

Hunger and appetite after single doses of marihuana, alcohol, and dextroamphetamine

Two separate experiments indicated that in most subjects, after oral administration of marihuana, total food intake, as well as reports of hunger and appetite, are increased. Drugs, such as dextroamphetamine and, to a lesser extent, alcohol reduced food consumption and appetite. Stimulation of appetite by marihuana is by no means invariable, occurring in only slightly more than half the subjects. Similar variations between individuals were observed in the case of responses to dextroamphetamine and alcohol.

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Marihuana smoking or hashish ingestion has long been reported to increase hunger and appetite. "Marihuana hunger" was described as coming on for 3 to 6 hours following the drug, with a special craving for sweets.¹ Another modern investigation² found that subjects did not experience hunger during the first 3 hours despite fasting; but when food was offered, they ate with great relish. Such reports apparently led to the assumption that marihuana lowers blood glucose. Several recent studies^{3, 4, 6} have, however, demonstrated that neither smoked marihuana in small doses nor orally ingested tetrahydrocannabinol (THC) in large doses has any significant effect on plasma glucose levels. To test whether or not marihuana stimulates hunger and appetite, food consumption was measured systematically after fasted subjects were treated with marihuana, alcohol,

dextroamphetamine, and a placebo in one experiment and after fed subjects received marihuana, alcohol, and placebo in a second experiment.

Methods

Experiment No. 1. Twelve normal young volunteers were chosen primarily on the basis of their being in good physical and emotional health and intelligent and cooperative enough to carry out the required procedures. All but one were men. Although most subjects had prior experience with small doses of marihuana and amphetamines, and all with alcohol, except for modest use of the latter, none were chronic or recent users of any of these drugs. Subjects were told which drugs were to be given and that one might be given twice.

Four trials were run at weekly intervals, with random assignment of the following four treatments: (1) marihuana prepared as an extract and calibrated for THC content, 0.5 mg. per kilogram⁵; (2) 95 per cent ethanol, 1 ml. per kilogram; (3) dex-

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troamphetamine sulfate, 0.2 mg. per kilogram; and (4) a placebo made by re-extracting marihuana from which all cannabinoids had previously been extracted. Subjects varied in weight between 66 and 91 kilograms. Total doses of drugs were: marihuana (as THC), mean dose 32 mg., range 27 to 39 mg.; dextroamphetamine, mean dose 15 mg., range 13 to 18 mg.; ethanol, mean dose 57 Gm., range 50 to 68 Gm.

Doses of each drug were administered in 180 ml. of a flavored, noncaloric soft drink. To mask taste differences further, doses were given with the subject blindfolded and the nostrils occluded. To the greatest extent possible, double-blind control was exercised, although various circumstances (distinctive taste and effects of alcohol and marihuana) mitigated against this.

Subjects were instructed not to take anything but water by mouth; i.e., no food or calorie-containing beverage after 7:30 P.M. the evening before the trial. They were put at rest in the fasting condition in the test room at 7:30 A.M. A number of preliminary tests were done over the next 30 minutes, including completion of a hunger questionnaire* and removal of blood samples for determination of glucose and free fatty acids. Drug was administered at 8 A.M. Offerings of food were first made at 11 A.M. and they were repeated at 11:30 A.M., 12 noon, and 1 P.M. Just prior to the first offering of food, the hunger questionnaire and blood samples were repeated. At the end of the trial, an appetite questionnaire,* concerned with enjoyment of food, was completed.

The hunger questionnaire asked subjects to rate on an 8 point scale their current degree of hunger (from "not hungry" to "hungriest ever") and their current feeling of satiety (from "empty" to "uncomfortably full"). A point was scored for each response, from 0 to 7 in the first instance, and

7 to 0 in the second. The appetite questionnaire asked the subject to rate the taste of the food offered at each trial over a spectrum ranging from "much worse than usual" to "much better than usual," using a 5 point scale scored from -2 to +2.

