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Action of Cannabidiol on the Anxiety and Other Effects Produced by Δ^9-THC in Normal Subjects

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Abstract. The object of the experiment was to verify whether cannabidiol (CBD) reduces the anxiety provoked by Δ^9-THC in normal volunteers, and whether this effect occurs by a general block of the action of Δ^9-THC or by a specific anxiolytic effect. Appropriate measurements and scales were utilized and the eight volunteers received, the following treatments in a double-blind procedure : 0.5 mg/kg Δ^9-THC, 1 mg/kg CBD. a mixture containing 0.5 mg 'kg Δ^9-THC and 1 mg/kg CBD and placebo and diazepam (10 mg) as controls. Each volunteer received the treatments in a different sequence. It was verified that CBD blocks the anxiety provoked by Δ^9-THC, however this effect also extended to marihuana-like effects and to other subjective alterations induced by Δ^9-THC. This antagonism does not appear to be caused by a general block of Δ^9-THC effects, since no change was detected in the pulse-rate measurements. Several further effects were observed typical of CBD and of an opposite nature to those of Δ^9-THC.

These results suggest that the effects of CBD, as opposed to those of Δ^9-THC, might be involved in the antagonism of effects between the two cannabinoids.

Key **words:** Cannabis – Cannabinoids – CBD – Δ^9-THC interaction – Anxiety

The extensive literature concerning the effects of *Cannabis sativa* and its constituents on man has been reviewed by many authors (Bech et al. 1974; Hollister 1971: Jones 1978).

The subjective changes provoked in man by the plant may be influenced by non-pharmacological variables, such as environment, personality. past experiences and the presumptions and attitude of the subject towards the drug (Cappel and Kuchar 1974; Carlin et al. 1972; Jones 1971; Klapper et al. 1972; Rossi et al. 1978: Weil et al. 1968). However, the influence of these variables does not appear to be very important when high doses of Δ^9-THC are introduced (Szara 1976).

Under these conditions referred psychotomimetic effects occur (body image distortion, depersonalization, visual distortions, coenesthetic hallucinations. dream-like fantasies and paranoid ideas) associated with a state of intense anxiety and panic (Meyer 1978).

The effect of the cannabinoid compounds, on anxiety in Particular, has been studied in volunteers under experimentally produced stress conditions. Pillard et al. (1974) studied the anxiety provoked in volunteers by the projection of a film and by speaking publicly after inhaling small doses of cannabis, and found no significant difference between those who had inhaled the drug and those who received placebo.

Another study showed that the inhalation of cannabis containing 14 mg of Δ^9-tetrahydrocannabinol (Δ^9-THC) produced an increase in the physiological response to stress, caused by the mental work of mathematical calculation. but had no effect on the anxiety of the subject, measured on a self-rating scale (Naliboff et al. 1976).

Gregg et al. (1976) have verified that subjects subjected to stress by oral surgery and pretreated with Δ^9-THC (0.022 and 0.044 mg/kg intravenously) showed a significantly higher level of anxiety than when pretreated with placebo or diazepam.

Besides these studies, some authors have observed that the administration of high doses of Δ^9-THC, in experiments which had not been designed to induce stress, produced intense anxiety in nearly all the volunteers (Malit et al. 1975: Tassinari et al. 1976).

Although Δ^9-THC is commonly accepted as the major psychoactive constituent of *Cannabis sativa*, recent reports have demonstrated that cannabidiol (CBD) influences the pharmacological activity of Δ^9-THC in animals and in man (Dalton et al. 1976; Davis and Borgen 1974; Fernandes et al. 1974; Karniol and Carlini 1973: Karniol et al. 1974). CBD may constitute up to 40 % of Cannabis sativa extracts (Grlic 1962) and is devoid of the typical THC-produced psychoactivity in man (Dalton et al. 1976; Hollister 1973; Karniol et al. 1974; Perez-Reyes et al. 1973).

