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THE EFFECT OF PROSTAGLANDIN E_1 ON RESPONSES OF SMOOTH MUSCLE TO CATECHOL AMINES, ANGIOTENSIN AND VASOPRESSIN

BY

S. W. HOLMES, E. W. HORTON AND I. H. M. MAIN

From the Miles-Ames Research Laboratories, Stoke Poges, Bucks.

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Reduction of the pressor responses to adrenaline in the rabbit following administration of prostaglandin E_1 has been confirmed. The effect is, however, nonspecific since noradrenaline, angiotensin and vasopressin are also antagonized. Analogous responses were observed in blood flow experiments on the cat hind limb but not on the rabbit isolated auricles or the rabbit isolated duodenum. Contractions of the cat nictitating membrane produced by sympathetic preganglionic stimulation or by adrenaline were not decreased following injection of prostaglandin E_1 but the relaxation period was shorter. Contractions of the rabbit vas deferens induced *in vivo* by adrenaline were smaller after prostaglandin E_1 and this effect tended to be long-lasting.

In 1938, Euler observed that pressor responses to adrenaline in the rabbit were reduced following an intravenous injection of prostaglandin. Steinberg, Vaughan, Nestel & Bergström (1963) have recently made a similar observation using pure prostaglandin E_1. These authors have also shown that the break-down of triglyceride in adipose tissue induced by catechol amines is antagonized. In this investigation we have confirmed the action of prostaglandin E_1 on pressor responses to catechol amines and have shown that this effect is nonspecific since responses to angiotensin and vasopressin are also reduced.

METHODS

Blood pressure experiments. Blood pressure was recorded from a carotid artery using either a mercury manometer or a Statham pressure transducer. Cats were anaesthetized with pentobarbitone sodium (40 mg/kg), rabbits and rats with urethane (1.75 g/kg) injected intraperitoneally. In some experiments rats were anaesthetized with ether and pithed using a strong wire introduced through an orbit and passed down the cerebrospinal axis.

Cat hind-limb blood flow. Cats, weighing 2.5 to 4.5 kg, were anaesthetized with pentobarbitone sodium (40 mg/kg) injected intraperitoneally. The trachea, a carotid artery and both external jugular veins were cannulated. Blood pressure was recorded by a mercury manometer. Venous outflow from a hind-limb was recorded by passing blood from the femoral vein through a Palmer drop-chamber connected to a Gaddum drop-recorder, the blood being returned into a jugular vein. The artery supplying the gracilis muscle was cannulated with fine polyethylene tubing connected to a three-way tap for retrograde intra-arterial injections. Heparin (1,000 U/kg) was injected intravenously and further doses of 500 U/kg were given every 2 hr. Contractions of the hind-limb muscles produced by stimulation of

the sciatic nerve (3 to 4 V, 0.2 msec duration, 6 shocks/min) ensured a brisk venous outflow throughout the experiment.

Nictitating membrane contractions. Nictitating membrane contractions were recorded isometrically using a Grass force-displacement transducer (model FTO3). The ipselateral preganglionic cervical sympathetic nerve was stimulated and intra-arterial injections were made retrogradely through a polyethylene cannula in the ipselateral lingual artery.

Rabbit isolated auricles. The method described by Burn (1952) was used. The auricles were suspended in a 4 ml. organ-bath containing Locke solution gassed with oxygen and their spontaneous contractions were recorded isometrically using a Grass force-displacement transducer (model FTO3).

Rabbit isolated duodenum. A 3 to 4 cm segment of duodenum was suspended in a 4 ml. organ-bath containing Tyrode solution at 35 to 36° C gassed with air. Longitudinal contractions were recorded isometrically with a frontal writing lever on a smoked drum. A tension of 1 g and a lever magnification of five-times were used. The dose cycle was 5 min with 40 sec contact.

Rabbit vas deferens. Male rabbits, weighing 2 to 3 kg, were anaesthetized with urethane (1.75 g/kg) injected intraperitoneally. The trachea, an external jugular vein and a carotid artery were cannulated. The abdomen was opened and the viscera were displaced to allow access to one vas deferens. The distal end was ligated and the proximal end was cannulated with a polyethylene cannula introduced through a small incision and tied in position. The cannula was filled with Tyrode solution and connected to a Statham pressure transducer. Intraluminal pressure was then recorded from this artificial blind sac of vas deferens. The preparation showed spontaneous activity and responded by contraction to intravenous injections of adrenaline.

