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Cannabidiol Attenuates the Appetitive Effects of Δ_9-Tetrahydrocannabinol in Humans Smoking Their Chosen Cannabis

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Worldwide cannabis dependence is increasing, as is the concentration of Δ_9-tetrahydrocannabinol (THC) in street cannabis. At the same time, the concentration of the second most abundant cannabinoid in street cannabis, cannabidiol (CBD), is decreasing. These two cannabinoids have opposing effects both pharmacologically and behaviorally when administered in the laboratory. No research has yet examined how the ratio of these constituents impacts on the appetitive/reinforcing effects of cannabis in humans. A total of 94 cannabis users were tested 7 days apart, once while non-intoxicated and once while acutely under the influence of their own chosen smoked cannabis on dependence-related measures. Using an unprecedented methodology, a sample of cannabis (as well as saliva) was collected from each user and analyzed for levels of cannabinoids. On the basis of CBD : THC ratios in the cannabis, individuals from the top and bottom tertiles were directly compared on indices of the reinforcing effects of drugs, explicit liking, and implicit attentional bias to drug stimuli. When intoxicated, smokers of high CBD : THC strains showed reduced attentional bias to drug and food stimuli compared with smokers of low CBD : THC. Those smoking higher CBD : THC strains also showed lower self-rated liking of cannabis stimuli on both test days. Our findings suggest that CBD has potential as a treatment for cannabis dependence. The acute modulation of the incentive salience of drug cues by CBD may possibly generalize to a treatment for other addictive disorders.
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INTRODUCTION

Cannabis is the world's most popular illicit substance. Although cannabis dependence was a rare phenomenon even a decade ago, data from the European Monitoring Centre for Drugs and Drug Abuse (EMCDDA, 2006) show that the numbers of people seeking treatment for dependence have increased markedly since 1999. Over a similar time period, there also seems to have been a marked change in the constituents of the cannabis available on the street.

Cannabis contains around 70 different chemicals, which are unique to the plant and called cannabinoids. The main psychoactive ingredient is Δ_9-tetrahydrocannabinol (THC) and this is thought to produce the effects that users seek (Curran *et al*, 2002). When given intravenously to healthy humans, THC produces psychotic-like and anxiogenic effects (D'Souza *et al*, 2004, 2008). In contrast, cannabidiol (CBD), another major constituent of most strains of cannabis, seems to have anti-psychotic properties (Zuardi *et al*, 2006), and is anxiolytic (Guimares *et al*, 1990) and may be neuroprotective in humans (Hermann *et al*, 2007). THC and CBD have been found to have opposing neuropharmacological actions—the former is an partial agonist, whereas the latter is an antagonist at CB1 and CB2 receptors (Pertwee, 2008). CBD has also been suggested to inhibit the reuptake of the endogenous cannabinoid, anandamide (Bitencourt *et al*, 2008). The relative THC/CBD ratio of cannabis varies greatly. Levels of CBD can range from virtually none to up to 40% (Hardwick and King, 2008). Higher levels of THC are found in hydroponically grown varieties such as 'skunk' and in cross-bred strains, which are increasingly dominating the illicit drug market.

In addition to effects on psychotic symptoms and anxiety, THC and CBD may have opposing effects in the processes involved in addiction. The reinforcing effects of THC have been repeatedly shown. Synthetic THC produces conditioned place preference in rats and decreases the threshold for intercranial self-stimulation in animal studies (see Cooper and Haney, 2009 for a review). CBD is not acutely reinforcing in rats (Vann *et al*, 2008). However, CBD has been shown to reverse the conditioned place preference effect induced by THC in CBD : THC ratios of 1 : 1 and 1 : 10 (Vann *et al*, 2008), suggesting that it may modulate the

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reinforcing effects of THC. CBD has also been suggested to have a function in the modulation of addictive behavior. Preclinical studies have shown that acute administration of CBD can enhance extinction of both cocaine and amphetamine conditioned place preference (Parker *et al*, 2004). CBD has also been found to attenuate the reinstatement of opioid seeking in rats (Ren *et al*, 2009).