The interaction of Δ^9-THC and CBD in normal volunteers has been studied by three independent groups with apparently contradictory results. Karniol et al. (1974), studying the interaction of the two cannabinoids administered orally, observed that CBD (15, 30 and 60 mg) diminished the subjective effects of Δ^9-THC (30 mg). Hollister and Gillespie (1975) did not observe any significant interaction between CBD (40mg) and Δ^9-THC (20 mg), administered orally. except for a tendency, observed with the mixture, to initially retard and then prolong the duration of the Δ^9-THC effect. Dalton et al. (1976) have verified that CBD (150 µg/kg) significantly attenuated the subjective effects produced by Δ^9-THC (25 µg/kg) when the two cannabinoids were inhaled simultaneously, but could detect no interaction with the pretreatment of CBD.

Karniol et al. (1974) suggested that CBD apparently provoked a qualitative change in the subjective effects of Δ^9-THC, reducing the component of anxiety induced by Δ^9-THC alone.

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The object of the present experiment is to confirm this previously uncontrolled observation, that is, that CBD diminished the anxiety produced by Δ^9-THC in normal volunteers, and to verify whether this effect occurs through a general block of the action of Δ^9-THC or through a specific effect on the anxiety.

The plan of this experiment was initially submitted to, and approved by an Institutional Committee of our University specifically created to evaluate plans for clinical research, from an ethical and scientific point of view.

Materials and Methods

Subjects

Eight normal volunteers participated in the experiment (six men and two women), all with a university education, aged between 20 and 38 years old (average 27) and weighing between 50 and 80 kg (average 67 kg). These volunteers, after being informed of the plan of the experiment, signed a declaration agreeing to participate in the research.

They were then all given a physical examination and a psychiatric interview, revealing that they had good physical and mental health. Five of the volunteers had already smoked marihuana previously, but not less than 15 days prior to the start of the experiment.

Procedure

Each volunteer participated in five experimental sessions, separated by a minimum interval of 1 week and conducted between 9 a.m. and 12 a.m. in a comfortable isolated room. In each session the volunteers received orally, in a double-blind procedure, one of the following treatments: Δ^9-THC (0.5 mg/kg); CBD (1 mg/kg); mixture (0.5 mg/kg Δ^9-THC + 1 mg/kg CBD); placebo and diazepam (10 mg). The diazepam was used to obtain a standard response to a classical anxiolytic agent, for comparison with the effects produced by the cannabinoids. The treatments were administered in a different sequence to each volunteer, in such a way that each treatment followed each of the others. Table 1 presents the protocol for each experimental session, with the times in which the various measurements were taken.

Table 1
Experimental protocol

Time (min)	Procedure
−15	Adaptation period
−10	Self-evaluation scales
− 5	Pulse rate measurement
0	Drug ingestion
30	Interview
60	Interview
65	Self-evaluation scales
70	Pulse rate measurement
120	Interview
125	Self-evaluation scales
130	Pulse rate measurement
180	Interview

Drugs

The Δ^9-THC (supplied by the National Institute of Mental Health, USA) and CBD (kindly provided by Dr. R. Mechoulam, Israel) were stored in alcohol solution (100 mg/ml). On the day of the experiment the necessary quantity was taken from the storage solution, made up to 1.5 ml with alcohol (ethanol − 99%, Merck Co.) and then added to 200 ml of artificial lemon juice. The diazepam, commercially available in tablets containing 10 mg (Valium, Hoffmann-La Roche), was powdered and placed inside opaque gelatine capsules. The lemon juice placebo contained only 1.5 ml of alcohol, and the placebo capsule contained 10 mg of lactose. The lemon juice and the capsule with the drug or placebo, depending on the treatment, were swallowed simultaneously by the volunteers in each session over a period of 5 min.

Measurements

Pulse. The increase in cardiac activity in man is one of the most pronounced physiological effects associated with Δ^9-THC (Jones 1978), following a strict dose − response relationship (Borg et al. 1975; Kiplinger et al. 1971; Miller and Cornett 1978).

Radial artery pulse rate was measured, at intervals indicated in the protocol, during periods of 5 consecutive min.

