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Cardiovascular effects of prostaglandins mediated by the central nervous system of the dog

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Summary

1. Prostaglandins A_1, E_1, $F_{1\alpha}$ and $F_{2\alpha}$ were infused into the vertebral artery of the chloralose-anaesthetized greyhound and the resulting cardiovascular responses were compared with those obtained on intravenous and intracarotid infusions in the same dose range.

2. Infusions of $PGF_{2\alpha}$ intravertebrally (4–64 (ng/kg)/min) caused an increase of blood pressure, tachycardia and a fall of central venous pressure. Cardiac output was increased and peripheral resistance was essentially unchanged. There was never any response to intravenous or intracarotid $PGF_{2\alpha}$ infusions in this dose range.

3. $PGF_{1\alpha}$ was found to have similar effects to $PGF_{2\alpha}$ but it was much less potent.

4. PGE_1 infusions (4–360 (ng/kg)/min) into the vertebral artery caused a tachycardia which was greater than that obtained with intracarotid or intravenous infusions, but there was no significant effect on blood pressure.

5. Infusions of PGA_1 caused a small fall of blood pressure accompanied by an increase of heart rate and the dose response relationships were similar for all three routes of administration.

6. It is concluded that some prostaglandins can activate cardioregulatory centres within the territory of distribution of the vertebral artery. Prostaglandin $F_{2\alpha}$ is the most potent of these.

Introduction

Prostaglandins and prostaglandin-like substances have been discovered in many animal tissues, including the brain. Several workers have identified prostaglandins E and F in the material released spontaneously and on excitation from the cat brain (Ramwell & Shaw, 1966 ; Coceani & Wolfe, 1965 ; Feldberg & Myers, 1966). Consequently there has been some speculation about their possible role in the central nervous system, where they may act as synaptic transmitters or be in some way connected with the formation or actions of cyclic AMP (Horton, 1969).

Prostaglandins also have significant effects on the cardiovascular system. The E and A series cause peripheral vasodilatation and a fall of blood pressure (Carlson & Orö, 1966 ; Bergström, Carlson & Orö, 1967). The effects of the F series are more complicated in that they vary with the species ; $PGF_{2\alpha}$ is depressor in the cat and rabbit (Änggård & Bergström, 1963 ; Horton & Main, 1965), but pressor in the rat and dog (DuCharme & Weeks, 1967) and in the spinal chick (Horton & Main,

1965). DuCharme & Weeks found that the pressor action of $PGF_{2\alpha}$ in dogs was accompanied by an increase in cardiac output and right atrial pressure, but the peripheral resistance remained unchanged. They suggested that the increased cardiac output was primarily due to peripheral venoconstriction.

The possibility that prostaglandins may have cardiovascular effects which are mediated by the central nervous system was suggested by Kaplan, Grega, Sherman & Buckley (1969). They performed cross-circulation experiments in dogs and, after section of the buffer nerves, found that the cardiovascular response to cranial artery infusions of PGE_1 was abolished by administration of hexamethonium. An alternative method of investigating the effect of prostaglandins on the brain is by infusion of the drugs into extracranial arteries of the intact dog and comparing the resulting cardiovascular response with that obtained on intravenous infusion at the same rate. A greater response on intra-arterial infusion indicates that the drug is having a specific effect within the area of distribution of the artery infused.

In this paper we show that some of the prostaglandins have striking cardiovascular effects when infused into the vertebral artery of the chloralose-anaesthetized greyhound at doses which have no effect when given either intravenously or into the carotid artery.

Methods

Greyhounds weighing between 20 and 30 kg were anaesthetized with intravenous chloralose (120–140 mg/kg) after premedication with morphine (2 mg/kg intravenously). The dogs were artifically ventilated throughout the experiments. Intravascular pressures were registered in mmHg (1 mmHg$\equiv$1·333 mbar) by Statham pressure transducers connected to polythene catheters. Heart rate was recorded from the electrocardiograph using a Grass cardiotachometer. Blood flow was measured with a Biotronex electromagnetic flowmeter. Cardiac output was measured by dye-dilution using a Gilford constant-flow system and indocyanine green as the indicator. The area of the dye curve was calculated by a Sanborn cardiac output computer. All data were recorded on a Grass model 7 polygraph.

