

*Short communications***Reduction by  $\Delta^9$ -tetrahydrocannabinol in the blood pressure of hypertensive rats bearing re-generated adrenal glands**

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A suspension of (-)- $\Delta^9$ -*trans*-tetrahydrocannabinol ( $\Delta^9$ -THC) (3 mg/kg body wt) was administered daily for one week by i.p. injection to female rats showing the syndrome of adrenal regeneration hypertension (ARH). Other ARH rats received no injections or injections of vehicle only. On the first day,  $\Delta^9$ -THC decreased the average blood pressure by  $38 \pm 6$  mmHg 1 h,  $31 \pm 5$  mmHg 3 h, and  $11 \pm 5$  mmHg 5 h after injection ( $n=10$ ). On subsequent days the acute effect disappeared, but statistically highly significant decreases were observed between the blood pressures of the  $\Delta^9$ -THC-treated group and those of the other two groups. Plasma corticosterone concentrations, measured on the eighth day of treatment, one hour after injection time, averaged  $26.1 \pm 2.7$   $\mu\text{g}/100$  ml in the untreated animals,  $26.6 \pm 2.0$   $\mu\text{g}/100$  ml in the vehicle-injected animals, and  $21.3 \pm 2.4$   $\mu\text{g}/100$  ml in the animals injected with  $\Delta^9$ -THC. The findings indicate that  $\Delta^9$ -THC, at a moderate dose for the rat, is capable of lowering the blood pressure in rats suffering from adrenal regeneration hypertension and that chronic administration of  $\Delta^9$ -THC does not appear to stimulate the pituitary-adrenal axis, in contrast to reported effects of acute administration (Barry, Perhach & Kubena, 1970).

The pharmacological effects of marihuana and its main active principle, (-)- $\Delta^9$ -*trans*-tetrahydrocannabinol ( $\Delta^9$ -THC), have been summarized in several recent reviews (Neumeyer & Shagoury, 1971; Gershon, 1970; Hollister, 1971). Investigations on blood pressure have largely been confined to normotensive subjects. Isbell, Gorodetzsky, Jasinski, Claussen, Von Spulak & Korte (1967) noted no significant changes upon administration of  $\Delta^9$ -THC to human volunteers, but a reduction of blood pressure has been observed in rats (Ho, An, Fritchie, Englert & McIsaac, 1971), dogs

(Garriott, Forney, Hughes & Richards, 1968) and cats (Dagirmanjian & Boyd, 1962) after synthetic tetrahydrocannabinol derivatives. Spontaneously hypertensive rats with an average blood pressure in excess of 200 mmHg, responded to a crude alcoholic extract of marihuana, administered intraperitoneally, by a highly significant, acute reduction in blood pressure to normotensive levels (Birmingham, Oliver, Possanza, Langlois & Stewart, 1972).

The present work deals with effects of  $\Delta^9$ -THC on the blood pressure of rats suffering from adrenal regeneration hypertension.

**Methods.**—Adrenal regeneration hypertension was induced in female Wistar rats (Canadian Breeding Laboratories) by the technique of Skelton (1955). Blood pressures were measured eight weeks after operation from the tail of conscious restrained rats with a Narco Biosystems electrophygmomanometer and Sanborn recorder. The animals were divided into groups of ten. One group received no injections; a second received daily injections of  $\Delta^9$ -THC (Lot. No. SSE 66906, Canadian Food and Drug Directorate), suspended in water with Tween 80 and administered intraperitoneally in the morning at a dose of 3 mg/kg body weight, for eight consecutive days. A third group received injections of vehicle only. The blood pressures of the three groups before the onset of the experiment averaged  $208 \pm 7$  (s.e.) mmHg,  $209 \pm 6$  mmHg and  $210 \pm 6$  mmHg, respectively. During the experiment, blood pressures were measured daily for seven days one hour before, and one, three and five hours after drug administration. On the eighth day, the rats were decapitated, 1 h after injections. Blood was collected from the neck into tubes containing heparin, and the pituitary, thymus, heart, kidney and adrenals were removed and weighed. Corticosterone concentration in the plasma was determined by the method of Zenker & Bernstein (1958).

**Results.**—The results are shown in Figure 1. On the first day of treatment,  $\Delta^9$ -THC caused a striking reduction in blood pressure from a preinjection value of  $200 \pm 6$  mmHg to a minimum of  $162 \pm 4$  mmHg 1 h after injection. On subsequent days, the acute effect disappeared but