Given the opposing neuropharmacological actions of THC and CBD, and the capacity of CBD to modulate the acute reinforcing effects of THC in rats, we hypothesized that CBD may also counteract some of the reinforcing effects of THC in humans. This study set out to test these hypotheses by using a novel methodology, which enabled analysis of cannabinoids in the cannabis actually smoked by each individual user.

To index relevant aspects of reinforcing effects, we aimed to tap into not only the explicit 'liking' of a drug, but also the implicit 'wanting' (Robinson and Berridge, 2008). One way in which the latter has been assessed is by examining attentional bias to drugs of abuse. It is well known that with the progression from drug use to abuse and on to dependence, a drug user's attention becomes drawn to drug-related stimuli more than earlier reinforcing 'natural' rewards (Robinson and Berridge, 2001) and this can be investigated by using attentional bias tasks. Degree of attentional bias predicts relapse in cigarette smokers (Waters *et al*, 2003) and opiate-dependent individuals (Marissen *et al*, 2006) and as such relates to level of dependence. Attentional bias toward cannabis-related stimuli has been earlier reported in cannabis users (Field *et al*, 2006), but no study has investigated the impact of smoking different strains of cannabis may have on such processes. We, therefore, used a 'dot-probe' paradigm as an attentional bias task to assess implicit wanting of both cannabis stimuli and food stimuli (as a natural reinforcer influenced by cannabis), and ratings of pleasantness to assess the explicit liking of the cannabis and food stimuli.

MATERIALS AND METHODS

Design and Participants

A repeated measures design compared a sample of 94 cannabis users aged between 16 and 24 years on two test occasions approximately 7 days apart. Inclusion criteria required that participants had English as a native language, were not dyslexic, had no history of psychotic illnesses, and had normal or corrected-to-normal color vision. Participants were also excluded if they gave a positive saliva sample (above cutoffs for cannabis use in the past 4–6 h) for THC or CBD on the non-intoxicated day. The cannabis-using group was required to use the drug at least once a month for at least 1 year. They were recruited by word of mouth and 'snowball sampling' (Solowij *et al*, 1992). Data are first reported on the overall sample; to facilitate analysis of the impact of THC and CBD, the sample was divided into upper and lower tertiles (each $n = 32$) on the basis of individual CBD : THC ratios in the cannabis actually smoked.

All participants provided written, witnessed, informed consent on both occasions. This study was approved by the UCL Graduate School Ethics committee and its aims were supported by the UK Home Office.

Procedure

All participants were tested on two separate occasions. One testing session occurred when cannabis users were under the influence of the drug (intoxicated day) and the other when drug free (drug-free day) with session order being counterbalanced. Participants were required to abstain from recreational drugs and alcohol for 24 h before testing commenced. A sample of the cannabis each participant smoked was taken on the intoxicated day and analyzed for levels of THC and CBD (Forensic Science Service, UK). Saliva samples were also taken for analysis of cannabinoids, a screening analysis was performed, and then confirmation analysis by liquid chromatography mass spectrometry. A urine sample was collected before cannabis use on the intoxicated day for later analysis of THC metabolite in urine. Instant urine tests were administered on the drug-free day to confirm abstinence from other drugs (opiates, cocaine, amphetamine, benzodiazepines, and other related compounds; a positive result for THC occurs if a minimum of 50 ng/ml of THC metabolite is present in the urine sample; however, THC remains detectable in the body for up to 4 weeks so 24-h abstinence of cannabis users was not verifiable). On the intoxicated day, participants smoked the cannabis at the site of testing in front of the experimenter, which was usually at their own home. They were asked to smoke an amount of cannabis that was typical for them to become 'stoned.' The experimenter weighed this sample before they made the 'joint' and then collected 0.3 g of the same cannabis for analysis. The experimenter noted whether the sample was 'skunk,' herbal cannabis, or resin. Participants then completed the assessments described below beginning 1–5 min after they had finished smoking. For cognitive and dependence-related measures, the task versions were balanced across the two testing days and session order. Participants also completed the *Severity of Dependence Scale* (Gossop *et al*, 1995), a brief 5-item questionnaire regarding their drug use, the *Wechsler Adult Reading Test* (WTAR; Wechsler, 2001) to estimate their reading ability as an analog of premorbid IQ, and self-reported their drug use in a drug history questionnaire. The assessments reported here formed part of a wider test battery on which data collection is still underway. After testing, participants were fully debriefed and compensated for their time.