Drugs were infused through a polythene catheter (external diameter, 1 mm), 5 mm of which was inserted centrifugally into one vertebral artery near its origin, the opposite vessel being ligated. To prevent accidental withdrawal of the catheter a small square of adhesive tape was attached to it immediately proximal to the point of entry and a ligature passed through the tape and tied loosely around the artery. This held the catheter in place satisfactorily without obstructing blood flow. Leakage from the catheter entry site was avoided by using a puncture needle with an external diameter smaller than that of the catheter (23 gauge Yale, B.D.). Carotid artery catheters were inserted in a similar fashion. Intravenous infusions were given through a polythene catheter inserted into a femoral vein. In all experiments infusions of the drugs were preceded and followed by control infusions of physiological saline (0·9% w/v NaCl) at the same rate (1 ml/min).

Prostaglandins were prepared as the sodium salt; each milligram was dissolved in 0·1 ml of 95% ethanol with the rapid addition of 0·9 ml of sodium carbonate (0·2 mg/ml). A final stock solution was prepared with normal saline and kept frozen when not in use. The drugs used were prostaglandin E_1 ($C_{20}H_{34}O_5$), prostaglandin A_1 ($C_{20}H_{29}O_4$), prostaglandin $F_{1\alpha}$ ($C_{20}H_{36}O_5$), prostaglandin $F_{2\alpha}$ ($C_{20}H_{34}O_5$), alpha-chloralose ($C_8H_{11}O_6Cl_3$) and morphine sulphate.

Results

Prostaglandin $F_{2\alpha}$

Effect on arterial pressure

Vertebral artery infusions of $PGF_{2\alpha}$ at rates of 100–1,600 ng/min caused a dose-dependent increase of arterial pressure. Figure 1 illustrates part of this dose-response curve. Neither intravenous nor carotid artery infusions in this dose range had any effect on arterial pressure. To demonstrate any effect by intravenous infusion it was necessary to give doses of 50 μg/min or higher (Fig. 2).

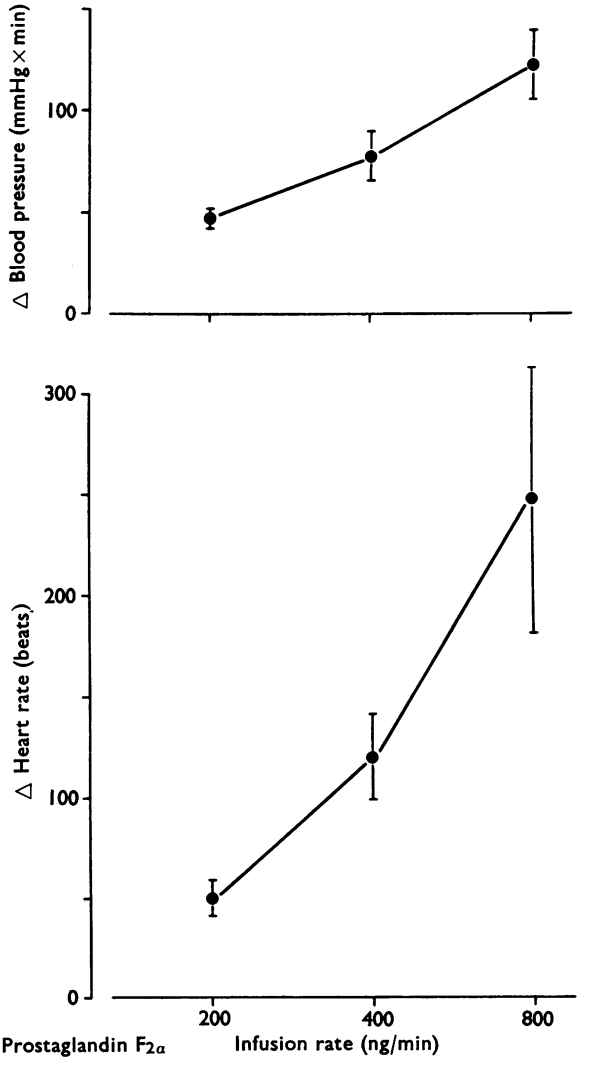

FIG. 1. Dose response curves for arterial pressure and heart rate changes (expressed as the integral) during vertebral artery infusions of prostaglandin $F_{2\alpha}$. Each point represents the mean from seven dogs and one standard error is shown. The infusions were of 5 min duration.

Effect on heart rate and central venous pressure

The rise of arterial pressure during intravertebral infusion of $PGF_{2\alpha}$ was accompanied by a tachycardia and a fall of central venous pressure. The mean dose-response curve rises sharply with increasing doses and above 800 ng/min infusion rate the heart rate usually failed to return completely to its pre-infusion level. There was never any heart rate response to intravenous or carotid artery infusions at these doses.

Effect on cardiac output and peripheral resistance

Cardiac output was measured in seven dogs during intravertebral infusions of 400 ng/min of $PGF_{2\alpha}$. The output was measured at 5 min intervals and the infusions were of 10 min duration. Two measurements were made before, two during and three after the infusion period. In every experiment the increase in blood pressure and heart rate during infusion of $PGF_{2\alpha}$ was accompanied by an increase in cardiac output, and a slight fall of total peripheral resistance occurred in some of the experiments towards the end of the 10 min infusion. The results from all seven experiments have been combined in the composite diagram shown in Fig. 3.

Effect on vertebral artery blood flow

An attempt was made in six dogs to measure the blood flow in the vertebral artery during infusions of prostaglandin. Only three of these experiments were successful owing to the short length of the vertebral artery available and artefacts produced by respiratory movements. In these experiments the flow usually increased slightly, presumably as a passive result of the increase of arterial pressure.

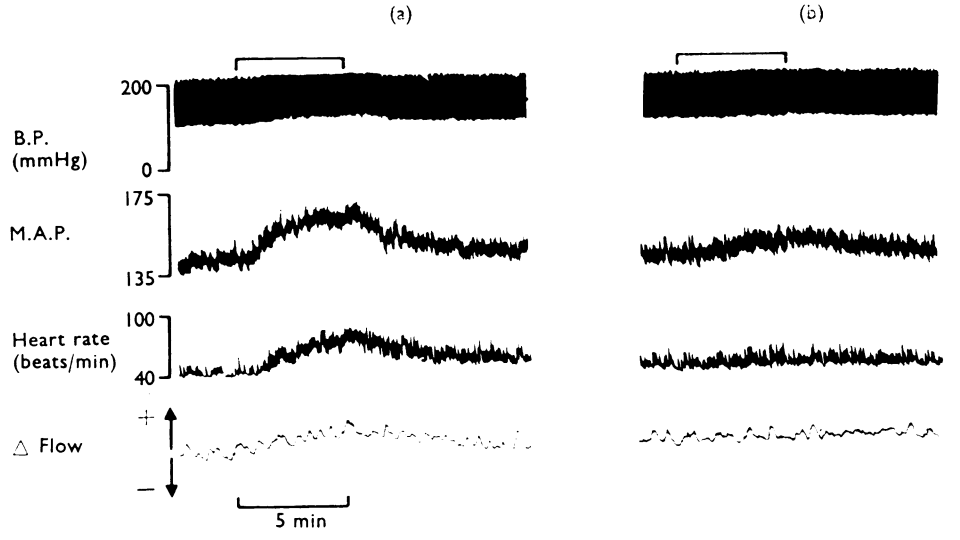

FIG. 2. Effect of prostaglandin $F_{2\alpha}$ infusions (a) into the vertebral artery at 0·4 μg/min and (b) intravenously at 50 μg/min. Pulsatile arterial pressure (B.P.), mean arterial pressure (M.A.P.), heart rate and vertebral artery blood flow are illustrated.

