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Subjective effects of cannabidiol in anxiety disorder and cannabinoid excretion in chronic daily cannabis smokers during sustained abstinence

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RESUMO

BERGAMASCHI, M. M. **Efeitos comportamentais do cannabidiol na ansiedade e eliminação de canabinóide durante abstinência em usuários crônicos de cannabis**. 2012. 114f. Tese (Doutorado). Faculdade de Ciências Farmacêuticas de Ribeirão Preto – Universidade de São Paulo, Ribeirão Preto, 2012.

Esta tese é dividida em três partes. A primeira parte consiste em investigar o efeito ansiolítico do canabidiol na ansiedade social através do teste de simulação de falar em público. Vinte e quatro sujeitos com ansiedade social, nunca tratados, receberam placebo ou canabidiol (CBD) 600 mg (n=12) em um estudo randomizado e duplo-cego. O mesmo número de indivíduos saudáveis realizaram o teste de simulação de falar em público sem receber medicação. A administração do CBD reduziu significativamente a ansiedade, sedação física e outros sentimentos e atitudes durante a fase de estresse, e diminui o nível de alerta na fase pré-estresse. O grupo placebo apresentou níveis elevado de ansiedade, sedação física, outros sentimentos e atitudes, e alerta comparado com o grupo controle. A pontuação do SSPS-N evidenciou aumento significativo durante o teste no grupo placebo, enquanto que o CBD reduziu estes níveis. Não houve diferenças significativas entre os grupos CBD e controle na SSPS-N e nos fatores sedação física, outros sentimentos e atitudes e alerta, da Visual Analogue Mood Scale (VAMS). A segunda parte do estudo avaliou a ansiedade em indivíduos saudáveis que receberam alta dose oral de rimonabanto e submetidos ao teste de simulação de falar em público, para melhor entendimento do possível mecanismo farmacológico para tratamento de transtornos de ansiedade. Vinte e quatro sujeitos saudáveis receberam placebo ou rimonabanto 90 mg (n=12) em um randomizado e duplo-cego. Não foi observado efeitos adversos significativo em ambos grupos. O grupo rimonabanto apresentou maiores níveis de ansiedade na fase pré-estresse e durante o estresse. Não houve diferença significativa quanto aos demais fatores avaliados entre os grupos. O aumento na ansiedade após administração do rimonabanto pode-se ao fato de haver diminuição no sistema endocanabinóide nos receptores CB1 e a possível modulação na ansiedade clínica e patológica. A terceira parte objetivou quantificar canabinóides no sangue total em usuários crônicos de cannabis durante abstinência supervisionada. Trinta usuários crônicos de cannabis, do sexo masculino, permaneceram no centro de pesquisa por até 33 dias, com coleta de sangue uma vez ao dia. Δ^9-tetrahidrocanabinol (THC), 11-hidróxi-THC (11-OH-THC) e 11-nor-9-carbóxi-THC (THCCOOH) foram quantificados no sangue por meio da cromatografia gasosa-espectrometria de massa bidimensional. Vinte e sete de 30 usuários foram positivos para THC no ingresso do estudo, com concentração mediana (variação) de 1.4 ng/mL (0.3–6.3). Níveis de THC diminuíram gradativamente com somente 1 de 11 participantes negativo no dia 26; 2 de 5 indivíduos permaneceram positivos para THC (0.3 ng/mL) por 30 dias. 5.0% dos sujeitos tiveram THC ≥1.0 ng/mL por 12 dias. Concentração mediana de 11-OH-THC foi 1.1 ng/mL no ingresso do estudo, sem valores ≥1.0 ng/mL após 24h. A taxa de detecção de THCCOOH foi 96.7% no ingresso, diminuindo gradativamente para 95.7 e 85.7% nos dias 8 e 22, respectivamente; 4 de 5 sujeitos permaneceram positivo para THCCOOH (0.6–2.7 ng/mL) após 30 dias e um permaneceu positivo no 33º dia. Foi detectado THC em alguns indivíduos por 30 dias, porém em baixas concentrações, devido a extensa eliminação do canabinóide em decorrência da exposição crônica.

Palavras-chave: canabidiol; rimonabanto; cannabis; teste de simulação de falar em público; transtorno de ansiedade social, usuários crônicos de cannabis

ABSTRACT

BERGAMASCHI, M. M. **Subjective effects of cannabidiol in anxiety disorder and cannabinoid excretion in chronic daily cannabis smokers during sustained abstinence**. 2012. 114p. Dissertation (Doctoral). School of Pharmaceutical Sciences of Ribeirão Preto – University of São Paulo, Ribeirão Preto, 2012.

