Interaction of Prostaglandin E_1 and Angiotensin II on Centrally Mediated Pressor Activities in the Cat[1] (37061)

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Several investigators have shown that angiotensin II produces a centrally mediated pressor effect when administered into the brain through the vertebral artery in doses which have little or no effect when given by the intravenous route. This has been demonstrated in dogs (1–3), rabbits (4), and cats (5).

Prostaglandins of the E group are known to lower arterial blood pressure in laboratory animals and for most species the effective concentration of prostaglandin E_1 (PGE_1) required to lower blood pressure ranges between 0.1 and 5 μg/kg (6). The possibility that PGE_1 may have centrally mediated cardiovascular effects was suggested by Kaplan *et al.* (7) who demonstrated a centrally mediated pressor effect in debuffered recipient dogs in cross-circulation experiments. Carlson and Orö (8) reported that infusion of PGE_1 into the common carotid artery of the dog increased the systemic blood pressure and that this effect could be abolished or reversed by ganglion blocking drugs. In the cat, Koss, Gray and Nakano (9) were unable to show a direct brain stem activation by PGE_1 when doses up to 1 μg/kg injected into the vertebral artery failed to produce demonstrable cardiovascular effects. The overall systemic vascular response to intravenous PGE_1 (4–8 μg/kg) in the cat was depressor in nature.

Since it has been demonstrated in this laboratory that both PGE_1 and angiotensin II produce a centrally induced pressor effect with very minute doses, the present studies were designed to investigate the possible interaction of these substances when administered *via* the vertebral artery.

Methods. Cats of either sex weighing between 2 and 4 kg were immobilized with halothane and anesthetized with α-chloralose (60 mg/kg dissolved in 5–10% sodium tetraborate solution) intravenously. The right femoral vein was cannulated for supplemental doses of the anesthetic and for intravenous infusions. A femoral artery was cannulated for recording of blood pressure by means of a Statham pressure transducer (P23AC) onto a Grass Model 7 polygraph. The trachea was cannulated and the animal was artificially respirated using a Harvard small animal respirator.

An incision was made from the sternum to the left axillary region, and the thoracic cavity was opened between the first and second rib. A polyethylene tube (PE10) was inserted into the left subclavian artery near, and proximal to, the exit of the left vertebral artery, passed down the latter artery to a distance of at least 2 cm and tied into position. The chest was then closed and 45–60 min were allowed for the blood pressure to stabilize before the administration of drugs.

For infusion purposes, aliquot portions of an ethanolic (absolute alcohol, 99%) solution of PGE_1 (0.5 mg/ml) were diluted with heparinized saline (50 units/ml). Angiotensin II was dissolved in normal saline, and heparin (50 units/ml) was added to the final dilution. Since the sensitivity of both angiotensin II and PGE_1, administered *via* the vertebral artery varied greatly from animal to animal, it was necessary to titrate each

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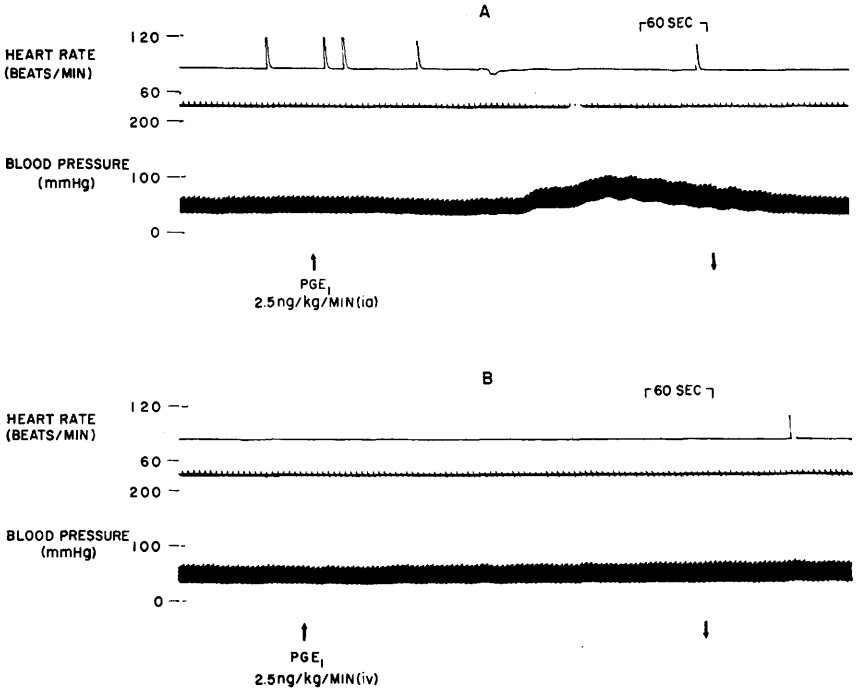

