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Mechanisms of reflex bradycardia and hypotension by metabolites of arachidonic acid in the cat

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1 In the cat, intravenous injections of arachidonic acid or prostaglandin (PG)$F_{2\alpha}$ caused significant reductions in mean arterial pressure and heart rate which were eliminated or significantly lessened, respectively, by previous administration of indomethacin. The bradycardia to intravenous prostacyclin (PGI_2) was unaffected by indomethacin.

2 In cats with bilateral ligation of the carotid arteries to eliminate competition between systemic baroreflexes and cardiopulmonary reflexes, PGI_2, $PGF_{2\alpha}$ and arachidonic acid caused significantly greater hypotension and bradycardia than in cats with intact carotid baroreflexes.

3 The bradycardia to PGI_2, $PGF_2\alpha$ and arachidonic acid was eliminated by bilateral vagal section or atropine.

4 PGE_1, PGE_2 and nitroprusside caused dose-related falls in mean arterial pressure and a small tachycardia.

5 In a small group of cats (7 of 67) nitroprusside also caused a reduction in heart rate which was eliminated by indomethacin.

6 We conclude that the reflex bradycardia to $PGF_{2\alpha}$, like that to arachidonic acid is, at least in part, the result of the stimulation of synthesis of another prostaglandin, most likely PGI_2.

Introduction

The hypotensive response and the selective vasodilatation in peripheral vascular beds following injection of prostacyclin (PGI_2) in the cat have been described previously (Lippton *et al.*, 1979). However, the effects of prostacyclin on heart rate and systemic reflexes were not studied. We have shown previously that in the dog the administration of prostacyclin or arachidonic acid results in a paradoxical reflex bradycardia and that this reflex also contributes to the hypotensive action of prostacyclin (Hintze *et al.*, 1979a). Under most conditions and in response to other prostaglandins as well, e.g. prostaglandin (PG)E_1 in the dog (Nakano & McGurdy, 1967) and the cat (Koss *et al.*, 1973), systemic arterial hypotension is accompanied by a baroreflex-mediated tachycardia (Heymans *et al.*, 1953).

The reflex effects following injection of $PGF_{2\alpha}$ in the cat are very similar to the reflex bradycardia and hypotension which were observed in the dog in response to PGI_2 (Hintze *et al.*, 1979a; 1981). Koss & Nakano (1976) have described these effects in the cat in detail and have concluded that the reflex bradycardia and hypotension result from stimulation of receptors located predominantly in the heart, and that both the afferent and efferent impulses travel in the vagus nerves. These authors also showed that the reflex effects of $PGF_{2\alpha}$ were abolished by the prostaglandin synthesis inhibitor, meclofenamic acid (Koss *et al.*, 1976). Furthermore, they proposed that meclofenamic acid was acting not as a prostaglandin synthesis inhibitor, but rather as a prostaglandin receptor blocker, as has been demonstrated in bronchial smooth muscle preparations (Collier & Sweatman, 1968) and in the anaesthetized rabbit (Levy & Lindner, 1971). These studies, however, were performed before the discovery of prostacyclin.

The purpose of our study was (1) to determine blood pressure and heart rate responses in the cat following injections of PGI_2, $PGF_{2\alpha}$, PGE_2, PGE_1 and nitroprusside and following stimulation of prostaglandin synthesis *in vivo* via the injection of arachidonic acid; (2) to determine the participation of afferent and efferent vagal fibres in these responses; and (3) to examine the effects of prostaglandin synthesis inhibition with indomethacin on the cardiovascular responses to arachidonic acid, the various prostaglandins and nitroprusside. This latter point is of special significance since indomethacin,

unlike meclofenamic acid has no prostaglandin receptor blocking activity (Flower, 1974; Robinson & Vane, 1974) and it seemed important to ascertain whether the bradycardia following the injection of $PGF_{2\alpha}$ might not be, at least partially, explained by the release of another prostaglandin. It was also of interest to learn whether an increase in prostaglandin synthesis followed by stimulation of myocardial ventricular receptors could result in a vagal reflex bradycardia, similar to the one caused by hypoxia (Thorén, 1973), coronary artery occlusion (Thorén, 1972) or haemorrhagic hypotension (Öberg & Thorén, 1972), and could thus be implicated in the reflex physiological control of cardiovascular function in the cat.

Methods

Cats of either sex, (3.2 ± 0.6 (s.d.) kg), were anaesthetized with intraperitoneal injections of Dialurethane (0.66 ml kg^{-1}, Ciba-Geigy) and a cannula was inserted in the right femoral artery (PE 100) for the recording of arterial pressure. A cannula was also placed in the femoral vein (PE 100) for the injection of drugs. The trachea was exposed through a midline neck incision and a tracheal cannula inserted in order to facilitate respiration. In some of the animals, the vagi were isolated bilaterally in the neck. The cats were warmed with a water circulating heating system (Thermo-rite), and temperature was monitored electronically (Yellow Springs Instruments).

