Inhibition of Venoconstrictor Responses by Prostaglandin E_1[1] (35137)

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Prostaglandins of the E series have been characterized as potent vasodilator substances, and it has been suggested that they may play an important role in modulating the effects of sympathetic nerve activity on the blood vessels (1, 2). In studies on the isolated perfused forelimb or hindlimb of the dog (3, 4), it was found that PGE_1 exerts a vasodilator effect not only on arterial but also on venous segments. Furthermore, PGE_1 has been reported to inhibit pressor (5–8) and vasoconstrictor responses (9, 10) to catecholamines and peptides.

In the present experiments, the effect of PGE_1 on venoconstrictor responses to nerve stimulation, norepinephrine and angiotensin was studied in the canine hindpaw and gracilis muscle.

Materials and methods. Male mongrel dogs weighing 22–30 kg were anesthetized with chloralose (50 mg/kg, iv) and urethane (500 mg/kg, iv), ventilated artifically and treated with decamethonium bromide (0.3 mg/kg, iv) and heparin (5 mg/kg). The hindpaw and gracilis muscle were isolated and perfused separately through the cranial tibial and the gracilis arteries with blood withdrawn from a femoral artery using a technique described previously (11). Flow to the hindpaw was maintained at 30 ml/min, and flow to the gracilis at 15 ml/min throughout the experiment. A small metatarsal vein and a small vein at the caudal end of the gracilis were cannulated upstream with polyethylene tubing (0.6-mm o.d.). Venous pressures were measured with Statham transducers (P 23 Gb) of low volume displacement (0.01 mm^3/100 mm Hg) and recorded on a Sanborn oscillograph. At constant flow, changes in small vein pressure reflected changes in venous resistance downstream from the point of pressure measurement. The sciatic and obturator nerves were cut and their distal ends were stimulated with square wave impulses of supramaximal voltage (20–25 V). Norepinephrine and angiotensin were injected in volumes of 0.1 ml into the perfusion tubing at a point upstream from the two perfusion pumps supplying the paw and muscle, so that equal concentrations of drugs reached both beds. Observations were made on responses to the vasoconstrictor interventions during an intra-arterial infusion of saline (0.07 ml/min) and again during an infusion of 0.07 ml/min of a solution of PGE_1[3] in saline which gave a concentration of 7×10^{-9} g/ml in the blood supplying both beds.

Results. Venous effects of PGE_1. In the paw, PGE_1 increased small vein pressure slightly but significantly ($p<0.01$) from an average of 13.4 ± SE 2.3 mm Hg to 15.4 ± 2.2 mm Hg in seven dogs. In the muscle, on the other hand, significant ($p < 0.01$) reductions in small vein pressure from 21.4 ± 1.7 to 18.2 ± 1.8 mm Hg were observed in five dogs.

Effect of PGE_1 on venoconstrictor responses. In the paw, there was significant inhibition of venoconstrictor responses to norepinephrine, nerve stimulation, and angiotensin (Table I). In the muscle, there was

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TABLE I. Effect of PGE$_1$ (7×10^{-9} g/ml) on Venoconstrictor Responses in Hindpaw and Gracilis Muscle.[a]

	Responses (Δ mm Hg) to							
	Nerve stimulation (Hz)			Norepinephrine (μg)			Angiotensin (μg)	
	1.5	3.0	6.0	0.03	0.1	0.3	0.3	1.0
Paw								
During infusion of saline								
$\bar{x} \pm$ SE	3.3 ± 0.6	7.8 ± 1.6	13.2 ± 2.8	1.6 ± 0.7	3.6 ± 1.6	10.8 ± 4.0	1.6 ± 0.6	5.8 ± 1.4
During infusion of PGE$_1$								
$\bar{x} \pm$ SE	0.7 ± 0.2	3.8 ± 0.7	7.3 ± 1.8	0.3 ± 0.2	1.1 ± 0.7	3.0 ± 3.0	0.2 ± 0.1	0.3 ± 0.2
n	(6)	(6)	(6)	(7)	(7)	(4)	(9)	(6)
p values[b]	<0.01	<0.05	<0.05	<0.05	<0.05	<0.01	<0.05	<0.05
Muscle							0.1	0.3
During infusion of saline								
$\bar{x} \pm$ SE	2.5 ± 1.5	3.3 ± 0.9	3.7 ± 1.2	2.4 ± 0.9	5.4 ± 2.2	8.8 ± 1.9	8.3 ± 2.9	15.5 ± 5.3
During infusion of PGE$_1$								
$\bar{x} \pm$ SE	2.0 ± 0.3	2.0 ± 0.6	3.0 ± 1.0	2.2 ± 1.5	4.0 ± 1.6	7.3 ± 3.5	3.8 ± 1.5	10.3 ± 3.4
n	(3)	(3)	(3)	(5)	(5)	(5)	(6)	(6)
p values	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	<0.05	<0.05

[a] Experiments included in this study are only those in which venoconstriction was observed in response to the interventions during the "control" saline infusion before PGE$_1$.

[b] Significance of difference in responses observed during PGE$_1$ and during "control" infusion of saline as compared by paired t tests.

minimal attenuation of venous responsiveness to angiotensin but not to nerve stimulation nor to norepinephrine (Table I).

Discussion. In previous studies we have reported that PGE$_1$ (7×10^{-9} g/ml) causes significant reductions in total resistance in the perfused gracilis muscle and hindpaw (9) without causing systemic effects. The venous responses observed in this study were small in magnitude. They indicate, however, that PGE$_1$ causes a decrease in venous resistance in skeletal muscle and a slight increase in venous resistance in the hindpaw. These findings are in agreement with observations made by Greenberg and Sparks (3) who reported increases in vascular capacity in the canine hindlimb after administration of intra-arterial PGE$_1$. One would expect that the contribution of muscular veins to vascular capacity would predominate over that of cutaneous veins in the hindlimb preparation which is primarily muscular. Daugherty and his collaborators (4) have observed that PGE$_1$ causes greater venodilatation in muscle than in skin in the canine forelimb and reported that active venodilatation took place in muscle.

The increase in venous resistance in the hindpaw which we observed may be an indirect effect of PGE$_1$ caused by the release of catecholamines (12). The veins draining the paw have a higher catecholamine content (13) and are more sensitive to norepinephrine (11) than those draining the muscle.

The interaction between the vasodilator effect of PGE$_1$ and its inhibitory effect on vasoconstrictor responses has not been clear. The studies on pressor responses in intact animals (5–8) indicate that inhibition of pressor responses to norepinephrine by PGE$_1$ was the result of the vasodilator effect of the prostaglandin. In contrast, studies on the mesoappendix of the rat (10) show a loss of vasoconstrictor responsiveness in the absence of vasodilatation. In earlier studies on the canine gracilis muscle and hindpaw, we ob-

served a dissociation of these two effects of PGE_1 on total vascular resistance (9). This dissociation was confirmed with respect to the venous responses in this study. In the muscle where PGE_1 caused venodilatation, the inhibitory effect on venoconstrictor responses was absent or minimal. In the paw, on the other hand, where PGE_1 had no venodilator effect but rather a slight venoconstrictor action, responses to nerve stimulation, norepinephrine and angiotensin were inhibited significantly.

Summary. PGE_1 caused venodilatation in the isolated perfused canine gracilis muscle but not in the perfused hindpaw. Venoconstrictor responses to nerve stimulation, norepinephrine, and angiotensin were inhibited significantly and uniformly in the paw but not in the muscle. The results indicate that inhibition of venoconstrictor responsiveness by PGE_1 is not associated with nor dependent upon a direct dilator action of the prostaglandin.

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