

Smoking Cue Reactivity in Schizophrenia: Effects of a Nicotinic Receptor Antagonist

Margaret A. Fonder, Kristi A. Sacco, Angelo Termine, Brigid S. Boland, Aisha A. Seyal, Melissa M. Dudas, Jennifer C. Vessicchio, and Tony P. George

Background: Rates of cigarette smoking in schizophrenia are higher than in the general population. To investigate differences in sensitivity to smoking cues between schizophrenia and control subjects, we compared smoking cue reactivity (CR) in schizophrenia versus control smokers with and without pretreatment with the nicotinic acetylcholine receptor (nAChR) antagonist mecamylamine (MEC).

Methods: Smoking CR in schizophrenia ($n = 22$) and nonpsychiatric control ($n = 20$) smokers was determined using exposure to smoking pictures. Three doses of MEC (0, 5, and 10 mg/day) were administered during the 3 test weeks to determine the role of nAChRs in mediating the smoking CR response.

Results: Eleven of 22 (50%) schizophrenia and 10 of 20 (50%) control smokers displayed smoking CR. Smoking CR was not significantly different between schizophrenia and control smokers in the placebo (0 mg/day) condition. However, MEC pretreatment produced a dose-dependent reduction of CR in schizophrenia smokers compared with placebo. There was no significant effect of MEC on CR in control smokers.

Conclusions: Our findings suggest that blockade of CR by MEC may be more robust in schizophrenia versus control smokers, possibly due to reduced nAChR levels in the brains of patients with schizophrenia.

Key Words: Schizophrenia, smoking, urges to smoke, cue reactivity, mecamylamine, human laboratory study

The prevalence of cigarette smoking in clinical samples of individuals with schizophrenia is 58% to 88%, compared with ~23% in the general population (Vocci and DeWit 1999; Lasser et al 2000; George and Vessicchio 2001). Given that smoking is the leading preventable cause of death in the United States (Thun et al 2000), this comorbid association of nicotine addiction with schizophrenia represents an important public health concern, especially given that rates of smoking-related medical illness are higher in schizophrenia compared with the general population (Lichtermann et al 2001). However, determinants of this comorbidity have not been fully elucidated.

Several recent studies have pointed to biological differences between schizophrenia patients and nonpsychiatric control subjects, which may render these patients more susceptible to nicotine addiction. For example, it appears that nicotinic acetylcholine receptors (nAChRs) may play a role in the pathophysiology of schizophrenia (Dalack et al 1998; Leonard et al 2000, 2001, 2002). Nicotine stimulates nAChRs located presynaptically on several neuronal types, including dopaminergic, glutamatergic, and gamma-aminobutyric acid (GABA)ergic neurons, thereby enhancing release of these neurotransmitters (McGehee et al 1995; George et al 2000a; Picciotto et al 2000). Chronic nicotine administration leads to the desensitization of nAChRs and leads to receptor upregulation (Picciotto et al 2000). Recently, it has been demonstrated that nAChR levels are decreased in the brains of schizophrenia patients at every smoking level

(Breese et al 2000), which may be an important determinant of the increased predisposition to nicotine dependence in these patients. Furthermore, it is well established that sensory gating abnormalities linked to low-affinity ($\alpha 7$; CHRNA7) nAChR function (P50 auditory evoked potentials) are common in schizophrenia and are transiently normalized by smoking and nicotine administration (Adler et al 1993, 1998; Freedman et al 1997; Leonard et al 2000, 2002). Other studies have shown that smoking and nicotine administration can (selectively) enhance neuropsychological performance in schizophrenia (Levin et al 1996; George et al 2002a; Smith et al 2002; Sacco et al 2004). Such procognitive effects of nicotine and smoking may further contribute to the vulnerability of these patients to the initiation and maintenance of nicotine dependence.

