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Cannabidiol inhibits the hyperphagia induced by cannabinoid-1 or serotonin-1A receptor agonists

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ABSTRACT

Δ9-THC is a component of *Cannabis sativa* that increases food intake in animals and humans, an effect prevented by selective CB1 receptor antagonists. Cannabidiol (CBD) is another constituent of this plant that promotes several opposite neuropharmacological effects compared to Δ9-THC. CBD mechanisms of action are still not clear, but under specific experimental conditions it can antagonize the effects of cannabinoid agonists, block the reuptake of anandamide and act as an agonist of 5-HT1A receptors. Since both the cannabinoid and serotoninergic systems have been implicated in food intake control, the aim of the present work was to investigate the effects caused by CBD on hyperphagia induced by agonists of CB1 or 5-HT1A receptors. Fed or fasted Wistar rats received intraperitoneal (i.p.) injections of CBD (1, 10 and 20 mg/kg) and food intake was measured 30 min later for 1 h. Moreover, additional fed or fasted groups received, after pretreatment with CBD (20 mg/kg) or vehicle, i.p. administration of vehicle, a CB1 receptor agonist WIN55,212-2 (2 mg/kg) or a 5-HT1A receptor agonist 8-OH-DPAT (1 mg/kg) and were submitted to the food intake test for 1 h. **C**BD by itself did not change food intake in fed or fasted rats. However, it prevented the hyperphagic effects induced by WIN55,212-2 or 8-OH-DPAT. These results show that CBD can interfere with food intake changes induced by a CB1 or 5-HT1A receptor agonist, suggesting that its role as a possible food intake regulator should be further investigate.

1. Introduction

The regulation of food intake is a complex interplay between the central nervous system (CNS) and the activity of several organs involved in energy homeostasis. It is one component of energy balance where endocrine signaling from the periphery to the CNS has a particularly important role (Woods and D'Alessio, 2008). In the CNS it involves several brain structures and effectors such as neuropeptides, monoamines, and the endocannabinoid system (Valassi et al., 2008).

Δ9-Tetrahydrocannabinol (Δ9-THC) is the main component of the *Cannabis sativa* plant, responsible for its behavioral effects as well as increased hunger. Two cannabinoid receptors have now been identified, named CB1 and CB2. The CB1 receptor is expressed mainly in several brain areas involved in appetite regulation such as the hypothalamus and nucleus accumbens, and peripherally in the liver, gastrointestinal tract, pancreas, adipose tissue and skeletal muscle (Di Marzo and Petrosino, 2007; Matias et al., 2008; Soria-Gomez et al., 2007). The CB2 receptors are predominantly expressed in immune cells such as monocytes, but are also present in the brain and cardiac muscle (Cavuoto et al., 2007; Fernandez-Lopez et al., 2007; Pacher and Ungvari, 2008).

The hyperphagic effect of Δ9-THC in rats is remarkably strong, causing animals to overconsume even when they are fed (Williams et al., 1998). This effect has been shown to be mediated by CB1 receptors, since it is reversed by the selective CB1 receptor antagonist SR141716A (rimonabant), but not the selective CB2 antagonist SR144258 (Williams and Kirkham, 2002). Similar CB1-mediated hyperphagic effects have also been reported following administration of the endocannabinoids anandamide and 2-arachidonoyl glycerol (2-AG) (Gomez et al., 2002; Hao et al., 2000; Jamshidi and Taylor, 2001; Kirkham et al., 2002; Williams and Kirkham, 1999). Both compounds are able to promote feeding when administered into hypothalamic nuclei and into the shell of the nucleus accumbens (Jamshidi and Taylor, 2001; Kirkham and Williams, 2001; Kirkham et al., 2002), regions associated with eating motivation (Kirkham et al., 2002; Schwartz et al., 2000). Moreover, acute or chronic administration of CB1 receptor antagonists such as rimonabant or AM251 suppresses food intake (Colombo et al., 1998; Vickers et al., 2003) and reduces the consumption of palatable food in laboratory animals (Gallate et al., 1999; Simiand et al., 1998). Together, these findings support a key role for endocannabinoids in the control of eating.

