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The effects of varenicline on stress-induced and cue-induced craving for cigarettes

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ABSTRACT

Background: Varenicline is a partial agonist of the $\alpha_4\beta_2$ nicotinic acetylcholine receptor approved by the FDA for the treatment of nicotine dependence. While the clinical efficacy of varenicline for smoking cessation is well-supported, its biobehavioral mechanisms of action remain poorly understood. This randomized, crossover, placebo-controlled, human laboratory study combines guided imagery stress exposure with in vivo presentation of cigarette cues to test the effects of varenicline on stress-induced and cue-induced craving for cigarettes.
Method: A total of 40 (13 females) daily smokers (≥10 cigarettes per day) completed a guided imagery exposure (stress and neutral) followed by the presentation of cigarette cues at the target dose of varenicline (1 mg twice per day) and on matched placebo.
Results: Multilevel regression models revealed a significant main effect of varenicline ($p < .01$) such that it reduced cigarette craving across the experimental paradigm, compared to placebo. There was also a significant medication × stress × trial interaction indicating that varenicline attenuated cue induced craving following neutral imagery but not when cues were preceded by stress induction (i.e., stress + cues).
Conclusions: These results elucidate the biobehavioral effects of varenicline for nicotine dependence and suggest that varenicline-induced amelioration of cigarette craving is unique to tonic craving and cue-induced craving following neutral imagery but does not extend to the combination of stress plus cues.

1. Introduction

Stress has been implicated as a central mechanism to drug relapse (Uhart and Wand, 2009), including cigarette smoking, with prospective research demonstrating that psychological stress and negative affect predict smoking lapses (Shiffman and Waters, 2004). In a recent study, 62% of smokers attributed their inability to stop smoking to stress (Hughes, 2009). Likewise, research has shown that cue-reactivity is a predictor of smoking behavior and relapse (Niaura et al., 1989; West, 2009), although recently this association has been called into question (Perkins, 2012). Preclinical studies provide compelling evidence of the ability of cue- and stress-exposure to reinstate nicotine-seeking behavior. For example, reintroduction to visual stimuli that had previously been paired with nicotine reinstated nicotine-seeking behavior in rats (Liu et al., 2006) and presentation of nicotine-associated cues following extinction produces reinstatement, above and beyond nicotine priming (LeSage et al., 2004). Likewise, preclinical models of stress exposure (e.g., foot shock paradigm) have supported stress-induced nicotine reinstatement (Buczek et al., 1999), which in turn represents a pharmacological treatment target (Yamada and Bruijnzeel, 2011; Zislis et al., 2007). Together, the preclinical data suggest that both cigarette cues and stress play a critical role in nicotine reinstatement and nicotine-seeking behaviors.

While preclinical studies have effectively dissociated mechanisms of stress- and cue-induced reinstatement, psychological models of craving argue that stress serves as an internal or affective cue, which in turn triggers craving in a similar fashion to smoking cues (Baker et al., 2004). Early experimental studies documented increases in smoking during conditions of stress (Schachter et al., 1977) and anxiety (Pomerleau and Pomerleau, 1987). In addition, several recent studies found that psychosocial stress, induced using the Trier Social Stress Test, reliably increases cigarette craving (Buchmann et al., 2010; Childs and de Wit, 2010) and that smokers have overall lower hormonal stress responsivity (al'Absi et al.,

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2003). Further, stress-induction using a personalized script was associated with decreased ability to resist smoking in the laboratory as well as potentiation of subjective reward from smoking (McKee et al., 2010).

This study extends the literature by testing the effects of varenicline on stress-induced craving followed by the presentation of smoking cues. As recommended by McKee (2009), human laboratory models should be validated with known medications before they can be used to screen for novel pharmacotherapies for smoking cessation (McKee, 2009). The present study is consistent with this approach and examines varenicline, a partial agonist of $\alpha_4\beta_2$ nicotinic acetylcholine receptors (nAChR) with proven efficacy as a pharmacotherapy for smoking cessation (Fagerstrom and Hughes, 2008; Gonzales et al., 2006; Oncken et al., 2006). Varenicline is a well-established and FDA-approved medication for smoking cessation. It has been hypothesized that binding of $\alpha_4\beta_2$ nAChR increases the dopamine tonus in the ventral tegmental area which in turn decreases craving for nicotine and alleviates nicotine withdrawal symptoms (Fagerstrom and Hughes, 2008). Varenicline blocks the effects of nicotine itself and recent studies suggest that it improves attention (Rhodes et al., 2012) and reduces craving and cigarettes per day among non-treatment seekers (Ashare et al., 2012). Preclinical studies suggested that varenicline significantly attenuated cue-induced nicotine reinstatement (Biala et al., 2011; Le Foll et al., 2011) and nicotine self-administration (Le Foll et al., 2011). In humans, varenicline reduced cue-induced cigarette craving as well as tonic levels of craving (i.e., steady state craving, non-cue induced) in a sample of daily smokers (Brandon et al., 2011). The present study extends the literature on the mechanisms of action of varenicline by testing its effects on stress-induced and cue-induced craving for cigarettes.

