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Acute Effects of Natural and Synthetic Cannabis Compounds on Prolactin Levels in Human Males

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MENDELSON, J. H., J. ELLINGBOE AND N. K. MELLO. *Acute effects of natural and synthetic cannabis compounds on prolactin levels in human males.* PHARMACOL BIOCHEM BEHAV **20**(1) 103–106, 1984.—Plasma prolactin levels were determined in 23 adult males prior to and following administration of Δ^9-tetrahydrocannabinol (THC) (17.5 mg orally), a synthetic cannabis compound, Nabilone (2 mg orally), a 1-g marihuana cigarette containing 1.83% THC, smoked under controlled conditions and placebo capsules and cigarettes for each of the active cannabis compounds. In order to control for possible influence of previous cannabis use history on prolactin response, three groups of subjects were studied—regular (daily) marihuana users, intermittent (weekly) marihuana users, and occasional (monthly) marihuana users. Each subject served as his own control for each drug condition. Double blind studies were conducted on a residential research ward. All baseline prolactin values were within the normal range for healthy adult males. There were no statistically significant differences in plasma prolactin levels among the three subject groups prior to administration of THC, Nabilone, marihuana or their respective placebos. There were no statistically significant changes in prolactin levels following TCH, Nabilone or marihuana smoking. Only placebo administration to regular and occasional marihuana users was followed by a significant increase in plasma prolactin levels. These findings indicate that acute administration of cannabis compounds, either orally or via smoking, does not significantly affect plasma prolactin levels in adult human males.

Prolactin Cannabis Marihuana Nabilone Δ^9-THC

IT has been consistently shown that Δ^9-tetrahydrocannabinol (THC) significantly affects prolactin levels in male and female rodents. An increase in serum prolactin levels was observed in male rats 24 hours following four consecutive daily intraperitoneal THC injections [5]. Administration of a single acute dose of THC to intact male rats [11,12], female rats [4] and ovariectomized rats [7] produced a significant suppression of plasma prolactin levels. Hughes and Tyrey [8] found that an intravenous injection of THC (4 mg/kg) delayed the initiation of the nocturnal prolactin surge induced experimentally by electrical stimulation of the cervix for about 1 hour but did not affect the amplitude and overall duration of the prolactin surge. When THC was administered in dosage of 1 mg/kg on a consecutive hourly basis during the period when prolactin levels normally increase in the female rat, the magnitude of prolactin surge was significantly depressed [8].

A possible adverse consequence of THC inhibition of prolactin secretion was studied by Borgen *et al.* [2], who observed high levels of post-natal mortality in rat pups born to mothers who had been chronically treated with THC during pregnancy. Borgen *et al.* [2] concluded that high post-natal mortality of rat pups occurred because of inadequate maternal lactation. Similar findings of adverse effects of perinatal THC exposure have been reported in mice [6,20]. Raine *et al.* [18] observed a delay in increments in plasma prolactin levels during the post-partum period in mice who had been chronically treated with THC during pregnancy. Bromley *et al.* [3] attempted to determine if THC suppression of prolactin levels during the post-partum period in mice might be due to a THC inhibition of the prolactin surge induced by suckling. A general THC disruption of maternal behavior, however, precluded attempts to obtain an unambiguous answer to this question. Tyrey and Hughes [21] were able to devise a urethane anesthesia procedure to circumvent more general disruption of nursing behavior induced by THC and were able to demonstrate a significant THC inhibition of suckling induced prolactin secretion.

Studies carried out with male and female rhesus monkey [1] have shown that THC produced a significant, but relatively brief, suppression of plasma prolactin levels. An average 84% decrease in plasma prolactin levels for both male and female rhesus monkeys was observed 30 to 180 min following administration of THC. Asch *et al.* [1] studied the site of THC inhibition on prolactin secretion by administering thyrotropin releasing hormone (TRH), which directly stimulates the release of prolactin from the pituitary. Administration of TRH 30 min following THC injection completely reversed THC suppression of prolactin levels. Asch *et al.* [1] concluded that THC inhibition of prolactin secretion is primarily due to the effects of the drug at a hypothalamic level.

