Yao *et al*, 2001). For example, high levels of superoxide dismutase (SOD), a key enzyme involved in the detoxification of superoxide radicals, have consistently been found in chronic schizophrenic patients (Yao *et al*, 1998; Zhang *et al*, 2003). Moreover, high levels of lipid peroxidation products have been reported in plasma (Mahadik *et al*, 1998), red blood cells (Herken *et al*, 2001) and cerebrospinal fluid of chronic schizophrenic patients (Lohr *et al*, 1990). In the current study, we therefore examined SOD and two related antioxidant enzymes: glutathione peroxidase (GSH-Px) and catalase (CAT). Furthermore, we assessed malondialdehyde (MDA) as an indicator of lipid peroxidation. MDA is a key index of membrane pathology, because it is formed from the decomposition of primary and secondary lipid peroxidation products.

Based on the higher smoking rates among schizophrenic patients and the close relationship between nicotine and oxidative stress, as well as the important role of free radicals in the pathophysiology of schizophrenia, we hypothesize that smoking could play a role in the altered antioxidant enzyme activities and levels of lipid peroxidation in schizophrenia. Because smoking is more common among men than women in both normal populations and schizophrenia, as well as gender differences in smoking behaviors, we included only male subjects. Thus, the purpose of this study was to determine (1) any differences in the psychiatric symptoms or in the side effects of antipsychotics in smokers and non-smokers with schizophrenia; (2) any differences in antioxidant enzyme activities and levels of lipid peroxidation in smokers and non-smokers with schizophrenia; (3) whether there were any relationships among altered antioxidant enzyme activities and levels of lipid peroxidation and psychopathological symptoms in smokers and non-smokers.

METHODS

We recruited 130 male schizophrenic inpatients from Beijing Hui-Long-Guan hospital, a Beijing-city-owned psychiatric hospital. All patients were diagnosed on the basis of the Structured Clinical Interview for DSM-IV (SCID). All schizophrenic patients had been receiving stable doses of oral antipsychotic drugs for at least 12 months before entry into the study. All patients were chronic, with

at least 5 years of illness, were Han Chinese, and were between 26 and 65 years old.

A complete medical history, physical examination and laboratory tests were obtained from all subjects. Any subjects with physical abnormalities were excluded. All subjects gave written informed consent, which was approved by the institutional Review Board, the Institute of Mental Health, Peking University. In addition, a current cigarette smoking questionnaire was administered to each patient. If the subjects identified themselves as a smoker, then further questions determined the average number of cigarettes per day in 1 week before entry into the study. If the subject was currently a non-smoker, further questions were asked regarding previous smoking behavior including whether or not they had quit smoking. Quitters were excluded from the present study. Based on the questionnaire responses, 104 (80%) were identified as 'smokers', whereas 26 (20%) were identified as 'nonsmokers'. The demographic comparisons of the two groups are shown in Table 1.

Clinical Measures

The patient's psychopathology was assessed on the day of the blood sampling using the Positive and Negative Syndrome Scale (PANSS), which was measured by two psychiatrists who had simultaneously attended a training session in the use of the PANSS before the study began. After training, repeated assessment showed that an inter observer correlation coefficient greater than 0.8 was maintained for the PANSS total score.

The same clinical psychiatrist measured parkinsonian side effects using the Simpson and Angus Rating Scale (SAS) to provide standardized objective assessments of rigidity, tremor, brady-kinesia and salivation. It consists of the following ten items: gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabellar tap, tremor and salivation. Each item is rated on a five-point scale (0–4). All items are assessed using clinical observation and neurological examination. Current treatment with anti-parkinsonian medication was also recorded.

Blood Sampling

Venous blood from the forearm vein was collected between 0700 and 0900 h following an overnight fast. Antioxidant enzymes and lipid peroxidation products were determined by a technician blind to the clinical status of subjects.

Determination of Antioxidant Enzymes and Lipid Peroxidation Products

SOD, GSH-Px and CAT activities were analyzed using established procedures. A full description of the assays has been given in our previous report (Zhang *et al*, 2006). Briefly, activity of plasma total SOD, GSH-PX or CAT activity was expressed as units per milliliter plasma (U/ml). The inter- and intra-assay coefficients of variation for SOD were 4.1% ($n = 8$) and 3.2% ($n = 8$), for GSH-PX were 4.8% ($n = 6$) and 5.7% ($n = 6$), and for CAT were 4.5% ($n = 5$) and 5.9% ($n = 5$), respectively. Lipid peroxidation levels