FIG. 1. Effect of PGE$_1$ (2.5 ng/kg/min) on blood pressure and heart rate of α-chloralose anesthetized cat when infused into the vertebral artery (A) and intravenously (B). (↑) Beginning of infusion; (↓) end of infusion.

cat in an attempt to determine the dose which would produce a pressor effect between 20 and 40 mm Hg. Whenever it was impossible to obtain a dose–response effect with the compound under investigation in a particular cat the smallest dose producing a maximal effect was utilized. Two cats were found to be relatively insensitive to the angiotensin II administered *via* the vertebral artery; however, the data were still included utilizing the lowest dose producing a relatively modest increase in mean blood pressure of 6 and 7 mm Hg, respectively (Table II). On the other hand two cats in this group were supersensitive to angiotensin II and 2.5 μg/kg/min administered *via* the vertebral artery produced increases in mean blood pressure of 50 and 55 mm Hg, respectively (Table II). Only one dose of either angiotensin II or PGE$_1$ was used in each cat. The interaction between angiotensin II and PGE$_1$ administered *via* the vertebral artery was investigated in a separate series of cats. The dose of angiotensin II producing a pressor effect of approximately 20 to 30 mm Hg and the dose of PGE$_1$ producing a pressor effect of approximately 10 to 15 mm Hg was determined for each animal.

Results and Discussion. When infused into the vertebral artery of the cat in doses ranging between 1 and 20 ng/kg/min for 4–6 min, PGE$_1$ increased the systemic blood pressure, within 2–5 min and heart rate was often but not always increased. Intravenous infusions using the same dose administered ia produced significantly less pressor effects. Figure 1 shows the results obtained in an experiment in which PGE$_1$ (2.5 ng/kg/min) was infused into the vertebral artery (A) and intravenously (B). Infusion into the vertebral artery raised the systemic blood pressure from 65/35 to 105/65 mm Hg, an increase of +40/30 mm Hg. Intravenous infusion of the same dose raised the blood pressure from 65/32 to 70/35 mm Hg, an increase of +5/3 mm Hg. There was no effect on the heart rate in either case. Table I summarizes the pressor effects of PGE$_1$ (2.5 to 20 ng/kg/min)

TABLE I. Effect of Prostaglandin E_1 on Arterial Blood Pressure of α-Chloralose Anesthetized Cats When Administered by Infusion into the Vertebral Artery (ia) and Intravenously (iv).

Dose (ng/kg/min)	Increase in blood pressure (mm Hg)					
	ia			iv		
	Systolic	Diastolic	Mean	Systolic	Diastolic	Mean
2.5	40	30	33	5	0	2
10.0	10	10	10	2	0	1
20.0	15	15	15	10	10	10
20.0	30	15	20	15	8	10
5.0	20	20	20	5	5	5
20.0	30	15	20	17	10	12
10.0	25	20	22	5	10	8
20.0	35	30	32	15	5	8
5.0	25	25	25	5	8	7
10.0	55	45	48	8	3	5
$\bar{X}$	28.5[a]	21.8[a]	24.5[a]	8.7	5.9	6.8
SE	±4.0	±3.6	±3.4	±1.7	±1.2	±1.0

[a] $p < .01$ when compared to response obtained on intravenous administration using Student's t test (paired).

via the vertebral artery (ia) and intravenously (iv) and Table II summarizes the pressor effects of angiotensin II (0.5 to 10 ng/kg/min) ia and iv. The increase in mean arterial pressure produced by PGE_1 ia was 24 ± 4 mm Hg (X ± SEM) whereas identical doses administered iv produced pressor effects of 7 ± 1 mm Hg ($p < 0.01$). Angiotensin II produced an increase in mean arterial pressure of 31 ± 5 mm Hg ia and 6 ± 2 mm Hg, iv ($p < 0.01$). The pressor response produced by each compound was therefore significantly greater when equi-doses were administered ia as compared to iv.

When a dose of PGE_1 which had only a slight pressor effect and a dose of angiotensin

TABLE II. Effect of Angiotensin II on Arterial Blood Pressure of α-Chloralose Anesthetized Cats When Administered by Infusion into the Vertebral Artery (ia) and Intravenously (iv).

