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Marijuana-Produced Changes in Pain Tolerance. Experienced and Non-Experienced Subjects[1]

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Abstract. The effect of marijuana and placebo on pain tolerance was compared in cannabis-experienced and naive subjects. A statistically significant increase in tolerance was observed after smoking marijuana. Although there was no statistically significant interaction between the drug effect and having had previous cannabis experience, there was a definite trend towards a greater increase in tolerance for the experienced (16 %) compared to the naive group (8 %).

This study is one in a series of ten experiments which were carried out by us in order to systematically study the effects of marijuana and a placebo on pain tolerance in both cannabis-experienced and naive subjects. The literature on cannabis effects on cutaneous pain is inconsistent. There have been reports that cannabis and THC increase, decrease and do not affect pain. Conflicting results like these are not uncommon in the pain literature as many physiological and psychological variables can affect pain, sensitivity and tolerance. Although it is important to study visceral pain experimentally, ethical considerations and present experimental techniques make it difficult to study more than cutaneous or surface pain. In this study we examined the effect of marijuana on pain toler-

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ance. In a previous experiment (4), we observed that marijuana, as compared to a placebo, produced no change in pain sensitivity in experienced or non-experienced subjects.

Materials and Methods

Subjects

Using a standardized smoke administration procedure, 16 volunteers experienced in the use of cannabis and 16 volunteer non-users each received 600 g of 1.3-percent Δ^9-THC marijuana and a placebo of THC-extracted marijuana double-blind on two different occasions, 7 days apart. Each group of 16 subjects contained eight males and eight females. One female subject from the experienced group failed to complete the experiment for personal reasons not related to the study. Prior to their participation, all subjects were examined by a physician and psychiatrist and judged physically fit and emotionally stable, received an explanation of what was involved, signed an informed consent form and were instructed to refrain from the use of alcohol for 24 h and all other drugs for 7 days prior to their participation in the two experimental sessions.

The two groups of subjects (experienced and non-experienced) were selected using a stratified random sampling technique matching as closely as possible on age and education from a pool of 1,500 volunteers. The match for education level was excellent and the match for age close. Both the mean and median age were greater for the non-experienced than for the experienced group (see table I). All subjects in the experienced group had been intoxicated previously by cannabis: their use during the past year ranged from two to 365 times. The mean use was 50.8 and median 12 times. No member of the non-experienced group reported ever having used cannabis or any other non-medical drug previously. Seven members of the experienced group reported previous experience with other non-medical drugs. The marijuana and placebo were administered double-blind to the subjects during two 24-hour visits, 1 week apart.

Drug Administration

In order to control precisely the amount of marijuana or placebo administered and to estimate accurately the amount of Δ^9-THC absorbed by the subjects, a smoking device was developed which consisted of: (1) a constant temperature burning chamber; (2) connected to a 4-liter smoke-collecting bottle which was (3) connected to a two-way anesthetic valve;

Table I. Subject profile

	Age	Education level (years)	Marijuana use during past year	Number of subjects having used other drugs non-medically
Experienced group (n = 15)	mean 28.5 median 27.5	mean 14.0 median 14.5	mean 50.8 median 12.0	7
Non-experienced group (n = 16)	mean 37.0 median 34.0	mean 14.7 median 14.5	0	0

(4) using forced air, the device delivered smoke to the mouth of the subject (5) who was instructed to breathe normally and not to hold the smoke. Calibration of our smoking device indicated that an average of 34 % (range 30–40 %) of the administered THC contained in the marijuana was retained by the subjects (for a description of the assay, see ref. 1). As an aid in maintaining the double-blind procedure, a different investigator administered the drug on each of the two occasions; the order of administration of the marijuana and placebo was randomly determined with one-half of the subjects receiving marijuana and one-half placebo on the first occasion.

Tests

In order to familiarize the subjects with the test procedure and to control for practice effects, two practice sessions, during which all the tests were given, were held on each occasion. The first session was 6 and the other 3 h prior to the pretest. The pretest was given 30–60 min prior to, and the post-test given beginning at, 15 min after smoking marijuana and placebo. The same test schedule, procedures and instructions, were followed, and given on all practice and test sessions. In addition to a test of pain tolerance, subjects also received tests of auditory fusion threshold and creativity. The fusion and creativity will be reported on in a future communication. Total test time for any subject at each test session was limited to 25 min in order not to fatigue the subjects and to try and test at a constant intoxication level; all subjects were tested individually and in private. The pain tolerance test always followed the measure of fusion threshold.

