Marijuana: Some Pharmacological Studies

Keyphrases ☐ Marijuana, effects—6-week pharmacological and toxicity study, rats ☐ Δ^9-Tetrahydrocannabinol, effects—6-week pharmacological and toxicity study, rats

Sir:

l-Δ^9-Tetrahydrocannabinol is the major psychoactive component of marijuana. Interest has developed in examining its effects in animals for the possible implications in humans. We wish to report studies on the pharmacology and toxicity of Δ^9-tetrahydrocannabinol in rats following repeated inhalation.

Δ^9-Tetrahydrocannabinol (10 mg.), prepared from the Δ^8-isomer as described in the literature (1), was dissolved in light petroleum ether (b.p. 30–60°) and injected into a half-length cigarette. The petroleum ether was allowed to evaporate, and the cigarettes were then mounted on wire at the bottom of large vacuum desiccators. Male Sprague-Dawley rats, 200–250 g., in groups of three were exposed to the smoke of Δ^9-tetrahydrocannabinol in the closed container every day for 10 min. excluding weekends for 6 weeks. A previous experiment using the same method with tritiated Δ^9-tetrahydrocannabinol had shown the retention of radioactivity in animals for 7 days after one exposure to the smoke (2).

Cardiovascular effects were evaluated by the measurement of blood pressure from the caudal artery with a physiograph. CNS activities were determined as the change in motor activity using an activity cage[1] and the time the animals were able to remain on a rotating rod. All pharmacological tests (six animals per group) were performed twice a week at least 18 hr. after an inhalation period to avoid the peak action of Δ^9-tetrahydrocannabinol (usually observable around 2–4 hr. after administration of the compound). Two control groups were used for comparison: one group inhaled the smoke from cigarettes without Δ^9-tetrahydrocannabinol and the other group were nonsmoking animals. The body weights of the three groups were also recorded weekly.

Animals were sacrificed at the end of the 6th week. Adrenals, brain, heart, kidneys, liver, lungs, testes, and spleen were carefully dissected and weighed to the milligram. All values were analyzed statistically using the Student *t* test. Slices of brain, kidney, liver, and lung were immediately fixed with 2% glutaraldehyde for histological studies. Plasma samples were obtained from the blood for determination of glutamic oxaloacetic transaminase and urea nitrogen.

[1] Metro Scientific Co.

A significant fall in blood pressure below that of both the cigarette control and nonsmoking animals was observed in rats that had repeatedly inhaled the smoke containing Δ^9-tetrahydrocannabinol for 5 and 6 weeks: 5th week, blood pressure (mm. Hg) 131.7 ± 6.06 (nonsmoking controls, A), 127.4 ± 4.18 (cigarette controls, B), 116.7 ± 9.83 (Δ^9-tetrahydrocannabinol-treated, C), no significant difference between A and B but a significant difference between B and C ($p < 0.05$) and A and C ($p < 0.01$); 6th week, 127.5 ± 2.74 (A), 124.2 ± 8.01 (B), 115.0 ± 6.32 (C), no significant difference between A and B, significant difference between B and C ($p < 0.10$) and A and C ($p < 0.001$). No significant change was noted before the 5th week.

Repeated inhalation of Δ-^{9}tetrahydrocannabinol resulted in a slightly increased motor activity of the animals at the final week of study. The increase was over both the cigarette control and nonsmoking groups ($p < 0.10$). The two control groups did not differ in motor activity. Although cigarette smoke impaired the animals' performance on the rotarod, no difference was observed between the cigarette- and Δ^9-tetrahydrocannabinol-treated animals.

When compared with the two groups of control animals, no weight variation in rats was detected during the 6 weeks of Δ^9-tetrahydrocannabinol inhalation. Nor did any variation occur in the weights of individual organs examined. Gross histological studies did not reveal any morphological changes due to the smoke containing Δ^9-tetrahydrocannabinol. Results from plasma glutamic oxaloacetic transaminase and urea nitrogen tests indicated no impairment of liver or kidney function. All these findings were obtained from only a 6-week study, and the results might be different if the length of exposure to Δ^9-tetrahydrocannabinol smoke was longer.

(1) R. Mechoulam, P. Braun, and Y. Gaoni, *J. Amer. Chem. Soc.*, **89**, 4552(1967).

(2) B. T. Ho, G. E. Fritchie, P. M. Kralik, L. F. Englert, W. M. McIsaac, and J. E. Idänpään-Heikkilä, *J. Pharm. Pharmacol.*, **22**, 538(1970).

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