Furthermore, there may be abnormalities in brain reward pathways in schizophrenia, such as the mesolimbic dopamine (DA) system (reviewed in Chambers et al 2001). In fact, common neurocircuitry may underlie both schizophrenia and drug addiction. The positive symptoms of schizophrenia (delusions, disorganized thinking and speech, hallucinations) may result from the hyperactivity of mesolimbic DA neurons projecting from the ventral tegmental area to the nucleus accumbens, and this is the target of antipsychotic drug effects on positive symptoms of the illness (Knable and Weinberger 1997). The mesolimbic DA system is implicated in addiction (Chambers et al 2001), as all addictive drugs, including nicotine, increase DA release in the nucleus accumbens, which appear to mediate drug reinforcement. Thus, schizophrenia patients may have increased susceptibility to nicotine and other drug addictions because of such hyperfunctional DA reward systems. Furthermore, the negative symptoms of schizophrenia (poverty of speech, blunted affect, loss of volition, social withdrawal) and cognitive deficits may relate to putative hypoactivity of DA neurons projecting to the frontal cortex (Knable and Weinberger 1997). Because nicotine enhances DA release in the prefrontal cortex, schizophrenia patients may be further prone to smoking as a means of self-medicating their negative symptoms and cognitive deficits (George et al 2002a; Sacco et al, in press).

In addition to its role in mediating the direct reinforcing effects of drugs of abuse, the mesolimbic dopamine system may also be involved in drug craving. It has been shown that stimuli

From the Program for Research in Smokers with Mental Illness (PRISM), Connecticut Mental Health Center, and Division of Substance Abuse, Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut.

Address reprint requests to Tony P. George, M.D., Associate Professor, Department of Psychiatry, Yale University School of Medicine, Room S-109, Substance Abuse Center, Connecticut Mental Health Center, New Haven, CT 06519; E-mail: tony.george@yale.edu.

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that elicit drug craving, such as drug-related cues (e.g., people, places, and things that increase drug craving due to conditioned associations), also cause increased DA levels in the nucleus accumbens (Stewart 2000). Thus, drug craving may be mediated by the same DA reward systems that are known to be hyperactive in schizophrenia patients. Hence, it is possible that the high rates of smoking among individuals with schizophrenia may be due, in part, to abnormally elevated levels of tobacco craving in response to smoking-related cues.

Cue reactivity (CR) paradigms monitor reactions of experienced drug users to drug-related stimuli. Exposure to such cues can produce physiological effects and robust craving in addicts (Carter and Tiffany 1999). Importantly, the craving associated with exposure to drug-related cues may contribute to drug relapse, both during habitual drug use and after the achievement of initial drug abstinence (Carter and Tiffany 1999). Thus, cue reactivity methodology may be used to investigate potential pharmacological treatments for decreasing drug craving and for relapse-prevention treatment. The present investigation assessed smoking cue reactivity in schizophrenia as compared with control smokers. Additionally, nAChR antagonist mecamylamine (MEC), which has modest selectivity for the $\alpha_4\beta_2$ and $\alpha_3\beta_4$ subunit containing forms of the high-affinity nAChR (Carter and Tiffany 1999; Picciotto et al 2000; Young et al 2001), was used to probe the role of central nAChRs in mediating the smoking cue reactivity response in both schizophrenic and control smokers. Our results suggest that while smoking cue reactivity does not differ between schizophrenia and control smokers matched for smoking consumption and nicotine dependence level, sensitivity to the effects of MEC on the smoking cue reactivity response is significantly enhanced in patients with schizophrenia.

Methods and Materials

Participants

Twenty-two schizophrenia and 20 nonpsychiatric control smokers were recruited from a study of cigarette smoking and cognitive function in schizophrenia (Sacco et al, *in press*). The protocol was approved by the Human Investigation Committee of the Yale University School of Medicine, and informed consent for study participation was obtained from all subjects by trained research staff. All smokers were heavy (≥ 15 cigarettes/day) smokers, with a Fagerstrom Test for Nicotine Dependence (FTND) score of 5 or higher, an expired breath carbon monoxide (CO) level >10 parts per million (ppm), and plasma cotinine level of >150 ng/mL (George et al 2002b; Sacco et al, *in press*). Patients met DSM-IV criteria for schizophrenia/schizoaffective disorder by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and were treated with a stable dose of antipsychotic medication (either typical or atypical antipsychotic); control smokers did not meet criteria for any current mental disorder.

