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Atomoxetine Attenuates Dextroamphetamine Effects in Humans

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Abstract

Background—Although preclinical studies support the contribution of the noradrenergic system activation in mediating the acute effects of amphetamines, these findings have not been followed up in clinical studies.

Objectives—To examine the effects of atomoxetine, a norepinephrine transporter inhibitor, on subjective, physiological, and plasma cortisol responses to dextroamphetamine in 10 healthy volunteers.

Methods—Subjects were randomly assigned to a sequence of atomoxetine (40 mg/day) or placebo treatments each lasting for 4 days. On Day 4 of each treatment period, responses to a single 20 mg/70 kg dose of dextroamphetamine were assessed

Results—Atomoxetine treatment attenuated dextroamphetamine-induced increases in systolic and diastolic blood pressure and plasma cortisol as well as the self-report ratings of “stimulated,” “high,” and “good drug effects.”

Conclusions—These findings are consistent with previous preclinical studies supporting the role of the noradrenergic system in mediating acute amphetamine responses.

Scientific significance—Atomoxetine's capacity to attenuate some of the physiological and subjective responses to dextroamphetamine supports its potential use for stimulant addiction.

Keywords

Atomoxetine; norepinephrine; dextroamphetamine

Introduction

Amphetamines are clinically used for treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. However amphetamines, especially methamphetamine, are also highly reinforcing and are commonly abused worldwide. The reinforcing effects of amphetamines are thought to be mediated by increased dopamine release, especially in the nucleus accumbens (1,²). However, in a study conducted by Brauer and De Wit, pimozone, a dopamine receptor antagonist did not alter dextroamphetamine-induced euphoria in healthy volunteers, suggesting non-dopaminergic contributions to the subjective effects of amphetamines (3). Consistent with these preclinical findings, the subjective effects of amphetamines in humans seem to be correlated with their capacity to release norepinephrine

but not dopamine (4). Further recent preclinical studies demonstrated that in doses equivalent to those used clinically, amphetamines release both norepinephrine and dopamine in the prefrontal cortex accompanied by minimal increases of dopamine in the nucleus accumbens (5). These findings further support the contribution of the noradrenergic system activation in mediating the acute effects of amphetamines (6).

The goal of this study was to determine the effects of atomoxetine on the acute dextroamphetamine responses. Atomoxetine is a selective norepinephrine transporter inhibitor, like reboxetine, and is marketed for the treatment of ADHD (7). Atomoxetine increases norepinephrine levels in the striatum and nucleus accumbens of rats (8), in contrast to amphetamines that increase both norepinephrine and dopamine levels in this brain region. Thus, treatment with atomoxetine would help to determine the contribution of norepinephrine in amphetamine responses in humans.

Methods

Participants

Three male and 7 female healthy controls were recruited from the New Haven area (8 African-Americans, 1 Caucasian, and 1 Asian-American). Three additional subjects were enrolled but did not complete the study due to poor intravenous access (n=1) or positive urine toxicology for cocaine during study participation (n=2) and were not included in subsequent analysis. The average age (with S.D.) of the subjects was 29.1 $\pm$ 6.4 years. Subjects were required to have normal physical, laboratory, and psychiatric examinations and no alcohol or drug dependence or abuse history. To minimize any confounding effects from nicotine or caffeine withdrawal, those who smoked over 5 cigarettes per day or drank more than 3 cups of coffee or caffeinated beverages per day were excluded from the study. All subjects provided informed consent prior to study entry. Experimental sessions were conducted in the Biostudies Unit located at the VA Connecticut Healthcare System (West Haven campus) and subjects were paid for participation. This study was approved by the VA Connecticut Healthcare System Human Subjects Subcommittee.

Design and Procedure

In this study, subjects participated in two treatment periods, each lasting for 4 days. Across the two treatment periods, subjects were assigned to a counterbalanced sequence of two treatment conditions: atomoxetine (40 mg/day) or placebo. These treatment periods were separated by a minimum of 4-day washout period to minimize carryover effects from study medications. During the first 3 days of each treatment phase, subjects participated in daily outpatient visits arriving at approximately at 8 AM to receive study medication and to monitor any medication effects. On day 4 of each phase, subjects participated in a laboratory session, which started at 8 AM and lasted approximately 6 hours. Before the sessions started an indwelling intravenous catheter was placed in the antecubital vein for blood drawing. After baseline measures were obtained, subjects received the daily dose of the study medication followed by a light meal. One hour after the medication treatment, subjects were first given a psychological stress and, 30 minutes afterwards, a physical stress which will be described elsewhere. Two hours after medication treatment, baseline subjective, physiological and cognitive measures were obtained followed by a 20 mg dose of dextroamphetamine. After the medication treatment, subjects stayed in the lab for 4 hours during which outcome measures were collected.

