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Rimonabant effects on anxiety induced by simulated public speaking in healthy humans: a preliminary report

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Abstract

Objective—We investigated the hypothesis that rimonabant, a cannabinoid antagonist/inverse agonist, would increase anxiety in healthy subjects during a simulation of the public speaking test.

Methods—Participants were randomly allocated to receive oral placebo or 90 mg rimonabant in a double-blind design. Subjective effects were measured by Visual Analogue Mood Scale. Physiological parameters, namely arterial blood pressure and heart rate, also were monitored.

Results—Twelve participants received oral placebo and 12 received 90 mg rimonabant. Rimonabant increased self-reported anxiety levels during the anticipatory speech and performance phase compared with placebo. Interestingly, rimonabant did not modulate anxiety prestress and was not associated with sedation, cognitive impairment, discomfort, or blood pressure changes.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

Conclusions—Cannabinoid-1 antagonism magnifies the responses to an anxiogenic stimulus without interfering with the prestress phase. These data suggest that the endocannabinoid system may work on-demand to counteract the consequences of anxiogenic stimuli in healthy humans.

Keywords

anxiety; public speaking test; rimonabant; SR141716; CB1 receptor

INTRODUCTION

Cannabis sativa induces multiple subjective effects including pleasure, relaxation, and anxiety relief (Hall and Solowij, 1998; Hall and Degenhardt, 2009; Zuardi *et al*., 2010). The growing understanding of endocannabinoid function raised interest in this system as a target for new drugs. In addition to synthetic cannabinoids (CBs), several CB1 receptor antagonists were developed, from which SR141716 (rimonabant) is the prototype (Engeli, 2012; Kirilly *et al*., 2012).

Studies focusing on anxiety-related responses revealed that delta-9-tetrahydrocannabinol (THC) and other CBs induce complex effects, depending on dose, environment, and subjects' previous experience (Viveros *et al*., 2005; Moreira and Wotjak, 2010). Endocannabinoid hydrolysis inhibitors generally induce anxiolytic effects (Kathuria *et al*., 2003; Patel and Hillard, 2006; Moreira *et al*., 2008; Haller *et al*., 2009). On the other hand, CB1 antagonists tend to increase anxiety-like behaviors, particularly in animals exposed to a highly aversive environment (Haller *et al*., 2004; Patel and Hillard, 2006), indicating that the endocannabinoid system may inhibit anxiety and fear responses, working on-demand to counteract consequences of highly-aversive stimuli (Moreira and Wotjak, 2010; Riebe *et al*., 2012). The limited available data emerged mainly after clinical investigation with rimonabant, which was removed from the market due to psychiatric side effects characterized by feelings of anxiety and depression (Christensen *et al*., 2007; Moreira and Crippa, 2009). Rimonabant's clinical profile suggests that blocking endocannabinoid actions increases anxiety, but this observation is confounded by the fact that psychiatric disorders are frequent comorbidities in the obesity (McIntyre *et al*., 2012). Therefore, in order to establish the role of CB1 receptors in anxiety modulation in humans, experimental studies are needed.

We evaluated the hypothesis that rimonabant would increase anxiety in healthy humans exposed to the simulation of the public speaking test. This model induces anxiety and is sensitive to both anxiolytic and anxiogenic drugs (McNair *et al*., 1982; Guimaraes *et al*., 1987; Bergamaschi *et al*., 2011). We analyzed drug effects at baseline and during the test, in order to investigate whether CB1 blockade selectively modified responses under high-anxiety levels.

METHODS

Subjects

Healthy participants were selected through a screening procedure described in the next section. Subjects were randomly allocated to receive placebo or 90 mg rimonabant in a double-blind study design. Groups were matched according to gender, age, years of education, socioeconomic status, body mass index, fear of public speaking [social phobia inventory; (Connor *et al*., 2000)] and general trait anxiety {Beck anxiety inventory [BAI]; (Beck *et al*., 1988; Cunha, 2001)}. No subject had a history of head trauma, neurological and psychiatric illness, substance abuse or major medical illnesses, and general medical condition based on a semi-standardized medical questionnaire and physical examination. Participants were all non-tobacco smokers and had not taken any prescribed medication for at least 3 months prior to the study. Subjects self-reported no cannabis or any other illegal drug use in their life. Women were required to have a negative pregnancy test prior to admission. Subjects provided a written informed consent after being fully informed about research procedures that were approved by the local institutional review board (HCRP No. 12407/2009), in accordance with the Declaration of Helsinki.

