Effects of orally administered delta-9-tetrahydrocannabinol in man

The effects of Δ^9-tetrahydrocannabinol (Δ^9-THC) administered orally at 2 dose levels were studied in a group of 7 healthy young adult males. Each subject was studied for 7 nights (2 drug, 5 placebo). Vital signs, subjective feelings, deep tendon reflexes, electrocardiogram, electroencephalogram, visual evoked responses, postural responses, time estimation and reaction time and sleep patterns were studied. At the doses studied, Δ^9-THC increased pulse rate, altered subjective feelings, and caused hyperreflexia and upset postural responses in the absence of visual cues. Some subjects also exhibited lowered oral temperature, changes in averaged visual evoked response, and alteration of sleep patterns.

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Delta-9-tetrahydrocannabinol (Δ^9-THC) (also known as delta-1-tetrahydrocannabinol) is generally considered to be the most potent psychoactive component of marihuana.[15] Isbell and associates[11] compared THC to marihuana and found little or no difference in the spectrum of effects. There have been a number of recent studies aimed at elucidating the effect of THC on specific aspects of behavior or on specific physiological parameters. In this study, we have attempted to determine the effect of THC on a number of behavorial and physiologic parameters in the same individuals under closely controlled conditions. We used this approach in order to obtain a broad overview of the effect of THC. Previous studies have been directed at a number of the parameters that we studied. Our findings are in agreement with a number of the previously reported studies, but we also report new observations on the effects of THC.

Materials and methods

Subjects. The study was conducted on seven healthy young male volunteers 24 to 28 years of age. Four were medical students (Subjects 1, 2, 3, and 6), two were laboratory technicians (Subjects 5 and 7), and one was a layman (Subject 4). One subject was a heavy user of marihuana (7, three times per week), three were regular users (1, 2, and 3, once a week), one (5) had smoked marihuana three times in a 3 year period, and two (4 and 6) had never knowingly used marihuana. All

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claimed to have abstained from the use of marihuana for at least 2 weeks preceding the study. The subjects understood and consented to the purpose and mechanics of the study. All claimed that the primary motivating factor for their participation was monetary. Each subject was given a complete physical examination and laboratory tests including urinalysis, complete blood count, and SMA-12. The electrocardiogram (ECG), electroencephalogram (EEG), and visual evoked response (VER) were also recorded.

The first subject was studied alone and the other 6 in groups of 2. The 7 experimental sessions for each group were spread over a 2-week period: 4 consecutive nights during the first week, 2 nights free over the weekend, followed by 3 consecutive nights in the second week. On the third or fourth night of the sequence, each subject received 200 μg per kilogram THC orally.* On the sixth or seventh night he received 300 μg per kilogram orally (Subject 1 received 400 μg per kilogram as the second dose). The experimental design was single blind. On every night of the study every subject received 1 oz. of flavored corn oil (Lipomul). On treatment nights, the appropriate dose of THC in alcoholic solution was suspended in the flavored corn oil emulsion. The study began at 6 P.M., subjects having fasted from 1 P.M. After changing to scrub suits an electrode harness was fixed to the subject. A subjective feeling checklist patterned after that of Jarvik, Abramson, and Hirsch[12] was filled out. Base line values were then established for vital signs, deep tendon reflexes, equilibrium, reaction time and time estimation, EEG, and VER. The test sequence was repeated at 1 hour intervals after the subject took 1 oz. of Lipomul vehicle or vehicle plus drug. At 11 P.M. the subjects went to sleep. During sleep, eye movements, muscle tone, and EEG were continuously monitored. The test sequence was repeated after the subjects awoke in the morning.

Reaction time–time estimation. This test consisted of a series of 9 tone stimuli followed by 9 light stimuli of approximately 1, 3, or 5 seconds duration presented in a random sequence with 3 stimuli of each time interval for each of the 2 sensory modalities. At the termination of a given stimulus the subject depressed a switch. The interval between termination of the stimulus and switch depression provided a measure of reaction time. The subject kept the switch depressed for a period he estimated to be equal to that of the auditory or visual stimulus. This was a measure of his ability to estimate stimulus duration.