Interviews and Spontaneous Reports. At set times during the session the experimenter encouraged the volunteer to describe what he was feeling, interrupting as little as possible during the report and then only to clarify obscure points. These interviews, as well as spontaneous reports of the volunteers, were recorded. The material obtained from these recordings was used for two purposes. One of them was the development of a summary of effects produced by the different treatments. at various times after ingestion of the drug, including only those changes which occurred in two or more of the volunteers; the other to obtain, for each session, a valuation of the observer in respect to the anxiety and typical effects of C. sativa. In order to do this, a transcription of the forty recordings (five from each volunteer) was given to two independent observers, who awarded marks for anxiety on a scale of 0 to 3 (0 = no anxiety; 1 = slight anxiety (insecurity): 2 = moderate anxiety: 3 = intense anxiety or panic) and for the typical effects of C. sativa on a scale of 0 to 4 as described previously by Karniol and Carlini (1973).

The results were compared to those obtained by self-evaluation.

Self-Rating Scales. The volunteers were submitted to four self-rating scales, at times indicated in the protocol

1. Spielberger's State- Trait Anxiety Inventor-v (STAI) (Spielberger 1970). A Portuguese form of STAI was used. developed and validated by Biaggio et al. (1977). STAI (A-trait) was applied to all the volunteers at the start of the first and last experimental sessions, while STAI (A-state) was applied in all the sessions, together with more self-rating scales.

2. *Addiction Research Center Inventory for Marihuana Effects (ARCI-Ma)* (Haertzen 1966). This scale has been shown to be sensitive to the effects of Δ^9-THC, following a dose-response relationship (Isbell and Jasinski 1969; Kiplinger et al. 1971).

3. *Analogue Self-Rating Scale for Subjective Feelings.* Apart from anxiety and the typical marihuana effects, detected

Table 2. Descriptive summary of the effects produced by the various treatments at different times after ingestion of the drug by eight normal volunteers (see text for details)

Time (min)	Treatments				
	Placebo	CBD	Diazepam	THC	THC + CBD
0–30	Sleepiness (2)		Sleepiness (2)	Difficulty in concentrating (5); Depersonalization (3); Dizziness (3); Change in body image (2); Paresthesia (2); Dry mouth (2); Restlesness (2)	Sleepiness (2)
30-60	Sleep .... (3)	Sleepiness (2)	Sleep .... (2) Dizziness (2)	Difficulty in concentrating (5); Anxiety (5); Hiperacusia (5) Depersonalization (4); Sleep (4); Change in body image (3); Resistance to communication (3); Dizziness (3); Dry mouth (3); Disconnected thonghts (2): Change in perception of time (2): Nausea (2)	Sleep. (4)
60 – 120	Sleep .... (5)	Sleepniness (2)	Sleep. (6)	Hiperacusia (5); Sleep. (5); Difficulty in concentrating (4); Resistance to communication (3): Change in body image (2); Disconnected thoughts (2); Anxiety (2); Visions of coloured geometric forms with the eyes closed (2); Paranoid ideas (2); Dizziness (2); A sensation of cold (2)	Sleep. (7): Difficulty in concentrating (3); Depersonal-ization (2): Paresthesia (2)
120-180	–	–	Sleep. (5)	Resistance to communication (5); Disconnected thoughts (4) : Sleep. (4) ; Tiredness (3); Anxiety (2); Dizziness (2)	Sleep. (5)

using the previous scales, we also tried to evaluate other subjective changes induced by the treatments using a analogue self-rating scale of sixteen items. Each item is composed of two adjectives with opposite feelings, separated by a 10 cm line on which the subject has to mark the point which best describes his feelings at the time (Bond and Lader 1974; Norris 1971).

4. *Scale of Bodily Symptoms.* The self-rating scale was of the same type described previously for subjective feelings and has already been used in other studies with drugs (Karniol et al. 1976, 1978).

Statistical Analysis

The correlation between the results of STAI (A-trait) taken during the first and last sessions, was tested using Pearson's correlation coefficient.

Spearman's correlation coefficient was used to analyse the correlation between the two observers evaluations, and between the average of those two evaluations (for anxiety and typical effects of Cannabis sativa) and the scores of STAI (A-state) and ARCI-Ma respectively.

