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The interplay of cannabinoid and NMDA glutamate receptor systems in humans: Preliminary evidence of interactive effects of cannabidiol and ketamine in healthy human subjects

Jaime E.C. Hallak [a,e,*], Serdar M. Dursun [b,e], Daniel C. Bosi [a], Ligia Ribeiro Horta de Macedo [a,e], João Paulo Machado-de-Sousa [a,e], João Abrão [f], José A.S. Crippa [a,e], Phillip McGuire [c,e], John H. Krystal [d], Glen B. Baker [b,e], Antonio W. Zuardi [a,e]

[a] Department of Neuroscience and Behavior, University of São Paulo, Ribeirão Preto, Brazil
[b] Neurochemical Research Unit, Department of Psychiatry, University of Alberta, Edmonton, Canada
[c] Institute of Psychiatry, King's College, London, UK
[d] Department of Psychiatry, Yale University, New Haven, USA
[e] National Institute of Sciences and Technology — Translational Medicine, CNPq, Brazil
[f] Anesthesiology, Department of Surgery, University of São Paulo, Ribeirão Preto, Brazil

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ABSTRACT

Background: Interactions between glutamatergic and endocannabinoid systems may contribute to schizophrenia, dissociative states, and other psychiatric conditions. Cannabidiol (CBD), a cannabinoid-1/2 (CB1/2) receptor weak partial agonist or antagonist, may play a role in the treatment of schizophrenia.
Objective: This study tested the hypothesis that CBD would attenuate the behavioral effects of the NMDA receptor antagonist, ketamine, in healthy human subjects.
Methods: Ten male healthy volunteers were evaluated twice in a randomized order. In both sessions they received ketamine (bolus of 0.26 mg/kg/1 min followed by IV infusion of 0.25 mg/kg over 30 min) preceded by either CBD (600 mg) or placebo. Psychopathology was assessed using the Brief Psychiatric Rating Scale (BPRS) and the CADSS (Clinician Administered Dissociative States Scale) at regular intervals from 30 min before to 90 min after ketamine administration.
Results: CBD significantly augmented the activating effects of ketamine, as measured by the activation subscales of the BPRS. However, CBD also showed a non-significant trend to reduce ketamine-induced depersonalization, as measured by the CADSS.
Conclusion: These data describe a complex pattern of psychopharmacologic interactions between CBD and ketamine at the doses of each agent studied in this experiment.

1. Introduction

The potential therapeutic effects of cannabidiol (CBD), a major constituent of the *Cannabis sativa* plant, are being studied because it produces some desirable effects without the psychotomimetic effects associated with Δ9-tetrahydrocannabinol (Δ9-THC) (Zuardi et al., 1982). It produces a complex dose-dependent profile of pharmacologic effects as a consequence of its multiple mechanisms of action, such as a non-competitive antagonism of cannabinoid-1 (CB1) receptors and an inverse agonism of cannabinoid-2 (CB2) receptors (Pertwee, 2008; Thomas et al., 2007), blockade of anandamide uptake, and inhibition of the enzymatic hydrolysis of anandamide (Bisogno et al., 2001). CBD also has an agonist activity at 5-HT_{1A} receptors (Russo et al., 2005), decreases the uptake of [^{3}H] adenosine (Carrier et al., 2006), and stimulates vanilloid receptors (Bisogno et al., 2001). In animals, many effects of CBD exhibit a biphasic or bell-shaped dose–response relationship, including the anxiolytic, antiemetic, neuroprotective, anti-inflammatory and sedative effects (Zuardi, 2008). Its actions at CB2 receptors appear to account for its anti-inflammatory actions (Thomas et al., 2007; Malfait et al., 2000). In humans, THC produces many signs and symptoms associated with schizophrenia (D'Souza et al., 2004), while CBD has few behavioral effects other than sedation at high doses (Hollister, 1973; Consroe et al., 1991; Zuardi et al., 1993). Several reports suggest that CBD attenuates the anxiogenic,

