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The insertion/deletion polymorphism in the angiotensin-converting enzyme gene and nicotine dependence in schizophrenia patients

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Abstract We investigated the relationship between the functional insertion/deletion (I/D) polymorphism in the angiotensin-converting enzyme (ACE) gene and the risk of nicotine dependence in Croatian schizophrenia patients. We also tested whether interactions between ACE-I/D polymorphism and smoking status affected the clinical psychopathology findings in patients as measured using Positive and Negative Symptom Scale (PANSS) scores. Polymerase chain reaction analysis was used to genotype 267 chronically ill schizophrenia patients (140 males/127 females). There were no significant differences in the distribution of ACE genotypes and alleles in male or female schizophrenia patients who were stratified based on their smoking status. However, there was a trend toward a difference in the ACE genotype distribution in female smokers vs. nonsmokers ($\chi^2 = 5.13$, $p = 0.077$) that was due mainly to the significant overrepresentation of ACE-ID heterozygous genotypes in female smokers compared to nonsmokers (62.3 vs. 42.0%, $p = 0.025$). ACE-ID heterozygous females had about a twofold higher smoking risk than ACE-II and ACE-DD homozygous carriers (OR = 2.29, 95% CI 1.1–4.7, $p = 0.026$). We observed no contribution of the ACE genotype-smoking interaction to PANSS psychopathology. This is the first study to investigate the possible association between ACE-I/D polymorphism and nicotine dependence in schizophrenia. Our results suggest that the ACE-I/D polymorphism may be relevant in determining the risk of nicotine dependence in female patients with schizophrenia while the ACE genotype-smoking interaction does not contribute to the clinical expression of schizophrenia.

Keywords Angiotensin-converting enzyme gene · Positive and Negative Syndrome Scale · Schizophrenia · Smoking

Introduction

The pleasurable effects of nicotine, the primary addictive component of tobacco smoke, are thought to be mediated by nicotine's ability to stimulate brain mesolimbic dopamine neurons. By acting on presynaptic nicotinic cholinergic receptors, nicotine is suggested to increase dopamine release and reuptake; in addition, by decreasing the activity of the monoamine oxidase enzyme, nicotine may inhibit dopamine degradation (Drew et al. 2000; Fowler et al. 2003; Iasevoli et al. 2013; Novak et al. 2010; Sagud et al. 2009; Severance et al. 2009). A worldwide meta-analysis revealed that the smoking rate in schizophrenia subjects is threefold greater than among healthy individuals and that the incidence of smoking is twofold higher than in subjects with other psychiatric illnesses (de Leon and Diaz 2005; Levin and Rezvani 2007; Zhang et al. 2012).

The etiology of such high rates of smoking in schizophrenia is not well understood. According to the self-medication hypothesis, smoking may have a beneficial effect in schizophrenia; by restoring dopaminergic

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transmission via central effects of nicotine on dopaminergic system, cigarette smoking may ameliorate cognitive deficits and may also decrease the severity of negative symptoms and the extrapyramidal side effects of antipsychotic medications that block postsynaptic dopamine D2 receptors (Laruelle et al. 2003; Sagud et al. 2009; Zhang et al. 2015; Winterer 2010). However, nicotine has been shown to increase the metabolism of antipsychotic drugs by approximately one-third, through the induced activity of the cytochrome family of enzymes (Misiak et al. 2015; Sagud et al. 2009; Winterer 2010; Zevin and Benowitz 1999). Thus, patients who smoke may be easily undertreated with antipsychotics; this under-medication may partially explain why smokers with schizophrenia have higher number of hospitalizations and more positive symptoms during acute episodes (Williams and Ziedonis 2004; Winterer 2010). Finally, the genetic hypothesis proposes that there is a shared genetic vulnerability i.e. that some genes, especially those in the dopamine signaling pathways, such as dopamine receptor D2 (DRD2), alpha7 nicotinic acetylcholine receptor (CHRNA7), and brain-derived neurotrophic factor (BDNF), might exert pleiotropic effects, contributing to both nicotine dependence and schizophrenia (de Leon and Diaz 2012; de Luca et al. 2004; Kelly and McCreadie 2000; Yoshimasu and Kiyohara 2003; Zhang et al. 2015).

