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THE EFFECTS OF SOME PROSTAGLANDINS ON RESPIRATION IN ANAESTHETIZED CATS

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1 Some prostaglandins have been found to be capable of affecting respiration in anaesthetized cats.

2 Prostaglandins E_1, E_2, $F_{2\alpha}$, A_1 and A_2 all elicited increases in respiratory frequency when administered to cats anaesthetized with either pentobarbitone or α-chloralose. This effect was abolished by bilateral vagotomy.

3 Prostaglandins of the E and A series, but not prostaglandin $F_{2\alpha}$, elicited increases in tidal volume which were accompanied by falls in systemic blood pressure in cats anaesthetized with pentobarbitone. The changes in blood pressure were also obtained in cats anaesthetized with α-chloralose, but not the tidal volume changes.

4 It is unlikely that the prostaglandins influenced respiration by direct actions on arterial chemoreceptors or baroreceptors.

5 Mechanisms by which the prostaglandins may be acting to affect respiration are discussed.

Introduction

Prostaglandins are known to be capable of influencing respiration. For example, in anaesthetized dogs prostaglandin E_1 has been observed to increase respiratory rate (Maxwell, 1967; Hirose & Said, 1971) and pulmonary ventilation (McQueen & Ungar, 1969). Experiments in man (Carlson, Ekelund & Orö, 1969) demonstrated that prostaglandin E_1 caused hyperventilation, the increase being mainly due to increased tidal volume, although increased respiratory frequency was observed with higher doses. Other prostaglandins have been found to affect respiration; both prostaglandins E_2 and A_1 increase alveolar ventilation (Said, 1968; Hirose & Said, 1971) while prostaglandin $F_{2\alpha}$ increases respiratory frequency but decreases alveolar ventilation in anaesthetized dogs (Said, Muren & Kirby, 1968). Prostaglandin $F_{2\alpha}$ also increases respiratory frequency in anaesthetized monkeys (White, Heaton & Denton, 1971).

It appears that no detailed investigation of the respiratory changes induced by prostaglandins has been performed and the object of the work described here was to examine some prostaglandins for respiratory effects in anaesthetized cats. The respiratory and vascular responses of anaesthetized cats to various prostaglandins are described and some mechanisms whereby prostaglandins may influence respiration are examined.

A preliminary account has been given of some of the work described in this paper (McQueen, 1972).

Methods

Experiments were performed on 21 cats of either sex weighing between 2.4 and 5.3 kg.

Anaesthesia

Cats were anaesthetized either by an intraperitoneal injection of pentobarbitone sodium (36 mg/kg body weight with supplements of 5 mg/kg body weight given intravenously during the experiment as needed) or by an intraperitoneal injection of α-chloralose, 90 mg/kg body weight. The chloralose was dissolved in hot 0.9% w/v sodium chloride solution (saline) and was cooled to body temperature before injection.

Surgical procedures

In all animals the trachea was cannulated in the neck. Rectal temperature was measured and maintained at 37° C.

A femoral vein was cannulated with a nylon

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catheter, the catheter tip lying in the inferior vena cava close to the junction of the venae cavae. This catheter was used for the intravenous administration of drugs and for the intravenous infusion of prostaglandins.

The right femoral artery was cannulated with a nylon catheter and this catheter was connected to a blood pressure transducer.

The right carotid artery was cannulated at the mid-cervical level with a nylon catheter, the catheter tip being positioned in the ascending aorta about 5 mm rostral to the aortic valves. This catheter was used for the intra-aortic (i. aort.) infusion of prostaglandins. The position of all the catheters was confirmed during post-mortem examination in each animal. In one cat one carotid artery was cannulated both ways and blood drawn from the lower carotid artery was pumped at constant flow to the distal part of the same artery, the contralateral carotid artery having been occluded. Part of the head vascular system was thus perfused at constant flow.

In two cats the left and right femoral arteries were cannulated with short nylon catheters and joined by a Y-piece to a blood pressure compensator. In another cat the abdomen was opened and the abdominal aorta was cannulated between the renal arteries and the inferior mesenteric arteries and connected to the blood pressure compensator. In cats in which a compensator was used, blood pressure was recorded from a brachial artery. The compensator used was as described by McQueen & Ungar (1971).