Abbreviations: CBD, cannabidiol; THC, tetrahydrocannabinol; CB1, cannabinoid-1; CB2, cannabinoid-2; NMDA, N-methyl-D-aspartate; PPI, prepulse inhibition; SCID-NP, structured clinical interview for the DSM-non-patient edition; SPSS, Severity of Psychosocial Stressors Scale for adults; BPRS, Brief Psychiatric Rating Scale; SIG, structured interview guide; CADSS, Clinician Administered Dissociative States Scale; RMANOVA, repeated measures analysis of variance.

* Corresponding author. Hospital das Clínicas da FMRP-USP, 3° andar, Av. Bandeirantes, 3900-Ribeirão Preto, CEP: 14048-900, SP, Brazil. Tel.: +55 16 3602 2853; fax: +55 16 3602 2703.
E-mail address: jhallak@fmrp.usp.br (J.E.C. Hallak).

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cognitive, and perceptual effects of THC (Zuardi et al., 1982; Hollister, 1973; Perez-Reyes et al., 1973; Karniol and Carlini, 1973; Leweke et al., 1999; Russo and Guy, 2006). Although a potent and selective CB1 receptor antagonist failed to show efficacy in treating schizophrenia (Meltzer et al., 2004), there is preliminary evidence suggesting that CBD might enhance antipsychotic treatment in some patients (Zuardi et al., 1995, 2006).

Studying the interactive effects of CBD and ketamine might improve our understanding of the interplay of CB1/2 and N-methyl-D-aspartate (NMDA) receptor systems and guide later studies of CBD pharmacotherapy for schizophrenia. The administration of the NMDA receptor antagonist ketamine has been used to model deficits in the NMDA receptor function that might contribute to cognitive impairments and symptoms associated with schizophrenia and other disorders (Krystal et al., 1999, 2003). Drugs that reduced the cognitive and behavioral effects of ketamine, such as mGluR2/3 agonists, later showed efficacy in treating symptoms of schizophrenia (Krystal et al., 2005a,b; Patil et al., 2007). Preclinical studies suggest that CBD attenuates prepulse inhibition (PPI) deficits and stereotypy produced by NMDA receptor antagonists (Long et al., 2006; Moreira and Guimaraes, 2005), but not memory impairments (Fadda et al., 2006).

The present preliminary study investigated the interactive effects of CBD and ketamine in healthy human volunteers using a double-blind placebo-controlled design. In contrast to studies of the interplay of CBD and THC, the current findings suggest a complex pattern of interacting behavioral effects of CBD and ketamine, including reductions in depersonalization symptoms, but worsening of activation.

2. Materials and methods

2.1. Participants

Ten healthy male subjects ranging in age from 20 to 36 years were recruited and consisted of 2 ethnicities (7 white and 3 mixed) of which 8 were single and 2 were married. Education ranged from 11 to 16 years. The subjects were recruited from the community by public advertisement and were compensated for their participation.

They were informed about the general psychological actions of ketamine and CBD and their possible adverse effects. After providing informed consent in their native language, the subjects underwent a structured interview (SCID-NP) (Spitzer et al., 1990) translated into Brazilian Portuguese (Del-Ben et al., 1996) and completed the Severity of Psychosocial Stressors Scale for adults (SPSS — American Psychiatric Association, 1994). We obtained medical history, physical examination and laboratory testing for toxicology on all subjects. Exclusion criteria included current or previous history of psychiatric disorder and/or family history of Axis-I psychiatric disorder in first degree relatives, alcohol or other substance dependence (excluding nicotine dependence), current clinical disease and scores of three or more on the SPSS. The subjects were required to abstain from psychoactive substance use for at least four weeks before the experiment and a toxicological screening was carried out prior to each experimental session; none of the subjects smoked tobacco or had a history of habitual alcohol consumption.

