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Olanzapine Attenuates Cue-elicited Craving for Tobacco

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Abstract *Rationale:* Recent biological conceptualizations of craving and addiction have implicated mesolimbic dopamine activity as a central feature of the process of addiction. Imaging, and pharmacological studies have supported a role for dopaminergic structures in cue-elicited craving for tobacco. *Objective:* If mesolimbic dopamine activity is associated with cue-elicited craving for tobacco, a dopamine antagonist should attenuate cue-elicited craving for tobacco. Thus, the aim of the present study was to determine whether an atypical antipsychotic (olanzapine, 5 mg) decreased cue-elicited craving for tobacco. *Method:* Participants were randomly assigned to 5 days of pretreatment with olanzapine (5 mg; n=31) or were randomly assigned to 5 days of a matching placebo (n=28). Approximately 8 h after the last dose, participants were exposed to a control cue (pencil) followed by exposure to smoking cues. Participants subsequently smoked either nicotine cigarettes or de-nicotinized cigarettes. *Results:* Olanzapine attenuated cue-elicited craving for tobacco but did not moderate the subjective effects of smoking. *Discussion:* This study represents one of the first investigations of the effect of atypical antipsychotics on cue-elicited craving for tobacco. The results suggest that medications with similar profiles may reduce cue-elicited craving, which in turn, may partially explain recent observations that atypical antipsychotics may reduce substance use.

Keywords Smoking · Nicotine · Craving · Olanzapine

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Introduction

There have been a number of new developments in smoking cessation research over the past decade, including the development of new pharmacological interventions (e.g. buproprion) as well as the refinement of existing behavioral and pharmacological interventions (e.g. nicotine replacement; see Niaura and Abrams 2002). Despite these new developments, the overall cessation success rate remains stagnant, suggesting that available treatments are only modestly effective for today's smokers. The lack of significant progress with respect to the success of smoking cessation interventions suggests that efforts to develop and test new interventions should be reinvigorated and that these efforts should be grounded in research on specific mechanisms that play an important role in the etiology of tobacco dependence and individual differences in the expression of these mechanisms.

Although there has been some debate over the definition of craving and its clinical relevance (see Tiffany 1995; Sayette et al. 2000), cue-elicited craving for tobacco is a construct that represents a useful laboratory target for intervention development (Hutchison et al. 2002). A number of studies have indicated that exposure to smoking cues (e.g. the sight and smell of a lit cigarette) markedly increases craving for tobacco (Niaura et al. 1988, 1992, 1998; Carter and Tiffany 1999; Hutchison et al. 1999; Tiffany et al. 2000; Sayette et al. 2001). In addition, cue-elicited craving for tobacco has been associated with relapse (Shiffman et al. 1996) and has been the focus of psychosocial and pharmacological intervention efforts (Goldstein 1999; Hutchison et al. 1999; Shiffman et al. 2000a,b; Durcan et al. 2002), although others have

suggested that its clinical relevance is questionable (Tiffany 1990, 1995).

At a biological level, craving has been linked to the actions of drugs on the mesolimbic dopamine pathway in the brain, and this substrate is thought to be an important mechanism in the etiology of tobacco and drug dependence (Wise 1988; Robinson and Berridge 1993; Berridge and Robinson 1998). Formally known as an incentive sensitization model of craving, this conceptualization suggests that repeated activation of the mesolimbic dopamine pathway produces the progressive attribution of incentive salience that is associated with neural representations of drug related stimuli, thus creating the motivational and appetitive properties of dependence that is sometimes described as "craving." The expression of this incentive salience or craving can be subsequently precipitated by cues associated with drug use. Consistent with the animal literature, a recent study indicated that exposure to smoking cues produced a hemodynamic response in some of these same brain regions in humans (e.g. the ventral tegmental area; Due et al. 2002).