Dose (ng/kg/min)	Increase in blood pressure (mm Hg)					
	ia			iv		
	Systolic	Diastolic	Mean	Systolic	Diastolic	Mean
1.0	10	5	7	0	0	0
10.0	50	35	40	15	15	15
2.5	55	55	55	5	5	5
2.5	50	50	50	0	0	0
0.625	8	5	6	0	0	0
2.5	40	40	40	10	15	13
5.0	25	20	22	5	5	5
3.5	55	40	45	10	5	7
7.0	45	25	32	5	0	2
7.5	20	15	17	15	5	8
0.625	30	25	27	15	10	12
$\bar{X}$	35.3[b]	28.6[a]	31.0[a]	7.3	5.5	6.1
SE	±5.29	±5.09	±5.03	±1.83	±1.71	±1.64

[a] Compared to response obtained on intravenous administration using Student t test (paired): $p < .01$; [b] $p < .001$.

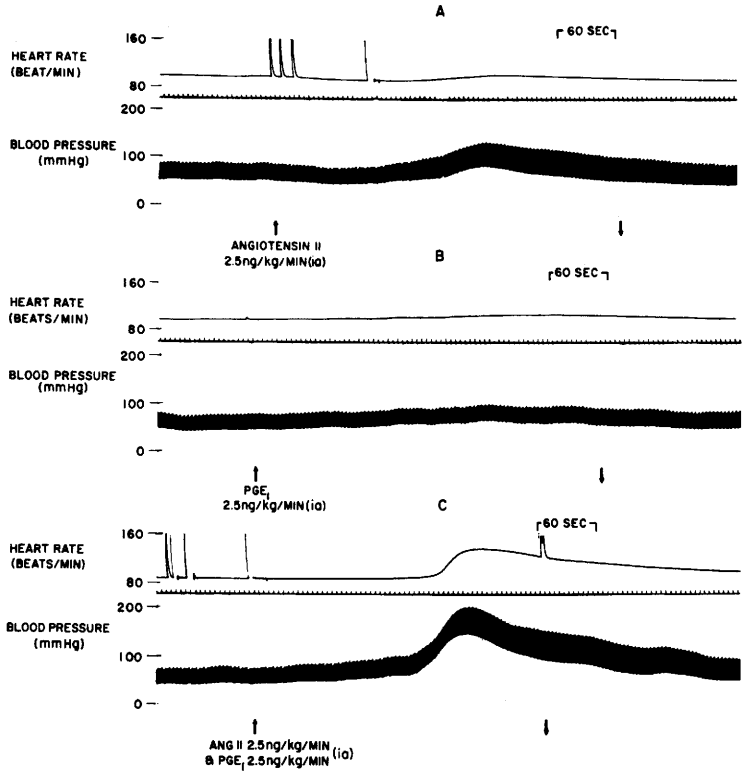

FIG. 2. Effects of angiotensin II (2.5 ng/kg/min) and PGE$_1$ (2.5 ng/kg/min) on the blood pressure and heart rate of α-chloralose anesthetized cat when infused into the vertebral artery separately (A and B) and simultaneously (C). (↑) Beginning of infusion; (↓) end of infusion.

II which produced pressor effects between 20 and 30 mm Hg were infused simultaneously into the vertebral artery, the resulting pressor response was greater than might be expected if the separate responses were additive.

Figure 2 shows the mean pressor effects of 2.5 ng/kg/min angiotensin II and 2.5 mg/kg/min PGE$_1$ infused separately and simultaneously into the vertebral artery. The pressor response was potentiated when the two compounds were infused simultaneously into the vertebral artery.

Table III summarizes the results of 8 similar experiments, in which there was potentiation of the pressor response when the drugs were infused simultaneously into the vertebral artery. Angiotensin II in doses of 0.5–5.0 ng/kg/min produced a mean pressor effect of 22 ± 3 mm Hg; PGE$_1$ in doses of 0.625–5.0 ng/kg/min produced pressor effects of 13 ± 1 mm Hg and the 2 compounds administered concomitantly produced mean pressor effects of 103 ± 10 mm Hg and this was significantly greater than the sum of the responses when the drugs were infused separately ($p < 0.05$).

