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Tiagabine affects the subjective responses to cocaine in humans

Mehmet Sofuoglu *, James Poling, Ellen Mitchell, Thomas R. Kosten

Yale University, School of Medicine, Department of Psychiatry and VA Connecticut Healthcare System, West Haven, CT, USA

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Abstract

In preclinical studies, medications which increase the synaptic GABA levels have been shown to block cocaine reinforcement. In this study, we examined the interaction between a GABA enhancing medication, tiagabine, and cocaine in cocaine users. A total of 7 subjects, 5 male and 2 female cocaine users had 2 experimental sessions. Before each session, subjects received either two oral doses of 4 mg of tiagabine or placebo. Starting 2 h after the second dose of medication treatment, subjects received an injection of saline followed by 2 escalating cocaine doses (0.15 and 0.3 mg/kg) intravenously. Tiagabine treatment did not affect the cocaine-induced blood pressure and heart rate changes. Tiagabine treatment attenuated the subjective ratings of "stimulated" and "crave cocaine" in response to cocaine administration. These results suggest that tiagabine treatment attenuates some of the subjective effects of cocaine without affecting its cardiovascular effects. GABA medications, including tiagabine, are currently being evaluated in controlled clinical trials for the treatment of cocaine dependence.

Keywords: Cocaine; Tiagabine; GABA

1. Introduction

The reinforcing effects of cocaine are thought to be mediated through the mesocorticolimbic dopamine (DA) system, which consists of DA neurons of the ventral tegmental area and their target projections, including the nucleus accumbens and the prefrontal cortex (Johanson and Fischman, 1989; Bardo, 1998; Koob, 1992; Tzschentke, 2001). Preclinical studies suggest an interaction between the brain GABA and DA systems. The brain areas which contain DA neurons such as the striatum and the nucleus accumbens also contain GABAergic synapses, suggesting anatomical connectivity between these two systems (McFarland and Kalivas, 2001). In addition, GABAergic medications modulate the effects of cocaine and the DA system. For example, treatment with vigabatrin, which increases GABA levels by inhibiting the breakdown of GABA, attenuates cocaine-induced locomotor activity and dopamine release in the nucleus accumbens in rats (Dewey et al., 1997; Gerasimov et al., 2001). Baclofen, a $GABA_B$ receptor agonist, attenuates cocaine self-administration in rats (Roberts et al., 1996; Shoaib et al., 1998; Campbell et al., 1999). These preclinical studies suggest the GABA system may be a useful target for the treatment of cocaine addiction.

In clinical trials, a number of GABAergic medications showed promising results for the pharmacotherapy of cocaine dependence. The GABAergic medications tested as treatment for cocaine dependence include tiagabine, topiramate, and baclofen (Shoptaw et al., 2003; Gonzalez et al., 2003; Kampman et al., 2004). Tiagabine is an anticonvulsant agent, which enhances synaptic GABA levels by selectively blocking the type I GABA reuptake transporter (GAT) (Schachter, 2001). A recent study investigating the efficacy of tiagabine for cocaine use with opioid dependent cocaine users maintained on methadone showed that tiagabine attenuated cocaine use measured with thrice weekly urine drug screening (Gonzalez et al., 2003).

Given the potential utility of tiagabine as a treatment of cocaine dependence, we decided to examine the interaction between tiagabine and cocaine. The goal of this study was to determine whether tiagabine treatment affects cocaine responses in controlled human laboratory settings. We hypoth-

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

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esized that tiagabine treatment would attenuate the subjective effects of cocaine.

2. Methods

2.1. Subjects

Five male and 2 female, non-treatment-seeking, crack cocaine users participated in the study. Five subjects were African-American, 2 were Caucasian. Three additional subjects were enrolled but were excluded for lack of venous access ($n=2$) and non-compliance ($n=1$) with study procedures and were not included in the analyses.

Subjects had an average age (SD) of 39.7 (3.0) years and average schooling of 12.1 (1.5) years. During the month before study participation, the average frequency of cocaine use was 13.7 (3.9) days and the amount spent on cocaine was $135 (124)/week (local cost of cocaine is around $80/g). Subjects had an average 19.1 (6.4) years of cocaine use. Subjects' current use of other drugs included cigarettes ($n=7$), alcohol ($n=5$) and marijuana ($n=3$).