Angiotensin-converting enzyme (ACE) catalyzes the conversion of angiotensin I to angiotensin II in the renin-angiotensin system (RAS) and inactivates bradykinin via the kinin-kallikrein system (Nawaz and Hasnain 2008; Song and Lee 2015). Several lines of evidence suggest that RAS, beyond its classical function in mediating the regulation of blood pressure, might also act as an important determinant in the etiology of conditions involving dopamine, such as substance addiction and psychiatric disorders, by influencing dopaminergic signaling (Jenkins et al. 1996, 1997; Obata et al. 2008). Notably, the neurotransmitter angiotensin II interacts with dopamine in mesocorticolimbic areas, and ACE modulates dopamine turnover in the rat striatum (Jenkins et al. 1996, 1997). In addition, there is decreased dopamine release in the rat striatum in response to captopril and enalaprilat, antihypertensive drugs that inhibit ACE activity (Obata et al. 2008).

To date, several reports have described significantly increased ACE activity in the brain as well as in various peripheral tissues (serum, plasma, etc.) of individuals with schizophrenia (Baskan et al. 2010; Gadelha et al. 2015; Wahlbeck et al. 1993). The most studied RAS-related polymorphic variant, a functional 287-base pair insertion/deletion (I/D) fragment that represents a polymorphism in intron 16 of the ACE gene, accounts for approximately 50% of the ACE levels (Rigat et al. 1990). The influence of the ACE-I/D polymorphism on the etiology of schizophrenia has been extensively investigated (Hui et al. 2014; Nadalin et al. 2012; Song and Lee 2015), but the results have been conflicting. Specifically, there is evidence of an association between the ACE-I/D polymorphism and elevated schizophrenia risk in Spanish and Turkish populations and in women with schizophrenia in the Iranian population (Crescenti et al. 2009; Kucukali et al. 2010; Mazaheri and Saadat 2015). Nevertheless, a meta-analysis of eight studies conducted mostly in European and Asian populations showed no significant associations between the ACE-I/D polymorphic variant and elevated schizophrenia risk (Song and Lee 2015). We recently observed that ACE-I/D polymorphism influenced the clinical expression of schizophrenia as measured via the Positive and Negative Syndrome Scale (PANSS) in a Croatian population (Nadalin et al. 2012). Specifically, we found that patients carrying the D allele in their ACE genotype (ACE-DD homozygous and ACE-ID heterozygous genotypes) had significantly higher negative and general PANSS scores compared to patients who were ACE-II homozygous. In addition, after adjustment for sex, we also observed that the presence of the D allele in the ACE genotype contributed to increased general symptom severity in men with schizophrenia.

Only a few studies have investigated a possible association between the ACE-I/D polymorphism and nicotine dependence (Baghai et al. 2008; Hubacek et al. 2001, 2004). While German ACE-DD homozygous individuals suffering from depression have a significantly higher risk of being smokers (Baghai et al. 2008), studies of healthy subjects in the Czech Republic and in Germany found no associations between ACE-I/D polymorphism and smoking risk (Baghai et al. 2008; Hubacek et al. 2004). Furthermore, the ACE-I/D polymorphism might influence smoking severity. Specifically, the ACE-DD homozygous genotype was associated with higher daily cigarette consumption in patients with depression as well as with a smoking history of a greater number of pack-years in healthy individuals in a German population (Baghai et al. 2008).

To the best of our knowledge, no studies have investigated a possible association between ACE-I/D polymorphism and nicotine dependence in schizophrenia. Based on the elevated smoking rate that is consistently observed in schizophrenia patients (de Leon and Diaz 2005; Zhang et al. 2012) and on the possible relevance of the ACE gene in schizophrenia and nicotine dependence via dopaminergic signaling (Obata et al. 2008; Song and Lee 2015), we investigated whether the risk for nicotine dependence in schizophrenia patients was associated with the ACE-I/D polymorphic variant. There is evidence suggesting that smoking might influence the clinical expression of schizophrenia (Xu et al. 2014; Yee et al. 2015), and we

found previously that the ACE-I/D polymorphism impacts schizophrenia severity (Nadalin et al. 2012). Accordingly, we further hypothesized that an interaction between smoking and ACE-I/D polymorphism might affect PANSS psychopathology scores in a group of patients with schizophrenia. Because of sex-specific differences in the effects of the ACE-I/D polymorphism in various diseases and conditions (Avila-Vanzzini et al. 2015; Higaki et al. 2000), including schizophrenia (Mazaheri and Saadat 2015; Nadalin et al. 2012, 2015), and because of observations of sex-gene interactions in the risk of nicotine dependence (Beuten et al. 2006; Nedic et al. 2010; Tochigi et al. 2007; Nadalin et al. 2016), we performed all analyses separately for male and female patients.

