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Acute Effects of Smoking Marijuana on Hormones, Subjective Effects and Performance in Male Human Subjects

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CONE, E. J., R. E. JOHNSON, J. D. MOORE AND J. D. ROACHE. *Acute effects of smoking marijuana on hormones, subjective effects and performance in male human subjects.* PHARMACOL BIOCHEM BEHAV **24**(6) 1749–1754, 1986.— Four healthy male subjects smoked two marijuana cigarettes or one marijuana cigarette and one placebo cigarette, or two placebo cigarettes on separate days in a random order crossover design. Each marijuana cigarette contained 2.8% delta-9-tetrahydrocannabinol (THC). Plasma hormones and THC were measured before and after each smoking session. Plasma LH was significantly depressed and cortisol was significantly elevated after smoking marijuana. Nonsignificant depressions of prolactin, FSH, testosterone and free testosterone and elevation of GH also occurred. Concurrent measures of subjective effects via subscales of the Addiction Research Center Inventory, Single Dose Questionnaire and a Visual Analog Scale were generally elevated. Significant impairment on a psychomotor performance task paralleled elevations in subjective effects, hormone effects and peak THC determinations. Although all the hormone effects were within normal basal ranges, interactions between these systems, and their effects on behavior cannot be discounted.

Marijuana Hormones Tetrahydrocannabinol THC Behavior Cortisol LH FSH Testosterone Prolactin GH Subjective effects

IN laboratory animals, the hormonal effects of delta-9-tetrahydrocannabinol (THC), the most active constituent of marijuana, are characterized by a suppression of circulating plasma levels of the gonadotropins, testosterone, prolactin, and thyrotropin and elevation of adrenal cortical steroids [13]. Less clear are the hormonal effects of marijuana usage in humans. One research group has reported dose-related decreases in the plasma testosterone levels of male subjects after chronic intensive use [17] as well as after controlled smoking of a standardized marijuana cigarette [18]. However, other studies with human males have found testosterone levels to be within normal limits after marijuana usage [4, 14, 23, 31]. Marijuana smoking also has been reported to suppress plasma levels of lutenizing hormone (LH) [18] and follicle stimulating hormone (FSH) [17] in males although these observations were not confirmed by other studies [14,23]. Further, a depression of growth hormone (GH) and cortisol response to insulin-induced hypoglycemia after prolonged administration of oral THC to male subjects has been reported [1] although another study in male volunteers found plasma cortisol levels unchanged after acute administration of oral THC except in cases where clinical signs of psychological stress were present [15]. Prolactin levels in human males after smoking a single marijuana cigarette were reported to be unchanged [22]. Serum triiodothyronine (T_3) levels were found to be significantly lower in male subjects of African origin who smoked marijuana regularly versus nonsmokers, whereas there was no significant difference in their testosterone levels [26].

THC-mediated stimulation of pituitary adrenocortical hormone secretion has been suggested to account for many of the behavioral, electroencephalographic and pharmacological actions of THC in animals [6]. In accord with this postulate, it is possible that THC-mediated release of ACTH or other neurohormones play a role in the behavioral effects of THC in humans. In view of the contradictory reports of the effects of marijuana on endocrine hormones in humans, we assessed the acute effects of smoking marijuana on a variety of plasma hormones in four male subjects. Determinations of plasma levels of selected hormones and THC were made at times when subjective measures and performance were maximally affected. The objective of this study

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was to determine if detectable changes in plasma hormones occur concurrently with the behavioral effects of marijuana, possibly lending support to the proposal of a hormone-behavior interaction induced by THC.

METHOD

Subjects

Four healthy male subjects with a history of frequent marijuana use participated in the study. The ages (years) and weight (kg) of the subjects were as follows: 22, 86.5; 26, 61.4; 33, 72.7; and 54, 85.2. The subjects participated as residents on a closed research ward under close surveillance. During the month prior to the present study, the subjects had participated in another study which involved passive exposure to marijuana smoke for a total of twelve 1-hr sessions; however, subjects had not smoked marijuana or received other drugs. The study was conducted under the guidelines for the protection of human subjects (45CFR46).