All subjects had normal physical, laboratory and psychiatric examinations, except drug use. All subjects were dependent on cocaine and those who were dependent on drugs other than cocaine and nicotine were excluded from the study. Current drug use was confirmed with urine toxicology screening. This study was approved by the VA Connecticut Healthcare System Human Subjects Subcommittee. Subjects signed an informed consent before study participation. Subjects were paid a total of $350 for study participation.

2.2. Study procedure

This was a double-blind, placebo-controlled, crossover study with one adaptation and 2 experimental sessions. For study participation, subjects were housed at the VA Connecticut Healthcare System for five days. Subjects had an adaptation session on the day of admission to orient them to the laboratory procedures. Two intravenous catheters were placed, one on each arm, for injection and blood drawing. Then, baseline measures including blood pressure, heart rate, ECG, and subjective measures were taken. Subjects first received an IV saline injection and 30 min later, a 0.3 mg/kg dose of IV cocaine to familiarize them with the IV injection and cocaine injection procedures, respectively.

Before each experimental session, subjects received the assigned medication treatment at 10 PM the night before and at 8 AM on the day of the experimental session. Starting 2 h after the AM medication treatment, subjects received an IV injection of saline followed by 2 escalating doses of IV cocaine, 0.15 and 0.3 mg/kg. Saline and cocaine injections were given 30 min apart to allow enough time for the heart rate and blood pressure changes to return to baseline levels. To ensure safety, subjects received the low dose cocaine (0.15 mg/kg), before the high dose (0.3 mg/kg). This cocaine dosing schedule was adapted from previous human laboratory studies (Walsh et al., 1994, 1996). Following a one-day washout, subjects were crossed over to the alternative treatment. Subjects were asked not to use any illicit drugs or alcohol during the study and their compliance was checked with urine drug screening and breathalyzer before the sessions. Subjects

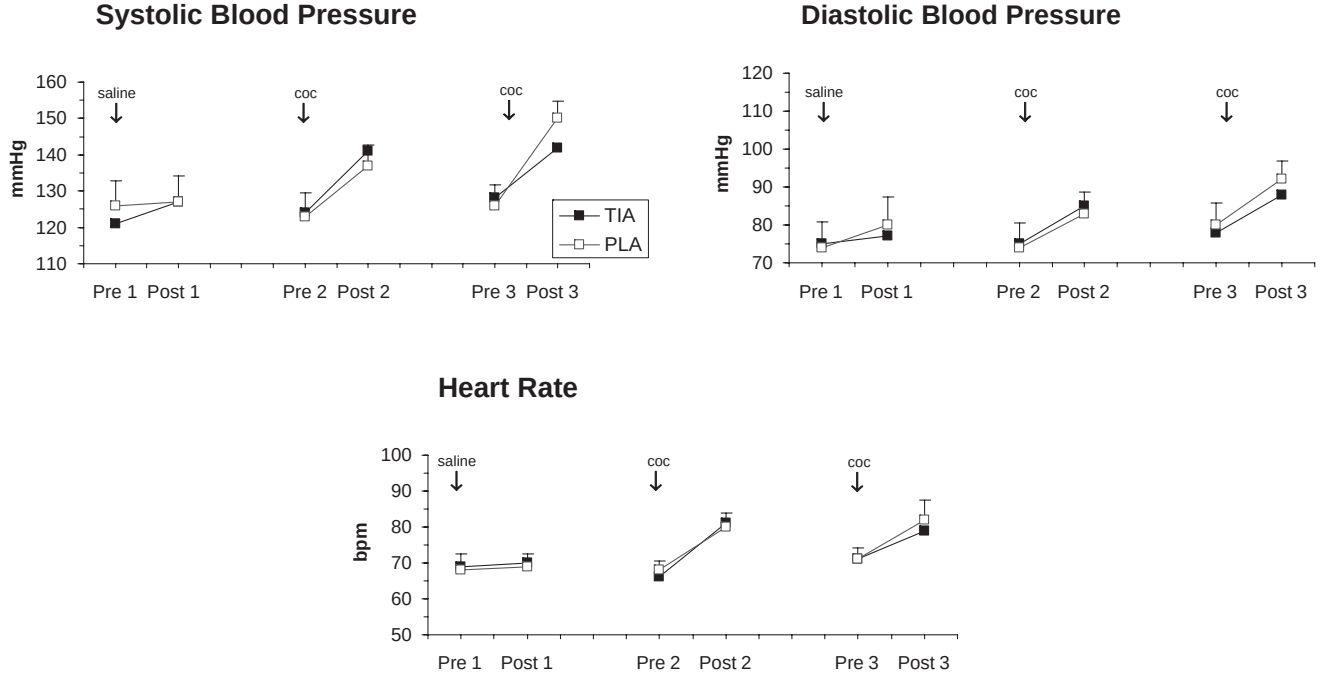

Fig. 1. Tiagabine effects on systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg) and heart rate (bpm) responses to IV saline and 2 escalating doses of cocaine (0.15 and 0.3 mg/kg), given 30 min apart. For clarity, only measurements taken 2 min before and 3 min after each cocaine administration are shown. Data shown are the average values (SEM).

