Pharmacology, Biochemistry and Behavior 92 (2009) 135–140

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Minocycline reduced craving for cigarettes but did not affect smoking or intravenous nicotine responses in humans

Mehmet Sofuoglu [a,*], Andrew J. Waters [b], Marc Mooney [c], Stephanie S. O'Malley [a]

[a] Yale University, School of Medicine, Department of Psychiatry and VA Connecticut Healthcare System, West Haven, CT, United States
[b] Uniformed Services University of the Health Sciences, Bethesda, Maryland, United States
[c] University of Minnesota, Minneapolis, Minnesota, United States

ARTICLE INFO

Article history:
Received 15 July 2008
Received in revised form 4 November 2008
Accepted 6 November 2008
Available online 13 November 2008

Keywords:
Nitric oxide
Nitric oxide synthase
Minocycline
Nicotine dependence
Intravenous nicotine

ABSTRACT

In recent preclinical studies, the role of nitric oxide (NO) in nicotine dependence has become increasingly evident. Inhibition of NO synthesis blocks acquisition of conditioned place preference, and attenuates the nicotine abstinence syndrome in rodents. These findings have not been followed up in human studies. In order to obtain preliminary data on NO inhibition in human smokers, we conducted a randomized, double-blind, crossover study (N=12) of minocycline, a tetracycline derivative antibiotic, that inhibits the neuronal nitric oxide (NO) synthase enzyme with resultant inhibition of NO production. Medication effects were assessed through a smoking choice procedure as well as subjective and physiological responses to nicotine administered via the intravenous route (IV). Minocycline treatment did not affect smoking self-administration in our choice procedure and did not affect most of the subjective responses to IV nicotine or sample smoking. Following IV nicotine administration, there was a greater reduction in craving for cigarettes under minocycline, compared to placebo. Similarly, smokers had greater reduction in their craving for cigarettes following sample smoking under minocycline treatment. These findings provide limited support for the potential use of minocycline as a treatment of nicotine dependence.

Despite advances in pharmacotherapy for nicotine dependence, including nicotine replacement therapy (NRT), sustained release (SR) bupropion, and varenicline (Cahill et al., 2007; Fiore et al., 2008; Stead et al., 2008), generally 70–90% resume smoking within a year of treatment. Accordingly, the mission to identify novel effective nicotine dependence pharmacotherapies continues, with a broad range of antidepressant, antianxiety, and other agents already evaluated or undergoing assessment. Given the grave consequences of the tobacco epidemic, innovative approaches to medications development are warranted. Recently, the role of nitric oxide (NO) in nicotine dependence has become increasingly evident. NO serves as a second messenger for the glutamate and dopamine receptors and facilitates nicotine's effects in the reward circuit (Schilstrom et al., 2004; Vleeming et al., 2002). Moreover, inhibition of NO synthesis by L-nitro-amino-methyl-ester (L-NAME) or 7-nitroindazole (7-NI) (Martin and Itzhak, 2000; Sahraei et al., 2004), blocked the acquisition of nicotine-induced place preference in mice (Martin and Itzhak, 2000; Sahraei et al., 2004), a model of the rewarding effects of nicotine. Of clinical interest, blockade of NO synthesis by nitro-L-arginine (L-NNA) also attenuated nicotine abstinence symptoms precipitated by the nicotinic antagonist mecamylamine (Malin et al., 1998). A number of clinically approved medications affect NO synthesis and other NO synthesis inhibitors are in development (Erdal et al., 2005). One widely used medication of the former class, minocycline, is a tetracycline derivative antibiotic that crosses the blood brain barrier (Allen, 1976; Macdonald et al., 1973) and has diverse CNS effects including anti-inflammatory and neuroprotective actions in doses used clinically (Jonas and Cunha, 1982; Stirling et al., 2005). Minocycline also inhibits the neuronal nitric oxide (NO) synthase enzyme, with resultant inhibition of NO production (Du et al., 2001). Based on this background, it is of interest to evaluate minocycline's effects on nicotine dependence. In order to obtain preliminary data on minocycline in nicotine dependent humans, we conducted a human laboratory study with a randomized, double-blind, crossover design. Medication effects were assessed through a smoking choice procedure as well as subjective and physiological responses to nicotine administered via intravenous route. We hypothesized that minocycline would result in reduced preference for cigarette puffs, nicotine withdrawal and craving, and physiological and subjective response to IV nicotine.