Food was offered in the form of a standard chocolate milk shake made according to the following recipe: homogenized whole milk, 240 ml.; skim milk powder, 60 Gm.; powdered chocolate, 25 Gm.; ice cream, 360 Gm. Ingredients were mixed in a blender immediately prior to use. Total volume was 800 ml. with approximately 1.5 calories and 0.6 Gm. of proteins per milliliter. The subjects knew that they would be offered chocolate milk shake, as it had previously been ascertained that this was acceptable to their tastes. The presentation was made in a covered box from which only a straw protruded, effectively masking any appreciation of the amount offered or consumed. They were instructed to drink to satiety or to the limit of the single offering, with the expectation that more food would be offered over the next 2 hours. The largest amount of milk shake offered at any single time was 480 ml.

Experiment No. 2. The general procedures used in the second experiment were similar to those used in the first experiment with the exceptions cited below. Twelve healthy subjects, all young men, were selected. All had some previous experience with marihuana, but at no greater frequency than twice monthly. Three trials were run at weekly intervals, with random assignment of the following treatments: (1) marihuana prepared as an extract calibrated to a dose of 0.35 mg. per kilogram of delta-1-THC; (2) ethanol, 95 per cent calibrated to a dose of 0.7 ml. per kilogram; (3) placebo (marihuana extract with all cannabinoids removed). Total doses of drugs were as follows: marihuana (as THC), mean dose 26 mg., range 20 to 29 mg.; ethanol, mean dose 43 Gm., range 27 to 52 Gm.

In this experiment, unlike the first, subjects were permitted to have their custom-

*Copies of the hunger and appetite questionnaires are available on request from author. These were devised by Sydnor B. Penick, M.D.

ary breakfast, with the specific instructions that, no matter what it was, it be the same on all 3 test days. Thus these subjects were in contrast to the fasted subjects in the first experiment. Offerings of food were made 2, 2½, 3½, 4½, and 5½ hours after the drug was given. The maximum amount of each offering was 240 ml of the chocolate milk shake. The hunger questionnaire was completed 1½, 3½, and 6 hours after each drug was given. The appetite questionnaire was completed at the end of each trial.

Results

Experiment No. 1. Ethanol ingestion, in the large amounts given in the fasting state, had an immediate and profound effect, readily recognized as alcoholic intoxication. Most subjects were also able to distinguish the effect of marihuana, which developed more slowly and was characterized by euphoria and sleepiness. The effects of dextroamphetamine were less readily evident. The placebo had no discernible effect, other than its unpleasant taste which resembled that of the marihuana extract.

The mean total intake of milk shake during the entire trial revealed that marihuana increased it as compared with placebo (731 ml. vs. 503 ml.), dextroamphetamine decreased in (390 ml.), and alcohol produced little change (511 ml.). Data from individual subjects were variable: 7 of 12 subjects consumed more food after marihuana, 2 showed no essential change, and 3 took less food. With dextroamphetamine and ethanol 7 and 6 subjects, respectively, ate less food; 2 and 3, respectively, showed no change, and 3 each consumed more food. These differences were not significant on chi square analysis. The acceptance of food offerings followed a similar pattern for each treatment. Of 48 offerings of food in any given trial, 31 were accepted after marihuana compared to 24 after placebo, 19 after dextroamphetamine, and 25 after alcohol. Despite these trends, the relatively small sample size and high variation between subjects ruled out a statistically sig-

nificant difference in total food intake between treatments on complex analysis of variance ($F = 2.06$; $df, 3$). As might have been expected, however, there were significant differences between subjects and between time periods.

The typical pattern of food intake over the four time periods is shown in Fig. 1. Following the 15 hour fast, substantial amounts were taken during the first two offerings of food but declined rapidly thereafter as satiety was reached. The pattern with dextroamphetamine followed that of placebo, except that smaller amounts were required during the first two offerings to attain satiety. The effect of alcohol was a slight decrease during the early stages of acute intoxication followed by increased consumption of food some 5 hours after the drug had been taken. The pattern following marihuana was like that after placebo initially, but at no point was it clear that satiation was complete. Analysis of variance showed a significant interaction between treatments at the last feeding period, in which both alcohol and marihuana were associated with greater intake of food than the other two treatments ($F = 2.93$; $df, 3$; $p < 0.025$).

