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CANNABIDIOL INTERFERES WITH THE EFFECTS OF Δ^9-TETRAHYDROCANNABINOL IN MAN

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Based on previous observations that cannabidiol (CBD) blocks some effects of Δ^9-tetrahydrocannabinol (Δ^9-THC) in laboratory animals, the present work was carried out to study possible interaction between CBD and Δ^9-THC in human beings. In a double blind procedure, 40 healthy male volunteers were assigned to 1 of 8 experimental groups, receiving per oral route, placebo, 30 mg Δ^9-THC, 15, 30 or 60 mg of CBD, and mixtures of 30 mg of Δ^9-THC plus either 15, 30 or 60 mg of CBD respectively. Pulse rate, time production tasks and psychological reactions were measured at several time intervals after drug ingestion. 30 mg Δ^9-THC alone increased pulse rate, disturbed time tasks and induced strong psychological reactions in the subjects. 15–60 mg of CBD alone provoked no effects. On the other hand, CBD was efficient in blocking most of the effects of Δ^9-THC when both drugs were given together. CBD also decreased the anxiety component of Δ^9-THC effects, in such a way that the subjects reported more pleasurable effects.

Δ^9-Tetrahydrocannabinol | Cannabidiol | Pulse rate | Time measurement
Pharmacological interaction | Marihuana | Mood
Cannabis sativa

1. Introduction

(–)-Δ^9-trans-tetrahydrocannabinol (Δ^9-THC) has been considered as the main active principle of *Cannabis sativa* and the pharmacological potency of the plant is usually attributed to its content of Δ^9-THC (Weil et al., 1968; Hollister, 1971). Several recent reports, however, state that in laboratory animals (Karniol and Carlini, 1972; Poddar and Ghosh, 1972; Carlini et al., 1974; Borgen et al., 1973) as well as in man (Galanter et al., 1973; Carlini et al., 1974) Δ^9-THC acts differently according whether it is administered pure or *in natura,* that is mixed with the other natural constituents of the plant. Galanter et al. (1973) suggested that pyrolysis of Δ^9-THC could be different in each situation. Studies carried out in our laboratory (Carlini et al., 1970; Karniol and Carlini, 1972) revealed that the activity in animals of several samples of marihuana differed widely, a fact which could not be attributed only to the different Δ^9-THC contents of the samples. It was then hypothesized that other cannabinoid compounds, among them cannabidiol (CBD) and/or cannabinol (CBN), could be interfering with Δ^9-THC effects on the animals. The hypothesis was further s rengthened by the observation that also in man the effects of several samples of *Cannabis sativa* were not only related to their Δ^9-THC content (Karniol and Carlini, 1972; Carlini et al., 1974). To test this hypothesis, experiments carried out with laboratory animals revealed that CBD was indeed able to block the excitatory effects of Δ^9-THC and to potentiate the depressant effects of Δ^9-THC (Karniol and Carlini, 1973b). As a consequence, both authors suggested that probably a mari-

huana sample containing a high percentage of CBD would induce less 'high' or psychotic-like effects on humans than would be expected from a consideration of its concentration of Δ^9-THC.

The present paper describes experiments undertaken to test this possibility. Under a double-blind procedure human volunteers received several dosages of either Δ^9-THC, CBD or mixtures of CBD *plus* Δ^9-THC.

2. Materials and methods

2.1. Drugs

(−)-Δ^9-trans-tetrahydrocannabinol, as an alcoholic solution kept in dark ampoules, was kindly provided by NIMH. Cannabidiol was purchased from Makor Chemicals Ltd., Israel.

2.2. Administration of the drugs

8 groups of 5 volunteers each received, respectively, placebo, 30 mg of Δ^9-THC, 15, 30 and 60 mg of CBD, and mixtures of 30 mg of Δ^9-THC *plus* either 15, 30 or 60 mg of CBD. The volunteers were told that they were participating in a marihuana experiment, but that they could be receiving a small or large dose or even placebo. The experimenter administering the drug was also 'blind' to the drug he was giving. The drugs were previously dissolved in 0.9 ml of ethanol and added to 200 ml of orange juice. As placebo 0.9 ml of ethanol in 200 ml of orange juice was used. The volunteers drank the selected dose at 9.00 am. They were previously instructed to refrain from alcoholic beverages for 24 hr before the experiment and to have only a slight breakfast (coffee, milk and one toast) on the experimental day. The oral route was preferred to avoid the possibility of eventual transformation of CBD into Δ^9-THC by heat due to smoking (Mikes and Waser, 1971).

