The effect of differing reserpine pretreatments on the cardiovascular response to tyramine

SIR,—Zaimis (1965, 1966) has shown that chronic treatment with small daily doses of reserpine in rats failed to cause a significant reduction in the cardiovascular response to tyramine although peripheral catecholamine levels were severely depleted. Since tyramine is thought to require endogenous catecholamines to exert at least some of its pharmacological effects (Burn & Rand, 1958; Muscholl, 1966) it was decided to investigate the responses to tyramine after chronic reserpine treatment. Four treatments were adopted: (A) Control animals received daily doses of vitamin C 20% w/v, 1 ml/kg intraperitoneally. (B) Reserpine 100 μg/kg daily in 20% w/v vitamin C intraperitoneally for three to four weeks. (C) Chronic treatment as in (B) followed by a single 5 mg/kg dose of reserpine intraperitoneally given 18 hr before the rats were used. (D) A single dose of 5 mg/kg reserpine intraperitoneally given 18 hr before the rats were used without prior chronic treatment.

All experiments were made using rats anaesthetized with pentobarbitone (60 mg/kg i.p.) and in which the blood pressure and heart rate were recorded. The results are shown in Table 1 and Fig. 1.

The cardiovascular responses to tyramine and bretylium were partly modified only by treatments (B) and (C) compared with control responses. The influence of these two treatments on the interaction of tyramine with the drugs listed in Table 1 did not indicate any qualitative differences in the nature of the response from that seen in control rats.

The effect of mecamylamine given after treatments (B) and (C) may indicate the presence of some residual sympathetic tone although it appears to be less than that obtained after treatment (A). It is possible therefore that after small daily doses of reserpine, sympathetic transmission, although impaired, still

TABLE 1. THE EFFECT OF DIFFERING RESERPINE PRETREATMENTS ON THE CARDIOVASCULAR RESPONSE TO TYRAMINE AND SOME OTHER DRUG-INDUCED RESPONSES IN ANAESTHETIZED RATS. Reserpine treatments: (A) 20% w/v vitamin C, 1 ml/kg daily (reserpine solvent); (B) reserpine, 100 μg/kg daily; (C) reserpine, 100 μg/kg daily + reserpine 5 mg/kg overnight; (D) reserpine, 5 mg/kg overnight.

Effect examined	Treatment			
	A	B	C	D
Mean initial resting blood pressure (mm Hg)	126·5 (140–110)	92·5 (110–70)	87 (110–82)	58 (75–45)
Mean initial heart rate (beats/min)	436 (468–396)	293 (336–276)	256 (276–228)	192 (220–156)
Pressor response to tyramine 25 μg i.v. (mm Hg)	29 (33–20)	19 (21–16)	14 (16–12)	0
Pressor response to tyramine after phentolamine 1 mg/kg + propranolol 2 mg/kg	Tyramine blocked			
Pressor response to tyramine 25 μg after desmethylimipramine 30 μg i.v.	Tyramine blocked			
Bretylium 6 mg/kg i.v.	Pressor + positive chronotropic effect			Pressor effect blocked + negative chronotropic effect
Pressor response to tyramine 25 μg after bretylium 5 mg/kg	Potentiated			"Restored"
Mecamylamine 1 mg/kg i.v.	Hypotensive + negative chronotropic effect			No effect

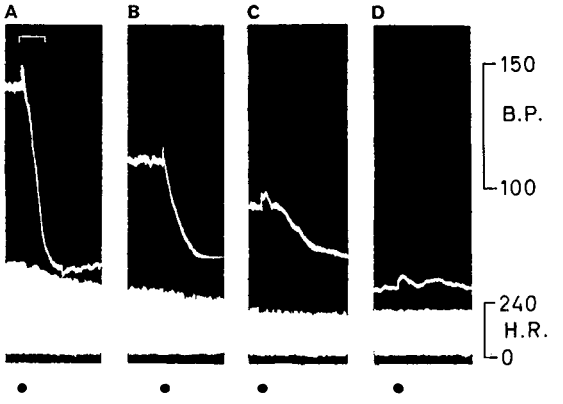

FIG. 1. The effect of mecamylamine 1 mg/kg i.v. (●) on the blood pressure (B.P.) (mm Hg) and heart rate (H.R.) (beats/min) of anaesthetized rats, after various reserpine pretreatments. Reserpine treatments: (A) 20% w/v vitamin C 1 ml/kg daily (reserpine solvent), (B) reserpine 100 μg/kg daily, (C) reserpine 100 μg/kg daily + reserpine 5 mg/kg overnight, (D) reserpine 5 mg/kg overnight. Time scale: 5 min.

functions to some extent despite the severe depletion of peripheral noradrenaline. This suggests the presence of small amounts of residual transmitter which could be sufficient to account for the pharmacological effect seen with tyramine. This is supported by the fact that increased sensitivity to noradrenaline exists in chronically treated rats (Zaimis, 1966) and that the action of the released noradrenaline is known to be enhanced by the tyramine itself (Muscholl, 1966). The single large dose of reserpine (treatment D) abolished the hypotensive effect of mecamylamine and the responses to tyramine.

