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The effects of endothelium-dependent vasodilators on cardiac output and their distribution in the anaesthetized rat: a comparison with sodium nitroprusside

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1 The effects of sodium nitroprusside, acetylcholine and bradykinin on cardiac output and its distribution were studied in the anaesthetized, vagotomised rat preparation by use of ^{113}Sn-labelled microspheres.

2 All three vasodilators lowered peripheral arterial blood pressure, but only bradykinin significantly reduced total peripheral resistance without reducing cardiac output. Bradykinin caused tachycardia, but this was offset by a reduction in stroke volume. These effects of bradykinin were not altered by indomethacin ($4\,mg\,kg^{-1}$). Acetylcholine and sodium nitroprusside both caused significant ($P < 0.05$) reductions in stroke volume and cardiac output.

3 Bradykinin reduced vascular resistance in the liver, stomach, small intestine, large intestine, pancreas/mesentery, epididimides, skeletal muscle and fat. These responses were not affected by indomethacin, whereas, the reduction in vascular resistance in the brain induced by bradykinin was abolished by indomethacin.

4 Acetylcholine caused a reduction in renal vascular resistance, where bradykinin had no effect. However, acetylcholine did not cause any haemodynamic changes in the bradykinin-sensitive intestinal vasculature.

5 Acetylcholine caused vasoconstriction in the coronary and epididymal vasculature. Bradykinin in the presence of indomethacin induced vasoconstriction in the skin.

6 In conclusion, the data show that, with the possible exception of the brain and the skin, the vasodilator actions of bradykinin can adequately be transduced (presumably by endothelium-derived relaxing factor, EDRF) in the absence of prostacyclin synthesis. Additionally, these results indicate that the vasculature of the stomach, pancreas/mesentery, epididimides and skeletal muscle are equally sensitive to both acetylcholine and bradykinin, whereas the kidneys showed selectivity towards acetylcholine and the intestines towards bradykinin. These results may indicate differential receptor populations.

Introduction

The vasodilator agents sodium nitroprusside, acetylcholine and bradykinin share a common mechanism of action, that of stimulating guanosine 3′:5′-cyclic monophosphate (cyclic GMP) production in the vascular smooth muscle cells. Sodium nitroprusside yields nitric oxide (Feelisch & Noack, 1987) which acts directly on the soluble guanylate cyclase to increase cyclic GMP. Bradykinin and acetylcholine on the other hand stimulate the release of endothelium-derived relaxing factor (EDRF) (Furchgott & Zawadzki, 1980), the activity of which is accounted for by nitric oxide (Palmer *et al.*, 1987). Bradykinin also releases prostacyclin (PGI_2) (Moncada *et al.*, 1979). Both EDRF and PGI_2 have short biological half-lives so they are likely to act as local vasodilators.

In isolated vascular smooth muscle, bradykinin and acetylcholine induce relaxation only through the release of PGI_2 and EDRF, whereas sodium nitroprusside yields nitric oxide to act on smooth muscle

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directly and so would be expected to be ubiquitous in its vasodilator actions. Its potency should be dependent upon factors such as vascular tone, the vessels' capacity for relaxation, the concentration of guanylate cyclase and substrate availability. Even so, there seems to be some vessel selectivity, as renal, splanchnic and cutaneous vascular beds in the rat selectively dilate to sodium nitroprusside (Flaim *et al.*, 1981).

A wide range of isolated vascular tissue preparations are relaxed by acetylcholine as long as they maintain their endothelium. Other vascular beds, inappropriate for *in vitro* study, could also be sensitive to acetylcholine and therefore contribute to a systemic depressor response. The hypotensive response to acetylcholine will depend on the same factors pertaining to sodium nitroprusside, but also on the cholinoceptor population of endothelium in individual vascular beds.

Bradykinin can release not only EDRF but also PGI_2. Thus, the vasodilator actions of bradykinin may not only depend on the same factors involved for nitroprusside or acetylcholine (receptor distribution and density), but also on the relative release of EDRF and PGI_2 upon receptor activation, and their possible additive or synergistic actions in different vascular beds.