1. Method

1.1. Participants

Seven female and 5 male non-treatment seeking smokers were recruited from the New Haven, Connecticut area. Four additional

* Corresponding author. Yale University, Department of Psychiatry, VA Connecticut Healthcare System, 950 Campbell Ave., Bldg. 36/116A4, West Haven, CT 06516, United States. Tel.: +1 203 937 4809; fax: +1 203 937 3478.
E-mail address: Mehmet.Sofuoglu@yale.edu (M. Sofuoglu).

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doi:10.1016/j.pbb.2008.11.004

Table 1
Experimental design

	Treatment period 1				Treatment Period 2		
Adaptation session	Days 1–2 outpatient visits	Day 3 (ES1) smoking behavior	Day 4 (ES2) IV nicotine responses	W	Days 1–2 outpatient visits	Day 3 (ES1) smoking behavior	Day 4 (ES2) IV nicotine responses

Note: ES: experimental session; W: washout.

participants were enrolled but dropped out of the study and were not included in the analyses. Eight participants were African-American, 3 were Caucasian, and 1 was Hispanic. The average age (SD) of the participants was 35.3 (7.4). On average, participants smoked 17.9 (4.5) cigarettes/day, and had a Fagerstrom Test for Nicotine Dependence (Heatherton et al., 1991) score of 6.6 (1.4). Participants had normal physical, laboratory and psychiatric examinations and were not dependent on drugs or alcohol other than nicotine. Participants provided written, signed consent before participating in the study. This study was approved by the VA Connecticut Healthcare System Human Subjects Subcommittee. Experimental sessions were conducted in the Biostudies Unit located at the VA Connecticut Healthcare System and participants were paid for participation.

1.2. Design and procedures

This was an outpatient randomized, double-blind, crossover study. The design is presented in Table 1. Following an adaptation session, participants had two 4-day treatment periods, in which they were assigned to a random sequence of minocycline (200 mg/day) or placebo treatment. These treatment periods were separated by a washout period lasting a minimum of 4 days. In the adaptation session, participants first received an IV saline injection followed by 2 escalating doses of IV nicotine (0.5 and 1.0 mg/70 kg), given 30 min apart. This procedure ensured that participants tolerated the IV saline and nicotine doses that were used in the experimental sessions. During the first 2-days of each treatment period, participants had daily clinic visits to receive the study medications and to complete outcome measures. Starting at midnight of Day 1, participants were asked to stop smoking until the morning of Day 3. To assure compliance with non-smoking instructions, participants were paid extra for not smoking. Abstinence from smoking was verified with expired carbon monoxide (CO; <10 parts-per-million).

On Day 3 (Choice Session), 2 h following study medication (minocycline or placebo) administration, smoking behavior was assessed using a choice procedure, as described below. Participants returned to the clinic on Day 4 (IV Nicotine Session), after overnight abstinence from smoking, where responses to IV nicotine were obtained. The two experimental sessions and the outpatient visits were scheduled at 8 AM.

Smoking Choice Procedure (Table 2a): Participants received 10 tokens at the beginning of the Smoking Choice Session, which could later be exchanged for money ($0.75/token) or 2 cigarette puffs. The choice procedure has been shown to be sensitive in demonstrating medication effects on smoking behavior (Tidey et al., 2000). We chose $0.75 as the token value, since this token value is expected to be sensitive to both increases and decreases in smoking behavior (Bisaga et al., 2007). This session started with sample smoking consisting of 2, 3 s cigarette puffs separated by a 20 s interval. The sample smoking allowed measurement of subjective responses to smoking following abstinence. Starting 15 min after the sample smoking episode and every 15 min thereafter until 2.5 h had elapsed (i.e., 15 min × 10 tokens), participants had the opportunity to exchange tokens for cigarette puffs or money.

Intravenous Nicotine Administration (Table 2b): For this procedure, participants had an indwelling catheter placed in an antecubital vein. After baseline measures were obtained, participants received an oral dose of either minocycline or placebo. Two hours after the medication administration, participants first received saline followed by two ascending doses of IV nicotine, 0.5 and 1.0 mg/70 kg, 30 min apart. Both 0.5 and 1.0 mg/70 kg dose of nicotine have been well tolerated and produced robust physiological and subjective responses in male and female smokers in our previous studies (Sofuoglu et al., 2003, 2005, 2006). These doses are within the range of nicotine delivered by smoking one cigarette, which is approximately 0.5 to 2 mg.

