Effects of cyclic AMP-affecting agents on contractile reactivity of isolated mesenteric and renal resistance arteries of the rat

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- 1 Effects of adenosine 3':5'-cyclic monophosphate (cyclic AMP)-affecting agents were compared in mesenteric and renal resistance arteries that had been isolated from 20 week old Wistar-Kyoto rats, chemically sympathectomized, stretched to their optimal diameter for mechanical performance and made to contract in response to 30 mM potassium.
- 2 In mesenteric resistance arteries, isoprenaline, dopamine, NaF, forskolin, isobutyl-methylxanthine, milrinone and dibutyryl-cyclic AMP induced relaxation. Clonidine induced further increases in tension that could be reduced by pertussis toxin and prazosin but not by yohimbine. Clonidine also reduced relaxant responses to isoprenaline.
- 3 In renal resistance arteries, isoprenaline and dopamine failed to induce relaxation. Compared to mesenteric resistance arteries, renal vessels were less sensitive to the relaxant effect of NaF, forskolin and isobutyl-methylxanthine. Relaxant responses to dibutyryl-cyclic AMP did not differ between the two resistance arteries.
- 4 Indirect evidence thus suggests that in mesenteric resistance arteries, adenylate cyclase is susceptible to pharmacological activation and inhibition and is functionally coupled to relaxation. The refractory nature of renal resistance arteries to the relaxant effects of isoprenaline and dopamine could be due primarily to absence of appropriate receptors and to a relatively low activity of adenylate cyclase.

Introduction

Selective renal vasodilatation could be beneficial for the therapy of hypertension (Struyker-Boudier, 1980; Ackerman *et al.*, 1983) and congestive heart failure (Renne, 1986; Dzau, 1987). This can be achieved by the use of prodrugs (Drieman *et al.*, 1990) and theoretically also by a direct action on vasodilator systems that are selectively present in renal blood vessels. The pharmacological properties of the renal vasculature differ both quantitatively and qualitatively from those in other organs. It is well known for instance that atrial natriuretic peptides and dopamine display in some species selectivity for the renal vasculature (Goldberg, 1984; Hintze *et al.*, 1985; De Mey *et al.*, 1987) and that there is a relative lack of postjunctional α_2 -adrenoceptors in renal blood vessels (Pettinger *et al.*, 1987; Wolff *et al.*, 1987; Edwards & Trizna, 1988). In addition, renal arteries, unlike arteries from other organs, fail to relax in response to β -adrenoceptor agonists (Bomzon, 1983; Boonen *et al.*, 1990). As for most aspects of vascular heterogeneity, the mechanisms that underly this latter regional difference are unclear.

β -Adrenoceptor agonists dilate blood vessels through activation of adenylate cyclase which leads to an increased sarcoplasmic concentration of adenosine 3':5'-cyclic monophosphate (cyclic AMP) and subsequent activation of cyclic AMP-dependent protein kinases (Kukovetz *et al.*, 1981; Krall *et al.*, 1983). β -Adrenoceptor-induced relaxation of vascular smooth muscle is reduced following prolonged exposure to agonist, ageing and hypertension (Triner *et al.*, 1975; Cohen & Berkowitz, 1976; Fleisch, 1980; Harden, 1983; Tsujimoto *et al.*, 1986). These changes have been attributed to alterations at the level of the β -adrenoceptors, the guanosine triphosphate (GTP)-binding regulatory proteins that link the receptors to the cyclase, the adenylate cyclase itself or to changes of cyclic AMP-dependent kinases (Bhalla *et al.*, 1976; Tsujimoto *et al.*, 1986; Asano *et al.*, 1988a,b).