This dissertation is divided into three parts. The first part aimed to investigate the cannabidiol anxiolytic effect in treatment-naïve individuals with social anxiety disorder through simulation of public speaking. Twenty-four never-treated social anxiety disorder subjects were allocated to receive 0 or 600 mg cannabidiol (CBD; n=12) in a double-blind randomized design. The same number of controls performed the simulation of a public speaking test without receiving any medication. Pretreatment with CBD significantly reduced anxiety, cognitive impairment, and discomfort in speech performance and significantly decreased alertness in their anticipatory speech. The placebo group displayed higher anxiety, cognitive impairment, discomfort, and alertness when compared with controls as assessed with the Visual Analogue Mood Scale (VAMS). The SSPS-N scores showed significant increases during testing of the placebo group that was almost abolished in the cannabidiol group. No significant differences were observed between the cannabidiol and control groups in SSPS-N scores or in cognitive impairment, discomfort, and alertness factors of the VAMS. The second part evaluated healthy subjects' anxiety during a public speaking test following a high rimonabant oral dose, to understand better the possible pharmacological approaches for anxiety disorder treatment. Twenty four participants were randomly allocated to receive 0 or 90 mg rimonabant (n=12) in a double-blind design. No significant adverse effects were reported in either group. Participants who received rimonabant showed increased anxiety levels compared to placebo during anticipatory speech and performance measurements. Rimonabant treatment did not affect sedation, cognitive impairment, discomfort, blood pressure, heart rate, self-statements during public speaking, or bodily symptoms scales. Increased anxiety may reflect lower endocannabinoid activity in CB1 receptors and CB1 receptor's possible role in modulation of anxiety and anxiety disorders. The third part aimed to monitor cannabinoid blood concentrations during sustained abstinence from chronic daily cannabis smoking. Thirty male chronic daily cannabis smokers resided on a secure clinical research unit for up to 33 days, with blood collected once daily. Δ^9-tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THCCOOH) whole blood concentrations were quantified by two-dimensional gas chromatography-mass spectrometry. Twenty-seven of 30 participants were THC-positive on admission, with a median (range) concentration 1.4 ng/mL (0.3–6.3). THC decreased gradually with only 1 of 11 participants negative at 26 days; 2 of 5 participants remained THC-positive (0.3 ng/mL) for 30 days. 5.0% of participants had THC ≥1.0 ng/mL for 12 days. Median 11-OH-THC concentrations were 1.1 ng/mL on admission, with no results ≥1.0 ng/mL 24h later. THCCOOH detection rates were 96.7 on admission, decreasing slowly to 95.7 and 85.7% on days 8 and 22, respectively; four of 5 participants remained THCCOOH positive (0.6–2.7 ng/mL) after 30 days and one remained positive on discharge at 33 days. THC was quantified in some participants for 30 days, albeit in low concentrations, due to the large cannabinoid body burden from extended exposure.

Keywords: cannabidiol; rimonabant; cannabis; simulated public speaking test; social anxiety disorder, chronic cannabis smokers

1. Introduction

1.1. Cannabis and Anxiety

Since early ages, *Cannabis sativa* (cannabis) is associated with psychotic symptoms, i.e. panic attack, anxiety, and fear (GROTENHERMEN, 2007; JOHNS, 2001; ZUARDI et al., 2006a), but anxiety symptoms receive little attention as to whether they would be related to psychotic (ARSENEAULT et al., 2004) or withdrawal symptoms (BUDNEY et al., 2004). However, chronic cannabis users report reduced anxiety after smoking cannabis, claiming it as the reason for prolonged cannabis use (ASHTON, 2001; LEE et al., 2009). However, one should consider factors that may be associated with increased anxiety after cannabis use such as duration and frequency of use, individual variability, presence of psychiatric symptoms, and environment (CRIPPA et al., 2009).

Results from epidemiological studies showed chronic cannabis users with high levels of anxiety (REILLY et al., 1998) and also found association with anxiety disorders with at least two-fold more probability than non-cannabis users (BUCKNER et al., 2008; SWADI; BOBIER, 2003). Another hypothesis for repeated cannabis use and development of dependence is self-medication of cannabis as an alternative to reduce anxiety (BONN-MILLER; ZVOLENSKY; BERNSTEIN, 2007; BUCKNER et al., 2007; BUCKNER et al., 2008; INSERM COLLECTIVE EXPERTISE CENTRE, 2001; REILLY et al., 1998). Anxiety associated with cannabis withdrawal symptoms usually manifests after 48 h of last cannabis use and persists for weeks (BUDNEY et al., 2004; HANEY, 2005). In psychiatric and drug treatment perspectives, detection of cannabis withdrawal syndrome is not straightforward as it is still not included in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) due to 'uncertain' clinical significance (AMERICAN PSYCHIATRIC ASSOCIATION, 1994).

The mechanisms by which cannabis induced anxiety and anxiety disorders were better described through clinical and animal studies. The most abundant psychoactive compound from cannabis extract, Δ^9-tetrahydrocannabinol (THC), can modulate serotonin, noradrenalin, and endocannabinoid systems, whose mechanism is complex and not fully understood (CRIPPA et al., 2009). Chronic cannabis use may also downregulate cannabinoid receptors with prolonged impairment (HIRVONEN et al., 2012). Future studies concerning cannabinoid

receptors density in human brain and endocannabinoid activity may provide better knowledge for the association between cannabis use and anxiety / anxiety disorders.

1.1.1. Cannabinoid Receptors

Two types of G-protein-coupled receptor are known, identified as cannabinoid receptor subtype 1 (CB1) and cannabinoid receptor subtype 2 (CB2) receptors (MATSUDA et al., 1990; MUNRO; THOMAS; ABU-SHAAR, 1993). CB1 receptors are located mainly in the central nervous system and highly expressed in the basal ganglia, hippocampus, amygdala, and cerebellum (GROTENHERMEN, 2004; HERKENHAM et al., 1990), while CB2 receptors are located in immune cells (BELTRAMO et al., 2006; GONG et al., 2006; ROSS et al., 2001; SKAPER et al., 1996; VAN SICKLE et al., 2005; WOTHERSPOON et al., 2005). The discovery of these receptors lead to identification of endogenous cannabinoid agonists (endocannabinoids) named N-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (DEVANE et al., 1992; MECHOULAM et al., 1995; SUGIURA et al., 1995).