Pain tolerance was measured with a pressure algometer. This simple device consists of a thumb holder and a hydraulically driven rod, 0.5 cm in diameter. Tolerance to pain is determined by placing the thumb in the algometer with the thumbnail directly under the 0.5-cm diameter flat-headed metal rod; pressure is then automatically and continually increased from 0 kg at a rate of 1 kg/0.75 sec until the subject pushes a stop button or until a maximum of 7-kg pressure is being applied to the thumb. A pressure of 7 kg was found to be just below the point at which damage to vessels, tissues, and the nail could occur. Three trials were conducted on each thumb, alternating hands on each trial. Half the subjects began with their left and half with their right hand. Pressure, rather than a thermal or electrical stimulus was employed to produce pain as we found it easier to control produced pain without any apparent tissue damage and resulted in less within-subject variability in tolerance thresholds.

Just prior to beginning the test, the subject was seated in front of the algometer and read the following instructions: 'In this experiment, pressure will be applied to the tip of your thumb. At first, you will feel a slight sensation of pressure. The pressure will increase and remain on, causing your thumb to begin to hurt. The sensation of pain will continue to get greater. Finally, the pain will become so great that you can no longer tolerate it and want the pain to stop. When you can no longer stand or tolerate the pain and want it to stop, push the stop button downward. The experimenter will show you how to stop the pressure. Remember you are to push the stop button or release button when you can no longer stand the pain and want it to stop. Do not push the button when the pain first begins. This is not an endurance test. Are there any questions? Now, tell me what you are going to do.'

Three subjective measures of intoxication were also employed: first, on each smoking occasion, the drug administrator made an appraisal of whether the subject was intoxicated or not intoxicated. This was done using the criteria of conjunctival redness, memory lapse, ability to carry on a coherent conversation and changes in affective state; second, immediately following the performance tests, the primary affect scale (PAS) was administered to each subject. This scale contains five subscales measuring anger, arousal, depression, fear and

happiness and takes a total of 4 min to administer (3, 6); and finally, on the second occasion, after completion of all testing, the subjects were asked to identify *a posteriori* the substance they received on each occasion.

Results and Discussion

A separate three-factor (drug, experience and sex) analysis of covariance, with repeated measures on one factor (drug) and pre-score as a covariate was used to compare changes in pain tolerance for the preferred and for the non-preferred hand. The pre-score was used as a covariate to control statistically for individual differences. The results for the analysis carried out for the preferred hand revealed a statistically significant change in performance under the marijuana condition relative to the placebo condition ($p < 0.05$). There were no other significant effects. Inspection of the data revealed that this significant difference resulted from an increase in pain tolerance after smoking marijuana relative to placebo. While there was no significant interaction between drug and experience, further examination of the data show a trend toward a greater increase in tolerance (16 %) for the experienced than for the non-experienced subjects (8 %). There were no statistically significant changes with the non-preferred hand (see fig. 1).

The results on the primary affect scale (PAS) indicate that marijuana produces an increase in happiness in both the experienced and non-experienced groups. A separate three-factor (drug, experience, sex) analysis of variance, with repeated measure on one factor (drug) was performed for each of the five PAS

