Reversal of adrenergic vasodepression

SIR,—Nearly twenty years ago Coret & Van Dyke (1948) reported the reversal of the adrenergic vasodepression observed in the cat after blockade of what are now called α-receptors, by doses of isoprenaline, 1·0 mg/kg. To explain this phenomenon they proposed the hypothesis that vascular smooth muscle was furnished with both excitatory and inhibitory "reactive patches," and that the adrenolytic drugs probably blocked most, but *not all*, excitatory patches and no inhibitory patches. The 1·0 mg/kg dose of isoprenaline was thought to remain loosely combined with the inhibitory patches for several minutes during which time they were inaccessible, but adrenaline still had access to the excitatory patches which had escaped the blocking drug. They suggested that the loose combination of isoprenaline and inhibitory patches gradually broke down so that the latter were again free to react with adrenaline and the depressor response returned. Since Butterworth (1963) has demonstrated the β-adrenergic blocking action of isoprenaline, these results of Coret & Van Dyke would seem to be quite comparable with those of Hull, Eltherington & Horita (1960) using the β-blocking agent, dichloroisoprenaline, and with those of Moreira & Osswald (1965) using the β-blocking agent, pronethalol. Although different terminologies are used, the proposed mechanisms would appear to be similar.

The experiments reported here demonstrate the phenomenon of "tapenolysis" in the femoral vascular bed independently of cardiac or central nervous system effects, or both.

Dogs of 9 to 15 kg were anaesthetised with pentobarbitone sodium, 32·5 mg/kg. Blood flow in the femoral artery was measured with an electromagnetic flow meter (Medical Avionics Model 6000) and recordings were made on a Honeywell Visicorder (Model 1508); intra-arterial injections were made through a polyethylene tube inserted into a small branch of the femoral artery. Isoprenaline hydrochloride, (–)-adrenaline bitartrate, (–)-noradrenaline bitartrate, phenoxybenzamine hydrochloride, dichloroisoprenaline hydrochloride, and pronethalol hydrochloride were the drugs used. The doses are expressed as the salts.

After the intra-arterial injection of 0·5–1·0 mg/kg of phenoxybenzamine the vasoconstrictor effect of adrenaline was changed to a purely vasodilator effect (Fig. 1). The subsequent injection of pronethalol, 100–300 μg/kg intra-arterially, caused a re-reversal of the adrenaline effects. The vasodilator effects of isoprenaline were markedly diminished by the treatment with intra-arterial pronethalol. We have found in the femoral vasculature, as others have found in systemic blood pressure, that "tapenolysis" is, with time, a completely reversible phenomenon.

In the ten experiments described above, the vasoconstrictor response to noradrenaline was unchanged, or only slightly reduced, by the phenoxybenzamine. In four other experiments the vasoconstrictor response was totally blocked by phenoxybenzamine and "tapenolysis" could not be demonstrated, i.e. intra-arterial doses of pronethalol up to 500 μg/kg which blocked the vasodilator response to isoprenaline blocked, but did not reverse, the vasodilator response to adrenaline.

In eight additional experiments the blockade of β-receptors in the leg was maintained by an intra-arterial infusion of dichloroisoprenaline (0·02–0·05 ml/min of a 0·5% solution). Under these experimental conditions the intra-arterial administration of phenoxybenzamine blocked the vasoconstrictor responses to adrenaline and noradrenaline equally. This is to be contrasted with the normal situation where it was found that the vasoconstrictor response to adrenaline could be reversed by a dose of phenoxybenzamine which had little or no effect on the vasoconstrictor response to noradrenaline.