Drugs

Dextroamphetamine administration. Dextroamphetamine, the dextrorotatory isomer of amphetamine, was obtained from Barr Laboratories (Pomona, New York). We used a single

20 mg/70 kg oral dose, which has previously been shown to produce typical amphetamine effects in healthy volunteers (9,¹⁰).

Atomoxetine administration. Atomoxetine (Strattera ®) was obtained from Eli Lilly (Indianapolis, IN). Atomoxetine was given at 40 mg/day, as a single daily dose, for 4 days. This is a typical starting dose of atomoxetine for the treatment of ADHD, while the maintenance dose for adults ranges from 40 to 100 mg/day. Following oral administration, peak plasma atomoxetine levels are reached within 2 hours. The elimination half-life of atomoxetine ranges from 5 to 20 hours (7).

Outcome Measures

The outcome measures consisted of endocrine, physiological, and subjective measures. The endocrine measure was plasma cortisol concentration, which is shown to increase in response to both amphetamine and atomoxetine administration (11-¹³). The mechanism for the cortisol release is thought to be mediated by norepinephrine's capacity to increase corticotrophin releasing hormone (CRH) at the paraventricular nucleus of the hypothalamus (14). For cortisol measures, blood samples were obtained just before, and 1, 2, and 3 hours after dextroamphetamine administration.

The physiological measures were systolic and diastolic blood pressure and heart rate, which were taken just before and 30, 60, 90, 120, 150 and 180 minutes after dextroamphetamine treatment.

The subjective measures included the Drug Effects Questionnaire (DEQ) and the Profile of Mood States (POMS). The DEQ was used to assess the acute subjective effects of dextroamphetamine. The items are "stimulated", "high", "anxious", "sedated", "down", "feeling the drug strength", "feel good drug effects", "feel bad drug effects", "want more drug", and "like the drug." Subjects rated these items on a 100 mm scale, from 0 "not at all" to 100 "extremely." The POMS is a 72-item rating scale used to measure the effects of medication treatments on mood (15). The DEQ and POMS were administered at the beginning of session, just before, and 30, 60, 90, 150 and 180 minutes after the dextroamphetamine treatment.

Statistical Analyses—To assess treatment effects, we used a mixed-effect repeated-measures crossover analysis using SAS Proc Mixed (version 9.13). For blood pressure, heart rate, POMS, and DEQ measurements, where multiple measurements were collected before and after each dextroamphetamine administration, a change score (maximum post dose score minus predose baseline) was used in the analysis. The structure of the analysis included a fixed main effect for treatment (placebo or atomoxetine), a random effect for participant and a blocking factor for treatment sequence. For plasma cortisol measurement, the analysis also included time of measurement (in hours) and an interaction between these two effects. A significance level of $p < 0.05$ was used for all analyses.

Results

Physiological responses (Figure 1)

In response to dextroamphetamine, a significant main effect for treatment was observed for systolic [$F(1, 18) = 8.8$; $p < 0.01$] and diastolic blood pressure [$F(1, 18) = 610.6$; $p < 0.01$], with lower responses under atomoxetine treatment. No treatment effect was observed for the POMS.

Subjective Responses (Figure 2)

In response to dextroamphetamine, a significant main effect for treatment was observed on the DEQ for the ratings of "stimulated" [$F(1, 9) = 5.9$; $p < 0.05$] "high" [$F(1, 9) = 5.4$; $p < 0.05$],

and “good drug effects” [$F(1, 9) = 5.3$; $p < 0.05$]. In all these items greater ratings were observed under placebo treatment.

Cortisol (Figure 3)

For cortisol responses, (Figure 3), there was a significant time [$F(1, 62) = 5.3$; $p < 0.05$], treatment [$F(1, 62) = 4.4$; $p < 0.05$] and treatment-by-time interaction [$F(1, 62) = 5.3$; $p < 0.05$], with greater values under placebo treatment.