We have compared the haemodynamic changes induced by nitroprusside, acetylcholine and bradykinin in the anaesthetized rat using a radioactive tracer microsphere technique. An account of some of this work was presented to the British Pharmacological Society meeting in Dublin (Thomas *et al.*, 1988).

Methods

Male Wistar rats (280–330 g, Tucks Ltd., Rayleigh, Essex) were anaesthetized with sodium pentobarbitone (Sagatal, May & Baker; 60 mg kg^{-1} i.p.) and prepared in a way similar to that described by Hiley & Thomas (1987a). Briefly, the right femoral artery was cannulated and connected to a Bell & Howell type 4-422-0001 pressure transducer for the measurement of systemic blood pressure on a Grass model 7D polygraph. The left femoral artery was cannulated and connected to a syringe pump (Perfusor VI, Braun, Melsungen, F.R.G.) for the withdrawal of blood and the left jugular vein was also cannulated for the administration of drugs. A polythene cannula (i.d. 0.04 mm; o.d. 1.80 mm) was introduced via the right common carotid artery into the left ventricle. The animals were ventilated with room air via a tracheal cannula at 58 strokes min^{-1} and a tidal volume of 14 ml kg^{-1} using a miniature ideal pump (Palmer Bioscience, Sheerness, Kent).

A stabilization period of 10–15 min was allowed after the surgical procedures and then arterial blood samples were taken so that pH and blood gases could be measured on a Corning 168 pH blood gas analyser. The animals were then vagotomised. Test drugs were administered and, during a stable depressor response of 75–100 mmHg to one of the vasodilators, 60,000–80,000 ^{113}Sn labelled microspheres (15 ± 3 μm diameter; NEN, Dreieich, F.R.G.), suspended by ultrasonication in 0.3 ml of 0.9% w/v saline containing 0.01% v/v Tween 80, were injected into the left ventricle over a period of 20 s. Concurrently, blood was withdrawn from the left femoral artery at a rate of 0.5 ml min^{-1} during and for 70 s after the introduction of the microspheres. Stable depressor responses to all of the agents used were obtained within 1 min of the start of drug infusion. The animals were then killed with an air embolism and the tissues dissected out, weighed and placed in vials for counting in an LKB 1282 CompuGamma, γ-scintillation counter.

The blood sample withdrawn during the microsphere injection was also counted as was any radioactive material remaining in the injection syringe and cannula. Cardiac output ((counts injected × pump speed)/blood sample counts) and tissue blood flow were determined as described by McDevitt & Nies (1976). The fraction of the cardiac output received by an organ is given by (counts in organ/counts injected), organ blood flow per unit mass by ((cardiac output × fraction of cardiac output received)/organ weight) and organ vascular resistance (assuming venous outflow pressure to be zero) by (mean arterial pressure at the mid-point of the microsphere injection/organ blood flow).

Drugs

All drugs were administered in saline as an intravenous infusion at 0.3 ml min^{-1}. Control animals received saline alone. Sodium nitroprusside was administered at 4 μg min^{-1}; acetylcholine iodide at 20 μg min^{-1} and bradykinin hydrochloride at 30 μg min^{-1} from a syringe pump (Perfusor VI, Braun, Melsungen, F.R.G.). Indomethacin, when used, was administered intravenously at a dose of 4 mg kg^{-1} before vagotomy. All drugs were purchased from Sigma Chemical Co., Poole, Dorset and prepared fresh daily in 0.9% w/v saline with the exception of indomethacin which was prepared as a 1 mg ml^{-1} solution in 5% w/v sodium bicarbonate.

Statistical comparison

All results are presented as mean ± s.e.mean of eight determinations. Statistical significance between groups was assessed by one-way analysis of variance

followed by a least significance difference (LSD) procedure (SPSS PC+; SPSS inc., Chicago, IL) and a value of P less than 0.05 was taken as significant.

Results

Blood gases and pH for the 40 animals in the study were stable within normal limits of 74.9 ± 2.3 for Po_2; 39.2 ± 0.7 for Pco_2 and 7.41 ± 0.01 for pH.