Procedures

Each subject completed 3 consecutive test days during each of 3 test weeks (Figure 1). During each study week, subjects received a different pretreatment MEC dose: 0 mg/day (placebo), 5 mg/day, or 10 mg/day, in twice daily dosing intervals using 2.5 mg active MEC and matching placebo tablets. Test weeks were separated by at least 7 days to minimize study medication carryover effects. Mecamylamine dose assignments across the 3 test weeks were counterbalanced to control for medication sequence effects. Study medications were administered to sub-

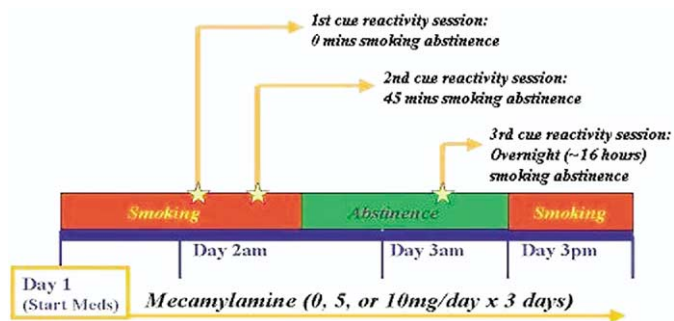


Figure 1. Single subject timeline for smoking cue reactivity session administration in schizophrenia (A) and control (B) smokers. Smoking cue reactivity assessment reported in the manuscript were derived from the Day 2 AM no-deprivation (0 minutes abstinence) condition.

jects (in twice daily dosing) on Day 1, Day 2, and Day 3 of each week (for a total of six doses per week). Take-home doses of study medications were given to subjects for the evenings of Day 1 and Day 2.

Subjects completed cue reactivity procedures during the study sessions on the mornings of Day 2 (Day 2 AM) and Day 3 (Day 3 AM). Smokers were permitted hourly smoke breaks during the Day 2 AM test session and were instructed to abstain from smoking on the evening of Day 2 after 6:00 PM. Subjects who successfully achieved overnight abstinence (expired CO level <10 ppm on Day 3 AM) were eligible to complete the Day 3 AM (acute abstinence) cognitive testing session. On completion of the Day 3 AM session, subjects resumed smoking. Subjects were paid \$25.00 for their completion of each Day 2 AM session and \$100.00 for the successful completion of the Day 3 AM testing session; smokers not meeting abstinence criteria by CO levels at the beginning of the Day 3 AM session were paid \$5.00 and rescheduled for the entire test sequence (Sacco et al, *press*). Subjects could therefore earn up to \$375.00 for completing all 3 test weeks.

There were three cue reactivity sessions per test week, each representing a different degree of nicotine withdrawal: 0 minutes smoking deprivation (first cue reactivity session during the Day 2 AM session, immediately after the first morning smoking break at approximately 10:20 AM); 45 minutes smoking abstinence (second cue reactivity session on Day 2 AM, approximately 11:05 AM); and overnight (16 hours; 960 minutes) smoking abstinence (Day 3 AM, after overnight smoking abstinence, approximately 10:20 AM). During each cue reactivity session, four cue types were presented: happy cue (photograph of person displaying positive emotions), sad cue (photograph of person displaying negative emotions), neutral cue (a blue screen), and smoking cue (photograph of an individual smoking). Nine different sets of cue presentation were used in a randomized, counterbalanced manner. Cue presentations were computerized and presented using PowerPoint 5.0 (Microsoft Corporation, Redmond, Washington) slides on a personal computer. Each cue exposure lasted 30 seconds. Happy/sad/neutral cue presentation order was randomized; smoking cues were always presented last in the sequence of four cue types. One study (McCusker and Brown 1991) found that drug-using subjects tend to show stronger responses to cues presented earlier in a sequence compared with those presented later. Thus, by presenting the smoking cue last, the present study garnered the most conservative smoking cue reactivity measures. Immediately following each cue exposure, subjects rated the intensity of their cigarette craving from 0 to 100

Table 1. Baseline Demographic and Clinical Characteristics of Schizophrenic and Control Smokers Completing Cue Reactivity Assessments

Variable	Schizophrenic Smokers (n = 22)	Control Smokers (n = 20)	p Value
Age	38.5 ± 7.8	42.2 ± 11.0	p = .21
Sex	14 M/8 F	10 M/10 F	p = .37
Race	8 W/12 AA/2 O	14 W/4 AA/2 O	p = .06
Cigarettes per Day	21.3 ± 12.5	20.5 ± 5.8	p = .80
Baseline CO Level	23.5 ± 9.1	22.0 ± 9.6	p = .61
FTND	6.4 ± 1.5	6.4 ± 1.4	p = .90
Baseline Cotinine (ng/mL)	445 ± 205	288 ± 89	p < .01
Years of Education	12.0 ± 2.5	14.4 ± 3.1	p < .01
Baseline BDI	8.4 ± 7.4	4.0 ± 3.3	p < .05
PANSS Positive	14.1 ± 2.3	n/a	-
PANSS Negative	13.1 ± 2.1	n/a	-
PANSS General	28.6 ± 3.6	n/a	-
PANSS Total	55.8 ± 6.0	n/a	-
Estimated WAIS-R IQ	84.6 ± 14.2	100.7 ± 12.9	p < .01
Antipsychotic Drug Class	17 ATP/5 TYP	n/a	-