Treatment

Each subject smoked two cigarettes on each of three consecutive days. The cigarettes were research marijuana cigarettes (NIDA Research Technology Branch) which contained 2.8% delta-9-THC (active, THC-containing cigarettes) or did not contain any detectable levels of THC (placebo cigarettes). Across the three days, each subject received each of the following three treatment (dose) conditions: two placebo cigarettes (i.e., the placebo condition); one placebo and one THC-containing cigarette (i.e., one cigarette condition); and two THC-containing cigarettes (i.e., two cigarette condition). The order in which each subject received the three dose conditions and the order of presentation of the marijuana cigarettes in the one marijuana cigarette dose condition was randomly assigned. Each dose condition was administered on a separate day and the smoking procedure was ad lib. The first cigarette was smoked at 8:30 a.m. and the second cigarette was smoked at 9:00 a.m.

Plasma Collection Procedures

Blood was obtained from each subject by venipuncture at 8:00 a.m. (pre-drug control), 9:30 a.m. (approximately 15 min after cessation of smoking) and 10:30 a.m. (approximately 75 min after cessation of smoking). Samples were collected in heparinized tubes and the plasma was separated from cells by centrifugation. The plasma was frozen immediately and stored at −20°C for subsequent analysis.

Hormone Analysis

Cortisol and prolactin were assayed by commercial kits from Nuclear-Medical Laboratories (Irving, TX). LH, FSH, GH, free testosterone and total testosterone were assayed by commercial kits from Diagnostic Products Corporation (Los Angeles, CA). All assays were performed in duplicate according to the procedures recommended by the manufacturer. Mean intra-assay coefficients of variation determined for all duplicate samples were as follows: Cortisol, 5.5%; prolactin, 10.3%; LH, 6.1%; FSH, 4.6%; GH, 17.1%; free testosterone, 5.7%; testosterone, 6.7%. Interassay variability was eliminated by assaying all samples in one run with the same reagents. The accuracy of each assay was assessed with the use of standard controls. Duplicate low, medium and high level standards (Tri-Level Ligand Assay Control

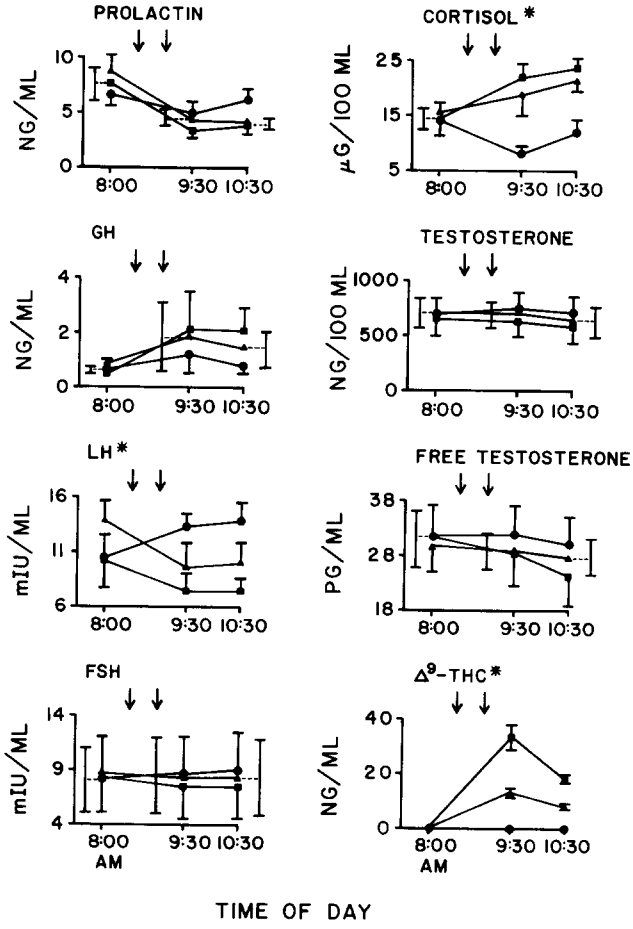

FIG. 1. Mean (±SE) plasma levels of hormones and delta-9-THC on days of subjects (N=4) smoking two marijuana cigarettes (■), one marijuana cigarette and one placebo marijuana cigarette (▲) or two placebo marijuana cigarettes (●). The two arrows indicate the times each subject began smoking each cigarette. A statistically significant ($p<0.05$) drug effect is indicated by *.