The pulse results, STAI (A-state) and ARCI-Ma, were expressed as differences from the pre-drug values and anal-Ysed by "split-plot" analysis of variance, with two fixed factors (drug and time) and interaction between them. In order to detect the differences between the averages in factors that showed significant differences by the analysis of variance, the group analysis technique, suggested by Scott and Knott (1974), was used, with some modifications introduced by Bussab (1976). The group analysis determines division of the averages into the most homogeneous groups possible, by minimizing the sum of the squares within the groups. Averages belonging to each group are statistically equal, while being statistically different from those belonging to the other groups.

The results of the analogue self-rating scale for subjective feelings and for bodily symptoms were analysed by non-parametric statistical methods. The results of each item were expressed as scores from 0 to 9, attributed according to the points marked by the volunteers on the 10 cm lines which, in order to analyse the results, were divided equally into ten intervals corresponding to the scores. The differences from the pre-drug values for each item, obtained 1 and 2 h after ingestion of the drug, were analysed using Friedman's analysis of variance, and in the case of significant differences the placebo was compared with the rest of the treatments using the Wilcoxon test (Siegel 1956). In a previous study the non parametric approach was considered more appropriate to analyse the Portuguese version of this scale (Zuardi and Karniol 1981).

Results

Interviews and Spontaneous Reports. With the material obtained from the interviews and the spontaneous reports of the volunteers it was possible to construct a descriptive summary of the effects produced by the different treatments at various times after ingestion of the drug (Table 2).

Table2 lists changes detected in two or more of the volunteers, the figures in brackets indicating the number of volunteers reporting the change. This summary shows the occurrence of sleep with all of the treatments, including placebo. Also note that Δ^9-THC produced a series of effects during all the sessions while the number of alterations caused

Table 3. The most homogeneous groups of drug effects in eight normal volunteers as obtained through group analysis. The frames indicate those groups of results which did not differ significantly, allowing them to be represented by a single average. The asterisks (*) mark those averages whose confidence interval does not contain a zero value. indicating a significant difference ($P \leq 0.05$) from the pre-drug measurement

Measurement	Time (h)	Treatments				
		Placebo	CBD	Diazepam	THC + CBD	THC
Pulse	1	−5.717*	−5.717*	−5.717*	7.625*	7.625*
	2	−9.838*	−9.838*	−9.838*	−2.238	−2.238
STAI (A-state)	1	*0.125*	0.125	3.125*	8.813*	15.938*
	2					
ARCI-Ma	1				9.643*	18.357*
	2					

by the mixture of the two cannabinoids was greatly reduced, occurring principally 2 h after taking the drug.

The recordings of the forty interviews and spontaneous reports (five for each volunteers) were also analysed by two independent observers, and the results of reliability showed significant correlations ($P < 0.001$) both for anxiety ($r = 0.847$), and for the typical effects of C. sativa ($r = 0.830$).

The averages of the evaluations of the two observers for anxiety and the typical effects of C. sativa were compared with the numerical changes observed in the results of STAI (A-state) and ARCI-Ma, respectively. For comparison we used the average of the numerical results of the self-rating scales, obtained 1 and 2 h after ingestion of the drugs, expressed as differences from the pre-drug values. The correlation coefficients between the evaluations of the observers and the self-rating scales were 0.743 for anxiety and 0.788 for the typical effects of C. sativa. In both cases the correlation was statistically significant ($P < 0.001$).

Pulse, STAI and ARCI-Ma. The eight volunteers who participated in this experiment produced an average result of 33.5 ± 8.66 for STAI (A-trait). The numerical results of the first session significantly correlated with those obtained in the last session ($r = 0.880$; $P < 0.01$), indicating a strong temporal stability.

The analyses of variance of the results of the pulse-rate. STAI (A-state) and ARCI-Ma measurements, expressed as differences from the pre-drug values, revealed that the influence of the drug factor on all three measurements was statistically significant, while the time and interaction (drug x time) factors significantly influenced only the pulse-rate.

