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FELINE ENDOTOXIN SHOCK: EFFECTS OF METHYLPREDNISOLONE ON KININOGEN-DEPLETION, ON THE PULMONARY CIRCULATION AND ON SURVIVAL

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1 *Escherichia coli* endotoxin, administered intravenously in a dose of 2mg/kg to pentobarbitone-anaesthetized, artificially ventilated cats resulted in pulmonary hypertension, systemic hypotension and an immediate (1–2 min) 30–40% reduction in plasma kininogen, an effect which probably indicates a release of plasma kinins.

2 Methylprednisolone (30 mg/kg), when administered 30 min before endotoxin, did not influence the endotoxin-induced pulmonary hypertension or systemic hypotension but completely prevented the depletion of plasma kininogen.

3 In spontaneously breathing cats, methylprednisolone, administered 30 min *after* endotoxin, caused a rapid repletion of kininogen and prolonged survival (47% at 6 h compared to 10% in the endotoxin-alone animals). Methylprednisolone did not appear to influence lactate production or the hyperventilation observed during the delayed endotoxin shock phase.

4 It is concluded that methylprednisolone does not prevent the release, by endotoxin, of a pulmonary vasoconstrictor prostaglandin, or its effects, but that perhaps by preventing kinin release it may reduce endotoxin-induced capillary leakage.

Introduction

There is considerable evidence that adrenocortical steroids are of value in the treatment of shock induced by bacterial endotoxins (Kadowitz & Yard, 1970; Berry, 1971; Rao & Cavanagh, 1971; Nicholas & Mela, 1975). The precise mechanisms of this protection are uncertain. One possibility is interference with the release of vasoactive agents by endotoxin or with their effects. These agents include histamine, plasma kinins and prostaglandins.

In a number of species marked pulmonary changes occur early in endotoxin shock. These changes include pulmonary vasoconstriction, increased airways resistance, reduced lung compliance, pulmonary oedema and reduced pulmonary gas exchange leading to an increased alveolar-arterial oxygen tension gradient and a reduced arterial oxygen tension (Kuida, Gilbert, Hinshaw, Brunson & Visscher, 1961, Gemer, Hayes, Ishikawa, Cuevas & Hirsch, 1973; Parratt, 1973; Parratt & Sturgess, 1976). Similar changes occur in patients with septic shock (Wilson, 1972a; Milligan, MacDonald, Mellon & Ledingham, 1974; Sykes, 1976). Recently it has been suggested that, at least in the cat, these pulmonary changes result partly from the liberation by endotoxin of a pulmonary vasoconstrictor, bronchoconstrictor prostaglandin (Parratt & Sturgess, 1975a; 1977).

In view of Wilson's work (1972b) on the effect of methylprednisolone in preventing cellular damage in the post-traumatic lung, we investigated the possibility that methylprednisolone might exert these beneficial pulmonary effects by interfering with the release by endotoxin of this prostaglandin, or with its action on the pulmonary circulation. This study also includes an account of the effects of methylprednisolone on the release of a plasma kinin, another highly vasoactive agent released in the early stages of endotoxin shock (Miller, Reichgott & Melmon, 1973). A preliminary account of some of this work was presented to a meeting of the Physiological Society (Al-Kaisi, Parratt, Siddiqui & Zeitlin, 1976).

Methods

Cats of either sex were anaesthetized with sodium pentobarbitone (30 mg/kg, i.p.), the chest was opened and the animals ventilated with room air using a Palmer positive-pressure pump (rate, 20/min; stroke

volume, 40–60 ml). Mid-oesophageal temperature was recorded with direct reading thermocouples (Ellab, Copenhagen). Systemic (carotid) arterial blood pressure and pulmonary artery pressure were measured as previously described (Parratt, 1973) and recorded, together with the electrocardiogram, on an eight-channel ink-jet writing recorder (Elema-Schönander mingograph 81).