In a total of 18 cats (Group I) dose-response curves were determined to intravenous arachidonic acid (AA) (1.0, 1.5, 2.0, 2.5, 3.0 mg), prostacyclin (PGI_2) (5, 20 and 40 μg), $PGF_{2\alpha}$ (10, 20 and 30 μg), nitroprusside (25, 50 and 100 μg), PGE_2 (5 and 10 μg) and PGE_1 (5 and 10 μg) and repeated after prostaglandin synthesis inhibition with indomethacin (5 mg kg^{-1}).

In 14 cats (Group II) the responses to AA (2.0 mg), PGI_2 (20 μg), $PGF_{2\alpha}$ (20 μg), PGE_1 (5 μg), PGE_2 (5 μg) and nitroprusside (25 μg) were examined before and after tying the carotid arteries bilaterally in the neck. This was done to diminish interference by the carotid sinus baroreflex.

In 35 cats (Group III) the carotid arteries were ligated bilaterally in the neck throughout the experiment. Dose-response curves were established to AA (1.0, 2.0 and 3.0 mg), PGI_2 (5, 20 and 40 μg), $PGF_{2\alpha}$ (10, 20 and 30 μg), PGE_1 (5 and 10 μg), PGE_2 (5 and 10 μg) and nitroprusside (25, 50 and 100 μg). Injections of these agents were repeated in a total of 27 cats after inhibition of prostaglandin synthesis with indomethacin, (5 mg kg^{-1}, $n = 15$), after administration of atropine (1 mg kg^{-1}, $n = 6$) and after bilateral vagal section ($n = 6$).

Mean and phasic arterial pressures were measured with Narco P1000A transducers and were recorded with a direct writing oscillograph (Narco). Heart rate was derived from the pressure pulse interval electronically with a biotachometer (Narco). Arachidonic acid (AA) (Nucheck) was prepared in 100 mM sodium carbonate in preweighed vials and stirred. Prostacyclin (PGI_2) was prepared in 1 M Tris pH 9.0 and diluted just before injection in 50 mM Tris, pH 7.5. Prostaglandins E_1 and E_2 were prepared in 100 mM sodium carbonate at a concentration of 1 mg ml^{-1}, frozen, thawed and diluted with normal saline just before use on the day of the experiment. Sodium nitroprusside (Fisher) was prepared in saline and stored at 5°C in the dark until use. $PGF_{2\alpha}$ (thromethamine salt) was made up in normal saline and frozen in aliquots that were thawed on the day of the experiment. Vehicles were tested and found to have no effects in the cats. All injections were given intravenously in amounts of 1 ml or less. Indomethacin (5 mg kg^{-1}) and atropine sulphate (1 mg kg^{-1}) were used to block prostaglandin synthesis and muscarinic receptors, respectively. Inhibi-

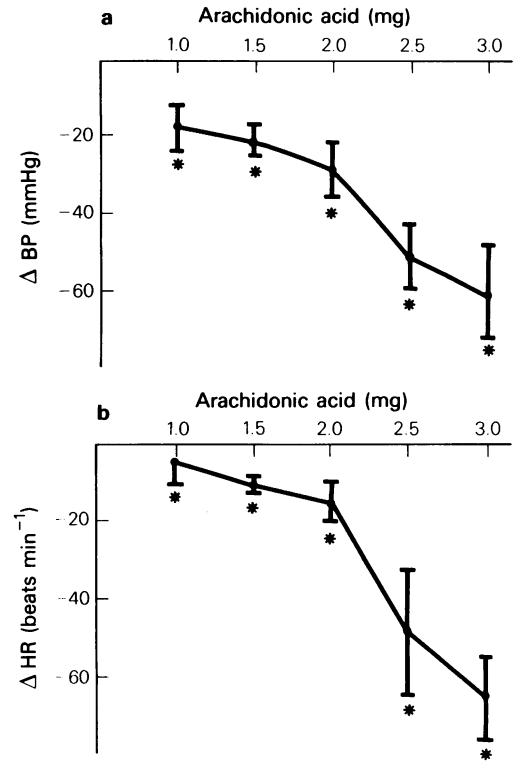

Figure 1 The effects of intravenous injections of arachidonic acid on (a) mean arterial pressure (ΔBP) and (b) heart rate (ΔHR) in the anaesthetized cat. Vertical lines represent s.e.mean, $n = 11$. $^*P < 0.05$, different from control value.

tion of prostaglandin synthesis or blockade of muscarinic receptors was verified with injections of arachidonic acid or acetylcholine. The test dose of AA used for assessment of the effects of indomethacin was the highest dose given in each experiment.

All statistical analyses to assess differences from control were done by using Student's *t* test for paired values (Snedecor & Cochran, 1967).