Assessments

Dot-probe task. A computer-based dot-probe paradigm was used to assess attentional bias to both drug- and food-related stimuli. The 10 color photographs of cannabis-related stimuli and 10 color photographs of food-related stimuli were used, with each image simultaneously paired with a neutral photograph matched as closely as possible for visual composition and complexity (see Figure 1 for an example). A total of 80 of the 160 total trials were critical trials of which 40 featured cannabis-related and 40 food-related stimuli, each presented twice for 250 ms and twice for 2000 ms. These two exposure times were used to

Figure 1 An example of a cannabis/neutral and a food/neutral-matched pair of images.

tap automatic (250 ms) and controlled (2000 ms) processing. The critical (food- or drug-related) images appeared once on the left and once on the right at each time interval. The side at which the probe appeared was counterbalanced across all the trials. An asterisk was used as the probe.

A total of 10 neutral practice trial pairs were used as training, followed by two blocks of 80 experimental trials. There was a short break between blocks. Each trial began with a central fixation cross shown for 1000 ms, after which a pair of matched images would appear, one on each side of the fixation cross, for either the long (2000 ms) or short (250 ms) duration. Both images then disappeared revealing the probe behind one of the two images. Participants were required to respond to the probe as quickly as possible by pressing a button corresponding to the relevant side of the screen. Attentional bias was calculated as the difference in reaction time between when the probe replaced the neutral compared with the incentive (drug/food) stimulus [Rtneutral—RTincentive], such that a greater difference indicated greater bias toward that stimulus.

Picture-rating task. After the dot-probe task, participants completed a picture-rating task as a measure of explicit liking for drug and food stimuli. They rated each picture earlier used in the dot-probe task on a 7-point scale, ranging from −3 (very unpleasant) to +3 (very pleasant).

Marijuana craving questionnaire (Heishman et al*, 2009).* A short 12-item questionnaire was given to assess current craving for cannabis.

Visual analog scale. A 100 mm visual analog scale (VAS) anchoring from 'not at all stoned,' to 'extremely stoned' was administered.

Statistical Analysis

Data are first reported on the overall sample. Owing to trace levels of CBD in the majority of the participants, therefore, we subdivided the groups on the basis of CBD > 1% and then excluded the middle third to compare equal group sizes who differed in their CBD content. Using the CBD : THC ratio groups, dependence-related data were subjected to a 2 × 2 repeated measures ANOVA with ratio (high CBD : THC; low CBD : THC) as the between subjects factor and day (intoxicated, drug free) as the within subjects factor. *Post hoc* comparisons were Bonferroni corrected one-way ANOVAs to explore interactions, or Bonferroni comparisons to explore main effects.

RESULTS

Demographics and Drug Use Data

Whole sample. Over the whole sample, the mean age of participants was 21.3 ± 1.42 years, there were 72 males and 22 females, and participants had spent a mean of 14.67 ± 2.11 years in education with a mean WTAR score of 42.86 ± 6.52. Cannabis was used as a mean of 13.9 ± 11.53 days per month.

Sub-group analyses. High CBD : THC ratio vs low CBD : THC ratio groups. There were no differences in demographic variables between these two cannabis smoking groups (Table 1). There were also no differences in self-reported use of cannabis or clinician rated dependence on the SDS. However, for drug use variables, individuals from the high CBD : THC ratio group drank alcohol more frequently than the low CBD : THC group [$F(1,57) = 4.32$, $p = 0.042$]. There were no significant group differences for when alcohol was last used before the non-intoxicated day.

