

## Acute Effects of Marihuana on Airway Dynamics in Spontaneous and Experimentally Induced Bronchial Asthma

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Although marihuana was used for the treatment of bronchial asthma in the past century (1), only recently has it been shown that smoking of marihuana or ingestion of its principal psychoactive ingredient,  $\Delta^9$ -tetrahydrocannabinol (THC), causes significant bronchodilatation in healthy young men (2,3). Whether similar effects could be elicited in subjects with bronchospastic disease was of interest because of the possibility that the irritant effect of marihuana smoke—which is probably responsible for the bronchitis attributed to heavy or chronic marihuana smoking (4,5)—might outweigh the bronchodilator properties of  $\Delta^9$ -THC and cause bronchospasm in patients with hyperreactive airways in contrast to the bronchodilatation observed in normal subjects. Therefore the acute effects of both smoked marihuana and oral  $\Delta^9$ -THC on plethysmographically determined airway resistance and specific airway conductance was investigated in a group of patients with clinically stable bronchial asthma. In addition, the effect of smoked marihuana on experimentally induced bronchospasm was evaluated.

### MATERIALS AND METHODS

Subjects included seven men and seven women, ages 19 to 74, with a diagnosis of bronchial asthma according to criteria established by the American Thoracic Society (6). Each subject had typical episodes of wheezing, cough, and dyspnea at least partially relieved by bronchodilator medication. At the time of study, all subjects were clinically stable; asthmatic symptoms were absent in five subjects and were of mild to moderate severity in the rest. With the exception of two subjects who probably had pulmonary emphysema in addition to bronchospastic disease, there was no evidence of other significant medical illness by history, physical examination, complete blood count, blood chemistries (SMA-12), routine urinalysis, electrocardiogram, and chest radiograph. Significant psychiatric illness was excluded on the basis of interviews with one of the investigators and, in most cases, evaluation of performance on the Minnesota Multiphasic Personality Inventory.

All subjects underwent screening pulmonary function studies, including spirometry using a 13.5-liter water spirometer (Warren E. Collins, Inc.), single-breath carbon monoxide diffusing capacity ( $D_{LCO}$ ) (7), and airway resistance ( $R_A$ ) and thoracic gas volume ( $V_{TG}$ ), using a 900-liter variable-pressure body plethysmograph (8,9). In order to assess the degree of reversible airway obstruction, spirometry was performed both before and 10 min following inhalation of 0.25 cc of isoproterenol HCl 1:200 via a DeVilbiss nebulizer connected to a positive-pressure breathing device powered by compressed air. In addition,  $R_A$  and  $V_{TG}$  were measured 15 min and immediately prior to inhalation of isoproterenol and 5 min following the bronchodilator. Physical characteristics and the results of screening pulmonary function studies for each subject are indicated in Table 1. In all subjects, flow rates or specific airway conductance ( $SG_A$ )—the ratio of the reciprocal of airway resistance to the simultaneously measured thoracic gas volume—increased more than 25% following isoproterenol inhalation, indicating the responsiveness of the airways to bronchodilator medication. In 10 subjects,  $R_A$  and  $V_{TG}$  were also measured 15, 30, and 60 min after the bronchodilator.

Of the 14 subjects, eight had smoked marihuana previously, seven only sporadically (less than one joint a month) and one regularly but mildly (one joint a week). None admitted to the use of drugs other than those prescribed for bronchial asthma and none were tobacco cigarette smokers. No subject had used marihuana within 7 days preceding the present study. In addition, bronchodilator medication was withheld for at least 8 hr before the study.

Two sets of experiments were performed to determine (1) effects on airway dynamics of smoked marihuana and oral  $\Delta^9$ -THC in stable asthmatic subjects and (2) effects of smoked marihuana on experimentally induced asthma.

#### Bronchial Effects of Marihuana in Stable Asthma

In each of 10 subjects (subjects 1 through 10, Table 1) experiments were carried out on four separate days beginning at 10 a.m., with at least 48 hr intervening between each study session. The subjects were informed that they would be randomly receiving marihuana or placebo.

##### *Smoked Marihuana*

During two of the four experimental sessions, subjects smoked 7 mg/kg body weight of a natural marihuana preparation containing either 0.0%  $\Delta^9$ -THC (serving as a placebo control) or 2.0%  $\Delta^9$ -THC, according to a random, double-blind crossover design. The THC content of the experimental preparation had previously been assayed by gas-liquid chromatography. The 0% preparation was obtained by extraction of the active cannabinoids from the natural material until assays for cannabinal, cannabidiol,  $\Delta^8$ -THC, and  $\Delta^9$ -THC were all 0.0%.