Given the importance of dopamine in terms of the attribution of incentive salience and expression of craving, pharmacological interventions that target the dopamine system could regulate craving, and by extension, drug taking behavior. However, some research has suggested that dopamine antagonists (e.g. haloperidol) may increase smoking in both normal (Dawe et al. 1995; Caskey et al. 1999, 2002) and schizophrenic individuals (McEvoy et al. 1995a), while dopamine antagonists may decrease smoking behavior (Caskey et al. 1999, 2002). Increased cigarette consumption in these individuals may be a compensatory behavior due to a loss in the rewarding value of nicotine or an effort to offset some of the negative side effects of haloperidol (e.g. sedation, confusion, motor dysfunction). In contrast, a recent study indicated that haloperidol decreased the consumption of both nicotine and de-nicotinized cigarettes (Brauer et al. 2001), and studies with atypical antipsychotics (e.g. clozapine) have suggested that these medications may reduce smoking and substance use more generally (McEvoy et al. 1995a,b; Green et al. 1999). The data from the study by Brauer et al. (2001) are consistent with the premise that dopamine antagonists might decrease cue-elicited craving for tobacco. On a related note, recent studies have suggested that olanzapine, an atypical antipsychotic that has a better side effect profile than traditional antipsychotic medications, reduced cue-elicited craving for alcohol (Hutchison et al. 2003). Given the contradictory findings with tobacco use, the question of whether pharmacotherapies that target dopamine receptors will prove to be beneficial remains unanswered.

The objective of the present study was to determine whether olanzapine decreases cue-induced craving and subsequent cigarette consumption. Because our previous work has suggested that olanzapine reduces cue-elicited craving for alcohol (Hutchison et al. 2003) and because clinical reports suggest that olanzapine reduces substance use (Lee et al. 1998; Green et al. 1999; Drake et al. 2000; Zimmet et al. 2000) and smoking behavior among schizophrenics (George et al. 2000), the present study tested the effect of olanzapine on cue-elicited craving for tobacco and subjective responses to nicotine administration. It was postulated that olanzapine would reduce cue-elicited craving for tobacco while having no significant effect on the rewarding effects of nicotine consumption. If dopamine receptors mediate the effect of smoking cues, we would expect olanzapine to attenuate craving relative to the inactive control medication.

Materials and methods

Participants

The study was approved by the University of Colorado Human Research Committee. All female subjects tested negative for pregnancy prior to participation, all subjects were required to have a breath alcohol level of zero before each session, and all subjects were required to be in excellent health as indicated by a thorough medical screening (e.g. medical exam, CBC, EKG, LFTs) to ensure that there were no contraindications for the use of the study medications. The research participants were screened medically at the University of Colorado General Clinical Research Center in Boulder. Of the 82 individuals who were initially enrolled into the study, 16 did not complete the study (eight in the olanzapine condition and eight in the placebo condition). In addition, six participants had a baseline CO less than 5 ppm and were excluded, leaving a final sample of 59 participants who completed both experimental sessions. The ethnic composition of the sample was 92% Caucasian, 3% African-American, 2% Asian, and 3% Hispanic. Table 1 provides the means and standard deviations for each medication group on a number of demographic and smoking history variables. *t*-Tests were used to confirm that the medication groups did not differ on these variables ($P>0.05$).

Table 1 Subject characteristics

Variable[a]	Placebo (n=28)	Olanzapine (n=31)
Age	20.6 (3.9)	22.3 (4.1)
Average no. cigarettes/day	15.2 (7.0)	15.6 (4.5)
Fagerstrom tolerance questionnaire	2.4 (1.6)	2.6 (1.5)
Baseline expired CO (ppm)	16.9 (10.4)	17.6 (11.2)
Baseline CO on nicotine day	8.6 (4.5)	10.3 (4.5)
Baseline CO on low nicotine day	10.5 (8.0)	10.8 (4.7)

[a]Standard deviations appear in parentheses next to the means of continuous variables.

Medication administration procedures

Volunteers were randomly assigned to receive either olanzapine (5 mg) or a placebo. Thirty-one participants (18 men, 13 women) received olanzapine and 28 (16 men, 12 women) received the placebo. The participants and the experimenter were blind to the medication condition. Participants were instructed to take five consecutive daily doses of the study medication prior to each of two experimental sessions scheduled 1 week apart. The first four doses were to be taken a few hours before bedtime to diminish the impact of any drowsiness experienced as a result of olanzapine. The last dose was taken 8 h before each of the experimental sessions. After taking each dose of medication, participants called the laboratory to confirm the time and date on which they took their dose. The medications were packed into an opaque capsule with 50 mg riboflavin, which is detectable in urine under ultraviolet light (Del Boca et al. 1996). In order to confirm that participants had taken the medication the night before the experimental session, a urine sample was collected in the morning of the experimental session and tested for riboflavin content under ultraviolet light. All of the participants took the medication as directed. At the end of each experimental session, participants were asked if they thought they had received olanzapine or the placebo in order to test the blind.