Ataxia and equilibrium. Ataxia and equilibrium impairment were evaluated by means of a modified Romberg (standing on 1 foot, arms at the side) and a simple heel-to-toe walk. Both tasks were performed with eyes open and closed. Responses were recorded on S-8 mm movie film on control and drug nights.

Electroencephalography. Gold-plated silver disc electrodes were fixed to the scalp with collodion. Orientation of the scalp leads was according to the 10-20 International Electrode System.[13] A base line EEG record was obtained at the beginning of every session. During base line recording preceding the initial session, each subject underwent provocative hyperventilation to exacerbate any latent EEG abnormality. All subjects were normal.

Visual evoked response. The VER was elicited by a strobe light fired at 1 Hz, positioned approximately 1 M from the subject's eyes. The subject was instructed to keep his eyes closed during the sampling period. The response was recorded on F.M. tape from a point 3 cm above the inion (Pz) referred to the right ear. From the tape, 128 responses were averaged using a Fabri-Tek 1010 digital signal averager. Analysis time was 500 msec.

Sleep patterns. The sleep records were obtained using the convention established by Rechtschaffen and Kales.[19] After collect-

*Ampules obtained from NIMH SSC Lot 6617 were labeled 95% Δ^9-THC; we subsequently learned that the lot contained 85% Δ^9-THC.

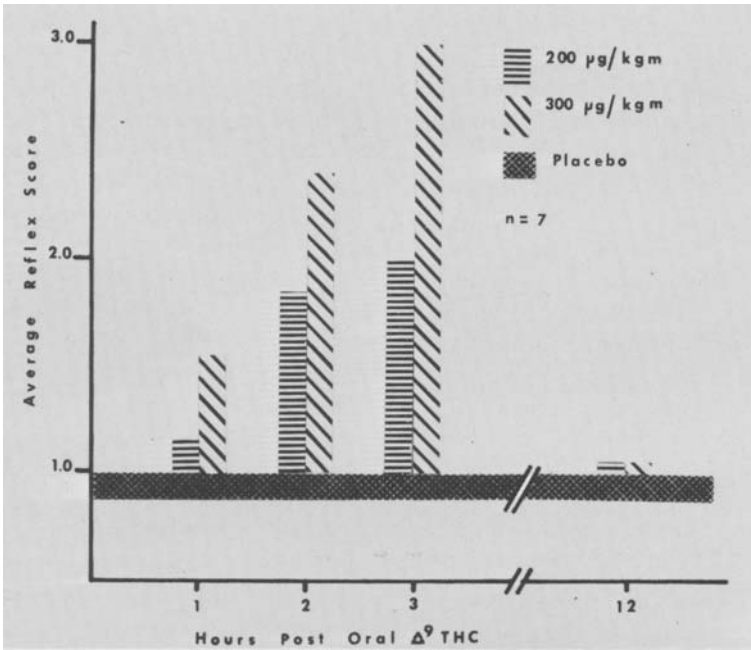

Fig. 1. Effect of oral Δ^9-THC on deep tendon reflexes. Hyperreflexia was arbitrarily scored from 1 to 3 with 3 representing marked augmentation. The averaged scores of all 7 subjects are plotted.

ing sleep records for the entire study, the records were coded and randomized. Every record was then scored in 10 second epochs by 2 investigators. After all records had been scored blind and tabulated, the code was broken to identify the record with regard to subject and session.

Results

Subjective feelings. Subjective feelings, both physical and perceptual-cognitive, were recorded periodically. Most subjects described the effects as neutral or pleasant. Two subjects reported unpleasant or fearful episodes for at least a short period of time after the 300 µg per kilogram dose. Comments such as: "I can't control my laughing," "A human being can't realize what I'm experiencing," "I understand hippies better now," "I have a lot of visual imagery," were also volunteered by the subjects. One striking behavioral effect in 5 of the 7 subjects was inappropriate "uncontrollable" laughter. All subjects displayed grinning ("shark smiles") when there was no apparent reason to do so.