To localize the steps within the receptor-cyclase-kinase chain that could be responsible for regional differences of β -adrenoceptor responses of vascular smooth muscle, we recorded effects of cyclic AMP-affecting agents on the contractile

reactivity of isolated mesenteric and renal blood vessels. The experiments were performed in vessels that were small enough to contribute to the regulation of mesenteric and renal vascular resistance *in vivo*. Parts of this study were presented at the 1989 summer meeting of the American Society for Pharmacology and Experimental Therapeutics (Heesen *et al.*, 1989).

Methods

Experiments were performed on resistance arteries isolated from 20-week-old male Wistar-Kyoto rats (local inbred, Rijksuniversiteit Limburg, Maastricht). The animals were killed by cervical dislocation and exsanguination. Fourth- to fifth-order side branches of the superior mesenteric artery and interlobar renal arteries were isolated and chemically sympathectomized with 6-hydroxydopamine (Aprigliano & Hermsmeyer, 1976). Two stainless-steel wires (diameter 40 μ m) were inserted in the lumen of the resistance arterial segments, which were then mounted horizontally in an organ chamber (volume 10 ml) between an isometric force transducer (Kistler Morse DSC6, Seattle WA, U.S.A.) and a displacement device (Mitutoyo, Tokyo, Japan) (Mulvany & Halpern, 1977; De Mey *et al.*, 1987). The organ chamber was filled with Krebs-Ringer bicarbonate solution (KRB, composition in mM: NaCl 118.3, KCl 4.7, CaCl₂ 2.5, MgSO₄ · 7H₂O 1.2, KH₂PO₄ 1.2, NaHCO₃ 25.0 and glucose 11) which was maintained at 37°C and continuously aerated with 95% O₂ and 5% CO₂. Before experimentation the resistance arterial segments were stretched to their individual optimal lumen diameter for mechanical performance (De Mey *et al.*, 1987). Their diameter was therefore initially set at 65 μ m and increased by 20 μ m increments at 10 min intervals. Intermittently, the preparations were exposed to activating solution (K-KRB, KRB in which all NaCl was replaced by an equimolar amount of KCl). This procedure was continued until maximal contractile responses to potassium were obtained. Subsequent experimentation was performed at this optimal diameter. In all experiments a mesenteric and a renal resistance-sized arterial segment from the same animal were mounted in the same organ chamber and were studied in parallel.

To study relaxant responses to pharmacological agents, the resistance arterial segments were first made to contract in

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response to 30 mM potassium by replacing the fluid in the organ chamber with a prewarmed and oxygenated solution containing four parts KRB and one part K-KRB. Changes with time of the response to this contractile stimulus were recorded in each individual experiment and were taken into account when evaluating the effects of agents added on top of the contraction induced by 30 mM potassium. The pharmacological agents that were used included (–)-isoprenaline sulphate, (±)-dopamine hydrochloride, prostaglandin E₂, forskolin, dibutyl-cyclic adenosine monophosphate, 3-isobutyl-1-methylxanthine, 6-hydroxydopamine hydrochloride, prazosin hydrochloride, and clonidine hydrochloride which were obtained from Sigma Chemicals (Saint Louis, MO, U.S.A.). Pertussis toxin was obtained from Janssen Chimica (Beerse, Belgium). The stable analogue of prostacyclin, iloprost and the inhibitor of phosphodiesterase III, milrinone were kind gifts from Shering AG and Sterling Winthrop, respectively.

Contractile responses were expressed as increases in wall tension (increases in force/2 × length of arterial segment). Effects of pharmacological agents were expressed as percentage change from the pre-existing contractile tension. Data are shown as means ± s.e.mean. Statistical significance of differences was evaluated by Student's *t* test for paired or unpaired observations or by analysis of variance followed by Bonferroni's *t* test, where applicable (Wallenstein *et al.*, 1980). *P* < 0.05 was taken to denote statistical significance.

