(tubocurarine, compound 48/80 and polysorbate 80) on melanophores. This suggests that the histamine liberators act on melanophores by a mechanism which is different to that of noradrenaline or adrenaline.

Histamine acted like the histamine liberators except that even with much higher doses (200 mg/kg as histamine acid phosphate) the degree of melanin concentration was less than that induced by histamine liberators. This dose of histamine was well-tolerated by the frogs which are known to be resistant to it (Rocha e Silva, 1955).

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November 4, 1966

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β-Adrenergic auto-inhibition of the effect of noradrenaline on avian pulmonary artery

SIR,—We have previously reported that the predominantly β-adrenergic amine, isoprenaline, exerts both β-adrenergic vasodilator and α-adrenergic vasoconstrictor effects on isolated vascular smooth muscle (Somlyo & Somlyo, 1964, 1966a). In contrast, noradrenaline is a predominantly α-adrenergic vasoconstrictor amine, and its β-adrenergic vasodilator effects have previously been demonstrated only after α-adrenergic blockade, *in vivo* (Brick, Hutchison & Roddie, 1966). In the absence of α-adrenergic blockade, noradrenaline is one of the most potent vasoconstrictors of large and medium vessels (Somlyo, Sandberg & Somlyo, 1965a; Somlyo & Somlyo, 1966b) when potency is judged by maximum isotonic response. We now find that, in certain types of vascular smooth muscle, noradrenaline, in the absence of α-adrenergic blocking agents, can exert sufficient β-adrenergic vasodilator activity to produce auto-inhibition of the α-adrenergic vasoconstrictor effect.

Right and left main branches of the pulmonary artery were obtained from rapidly exsanguinated chickens. The preparation of helically-cut vascular strips and recording methods employed in our laboratory have been reported in detail (Somlyo & Somlyo, 1964; Somlyo, Sandberg & Somlyo, 1965a,b; Somlyo, Woo & Somlyo, 1965; Woo & Somlyo, 1966). The temperature for the present experiments was maintained at $41{\cdot}5 \pm 0{\cdot}5°$. Loading tensions applied were 2 g for pulmonary and 3 g for sciatic artery strips.

Fig. 1 shows the effect of the β-adrenergic blocking agent, pronethalol, on cumulative dose-response curves of pulmonary (1A) and sciatic (1B) artery strips to noradrenaline. Auto-inhibition of α- by β-adrenergic effect in pulmonary vascular smooth muscle is indicated by the maximum contractile effect, which is increased by β-adrenergic blockade, being depressed. Similar results were obtained in another group of 5 pulmonary arteries, suspended in Mg-free Krebs solution. The maximum isotonic response of the two pooled groups

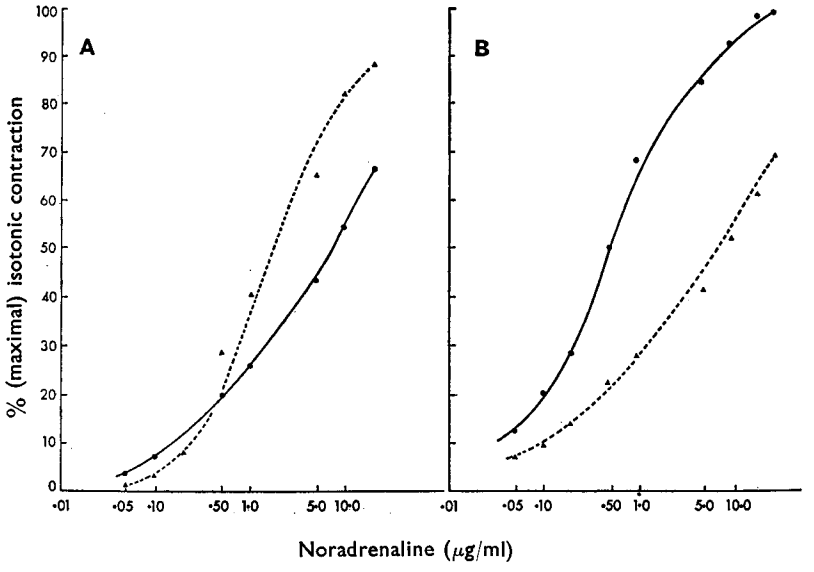

FIG. 1. Cumulative dose-response curves of chicken pulmonary (A) and sciatic (B) artery strips to noradrenaline: effect of pronethalol. Circles represent control responses, triangles the responses in the presence of pronethalol 10 μg/ml. Each curve represents the mean of five experiments.