Drugs. These were (−)-adrenaline acid tartrate (B.D.H.); (−)-noradrenaline bitartrate (Levophed, Bayer); valyl[5]angiotensin II aspartyl-β-amide (Hypertensin, Ciba); vasopressin injection B.P. (Pitressin, Parke, Davis & Co.); and histamine acid phosphate (B.D.H.).

RESULTS

Blood pressure experiments. Following an intravenous injection of prostaglandin E_1 (10 μg/kg) into the rabbit, pressor responses to adrenaline were smaller than before (Fig. 1*a*). Although responses to successive doses of adrenaline gradually increased, complete recovery was long-delayed (15 to 30 min) and in some experiments did not occur. Similar reductions in pressor responses to both adrenaline and noradrenaline were also observed in the cat and the rat. In the experiment illustrated in Fig. 1*b* pressor responses to 0.2 μg noradrenaline in the rat anaesthetized with urethane did not return to their former magnitude during the course of the experiment after an intravenous injection of prostaglandin E_1.

This effect was not specific for catechol amines. Pressor responses both to angiotensin and to vasopressin were similarly reduced following injection of prostaglandin E_1. In an experiment on a pithed rat illustrated in Fig. 1*c*, the pressor response to 2.5 mU of vasopressin was similarly reduced.

Blood flow experiments. Vasoconstrictor responses to intra-arterial injections of adrenaline, noradrenaline or angiotensin into the hind limb of the cat were reduced following an intra-arterial injection of prostaglandin E_1 (Fig. 2). In one experiment as little as 32 ng of prostaglandin E_1 caused detectable inhibition of the vasoconstriction due to 100 ng of noradrenaline and in the same animal 500 ng of prostaglandin E_1 almost completely abolished the response to 100 ng of nor-

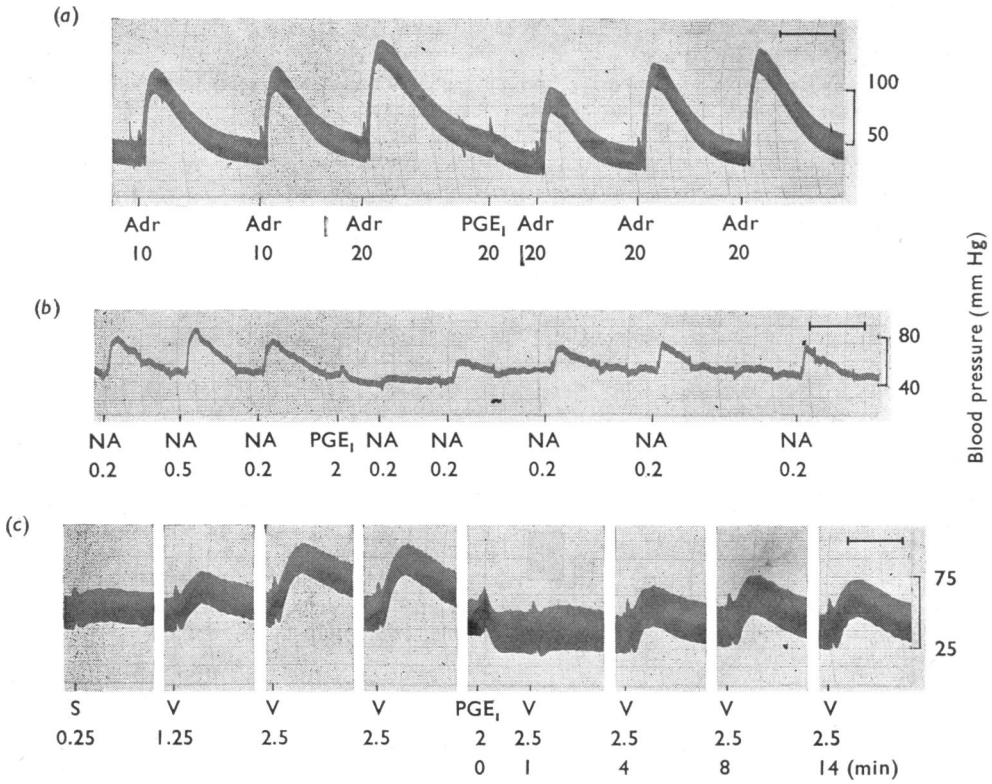

Fig. 1. Records of carotid arterial blood pressure from: (*a*) a rabbit (2 kg) anaesthetized with urethane; (*b*) a rat (290 g) anaesthetized with urethane; and (*c*) a pithed rat (200 g). Drugs were injected intravenously. Adr=adrenaline (μg); NA=noradrenaline (μg); V=vasopressin (mU); PGE_1=prostaglandin E_1 (μg); S=saline (ml.). Time calibrations are 1 min. In (*c*) the lower figures indicate times in minutes after administration of prostaglandin E_1 at which doses of vasopressin were given.

