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The acute effects of tetrahydrocannabinol on auditory threshold and frequency resolution in human subjects

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Aims: The study was designed to investigate the acute effects of ingested tetrahydrocannabinol (THC) on auditory function. Methods: Eight male subjects (aged 22–30 years), who had previous experience of cannabis use, took part in this study. They performed air conduction pure tone audiometry in both ears over 0.5–8 kHz. A simple test of frequency selectivity by detecting a 4-kHz tone under two masking noise conditions was also carried out in one ear. Three test sessions at weekly intervals were carried out, at the start of which they ingested a capsule containing either placebo, or 7.5 or 15 mg of THC. These were administered in a randomized cross-over, double-blind manner. Auditory testing as described above was carried out 2 hours after ingestion. Blood samples were also obtained at this time point and assayed for Δ9- and 11-OH-THC levels. Results: No significant changes in threshold or frequency resolution were seen with the dosages employed in this study. Conclusions: This suggests that THC at the plasma levels attained in this study does not have a profound effect on the processing of elementary stimuli by the auditory pathway. *Human & Experimental Toxicology* (2002) **21**, 289–292.

Key words: frequency resolution; oral dosing; plasma levels; pure tone audiometry; tetrahydrocannabinol

Introduction

The use of cannabis as a 'recreational' drug is widespread.[1–3] Amongst the effects reported by users is an apparent increased sensory awareness, including auditory sensation.[1,2] Most studies investigating the effect of cannabis on various aspects of auditory function were carried out in the late 1960s and early 1970s.[4–10] The more detailed of these studies looked at the effects of cannabis on the higher cortical processing of auditory information.[4–6] In the acute studies, cannabis was smoked from cigarettes containing a known weight of Δ9-tetrahydrocannabinol (THC), with the amount taken up by the subject assumed to be proportional to the amount in the cigarette.

The study presented here was carried out as part of a larger, detailed investigation of the acute effects of ingested Δ9-THC on cardiovascular and psychological functions. Plasma levels of Δ9-THC, and its active metabolite 11-OH-THC, were measured. Within the present study, it was decided to use the detection thresholds to pure tone stimuli to provide a measure of the effects of THC on auditory perception. A simple measure of frequency selectivity was also chosen, which would provide an additional measure of the effects of THC on primary processing at the level of the peripheral auditory system.

Subjects and methods

The study was designed as a randomized, double-blind, cross-over trial, looking at the effects of Δ9-THC on cardiovascular function and on aspects of psychological performance. Eight subjects from the main study agreed to undergo testing of auditory function. All subjects were male, aged 22–30 years, and had been regular cannabis users for at least a year prior to the study. They abstained from its use for two weeks prior to the study (checked by urine testing). Subjects were under direct medical supervision at all times during the study. Ethical permission for the study was obtained from St. Mary's Hospital Local Research Ethics Committee. The nature of the study was explicitly discussed

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with volunteers and all gave their informed and written consent prior to taking part in it.

Before auditory testing, a hearing questionnaire was completed to identify any aspects of medical history that could contribute to a pre-existing auditory deficit. These included birth trauma; familial deafness; diseases implicated in hearing loss, e.g., meningitis; history of chronic middle ear disease or ear surgery; concurrent or previous use of other known ototoxic agents, e.g., aminoglycosides; and a significant history of noise exposure.[11] All eight subjects passed the screening. A prestudy audiogram was then performed to establish that their auditory thresholds were within normal, age-adjusted limits.[11] Power calculations based on the prestudy thresholds showed that changes in thresholds of 10 dB or greater would be detectable with a minimum of 80% power across the frequencies measured.

During the study, subjects were told not to use cannabis or other psychoactive agents that could confound the effect of the drug given in the study. All subjects were instructed to consume a low-fat breakfast on the mornings of the test days and were provided with a standardized low-fat lunch and snacks throughout the test days and had to refrain from drinking any caffeine or alcoholic beverages on these days. Cigarette smoking was also not allowed on test days. Subjects attended three experimental sessions at weekly intervals. At the start of each session, each subject was asked to swallow a capsule that contained placebo (0 mg of THC), 7.5 mg of THC (low dose) or 15 mg of THC (high dose).