In contrast to these studies with experimental animals, two studies in human males have not revealed any significant acute effects of cannabis compounds on plasma prolactin levels. Kolodny *et al.* [10] found no significant changes in

prolactin levels in males following marihuana smoking. Lemberger *et al.* [14] did not observe any significant alterations in serum prolactin levels in males following parenteral administration of THC in studies carried out under double blind conditions.

The purpose of the present study was to determine more precisely if the type of cannabis compound (natural vs. synthetic), route of administration (oral ingestion vs. smoking) or past history of cannabis use influenced plasma prolactin levels following acute administration of these drugs under double blind conditions.

METHOD

Subjects

Twenty-four healthy adult males were recruited through newspaper advertisements and provided informed consent for participation in the study. All subjects selected were in good health according to medical and mental status examinations; electrocardiograms and blood and urine laboratory screening tests were normal. No subject reported use of drugs other than marihuana and none had a past history of drug dependence, alcohol abuse or alcohol dependence.

Subjects were divided into three groups of eight on the basis of their reported frequency of marihuana use. *Regular* users were subjects who smoked 1–3 marihuana cigarettes *per day* and had maintained this pattern of marihuana use for at least one year. Eight subjects with a mean age of 26.8 yr (range 23–30 yr) and a mean weight of 163.8 pounds (range 140–216 pounds) were regular marihuana users. *Intermittent* users smoked 1–3 marihuana cigarettes *per week* and had maintained this pattern of marihuana use for at least one year. Eight subjects with a mean age of 25.3 yr (range 22–30 yr) and a mean weight of 158.6 pounds (range 131–181 pounds) were intermittent marihuana users. *Occasional* users smoked 1–3 marihuana cigarettes *per month* and had maintained this pattern of marihuana use for at least one year. Eight subjects with a mean age of 24.4 yr (range 22–28 yr) and a mean weight of 164.1 pounds (range 133–192 pounds) were occasional users. Final data are reported on 23 subjects; one subject (an intermittent user) left the study after the first experimental day.

Drugs

The effects of six compounds were studied: Nabilone (2 mg oral dose); Nabilone placebo; a 1-g marihuana cigarette containing 1.83% THC; a standardized placebo cigarette; oral THC (17.5 mg) and oral THC placebo capsules. These drugs were administered under double blind and double dummy conditions to control for two routes of administration; e.g., cigarettes and oral capsules. Marihuana and placebo cigarettes were provided by the National Institute on Drug Abuse.

The dose of Nabilone (2 mg) selected for study was based on the clinically effective dose [13]. A slightly larger dose of Nabilone (2.5 mg) would probably induce postural hypotension and place subjects at unnecessary risk for an adverse drug side effect. The oral doses of Δ^9-THC (17.5 mg) and Nabilone (2 mg) are the currently utilized and recommended clinical doses of these drugs as antiemetics for use as adjuncts to cancer chemotherapy [13]. Isbell and associates [9] have shown that the potency of THC after smoking (as determined from changes in peak pulse rate) is approximately 2.6 times that after oral ingestion. The marihuana cigarettes used in the study contained 1.83% THC in each 1-g cigarette. Observations of smoking behavior suggested that subjects actually inhaled only 1/3 of the total pyrolyzed material in any cigarette or approximately 6.1 mg THC.

Sequence of Procedures

Each subject served as his own control over five consecutive days. On days 1 through 4, subjects remained on the research ward from 1800 hr each evening until 0700 hr the following morning when they could leave to attend usual school or job activities. Each subject provided a urine sample for drug screening when he reported to the laboratory each evening. All samples were negative for the presence of psychoactive drugs.

