

THE EFFECTS OF PROSTAGLANDINS E_1 , E_2 AND $F_{2\alpha}$ ON VAGAL BRADYCARDIA IN THE ANAESTHETIZED MOUSE

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- 1 In anaesthetized mice prostaglandins E_1 and E_2 reduced the bradycardia caused by electrical stimulation of the sectioned peripheral vagus nerve; prostaglandin $F_{2\alpha}$ produced only a slight inhibition of the vagal response.
- 2 None of the prostaglandins studied affected acetylcholine-induced bradycardia.
- 3 Prostaglandins modify parasympathetic nerve activity *in vivo* presumably by a pre-synaptic action.

Introduction

Certain criteria must be satisfied for prostaglandins to modulate the release of autonomic neurotransmitter substances by an endogenous feedback mechanism.

In recent years, several reports have shown that prostaglandins of the E series may reduce the responses of isolated cardiac preparations to both sympathetic (Hedqvist, Stjarne & Wennmalm, 1970; Hedqvist & Wennmalm, 1971) and parasympathetic nerve stimulation (Wennmalm & Hedqvist, 1971; Hadhazy, Illés & Knoll, 1973). This evidence, together with reports that prostaglandin-like substances may be released upon sympathetic (Sammuelsson & Wennmalm, 1971) and also upon parasympathetic nerve stimulation (Coceani, Pace-Asciak, Volta & Wolfe, 1967; Junstad & Wennmalm, 1974), indicates a possible involvement of prostaglandins in the transmission process.

The aims of the current studies were to see whether certain prostaglandins were capable of inhibiting the effects of cardiac vagal stimulation in anaesthetized mice.

Methods

Male mice of Tuck No. 1 strain, weighing 25-40 g were anaesthetized with a mixture of chloralose (100 mg/kg) and hexobarbitone (100 mg/kg) administered via an indwelling cannula in the caudal vein which also served for all subsequent injections. The animals were artificially ventilated at 90 strokes/min, with a volume of approximately 0.5 ml. Blood pressure and integrated heart rate were measured from the cannulated left common carotid artery. On each side of the neck the

cervical vagus and sympathetic nerves (Large, 1975) were separated and sectioned; bipolar platinum electrodes were used to stimulate the cardiac end of the right or left vagus with rectangular pulses of 0.5 ms duration at supramaximal voltage (6-12V) with liquid paraffin for insulation. The initial mean arterial blood pressure was 44 ± 2 mmHg (mean \pm s.e.) and the initial heart rate 455 ± 11 beats/minute.

The vagus nerve was initially stimulated with 1 Hz and the frequency progressively changed through 2, 5, 10, 20 to 50 Hz as the heart rate stabilized at each frequency. The blood pressure and heart rate having returned to resting values, the vagus nerve was then stimulated intermittently with a selected frequency every 3 min using a constant number of shocks (50, 100 or 200). Following two consecutive control responses, S_1 and S_2 , an intravenous injection of prostaglandin E_1 , E_2 or $F_{2\alpha}$ was made 10-20 s prior to obtaining the third response, S_3 . The bradycardia induced by vagal stimulation in the presence of the prostaglandin was compared with that in its absence by the change in the ratios, S_2/S_1 and S_3/S_2 . Differences between the ratios S_2/S_1 and S_3/S_2 were analysed by Student's *t*-test.

A similar procedure was adopted to investigate the effects of the prostaglandins on the bradycardia induced by intravenous acetylcholine but, in order to obtain bradycardia, physostigmine had to be given beforehand.

Results

Prostaglandins E_1 and E_2 (in doses from 2.5 to 20 μ g/kg) produced a fall in both systolic and

diastolic pressures, the magnitude of which was dependent upon the resting blood pressure. In most experiments heart rate was unaffected though occasionally a tachycardia not exceeding 10 beats/min was seen. By contrast, prostaglandin $F_{2\alpha}$ (10 or 20 $\mu\text{g/kg}$) produced a rise in both systolic and diastolic pressures, with little change in the resting heart rate.

The bradycardia induced by stimulating the cardiac end of the cut vagus nerve could be inhibited by the prior administration of prostaglandin E_1 or E_2 . This inhibitory effect was of short duration, responses returning to control levels usually within a 6 min period. A slight inhibition of vagal bradycardia was seen with prostaglandin $F_{2\alpha}$ although no differences were observed between the two dose levels employed. More experiments are needed to determine if larger doses of prostaglandin $F_{2\alpha}$ could produce further inhibition. Some of these results are illustrated in Table 1. The effect of the E prostaglandins was, however, dose-dependent in that progressively greater inhibition occurred as the dose was raised. A statistical analysis has only been possible so far on the results obtained with 10 $\mu\text{g/kg}$ prostaglandin E_1 and E_2 .