Procedure

Participants were scheduled for one baseline and two experimental sessions, approximately 1 week apart. Participants were instructed not to drink alcohol for 24 h, consume caffeine for 2 h, or to smoke for 8 h before arriving at the laboratory. Participants attended the baseline session, where they signed consent forms and completed questionnaires (see "Individual difference measures" below). Participants were scheduled for the first of the two experimental sessions 1 week later. Participants received three nicotine cigarettes during one of the experimental sessions and three de-nicotinized cigarettes during the other experimental session in a crossover design. Participants smoked either three nicotine (1.1 mg) cigarettes separated by 25 min or smoked three de-nicotinized cigarettes containing trace amounts of nicotine (0.07 mg) separated by 25 min (for description of research cigarettes; see Pickworth et al. 1999). The inter-cigarette interval was designed to allow the participants enough time to complete measures and relax between each cigarette. The de-nicotinized cigarettes were used in order to control for CO and tar content as well as the physical action of smoking. The de-nicotinized cigarettes were not expected to deliver a psychoactive dose of nicotine (Pickworth et al. 1999). After smoking each cigarette, the participants completed subjective measures of craving and smoking satisfaction and affect (see "Experimental session measures" below).

The order of the two sessions was counterbalanced across participants such that half of the participants smoked the nicotine cigarettes on the first session and half of the participants smoked the de-nicotinized cigarettes on the first session. Participants smoked the cigarettes following standardized audio-taped instructions. Individuals were required to inhale from the cigarette for a count of 2 s, then hold the smoke in their lungs for a count of 3 s, and then asked to exhale and wait for 20 s, such that each individual received 12 puffs from each cigarette over the course of 5 min. The puffing procedure was designed to standardize nicotine consumption across participants, consistent with previous studies (Hutchison et al. 2000). All experimental sessions occurred in the morning (before noon). Each of the two sessions was scheduled at the same time for a given subject and baseline CO measures were taken at the beginning of each of these sessions. The entire session lasted approximately 4 h.

Participants completed a smoking cue reactivity assessment at the beginning of each of the experimental sessions. Following previously published procedures (Sayette and Hufford 1994; Hutchison et al. 1999), participants were first exposed to control cues by asking them to hold a pencil for 3 min. The exposure to the control cue was followed by an assessment of craving and a 5-min interval prior to exposure to the smoking cue. Exposure to the smoking cue consisted of instructing the participants to remove one of their preferred brand of cigarettes from a pack and light it without putting it in their mouths by holding it in the flame for several seconds. Participants were then instructed to focus their attention on the lit cigarette. Participants completed measures of craving, attention, and affect before and after each exposure.

Individual difference measures

A *demographics questionnaire* was used to collect information on age, sex, marital status, socioeconomic status (SES), occupation, income, education, and race before the first session.

A *smoking history questionnaire* was used to collect information on frequency and quantity of tobacco use prior to the study, number of previous quit attempts, age when first cigarette was smoked, and number of years as a regular smoker.

The *Fagerstrom tolerance questionnaire* (FTQ) was used to collect information on the severity of nicotine dependence.

Expired carbon monoxide (CO) was also collected prior to each session using a Vitalograph CO monitor to verify compliance with the abstinence instructions (i.e. expired CO less than 10 ppm).

Experimental session measures

Craving measure The craving measure consisted of five items that were rated on a scale of 0–100 and that were

averaged to form a craving scale (Shiffman et al. 2003). The five items included "I crave a cigarette right now," "I have an urge for a cigarette," "I have a desire for a cigarette right now," "If it were possible, I would smoke now," and "All I want right now is a cigarette." Cronbach's alpha for the scale was greater than 0.90 in previous studies, suggesting good internal consistency (Hutchison et al. 2000; Shiffman et al. 2003).