Vital signs. Six of the 7 subjects had increases in pulse rate following the 300 µg per kilogram oral dose of THC. In three subjects (2, 3, and 7) the increased pulse rate persisted for approximately 12 hours. Only one subject (1) had an appreciable pulse rate increase after 200 µg per kilogram.

The effect of THC on temperature was variable. There was no statistically significant alteration of oral temperature, although four subjects exhibited lowered oral temperature 2 to 3 hours after ingestion of 300 µg per kilogram THC (Subject 3, 97°, 4, 96°, 5, 96.5°, and 7, 96°). The ambient temperature in the clinical neuropharmacology laboratory ranged from 72° to 74° F. at all times.

No consistent alteration of respiratory rate or pupil size was noted. Conjunctival congestion was seen in all subjects following both doses of THC.

Deep tendon reflexes. Deep tendon reflexes were scored on an arbitrary scale by the consensus of two investigators. Responses were also recorded on S-8 mm

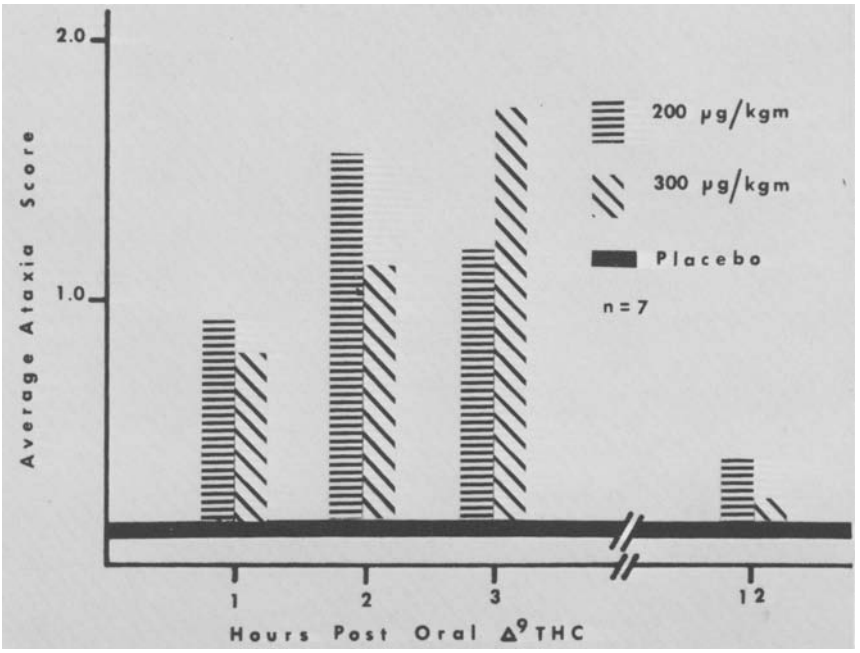

Fig. 2. Effect of oral Δ^9-THC on ataxia (no visual cues). Ataxia was arbitrarily scored from 0 to 2 with 2 representing marked effects. The averaged scores of all 7 subjects are plotted.

movie film, and the film was reviewed to confirm the scores. A number of deep tendon reflexes (brachioradialis, biceps, and triceps of the arm and patellar and Achilles of the leg) were elicited bilaterally. Both doses of THC (200 μg per kilogram and 300 μg per kilogram) produced hyperreflexia in every subject in our study. One subject (5) exhibited a well-sustained patellar clonus after the higher dose. It was our impression that the patellar response was the one most affected by THC. Fig. 1 illustrates the increase in average reflex scores. Note that the hyperreflexia returned to control levels within 12 hours after administration of THC. There was a statistically significant dose-response relationship between hyperreflexia and 0, 200, and 300 μg per kilogram of orally administered THC (Wilcoxon Signed Rank Test). The onset of action was between 0 and 1 hour, and the duration of action was more than 3 but less than 12 hours.

Ataxia-equilibrium impairment. Ataxia-equilibrium impairment was scored on an arbitrary scale using the method outlined for the reflex changes. The modified Romberg was performed first with the eyes open and immediately after with the eyes closed. The "heel-to-toe" walk was then done with and without visual cues.