M, male; F, female; W, white; AA, African American; O, other; CO, carbon monoxide; FTND, Fagerstrom Test for Nicotine Dependence; BDI, Beck Depression Inventory; PANSS, Positive and Negative Syndrome Scale; WAIS-R IQ, Wechsler Adult Intelligence Scale-Revised Intelligence Quotient; ATP, atypical antipsychotic; TYP, typical antipsychotic.

millimeters on a visual analogue scale (VAS) (Hutchison et al 1999). As control assessments, subjects also rated happiness, sadness, and hunger using VAS. Measurements of blood pressure, heart rate, respiration rate, and body temperature were recorded immediately before and after each cue reactivity session.

Data Analysis

Cue reactivity for a given experimental session was defined as follows: (Urge to smoke following exposure to smoking cue)-(Baseline urge to smoke). Because some smokers were not reactive to smoking cues (e.g., CR ≤ 0), it was important to distinguish cue reactors from nonreactors for the purpose of the final data analysis. Reactors were defined as those subjects demonstrating positive cue reactivity (CR > 0) in the 0 minutes abstinence, placebo (0 mg/day) condition (Carter and Tiffany 1999). Smoking subjects who were judged to be nonreactors were eliminated from subsequent cue reactivity analyses.

The demographic and clinical characteristics of the entire subject sample (schizophrenia smokers and control smokers) and for comparisons of reactor and nonreactor populations within each study group were analyzed using independent samples *t* tests (continuous variables) and chi-square tests (categorical variables).

Within-group analyses of CR as a function of mecamlamine dose (0 mg/day, 5 mg/day, or 10 mg/day) were conducted for each smoking deprivation condition (0, 45, 960 minutes) using one-way analyses of variance (ANOVAs). Bonferroni post hoc analyses were performed to compare each group's CR levels at 5 mg/day and 10 mg/day with levels in the 0 mg/day condition. For between-group analysis, two-factor ANOVAs to detect MEC Dose × Diagnosis interactions were used to compare the CR of schizophrenic smokers versus control smokers during the three abstinence length conditions. Similar analyses were conducted for cue-induced physiological changes. Data analysis was per-

formed using the Statistical Package for the Social Sciences (SPSS Inc., Cary, North Carolina) version 12.0 software.

Results

Demographic and Clinical Characteristics of Study Subjects

The demographic and clinical characteristics of schizophrenia and control smokers completing cue reactivity assessments are given in Table 1. Demographic differences between groups included increased depression scores and reduced Wechsler Adult Intelligence Scale-Revised (WAIS-R) full-scale intelligence quotient (IQ) estimated scores and educational attainment in the schizophrenia group. Consistent with our previous studies (George et al 2002a; Sacco et al, in press), patients and control subjects were closely matched on daily smoking consumption, FTND scores, and CO levels, but there were significantly higher levels of plasma cotinine in smokers with schizophrenia as compared with control subjects. Of the schizophrenia smokers (n = 22), 11 (50%) were classified as cue reactors. In the control smoker sample (n = 20), 10 (50%) smokers met cue reactivity criteria. Demographic and clinical characteristics of reactors and nonreactors in the schizophrenia and control smoker samples are given in Tables 2 and 3, respectively. There were no significant demographic differences between schizophrenia smokers who were reactors and those who were nonreactors (Table 2), nor were there significant differences between control reactors and nonreactors (Table 3).