Set A, B, C, Ortho Diagnostic Systems, Raritan, NJ) were assayed concurrently with subject samples. All standard determinations fell within the expected range of the manufacturer's assay data for the cortisol, prolactin, LH and FSH assay. Testosterone standard determinations were within the expected range for the high standard (8.89 ng/ml) but assayed approximately 18% and 29% lower than the medium (4.45 ng/ml) and the low standard (0.66 ng/ml), respectively. The accuracy of the free testosterone assay was assessed with CON6 standards (Diagnostic Products Corporation, Los Angeles, CA). Mean determinations were 13% lower than the low standard (4.7 pg/ml) and 34% and 15% higher than the medium and high standard, respectively. The accuracy of the GH assay was assessed with bilevel controls from Diagnostic Products Corporation (HGH1 and HGH2). All standard determinations fell within the expected range published by the manufacturer.

The human serum calibrators for the LH assay were standardized in terms of the World Health Organization's First International Reference Preparation of LH for Immunoassay, number 68/40 where assay units mIU/ml × 0.6 equals

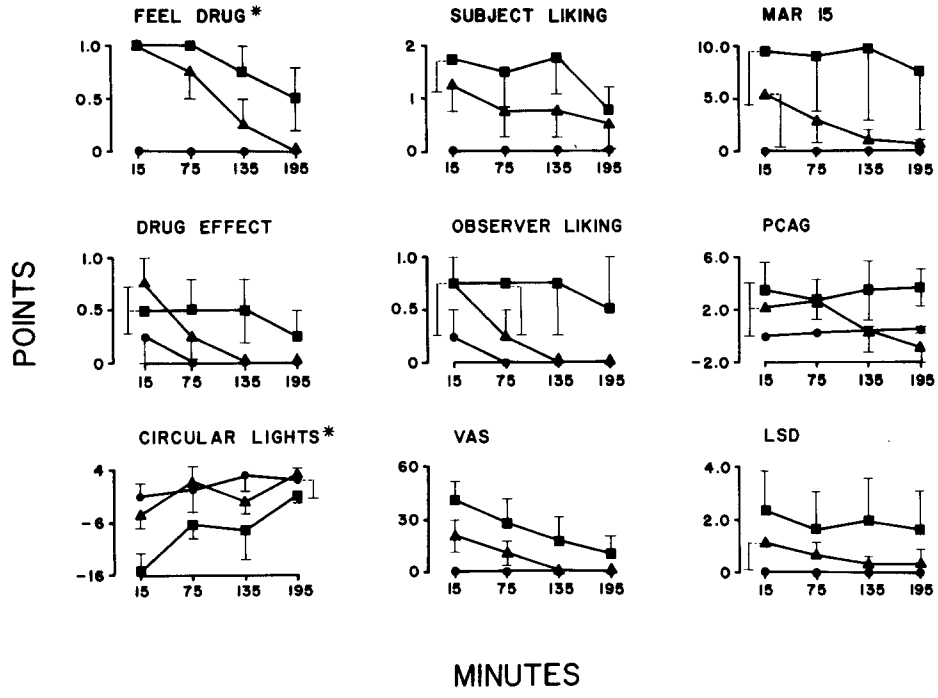

FIG. 2. Mean (±SE) subjective and performance effects (minus predrug control measures) of subjects (N=4) after smoking two marijuana cigarettes (■), one marijuana cigarette and one placebo marijuana cigarette (▲) or two placebo marijuana cigarettes (●). A statistically significant ($p<0.05$) drug effect is indicated by *.

mIU/ml (1st IRP 68/40). Calibrators for FSH were standardized against the World Health Organization's Second International Reference Preparation of FSH (2nd IRP-HMG). Calibrators for GH were standardized against the World Health Organization's International Reference Preparation of Human GH for Immunoassay, number 66/217.

Delta-9-THC Analysis

Plasma levels of delta-9-THC were measured by radioimmunoassay [3].