Prostaglandin $F_{1\alpha}$

Prostaglandin $F_{1\alpha}$ was found to have the same balance of effects as $PGF_{2\alpha}$ when infused into the vertebral artery, but it was much less potent. Infusion rates of 9–60 μg/min were required to obtain rises of blood pressure and heart rate comparable with those obtained with $PGF_{2\alpha}$ infusions at 400–800 ng/min (Fig. 4). Intravenous and intracarotid infusions at these rates had no effect on either heart rate or blood pressure.

Prostaglandin E_1

Intravertebral infusions of PGE_1 in the dose range 0·1–9 μg/min caused a tachycardia which was greater than that obtained with intravenous or carotid artery

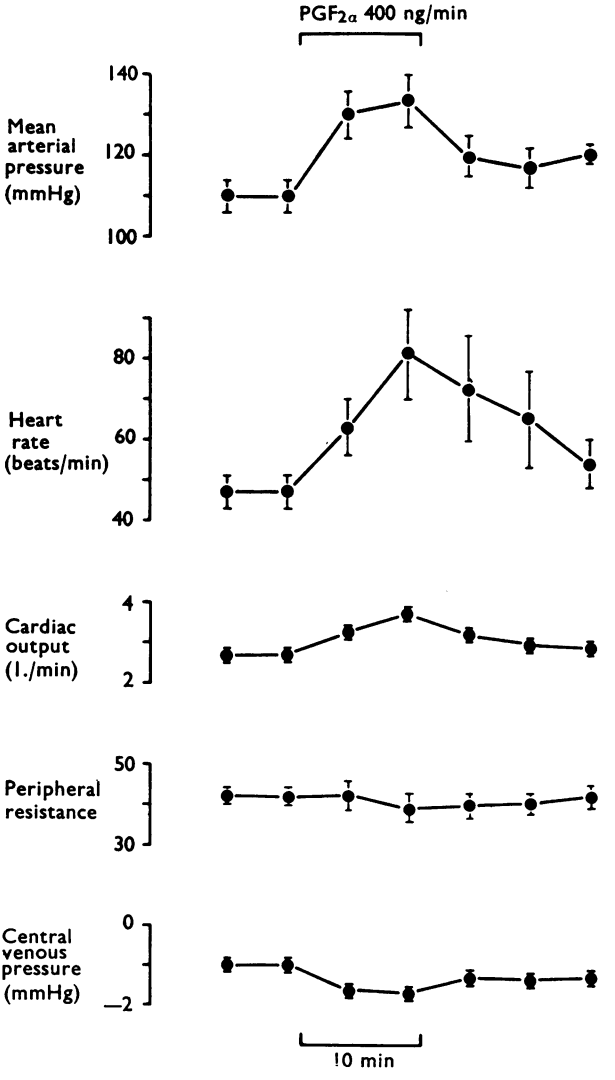

FIG. 3. Effect of prostaglandin $F_{2\alpha}$ infusions at 400 ng/min for 10 min on mean arterial pressure, heart rate, cardiac output, peripheral resistance $\left(\frac{\text{arterial pressure}}{\text{cardiac output}}\right)$ and central venous pressure. Each point represents the mean of seven dogs and one standard error is shown.

infusions at the same rate, but there was no significant change in arterial pressure (Figs. 5 and 6). The heart rate response often exhibited tachyphylaxis.

Prostaglandin A_1

Infusions of PGA_1 into the vertebral artery, intravenously or into the carotid artery at 0·1–9 μg/min caused a rise in heart rate accompanied by a small fall of arterial pressure. The magnitude of the responses was similar for all three routes of administration.

