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Enhancement of the convulsant action of thiosemicarbazide in mice

Reserpine-like agents enhance seizure suceptability to leptazol (Chen, Ensor & Bohner, 1954) and reduce the effectiveness of most, if not all, anticonvulsants in mice (Chen & others, 1954; Gray, Rauh & others, 1958, 1963; Mennear & Rudzik, 1966). I have now made experiments on the effects of two catecholamine-depleting agents on the convulsant activity of thiosemicarbazide.

Male albino mice (Harlan Industries), 18–22 g, were housed in groups of 25 before experimentation and then individually after intraperitoneal injection of 100 mg/kg of thiosemicarbazide. Ten mice were used in each experimental group.

α-Methyltyrosine, suspended in corn oil, was administered intraperitoneally in three daily doses of 150 mg/kg. Ninety min after the administration of the third dose the mice received an intraperitoneal injection of thiosemicarbazide. The second catecholamine depletor, Ro4-1284 (2-ethyl-1,2,3,4,6,7-hexahydro-2-hydroxy-3-isobutyl-9,10-dimethoxy-11b*H*-benzoquinolizine), was administered in an intraperitoneal dose of 20 mg/kg simultaneously with the dose of thiosemicarbazide. Three end points were measured; the onset time for clonic seizures; the onset time for tonic seizures and the time of death.

The results summarized in Table 1 show the potentiating effect of Ro4-1284 on the convulsant action of thiosemicarbazide. In control mice the mean latency time for the onset of the initial clonic seizure was 41 ± 4 min and tonic seizures developed

Table 1. *Effect of* Ro4-1284* *and α-methyltyrosine‡ (α-MT) on the convulsant action of thiosemicarbazide†*

	Ro4-1284*			α-Methyltyrosine		
End point	Treatment	Min to end point ± s.e.	P	Treatment	Min to end point ± s.e.	P
Clonic seizure	Control	41 ± 4	<0·05	Control	31 ± 2	n.s.
	Ro4-1284	30 ± 2		α-MT	36 ± 4	
Tonic seizure	Control	46 ± 4	<0·01	Control	36 ± 2	n.s.
	Ro4-1284	30 ± 2		α-MT	36 ± 4	
Death	Control	54 ± 2	<0·001	Control	49 ± 3	<0·05
	Ro4-1284	30 ± 2		α-MT	37 ± 4	

* 20 mg/kg i.p. † 100 mg/kg i.p. ‡ 150 mg/kg/day for 3 days.

after a further latency of approximately 5 min. In these animals the initial tonic seizure was seldom terminal and the mean survival time after the onset of seizure activity was 13 min. In mice pretreated with Ro4-1284 the effects of thiosemicarbazide were produced significantly sooner than after the administration of the convulsant alone. The initial clonic seizure appeared after only 30 ± 2 min and proceeded immediately into the tonic phase. Similarly, all animals which had received both Ro4-1284 and thiosemicarbazide died during this initial convulsive episode.

Unlike Ro4-1284, α-methyltyrosine did not significantly alter the onset time of the initial clonic seizure induced by thiosemicarbazide (Table 1). A striking similarity between the effects of α-methyltyrosine and Ro4-1284 was however noted. The initial clonic seizure in the α-methyltyrosine-treated animals uniformly proceeded directly into the tonic phase of the seizure pattern. Also, all but one of the α-methyltyrosine-treated animals died during the first seizure. The animal which did not die during the initial seizure survived only 3 min after the onset of convulsive activity. The mean survival time after onset of convulsions in control mice was 18 min.

The results of these experiments clearly demonstrate that both Ro4-1284 and α-methyltyrosine markedly enhance the convulsant activity of thiosemicarbazide. The mechanism of potentiation of thiosemicarbazide and other seizure-inducing treatments by these agents remains obscure. Because both Ro4-1284 and α-methyltyrosine are known to influence the disposition of brain catecholamines, it is tempting to attribute these results to a lowering of brain amines.

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