Short communications

Distribution of tritium labelled Δ^1-tetrahydrocannabinol in the rat brain following intraperitoneal administration

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Tritiated Δ^1-tetrahydrocannabinol was injected intraperitoneally into rats and its distribution measured in the brain for up to 30 days after administration. The results showed that there was no selective distribution in any one area of the brain. The maximum levels of radioactivity occurred 1 h after the injection of the tetrahydrocannabinol, thereafter the levels fell very slowly, with demonstrable activity still present at the end of 30 days.

Miras (1964) found that 1·5 h after the intraperitoneal injection of ^{14}C tetrahydrocannabinol (^{14}C THC), 0·18% of the injected dose was present in the brain, compared with about 5% in the liver. In the same paper Miras reported that after the administration of cannabis to rats there was a potentiation of barbiturate sleeping time, which could be detected for up to 30 days. More recently Agurell, Nilsson, Ohlsson & Sandberg (1969) have found that after an intraperitoneal injection of $^3H\Delta^1$-THC the compound was eliminated very slowly, with less than 50% eliminated in the first week.

We thought it would be of interest to investigate the regional distribution of $^3H\Delta^1$-THC in the brain following an intraperitoneal injection of the drug, and also how long the radioactivity remained in the brain. As a consequence of the results which we obtained we reinvestigated the effects of cannabis on barbiturate sleeping time.

Methods.—*Radioactive studies.* Approximately 100 mg ^3H-THC was prepared according to the method of Agurell *et al.* (1969). The activity of the product was 91 μCi/mg. The compound was stored as a 10 mg/ml solution in toluene under nitrogen gas at −20° C. Directly before use the toluene was evaporated with a stream of nitrogen and the ^3H-THC was suspended in normal saline (0·9% NaCl) containing 4% Tween 80, to give a concentration of 5 mg THC/ml. Wistar rats (120–150 g) of either sex were injected with 10 mg/kg THC intraperitoneally; control rats were injected with a similar volume of 0·9% NaCl containing 4% Tween 80. Six animals were killed at each of the following times: 20 min, 1, 2, 4 or 6 h and 7, 14, 21 or 30 days after the administration of the drug. The brains were removed and dissected into the following areas—cerebellum, cerebral cortex, hippocampus, medulla and pons, remainder of brain. A small portion of each area was weighed and transferred to a scintillation counting vial containing 'Soluene 100' to dissolve the tissue. When the tissue had dissolved, scintillator was added and the radioactivity measured in a Packard Tri-carb Scintillation Counter.

Barbiturate sleeping time. Twelve female Wistar rats (120–200 g) were injected intraperitoneally with 100 mg/kg cannabis resin extract (containing approximately 200 mg Δ^1-THC/g extract) dissolved in olive oil. Twelve control animals were injected by the same route with a similar volume of olive oil. After 14 days the rats were injected with sodium hexobarbitone (100 mg/kg) and the sleeping time measured.

Results.—The distribution of $^3H\Delta^1$-THC in the different areas of the brain at the various time intervals after administration is shown in Table 1. There are no significant differences in the levels of $^3H\Delta^1$-THC between any of the areas studied. The radioactivity in the brain rose rapidly, reaching a maximum level at 1 hour. The level then fell very slowly with two-thirds of the maximum radioactivity still present after 6 hours. By interpolation from the 1 and 2 h values, the level in the brain at 1·5 h would be approximately 0·2% of the total injected radioactivity. Seven days after the administration of the ^3H-THC there was still an appreciable amount of radioactivity in the brain, about a quarter of that seen after 1 h, and radioactivity could still be detected 30 days after the administration of the drug. In the control rats the average sleeping time following the injection of sodium hexobarbitone (100 mg/kg) was $25{\cdot}25 \pm 3{\cdot}51$ min (S.E. of mean), compared with the cannabis treated animals which was $27{\cdot}5 \pm 1{\cdot}56$ min.

TABLE 1. *Distribution of radioactivity in different areas of rat brain at various times after injection of* $^3H\Delta^1$*-THC*

Area	20 min	1 h	2 h	4 h	6 h	7 days	14 days	21 days	30 days
Cerebral cortex	3,526±95	6,438±61	5,415±260	5,579±214	3,853±248	1,454±65	326±12	104±15	43±4
Hippocampus	3,058±114	6,054±104	5,169±201	5,686±212	3,987±263	1,513±72	337±11	109±15	41±5
Cerebellum	3,362±181	6,303±189	5,594±365	5.933±348	3,980±353	1,478±119	334±19	107±20	33±6
Medulla and pons	3,300±21	6,056±277	5,753±440	6,086±376	3,899±324	1,405±107	337±12	126±23	51±9
Remainder	3,484±169	6,487±69	5,710±403	6,039±329	3,970±356	1,471±115	330±14	125±34	44±7
Average	3,346	6,276	5,528	5,864	3,937	1,464	333	114	42

Results expressed as d.p.m. $\times 10^{-2}$/g brain tissue ±S.E. $\times 10^{-2}$

(S.E. of mean). The difference between these times is not significant.

Discussion.—The lack of any significant differences in the radioactivity found in the different areas of the brain following the administration of $^{3}H\Delta^{1}$-THC is of interest. THC is a highly lipophilic drug with an octanol: water partition ratio higher than most of the barbiturates (Gill, Paton & Pertwee, 1970) and it would be expected that a higher concentration of THC would be found in white matter than in grey matter. These experiments do not indicate whether the THC was evenly distributed throughout the tissue or whether it became bound to specific sites. If a labelled sample of THC can be obtained with a high enough specific activity, it is hoped to extend these observations using autoradiography.

The percentage of the total dose injected which was found in the brain after 1·5 h was similar to that reported by Miras (1964). We observed a 50% decline in brain levels after 1 week following an intraperitoneal injection. This represents an appreciable amount present after 1 week and may partially explain the long lasting effects of THC in monkeys as shown by Scheckel, Boff, Dahlem & Smart (1968). Our results are in contrast to those of Ho, Fritchie, Kralik, Englert, McIsaac & Idänpään-Heikkilä (1970) who found that following the administration of ^{3}H-THC by inhalation there was less than a 25% decline in brain levels after 1 week.

We were unable to confirm the results of Miras (1964) that cannabis potentiated barbiturate sleeping time up to 30 days after administration, as we observed no effects after 14 days.

The results which we have obtained together with the work of previous workers indicate that THC is retained for long periods by brain tissue, consequently the habitual use of cannabis could result in high accumulation of THC in brain.

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