Over the dose range studied, we could detect no effect on performance of either of these tests as long as the subject was allowed to keep his eyes open. When the eyes were closed, all 7 subjects exhibited some degree of disruption in both the Romberg and heel-to-toe tasks. After the higher THC dose, in the absence of visual cues, the ataxia and equilibrium impairment were marked. Average ataxia scores (no visual cues) over the 12 hour test periods are plotted in Fig. 2. Some residual ataxia persisted 12 hours after drug administraton. Doses of 200 or 300 μg per kilogram THC produced significant levels of ataxia, but it was not possible to distinguish between the ataxic effects of 200 or 300 μg per kilogram THC in the group as a whole. In a number of individual subjects, a clear dose-response relationship was observed.

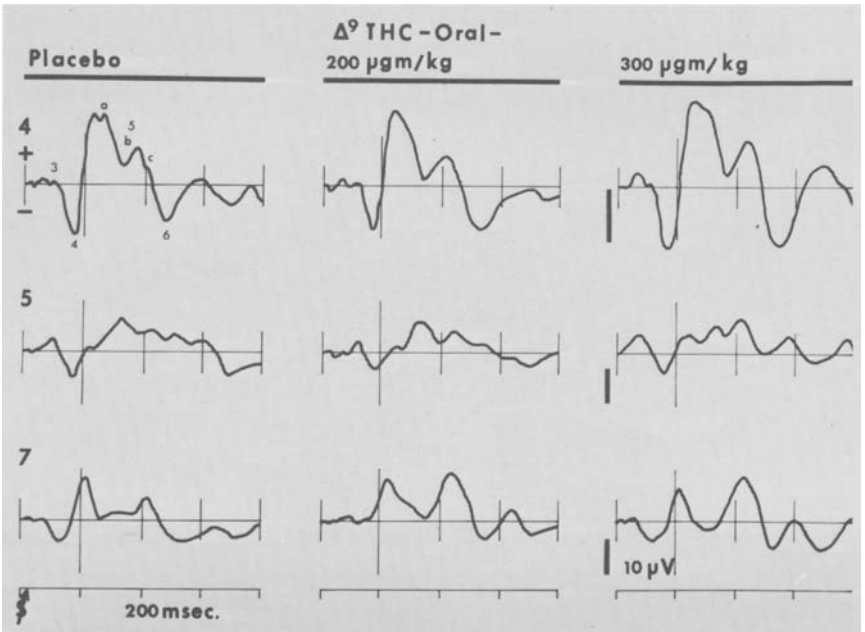

Fig. 3. Effect of oral Δ9-THC on the visual evoked responses at 2 dose levels. Responses recorded 3 to 4 hours after placebo and drug. Each potential represents the average of 128 responses. Flash rate was 1 Hz. Negativity is down. (Waveform designation after Gastaut, H., and Regis, H.[6])

Babinski and finger-to-nose tests were done on most subjects during the height of the drug response. No impairment was noted. No nystagmus was detected in any of the subjects after THC administration.

Reaction time–time estimation. We were unable to detect a significant alteration in ability to estimate the duration of a tone or light stimulus when the stimulus duration for either sensory modality ranged between 1 and 5 seconds. After the 300 μg per kilogram THC dose, 1 subject "forgot" to release the signal key after an auditory stimulus. No significant alteration of the average reaction time to either visual or auditory stimuli was detected.

EEG and VER. EEG and VER were recorded at 1 hour intervals after administration of either placebo or THC. The EEG was monitored during and following acquisition of the VER. The traces following termination of the VER stimulation sequence were used for comparison of control with THC patterns.

No changes were observed in symmetry or synchrony of the EEG. No abnormal waveforms or consistent shifts in dominant or secondary EEG frequency could be detected by visual examination of the records.

Subjects 4 and 7 exhibited changes in amplitude and latency of the VER that were more apparent after the 300 μg per kilogram dose (Fig. 3). There was an increase in the latency of the 5-b-c waves (convention of Gastaut and Regis[6]) in both. Subject 4 also displayed a 20% increase in the amplitude of the 3-4-5 complex. The VER of Subject 7 showed an increase in the amplitude of the late wave components. The other 5 subjects showed variable and minor shifts in the amplitude of the later VER wave components (e.g., Subject 5, Fig. 3).