Mean scores on the hunger questionnaire are shown in Table I. Ordinarily, continued fasting might have been expected to increase hunger slightly from the time of beginning the trial until shortly before the first offering of food. Such was the case for all treatments but dextroamphetamine, which made hunger less intense. The greatest increment in hunger followed marihuana. Following three opportunities to take food, subjects treated with marihuana reported more persisting hunger than did the others. In terms of appreciation of food as judged by the appetite questionnaire and compared with scores obtained after placebo, after marihuana 8 patients reported improved appetite and 4 reported diminished appetite. After dextroamphetamine, 4 reported enhanced appetite, 5 reported diminished appetite, and 3 unchanged appetite. Ethanol produced

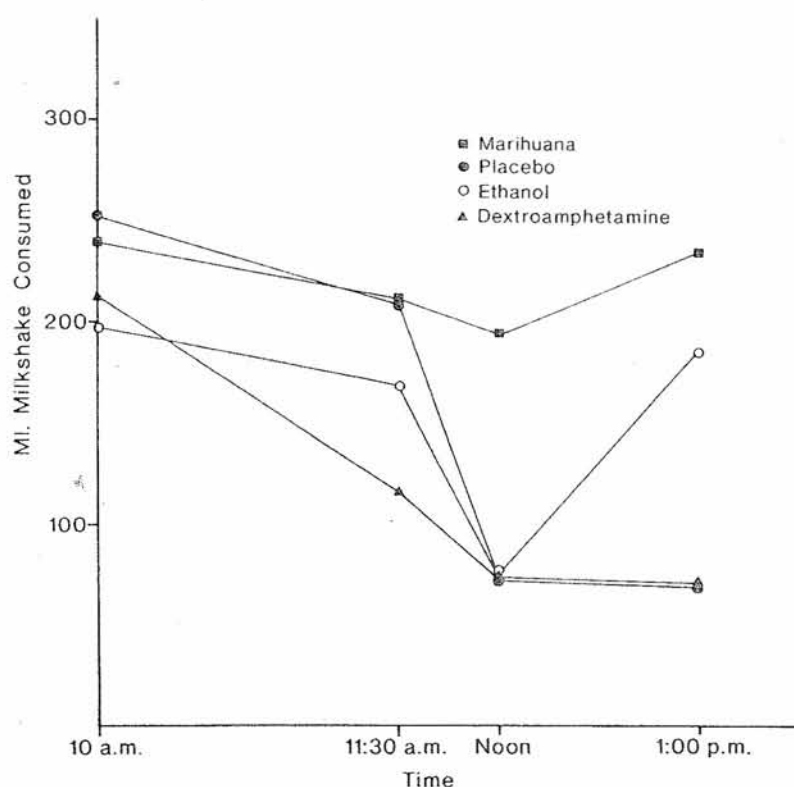


Fig. 1. Pattern of total intake of food at each time for four treatments.

an equal division, 4 reporting improvement, 4 reporting impairment, and 4 reporting no change.

Compared to pretreatment values, plasma free fatty acids (FFA) fell significantly during treatment with placebo and alcohol, rose significantly with dextroamphetamine, and were unchanged by marihuana (Table I). Analysis of variance of the plasma FFA values during the drug conditions revealed that levels were significantly higher after dextroamphetamine and lower after ethanol than they were after placebo and marihuana. The correlation in percentage change in plasma FFA levels and total amount of food consumed was undertaken to determine if change in plasma FFA levels might be an indicator of hunger. The correlations were only weakly negative ($r = -0.18$). Absolute levels of FFA in the fasting state, paired to any drug being given, were correlated with reports of hunger only weakly ($r = 0.18$). Plasma glucose values

Table I. Mean values of hunger questionnaire scores, plasma free fatty acids, and plasma glucose

Treatment	Before	2½ hr.	4½ hr.	7 hr.
<i>Hunger questionnaire</i>				
Placebo	4.8	5.0	3.8	4.1
Dextroamphetamine	5.0	4.3	3.7	3.7
Alcohol	4.6	4.8	3.4	3.5
Marihuana	4.8	5.8	4.5	4.0
<i>Plasma free fatty acids</i>				
Placebo	507	464*		
Dextroamphetamine	602	707†		
Alcohol	416	288*		
Marihuana	479	430		
<i>Plasma glucose</i>				
Placebo	86	85		
Dextroamphetamine	86	90		
Alcohol	87	84		
Marihuana	85	84		

* $P < 0.05$.