Bilateral vagotomy increased the systemic mean arterial pressure (MAP) by 25 ± 3 mmHg and heart rate by 33 ± 5 beats min^{-1} ($n = 40$). As may be seen in Table 1, all three vasodilators produced significant decreases in MAP compared to saline-treated controls. The total peripheral resistance (TPR) for the vagotomised control animals was 5.5 ± 0.75 mmHg ml^{-1} min 100 g body weight and this was decreased by bradykinin alone (34%) and by bradykinin after indomethacin (47%). No significant change in TPR was observed for the acetylcholine- or nitroprusside-treated groups.

Administration of bradykinin with or without indomethacin produced a significant ($P < 0.05$) tachycardia of 33 ± 13 and 43 ± 6 beats min^{-1}, respectively. However, this positive chronotopic effect was not accompanied by an increase in cardiac output, indicating a decrease in stroke volume of approximately 20% (Table 1). A significant reduction in stroke volume occurred during the administration of both sodium nitroprusside (38%) and acetylcholine (48%). This reduction in stroke volume is reflected by the significant depression in cardiac output brought about by these two agents (Table 1).

Bradykinin caused a reduction in vascular resistance in the liver (35%), stomach (72%), small intestine (40%), large intestine (37%), pancreas/mesentery (73%), epididimides (61%), skeletal muscle (77%) and fat (63%). These responses were not affected by indomethacin (Figure 1). In those organs where vascular resistance was reduced by more than 60% there was a resultant increase in blood flow (Table 3). Similarly, in those organs where the percentage of the cardiac output received could be calculated, i.e. all but the skeletal muscle and fat, this parameter was also increased when the vascular resistance had been reduced by more than 60% (Table 2).

Bradykinin also reduced the vascular resistance in the brain by 49% but, unlike other vascular beds, the effect was abolished by indomethacin (Figure 1). This abolition of the vasodilator response to bradykinin was accompanied by reductions both in cerebral blood flow to 71% of the perfusion rate during bradykinin alone (Table 3) and in the percentage of the cardiac output received by the brain (Table 2).

Bradykinin alone had no effect on cutaneous vascular resistance, but in the presence of indomethacin the response to bradykinin infusion was a 42% increase in vascular resistance. Similarly, an increase in vascular resistance was observed in the heart (182%) and testes (42%) during the adminis-

Table 1 Effect of nitroprusside and endothelium-dependent vasodilators on central haemodynamics in the anaesthetized rat

	Mean arterial pressure (mmHg)	*Heart rate* (beats min^{-1})	*Cardiac index* ($ml\,min^{-1}$ $100\,g^{-1}$ body wt.)	*Stroke volume* (ml)	*TPR* ($mmHg\,ml^{-1}$ min 100 g body wt)
Saline	151.2 ± 6.0	440 ± 23	30.0 ± 3.3	0.21 ± 0.03	5.5 ± 0.75
	-2.2 ± 2.4	$+3 \pm 5$			
Sodium nitroprusside	92.0 ± 8.0*	485 ± 9*	22.4 ± 2.2*	0.13 ± 0.01*	4.2 ± 0.37
	-69.6 ± 6.1*	$+18 \pm 7$			
Bradykinin	83.7 ± 11.3*	498 ± 16*	26.9 ± 3.4	0.17 ± 0.02	3.4 ± 0.47*
	-80.2 ± 3.8*	$+33 \pm 13$*			
Bradykinin and indomethacin	79.3 ± 8.2*	512 ± 11*	28.2 ± 2.2	0.19 ± 0.01	2.9 ± 0.32*
	-79.3 ± 9.8*	$+43 \pm 6$*			
Acetylcholine	81.2 ± 8.4*	459 ± 7	16.2 ± 3.0*	0.11 ± 0.01*	5.1 ± 0.38
	-82.5 ± 13.7*	-6 ± 5			

Sodium nitroprusside ($4\,\mu g\,min^{-1}$); bradykinin ($30\,\mu g\,min^{-1}$); bradykinin ($30\,\mu g\,min^{-1}$) plus indomethacin ($4\,mg\,kg^{-1}$); acetylcholine ($20\,\mu g\,min^{-1}$).
Where two numbers are given in a column, the upper values are those recorded during the microsphere injection. The lower value is the change in the parameter observed upon the administration of either saline or vasodilator. Cardiac index is the absolute value calculated by the microsphere method. TPR is the total peripheral resistance calculated from the cardiac index and mean arterial pressure during the microsphere injection, assuming central venous pressure to be zero. Stroke volume is also an absolute value calculated from the cardiac output (without normalisation to body weight) and the heart rate at the time of the microsphere injection. * Significant differences ($P < 0.05$) between the saline control and experimental groups.