2.3. Selection of subjects

After personal invitation, 50 male volunteers were submitted to physical examination, ECG and psychiatric interview, 2 to 6 days before the experimental day. 10 persons were refused due to past history of either allergy, cardiac disease or psychotic episodes. The 40 selected volunteers were 24 medical students and 16 medical doctors with ages and weights, varying from 21 to 34 years and from 50 to 91 kilograms. They were distributed into the several groups, balanced for age and weight. 22 of the volunteers referred to previous occasional use of marihuana.

2.4. Test procedure

The volunteers were received in an isolated laboratory and were told in detail how the experiment would be developed. They were then asked to be seated and to relax while pulse rate was measured 5 times at 1-min intervals. Following that the subjects were submitted to a time production task, that is they were asked to produce a 60-sec interval, 10 times. The 5 first estimations (Estimation T1) were without feedback and the following 5 with feedback (Estimation T2), the experimenter saying either 'correct', 'too short' or 'too long' immediately after each estimation. The subjects were then allowed 5 min to ingest the 200 ml of orange juice with the drugs. After ingestion, pulse rate measurements were performed at every 20-min intervals. 45, 95 and 180 min after ingestion (or 80, 125 and 215 min after beginning of experiment) the subjects were again submitted to the time tasks without feedback (Estimations T3, T5 and T7) and with feedback (Estimations T4, T6 and T8). The estimations, with and without feedback, were intercalated (T3, T4, T5, etc.) and in each one of them the subjects were asked to produce the 1-min interval 5 times. Finally, at 55, 95, 155 and 185 min after ingestion, the experimenter interviewed the subjects asking questions about and recording their feelings and sensations. The psychological effects of drug action were graded from 0 to 4, according to a scale of subjective symptoms previously described (Karniol and Carlini, 1973a; Carlini et al., 1974).

3. Results

3.1. Pulse rate

The results are summarized in table 1. All 5 subjects under 30 mg Δ^9-THC alone showed an accentuated acceleration of pulse rate averaging 35% increase,

Table 1
Change in pulse rate of human beings after ingestion of placebo, 30 mg Δ^9-THC, 15, 30 and 60 mg CBD, and mixtures of 30 mg of Δ^9-THC plus either 15, 30 or 60 mg CBD.

Drug	Dose (mg)	Change in pulse rate (± SE) at several time intervals after drug ingestion[a]						
		30	50	70	90	110	150	170 min
Placebo	0.9 ml	96.6 ± 2.8	98.2 ± 3.7	92.4 ± 2.4	91.8 ± 3.9	88.8 ± 3.5	86.8 ± 2.7	87.0 ± 4.7
CBD	15	95.4 ± 3.0	97.2 ± 1.9	93.4 ± 3.2	94.6 ± 2.3	91.2 ± 1.0	91.0 ± 2.4	89.4 ± 3.0
CBD	30	98.4 ± 1.4	97.6 ± 2.3	97.0 ± 1.6	93.8 ± 0.8	89.2 ± 2.6	87.4 ± 1.0	84.6 ± 1.6
CBD	60	96.4 ± 3.3	96.6 ± 5.8	93.6 ± 4.8	90.8 ± 3.3	87.2 ± 4.4	86.8 ± 4.2	86.8 ± 4.8
Δ^9-THC	30	123.6 ± 7.6[b]	135.2 ± 8.7[b]	133.4 ± 5.5[b]	130.2 ± 8.2[b]	119.4 ± 6.8[b]	110.2 ± 4.4[b]	109.4 ± 3.6[b]
Δ^9-THC + CBD	30 + 15	132.8 ± 8.0[b]	153.2 ± 16.0[b]	155.0 ± 13.8[b]	142.6 ± 17.5[b]	131.8 ± 13.1[b]	117.4 ± 7.0[b]	121.0 ± 11.4[b]
Δ^9-THC + CBD	30 + 30	102.8 ± 5.2[c]	111.8 ± 5.8[c]	109.0 ± 7.2[c]	105.4 ± 6.2[c]	102.4 ± 6.6	103.6 ± 13.1	99.6 ± 10.0
Δ^9-THC + CBD	30 + 60	100.2 ± 4.1[c]	106.2 ± 4.4[c]	100.6 ± 4.0[c]	100.0 ± 4.2[c]	100.2 ± 4.5[c]	95.8 ± 3.6[c]	95.6 ± 2.8[c]

