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Δ^9-Tetrahydrocannabinol reduces brain regional histamine concentrations

M.R. Fennessy, S.J. Lewis*, D.A. Taylor** & A.J.M. Verberne

Department of Pharmacology, University of Melbourne, Parkville, Victoria, 3052; Department of Medicine*, Clinical Pharmacology & Therapeutics Unit, University of Melbourne, Austin Hospital, Heidelberg, Victoria, 3084 and School of Pharmacology**, Victorian College of Pharmacy, Parkville, Victoria, 3052, Australia

The effect of Δ^9-tetrahydrocannabinol (Δ^9-THC) on rat brain regional histamine concentrations was examined. Δ^9-THC reduced the histamine concentration of the hypothalamus, midbrain and cortex. It is suggested that Δ^9-THC may release histamine in the rat brain and that this amine may mediate some of the pharmacological effects of Δ^9-THC.

Introduction Despite a considerable number of investigations into the mode of action of the tetrahydrocannabinols (THCs), many questions remain unanswered (for review, see Burstein & Hunter, 1981). Many of the pharmacological and neurochemical effects of the THCs are stereospecific (Edery, Grunfeld, Ben-Zvi & Mechoulam, 1971; Revuelta, Cheney, Costa, Lander & Mechoulam, 1980) and a distinct structure-activity relationship for the THCs, and their synthetic derivatives, has been demonstrated (Mechoulam, McCallum & Burstein, 1976; Mechoulam, Lander, Varkony, Kimmel, Becker, Ben-Zvi, Edery & Porath, 1980). This evidence strongly suggests that the THCs exert their pharmacological effects through specific receptors. These receptors presumably would be located on particular neurones in the central nervous system. Accordingly, many investigators have examined the neurochemical effects of the THCs and have implicated central 5-hydroxytryptaminergic (Taylor & Fennessy, 1978), dopaminergic (Bhattacharya, Aulakh, Pradhan, Ghosh & Pradhan, 1980), noradrenergic (Mazurkiewicz-Kwilecki & Filczewski, 1973), cholinergic (Revuelta *et al.*, 1980) and GABA-ergic (Revuelta, Cheney, Wood & Costa, 1979) mechanisms. Despite this considerable neurochemical investigation, the possible involvement of brain histaminergic mechanisms in the effects of the THCs has not been examined, even though histamine is considered to be a putative neurotransmitter in the mammalian CNS (Schwartz, Pollard & Quach, 1980; Lomax & Green, 1981). Glick & Crane (1978) have reported that microinjections of histamine into specific rat brain sites produce hypothermia, catalepsy, increased grooming and irritability (squealing, jumping and biting in response to touch). Since such behavioural and physiological effects are similar to those produced by an acute dose of Δ^9-THC (Fennessy & Taylor, 1977; Taylor & Fennessy, 1977), it is of importance to investigate, as a preliminary study, the effects of Δ^9-THC on brain regional histamine concentrations in the rat.

Methods Male albino Wistar rats weighing 220–260 g were used. All experiments were performed in a room with an ambient temperature of 21 ± 1°C. Δ^9-THC was suspended in normal saline (0.9% w/v NaCl solution) using polyvinylpyrrolidone (PVP) according to the method of Fenimore & Loy (1971). For the intravenous (i.v.) injection of drugs, cannulae were implanted into the external jugular veins of individually-caged rats according to the method of Fennessy & Taylor (1977). Rats were allowed 48 h to recover before the injection of either Δ^9-THC (2 mg/kg, i.v.) or the vehicle PVP (40 mg/kg, i.v.) in volumes of 1 ml/kg body weight. After 30 or 120 min, the rats were decapitated, their brains rapidly removed, blotted free of blood and placed on an ice-cold glass plate for dissection. The chilled brains were dissected into five regions (hypothalamus, cortex, cerebellum, midbrain and medulla oblongata/pons) according to the method of Glowinski & Iversen (1966). The dissected tissues were stored at −20°C until they were assayed. Brain regional histamine concentrations were determined spectrophotofluorometrically following column chromatographic isolation of this amine using the weak cation exchange resin Bio-Rex 70 as described previously (Lewis, Fennessy, Laska & Taylor, 1980). For testing the statistical significance of differences between means, Student's *t* test was used.

