The effect of reserpine on amphetamine toxicity in aggregated mice

SIR,—The enhancing effect of aggregation on the toxicity of amphetamine (Chance, 1946; Hohn & Lasagna, 1960; Mennear, 1965), can be prevented by prior administration of chlorpromazine (Lasagna & McCann, 1957), reserpine (Burn & Hobbs, 1958) and α- or β- adrenergic blocking agents (Mennear & Rudzik, 1965).

We have found the protection given by reserpine against the toxicity of amphetamine to be dependent on the dose of reserpine. Thus, doses of reserpine greater than 0·8 mg/kg intraperitoneally did not protect aggregated animals against amphetamine toxicity.

Male albino mice (Harlan Industries), 18–26 g, were given doses of reserpine 18–24 hr before (+)-amphetamine sulphate, 20 mg/kg i.p. Immediately after the administration of the amphetamine the mice were aggregated in groups of ten, in wire mesh cages measuring 15 cm on each side. The adrenergic blocking agents, MJ-1999 [4-(2-isopropylamino-1-hydroxyethyl)methane sulphonanilide], and phenoxybenzamine were administered 30 min before amphetamine was given to resperpine-pretreated animals.

In Table 1 it is seen that only doses of reserpine ranging from 0·1 to 0·8 mg/kg were effective in reducing the toxicity of amphetamine in aggregated mice. Doses of reserpine greater than 0·8 mg/kg did not reduce the % mortality produced by the 20 mg/kg dose of amphetamine.

TABLE 1. EFFECT OF VARYING DOSES OF RESERPINE ON THE TOXICITY OF AMPHETAMINE IN AGGREGATED MICE

Reserpine dose (mg/kg i.p.)	No. dead / No. tested	% Mortality
—	35/40	88
0·05	9/10	90
0·1	9/30	30
0·2	6/20	30
0·4	4/20	20
0·8	11/20	55
1·0	8/10	80
1·6	16/20	80
3·0	8/10	80
6·4	16/20	80

The β-adrenergic receptor blocking drug MJ-1999 (30 mg/kg i.p.) and the α-adrenergic receptor blocking agent phenoxybenzamine (10 mg/kg i.p.) antagonized the toxicity of amphetamine in groups of ten animals pretreated with doses of reserpine (1·0, 1·6, 3·0 and 6·4 mg/kg), only one death was recorded of the 100 animals tested; this was at a dose of 1·6 mg/kg i.p. reserpine + phenoxybenzamine.

The protective effect of low doses of reserpine on the toxicity of amphetamine in aggregated mice has been previously reported by Moore (1964). The lack of protection after large doses of reserpine was unexpected and may involve a toxicity of the reserpine itself. Since MJ-1999 and phenoxybenzamine are capable of blocking the toxicity of (+)-amphetamine after large doses of reserpine, the mechanism of action of reserpine in these tests remains obscure.

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References

Burn, J. H. & Hobbs, R. (1958). *Archs int. Pharmacodyn. Thér.*, **113**, 290–295.
Chance, M. R. A. (1946). *J. Pharmac. exp. Ther.*, **87**, 214–219.
Hohn, R. & Lasagna, L. (1960). *Psychopharmacologia*, **1**, 210–220.
Lasagna, L. & McCann, W. P. (1957). *Science, N.Y.*, **125**, 1241–1242.
Mennear, J. H. (1965). *Psychopharmacologia*, **7**, 107–114.
Mennear, J. H. & Rudzik, A. D. (1965). *Life Sci.*, **4**, 1425–1432.
Moore, K. E. (1964). *J. Pharmac. exp. Ther.*, **144**, 45–51.

Desipramine and potentiation of noradrenaline in the isolated perfused renal artery

SIR,—Recently it was reported that desipramine potentiates the pressor effect of directly acting sympathomimetic amines in cats or rabbits (Sigg, Soffer & Gyermek, 1963) and in rats (Bonaccorsi, 1966). This action was thought to be the result of an inhibition of the uptake of noradrenaline by nerve endings (Iversen, 1965). We have now examined the interaction of desipramine and noradrenaline in an isolated sympathetically innervated peripheral tissue.

The isolated renal artery of the rat was found to show a constriction with a single dose of 0·1 μg of noradrenaline. The artery, removed from 200 $\pm$ 20 g Sprague-Dawley male rats, was cannulated and perfused by means of a peristaltic pump under constant flow with Krebs-bicarbonate solution (6–7 ml/min.) gassed with 95% oxygen and 5% carbon dioxide. There was about 5 mm of artery between the tip of the cannula and the open end through which perfusion fluid emerged. Under resting conditions the pressure was 40–50 mm Hg.

The constrictor response of the vessel was measured by raising the perfusion pressure recorded by a mercury manometer on a kymograph. The renal artery was immersed in a 50 ml bath with overflow and containing its own perfusion fluid at 37°.

TABLE 1. EFFECT OF COCAINE AND DESIPRAMINE ON PRESSOR RESPONSE OF ISOLATED RENAL ARTERY OF RAT TO NORADRENALINE

Perfusing pressure values (mm Hg) and resistance (R)[1] in presence of noradrenaline (bitartrate salt) before and after treatment with cocaine or desipramine

	0·25 μg		1·0 μg		4·0 μg	
	mm Hg $\pm$s.e.	R	mm Hg $\pm$s.e.	R	mm Hg $\pm$s.e.	R
7 experiments. Drug: cocaine, $2·9 \times 10^{-5}$M						
Before drug	61·2 $\pm$ 3·3	9·4 $\pm$ 0·5	81·9 $\pm$ 5·0	12·6 $\pm$ 0·8	104·4 $\pm$ 7·6	16·0 $\pm$ 1·1
After drug	71·2 $\pm$ 3·3**	10·9 $\pm$ 0·4**	98·1 $\pm$ 4·6*	15·1 $\pm$ 0·6*	123·2 $\pm$ 7·7†	18·9 $\pm$ 1·1*
8 experiments. Drug: desipramine, $6·6 \times 10^{-6}$M						
Before drug	64·7 $\pm$ 1·5	9·9 $\pm$ 0·3	86·5 $\pm$ 2·8	13·1 $\pm$ 0·5	112·3 $\pm$ 4·3	17·1 $\pm$ 0·8
After drug	73·0 $\pm$ 2·6§	11·2 $\pm$ 0·6§	106·4 $\pm$ 4·4**	16·2 $\pm$ 0·9§	142·6 $\pm$ 6·5*	21·8 $\pm$ 1·3**

The basal pressure was 45 $\pm$ 5 mm Hg. Optimal potentiation was obtained after 60 min of perfusion with desipramine and 10 min after perfusion with cocaine.
* $P < 0·001$, ** $P < 0·002$. † $P < 0·005$. § $P < 0·01$.
[1] Resistance = pressure (mm Hg)/flow (ml/min)

(–)-Noradrenaline (as bitartrate salt) was always injected in a volume of 0·1 ml through rubber tubing interposed just upstream from the cannula. For each preparation, the dose-response curve for noradrenaline was first established and the artery was then perfused with a solution containing desipramine, as hydrochloride, or cocaine, as hydrochloride. The dose-response curve of noradrenaline was then determined again. The sensitivity of preparations to