Results

Group I

Injections of arachidonic acid caused dose-related reductions in mean arterial pressure and heart rate (Figure 1) which were totally abolished after prostaglandin synthesis inhibition. In a similar fashion, injection of $PGF_{2\alpha}$ in doses of 10, 20 and 30 μg caused significant falls in mean arterial pressure from 135 ± 7.6 mmHg by -16 ± 8.9, -29 ± 6.6 and -29 ± 6.9 mmHg, respectively. Indomethacin reduced significantly ($P < .01$) the fall in arterial pressure following injections of similar doses of $PGF_{2\alpha}$ (-7.6 ± 7.6, -5.0 ± 4.1 and -10 ± 6.6 mmHg). $PGF_{2\alpha}$ also reduced heart rate from 190 ± 8.1 beats min^{-1} by -5.3 ± 5.1, -25 ± 6.3 and -42 ± 11.4 beats min^{-1} (Figure 2). Indomethacin lowered baseline heart rate to 174 ± 6.2 beats min^{-1} and eliminated the bradycardia to each dose of $PGF_{2\alpha}$ (-4.6 ± 4.3, -1.0 ± 3.4 and -10 ± 5.6 beats min^{-1}). Injections of prostacyclin (5, 20 and 40 μg, $n = 15$) caused large falls in mean arterial pressure from 129 ± 8.1 mmHg by -20 ± 2.8, -51 ± 4.8 and -59 ± 3.6 mmHg, respectively, and variable changes in heart rate ($+2.6 \pm 4.9$, -12 ± 8.7 and -15 ± 9.3 beats min^{-1} from 192 ± 11 beats min^{-1}). Indomethacin had no effect on the hypotension and bradycardia to PGI_2. Both PGE_1 and PGE_2 (5 μg and 10 μg, $n = 11$) caused reductions in mean arterial pressure. At a dose of 10 μg they lowered blood pressure from 127 ± 8.5 mmHg by -44 ± 4.3 and -35 ± 4.4 mmHg, changes that were unaffected by indomethacin. These prostaglandins had inconsistent effects on heart rate; for instance PGE_1, had no statistically significant effect either before (-0.4 ± 11.2 beats min^{-1}) or after (-12 ± 10.0 beats min^{-1}) indomethacin. Sodium nitroprusside (25, 50, 100 μg, $n = 11$) caused dose-related falls in mean arterial pressure (-34 ± 3.2, -43 ± 4.3 and -51 ± 4.3 mmHg, from 121 ± 9.6 mmHg). Heart rate increased significantly at each dose of nitroprusside (from 188 ± 8.5 by 15 ± 2.8, 19 ± 3.4 and 15 ± 7.2 beats min^{-1}, respectively). After inhibition of prostaglandin synthesis heart rate increased by a similar degree (from 166 ± 7.6 by 17 ± 4.5, 25 ± 5.6 and 24 ± 6.6 beats min^{-1}, respectively).

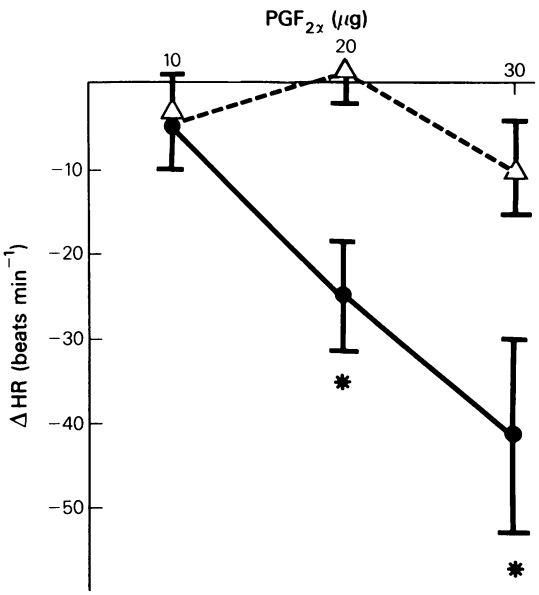

Figure 2 The effect of intravenous injections of prostaglandin (PG) $F_{2\alpha}$ on heart rate (ΔHR) in the anaesthetized cat before (solid line) and after treatment with indomethacin (dashed line). Vertical lines represent s.e.mean, $n = 11$. $^*P < 0.05$, different from control value.

Interestingly, in 7 out of a total of 67 cats studied, sodium nitroprusside caused bradycardia when injected at all three doses tested. All cats, regardless of the planned protocols, which initially responded to nitroprusside with a bradycardia were placed into this experimental group. Reduction in heart rate was eliminated by inhibition of prostaglandin synthesis with indomethacin. For instance, the bradycardia (-19 ± 2.6 from 188 ± 8.5 beats min^{-1}) initially observed following injection of 50 μg nitroprusside was reversed to tachycardia ($+11 \pm 6.8$ from 166 ± 11 beats min^{-1}) after indomethacin. In these cats the fall in blood pressure to nitroprusside was also attenuated after indomethacin, but changes in blood pressure and heart rate to AA, PGI_2 and $PGF_{2\alpha}$ were not different from those in other cats in group I.