[a] The change was calculated considering the average of the 5 pre-drug as 100%, and comparing it with each post-drug value.
[b] Student's t-test ($p \leq 0.05$). Comparison made with placebo group.
[c] Student's t-test ($p \leq 0.05$). Comparison made with 30 mg Δ^9-THC group.

Table 2
Effects of placebo, 30 mg Δ^9-THC, 15, 30, 60 mg of CBD and mixtures of 30 mg of Δ^9-THC plus either 15, 30 or 60 mg of CBD on a time production task by human beings. Measures without (T_1, T_3, T_5, T_7) and with feedback (T_2, T_4, T_6, T_8).

Drug	Dose (mg)	Mean production[a] in seconds ± SE at several times after treatments							
		T_1[b]	T_2[b]	T_3	T_4	T_5	T_6	T_7	T_8
Placebo	0.9 ml			58.3 ± 1.0	59.6 ± 0.6	59.4 ± 0.7	59.6 ± 0.7	57.8 ± 1.4	59.9 ± 0.6
CBD	15			49.0 ± 1.8[c]	61.7 ± 1.4	54.0 ± 1.1[c]	62.0 ± 1.1	55.1 ± 1.5	62.4 ± 1.3
CBD	30			60.0 ± 1.5	60.5 ± 1.0	55.8 ± 1.8	59.4 ± 0.8	58.4 ± 2.1	60.5 ± 1.3
CBD	60			57.1 ± 1.2	59.8 ± 1.0	56.8 ± 0.8[c]	60.9 ± 0.7	62.4 ± 1.0[c]	60.6 ± 0.6
		58.3 ± 3.1	59.8 ± 2.1						
Δ^9-THC	30			33.6 ± 2.1[c]	40.2 ± 2.6[c]	39.6 ± 2.1[c]	49.2 ± 3.3[c]	39.9 ± 2.5[c]	51.0 ± 2.7[c]
Δ^9-THC + CBD	30 + 15			49.2 ± 3.0[cd]	57.9 ± 1.9[d]	54.4 ± 2.7[d]	62.7 ± 2.5[d]	55.7 ± 2.3[d]	63.2 ± 2.3[d]
Δ^9-THC + CBD	30 + 30			51.8 ± 2.1[cd]	56.6 ± 2.0[d]	50.9 ± 1.5[cd]	55.8 ± 1.8	45.8 ± 1.7[c]	56.7 ± 2.3
Δ^9-THC + CBD	30 + 60			50.0 ± 1.4[cd]	58.4 ± 1.7[d]	54.7 ± 1.5[cd]	59.9 ± 2.2[d]	56.9 ± 2.4[d]	57.9 ± 1.2[d]

[a] The values below represent the average of 25 estimations performed under each drug treatment (5 estimations per each of the 5 subjects).
[b] T_1 and T_2 obtained before drug ingestion represent the entire population utilized (40 subjects).
[c] Comparison made with placebo group (p at least ≤ 0.05; Student's t-test).
[d] Comparison made with 30 mg Δ^9-THC group (p at least ≤ 0.05; Student's t-test).

as compared to the pre-drug levels, 50 min after drug administration. At this time, Δ^9-THC ingested together with 15 mg of CBD increased pulse rate by 53%. However, 30 and 60 mg of CBD reduced the acceleration of pulse rate induced by Δ^9-THC. For example, the volunteers under 30 mg of Δ^9-THC *plus* 60 mg of CBD averaged at most 6.2% increase of pulse rate, which contrasts with the result obtained with Δ^9-THC alone. On the other hand, the doses of CBD alone did not significantly change pulse rate. Finally, table 1 shows that the peak affect of Δ^9-THC on pulse rate occurred at about 50–70 min after drug ingestion.