Results

Sympathectomized resistance arteries that had been isolated from rat mesenteries and kidneys had comparable optimal diameters (Table 1). Maximal contractile responses to 125 mM potassium were significantly larger in mesenteric than renal preparations (Table 1). Potassium (30 mM) induced responses that reached 70 to 80% of the maximal response to depolarization in both the mesenteric and the renal resistance arteries (Table 1). In neither mesenteric nor renal preparations was the amplitude of the contractile response to 30 mM potassium significantly affected by the presence of either 1 μM prazosin alone or of both 1 μM prazosin and 1 μM propranolol (data not shown). Exposure of mesenteric and renal resistance arteries to pertussis toxin (1 μg ml⁻¹) for 90 min did not affect their resting wall tension. Following pretreatment with the toxin, responses to 125 mM potassium were reduced in mesenteric resistance arteries and increased in renal vessels (Table 1). The relative amplitude of responses to 30 mM potassium was reduced in mesenteric preparations and not affected in renal resistance arteries that had been exposed to pertussis toxin (Table 1).

In the presence of 1 μM prazosin, mesenteric resistance arteries that had been made to contract with 30 μM potassium

responded to isoprenaline with concentration-dependent relaxations. Renal resistance arteries failed to respond to isoprenaline (Figure 1 and Table 2). Similarly, mesenteric but not renal resistance arteries, relaxed in response to dopamine when they had been made to contract with 30 mM potassium in the presence of both prazosin (1 μM) and propranolol (1 μM) (Table 2). Similar observations were obtained with the D₁-receptor agonist, fenoldopam (0.1 to 100 μM, *n* = 4, not shown).

Prostaglandin E₂ and the stable analogue of prostacyclin, iloprost, which in a variety of systems have been observed to stimulate the production of cyclic AMP (Gryglewski *et al.*, 1988), did not induce relaxation in either type of resistance artery. Prostaglandin E₂ rather increased contractile responses to 30 mM potassium in both the mesenteric and renal preparations (Table 2). The maximal effect and sensitivity for prostaglandin E₂ did not differ between the two types of resistance artery (Table 2). Iloprost, on the other hand, increased contractile responses in the renal resistance arteries but did not affect mesenteric resistance arteries (Table 2).

NaF, which in combination with trace amounts of aluminium ions directly activates GTP-binding regulatory proteins (Sternweis & Gilman, 1982), caused biphasic effects in precontracted resistance arteries (Figure 2). Low concentrations of NaF induced relaxation, while concentrations of NaF above 10 mM induced transient further increases in tension. The relaxant effect induced by 3 mM NaF was significantly larger in mesenteric (67 ± 4%, *n* = 6) than renal (42 ± 8%, *n* = 6) resistance arteries. Forskolin, a diterpene that directly activates the catalytic subunit of adenylate cyclase (Seamon & Daly, 1981), caused concentration-dependent relaxations in both precontracted mesenteric and renal resistance arteries (Figure 3). The mesenteric preparations were significantly more sensitive to forskolin than the renal vessels (Table 2). Forskolin fully relaxed mesenteric and renal resistance arteries that had been contracted with 30 mM potassium (Table 2).

In contrast to receptor-mediated and direct activators of adenylate cyclase, dibutyl-cyclic AMP similarly relaxed precontracted mesenteric and renal resistance arteries (Figure 4). Neither the sensitivity for, nor the maximal effect of the degradation-resistant analogue of cyclic AMP, differed significantly between both types of resistance arteries (Figure 4).

We considered whether in addition to the presence of appropriate receptor sites and of adenylate cyclase, differences in the activity of phosphodiesterases and in receptor-mediated inhibition of adenylate cyclase could also contribute to regional differences in responsiveness to cyclic AMP affecting agents. Isobutyl-methylxanthine and milrinone, a non-selective phosphodiesterase inhibitor and an inhibitor of phosphodiesterase III, respectively (Weishaar *et al.*, 1986), induced

Table 1 Effects of pertussis toxin (PTX) on contractile responses to potassium in isolated mesenteric and renal resistance arteries*