Group II

In an attempt to eliminate the variability of the heart rate responses to the various prostaglandins in 14 cats the carotid arteries were ligated bilaterally in the neck and selected doses of each drug were again injected. The hypotensive effects of $PGF_{2\alpha}$ (20 μg), AA (2 mg) and PGI_2 (20 μg) were potentiated (Figure 3), as were the responses to 5 μg of PGE_1, (from -37 ± 4.1 to -54 ± 5.5 mmHg), 5 μg of PGE_2 (from

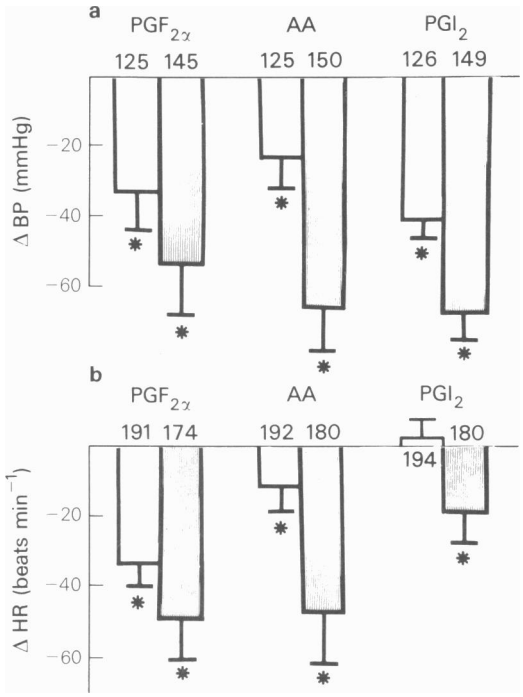

Figure 3 The effect of bilateral ligation of the common carotid arteries (shaded columns) on the (a) changes in mean arterial pressure (ΔBP) and (b) heart rate (ΔHR) induced by intravenous injections of prostaglandin (PG) $F_{2\alpha}$ (20 μg), arachidonic acid (AA) (2 mg) and PGI_2 (20 μg) into anaesthetized cats. The open columns show the responses of the same animals, with intact carotid baroreflexes, to these agents. Control values for mean arterial pressure and heart rate are shown at the base of each column. *$P < 0.05$, responses significantly different from baseline values. Vertical lines represent s.e.mean; $n = 14$.

-10 ± 3.3 to -27 ± 4.7 mmHg) and 25 μg of nitroprusside (-36 ± 3.7 to -47 ± 6.4 mmHg). The bradycardia (Figure 3) to $PGF_{2\alpha}$, AA and PGI_2 was potentiated, whereas the tachycardia to PGE_1, (17 ± 4.3 beats min^{-1}), PGE_2 (19 ± 2.5 beats min^{-1}) and nitroprusside (13 ± 4.2 beats min^{-1}) was essentially unchanged (21 ± 3.4, 12 ± 4.4 and 8 ± 2.7 beats min^{-1}, respectively).

Group III

In this part of the study carotid arteries of cats were ligated bilaterally in the neck at the beginning of the experiment.

The effects of AA (3 mg), PGI_2 (20 μg) and $PGF_{2\alpha}$ (20 μg) before and after muscarinic receptor blockade (atropine) are shown in Figure 4. Arachidonic acid caused dose-related falls in mean arterial pressure which were unaffected by muscarinic blockade (Figure 4) but totally eliminated by bilateral vagal section (Table 1). The bradycardia following stimulation of prostaglandin synthesis with AA was also dose-related (Figures 4 and 5) and was eliminated by either muscarinic receptor blockade or bilateral vagal section (Table 1). Indomethacin abolished the response to the highest dose of AA (3 mg), indicating that blockade of prostaglandin synthesis was complete.

$PGF_{2\alpha}$ (Tables 2 and 3; Figures 4 and 5) caused a reduction in blood pressure which was attenuated by prostaglandin synthesis inhibition, reversed to hypertension after atropine and was eliminated by bilateral vagal section. The bradycardia to $PGF_{2\alpha}$ was not dose-related but was inhibited by pretreatment with indomethacin and eliminated by either muscarinic receptor blockade (Figure 4) or bilateral vagal section.

Table 1 Effects of arachidonic acid on heart rate and blood pressure in the cat

	Control mean arterial pressure (mmHg)	n	*Change in mean arterial pressure (mmHg)*		
Dose of AA (mg)			1.0	2.0	3.0
No treatment	139 ± 4.6	35	−24 ± 4.6*	−53 ± 6.4*	−75 ± 5.3*
Atropine	134 ± 11	6	−13 ± 4.8*	−43 ± 2.8*	−72 ± 4.0*
Vagal section	153 ± 17	6	−1.0 ± 13	−13 ± 21†	−10 ± 30†
	Control heart rate (beats min^{-1})	n	*Change in heart rate (beats min^{-1})*		
Dose of AA (mg)			1.0	2.0	3.0
No treatment	178 ± 4.9	35	−13 ± 3.5*	−40 ± 7.1*	−65 ± 6.1*
Atropine	177 ± 14	6	+3.0 ± 3.1†	+7.0 ± 7.4†	−15 ± 8.3†
Vagal section	203 ± 9.8†	6	+3.0 ± 3.8†	+3.3 ± 4.6†	+6.7 ± 6.8†

Values shown are the mean ± s.e.mean; n = number of cats used in each group. *Indicates values significantly different from control; †indicates values significantly different from the no treatment group ($P < 0.05$).

