Pharmacology Biochemistry & Behavior, Vol. 23, pp. 765–768, 1985. © Ankho International Inc. Printed in the U.S.A. 0091-3057/85 $3.00 + .00

Acute Effects of Marihuana on Luteinizing Hormone in Menopausal Women

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Received 10 September 1984

MENDELSON, J. H., P. CRISTOFARO, J. ELLINGBOE, R. BENEDIKT AND N. K. MELLO. *Acute effects of marihuana on luteinizing hormone in menopausal women.* PHARMACOL BIOCHEM BEHAV **23**(5) 765–768, 1985.— Plasma luteinizing hormone (LH) levels were determined under double blind crossover conditions in 10 healthy menopausal adult females prior to and following smoking of a 1-g marihuana cigarette containing 1.83% Δ^9-tetrahydrocannabinol (THC) and a 1-g marihuana placebo cigarette. A significant increase in pulse rate and levels of intoxication occurred after marihuana smoking but not after smoking placebo cigarettes. LH levels determined before administration of marihuana and placebo cigarettes were not significantly different and were within the range of normal values for healthy menopausal women. No significant differences were found between LH levels following marihuana and placebo smoking.

Marihuana Luteinizing hormone Menopause Women

OVARIECTOMIZED female rodents and menopausal women have LH levels which are significantly greater than observed in females with normal ovarian function. THC (1 to 5 g mg/kg IV) produced a dose-dependent suppression of LH which occurs within 1 hr following drug administration [6]. A very low dose of THC (62.5 mcg/kg) administered to ovariectomized rats rapidly suppressed LH release and reduced serum LH concentration by 40 to 68% [15]. In ovariectomized rhesus monkeys with high basal levels of LH, a single intramuscular dose (2.5 mg/kg) of THC significantly suppressed plasma luteinizing hormone levels for 12 to 24 hours [12]. In the ovariectomized female rhesus monkey the degree of LH suppression was not correlated with THC dose but the duration of LH suppression was dose-dependent [12,13].

These observations in rat and rhesus monkey suggested that THC might suppress LH levels in menopausal women. Since LH surges during menopause have been correlated with the subjective sensation of hot flashes, increases in body temperature, and dysphoria [14], it was postulated that a cannabis-induced suppression of LH may be useful for the treatment of some of the adverse concomitants of the menopausal syndrome.

METHOD

Ten healthy adult females recruited by newspaper advertisement provided informed consent for their participation in the study. All were normal, healthy women as determined by evaluation of medical and mental status history plus appropriate physical examination, blood hemograms and blood chemistry studies.

The mean age of the women was 54 (range 50–56) and their mean weight was 68 kg (range 48–108 kg). Cessation of regular menstrual periods had occurred for all subjects at least one year prior to the study. The mean age of onset of menopause was 51 years (range 48–53 years). The mean age of menarche was 13 years (range 11–17 years) and the mean duration of menstruation was 38 years (range 30–40 years).

None of the women had a history of past or current alcohol or drug abuse. Only two subjects reported ingesting over 10 beverage alcohol drinks during the month prior to admission. Seven women had a history of tobacco use but only two were current cigarette smokers. Six women reported past history of physician prescribed stimulants or depressants but none were currently using any psychoactive drugs. Six subjects reported no past history of cannabis use; four subjects reported a total of 7 experiences with the drug.

Procedure

Subjects served as their own controls for evaluating the effects of marihuana cigarette or placebo cigarette smoking on plasma LH levels. Marihuana and placebo cigarette smoking were carried out under double blind crossover study conditions approximately 11 days apart. Five subjects received marihuana and 5 received placebo on the first study day. On each study day the subjects reported to the research facility at 0900 hr following a 12-hr fast. A 0.9% saline solution was slowly infused via an indwelling intravenous catheter which was utilized for subsequent blood plasma sampling. Subjects were not permitted to smoke tobacco cigarettes or consume food but could drink fruit juices. During the study subjects could listen to the radio, watch television or read.

