Letters to the Editor

Changes in sensitivity to noradrenaline in rats pretreated with reserpine

SIR,—Pretreatment with reserpine increases the sensitivity of the cardiovascular system of the cat to the actions of noradrenaline (Bein, 1953; Burn & Rand, 1958; Fleming & Trendelenburg, 1961). Similar observations were made using the anaesthetised dog and the rabbit isolated atria (Maxwell, Povalski & Plummer, 1959; Macmillan, 1959). Recently Bhagat & Shidemann (1963) and Bhagat, Booker & West (1964) did not observe increased sensitivity to noradrenaline in isolated atria of rats pretreated with reserpine and suggested that the sensitising action of reserpine varied according to the animal species and organ used. On the other hand, we have now found reserpine pretreatment to potentiate the pressor action of noradrenaline in the rat. The conflicting results would not therefore seem to be explained by the use of different species; rather that the explanation lies with the method used to demonstrate noradrenaline sensitivity.

Male rats, Sprague-Dawley, 350–450 g, were treated with a single intraperitoneal injection of reserpine (Serpasil, Ciba). 48 to 168 hr later the animals were anaesthetised with ethylurethane, 1·25 g/kg, i.p., and the carotid artery cannulated. Arterial blood pressure was recorded via the cannula by a pressure transducer (Statham P23 AC) and displayed on an ink-writing oscillograph (Grass Polygraph). Heparin was given intravenously (5 mg/kg). Noradrenaline was injected into the jugular vein of alternate animals as a logarithmic series of either progressively increasing or progressively decreasing doses. Sufficient time was taken between successive doses of noradrenaline to allow for complete recovery.

TABLE 1. EFFECT OF RESERPINE PRETREATMENT ON PRESSOR RESPONSES OF ANAESTHETISED RATS TO NORADRENALINE

Treatment	mg/kg i.p.	Time after reserpine (hr)	No. of exp.	Mean response (mm Hg ± s.e.) to noradrenaline base (μg)			
				0·25	0·5	1	2
Saline ..	—	—	15	35·7 ± 3·4	47·7 ± 4·6	61·3 ± 5·3	83·0 ± 6·1
Reserpine ..	5	48	15	39·8 ± 3·1	53·1 ± 4·1	78·5 ± 7·5	94·2 ± 7·4
Reserpine ..	5	72	15	42·2 ± 4·7	60·6 ± 5·4	87·6*± 8·3	109·7†± 6·5
Reserpine ..	5	96	13	43·6 ± 4·3	59·5 ± 6	75·1 ± 5·2	98·6 ± 5·8
Reserpine ..	5	168	10	41·0 ± 7·3	49·2 ± 6·3	68·6 ± 6·7	83·5 ± 6·3
Reserpine ..	2·5	72	17	56·5†± 5·6	67·5*± 5·4	94·6†± 5·6	113·5†± 6·6
Reserpine ..	2·5	96	7	35·0 ± 2·3	50·5 ± 5·4	73·7 ± 6·2	90·1 ± 7·8

* $P < 0.05$. † $P < 0.01$.

Table 1 shows that a single injection of 5 mg/kg of reserpine induced a moderate increase of sensitivity to noradrenaline within 48 hr. Maximal increase in sensitivity was achieved by 72 hr and then declined slowly; 7 days after reserpinisation the responses to noradrenaline had returned to normal. A smaller dose of reserpine (2·5 mg/kg) also produced an increase in sensitivity to noradrenaline in 72 hr; however, the increase in sensitivity was larger but declined more rapidly. Basal blood pressure and body temperature of reserpinised rats were not significantly different from those of controls, and the

increased sensitivity was not due to non-specific factors like reduced food or water intake which occurs in reserpinised animals.

Studies in this laboratory (Giachetti & Montanari, unpublished observations) showed that the concentration of heart noradrenaline in rats treated with 5 mg/kg of reserpine is 5% of controls at 24 hr, 18% at 48 hr, and 25% at 72 hr, and so the increased sensitivity to the pressor action of noradrenaline is not directly related to the decreased concentration of the amine in the heart. These last results agree with those reported by Trendelenburg & Weiner (1962). The time elapsing after the administration of reserpine seems more important for the development of increased sensitivity. Similar conclusions were previously reached for the pressor action of noradrenaline in the cat by Fleming & Trendelenburg (1961). In our view the potentiation of noradrenaline by reserpine cannot be explained on the basis of an impairment of the uptake mechanism for the amine. Giachetti & Montanari (unpublished) have also shown that although treatment with reserpine (5 mg/kg, i.p.) reduced the uptake of injected tritiated noradrenaline into the rat heart, the effect was short-lived. The capacity of the rat heart to take up and bind the tritiated amine fully recovered within 48 hr of reserpine treatment.

The cardiovascular system of the rat can be made more sensitive to noradrenaline by reserpine. Rats need a larger dose of the alkaloid than do other animal species for the potentiation of noradrenaline effects, but this applies also to other actions of reserpine such as hypothermia and sedation. It is difficult to reconcile our findings using an *in vivo* technique with those obtained by Bhagat & others (1964) using the isolated atria. It may be noteworthy to recall, however, that some organs from reserpinised animals, for example the nictitating membrane and the iris of the cat, do not show increased sensitivity to noradrenaline *in vitro*, but do so *in situ* (Burn & others, 1959; Marley, 1962).

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September 21, 1964

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