The negative chronotropic effect of bretylium observed after treatment (D) is in accord with the results of Gaffney (1961) on the isolated reserpinized dog heart-lung preparation.

Irrespective of the form of treatment employed, bretylium potentiated tyramine; this effect is most probably due to the monoamine oxidase inhibitory property of this drug (Furchgott & Sanchez-Garcia, 1966; Clarke & Leach, unpublished).

Chronic treatment terminated with a large single dose of reserpine fails to abolish the effects of tyramine, bretylium or mecamylamine. These animals also appeared more active and showed less ptosis and diarrhoea than animals under treatment (D). It is possible that the persistence of low concentrations of reserpine in rat tissues during chronic treatments leads to the development of some form of "resistance" to this drug. Cass & Callingham (1964) noted an "escape" from the depleting action of reserpine after small daily doses and there is evidence (Carlsson, 1966) of a small labile pool of catecholamines which are more resistant to chronic reserpine treatment than the bulk of endogenous amines.

Postgraduate School of Studies in Pharmacology,
University of Bradford,
Bradford.
May 12, 1967

D. E. CLARKE

References

Burn, J. H. & Rand, M. J. (1958). *J. Physiol., Lond.*, **144**, 314–336.
Cass, R. & Callingham, B. A. (1964). *Biochem. Pharmac.*, **13**, 1619–1625.
Carlsson, A. (1966). *Pharmac. Rev.*, **18**, 541–549.
Furchgott, R. F. & Sanchez-Garcia, P. (1966). *Pharmacologist*, **8**, 176.
Gaffney, T. E. (1961). *Circulation Res.*, **11**, 83–88.
Muscholl, E. (1966). *Pharmac. Rev.*, **18**, 551–559.
Zaimis, E. (1965). *Proc. R. Soc. Med.*, **58**, 1067–1070.
Zaimis, E. (1966). In *Antihypertensive Therapy: Principles and Practice*, editor Gross, F., pp. 59–70, Berlin: Springer.

The influence of blood pressure on the responses of the nictitating membrane of the cat to sympathetic stimulation

SIR,—We have observed in cats anaesthetized with chloralose that the responses of the nictitating membrane were reduced when the blood pressure was reduced to 45 mm Hg.

Cats were anaesthetized with chloralose, 7·5 ml/kg of a 1% w/v solution in 0·9% w/v saline, administered intravenously after induction with ether. Carotid arterial blood pressure was recorded by means of a mercury manometer and contractions of the nictitating membrane by a frontal writing lever (15 times magnification, 8 g tension). The responses of the membrane to intravenously administered noradrenaline (50 μg) and adrenaline (40 μg) and to post-ganglionic nerve stimulation (10 V; 1 msec duration; 1, 5, 10 and 20 pulses/sec for 20 sec)

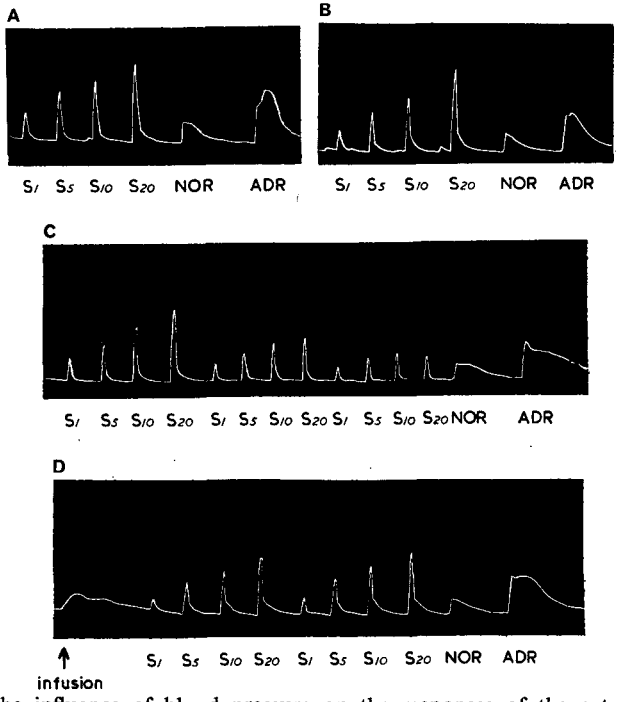

FIG. 1. The influence of blood pressure on the responses of the cat nictitating membrane to postganglionic stimulation of the ascending cervical sympathetic nerve (S) and to intravenous injections of 50 μg noradrenaline (NOR) and 40 μg adrenaline (ADR). Stimulus parameters 10 V, 1 msec duration at 1, 5, 10 and 20 pulses/sec for 20 sec. Between A and B the blood pressure was reduced by haemorrhage from 110 mm to 60 mm Hg. Between B and C the blood pressure was further reduced to 45 mm Hg. D shows the effect of restoring the blood pressure to 110 mm Hg by infusing the blood collected during haemorrhage.