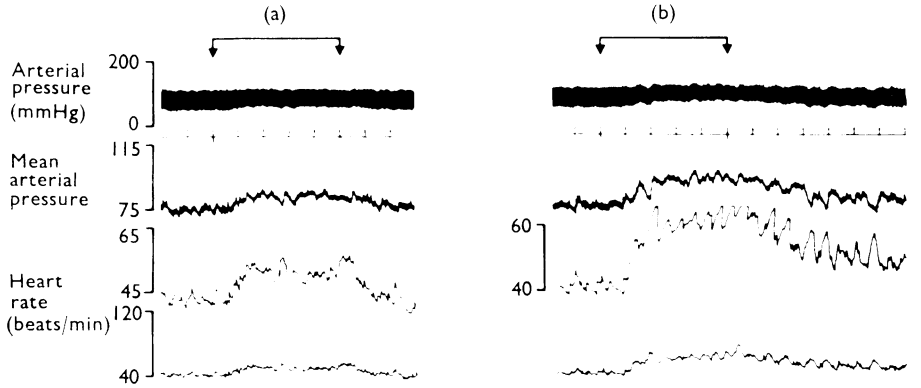

FIG. 4. Effect of a 5 min infusion of (a) prostaglandin $F_{1\alpha}$ at 9 μg/min and (b) prostaglandin $F_{2\alpha}$ at 0·9 μg/min in the intact dog. The traces show pulsatile arterial pressure, mean arterial pressure and heart rate at two different gain factors. Time scale: 1 division = 1 min.

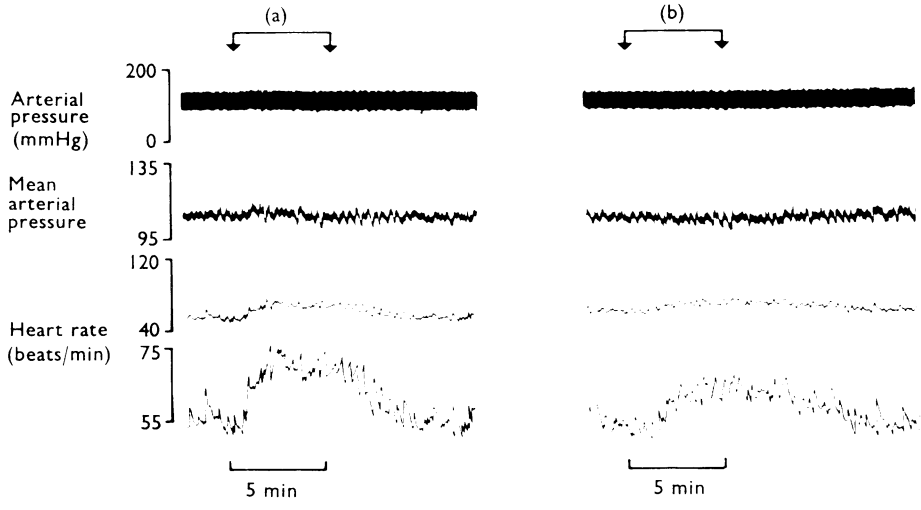

FIG. 5. Effect of prostaglandin E_1 infusions at 3 μg/min for 5 min (a) into the vertebral artery and (b) intravenously. Pulsatile arterial pressure, mean arterial pressure, and heart rate at two different gain factors are shown.

Discussion

These results show that some prostaglandins, in doses which have no effect when given intravenously, have cardiovascular effects on infusion into the vertebral artery. It can therefore be concluded that they produce these effects by activating some structure or structures within the territory of distribution of the vertebral artery, and it seems probable that the site of action is within the central nervous system.

Prostaglandins $F_{2\alpha}$ and $F_{1\alpha}$ both cause an increase in blood pressure, heart rate and cardiac output and a fall of central venous pressure. Peripheral resistance is essentially unchanged. DuCharme & Weeks (1967) have suggested that the increased cardiac output observed on intravenous injection of $PGF_{2\alpha}$ (10 μg/kg) in dogs was due to an increase in central venous pressure resulting from peripheral venoconstriction. Such a mechanism cannot account for the increase of cardiac output in our experiments because central venous pressure fell.