Measurement of Subjective Effects

Subjective effects were assessed at 60 min (7:30 a.m.) and 30 min (8:00 a.m.) before smoking (i.e., pre-drug controls) and at intervals of approximately 15 min (9:30 a.m.), 75 min (10:30 a.m.), 135 min (11:30 a.m.) and 195 min (12:30 p.m.) after smoking the second cigarette. Subjective effects were measured with subscales of the Addiction Research Center Inventory (i.e., MAR 15, MBG, LSD, PCAG) [12], and the Single Dose Questionnaire [10] which includes subject ratings, i.e., Feel Drug and Subject Liking, as well as observer ratings, i.e., Drug Effect and Observer Liking. A 200 mm Visual Analog Scale (VAS) also was employed which involved rating drug effects as "high" (positive effects), "neutral" (no effects), or "bad" (negative effects); subjects rated these effects by placing a mark along the line on the left, center, or right-hand portions of the line respectively.

Measurement of Psychomotor Performance Effects

Psychomotor performance was evaluated through the use of the circular lights task; this task was performed at the same times as described above for the subjective effects. The circular lights task has been used extensively to quantitate psychomotor impairment produced by CNS depressants [30]. The task requires rapid hand-eye coordination on the part of subjects who are to press a randomly-illuminated series of buttons for a 60 second interval. The data were collected as the number of correct button presses per 60 sec.

Statistical Analyses

For all data analysis, the mean of the two predrug controls was subtracted from each post-drug response and a one-way analysis of variance (ANOVA) was performed on the difference scores to determine the presence of a significant effect ($p<0.05$) of treatment condition.

RESULTS

Hormones and Delta-9-THC

Immediately following the smoking of one or two marijuana cigarettes (2.8% delta-9-THC) plasma LH was significantly depressed and cortisol was significantly elevated from placebo conditions (Fig. 1). A dose related response between the one and two cigarette conditions for these measures was apparent but was not significant. A slight elevation of GH and slight depressions of prolactin, FSH, testosterone and free testosterone were noted but were not significant. Predrug control measures were similar for all three treatments with all of the hormones except for the

elevated predrug LH measure in the one cigarette condition. Intersubject variability was relatively high for all hormone measures but was greatest for GH, FSH and free testosterone.

Mean plasma levels of THC were 13.0 ng/ml and 33.7 ng/ml at 9:30 a.m. following the smoking of one and two marijuana cigarettes, respectively (Fig. 1). By 10:30 a.m. mean drug levels had declined to 8.1 ng/ml and 18.5 ng/ml. Detectable levels of THC were not present following the smoking of placebo cigarettes.

Subjective and Performance Effects

There was a significant increase in the Feel Drug scale of the Single Dose Questionnaire after smoking marijuana (Fig. 2). A similar response was obtained with the Subject Liking, MAR 15 and Drug Effect scales although these were nonsignificant. Nonsignificant increases also were obtained with the Observer Liking, PCAG, VAS and LSD scales; the MBG scale (not shown) was not affected. Generally, subjective effects were maximal at 15 min and declined to near baseline by 135 to 195 min after smoking one marijuana cigarette. After smoking two marijuana cigarettes, responses were higher and remained elevated at 195 min.

Placebo responding generally was absent in the reporting of subjective effects by the four subjects but was slightly evident at the 15 min response of the nurse observer (Drug Effect, Observer Liking). Also, considerable intersubject variability was apparent in all subjective measures following smoking marijuana, however the subjects were clearly able to distinguish placebo from marijuana.

Circular lights performance was significantly impaired (i.e., decreased scores) only with the high dose condition (i.e., two cigarettes). With this dose, performance was maximally impaired at 15 min but had returned to pre-drug levels by 195 min. Performance under the placebo condition was relatively constant although there was a slight upward trend across time; under the one cigarette condition, performance was more erratic.