were not permitted to eat or smoke for approximately 5 h during the sessions.

2.3. Drugs

Cocaine hydrochloride was obtained from the Sigma-Aldrich (St. Louis, MO). The cocaine doses were 0.15 and 0.3 mg/kg injected intravenously over 60 s. At this dose range, cocaine has elicited reproducible subjective and physiological effects safely in previous human studies (Haney et al., 1998; Sofuoglu et al., 2004).

Tiagabine (Gabitril®) was obtained from Cephalon (West Chester, PA). Following oral administration, tiagabine is rapidly absorbed, reaching peak plasma levels within 2 h. Tiagabine has an elimination half-life of 5–9 h (Genton et al., 2001). Before each experimental sessions, subjects were given 2 oral doses of 4 mg tiagabine, the usual starting dose for tiagabine, or placebo. The order of medication treatment (tiagabine or placebo) was counterbalanced in blocks of two.

2.4. Medical monitoring and safety

During sessions, cardiac rhythm was monitored continuously and 12-lead ECGs were taken before and at the end of each session. Subjects remained in the laboratory until all vital signs returned to baseline levels. A physician was present during all the sessions to monitor the subjects.

2.5. Outcome variables

The main outcome variables were physiological, subjective, and biochemical measures. Physiological measures were systolic and diastolic blood pressure, and heart rate, which were taken at −2, 3, 5, 10 and 15 min in relation to cocaine deliveries. Subjective effects of cocaine were measured by the Cocaine Effects Questionnaire (CEQ) on a VAS. The CEQ consists of 5 items: feel high, feel stimulated, crave cocaine, heart racing/pounding, and feel the effects of last dose. The CEQ was given 4.5 min before and 2.5, 10 and 15 min after each dose. The POMS (McNair et al., 1971) was used to measure the effects of treatments on mood. The POMS is a 72-item rating scale with 6 subscales: (1) composed-anxious; (2) agreeable-hostile; (3) elated-depressed; (4) confident-unsure; (5) energetic-tired; (6) clear headed-confused. The POMS was given twice: at the beginning and end of each experimental session.

Plasma cocaine concentrations were assessed at baseline and 5 min after the low and high dose of cocaine administration.

2.6. Statistical analysis

To assess treatment effects on the physiological and subjective measures, a mixed-effects repeated-measures cross-over analysis was conducted using SAS. The structure of the analysis included a fixed main effect for treatment (placebo or tiagabine), dose (saline, 0.15 and 0.3 mg/kg cocaine), another for the effect of time since delivery of saline or cocaine, and the interaction of these three effects. Also included were a random effect for subject, allowing for a compound-symmetric covariance structure for all responses on a particular subject. For the CEQ and physiological measures, significant treatment effects were further analyzed using peak-change scores (maximum post-dose minus pre-dose) as dependent variables. Peak change score was chosen as a measure for the magnitude of response with each delivery of cocaine. A significance level of 0.05 was used for all analyses.