Positive affect/negative affect scale (PANAS) This was used to collect information on mood at the follow-up visits. The PANAS is a reliable and valid measure of both positive and negative affect with alphas of 0.84–0.90 (Watson et al. 1988).

Hedonic scale (HS) This measure assessed the hedonic value of the cigarettes by asking each participant to rate the cigarettes in terms of "enjoyable" and "satisfying" on a scale from 0 (not at all) to 10 (extremely).

Sedation and stimulation The biphasic alcohol effects scale (BAES) was used to collect information on changes in self-reported sedation and stimulation after smoking. The BAES has previously demonstrated reliability and validity in investigations of the stimulatory and sedative effects of alcohol (Martin et al. 1993) and for assessing medication effects (Swift et al. 1994). The sedation and stimulation subscales each consist of seven items rated from 0 (least) to 10 (most).

Results

To assess the integrity of the blind, a χ^2 test was performed on the item asking participants to guess which medication they received at the end of each experimental session. The tests were non-significant ($P>0.05$), suggesting that participants were unable to distinguish between the placebo and olanzapine. Similar tests were conducted on items asking participants to guess whether they had smoked the nicotine cigarettes or de-nicotinized cigarettes. These tests were significant ($P<0.05$), with 68% of the participants correctly identifying the de-nicotinized cigarettes and 70% of participants correctly identifying the nicotine cigarettes. Olanzapine had no effect on the ability of participants to correctly identify the cigarettes ($P>0.05$).

Cue-elicited craving

To analyze reactivity to smoking cues, a 2×2×2 mixed design analyses of variance (ANOVAs) were conducted on the craving scale score, where type of cue (control cue versus smoking cue) was a two-level, within-subjects factor, session (first versus second experimental session) was a two-level, within-subjects factor, and medication (olanzapine or placebo) was a two-level between-subjects factor.

The analyses revealed a significant main effect for cue [$F(1,57)=29.01$, $P<0.001$], indicating that smoking cues significantly increased craving. There was also a significant medication by cue interaction [$F(1,57)=5.10$, $P<0.05$], such that olanzapine attenuated cue-elicited craving. There were no other significant main or interaction effects and no effects involving session ($P>0.05$). Given the overall medication by cue interaction and the lack of an effect for session, the means were collapsed across session and presented in Fig. 1.

Effects of smoking

To address the subjective effects of nicotine, a series of 3×2×2 ANOVAs were conducted where cigarette (first, second, or third cigarette) was a three-level within-subjects factor, nicotine (nicotine versus de-nicotinized) was a two-level within-subjects factor, and medication (olanzapine versus placebo) was a two-level between-subjects factor. The dependent variables examined were the craving scale score, positive affect, negative affect, and the hedonic scale score.

Craving measure Analyses revealed a significant main effect for nicotine [$F(1,55)=18.48$, $P<0.001$], such that nicotine cigarettes decreased craving (see Fig. 2). There was also a significant effect for cigarette [$F(2,110)=35.54$, $P<0.001$], such that craving generally decreased across cigarettes regardless of nicotine condition, suggesting that placebo cigarettes also reduced craving. There were no significant effects involving medication ($P>0.05$).

Positive affect There were no main or interaction effects for medication ($P>0.05$). There was a main effect for cigarette [$F(2,110)=10.59$, $P<0.01$], and a significant