While the neuronal role of CB2 receptors is still unknown, increased interest emerged on the neuropharmacology of CB1 receptors. Activation of the CB1 receptor can modulate neurotransmitter release by inhibition of excitatory and inhibitory transmitters by elevation of intracellular calcium (DE PETROCELLIS; DI MARZO, 2009; HOWLETT et al., 2002) and inhibition of adenylate cyclase, which converts adenosine-5'-triphosphate (ATP) to cyclic adenosine monophosphate (cAMP) (GROTENHERMEN, 2004). However, the mechanism *per se* remains more complex, as these receptors can affect the homeostasis of other neurotransmitters, i.e., acetylcholine, noradrenaline, dopamine, 5-hydroxytryptamine (5-HT), gamma-aminobutyric acid (GABA), glutamate, D-aspartate, and cholecystokinin (PERTWEE; ROSS, 2002; SZABO; SCHLICKER, 2005). In addition to pharmacological modulation of cannabinoid receptors, (endo)cannabinoids can exert multiple actions through diverse mechanisms via transient receptor potential vanilloid (TRPV), orphan G-protein-coupled receptors (GPR55), α-receptors, and endocannabinoid modulation by cannabinoids, i.e., cannabidiol (CBD) inhibits anandamide reuptake (IZZO et al., 2009).

As more than 80 known cannabinoids are located in the *Cannabis sativa* plant (ZUARDI; CRIPPA; HALLAK, 2010), the plethora of pharmacological effects remains unknown, with the most abundant and studied compounds, THC and CBD, as potential

therapeutic agents for diverse disorders (PERTWEE, 2008; ZUARDI, 2008; ZUARDI; CRIPPA; HALLAK, 2010).

1.2. Cannabidiol

CBD is a component of *Cannabis sativa* and constitutes up to 40% of plant extracts (GRLIC, 1962). However, CBD concentrations are highly variable and depend on growing conditions, different phenotypes of illicit cannabis, and on the plant parts analyzed (MEHMEDIC et al., 2010; POTTER; CLARK; BROWN, 2008). Evidence suggests that CBD potency decreased in recent years, while THC concentrations increased, as varieties such as sensimilla ('skunk'), provided by illegal cannabis growers, currently dominate cannabis supply in many countries (POTTER; CLARK; BROWN, 2008). CBD induces markedly different psychological effects compared to the best known cannabis compound, THC (PEREZ-REYES et al., 1973; ZUARDI et al., 1982). Despite presenting low affinity for CB1 and CB2 receptors, CBD can still interact with these receptors at doses equal to or lower than 1 μM. Therefore, there is no certainty about whether this antagonism is non-competitive. CBD can also act as a CB1 receptor inverse agonist at concentrations below those needed to bind to the CB1 orthosteric site. Moreover, CBD can antagonize THC effects via non-CB1/CB2 receptors such as GPR55, which is activated by THC and blocked by CBD (PERTWEE, 2008). The time between CBD and THC intake, as well as the CBD/THC ratio, seem to play an important role in the interaction between these two cannabinoids. CBD can increase the potency of THC by pharmacokinetic interaction if CBD is administered before THC, or a pharmacodynamic interaction may occur when both cannabinoids are taken together, mainly at a high dose ratio of CBD/THC (ZUARDI; HALLAK; CRIPPA, 2012).

CBD was first isolated by Adams *et al*. in 1940 (ADAMS; HUNT; CLARK, 1940) and its structure was identified 23 years later (MECHOULAM; SHVO, 1963). Since then, a considerable number of published articles describe its chemistry, biochemistry, pharmacology, and clinical effects. By 2000, the primary research topics regarding possible therapeutic effects of CBD were related to its antiepileptic, sedative, anxiolytic, and antipsychotic activities (CUNHA et al., 1980; ZUARDI et al., 2006a). The last decade has shown a notable increase in scientific literature on CBD, owing to the identification of its anti-inflammatory and neuroprotective effects. These studies raised the possibility of CBD's therapeutic effects for diverse conditions including dementias, cerebral ischemia, diabetes, inflammatory diseases, nausea, and psychiatric disorders (ZUARDI, 2008). This wide range of therapeutic effects can be explained by CBD's multiple mechanisms of action. Despite its low affinity for CB1 and CB2 receptors, CBD is capable of antagonizing CB1 / CB2 receptor agonists at reasonably low concentrations. At CB2 receptors, CBD acts as an inverse agonist.

Other mechanisms of action include antagonism of the recently discovered GPR55 receptor; transient receptor potential vanilloid subtype 1 (TRPV1) agonist; transient receptor potential vanilloid subtype 2 (TRPV2) agonist; 5-hydroxytryptamine receptor subtype 1A (5-HT_{1A}) agonist; antagonism of the putative abnormal-CBD receptor; and regulation of intracellular [Ca^{2+}] (IZZO et al., 2009). Inhibition of adenosine uptake leads to increased adenosine signaling, which may explain the ability of CBD to decrease inflammation and provide neuroprotective effects (CARRIER; AUCHAMPACH; HILLARD, 2006; CASTILLO et al., 2010). A similar mechanism also was reported for CBD, suggesting that this cannabinoid could block anandamide uptake and inhibit its enzymatic hydrolysis (LIGRESTI et al., 2006).