2.2. Methods

The volunteers participated in two double-blind test days. The subjects were told not to consume any alcohol for 24 h and caffeine for at least 4 h before each visit to the laboratory. They were advised to have at least 6 h of sleep the night before the experiment and to have a normal breakfast. They were randomly divided into two groups of five subjects. Each participant was evaluated on two different occasions, 1 week apart. In the first session, after a 30-min period of adaptation, the subjects were given a single dose of oral CBD (600 mg) or placebo, in a double-blind procedure. The sessions were held in the morning (between 0800 and 1200) to minimize the effects of circadian variation. In the second session, an identical procedure was followed except that the remaining drug was administered (i.e. those given CBD in the first session received placebo in the second and vice versa). The subjects were informed that they would receive CBD and placebo, but they were not told in which order. The investigators were also blind to the content of the capsules. At 65 min after the intake of the capsules the subjects received an intravenous infusion of S-ketamine solution (Ketalar® — *Parke-Davis*) in 0.9% saline containing 0.26 mg/kg of the drug in bolus; subsequently, an infusion pump with ketamine solution (0.25 mg/kg) was administered for 30 min, on both test days. During the procedure continuous electrocardiogram and automatic blood pressure measures were assessed. This time schedule was designed to allow CBD to reach its peak blood level. The behavioral and subjective effects of ketamine and CBD were assessed using the version of the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) modified by Bech (Bech et al., 1986) and translated into Brazilian Portuguese (Zuardi et al., 1994). The BPRS was divided into four factors: negative, positive, anxiety/depression and psychomotor activation (Crippa et al., 2002). The interviews were performed by one of the authors using a structured interview guide (SIG), which has been shown to enhance test–retest reliability of the BPRS (Crippa et al., 2001). We also administered the Clinician Administered Dissociative States Scale (CADSS) (Bremner et al., 1998), translated into Portuguese specifically for this trial. The CADSS comprises 19 subjective items, divided into 3 components: depersonalization (items 3 to 7), derealization (items 1, 2, 8–13, 16–19) and amnesia (items 14 and 15). Both scales were applied immediately before the CBD or placebo ingestion and 65 min after CBD or placebo administration (prior to ketamine infusion). The BPRS was administrated 5, 30, 60, 90 and 120 min after administration of ketamine, and the CADSS was administered 90 min after the ketamine bolus.

3. Data analysis

The blood pressure and heart rate data were analysed using a two-factor repeated measures analysis of variance (RMANOVA) with Greenhouse–Geiser corrections to the degrees of freedom to correct for a lack of sphericity. The factors analysed were group (CBD or placebo), time and the group by time interaction. The BPRS total and factor scores were analysed using the nonparametric method of Brunner (Brunner et al., 2002) for group, time and group by time interaction. The CADSS total and factor results were evaluated comparing the scores before and after ketamine administration, using paired t-tests. For the BPRS and CADSS factors we conducted post-hoc tests, adjusting the significance level for the number of factors of each test.

4. Results

Of the 10 selected subjects, one was excluded from CADSS analyses (due to nausea and vomiting) before the last response of this scale.

4.1. Physiological measures

RMANOVA revealed significant time effects for systolic ($F_{45,5} = 17.4$; $p < 0.001$) and diastolic ($F_{45,5} = 17.6$; $p < 0.001$) blood pressures and heart rate ($F_{45,5} = 12.7$; $p < 0.001$), indicating that ketamine significantly increased these physiological measures. There were no significant group effects on systolic ($F_{9,1} = 1.0$; $p = 0.347$) and diastolic ($F_{9,1} = 3.2$; $p = 0.105$) blood pressures, indicating that there were no differences between the CBD or the placebo pretreatment. There were no significant group by time interactions for either measure ($F_{45,5} = 0.8$; $p = 0.537$ and $F_{45,5} = 0.3$; $p = 0.916$, respectively). Similarly, there was no heart rate difference between the CBD and the placebo pretreatment, (drug effect: