The role of dopamine in sound-induced convulsions

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Investigations concerned with the role of brain biogenic amines in convulsive seizures have led to widespread agreement that endogenous noradrenaline functions as a modulator of experimentally-induced convulsions (Lehman, 1967; Bourn, Chin, & Picchioni, 1972; Jobe, Picchioni, & Chin, 1973, a,b,c; Wenger, Stitzel, & Craig, 1973; Jobe, Stull, & Geiger, 1974). The role of dopamine in this condition is less clear. While there is evidence that dopamine may act to suppress seizure discharge, (DeSchaepdryver, Piette, & Delaunois, 1962; Goldberg & Salama, 1969; Boggan & Seiden, 1971; Stull, Jobe & others, 1973), This hypothesis is not supported by the work of Pfeifer & Galambos (1967). Jobe & others (1973a,b,c), and Wenger & others (1973).

The purpose of the present study was to demonstrate whether selective impairment of dopamine function, accomplished by administration of 6-hydroxydopamine following pretreatment with desipramine, would result in alteration of audiogenic seizure severity.

Female rats from The University of Arizona strain of audiogenic rats were used. Only animals having a minimal audiogenic response score (ARS) of 2 or 3 (see below), were included. All rats received implantations of permanent intracerebroventricular cannulae. Seven days after cannulation, animals were tested for minimal audiogenic seizure response and were divided into four groups of 12 rats. Treatments were as follows: Group I (controls), 20 μl of normal saline containing 0·01% ascorbic acid was injected into the ventricle 1 h following intraperitoneal injection of deionized water, 1 ml kg^{-1}; Group II, 20 μl of saline-ascorbic acid vehicle was injected intraventricularly 1 h following an intraperitoneal injection of desipramine 25 mg kg^{-1} in a volume of 1 ml kg^{-1}; Group III, 200 μg of 6-hydroxydopamine in 20 μl of saline-ascorbic acid vehicle was injected intraventricularly 1 h after an intraperitoneal injection of deionized water, 1 ml kg^{-1}; Group IV, 200 μg of 6-hydroxydopamine in saline-ascorbic acid vehicle was injected intraventricularly 1 h following intraperitoneal injection of desipramine, 25 mg kg^{-1} in a volume of 1 ml kg^{-1}.

Seven days after treatment, 5 rats from each group were killed and brain regions assayed for noradrenaline and dopamine. Brains were dissected by a modification of the method of Glowinski & Iversen (1966), and were divided into: cerebral cortex, nucleus caudatus putamen (striatum), pons-medulla (brainstem), hypothalamus, spinal cord (from directly below the level of the medulla through mid-thoracic vertebrae), and the remainder of the brain. Noradrenaline and dopamine were assayed by the method of Cox & Perhack (1973), an iodine oxidation method, allowing determination of both amines from the same sample after adsorption on alumina.

Rats not killed for regional brain assays were tested for ARS. Seizure severity was measured by a scoring

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Table 1. *The effect of intraventricular injection of 6-hydroxydopamine (6-OHDA) after intraperitoneal injection of desipramine on regional brain noradrenaline (NH) and dopamine (DA) concentrations.*

	% control catecholamine concn[a] ± s.e.m.					
	Desipramine[b]		6-OHDA[c]		Desipramine[d] + 6-OHDA	
Brain region	NA	DA	NA	DA	NA	DA
Cortex	98·7 ± 4·6 NS	98·8 ± 4·8 NS	11·8 ± 2·4 ($P<0·005$)	38·6 ± 1·9 ($P<0·005$)	89·8 ± 4·2 NS	19·7 ± 2·5 ($P<0·005$)
Spinal cord	102·6 ± 7·5 NS	100·0 ± 18·8 NS	34·5 ± 3·9 ($P<0·005$)	95·0 ± 9·6 NS	95·5 ± 76·8 NS	101·7 ± 16·7 NS
Striatum	96·1 ± 5·2 NS	101·5 ± 1·7 NS	20·5 ± 2·7 ($P<0·005$)	50·9 ± 1·7 ($P<0·005$)	81·7 ± 8·6 NS	49·1 ± 2·0 ($P<0·005$)
Hypothalamus	104·4 ± 3·4 NS	110·7 ± 6·3 NS	30·1 ± 1·4 ($P<0·005$)	24·0 ± 8·3 ($P<0·005$)	95·0 ± 4·2 NS	24·9 ± 4·9 ($P<0·005$)
Pons-medulla	98·8 ± 1·5 NS	104·6 ± 5·6 NS	31·5 ± 3·9 ($P<0·005$)	92·6 ± 6·8 NS	94·1 ± 2·1 NS	80·0 ± 4·8 ($P<0·01$)
Remainder	94·5 ± 3·6 NS	95·7 ± 3·1 NS	4·9 ± 0·8 ($P<0·005$)	92·4 ± 2·7 NS	95·6 ± 4·0 NS	95·7 ± 3·7 NS