Evidence of CBD anxiolytic effects first appeared in the mid 1970s. Fifteen to 60 mg oral CBD significantly attenuated anxiety, heart rate, and panic induced by 30 mg THC in healthy male participants (KARNIOL et al., 1974). Further studies in animals and humans employing anxiogenic models elucidated CBD's anxiolytic effect. Two initial animal studies reported conflicting results. First, Silveira Filho and Tufik (SILVEIRA; TUFIK, 1981) showed that a high 100 mg/kg CBD dose had no effect on conflict behavior, whereas Zuardi and Karniol (ZUARDI; KARNIOL, 1983) showed that low 10 mg/kg CBD doses decreased conditioned emotional responses in rats. These findings were explained by Guimarães and co-workers (GUIMARAES et al., 1990), who demonstrated in the elevated plus-maze test in rats that CBD has an inverted U-shape dose-effect anxiolytic curve with narrow doses range (2.5 – 10mg/kg). Following this finding, others animal studies confirmed CBD's anxiolytic effect in the elevated plus-maze anxiety model (CAMPOS; GUIMARAES, 2009; 2008; GOMES; RESSTEL; GUIMARAES, 2011; GUIMARAES et al., 1994; ONAIVI; GREEN; MARTIN, 1990), Vogel conflict test (CAMPOS; GUIMARAES, 2008; GOMES; RESSTEL; GUIMARAES, 2011; MOREIRA; AGUIAR; GUIMARAES, 2006), contextual conditioned fear paradigm (LEMOS; RESSTEL; GUIMARAES, 2010; RESSTEL et al., 2006), marble burying test for obsessive-compulsive disorder (CASAROTTO et al., 2010) and attenuation of acute stress responses (RESSTEL et al., 2009).

Direct CBD administration into brain investigates the regions where CBD exerts its anxiolytic effect. Microinjection into the dorsolateral periaqueductal gray (dlPAG) (CAMPOS; GUIMARAES, 2009; 2008) and bed nucleus of the stria terminalis (BNST) (GOMES et al., 2012; GOMES; RESSTEL; GUIMARAES, 2011) in rats suggested that this cannabinoid interacted with 5HT1A (RUSSO et al., 2005; ZANELATI et al., 2010) and TRPV1 to produce anxiolytic-like effects. Another finding (LEMOS; RESSTEL; GUIMARAES, 2010) showed that CBD attenuated the conditioned fear response by paw

shock in rats when CBD is injected into medial prefrontal cortex (mPFC) at the prelimbic region, while anxiogenic response was observed when CBD was injected into the infralimbic prefrontal cortex. In addition, CBD also promoted contextual fear memory extinction after intracerebral ventricular administration antagonized by the cannabinoid (CB1)-antagonist SR141716 (rimonabant), suggesting the role of CB1 receptor on fear extinction (BITENCOURT; PAMPLONA; TAKAHASHI, 2008).

CB1 receptor involvement in anxiety modulation was reported previously (CASAROTTO et al., 2010), but interest increased when the first CB1 receptor antagonist rimonabant was released in the market for obesity treatment in 2006 (MOREIRA; CRIPPA, 2009). Rimonabant was withdrawn from the market two years later due to potential serious psychiatric side effects, i.e. anxiety (MOREIRA; CRIPPA, 2009). CB1 receptors are located primarily in the human central nervous system, particularly those regions responsible for emotions, i.e. hippocampus, amygdala, periaqueductal gray, prefrontal cortex, and hypothalamus (HERKENHAM et al., 1990). CB1 receptor location also explains the reason cannabis smokers experience feelings of relaxation and reduced anxiety (HALL; SOLOWIJ, 1998), also attributed to the role of the endocannabinoid system. The mechanism remains unclear, as antagonism of this receptor is related to anxiogenic-like effects in animals (MOREIRA; CRIPPA, 2009), as observed with administration of THC, a CB1 receptor agonist, in humans and animals (HOWLETT, 1995; KARNIOL; CARLINI, 1973; PERTWEE, 2008; 1997). This controversy could be related to the fact that THC is a partial agonist at CB1 receptors (PERTWEE, 2008) and depending upon several factors, may either facilitate or decrease endocannabinoid transmission.

Thus, pre-clinical studies suggest CBD anxiolytic effects related to specific brain areas modulating emotion and anxiety. Indeed, these findings were also confirmed in clinical human trials. Early studies in healthy participants showed that CBD decreased anxiety provoked by THC, suggesting a non-selective antagonism (ZUARDI et al., 1982).