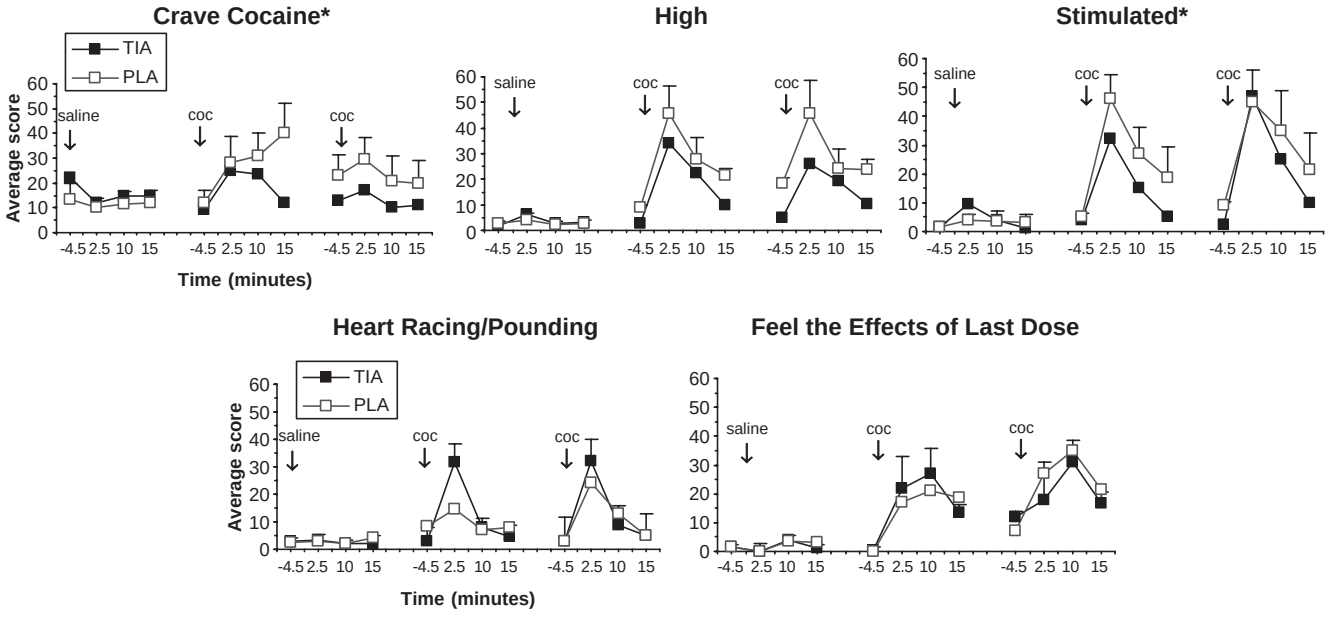

Fig. 2. Tiagabine effects on average subjective responses using CEQ to IV saline and 2 escalating doses of cocaine (0.15 and 0.3 mg/kg), given 30 min apart. The measurements were obtained 4.5 min before and 2.5, 10 and 15 min after saline and cocaine administration. Data shown are the average values (SEM) and significant group difference ($P<0.05$) are indicated by an asterisks (*).

3. Results

3.1. Physiological response

No significant treatment effects were observed for heart rate [$F(1,198)=1.1$; $p=0.3$], systolic [$F(1,198)=0.2$; $p=0.6$], or diastolic blood pressure [$F(1,198)=1.6$; $p=0.2$]. Significant time and dose effects were observed for heart rate, systolic and diastolic pressure [all $p<0.0001$]. Neither treatment-by-time or treatment-by-dose interactions were significant for heart rate, systolic or diastolic blood pressure (all $p>0.05$) (Fig. 1).

3.2. Subjective response

Significant treatment effects were observed for the rating of "stimulated" [$F(1,150)=4.9$; $p<0.05$], and "crave cocaine" [$F(1,150)=6.2$; $p<0.05$], with attenuated responses with tiagabine treatment. Treatment effects were not significant for the rating of "high" [$F(1,150)=3.5$; $p=0.06$], "heart racing/pounding" [$F(1,138)=0.1$; $p=0.7$], and "feel the effects of last dose" [$F(1,150)=0.03$; $p=0.9$]. All 5 CEQ items showed a significant time effect (all $p<0.001$), without a significant treatment by time interaction ($p>0.05$). A significant dose effect was observed for the rating of "high" [$F(2,150)=32.4$; $p<0.0001$], "stimulated" [$F(2,150)=24.6$; $p<0.0001$], and "crave cocaine" [$F(2,150)=5.2$; $p<0.01$], due to greater responses to cocaine (0.15 and 0.3 mg/kg) compared to saline. Treatment-by-dose interaction was significant for "crave cocaine," [$F(2,150)=4.9$; $p<0.01$], with attenuated responses under tiagabine treatment. Further analyses with peak change scores did not show significant treatment effects for the rating of "crave cocaine" and "feel stimulated" ($p>0.05$).

Since sedation is one the side effects of tiagabine, the energetic-tired subscale of the POMS was of particular interest. This subscale showed no treatment [$F(1,15)=0.4$; $p=0.6$] or treatment-by-time [$F(3,15)=0.6$; $p=0.6$] interaction. Similarly, the other subscales of the POMS showed no treatment or treatment-by-time interactions (Fig. 2).