Patients and methods

Study participants

Our study group included 267 chronically ill schizophrenia in-patients who were treated at the Department of Psychiatry in the Clinical Hospital Center in Rijeka, Croatia ($n = 179$) or at the Psychiatric Hospital in Rab, Croatia ($n = 88$) due to an acute exacerbation of schizophrenia symptoms. Table 1 shows the patients' demographic and clinical characteristics. Their diagnoses were assessed by at least two psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria using structured clinical interviews. PANSS psychopathology evaluation was performed at the time of each patient's last admission during an acute state of the illness that required hospitalization.

All patients were treated with a stable antipsychotic medication regimen for at least 12 months before they entered the study. Antipsychotic polytherapy was used in two-thirds of the patients, while one-third of them received monotherapy. The patients received the following drugs: risperidone ($n = 90$), clozapine ($n = 84$), olanzapine ($n = 81$), quetiapine ($n = 71$), haloperidole ($n = 42$), fluphenazine ($n = 37$), paliperidone ($n = 34$), aripiprazole ($n = 27$), levomepromazine ($n = 25$), ziprasidone ($n = 23$), sulpiride ($n = 21$), and amisulpride ($n = 9$). The antipsychotic promazine was also prescribed to many patients ($n = 114$), usually in smaller doses (75–150 mg per day), when anxiolytic or hypnotic drugs, such as benzodiazepines or barbiturates, were not sufficiently effective. The mean antipsychotic dose (converted to chlorpromazine equivalents) was 550 ± 250 mg per day (Woods 2003).

The psychiatrists obtained information about the patients' smoking status via a questionnaire. Smokers were defined as individuals who smoked more than one cigarette each day who had smoked for more than one year. Nonsmokers were defined as those who had smoked fewer than 100 cigarettes during their lifetime. Former smokers were characterized as individuals who had previously smoked more than one cigarette each day but who had quit smoking more than one year before the questionnaire was filled out (de Leon and Diaz 2005; Guo et al. 2007). Quitters and ex-smokers were excluded from the study.

All clinical and laboratory investigations were conducted in accordance with the ethical standards of the latest version of the Declaration of Helsinki. After the study's purpose and methods had been described, the patients provided written informed consent to participate in the study, which was approved by the Ethics Committee of the School of Medicine, University of Rijeka, Croatia.

Genotyping

Genomic DNA was extracted from whole blood using the FlexiGene DNA kit 250 (QIAGEN GmbH, Hilden, Germany) according to the manufacturer's instructions. Polymerase chain reaction (PCR) based genotyping was performed in the Laboratory for Molecular Genetics (Department of Biology and Medical Genetics, School of Medicine, Rijeka) using protocols that were described previously (Rigat et al. 1990). To exclude mistyping of the ACE-ID heterozygotes as ACE-DD homozygotes, all

Table 1 Characteristics of the schizophrenia patients in this study

	Males ($n = 140$)	Females ($n = 127$)
Age, years	40.6 ± 12.0	42.9 ± 11.8
Age at first hospitalization	26.2 ± 7.6	27.6 ± 8.2
PANSS positive symptom score	26.6 ± 5.3	25.2 ± 5.6
PANSS negative symptom score	29.5 ± 6.4	28.4 ± 6.9
PANSS general psychopathology score[a]	53.1 ± 7.8	50.7 ± 7.9
PANSS total score[b]	109.2 ± 15.1	104.3 ± 15.8
Smokers/nonsmokers	99/41	77/50

PANSS Positive and Negative Syndrome Scale

Males vs. females: [a] $F = 4.00$, $p = 0.047$; [b] $F = 4.35$, $p = 0.039$

ACE-DD genotypes were confirmed using insertion-specific PCR (Shanmugam et al. 1993).

Statistical analysis

The ACE genotype and allele distributions among smokers and nonsmokers, as well as the observed and expected genotype proportions according to the Hardy–Weinberg equilibrium, were compared by the Chi-square (χ^2) test. Odds ratios (OR) and 95% confidence intervals (CIs) were used to examine the strength of the association between the ACE-ID heterozygous genotype and the risk for being a smoker among female patients. The factorial analysis of variance (ANOVA) was used to test the possible interaction between ACE genotype and smoking status on positive, negative, general, and total PANSS psychopathology scores. Probability (p) values less than 0.05 ($p < 0.05$) were considered statistically significant. All statistical analyses were conducted using Statistica for Windows, version 12.