1.3. Drugs

1.3.1. Nicotine and minocycline administration

Nicotine bitartrate was obtained from Interchem Corporation (Manchester, Connecticut). Nicotine samples were prepared by a research pharmacist at the VA CT Healthcare System. A saline injection was followed by two nicotine injections (0.5 and 1.0 mg/70 kg). Nicotine was administered in 5 mL volume over 60 s intravenously via a catheter located in a forearm vein. The injections were given 30 min apart.

Minocycline (Dynacin®) was administered at 200 mg/day, as a single dose, for 4 days. This dose is within the range of usual daily dose of minocycline used for the treatment of infections (Jonas and Cunha 1982). Further, two recent trials have utilized a 200 mg/day dose of minocycline in studies of Parkinson's disease and acute stroke (Lampl et al., 2007; The NINDS NET-PD Investigators, 2006). Following oral administration, peak plasma levels of minocycline are reached within 1–4 h. The elimination half-life of minocycline ranges from 11 to 24 h. Minocycline was administered in the clinic daily by the study nurse.

1.4. Measures

The outcome measures tapped behavioral, biochemical, physiological, subjective, and cognitive domains. Smoking behavior was assessed through a choice procedure, i.e., number of cigarette puff selections. Biochemical measures were expired CO and plasma cotinine concentrations to verify abstinence from smoking and level of smoking, respectively. Blood samples were obtained at baseline and before the IV Nicotine Sessions. The physiological measures were systolic and diastolic blood pressures and heart rate, which were taken before medication treatment and every 20 min for 2 h afterwards. Additional physiological measures were taken at −5 and 1, 2, 3, 5, 8, 10, and 15 min in relation to saline or nicotine deliveries.

The subjective measures included the Drug Effects Questionnaire (DEQ), Cigarette Evaluation Scale (CES), Nicotine Withdrawal Symptom Checklist (NWSC), Positive and Negative Affect Schedule (PANAS) and Profile of Mood States (POMS). The DEQ was used to measure acute effects from intravenous nicotine and consisted of 5 items: drug strength, good effects, bad effects, head rush and like the drug. Participants rated these effects on a 100 mm scale, from “not at all” to “extremely.” The DEQ was given just before and 1, 3, 5, 8, 10, and 15 min after saline or nicotine administration. The Cigarette Evaluation Scale

Table 2a
Schedule of events: experimental session 1

Time	Measures and events
Baseline	CO, HR/BP, POMS, NWSC, PANAS
8:00 AM	Medication treatment (minocycline or placebo)
8:30 AM	Snack
10:00 AM	Cognitive testing, HR/BP, DEQ, NWSC, PANAS Smoking period starts
12:30	Smoking period ends HR/BP, POMS, NWSC, PANAS

Note: CO: alveolar carbon monoxide; HR/BP: heart rate/blood pressure; POMS: profiles of mood states; NWSC: Nicotine Withdrawal Symptom Checklist; PANAS: Positive and Negative Affect Schedule; DEQ: Drug Effects Questionnaire.

Table 2b
Schedule of events: experimental session 2

Time	Measures and events
Baseline	CO, nicotine levels, HR/BP, POMS, NWSC, PANAS
8:00 AM	Medication treatment (minocycline or placebo)
8:15 AM	Snack
10:00 AM	HR/BP, DEQ, NWSC
	Nicotine 0 mg
10:01	HR/BP, DEQ
10:02	HR/BP
10:03	HR/BP, DEQ
10:05	HR/BP, DEQ
10:08	HR/BP, DEQ
10:10 am	HR/BP, DEQ
10:15 min	HR/BP, DEQ
	Nicotine 0.5 mg/70 kg
10:45	Nicotine 1 mg/70 kg
12:15	HR/BP, POMS, NWSC, PANAS

Note: The same measures were obtained following saline and each nicotine administration. For brevity, only the measures after saline are shown. For abbreviations see Table 2a.

(CES) was used to measure the subjective effects of smoking under each of the treatment conditions (Cappelleri et al., 2007; Westman et al., 1992). This scale assesses satisfaction, taste, and smoking-induced changes in dizziness, calm, concentration, wakefulness, hunger, nausea, irritability, throat and chest sensations, and craving on a seven-point ratings (from 1 = "not at all" to 7 = "extremely").