Baseline Urge to Smoke and Smoking Cue Reactivity in Schizophrenic Versus Control Smokers: Effects of Abstinence Duration and Mecamlamine Pretreatment

On the first day of testing (Day 2 AM), schizophrenia patients (SZ) smoked more cigarettes prior to the baseline cue reactivity session (Day 2AM; nondeprived) compared with control subjects (CON), but this difference was nonsignificant (SZ 9.88 ± 4.65 versus CON 6.75 ± 2.05 cigarettes; *t* = 1.74, *df* = 14, *p* = .10). These high levels of cigarette consumption prior to the first (nondeprived) smoking CR session led to low levels of baseline

Table 2. Baseline Demographic and Clinical Characteristics of Schizophrenic Smokers as a Function of Cue Reactivity Status

Variable	Reactors (n = 11)	Nonreactors (n = 11)	p Value
Age	37.6 ± 9.2	39.4 ± 6.3	p = .60
Sex	6 M/5 F	8 M/3 F	p = .38
Race	5 W/4 AA/2 O	3 W/8 AA/2 O	p = .15
Cigarettes per Day	23.2 ± 11.1	19.3 ± 14.0	p = .48
Baseline CO Level	22.9 ± 12.3	24.2 ± 3.0	p = .75
FTND	6.5 ± 1.6	6.4 ± 1.4	p = .89
Baseline Cotinine (ng/mL)	403.2 ± 134	504.7 ± 280	p = .40
Years of Education	11.7 ± 1.1	12.3 ± 3.4	p = .62
PANSS Positive	14.0 ± 3.0	14.1 ± 1.4	p = .93
PANSS Negative	12.6 ± 2.4	13.6 ± 1.7	p = .27
PANSS General	28.1 ± 3.9	29.1 ± 3.4	p = .53
PANSS Total	54.7 ± 6.8	56.8 ± 5.2	p = .43
Baseline BDI	5.4 ± 4.9	11.5 ± 8.3	p = .07
Estimated WAIS-R IQ	81.6 ± 11.3	87.5 ± 16.7	p = .35
Antipsychotic Class	9 ATP/2 TYP	8 ATP/3 TYP	p = .61

M, male; F, female; W, white; AA, African American; O, other; CO, carbon monoxide; FTND, Fagerstrom Test for Nicotine Dependence; PANSS, Positive and Negative Syndrome Scale; BDI, Beck Depression Inventory; WAIS-R IQ, Wechsler Adult Intelligence Scale-Revised Intelligence Quotient; ATP, atypical antipsychotic; TYP, typical antipsychotic.

Table 3. Baseline Demographic and Clinical Characteristics of Control Smokers as a Function of Cue Reactivity Status

Variable	Reactors (n = 10)	Nonreactors (n = 10)	p Value
Age	43.9 ± 8.1	40.4 ± 13.9	p = .50
Sex	6 M/4 F	4 M/6 F	p = .37
Race	6 W/3 AA/1 O	14 W/4 AA/2 O	p = .31
Cigarettes per Day	22.2 ± 5.9	18.8 ± 5.6	p = .20
Baseline CO Level	22.1 ± 7.4	22.6 ± 11.6	p = .76
FTND	6.7 ± 1.6	6.0 ± 1.0	p = .27
Baseline Cotinine (ng/mL)	307.6 ± 86	266.5 ± 92	p = .36
Years of Education	14.5 ± 3.4	14.3 ± 2.8	p = .89
Baseline BDI	3.0 ± 2.5	5.0 ± 3.8	p = .18
Estimated WAIS-R IQ	97.2 ± 13.6	104.1 ± 11.8	p = .24

M, male; F, female; W, white; AA, African American; O, other; CO, carbon monoxide; FTND, Fagerstrom Test for Nicotine Dependence; BDI, Beck Depression Inventory; WAIS-R IQ, Wechsler Adult Intelligence Scale-Revised Intelligence Quotient.

urges to smoke (BLUTS) in both schizophrenia and control smokers (Figure 2A). In the placebo (0 mg/day) condition, BLUTS increased as a function of abstinence duration in both schizophrenia ($F = 15.38, df = 2,29, p < .001$) and control ($F = 18.73, df = 2,27, p < .001$) smokers (Figure 2A). Furthermore, with increasing abstinence duration, there was a decrease in smoking cue reactivity in both schizophrenia ($F = 11.52, df = 2,29, p < .001$) and control smokers ($F = 12.22, df = 2,27, p < .001$) (Figure 2B); in the overnight abstinence (960-minute) condition, there was negligible smoking CR, so these data were not further analyzed. The increase in BLUTS with increasing abstinence duration was not altered by MEC at the 5 mg/day and 10 mg/day doses (data not shown). There were no differences in BLUTS between schizophrenic smokers and control smokers ($t = 1.21, df = 19, p = .24$) and no effects of MEC dose ($F = .05, df = 2,59, p = .95$) on BLUTS (Figure 3). There were no significant effects of neutral, happy, or sad cue exposure on BLUTS or smoking CR in either schizophrenic smokers or control smokers (data not shown).