Cannabidiol (CBD) is another constituent of *C. sativa* that may constitute up to 40% of cannabis extracts (Grlie, 1976) and does not cause the typical psychological effects of Δ9-THC (Zuardi et al., 1982).

Abbreviations: 2-AG, 2-arachidonoyl glycerol; CBD, Cannabidiol; 5-HT, serotonin; Δ9-THC, Δ9-tetrahydrocannabinol.

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Moreover, CBD has been shown to antagonize several Δ9-THC effects (D'Souza et al., 2004) and may have anti-psychotic (Zuardi et al., 2006), anxiolytic (Guimaraes et al., 1990; Resstel et al., 2006), antidepressant (Zanelati et al., 2010) and neuroprotective (Hermann et al., 2007) properties.

The mechanisms of CBD effects are not altogether clear. Although it has a low affinity for CB1 receptors (Petitet et al., 1998; Thomas et al., 1998) it could antagonize the effects of cannabinoid agonists (Pertwee et al., 2002; Zuardi et al., 1981). Moreover, CBD blocks the reuptake of anandamide (Bisogno et al., 2001) and acts as an agonist at 5-HT1A receptors (Resstel et al., 2009; Russo et al., 2005; Zanelati et al., 2010). Central serotoninergic systems are also involved in the regulation of eating behavior (Leibowitz, 1990; Leibowitz and Alexander, 1998) and the 5-HT1A receptor agonist 8-OH-DPAT induces hyperphagia in satiated rats (Dourish et al., 1985).

Therefore, based on these pieces of evidence, the present study was aimed at investigating the effects of CBD on food intake changes induced by CB1 and 5-HT1A receptor agonists.

2. Methods

2.1. Animal preparation

Male Wistar rats ($n=120$) weighing 230–270 g were used. Animals were kept in the Animal Care Unit of the Department of Pharmacology, School of Medicine of Ribeirão Preto, University of São Paulo. Rats were housed in plastic cages under standard laboratory conditions, under a 12-h light–dark cycle (lights on from 06:00 to 18:00 h), with free access to food and water (according to the experiment). All experimental procedures were carried out during the lights-on cycle. The institution's animal ethics committee approved the animal housing conditions and experimental procedures.

2.2. Drug injections

The following drugs were used: CBD (THC Pharma, Frankfurt, Germany, 1, 10 or 20 mg/kg), suspended in polyoxyethylenesorbitan monooleate (Tween 80) 2%-saline (Resstel et al., 2006); 8-OH-DPAT (Tocris, USA, 1 mg/kg, dose based on Hutson et al., 1988) and WIN55,212-2 (Tocris, USA, 2 mg/kg, dose based on Merroun et al., 2009), dissolved in sterile saline solution. The solutions were prepared immediately before use and injected intraperitoneally in a volume of 1 mL/kg. The appropriate vehicles were used in each experiment.

2.3. Experimental protocol

2.3.1. Experiment 1—Effect of CBD on fed and fasted animals

One day before the test, the rats were divided into two groups: animals that had access to food (fed) and 18 h food-deprived animals (fasted) (Kittner et al., 2006; Scopinho et al., 2008). On the next day, in the morning (between 7 and 12 a.m.), the animals were placed individually in plastic cages (test cage) inside a soundproof room. After 30 min of environmental adaptation, both groups of rats received a single intraperitoneal (i.p.) injection of one of the following drugs: vehicle ($n=5$) or CBD (1, 10 or 20 mg/kg, $n=5$ for each dose). Thirty minutes later they were submitted to the food intake test where a petri dish with previously weighed food pellets was placed in the test cage. The food intake test lasted for 1 h, and the petri dish was reweighed to calculate food intake. Food spillage on the cage floor was also considered and weighed. No water was available during the trials.