Sleep patterns. Fig. 4 summarizes the effect of THC on sleep patterns. It is clear from these data that THC did not produce a consistent pattern of sleep alteration in the group as a whole. Individuals exhibited what appeared to be drug-related changes in sleep patterns. Subject 1 had reduced rapid eye movement (REM) on the nights

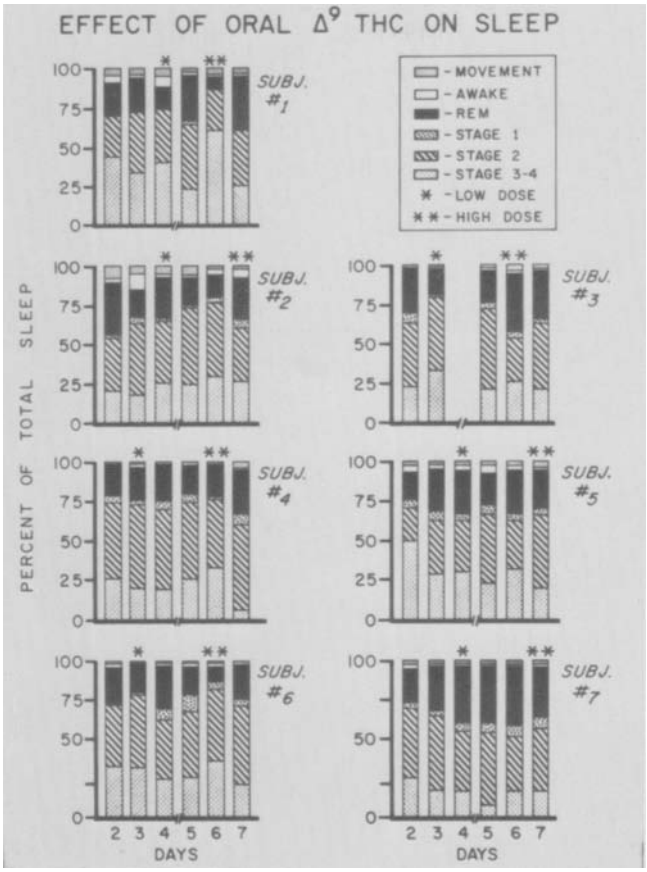

Fig. 4. Sleep patterns of all subjects. Low dose = 200 μg per kilogram; high dose = 300 μg/kg Δ^9-THC. All other bars represent placebo. Night 1 of the study (placebo) was not included in the graph.

he received THC. Subject 6 exhibited a similar REM reduction after the 300 μg per kilogram dose of THC. Both exhibited rebound increase in per cent of REM sleep on the night following drug-induced REM sleep loss. The same two subjects exhibited increased per cent of time spent in the deeper stages of sleep (stages 3-4) on the THC nights. This effect was greater after the high dose. Subject 4 showed an increase in per cent of REM sleep on the night following the high THC dose, suggesting the possibility of a REM rebound effect. In Subjects 2, 5, and 7, THC had no appreciable effect on REM sleep. Subject 3 had an increase in per cent of REM sleep after the high dose of THC.

We considered the possibility that there could be a shift in the distribution of sleep stages related to THC administration. To test this hypothesis, we analyzed REM and non-REM stage content during the first 2 hours and the first and second half of sleep. No drug-related changes were detected. In Fig. 4, the analysis of sleep records from night 1 of the study was not included in the tabulation since it was felt that sleep patterns on the initial night would be atypical due to the novelty of the experimental situation.[1]

Discussion

Within 30 to 90 minutes after ingestion of the 200 or 300 μg per kilogram dose of THC, every subject correctly reported that he had received "marihuana." The 2 subjects who had no previous marihuana experience reported feeling strange, different,

or otherwise indicated that they had received something in addition to the usual placebo. We had only one instance of a "false positive." Subject 7 reported that he "might have received the drug" approximately 25 minutes after placebo on night 3 of his run. Within 10 minutes of his initial report, he positively stated that he had not received marihuana.

