the result of release of 5-HT, and preliminary results suggest that the hypotensive action of L-dopa in dogs may be similarly mediated.

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Potentiation of leptazol seizures by 6-hydroxydopamine

A considerable body of evidence suggests that monoaminergic systems in the brain act to decrease the seizure susceptibility of animals (reviewed by Maynert, 1969). For example, injections of monoamine oxidase inhibitors, which raise brain monoamine levels, inhibit audiogenic seizures in rodents (e.g. Lehmann & Busnel, 1963), while treatment with 5-hydroxytryptophan, the immediate precursor of 5-hydroxytryptamine, decreases the photogenic seizure response of epileptic baboons (Wada, Balzamo & others, 1972). Conversely, administration of L-amino-acid decarboxylase inhibitors or reserpine, which non-specifically lower the levels of monoamines, increases seizure susceptibility (e.g. Jenney, 1954; Rudzik & Mennear, 1966).

It is of interest to determine the extent of the participation of catecholaminergic systems as opposed to 5-hydroxytryptaminergic systems in these effects. Unfortunately, however, the non-specificity of the pharmacological treatments previously employed does not permit such a discrimination. Non-specificity must be considered even when putative neurotransmitters or their precursors are administered, since there is evidence for the uptake of externally applied doses of these agents into cells that do not normally contain them (e.g. Butcher, Engel & Fuxe, 1972; Ng, Chase & others, 1972).

The use of 6-hydroxydopamine (6-OHDA) provides a partial solution to this question since relatively small doses of this drug injected intracerebrally have been shown to produce selective destruction of catecholaminergic but not 5-hydroxy-

tryptaminergic or other neural systems (e.g. Uretsky & Iversen, 1970; McGeer, Fibiger & others, 1973). We therefore examined the convulsive effects of subcutaneous leptazol injections in normal rats and in rats whose central catecholamines had been destroyed by intracerebral 6-OHDA.

Five male hooded rats, 200–250 g, were given an intraperitoneal injection of the monoamine oxidase inhibitor tranylcypromine sulphate at a dose of 5 mg kg^{-1}. Thirty min later the rats were anaesthetized with ether, and 250 μg of 6-OHDA dissolved in 25 μl of 0·9% NaCl with ascorbic acid (1 mg ml^{-1}) was injected into the lateral ventricle of each rat. Five control rats were treated in the same manner except that no 6-OHDA was contained in the solution injected intraventricularly. Thirty to 45 days after treatment each rat received a subcutaneous injection of leptazol into the caudal back. The dose administered was 70 mg kg^{-1}, the CD 97 for clonic convulsions (Swinyard, 1969). Each rat was then placed in a test cage and the occurrence of behavioral seizures was observed for one hour.

As shown in Table 1, the rats that had received 6-OHDA displayed a shorter latency to the first myoclonic jerk (Mann-Whitney $U = 3$, $P = 0{\cdot}028$), a shorter latency to the first convulsion ($U = 1$, $P = 0{\cdot}008$), and a longer duration of the first convulsion ($U = 0$, $P = 0{\cdot}004$) than the control rats. Three of the 6-OHDA rats subsequently exhibited a second generalized convulsion of extremely long duration, while only one control rat had a second clonic convulsion and that of a brief duration. Perhaps the most significant finding is that four of the 6-OHDA-treated rats displayed a tonic extension during their first convulsion, while none of the control rats displayed anything more than clonic manifestations. This difference between the groups is highly significant (Fisher's exact probability test, $P = 0{\cdot}0007$). There were also episodes of tonic extension during the second convulsion in two of the three 6-OHDA rats displaying a second convulsion, while only the expected clonic manifestations appeared in the sole control rat exhibiting more than one convulsion.

Two weeks after the leptazol study four control rats and the four surviving 6-OHDA treated rats were killed by cervical fracture, and their brains were removed. The brains were divided into a midbrain, hypothalamic, and caudate component according to a previously described method (Fibiger & McGeer, 1971), and tyrosine

Table 1. *Convulsive effects of leptazol in control and 6-OHDA treated rats.*

	Latency to first myoclonic jerk	Latency to first convulsion	Duration of first convulsion	Latency to second convulsion	Duration of second convulsion
Controls	14:20	33:05	28 s	—	—
	33:00	— (60:00)	— (0)	—	—
	12:08	20:08	27	—	—
	5:40	21:15	45	—	—
	7:22	10:24	41	27:05	38 s
	$\bar{X}$=14:28	$\bar{X}$=28:58	$\bar{X}$=28·2s		
6-OHDA	7:45	11:15	*70 s	—	—
	6:45	9:53	*72	20:00	*630 s
	4:50	7:00	110	—	—
	5:30	6:35	*80	12:03	502† s
	2:55	5:29	*66	52:30	*1800‡ s
	$\bar{X}$= 5:33	$\bar{X}$= 8:02	$\bar{X}$=79·6 s		

* Convulsion included tonic extension.
† Convulsion terminated with i.p. administration of 30 mg kg^{-1} phenobarbitone sodium followed by death.
‡ Convulsion terminated 10 min after i.p. administration of 1·25 mg kg^{-1} diazepam.

Table 2. *Effect of 6-hydroxydopamine on tyrosine hydroxylase activity (n mol dopa g^{-1} tissue h^{-1}) in 3 brain regions.*

	Control	6-Hydroxydopamine
Midbrain	22·0±2·4	6·3±1·6*
Hypothalamus	29·9±6·4	17·5±1·5*
Striatum	110·5±11·4	18·2±7·6*

Data represent mean (± s.d.) of 4 animals in each group. Tyrosine hydroxylase activity was measured by the method of McGeer, Gibson & McGeer (1967).

* Significantly different from controls $P<0·03$.

hydroxylase levels in each of these areas were measured using the method of McGeer, Gibson & McGeer (1967). The results are seen in Table 2, and it is obvious that the 6-OHDA treatment produced highly significant decreases in tyrosine hydroxylase activity in all three brain regions.

Since destruction of central catecholaminergic systems by intracerebral injection of 6-OHDA greatly potentiates convulsions induced by leptazol, we conclude that these systems normally participate in the suppression of seizure activity. It is possible of course that 5-hydroxytryptaminergic or other neurochemical systems also exert a suppressive influence on seizures, an issue which cannot be resolved on the basis of these results. However, the antiseizure activity of non-catecholaminergic systems, if it occurs, is clearly not sufficient to compensate for the effects of selective catecholaminergic destruction.

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