2.3.2. Experiment 2—Effect of CBD on hyperphagia induced by WIN55,212-2

One day before the test the animals were divided into two groups: those that had access to food (fed) and 18 h food-deprived animals (fasted). On the next day, animals were tested after being submitted to the previously described conditions of adaptation. The two groups of animals were injected with CBD (20 mg/kg, $n=5$) or vehicle ($n=5$). After 15 min they received WIN55,212-2 (2 mg/kg, $n=5$) or vehicle ($n=5$) and 15 min later were submitted to the food intake test, which lasted 1 h.

2.3.3. Experiment 3—Effect of CBD on hyperphagia induced by 8-OH-DPAT

One day before the test the animals were divided into two groups: those that had access to food (fed) and 18 h food-deprived animals (fasted). On the next day, animals were tested after being submitted to the previously described conditions of adaptation. The two groups of animals were injected with CBD (20 mg/kg, $n=5$) or vehicle ($n=5$). Fifteen minutes later they received 8-OH-DPAT (1 mg/kg, $n=5$) or vehicle ($n=5$). Fifteen minutes after the last injection, the animals were submitted to the food intake test, which lasted 1 h.

2.4. Statistical analysis

The results were analyzed by a two-way ANOVA (factors: treatment and condition). When indicated post-hoc analyses were done using the Bonferroni test. Probability less than 0.05 was accepted as significant.

3. Results

3.1. Effect of CBD on fed and fasted animals

The amount of food ingested by fasted animals was significantly higher than fed animals (condition factor, $F_{1,32}=199$, $p<0.0001$). CBD did not change food intake in neither group (treatment factor $F_{3,32}=0.09$, $p>0.05$ and there was no interaction between factors $F_{3,32}=1.3$, $p>0.05$) (Fig. 1).

3.2. Effect of CBD on hyperphagia induced by WIN55,212-2

CBD decreased the hyperphagia induced by WIN55,212-2 in both fed and fasted rats (treatment factor $F_{3,30}=57.7$, $p<0.0001$, interaction between factors, $F_{3,30}=1.7$, $p>0.05$) (Fig. 2).

3.3. Effect of CBD on hyperphagia induced by 8-OH-DPAT

CBD decreased the hyperphagia induced by 8-OH-DPAT in both fed and fasted rats (treatment factor $F_{3,32}=21.5$, $p<0.0001$, interaction between factors, $F_{3,32}=1.4$, $p>0.05$) (Fig. 3).

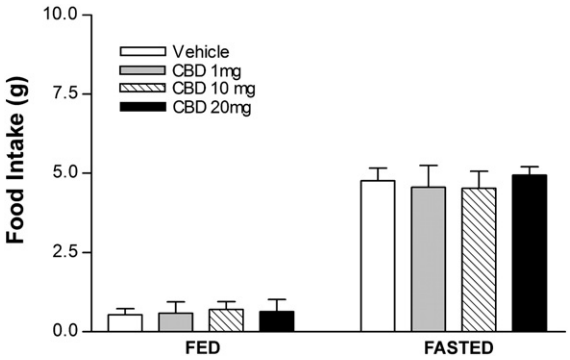

Fig. 1. Effects of systemic injection of vehicle ($n=5$/group) or 1, 10 or 20 mg/kg of CBD ($n=5$/group) on food intake (g) by fed or fasted rats. Columns represent the means and bars represent the SEM.

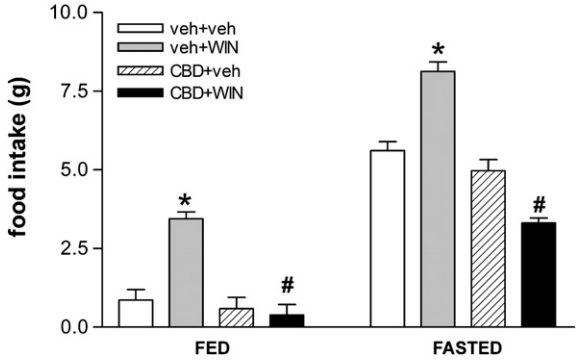

Fig. 2. Effects of systemic injection of vehicle + vehicle (veh, $n=4$), vehicle + WIN55,212-2 (WIN, 2 mg/kg, $n=5$), CBD (20 mg/kg) + vehicle ($n=5$), CBD (20 mg/kg) + WIN (2 mg/kg, $n=5$), on food intake (g) by fed or fasted rats. Columns represent the means and bars represent the SEM, $^{*}p<0.0001$ compared to respective vehicle + vehicle group; $\#p<0.0001$ compared to respective vehicle + WIN group.

