The effect of Δ^9-tetrahydrocannabinol on brain amine concentration and turnover in whole rat brain and in various regions of the brain

Most of the early reports concerning the effects of cannabis on the putative neurotransmitter amines in the central nervous system used impure extracts of varying origin. However, even since the identification of Δ^9-tetrahydrocannabinol (THC) as the major psychoactive component of cannabis, there have been many contradictory reports about the effects of this substance on both endogenous levels and turnover of brain noradrenaline, dopamine and 5-hydroxytryptamine (5-HT). In experiments where rats were used, most authors have reported no change in endogenous concentrations of dopamine (Maitre, Staehelin & Bein, 1970; Leonard, 1971; Maitre, Baumann & Delini-Stula, 1972), no change in noradrenaline concentrations in whole brain (Leonard, 1971; Maitre & others, 1970; Schildkraut & Efron, 1971; Maitre & others, 1972), with either an increase (Sofia, Dixit & Barry, 1971; Schildkraut & Efron, 1971) or no change (Gallagher, Sanders-Bush & Sulser, 1972; Leonard, 1971) in 5-HT concentrations. Studies with mice have not necessarily yielded the same results or trends (see e.g. Holtzmann, Lovell & others, 1969). Reports on amine concentrations in various brain regions and amine turnover in these regions, are even more scanty (see e.g. Colombini, Westfall & McCoy, 1970; Constantinidis & Miras, 1971).

In view of the still confused state of the literature, and because of the importance of determining any effect that acute administration of THC might have on brain amines for the interpretation of previous work from this laboratory (see Chesher, Hazleton & others (1972); Chesher, Dahl & others, 1973; Anderson, Jackson & Chesher, 1974; Chesher & Jackson, 1974; Chesher, Jackson & Starmer, 1974), we examined the effects of THC on 5-HT, dopamine and noradrenaline concentrations, both in whole brain and in various parts of the brain. In addition, using the synthesis inhibition method, we examined noradrenaline and dopamine disappearance. Male Wistar rats (150–350 g), random bred, kept on a light-dark cycle of 0700–1800 h and 1800–0700 h respectively, at 22 ± 2°, were matched according to weight into THC-treated and vehicle control treated groups. THC, dissolved in a stock solution of propylene glycol (kept at −20°), was prepared immediately before administration as a suspension in Lissapol-Dispersol (ICI) (Whittle, 1964) to give a concentration of propylene glycol in lissapol of 5% v/v. Both THC and the vehicle were administered by gavage in a dose volume of 10 ml kg^{-1}, and because cannabis produces hypothermia (Garratini, 1965; Gill, Paton & Pertwee, 1970), after cannabis administration all rats were kept at 31°, the approximate thermally neutral zone for rats (Herrington, 1940). Animals were always killed between 10.00 and 12.00 h to control for diurnal variation. In all experiments THC in a dose of 20 mg kg^{-1} (or vehicle) was administered 1 h before death (except in turnover studies where a dose of 60 mg THC kg^{-1} was given with 30 min premedication period); 30 min to 2 h is the time at which maximum behavioural changes occur after acutely administered THC in both rats and mice (Dewey, Harris & Kennedy, 1972; Drew, Miller & Wikler, 1972; Gallagher & others, 1972; Chesher & others, 1973). Individual brains were removed immediately after decapitation and dissected essentially by the method of Glowinski & Iversen (1966) and noradrenaline and dopamine extracted and assayed according to Welch & Welch (1969) and 5-HT extracted according to Bogdanski, Pletscher & others (1956), and assayed according to Snyder, Axelrod & Zweig (1965). Most data are presented as the mean amine concentration (ng g^{-1} wet weight) ± s.e.m., uncorrected for recovery (which were from all experiments) for dopamine 57 ± 1% (n = 136); noradrenaline 59 ± 1% (146); 5-HT 52 ± 1% (114), the theoretically maximum recoveries being 68, 70 and 73% respectively. Table 1 shows that no significant changes were observed in either

Table 1. *The effect of Δ^9-THC (20 mg kg^{-1}) administered 1 h before death on endogenous concentrations of rat brain catecholamines and 5-HT.* The data are uncorrected for recovery (see text) and represent the ng of amine g^{-1} wet weight of tissue ± s.e.m. The number of observations is in brackets. C = vehicle controls, T = THC treated.