adrenaline. Similar results were obtained with adrenaline and angiotensin but responses to neither drug appeared as sensitive to prostaglandin E_1 as that to noradrenaline. The effect of prostaglandin E_1 on the vasodilatation due to isoprenaline (100 ng) was insignificant for doses of prostaglandin up to 5 μg. Inhibition of the response to the vasoconstrictor drugs was maximal immediately after the prostaglandin had been administered, with a gradual return to normal in 5 to 15 min. Similar effects were found when other vasodilator drugs, for example histamine and bradykinin, were injected in place of prostaglandin E_1.

Contractions of the cat nictitating membrane. The force of contraction of the nictitating membrane in response either to sympathetic preganglionic stimulation or to intra-arterial injection of adrenaline was not reduced after administration of prostaglandin E_1 in doses up to 20 μg/kg. However, the duration of the contraction was markedly reduced (Fig. 3).

Responses of other smooth muscle preparations. Increased force of contraction of the rabbit isolated auricles following administration of isoprenaline or adrenaline

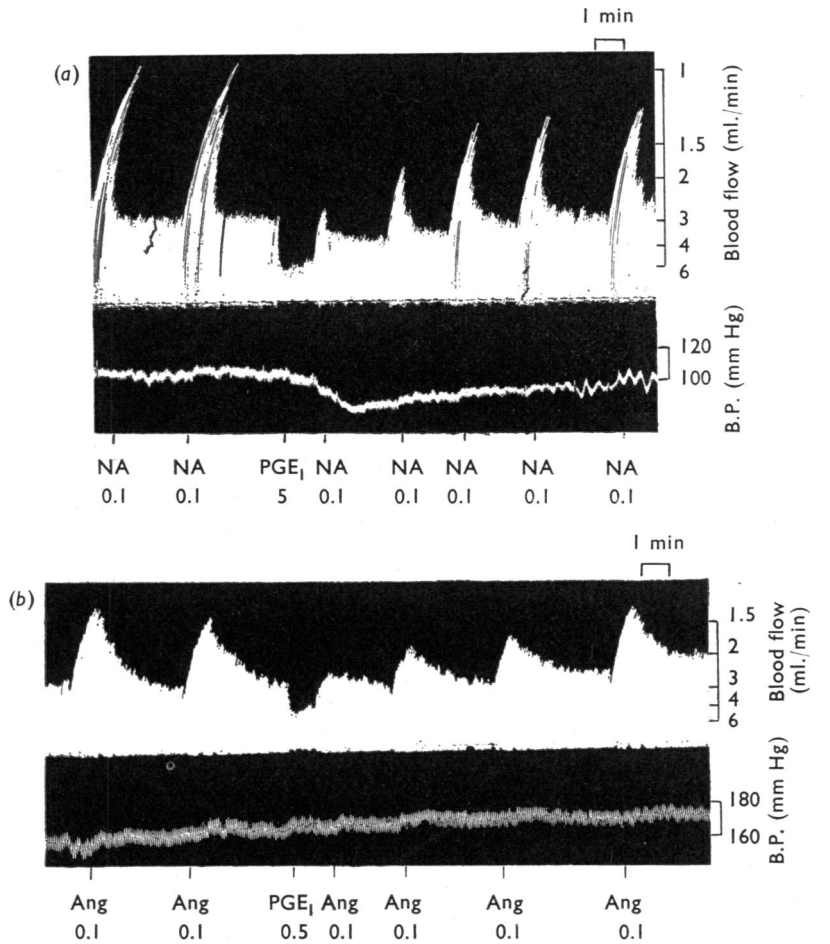

Fig. 2. Records from cats (*a*, 2.2 kg; *b*, 2.5 kg) anaesthetized with pentobarbitone sodium, 40 mg/kg injected intraperitoneally. Upper trace, hind-limb blood flow; lower trace, carotid arterial blood pressure. Drugs were injected retrogradely into the femoral artery from a cannula in the artery to the gracilis muscle. Time calibrations are 1 min. All doses in μg. NA=noradrenaline; PGE_1=prostaglandin E_1; Ang=angiotensin II.