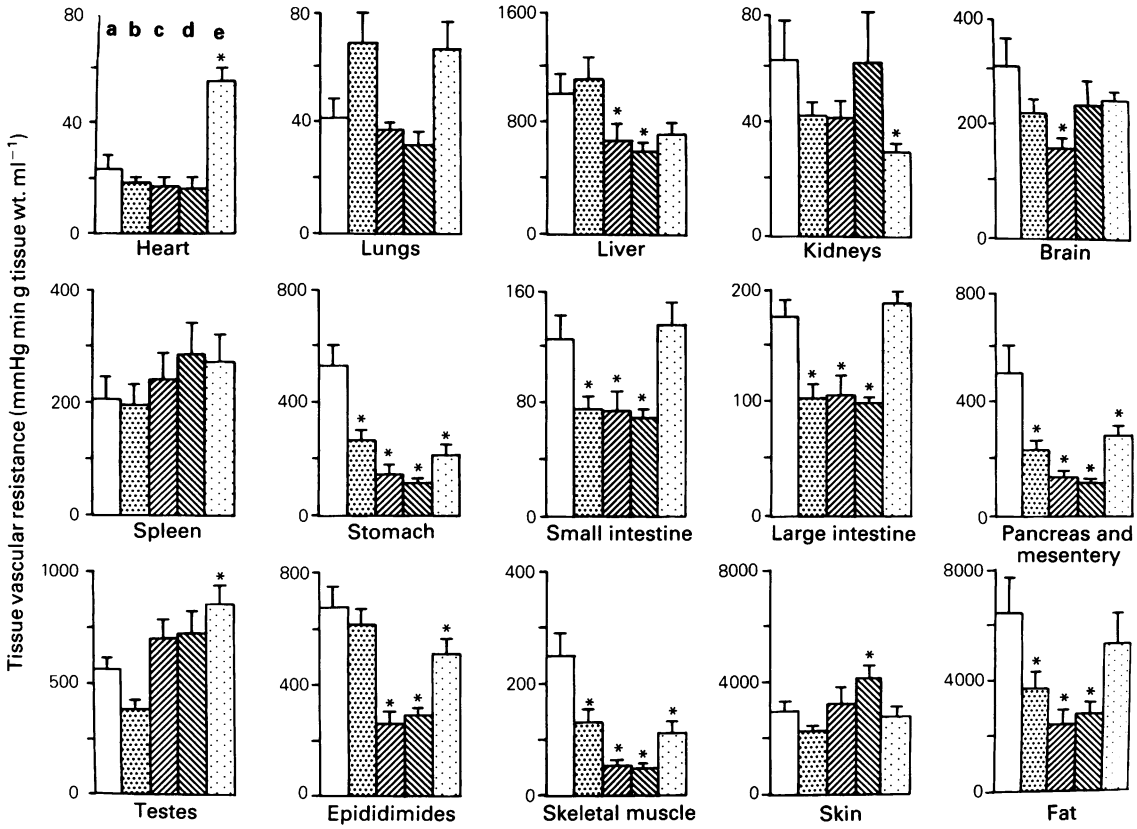

Figure 1 The effects of infusions of sodium nitroprusside (4 μg min^{-1}, column b), bradykinin (30 μg min^{-1}) in the absence (column c) and presence (column d) of indomethacin (4 mg kg^{-1}) and acetylcholine (20 μg min^{-1}) (column e) on the vascular resistance in individual organs. The results are expressed as means of 8 determinations with vertical bars showing s.e.mean. * Significant differences ($P < 0.05$) between groups and saline controls (column a).