In three cats, anaesthetized with pentobarbitone and artificially ventilated, the thorax was opened by splitting the sternum in the mid-line. The internal thoracic vessels were ligated. A nylon catheter was positioned in a pulmonary vein via an incision made in the left auricle. This catheter was connected to a blood pressure transducer and a record obtained of pulmonary venous pressure. A similar catheter was positioned in the right ventricle via an incision made in the right auricle. This catheter was connected to a blood pressure transducer and a record obtained of right ventricular pressure. Prostaglandins could be infused into either of these catheters. The chest was closed, the pneumothorax reduced, and the animal allowed to breathe spontaneously. Results from these experiments were not incorporated with those obtained in other experiments because the experimental technique (opening and closing the thorax) differed.

Both vagus nerves were dissected in the neck and loops placed around them preparatory to cutting. In two cats the carotid sinus nerves on both sides were dissected and looped in preparation for sectioning during the experiment.

Recording procedure

In each experiment the tracheal cannula was connected to a pneumotachograph head. In early experiments the pneumotachograph was a Mercury Electronics M3 micromanometer with a V2 continuous integrator, a signal proportional to volume being obtained. In later experiments a Mercury Electronics CS3c integrating pneumotachograph was used in conjunction with a Palmer time clock (2112). A cumulative record of total volume inspired over a period of 30 s was measured and recorded on the pen recorder. A 'staircase' tracing was obtained giving a breath by breath record of respiration, with the overall height being proportional to the respiratory volume in half a minute.

Blood pressure

Arterial or venous blood pressure was recorded by connecting a blood pressure transducer (Consolidated Electrodynamics, Type 4-326-L212) to a catheter and recording the transducer output on a pen recorder (1 mmHg = 1.333 mbar). All animals were injected intravenously with 1000 i.u./kg heparin to prevent blood clotting.

Blood flow

In two cats blood flow in a carotid artery was monitored with an electromagnetic flow probe (MDQ 7020 SCF 2 mm, Statham) connected to a Statham Blood Flow meter (SP 2200). The meter output was recorded by the pen recorder.

Blood gas analysis

In two cats blood from a cannulated femoral artery was sampled before, during and after a prostaglandin infusion. P_aCO_2 P_aO_2 and pH were estimated by means of a Radiometer BMS 3 meter with PHM 71, PHA 930, and PHA 931 attachments.

Recorder

A Devices M4 Hot-stylus recorder with DC2d pre-amplifiers was used. Pens gave a frequency response flat to 75 Hz.

Drugs

The following drugs were used, dissolved in saline unless otherwise indicated:

Prostaglandins E_1 E_2, $F_{2\alpha}$, A_1 and A_2. Stock solution of 1 mg/ml in 10% ethanol: 90% 0.9% w/v aqueous sodium chloride kept frozen (−20° C)

and diluted with saline before use. Working solutions of all the prostaglandins were 10 μg/ml. The prostaglandins used were generously supplied by Dr J.E. Pike of The Upjohn Company, Kalamazoo, Michigan.

Atropine sulphate, histamine acid phosphate, α-chloralose, sodium cyanide (B.D.H. Chemicals Ltd), pentobarbitone sodium (Abbott Laboratories Ltd), mepyramine maleate (May and Baker Ltd), heparin B.P. (Weddel Pharmaceuticals Ltd), propranolol (I.C.I. Ltd) and isoprenaline sulphate B.P. (Boots Ltd).

The doses refer to the salts.

Drug administration

Drugs were either injected, or infused by means of a Watson Marlow MRHE 200 pump. It was noted during the course of the investigation that the response to prostaglandins varied from animal to animal, as did the frequency with which doses of prostaglandin could be administered. In general, a 6 min cycle was followed for prostaglandins E_1 and E_2, with a 10 min time cycle for prostaglandins A_1, A_2 and $F_{2\alpha}$. The doses administered provoked respiratory responses which were submaximal.

Measurement of responses

The responses were measured at 60 s after the start of the 30 s infusion. At this time a maximal respiratory and vascular response was observed, regardless of the dose of prostaglandin administered.

The variables measured were respiratory minute volume (RMV), respiratory rate or frequency (f) and blood pressure (BP). Tidal volume (V_t) was calculated from RMV and f. The results obtained for each set of circumstances (i.e. type of prostaglandin, route of infusion, whether or not vagotomized) were pooled and are expressed as the mean control value ± s.e. mean and the mean incremental change ± s.e. mean.