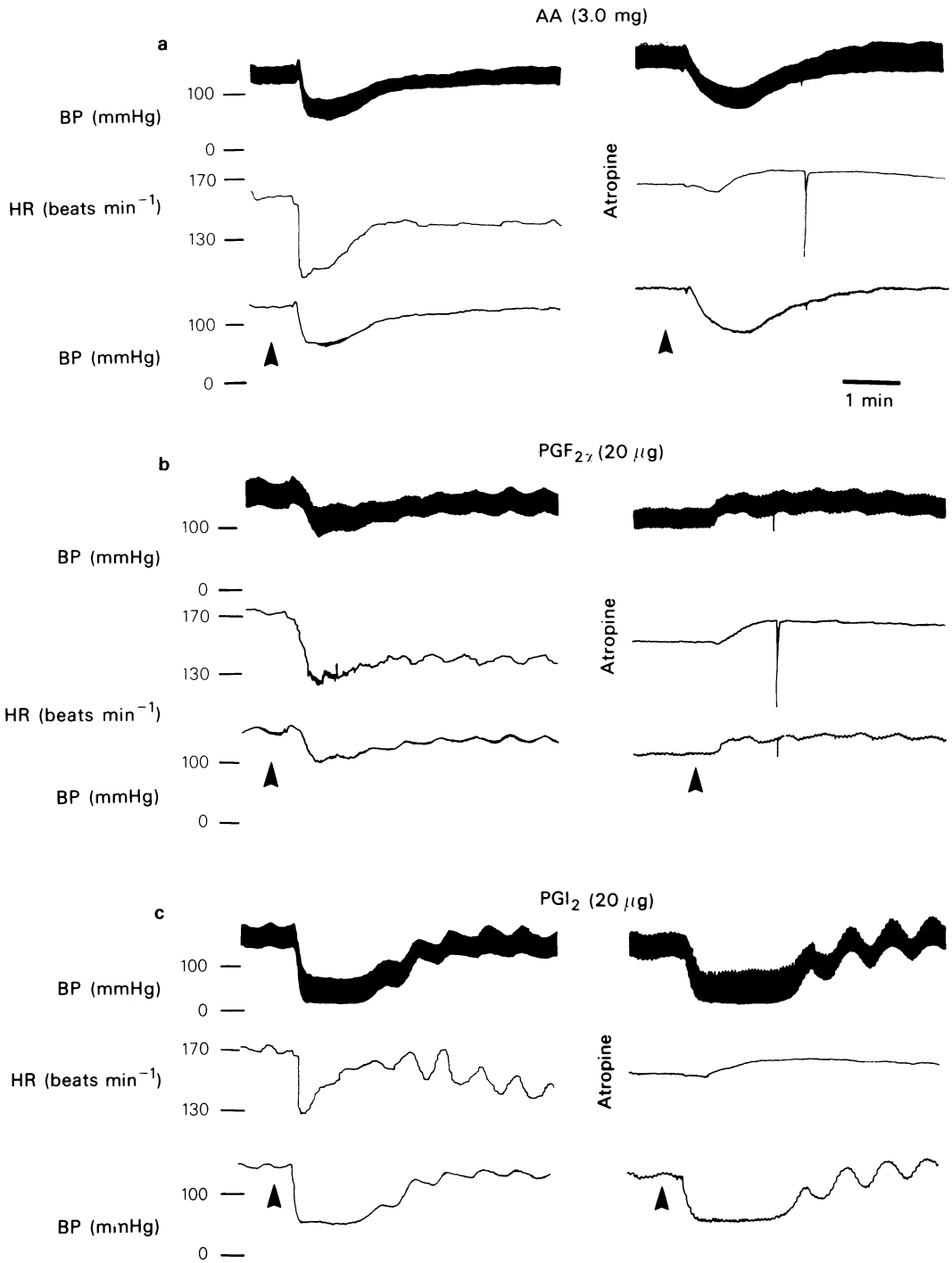

Figure 4 Traces showing the effects intravenous injections of (a) arachidonic acid (AA, 3.0 mg), (b) prostaglandin (PG) $F_{2\alpha}$ (20 μg) and (c) PGI_2 (20 μg) on both phasic (BP) and mean (BP) arterial pressure and heart rate (HR) in the cat. Whereas muscarinic receptor blockade using atropine (right-hand traces) eliminated the bradycardia to all three agents, the hypotensive action of only $PGF_{2\alpha}$ was abolished and was actually reversed to a hypertensive response by the administration of atropine. This record is from a single cat.

