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

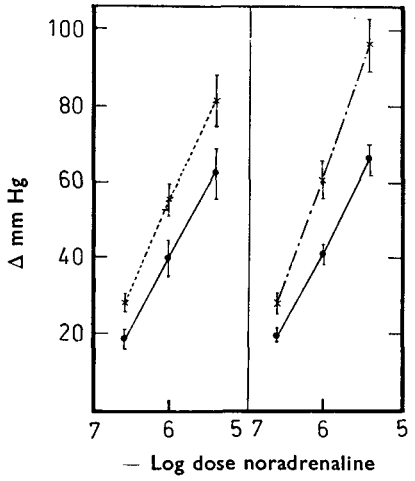

FIG. 1. Effect of cocaine and desipramine on the dose-response curve of noradrenaline in isolated perfused renal artery of rat; before ● — ● and after perfusion of artery with cocaine $2{\cdot}9 \times 10^{-5}$M (× - - - - ×) and desipramine $6{\cdot}6 \times 10^{-8}$M (× ·—·—· ×).

noradrenaline in control experiments did not change significantly for several hours. Cocaine and desipramine did not show any effect on the baseline perfusion pressure. The results obtained are reported in Table 1 and in Fig. 1. Both cocaine ($2{\cdot}9 \times 10^{-5}$M) and desipramine ($6{\cdot}6 \times 10^{-8}$M) shift the dose-response curve of noradrenaline to the left.

The onset of the potentiating effect of desipramine required a longer time (60 min) than did that of cocaine (10 min).

These results are consistent with those obtained in rats in which the blood pressure response was measured (Bonaccorsi, 1966). They are also in agreement with the facts reported by Iversen (1965), who established that the ED50 of desipramine needed to inhibit the uptake of noradrenaline in the isolated rat heart was $1{\cdot}3 \times 10^{-8}$M, a concentration close to ours ($6{\cdot}6 \times 10^{-8}$M) shown here to potentiate noradrenaline contraction in the renal isolated artery.

The present results support the hypothesis that desipramine increases the pharmacological effect of noradrenaline by preventing its uptake by the arterial wall.

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References

Bonaccorsi, A. (1966). *J. Pharm. Pharmac.*, **18**, in the press.
Iversen, L. L. (1965). *J. Pharm. Pharmac.*, **17**, 62–64.
Sigg, E. B., Soffer, L. & Gyermek, L. (1963). *J. Pharmac. exp. Ther.*, **142**, 13–20.

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