1.2.1 Cannabidiol and Social Anxiety

Fear of public speaking is one of the pivotal symptoms of social anxiety disorder (SAD) (STEIN; STEIN, 2008). Thus, experimental models based on fear were developed to assess effects of substances on anxiety (HALLAK et al., 2010a; MCNAIR et al., 1982). Zuardi and co-workers (ZUARDI et al., 1993) evaluated CBD's effect on reduction of anxiety during the simulation of public speaking test (SPST) in healthy subjects. This test consisted of

participants speaking in front of the camera while viewing his/her own image on a TV screen. They were also told that the speech would be recorded and further analyzed by a psychologist. A single 300 mg CBD dose significantly reduced post-stress anxiety compared to placebo. A subsequent study performed in treatment-naïve social phobic subjects (BERGAMASCHI et al., 2011a) showed that 600 mg CBD administered 80 minutes before SPST-mitigated anxiety provoked by SPST during the speech. Furthermore, CBD also reduced cognitive impairment and negative self-evaluation compared to placebo before and during the speech, indicating that CBD was able to decrease anxiety *per se* and that it also positively affected self-evaluation during public speaking, crucial for SAD patient therapy. Negative self-evaluation is one of the pivotal aspects of this disorder.

A functional neuroimaging study (CRIPPA et al., 2004) employing single photon emission computed tomography (SPECT) in healthy participants evaluated CBD effects in neural activity in those brain areas modulating anxiety. This test consisted of 0 or 400 mg CBD administration with SPECT image acquisition and subjective ratings performed 110 minutes after CBD intake. This test is considered anxiogenic *per se*, as participants often report increased anxiety before scanning. This study showed that 400 mg CBD could modulate brain activity in regions related to emotion and anxiety, i.e. decrease neural activation in the left amygdala-hippocampal complex and left posterior cingulate gyrus, also related to brain activity modulation by benzodiazepines (i.e. diazepam) and selective serotonin reuptake inhibitors (i.e. citalopram).

Another study investigated regional brain function during emotional processing by functional magnetic resonance imaging (fMRI) (FUSAR-POLI et al., 2009). Functional MRI is a modern imaging technology providing sensitive non-invasive imaging of physiological changes (MATTHEWS; HONEY; BULLMORE, 2006). Administration of 600 mg oral CBD reduced brain activity in the amygdala and anterior and posterior cingulate cortex and decreased skin conductance response when participants were presented fearful faces which elicited different levels of anxiety. A subsequent study investigated connectivity during emotional processing by the fearful face stimuli task. As predicted, CBD modulated prefrontal and subcortical region activity, reducing connectivity between anterior cingulate cortex and amygdala (FUSAR-POLI et al., 2010).

Crippa and co-workers (CRIPPA et al., 2011) conducted the first study evaluating CBD neural effects in treatment-naïve social anxiety disorder participants. Subjects with generalized SAD received 400 mg oral CBD according to the same study design as the previous SPECT study in healthy participants (CRIPPA et al., 2004). CBD decreased activity

in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus. Interestingly, CBD administration in these SAD subjects did not provoke sedation or alteration in hypothalamic activity, as previously reported (BERGAMASCHI et al., 2011a). In total, these results support the anxiolytic effect of CBD as related to its activity in limbic and paralimbic brain areas.

Although animal and human studies demonstrate significant and strong evidence of CBD's anxiolytic effect, the SAD results must be carefully considered. First, healthy participants in clinical studies have no history of psychiatric disorder or drug abuse. Second, to date, these are only two SAD studies on human pathological anxiety. These participants were treatment-naïve and had no comorbidities. It is known that SAD has an early age of onset and high rate of comorbidity (FILHO et al., 2010) that can affect therapy efficacy, as medication and cognitive behavioral therapy are required (DAVIDSON, 2006; STEIN; STEIN, 2008). Third, after an acute therapeutic response is achieved, long-term treatment is needed to prevent return of symptoms after treatment is stopped. To date, no chronic clinical studies have evaluated CBD's anxiolytic effects.

In conclusion, CBD therapy is a good approach for pharmacological treatment of social anxiety disorder, as acute administration achieves rapid therapeutic effects. However, further clinical trials with larger sample sizes and chronic administration with post-treatment follow-up are needed to confirm these findings.

1.2.2. Cannabidiol Safety in Humans

1.2.2.1. Acute Studies

In the 1970s, human studies showed that oral CBD intake from 15 to 160 mg (CARLINI; MASUR; MAGALHÃES, 1979; HOLLISTER, 1973; KARNIOL et al., 1974), inhalation of 0.15mg/kg body weight (bw) (DALTON et al., 1976), or intravenous injection from 5 to 30 mg (HOLLISTER, 1973; PEREZ-REYES et al., 1973), did not produce adverse effects. CBD did not interfere with several psychomotor and psychological functions. CBD did not affect heart rate, blood pressure, or performance in the verbal paired-associate learning test at doses up to 600 mg (BERGAMASCHI et al., 2011a; CONSROE et al., 1979; KARNIOL et al., 1974; ZUARDI et al., 1982). Subsequent studies on CBD's antipsychotic effects did not report adverse side effects (BHATTACHARYYA et al., 2010; HALLAK et al., 2011; HALLAK et al., 2010b).

1.2.2.2. Chronic studies

Chronic daily oral 10 mg CBD administration for 21 days did not induce changes in neurological [including electroencephalogram (EEG)], clinical [including electrocardiogram [EKG)], psychiatric, blood, or urine examinations (MINCIS et al., 1973). Likewise, oral CBD administration in healthy participants (3 mg/kg bw daily for 30 days) and in epileptic patients (200-300 mg daily for 135 days) was well-tolerated and no signs of toxicity or serious side effects were detected on neurological and physical examinations, blood and urine analysis, or EKG and EEG, which were performed at weekly intervals (CUNHA et al., 1980).