TABLE 1. Anthropomorphic and base-line pulmonary function data

| Subject | Sex | Height<br>(cm) | Weight<br>(kg) | Age<br>(years) | FVC<br>(% predicted*) | FEV <sub>1</sub> <sup>b</sup><br>(% predicted*) |                   | SGA <sup>†</sup><br>(cm H <sub>2</sub> O/sec) |                   | V <sub>TG</sub><br>(liters) |                   | D <sub>L</sub> CO<br>(% predicted) |
|---------|-----|----------------|----------------|----------------|-----------------------|-------------------------------------------------|-------------------|-----------------------------------------------|-------------------|-----------------------------|-------------------|------------------------------------|
|         |     |                |                |                |                       | B.B. <sup>c</sup>                               | A.B. <sup>d</sup> | B.B. <sup>c</sup>                             | A.B. <sup>d</sup> | B.B. <sup>c</sup>           | A.B. <sup>d</sup> |                                    |
| 1       | F   | 154            | 67             | 74             | 106                   | 62                                              | 81                | 0.077                                         | 0.090             | 2.80                        | 2.02              | 95                                 |
| 2       | M   | 193            | 84             | 31             | 111                   | 96                                              | 106               | 0.163                                         | 0.254             | 3.95                        | 3.06              | 60                                 |
| 3       | M   | 172            | 69             | 26             | 87                    | 60                                              | 75                | 0.048                                         | 0.127             | 5.14                        | 3.12              | 118                                |
| 4       | M   | 180            | 72             | 61             | 62                    | 26                                              | 29                | 0.062                                         | 0.082             | 5.78                        | 5.30              | 103                                |
| 5       | M   | 174            | 68             | 22             | 94                    | 86                                              | 98                | 0.179                                         | 0.335             | 2.79                        | 2.50              | 100                                |
| 6       | F   | 170            | 52             | 24             | 96                    | 73                                              | 92                | 0.100                                         | 0.174             | 3.87                        | 3.94              | 104                                |
| 7       | M   | 171            | 70             | 22             | 102                   | 93                                              | 95                | 0.093                                         | 0.122             | 2.64                        | 2.28              | 41                                 |
| 8       | F   | 158            | 66             | 59             | 77                    | 57                                              | 77                | 0.075                                         | 0.107             | 3.32                        | 2.79              | 100                                |
| 9       | F   | 163            | 59             | 27             | 95                    | 46                                              | 76                | 0.053                                         | 0.098             | 4.11                        | 2.83              | 104                                |
| 10      | F   | 168            | 66             | 28             | 86                    | 75                                              | 78                | 0.124                                         | 0.234             | 3.09                        | 2.80              | 97                                 |
| 11      | M   | 172            | 61             | 24             | 96                    | 64                                              | 73                | 0.076                                         | 0.106             | 5.21                        | 4.23              | 98                                 |
| 12      | F   | 166            | 61             | 56             | 100                   | 75                                              | 132               | 0.127                                         | 0.203             | 3.35                        | 3.04              | 106                                |
| 13      | M   | 170            | 61             | 19             | 117                   | 85                                              | 97                | 0.143                                         | 0.208             | 3.64                        | 3.57              | 110                                |
| 14      | F   | 162            | 54             | 40             | 98                    | 77                                              | 85                | 0.132                                         | 0.170             | 3.20                        | 3.00              | 138                                |
| MEAN    |     | 170            | 65             | 37             | 95                    | 70                                              | 85                | 0.104                                         | 0.165             | 3.78                        | 3.18              | 95                                 |
| ± SD    |     | 10             | 8              | 18             | 14                    | 19                                              | 23                | 0.040                                         | 0.074             | 0.98                        | 0.85              | 26                                 |

<sup>a</sup> FVC = forced vital capacity.<sup>b</sup> FEV<sub>1</sub> = forced expired volume in 1 sec.<sup>c</sup> B.B. = before bronchodilator.<sup>d</sup> A.B. = after bronchodilator.\* Predicted values for FVC and FEV<sub>1</sub> and for D<sub>L</sub>CO were based on the regression equations of Kory and associates (10) and of Hammer and Meade as reported by Cotes (11), respectively.

† Predicted value for our laboratory is 0.250 ± 0.043 (SD).

A uniform smoking technique was used in an effort to standardize the amount of volatilized  $\Delta^9$ -THC delivered in the inhaled material. Subjects inhaled the cigarette deeply for 2 to 4 sec, held their breath for 15 sec, resumed normal breathing for about 5 sec and then repeated these maneuvers until the cigarette was consumed, over a period of approximately 10 min. The cigarette butt, or "roach", was held with forceps in order to permit nearly complete consumption of the roach in which the volatilized cannabinoids are concentrated.

The following characteristics were measured 15 min before and immediately before smoking marihuana or placebo (initial control period) and immediately, 5, 10, 15, 30, 60, 90, and 180 min after completion of smoking:  $R_A$ ,  $V_{TG}$ , respiratory rate, heart rate (determined from the electrocardiogram), and systolic and diastolic blood pressure. In addition, in order to provide a rough assessment of the degree of intoxication, at each time interval following the smoking of marihuana and placebo, the seven subjects who had previous experience with cannabis were asked to estimate how "high" they felt on a 0-7 scale in which 7 represented the "highest" they had ever felt following marihuana.

#### *Oral $\Delta^9$ -THC*

During the remaining 2 study days, after an overnight fast, using a random double-blind design, subjects ingested either placebo or 15 mg synthetic  $\Delta^9$ -THC dissolved in sesame oil and made up into identical-appearing gelatin capsules. Measurements of the same characteristics as those determined in the smoking studies and scoring of subjective degree of intoxication were carried out 30 min before and immediately before oral administration of the drug (initial control period) and 30, 60, 90, 120, 180, 240, 300, and 360 min after ingestion. The order of the smoking and oral experiments was randomized among the study subjects.