The POMS bipolar, a 72-item rating scale (McNair et al., 1988), was used to measure the effects of medication treatments on the mood. The POMS has 6 subscales: (1) composed–anxious; (2) agreeable–hostile; (3) elated–depressed; (4) confident–unsure; (5) energetic–tired; (6) clear headed–confused. The PANAS is a 20-item scale that assesses both negative and positive affective states (Watson et al., 1988). Participants rate adjectives describing affective states on a scale of 1 to 5 using a specified time period (i.e., now, today, past week, etc.). This scale is sensitive to the affective symptoms of tobacco withdrawal (Kenford et al., 2002). The NWSC measures withdrawal symptoms from tobacco and includes items of cigarette craving, irritability/anger, anxiety, difficulty concentrating, restlessness, increased appetite, depressed or sad mood, and insomnia (Hughes and Hatsukami, 1986, 1997). We used a modified version of the NWSC in which participants were asked to rate these symptoms on a 100 mm scale, from "not at all" to "extremely" (e.g., Buchhalter et al., 2005). The "cigarette craving" item from the NWSC was also given during the session on Day 4 to measure changes in urges to smoke in response to intravenous nicotine. The NWSC, POMS, and PANAS were given daily during the study, On Day 4, the cigarette craving item from the NWSC was given at baseline, before saline and nicotine administrations and at the end of the session.

Cognitive Performance was measured with the Sustained Attention to Response Test (SART) (Robertson et al., 1997; Sofuoglu et al., 2008a). The SART assesses the ability to withhold responses to an infrequently occurring target. The SART was administered on Days 1, 2 and 3 of each treatment phase. On Day 3, the SART was administered 2 h after medication treatment. Due to experimenter error, one participant did not complete the SART. Data from 2 sessions was missing for an additional two participants.

1.5. Statistical analysis

Study outcomes were analyzed using a mixed-effect repeated-measures crossover models using the Statistical Analysis System, Version 9.1.3. (SAS Institute Inc., 2007). Each model included fixed main effect terms for treatment (placebo or minocycline), and time of measurement (day in the study or time since medication administration), as well as the interaction of these two effects. We also included a random effect for participant and a blocking factor for treatment sequence. Values of $p<0.05$ were considered statistically significant, based on two-tailed tests, unless otherwise specified. Significant treatment or treatment by time interactions ($p<0.05$) was followed by post hoc comparisons, with Tukey adjustments to prevent the Type I error rate. For blood pressure, heart rate and DEQ measurements during IV nicotine administration, where multiple measurements were collected before and after each dose, a change score (maximum post dose score minus predose baseline) was used in the analysis.

2. Results

2.1. Smoking behavior

There was no treatment effect on smoking self-administration [$F(1,11)=0.7$; $p>0.05$]. Participants exchanged an average (SD) of 7.3 (0.9) tokens for cigarette puffs under placebo treatment, and 7.4 (1.0), under minocycline treatment.

2.2. Plasma cotinine measurements and breath CO levels

Baseline cotinine (SEM) levels were 236 ng/mL (32). Cotinine levels (SEM) on the last day of each treatment (IV Nicotine Session) were 207 ng/mL (32) for the placebo, and 184 ng/mL (29) ng/mL for the minocycline treatment [$F(1,11)=1.5$; $p>0.2$]. Smoking abstinence before the sessions were verified by CO levels <10 ppm.