The dose is expressed as μg/kg, this being the total quantity administered over a period of 30 s at a constant rate of infusion.

Statistical analysis

The null hypothesis that the incremental changes observed were not different from zero was tested using a paired t test on data obtained with prostaglandins E_1 and $F_{2\alpha}$. A t test was applied to incremental changes obtained under different test situations (e.g. i.v.: i. aort; before : after vagotomy). The difference was said to be statistically significant if P was less than 0.05.

Prostaglandins E_2, A_1, and A_2 were found, from a limited number of tests, to evoke changes similar to those seen with E_1. Because the responses to prostaglandin E_1 had been extensively examined, further experiments with these other prostaglandins were not performed.

Results

Prostaglandins E_1 and $F_{2\alpha}$ were investigated for their ability to evoke respiratory changes. Prostaglandins E_2, A_1 and A_2 were found to be similar to E_1 in their ability to affect respiration, and the results obtained with these prostaglandins will be described qualitatively. Prostaglandins A_1 and A_2 were about twice as potent as E_1 in eliciting respiratory rate increases and hypotension. The main difference between the E and A series was that the latter caused sizeable falls in BP when infused i.v., comparable with the effect seen on i. aort. infusion of the same dose.

Prostaglandin E_1

Data obtained from experiments with prostaglandin E_1 are summarized in Table 1. When infused either i.v. or i. aort. prostaglandin E_1 evoked a dose-dependent increase in f and RMV; V_t increased on i. aort. infusion but decreased on i.v. administration. The change in f started about 10 s after the start of an i.v. infusion and continued for the duration of the infusion, at least up to 4 min which was the longest infusion period studied. The rate increase was sometimes preceded by one deep breath or by a period of respiratory inhibition (Figure 1).

On i. aort. infusion prostaglandin E_1 evoked an increase in f, an increase in V_t and a fall in BP. The f increase started about 24 s after the start of the infusion and the V_t increase was greatest at the time when the hypotension was maximal (Figure 2). The f increase obtained on i.v. administration of prostaglandin E_1 was significantly bigger than that obtained on i. aort. administration ($P < 0.05$) although smaller doses of prostaglandin E_1 were administered i. aort. before vagotomy in order to avoid obtaining large vascular effects. In those experiments in which equal doses were infused by the two routes, the f response was always greatest on i.v. infusion. The RMV increase was greatest on i. aort. infusion ($P < 0.01$) and the BP fall was greatest with i. aort. infusions ($P < 0.01$).

Bilateral vagotomy significantly reduced the f increase ($P < 0.01$ for either route) but the V_t increase observed on i. aort. infusions was still

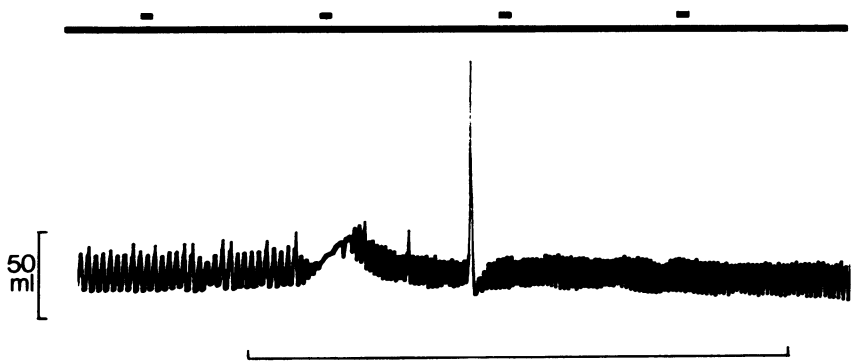

Fig. 1 Cat (male, 4.4 kg) anaesthetized with pentobarbitone. Prostaglandin E_1, 12 μg/kg, infused over a period of 3 minutes. Record, from above downwards: 1 min time marker; breath by breath record of respiration; marker indicating period during which prostaglandin E_1 was infused.

present after vagotomy, although reduced in magnitude. The i. aort. RMV increase was significantly reduced by vagotomy ($P < 0.01$) and bilateral vagotomy also resulted in prostaglandin E_1 evoking a bigger depressor response ($P < 0.05$ pre/post vagotomy) although the response to i. aort. infusions was not significantly affected.

In two experiments measurements of P_aCO_2 were made before and during the RMV increases evoked by prostaglandin E_1 infusions and it was found that alveolar hyperventilation was occurring since the P_aCO_2 fell.

