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SHORT COMMUNICATIONS

1 - Δ^9-Tetrahydrocannabinol—Effects on the urinary excretion of 5-hydroxyindole acetic acid

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1 - Δ^9-TETRAHYDROCANNABINOL (Δ^9-THC), the major active constituent in cannabis preparations[1–4] is being used as a tool in the studies of the neuropharmacological effects of cannabis. Holtzman *et al.*[5] have studied the effects of the drug on the brain amine levels and reported that Δ^9-THC elevates the 5-hydroxytryptamine (5-HT) content in the rat brain without any significant change in the 5-hydroxyindole acetic acid (5-HIAA) level. But LSD, the well known psychotomimetic agent, raises the 5-HT level in the brain with a simultaneous reduction of the 5-HIAA content and, therefore, it has been concluded that this drug either increases the "binding" or reduces the metabolism of 5-HT in the brain.[6] Obviously, the exact mechanism responsible for the increase in the 5-HT concentrations in the brain due to Δ^9-THC is not clear.[5] In an attempt to understand further the effects of Δ^9-THC on the metabolism 5-HT, the urinary excretion of 5-HIAA has been studied.

Materials and Methods

Male albino rats weighing 100–120 g were used. Urine was collected over 1 ml of 2 N HCl for 16 hr, during which period food was removed from the metabolism cages. Saline-Tween 80 suspension of Δ^9-THC* (0·5 ml) was injected intraperitoneally at 10 and 100 mg/kg doses. In some experiments the treatment was continued for 7 consecutive days and urine was collected following the last injection. Control rats received saline-Tween vehicle in equivalent volume by the same route. Urines were frozen pending analysis. 5-HIAA in pooled urine was estimated by the method of Udenfriend *et al.*,[7] as modified by Bertlet.[8] Values reported have been corrected for "recovery" by duplicate analysis of each pooled sample. Δ^9-THC apparently did not interfere with the spectrophotometric assay of 5-HIAA. Creatinine was estimated by the sodium picrate method after extraction of the urine with peroxide free ether as described by Taussky.[9]

Results and Discussion

In Fig. 1 is presented the effect of Δ^9-THC on the excretion of 5-HIAA in albino rats and it will be evident therein that the drug elevated the 5-HIAA content in the urine. While a slight, but statistically insignificant, rise (6 per cent) was observed following a single injection at 10 mg/kg dose, the treatment for 7 consecutive days at the same dose level caused a moderate increase (16 per cent, $P < 0{\cdot}05$). However, the latter rise was still less marked than that (22 per cent, $P < 0{\cdot}05$) due to a single massive dose of the drug (100 mg/kg). Since the excretion of creatinine did not significantly change in all experiments after Δ^9-THC administration, the glomerular filtration was not affected by the drug and therefore, any change in the 5-HIAA excretion due to the cannabinol may be assumed to be absolute.

Holtzman *et al.*[5] observed that Δ^9-THC at 10–100 mg/kg doses increased the 5-HT content in the rat brain to the extent of 15–25 per cent and although slightly raised, 5-HIAA concentrations in the brain did not show statistically significant changes with either dose or time. In view of the above report, the results of the present study indicate that the effects of Δ^9-THC on the metabolism of 5-HT in other organs should be investigated in order to understand the significance of the changes in the 5-HIAA content in the urine. Since the 5-HIAA content in the urine reflects the overall 5-HT metabolism in an animal, the changes in brain 5-HT may not always be correlated with the changes in the urinary 5-HIAA following a drug treatment. Thus, in Bertlet's experiments,[8] although chlorpromazine (20 mg/kg) did not significantly alter the brain 5-HT content, the amount of 5-HIAA excreted in the urine was considerably reduced. Furthermore, a drug may differentially affect the 5-HT metabolism in various organs, such as brain, liver, kidney, heart and spleen. In fact, chlorpromazine, BOL and LSD have been shown to behave in this way.[10] LSD reduces the excretion of 5-HIAA in the urine,[11] while Δ^9-THC is observed in the present studies to increase the same. It is probable that the mode of

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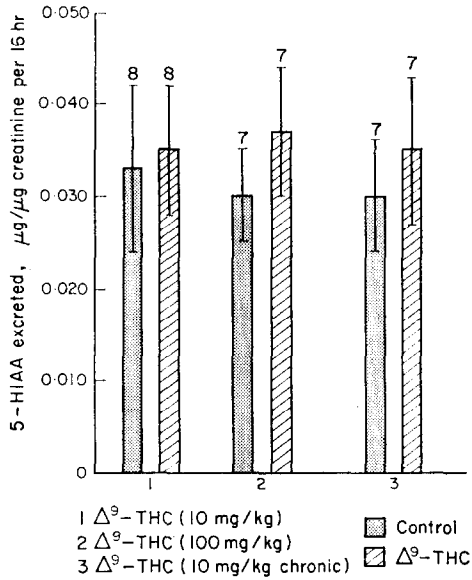

FIG. 1. Effects of 1 - Δ^9-tetrahydrocannabinol (Δ^9-THC) on the urinary excretion of 5-hydroxyindole acetic acid (5-HIAA) in albino rats. Each column depicts a mean value, the standard error and number of experiments being shown by a vertical bar and numeral at the end of the column respectively.

Mean value ± S.E. for creatinine excreted:
(μg/g body weight/16 hr)

	1	2	3
Control	12·3 ± 3·4	12·2 ± 3·0	10·3 ± 2·6
Δ^9-THC	10·8 ± 2·6	11·8 ± 2·3	10·2 ± 2·3

* $P < 0.05$.

action of the two psychotomimetic agents, LSD and Δ^9-THC on the metabolism and/or turnover of 5-HT is different.

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