Interaction between delta-6-tetrahydrocannabinol (delta-6-THC) and lithium at the blood brain barrier in rats

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Summary. Neither the acute nor the chronic i.p. administration of delta-6-tetrahydrocannabinol affected the passage of lithium from blood to brain in normal rats.

This report outlines the data obtained in a study of the interaction between delta-6-tetrahydrocannabinol (delta-6-THC) and lithium at the blood brain barrier of normal rats, and shows that neither the acute nor the chronic administration of delta-6-THC affects passage of the lithium ion from blood to brain of the normal rat.

This study was initiated because of a) our interest in lithium as a clinically useful but potentially toxic therapeutic agent, b) THC's known qualitative and quantitative effects on the EEG[2-4], and c) after a report appeared in 1975[5] which described that THC could modify the blood brain barrier. The authors[5] outlined the appearance of convulsions in dogs into which penicillin had been injected and which had simultaneously smoked marihuana and concluded that some active ingredient in the marihuana smoke had altered the permeability of the dog's blood brain barrier, thus allowing the penicillin convulsions to ensue as if the penicillin had been applied directly to the dog's central nervous system. This report led us to speculate that one of the active ingredients of marihuana (in our case the delta-6-THC derivative - about as active as delta-1-THC and with similar psychological effects in man[6,7]) might alter the blood brain barrier in such a way so as to enhance the passage of the lithium ion into the brain, and thus possibly allow therapeutic maintenance in manic-depressive illness at lower dosage levels with resultant prevention and/or lessening of lithium's potential toxicity.

Method. The 56 male Sabra rats, weighing between 250 and 350 g, used in this study were housed 5 per cage and allowed free access to food and water until sacrificed.

Lithium ion, in the form of its chloride salt, was slowly infused (2-3 min) into the rat's tail vein at a concentration of 7.5 mEq/kg in a total volume of 0.2 ml/200 g b.wt. 2 or 24 h after administering the lithium, the animals were sacrificed by decapitation. Blood was collected from the severed neck vessels, centrifuged immediately and plasma stored at $-10\,^{\circ}C$ until assayed for lithium. At the time of assay, the plasma samples were diluted 1:3 or 1:5 with distilled water as required. At sacrifice, the brains were removed within 1-3 min, dried, weighed and dissolved in 6 ml of soluene-100 as described by Bond et al.[8]. Prior to assay, each brain sample was diluted 2-3fold with 1.4-dioxan as required[8]. The lithium ion was determined by atomic absorption spectrophotometry, using a Perkin Elmer 403 Atomic Absorption Spectrophotometer[9], adjustments according to the Perkin Elmer Analytical Methods Manual. Standard curves in distilled water, plasma and soluene-dioxan were simultaneously carried out with each assay, and each assay included a control tissue (brain) and plasma blank (plasma and brain taken from an untreated animal).

Delta-6-THC[10] was dissolved in ethanol/propylene glycol (1:10), acutely injected in a dose of 10 mg/kg i.p. (0.2 ml/200 g b.wt) 1 h prior to the administration of lithium and also injected chronically for 1 week in a dosage schedule of 1 mg/kg/day i.p. (0.2 ml/200 g b.wt), the animals being administered the lithium 1 h following the last dose of THC and sacrificed at 2 or 24 h thereafter as described above.

Results and discussion. The results are detailed in the table. Our control lithium data are in agreement with the rat blood-brain kinetic lithium data reported by Ebadi et al.[11] and it is clear that neither the acute nor the chronic administration of delta-6-THC affects the passage of lithium from the blood to the brain in our experimental animals. THC appears to have no potential role in lithium therapy.

Concentration of lithium in blood and brain with or without delta-6-THC*

	At 2 h		At 24 h	
	Blood (mean ± SEM)	Brain (mean ± SEM)	Blood (mean ± SEM)	Brain (mean ± SEM)
Acute control (7.5 mEq/kg Li**)	3.86±0.36 (13)***	0.58±0.06 (13)	1.87±0.26 (8)	1.00±0.13 (9)
Acute delta-6-THC (10 mg/kg i.p., 1 h prior to 7.5 mEq/kg Li)	4.02±0.56 (10)	0.60±0.11 (10)	2.01±0.65 (4)	0.89±0.24 (4)
Chronic vehicle control (ethanolpropylene glycol (1:10), 0.2 ml/200 g/day for 1 week prior to 7.5 mEq/kg Li)	3.83±0.68 (5)	0.54±0.14 (5)	1.27±0.40 (5)	1.22±0.19 (5)
Chronic delta-6-THC (1 mg/kg/day for 1 week prior to 7.5 mEq/kg Li)	4.78±0.43 (8)	0.90±0.14 (7)	1.62±0.35 (8)	1.51±0.17 (8)

* Delta-6-tetrahydrocannabinol. ** Lithium.
*** The figures within all the brackets represent the number (n) of animals in each set of experiments.

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