Within-group analyses of MEC effects on smoking cue reactivity in schizophrenia and control smokers were performed. In the schizophrenia smoker group, there was a significant effect of MEC dose on smoking cue reactivity at the 0-minute abstinence condition assessed by one-way ANOVA ($F = 4.84, df = 2,29, p = .02$) (Figure 4). Bonferroni post hoc analyses revealed a trend toward a reduction in smoking cue

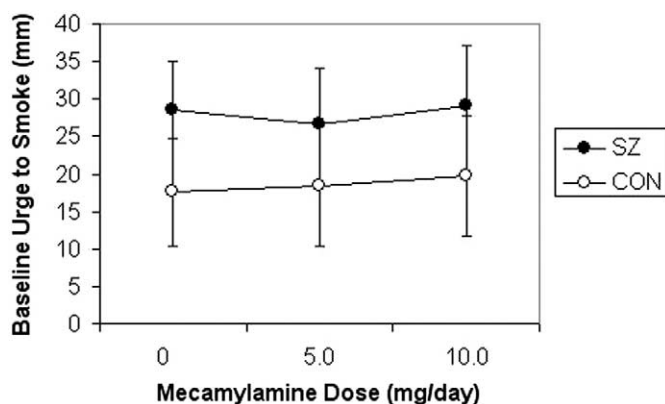


Figure 3. Baseline urge to smoke (BLUTS) in schizophrenia and control smokers: Effects of mecamylamine pretreatment. Data points are presented as means + SE. SZ, schizophrenia patients; CON, control subjects.

reactivity at the 5 mg/day dose ($p = .12$) and a significant reduction at the 10 mg/day ($p = .02$) dose compared with placebo (0 mg/day). In the 45-minute and 960-minute deprivation conditions (see Figure 2B), the magnitude of CR was reduced compared with the no-deprivation condition. We observed no significant effects of MEC dose in either the 45-minute ($F = 1.15, df = 2,29, p = .33$) or the 960-minute ($F = .01, df = 2,29, p = .99$) deprivation conditions. In control smokers, MEC caused a slight (~15%) but nonsignificant decrease in smoking cue reactivity at the 0-minute abstinence condition (Figure 2) ($F = .92, df = 2,27, p = .41$). Finally, there was a significant Diagnosis x MEC Dose interaction for smoking CR at the 0-minute abstinence condition ($F = 2.81, df = 5,53, p < .05$) but not in the 45-minute ($F = 1.28, df = 5,50, p = .29$) or 960-minute deprivation conditions ($F = .99, df = 5,53, p = .43$). Using pairwise comparisons, smoking CR was compared between schizophrenia patients and control subjects, and no significant differences were found between schizophrenic smokers and control smokers at the 0-minute abstinence condition at the 0 mg/day ($p = .29$) or 5 mg/day ($p = .67$) doses, but a trend for between-group differences was observed at the 10 mg/day dose ($p = .09$) (Figure 4).

Physiological Responses to Smoking Cues in Schizophrenia Versus Control Smokers

In each diagnostic group, physiological responses (e.g., heart rate, temperature, systolic and diastolic blood pressure)