A groups analysis was also performed on these results and the most homogeneous groups are presented in Table 3. The frames in the table indicate those groups of results which did not differ significantly, allowing them to be represented by a single average. The asterisks (*) mark those averages different from zero, i.e., those averages whose confidence interval does not contain a zero value. This indicates a significant difference between pre- and post-drug measurements. For ARCI-Ma only the results obtained with Δ^9-THC and the mixture of the two cannabinoids were analysed because the other treatments had a high zero result frequency. The data obtained by group analysis shows that the pulse-rate dropped significantly, as it did during the sessions with placebo, CBD and diazepam. On the other hand, Δ^9-THC and the mixture produced an increase in the pulse-rate, compared to the pre-drug values during the first hour, with no significant change in the second hour. The effect of Δ^9-THC on the pulse-rate did not differ significantly from that caused by the mixture of the two cannabinoids. Furthermore, STAI (A-state) and ARCI-Ma produced similar results for the first and second hours. In the case of STAI (A-state), only CBD was equivalent to the placebo, not showing significant differences from the pre-drug values. Most treatments produced an increase in the STAI (A-state) result, the highest value being with Δ^9-THC, followed by the mixture, and finally diazepam. The changes in the numerical results for ARCI-Ma, in the sessions with the mixture, were also significantly less than those observed with Δ^9-THC.

Analogue Self-Rating Scale for Subjective Feelings. Figure 1 represents treatments comparisons with placebo during the second hour after ingestion of the drugs, for those items whose analysis of variance showed significant differences between the treatments and for which at least one of the treatments differed statistically from placebo. The data presented in the figure indicate the significant effects of diazepam ("drowsy"), of CBD ("quick-witted" and "clear-minded") and of Δ^9-THC ("feeble", "incompetent", "muzzy", "discontented","troubled" and "withdrawn"). It is clear that in some items (e.g. "alert-drowsy", "strong-feeble", "incompetent-proficient", '*mentally-slow-quick-witted", and "muzzy-clear-minded") there is a tendency for Δ^9-THC and CBD to effect opposite feelings. The changes in feeling caused by the two cannabinoids in the item "muzzy-clear-minded" were significantly different from placebo. With the mixture of the two cannabinoids the changes were not significant in any of the items.

During the first hour only the results with Δ^9-THC differed significantly in some items (e.g., "discontented". "feeble". "clumsy". "incompetent" and "muzzy").

As we have carried out multiple testing against placebo after Friedman's analysis, the possibility exists of an inflation of the significance levels.

Scale of Self-Evaluation for Bodily Symptoms. Friedman's analysis of variance revealed no significant difference between the treatments for any of the items in the scale of bodily symptoms.

Discussion

A summary of the effects produced by the different treatments (Table 2) illustrates, in descriptive form. the principle changes which the volunteers showed in the present experi-

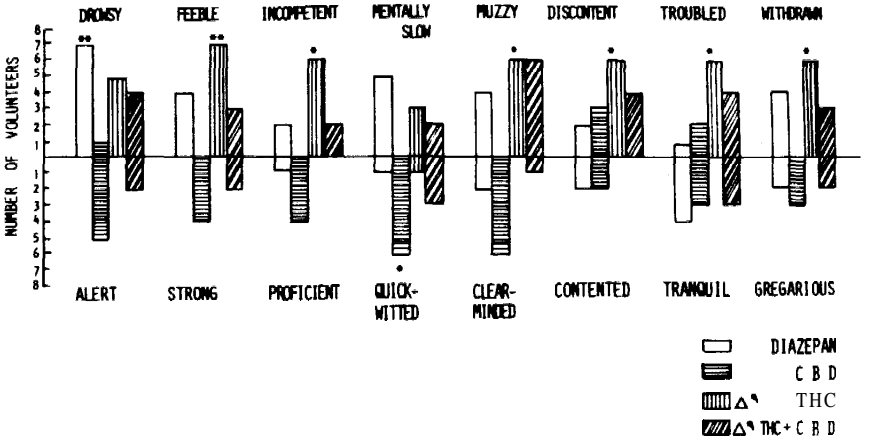

Fig. 1
Comparison of the effects, in eight normal volunteers, of the various treatments with placebo. 2 h after ingestion of the drugs. The columns represent the number of volunteers whose changes from the pre-drug value, when compared with the changes observed with placebo, alter as shown using the four shades. The asterisks indicate treatments which the Wilcoxon test demonstrated to differ significantly from the placebo [$P < 0.05$ (*), $P < 0.02$ (**)]