Results Preliminary studies demonstrated that PVP (1–100 mg/kg, i.v.), compared to saline control, did not affect brain histamine concentration. The data in Table 1 show that Δ^9-THC (2 mg/kg, i.v.) produces statistically significant reductions in the histamine concentrations of the hypothalamus, mid-

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Table 1 The effect of Δ^9-tetrahydrocannabinol (Δ^9-THC, 2 mg/kg, i.v.) and polyvinylpyrrolidine (PVP, 40 mg/kg, i.v.) on brain regional histamine concentrations of the rat 30 and 120 min after administration

Brain region	*Time (min)*	*Histamine concentration (ng/g)*		*% of PVP control*
		PVP	*Δ^9-THC*	
Hypothalamus	30	237.7 ± 9.8	128.9 ± 25.0*	54.2 ± 7.0
	120	192.6 ± 21.4	198.8 ± 21.4	103.2 ± 16.0
Midbrain	30	46.3 ± 8.5	18.4 ± 2.4*	39.7 ± 18.5
	120	39.9 ± 6.1	29.7 ± 4.9	74.4 ± 17.8
Cortex	30	21.6 ± 2.3	6.1 ± 1.0*	28.2 ± 10.7
	120	22.0 ± 2.9	19.0 ± 2.1	86.4 ± 15.6
Medulla oblongata/pons	30	34.5 ± 4.8	28.9 ± 4.4	83.8 ± 17.5
	120	30.4 ± 3.2	20.0 ± 1.5*	65.8 ± 11.0
Cerebellum	30	40.7 ± 3.8	32.4 ± 4.8	79.6 ± 13.2
	120	36.3 ± 2.8	31.7 ± 3.3	87.3 ± 11.1

Values are means ± s.e.mean, $n = 5$ rats per group.
*$P < 0.05$ compared to the PVP control.

brain and cortex 30 min after administration. The histamine concentrations in these brain regions were not significantly different from those of the PVP control concentrations 120 min after Δ^9-THC administration. However, a significant reduction in the histamine concentration of the medulla oblongata/pons was observed 120 min but not 30 min after Δ^9-THC. With respect to brain regional sensitivity towards Δ^9-THC, the largest reductions in histamine concentrations occurred within the cortex (71.8%), midbrain (60.3%) and hypothalamus (45.8%) 30 min after administration. On the other hand, a significant reduction in histamine concentration occurred in the medulla oblongata/pons (34.2%) 120 min after Δ^9-THC. The dose of Δ^9-THC used did not produce any statistically significant change in the histamine concentration of the cerebellum at either 30 or 120 min.

Discussion The present study has demonstrated that acute administration of Δ^9-THC (2 mg/kg, i.v.) reduces the histamine concentration of several regions of the rat brain. Although the decrease in brain regional histamine concentration may result from a Δ^9-THC-induced increase in the release of this amine, it may conceivably also occur via a decrease in histamine synthesis through inhibition of histidine decarboxylase. However, it is considered that the former is the more reasonable explanation since the pharmacological effects of Δ^9-THC, such as hypothermia, catalepsy and irritability, are consistent with the effects produced by centrally administered histamine (Glick & Crane, 1978). In addition, only specific types of compounds (usually derivatives of histamine) are potent inhibitors of histidine decarboxylase (Taylor & Snyder, 1972; Kollonitsch, Patchett, Marburg, Maycock, Perkins, Doldouras, Duggan & Aster, 1978). Although histamine is thought to be stored in both neurones and mast-cells, the results of the present study suggest that Δ^9-THC primarily affects neuronal release since the Δ^9-THC-induced decreases in the histamine concentrations of the hypothalamus, cortex and midbrain were not maintained for 2 h. If mast-cell degranulation was involved, then the concomitant decrease in the histamine concentration would be expected to be maintained for at least 4–8 h due to the slow recovery rate of histamine stores within these cells (Martres, Baudry & Schwartz, 1975). Furthermore, the site of the hypothermic action of Δ^9-THC as proposed by Hosko, Schmeling & Hardman (1981), that is the caudal brain stem, coincides with the origins of an ascending histaminergic neuronal projection which courses through the hypothalamus via the medial forebrain bundle (Garbarg, Barbin, Feger & Schwartz, 1974). This pathway then innervates both the whole telencephalon and also the hippocampus (Barbin, Garbarg, Schwartz & Storm-Mathisen, 1976). As such, it can be envisaged that stimulation of the histaminergic cell bodies by Δ^9-THC would result in release of histamine in brain regions such as the cortex, midbrain and hypothalamus. Since no high-affinity reuptake mechanism for histamine has been shown (Tuomisto, Tuomisto & Walaszek, 1975), a decrease in the histamine concentrations of these brain regions should follow.

In conclusion, Δ^9-THC appears to release histamine in the CNS of the rat and, as such, it is suggested that histamine may mediate some of the pharmacological effects of Δ^9-THC.

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