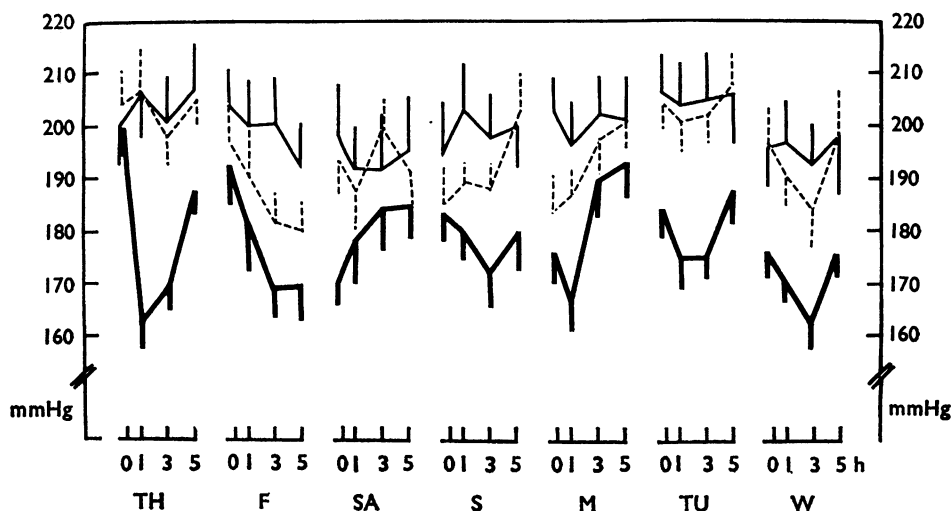


FIG. 1. Effect of  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC) on the blood pressure of female rats showing adrenal regeneration hypertension.  $\Delta^9$ -THC (3 mg/kg body wt) was administered, daily for one week by i.p. injection at 0 time (10.00 hours). Blood pressures were determined before injection (first value of each curve), and 1, 3 and 5 h after injection. Heavy solid curves, rats injected with  $\Delta^9$ -THC; light solid curves, uninjected rats; broken curves, rats injected with vehicle only. Vertical bars indicate S.E.M. ( $n=10$ ). The analyses of variance of unpartitioned data and of data partitioned into days or hours, indicated in all cases highly significant differences associated with group means. Individual comparisons between uninjected and  $\Delta^9$ -THC injected animals gave highly significant differences for each day ( $F=26.3, 14.8, 7.0, 17.2, 16.5, 25.9, 24.6$ ; df 1 and 108;  $F(0.01)=6.9$ ), for each hour ( $F=24.2, 46.4, 40.2, 17.6$ ; df 1 and 189;  $F(0.001)=12.0$ ), and for unpartitioned data ( $F=123.9$ ; df 1 and 756); comparison between vehicle injected and  $\Delta^9$ -THC injected animals gave significant differences for each day, excepting the second, ( $F=25.8, 2.64, 5.66, 5.65, 5.38, 25.1, 19.2$ ; df 1 and 108;  $F(0.05)=4.0$ ), for each hour ( $F=11.0, 25.6, 22.6, 15.5$ ; df 1 and 189;  $F(0.01)=6.8$ ), and a highly significant difference for unpartitioned data ( $F=65.3$ ; df 1 and 756); differences between vehicle injected and uninjected animals were only significant for unpartitioned data ( $F=6.62, P<0.01$ ).

highly significant differences between the blood pressure of the  $\Delta^9$ -THC injected group and the other two groups were observed and assessed by analysis of variance (see legend to Figure 1). The reduction in blood pressure was also evident in measurements taken 23 h after the preceding administration of the drug; these values averaged  $176 \pm 4$  mmHg on the seventh day in the  $\Delta^9$ -THC treated group,  $197 \pm 7$  mmHg in the vehicle-treated group and  $196 \pm 7$  mmHg in the uninjected group.

The plasma corticosterone values, obtained on the eighth day, 1 h after injection time, averaged  $26.1 \pm 2.7$   $\mu\text{g}/100$  ml in the untreated,  $26.6 \pm 2.0$   $\mu\text{g}/100$  ml in the vehicle-treated, and  $21.3 \pm 2.4$   $\mu\text{g}/100$  ml in the  $\Delta^9$ -THC treated rats. No significant differences in body and organ weights were observed.

**Discussion.**—This study indicates that  $\Delta^9$ -THC is capable of lowering the blood pressure in rats suffering from one form of experimentally induced hypertension. A

significant reduction in pre-injection blood pressure was achieved with the administration of a daily injection of 3 mg/kg, a moderate dose for the rat and it was not accompanied by pronounced somatic side effects. Although not apparent when absolute values are considered, the immediate changes following the daily injection of  $\Delta^9$ -THC became less pronounced. This could indicate that some tolerance to  $\Delta^9$ -THC developed or that the effect of  $\Delta^9$ -THC depends on the absolute blood pressure. Contrary to the results reported for acute administration (Barry, Perhach, & Kubena, 1970), chronic administration for a period of one week did not raise the plasma concentrations of corticosterone but, if anything, lowered them. Unfortunately we did not measure the effect of a single injection of  $\Delta^9$ -THC on plasma corticosterone levels of the hypertensive animals. It is therefore not possible to decide whether the lack of effect on corticosterone levels was the result of the

development of tolerance to  $\Delta^9$ -THC. Whether  $\Delta^9$ -THC modifies the pattern of adrenocortical steroids secreted remains to be assessed. The site of action of  $\Delta^9$ -THC in lowering blood pressure also awaits to be established.

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