Marijuana smoking and reduced pressure in human eyes: drug action or epiphenomenon? MERTON C. FLOM, ANTHONY J. ADAMS, AND REESE T. JONES.

Normal pressure within the human eye was reduced after smoking a socially relevant dose of marijuana (12 mg. Δ9-tetrahydrocannabinol), but only for light to moderate users who experienced a substantial "high" and a state of peaceful relaxation from the experimental dose. Analysis suggests an indirect effect of the drug associated with relaxation—a psychophysiologic state that can be produced by drug and nondrug means.

Marijuana has been reported to reduce the pressure within the human eye. The normal intraocular pressure (IOP) of about 15 mm. Hg was found to drop after smoking 18 mg. of Δ9-tetrahydrocannabinol (Δ9-THC). This result apparently led to the experimental use of marijuana in a patient with glaucoma for whom the abnormally high IOP dropped from a presmoke level of 29 mm. Hg to 17 mm. Hg about 45 minutes after smoking; the treatment effect lasted more than 4 hours. Although the mechanism of the drug action in reducing IOP is not yet understood, there is interest in using marijuana for the treatment of glaucoma.

Our experiments on the influence of marijuana and other drugs on several vision functions included measurements of IOP. We found marked individual differences in the IOP changes after smoking marijuana. IOP decreased only in those subjects whose experience was limited to moderate use and for whom the experimental dose produced a substantial "high" and peaceful relaxation. These results have implications for the possible therapeutic use of marijuana, and suggest a nondrug mechanism in the control of elevated IOP.

Methods. Fifteen young male adults (18 to 30 years of age) experienced in smoking marijuana participated in the IOP phase of the study. Their experience ranged from smoking an average of one cigarette per month to an average of several per day. These paid volunteer subjects were instructed to take no drugs (including alcohol) for 24 hours before the experiment and to eat a light, low-fat breakfast on the day of the tests. Food and fluid intake during the experiments was controlled. The experiments were conducted double-blind with marijuana and marijuana placebo being given on alternate experimental days.
Table 1. Subjects are ranked according to their change from baseline intraocular pressure (IOP) 80 minutes after smoking 12 mg. of natural THC relative to the change from baseline IOP 80 minutes after smoking placebo. Also tabulated are the maximum per cent increase in pulse rate, the subject’s maximum assessment of his “high” on a 0 to 100 scale, and the subject's score on a 6-item scale pertaining to peaceful relaxation and tiredness extracted from a 272-item check list comprising the Subjective Drug Effects Questionnaire. The last column ranks the subjects according to previous experience in smoking marijuana, rank 1 being assigned to the heaviest use. Spearman rank correlation coefficients (r) are read across the bottom. For significance at the 0.05 level, r > 0.44; 0.01 level, r > 0.62. Thus, the correlation (+0.11) between IOP drop and the maximum pulse increment after smoking marijuana is statistically insignificant. However, IOP drop is significantly correlated with the other three variables (+0.57, +0.83, and -0.61) indicating that subjects who had the larger IOP decreases after smoking marijuana tended (1) to feel more “high,” (2) to experience more of six symptoms on the Subjective Drug Effects Questionnaire relating to peaceful relaxation and tiredness, and (3) to be less experienced in using marijuana.

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>IOP change (mm. Hg)</th>
<th>Maximum pulse increment (per cent)</th>
<th>Maximum high rating (0-100)</th>
<th>SDEQ score (0-6)</th>
<th>Marijuana experience (Rank)</th>
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Correlation coefficients:

- IOP: +0.11
- Pulse: +0.57
- High: +0.83
- SDEQ: -0.61

IOP measurements were obtained following instillation of one drop of 0.5 per cent ophthalmic solution of proparacaine hydrochloride onto the cornea. A Mackay-Marg tonometer was used for all IOP measurements and a Goldmann tonometer at some trials for comparison. After several trials to establish the presmoke IOP baseline, the subject smoked a 0.8 Cm. cigarette that contained either marijuana placebo material or natural marijuana plant material with 12 mg. THC, a socially relevant dose. The cigarette was smoked in the subject's usual style in about 10 minutes.