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TABLE 1

PLASMA LH (LER-907 ng/ml) VALUES PRIOR TO (−120 MIN TO 0) AND FOLLOWING (0 TO +180 MIN) ACUTE MARIHUANA SMOKING

Marihuana	Mean	323	215	257	235	220	254	233	230	211	273	244	202	216	262	234
N=10	S.D.	101	58	103	89	78	91	116	86	50	122	120	133	86	57	64
	S.E.	32	26	46	40	35	41	52	38	23	54	54	60	39	25	29
Placebo	Mean	300	291	244	227	238	270	263	273	255	267	280	227	247	272	252
N=10	S.D.	90	110	134	104	128	166	109	156	123	143	126	120	107	102	116
	S.E.	29	49	60	47	57	74	49	70	55	64	57	54	48	46	52
Time		−120	−90	−60	−30	0	+15	+20	+25	+30	+45	+60	+90	+120	+150	+180

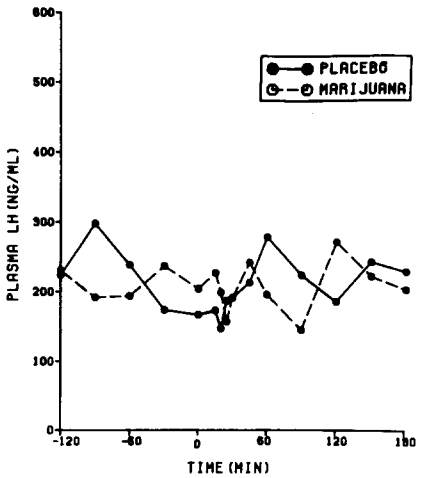

FIG. 1. Plasma LH levels for a single subject prior to and following placebo or marihuana cigarette smoking at 0 time.

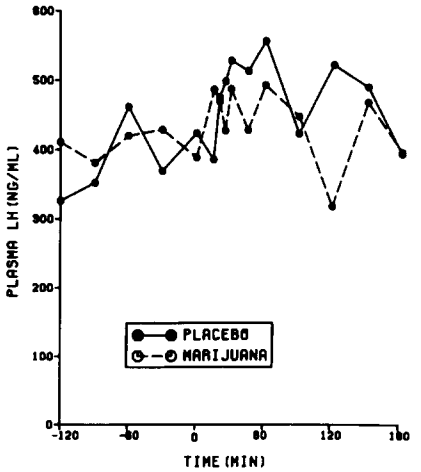

FIG. 2. Plasma LH levels for a single subject prior to and following placebo or marihuana cigarette smoking at 0 time.

Blood samples were collected every 30 min for 2 hr *prior* to marihuana or placebo cigarette smoking and at 15, 20, 25, 30, 45, 60, 90, 120, 150, and 180 min *after* smoking. At these times pulse rate and level of intoxication were also determined. Pulse rate was measured manually at the site of the radial artery. Level of intoxication ("high") was measured with an 11 point scale which ranged from 0 ("no effect; not high at all") to 10 ("highest ever"). A similar level of intoxication scale has been used previously for assessing acute marihuana intoxication [5, 8, 10].

One gram marihuana cigarettes containing 1.83% Δ^9-THC and marihuana placebo cigarettes containing cannabis leaves from which all psychoactive materials had been extracted were obtained from NIDA. Smoking of marihuana and placebo cigarettes were carried out with a controlled inhalation paradigm. Subjects were instructed to take and maintain a deep inhalation for 2–5 sec every 30 sec. Cigarettes were smoked until no more than 10 mm of the cigarette remained. The process was completed within approximately 15 min following initiation of smoking.

LH was assayed as described previously [7]. Results are expressed as ng LER-907 standard/ml plasma. Mean intra- and interassay CV's were 7 and 11 percent.

RESULTS

A significant increase in pulse rate occurred following marihuana smoking (ANOVA $p<0.01$) but no statistically significant changes in pulse rate occurred following placebo smoking. The statistically significant increase in pulse rate following marihuana smoking was detected at +15 min and persisted until +120 min.

ANOVA revealed a significant increase ($p<0.01$) in level of intoxication following marihuana smoking. Onset of a statistically significant increase in level of intoxication was detected at +15 min and persisted through +180 min.

Pulse rate increment and level of intoxication were highly correlated following marihuana smoking ($r=0.883, p<0.001$). No significant correlations were found after placebo smoking.

Table 1 presents plasma LH levels prior to and following marihuana and placebo cigarette smoking. Analysis of variance (ANOVA) revealed no significant differences in plasma LH levels prior to marihuana smoking (−120 min to 0 min) and no significant differences in plasma LH levels following marihuana or placebo cigarette smoking (0 to +180 min).