The increased pulse rate we observed is in agreement with the findings of a number of other investigators.[9, 11, 20, 21] The fact that 3 of the 7 subjects had elevated pulse rates 12 hours after oral administration of 300 μg per kilogram indicates a long duration of action for orally administered THC. The pulse rate in all subjects was within the control range within 24 hours.

In animal studies, THC and related compounds produce a centrally mediated fall in blood pressure.[3, 7, 10] In the dose range we studied there were no significant alterations of systolic, diastolic, or mean blood pressure in the standing and supine positions.

Although THC at both dose levels did not produce significant depression of body temperature in the group as a whole, 4 of the 7 subjects had some depression of sublingual temperature. Hollister, Richards' and Gillespie's group[9] reported that temperature was not affected, while Isbell and associates[11] reported consistent depression of oral temperature after ingestion of THC.

Domino[4] has described slight hyperreflexia after marihuana smoking. Marked hyperreflexia in animals after DMHP, the dimethyl heptyl pyran derivative of THC, has also been reported.[5] The hyperreflexia we noted was distinct, and in 1 subject definite patellar clonus was elicited after 300 μg per kilogram. It should be noted that Hollister, Richards, and Gillespie[9] did not observe hyperreflexia after oral doses of THC up to 946 μg per kilogram.

A few investigators have noted some disruption of equilibrium and ataxia. The latter has been measured by instrumental techniques.[14] We were unable to detect any observable signs of equilibrium loss with a simple modified Romberg test and a heel-to-toe task. However, when visual cues were withheld, there was a decrement in the performance of every subject in both tests. In the absence of visual cues ataxia persisted at a significant level for more than 12 hours.

Our data on hyperreflexia and ataxia in the absence of visual cues suggests a specificity of action of THC for different functional systems. It was possible to demonstrate significant dose-response relationships for the effect of THC on deep tendon reflexes. Dose-response relationships could not be established for ataxia, but it was possible to differentiate between THC and placebo on the basis of ataxia. The duration of action in the two systems differed significantly.

Hollister,[8] Melges and associates,[16] Clark, Hughes, and Nakashima[2] and others have reported alteration in time sense. Our reaction time–time estimation test provided a highly objective measure of ability to estimate the duration of a stimulus immediately following the stimulus. The technique also provided a measure of reaction time. By using visual and auditory stimuli it became theoretically possible to determine whether THC would differentially affect the response to a stimulus to either sensory modality. We were unable to detect significant effect on time estimation or reaction time, although after the 300 μg per kilogram dose, there seemed to be a trend toward increased reaction time for the visual stimulus.

The very short stimulus duration (1 to 5 seconds) and the simplicity and immediacy of the response situation may account for the ability of the subjects to perform adequately after THC. A number of subjects commented that they were able to pull themselves together or "come down" when it was necessary to do so. It is interesting that they were able to "come down" for time estimation (a cognitive task) but were unable to do so

for the eyes closed Romberg or heel-to-toe tasks.

No consistent significant change in VER was observed in the group as a whole. In 2 subjects there was a shift in the latency of those elements occurring 200 or more milliseconds post stimulus. The same subjects also exhibited an increased peak-to-peak amplitude of the VER.

In a recent study Pivik and associates[18] described the effect of orally administered THC on human sleep patterns. In a very well-controlled study, they showed a small but statistically significant reduction in REM sleep in 4 young males who received 60 to 270 μg per kilogram of THC. REM sleep reduction occurred during the second half of the sleep period. In a previous study,[17] Pivik and his asociates demonstrated a trend (not statistically significant) toward REM sleep reduction. In our protocol, the subjects were not allowed to sleep during the first 4 hours after THC. This period coincides with the initial half of the sleep period of Pivik's protocol. Although we analyzed our sleep data in half-night segments, we did not detect a significant REM sleep shift for the group as a whole in either the first or second half of the sleep period. The first half of the sleep period in our protocol would coincide with the second half of the sleep period in the Pivik study (4 to 8 hours post THC). Pivik also demonstrated an increment in stage 4 sleep after THC. Two of the subjects in our series exhibited an increase in stage 3 to 4 sleep after THC. Following the high dose, 3 of the subjects also showed a reduction in waking time.

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