PGE_1 has an effect on heart rate without change of arterial pressure. Intravertebral infusions caused a tachycardia which was always greater than that obtained on intravenous infusions at the same rate. Therefore the response to vertebral artery infusion must be due, in part at least, to activation of some area in its territory

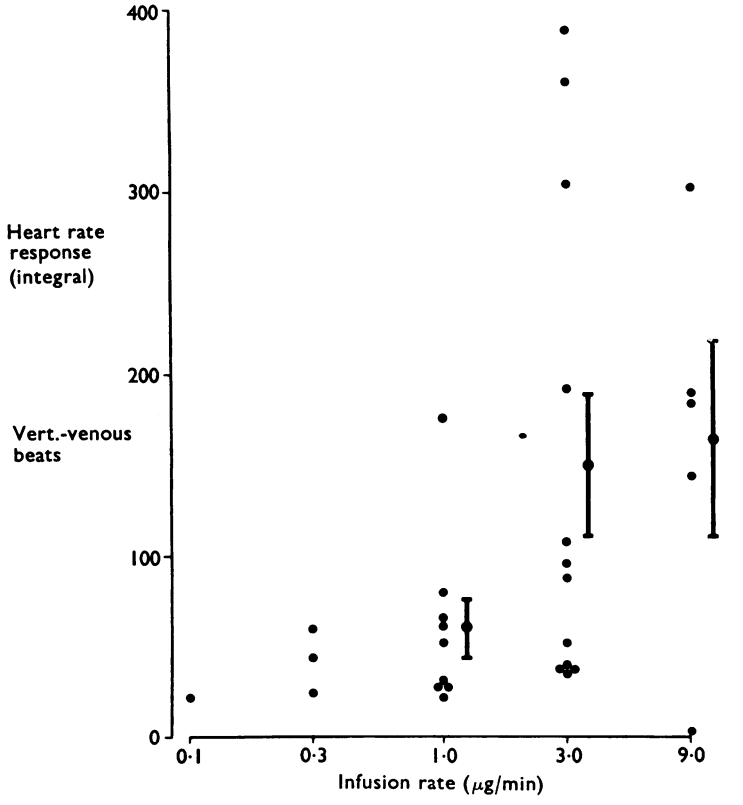

FIG. 6. Dose response curve for the difference in heart rate response between vertebral artery and venous infusions of PGE_1 (twelve dogs); the complete range of doses was not given in every dog. The integrals of the heart rate responses were measured and the difference between the response to vertebral artery and intravenous infusions at any one dose in the same dog calculated. The infusions were of 5 min duration.

of distribution and cannot all be due to recirculation because about 95% of PGE_1 is removed or inactivated during its passage through the lungs (Piper, Vane & Wyllie, 1970). We cannot definitely say whether PGA_1 has any central effects since neither intravertebral nor intracarotid infusions caused a significantly greater cardiovascular response than intravenous infusions.

The experiments described here provide no information about the mechanism of action of the prostaglandins. One possibility is that prostaglandins selectively constrict cerebral blood vessels and that the cardiovascular changes are the result of ischaemia of the autonomic centres. This seems unlikely because the prostaglandins producing the most striking cardiovascular changes (the F series) had no significant effect on vertebral vascular resistance. Furthermore, vertebral artery infusions of noradrenaline in doses which are strongly constrictor have no specific cardiovascular effects (Lowe & Scroop, 1969), whereas two vasodilators, acetylcholine (Scroop, 1969) and bradykinin (Lang & Pearson, 1968), have both been shown to have central cardiovascular effects.

Prostaglandin $F_{2\alpha}$ was the most potent of the prostaglandins we have studied and the concentration reaching the brain in our experiments can be calculated approximately; blood flow in one vertebral artery of the greyhound, with the contralateral vessel clamped, has been measured in previous experiments (Lowe & Scroop, 1969) and found to be 30–50 ml/min. In our experiments the flow changed little during infusion of $PGF_{2\alpha}$. Thus, on infusion of 400 ng/min of $PGF_{2\alpha}$, the approximate concentration in the vertebral artery would be 10 ng/ml. The rapid destruction of prostaglandins by the lungs suggests that, although stable in blood, they will not normally be found in arterial blood, and they would probably never be present in vertebral artery blood in the high concentration whose effects we have studied. However, it does not necessarily follow that in our experiments the concentrations achieved at the receptors are also unphysiological; if the prostaglandins function as neurotransmitters, the local concentration could be many times higher than in arterial blood.

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