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CARDIOVASCULAR ACTIONS OF PROSTAGLANDIN C IN THE CAT AND DOG

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1 Prostaglandin C_2 causes a prolonged fall in arterial blood pressure in the cat.

2 At constant heart rate this fall in arterial pressure is accompanied by falls in stroke volume, left ventricular end diastolic pressure, and left ventricular dP/dt *max.*

3 If mean aortic pressure and left ventricular end diastolic pressure are held constant as well as heart rate, prostaglandins C_2 and E_2 do not affect dP/dt *max* in the cat.

4 In the dog, under similarly controlled conditions, prostaglandins C_2 and E_2 raise dP/dt *max.*

5 We conclude that prostaglandins E_2 and C_2 have no direct inotropic action in the cat, but both have a direct positive inotropic action in the dog.

Introduction

Prostaglandins of the E and A series lower the blood pressure of a large number of mammalian species, mainly by a direct dilator action on arteriolar smooth muscle (see Nakano, 1973 for references). Prostaglandins A are converted to the isomeric prostaglandins C by an enzyme present in the plasma of a number of species, including the cat and dog (Jones, 1972a; Jones, Cammock & Horton, 1972; Jones & Cammock, 1973). It has been shown that prostaglandins C_1 and C_2 are several times more potent as vasodilators in the cat than the precursor prostaglandins A and that the former have a more prolonged effect than the corresponding prostaglandins E (Jones, 1972b). The prostaglandins C pass through the pulmonary circulation of the cat with negligible loss of depressor activity (Jones & Cammock, 1973) unlike the prostaglandins E, which, as shown by previous workers (Ferreira & Vane, 1967; Horton & Jones, 1969) are extensively metabolized by the lung. Thus it is possible that this prolonged effect is simply a reflection of the longer half-life of prostaglandins C in the circulation.

Preliminary investigations, however, revealed that following the intravenous injection of prostaglandin C_2 into the cat a biphasic change in cardiac output occurred, a transient rise followed by a fall, the latter coinciding with the prolonged depression of arterial blood pressure. The experiments described in this paper were designed to elucidate whether prostaglandins C have actions on the cardiovascular system, other than dilatation of arterioles, which could contribute to the depression of cardiac output. We considered three possible actions:

(1) A negative inotropic action on the heart.

(2) Contractility depressed by the fall in arterial pressure.

(3) A reduction of venous return.

Since prostaglandins affect arterial pressure, heart rate and central venous pressure, and since these three factors themselves affect the mechanical performance of the heart, we used a preparation in which they could be held constant.

Prostaglandins E have been reported to increase myocardial contractile force in the dog, but not under conditions of constant heart rate and pressure (Nakano & McCurdy, 1967, 1968; Nakano & Cole, 1969; Emerson, Jelks, Daugherty & Hodgman, 1971). We therefore extended our study to the dog and included prostaglandins E_2 for comparison.

Methods

Cats weighing between 3.0 and 5.3 kg were anaesthetized by an intraperitoneal injection of pentobarbitone sodium (40 mg/kg). Dogs weighing between 5 and 7 kg were anaesthetized by an intravenous injection of pentobarbitone sodium (30 mg/kg). Subsequently, a constant level of anaesthesia was maintained by a continuous intravenous infusion of pentobarbitone sodium.

The animals were ventilated with oxygen by a Starling 'Ideal' Pump. Throughout the experiment, samples of arterial blood were withdrawn at intervals for measurement of pH, P_{CO_2} and P_{O_2} in a Radiometer BMS3 analyser. Arterial P_{CO_2} was

kept as near as possible to 28 Torr in the cat and 40 Torr in the dog by adjusting the stroke of the respiratory pump. Plasma bicarbonate concentration was determined using the nomogram of Siggaard-Anderson (1963) and corrected to 18 mM in the cat and 25 mM in the dog by intravenous injection of an appropriate volume of 1 M sodium bicarbonate solution.

The chest was opened by splitting the sternum in the mid line. The heart was denervated by cutting its sympathetic nerves and the cervical vagi. A small bipolar platinum electrode was inserted into the right auricular appendage and the heart was paced with 5 V pulses of 5 ms duration at a frequency just faster than the spontaneous rate. An electromagnetic flow probe (Statham Q series) was placed around the ascending aorta. Aortic blood pressure was recorded from a catheter inserted through the right common carotid artery.

A metal cannula (2 mm internal diameter) with side holes was inserted through the apical dimple of the left ventricle to record pressure in the ventricular cavity. A consolidated Electrodynamics L223 transducer was attached to the cannula, the whole system having a frequency response flat to more than 40 Hz. The pressure signal was connected to analogue computing circuits to derive the rate of change of ventricular pressure (dP/dt) and left ventricular end diastolic pressure (LVEDP) beat by beat. The pacemaker was synchronized to the clock of the analogue computer.