Prostaglandin $F_{2\alpha}$

Data obtained from experiments with prostaglandin $F_{2\alpha}$ are summarized in Table 2. Prostaglandin $F_{2\alpha}$ when infused i.v. increased respiratory rate, this increase often being prolonged following a 30 s infusion (Figure 3). No significant change in

Table 1 Prostaglandin E_1 (PGE_1) infused i.v. or i. aort. before and after bilateral vagotomy, pentobarbitone anaesthesia

	Intravenous					
	Before vagotomy			*After vagotomy*		
	Control	*Increment*	P	*Control*	*Increment*	P
f (breaths/min)	22 ± 2.1	9.5 ± 1.0	<0.01	17 ± 1.3	0.4 ± 0.5	*
V_t (ml)	30 ± 1.7	−1.6 ± 0.6	<0.01	38 ± 3.1	4.2 ± 1.7	<0.05
RMV (ml/min)	660 ± 36	160 ± 20	<0.01	570 ± 44	104 ± 41	<0.05
BP (mmHg)	140 ± 2.7	−17 ± 1.8	<0.01	130 ± 7.1	−24 ± 3.8	<0.01
			Intra-aortic			
f (breaths/min)	16 ± 2.1	5.7 ± 0.9	<0.01	16 ± 0.4	1.7 ± 0.9	*
V_t (ml)	33 ± 1.4	22 ± 6.8	<0.01	37 ± 5.3	7.8 ± 2.5	<0.05
RMV (ml/min)	520 ± 72	610 ± 120	<0.01	590 ± 93	180 ± 54	<0.05
BP (mmHg)	140 ± 6.8	−53 ± 4.1	<0.01	130 ± 14	−52 ± 9.5	<0.01

i.v. before vagotomy	59 tests in 10 cats.	Dose PGE_1 = 3.4 ± 0.2 μg/kg	
i.v. after vagotomy	21 ,, ,, 8 ,,	,, ,,	3.9 ± 0.4 ,,
i. aort. before vagotomy	12 ,, ,, 4 ,,	,, ,,	1.9 ± 0.2 ,,
i. aort. after vagotomy	8 ,, ,, 5 ,,	,, ,,	2.8 ± 0.3 ,,

Data are shown as mean ± s.e. * indicates $P > 0.05$.

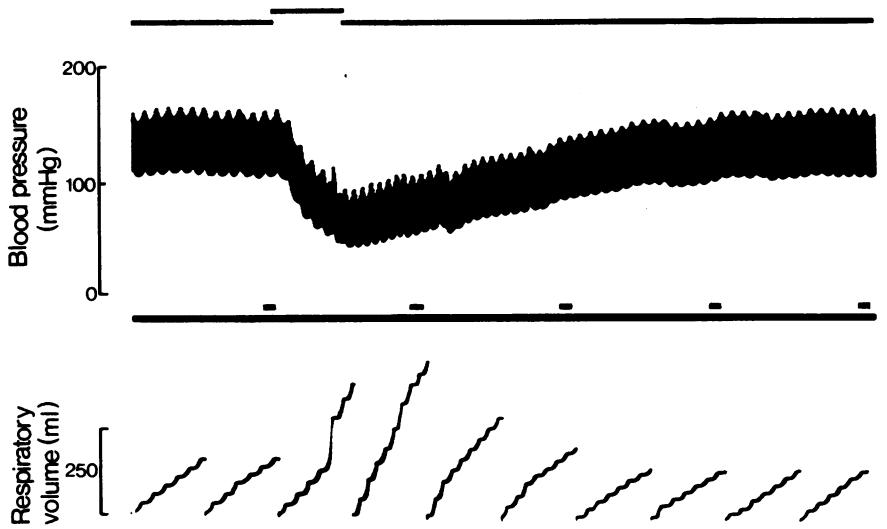

Fig. 2 Cat (male, 3.5 kg) anaesthetized with pentobarbitone. Prostaglandin E_1, 0.9 μg/kg, infused i. aort. over a period of 30 seconds. Record, from above downwards: event marker; arterial blood pressure; 1 min time marker; breath by breath record of respiration, total height representing the respiratory volume in 30 seconds.

f was observed on i. aort. infusion either before or after vagotomy and there was no significant change in V_t following prostaglandin $F_{2\alpha}$ administration by either route, and vagotomy did not alter this. Blood pressure fell slightly when prostaglandin $F_{2\alpha}$ was infused i.v. but not when infused i. aort. The *f* increase seen on i.v. administration was markedly reduced after bilateral vagotomy ($P < 0.01$).