All natural marihuana and synthetic THC preparations were obtained from the National Institute of Mental Health under whose direction all extraction, blending, assay, and synthetic procedures had previously been performed.

#### *Effects of Marihuana on Experimentally Induced Bronchospasm*

Seven asthmatic subjects (subjects 7 through 14, Table 1) were studied, five subjects on eight separate occasions, two subjects on four separate occasions.

In four experimental sessions, two sets of control plethysmographic measurements of  $R_A$  and  $V_{TG}$  were performed 15 min apart. Bronchospasm was then induced in each of six subjects by inhalation of the same dose of methacholine (0.25 to 0.50 cc of a 0.025 to 0.25% nebulized solution of methacholine), which had previously been shown to reduce  $SG_A$  by approximately 35 to 55% in that subject. Immediately thereafter subjects smoked a joint containing 500 mg marihuana assayed at 2.0%  $\Delta^9$ -THC or 0.0%  $\Delta^9$ -THC (placebo) or inhaled 0.25 cc of aerosolized saline or 0.5% isoproterenol according to a single-blind experi-

mental protocol. Plethysmographic measurements were then repeated immediately and 5, 10, 15, 30, and 60 min after smoking or aerosol inhalation.

In four other sessions, after control measurements of  $R_A$  and  $V_{TG}$ , six subjects were exercised on a treadmill or on a bicycle ergometer. During each session steady exercise was performed by each subject over the same time period (5 to 10 min) using the same work-load (200 to 650 kilopond m/min on the bicycle ergometer or 1 to 3.5 mph at a 0 to 10% grade on the treadmill) which had previously been demonstrated to acutely decrease specific airway conductance in that individual by approximately 25 to 50%. Immediately thereafter subjects either smoked 2.0% marihuana or placebo or inhaled isoproterenol or saline in a single-blind manner, following which serial plethysmographic measurements were repeated.

## CALCULATIONS

### Stable Asthma

From each set of measurements of  $R_A$  and  $V_{TG}$ ,  $SG_A$  was calculated in order to correct for changes in  $R_A$  secondary to changes in lung volume (12). For each subject, at each time interval following inhalation of isoproterenol or the smoking or ingestion of the test agent, percent changes in each of the measured characteristics were calculated from the average of the two control values. Individual percent changes were averaged for each inhaled or ingested agent separately for all subjects at each time interval. The absolute ratings of subjective degree of intoxication were averaged at each time interval for each type of experimental preparation. Using Student's *t* test, statistical significance was determined (1) for the average percent change in each characteristic for each experimental preparation compared with initial control values, (2) for the percent changes following smoked marihuana and oral THC compared with placebo using paired observations, and (3) for the differences of the mean scores from zero for the level of "high" following smoked marihuana and oral  $\Delta^9$ -THC.

### Experimentally Induced Bronchospasm

For each subject, percent changes in  $SG_A$  after methacholine inhalation or exercise at each time interval following smoking of marihuana or placebo or inhalation of isoproterenol or saline were calculated from the average of the two pre-methacholine or preexercise control values. Using Student's *t* test, statistical significance was determined (1) for the average percent changes in  $SG_A$  from initial control values and (2) for the percent changes following marihuana compared with placebo or saline and following isoproterenol compared with saline or marihuana using paired observations.

TABLE 2. Mean  $\pm$  SE initial control cardiopulmonary values

|                             | $R_A$ (cm H <sub>2</sub> O/<br>liter/sec) | $V_{TG}$<br>(liter) | SG <sub>AW</sub><br>(cm H <sub>2</sub> O/sec) | Heart rate<br>(beats/min) | Respiratory<br>rate<br>(breaths/min) | Systolic<br>blood pressure<br>(mm Hg) | Diastolic<br>blood pressure<br>(mm Hg) |
|-----------------------------|-------------------------------------------|---------------------|-----------------------------------------------|---------------------------|--------------------------------------|---------------------------------------|----------------------------------------|
| Smoked 2%<br>marihuana      | 2.49 $\pm$ 0.25                           | 3.86 $\pm$ 0.28     | 0.120 $\pm$ 0.015                             | 88.3 $\pm$ 5.6            | 19.9 $\pm$ 1.4                       | 120 $\pm$ 4                           | 75.3 $\pm$ 1.6                         |
| Smoked placebo<br>marihuana | 2.48 $\pm$ 0.20                           | 3.87 $\pm$ 0.32     | 0.118 $\pm$ 0.013                             | 84.7 $\pm$ 4.7            | 17.4 $\pm$ 1.4                       | 117 $\pm$ 3                           | 75.4 $\pm$ 1.0                         |
| Oral $\Delta^9$ -THC        | 2.78 $\pm$ 0.28                           | 3.84 $\pm$ 0.33     | 0.112 $\pm$ 0.016                             | 78.0 $\pm$ 1.8            | 18.2 $\pm$ 1.3                       | 117 $\pm$ 3                           | 76.4 $\pm$ 1.7                         |
| Oral placebo                | 2.88 $\pm$ 0.26                           | 4.03 $\pm$ 0.41     | 0.104 $\pm$ 0.015                             | 77.2 $\pm$ 2.6            | 17.0 $\pm$ 1.6                       | 117 $\pm$ 3                           | 77.2 $\pm$ 2.5                         |
| Inhaled<br>isoproterenol    | 3.17 $\pm$ 0.25                           | 3.76 $\pm$ 0.33     | 0.103 $\pm$ 0.017                             | 80.8 $\pm$ 4.3            | —                                    | 124 $\pm$ 4                           | 79.1 $\pm$ 2.4                         |

## RESULTS

## Stable Asthma

Average initial control values for the measured characteristics during each experimental session are indicated in Table 2. There were no significant differences between the mean base-line values obtained on separate days.