Table 1 Demographic and CBD and THC Data Across the Two User Groups in the Sample

	Low CBD : THC ratio ($N = 30$), mean (SD)	High CBD : THC ratio ($N = 31$), mean (SD)
Age	21.19 ± 1.53	21.6 ± 1.22
Number of years in education	14.55 ± 1.85	15 ± 1.78
Age at which cannabis first tried	15.34 ± 2.36	14.77 ± 1.98
How often cannabis is used (days per month)	13.33 ± 10.93	14.55 ± 12.3
Time to smoke 1/8th ounce of cannabis (days)	11.43 ± 12.90	25.00 ± 35.60
SDS total	3.06 ± 2.7	2.8 ± 2.28
Total WTAR score	42.78 ± 4.99	44.17 ± 6.53
Number of units used per session	10 ± 4.6	8.44 ± 4.43
How often is alcohol drunk (days per month)	8.6 ± 5.88	12.27 ± 7.4*
Number of days since last alcohol use	5.067 ± 10.929	10.138 ± 38.80
Salivary THC intoxicated (ng/ml)	21.20 ± 42.7	15.97 ± 28.81
Salivary CBD intoxicated (ng/ml)	0.14 ± 0.51	2.48 ± 7.17
CBD content (% of sample)	0.14 ± 5.41	2.64 ± 2.54*
THC content (% of sample)	11.92 ± 5.41	7.74 ± 4.20*
CBD : THC ratio (CBD/THC)	*0.01 ± 0.01*	*0.35 ± 0.31* *
Urinary THC acid : creatinine ratio	*90.78 ± 187.88*	*49.54 ± 109.27*

Abbreviations: SDS, severity of dependence scale; WTAR, Wechsler test of adult reading. *$p < 0.05$.

There was significantly greater THC content [$U = 286.0$, $p = 0.002$] and lower CBD content [$U = 76.0$, $p < 0.001$] in the low CBD : THC ratio group.

Salivary levels on the intoxicated day showed only a trend for a group difference in CBD [$U = 248.5$, $p = 0.099$], but no differences in salivary levels of THC.

No significant difference was found between the two groups of urinary levels of THC acid from the samples taken on the intoxicated day. From the instant drug test results on the non-intoxicated, day, χ^2 analysis found no significant group differences in positive results for THC metabolite. The χ^2 analysis also found a significant difference in the type of cannabis smoked between the groups [$\chi^2(4) = 43.79$, $p < 0.001$] reflecting that all the low CBD : THC ratio group had smoked 'skunk' varieties (see Table 2).

Dependence-related measures. Dot-probe task Reaction times <100 ms or >1000 ms were excluded from the analysis in line with earlier dot-probe studies (Duka and Townshend, 2004) and this excluded two participants, one from each CBD : THC ratio group. A $2 \times 2 \times 2 \times 2$ repeated measures ANOVA with the additional within subjects factors of stimulus type (food, drug) and picture duration (short, long) found a significant day × CBD : THC ratio × duration interaction [$F(1,57) = 6.31$, $p = 0.015$] and a trend for a day × type interaction [$F(1,57) = 3.31$, $p = 0.073$]. *Post-hoc* exploration of the three-way interaction showed that the significant day × ratio group interaction was attributable to greater bias to both types of stimuli in the low CBD : THC ratio group at the short picture presentation interval on the intoxicated day [$F(1,57) = 5.63$, $p = 0.021$], but no difference on the non-intoxicated day (see Figure 2a).

Table 2 Types of Cannabis Collected, Number of Samples in Each Group, and Corresponding Means (± SD) of CBD/THC Ratios in Each Sample

	Low CBD : THC ratio	High CBD : THC ratio	CBD/THC, mean ± SD
Skunk	32	6	0.02 ± 0.02
Herbal	0	11	0.24 ± 0.35
Resin	0	15	0.53 ± 0.22

Picture-rating task. A $2 \times 2 \times 3$ repeated measures ANOVA of ratings of pleasantness of the pictures presented in the dot-probe task, with the additional factor of stimulus type (food, drug, neutral) yielded a significant CBD : THC ratio × stimulus type interaction [$F(2,118) = 4.29$, $p = 0.016$], as well as main effects of stimulus type[$F(2,118) = 46.52$, $p < 0.001$] and CBD : THC ratio [$F(1,59) = 7.61$, $p = 0.008$], but not day. Exploration of the interaction, depicted in Figure 2b, shows significantly lower ratings of pleasantness for drug stimuli in the high CBD : THC ratio group [$F(1,59) = 12.44$, $p = 0.001$], a trend for lower ratings of pleasantness for food stimuli in the high CBD : THC ratio group [$F(1,59) = 2.81$, $p = 0.099$], but no group differences in ratings of neutral stimuli.