While there is considerable evidence that angiotensin II produces its centrally mediated pressor effect of activation of central sympathetic mechanisms (10–12) the actual site(s) of action is still not quite clear. The ventromedial hypothalamic nucleus (13), the area postrema in the lower medulla (14–16), and the subnucleus medialis in the midbrain (17, 18) have been suggested as the possible sites for the central pressor action of angiotensin II. Although prostaglandin E$_1$ is generally known to produce a depressor effect in the animal species studied by peripheral vasodilation, a possible centrally mediated pressor effect was observed in dogs by Carlson and Orö (8) who demonstrated a slight pressor effect when PGE$_1$ was infused into a common carotid artery. Kaplan *et al.* (7) showed in

TABLE III. Effects of Angiotensin II and PGE_1 on Arterial Blood Pressure of α-Chloralose Anesthetized Cats When Administered by Infusion into the Vertebral Artery Individually and Simultaneously.

Angiotensin II		PGE_1		Sum of responses to angiotensin II and PGE_1 (a) (mm Hg)	Angiotensin II and PGE_1 simultaneous (b) (mm Hg)	Excess of (b) over (a) (mm Hg)
Dose (ng/kg/min)	Increase in blood pressure (mm Hg)	Dose (ng/kg/min)	Increase in blood pressure (mm Hg)			
5.0	25	2.5	14	39	96	57
2.5	24	2.5	13	37	95	58
2.5	38	0.625	10	48	82	34
1.0	20	2.5	15	35	158	123
0.5	14	2.5	17	31	110	79
5.0	18	5.0	13	31	93	35
0.625	25	1.25	10	35	128	93
2.5	14	2.5	15	29	63	34
$\bar{X}$	22.3		13.4	35.6	103.1	67.5[a]
SE	±2.76		±0.86	±2.1	±10.3	±10.6

[a] Significantly greater than the sum of the responses (a) when the two drugs are administered separately, $p < .05$ using Student's t test (paired).

dogs that the carotid sinus baroreceptors may be involved in the peripheral depressor effects of PGE_1 whereas the central nervous system *per se* is involved in pressor effect that is abolished by ganglionic blockade. In unanesthetized decerebrate cats, Avanzino, Bradley and Wolstencroft (19) used the method of iontophoresis to demonstrate the excitatory action of prostaglandin E_1 on some brain stem neurones in the medulla and caudal pons areas of the brain.

The results of the work presented here show a centrally mediated pressor effect in the cat when very low doses of PGE_1 are infused into the vertebral artery. When administered by the intravenous route, it is probable that these low doses which appear to be below the threshold for direct peripheral vasodilatation stimulate PGE_1-sensitive neurones in the brain. The rapid removal of the drug by the lungs could then explain the smaller pressor effect when given by the intravenous route than when infused into the vertebral artery.

Doses of PGE_1 which produce slight effects have been shown here to potentiate the pressor effects of angiotensin II when the two drugs are infused simultaneously into the vertebral artery. Daniels and Buckley (20) have suggested an interrelationship between endogenous norepinephrine, calcium ions and central adrenergic pressor mechanisms stimulated by angiotensin II. From data obtained in experiments on the rat stomach, Coceani *et al.* (21) concluded that PGE_1 causes retention of calcium during an efflux phase and accumulates this calcium in a slowly exchangeable pool. On the guinea pig myometrium PGE_1 has been shown to increase the responses to other spasmogens in concentrations which has no spasmogenic action (22). Though this potentiation by PGE_1 has been shown on different tissues, it is not inconceivable that calcium ions may be similarly involved in the potentiation by PGE_1 of the centrally mediated pressor effect of angiotensin II involving central neurones.

Potentiation could only be demonstrated when the two drugs were infused simultaneously into the vertebral artery and not when administered concomitantly *via* the femoral vein. This could be due to either a transient action by PGE_1 on membranes to facilitate the accessibility of receptors sensitive to angiotensin II, or a possible increase in the sensitivity of angiotensin receptors themselves, although there is the possibility that the low doses of PGE_1 affected peripheral sites to potentiate the central pressor activity of angiotensin II.

Summary. Low doses of PGE_1 (1–20 ng/kg/min) infused into the vertebral artery elevated the arterial blood pressure in anesthe-

tized cats. When administered by infusion *via* the femoral vein, identical doses of PGE_1 produced pressor effects which were less intense than that produced by the arterial route. Low doses of PGE_1 which have slight pressor effects when infused into the vertebral artery were shown to potentiate the centrally mediated pressor effect of angiotensin II when the two drugs were infused simultaneously into the vertebral artery of cats.

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