Chloralose anaesthesia

A series of experiments was performed on cats anaesthetized with α-chloralose in order to

Table 2 Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) infused i.v. or i. aort. before and after bilateral vagotomy, pentobarbitone anaesthesia

	Before vagotomy			*After vagotomy*		
	Control	*Increment*	P	*Control*	*Increment*	P
			Intravenous			
f (breaths/min)	19 ± 1.4	6.4 ± 1.1	0.01	14 ± 1.0	0.7 ± 0.8	*
V_t (ml)	32 ± 2.5	−1.7 ± 1.4	*	49 ± 2.2	3.5 ± 3.9	*
RMV (ml/min)	540 ± 32	160 ± 49	0.01	660 ± 45	79 ± 84	*
BP (mmHg)	130 ± 4.3	−10 ± 4.8	0.05	130 ± 10	−3.1 ± 6.1	*
			Intra-aortic			
f (breaths/min)	17 ± 1.8	3.7 ± 1.7	*	16 ± 0.9	−1.5 ± 1.3	*
V_t (ml)	33 ± 0.7	5.0 ± 2.1	*	44 ± 3.6	2.5 ± 5.9	*
RMV (ml/min)	540 ± 55	220 ± 55	0.05	700 ± 63	−22 ± 110	*
BP (mmHg)	130 ± 10	−2.2 ± 5.3	*	130 ± 11	−8.1 ± 8.7	*

i.v. before vagotomy	23 tests in 8 cats.	Dose $PGF_{2\alpha}$ = 3.2 ± 0.3 μg/kg	
i.v. after vagotomy	6 „ „ 3 „	„ „	3.0 ± 0.4 „
i. aort. before vagotomy	7 „ „ 4 „	„ „	2.6 ± 0.4 „
i. aort. after vagotomy	8 „ „ 5 „	„ „	3.2 ± 0.5 „

Data are shown as mean ± s.e. * indicates $P > 0.05$.

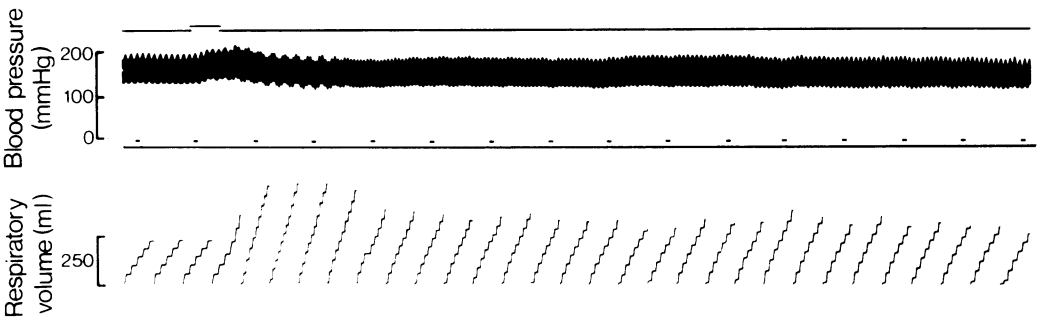

Fig. 3 Cat (female, 2.9 kg) anaesthetized with pentobarbitone. Prolonged response to an infusion of prostaglandin $F_{2\alpha}$ (4.1 μg/kg over a 30 s period) into the abdominal aorta. Record, from above downwards: event marker; arterial blood pressure; 1 min time marker; breath by breath record of respiration, total height representing the respiratory volume in 30 seconds.