Blood samples (0.6 ml) were taken, without exposure to air, from the catheter in the carotid artery and analysed for O_2 and CO_2 tensions, and for pH, using appropriately calibrated electrode systems (Parratt, 1973). Blood gas tensions, and pH, were corrected for any temperature difference between the electrode system (usually 37.3°C) and the animals mid-oesophageal temperature by means of a blood-gas calculator (Severinghaus, 1966). Arterial blood samples (2 ml) were also taken for the extraction of kininogen by the method of Brocklehurst & Zeitlin (1967). The samples were immediately added to 6 ml of pre-cooled (4°C) 90% ethanol. The denatured plasma protein was suspended in 6 ml 0.9% w/v NaCl solution (saline) for homogenization and 0.2 ml of this homogenate was incubated with 200 μg of crystalline trypsin for 30 minutes. The reaction was stopped by heating in boiling water for 10 min and the liberated kinin assayed on the stilboestrol-treated rat isolated uterus, bathed in de Jalon's solution containing 1 μg/ml atropine sulphate, in a 5 ml organ bath. The bath temperature was 33°C and the solution was gassed with 95% O_2 and 5% CO_2. The kinin concentrations of the samples were assayed by close bracketing between doses (usually 1.0 and 1.2 ng) of purified bradykinin (Sandoz, Basle). Total plasma protein was estimated by the Biurett method using a Boehringer test kit. Each time blood was removed from the cat it was replaced by an equal volume of dextrose-saline solution.

For studies designed to determine the effects of methylprednisolone on the secondary, delayed shock phase (Parratt & Sturgess, 1975b) cats were anaesthetized as described above but were not subjected to thoracotomy. Only carotid arterial and right atrial pressures, temperature and the electrocardiogram were recorded in these spontaneously breathing animals. Arterial lactate was measured as described previously (Parratt & Sturgess, 1975b).

All the cats received *Escherichia coli* endotoxin (Difco Laboratories, 055:B5) suspended in saline and administered slowly, by intravenous injection, in a dose of 2 mg/kg. Methylprednisolone sodium succinate (Solumedrone, Upjohn Laboratories, Sussex) was injected intravenously in a dose of 30 mg/kg.

Results

The effect of endotoxin on plasma kininogen and on systemic and pulmonary arterial pressures

Two groups of cats were studied (Table 1); in the first, blood samples were taken for kininogen analysis before, and 5, 15, 30 and 60 min after, the injection of endotoxin. In the second series, samples were taken 1–2 min after endotoxin (i.e. at the height of the pulmonary pressor response) and again after 30 min; the effect of endotoxin on plasma protein was also examined in this second group of cats. They were later used to examine whether methylprednisolone influenced plasma kininogen depletion when administered 30 min after endotoxin. It is clear that the administration of endotoxin resulted in a considerable (30–40%) and immediate (within 1–2 min) depletion of plasma kininogen and that this was unrelated to changes in packed cell volume (Table 1). It was also unrelated, at least initially, to changes in total plasma protein. Thus immediately before endotoxin the plasma protein was 6.26 ± 0.12 g/100 ml plasma; 2 min after endotoxin, when plasma kininogen was already reduced by 30% (Table 1), it was 6.38 ± 0.21 g/100 ml. Thereafter it was decreased to 6.01 ± 0.17 g/100 ml ($P < 0.05$) after 30 minutes.

The immediate haemodynamic responses of anaesthetized, artificially ventilated cats to *E. coli*

Table 1 Effects of endotoxin on plasma kininogen levels (as μg bradykinin equivalents/ml plasma) and on packed cell volume (%s in brackets) in anaesthetized cats

	Pre-endotoxin	*After endotoxin*				
		+1.5 min	*+5 min*	*+15 min*	*+30 min*	*+1 h*
Series 1 ($n=5$)	2.75 ± 0.08 (33.8 ± 1.6)		1.88 ± 0.12* (33.2 ± 1.5)	1.69 ± 0.09* (32.8 ± 1.3)	1.41 ± 0.10* (32.2 ± 1.2)	1.80 ± 0.23** (31.8 ± 1.2)
Series 2 ($n=7$)	2.58 ± 0.18 (35.2 ± 2.1)	1.8 ± 0.1** (31.7 ± 3.2)			1.54 ± 0.04* (35.3 ± 2.4)	

Values are mean ± s.e. mean.
* $P < 0.001$; ** $P < 0.01$.

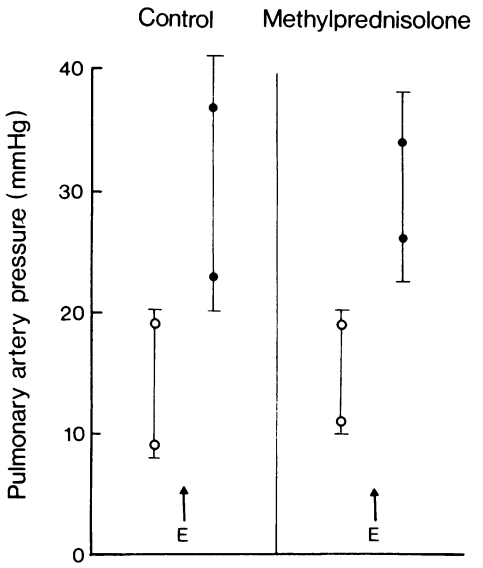

Figure 1 Effects of endotoxin (E) on pulmonary artery pressure (systolic and diastolic, mmHg) in control cats and in cats pretreated with methylprednisolone (30 mg/kg) 30 min previously. The open circles represent mean values before endotoxin and the closed symbols mean values 3 min after endotoxin. The short vertical lines above systolic pressures and below the diastolic pressures represent the s.e. mean; the continuous vertical line joining systolic and diastolic pressures represents the pulmonary pulsatile pressure.