MCQ (Table 3) There were no group differences in craving as assessed by the Marijuana Craving Scale across the 2 days.

VAS (Table 3) There were no group differences in 'stoned' ratings on either day and both groups had similarly higher ratings on the intoxicated compared with the drug-free day [$F(1,59) = 299.53$, $p < 0.001$].

DISCUSSION

The main findings of this study were of reduced attentional bias to drug and food stimuli in intoxicated individuals smoking cannabis with a high CBD : THC ratio. We also found evidence of an overall reduction in ratings of liking of drug stimuli in high CBD : THC cannabis smokers.

Attentional Bias to Drug Stimuli

Attentional bias to drug stimuli in users when they were drug free was observed in both CBD : THC groups at the short, but not the long stimulus exposure interval. This differentiation most likely reflects automatic processing at the short interval and accords with 'incentive sensitization' processes described in Robinson and Berridge's (1993, 2003) model of addiction, which is thought to be an automatic process. The presence of an attentional bias at this short time interval is consistent with some other studies (eg Morgan *et al*, 2008). In drug users, incentive sensitization is thought to accumulate over time, whereby drugs of abuse come to grab attention or act as 'motivational magnets,' eventually more so than natural reinforcers in

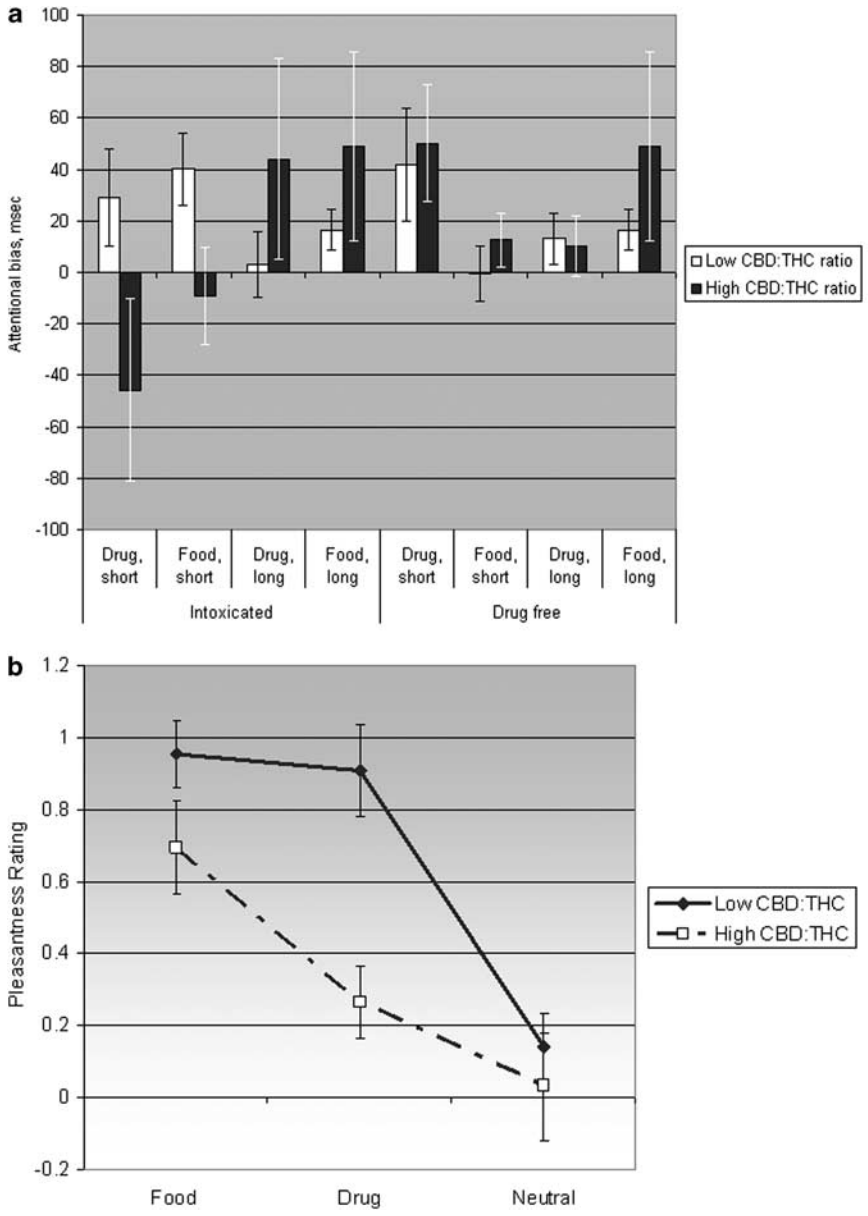

Figure 2 (a) Attentional bias to food and drug stimuli across day, CBD : THC ratio group, and picture presentation interval. (b) Pleasantness rating across stimulus type and CBD : THC ratio group across both days.

Table 3 Means (± SD) on Self-Ratings of Marijuana Craving and 'stoned' of Each CBD : THC Group Across Test Days

	Low CBD : THC ratio, $n = 30$, mean ± SD		**High CBD : THC ratio, $n = 31$, mean ± SD**	
	Intoxicated	**Drug free**	**Intoxicated**	**Drug free**
MCQ	40.52 ± 11.94	41 ± 12.35	37.88 ± 10.48	36.28 ± 11.55
Ratings of 'stoned'	6.63 ± 2.0	1.34 ± 1.41	6.45 ± 1.94	1.33 ± 1.06

the environment (Berridge *et al*, 2009). The present findings are consistent with those of earlier studies showing that cannabis, such as other recreational drugs, elicits attentional bias in its users (Field *et al*, 2006).