Screening procedure and clinical assessment

Participants, recruited by telephone and printed advertisements, were screened through self-assessment diagnostic instruments. Participants who scored BAI <10, fast alcohol screening test <3 (Hodgson *et al*., 2002; Meneses-Gaya *et al*., 2010), and Patient Health Questionnaire-9 < 10 (Lowe *et al*., 2004; de Lima Osorio *et al*., 2009), were invited to attend an interview for diagnosis absence through the full structured clinical interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, clinical version (First *et al*., 1997), translated into Portuguese (Del-Ben *et al*., 2001), by one examiner familiar with the instrument.

Drug preparation

Rimonabant (90 mg; Acomplia®, Sanofi-Aventis, Brazil) or wheat flour (placebo) were administered inside an identical gelatin capsules. Rimonabant dose was selected based on previous studies demonstrating that this was the minimum required dose to acutely block the CB1 receptor (Huestis *et al*., 2001; Gorelick *et al*., 2006), and participants who received rimonabant only reported no significant physiological or psychological effects compared with other groups, attesting that this 90 mg dose is safe in humans in controlled clinical study.

Psychological and physiological measurements

The state-anxiety level and other subjective states were evaluated during the test through the Visual Analogue Mood Scale (VAMS) Portuguese version (Norris, 1971; Zuardi and Karniol, 1981), grouped into four factors: (i) anxiety; (ii) sedation; (iii) cognitive impairment; and (iv) discomfort (Hallak *et al*., 2010). Systolic blood pressure, diastolic blood pressure, and heart rate (HR) were measured by multiparametric monitor (Monitor DX 2022, Dixtal, Brazil).

Procedure

The simulation of the public speaking test was the same as used by McNair *et al*. (McNair *et al*., 1982) with minor modifications (Hallak *et al*., 2010; Bergamaschi *et al*., 2011). Each subject participated in only one experimental session in a double-blind design. Subjects were told to have a light breakfast 2 h prior to the session. The experimental session was conducted in a sound attenuated and temperature-controlled room beginning at 08:00. After a 15-min adaptation period, baseline measurements (B) were taken followed by a single 90 mg rimonabant or placebo dose in a double-blind randomized procedure. Prestress measurements (P) were made 2 h after drug ingestion. Immediately, thereafter, the subject received instructions and had 2 min to prepare a 4-min speech about 'the public transportation system of your city'. He/she also was told that the speech would be recorded on videotape and later analyzed by a psychologist. Anticipatory speech measurements (A) were taken before the subject started speaking. When speaking before the camera began, subjects viewed their own image on the television screen. The speech was interrupted in the middle and speech performance measurements (S) obtained. The speech was recorded for additional 2 min. Poststress measurements (F1 and F2) were made 15 and 35 min after the end of the speech, respectively. Participants were monitored 1 week and 1, 3, and 6 months after study procedure to assess occurrence of depressive symptoms.

Statistical analysis

Clinical and demographic characteristics were investigated *via* boxplot and Shapiro–Wilk normality tests; therefore, they were analyzed by nonparametric tests (gender, socioeconomic level, BAI, and social phobia inventory) and by analysis of variance (ANOVA) for one factor, (age and body mass index). VAMS scores, diastolic and systolic pressures and HR were calculated as previously described (Bergamaschi *et al*., 2011). The two treatments were compared in each phase, taking into account baseline values. Statistical tests were conducted with SPSS version 19.0 (Chicago, IL, USA) and considered significant if two-tailed $p < 0.05$.

RESULTS

Twenty four subjects enrolled in the study. Participants' clinical and demographic characteristics are shown in Table 1. No significant differences were observed between groups.

Psychological measures

Repeated-measures ANOVA for the VAMS anxiety factor showed a significant effect of phases ($F_{3.17, 69.68} = 9.81$; $p < 0.0001$) and phase by group interaction between baseline and anticipatory speech ($F_{1, 22} = 4.53$; $p = 0.045$) and baseline and performance measurements ($F_{1, 22} = 4.36$; $p = 0.049$). VAMS sedation factor showed only a significant effect of phase ($F_{3.80, 83.59} = 11.62$; $p < 0.0001$), and no significant effects of phase and phase by group interaction were observed in the VAMS cognitive impairment and discomfort factors (Figure 1). The VAMS' item 'happy–sad' was used to assess depression symptom during study procedure and showed no significant difference of phase by group interaction

($F_{3.89, 85.51} = 1.40$, $p = 0.243$). Participants were monitored for up to 6 months and reported no depressive symptoms.