† $P < 0.01$; t test, correlated mean, 2 trial.

showed little change during any of the four treatments, which were not appreciably different from each other. Inspection of data from individual subjects revealed no clinically significant changes in any instance.

Experiment No. 2. The mean total intake of milk shake during the second experiment virtually duplicated the results of the first one. After marihuana, mean intake was 777 ml. compared with 603 after placebo and 540 after alcohol. Data from individual subjects were variable: 7 consumed more food after marihuana than after placebo, in the other 5 it was about the same in both cases; only one increased food intake after alcohol, 4 decreased food intake, and the remaining 7 subjects consumed about as much as they did after placebo. Of 60 offerings of food in each trial, 42 were accepted following marihuana, 30 following ethanol, and 33 following placebo. These trends were comparable to those in the first experiment.

Analysis of variance of total food intake revealed a significant difference between treatments ($F = 10.6$; $df, 2$; $p = 0.001$) as well as between subjects ($F = 6.7$; $df, 11$; $p = 0.0005$). Correlated t tests (2 tailed) revealed a significant difference between total food intake following marihuana compared with alcohol ($t = 4.7$; $p = 0.001$) and placebo ($t = 3.3$; $p = 0.01$). The difference between placebo and alcohol was not significant. In this experiment, therefore, the results are clear that marihuana caused an increase in food intake.

The pattern of food intake in fed subjects differed somewhat from that in fasted subjects. Marihuana did not produce a sustained level of food intake but rather a pattern in which satiety tended to be reached after the $3\frac{1}{2}$ hour feeding. The pattern of food intake was similar among the three treatments, although more food was taken following marihuana at each time period except the last.

Initial mean hunger scores were virtually identical for three treatments. Al-

though they rose progressively at $1\frac{1}{2}$ and $3\frac{1}{2}$ hours, the increases were parallel for all three. Following the $5\frac{1}{2}$ hour feeding, subjects reported somewhat less hunger following marihuana, presumably due to over-satiation. Seven subjects treated with marihuana reported enhancement of appetite, 4 no difference, and 1 less appetite as compared to those treated with placebo. Alcohol reduced appetite in 5 subjects, increased it in 1, and had no effect in 6.

Discussion

Marihuana tended to increase appetite and food consumption, while dextroamphetamine and, to a lesser extent, alcohol tended to decrease appetite and food consumption. Marihuana was shown to increase total food intake to a statistically significant degree in experiments which involved the fed subjects. Similar trends were found in relation to the number of offerings of food which were accepted, the greatest number being after marihuana in each experiment. These results confirm the notion that marihuana has a stimulating effect on appetite and food consumption. It is of interest that fed subjects were more sensitive to these effects than were the fasted subjects. One may speculate that the stress of fasting may increase variability, thus making it a relatively poor control measure.

In both experiments there was a great individual variation in response to drugs. Only slightly more than half of all subjects ate more food after marihuana than after placebo. Occasional instances occurred in which results were opposite to expectations. One subject took more food following dextroamphetamine than after either placebo or marihuana. The stimulation or suppression of food intake, at least following single doses of drugs, is variable among different individuals. Allowing for the distinct possibility of a positive bias toward reports of enhanced hunger and appetite following marihuana, due to the fairly easy identification of the drug from its clinical actions, results of the present

study scarcely support the stand that the drug reliably stimulates hunger and appetite. But neither did all patients treated with dextroamphetamine respond with appetite diminution, although many do.

One of the reasons for the prevalent belief that marihuana enhances food intake in all persons is the fact that marihuana is often taken in social groups. Assuming that a majority of persons within such groups actually experience an increase in appetite, it is very likely that these effects would spread to other members of the group. Although it has not been clearly documented, it seems reasonable that marihuana may have the effect of increasing suggestibility. In such a case, the group pressure of a majority experiencing a particular effect would be strong for the others.

As in a previous study,² marihuana had no effect on plasma levels of glucose and FFA. Since prevailing levels of plasma FFA may in part be a reflection of the degree of the postabsorptive state, it is of interest that changes in the levels during the first 2½ hours following drug did not correlate with food intake. Neither did they corre-

late with hunger scores as reported in the fasting state prior to any drug given. It would appear that the sensation of hunger is independent of FFA levels.

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