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Riluzole and d-amphetamine interactions in humans

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Abstract

In preclinical studies, medications which decrease glutamate release have been shown to block some of the effects of psychostimulants. One such medication is riluzole, marketed for the treatment of Amyotrophic Lateral Sclerosis (ALS). The goal of this study was to determine riluzole's effects on acute physiological and subjective responses to d-amphetamine in healthy volunteers. Seven male and 5 female subjects participated in an outpatient double-blind, placebo-controlled, crossover study. Across 4 sessions, subjects were randomly assigned to a sequence of 4 oral treatments: placebo, 20 mg d-amphetamine alone, 100 mg riluzole alone, or d-amphetamine plus riluzole. Outcome measures included heart rate, blood pressure, plasma cortisol, performance on the Sustained Attention to Response Test (SART), and subjective measures. D-amphetamine increased heart rate, blood pressure and plasma cortisol levels while inducing psychostimulant-type subjective effects. On the SART, d-amphetamine enhanced the speed of correct responses but also significantly increased the number of errors of commission. Riluzole at 100 mg did not block, the typical subjective and physiological responses to 20 mg d-amphetamine. Riluzole alone induced amphetamine-like subjective responses. On the SART test, riluzole increased the number errors of commission, but unlike d-amphetamine, did not speed reaction time. The mechanism accounting for these findings is unclear, but may involve processes other than decreased glutamate release by riluzole. The effects of glutamate medications on psychostimulant responses need to be further examined.

Keywords

AMPA; d-amphetamine; dopamine; glutamate psychostimulant; riluzole

1. Introduction

Amphetamines are prototypical psychostimulants that produce a range of behavioral, cognitive, and physiological effects. In humans, amphetamines increase arousal, heart rate, blood pressure, and release of stress hormones as well as producing feelings of well-being, and decreasing appetite (Seiden et al. 1993). In addition to their clinical use for treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy, amphetamines, especially

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methamphetamine, are also highly reinforcing and are commonly abused worldwide (Ahmad 2003). The reinforcing effects of amphetamines are thought to be mediated by activation of the mesocorticolimbic dopamine system, an essential component of the brain reward circuit (Bardo 1998; Koob 1992; Tzschentke 2001). As a result, amphetamines have been proposed to be useful tools to probe the brain reward circuit (Cardenas et al. 2002; Tremblay et al. 2002). Changes in functioning of the brain reward system have been implicated in many neuropsychiatric conditions including major depression, schizophrenia and drug addiction.

A growing body of evidence suggests that glutamatergic transmission also contributes to the rewarding and addictive effects of psychostimulants (Kalivas et al. 2003). For example, glutamatergic input to the ventral tegmental area (VTA) or nucleus accumbens increases dopaminergic transmission in the mesocorticolimbic pathway. Similarly, dopaminergic activation by repeated stimulant treatment increases glutamate release in the nucleus accumbens (Tzschentke and Schmidt 2003). Blockage of NMDA or AMPA type glutamate receptors has blocked amphetamine effects in preclinical models of addiction (Kelley 2004). Since glutamate is the primary neurotransmitter for learning and memory, its simultaneous activation with the dopaminergic system has been suggested to mediate the neuronal changes that lead to addictive behavior and relapse (Lapish et al. 2006).

In spite of these promising preclinical findings, the interaction between the dopaminergic and glutamatergic systems has not been well examined in humans. This is partly due to the limited number of glutamatergic medications available for human use. One such medication is riluzole, an anti-glutamate medication marketed for the treatment of Amyotrophic Lateral Sclerosis (ALS, Lou Gehrig's disease). Riluzole's pharmacological effects include inhibition of glutamate release, blockage of sodium channels, and direct stimulatory effects on the AMPA/kainate type of glutamate receptors (Doble 1996). riluzole is currently being examined for the treatment of obsessive compulsive disorder (OCD), anxiety disorders, schizophrenia, and depression (Coric et al. 2005; Sanacora et al. 2004; Zarate et al. 2005).

Riluzole's interaction with psychostimulants has been examined in preclinical rodent models of amphetamine addiction. Riluzole at 4 mg/kg blocked amphetamine and morphine-induced conditioned place preference in rats (Tzschentke and Schmidt 1998). Similarly, riluzole at 10 mg/kg moderately attenuated amphetamine-induced locomotion in rats (Lourenco Da Silva et al. 2003). Another study examined the effect of riluzole on the induction and expression of stimulant sensitization (Itzhak and Martin 2000). While riluzole had no effect on sensitization to cocaine, it attenuated the expression of sensitization to amphetamines. Altogether, these studies suggest that riluzole may attenuate the rewarding effects of the prototypical psychostimulant, amphetamine.