Discussion

Atomoxetine treatment attenuated the rating of “stimulated,” “high,” and “good drug effects” in response to dextroamphetamine in healthy controls. Recently, Stoops et al. reported that atomoxetine treatment did not affect the subjective effects of intranasal cocaine in stimulant users (16). Based on the similarities between the actions of stimulants, one may expect atomoxetine to act similarly on cocaine and amphetamine responses. However, there are significant differences between the pharmacological effects of cocaine and amphetamines. Most importantly, accumulating evidence indicates that norepinephrine contributes more to the effects of amphetamine than to the effects of cocaine. In a recent study, dextroamphetamine and methamphetamine were 5-9 times more potent at the norepinephrine transporter than the dopamine transporter (17). In contrast, cocaine was equally potent at norepinephrine transporter and dopamine transporter (17). In another study, the initiation of psychomotor sensitization to dextroamphetamine, but not to cocaine, was dose-dependently inhibited by an α_1 -adrenergic blocker prazosin or by an α_2 -adrenergic agonist clonidine in rats (18). Our findings are consistent with these preclinical studies suggesting that norepinephrine contributes to acute amphetamine responses, including its subjective effects.

Atomoxetine treatment attenuated the dextroamphetamine-induced systolic and diastolic blood pressure increases. These findings support the safety of atomoxetine when co-administered with amphetamines. Similarly, amphetamine-induced cortisol release was attenuated by atomoxetine treatment. Consistent with our findings, in a recent study, 3 days of reboxetine treatment, an inhibitor of norepinephrine transporter, attenuated the plasma norepinephrine response to a cold pressor test without changing the baseline plasma norepinephrine levels (19). Altogether, these findings suggest that treatment with norepinephrine transporter inhibitors may decrease endocrine responses mediated by central noradrenergic receptors.

What are the mechanisms by which atomoxetine attenuates some of the subjective, physiological, and cortisol responses to dextroamphetamine? As many preclinical and clinical studies indicate, norepinephrine transporter inhibitors acutely increase synaptic levels of norepinephrine. However, with prolonged treatment, norepinephrine response to pharmacological and behavioral challenges is attenuated while the tonic norepinephrine activity stays elevated. This is possibly due to neuroadaptation including both increased stimulation of inhibitory α_2 adrenergic auto-receptors and down-regulation of the post-synaptic noradrenergic receptors (20), although the exact mechanisms of these changes remain to be elucidated.

This study had several limitations. First, the sample size was relatively small with only 10 subjects. However, the crossover design is likely to reduce variance in examining atomoxetine effects in amphetamine responses. Second, the study duration was only four days. Longer treatment duration could have addressed whether chronic treatment with atomoxetine would lead to different results. Third, this study only examined a single 40 mg/day dose of atomoxetine and a single 20 mg dose of dextroamphetamine. Fourth, the amphetamine treatment had no placebo control, which could have allowed a more clear evaluation of atomoxetine effects on

amphetamine responses. This may be especially important for subjective measures which may be affected by subject expectations.

To summarize, atomoxetine treatment at 40mg/day attenuated some of the subjective, physiological, and endocrine effects of dextroamphetamine. These findings are consistent with previous preclinical studies supporting the role of the noradrenergic system in mediating acute amphetamine responses. Further studies are warranted to examine the therapeutic utility of atomoxetine for amphetamine addiction.

Acknowledgments

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Fig. 1.

The average (with standard error of the mean - SEM) systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) responses to 20 mg/70 kg dextroamphetamine administration under 40 mg/day atomoxetine (ATX) or placebo (PLA) conditions. Bars represent the change (maximum post dose-baseline). Significant ($p < 0.05$) treatment differences are indicated by asterisks (*).

Fig. 2.

The average (SEM) ratings (from 0 to 100) of subjective responses to 20 mg/70 kg dextroamphetamine administration under 40 mg/day atomoxetine (ATX) or placebo (PLA) conditions. Bars represent the change (maximum post dose-baseline). Significant ($p < 0.05$) treatment differences are indicated by asterisks (*).

Fig. 3.

The average (SEM) plasma cortisol ($\mu\text{g/dL}$) responses to 20 mg dextroamphetamine administration under 40 mg/day atomoxetine (ATX) or placebo (PLA) conditions. Measurements were taken at 0, 60, 120, and 180 minutes in relation to amphetamine administration. A significant treatment effect was observed for plasma cortisol response ($p < 0.05$). Significant treatment differences ($p < 0.05$) at each time point are indicated by an asterisks (*).