Acetylcholine (2.5 $\mu\text{g/kg}$) produced only vasodepression but in the presence of physostigmine salicylate (100 $\mu\text{g/kg}$) it caused a larger fall in blood pressure and also a bradycardia of 92 ± 6 beats/minute. As may be seen from Table 1 this bradycardia was unaffected by any of the prostaglandins. Physostigmine also enhanced the responses to vagal stimulation but did not modify the inhibitory effects of prostaglandin E_1 or E_2 .

Since the E prostaglandins were more potent than prostaglandin $F_{2\alpha}$ in reducing the vagal bradycardia, experiments were carried out to determine whether the inhibition was consequent upon the fall in blood pressure produced by the E prostaglandins. Neither bradykinin (0.5–5 $\mu\text{g/kg}$), which caused a prolonged fall in blood pressure, nor acetylcholine (2–5 $\mu\text{g/kg}$) modified the response to vagal stimulation.

Discussion

These results demonstrate that prostaglandins E_1 , E_2 and, to a lesser extent, $F_{2\alpha}$ can reduce the responses of the heart *in vivo* to parasympathetic nerve stimulation. These inhibitory effects appear to be presynaptic in nature.

Since the acetylcholine-induced bradycardia was unaffected by any of the prostaglandins it is tempting to conclude that these substances were preventing the release of acetylcholine from the parasympathetic nerve endings, though an effect on ganglionic transmission cannot be excluded. Vasodepression as such was not responsible for the inhibitory effect of the E prostaglandins since neither bradykinin nor acetylcholine were capable of reducing the responses to vagal stimulation. Furthermore larger doses of E prostaglandins, which did not always produce a greater fall in blood pressure, caused a greater inhibition of the bradycardia.

Benz & Salzmann (1974) stated that prostaglandins did not modify vagal activity in the anaesthetized cat, despite observing a small

Table 1 Effect of intravenous prostaglandins (PGs) on the bradycardia induced in anaesthetized mice either by electrical stimulation of the vagus nerve or by acetylcholine

	Control			PGE_1 (10 $\mu\text{g/kg}$)		PGE_2 (10 $\mu\text{g/kg}$)		$PGF_{2\alpha}$ (10 or 20 $\mu\text{g/kg}$)	
	Mean ΔHR	S_2/S_1 †	n	S_3/S_2	n	S_3/S_2	n	S_3/S_2	n
‡ Acetylcholine									
2 to 5 $\mu\text{g/kg}$	92	0.97 ± 0.02	12	0.99 ± 0.04	6	0.97 ± 0.09	3	1.02 ± 0.04	3
10 Hz 5 s	88	0.97 ± 0.02	12	$0.42 \pm 0.09^{***}$	4	$0.46 \pm 0.05^{***}$	4	0.95 ± 0.03	4
10 Hz 10 s	124	1.03 ± 0.02	20	$0.38 \pm 0.12^{***}$	6	$0.36 \pm 0.06^{***}$	8	$0.92 \pm 0.03^{**}$	6
20 Hz 5 s	125	1.05 ± 0.01	7	$0.53 \pm 0.13^{***}$	3	$0.54 \pm 0.08^{***}$	4	—	—
20 Hz 10 s	137	0.99 ± 0.04	8	$0.55 \pm 0.16^{**}$	3	$0.39 \pm 0.11^{***}$	5	—	—
50 Hz 2 s	272	1.04 ± 0.03	5	0.25	2	$0.62 \pm 0.13^*$	3	—	—

All values are means \pm s.e. mean. † S_1 and S_2 are two successive control responses just prior to S_3 which is the response obtained 10 to 20 s after injection of the prostaglandin. ‡ Responses to acetylcholine were obtained after the administration of physostigmine salicylate (100 $\mu\text{g/kg}$) both drugs being given intravenously.

Comparison of ratio S_2/S_1 with appropriate S_3/S_2 ; Student's *t* test, *P* values: * < 0.05 > 0.01; ** < 0.01 > 0.001; *** < 0.001. There were no statistically significant differences between any pairs of S_3/S_2 values for a given prostaglandin during the periods of nerve stimulation.

reduction in the magnitude of the vagal bradycardia with prostaglandins E_1 or $F_{2\alpha}$, whilst E_2 was without activity. Although species differences may exist, a direct comparison of results is difficult, since in their experiments the prostaglandins were given by intravenous infusion at rates from 0.001 to 1.0 $\mu\text{g}/\text{minute}$.

Our results suggest that prostaglandins, particularly of the E series, may modulate the release of

the parasympathetic neurotransmitter and demonstrate that inhibitory effects can occur *in vivo*.

At present we are studying the effects of prostaglandin-synthetase inhibitors on this phenomenon and also the actions of prostaglandins on sympathetic function in mice.

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