While preclinical findings suggest a role for riluzole in antagonizing amphetamine effects, no research has extended these observations to humans. To better understand the glutamatergic contributions to any psychostimulant effects in humans, we examined the interactions between riluzole and d-amphetamine in healthy human volunteers using an outpatient, double-blind, placebo-controlled, crossover design.

2. Methods and Materials

2.1 Subjects

Seven male and 5 female healthy controls were recruited from the New Haven area (6 African-Americans, 4 Caucasians, and 2 Hispanics). Three additional subjects were enrolled but did not complete the study for personal reasons and were not included in the analysis. The average age (SD) of the subjects was 27.7 years (6.9). Subjects were required to have normal physical, laboratory and psychiatric examinations. None of the subjects were dependent on alcohol or

on any drugs except nicotine. To minimize any confounding effects from nicotine or caffeine withdrawal, those who smoked over 5 cigarettes per day and 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.

2.2 Procedures

In this double-blind, placebo-controlled, crossover study, subjects had 4 separate outpatient experimental sessions. Across 4 sessions, subjects were randomly assigned to a sequence of 4 treatment conditions which included oral placebo, d-amphetamine (20 mg) alone, riluzole (100 mg) alone, or d-amphetamine (20 mg) plus riluzole (100 mg). Before the sessions started, an indwelling intravenous catheter was placed in the antecubital vein for blood drawing and safety precaution. After baseline measures were obtained, subjects received the study medication followed by a light meal. The sessions started at 8 am and were 3 to 9 days apart to minimize the carryover effects from d-amphetamine and riluzole.

2.3 Drugs

Amphetamine and riluzole administration—D-amphetamine, the dextrorotatory isomer of amphetamine, was obtained from Barr Laboratories (Pomona, New York). D-amphetamine is used for the treatment of ADHD and narcolepsy at a dose range from 5–60 mg/day (PDR, 2007). In this study, we used a single 20 mg oral dose, which has been shown to produce typical amphetamine effects in healthy volunteers (e.g., Brauer and de Wit 1996; Fillmore et al. 2003; Tidey et al. 2000). Following oral administration, peak plasma levels of d-amphetamine are reached within 1–3 hours. The elimination half-life of d-amphetamine is 10 to 13 hours (PDR, 2007). Riluzole (Rilutek®) was obtained from Aventis Pharmaceuticals Inc. (Bridgewater, NJ). The recommended dose of riluzole for the treatment of ALS is 100 mg/day (PDR, 2007). Following oral administration of riluzole, peak plasma levels are reached within 1 to 1.5 hours. The elimination half-life of riluzole is 12–14 hours (PDR, 2007). Riluzole was administered as a 100 mg single dose, alone or together with a 20 mg d-amphetamine.

2.4 Outcome measures

The outcome measures consisted of endocrine, physiological, subjective, and cognitive performance measures. Baseline assessments were made before administration of study medications. The endocrine measure was plasma cortisol concentration, which is sensitive to amphetamine administration (Grady et al. 1996; Seiden et al. 1993). For cortisol measures, blood samples were obtained at the beginning of each session and 1, 2 and 3 hours after amphetamine administration.

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

The subjective measures included the Drug Effects Questionnaire (DEQ), Addiction Research Center Inventory (ARCI)-short form, and the Profile of Mood States (POMS). These 3 subjective scales were given before, and 30, 60, 90, 150 and 180 minutes after the medication treatment. The DEQ was used to assess the acute subjective effects of d-amphetamine. The items are stimulated, high, anxious, sedated, down, feeling the drug strength, feel “good” drug effects, feel “bad” drug effects, and wanted more of the drug they received, and “like the drug.” Subjects rated these items on a 100 mm scale, from 0 “not at all” to 100 “extremely.” The ARCI consists of 49 true or false questions that are scored as five subscales: drug-induced

euphoria (Morphine-Benzedrine Group; MBG), stimulant-like effects (Amphetamine; A), intellectual efficiency and energy (Benzedrine Group; BG), dysphoria (Lysergic Acid; LSD), and sedation (Pentobarbital-Chlorpromazine; PCAG) (Martin et al., 1971).