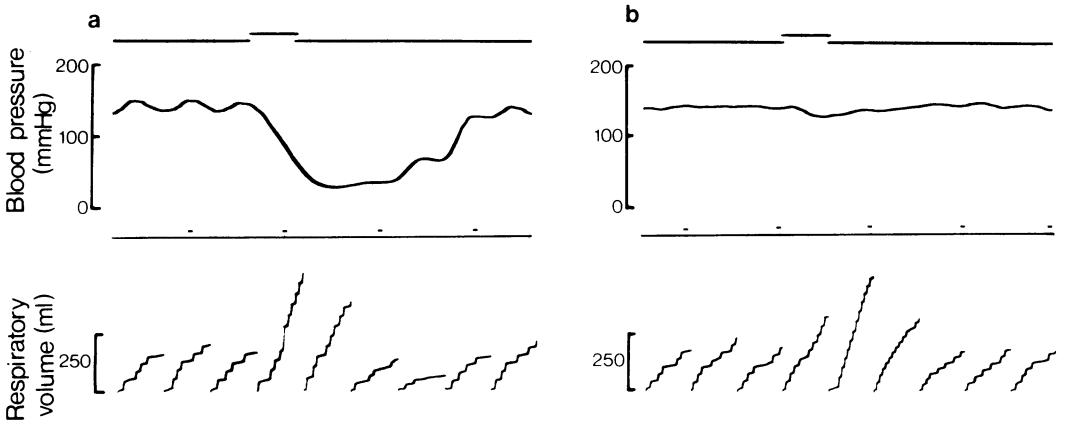

Fig. 4 Cat (male 3.0 kg) anaesthetized with pentobarbitone. (a) Prostaglandin E_2, 2.7 μg/kg, infused i. aort. over a 30 s period; (b) prostaglandin E_2, 2.7 μg/kg, infused i. aort. over a 30 s period, with blood pressure compensator connected to the abdominal aorta. Record details as in Fig. 2, excepting that the mean blood pressure is shown.

examine the possibility that the changes observed in cats anaesthetized with pentobarbitone were peculiar to the anaesthetic agent. Some of the results obtained are summarized in Table 3. Prostaglandin E_1 evoked an increase in respiratory rate when administered either i.v. or i. aort. as did $F_{2\alpha}$ i.v., and these increases were significantly reduced after vagotomy ($P < 0.01$). V_t fell on i.v. administration, but there was no significant change when the prostaglandin was infused i. aort. RMV was not significantly affected by prostaglandin E_1 i.v., but it was increased by E_1 or $F_{2\alpha}$ administered i. aort. BP fell when prostaglandin E_1 was infused i.v. and a bigger fall was obtained when it was infused i. aort. ($P < 0.01$). Prostaglandin $F_{2\alpha}$ did not significantly affect blood pressure.

Blood pressure compensation

In three cats anaesthetized with pentobarbitone the mean arterial blood pressure was compensated. The results obtained are illustrated by Figure 4. BP compensation reduced the increase in V_t and a larger increase in f was obtained. After bilateral vagotomy BP compensation reduced the tidal volume increment evoked by prostaglandin E_1 by about 60%.

Blood flow to the head

When carotid blood was pumped to the head at constant flow changes in respiration followed the intravenous or intra-arterial (descending aorta)

Table 3 Cats anaesthetized with chloralose. Infusions of prostaglandin E_1 (PGE_1) or $F_{2\alpha}$ ($PGF_{2\alpha}$)

	PGE_1 i.v.			*PGE_1 .. aort.*			*$PGF_{2\alpha}$ i.v.*		
	Control	*Increment*	P	*Control*	*Increment*	P	*Control*	*Increment*	P
f (breaths/min)	15 ± 0.7	5.1 ± 1.2	<0.01	15 ± 0.7	3.5 ± 0.8	<0.01	16 ± 0.5	7.1 ± 1.6	<0.01
V_t (ml)	26 ± 1.5	−3.5 ± 0.8	<0.01	21 ± 1.2	4.0 ± 2.1	*	27 ± 2.2	−4.5 ± 1.4	<0.01
RMV (ml/min)	380 ± 27	65 ± 35	*	310 ± 23	160 ± 49	<0.05	440 ± 33	79 ± 24	<0.01
BP (mmHg)	130 ± 5.8	−23 ± 4.9	<0.01	130 ± 3.3	−67 ± 3.1	<0.01	120 ± 3.8	−7.8 ± 10	*

PGE_1 i.v. 16 tests in 5 cats. Dose = 3.7 ± 0.5 μg/kg
PGE_1 i. aort. 7 " " 3 " " 3.5 ± 0.6 "
$PGF_{2\alpha}$ i.v. 13 " " 4 " " 3.6 ± 0.4 "
Values are shown as the mean ± s.e. $P > 0.05$ = *.