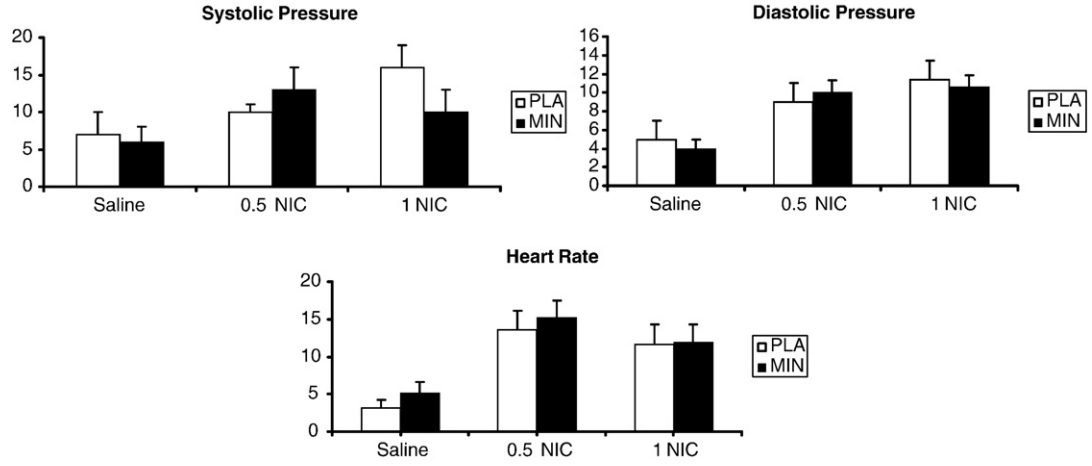

Fig. 1. The average (with standard error of the mean — SEM) systolic blood pressure, diastolic blood pressure and heart rate responses to saline, 0.5 and 1.0 mg/70 kg intravenous nicotine under placebo and minocycline conditions. Bars represent the change (maximum post dose-baseline). Measurements were taken 5 min before and 1, 2, 3, 5, 8 and 10 min after each injection.

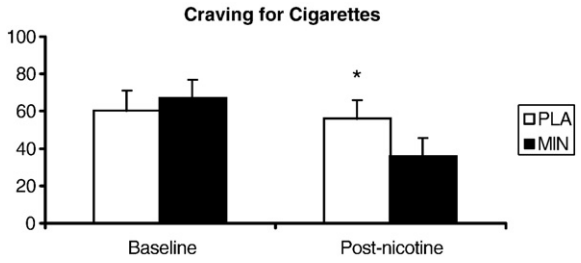

Fig. 2. The average (with SEM) ratings of cigarette craving in response to saline and nicotine administration. The measurements shown were taken at baseline and 30 min after 1.0 mg nicotine administration. * indicates a significant treatment-by-time interaction.

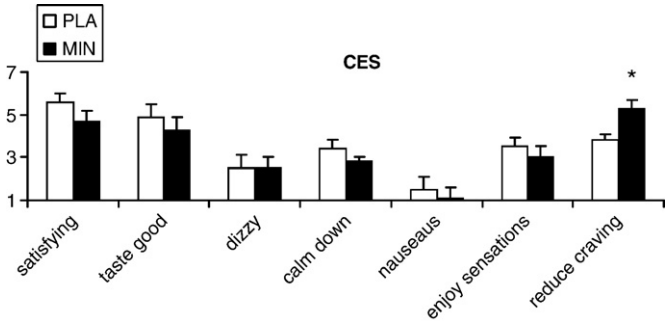

Fig. 4. The average (with SEM) ratings of subjective responses to sample smoking measured with the Cigarette Evaluation Scale (CES). The measurements were obtained after 2 puffs of a cigarette.* indicates a significant treatment effect.

2.3. Physiological response to IV nicotine

There was no treatment effect on IV nicotine responses for heart rate [$F(1,55)=1.5$; $p>0.05$], systolic [$F(1,55)=1.2$; $p>0.05$] or diastolic [$F(1,55)=0.2$; $p>0.05$] blood pressure. As shown in Fig. 1, there was a significant nicotine dose effect for the heart rate, systolic and diastolic blood pressures ($p<0.001$). Pairwise comparisons indicated that responses for all 3 outcomes were higher under the 0.5 mg or 1.0 mg nicotine than under the placebo condition ($p<0.05$).

2.4. Tobacco withdrawal severity and mood measures

There was no treatment effect on the total NWSC scores during the first 3 days of each treatment period [$F(1,55)=0.2$; $p>0.05$]. There was a significant main effect for time [$F(3,77)=5.1$; $p<0.01$], with increased withdrawal severity over time. For the individual items, a significant treatment-by-time interaction was observed for "depressed mood," with lower rating under minocycline treatment [$F(3,77)=2.9$; $p<0.05$]. In response to IV nicotine administration, cigarette craving showed a significant treatment-by-time interaction, (Fig. 2) with greater decreases under the minocycline condition [$F(4,99)=2.9$; $p<0.05$].

No treatment effects were observed for any of the PANAS and POMS subscales.