Results

The smoking rate was higher for both male and female schizophrenia patients compared to the rate in the general population, with about two-thirds of the patients classified as smokers (Table 1). Interestingly, we found that the prevalence of nicotine dependence did not differ significantly with respect to sex ($p > 0.05$). Table 2 shows the allele and genotype frequencies for the ACE-I/D polymorphism according to patient smoking status. The statistical power of our study was 100% for detecting a 1.5-fold increase in the ACE-D allele frequency and 98% for detecting a 1.5-fold increase in the ACE-I allele frequency. The ACE genotype distributions in male and female patients, in male smokers and nonsmokers, and in female nonsmokers were all consistent with the Hardy–Weinberg equilibrium ($p > 0.05$ for all). However, the ACE genotype distribution in female smokers deviated slightly from the Hardy–Weinberg equilibrium due to an excess of ACE heterozygous (ID) genotypes ($\chi^2 = 5.99$, $p = 0.024$). The allele and genotype frequencies of the ACE-I/D polymorphism were similar to those we reported in our previous studies (Nadalin et al. 2012, 2015) and were not different from those observed in the European population (http://www.ncbi.nlm.nih.gov/snp/?term=rs1799752). Moreover, no significant differences were found in the ACE genotype and allele distributions between groups of male and female schizophrenia patients ($p > 0.05$). We did not find any significant differences in the distribution of the ACE genotypes and alleles in either male or female patients who were stratified according to their smoking status (Table 2). However, we observed a trend towards a difference in the ACE genotype distribution in female smokers compared to female nonsmokers ($\chi^2 = 5.13$, $p = 0.077$) that was due mainly to significant overrepresentation of the ACE-ID heterozygous genotype in female smokers compared with nonsmokers (62.3 vs. 42.0%, $p = 0.025$). Furthermore, the ACE-heterozygous females (ID) had about a twofold

Table 2 The frequency of ACE genotypes and alleles according to smoking status[a]

	Males		
	Smokers ($n = 99$)	Nonsmokers ($n = 41$)	
DD	32 (32.3)	11 (26.8)	$\chi^2 = 1.43$, df = 2, $p = 0.495$
ID	45 (45.5)	17 (41.5)	
II	22 (22.2)	13 (31.7)	
D allele	109 (55.1)	39 (47.6)	$\chi^2 = 1.31$, df = 1, $p = 0.253$
I allele	89 (44.9)	43 (52.4)	
	Females		
	Smokers ($n = 77$)	Nonsmokers ($n = 50$)	
DD	18 (23.4)	19 (38.0)	$\chi^2 = 5.13$, df = 2, $p = 0.077$
ID	48 (62.3)	21 (42.0)	
II	11 (14.3)	10 (20.0)	
ID vs. II + DD			OR = 2.29, 95% CI 1.1–4.7, $p =$ **0.026**
D allele	84 (54.5)	59 (59.0)	$\chi^2 = 0.49$, df = 1, $p = 0.484$
I allele	70 (45.5)	41 (41.0)	

ACE angiotensin-converting enzyme, *CI* confidence interval, *OR* odds ratio

[a] Data are reported as *n* (%)

p value less than 0.05 were considered statistically significant

higher risk of becoming smokers than the ACE-II and ACE-DD homozygous carriers (OR = 2.29, 95% CI 1.1–4.7, $p = 0.026$).

We also investigated whether the ACE genotype interacted with patient smoking status to contribute to the clinical expression of schizophrenia, which was measured using PANSS scores. We found no ACE genotype-smoking interaction with the PANSS scores for either male or female patients ($p > 0.05$ for both; Supplementary Table 1).

Discussion and conclusions

Due to their high smoking rate, schizophrenia patients represent a particularly interesting model group for studying the etiology of nicotine dependence (de Leon and Diaz 2005; Levin and Rezvani 2007). The ACE-I/D polymorphic variant has been intensively investigated in schizophrenia (Hui et al. 2014; Nadalin et al. 2012; Song and Lee 2015) and was associated with schizophrenia severity in our recent study (Nadalin et al. 2012). Here we investigated whether the ACE-I/D polymorphism might influence the risk of nicotine dependence in Croatian schizophrenia patients and whether an interaction between this variant and smoking status might contribute to baseline psychopathology data as measured using PANSS scores.

Functional analysis of the ACE-I/D polymorphism, which was first described over two decades ago, indicates that the homozygous ACE-DD genotype is associated with tissue and plasma enzyme levels that are almost twice as high as those in subjects with the homozygous ACE-II genotype (Rigat et al. 1990). In line with this, we initially speculated that patients with the ACE-DD genotype might release dopamine at higher levels in their brains and might consequently be more vulnerable to developing nicotine dependence. However, our data indicated a greater risk for smoking in female patients who were heterozygous for the ACE genotype (ID), which argues against this hypothesis (Table 2). Moreover, our results disagree with previous reports about the ACE-I/D polymorphism and nicotine dependence: no associations between smoking and ACE-I/D polymorphism in healthy individuals from the Czech Republic and Germany were observed, and there were positive associations between the risk of being a smoker and ACE-DD homozygosity among patients suffering from depression in a German population (Baghai et al. 2008; Hubacek et al. 2004). Furthermore, although evidence suggests that nicotine as well as ACE and/or angiotensin II potentiate dopamine release in same signaling pathway i.e. the mesolimbic dopaminergic reward pathway (Jenkins et al. 1996, 1997; Sagud et al. 2009), we found that the ACE genotype-smoking interaction had no significant influence on PANSS psychopathology scores (Supplementary Table 1).