The POMS is a 72-item rating scale used to measure the effects of medication treatments on mood (McNair et al. 1971). The POMS has 6 subscales: (1) composed-anxious; (2) agreeable-hostile; (3) elated-depressed; (4) confident-unsure; (5) energetic-tired; (6) clear headed-confused. For all subscales, higher scores are reflective of more positive mood states.

The Sustained Attention to Response Test (SART) assesses the ability to withhold responses to an infrequently occurring target. Inappropriate responses on the SART have been interpreted as a result of a “drift” from controlled processing into more automatic responding occurring as a result of impaired sustained attention. Performance on the SART correlates with other tests of sustained attention (Robertson et al. 1997), time-of-day (Manly et al., 2002) and subjective sleepiness (Manly et al. 2002), and discriminates ADHD cases from controls (Shallice et al. 2002), and depressed men from non-depressed men (Farrin et al. 2003).

The SART was presented using E-Prime, Version 1.1. In this 4.5 min task, 225 single digits (25×9 digits) were presented on a computer monitor. Each digit was presented for 250 ms, and was immediately followed by a mask for 900 ms. (The time between digit onsets was therefore always 1150 ms). The mask consists of a ring with a diagonal cross in the center. Subjects were instructed to press a spacebar to every digit except the 3, and to give equal importance to speed and accuracy. Responses were allowed during the presentation of both the digit and mask. The digits were presented in a different random order for each subject. There were 18 practice trials, containing 2 no-response targets (3s). We estimated the internal reliability by computing error rates on even/odd trials for each subject, correlating these measures, and applying the Spearman-Brown formula to derive the split-half reliability coefficient (Parrott 1991); the split-half reliability of erroneous responses to the 3 was good in all 4 conditions (rs ranging from .94 to .98). The SART was administered 2 hours after medication administration. For the SART, the primary outcome measure was the number of errors of commission (out of 25) on the no-response target (pressing the spacebar to 3). The number of errors of omission (not pressing the spacebar on response targets (digits other than 3), and the mean correct reaction times to response targets, were also measured. RTs < 100 ms were discarded from analyses.

2.5 Statistical Analysis

We conducted mixed-effects repeated-measures analyses using SAS Proc Mixed, version 9.13. We summarized treatment effects (except the SART), as the area under the curve (AUC) of the response function, using the trapezoidal method. All models included fixed main-effect estimates for amphetamine (0 mg or 20 mg), riluzole (0 mg or 100 mg) and their interaction. We also included a random effect for subject and a blocking factor for treatment sequence. Significant treatment or treatment-by-treatment interactions ($p < 0.05$) were followed by post hoc group comparisons using Fisher's LSD.

3. Results

3.1 Physiological responses

Analyses of physiological response showed d-amphetamine treatment effects for heart rate [$F(1, 30) = 16.9$; $p < 0.001$], systolic [$F(1, 30) = 22.0$; $p < 0.0001$] and diastolic blood pressure [$F(1, 30) = 10.1$; $p < 0.01$], with higher responses under d-amphetamine treatment (Figure 1).

3.2 Subjective responses

3.2.1 DEQ—For the DEQ (Figure 2), a significant main effect for d-amphetamine was observed for the rating of “stimulated” [$F(1, 30) = 6.4$; $p < 0.05$], “good effects” [$F(1, 30) = 6.3$; $p < 0.05$], “want more drug” [$F(1, 30) = 6.2$; $p < 0.05$], and “drug liking” [$F(1, 30) = 5.6$; $p < 0.05$]. Post hoc comparisons indicated greater values under d-amphetamine treatment. A main effect for riluzole was observed for the rating of “high” [$F(1, 30) = 4.2$; $p < 0.05$], and “down” [$F(1, 30) = 6.8$; $p < 0.05$]. Under riluzole treatment the rating of “high” was higher and the rating of “depressed” was lower. For the rating of “anxious,” a significant d-amphetamine-by-riluzole interaction was observed [$F(1, 30) = 4.6$; $p < 0.05$], reflecting a greater endorsement of anxiety for the d-amphetamine plus riluzole condition compared to placebo ($p < 0.05$).

3.2.2. ARCI—For the ARCI, a significant main effect for d-amphetamine was observed for MBG subscale [$F(1, 30) = 5.2$; $p < 0.05$], with greater responses under d-amphetamine treatment ($p < 0.05$).