Physiological measures

Systolic and diastolic pressure did not show significant repeated-measures ANOVA effect in phases and phase by group interaction. HR showed a significant effect of phase ($F_{3.97, 87.31} = 6.46$; $p < 0.0001$) (Figure 2).

DISCUSSION

This study documents that the CB1 receptor antagonist/inverse agonist, rimonabant, increases anxiety induced by public speaking in healthy humans. The anxiogenic effects occurred selectively during anticipatory and performance speech, without interfering with the prestress phase, meaning that the drug effects occurred selectively in response to an aversive situation. Endocannabinoids implication with social anxiety is in accordance with dense expression of CB1 receptors in brain regions related to anxiety, fear, and aversion, including the medial prefrontal cortex, hippocampus, amygdala, and periaqueductal gray (Howlett *et al*., 2002; Mackie, 2005).

Preclinical studies showed that anxiogenic-like effects of CB1 antagonists tend to be more evident when animals are subjected to high levels of aversion (Haller *et al*., 2004; Jacob *et al*., 2012). Anandamide-hydrolysis inhibitors are more efficacious as anxiolytic drugs, when tested in a highly aversive environment (Naidu *et al*., 2007; Haller *et al*., 2009). The basal levels of endocannabinoid synthesis and release tend to be low; however, the activity of this system is enhanced in response to neural activation when experimental animals are exposed to threatening stimuli, when endocannabinoids would work to counteract fear responses (Moreira and Wotjak, 2010; Riebe *et al*., 2012). This would explain why CB1 antagonists tend to modify behavioral responses preferentially under high levels of aversion, without significant baseline effects.

An experimental study with healthy volunteers revealed that rimonabant reduced incidental recall of positive self-relevant adjectives (Horder *et al*., 2009). The role for the endocannabinoid system in anxiety emerged primarily from clinical trials of rimonabant's effect on obesity and related metabolic disorders treatment (RIO Studies). These investigations revealed that anxiety and depression are important side effects of this drug, as compared with placebo (Christensen *et al*., 2007). The absence of significant difference on the VAMS' item 'happy–sad' is in accordance with previous studies that showed acute 90 mg rimonabant administration was well tolerated and no serious adverse events (Huestis *et al*., 2007), and chronic and multiple rimonabant intake increase depression incidence (Christensen *et al*., 2007; Mitchell and Morris, 2007).

The present work indirectly suggests that facilitating CB1 receptor signaling may alleviate the consequences of aversive stimuli with important implication in the treatment of psychiatric disorders. Rimonabant increased self-reported anxiety induced by public speaking in healthy subjects, without interfering with prestress levels, supporting the notion that the endocannabinoid system may work on-demand to counteract the consequences of

aversive stimuli. Additional double-blind, placebo controlled trials are desirable to determine the precise endocannabinoids mechanism in anxiety and anxiety disorders.

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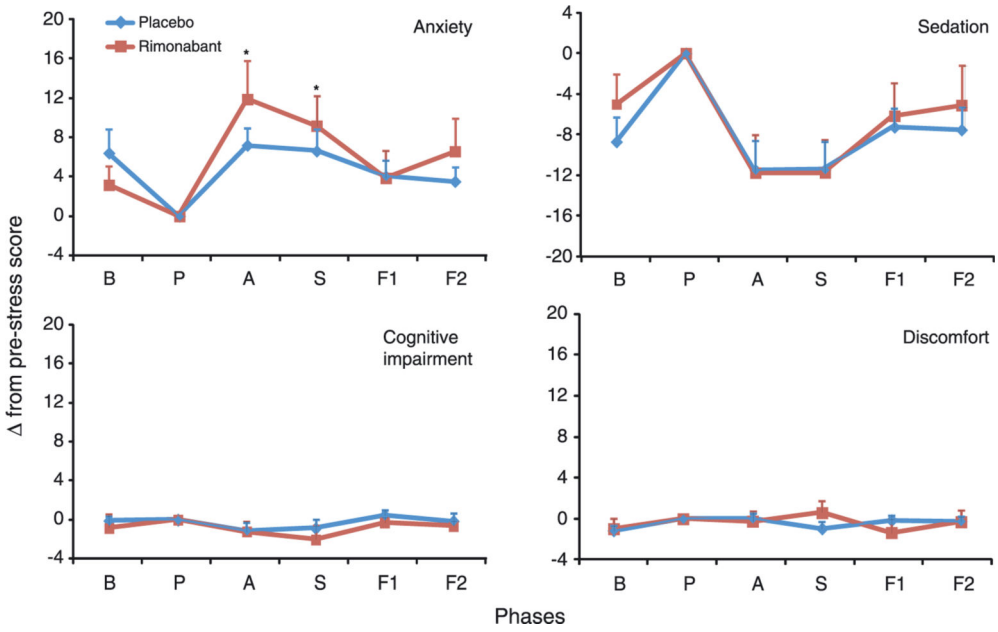