Interestingly, our analyses of the possible association between ACE-I/D polymorphism alone and PANSS psychopathology scores did not support the results of our previous study (Nadalin et al. 2012), since this study found that the ACE-I/D variant had no significant impact on any of the PANSS scores (data not shown). Nevertheless, it should be noted that novel findings likely reflect the rather complex relationship between ACE genotype and ACE levels in schizophrenia patients (Baskan et al. 2010; Gadelha et al. 2015). For instance, the study carried out by Baskan et al. (2010) yielded unexpected results in that they found that there were no significant differences in serum ACE levels based on different ACE genotypes in a patient group. In addition, a recent study by Gadelha et al. (2015) calculated delta-ACE values in schizophrenia patients by subtracting the mean ACE activity value in control subjects with particular genotypes from the observed plasma ACE activity value in schizophrenia patients with the same genotype. Their findings suggest that delta-ACE values are much better predictors of schizophrenia diagnosis than either ACE dichotomized values (high/low) or ACE-I/D polymorphism genotype alone.

Several findings could account for the gender specific differences in the ACE-I/D polymorphism observed in this study (Gallagher et al. 1999; Sanada et al. 2001; Sumino et al. 2003). It has been shown that estrogen replacement therapy in postmenopausal women may result in the genotype-associated decrease in ACE activity: a significant decrease in plasma ACE activity was observed either in women with the ACE-ID and ACE-II genotypes (Sanada et al. 2001), or in those with the ACE-ID and ACE-DD genotypes (Sumino et al. 2003). Moreover, there is also evidence that estrogen may influence dopaminergic neurotransmission, since it has been observed that estrogen treatment reduces dopamine receptor D2 levels in several rat brain regions (Chavez et al. 2010).

This study has several limitations. Our sample was relatively small, so there is a possibility that some minor effects were not detected. In addition, the study only included patients who were hospitalized, and, therefore, they had more severe psychopathology and longer illness duration than typical psychotic outpatients or first-episode/drug-naïve schizophrenia patients. Moreover, the current sample lacked a healthy control group, and data regarding smoking status were based exclusively on self-reporting. Finally, all patients were under antipsychotic treatment; there is evidence that antipsychotic medications may reduce or increase ACE expression/activity (Beckmann et al. 1984; Wahlbeck et al. 1993, 1998).

In conclusion, our results suggest that the ACE-I/D polymorphism may be relevant in determining the risk of

nicotine dependence in women with schizophrenia. They also indicate that the ACE genotype-smoking interaction has no significant influence on the clinical expression of schizophrenia in either male or female patients. According to the studies investigating an association between the ACE-I/D polymorphism and nicotine dependence among healthy controls and patients with depression, our findings indicated that the mechanism by which ACE-I/D polymorphism contributes to the risk of nicotine dependence in schizophrenia may be different than in other diseases and conditions (Baghai et al. 2008; Hubacek et al. 2004). Furthermore, there was a weak but significant overrepresentation of ACE-ID heterozygous genotypes in female smokers vs. nonsmokers (62.3 vs. 42.0%, $p < 0.05$), which may suggest that intermediate ACE levels (rather than decreased or increased ACE levels) are responsible for the greater risk of nicotine dependence in schizophrenia.

Although our sample size was small, the strength of this study is in that it was conducted in a tightly defined, severe schizophrenia cohort. However, larger studies, as well as studies that include participants with other neuropsychiatric disorders, plus an assessment of nicotine dependence that uses more specific methods (e.g. the Fagerstrom test for nicotine dependence, "pack-year" smoking history, etc.) are needed to verify our findings. It also seems important to clarify the underlying molecular mechanisms that may link the ACE-I/D polymorphic variant with dopaminergic signaling. Another issue that should be considered is that both ACE and angiotensin II have other potential substrates, some of which influence dopaminergic neurotransmission and are proposed to be associated with schizophrenia, such as substance P and neurotensin (Arinami et al. 1996; Azmi et al. 2006; Binder et al. 2001; Gadelha et al. 2015; Krasnova et al. 2000).

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