Results. The mean IOP before smoking marijuana was 14.6 mm. Hg (S.D. = 2.3); before smoking placebo it was 15.2 mm. Hg (S.D. = 2.6). The time courses of IOP for the marijuana and placebo treatments are shown for the group as a whole in Fig. 1. (The placebo curve was displaced downward to equate the mean presmoke IOP values.) It is seen that the average IOP dropped more after smoking marijuana than placebo. The greatest mean drop in IOP for the group occurred 80 minutes after marijuana (mean = 2.1 mm. Hg, S.D. = 2.0). For placebo it occurred 30 minutes after smoking (mean = 0.6 mm. Hg, S.D. = 2.1). What is important in this experiment is how much the subjects’ IOP changed after smoking marijuana compared to the change after smoking placebo. Analysis of the data was performed with the Walsh test, a nonparametric statistic designed for two related samples of small size (N = 4 to 15). With this test it was determined that the marijuana-induced IOP changes relative to the placebo-induced IOP changes were not significant at the 0.05 level at any of the measurement times except at 80 minutes postsmoke where the relative IOP decrease was significant at the 0.01 level. Thus, while the mean relative IOP drop 80 minutes after smoking marijuana was small, the chances...
that it could have occurred by chance are less than 1 in 100. At 80 minutes after smoking, when IOP for the marijuana treatment was at its minimum, the radial pulse rate for the group had declined to its presmoke level but the subjects' average "high" rating was still at about 70 per cent of its maximum (Fig 1).

Only 7 out of 15 subjects exhibited a clear decline in IOP after marijuana. These subjects appeared less anxious, more relaxed, and more sleepy during the experiment than the subjects who had little or no IOP drop. An item analysis was performed on the responses to a Subjective Drug Effects Questionnaire (SDEQ) given to each subject at the end of the day's trials. Subjects with greater-than-mean IOP drop after marijuana reported the following symptoms significantly more often (p = 0.03 by the Fisher exact probability test) than did subjects with less-than-mean pressure drop: thinking seemed fuzzier, eyes felt as if closed, arms or legs felt weaker, felt more at peace with the world, felt dozy, and thoughts moved slower. Other related symptoms checked more often by subjects with above-average IOP drop were: felt pleasantly tired and sleepy (p = 0.08) and felt sleepier (p = 0.12).

Correlational analysis was performed on post-marijuana IOP change and several relevant variables (Table 1). Two points deserve mention. First, IOP change is independent of pulse-rate increment, but it is positively related to the maximum "high" rating and to the score on the 6-item SDEQ scale pertaining to peaceful relaxation and tiredness. Second, amount of marijuana experience is inversely related to IOP drop and to both subjective measures (maximum "high" rating and the 6-item SDEQ score); marijuana experience is inversely related to pulse increase.

Blood plasma concentration of Δ9-THC has been reported by Galanter and co-workers to be highly correlated with increase in pulse rate. Dose of smoked marijuana has been found to be related to heart rate increase. Volavka and co-workers believe heart rate increase is so closely related to marijuana dose that it can be used as a bioassay of THC. To the extent that the reported relationship between blood THC and pulse rate holds in our sample, IOP drop would be independent of plasma THC concentration. In any case, IOP drop in our subjects is related more to the subjective effects of smoking marijuana than to the increase in pulse rate.

Tolerance to certain marijuana effects is indicated from our results (Table 1). Individuals who used marijuana the most tended to have little or no IOP drop (r = 0.61), and reported few drug-induced symptoms of peaceful relaxation and tiredness (r = 0.78). Subjects who used marijuana at least four times per week and stayed "stoned" all day on about half the smoking occasions (Table 1, subjects 007 and 015) exhibited little or no IOP drop; of nine subjects with less than this usage, seven exhibited a clear drop in IOP (Table 1, first seven subjects). Also, the "high" ratings of the more frequent users were lower than those for less experienced users (r = -0.61) which, however, may be attributed to a scaling factor since a rating of 100 is defined as the "highest" a subject has ever felt after smoking marijuana.

**Discussion.** The mechanism by which marijuana reduces IOP is not understood. Green and Pederson applied THC directly to the excised ciliary body of rabbit and found a pronounced decrease in fluid secretion and increase in ultrafiltration. Of these two changes, only the decreased secretion is consistent with the marijuana-induced IOP drop they observed in rabbit. For man, they emphasized that, "if, however, one accepts the view that ultrafiltration is the most important process in aqueous formation . . . then one must look elsewhere for a suitable explanation." Blood pressure changes are not likely to have produced the IOP decreases that occurred in our subjects after smoking marijuana cigarettes containing 12 mg. THC (1.5 per cent THC). Marijuana research has consistently shown no significant changes in blood pressure in man following intake of low to moderate doses (such as we used) and only a slight increase with doses of 2.9 per cent. Hollister has reported blood pressure reducing effects of THC only at doses so high as to produce severe mental effects in man. Our THC doses were far below these high levels, and probably produced no changes in blood pressure that could account for the IOP decreases.