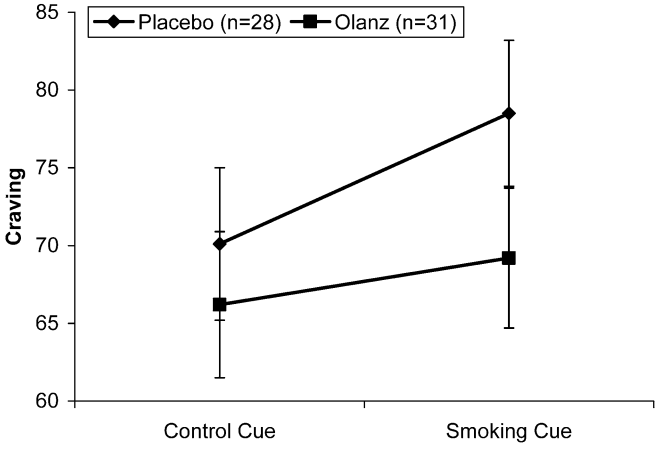

Fig. 1 Means and standard errors for craving scores after exposure to control cues and smoking cues collapsed across *Session 1* and *Session 2*. Analyses indicated a significant medication by cue interaction ($P<0.05$) such that olanzapine decreased cue-elicited craving for tobacco. Simple effects tests indicated that exposure to smoking cues significantly increased craving in the placebo condition ($P<0.001$). There was only a marginally significant increase in the olanzapine condition ($P=0.05$)

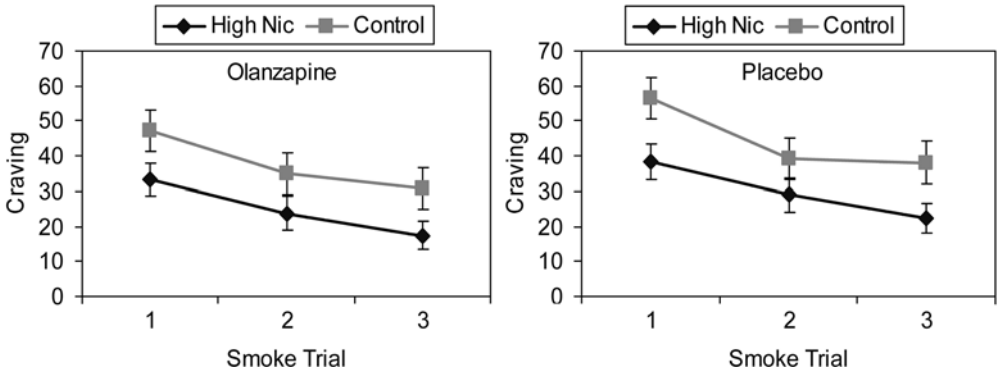

Fig. 2 Means and standard errors for craving scores after smoking each cigarette. Analyses indicated a main effect for nicotine, such that cigarettes containing nicotine resulted in a significantly lower craving as compared to the control cigarettes ($P<0.05$). There were no significant effects for medication

effect for nicotine [$F(1,55)=4.92$, $P<0.05$], such that positive affect was increased across cigarettes and was greater when participants received the nicotine cigarettes.

Negative affect Analyses revealed a significant effect for cigarette [$F(1,10)=3.68$, $P<0.05$], such that negative affect decreased across cigarettes. There were no other significant main effects or interactions ($P>0.05$).

Hedonic scale Analyses revealed a significant main effect for nicotine [$F(1,55)=44.97$, $P<0.001$], such that the nicotine cigarettes were much more rewarding than the de-nicotinized cigarettes. There was also a significant effect for cigarette [$F(2,110)=22.16$, $P<0.001$], such that the hedonic value of the cigarettes generally decreased across cigarettes. There were no significant effects involving medication ($P>0.05$).

Sedation Analyses indicated a main effect for nicotine [$F(1,49)=4.63$, $P<0.05$], such that the nicotine cigarettes decreased sedation. There was also a main effect for cigarette [$F(2,98)=10.23$, $P<0.01$], indicating that sedation generally decreased across cigarettes. There were no main or interaction effects involving medication ($P>0.05$), suggesting that olanzapine did not produce significant sedation.

Stimulation Analyses indicated a main effect for cigarette [$F(2,110)=8.91$, $P<0.01$], indicating that stimulation generally increased across cigarettes. There were no main or interaction effects involving medication ($P>0.05$) or nicotine, suggesting that olanzapine and nicotine did not produce significant changes in stimulation.

Discussion

The findings of the present study indicate that olanzapine attenuates cue-elicited craving for tobacco but does not influence the rewarding effects of smoking. From a theoretical perspective, it is not surprising that olanzapine reduces the appetitive value of alcohol and drug while having minimal influence over the rewarding or hedonic aspects of alcohol and drug use. One of the prominent theories of addiction has suggested that mesolimbic dopamine circuitry subserves the attribution of incentive salience (i.e. "wanting") rather than the hedonic aspects of drug use behavior (i.e. "liking"; see Robinson and Berridge 1993; Berridge and Robinson 1998). In addition, these results are consistent with other recent studies that have suggested that dopamine antagonists may reduce the appetitive aspects of smoking behavior (Brauer et al. 2001) and studies that have suggested that olanzapine reduces craving for alcohol (Hutchison et al. 2001).