## Smoking Studies

The average percent changes in  $SG_A$  following smoked marihuana, smoked placebo marihuana and inhaled isoproterenol are shown in Fig. 1. Following placebo,  $SG_A$  did not change significantly. After 2% marihuana, average  $SG_A$  increased immediately and remained elevated (33 to 48% above initial control values) for at least 2 hr. These increases were statistically significant ( $p < 0.05$ ) compared with both control values and placebo.  $V_{TG}$  did not change following placebo but decreased slightly (4 to 13%) but significantly ( $p < 0.05$ ) compared with base-line and/or placebo for at least 5 hr following 2% marihuana. Changes

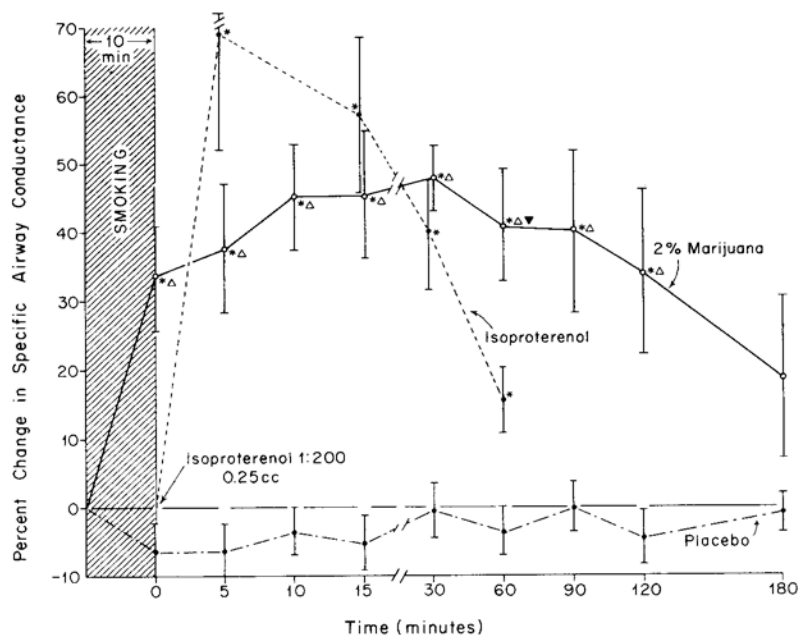


FIG. 1. Average percent change in  $SG_A$  as a function of time following the completion of smoking of 2% marihuana and of placebo and following the inhalation of isoproterenol. Vertical bars represent 1 SEM for this and subsequent figures. \*Significantly different from initial control values ( $p < 0.05$ ).  $\Delta$ , Significantly different from placebo, paired  $t$  test ( $p < 0.05$ ).  $\nabla$ , Significantly different from isoproterenol, paired  $t$  test ( $p < 0.05$ ).

in  $R_A$  following marihuana generally paralleled the changes in  $SG_A$  but were of lesser magnitude because of the associated decreases in  $V_{TG}$ .

For comparison with the changes following marihuana, average percent changes in  $SG_A$  following inhalation of 1,250  $\mu$ g isoproterenol are also shown in Fig. 1. During the first 15 min following isoproterenol,  $SG_A$  increased to levels greater than those observed following 2% marihuana, although these differences were not statistically significant. By 60 min following isoproterenol,  $SG_A$  was elevated only slightly and significantly less than following marihuana ( $p < 0.05$ ). Over the first 30 min following isoproterenol inhalation,  $V_{TG}$  was significantly reduced to a degree similar to that noted following marihuana. By 60 min following isoproterenol,  $V_{TG}$  had returned essentially to normal.

The average percent changes in heart rate after smoking of marihuana or placebo and inhalation of isoproterenol are shown in Fig. 2. Pulse rate fell gradually following placebo to levels slightly but significantly below base-line values at 30 to 120 min. Following 2% marihuana, pulse rate increased immediately and remained elevated for 30 min by amounts (7 to 22%) significantly different from the changes following placebo to levels which at 90 to 120 min were significantly below initial control values ( $p < 0.05$ ) but were not significantly different from the changes following placebo. Pulse rate increased following