CBD was evaluated for symptomatic efficacy and safety in 15 neuroleptic-free patients with Huntington's disease. Effects after oral CBD (10 mg/kg bw /day for 6 weeks) or placebo (sesame oil for six weeks) were evaluated weekly according to a double-blind, randomized crossover design. CBD showed no significant or clinical differences compared to placebo in the cannabis side effect inventory, clinical laboratory tests, or other safety outcome variables. Also, weekly plasma CBD concentrations by gas chromatography–mass spectrometry (GCMS; mean range 5.9 to 11.2 ng/mL), did not differ significantly over six weeks of CBD administration (CONSROE et al., 1991).

A previous case report of a teenager diagnosed with schizophrenia who experienced severe side effects after treatment with conventional antipsychotics demonstrated significant symptom improvement with no adverse effects after hospitalization and four weeks of treatment with increasing CBD doses up to 1,500 mg/day (ZUARDI et al., 1995). More recently, CBD monotherapy was administered to three patients with treatment-resistant schizophrenia (initial oral 40 mg dose, increasing to 1,280 mg/day for up to four weeks) with no side effects reported, even at the highest dose (ZUARDI et al., 2006b). A similar result was observed in two patients with bipolar affective disorder who received CBD (600-1,200 mg/day) for up to 24 days (ZUARDI et al., 2010). A double-blind study with 42 patients diagnosed with schizophrenia or schizophreniform disorder (diagnosed by DSM-IV) in an acute episode showed that an 800 mg CBD dose significantly reduced psychotic symptoms after two to four weeks of treatment and induced fewer side effects such as extrapyramidal symptoms, increased prolactin levels, and weight gain compared to amisulpride (LEWEKE et al., 2007).

CBD efficacy and safety for Parkinson’s disease patients with psychotic symptoms were evaluated in a four week open trial. Flexible oral CBD dosing ranged from 150 to 400 mg/day in the last week. Patients’ usual treatments showed that psychotic symptoms were

significantly reduced; cognitive and motor symptoms were not affected by the cannabinoid and no serious side effects were reported (ZUARDI et al., 2009). A double-blind placebo controlled trial is currently underway by Zuardi's group to evaluate CBD efficacy, safety, and tolerability in patients with Parkinson's disease and psychosis.

Finally, a 19-year old female with a history of cannabis addiction received 300 mg CBD on day 1, 600 mg/day divided into two doses on days 2 through 10, and 300 mg CBD on day 11. During CBD treatment, the patient did not report any cannabinoid withdrawal symptoms and did not experience anxiety or dissociative symptoms (CRIPPA; ZUARDI; HALLAK, 2010) as assessed by standardized rating scales. Some clinical trials in multiple sclerosis showed that 1:1 mix THC and CBD, available as an oromucosal spray (Sativex®), at doses ranging from 2.5 to 120 mg of each cannabinoid, showed no adverse effects on cognition or mood (WADE et al., 2004), other than those observed with psychoactive drugs for pain treatment (NOTCUTT et al., 2004).

1.3. Rimonabant

Rimonabant is a CB1 receptor inverse agonist or antagonist developed for its anti-obesity and anti-tobacco smoking effects at a therapeutic dose of 5 or 20 mg/day (DESPRES; GOLAY; SJOSTROM, 2005; LE FOLL et al., 2008; PI-SUNYER et al., 2006; VAN GAAL et al., 2005; VAN GAAL et al., 2008b). CB1 receptor antagonist development provided a powerful tool for investigating the endocannabinoid system in animals and humans. *In vitro* studies showed rimonabant antagonized cannabinoids effects, further confirmed by rodent studies (RINALDI-CARMONA et al., 1995; RINALDI-CARMONA et al., 1996). In humans, pretreatment with 90 mg rimonabant significantly antagonized THC effects, documenting for the first time that THC's effects were modulated through the CB1 receptor and that the interaction was pharmacodynamic rather than pharmacokinetic in nature (HUESTIS et al., 2007; HUESTIS et al., 2001).

Evidence for rimonabant's anti-obesity effect in animals showed central and peripheral action on fat metabolism by inducing weight loss and decreasing food intake (KUNOS, 2007; PAGOTTO et al., 2006). This CB1 receptor antagonist was recently approved for anti-obesity treatment but withdrawn from the market due to adverse psychiatric effects such as anxiety and depression (CHRISTENSEN et al., 2007; DESPRES; GOLAY; SJOSTROM, 2005; DESPRES et al., 2009; NISSEN et al., 2008; PI-SUNYER et al., 2006; ROSENSTOCK et al., 2008; RUCKER et al., 2007; SCHEEN et al., 2006; VAN GAAL et al., 2008a; VAN GAAL et al., 2005). However, participants' inclusion with previous depression history and other significant psychiatric disease may have contributed to the observed adverse effects (MOREIRA; CRIPPA, 2009). Rimonabant was also investigated for other therapeutic applications, including tobacco (RIGOTTI et al., 2009) and alcohol cessation (GEORGE et al., 2010; SOYKA et al., 2008). Rimonabant did not affect cardiac function (arterial blood pressure, heart rate, renal function and *urine albumin* / c*reatinine* ratio in humans (ROSENSTOCK et al., 2008).