On three of the four drug days subjects received only one dose of an active drug (Nabilone capsule, THC capsule, or marihuana cigarette). In addition, subjects received two placebos to control for two different routes of administration (oral or smoking). On one study day, subjects received no active drug but were given three placebos (marihuana placebo cigarette, Nabilone placebo, and THC placebo). Drugs and placebos were administered according to a 4×4 Latin square design to control for sequence effects.

Questionnaire instruments were administered to assess the type and quality of subjective drug effects and included a Profile of Mood States (POMS) and a "High" scale to assess subjects' levels of intoxication. On the fifth study day, each subject's drug preference was assessed in an operant work-contingent choice procedure. The questionnaire and operant performance data will be reported separately.

Blood samples (10 ml) for prolactin analysis were obtained at 1800 hr (1.5 hr prior to drug or placebo administration) and at 2230 hr (3 hr after drug or placebo capsule administration and 2 hr following marihuana or placebo cigarette smoking). Statistical analysis of these data was carried out with paired t tests for related samples.

Prolactin Radioimmunoassay

Plasma prolactin concentrations were determined by a double antibody radioimmunoassay similar to that described by Midgley [16] for gonadotropins. Anti-prolactin serum was obtained from the National Institute of Arthritis, Metabolism and Digestive Diseases, National Pituitary Agency, University of Maryland School of Medicine. The First International Reference Preparation (75/504) was obtained from the National Biological Standards Board, National Institute for Biological Standards and Control, London. Goat anti-rabbit gamma globulin (GARGG) was purchased from Calbiochem, La Jolla, CA. Radioiodinated human prolactin was supplied by Cambridge Medical Diagnostics, Billerica, MA. All results are expressed as ng/ml 1st IRP, 75/504 (1 mIU=30.8 ng). The assay sensitivity was 3 ng/ml. Intra- and interassay coefficients of variation were 6.5% and 15.7%, respectively. All samples from an individual subject were analyzed in the same assay.

RESULTS

Table 1 presents plasma prolactin levels (ng/ml) for regular, intermittent, and occasional marihuana smokers following placebo, THC, marihuana and Nabilone administration. All plasma prolactin levels prior to and following administration of THC, marihuana, and Nabilone are within the normal basal values for healthy adult males. The average prolactin level for normal adult males determined in our laboratory is 6.5±2.4 ng/ml (range: 2–16 ng/ml).

TABLE 1

PLASMA PROLACTIN (ng/ml) (MEAN ± S.E.)

	Placebo		THC		Marihuana		Nabilone	
Subjects	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Regular Users N=8	7.4 ± 2.6	13.7 ± 4.9*	6.6 ± 2.3	5.6 ± 2.0	7.1 ± 2.5	6.7 ± 2.4	6.9 ± 2.4	7.1 ± 2.5
Intermittent Users N=7	6.7 ± 2.5	7.8 ± 2.3	5.8 ± 2.2	5.4 ± 2.1	5.6 ± 2.1	5.9 ± 2.2	6.0 ± 2.1	6.9 ± 2.4
Occasional Users N=8	7.6 ± 2.7	10.1 ± 3.6*	7.1 ± 2.7	4.5 ± 1.7	5.5 ± 2.0	7.3 ± 2.6	7.3 ± 2.8	6.4 ± 2.4

*Different from pre value $p<0.05$.

There were no statistically significant increases or decreases in plasma prolactin levels following THC, marihuana or Nabilone administration. A statistically significant increase in plasma prolactin levels (compared with pre-placebo values) occurred in regular and occasional users following placebo administration. Intermittent users did not have any statistically significant change in plasma prolactin levels following placebo administration. Although regular and occasional users had a statistically significant increase in prolactin levels following placebo, this is probably not biologically significant since all values were within the normal range for healthy adult males studied in our laboratory.