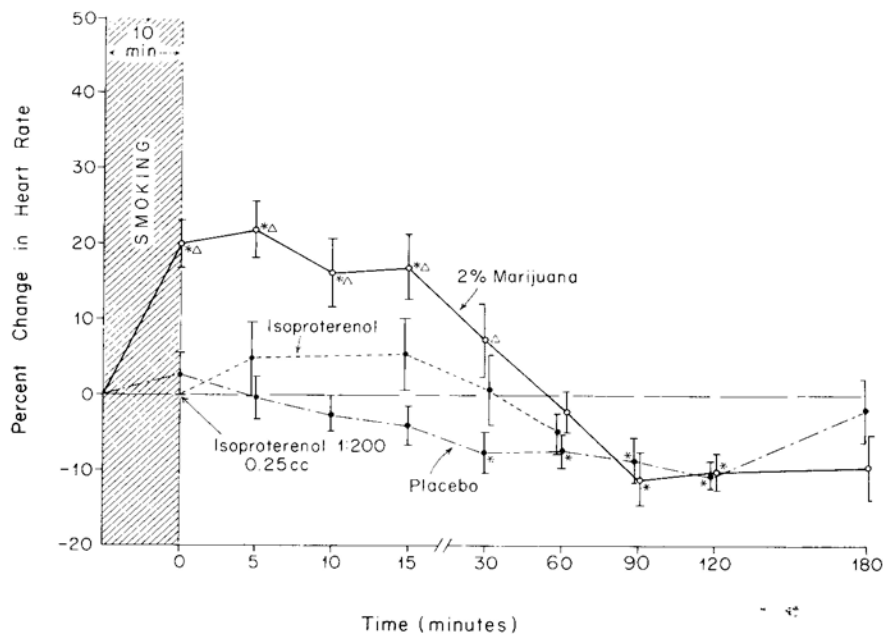


FIG. 2. Average percent change in heart rate with time following completion of smoking of 2% marihuana and of placebo and of inhalation of isoproterenol. \* Significantly different from initial control values ( $p < 0.05$ ).  $\Delta$ , Significantly different from placebo, paired  $t$  test ( $p < 0.05$ ).

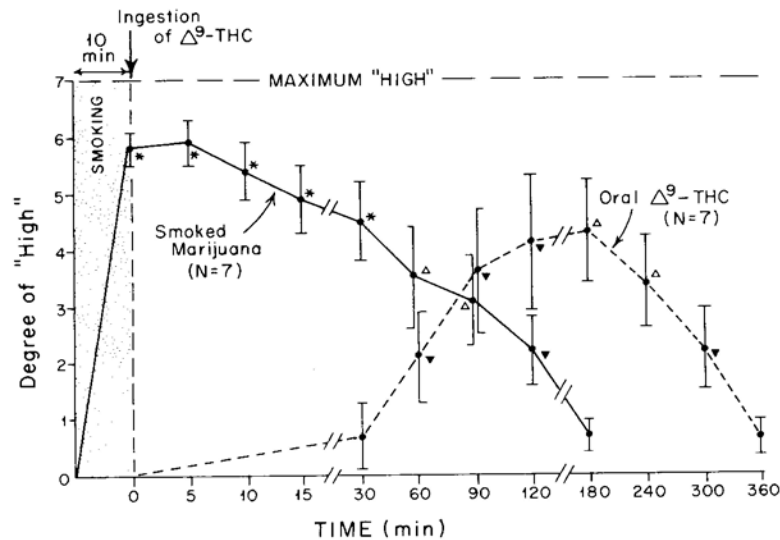


**FIG. 3.** Mean scores for subjective degree of intoxication with time following completion of smoking 2% marihuana and ingestion of 15 mg  $\Delta^9$ -THC in seven asthmatic subjects who had smoked marihuana previously (See text). \* Significantly different from zero ( $p < 0.001$ ).  $\Delta$ , Significantly different from zero ( $p < 0.01$ ).  $\nabla$ , Significantly different from zero ( $p < 0.05$ ).

isoproterenol, but the increase was not statistically significant at the  $p < 0.05$  level.

No significant changes in systolic or diastolic blood pressure or in respiratory rate were observed following placebo, marihuana, or isoproterenol.

All subjects admitted to a definite feeling of intoxication following marihuana, whereas all but one subject had either no change or minimal change in state of consciousness following placebo. That subject (subject 1, Table 1) who had not had any previous exposure to cannabis, felt sleepy, lightheaded, and jittery after both marihuana and placebo. The scores for subjective degree of "high" following marihuana revealed a maximal feeling of intoxication over the 5-min period immediately following the completion of smoking with a gradual decline thereafter (Fig. 3). By 2 hr the magnitude of the "high" was approximately one-third of the peak level and by 3 hr the "high" had essentially dissipated.

#### Oral Studies

$SG_A$  increased modestly (14 to 19%) but significantly ( $p < 0.05$ ) at 60 to 120 min following ingestion of 15 mg  $\Delta^9$ -THC, whereas placebo was not associated with any significant changes (Fig. 4).  $V_{TG}$  did not change significantly following either placebo or THC. As noted with smoked marihuana, decreases in  $R_A$  following oral THC paralleled the increases in  $SG_A$  except that  $R_A$  was still significantly reduced ( $-10.2 \pm 3.6$  and  $-12.9 \pm 3.3$ ;  $p < 0.05$ ) at 3 and 4 hr, respectively.

No alterations in respiratory rate or systolic and diastolic pressure were observed following oral  $\Delta^9$ -THC or placebo.