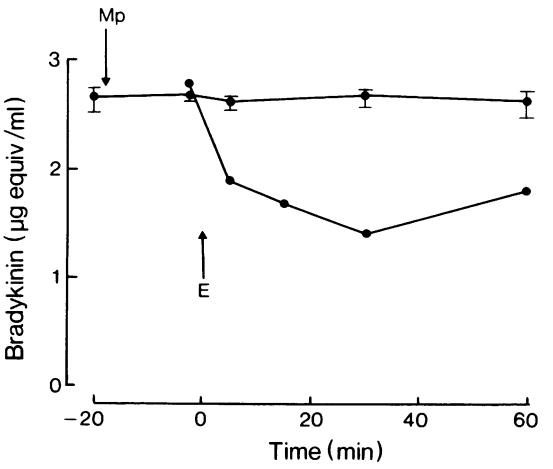

Figure 2 The effect of pretreatment with methylprednisolone (Mp; 30 mg/kg) on endotoxin-induced plasma kininogen depletion. In cats not treated with methylprednisolone (lower curve) there is a marked depletion of kininogen after the administration of endotoxin (at E). No such depletion is observed (top curve) in animals pretreated with methylprednisolone. The detailed values for the endotoxin-alone experiments are given in Table 1 (series 1).

endotoxin have already been documented (Parratt, 1973). In this particular study there was an immediate increase in pulmonary artery pressure, bradycardia and a marked, though transient, reduction in systemic arterial pressure (Table 2).

Direct haemodynamic effects of methylprednisolone

Methylprednisolone was administered intravenously, in a dose of 30 mg/kg to a group of 7 anaesthetized cats. There was a moderate (20 mmHg) but transient, reduction in systemic arterial pressure within 1–2 min of the injection (from 113 ± 6 mmHg systolic and 89 ± 9 mmHg diastolic before the administration of methylprednisolone to 93 ± 5 and 62 ± 9 mmHg respectively after 1–2 min; $P < 0.01$). Systemic arterial pressure returned to control levels within 5–10 minutes. There were no significant effects on heart rate (208 ± 11 beats/min before and 204 ± 13 beats/min after the injection), pulmonary arterial pressure (20 ± 11 mmHg systolic and 11 ± 1 mmHg diastolic before methylprednisolone and 18 ± 1 mmHg systolic and 11 ± 1 mmHg diastolic 1–2 min after the injection), plasma kininogen (2.66 ± 0.10 μg bradykinin equivalent/ml plasma before and 2.66 ± 0.11 μg/ml 20 min afterwards) or on packed cell volume ($33.1 \pm 2.1\%$ before and $33.1 \pm 1.8\%$ after).

The effects of pretreatment with methylprednisolone on the acute haemodynamic response to endotoxin and on endotoxin-induced plasma kininogen depletion

The haemodynamic effects of endotoxin when given to cats 30 min after pre-treatment with methylprednisolone (30 mg/kg) are summarized in Table 2. There was no modification either of the immediate systemic hypotension, or of the marked pulmonary pressor response (Figure 1). However, endotoxin-induced depletion of plasma kininogen was not observed in these cats (Figure 2), neither was there any change in packed cell volume ($33.14 \pm 1.75\%$ before endotoxin and $29.7 \pm 2.1\%$, $30.5 \pm 2.0\%$ and $28 \pm 2.0\%$, 5, 30 and 60 min after endotoxin).