2.5. Subjective responses to cigarette smoking and IV nicotine

The subjective responses to sample smoking, measured with CES, a significant treatment effect was observed for the rating of "reduced craving for cigarettes" [$F(1,11)=8.5$; $p<0.05$], 5.4 (1.3) and 3.7 (2.0) under minocycline and placebo conditions, respectively. Other CES items did not show treatment effects (Fig. 3).

The treatment effects on the subjective response to IV nicotine measured with DEQ are shown in Fig. 4 There was no treatment effect for the rating of drug strength [$F(1,54)=0.07$; $p>0.05$], good effects [$F(1,54)=0.02$; $p>0.05$], bad effects [$F(1,54)=0.02$; $p>0.05$], head rush [$F(1,54)=0.04$; $p>0.05$] or drug liking [$F(1,54)=0.3$; $p>0.05$]. As expected, there was a significant nicotine dose effect for all 5 DEQ items ($p<0.001$). Pairwise comparisons indicated that the responses under the placebo were less than the 0.5 or 1.0 mg nicotine conditions ($p<0.05$).

2.6. Performance measures

Table 3 summarizes the results of the SART. No effects involving treatment were observed on the SART ($p>0.05$).

3. Discussion

Minocycline treatment did not affect smoking self-administration in our choice procedure. Smokers chose cigarette puffs in approximately 70% of opportunities under placebo or minocycline treatment, with a token value of $0.75. These findings are consistent with a recent study by Bisaga and coworkers (2007) which demonstrated an increase in token exchange rate for cigarette puffs in a range of token

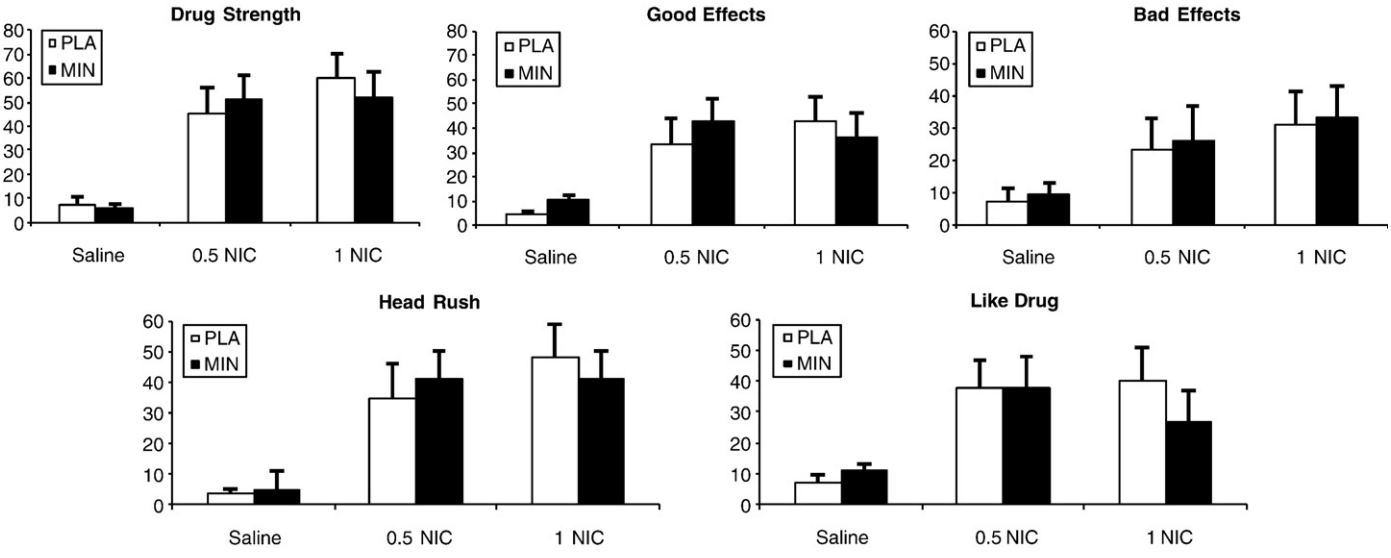

Fig. 3. The average (with SEM) subjective responses to saline, 0.5 and 1.0 mg/70 kg intravenous nicotine under placebo and minocycline conditions. Bars represent the change (maximum post dose-baseline). Measurements were taken just before and 1, 3, 5, 8 and 10 min after each injection.