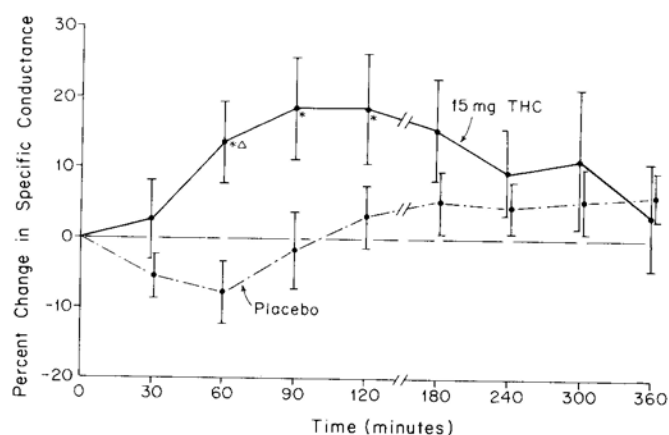


FIG. 4. Average percent change in  $SG_A$  as a function of time following the ingestion of 15 mg  $\Delta^9$ -THC and of placebo. \* Significantly different from initial control values ( $p < 0.05$ ).  $\Delta$ , Significantly different from placebo, paired  $t$  test ( $p < 0.05$ ).

A subjective "high" was first experienced 1 hr following ingestion of THC, reached a peak at 2 to 3 hr, then declined gradually and was gone by 6 hr. The placebo preparation was not associated with any significant change in consciousness.

#### Experimentally Induced Bronchospasm

There were no significant differences between the mean initial control values of  $SG_A$  obtained during each experimental session for methacholine- or exercise-induced bronchospasm (Table 3). The mean percent changes in  $SG_A$  following smoked marihuana and placebo and inhaled isoproterenol and saline after metha-

TABLE 3. Experimentally induced bronchospasm: mean values ( $\pm$  SE) for initial control specific airway conductance ( $\text{sec}^{-1}\text{cm H}_2\text{O}^{-1}$ )

| Drug                     | Methacholine-induced bronchospasm ( $N=6$ ) | Exercise-induced bronchospasm ( $N=6$ ) |
|--------------------------|---------------------------------------------|-----------------------------------------|
| Smoked 2% marijuana      | $0.058 \pm 0.004$                           | $0.091 \pm 0.098$                       |
| Smoked placebo marijuana | $0.076 \pm 0.016$                           | $0.092 \pm 0.015$                       |
| Inhaled isoproterenol    | $0.081 \pm 0.18$                            | $0.086 \pm 0.006$                       |
| Inhaled saline           | $0.079 \pm 0.015$                           | $0.087 \pm 0.014$                       |

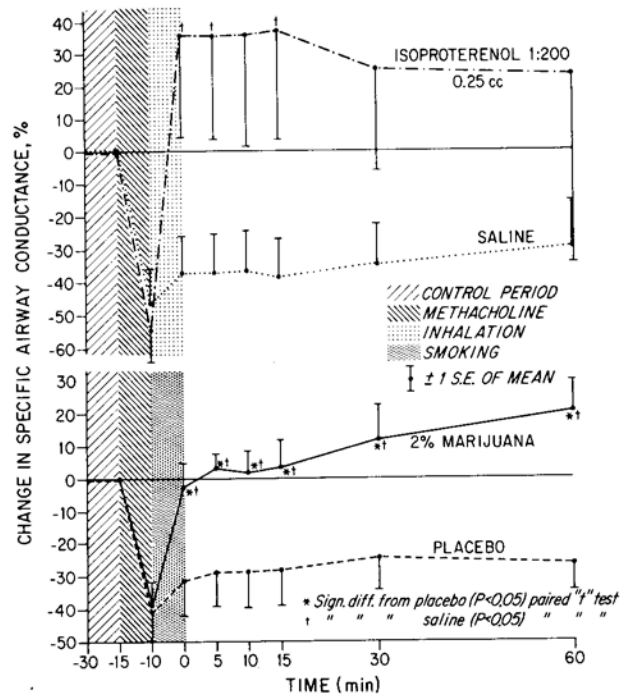


FIG. 5. Average percent change in  $SG_A$  from initial control values with time following smoking of 2% marihuana and placebo and following inhalation of 0.25 cc of 0.5% isoproterenol and saline after methacholine-induced bronchospasm ( $N=6$ ).

choline-induced bronchospasm are shown in Fig. 5. Methacholine inhalation resulted in significant bronchoconstriction with average reductions in  $SG_A$  of 40 to 55%. Following subsequent placebo marihuana smoking, or saline inhalation,  $SG_A$  increased only slightly, whereas 2% marihuana and isoproterenol each resulted in a prompt return of  $SG_A$  to control values significantly different from values following placebo and saline. Although the mean postisoproterenol values for  $SG_A$  were greater than those following smoked marihuana, these differences were not statistically significant.

The average percent changes in  $SG_A$  following each test preparation after exercise-induced bronchospasm are shown in Fig. 6. Exercise resulted in an average reduction in  $SG_A$  of 30 to 39%. There was a gradual return to control values over the ensuing 60 min following placebo and saline. Following marihuana, on the other hand,  $SG_A$  returned promptly to preexercise values significantly different from values following placebo and saline for 15 to 60 min. Isoproterenol caused an immediate increase in  $SG_A$  to values that significantly exceeded those following saline and marihuana for 30 to 60 min.