DISCUSSION

The lack of concordance between the pronounced acute effects of cannabis compounds on prolactin levels in experimental animals and humans can be explained by a number of factors. First, species differences are undoubtedly of primary importance. In rodents, prolactin serves not only as the lactogenic tropic hormone but also has primary luteotropic effects. Cannabis induced suppression of prolactin secretion in rodents is not due to direct inhibition of pituitary function but effects upon central neuroendocrine control of the pituitary [7]. Therefore, differences in cannabis effects upon prolactin secretion in experimental animals, in contrast to humans, may involve species differences in the control of prolactin secretion at suprapituitary sites in the brain.

A second and more parsimonious explanation for differences in acute cannabis effects on prolactin secretion in experimental animals and humans is the dose level of cannabis compounds which has been administered to the different species. In general, dose levels of cannabis compounds administered to both rodents and sub-human primates have been significantly greater than cannabis dosage either experimentally or self-administered to humans (even when dose levels are corrected for square meters of body surface area for the different species).

A third factor which must be considered for comparison of acute cannabis effects on prolactin secretion in experimental animals and humans is drug tolerance. Smith and her associates [19] have reported recently that tolerance develops in the female rhesus monkey to disruptive effects of THC on the primate menstrual cycle. All of the male subjects who participated in this study, including occasional users, had prior experience with marihuana smoking. Although the regular marihuana users involved in this study had a past history of relatively heavy marihuana use in comparison to the intermittent and occasional users, it is possible that tolerance to marihuana effects on prolactin secretion may occur as a consequence of use of relatively small amounts of cannabis compounds.

Markianos and Stefanis [15] have reported that smoking 1.5 g of "cannabis oil" mixed in tobacco produced a small increase in prolactin levels 30 min following smoking. But prolactin levels were not significantly different from baseline controls 120 min following smoking. The prolactin levels observed by Markianos and Stefanis [15] were essentially within the same range of normal basal prolactin levels observed in healthy males. While it is possible that larger doses of cannabis compounds than those employed in this study might alter prolactin levels, acute administration of larger doses of smoked marihuana, THC, or Nabilone would likely produce a number of adverse side effects which could indirectly influence prolactin secretion. There were no adverse side effects following acute administration of cannabis compounds in this study.

All groups of subjects had an increase in prolactin levels following placebo administration which achieved statistical significance for the regular and occasional users. It is possible that a stress induced elevation of prolactin occurred following placebo smoking because the subjects anticipated but did not attain a drug-induced change in mood. It is also possible that the experimental procedure per se induced a stress response. Absence of change in plasma prolactin levels following administration of THC, marihuana cigarettes or Nabilone may have been due to a suppression of stress induced prolactin levels in human males by cannabis compounds. Cannabis compounds may inhibit or attenuate physiological concomitants of human stressors. This hypothesis should be explored within the context of studies designed to elucidate the reinforcing properties of cannabis use and abuse.