ment. This summary suggests that the experimental situation might have favoured the occurrence of sleep in the volunteers, considering the high frequency with which this occurred in the sessions with placebo. Furthermore Δ^9-THC produced a series of changes not unlike the clinical syndrome described previously by Hollister et al. (1968) for this cannabinoid. These effects are markedly reduced with the simultaneous administration of CBD, which agrees with the previous verifications of Karniol et al. (1974) and Dalton et al. (1976), but differs from the observation of Hollister and Gillespie (1975).

The quantitative study of these changes was made possible by the use of scales of self-evaluation. The numerical results of ST.41 A-state and ARCI-Ma correlated significantly with the marks allocated by the two independent observers for anxiety and the typical effects of C. sativa, respectively, suggesting that the volunteers were able to evaluate themselves accurately while under the effect of the drugs.

The analysis of the results for anxiety showed that no changes occurred during the sessions with placebo, suggesting that the experimental conditions were neutral for anxiety (Table 3). Perhaps for this reason. it had not been possible to detect a probable anxiolytic effect of CBD alone.

Diazepam, the drug standard for anxiety analysis, paradoxically provoked a small and significant increase in the levels of anxiety (Table 3). Anxiety caused by some side-effects, such as dizziness, in the volunteers who showed some degree of anxiety with diazepam perhaps accounts for this paradoxical effect.

The results also confirm that after ingestion of Δ^9-THC the volunteers experienced a large increase in the level of anxiety, which agrees with various previous descriptive reports (Karniol et al. 1974; Malit et al. 1975: Tassinari et al. 1976) and supports the suggestion of a possibly anxiogenic effect of this cannabinoid, This Δ^9-THC effect was particularly antagonized when CBD was administered simultaneously, confirming the observation made by Karniol et al. (1974).

The antagonism of effects between the two cannabinoids is not restricted to anxiety. The subjective changes provoked by Δ^9-THC detected by ARCI-Ma and the analogue self-rating scale for subjective feelings also diminished with the simultaneous administration of CBD, suggesting an antagonism not selective to the subjective effects of Δ^9-THC.

However, not all the effects of Δ^9-THC were antagonized by CBD. Contrary to what occurred with the subjective changes. the tachycardia obtained with Δ^9-THC was not significantly blocked by CBD (Table3).

These results can be understood if one considers that these two types of effect would probably be mediated by different mechanisms (Agurell et al. 1976: Galanter et al. 1972; Martz et al. 1972). With this in mind, it does not seem feasible that the antagonism observed on the scales of self-evaluation might be attributed to a general block of Δ^9-THC effects.

Of the various mechanisms that might be involved in this antagonism, one ought to consider the possibility that it results from a combination of independent and opposing effects of the two cannabinoids. Although CBD has no psychotomimetic effects on man (Dalton et al. 1976; Hollister 1973: Karniol et al. 1974; Perez-Reyes et al. 1973), it has been demonstrated to be pharmacologically active in both laboratory animals (Carlini et al. 1973; Davis and Borgen 1974; Karniol and Carlini 1973; Monti et al. 1977) and in man (Carlini et al. 1979; Cunha 1979). In the present experiment it was possible to detect subjective changes provoked by CBD alone using the analogue self-rating scale for subjective feelings ("quick witted" and "clear-minded" – Fig. 1). In one of the items on the scale ("muzzy-clear-minded") CBD caused significant changes, to the same extent as did 4 ^{9}-THC but with opposite feelings, and when administered simultaneously there was no detectable effect. Various other items also show this tendency (Fig. 1), suggesting that the combination of independent and opposing effects of the two cannabinoids might contribute to the observed antagonism.

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