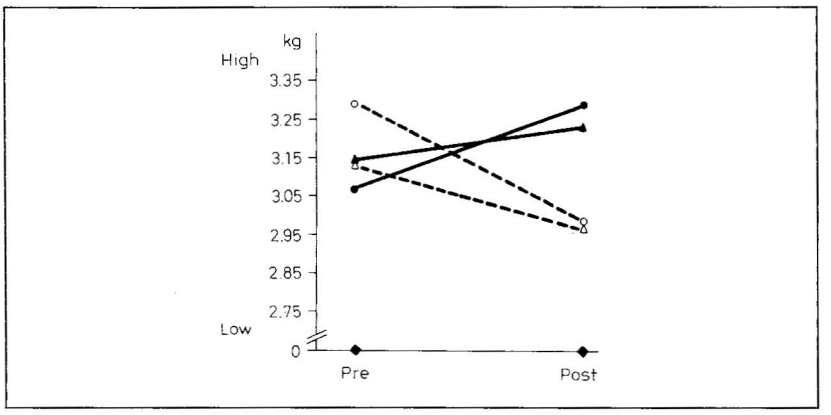

Fig. 1. Pre- and post-*pain tolerance* scores for both the experienced and non-experienced groups. ● = Experienced marijuana; ▲ = non-experienced marijuana; ○ = experienced placebo; △ = non-experienced placebo.

scales. The results of these analyses of variance show a significant difference between the change in happiness under marijuana as compared to placebo. Inspection of these data show this difference to be due to an increase in happiness under marijuana as compared to placebo. There were no significant differences between the experienced and non-experienced or male and female subjects. The interaction between sex and drug was also not significant. These analyses did not indicate any change on the other PAS scales. In addition to producing a change in the PAS happiness score, marijuana produced a clinically observed state of intoxication in 13 of 15 experienced and 11 of 16 non-experienced subjects. A χ^2 calculated to determine whether the degree of observed intoxication was related to having had previous experience with marijuana indicated that there was a significant relationship ($\chi^2 = 5$ $p < 0.05$).

The ability to make a correct *a posteriori* identification of the drug condition, also appears related to having had some previous cannabis experience. A Fisher exact probability test indicated that there was a significant relationship ($p < 0.02$) between making a correct *a posteriori* identification and having had previous cannabis experience (experienced group, 15 of 15 correct and non-experienced 11 of 15 correct). Separate one-tailed binomial tests were carried out for each group to determine whether the rate of correct identification was better than chance. These tests showed that the experienced group correctly identified the marijuana condition statistically significantly better than was possible by chance ($p < 0.01$). While the correct identification rate for the non-experienced group was not significantly better than chance there was a trend in this direction ($p < 0.1$).

The results of this study and our previous finding of no effect on pain sensitivity are contrary to the findings of *Hill et al.* (2) who reported increased sensitivity to and reduced tolerance for pain after smoking marijuana. In trying to account for these differences one notes that *Hill et al.* (2) estimate that 12 mg of THC was delivered to their subjects while we estimate that 7.5 mg was delivered in our study. Secondly, they employed an electrical stimulus while we employed pressure. We doubt that a larger dosage would produce an opposite effect although it is possible. On the other hand, it is not uncommon for different pain stimuli to produce different effects.

The observation of a greater effect in experienced than non-experienced subjects is consistent with previous findings. In a study on perceptual-motor coordination employing the same procedures as we used in this study, we observed impairments in coordination after smoking marijuana which were greater in experienced than in non-experienced subjects (5). *Weil et al.* (7) also found a difference, as they reported a greater increase in heart rate of users than non-users. This was replicated in a recent study by *Clark et al.* (1) in which they found not only a greater increase in heart rate but also a higher rate of rise in diastolic pressure in cannabis-experienced than in non-experienced subjects.

This tendency towards a greater effect in experienced than non-experienced subjects is also present in our clinical observations and in the subjects' ability to make an *a posteriori* identification of the drug condition. In a total of four experiments (1, 4, 5) (including this one) conducted under exactly the same conditions, we observed a relationship between previous cannabis experience and both clinical symptomatology and substance identification ability. In those cases where no significant interaction was observed, a trend towards greater intoxication in the experienced subjects was still observed. *Casswell and Marks* (8), in another controlled laboratory comparison of cannabis effects on experienced and naive subjects obtained reports on subjective state. These included ratings by the subjects on the strength of the cigarettes smoked, the extent of its effect and which if any of 14 symptoms or systems were affected. There was a significant drug and dose effect on all three measures but no significant interaction between drug effect and previous experience '... although there was a slight tendency in all three conditions for the experienced subjects to rate more variables as affected than naive subjects'. The results just discussed lead us to a conclusion that marijuana produces similar but more pronounced effects in experienced than in naive subjects the magnitude of which are dependent on the behavior being studied.

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