When intoxicated with their own chosen cannabis, only the low CBD : THC group showed an attentional bias to drug stimuli. In contrast, the high CBD : THC group showed no evidence of any bias. Thus, even when intoxicated, cannabis stimuli grabbed the attention of the low CBD : THC smokers. One might expect that having smoked cannabis, both groups would reach a level of satiety and so attentional bias would reduce as motivational state is thought to modulate the magnitude of conditioned responses on this task (Duka and Townshend, 2004). However, some research suggests that endocannabinoids may modulate afferent satiety signals (Rodriguez *et al*, 2001), related to cannabis' capacity to stimulate appetite, which could explain this finding in the low CBD : THC group.

Higher levels of CBD seemed to remove the attentional bias to drug stimuli at the short picture presentation interval. Owing to the short presentation time (250 ms), this

is very unlikely to be a conscious mechanism of attention aversion. Instead, it may reflect automatic or non-conscious processing, of which the individual is unaware. This is commensurate with a lack of CBD : THC group differences in explicit processing engaged both at the longer stimulus exposure time in the attentional bias and in self-ratings of craving and dependence on questionnaire measures. At longer durations, drug users may use conscious attentional aversion mechanisms, as drug stimuli may provoke undesired craving. Greater automatic attentional bias to drug-related stimuli has been shown to predict relapse in cigarette smokers (Waters *et al*, 2003) and opiate users (Marissen *et al*, 2006), respectively. Our present findings may, therefore, also shed new light on the increasing incidence of cannabis dependence, as the CBD content of street cannabis has been declining over the past 20 years (Hardwick and King, 2008). Recent research has also shown training attentional bias away from alcohol stimuli to be effective in reducing alcohol consumption, and this effect was still evident at a 3-month follow-up (Fadardi and Cox, 2009), therefore, CBD might be a potentially beneficial adjunct in this training.