3.2.3 POMS—No significant treatment effects were observed for any of the POMS subscales.

3.3 Cortisol Response

For cortisol responses, (Figure 3), there was a significant d-amphetamine treatment effect [$F(1, 30) = 28.1$; $p < 0.0001$], with greater values under d-amphetamine treatment.

3.4 Cognitive Response

Due to computer or subject error, there were 3 sessions in which there were no spacebar presses recorded; the primary analyses were conducted on the data from the 10 subjects with complete data (Table 1). For errors of commission (pressing spacebar on a 3), there were main effects of d-amphetamine [$F(1, 26) = 4.76$; $p < 0.05$] and riluzole [$F(1, 26) = 4.09$; $p = 0.05$], but no interaction. Pairwise comparisons showed that d-amphetamine plus riluzole, d-amphetamine, and riluzole conditions had higher error rates than placebo ($p < 0.05$). For RTs on correct responses, there was a main effect of d-amphetamine [$F(1, 26) = 7.93$; $p < .01$], but not riluzole, and no interaction. Pairwise comparisons showed that d-amphetamine plus riluzole and d-amphetamine had faster reaction times than placebo ($p < 0.05$). There were no effects on errors of omission.

4. Discussion

The goal of this study was to evaluate the interaction between d-amphetamine and riluzole using multiple outcome measures. D-amphetamine produced typical subjective psychostimulant effects including increase in MBG (drug-induced euphoria) subscale of ARCI, and rating of drug liking. D-amphetamine also increased the heart rate, blood pressure, as well as plasma cortisol levels. These findings were consistent with those from previous studies which also administered amphetamines to healthy volunteers (e.g., Brauer and de Wit 1996; Grady et al. 1996; Jayaram-Lindstrom et al. 2004).

On the SART, d-amphetamine enhanced the speed of correct responses but at a cost: d-amphetamine also significantly increased the number of errors of commission. Stimulants, including amphetamines, have been shown to alleviate fatigue, enhance vigilance and performance speed (Koelega 1993). However, the effects of stimulants on tasks with a response-inhibition component may be more complex. In 2 recent studies, Fillmore et al. have reported that amphetamines can worsen response inhibition assessed using a go/no go task under certain conditions (Fillmore et al. 2003), although they may have no effect on a stop-signal task (Fillmore et al. 2005). Similarly, in our study, d-amphetamine treatment was associated with decreased response inhibition on the SART. These findings are important since

stimulant use is associated with poor impulse control and risk-taking behavior (Moeller et al. 2001; Hoffman et al. 2006; Semple et al. 2005). A better characterization of the mechanisms linking psychostimulant use and impulsivity may ultimately lead to better treatment strategies for psychostimulant addiction.

Riluzole increased the DEQ ratings of “high” and decreased the ratings of “down.” When combined with d-amphetamine, riluzole enhanced amphetamine-induced rating of “anxious” on the DEQ. Riluzole alone did not affect heart rate, blood pressure, or cortisol levels. In the SART test, riluzole increased the number errors of commission, but unlike d-amphetamine, it did not speed the reaction time. Overall, the subjective effects from riluzole were somewhat similar to those of d-amphetamine.

As summarized in the introduction, preclinical studies have found that riluzole reduced amphetamine effects in rats. These preclinical findings were not supported in our human study, which found stimulant-like effects by riluzole. The reasons for this discrepancy between the results of these preclinical studies and ours are not clear. Possibilities include species differences (rodents vs. humans) and differences in outcome measures. The outcome measures in preclinical studies were conditioned place preference (Tzschentke and Schmidt 1998) and sensitization to psychomotor activation by amphetamines (Itzhak and Martin 2000; Lourenco Da Silva et al. 2003), compared to the subjective and physiological and cognitive outcomes in our study. In addition, complex pharmacological effects of riluzole might have contributed to our findings. Riluzole has multiple pharmacological effects including inhibition of glutamate release, blockage of sodium channels and direct stimulation of AMPA-type glutamate receptors. Our findings are not consistent with decreased glutamate release by riluzole, which would be expected to be opposite of psychostimulant effects. One intriguing possibility is enhancement of AMPA transmission by riluzole, which has been demonstrated in a recent study (Du et al. 2006). In that study, riluzole or lamotrigine, but not valproate, increased the surface expression of GluR1 or GluR2, AMPA receptor subunits, in hippocampal neurons, which resulted in enhanced AMPA transmission. Elevations of either Glu1 and Glu2 have been shown to enhance behavioral responses to stimulants (Mead and Stephens 2003; Sun et al. 2005). Interestingly, elevation of GluR1 expression is also associated with resistance to reinstatement of drug use in animal models of relapse (Sutton et al. 2003). Thus, riluzole-induced enhancement of the AMPA transmission may enhance acute amphetamine effects, while preventing relapse. These possibilities, however, need to be tested in future studies.

