Tolerance to Delta-9-Tetrahydrocannabinol in the Spontaneously Hypertensive Rat[1] (36957)

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Administration of delta-9-tetrahydrocannabinol (THC) to the anesthetized dog produces a marked and prolonged hypotension (1). In normal man, marihuana extracts or THC, which produce marked psychological alterations, do not alter blood pressure in a systematic fashion (2–4).

In the present experiments, the effects of THC and of marihuana extract distillate (MED) were evaluated in spontaneous hypertensive rats (SHR). This strain has been used to test the efficacy of different antihypertensive drugs (5). Because of the rapid development of tolerance (6) to many of the effects of THC, the drug was administered over a period of several days.

Materials and Methods. Two groups of 12 SHR were fed through a stomach tube 5 to 25 mg/kg of THC in 3% cornstarch with Tween 80. In a first series of experiments, 5 mg/kg THC was administered to 12 hypertensive rats for 5 days. In a second series, dosage of THC was increased over a period of 10 days to 25 mg/kg. In a third group of 12 SHR, MED was administered in dosages containing 5 to 25 mg of THC. Blood pressure was measured daily by the tail plethysmography method and heart rate was computed. Measurements were made once daily in the morning for 3 days, to obtain mean control values. During the test period, measurements of blood pressure were performed once daily 24 hr after administration of the drug. The animals were also weighed daily.

Results. Following administration of 5 mg/kg THC, a significant decrease in blood pressure was observed during the first 2 days after treatment. The maximum decrease occurred 24 hr after the first dose (21 mm Hg ± 3). However, by the third day, blood pressure was not significantly different from control. The animals lost weight significantly throughout the period of treatment (Fig. 1).

In a second series of experiments, increasing the dosage of THC to 10 and 25 mg/kg produced only transient decreases in blood pressure, while weight loss was maintained throughout the period of treatment (Fig. 2). Heart rate, measured 24 hr after treatment with THC, was not significantly different from control. Significant bradycardia was only observed 3 hr after administration of the highest dose (25 mg/kg). After repeated administration of the higher dosage of THC, the animals displayed aggressive behavior, inflicting wounds upon each other.

Similar results were observed when the

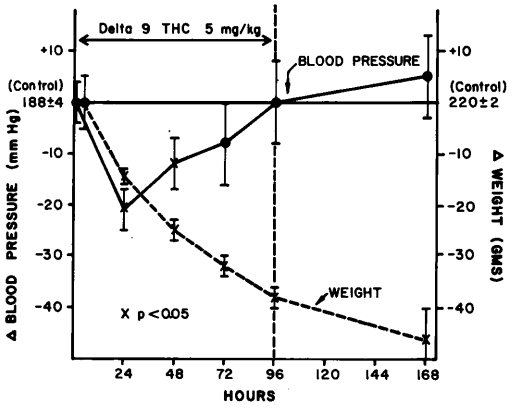

FIG. 1. The development of tolerance to the hypotensive effects of increasing dosage of delta-9-THC in spontaneous hypertensive rats (SHR). The data represent mean changes from control ± SE. Weight loss is maintained below control in the presence of a return of blood pressure to control value. * Significant ($p < 0.05$).

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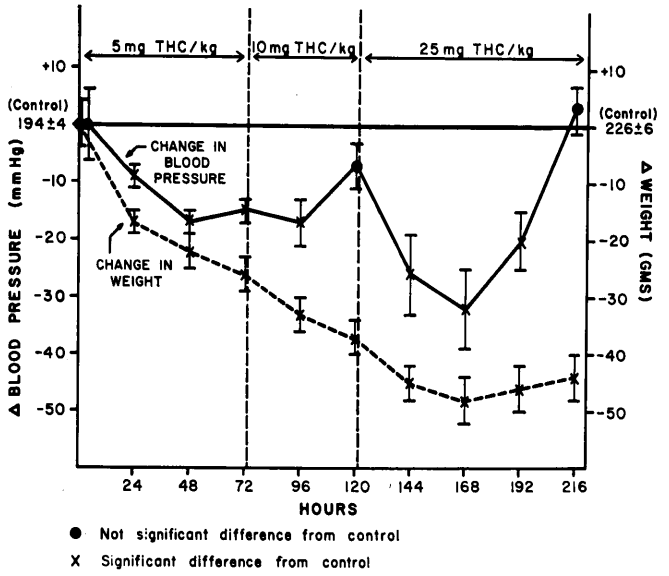

FIG. 2. Effects of delta-9-THC orally administered (5 to 25 mg/kg daily on blood pressure and body weight of spontaneous hypertensive rats (SHR). The data represent mean changes from control ± SE. Note the rapid development of tolerance to the hypotensive effects of THC in the presence of continued weight loss. * Significant ($p < 0.05$).

animals were given per os MED containing equivalent amounts of THC in sesame oil. In this group, animals were weighed during the period which followed cessation of MED administration. All rats had returned to control weight between Days 11 and 17 which followed the last dose (which contained 25 mg THC). One month later the animals were still gaining weight, but weighed less than controls of the same age and had not recovered the weight loss suffered during the experimental period. Manning *et al.* (7) reported similar results.

Control SHR fed with the vehicle, cornstarch and Tween 80, did not present any change in blood pressure over a period of 7 days and did not lose weight.

Discussion. Tolerance to the hypotensive effects of THC and marihuana extract develops rapidly in the spontaneous hypertensive rat. These results are at variance with those reported by Birmingham *et al.* (8) who administered the drug intraperitoneally and who report that "chronic administration of a moderate dose of THC causes a progressive fall in the blood pressure of hypertensive rats." In the present experiment the maximum fall in blood pressure observed with the highest dose did not exceed 40 mm Hg, and only transiently brought the pressure below 150 mm Hg in two animals. This is in contrast with other hypotensive drugs such as hydralazine, methyldopa or reserpine, which lower blood pressure below 120 mm Hg for 6 mo or more when administered chronically to the SHR (5).

The significant progressive loss of weight of the animals during administration of THC is also maintained several days after cessation of treatment. These data are in agreement with those reported by others who showed that this weight loss could be related to an anorectic effect of THC (8). It would seem that hypertensive rats will develop tolerance more slowly to the anorectic effects of THC than to its hypotensive effects. If the hypotensive effect of THC is due to peripheral vasodilatation, as suggested by Beaconfield, Ginsburg and Rainsbury (9), it would appear that tolerance to the peripheral autonomic effects of THC develops more rapidly than tolerance to its central effects.

Summary. Tolerance to the hypotensive effects of 5 to 25 mg/kg of delta-9-THC orally administered develops in spontaneous hypertensive rats within 9 days. The weight

loss produced by similar doses is maintained throughout the period of therapy.

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