Effects of methylprednisolone, administered after endotoxin, on kininogen depletion, on the delayed shock phase and on survival

It was of interest to determine whether, as well as preventing endotoxin-induced kininogen depletion when given before endotoxin, methylprednisolone modified kininogen depletion when administered after

Table 2 Haemodynamic effects of endotoxin in open-chest cats pretreated with either saline (control; C) or methylprednisolone (Mp) 30 mg/kg given 30 min previously

		Carotid blood pressure (mmHg)				*Pulmonary artery pressure (mmHg)*				*Heart rate (beats/min)*	
		Systolic		*Diastolic*		*Systolic*		*Diastolic*			
		C	*Mp*	*C*	*Mp*	*C*	*Mp*	*C*	*Mp*	*C*	*Mp*
Pre-endotoxin		110 ± 5	121 ± 11	83 ± 5	85 ± 10	19 ± 1	18 ± 1	9 ± 1	11 ± 1	196 ± 8	203 ± 16
Post-endotoxin	+1 to 2 min	75 ± 9*	66 ± 13*	50 ± 8*	37 ± 9*	34 ± 3*	34 ± 4*	24 ± 2*	26 ± 3*	168 ± 10*	162 ± 20*
Post-endotoxin	+30 min	99 ± 6	99 ± 9	68 ± 5	60 ± 7	25 ± 2	18 ± 2	13 ± 1	12 ± 2	208 ± 8	196 ± 18

Values are means ± s.e. mean of 8 to 13 observations.
* $P < 0.01$.

Table 3 Haemodynamic and metabolic effects of endotoxin in spontaneously-breathing anaesthetized cats administered either saline (control, C; $n = 10$) or methylprednisolone (Mp; 30 mg/kg; $n = 17$) 30 min after endotoxin

	Carotid blood pressure (mmHg)				*Arterial blood pH (units)*		*Arterial lactate (mg/100 ml)*		*Survivors (%)*	
	Systolic		*Diastolic*							
	C	*Mp*	*C*	*Mp*	*C*	*Mp*	*C*	*Mp*	*C*	*Mp*
Pre-endotoxin	134 ± 7	128 ± 7	104 ± 7	102 ± 7	7.36 ± 0.02	7.38 ± 0.02	4.9 ± 1.8	4.8 ± 1.8	—	—
Post-endotoxin										
+2–3 min	90 ± 12*	75 ± 10*	67 ± 12*	57 ± 8*	—	—	—	—	100	100
+1 h	105 ± 7	106 ± 6	75 ± 8*	68 ± 5	7.25 ± 0.03*	7.38 ± 0.02	23 ± 4*	17 ± 2*	100	100
+2 h	119 ± 7	84 ± 4	82 ± 9	68 ± 4	7.36 ± 0.03	7.41 ± 0.02	18 ± 3*	19 ± 2*	100	100
+3 h	111 ± 8	130 ± 5	90 ± 6	90 ± 6	7.39 ± 0.01	7.39 ± 0.02	22 ± 5*	22 ± 3*	90	100
+4 h	110 ± 11	128 ± 4	77 ± 14	79 ± 8*	7.32 ± 0.03	7.39 ± 0.02	23 ± 5*	22 ± 3*	70	88
+5 h	88 ± 19*	95 ± 14	62 ± 19	79 ± 11	7.24 ± 0.14*	7.43 ± 0.05	31 ± 8*	22 ± 3*	50	77
+6 h	52	110 ± 7	36	77 ± 11*	7.41	7.42 ± 0.06	27.5	25 ± 5*	10	47

Values are means ± s.e.mean.
* $P < 0.01$.

endotoxin. Seven cats (series 2, Table 1) were used for this study; all exhibited a marked pulmonary pressor response to endotoxin and all showed marked depletion of plasma kininogen at 30 min (Table 1). Methylprednisolone was given 31 min after the administration of endotoxin and, within a further 30 min, the plasma kininogen had returned to normal levels (from 1.54 ± 0.04 μg bradykinin equivalents/ml plasma immediately before methylprednisolone to 2.49 ± 0.19 μg/ml, a value not significantly different from the pre-endotoxin level of 2.58 ± 0.18 μg/ml). Methylprednisolone, administered at this time after endotoxin, did not affect packed cell volume (35.3 ± 2.4 to $36.7 \pm 2.5\%$) or plasma protein (6.01 ± 0.17 to 5.81 ± 0.16 mg/100 ml plasma) nor did it modify the endotoxin-induced hypotension. In fact there was some evidence in the group of spontaneously breathing cats (see below) that methylprednisolone administered 30 min after endotoxin delayed the recovery of systemic pressure (values at 1 h and 2 h in Table 3).