Table 1 Demographics of Smokers and Non-Smokers with Schizophrenia

Variable	Smokers (n = 104)	Non-smokers (n = 26)	F or χ^2	df	p
Age (years)	50.3 ± 8.1	55.1 ± 7.1	F = 7.62	1,127	0.007
Education (years)	9.4 ± 2.4	10.2 ± 2.7	F = 1.86	1,128	0.18
Duration of illness (years)	26.0 ± 7.7	32.4 ± 10.2	F = 12.4	1,127	0.001
Age of onset (years)	24.4 ± 6.1	23.6 ± 5.1	F = 0.35	1,128	0.56
Body Mass Index (kg/m ²)	23.9 ± 3.9	24.4 ± 3.6	F = 0.25	1,127	0.71
Hospitalization numbers	4.0 ± 2.2	4.0 ± 2.1	F = 0.007	1,128	0.93
Anti-parkinsonian drugs	33 (31.7%)	8 (30.8%)			
Antipsychotic types			$\chi^2 = 0.193$	2	0.91
Clozapine	44 (42.3%)	12 (46.2%)			
Risperidone	11 (10.6%)	3 (11.5%)			
Typicals	49 (47.1%)	11 (42.3%)			
Subtypes of schizophrenia			$\chi^2 = 3.70$	3	0.30
Paranoid type	36 (34.6%)	12 (46.2%)			
Disorganized type	14 (13.5%)	2 (7.8%)			
Residual type	11 (10.6%)	5 (19.2%)			
Undifferentiated type	43 (41.3%)	7 (26.6%)			

were monitored by determining the end product of lipid peroxidation MDA using the thiobarbituric acid method. Malondialdehyde results were expressed as nmol/mL.

Statistical Analysis

Demographic characteristics of the smoker and nonsmoker groups were compared using analysis of variance (ANOVA) for continuous variables and chi-squared for categorical variables. As MDA, SOD, GSH-Px and CAT, as well as clinical variables, were all normally distributed in both smoker and nonsmoker groups (Kolmogorov-Smirnov one-sample test), the principal analysis consisted of one-way ANOVA. Because of group differences in age and duration of illness, analysis of covariance was also performed with these covariates. Correlation among biochemical and clinical ratings (eg number of cigarettes smoked) was examined by Pearson correlation coefficients. As both age and education were negatively correlated with cigarettes smoked among all subjects (both $p < 0.05$), a partial correlation was also calculated, with age and education. For the multiple comparisons, we used multivariate regression analysis.

RESULTS

Symptoms and Demographics

The smoker group scored lower than the nonsmoker group on the positive (14.5 ± 6.3 vs 17.5 ± 4.9) ($F = 5.17$, $df = 1,128$, $p < 0.002$), but not the negative, symptom subscales of the PANSS (24.0 ± 5.9 vs 25.8 ± 6.4 ; $F = 0.66$; $df = 1,128$; NS). However, a greater number of cigarettes smoked was significantly associated with fewer negative PANSS symptoms ($r = -0.23$, $p = 0.02$). The SAS total score did not differ

between the two groups and was not correlated with the number of cigarettes smoked. Although Table 1 shows significant differences in age ($F = 7.62$, $df = 1,127$, $p = 0.007$) and duration of illness ($F = 12.4$, $df = 1,127$, $p = 0.001$), when both were added as covariates both PANSS symptom associations remained significant.

Antioxidant Enzyme Activities and MDA Levels

The activities of the three enzymes were positively correlated: CAT activity with SOD ($r = 0.23$, $p = 0.04$) and GSH-Px ($r = 0.24$, $p = 0.02$). The CAT activity was significantly higher in smokers than in non-smokers (2.9 ± 0.3 vs 1.6 ± 0.2 U/ml) ($F = 4.39$, $df = 1,91$, $p = 0.04$), and greater SOD activity correlated more cigarettes smoked ($r = 0.24$, $df = 76$, $p = 0.04$), even after covarying for age and education ($r = 0.27$, $df = 61$, $p = 0.03$). Consistent with some protection against rather than response to oxidative stress, MDA was significantly lower in smokers than in non-smokers (9.2 ± 0.7 vs 14.4 ± 1.7 nmol/ml) ($F = 7.03$, $df = 1,95$, $p = 0.01$).

In addition, a four-to-one matching of smokers to non-smokers was carried out thereby minimally reducing the sample size to 24 non-smokers and 96 smokers in a secondary analysis. This eliminated the age and duration of illness difference, but the primary results on the PANSS and biological measures were unchanged (date not shown).

