A possible role for 5-hydroxytryptamine in drug-induced seizures

The pattern of convulsive seizures seen in rats injected with leptazol (pentylenetetrazol) was used to test the anticonvulsive properties of several drugs that affect brain monoamine metabolism. Seizures were measured after 40 mg/kg of leptazol followed by other drug treatment according to the following index. Phase I: no seizure (A) or mild myoclonic head jerk (B). Phase II: clonic-tonic convulsions (C) and loss of righting reflex for 3 s or less (D). Phase III: loss of righting reflex for 5–10 s (E) and prolonged loss of righting reflex, over 2 min (F). Phase IV: death (G). All injections were given intraperitoneally. The latency period before seizure was 75 s ($\pm$10 s). When phenobarbitone (6 mg/kg) was given 1 h before leptazol, an increase in the rat seizure threshold was seen (Table 1). Treatment with the peripheral decarboxylase inhibitor Ro 4–4602 [*N*-(DL-seryl-N^1-2,3,4-trihydroxybenzyl)hydrazine] followed 30 min later by 100 mg/kg of 5-hydroxytryptophan (5-HTP) 1 h before leptazol, resulted in no seizures in 35% of the rats while the remaining 65% had only a mild myoclonic head jerk (Table 1). At the same doses, single injections of either Ro 4–4602 or 5-HTP did not alter the susceptibility of the animal to leptazol compared with the controls.

Table 1. *Relative seizure susceptibility to leptazol after various drugs.* Phase I, indicates no or very mild seizure; Phase II, moderate seizure; Phase III, severe convulsions, Phase IV, death. Numbers indicate % rats; total number of animals are shown in parenthesis. Comparatively good protection in phenobarbitone-treated rats (75% under Phase II) while excellent protection is seen after Ro 4–4602 + 5-HTP (100% Phase I).

	Dose mg/kg	Phase I		Phase II		Phase III		Phase IV
		A	B	C	D	E	F	G
Disulfiram*	3×100	—	—	10 (1)	10 (1)	80 (8)	—	—
α-Methyltyrosine*	3×100	—	—	10 (1)	20 (2)	70 (7)	—	—
Ro 4–4602*	50	—	5 (1)	5 (1)	5 (1)	70 (14)	—	15 (3)
5-HTP*	100		5 (1)	30 (6)	5 (1)	60 (12)	—	—
Phenobarbitone†	6	10 (2)	5 (1)	55 (11)	30 (6)	—	—	—
Ro 4–4602 + 5-HTP‡	50+100	35 (7)	65 (13)	—	—	—	—	—
Leptazol	40	—	—	10 (8)	5 (4)	80 (64)	2·5 (2)	2·5 (2)

* $P = > 0{\cdot}05$ (n.s.). † $P = < 0{\cdot}01$. ‡ $P = < 0{\cdot}001$.

The dopamine-β-hydroxylase inhibitor disulfiram and the tyrosine hydroxylase inhibitor α-methyl tyrosine when given at 100 mg/kg daily for 3 days did not significantly change the rat seizure threshold when compared to leptazol controls. Both these compounds can reduce brain catecholamines by inhibiting the formation of either noradrenaline or dopamine (Musacchio, Kopin & Snyder, 1964; Corrodi & Hanson, 1966).

Similarly, the tryptophan hydroxylase inhibitor *p*-chlorophenylalanine (p-CPA) was administered for 3 days at 100 mg/kg daily but with leptazol reduced to 35 mg/kg. At this last dose, 45% of the leptazol controls had no seizure, 25% had clonic-tonic convulsions and 30% had brief loss of righting reflex 5–10 s (Table 2). After *p*-CPA, however, the seizure pattern was exacerbated. In addition, 24 h after a strong single dose of *p*-CPA (316 mg/kg) all rats had severe loss of righting reflex when challenged with 35 mg/kg of leptazol (Table 2).

Table 2. *Seizure susceptibility in* p-*chlorophenylalanine* (*p-CPA*)*-treated rats.* Leptazol was reduced to 35 mg/kg for better evaluation of the *p*-CPA effect. Rats treated for 3 days with 100 mg/kg daily of *p*-CPA show a decrease in seizure threshold with 65% in Phase III, severe convulsions. Susceptibility to leptazol is markedly enhanced after a single strong dose of *p*-CPA as seen by 100% Phase III, severe convulsions, versus 70% leptazol controls Phase I and II. *P* values as in Table 1.

	Dose mg/kg	Phase I		Phase II		Phase III		Phase IV
		A	B	C	D	E	F	G
p-CPA‡	316	—	—	—	—	—	100 (20)	—
p-CPA†	3×100	20 (4)	—	—	15 (3)	25 (5)	40 (8)	—
Leptazol	35	45 (9)	—	25 (5)	—	36 (6)	—	—

The brain 5-HT after 316 mg/kg of *p*-CPA has been reported (Koe & Weissman, 1966) to decrease to 11% of control values as opposed to 21% of control levels following *p*-CPA for 3 days at 100 mg/kg.

p-CPA can reduce the shock intensity threshold for tonic extension in rats (Koe & Weissman, 1968) and also lower the resistance of mice to electroshock seizures (Chen, Ensor & Bohner, 1968). 5-HT, on the other hand, is reported (Laborit, Coirault & others, 1958) to protect animals subjected to convulsive fits induced by oxygen under high pressure. Moreover, many anticonvulsive compounds such as phenobarbitone, diphenylhydantoin, nitrozepam and others, have been shown to selectively increase 5-HT in animals in no other organ but the brain (Bonnycastle, Giarman & Paasonen, 1957).

Our experiments suggest that affecting brain 5-HT levels with 5-HTP in conjunction with a peripheral decarboxylase inhibitor, may result in decreased neuronal excitability induced by leptazol. It also seems that adequate penetration of 5-HTP into brain tissue cannot be achieved effectively without prior inhibition of peripheral decarboxylase activity (de la Torre, 1968). This is due to extracerebral decarboxylation and conversion of the injected 5-HTP to 5-HT which remains at the brain capillary level until breakdown by monoamine oxidase (de la Torre, 1970).

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