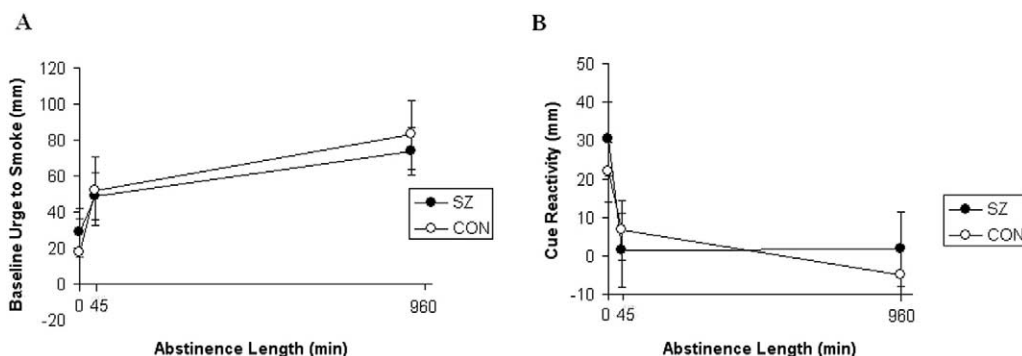


Figure 2. Effects of smoking abstinence duration on (A) baseline urge to smoke (BLUTS) and (B) smoking cue reactivity in schizophrenia (SZ; n = 11) and control (CON; n = 10) smokers. Data points are presented as means + SE. (A) SZ: 0-45 min, $p < .05$; 0-960 min, $p < .001$; 45-960 min, $p < .01$; CON: 0-45 min, $p < .01$; 0-960 min, $p < .001$; 45-960 min, $p < .01$. (B) SZ: 0-45 min, $p < .001$; 0-960 min, $p < .001$; 45-960 min, $p = .96$. SZ, schizophrenia patients; CON, control subjects.

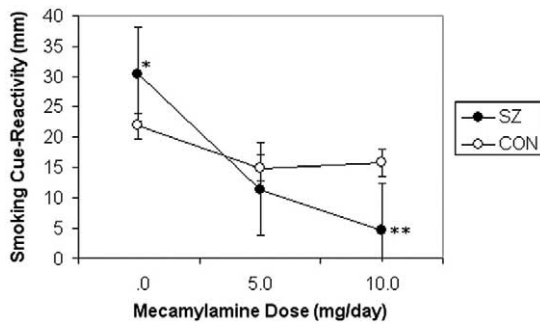


Figure 4. Smoking cue reactivity in schizophrenia and control smokers: Effects of mecamylamine pretreatment. Data points are presented as means + SE. * $p = .12$ vs. 5.0 mg/day; $p = .02$ vs. 10.0 mg/day within SZ group; $p = .29$ for SZ versus CON comparison at 0 mg/day; ** $p = .09$ for SZ versus CON comparison at 10.0 mg/day. SZ, schizophrenia patients; CON, control subjects.

to smoking cues were obtained before and after cue presentation sessions. Within-group analyses revealed no significant effects of either smoking, neutral, happy, and sad cue presentation ($p = \text{NS}$, all cue types) or MEC dose ($p = \text{NS}$) in either schizophrenia ($n = 11$) or control ($n = 10$) cue reactor physiological responses to smoking cues at the 0-minute, 45-minute, and 960-minute abstinence conditions (data not shown). Nonreactors also showed minimal physiological reactivity to smoking cue exposure (data not shown).

Discussion

This preliminary study demonstrated that exposure to smoking cues increased urges to smoke in satiated schizophrenia and control smokers and that smoking cue reactivity was of similar magnitude in schizophrenia and control smokers matched for levels of daily smoking consumption and level of nicotine dependence. Consistent with previous reports, approximately 50% of smokers (e.g., both schizophrenia and control subjects) did not exhibit smoking cue reactivity (Carter and Tiffany 1999). In smoking cue reactors, the central nicotinic acetylcholine receptor antagonist mecamylamine attenuated smoking cue reactivity more robustly in schizophrenia as compared with control smokers, and this diagnostic difference in the effects of MEC on smoking CR was supported by a significant Diagnosis \times MEC Dose interaction. Thus, further studies of smoking cue reactivity in schizophrenia and control smokers are warranted.

It is interesting to note that MEC did not alter baseline urges to smoke in either schizophrenia or control smokers, which is consistent with reports that this nAChR antagonist does not alter or precipitate tobacco withdrawal in nicotine-dependent smokers (Eissenberg et al 1996) and does not alter tobacco craving in schizophrenia and control smokers (Sacco et al, in press). As expected, BLUTS increased with increasing abstinence duration (Carter and Tiffany 1999), and this was accompanied by a decrease in smoking cue reactivity, especially with overnight (~16 hours) smoking deprivation (Hutchison et al 1999). Accordingly, we determined the effects of MEC on smoking CR in the nondeprivation (0 minutes abstinence) condition where smoking CR was most robust. Given the lack of effect of this antagonist on BLUTS, we are confident that the effects of MEC on smoking CR observed in this study are specific to cue reactivity and not as a result of nonspecific reductions of nicotine craving and withdrawal.