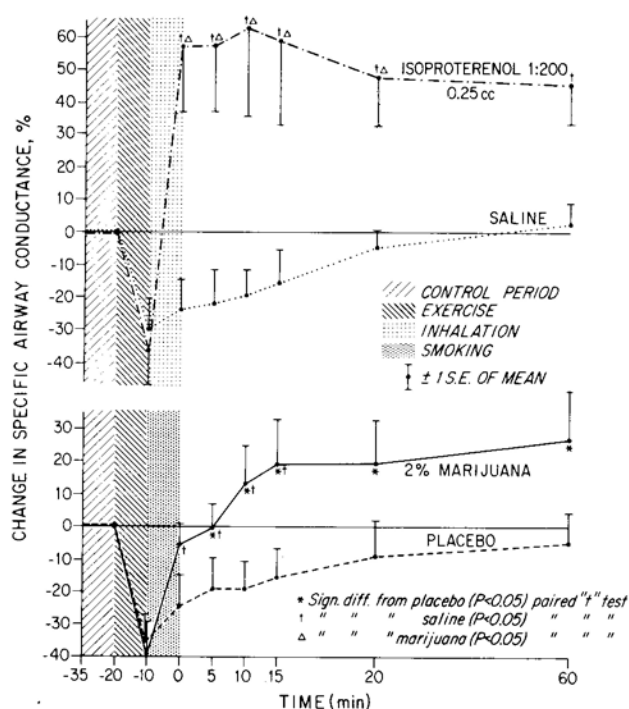


FIG. 6. Average percent change in  $SG_A$  from initial control values with time following smoking of 2% marihuana and placebo and following inhalation of 0.25 cc of 0.5% isoproterenol and saline and after exercise-induced bronchospasm ( $N=6$ ).

## DISCUSSION

### Stable Asthma

#### Smoked Marihuana

The significant increases in  $SG_A$  following the smoking of marihuana compared with placebo suggests that inhaled marihuana causes airway dilatation in asthmatic subjects and is consistent with findings previously reported in individuals without airways disease (2,3). The dilatation was not due to an increase in lung volume (12) since  $V_{TG}$  fell significantly in parallel with the rise in  $SG_A$ . The observed decrease in  $V_{TG}$  is consistent with a reduction in air-trapping secondary to the decrease in bronchomotor tone. Also the volume history of the lung—i.e., the deep, sustained inhalation breathing pattern—does not explain the increase in  $SG_A$  following marihuana smoking compared to placebo smoking since the breathing patterns were similar.

Because there was a significant correlation between the individual increases

in  $SG_A$  following marihuana and the magnitude of the subjective "high" ( $r = 0.52$ ,  $p < 0.01$ ), the possibility that the observed bronchodilatation was causally related either to the psychological effects of marihuana or to other effects of cannabis on the central nervous system deserves consideration. Despite the significant correlation between the degree of marihuana-induced bronchodilatation and the level of intoxication, the time sequences for these changes were somewhat different in that the bronchodilator effect at 2 hr was similar in magnitude to that noted immediately following smoking (Fig. 1), whereas by 2 hr the "high" had fallen to less than one-half the level experienced immediately after smoking (Fig. 3). These temporal differences do not exclude the possibility that the emotional changes experienced soon after smoking triggered a chain of reactions that eventuated in a relaxation of bronchomotor tone of longer duration than the initiating emotional stimulus. However, the fact that significant bronchodilatation following 2% marihuana has also been noted in nonasthmatic individuals (2,3) suggests that the dilator effect observed in our asthmatic subjects is probably not predominantly of psychogenic origin; there is no evidence that bronchomotor tone in normal man is influenced significantly by emotional factors. Moreover, although three of our subjects who had had no previous exposure to cannabis experienced a less euphoric "high" than the others, there was no difference in the degree of bronchodilatation observed in these individuals and those who had smoked marihuana previously, suggesting that the pleasure associated with the "high" was probably not related to the relaxant effect on the airways.

The fact that the smoking of placebo marihuana did not cause a significant fall in  $SG_A$  is surprising since the inhalation of particulate matter in the smoke would be expected to cause reflex bronchoconstriction (13), particularly in asthmatic subjects whose airways are more reactive to nonspecific irritants than those of subjects without airways disease (14). In the present study, the failure of the airways to constrict following smoked placebo may have been due to a balancing out of the constrictor effect of inhaled irritants either by unidentified bronchodilator compounds in marihuana that are not alcohol-extractable or by a nonspecific placebo bronchodilator response to the expectation of a pleasant experience. In an earlier study it was shown that the airways of normal subjects also do not constrict following the smoking of the placebo preparation but do constrict following cigarette smoking (3). The fact that pulse rate fell following placebo, in contrast to the significant and expected rise (15) following 2% marihuana (Fig. 2), is more in favor of a placebo phenomenon than a pharmacological response to a bronchodilator principle in the THC-extracted marihuana preparation.

Although the maximal mean change in  $SG_A$  following smoking of 2% marihuana (48%) was less than that following inhalation of 1,250  $\mu$ g isoproterenol HCl (69%), the bronchodilator effect of marihuana was more sustained than that of isoproterenol, consistent with the metabolism of  $\Delta^9$ -THC to physiologically active compounds (16) in contrast to the rapid conversion of isoproterenol to inactive metabolites (17).