This study enrolled non treatment-seeking daily smokers in a placebo-controlled, randomized, crossover study of varenicline (1 mg twice per day). The human laboratory design combined stress induction, using guided imagery procedures (Sinha, 2009) followed by the systematic presentation of cigarette cues (Monti et al., 1987). This study tested whether varenicline attenuates stress-induced and cue-induced craving for cigarettes in daily smokers. Based on the emerging literature on the effects of varenicline on cigarette craving (Ashare et al., 2012; Brandon et al., 2011), we hypothesized that varenicline would attenuate craving for cigarettes after stress induction and after presentation of smoking cues, compared to placebo.

2. Method

2.1. Participants

Participants ($n = 40$, 13 females) were healthy daily smokers ($\geq$10 cigarettes per day) between the ages of 18 and 55. Exclusion criteria were the following: (1) more than 3 months of smoking abstinence in the past year; (2) self-reported use of cocaine, methamphetamine, heroin or other illicit drugs (other than marijuana) in the past 60 days (verified by urine toxicology screen); (3) lifetime history of psychotic disorders, bipolar disorder, or major depression with suicidal ideation; (4) self-reported current feelings of active suicidality, as indicated by a score $\geq$2 on the suicidal ideation item of the BDI-II; (5) self-reported symptoms of depression in the moderate range, as indicated by a score $\geq$20 on the BDI-II; (6) currently taking insulin or oral hypoglycemic medication; (7) serious medical illness present during the physical exam and laboratory tests; and (8) pregnancy, as verified by a urine pregnancy screen.

The majority of randomized participants ($n = 40$) were male ($n = 27$, 67.5%) and the average age was 36.03 (SD = 10.13). The ethnic composition of the randomized sample was 32.5% Caucasian, 32.5% African American, 5% Latino, 2.5% Asian, 25% Mixed Ethnicity, and 2.5% did not report. The average score on the Fagerstrom Test of Nicotine Dependence (FTND) was 4.03 (SD = 1.76). The average number of cigarettes on a typical day in the past month was 14.87 (SD = 5.85) and the average carbon monoxide (CO) level at baseline was 17.50 ppm (SD = 11.09). Participants reported drinking, on average, once per week and consuming 4.20 drinks per drinking occasion (SD = 4.78). The average score on the Alcohol Use Disorders Identification Test (AUDIT; Allen et al., 1997) was 3.13 (SD = 3.43).

2.2. Procedures

Study procedures were approved by the Human Research Committee at the University of California, Los Angeles and all participants provided written informed consent after receiving a full explanation of the study. Following telephone screening, participants completed an in-person assessment visit. Eligible participants based on the in-person assessment were invited for a physical exam. Self-reported smoking pattern was verified by a urine cotinine test, and only participants whose cotinine test was consistent with regular smoking ($\geq$100 ng/mL of cotinine) were enrolled in the study. Self-reported drug use was verified by a urine toxicology screen and individuals who tested positive for drugs (other than marijuana) were excluded. Medically eligible participants were then randomized to receive the first study medication (varenicline or placebo) for a total of 10 days. On medication day 10, participants completed the first laboratory experimental session consisting of guided imagery exposure (stress and neutral) followed by the presentation of cigarette cues. After the first session, participants were given the second study medication (varenicline or placebo) for a total of 10 days and returned to the laboratory on medication day 10 to complete the second experimental session. Participants were required to abstain from smoking for 12 h prior to each experimental session. Expired carbon monoxide levels of less than 10 ppm (or below 50% of initial baseline value) were used to verify overnight smoking abstinence, and breathalyzers were used to ensure a breath alcohol concentration of 0.000 g/dl at testing.

A total of 536 individuals were screened over the phone, of whom 167 were initially eligible and invited for an in-person screening session. Of the 167 recruits invited, 109 completed the in-person screening visit and of those, only 58 were eligible and therefore invited to complete the physical exam. A total of 46 participants completed the physical and 40 were medically eligible, all of whom were randomized to receive the study medication or matched placebo. Of the 40 randomized participants, 2 did not return for the experimental session and 1 completed only one medication condition, resulting in 37 completers.

2.3. Stress-induction and smoking cue

During the initial screening session, participants completed individual differences measures, received standardized relaxation training and imagery training, and provided detailed descriptions of two recent stressful life events and one neutral event. This information was used to generate tape recorded personalized scripts for the neutral and stressful experimental conditions, following well-established procedures (Sinha, 2009; Sinha et al., 1992, 2000). Participants were asked to identify and describe recent stressful experiences and to rate them on a 0–10 Likert scale, where 10 is the most stressful. Only stressful events rated $\geq$8 were used in script development. Stressful events that were resolved were not used in script development to ensure the salience of the stimuli presented. All scripts were evaluated by the first author (LR) for stressful and neutral content prior to implementation. Different stressful events