Figures 1 and 2 present individual data for 2 representative subjects. One subject (Fig. 1) had LH levels which ranged from 150 to 300 ng/ml and a second subject (Fig. 2) had a higher range of LH values (300 to 550 ng/ml). Analysis of variance revealed no statistically significant differences between LH values prior to and following marihuana and placebo cigarette smoking. Analysis of variance for the remaining 8 subjects who participated in the study did not reveal any statistically significant changes in LH values as a

consequence of either marihuana or placebo cigarette smoking.

DISCUSSION

Subjects who participated in this study had a pulse rate increment averaging 14 beats/min following marihuana smoking. The increase in pulse rate was detected 15 min after initiation of smoking and persisted for 2 hours. Increased pulse rate following marihuana use has been one of the most consistently reported physiologic concomitants of marihuana use by humans [2,11]. Pulse rate changes observed in this study with post-menopausal women who were relatively naive marihuana users were similar to the magnitude and duration of pulse rate increments observed in younger women with long histories of marihuana use [5].

The level of intoxication following marihuana smoking by post-menopausal women was also very similar to intoxication levels observed in younger women following marihuana smoking [5]. There was a strong positive correlation ($p<0.001$) between increments in pulse rate and level of intoxication found in this study with post-menopausal women. These data are similar to observations for a cohort of younger women studied under identical conditions in our laboratory [5].

Although determination of plasma levels of Δ^9-THC or THC metabolites was not carried out in this study, data obtained for pulse rate and levels of intoxication indicate that marihuana induced significant behavioral and physiologic changes which did not occur following placebo cigarette smoking. Unfortunately, it would be difficult to infer the effects of actual levels of Δ^9-THC or its metabolites even if plasma levels of Δ^9-THC, 11-hydroxy TCH and 9-carboxy THC had been determined. The highly complex pharmacokinetics and pharmacodynamics of Δ^9-THC and its metabolites has impeded the development of dose-effect relationships between plasma levels, active tissue site levels, sequestered tissue levels and biologic concomitants of acute and chronic drug administration [4].

Although the neurochemical and neurophysiologic sites of action of cannabis compounds in the central nervous system remain to be elucidated, it has been postulated that marihuana may affect adrenergic and dopaminergic systems [11]. There is also evidence that LH secretory activity in post-menopausal women may be more sensitive to the inhibitory action of drugs which affect adrenergic or dopaminergic pathways in the brain and hypothalamus. For example, Grossman and his associates [3] have found that long acting analogs of met-enkephalin produce a greater decrement in plasma LH in menopausal women than in younger subjects. However, we have been unable to substantiate that marihuana selectivity inhibits LH secretory activity in post-menopausal women and we have also failed to observe any selective inhibitory effects of ethanol on LH levels in similar cohorts of women [9].

The THC dose (approximately 18 mg) in the marihuana cigarettes smoked in this study were larger than doses of THC which have been shown to rapidly suppress LH release and reduce serum LH concentrations in ovariectomized rats [15]. However, the dose of THC was smaller than the single intramuscular dose of 2.5 mg/kg which induced significant suppression of luteinizing hormone levels for 12 to 24 hr in rhesus monkeys [12]. An equivalent dose of THC (2.5 mg/kg) for human females would have necessitated administration of approximately 100 mg of THC or the equivalent of smoking 5 to 6 1-g marihuana cigarettes containing 1.8% THC. Administration of larger doses of THC via marihuana smoking to our subjects would not have been ethically feasible because of the risk of inducing severe marihuana-related intoxication in relatively naive (with respect to past history of marihuana use) individuals.

In summary, our study suggests that menopausal women are less sensitive to marihuana-induced suppression of luteinizing hormone levels than rodents [1, 6, 11, 15] and monkey [12,13]. However, our data do not unequivocally rule out the possibility that natural or synthetic cannabis compounds may be useful for the treatment of dysphoria associated with the menopause. It is possible that adverse menopausal symptoms may be ameliorated by compounds which have no effect on LH secretory activity.

ACKNOWLEDGEMENTS

This study was supported in part by Grants DA 00064, DA 02905, and DA 00101 from the National Institute on Drug Abuse. We acknowledge the National Hormone and Pituitary Program, supported by NIDDK and NICHHD for providing LH radioimmunoassay materials.

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