Table 2 Percentage of cardiac output received by individual vascular beds after administration of vasodilators

Vascular bed	*Control*	*SNP*	*Bk*	*Bk + Indo*	*ACh*
Heart	10.33 ± 1.52	9.14 ± 1.06	7.61 ± 1.09	6.79 ± 0.65*	3.47 ± 0.45*
Lungs	9.70 ± 4.09	6.19 ± 3.18	6.85 ± 3.36	4.57 ± 0.67	3.77 ± 0.42
Liver[a]	3.03 ± 0.54	1.97 ± 0.37	3.05 ± 0.47	2.47 ± 0.18	3.80 ± 0.48
Kidneys	10.12 ± 0.86	9.52 ± 0.92	7.56 ± 0.75*	6.18 ± 1.15*	16.01 ± 0.68*
Spleen	0.93 ± 0.09	0.72 ± 0.11	0.43 ± 0.08*	0.36 ± 0.06*	0.66 ± 0.10*
Stomach	0.54 ± 0.04	0.87 ± 0.11*	1.27 ± 0.13*	1.26 ± 0.13*	1.21 ± 0.10*
Small intestine	10.70 ± 0.97	13.40 ± 0.71	11.08 ± 0.96	9.23 ± 0.44	9.51 ± 0.70
Large intestine	3.30 ± 0.32	3.94 ± 0.45	3.31 ± 0.32	3.02 ± 0.22	3.02 ± 0.34
Pancreas and mesentery	1.73 ± 0.17	2.81 ± 0.28*	4.03 ± 0.46*	3.95 ± 0.20*	2.65 ± 0.20*
Testes	0.86 ± 0.05	1.05 ± 0.13	0.45 ± 0.03*	0.37 ± 0.02*	0.58 ± 0.04*
Epididimides	0.23 ± 0.02	0.20 ± 0.02	0.39 ± 0.05*	0.31 ± 0.02*	0.29 ± 0.03
Brain	1.22 ± 0.16	1.25 ± 0.18	1.41 ± 0.21	0.82 ± 0.10†	1.31 ± 0.10

Values are given as the mean ± s.e.mean of 8 determinations for each group. Statistical significance from controls was determined by analysis of variance followed by a least square difference analysis. * $P < 0.05$ from saline controls. † $P < 0.05$ from bradykinin-treated group.

[a] Hepatic artery.

SNP: sodium nitroprusside (4 μg min^{-1}); Bk: bradykinin (30 μg min^{-1}); Bk + Indo: bradykinin (30 μg min^{-1}) plus indomethacin (4 mg kg^{-1}); ACh: acetylcholine (20 μg min^{-1}).

Table 3 Tissue blood flow (ml min^{-1} g^{-1} tissue wt) after administration of vasodilators

Vascular bed	*Control*	*SNP*	*Bk*	*Bk + Indo*	*ACh*
Heart	8.46 ± 1.72	5.52 ± 0.87*	5.48 ± 0.88*	5.60 ± 0.74	1.55 ± 0.13*
Lungs	6.34 ± 2.94	3.91 ± 2.49	2.34 ± 0.14	2.85 ± 0.33	1.45 ± 0.30
Liver[a]	0.17 ± 0.03	0.09 ± 0.02*	0.16 ± 0.03	0.14 ± 0.01	0.13 ± 0.02
Kidneys	3.12 ± 0.49	2.31 ± 0.20	2.40 ± 0.34	2.20 ± 0.48	2.95 ± 0.30
Spleen	0.93 ± 0.15	0.58 ± 0.11*	0.50 ± 0.14*	0.38 ± 0.08*	0.40 ± 0.10*
Stomach	0.32 ± 0.04	0.38 ± 0.04	0.66 ± 0.08*	0.72 ± 0.06*	0.40 ± 0.03
Small intestine	1.37 ± 0.17	1.29 ± 0.15	1.28 ± 0.19	1.19 ± 0.08	0.70 ± 0.07*
Large intestine	0.93 ± 0.08	0.90 ± 0.10	0.89 ± 0.12	0.84 ± 0.06	0.47 ± 0.04*
Pancreas and mesentery	0.38 ± 0.06	0.44 ± 0.04	0.73 ± 0.09*	0.78 ± 0.07*	0.30 ± 0.03
Testes	0.28 ± 0.02	0.25 ± 0.03	0.13 ± 0.02*	0.12 ± 0.01*	0.10 ± 0.01*
Epididimes	0.24 ± 0.02	0.16 ± 0.02	0.37 ± 0.06*	0.29 ± 0.03	0.17 ± 0.02
Skeletal muscle[b]	0.08 ± 0.02	0.10 ± 0.03	0.16 ± 0.02*	0.22 ± 0.05*	0.09 ± 0.01
Skin	0.06 ± 0.01	0.04 ± 0.01	0.03 ± 0.01*	0.02 ± 0.01*	0.03 ± 0.01*
Fat	0.03 ± 0.01	0.03 ± 0.01	0.05 ± 0.01	0.03 ± 0.01	0.02 ± 0.01
Brain	0.57 ± 0.08	0.44 ± 0.05	0.58 ± 0.06	0.41 ± 0.06†	0.34 ± 0.02*

