Δ¹-Tetrahydrocannabinol, Synhexyl and Marijuana Extract Administered Orally in Man: Catecholamine Excretion, Plasma Cortisol Levels and Platelet Serotonin Content*

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Abstract. Measurements of catecholamine excretion, plasma cortisol and platelet serotonin concentration were done in the course of experiments in which human volunteers were given sizable oral doses of Δ¹-tetrahydrocannabinol, synhexyl or marijuana extracts. A transient rise in epinephrine excretion was observed following THC but seemed best explained by the anticipatory stress of the experiment or the rapid onset of unfamiliar symptoms. A decreased turnover of catecholamines or a shift in the degradative pathways of catecholamines from the oxidative to the reductive route was suggested by the decrease in VMA excretion following synhexyl. Plasma cortisol was unchanged except in the presence of clinically obvious psychological distress on the part of the patient. Platelet serotonin was unchanged.

The lack of major effects of marijuana-like drugs on these and other clinical measurement of stress corroborates the clinical observation that drugs of this type seem to be less stressful than the usual psychotomimetics. The pronounced euphoriant and sedative effect of marijuana may ameliorate the stress of the psychotomimetic experience.

Key-Words: Marijuana — Tetrahydrocannabinol — Catecholamines — Cortisol — Serotonin.

The recent availability of synthetic 1-Δ¹-trans-tetrahydrocannabinol (THC), as well as the development of gas liquid chromatographic techniques for quantifying doses of marijuana extract based on THC content have made possible modern clinical pharmacologic studies of these drugs. The synthetic Δ³-THC analogue, synhexyl, which can also be given in quantitative doses, was also available for study. In the present report, we

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shall be concerned with the effects on catecholamine excretion, plasma cortisol levels and platelet serotonin content of substantial doses of these materials administered orally to man. As accurate determinations of these biochemical measures are fairly recent, no previous measurements of this type have been reported with marijuana-like drugs.

Methods

Excretion of catecholamines and plasma cortisol levels were measured in the context of a clinical experiment comparing the effects of graded doses of THC and synhexyl in normal volunteer subjects. The latter were predominantly medical students, graduate students or hospital staff. The range of doses varied from 30 to 70 mg of THC and 50 to 150 mg of synhexyl given orally on separate occasions (Hollister, Richards, and Gillespie, 1968). After equilibrating at a resting, fasted state in the early morning hours, a two-hour collection of urine was made prior to giving the test dose of drug, followed by two successive two-hour collections. Determination of urinary epinephrine, norepinephrine, metanephrines and vanilmandelic acid (VMA) was done on each sample by techniques previously described (Hollister and Moore, 1967; ibid, 1968). Creatinine excretion was also measured, values for the catecholamines being adjusted to mg creatinine excreted as well as to a time-base. The level of excretion during the control period was compared with that over the first two-hour period as well as over the entire four-hour period. Although 12 subjects provided these data, 2 did not provide a two-hour urine specimen, but only a pooled four-hour specimen. Blood was drawn for determination of plasma cortisol levels just prior to the dose of drug and four hours later. Cortisol levels were measured by usual methods (Mattingly, 1962).

A second experiment was performed in which subjects in a rested and fasting state were given three oral doses of marijuana extract quantified for THC content, as well as a "placebo", consisting of an extract of marijuana from which the cannabinoids had been removed by prior extraction. Although pharmacologically inactive, the latter material retained the disagreeable taste of the other extracts, so that double blind control and random assignment of doses was possible. Doses of 15 to 25 mg of THC equivalent were considered "low", 30 to 45 mg, "medium," and 45 mg or more as "high." Most of the subjects received a series which ran, in order of ascending dose: placebo, 15 mg, 30 mg and 45 mg. Eight subjects completed the full course; others only a partial course. The details of the clinical aspects of this experiment will be reported separately. In addition, a number of subjects were given single doses of marijuana extract, usually in the medium or high dose range, and their relevant data has been pooled with the others. In these experiments,