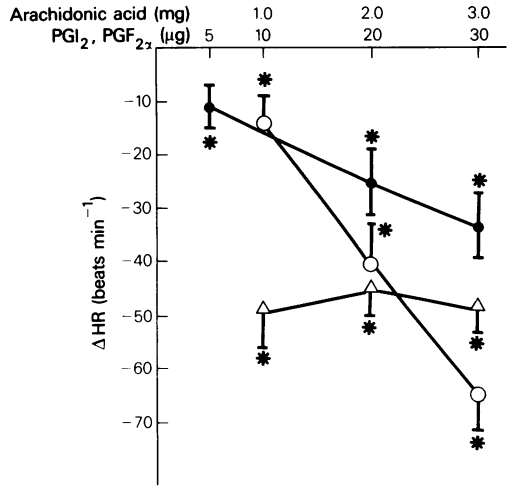

Figure 5 The effects of arachidonic acid (open circles), prostaglandin (PG) I_2 (closed circles) and $PGF_{2\alpha}$ (open triangles) on heart rate (ΔHR) in cats in which the carotid arteries had been previously ligated. *$P<0.05$, different from control values. Vertical lines represent s.e.mean.

Prostacyclin (Tables 2 and 3, Figures 4 and 5) caused dose-related falls in mean arterial pressure and heart rate. The hypotension was unaffected by inhibition of prostaglandin synthesis, administration of atropine or bilateral vagal section. The bradycardia on the other hand was eliminated by atropine and bilateral vagal section but was unaffected by prostaglandin synthesis inhibition.

Sodium nitroprusside (Tables 2 and 3) caused dose-related falls in mean arterial pressure which were unaffected by indomethacin, atropine or bilateral vagal section. Similarly, the changes in heart rate were unaffected by indomethacin, atropine or bilateral vagal section.

PGE_1 at a dose of 10.0 μg, reduced arterial pressure by -53 ± 3.9 mmHg from 139 ± 4.8 mmHg, an effect which was unaffected by indomethacin (-47 ± 4.2 mmHg), by muscarinic receptor blockade (-47 ± 13 mmHg), or by bilateral vagal section (-44 ± 13 mmHg). The increase in heart rate to PGE_1, 14 ± 2.8 beats min^{-1} from 177 ± 5.2 beats min^{-1}, was also unaffected by indomethacin, atropine or bilateral vagal section.

The hypotension resulting from injections of PGE_2, 5.0 and 10.0 μg, -35 ± 3.5 and -46 ± 3.7 mmHg, respectively, was unaffected by indomethacin, atropine or bilateral vagal section. For instance, the reduction in mean arterial pressure to PGE_2 (10 μg) was -52 ± 6.4 mmHg after indomethacin, -49 ± 4.5 mmHg after atropine and -54 ± 11 mmHg after bilateral vagal section. Indomethacin, atropine and bilateral vagal section had no effect on the tachycardia to PGE_2.

Discussion

It has been shown previously that AA and prostacyclin cause a vagal reflex bradycardia in the dog (Hintze

Table 2 Effects of $PGF_{2\alpha}$, PGI_2 and nitroprusside on mean arterial pressure in the cat

	Control mean arterial pressure (mmHg)	n	*Change in mean arterial pressure* (mmHg)		
Dose $PGF_{2\alpha}$ (μg)			10	20	30
No treatment	142±5.0	35	−39±8.2*	−50±7.3*	−52±6.6*
Indomethacin	152±7.8	15	−19±10†	−12±9.5†	−11±3.0†
Atropine	141±16	6	+17±2.1†	+25±3.2*†	+24±3.0*†
Vagal section	166±12	6	+7±5.1†	−1±10†	+3±8.7†
Dose PGI_2 (μg)			5	20	40
No treatment	137±5.1	35	−48±3.3*	−74±4.1*	−83±4.5*
Indomethacin	147±8.5	15	−46±5.0*	−68±8.2*	−73±5.1*
Atropine	153±13	6	−49±13*	−84±4.9*	−93±4.6*
Vagal section	154±17	6	−47±7.4*	−68±9.4*	−88±9.2*
Dose of nitroprusside (μg)			25	50	100
No treatment	144±5.2	35	−56±3.5*	−67±3.7*	−80±3.8*
Indomethacin	138±9.1	15	−44±4.3*	−59±4.5*	−72±4.6*
Atropine	143±11	6	−48±13*	−63±12*	−81±11*
Vagal section	158±13	6	−51±9.5*	−73±8.9*	−85±6.5*

Values shown are the mean±s.e.mean; n = number of cats used in each group. *Indicates values significantly different from control; †indicates values significantly different from the no treatment group ($P<0.05$).