4. Discussion

Systemic administration of CBD caused no changes in food intake in either fed or fasted rats. This result is in agreement with the findings of Wiley et al. (2005). They showed in mice that CBD failed to alter either food intake or locomotor activity at doses that were up to 10-fold greater than those of Δ9-THC. Although there was a trend, Riedel et al. (2009) have also recently failed to show a significant hypophagic effect of CBD (10 mg/kg) in mice.

CBD, however, was able to prevent the hyperphagic effects of the CB1 receptor agonist WIN55,212-2. CBD has been shown to interfere with several effects mediated by CB1 receptor agonists or partial agonists such as THC (Carlini et al., 1970; Karniol and Carlini, 1973; Zuardi et al., 1981). In the same study where CBD failed to change food intake by itself, it showed synergic effects with a Cannabis extract containing mainly the phytocannabinoid Δ9-tetrahydrocannabivarin, an effect that has been attributed to a CBD-induced block of residual THC contained in the extract (Riedel et al., 2009). A recent clinical study showed that smokers of high CBD:THC strains presented reduced attentional bias to drug and food stimuli compared with smokers of low CBD:THC (Morgan et al., 2010). The authors explained this finding by a possible antagonistic or inverse agonistic property of CBD at CB1 receptors (Pertwee, 2008).

Although the effects of Δ9-THC have been proposed to be mediated by a partial agonism at central CB1 receptors (Pertwee, 2008), the precise molecular mechanism of action of CBD is unclear and may involve a wide variety of mechanisms (Izzo et al., 2009; Mechoulam et al., 2007). In spite of its low affinity for CB1 and CB2 receptors, CBD is capable of antagonizing CB1/CB2 receptor agonists at reasonably low concentrations (Thomas et al., 2007). It is also able to antagonize, at low concentrations, the new putative cannabinoid receptor GPR55 (Ryberg et al., 2007). Finally, CBD can block anandamide uptake and inhibit its enzymatic hydrolysis (Bisogno, 2008).

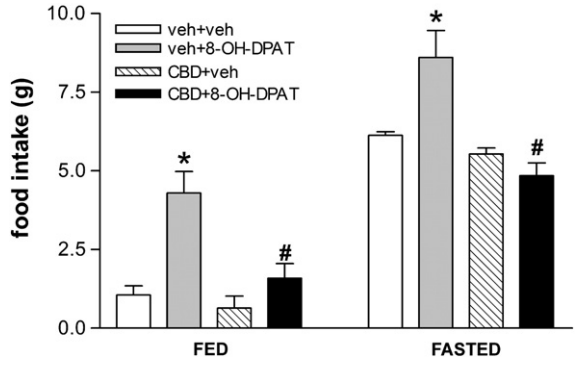

Fig. 3. Effects of systemic injection of vehicle + vehicle (veh, $n=5$), vehicle + 8-OH-DPAT (1 mg/kg, $n=5$), CBD (20 mg/kg) + vehicle ($n=5$), CBD (20 mg/kg) + 8-OH-DPAT (1 mg/kg, $n=5$), on food intake (g) by fed or fasted rats. Columns represent the means and bars represent the SEM, $^{*}p<0.0001$ compared to respective vehicle + vehicle group; $\#p<0.0001$ compared to respective vehicle + 8-OH-DPAT group.