(10 strips) to noradrenaline was 36·6% ±10·2 greater in the presence of pronethalol 10 μg/ml ($P < 0.01$). The dose-response curves of sciatic artery strips (1B) exhibited no auto-inhibition with the same concentrations of noradrenaline. In these preparations a non-specific, depressant effect of pronethalol significantly ($P < 0.01$) depressed the contractile response to noradrenaline. A depressant action of pronethalol on intestinal smooth muscle has also been demonstrated (Woo & Somlyo, 1966). This non-specific effect of pronethalol was presumably responsible for the diminished responses of pulmonary artery strips to low (<0·5 μg/ml) concentrations of noradrenaline and the absence of a pure parallel shift in Fig. 1A.

Individual (rather than cumulative) dose-response curves obtained with pulmonary arterial strips showed the descending limb configuration characteristic of auto-inhibition (Bijlsma, Werff & Julius-Bijlsma, 1961; Ariens & Simonis, 1964).

Acknowledgements. This study has been supported by NSF Grant B6–2069 R and NIH Grants HE 08226 and I-K3-HE 17, 833. Pronethalol was kindly provided by Dr. A. Sahagian-Edwards as a gift from Ayerst Laboratories.

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Antihypertensive effect of methyldopa in metacorticoid immunosympathectomized rats

SIR,—It is now generally accepted that methyldopa (α-methyldihydroxyphenylalanine) is an effective antihypertensive agent. Day & Rand (1963) proposed that methyldopa lowered the blood pressure by acting as a weak false sympathetic neurotransmitter. This hypothesis is inconsistent with the observation that administration of methyldopa did not inhibit the effect of sympathetic nerve stimulation (Stone, Ross, Wenger, Ludden, Blessing, Totaro & Porter, 1962; Varma & Benfey, 1963) and did not reduce the release of noradrenaline after stimulation of sympathetic nerves (Davies, 1966). Indeed, Nickerson (1965) pointed out that "the role of catecholamine depletion or, indeed, of any action on catecholamine metabolism in the antihypertensive effect of methyldopa, requires re-evaluation".

Since almost complete destruction of the peripheral sympathetic system can be produced in mammals by immunosympathectomy (Levi-Montalcini & Booker, 1960; Levi-Montalcini & Angeletti, 1962), it became possible to test whether the antihypertensive action of methyldopa is due to a reduction in peripheral sympathetic activity and whether a fully active sympathetic system is essential for experimental hypertension.

Immunosympathectomy was produced by subcutaneous injection of 0·2 ml of 61,000 anti-units/ml of bovine anti-serum to nerve-growth factor (kindly supplied by Dr. R. K. Richards, Abbott Laboratories, Chicago) in 1–2 days-old Sprague-Dawley rats. The effectiveness of this treatment producing immunosympathectomy has been described by Iversen, Glowinski & Axelrod (1966). The treated and untreated litter mate controls were raised together. Noradrenaline (equivalent) was assayed biologically on isolated rabbit aortic strip (Helmer, 1961). Treated rats exhibited marked ptosis of the eye lids. The daily urinary excretion of catecholamine (as noradrenaline equivalent) was $2{\cdot}1 \pm 0{\cdot}5$ μg/kg in treated rats and $5{\cdot}6 \pm 1{\cdot}2$ μg/kg in normal rats. Myocardial noradrenaline in 3 treated rats was $0{\cdot}22 \pm 0{\cdot}22$ μg/g and in 3 normal controls was $1{\cdot}26 \pm 0{\cdot}23$ μg/g. The responses of the isolated atria of untreated rats (6 preparations) to tyramine were negligible. Approximately 2 months after birth, the rats were used for inducing metacorticoid hypertension. Rats were anaesthetized with an intraperitoneal injection of pentobarbitone sodium (30 mg/kg), one kidney was removed and a 20 mg desoxycorticosterone acetate pellet contained in 50 mg beeswax was implanted under the skin. Animals were maintained on 1% sodium chloride instead of water. The systolic blood pressure in the unanaesthetized rat was determined by the tail cuff method by means of an Electrosphygmograph (E & M Instruments). Methyldopa (200