Table 3 Effects of $PGF_{2\alpha}$, PGI_2 and nitroprusside on heart rate in the cat

	Control heart rate (beats min^{-1})	n	*Change in heart rate* (beats min^{-1})		
Dose of $PGF_{2\alpha}$ (μg)			10	20	30
No treatment	184±4.7	35	−49±7.2*	−45±4.9*	−48±4.8*
Indomethacin	176±11	15	−26±7.0*	−27±8.2*†	−29±8.6*†
Atropine	176±13	6	+1±1.4†	0±3.1†	−3±2.4†
Vagal section	204±8.1†	6	0±1.8†	−1±2.1†	−2±2.5†
Dose of PGI_2 (μg)			5	20	40
No treatment	184±5.0	35	−11±3.5*	−25±5.7*	−33±6.0*
Indomethacin	165±10	15	−4±3.3	−22±8.6*	−28±10*
Atropine	177±10†	6	+7±3.0†	+18±4.4*†	+20±6.1*†
Vagal section	200±8.6†	6	+4±1.0*	+9±5.2†	+12±5.9†
Dose of nitroprusside (μg)			25	50	100
No treatment	188±4.8	35	+1.4±2.0	+3.5±2.4	+2.0±3.3
Indomethacin	162±13	15	+11±3.0*	+14±3.6*	+16±4.4*
Atropine	178±12	6	+5±1.7*	+8±1.6*	+9±1.7*
Vagal section	203±8.2†	6	−3.3±1.3	−1.7±4.0	−2.3±3.3

Values shown are the mean±s.e.mean; n = number of cats used in each group. *Indicates values significantly different from control; †indicates values significantly different from the no treatment group ($P<0.05$).

et al., 1979a; Chapple *et al.*, 1980; Chiavarelli *et al.*, 1982). Previous studies of the effects of prostacyclin in the cat (Lippton *et al.*, 1979) have demonstrated systemic and pulmonary vasodilatation but not the reflex bradycardia which we observed. This reflex which is activated during systemic production of prostaglandins and following injection of PGI_2 is similar to the one induced by $PGF_{2\alpha}$ and results, most likely, from stimulation of vagal afferent fibres which originate in the cardiopulmonary region (Koss *et al.*, 1973; Koss & Nakano, 1976). The bradycardia is due to release of acetylcholine from the vagus nerve since it was abolished by muscarinic receptor blockade in our study. Whereas, the hypotensive effect of AA is partially reflex, as it was attenuated by vagal section, the hypotension caused by PGI_2 is most likely due to a direct effect on vascular smooth muscle since it was unaffected by vagal nerve section. Arachidonic acid caused dose-related falls in mean arterial pressure and heart rate, a result which suggests that the *in vivo* production of prostaglandins may cause graded reductions in both arterial pressure and heart rate (Figure 1, Table 1). In previous experiments, in the anaesthetized dog, we found no strict dose-response relationship between PGI_2 and changes in heart rate (Hintze *et al.*, 1981). However, when the carotid baroreflex was eliminated or diminished by ligating the carotid arteries bilaterally, a dose-response relationship was found (Hintze *et al.*, 1979b). This result is due to the direct vasodilator effects of PGI_2 and relates to its possible role as a circulating hormone (Moncada *et al.*, 1978). Since we obtained similar results in the cat, we decided to ligate bilaterally the carotid arteries. This had the effect of potentiating the responses to PGI_2, $PGF_{2\alpha}$ and AA in our experiments, most likely by eliminating the antagonism between cardiopulmonary receptors which are directly stimulated by prostaglandins, and the baroreflexes which are activated by hypotension.

PGE_1, PGE_2 and nitroprusside caused hypotension and either no change in heart rate or a slight tachycardia. Since the hypotension is a direct effect of the drugs, these alterations were unaffected by pretreatment with atropine or bilateral vagal section. The tachycardia results from activation of the systemic arterial baroreflexes and involves withdrawal of vagal tone and augmentation of β-adrenergic tone (Heymans *et al.*, 1953).

Inhibition of prostaglandin synthesis with indomethacin had no major effects on the cardiovascular responses to PGI_2, PGE_1, PGE_2 or nitroprusside. In contrast, the bradycardia and hypotension which result from injection of AA were abolished by indomethacin. This is consistent with the fact that AA administration causes the production of vasoactive prostaglandins *in vivo*. We have previously shown that the coronary vasodilatation which results from the intracoronary injection of AA in the dog (Hintze & Kaley, 1977) and the Bezold-Jarisch-like reflex which results from systemic injection of AA (Hintze *et al.*, 1979a, 1981) are eliminated by pretreatment with indomethacin.