DISCUSSION

The profile of marijuana-induced hormonal effects in the four male subjects was qualitatively similar in most respects to responses found in animal studies [13], but differed somewhat from results in earlier human studies. Current findings of a significant elevation of cortisol and a significant depression of LH are in contrast to studies where no effects of marijuana on these hormones were observed [14, 15, 23]. This study also failed to confirm earlier reports of a significant reduction in plasma testosterone levels in human males after smoking marijuana [18] although there were slight trends indicating reductions of free and total plasma testosterone (Fig. 1). Other studies also have found a lack of a significant effect of smoking marijuana on testosterone levels [4, 14, 23, 31]. Prolactin and FSH levels were not significantly affected after acute smoking of marijuana in the current study although some slight reductions were evident. This is in agreement with other studies with human males in which prolactin or FSH levels were unchanged after acute administration of THC or marijuana [14,22]. Overall, the lack of marijuana effects on testosterone, prolactin and FSH are generally consistent with most other studies; however, the present findings of increased cortisol and decreased LH seem to contradict findings of earlier human studies. The small number of subjects (i.e., four) and differences in subject population, marijuana dosage, sampling times and methodological detail, could possibly account for discrepancies between the present and previous studies.

The profiles of marijuana-induced subjective effects and plasma THC levels of this study were in close agreement with other studies involving humans smoking marijuana [2, 16, 19, 28]. In these earlier studies both subjective ratings and plasma THC generally declined to near baseline levels within 3 hr after smoking one marijuana cigarette similar to that found in the current study. As expected, following the smoking of two marijuana cigarettes subjective effects and plasma THC levels were higher and of longer duration. A significant performance impairment with the circular lights task at times corresponding with the elevations in subjective effect measurements is also consistent with reports of psychomotor impairment following smoking marijuana [27].

The subjective effects and performance impairment observed with marijuana in human studies are similar to effects produced by other central nervous system depressants. The hormonal profile of effects also resembles that of other depressants with one major exception, i.e., the lack of a significant elevation of prolactin levels. The robust increase in prolactin levels usually associated with depressants like alcohol [7] and barbiturates [33] and with opioids such as morphine [9] does not occur with marijuana. Both ACTH and beta-endorphin have been shown to share a common precursor [20] and are secreted concomitantly [11]. A rise in beta-endorphin levels would be expected to produce an increase in prolactin [9]. Stressful stimuli also provoke increases in ACTH, cortisol and beta-endorphin levels which are usually accompanied by increases in prolactin levels [29]. Obviously marijuana and stress differ in the manner in which they influence cortisol and prolactin secretion.

Although the hormonal changes observed in this study are not significant physiologically (i.e., none were outside of reported normal ranges) the potential remains for a marijuana induced hormone-behavior interaction. The subjective, hormonal and psychomotor effects occurred concurrently, thus it is possible that the change in hormone levels as a result of smoking marijuana influenced CNS function and human behavior. It has been shown that a dose of 3 mg/kg of THC administered intraperitoneally to adrenalectomized rats produced a nonsignificant elevation of ^{3}H-corticosterone uptake in the hippocampus and septum, whereas a dose of 9 mg/kg of THC significantly ($p<0.01$) reduced uptake [6]. Since the hippocampus and septum may exert a feedback regulation on the hypothalamic-pituitary-adrenal axis, loss of inhibitory feedback in the presence of high levels of THC may trigger release of ACTH [25]. Both THC and ACTH produce similar behavioral effects in rats including extinction of avoidance responding, production of enhanced fear and facilitation of acquisition of the avoidance task [25]. It also is significant that ACTH fragments (ACTH 1–24 and ACTH 1–10) are euphorigenic in man [8]. Together with these similarities, however, discrepancies between the effects of ACTH and THC do exist. ACTH 4–10 has been shown to reduce performance deficits and enhance attention and short-term visual memory whereas THC generally produces performance deficits [27] and short-term memory losses [5].

LH is another hormone which has been associated with overt behavioral effects. Increased levels of LH have been associated with antemortem violence [24] and feelings of hypophoria [21]. However it is not known whether depres-

sion of LH levels as seen in the present study might be associated with decreased aggression. Suggestive evidence has been offered that use of marijuana may lead to reduced probability for human aggression [32].

While the data from the present study are limited by the fact that only four male subjects participated, it is clear that the use of marijuana concurrently affects hormonal systems and behavior. Understanding how these systems interact and the extent of their influence on human mood state and behavior would significantly advance our understanding of the actions of marijuana.

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