THC and CBD Effects on Explicit Liking

Cannabis users in this study who smoked high CBD cannabis rated their explicit liking for the drug stimuli as less than the low CBD group. This subjective measure of 'liking' can be thought of as reflecting hedonic processes involved in drug abuse. The endocannabinoid system is known to be involved in mediating 'liking' reactions and microinjection of anandamide into the nucleus accumbens doubles the level of 'liking' of sucrose taste in rats (Mahler *et al*, 2007). Given that the high CBD cannabis users are smoking as much cannabis as the low CBD group, that they explicitly 'like' the drug less may seem counterintuitive. However, this may relate to the notion that it is implicit drug 'wanting' and not explicit 'liking' that mediates drug seeking behavior, which is particularly evident in drug addicts who will continue wanting the drug, in the absence of any explicit liking (Robinson and Berridge, 2003). When drug free, there was no difference in implicit attentional bias across the groups, which is tentative support for the suggestion that it is this process and not explicit 'liking' that mediates cannabis use.

Attentional Bias to Food Stimuli

We expected that acute cannabis would increase bias to food stimuli, in line with the drug's well-documented abilities to promote eating (Chopra and Chopra, 1957). The findings in the low CBD : THC group, at the short time interval, were consistent with this. Earlier work has shown that the appetite stimulating, or hyperphagic, actions of THC are mediated predominantly by CB1 receptors (Chopra and Chopra, 1957). Our findings are thus compatible with suggestions based on animal research that CB1 agonists increase the incentive value, or salience, of food (Kirkham, 2009). That higher CBD : THC ratios in the cannabis markedly attenuated acute bias to food stimuli may be explained by the antagonistic, or even inverse agonistic, properties of CBD at the CB1 receptor (Pertwee, 2008). Earlier research has shown that the CB1 antagonist, rimonabant, reduces desire to eat in humans consistent with its earlier use in the treatment of obesity (Christensen *et al*, 2007). However, rimonabant was recently withdrawn from clinical use because of reports of depression and anxiety after treatment (Taylor, 2009). As CBD possesses a different mechanism of CB1 antagonism to rimonobant, and a much better side-effect profile, these preliminary findings may suggest a clinical use for CBD in the treatment of obesity. However, clearly to establish this, studies would need to control for many factors not assessed here, such as food satiety and body weight.

Limitations

This study was subject to some limitations. Estimates of THC levels in urine at baseline were not taken on the intoxicated test day and these may have varied between subjects, which may possibly have influenced results on the drug-free day. In addition we did not breathalyze subjects on the testing days; however, none showed any visible signs of acute alcohol intoxication, as rated by the experimenter. There were no differences between the groups in levels of salivary THC on the intoxicated day, which is interesting as levels of THC in the cannabis were significantly lower in the high CBD : THC group. However, salivary estimates of metabolites of cannabis are not possible; therefore, it is possible that salivary THC and CBD levels are as a result of contamination of the oral cavity and may be inaccurate measures of true cannabis consumption.

Conclusions

When people are given a choice between marijuana cigarettes with different THC concentrations, those with higher THC content are preferred over those containing lower THC concentrations (Chait and Zacny, 1992; Kelly *et al*, 1997). The constituents of street cannabis have changed over the past decade or so with high THC, low CBD strains such as skunk and sinsemilla now dominating the market (Hardwick and King, 2008). This change was thought to be in part to be driven by user preference for lower CBD strains, because of CBD's potential to modulate the psychotomimetic effects of the drug and reduce the 'stoned' feeling (Zuardi *et al*., 2006). However, the findings of this study suggest instead that one reason may be CBD's capacity to modulate both the 'wanting' and the 'liking' of THC without affecting the 'stoned' feeling. Our findings suggest that lower CBD in cannabis may result in greater salience of drug cues when intoxicated, potentially invoking more associative learning around drug cues in users of high THC/low CBD cannabis, which could speculatively result in a higher chance of later addiction. The research reported here also contributes to the growing body which suggests a range of potential therapeutic uses of CBD, including the ability to acutely modulate the reinforcing properties of drugs.

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DISCLOSURE

The authors declare no conflict of interest.

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