The bradycardia following the injection of nitroprusside in a subgroup of our cats ($n=7$) was abolished by indomethacin, suggesting that nitroprusside may release a prostaglandin which activates a vagal reflex. A portion of the hypotension in these cats was eliminated by inhibition of prostaglandin synthesis. This indicates that either the released prostaglandin(s) causes a potent, direct vasodilatation or that a component of the reflex involves withdrawal of adrenergic tone or activation of sympathetic cholinergic vasodilator pathways which are known to be active in the cat (Folkow & Rubinstein, 1965; Takeuchi & Manning, 1971). These findings may be comparable to those seen in a small group of patients with myocardial infarction in whom a vasovagal reaction occurs during administration of therapeutic doses of nitroglycerine (Come & Pitt, 1976). Nitroglycerine also releases PGI_2 from cultured human endothelial cells (Levin *et al.*, 1981). Furthermore, Morcillio *et al.* (1980) have demonstrated a significant rise in coronary sinus PGE during infusion of nitroglycerine in dogs. In that study the hypotension to nitroglycerine was attenuated, while the tachycardia was potentiated and the release of PGE was abolished after treatment with indomethacin.

Prostaglandin $F_{2\alpha}$ caused a potent, vagal reflex bradycardia and reflex hypotension in our experiments, as previously shown by Koss & Nakano (Koss *et al.*, 1973; 1976; Koss & Nakano, 1976). This response seems to be specific for $PGF_{2\alpha}$ since other F prostaglandins, including $PGF_{1\alpha}$ and $PGF_{1\beta}$, cause minimal effects and also, because a stable, 15-methyl derivative of $PGF_{2\alpha}$ has more pronounced and longer-lasting effects than does $PGF_{2\alpha}$ itself (Koss, 1976). The above authors also described the relative roles of changes in peripheral resistance and cardiac output in the hypotension following the administration of $PGF_{2\alpha}$. Under certain conditions the vagal reflex actions of $PGF_{2\alpha}$ may even result in cardiac arrythmias (Koss & Nakano, 1974). It is interesting to note that in our experiments the hypotensive effects of $PGF_{2\alpha}$ were eliminated by atropine whereas the hypotensive actions of arachidonic acid and PGI_2 were unaffected. Blocking muscarinic receptors might reduce the hypotension due to elimination of the bradycardia and subsequent reduction in cardiac output or, on the other hand, may block peripheral cholinergic vasodilatation directly. In this respect, Folkow & Rubinstein (1965) have shown that hypothalamic stimulation causes cholinergic vasodilatation in skeletal muscle, and Takeuchi & Manning (1971) have demonstrated that during baroreceptor stimulation there is similar vasodilatation in the cat.

The diminution of the bradycardia to $PGF_{2\alpha}$ following administration of an inhibitor of prostaglandin synthesis, meclofenamic acid, in studies by Koss *et al.* (1976) was somewhat unexpected. However, these authors attributed the action of meclofenamic acid to its efficacy as a prostaglandin $F_{2\alpha}$ receptor blocker, as originally demonstrated in the anaesthetized rabbit (Levy & Lindner, 1971). In the present study we found that another prostaglandin synthesis inhibitor, indomethacin, a drug that has no prostaglandin receptor blocking activity (Flower, 1974; Robinson & Vane, 1974), also significantly reduced the bradycardia to $PGF_{2\alpha}$. This finding is consistent with the hypothesis that $PGF_{2\alpha}$ stimulates the synthesis of another prostaglandin, in this case most probably PGI_2, which in turn activates cardiopulmonary receptors to cause a vagal reflex bradycardia in the cat. De Deckere *et al.* (1979) have recently shown that $PGF_{2\alpha}$ releases both PGE_2 and PGI_2 in the isolated perfused rat heart and previous work by Murota *et al.* (1978) suggested that increased release of AA from cultured fibroblasts occurs following administration of $PGF_{2\alpha}$. Since the reflex bradycardia to $PGF_{2\alpha}$ was not totally eliminated by indomethacin in our study, the indication is that a portion of this response may be a result of direct activation of cardiopulmonary receptors by $PGF_{2\alpha}$. The elimination of the bradycardia to $PGF_{2\alpha}$ by meclofenamate in studies by Koss *et al.* (1976) might have been due to a combined effect of $PGF_{2\alpha}$ receptor blockade and inhibition of prostacyclin synthesis by this drug. $PGF_{2\alpha}$ may also have direct reflex effects independent of other prostaglandins in the dog (Ducharme *et al.*, 1978). It is noteworthy too, that in our study there is a rise in blood pressure to $PGF_{2\alpha}$ (Table 3, Figure 4) after the administration of atropine. It is likely that this effect opposes the reflex fall in blood pressure and heart rate produced by $PGF_{2\alpha}$ in the absence of atropine.

The physiological role of the reflex bradycardia and hypotension which is elicited by PGI_2, $PGF_{2\alpha}$ and stimulation of prostaglandin synthesis by AA is difficult to assess, since the existence and importance of cardiopulmonary reflexes is still questionable (Donald & Shepard, 1978). On the other hand, unlike veratridine, prostaglandins are naturally occurring substances and thus may have a potential role in the physiological control of cardiac function (Mullane *et al.*, 1979; Kaley *et al.*, 1980). In the cat, ventricular reflexes are activated during hypoxia (Thorén, 1973), coronary artery occlusion and haemorrhage (Thorén, 1972) leading to a vagal reflex bradycardia. The role of prostaglandins in these responses has not, as yet, been evaluated.

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