We also evaluated the effects of CBD over another drug capable of causing hyperphagia in rats, the serotoninergic agonist 8-OH-DPAT. Serotonin (5-HT) plays an important role in the control of feeding behavior (Blundell, 1977, 1984; Simansky, 1996). 5-HT acts at a number of different receptor subtypes (Hoyer et al., 2002) and it has been generally found that drugs that are agonists at these multiple 5-HT receptors decrease food intake (Blundell, 1984). The 5-HT1A receptor agonist 8-OH-DPAT, however, has been shown to produce hyperphagia in fed rats (Dourish et al., 1985; Ebenezer, 1992). Similar effects on food intake were obtained with other 5-HT1A receptor agonists, such as buspirone and gepirone (Ebenezer and Parrott, 1993; Fletcher and Davies, 1990; Gilbert and Dourish, 1987). The mechanism by which these 5-HT1A receptor agonists increase feeding has been the subject of much research. Electrophysiological, neurochemical, and behavioral studies have suggested that they act at 5-HT1A somatodendritic autoreceptors in the raphe nuclei to decrease 5-HT function in the central nervous system (Bendotti and Samanin, 1986; Hjorth and Magnusson, 1988; Sharp et al., 1990; Sprouse and Aghajanian, 1987). Thus, their mechanism of action remains consistent with the putative inhibitory role of 5-HT in the control of ingestive behavior. CBD can act as a 5-HT1A receptor agonist (Bisogno, 2008) and this mechanism has been related to several effects mediated by this drug, such as anxiolytic and antidepressant effects (Campos and Guimaraes, 2008; Zanelati et al., 2010). Considering this, the inhibitory effect on 8-OH-DPAT-induced hyperphagia is somehow surprising. It is possible, however, that CBD is producing its effect on food intake by acting, at these doses, at post-synaptic 5-HT1A receptors (Campos and Guimaraes, 2008) or by a different mechanism. For example, several studies have demonstrated that cannabinoids modulate the synthesis, release and turnover of 5-HT in the projection areas of the dorsal raphe nucleus (Egashira et al., 2002; Nakazi et al., 2000; Sagredo et al., 2006; Tzavara et al., 2003). By antagonizing CB1-mediated inhibitory action on serotonin release, CBD could be reversing the consequences of decreasing 5-HT neuronal activity by 5-HT1A agonists.

Food intake was evaluated for only 1 h and without allowing for concomitant water ingestion. While this latter condition does not seem to conform to normal eating behavior, several studies in the literature have used a similar protocol (Higgs et al., 2005; Kittner et al., 2006; Petrovich et al., 2007; Scopinho et al., 2008). CBD, however, was only effective when food intake was pharmacologically stimulated. Therefore, even though both the cannabinoid and serotoninergic systems have been related to food intake control, the present results do not allow for a conclusion on the usefulness of this drug for treating eating disorders. Further studies, addressing those limitations (duration of the drug effect, effects in animals allowed to freely drink during the test) as well as investigating CBD effects on other hyperphagic stimuli and situations need to be performed.

Even so, the present results, by suggesting that CBD can specifically attenuate the hyperphagic stimulus of CB1 or 5HT1A agonists, could indicate another potential clinical use of this drug. This is particularly important considering that the CB1 receptor antagonist, rimonabant, an effective drug in reducing the desire to eat in humans that was being employed as a therapeutic agent for the treatment of obesity (Christensen et al., 2007), was recently withdrawn from clinical use because of collateral effects such as depression and anxiety (Taylor, 2009). CBD, on the other hand, is devoid of these side effects. On the contrary, pre-clinical and clinical findings suggest that it has anxiolytic and antidepressant properties (Guimaraes et al., 1990; Zanelati et al., 2010).

In conclusion, the present results indicate that CBD, although not decreasing food intake by itself, can prevent the hyperphagic effects of CB1 and 5-HT1A receptor agonists. Since this drug apparently lacks the side-effects previously reported with the CB1 receptor antagonist rimonabant, it could be useful for the treatment of eating disorders.

Conflicts of interest

The authors state no conflict of interest.

Declaration

The Institution's Animal Ethics Committee approved the housing conditions and experimental protocols.

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