DISCUSSION

We found fewer positive symptoms in schizophrenic smokers than in non-smokers, and that smokers had significantly increased CAT activity and decreased MDA levels. Furthermore, smoking a greater number of cigarettes

correlated with fewer negative symptoms and with greater SOD activity. As expected, the activities of the three enzymes were positively correlated.

Clinical data suggest a complex association between smoking and symptoms of schizophrenia (Dalack *et al*, 1998). For example, some earlier studies such as Goff *et al* found more positive and negative symptoms in smokers than in non-smokers (Goff *et al*, 1992), although others such as Ziedonis *et al* described fewer negative symptoms in heavy smokers compared to light smokers and non-smokers with schizophrenia (Ziedonis *et al*, 1994). More recent work by Aguilar *et al* found fewer positive symptoms in smokers than in non-smokers (Aguilar *et al*, 2005). Furthermore, smoking high-nicotine cigarettes reduced negative symptoms compared to smoking de-nicotinized cigarettes (Smith *et al*, 2001). Patkar *et al* (2002) like us also found that smoking was associated with significantly fewer negative symptoms in schizophrenia. Thus, newer studies suggest that smoking may be associated with fewer negative and positive symptoms in schizophrenia.

Our finding of increased CAT activity in smokers and greater SOD activity with greater cigarette consumption is consistent with tobacco smoke leading to oxidative stress and stimulating the protective actions of these enzymes to reverse this stress. In non-schizophrenic smokers, MDA also increases as a product of this oxidative stress (Altuntas *et al*, 2002; Ozguner *et al*, 2005; Solak *et al*, 2005). However, the lower MDA levels in schizophrenic smokers suggests that tobacco smoke increases the activity of these antioxidant enzymes more than is needed to simply counteract the peroxidation effects of tobacco smoke. This excess enzyme activity could offer some protection from lipid peroxidation that otherwise occurs in schizophrenia. Peroxidation damage to dopamine neurons may occur in schizophrenia through subcortical dopamine hyperactivity, because excess catecholamines can auto-oxidize to form free radicals as well as form the toxic dopamine metabolite—6-hydroxydopamine (Lohr and Browning, 1995; Davis *et al*, 1991).

Nicotine can reduce this peroxidation through several mechanisms and one of these mechanisms also could reduce the positive symptoms of schizophrenia. Nicotine itself reduces lipid peroxidation that is owing to 6-hydroxydopamine autoxidation (Soto-Otero *et al*, 2002). Furthermore, nicotine can reduce the ability of free radicals to produce 6-hydroxydopamine, which supports an antioxidant mechanism for nicotine's protective effect (Linert *et al*, 1999). Some component of tobacco smoke also appears to inhibit monoamine oxidase and this also might decrease free radical formation (Mazzio *et al*, 2005). Furthermore, chronic nicotine administration decreases basal firing rates in the ventral tegmental area dopamine neurons owing to desensitization of the nicotinic receptors (Rasmussen and Czachura, 1995), and chronic nicotine treatment decreases dopamine catabolism in the dorsal striatum (Kirch *et al*, 1987). Reducing this subcortical dopamine hyperactivity would reduce the positive symptoms in schizophrenia (Davis *et al*, 1991), as well as decreasing the excess dopamine and the production of 6-hydroxydopamine (Dalack *et al*, 1998; Davis *et al*, 1991). Thus, long-term smoking may have several mechanisms that reduce lipid peroxidation in schizophrenia, and like PD, another disease of deteriorating dopamine neurons,

tobacco smoking is associated with milder symptoms (Morens *et al*, 1995).

This study is limited by its sample of chronically hospitalized male patients with more severe psychopathology and longer duration of illness than typical psychotic outpatients or first episode and drug-naïve patients with schizophrenia. Nevertheless, schizophrenic patients who smoke appear to have fewer psychotic symptoms and decreased lipid peroxidation in the context of significantly elevated anti-oxidant enzyme activities. This elevated enzyme activity is consistent with the oxidative stress induced by tobacco smoke, but this stimulated activity appears to overshoot the level needed to reverse the tobacco smoke stress and to possibly reverse a baseline level of ongoing lipid peroxidation associated with schizophrenia itself, chronic antipsychotic medications or some other unidentified cause.

ACKNOWLEDGEMENTS

This study was funded by the Stanley Medical Institute Foundation (03T-459 and 05T-726) (XYZ), and the Department of Veterans Affairs, VISN 1, Mental Illness Research, Education and Clinical Center (MIRECC) and National Institute on Drug Abuse K05-DA0454 and P50-DA18827 (TRK).

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