3.3. Plasma cocaine measurements

Tiagabine did not affect plasma cocaine concentrations after cocaine injections. Under tiagabine treatment, the average (SD) peak cocaine concentrations following the 0.15 and 0.3 mg/kg cocaine, were 177(48) and 364(65) ng/ml, respectively. Under placebo treatment, the corresponding values were 163 (49) and 366 (75) ng/ml, respectively.

4. Discussion

In this study, tiagabine treatment attenuated some of the subjective effects from escalating doses of intravenous cocaine given to cocaine users. The subjective ratings of "stimulated," and "crave cocaine" were attenuated with tiagabine, while the rating of "high," "heart racing/pounding" and "feel the effects of last dose" were not affected by tiagabine treatment. These findings further extend the human laboratory studies examining the interactions between GABergic medications and cocaine. Previous human studies using tiagabine, gabapentin and baclofen in conjunction with cocaine have yielded mixed results (Lile et al., 2004a,b; Hart et al., 2004). In contrast to our findings, a recent study reported no effects from tiagabine (single 4 or 8 mg) treatment on the subjective responses to orally administered cocaine (Lile et al., 2004b). These conflicting findings could be due to a number of methodological differences between these two studies. Most notably, our study used intravenous cocaine administration, in contrast to the oral form of cocaine administration in the other study (Lile et al., 2004b). Although, cocaine elicits qualitatively similar subjective and cardiovascular effects following oral versus intravenous administration, the time course is faster following intravenous route (Smith et al., 2001). Intravenous cocaine is also approximately 10 times more potent than the oral form (Smith et al., 2001), suggesting that subjects in our study received twice as much cocaine than the Lile et al. study (0.45 mg/kg IV versus 150 mg orally). In our study, tiagabine was administered in two divided doses starting the night before the session, compared to acute single dose administration in the other study (Lile et al., 2004b). In addition, compared to a single dose of cocaine in the Lile et al. study, subjects in our study received 2 increasing doses of cocaine, which may have resulted in the development of tolerance to cocaine's effects. Acute tolerance may explain the lack of dose related response to cocaine-induced subjective and physiological effects in this study. Further studies are needed to determine whether route of cocaine administration or acute tolerance with repeated cocaine deliveries affect the interaction between GABAergic medications and cocaine.

In another study by the same group, $GABA_B$ receptor agonist baclofen treatment (a single 10, 20 or 30 mg) did not affect the subjective responses to intranasal cocaine (Lile et al., 2004a). These results did not support the preclinical studies which reported decreased cocaine self-administration with baclofen (Roberts et al., 1996; Shoaib et al., 1998; Campbell et al., 1999). In a recent human laboratory study, gabapentin treatment (600 or 1200 mg/day), compared to placebo, attenuated some of the subjective effects of smoked cocaine including the rating "good effects" and "anxious." (Hart et al., 2004) Although its exact mechanism of action is unknown, gabapentin treatment, similar to tiagabine, is associated with increased brain GABA levels (Kuzniecky et al., 2002). Future studies correlating changes in the brain GABA levels and cocaine responses following tiagabine or gabapentin treatment will be helpful to better understand the role of the GABA system in cocaine addiction. Interestingly, both this study and Hart et al. (2004) study, which reported attenuation of subjective cocaine effects by GABA enhancing agents, used intravenous or smoked cocaine. In contrast, the other two studies, which reported no effects from GABA enhancing agents used oral or intranasal cocaine administration (Lile et al., 2004a,b). How route of cocaine administration influence medication effects on cocaine responses has not been systematically examined.

This study has several limitations. First, we used only one dose size of tiagabine, which was the usual starting dose of tiagabine. This study did not examine the dose-effect relationship for tiagabine effects on cocaine responses. Having more than one dose of tiagabine would be helpful to examine the dose-effect relationship for tiagabine effects on cocaine responses. Second, the duration of treatment was brief: subjects received two administrations of tiagabine treatment. It is possible that a longer tiagabine treatment may lead to different results than acute treatment. Third, our sample was relatively small, especially to examine gender and other individual differences that may have affected tiagabine and cocaine interactions.

To summarize, tiagabine treatment attenuated some of the subjective effects of cocaine in cocaine users. Further studies are warranted to examine the therapeutic effects of tiagabine for cocaine dependence.

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