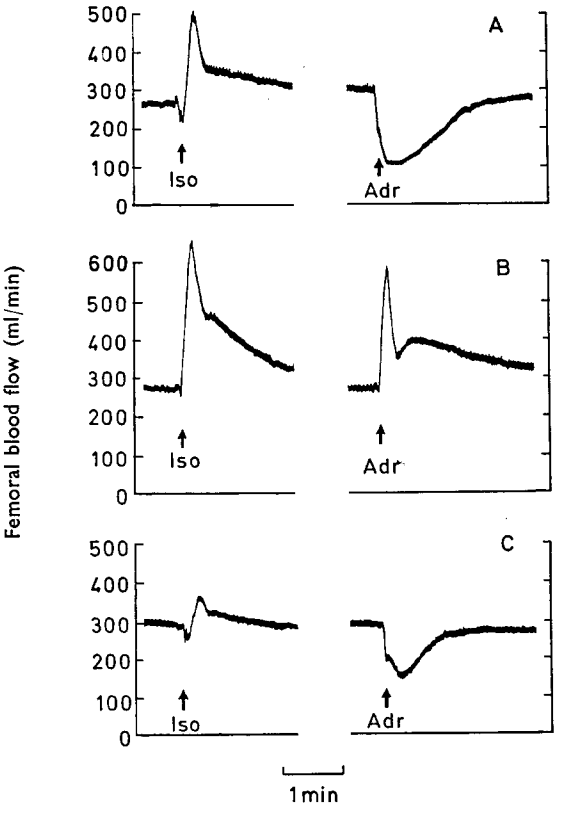

FIG. 1. Blood flow in the femoral artery of a dog, measured with an electromagnetic flowmeter. Drugs administered intra-arterially through a polyethylene tube inserted into a small arterial branch. Isoprenaline (Iso), 0·05 μg/kg i.a., administered at 09.07 hr in A, 10.05 hr in B and 10.36 hr in C. Adrenaline (Adr), 0·1 μg/kg i.a., administered at 09.12 hr in A, 10.12 hr in B and 10.23 hr in C.

Phenoxybenzamine, 500 μg/kg i.a., was administered between A and B. Pronethalol, 300 μg/kg i.a., was administered between B and C.

An attempt was made to demonstrate "tapenolysis" in the femoral vascular bed in four experiments using ephedrine instead of a β-blocking agent. Intra-arterial doses of 100–500 μg/kg of ephedrine did not affect the vasodilator response of the femoral vascular bed to adrenaline after phenoxybenzamine. Nor was the vasodilator response to isoprenaline affected by the ephedrine.

It would seem that there are two different mechanisms for the reversal of adrenergic vasodepression. The first involves the reversal of the depressor action of adrenaline in phenoxybenzamine-treated animals and is induced by β-blocking agents. It is demonstrable in the femoral vasculature. The second involves a reversal of the vasodepressor action of isoprenaline in normal animals, and is induced by a variety of vasoconstrictor substances (Lands, Luduena, Grant, Ananenko & Tainter, 1950; Walz, Koppanyi & Maengwyn-Davies, 1960; Levy & Ahlquist, 1961). An alteration of the availability of α- and β- receptors, as first proposed by Coret & Van Dyke (1948), would seem to

explain the first phenomenon; increased cardiac output in the presence of a sustained vasoconstriction, as first suggested by Lands & others (1950), would seem to explain the second phenomenon.

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Effects on lipomobilisation of the β-adrenergic blocking drugs, propranolol and INPEA

SIR,—An increase of plasma free fatty acids (FFA) occurred within 60 min after subcutaneous administration of propranolol [1-isopropylamino-3-(1-naphthyloxy)-2-propanol hydrochloride] (Black, Crowther, Shanks, Smith & Dornhorst, 1964) to rats. The rise was more evident with low doses and disappeared with increasing dosage (Table 1). In contrast, (±)-INPEA (*N*-isopropyl-*p*-nitrophenylethanolamine hydrochloride) (Somani & Lum, 1965) diminished plasma FFA at lower doses while, at greater doses, it did not induce significant changes in FFA level. The results obtained with the two optical isomers seem to indicate that a mild lipid-mobilising power is linked only to (−)-INPEA (Table 1).

The lipomobilising activity of propranolol *in vivo* was prevented by previous reserpinisation or treatment with dibenzyline (Table 2). Thus propranolol action on lipolysis *in vivo* is apparently an indirect adrenergic one.

Regarding the antagonistic action against the noradrenaline-induced lipomobilisation, propranol and (±)-INPEA are equally active *in vivo* (Table 3). The inhibitory power of INPEA appears to be greater in the (−)-isomer (Table 3).

In vitro propranolol and INPEA did not show any intrinsic lipomobilising activity on rat epididymal adipose tissue. On the contrary, at high concentrations (2 and 20 × 10^{-5}M) they depressed the basal lipolytic activity.

The antagonism of propranolol and INPEA against the FFA mobilisation stimulated by noradrenaline *in vitro* was studied according to a procedure previously described (Fassina, Tóth & Santi, 1965). The curves obtained by plotting the log concentration of noradrenaline against the amount of FFA released in the presence of increasing concentrations of propranolol and INPEA, indicate that the two β-adrenergic blocking drugs behave as competitive antagonists. The pA_2 values (Schild, 1947) (calculated when the effect of noradrenaline was 50% of the maximal) show that (−)-INPEA ($pA_2 = 6{\cdot}32$) is less active than propranolol ($pA_2 = 6{\cdot}75$) whilst (+)-INPEA ($pA_2 = 4{\cdot}20$) has a very small activity. From these values the affinity of (−)-INPEA for the lipid mobilising sites affected by noradrenaline gives results about 130 times higher than that of (+)-INPEA and 3 times lower than that of propranolol. This