In terms of neuropharmacological activity, the principal agents are considered to be the Δ9 isomer of THC, along with its metabolite, 11-OH-THC. They are also considered to be equivalent in terms of effect.[1,2] Ingestion of THC normally leads to peak levels of both Δ9- and 11-OH-THC about 2 hours later,[1,2,12] and audiometric testing was carried out at that time after ingestion. Plasma levels of Δ9- and 11-OH-THC were determined by HPLC.[13] Blood samples were taken 0, 1, 2, 4, 6, 8, 24 and 48 hours after ingestion, centrifuged, separated and the plasma stored at −20°C in silanized glass tubes until analysed.

Two hours after taking the capsule, pure tone audiometric testing was carried out at 0.5, 1, 2, 4 and 8 kHz, using a KD-29 audiometer (PC Werth, Clapham, UK). Pure tone stimuli were delivered over TDH 39P headphones fitted with audiocups. Threshold values measured as decibel hearing level (HL) at each frequency were obtained to within 5-dB resolution, according to a recognized protocol.[14] All test sessions were carried out at a similar time of day (i.e., 10 a.m.–12 p.m.) in a quiet, isolated room. Ambient noise level in the room was low, satisfying recommended criteria for carrying out air conduction audiometry.[15] The acoustic output of the audiometer was calibrated in accordance with the clinical standard BS 2497.[16] The calibration was rechecked at the end of the study.

Following pure tone audiometry (PTA), a simple measure of frequency resolution at 4 kHz was performed, using an adaptation of the psychophysical test developed by Stone *et al*.[17] Of the original eight subjects, five agreed to take part in this further audiometric test, which was carried out in the right ear at each test session.

Subjects were required to detect the presence of a 4-kHz pure tone in the presence of a 0.8-octave (3.2 kHz) band noise centred on 4 kHz. They were then required to detect the 4-kHz tone in 'notched noise', in which the masking noise included a 0.3-octave (1.2 kHz) notch centred about 4 kHz. The notch was flanked by 0.4-octave (1.6 kHz) noise bands. The overall level of masking noise under both conditions was about 70 dB SPL. The difference between the detection thresholds for the non-notched and notched noise was used as the measure of psychophysical frequency selectivity.

Data analysis

Student's t test was applied to the plasma levels of Δ9- and 11-OH-THC. Friedman's two-way ANOVA[18] was used for analysis of the threshold data, each frequency in both ears analysed independently. A significance level of $P < 0.05$ was adopted throughout.

Results

Plasma levels of Δ9- and 11-OH-THC

As Δ9- and 11-OH-THC are the principal psychoactive agents in or derived from THC,[1,2] their concentrations were summated prior to statistical analysis. At 2 hours after capsule ingestion, mean levels of the low and high dose were 6.92 ± 1.4 SE ($n=8$) and 15.25 ± 1.6 SE ($n=8$) ng/mL, respectively. These means were significantly different at $P < 0.001$. The placebo dose gave values below the detection limit (< 0.5 ng/mL) of the technique.

Effects on PTA thresholds

The median thresholds for both ears after placebo treatment over 0.5–8 kHz fell between 5 and 15 dB HL. There was no evidence of any significant change in median thresholds after the low- or high-dose treatments. The median thresholds (with ranges) at each frequency for each ear and treatment are summarized in Table 1. These thresholds were also

Table 1 Median decibel HL thresholds with ranges for treatments, frequency and ear