Amine		Whole brain	Neostriatum	Hypothalamus plus mid-brain thalamus	Cerebellum	Ponsmedulla
NA	C	242 ± 5 (10)	907 ± 72 (6)	726 ± 49 (6)	144 ± 9 (6)	397 ± 18 (6)
	T	255 ± 8 (12)	1032 ± 102 (4)	725 ± 55 (4)	149 ± 18 (4)	375 ± 22 (4)
DA	C	362 ± 15 (9)	5509 ± 314 (7)	263 ± 69 (4)		
	T	377 ± 14 (12)	5856 ± 298 (4)	154 ± 67 (4)		
5-HT	C	262 ± 11 (9)	456 ± 69 (6)	576 ± 67 (7)	70 ± 9 (6)	407 ± 29 (7)
	T	269 ± 8 (13)	301 ± 27 (5)	523 ± 66 (6)	52 ± 14 (5)	426 ± 29 (6)

Table 2. *The effect of Δ^9-THC (60 mg kg^{-1}) administered 2 h before α-MT (see text) on the rate of amine depletion in rat brain.* The data are expressed as a percentage of normal values ± s.e.m. The normal values are considered as 100% in each case. C = vehicle controls, T = THC treated. The values in brackets represent the sum of control and treated observations.

		Brain region % depletion			
Amine		Whole brain	Neostriatum	Hypothalamus plus midbrain Thalamus	Ponsmedulla
NA	T	59 ± 10 (12)	42 ± 12 (7)	19 ± 11 (7)	48 ± 6 (7)
	C	51 ± 9 (12)	45 ± 8 (7)	24 ± 6 (7)	38 ± 5 (7)
DA	T	61 ± 3 (12)	54 ± 9 (7)		
	C	65 ± 6 (12)	60 ± 6 (7)		

whole brain concentrations of dopamine, noradrenaline or 5-HT, or in noradrenaline or 5-HT concentrations in the neostriatum, hypothalamus plus mid-brain thalamus, cerebellum or ponsmedulla, or in dopamine concentrations in neostriatum or hypothalamus plus mid-brain thalamus. Using DL-α-methyl-*p*-tyrosine methyl ester hydrochloride (α-MT), dissolved in saline, administered intraperitoneally 3 h before death (2 h before the THC), in a dose of 250 mg kg^{-1}, we were unable to detect any changes in either whole brain noradrenaline or dopamine disappearance rate, or noradrenaline disappearance in the neostriatum, hypothalamus plus mid-brain thalamus or pons medulla, or dopamine in the neostriatum (Table 2). In other experiments, using an extract containing 33% Δ^9-THC, 6% Δ^8-THC and 21% cannabidiol (see Chesher & others, 1973 for method of extract preparation), doses as high as the equivalent of 80 mg THC kg^{-1} in extract form were also ineffective in modifying whole rat brain amine levels (Bracs, Jackson & Chesher, unpublished observations). Also, other experiments examining noradrenaline and dopamine disappearance rates with 20 mg THC kg^{-1} revealed no significant differences (Bracs, Jackson & Chesher, unpublished). The data presented here confirm results from previous studies (see above references) that comparatively high doses of THC are without effect on either endogenous con-

centrations of 5-HT, noradrenaline or dopamine or on dopamine and noradrenaline turnover; this supports a previous suggestion that at least some of the acute behavioural effects of THC in laboratory animals are exerted independently of an effect on brain neurotransmitter function (Chesher & others, 1974). However, it should be noted that some species differences may be involved, as Holtzmann & others (1969) and Welch, Welch & others (1971) have reported increased 5-HT brain concentrations in mice after Δ^9-THC, with dose-dependent changes in noradrenaline and 5-HT reported by Ho, Taylor & others (1972). Although chronic studies, in contrast to acute studies, have reported some changes in 5-HT and noradrenaline in rat brain after THC treatment (Ho, Taylor & Englert, 1973), from the data reported here it appears unlikely that behavioural effects produced in rats after acute THC administration are a result of any marked effect on brain function mediated by noradrenaline or dopamine.

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