The finding that MEC reduces smoking cue reactivity more

robustly in smokers with schizophrenia as compared with control smokers may be attributable to the recent observation from postmortem studies that central nAChR levels are decreased in the brains of schizophrenia patients at every smoking level (Breese et al 2000; Leonard et al 2000). Thus, these preliminary findings suggest a correlation between smoking cue reactivity and brain nAChR levels in schizophrenia, specifically, the lower the level of brain nAChRs, the greater the blockade of smoking cue reactivity. Although there appear to be differential effects of MEC on smoking cue reactivity in schizophrenia versus control smokers, these groups did not differ in sensitivity to smoking cues per se, since smoking cue reactivity was of similar magnitude in schizophrenia and control smokers in the placebo condition. This suggests that while smoking cue reactivity is not different in schizophrenia and control smokers, there may be differential responses in smoking cue reactivity in response to pretreatment with a nAChR antagonist, likely related to increased sensitivity to MEC in schizophrenia due to reduced high-affinity nAChR expression. Therefore, we hypothesize that nAChR-mediated neurotransmission and resultant effects on DA, glutamatergic, and GABAergic function in relevant mesocorticolimbic pathways would be specifically reduced by MEC in schizophrenia, leading to a selective suppression of cue reactivity compared with control subjects. Our results are also consistent with a growing literature suggesting diagnosis-specific differences of the effects of nicotine and nicotinic agents on cognitive and affective measures in patients with schizophrenia (Adler et al 1993; Olincy et al 1998; Depatie et al 2002; George et al 2002a; Avila et al 2003; Sacco et al, in press), which collectively suggest that these differences may constitute a biological vulnerability to nicotine dependence in these patients. Furthermore, this finding may have implications for the development of pharmacotherapies for nicotine dependence in smokers with schizophrenia and for the treatment of schizophrenia symptomatology with nAChR agonists. For example, the antidepressant agent bupropion, which has high-affinity nAChR antagonist properties (Slemmer et al 2000), is superior to placebo for smoking cessation and reduction in schizophrenia patients and reduces negative symptoms of this illness without altering positive symptoms of schizophrenia (Evins et al 2001; George et al 2002b).

There were no consistent effects of smoking (neutral, happy, and sad) cues on any of the physiological indices assessed (heart rate, blood pressure, body temperature) in any subject group; rather, the observed physiological changes following cue exposure seemed to represent random physiological fluctuations. It is possible that modest physiological trends went undetected due to substantial subject variability on these measures, our lack of continuous monitoring of these physiological parameters, and our small group sample sizes. However, the present finding is not wholly inconsistent with published reports. For example, Drobles and Tiffany (1997) found that whereas smokers exposed to smoking cues experienced large changes in self-reported craving, their physiological reactions to these cues were modest and often inconsistent with self-reports. In fact, this discrepancy between the magnitudes of subjective and physiological measures of cue reactivity is widely recognized. In their meta-analysis of cue reactivity in addiction research, Carter and Tiffany (1999) note that although drug cues can consistently elicit increases in self-reported craving and physiological reactions, there is typically a large difference in the size of these effects. This

may be due to the fact that while self-reports of craving are strongly cue-specific, physiological responses are governed by a variety of factors other than cue exposure. It is also possible that the large self-report effect sizes are reflective of subject conformity to presumed experimenter expectations, while physiological responses are more difficult to tailor in this manner. Furthermore, there is evidence that smoking cue reactivity elicited by imaginal cues is less robust than that induced by in vivo (e.g., handling of smoking paraphernalia) cues (Hutchison et al 1999), and this could have been an additional reason for the lack of correlation between cue reactivity and physiological activation.

It should be noted that cigarette smoking schizophrenia patients in this sample were prescribed antipsychotic drugs (APDs) but that control smoking subjects were not. While it is possible that this may have contributed to the differential effects on MEC on smoking cue reactivity in schizophrenia versus control subjects, we think this possibility is unlikely due to the within-subject design for administration of MEC study medication. Nonetheless, it is possible that a MEC-APD interaction may have altered smoking CR responses in schizophrenia versus control smokers and further validation of the present findings is certainly warranted, including studies in antipsychotic-free schizophrenia patients.

Although these results are preliminary, our findings may contribute to our current understanding of the role of central nAChRs in mediating the subjective responses of cigarette smokers to smoking-related environmental cues. Furthermore, the apparent blockade of smoking cue reactivity by MEC might suggest that nAChR antagonism could be an effective pharmacological intervention treatment for nicotine dependence in schizophrenia. Accordingly, this may be a significant development, especially since current smoking cessation interventions have been only modestly successful in schizophrenia (Addington et al 1998; George et al 2000b, 2002b; Evins et al 2001).

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