Treatment	*Frequency (kHz)*				
	0.5	*1*	*2*	*4*	*8*
Right ear: median threshold, dB HL (range)					
Placebo	10 (5–20)	10 (5–20)	15 (5–20)	12.5 (5–20)	7.5 (5–25)
Low dose	12.5 (5–15)	10 (5–20)	7.5 (5–20)	15 (5–25)	7.5 (5–15)
High dose	15 (5–20)	10 (5–15)	15 (5–20)	10 (5–20)	7.5 (5–30)
Left ear: median thresholds, dB HL (range)					
Placebo	15 (10–20)	7.5 (5–20)	5 (5–10)	12.5 (5–15)	5 (5–15)
Low dose	12.5 (5–25)	7.5 (5–15)	7.5 (5–15)	7.5 (5–20)	10 (5–15)
High dose	12.5 (5–20)	5 (5–15)	5 (5–15)	7.5 (5–15)	5 (5–30)

Friedman's two-way ANOVA returned S values between 0.1 and 2.47. For $n=8$ and 2 df, corresponding P values fell between 0.9 and 0.29.

directly comparable with the prestudy PTA threshold values.

Effects on 4-kHz masking thresholds

The median placebo threshold for the non-notched masking condition was 52 dB HL (range 49–57 dB). The difference between it and the 0.3-octave notched masking conditions was 25 dB (range 18–31 dB). No significant change in these values was seen after the low- or high-dose cannabinol treatment, or from the prestudy results.

Discussion

The findings from this study show that 2 hours after ingestion of the low- and high-dose cannabinol capsule, appreciable levels of Δ9- and 11-OH-THC were present in plasma. These levels were not found to be associated with any acute elevation in standard pure tone auditory threshold. The absence of any effect on standard pure tone auditory thresholds is consistent with the earlier reports of Spector and Liedgren *et al.*[8,9] However, the study by Spector was not concerned with acute effects of cannabis on hearing and did not involve smoking or ingestion of cannabis prior to performing audiometry. Instead, hearing thresholds were measured in a group of 65 subjects who had reported cannabis smoking habits, which were known to be highly variable.

The study by Liedgren *et al.* involved 30 subjects of whom 15 smoked a cigarette containing 8 mg of THC, and 15 smoked a placebo. Hearing was examined about 15–30 min after smoking the cigarette. Plasma levels of the active components in the study of Liedgren *et al.* may have been comparable to those observed here, although pyrolysis may have reduced the effective amount of THC entering the blood.[1]

The number of subjects in our study was relatively small, and limited the power of the study to reveal a threshold shift of 10 dB or more. The within-subject cross-over design of the study, however, did enable any effect of the two dose levels on hearing to be assessed in the same subjects. The results could then be directly compared with plasma THC concentrations, which had not been done in previous studies. From the present study, mean plasma levels up to 15 ng/mL (Δ9- and 11-OH-THC combined) were not found to be associated with any marked changes in auditory threshold.

The task of detecting a pure tone in the presence of a competing noise background represents a higher order of signal processing than detection of a single pure tone alone. The cochlea is considered to be the principal physiological processing site for this task.[19] Notwithstanding the small number of subjects investigated, the absence of any marked effect on frequency resolution suggests that cannabis seemed not to have directly affected this process, at least when present at plasma concentrations sufficient to have marked subjective and objective effects on psychological function.[1–3]

The apparent absence of effect at the level of the cochlea does not imply that the potential effects of cannabis on the cochlea or on higher auditory processing should not be further investigated. The cochlea is also responsible for the temporal resolution of auditory stimulus and the coding of its intensity.[20] The effect of cannabis on these processes should also be examined for any evidence of activity at the cochlea level. The results of earlier psychological studies showed that cannabis adversely affected responses to auditory signals requiring increased attention or vigilance.[4–7] An electrophysiological study by Roth *et al.* also found that there was a significant decrease in the late components (>100 ms) of the auditory-evoked response after smoking a cigarette containing 10 mg of Δ9-THC.[10]

Given the prevalence and likelihood of the continuing use of cannabis as a recreational drug, there are considerable grounds for a further comprehensive and systematic study both of the acute and chronic effects of cannabis on the auditory system. Effects may well be demonstrated, though it is likely that they would involve processing higher in the auditory pathway.

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