Several mechanisms may be proposed to increase anxiety and depressive symptoms after rimonabant administration. One hypothesis would be that the endocannabinoid system maintains a neurochemical balance between glutamate and GABA neurotransmission (MOREIRA; LUTZ, 2008). Indeed, blockade of the CB1 receptor could affect neurotransmitter activity by inhibiting GABA and increasing glutamatergic activity (MOREIRA; LUTZ, 2008). Another hypothesis could be the endocannabinoid anandamide activity at CB1 or TRPV1, whereas anandamide activation of CB1 receptors produces

anxiolytic effects while activation of TRPV1 can induce aversive reactions (MOREIRA; CRIPPA, 2009).

In light of this CB1 receptor antagonist action, healthy humans received up to 90 mg rimonabant to evaluate whether blockade of this cannabinoid receptor could mitigate effects of smoked cannabis. Lower rimonabant doses did not significantly affect subjective measurements, while 90 mg rimonabant attenuated subjective effects with no significant adverse effects and no pharmacokinetics interaction with THC (GORELICK et al., 2006; HUESTIS et al., 2001). Conversely, increased anxiety was observed in animals (COMPTON et al., 1996; NAVARRO et al., 1997; RICHARDSON; AANONSEN; HARGREAVES, 1997; SANTUCCI et al., 1996; TERRANOVA et al., 1996). Further studies confirmed the safety of 40 mg rimonabant administration to humans for up to 15 days without significant adverse effects (GORELICK et al., 2006; HUESTIS et al., 2007; HUESTIS et al., 2001).

1.4. Cannabinoid Blood Pharmacokinetics

THC, the main psychoactive constituent of cannabis, is lipophilic (GARRETT; HUNT, 1974; THOMAS; COMPTON; MARTIN, 1990), thermolabile (JOHNSON et al., 1984), and sensitive to oxidation (AGURELL; LEANDER, 1971; FAIRBAIRN; LIEBMANN; ROWAN, 1976). The most common route of cannabis intake is through smoking, although oral dronabinol, CBD capsules, and other routes of administration are also applied (CRIPPA; ZUARDI; HALLAK, 2010; GROTENHERMEN, 2003; HUESTIS, 2007).

THC and metabolites' peak plasma concentration occur approximately 15 min after smoking initiation (HUESTIS; HENNINGFIELD; CONE, 1992; SCHWOPE et al., 2011a). Due to uncertain smoking topography and consequent drug delivery, cannabinoids have low bioavailability around 10-50% (AGURELL et al., 1986; LINDGREN et al., 1981; OHLSSON et al., 1982). Peak THC plasma concentration after oral intake is 1 - 6 h, (OHLSSON et al., 1980) (TIMPONE et al., 1997; WALL et al., 1983) and demonstrate lower bioavailability than smoked route due to first-pass liver metabolism and acid pH in the stomach (GARRETT; HUNT, 1974). Steady-state volume of distribution is 3.4 L/Kg (GROTENHERMEN, 2003; STICHT; KÄFERSTEIN, 1998), with 95-99% plasma THC bound to proteins in plasma (GROTENHERMEN, 2003; HUESTIS, 2005). Extended cannabinoid excretion due to extensive body burden (HUESTIS, 2005) (HARVEY; LEUSCHNER; PATON, 1982; HO et al., 1970; LEUSCHNER et al., 1986) can be observed in plasma and blood for at least seven days of sustained abstinence (KARSCHNER et al., 2009a; KARSCHNER et al., 2009b) and is present in brain when no longer present in blood (MURA et al., 2005).

Hydroxylation and oxidation of THC by cytochrome P450 (CYP) is the main metabolism pathway (MATSUNAGA et al., 1995; NARIMATSU et al., 1992) with about 100 identified metabolites (HARVEY; SAMARA; MECHOULAM, 1991), mainly by CYP2C9, 2C19, and 3A4 (HUESTIS, 2005) and other tissues such as heart and lung (NAKAZAWA; COSTA, 1971; WIDMAN et al., 1975). Phase I hydroxylation forms the psychoactive metabolite 11-hydroxy-THC (11-OH-THC) and subsequent oxidation to non-psychoactive 11-nor-9-carboxy-THC (THCCOOH) metabolite (HUESTIS, 2005). Phase II conjugation of glucuronic acid (and lesser extend of sulfate, glutathione, amino acids, and fatty acids) to THCCOOH increases water solubility, facilitating urinary excretion (BLACKARD; TENNES, 1984). After smoking a 1.75% or 3.55% cannabis cigarette, THC concentration increased rapidly with mean peak concentrations at 8.4 min at 84.3 and 162.2 ng/mL for the low and high doses, respectively. Time of last THC detection was longer for the high doses

than the low doses, detected for maximum of 27 h (HUESTIS; HENNINGFIELD; CONE, 1992).