In our study, riluzole did not significantly affect d-amphetamine-induced cortisol release. One notable effect was delay in peak plasma cortisol levels under riluzole plus d-amphetamine treatment, compared to d-amphetamine alone (2 hours vs. 1 hour). Similarly, in a study with 9 elderly healthy controls, under riluzole at 150 mg for 2 days, a trend was observed for attenuated ACTH and cortisol response to physical but not psychological stress (Kniest et al. 2001). These preliminary findings were attributed to reduced HPA-axis activation by riluzole due to its anti-glutamate effects. Glutamate activates the HPA-axis by stimulating CRH in the paraventricular area of hypothalamus and reduction of glutamatergic transmission has attenuated CRH release (Patchev et al. 1994; Ziegler et al. 2005).

This study has several limitations. First, only one dose of riluzole and d-amphetamine were used and as a result the study did not examine the dose-effect relationship for riluzole effects on d-amphetamine responses. Second, the study did not assess amphetamine plasma levels, which would be helpful to determine whether riluzole's effects on d-amphetamine responses were mediated by pharmacokinetic mechanisms. Similarly, assessment of amphetamine choice behavior would be helpful in evaluating the potential utility of riluzole as a treatment medication for amphetamine addiction. Fourth, our sample were healthy volunteers and the generalizability of these findings to stimulant users needs to be determined in future studies.

To summarize, riluzole at 100 mg did not block, the typical subjective and physiological response to 20 mg d-amphetamine in healthy volunteers. Riluzole alone induced amphetamine-like subjective responses. The mechanism accounting for these findings may involve processes other than decreased glutamate release by riluzole including increased AMPA transmission. The interaction between glutamatergic medications and psychostimulant responses need to be further examined.

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Fig. 1.

Heart rate (a), systolic (b), and diastolic blood pressure (c) responses under 20 mg d-amphetamine (DAMP), 100 mg riluzole (RIL), 20 mg DAMP plus 100 mg RIL (DAMP+RIL), or placebo (P) conditions. Measurements were taken before and 30, 60, 90, 120, 150 and 180 minutes after medication administration. All 3 outcomes showed significant d-amphetamine effect, with higher responses under d-amphetamine treatment.

Fig. 2.

Subjective responses to selected items on DEQ under 20 mg d-amphetamine (DAMP), 100 mg riluzole (RIL), 20 mg DAMP plus 100 mg RIL (DAMP+RIL), or placebo (P) conditions. Bars represent the area under the curve (AUC) values for measurements were taken before and 30, 60, 90, 150, and 180 minutes after medication administration. A significant effect for d-amphetamine was observed for “stimulated,” “good effects,” “want more drug” and drug liking and a significant effects for riluzole was observed for “high” and “down.” There was a significant riluzole-by-d-amphetamine interaction for “anxious,” with greater ratings under d-amphetamine plus riluzole condition compared to placebo ($p < 0.05$), indicated by an asterisks (*)

Fig. 3.

Plasma cortisol ($\mu\text{g/dL}$) responses under 20 mg d-amphetamine (DAMP), 100 mg riluzole (RIL), 20 mg DAMP plus 100 mg RIL (DAMP+RIL), or placebo (P) conditions. Measurements were taken before and 60, 120, and 180 minutes after medication administration. A significant d-amphetamine effect was observed for plasma cortisol response ($p < 0.05$).

Table 1**Mean (SE)** on the SART (n = 10).

	Placebo	d-amphetamine	riluzole	d-amphetamine + riluzole
Errors on 3s (/25)	7.9 (2.7)	11.1 (2.7)	10.9 (2.7)	12.0 (3.1)
Errors on non-3s (/200)	1.5 (0.6)	1.6 (0.5)	3.3 (1.2)	4.5 (2.7)
Mean RT (ms)	374 (37.0)	343 (31.1)	365 (31.5)	342 (38.6)