Conversely, the findings of the present study contradict theories of drug use behavior that emphasize the importance of dopamine in terms of pleasure, reward, and reinforcement and contradict recent studies suggesting that dopamine antagonists decrease the rewarding aspects of smoking, thereby increasing tobacco use (Caskey et al. 1999, 2002). These studies noted changes in smoking topology after haloperidol treatment but did not detect any changes on measures of positive mood. It is possible that no changes in positive mood were observed because dopamine antagonists do not have an effect on the positive affect generated by smoking, consistent with the present study. It is also possible that the assessment of mood was not optimal for detecting an effect in the previous studies, given that the assessment of mood occurred 30 min after smoking.

Despite this preliminary work, it has yet to be determined whether the effect of olanzapine on cue-elicited craving for tobacco might translate into a reduction in tobacco use behavior. However, there is some evidence to suggest that atypical antipsychotics may produce decreases in tobacco use and craving. For example, a recent smoking cessation trial in schizophrenics suggested that the combination of nicotine replacement therapy (NRT) and atypical antipsychotics were more than twice as effective as NRT and typical antipsychotics (George et al. 2000). The authors of the study noted that olanzapine and risperidone were associated with the greatest success. Likewise, a comparison between olanzapine and valproic acid in bipolar patients indicated that olanzapine significantly reduced self-reported smoking. In addition, several studies have suggested that atypical antipsychotics reduce alcohol and drug use behavior in psychiatric patients (Lee et al. 1998; Green et al. 1999; Drake et al. 2000; Zimmet et al. 2000). However, it is not clear how these medications may

influence smoking behavior in non-psychiatric populations. Future studies will need to address this question.

It is also interesting to note that de-nicotinized cigarettes reduced craving for cigarettes immediately after smoking, as illustrated in the present study (Fig. 2) and in other research (e.g. Butschky et al. 1995; Pickworth et al. 1999; Brauer et al. 2001). Furthermore, results of the present study illustrate that repeated administration of the de-nicotinized cigarettes continues to decrease cigarette craving. These results extend the findings of Dallery et al. (2003), where placebo cigarette smoking in a rapid smoking or in a paced smoking paradigm, decreased urges to smoke and smoking. The ability of the placebo cigarettes to diminish urge to smoke has been attributed to the stimulation of sensory cues associated with the inhalation of tobacco smoke or from components of tobacco smoke other than nicotine (Robinson et al. 2000). It is interesting that olanzapine was evidently able to diminish the cigarette craving induced by holding and attending (but not smoking) a lit cigarette but unable to diminish placebo cigarette-induced reduction in cravings. These results tentatively suggest that the neural mechanisms responsible for cigarette craving and smoking urge are heterogeneous and may be influenced by diverse behavioral or pharmacological manipulations.

Several limitations of the present study need to be addressed. The present study only used a single dose of olanzapine. This dose was chosen for practical reasons. Higher doses would have been impractical due to side effects. In addition, previous studies have documented that 5 mg is sufficient for reducing cue-elicited craving for alcohol (Hutchison et al.2001, 2003). Therefore, it is not clear whether higher doses may actually reduce the rewarding effects of smoking in humans. The addition of an active medication that controls for activity at 5-HT_2 receptors and the general sedative effects of olanzapine (e.g. cyproheptadine) would also be useful in future studies. The present study with olanzapine utilized a placebo control which does not control for the effects of olanzapine on 5-HT_2 receptors, histamine receptors, and the non-specific sedating effects of the medication. Thus, expectancies regarding the effects of the medication and/or the effects of the medication on 5-HT_2 or histamine receptors of the medication cannot be excluded as explanations for the results. Given that other studies with olanzapine have utilized active controls, future studies should be able to resolve some of these interpretive issues. Finally, the generalizeability of the results may be somewhat limited, given that the present sample was young with low nicotine dependence scores.

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