CBD has a similar pharmacokinetics pattern as THC, with bioavailability ranging from 11-45% (AGURELL et al., 1981; SAMARA; BIALER; MECHOULAM, 1988) and greater volume of distribution (30 L/Kg) than THC (OHLSSON et al., 1984). CBD metabolism mainly occurs through C-9 and side-chain oxidation and also as cyclized THC and cannabinol (AGURELL et al., 1986; HARVEY; MARTIN; PATON, 1978; HARVEY; MECHOULAM, 1990). Besides significant metabolism by liver enzymes (HUESTIS, 2005), a high percentage of free-CBD is excreted in feces (PATON; PERTWEE, 1972; WALL; BRINE; PEREZ-REYES, 1976). CBD can also alter the pharmacokinetics of other drugs by inactivation of CYP 2C 2D6, 3A4 (BORNHEIM; CORREIA, 1991; 1990; JAEGER; BENET; BORNHEIM, 1996; KLEIN et al., 2011; YAMAORI et al., 2011), decreasing 11-OH-THC and THCCOOH concentrations as a result of covalent binding of CBD metabolite to CYP (BORNHEIM et al., 1994). Chronic CBD treatment showed increased CYP 2B activity, inducing drug metabolism. Besides the ability of CBD to affect THC pharmacokinetics (AGURELL et al., 1985; MCARDLE et al., 2001), CBD extracts or concomitant CBD/THC administration at equivalent dose ratio showed no pharmacokinetics interaction (KARSCHNER et al., 2011) or effect on CYP activity (STOTT et al., 2005).

Cannabinoids half-lives are difficult to measure due to large body burden and sustained drug elimination over days (GROTENHERMEN, 2003). In a recent pharmacokinetics study (SCHWOPE et al., 2011a), participants smoked a 6.8% THC cannabis cigarette. Peak THC and CBD whole blood concentrations were 50 and 1.3 ng/mL, respectively, while plasma concentrations were 76 (THC) and 2 ng/mL (CBD) 15 min after starting smoking. Plasma CBD concentrations was detected up to 1 h after smoking, while THC was still detected in plasma specimens 22 h after smoking. Little is known concerning CBD pharmacokinetics after oral administration and its elimination in urine. Peak CBD concentration was achieved 76.3 min. after oral 2.5 mg CBD intake at mean plasma concentration 2.5 ng/mL (GUY; ROBSON, 2003). In another study with CBD oral administration, participants received 300 mg CBD and mean blood concentrations at 1 and 2 h after administration were 4.7±7.0 and 17±29 ng/mL, respectively (FUSAR-POLI et al., 2009).

1.5. Summary

Cannabidiol anxiolytic effects have not been studied in treatment-naïve social anxiety disorder participants during the public speaking simulation task. Furthermore, there are currently no studies regarding the effects on anxiety after administration of the CB1 receptor antagonist (rimonabant) in healthy humans during the public speaking simulation task. This protocol was approved by Clinics Hospital of Ribeirão Preto of University of São Paulo Institutional Review Board and participants provided written informed consent. The results from these studies would improve knowledge of subjective effects during controlled conditions of experimental anxiety and the therapeutic effect of cannabidiol, a *Cannabis sativa* constituent, which would assist further studies focusing on anxiety treatment. In light of the difficulty in social anxiety disorder treatment with low rates of success, discovery of new potential drugs with rapid onset, minimal side effects, and high efficacy are strongly needed.

Whole blood cannabinoid pharmacokinetics has not been determined in chronic heavy cannabis users during sustained abstinence. The protocol was approved by the National Institute on Drug Abuse (NIDA, Baltimore, MD, USA) Institutional Review Board (IRB) and participants provided written informed consent. This research was done through a doctorate exchange between the School of Pharmaceutical Sciences of Ribeirão Preto and NIDA during 2010 and 2011, generously granted by CAPES (Federal Agency of Support and Evaluation of Graduate Education). Previous studies showed cannabinoids were detected in plasma and whole blood for at least a week in chronic cannabis users during sustained abstinence, leading to questions regarding the duration of cannabinoids excretion. This study would provide important information concerning public safety and assist in the development of evidence-based drug policy and legislation.

2. Conclusions

Cannabidiol has extensive pharmacological effects by multiple mechanisms (IZZO et al., 2009). Previous studies demonstrated anticonvulsant, antipsychotic, antidepressant and anxiolytic effect of CBD in psychiatry (CRIPPA; ZUARDI; HALLAK, 2010). Chapter 3 extended the knowledge CBD anxiolytic effect in SAD participants. A single dose of CBD significantly reduced anxiety, cognitive impairment, and discomfort at speech performance and significantly decreased alertness at anticipatory speech. Acute CBD administration mitigated the increase of negative self-evaluation during public speaking and the self-report of somatic symptoms, with no effects on physiological measures.

Chapter 4 provided addition information about anxiogenic-like behavior after acute blockade of CB1 receptor in humans submitted to controlled conditions of experimental anxiety. Rimonabant administration had no effect on VAMS factors besides ‘anxiety’ and no effect on other measurements. This finding can extended our knowledge about neurobiological mechanisms of anxiety and the possible role of endocannabinoids in anxiety / anxiety disorders. However, additional studies are necessary to investigate modulation of endocannabinoids as alternative for SAD treatment.

Cannabinoids quantification in whole blood presented in Chapter 5 provided novel insight into THC, 11-OH-THC and THCCOOH excretion over days to weeks. These novel data provide important information regarding extended cannabinoid excretion in chronic daily cannabis smokers and impact development of *per se* laws to reduce morbidity and mortality from cannabis-impaired driving.

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