Values are given as the mean ± s.e.mean of 8 determinations for each group. Statistical significance from controls was determined by analysis of variance followed by a least square difference analysis. * $P < 0.05$ from saline controls. † $P < 0.05$ from bradykinin-treated group.

[a] Hepatic artery; [b] pectoral muscles.

SNP: sodium nitroprusside (4 $\mu g\,min^{-1}$); Bk: bradykinin (30 $\mu g\,min^{-1}$); Bk + Indo: bradykinin (30 $\mu g\,min^{-1}$) plus indomethacin (4 $mg\,kg^{-1}$); ACh: acetylcholine (20 $\mu g\,min^{-1}$).

tration of acetylcholine (Figure 1). In all of these vascular beds this corresponded to a significant reduction in blood flow (Table 3) and in the percentage of the cardiac output received (Table 2).

As may be seen in Figure 1 not all tissues responded similarly to the two endothelium-dependent vasodilators. As described earlier, acetylcholine caused an increase in coronary vascular resistance whereas bradykinin was without effect. Conversely, bradykinin was inactive on the renal vasculature, whereas acetylcholine caused a significant reduction (53%) in the vascular resistance of this organ. This reduction in renal vascular resistance was reflected as an increase in the fraction of the cardiac output received by the kidneys (Table 2) but, due to the depression of cardiac output (Table 1), the reduction in vascular resistance was insufficient to affect absolute blood flow (Table 3). Other vascular beds, namely the small and large intestines, responded to bradykinin with significant reductions in vascular resistance (40% and 37%, respectively) but the same two organs were unresponsive to acetylcholine. From comparisons made between the effects of bradykinin and acetylcholine on vascular resistance and blood flow it is apparent that for bradykinin, reductions in resistance of >60% usually resulted in increases in blood flow whereas with acetylcholine, due to the reduction in cardiac output, there was no augmentation of blood flow in any of the tissues studied even though it caused reductions in resistance of up to 53% and 60% in the kidneys and stomach, respectively.

Whereas most of the tissues studied responded to one of the agents tested it is noteworthy that none of these vasodilators had any effect on the vascular resistance of the lungs and spleen (Figure 1).

Discussion

All the vasodilators tested significantly lowered peripheral blood pressure but only bradykinin decreased total peripheral resistance to a point that attained a level of significance of $P < 0.05$. Nitroprusside has previously been shown to decrease TPR, for example by 47% in the rhesus monkey (Sivarajan *et al.*, 1985). The somewhat smaller reduction in TPR observed in this study may be explained by the fact that our animals were vagotomized and hence had a high central sympathetic outflow with consequent greatly elevated vascular tone. Under these conditions there may have been some venous pooling resulting in reduced venous return and subsequent reduction in stroke volume and cardiac output. This reduction in cardiac output and minimal effect on peripheral resistance, due to venodilatation leading to a diminished venous return, is an effect previously associated with nitroprusside under normal circulatory conditions (Pouleur *et al.*, 1980). However, our 25% reduction of TPR by nitroprusside is similar to that of Vetterlein *et al.* (1979), from whose results a reduction of approximately 27% can be calculated for a 39% fall in blood pressure.