3.2. Time production task

30 mg of Δ^9-THC markedly affected time production of the subjects, when compared with the placebo group, at times T3, T5 and T7 (without feedback), respectively, 45, 95 and 180 min after ingestion (table 2). Thus, the average productions in these 3 occasions were below 40 sec. At estimations with feedback (T4, T6 and T8) the underproduction induced by Δ^9-THC was also clear although not as dramatic as in the measures without feedback (table 2). 15–60 mg of CBD were practically without effect; only in 4 of the 18 measurements were there significant effects.

On the other hand, CBD blocked the effects of Δ^9-THC. Thus, even 15 mg of CBD significantly reduced the underproduction induced by Δ^9-THC. The larger doses of CBD were also efficient in blocking the effects of Δ^9-THC. It is also interesting that in the measures without feedback (T3, T5 and T7) the deviations produced by the subjects receiving the mixtures of drugs were larger than those found with feedback (measures T4, T6 and T8). Actually, in none of the latter measures were there statistically significant differences from the placebo group.

3.3. Psychological effects

Table 3 shows the psychological reactions reported by the subjects. Ingestion of placebo or of the several doses of CBD did not provoke effects except in 2 subjects (1 with 15 and the other with 30 mg of CBD) who reported discrete changes that were recorded as grade 1. 30 mg of Δ^9-THC provoked strong reactions, and in 4 of the 5 subjects they were scored as the maximum grade 4. These effects usually started 30–50 min after ingestion and reached a peak 30 to 60 min later, gradually subsiding within the next 2 to 3 hr. In general the symptoms appeared in 'waves' during which the subjects reported strong feelings of anxiety reaching sometimes a near panic state. During the interval between 'waves' the subjects were less anxious.

When CBD was given together with Δ^9-THC the latter drug induced weaker effects; even 15 mg of the former drug was able to considerably mitigate the

Table 3
Distribution of subjects in a scale of psychological reactions according to the effects produced by 30 mg Δ^9-THC, 15, 30 and 60 mg of CBD and mixtures of 30 mg Δ^9-THC plus either 15, 30 or 60 mg of CBD.

Drug	Dose	Number of subjects with psychological reactions graded as					Median
		0	1	2	3	4	
Placebo	0.9 ml	5	0	0	0	0	0
CBD	15	4	1	0	0	0	0
CBD	30	4	1	0	0	0	0
CBD	60	5	0	0	0	0	0
Δ^9-THC	30	0	0	1	0	4	4[a]
Δ^9-THC + CBD	30 + 15	0	0	3	0	2	2[a]
Δ^9-THC + CBD	30 + 30	0	3	1	0	1	1[ab]
Δ^9-THC + CBD	30 + 60	0	2	3	0	0	2[ab]

[a] and [b] Comparisons made, respectively, with placebo and 30 mg Δ^9-THC groups. Mann–Whithney U-test (p at least ≤ 0.05).

psychological reactions induced by 30 mg of Δ^9-THC. Furthermore, when 60 mg of CBD was given mixed with the 30 mg dose of Δ^9-THC, none of the subjects presented reaction classified as grade 4. The interference of CBD on the effects of Δ^9-THC was not restricted in altering quantitatively the intensity of the psychological reactions. CBD also changed the symptoms, in such a way that the subjects receiving the mixtures showed less anxiety and panic but reported more pleasurable effects.