In the cat, mean arterial pressure (MAP) was held constant by compression of the descending aorta against a cotton tape which had been previously placed around it, and LVEDP was held constant by injection or removal of blood or dextran solution. In the dog, a compressed air blood pressure compensator was connected to both femoral arteries and also through a Watson-Marlow MHRE pump and a reservoir to the left auricle. With this system, fluid could be transferred from the venous to the arterial sides of the circulation and *vice versa* and both arterial pressure and LVEDP could be controlled.

Prostaglandin solutions were infused into the left ventricular cavity through the indwelling catheter at a rate of 0.5 or 1.0 ml/minute. Since prostaglandin C_2 is unstable under alkaline conditions, fresh solutions were prepared in 0.9% w/v NaCl solution at pH 5.5, from a 3 mg/ml stock solution in methanol at the start of each experiment.

Two kinds of tests were performed. In one series (controlled tests) MAP and LVEDP were held constant during the prostaglandin infusion, so that only direct actions on the heart were seen. In the other series (uncontrolled tests) MAP and LVEDP were allowed to change freely under the action of the drug, so that actions on cardiac performance secondary to changes in arterial pressure and venous return were seen. Uncontrolled tests were only performed on cats. In the dog, the direct action seen in the controlled tests would have masked any quantitative information about indirect actions.

After the first infusion of prostaglandin E_2 or C_2 there was marked tachyphylaxis in the responses to further doses of prostaglandins. We therefore adjusted the dose to keep the same order of fall in blood pressure in the controlled tests. Similar allowance was made for the variation, greater than tenfold, in sensitivity to prostaglandins between animals.

MAP, LVEDP and dP/dt *max* were recorded on magnetic tape and later analysed by a PDP8 digital computer. For every test the mean values of these parameters were computed for ten consecutive beats before, and at the end of, a 2 min infusion of the prostaglandin.

Prostaglandin E_2 was supplied by Dr J.E. Pike, of the Upjohn Co., Kalamazoo, Michigan, U.S.A.

Prostaglandin C_2 was prepared from prostaglandin A_2 with rabbit plasma prostaglandin A isomerase bonded to Sepharose 4B gel (Jones, 1974).

Results

Uncontrolled tests in the cat

Table 1 shows the results obtained when LVEDP and MAP were allowed to change freely during an infusion of prostaglandin C_2. In all thirteen tests, MAP and dP/dt *max* fell. In 11 out of 13 tests, LVEDP also fell.

Table 1 The effects of prostaglandin C_2 (0.06-5.5 $\mu g\ kg^{-1}\ min^{-1}$) on left ventricular end diastolic pressure (LVEDP), mean arterial pressure (MAP) and dP/dt *max* in cats when no constraints were applied

State	*LVEDP (mmHg)*	*MAP (mmHg)*	*dP/dt max (mmHg/s)*
Baseline	3.2	97	2220
Test	2.7	59	1410
Change with s.e. mean	−0.5 ± 0.1	−38 ± 6	−810 ± 170

The figures quoted are the means for 13 tests in 5 cats.

Controlled tests in the cat

The results of the controlled tests for the various infusion rates of prostaglandins C_2 and E_2 are shown in Table 2. There were no consistent changes in LVEDP, MAP or d*P*/d*t max*. It can thus be concluded that neither prostaglandin C_2 nor E_2 has a direct inotropic action on the cat's heart.

Controlled tests in the dog

The effects of prostaglandins C_2 and E_2 were investigated in the dog. While LVEDP and MAP were held constant, an increase in d*P*/d*t max* occurred in all ten tests indicating a positive inotropic action on the myocardium. The results are shown in Table 3.

Discussion

We have shown that doses of prostaglandin C_2 which lower the arterial blood pressure of the cat also lower its LVEDP, and d*P*/d*t max*. The effect on d*P*/d*t max* is not seen in the paced heart if both LVEDP and MAP are held constant. This is also true with prostaglandin E_2. We conclude that these prostaglandins have no direct inotropic action on the cat heart.

The explanation for the fall in cardiac output seen in our preliminary experiments with prostaglandin C_2 must therefore lie in an action on the peripheral circulation. The fall in d*P*/d*t max* in the uncontrolled state can be accounted for partly by the fall in arterial pressure and partly by the fall in LVEDP. The fall in LVEDP, in conjunction with a fall in cardiac output, indicates a reduced venous return. The mechanism of this reduction in venous return is not known. Von Euler (1939) found that a crude prostaglandin extract increased portal venous pressure and caused blanching of the liver. Pooling of blood in the portal circulation, due to constriction of vessels in the liver would reduce venous return. Another possibility is that prostaglandin C_2 may dilate capacitance vessels. This could be a direct action on smooth muscle, or an

Table 2 The effects of prostaglandin C_2 (PGC_2) and E_2 on d*P*/d*t max* of the cat heart when left ventricular end diastolic pressure (LVEDP) and mean arterial pressure (MAP) were maintained at the resting level (controlled test)

PG	*State*	*LVEDP (mmHg)*	*MAP (mmHg)*	*dP/dt max (mmHg/s)*
C_2	Baseline	3.3	115	2510
	Test	3.4	116	2550
	Change with s.e. mean	0.1 ± 0.1	1 ± 1	40 ± 20
E_2	Baseline	3.6	118	3020
	Test	3.7	119	2880
	Change with s.e. mean	0.1 ± 0.1	1 ± 1	−140 ± 270

The figures quoted are the means of 6 tests for each prostaglandin in three cats. The infusion rates varied between 0.06 and 5.5 $\mu g\ kg^{-1}\ min^{-1}$ for prostaglandin C_2 and 0.3 and 2.8 $\mu g\ kg^{-1}\ min^{-1}$ for E_2.