*Oral  $\Delta^9$ -THC*

The small but significant increases in  $SG_A$  and decreases in  $R_A$  following oral  $\Delta^9$ -THC indicate that this component of natural marihuana has a systemically active bronchodilator effect in asthmatics beginning 1 hr and lasting as long as 4 hr after ingestion of the drug. However, this bronchodilator effect was fractionally smaller in magnitude than that previously noted in normal subjects following the same dose of THC (3). Moreover, heart rate did not increase significantly (maximum mean increase  $9 \pm 7\%$ ) following oral administration of 15 mg  $\Delta^9$ -THC in our asthmatic subjects in contrast to the significant increases ( $19 \pm 7\%$ ) previously noted in normal subjects (3). These discrepancies in the responses of normal, experienced cannabis users and relatively inexperienced asthmatic individuals to oral THC may be due to differences in absorption of the drug from the gastrointestinal tract, metabolism of THC to the active agent, or tissue responsiveness. With regard to the first two possibilities, comparison of plasma levels of  $\Delta^9$ -THC and its metabolites following oral administration of the drug in both experienced and naive individuals with and without asthma would be of interest.

*Experimentally Induced Asthma*

The 40 to 55% reduction in  $SG_A$  following inhalation of  $\leq 0.5$  cc of 0.025 to 0.25% methacholine noted in our subjects is consistent with the known bronchial hyperreactivity of asthmatic subjects to muscarinic stimulation (18). The similar magnitude and duration of the bronchoconstriction which persisted for up to 30 to 60 min following both saline and placebo marihuana indicated that any bronchial irritant effect of marihuana smoke was not sufficient to aggravate existing acute bronchospasm. Comparison of the responses to 2% marihuana and isoproterenol indicates that inhaled  $\Delta^9$ -THC has as prompt and sustained a bronchodilator effect in acute methacholine-induced bronchospasm as inhalation of a  $\beta$ -adrenergic agonist.

The 30 to 40% decrease in  $SG_A$  after mild to heavy exercise for 5 to 10 min is consistent with postexercise bronchospasm (19). The gradual return of  $SG_A$  to control values over the ensuing 30 to 60 min following placebo or saline is characteristic of the time course of untreated exercise-induced asthma (19). The observation that 2% marihuana smoking resulted in a rapid increase in  $SG_A$  to values significantly greater than those following placebo or saline indicates that inhaled THC is capable of promptly relieving exercise-induced bronchoconstriction. Comparison of the responses to 2% marijuana and 0.25 cc 0.5% isoproterenol, however, reveals that in the doses used the latter causes a significantly greater degree of bronchodilatation in exercise-induced asthma.

Although the mechanism of exercise-induced asthma is not known, the absence

of any effect of atropine on postexercise bronchospasm (20,21) suggests that the bronchospasm is not reflexly mediated by cholinergic efferents. The effectiveness of marihuana in relieving postexercise bronchoconstriction is therefore consistent with previous findings (22) indicating that marihuana-induced bronchodilatation is not mediated by an atropine-like effect.

In summary, in clinically stable asthmatic subjects with minimal to moderate bronchospasm, both smoked marihuana and oral  $\Delta^9$ -THC result in bronchodilatation lasting as long as 2 hr and 4 hr, respectively. Smoked marihuana promptly reversed experimentally induced bronchoconstriction and its effect was comparable to that of isoproterenol in methacholine-induced asthma but less than that of isoproterenol in exercise-induced bronchospasm. Since only the *acute* effects of marihuana smoking on airway dynamics in subjects with bronchospastic disease were studied, the results do not preclude the possibility that *chronic* marihuana smoking might aggravate existing bronchial pathology in these same individuals. Moreover, the profound psychotropic effect of marihuana and  $\Delta^9$ -THC, in addition to such side effects as tachycardia and the atropine-like drying effect, may severely limit any potential clinical therapeutic usefulness.

### SUMMARY

Previous studies have shown that both smoked marihuana and oral  $\Delta^9$ -tetrahydrocannabinol (THC) produce significant acute bronchodilatation in healthy young males. We present data on 10 subjects with clinically stable bronchial asthma of mild to moderate severity in whom acute effects of smoked 2% natural marihuana (7 mgm/kg) and oral  $\Delta^9$ -THC (15 mgm) on plethysmographically determined airway resistance ( $R_{AW}$ ) and specific airway conductance ( $SG_{AW}$ ) were compared with those of placebo using a double-blind crossover technique. After smoked marihuana,  $SG_{AW}$  rose immediately and remained significantly elevated (33 to 48% above initial control values) for at least 2 hr, whereas  $SG_{AW}$  did not change after placebo. The peak bronchodilator effect of 1250  $\mu$ g of isoproterenol was greater than that of marihuana, but the effect of marihuana lasted longer. After ingestion of 15 mgm of THC,  $SG_{AW}$  was elevated significantly at 1 and 2 hr, and  $R_{AW}$  was reduced significantly at 1 to 4 hr, whereas no changes were noted after placebo.

In 6 asthmatic subjects, bronchospasm ( $> 30\%$  decrease in  $SG_{AW}$ ) was induced by exercise on a bicycle ergometer or treadmill or by inhalation of 0.25 to 1.25 mgm methacholine. Following induction of bronchospasm, subjects smoked 2% marihuana or placebo or inhaled 1,250  $\mu$ g isoproterenol or saline in a single-blind fashion. Bronchospasm was promptly reversed by smoked marihuana and inhaled isoproterenol but not by smoked placebo or inhaled saline.

The above findings indicate that in stable asthmatics smoked marihuana and oral THC cause significant bronchodilatation of at least 2 hr duration and that smoked marihuana is capable of reversing experimentally induced bronchospasm.

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