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REFERENCES

1. Asch, R. H., C. G. Smith, T. M. Siler-Khodr and C. J. Pauerstein. Acute decreases in serum prolactin concentrations caused by delta-9-tetrahydrocannabinol in nonhuman primates. *Fertil Steril* **32:** 571–575, 1979.
2. Borgen, L. A., W. M. Davis and H. B. Pace. Effects of synthetic Δ^9 tetrahydrocannabinol on pregnancy and offspring in the rat. *Toxicol Appl Pharmacol* **20:** 480–486, 1971.
3. Bromley, B. L., J. Rabii, J. H. Gordon and E. Zimmerman. Delta-9-tetrahydrocannabinol inhibition of suckling-induced prolactin release in the lactating rat. *Endocrinol Res Commun* **5:** 271–278, 1978.
4. Chakravarty, I., A. R. Sheth and J. J. Ghosh. Effect of acute Δ^9-tetrahydrocannabinol treatment on serum luteinizing hormone and prolactin levels in adult female rats. *Fertil Steril* **26:** 947–948, 1975.
5. Daley, J. D., L. A. Branda, J. Rosenfeld and E. V. Younglai. Increase of serum prolactin in male rats by (minus)-trans-delta-9-tetrahydrocannabinol. *J Endocrinol* **63:** 415–416, 1974.
6. Hatoum, N. S., W. M. Davis, M. A. Elsohly and C. E. Turner. Perinatal exposure to cannabinchromene and delta-9-tetrahydrocannabinol: separate and combined effects on viability of pups and on male reproductive system at maturity. *Toxicol Lett* **8:** 141–146, 1981.
7. Hughes, C. L., J. W. Everett and L. Tyrey. Delta-9-tetrahydrocannabinol suppression of prolactin secretion in the rat: lack of direct pituitary effect. *Endocrinology* **109:** 876–880, 1981.
8. Hughes, C. L. and L. Tyrey. Effects of (−)-trans-delta-tetrahydrocannabinol on serum prolactin in the pseudopregnant rat. *Endocrinol Res Commun* **9:** 25–36, 1982.
9. Isbell, H., C. W. Gorodetzsky and D. Jasinski. Effects of (−) Δ^9 trans-tetrahydrocannabinol in man. *Psychopharmacologia* **11:** 184–188, 1967.
10. Kolodny, R. C., W. H. Masters, R. M. Kolodner and G. Toro. Depression of plasma testosterone levels after chronic intensive marihuana use. *N Engl J Med* **290:** 872–874, 1974.
11. Kramer, J. and M. Ben-David. Suppression of prolactin secretion by acute administration of delta-9-THC in rats. *Proc Soc Exp Biol Med* **147:** 482–484, 1974.
12. Kramer, J. and M. Ben-David. Prolactin suppression by (−) delta-9-tetrahydrocannabinol (THC): involvement of serotonergic and dopaminergic pathways. *Endocrinology* **103:** 452–457, 1978.
13. Lemberger, L. and H. Rowe. Clinical pharmacology of Nabilone, a cannabinol derivative. *Clin Pharmacol Ther* **18:** 720–726, 1975.
14. Lemberger, L., R. Crabtree, H. Rowe and J. Clemens. Tetrahydrocannabinols and serum prolactin levels in man. *Life Sci* **16:** 1339–1343, 1973.
15. Markianos, M. and C. Stefanis. Effects of acute cannabis use and short-term deprivation on plasma prolactin and dopamine-β-hydroxylase in long-term users. *Drug Alcohol Depend* **9:** 251–255, 1982.
16. Midgley, A. R. Radioimmunoassay: A method for human chorionic gonadotropin and human luteinizing hormone. *Endocrinology* **79:** 10–18, 1966.
17. Midgley, A. R., G. D. Niswender and R. W. Rebor. Principles for the assessment of the reliability of radioimmunoassay methods (precision, accuracy, sensitivity, specificity). *Acta Endocrinol* Suppl **142:** 163–184, 1969.
18. Raine, J. M., D. R. Wing and W. D. Paton. The effects of delta-l-tetrahydrocannabinol on mammary gland growth, enzyme activity and plasma prolactin levels in the mouse. *Eur J Pharmacol* **51:** 11–17, 1978.
19. Smith, C. G., R. G. Almiriz, J. Barenberg and R. H. Asch. Tolerance develops to the disruptive effects of Δ^9-tetrahydrocannabinol in primate menstrual cycle. *Science* **219:** 1453–1455, 1983.
20. Szepsenwol, J., J. Fletcher, G. L. Murison and E. Toro-Goyco. Long-term effects of delta-9-tetrahydrocannabinol in mice. In: *Marihuana: Biological Effects, Advances BioScience*, vol 22–23, edited by G. G. Nahas and W. D. M. Paton. New York: Pergamon Press, 1979, pp. 359–370.
21. Tyrey, L. and C. L. Hughes. Inhibition of suckling-induced prolactin secretion by Δ^9-tetrahydrocannabinol. In: *Cannabinoids 82*, edited by S. Agurell, W. L. Dewey and R. Willette. New York: Academic Press, 1983, in press.