Effects of cocaine on brain noradrenaline in relation to toxicity and convulsions in mice

SIR,—Decreases in the concentration of noradrenaline in the brain have been reported when stress is induced by drugs (Vogt, 1954), electric shock (Maynert & Levi, 1964), or by audiogenic seizures (Breitner, Picchioni & Chin, 1963). Sensory stimulation also increases the toxicity of amphetamine (Cohen & Lal, 1964) and hence, presumably, stress. Sensory stimulation, including aggregation in mice, also enhances the effect of amphetamine on the brain concentration of noradrenaline (Moore, 1963; Lal & Chessick, 1964). Recently, it was reported that the toxicity of cocaine in mice is heightened by several types of sensory stimulation, including aggregation (Lal & Chessick, 1965). We now report the reaction between the toxicity of cocaine during sensory stimulation and the effect of cocaine on the brain concentration of noradrenaline.

Adult male HA/ICR albino mice were housed under conditions almost identical to "aggregation". Cocaine hydrochloride, 10 ml/kg, in physiological saline was injected intramuscularly. Immediately after injection, the animals were isolated one per cage, or aggregated, 10 per cage (Cohen & Lal, 1964). The surviving mice were decapitated, but mice found dead were not used. The brains of three mice were pooled and the concentration of noradrenaline measured fluorimetrically by the method of Crout, Creveling, & Underfriend (1961) modified by Harvey (1965).

A small but significant decrease in the concentration of brain noradrenaline was found at 0·5 and 1 hr after the administration of 100 mg/kg cocaine (Table 1). The animals recovered from the central stimulant effects of cocaine within 2 hr. The effects of isolation and aggregation on brain noradrenaline, on toxicity, and on convulsions are compared in Table 2. The data confirm the earlier report (Lal & Chessick, 1965) that aggregation increases the toxicity in mice treated

TABLE 1. EFFECT OF 100 mg/kg COCAINE ON THE CONCENTRATION OF NORADRENALINE IN THE BRAINS OF MICE

Hr after injection	Noradrenaline ± s.e. mean		Change %	P*
	Control	Treated		
0·5	0·36 ± 0·006 (18)†	0·33 ± 0·012 (18)	−8	0·05
1·0	0·32 ± 0·010 (18)	0·26 ± 0·023 (24)	−19	0·01
2·0	0·29 ± 0·015 (9)	0·31 ± 0·011 (15)	+6	n.s.
4·0	0·25 ± 0·013 (12)	0·26 ± 0·009 (9)	+4	n.s.

* Significance calculated on the basis of "Student's t", two-tailed.
† No. of animals in parentheses.

TABLE 2. EFFECTS OF ISOLATION AND AGGREGATION ON BRAIN NORADRENALINE, TOXICITY, AND CONVULSIONS IN MICE TREATED WITH COCAINE (100 mg/kg)*

Experimental condition	Noradrenaline† µg/g wet weight ± s.e. mean	Change %	P§	Dead‖ total	Convulsed total
Isolation—					
Control	0·30 ± 0·018 (18)‡			0/20	0/10
Treated	0·23 ± 0·023 (24)	−23	0·05	4/20	9/10
Aggregated—					
Control	0·32 ± 0·010 (30)			0/20	0/20
Treated	0·26 ± 0·017 (33)	−19	0·01	21/30	9/10

* The estimations of noradrenaline, toxicity, and convulsion figures are based on three different groups of animals. The toxicity and convulsion data presented are typical of the effect.
† 1 hr after injection.
‡ No. of animals in parentheses.
§ Significance calculated on the basis of "Student's t", two-tailed.
‖ 4 hr after injection.

with cocaine. The effect on brain noradrenaline does not seem to be related to the toxicity of the drug, but rather to the convulsive state. The convulsions were violent and clonic in nature, and appeared within 30 min of injection.

Thus cocaine can cause a small but significant decrease in the concentration of noradrenaline in the brain. Although the change is small compared with the total amount of noradrenaline in the brain, it is important when compared with the size of the noradrenaline pool proposed to be involved in physiological nerve activity (Kopin, 1964). In contrast to amphetamine, the effect of cocaine on brain noradrenaline seems to be identical under conditions of aggregation or isolation. Thus, there is either a different mechanism for the increased lethality of amphetamine and cocaine under sensory stimulation, or the noradrenaline-depleting action of convulsions obscured the differences between isolated and aggregated mice.

Acknowledgement. The technical assistance of Mrs. Clara Lastre and interest of Dr. John A. Harvey are acknowledged. The participation of Frank Grabarits was supported in part by USPHS Predoctoral Fellowship MH-15, 559.

Psychiatry Service,
Veterans Administration Research Hospital,
Chicago, Illinois.
December 3, 1965

FRANK GRABARITS*
HARBANS LAL†
RICHARD D. CHESSICK‡

* Present address: Department of Psychology, University of Chicago, Chicago, Illinois.

† Present address: Department of Pharmacology, University of Kansas, Lawrence, Kansas.

‡ Present address: 25 E. Washington St., Chicago, Illinois.

References

Breitner, C., Picchioni, A. & Chin, L. (1963). *J. Neuropsychiat.*, **5**, 153–158.
Cohen, M. & Lal, H. (1964). *Nature, Lond.*, **201**, 1037.
Crout, J. R., Creveling, C. R. & Udenfriend, S. (1961). *J. Pharmac. exp. Ther.*, **132**, 269–277.
Harvey, J. A. (1965). *Ibid.*, **147**, 244–251.
Kopin, I. J. (1964). *Pharmac. Rev.*, **16**, 179–191.
Lal, H. & Chessick, R. D. (1964). *Life Sci.*, **3**, 381–384.
Lal, H. & Chessick, R. D. (1965). *Nature, Lond.*, **208**, 295–296.
Maynert, E. W. & Levi, R. (1964). *J. Pharmac. exp. Ther.*, **143**, 90–95.
Moore, K. E. (1963). *Ibid.*, **142**, 6–12.
Vogt, M. (1954). *J. Physiol., Lond.*, **123**, 451–481.