[a] Catecholamine concentration was determined 7 days following injections. n = 5.
[b] Desipramine HCl, 25 mg kg^{-1}, i.p. + intraventricular injection of saline-ascorbic acid vehicle, 20 μl, 1 h later.
[c] Distilled water, 1 ml kg^{-1}, i.p. + intraventricular injection of 6-OHDA, 200 μg/20 μl, 1 h later.
[d] Desipramine HCl, 25 mg kg^{-1}, i.p. + intraventricular injection of 6-OHDA, 200 μg/20 μl, 1 h later.

Table 2. *The effect of intraventricular injection of 6-hydroxydopamine after pretreatment with desipramine on audiogenic response score.*

	Audiogenic seizure response score ±s.e.m.			
	Control[a]	Desipramine[b]	6-OHDA[c]	Desipramine +6-OHDA[d]
Pre-treatment[e]	2·4 ± 0·3	2·9 ± 0·5	3·0 ± 0·4	2·6 ± 0·5
Post-treatment[f]	2·6 ± 0·3	3·1 ± 0·4	7·1 ± 0·9 ($P<0·001$)[g]	3·0 ± 0·6

a. Distilled water, 1 ml kg^{-1}, i.p. + intraventricular injection of saline-ascorbic acid vehicle, 20 µl, 1 h later.
b. Desipramine HCl, 25 mg kg^{-1}, i.p. + intraventricular injection of saline-ascorbic acid vehicle, 20 µl, 1 h later.
c. Distilled water, 1 ml kg^{-1}, i.p. + intraventricular injection of 6-OHDA, 200 µg/20 µl, 1 h later.
d. Desipramine HCl, 25 mg kg^{-1}, i.p. + intraventricular injection of 6-OHDA, 200 µg/20 µl, 1 h later.
e. Rats were tested for minimal response 7 days after surgery, 2 days before injections. n = 7.
f. Rats were tested for ARS 7 days after injections.
g. Compared to pretreatment Audiogenic Response Score.

system with a range of 1 to 9, with the least severe score (score of 1) consisting of running activity only, and the most severe (score of 9) consisting of running activity followed by convulsive activity progressing to full tonic extension of the hind limbs (Jobe & others, 1973a). Seizures were induced by ringing two electric bells producing approximately 120 db inside a soundproof testing chamber.

Desipramine produced no significant change in concentration of catecholamines in any region of the brain that was assayed (Table 1) and it caused no significant change in ARS (Table 2). 6-Hydroxydopamine caused significant reduction of noradrenaline concentration in all six regions of the cns assayed (Table 1); significant reduction of dopamine in the cortex, striatum, and hypothalamus (Table 1), and a significant increase of ARS (Table 2). In comparison, the combination treatment of desipramine followed by 6-hydroxydopamine produced no significant change in noradrenaline concentration in any of the six regions assayed, a significant decrease in dopamine concentration in the cortex and striatum (Table 1), and no significant change in ARS (Table 2).

Depletion of noradrenaline by 6-hydroxydopamine was effectively prevented by pretreatment with desipramine, whereas dopamine depletion in the cortex and striatum was not prevented. If dopaminergic transmission were a significant factor in inhibitory modulation of audiogenic seizures, either the intracortical or the nigrostriatal dopamine system, or both would probably be involved, since these are the two most widespread dopaminergic systems described in the brain. Since dopamine in both of these systems was severely and selectively depleted without an increase of audiogenic seizure severity, we consider it unlikely that dopamine is involved as an inhibitory modulator of audiogenic seizures.

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