Table 3
Summary statistics on the SART ($n=11$) (note * due to missing data, $n=10$)

	Placebo			Minocycline		
	Day 1*	Day 2	Day 3	Day 1*	Day 2	Day 3
Errors on 3s (/25)	11.8 (6.09)	12.5 (6.8)	11.0 (7.0)	9.9 (6.8)	10.5 (6.7)	10.5 (5.5)
Errors on non-3s (/200)	8.40 (15.1)	11.7 (19.9)	5.54 (6.3)	6.7 (7.9)	11.4 (15.2)	7.73 (10.7)
Mean RT for correct presses (ms)	355.1 (81.4)	377.6 (92.4)	380.4 (77.8)	383.1 (120.0)	412.0 (95.4)	400.9 (73.4)

values from $0.5 to $2. In that study, token exchange rate was 100 and 80%, for token values of $0.50 and $1 respectively, demonstrating the sensitivity of the choice-procedure to changes in alternative reinforcer values (i.e., money).

Our model examined responses to IV nicotine, in addition to cigarette smoking. The advantage of IV nicotine is fast and accurate dose delivery and the ability to produce consistently both subjective and physiological effects. As demonstrated in previous studies, IV nicotine is reinforcing and readily self-administered by smokers (Harvey et al., 2004; Sofuoglu et al., 2008b). Examining nicotine as well as cigarette smoking responses helped to assess medication effects on both nicotinic and non-nicotinic components of tobacco addiction, since cigarette smoke contains many other compounds other than nicotine (Hoffmann and Wynder, 1986). Minocycline did not affect most of the subjective responses to IV nicotine or sample smoking. One exception was the rating of cigarette craving. Following IV nicotine administration, there was a greater reduction in craving for cigarettes under minocycline, compared to placebo. Similarly, smokers had greater reduction in their craving for cigarettes following sample smoking under minocycline treatment, compared to placebo. As demonstrated in a recent field study, smoking reliably reduces craving (Carter et al., 2008); a medication that facilitates this craving reduction may attenuate ad libitum smoking. Future research can also determine whether minocycline reduces cue-induced craving.

Consistent with many previous studies, tobacco withdrawal severity increased over 3 days of cigarette abstinence. Minocycline treatment did not affect the severity of tobacco withdrawal symptoms. One exception was feeling depressed or sad mood, which was attenuated under the minocycline treatment condition. However, minocycline did not affect the rating of elated-depressed subscale of the POMS. Interestingly, preclinical studies and anecdotal evidence from humans support antidepressant effects of minocycline (Pae et al., 2008). Whether minocycline will have efficacy for depression or depressed mood associated with tobacco withdrawal remains to be examined in future studies.

What are the implications of our findings? As mentioned before, NO inhibitors have shown promising results for nicotine addiction in preclinical studies. Unfortunately, the NO inhibitors used in these preclinical studies are not approved for human use. Minocycline, in clinically used doses, has been shown to inhibit NO synthesis (Kim et al., 2004; Sadowski and Steinmeyer, 2001); however, it has not been examined in preclinical models for nicotine addiction. To fully evaluate the potential use of NO inhibitors for nicotine addiction, further studies using other NO inhibitors, especially those selective for neuronal type, as they become available, are warranted.

This study also had several limitations. First, dose-dependent effects of minocycline were not examined. We selected a clinically used dose of minocycline, which has also been used in many clinical trials for neuropsychiatric conditions including Huntington's disease, Alzheimer's disease, stroke and schizophrenia (Thomas et al., 2004). Second, the study had a 4-day treatment duration. It is possible that longer treatment duration might be associated with different treatment effects. Third, participants were non-treatment seeking smokers who were not motivated to quit. The generalizability of our findings to treatment-seeking smokers may be limited.

To summarize, we detected no differences between minocycline and placebo on most of the measures of behavioral, biochemical, physiological, subjective, and cognitive domains. Minocycline treatment was associated with modest improvement in depressed mood and greater reduction in craving for cigarettes following smoking in abstinent smokers.

Acknowledgments

This research was supported by the Veterans Administration Mental Illness Research, Education and Clinical Center (MIRECC) and NIH grants P50-AA-015632, K02-DA-021304 (MS), K01-DA-019446 (MM), and K05-AA-014715 (SSO). We would like to thank Ellen Mitchell, R.N., Lance Barnes, and Stacy Minnix for technical assistance.

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