In our study, the observed decrease in IOP in 7 out of 15 subjects could have resulted from a direct effect of marijuana on the ocular fluid dynamics. On the other hand, part of the marijuana-induced IOP drop may have been an epiphenomenon or secondary effect associated with the subjective state created by the drug. Indeed, we found that "high" rating and the 6-item SDEQ (relaxation) score were significantly correlated with IOP drop, and we conjectured from pulse-rate analysis that blood THC was probably not associated with the observed IOP decreases.

The idea that IOP can be reduced through changes in the psychophysiological state of the subject is supported by reports of IOP decline following exercise, by the successful treatment of primary glaucoma at health resorts that emphasize therapeutic exercise and mineral baths, and by the clinical observation that some glaucoma patients show substantially lowered IOP after a day of hospital bed rest with no change in therapeutic drug usage. Moreover, the IOP drop following ingestion of ethyl alcohol has a
longer duration (about 4 hours) than can be accounted for on the basis of rapid change in blood osmotic pressure or suppression of the antidiuretic hormone. Perhaps the relatively prolonged IOP decline is related to the sustained relaxing effect of alcohol. In pilot experiments with chlordiazepoxide hydrochloride (an anti-anxiety and muscle-relaxing drug with no known diuretic properties), we found that a 50 mg dose produced an IOP drop of about 5 mm Hg lasting about 3 hours in each of three normal subjects.

Social use of marijuana, particularly in relatively inexperienced users, may lead to unusually low IOP. Several of our subjects had post-marijuana IOP measurements as low as 7 or 8 mm Hg. Therapeutic use of marijuana for the treatment of glaucoma seems premature considering the present state of knowledge of the drug's action. Our results suggest an indirect effect of the drug associated with relaxation and tiredness—a psychophysiological state that can be produced by drug and nondrug means. However, heavy use of marijuana appears to prevent an IOP drop after smoking the drug. If IOP can be reduced by marijuana, alcohol, or chlordiazepoxide (drugs which tend to produce relaxation) as well as by nondrug means such as mild exercise, mineral baths, or hospital rest, then it seems legitimate to propose that the search for means of controlling or preventing high IOP should include the possible role of relaxation.

From the Smith-Kettlewell Institute of Visual Sciences, Pacific Medical Center, San Francisco, and the University of California (School of Optometry, Berkeley; School of Medicine, San Francisco). This study was supported in part by contracts (DADA17-75-C-2053 and DADA17-75-C-3106) from the United States Army Medical Research and Development Command to the Visual Sciences Division of the Optical Sciences Group, San Rafael, Calif., and by a grant from the National Institutes of Health (MH15842) to Dr. Jones. Submitted for publication May 21, 1974. Reprint requests: Dr. M. C. Flom, School of Optometry, University of California, Berkeley, Calif. 94720.

Key words: marijuana, intraocular pressure, relaxation, alcohol, tranquilizer, socially used drugs, tonometry, tetrahydrocannabinol, glaucoma, chlordiazepoxide hydrochloride.

REFERENCES


Histological observations in the normal monkey lateral geniculate nucleus.

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As a basis for studies of the histologic effect of visual deprivation, cell section areas were determined in all six laminae from the anterior, central, and posterior regions of both lateral geniculate nuclei (LCN) from a normal macaque monkey. No significant cell size variations existed between the right and left LCN's, between the contiguous parvocellular and magnocellular laminae of the same LCN, and between parvocellular sizes in various regions of the LCN's. In the magnocellular laminae, cell section areas increased in an anteroposterior direction.

The macaque lateral geniculate nucleus (LCN) is composed of six well-defined layers which contain neurons from crossed and uncrossed optic fibers from each eye. These layers are numbered from one to six in a ventrodorsal direction. Layers one and two contain large cells (magnocellular layers) and three to six small cells (parvocellular layers). Crossed fibers terminate in layers one, four, and six and uncrossed fibers in layers two, three, and five. Thus, ganglion cells from corresponding retinal elements are situated in contiguous layers except for the most anterior part of each LCN (monocular segment) which...