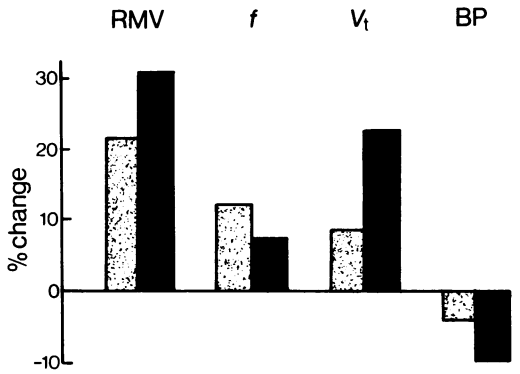

Fig. 5 Vagotomized cat (female, 3.6 kg) anaesthetized with pentobarbitone, showing the response to prostaglandin E_1 (3.1 μg/kg infused over a 30 s period) obtained before (stippled column) and after (solid column) bilateral sinus nerve section.

administration of prostaglandin E_1; injection of prostaglandin E_1 into the head perfusion circuit did not evoke any respiratory changes until the prostaglandin had had time to recirculate. It appears, therefore, that prostaglandins do not affect respiration by actions within the vascular territory perfused by the carotid arteries, and also that even when part of the CNS is perfused at constant flow, respiratory changes are still obtained.

Experiments with an electromagnetic flow probe positioned around a common carotid artery revealed that flow in this vessel increased on i.v. administration of prostaglandin E_1 but decreased on i. aort. administration. Flow in the vertebral arteries would be expected to follow the direction of flow in the carotid arteries, and so it may be concluded that blood flow to the CNS increases during i.v. prostaglandin E_1 administration, even though systemic blood pressure falls, and that blood flow to the CNS falls during i. aort. administration.

Carotid sinus denervation

In two experiments on vagotomized cats anaesthetized with pentobarbitone the respiratory response to prostaglandin E_1 was examined before and after bilateral sectioning of the carotid sinus nerves. The results obtained are illustrated by Figure 5. The RMV increment was further increased following sinus denervation and this was associated with a larger fall in blood pressure and an increase in V_t. The evidence argues against any direct activation of either the carotid chemoreceptors or baroreceptors.

Pulmonary vascular responses

In three cats anaesthetized with pentobarbitone no significant change in central venous pressure was observed for any of the prostaglandins administered by either the venous or arterial route.

Catheters were positioned in a pulmonary vein and in the right ventricle in three cats. Pressure recordings in the spontaneously breathing animals showed no consistent change in right ventricular pressure with prostaglandins E or A, although $F_{2\alpha}$ caused a rise in pressure. Pulmonary venous pressure was reduced slightly by prostaglandin $F_{2\alpha}$, increased slightly by E_1 and E_2 and not affected by A_1 or A_2 on i.v. infusion.

Infusions of prostaglandin into the right ventricle evoked respiratory changes similar to those seen on i.v. administration, and infusion into a pulmonary vein elicited a response akin to that seen on i. aort. administration. The 'receptors' for the *f* response seem therefore to be located in the vascular territory between the right ventricle and the larger pulmonary veins.

Blocking drugs

Mepyramine. It has been suggested (Willis, 1969) that prostaglandin E_1 may act in some situations by releasing histamine from mast cells. In the present work two experiments were performed on pentobarbitone anaesthetized cats in which prostaglandin E_1 was infused before and after 0.33 mg/kg mepyramine, a dose which blocked the vascular response to injections of histamine. The respiratory effect evoked by prostaglandin E_1 was not markedly altered by mepyramine, thereby suggesting that this prostaglandin does not produce its respiratory effect via histamine release. It is also unlikely that it acts by liberating 5-hydroxytryptamine (Thompson & Angulo, 1969).

Propranolol. In two vagotomized cats anaesthetized with pentobarbitone, isoprenaline elicited an increase in RMV, due mainly to increased V_t, and a BP fall. Prostaglandin E_1 produced similar effects, except that the RMV change was associated with an *f* increase. Propranolol (0.25 mg/kg i.v.) abolished the vascular and respiratory responses to isoprenaline without altering the changes evoked by prostaglandin E_1. It is unlikely, therefore, that prostaglandin E_1 produces its effects by actions, direct or indirect, at β-adrenoceptors.

Discussion

Prostaglandins have been shown in the present study to be capable of affecting respiration in anaesthetized cats. The findings are in general agreement with observations made in other species (see Introduction).