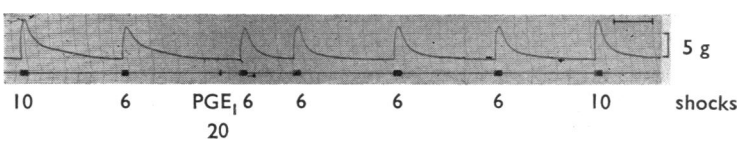

Fig. 3. Cat (2.35 kg) anaesthetized with pentobarbitone sodium, 40 mg/kg injected intraperitoneally. Isometric contractions of a nictitating membrane in response to stimulation of the ipselateral preganglionic cervical sympathetic nerve with 5 V shocks of 1 msec duration. Figures indicate number of shocks. PGE_1=prostaglandin E_1 (μg) injected retrogradely through a cannula in a lingual artery. Time calibration, 30 sec.

was not altered by prostaglandin E_1 in concentrations up to 2.5 μg/ml. Similarly, relaxations of the rabbit isolated duodenum induced by adrenaline were unaltered by prostaglandin in a dose which itself caused contraction of the muscle.

Contractions of the rabbit vas deferens induced *in vivo* by adrenaline were, however, reduced following administration of prostaglandin E_1 (Fig. 4). This effect was also observed in the rabbit vas deferens *in vitro*.

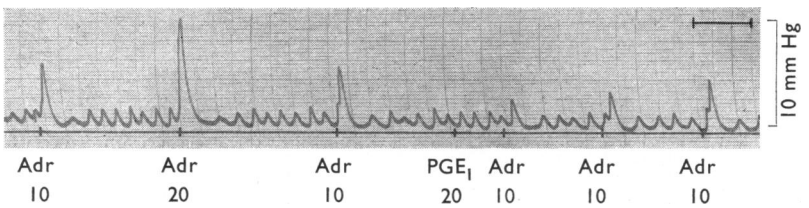

Fig. 4. Rabbit (2 kg) anaesthetized with urethane injected intraperitoneally (1.75 g/kg). Records of the intraluminal pressure of one vas deferens *in vivo*. Adr=adrenaline, PGE_1=prostaglandin E_1, each injected intravenously. Doses are in μg. Time calibration, 1 min.

DISCUSSION

Effect of prostaglandin E_1 on vascular smooth muscle. The experiments described here indicate that the antagonism of pressor responses to catechol amines reported by Euler (1938) and Steinberg *et al.* (1963) is nonspecific since responses to angiotensin and vasopressin are similarly affected. This lack of specificity has been demonstrated both on blood pressure and on blood flow. Similar antagonism of responses to catechol amines was observed when other depressor substances such as bradykinin were used instead of prostaglandin E_1. Such "physiological" antagonism might be expected to occur from algebraic summation of effects when a pressor and depressor substance are injected either simultaneously or within a short time of each other, but there is the alternative possibility, mentioned by Steinberg *et al.* (1963), that prostaglandin E_1 blocks a biochemical sequence of events initiated by vasoconstrictor substances, but has no vascular effects in the absence of these substances. From the experiments described here we conclude that, if the latter is the actual mechanism, the site of block must be somewhere on the final common path for the actions of catechol amines, angiotensin and vasopressin.

Effect of prostaglandin E_1 on other smooth muscle preparations. Prostaglandin E_1 also modified responses of other smooth muscle preparations. Contractions of the rabbit vas deferens induced by adrenaline were reduced, although resting tone and spontaneous contractions were unaffected. On the cat nictitating membrane, prostaglandin E_1 did not reduce the size of contractions in response to sympathetic nerve stimulation or to injection of adrenaline, but recovery time was shortened.

Whether these actions of prostaglandin are of any physiological significance is unknown. It is clear that prostaglandins are of much wider distribution in the body than was formerly suspected and we suggest that their presence in organs

containing smooth muscle may be associated with a function as local mediators of smooth muscle inhibition. The finding that break-down of triglyceride is also modified (Steinberg *et al.*, 1963) shows that the action of prostaglandins is not restricted to smooth muscle. It is possible that prostaglandins inhibit a biochemical pathway which is activated by different substances and which is common to several different tissues. Consequently this inhibition may lead to entirely different effects depending upon the tissue.

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