A more detailed study of the effect of methylprednisolone on the delayed endotoxin-shock phase was examined in 17 spontaneously breathing cats. The drug was again administered in a dose of 30 mg/kg, 30 min after endotoxin and effects on blood pressure, heart rate, arterial blood gases, pH and lactate were compared with those obtained in a group of 10 cats given only endotoxin. The results are summarized in Table 3. The greatest effect was the increased survival in the cats administered methylprednisolone; 8 out of 17 (47%) were alive at 6 h after endotoxin compared with only 1 (10%) of the group administered endotoxin alone. Systemic arterial pressure was reasonably well maintained in the survivors (110 ± 7 mmHg systolic and 77 ± 11 mmHg diastolic at 6 h) although there was no difference between the two groups with regard to lactate production (Table 3). Arterial blood pH was well maintained, especially in the methylprednisolone group, because of the substantial degree of hyperventilation. For example, the arterial P_{CO_2} before endotoxin in this group was 34 ± 1 mmHg (within the normal range for spontaneously breathing cats; Parratt, 1973); after 4 h of shock it was reduced to 25 ± 4 mmHg ($P < 0.01$) and after 5 h to 21 ± 3 mmHg ($P < 0.001$). In one of the cats it was only 13 mmHg at 6 h (from the control level of 37 mmHg). This hyperventilation resulted in a gradually increasing arterial P_{O_2} (from 99 ± 3 mmHg before, to 107 ± 5, 111 ± 7 and 116 ± 7 mmHg, 4, 5 and 6 h after endotoxin). Similar changes in arterial P_{CO_2} and P_{O_2} were also observed in the cats given only endotoxin.

Discussion

Our initial hypothesis that methylprednisolone might prevent the pulmonary effects of bacterial endotoxin by inhibiting the release, or actions, of the vasoconstrictor, bronchoconstrictor, prostaglandin was not supported by these studies. The pulmonary hypertension and oedema that result from the administration of endotoxin in anaesthetized cats were unaffected by methylprednisolone (Figure 1). However, there were three positive effects of methylprednisolone, prevention of the kininogen depletion that resulted from endotoxin administration (Table 1), a rapid repletion of kininogen when given after endotoxin, and increased survival when assessed at 6 hours.

It is clear from these experiments that, in the cat, as in subhuman primates (Herman, Oshima & Erdös, 1974), endotoxin decreases the concentration of plasma kininogen. Such a depletion of kininogen can be equated with the liberation of plasma kinins since there were no significant changes in packed cell volume or in total plasma protein. Other studies have demonstrated that there is a significant correlation between kinin production and kininogen depletion when endotoxin is added to human plasma (Nies & Melmon, 1971) and that free kinins appear in the blood after the administration of endotoxin to human subjects (Kimball, Melmon & Wolff, 1972) and to monkeys (Nies, Forsyth, Williams & Melmon, 1968). We made no attempt to demonstrate a release of free kinins since recoveries of added bradykinin to cat blood were too variable. Recovery of added bradykinin to blood, and other fluids, obtained from other species have been perfectly satisfactory (Brocklehurst & Zeitlin, 1967).

The mechanism by which methylprednisolone prevents kininogen depletion by endotoxin is obscure and any explanation would need to take into account the rapid repletion of the kinin precursor when the drug is administered early in endotoxin shock. In monkeys, the administration of endotoxin leads to activation of plasma kallikrein and ultimately, to a reduction in its concentration in the plasma; a reduction in plasma kallikrein was not seen in monkeys treated with methylprednisolone (Herman *et al.*, 1974). This could indicate that methylprednisolone prevents an effect of endotoxin on complement, on Hageman factor, on plasminogen, or more likely, that it interferes with the interrelationship between endotoxin and granulocytic leucocytes (Miller, Webster & Melmon, 1975), perhaps by stabilizing the cell membrane. There is evidence for at least one of these possibilities; in rats, endotoxin results in a 28% reduction in Hageman factor, an effect completely prevented by pretreatment with glucosteroids (Latour & Leger, 1975).

Whether the effects of methylprednisolone on the kallikrein-kinin system (Table 1) and on survival (Table 3) are related is uncertain. There certainly appears to be no relationship between kinin production and the early (0–30 min) hypotensive phase of endotoxin shock in the cat. The reasons for

this are twofold: (i) Despite the failure of endotoxin to reduce plasma kininogen in cats pretreated with methylprednisolone, the initial reduction in blood pressure following endotoxin administration was still evident (Table 2). (ii) Repletion of kininogen by methylprednisolone, when administered 30 min after endotoxin, did not result in a faster recovery from systemic hypotension; in fact recovery appeared to be delayed (Table 3). However, it is conceivable that by preventing the release of free kinins from plasma kininogen, methylprednisolone might prevent the egress of fluid from the circulation into the tissues, an effect which would presumably result from the marked action of the plasma kinins on capillary permeability.

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