The results obtained make it possible to eliminate certain potential mechanisms from involvement in the respiratory response to prostaglandin administration. Thus, the respiratory stimulating property of the prostaglandins examined did not appear to be associated with actions at histamine receptors or β-receptors; indirect evidence suggests that 5-hydroxytryptamine is unlikely to be involved. Direct actions of the prostaglandins on either the carotid baroreceptors or chemoreceptors also appeared unlikely, and McQueen & Belmonte (1974) have since confirmed this using electrophysiological techniques. The possibility that the respiratory changes observed were secondary to changes in bronchial structures was considered. It is unlikely that the *f* change, the effect most associated with the pulmonary system in the present work, is secondary to changes in bronchial tone because Hirose & Said (1971) demonstrated that in dogs anaesthetized with pentobarbitone, prostaglandin E_1 evokes an increase in *f* without altering dynamic lung compliance or airway resistance. However, it is possible that the cat may differ from the dog in this respect.

It has not been possible in the present investigation to determine how the prostaglandins elicit the respiratory changes observed, but some evidence has been obtained which implicates certain mechanisms and this will be discussed below in terms of V_t and *f* changes.

Tidal volume

The results demonstrated that the tidal volume increase was usually preceded by a fall in mean blood pressure (see Figure 2). Prostaglandin $F_{2\alpha}$ which did not possess much depressor activity, did not cause a significant increase in V_t. Lowering the BP by use of a compensator or a dilator drug such as isoprenaline also increased V_t. The fall in BP and the increase in V_t were both greatest when the prostaglandin (E or A series) was administered into the ascending aorta. Results from experiments with a blood pressure compensator (Fig. 4) suggest that the BP fall evokes an increase in V_t, this increase tending to mask part of the rate increase elicited by the prostaglandin. It is known that a reduction in blood flow to the CNS in cats stimulates respiration, while an increase in flow depresses respiration (Schmidt, 1928). A possibility is therefore that prostaglandins which increase V_t do so at least partly as a consequence of reduced blood flow to the CNS, and this is supported by the evidence that the V_t increase is associated with reduced blood flow in the carotid

artery. However, blood pressure reduction also removes inhibitory tone from the baroreceptors and such removal leads to an increase in respiration (Heymans & Neil, 1958). It will be necessary to perform further studies in order to determine the extent to which flow changes, removal of inhibitory baroreceptor tone, or other mechanisms contribute to the V_t response.

It appears that the V_t changes are not seen in animals anaesthetized with α-chloralose, although the blood pressure fall is observed on prostaglandin administration. The reason for this difference between α-chloralose and pentobarbitone will need further investigation.

Respiratory frequency

The *f* increase was observed with all the prostaglandins examined, under both pentobarbitone and α-chloralose anaesthesia. It was most apparent on i.v. administration and took about 14 s longer to develop on i. aort. administration. The region from which the response appeared to be most readily elicited lay between the right ventricle and the large pulmonary veins. These observations, coupled with the finding that the *f* response was virtually abolished after bilateral vagotomy, suggests that the effect may be due to actions at a sensory receptor with vagal afferents.

In the present study it has not proved possible to establish the precise site and type of receptor which may be involved in the *f* response. Daly, Ludnay, Todd & Verney (1937) and Aviado, Li, Kalow, Peskin, Turnbull & Hess (1951) described receptors in the pulmonary venous system of dogs which provoked an increase in respiratory rate when activated by increased pulmonary venous pressure. However, only slight and variable effects on pulmonary vascular pressure were observed in the present experiments. The possibility that extensive changes in tone of pulmonary venules might occur without this being reflected in changes of pulmonary venous pressure should be borne in mind.

The receptors described by Paintal (1955) are unlikely to be involved because the delay in onset of the *f* response after i.v. administration of prostaglandin, 10 s, is longer than would be anticipated for direct stimulation of these receptors, unless a prostaglandin metabolite is the active agent.

It might be argued that bilateral vagotomy so alters respiratory control that it becomes difficult to establish whether prostaglandins are acting via vagal afferents to affect *f*. Electrophysiological experiments could be performed in order to investigate directly the question of whether prostaglandins affect pulmonary sensory receptors.

The possibility of prostaglandin actions within the brain stem has not been excluded by the present study and should also be investigated.

Respiratory changes can cause reflex alterations through the lung inflation reflex (Scott, 1966). When examining prostaglandins for effects in whole animals it would seem advisable to note that prostaglandins are capable of eliciting respiratory changes.

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