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Short Report

An Abstinence Syndrome Following Chronic Administration of Delta-9-Tetrahydrocannabinol in Rhesus Monkeys

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Abstract. Chaired, chronically catheterized rhesus monkeys were administered IV delta-9-tetrahydrocannabinol (THC), 0.5 mg/kg every 6 h for 3 weeks. Following the first THC injection, the animals appeared heavy-lidded, immobile, and unresponsive to observation. Tolerance developed to these behaviors during the 3 weeks of THC administration, although the animals remained subdued compared to baseline. Following discontinuation of THC, animals showed an increase in gross movement, eye contact, and tooth baring of greater frequency and/or duration than observed before THC. This presumably represents a cannabis abstinence syndrome.

Key words: Chronic delta-9-tetrahydrocannabinol (THC) – Cannabis – Marijuana – Tolerance – Dependence – Abstinence – Behavior – Rhesus monkey

Tolerance and abstinence to THC, the major active ingredient in marijuana, are observed in rhesus monkeys when high dosing levels are employed (McMillan et al. 1971; Stadnicki et al. 1974). When lower doses are used, 0.4 – 2 mg/kg/day for 30 days, tolerance and abstinence have been reported by some investigators and not by others (Deneau and Kaymakcalan 1971; Harris et al. 1974). In all studies, behavioral changes such as ptosis, irritability, increased aggressiveness, and anorexia were reported but not quantified. We have been studying behavioral and cardiovascular effects of prolonged THC administration in conscious rhesus monkeys. We report here the course of tolerance to the behavioral effects during 3 weeks of THC administration and the occurrence of an abstinence syndrome following discontinuation of dosing.

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Materials and Methods

Four male rhesus monkeys weighing from 4 – 5.5 kg at the start of the experiment were anesthetized and arterial and venous catheters placed into the abdominal vessels through the external iliac vessel. Following 2 weeks recovery from surgery, a 6 week experimental session ensued. The session consisted of 1 week of vehicle injections, 3 weeks of THC injections, and 2 weeks of post-THC vehicle injections. Two mg/kg/day of drug and/or vehicle was administered into the venous catheter in equally divided bolus doses every 6 h by Harvard pump in conjunction with timing and switching circuitry. THC dosing started at 4 p.m. 7 days after vehicle injection was first administered. THC was prepared from National Institute on Drug Abuse stock of 20 mg/ml THC in ethanol. The appropriate dose in ethanol was sonicated in 0.5 ml of 0.05 ml/ml of emulphor (EL 620, Gaff Corp., New York, NY) and saline. Appropriate volumes of this solution were brought to a 2 ml total with saline for each injection. An initial pilot study using three rhesus monkeys whose data are not presented here was conducted twice weekly in order to compile a list of behaviors which changed reliably with drug condition and for which there was a high interrater reliability. In the pilot studies, behavioral changes following termination of THC administration lasted 2 – 4 days. In the final study presented here, observations were done starting at 4:20 p.m. for a 3 min period by one rater once a week for each experimental week in order to minimize interference with cardiovascular measurements done concurrently. The occurrence of specified behaviors was scored by depressing switches that resulted in a line deflection on a multichannel event recorder for the duration of the designated behavior. Each behavior occurrence from momentary to 1.5 s duration was counted as one event. The resulting count of events was analyzed by repeated measures analysis of variance and student Newman Keuls post-tests.

Results and Discussion

Figure 1 shows the total number of occurrences of selected behavioral events for the four animals during observation periods for baseline, THC, and post-THC weeks. Tolerance to the initial drug effect occurred both to that set of behaviors initially elicited by THC (staring and averting head) and to that set of behaviors initially suppressed by the drug (gross movement and eye contact/tooth baring). Hower, during the first post-THC week, all four animals showed a substantial

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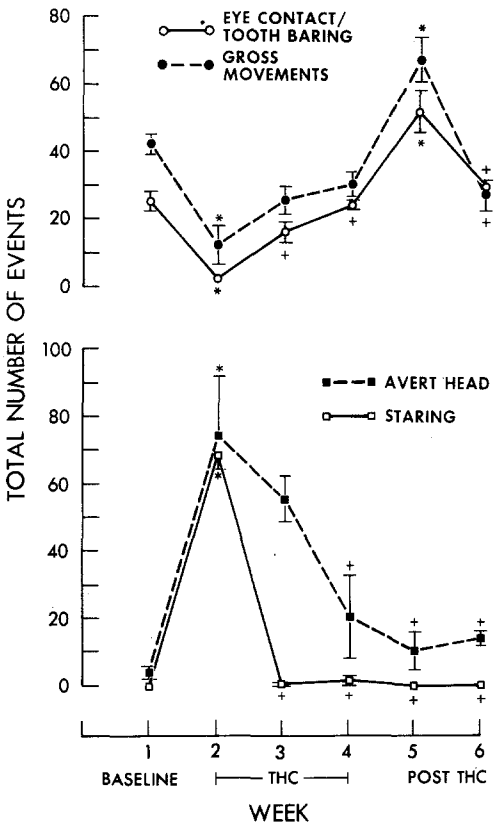

Fig. 1. Occurrence of selected behaviors in chaired rhesus monkeys during 3 min of observation on day 7 of vehicle administration (baseline), days 1, 8, and 20 of THC dosing (THC) and days 3 and 12 of vehicle after THC (post-THC). Data points are the mean of four animals and associated SE's. * different from baseline; $P \leq 0.01$. +indicates different from week 2 (first THC week), $P \leq 0.01$

increase only in those behaviors initially suppressed by THC administration (gross movement, eye contact/tooth baring). By the second post-drug week, occurrence of all behaviors was similar to that during baseline week.

We have confirmed previous reports that tolerance develops to the sedative effects of THC during prolonged administration. We have demonstrated a rebound in the number of events of selected behaviors following cessation of THC treatment. The rebound presumably represents a cannabis abstinence syndrome. Suppression and rebound, especially of REM sleep, are sometimes interpreted as indications of the dependence liability of a drug (Oswald et al. 1969). However, rebound has been reported for drugs not considered addiction risks (Hökfelt et al. 1970). Further, the initial issue of the relationship of REM suppression, rebound, and dependence liability has not been settled (Feinberg et al. 1969). The observation of an abstinence syndrome in rhesus monkeys is consistent with observations made in humans after 2–3 weeks of high dose oral THC (Benowitz and Jones 1975; Jones and Benowitz 1976).

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