Table 3 The effects of prostaglandins C_2 and E_2 (0.07-1 $\mu g\ kg^{-1}\ min^{-1}$) on d*P*/d*t max* of the dog heart when left ventricular end diastolic pressure (LVEDP) and mean arterial pressure (MAP) were maintained at the resting level (controlled tests)

PG	*State*	*LVEDP (mmHg)*	*MAP (mmHg)*	*dP/dt max (mmHg/s)*
C_2	Baseline	2.3	72	1140
	Test	2.4	71	1550
	Change with s.e. mean	0.1 ± 0.1	−1 ± 1	410 ± 116
E_2	Baseline	2.8	74	1160
	Test	2.8	74	1710
	Change with s.e. mean	0 ± 0.1	0 ± 1	550 ± 100

The figures quoted are the means of 4 tests with prostaglandin C_2 and 6 tests with E_2 in 3 dogs.

inhibition of adrenergic venomotor tone. Death from circulatory collapse, which is seen with large doses of prostaglandin C_2 in the cat can be explained by the combination of vasodilatation and reduced venous return.

In contrast with their actions in the cat, prostaglandins C_2 and E_2 exert positive inotropic actions in the dog. The two compounds are of the same order of potency. Since our measurements were made at constant heart rate, LVEDP and MAP, the changes in dP/dt *max* seen in Table 3 indicate the extent of the direct inotropic action in the absence of effects secondary to peripheral vascular actions of the prostaglandins.

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References

EMERSON, T.E. Jr, JELKS, G.W., DAUGHERTY, R.M. Jr. & HODGMAN, R.E. (1971). Effects of prostaglandin E_1 and $F_{2\alpha}$ on venous return and other parameters in the dog. *Amer. J. Physiol.*, **220**, 243-249.

EULER, U.S. von (1939). Weitere Untersuchungen über. Prostaglandin die physiologisch aktive Substanz gewisser. Genitaldrüsen. *Skand. Arch. Physiol.*, **81**, 65-80.

FERREIRA, S.H. & VANE, J.R. (1967). Prostaglandins: their disappearance and release into the circulation. *Nature, Lond.*, **216**, 868-873.

HORTON, E.W. & JONES, R.L. (1969). Prostaglandins A_1, A_2 and 19-hydroxy A_1; their actions on smooth muscle and their inactivation on passage through the pulmonary and hepatic portal vascular beds. *Br. J. Pharmac.*, **37**, 705-722.

JONES, R.L. (1972a). 15-hydroxy-9-oxoprosta-11, 13-dienoic acid as the product of a prostaglandin isomerase. *J. Lipid Res.*, **13**, 511-518.

JONES, R.L. (1972b). Properties of a new prostaglandin. *Br. J. Pharmac.*, **45**, 144-145P.

JONES, R.L. (1974). Inhibitors of rabbit plasma prostaglandin A isomerase. *Biochem. J.*, **139**, 381-389.

JONES, R.L. & CAMMOCK, S. (1973). Purification, properties and biological significance of prostaglandin A isomerase. In: *Advances in the Biosciences*, **9**, pp. 61-70., ed. Bergström, S. Vieweg, Oxford: Pergamon Press.

JONES, R.L., CAMMOCK, S. & HORTON, E.W. (1972). Partial purification and properties of a prostaglandin A isomerase. *Biochim. biophys. Acta*, **280**, 588-601.

NAKANO, J. (1973). General pharmacology of the prostaglandins. In: *The Prostaglandins*, Chapt. II, pp. 41-67., ed. Cuthbert, M.F. London: Heinemann.

NAKANO, J. & COLE, B. (1969). Effects of prostaglandins E_1 and $F_{2\alpha}$ on systemic, pulmonary and splanchnic circulations in dogs. *Amer. J. Physiol.*, **217**, 222-227.

NAKANO, J. & McCURDY, J.R. (1967). Cardiovascular effects of prostaglandin E_1. *J. Pharmac. exp. Ther.*, **156**, 538-547.

NAKANO, J. & McCURDY, J.R. (1968). Hemodynamic effects of prostaglandins E_1, A_1 and $F_{2\alpha}$ in dogs. *Proc. Soc. exp. Biol. Med.*, **128**, 39-42.

SIGGAARD-ANDERSON, O. (1963). Blood Acid-Base alignment nomogram. *Scand. J. Clin. Lab. Invest.*, **15**, 211-217.

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