Figure 1.

Changes in Visual Analogue Mood Scale factors induced by simulation of the public speaking test. B, baseline; P, prestress; A, anticipatory speech; S, speech performance; F1, poststress 1; and F2, poststress 2. Points indicate mean and vertical bars indicate standard error of the mean. *Indicates significant differences from placebo group ($p < 0.05$)

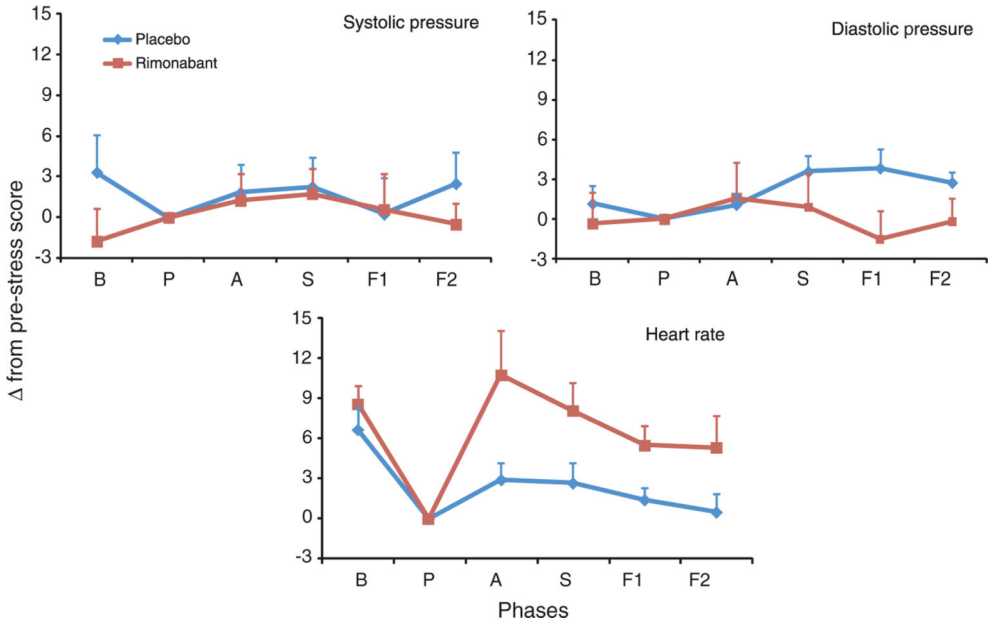

Figure 2.

Changes in heart rate, systolic, and diastolic pressure induced by simulation of public speaking test. B, baseline; P, prestress; A, anticipatory speech; S, speech performance; F1, poststress 1; and F2, poststress 2. Points indicate mean and vertical bars indicate standard error of the mean

Table 1

Clinical and demographic characteristics of participant groups

	Placebo	Rimonabant	*p*
Male/female	6/6	6/6	1.00
Age [mean (SD)]	24.5 (4.9)	24.9 (3.7)	0.82
Socioeconomic level[a] [Median (range)]	2.5 (1.0–3.0)	2.0 (1.0–4.0)	0.93
Body mass index [BMI, mean (SD)]	23.8 (4.6)	23.4 (3.3)	0.85
Social Phobia Inventory [SPIN, mean (SD)]	4.3 (3.1)	6.8 (5.9)	0.34
Beck Inventory Anxiety [BAI, mean (SD)]	2.0 (1.7)	3.9 (3.4)	0.20

SD, standard deviation;

[a]Socioeconomic level was assessed by the Brazil Socioeconomic Classification Criteria.