4. Discussion

The effects observed in our subjects after a 30-mg dose of Δ^9-THC have been described before. Thus, Isbell et al. (1967), Tinklenberg et al. (1972), Hosko et al. (1973) and Karniol and Carlini (1973a) have also reported pulse rate increase, impaired production of a time interval, and psychological effects induced by Δ^9-THC. On the other hand, 15–60 mg of CBD was without any noticeable effects, confirming previous results that CBD even when given chronically at a daily dose of 10 mg for 21 days is inactive (Mincis et al., 1973).

The effects of Δ^9-THC on time production deserve further attention.

Recently, Tinklenberg et al. (1972) reported a significant underproduction of time intervals by subjects receiving marihuana but not after alcohol. They explained this as an acceleration of the 'internal clock', due to an increase of mental events per unit of geophysical time caused by marihuana, so that 'inner time' is fast compared to geophysical time. On the other hand, table 2 shows that at production tasks without feedback (T3, T5 and T7) the errors were larger than at estimations with help (T4, T6 and T8). This observation had been previously reported by Carlini et al. (1974) when comparing the effects of marihuana samples on only 2 time productions (corresponding to the present productions T3 and T4). These authors interpreted this either as an interference of the experimenter (giving feedback) on the subjective effects of the drugs or as a very short activity of Δ^9-THC on the time production abilities of the subjects. Our present results favor the former interpretation, since in 6 more time tasks the subjects made larger underproductions at those without feedback, regardless of the time elapsing since drug ingestion. It seems that when the drugged subjects are left indisturbed (without feedback), the drug effects may manifest themselves more freely; and, as a consequence, the rapid flow of ideas could more readily impair concentration. It is possible therefore, that the experimenter can limit the psychological manifestation of Δ^9-THC, and when drugged subjects are administered batteries of tests and other procedures, the total manifestations of a 'high' may not be seen.

The major finding of the present work is the clear interaction observed between CBD and Δ^9-THC. 15 to 60 mg of CBD were able to attenuate several effects of Δ^9-THC, such as pulse rate acceleration (table 1), time production impairment (table 2) and psychological disturbances (table 3). These data corroborate previous findings with laboratory animals which have shown that CBD blocks some effects of Δ^9-THC (Karniol and Carlini, 1973b), and add further support to the suggestion that data obtained with inferior mammals may be of importance to understand or even to predict the effects of cannabinoid compounds on human beings (Carlini et al., 1972, 1974; Karniol and Carlini, 1973a). The mechanisms by which GBD counteracts the effects of Δ^9-THC on humans is not known at present. However, Karniol and Carlini (1973b) recently discussed several possibilities when reporting on the pharmacological interaction between the 2 compounds in laboratory animals.

The observed blockade of Δ^9-THC effects by CBD further suggests that if only the Δ^9-THC content of marihuana plants or their extracts is taken into consideration, experiments performed with these materials may lead to erroneous conclusions. Since CBD content varies widely according to the origin of the plant used (Doorenbos et al., 1971), it is possible that the discrepancies in potency commonly found by the authors are due to the CBD content, despite previous calibration of the Δ^9-THC amounts delivered to the subjects. In this respect Doorenbos et al. (1971) and Fetterman et al. (1971) state that marihuana cultivated as intoxicant has low CBD content and high Δ^9-THC, whereas plant cultivated for fiber production yields little Δ^9-THC and more CBD. Another interesting point is that CBD not only decreased but also changed the type of psychological reactions induced by Δ^9-THC. 4 of the 5 volunteers receiving Δ^9-THC alone were very anxious concerning the ef-

fects they were feeling. CBD, in all doses used, was able to partially block this anxiety component of Δ^9-THC action, leaving the subjects less tense and enjoying the experiment more. Therefore, it is possible that CBD could also qualitatively modulate the effects of Δ^9-THC in such a way that, depending upon the relative content of both compounds, in a marihuana sample, 'bad' or 'good' trips would be experienced by the users.

The interaction between CBD and Δ^9-THC, may be an indication that other cannabinoids, among the many compounds present in the plant (Mechoulam, 1970), may also interfere with Δ^9-THC effects. In this respect, cannabinol has been recently suggested as a candidate for this role (Krantz et al., 1971; Karniol and Carlini, 1972).

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