Our results show that bradykinin caused a reduction in vascular resistance in a wide range of tissues including the hepato-splanchnic area, the epididimides, skeletal muscle and skin. In all of these tissues the response to bradykinin was not affected by the administration of indomethacin, suggesting that these effects are mediated via a vasodilator other than PGI_2. It is likely that the responses to bradykinin in these tissues were transduced by EDRF since bradykinin is a potent releaser of EDRF *in vitro* (see Furchgott, 1984).

Interestingly, the reduction in vascular resistance caused by bradykinin in the brain was abolished by indomethacin suggesting that, in this vascular bed, PGI_2 is the main mediator of the bradykinin effects. Abdel-Halim *et al.* (1980) have shown that 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$), the primary metabolite of PGI_2, is the predominant prostaglandin in cerebral vessels occurring in 5–10 fold higher levels than the second most important prostaglandin $PGF_{2\alpha}$. It is possible that bradykinin has an important role to play in the control of cerebral blood flow for it is a potent vasodilator of human and feline pial arteries (Wahl *et al.*, 1983). Bradykinin is also present in brain tissue (Côrrea *et al.*, 1979; Chao *et al.*, 1983; Perry & Snyder, 1984) and cerebrospinal fluid (Thomas *et al.*, 1984) and is a mediator in vasogenic brain oedema (Unterberg & Baethmann, 1984; Maier-Hauff *et al.*, 1984). When administered centrally it is known to have profound effects on peripheral blood flow and distribution (Hiley & Thomas, 1987b).

Vasoconstriction was also seen after administration of bradykinin in this study. In the cutaneous vascular bed, bradykinin alone had no effect, but in the presence of indomethacin the peptide caused an increase in vascular resistance and a subsequent decrease in blood flow. In the rat, the skin is a major homeothermic organ and consequently must have a high degree of vascular control. It is possible, therefore, that when PGI_2 production is suppressed the net effect of bradykinin stimulation of the endothelial cells is the release of a constricting factor, possibly the vasoconstrictor peptide produced by cultured endothelial cells described by Hickey *et al.* (1985) or endothelin (Yanagisawa *et al.*, 1988). This may also account for the increased vascular resistance seen with acetylcholine in the testes. Increases in vascular resistance and reduced blood flow were also seen in response to acetylcholine in the heart, an effect which may be associated with coronary autoregulation. During acetylcholine infusion the pressure-rate index, an indicator of myocardial oxygen consumption (Baller *et al.*, 1981), is reduced by approximately 44%, the largest reduction seen with any of the compounds studied. Hence, one consequence of this fall in myocardial oxygen demand may be a reduction in coronary flow.

The fact that sodium nitroprusside did not cause a generalized vasodilatation was unexpected, but Vetterlein *et al.* (1979) observed that the only haemodynamic changes following sodium nitroprusside administration were significant decreases in splenic and renal blood flow. In our experiments, sodium nitroprusside showed selectivity for the vasculature of the splanchnic area, skeletal muscle and epididymal fat pad. This pattern of selective vasodilatation was similar to that observed for bradykinin, whereas with acetylcholine the kidneys were dilated with no effect on the intestine. This may indicate a different distribution of the receptor populations for acetylcholine and bradykinin, and reflect a heterogeneous nature of arterial endothelial cells, comparable to that already observed between species (Auerbach *et al.*, 1982) and arteries and veins (De Mey & Vanhoutte, 1982). The vasodilator activity of acetylcholine in the stomach has been previously described in the rat (Vetterlein *et al.*, 1979). Acetylcholine also dilates the vasculature of the rat stomach (Kitagawa *et al.*, 1987) and the vasodilatation is not inhibited by indomethacin but is reduced by quinacrine, *p*-bromophenacyl bromide and nordihydroguaiaretic acid. Although these inhibitors are no longer regarded as positive indicators of the origins of EDRF (Förstermann *et al.*, 1988) they do, however, suggest the involvement of an endothelium-dependent factor other than PGI_2.

In conclusion, although the vasodilator effects of sodium nitroprusside, acetylcholine and bradykinin show similarities in their mode of action, there are some considerable differences in their target vascular beds. These differences may reflect an organ specific distribution of receptors and the possibility therefore exists of further exploitation of this for the development of organ-specific vasodilators.

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