Resistance artery	Mesenteric	Renal
Optimal diameter, <i>n</i> = 24 (μm)	265 ± 10	295 ± 11
Before PTX, <i>n</i> = 24		
125 mM K ⁺ (mN mm ⁻¹)	2.5 ± 0.3	1.7 ± 0.3*
30 mM K ⁺ (/K125)	0.701 ± 0.063	0.774 ± 0.045
After PTX, <i>n</i> = 6		
125 mM K ⁺ (mN mm ⁻¹)	1.5 ± 0.6†	2.6 ± 0.6
30 mM K ⁺ (/K125)	0.465 ± 0.065†	0.793 ± 0.059*

* Data are shown as means ± s.e.mean for isolated sympathectomized resistance arteries, before and after 90 min exposure to PTX 1 μg ml⁻¹. Contractile responses to 125 mM potassium were expressed as increases in wall tension; those to 30 mM potassium as a fraction of the response to 125 mM potassium. * and †: The difference between mesenteric preparations and between observations before and after exposure to PTX is statistically significant.

Figure 1 Effects of isoprenaline in isolated mesenteric (□) and renal (●) resistance arteries that had been contracted with 30 mM potassium in the presence of 1 μM prazosin. The data are expressed as a percentage of the response to potassium in the absence of agonist (for absolute value see Table 1) and are shown as means (*n* = 24) with s.e.mean indicated by vertical bars.

Table 2 Effects of pharmacological agents in precontracted resistance arteries*

Resistance artery	Maximal effect (% change)		Sensitivity (-log M ED ₅₀)	
	Mesenteric	Renal	Mesenteric	Renal
Control				
Isoprenaline ^b (24)	-84 ± 1	+11 ± 2*	7.5 ± 0.2	<5*
Forskolin (12)	-97 ± 1	-100 ± 0	6.5 ± 0.2	5.8 ± 0.2*
Dopamine ^{b,c} (6)	-48 ± 3	-0 ± 6*	6.2 ± 0.4	<5*
Prostaglandin E ₂ (6)	+128 ± 79	+106 ± 16	7.2 ± 0.2	6.9 ± 0.3
Iloprost (6)	+9 ± 3	+99 ± 36*	<5	6.7 ± 4*
Isobutyl-methylxanthine (6)	-92 ± 2	-90 ± 5	6.1 ± 0.1	5.5 ± 0.2*
Milrinone (6)	-89 ± 3	-92 ± 4	5.2 ± 0.3	5.3 ± 0.3
In presence of 10 µM clonidine				
Isoprenaline ^b (6)	-42 ± 11†	-1 ± 8*	7.7 ± 0.2	<5*
Forskolin (6)	-98 ± 1	-100 ± 0	6.5 ± 0.3	5.3 ± 0.2*†

* Data are shown as means ± s.e.mean for isolated sympathectomized resistance arteries that had been made to contract with 30 mM potassium. A negative effect indicates relaxation; a positive effect a further increase in tension. For agents that hardly induced an effect the change induced by 10⁻⁵ M was taken as the maximal effect. The number of observations is given in parentheses.

^b In the presence of 1 µM prazosin.

^c In the presence of 1 µM propranolol.

* and †: The difference between mesenteric preparations and between observations in the absence and presence of clonidine is statistically significant.

relaxation in both mesenteric and renal resistance arteries. Mesenteric resistance arteries were more sensitive to isobutyl-methylxanthine than renal preparations (Table 2). Milrinone, on the other hand, had a similar effect on both types of resistance arteries (Table 2).

Up to 10 µM clonidine failed to induce contraction in resting mesenteric or renal resistance arteries (Table 3). In vessels that had been made to contract with 30 mM potassium, the α₂-adrenoceptor agonist induced further increases in tension

Figure 2 Tracings of isometric wall tension versus time obtained in an isolated renal (a) and mesenteric artery (b) of the same rat. The tracings illustrate the effect of increasing concentrations of sodium fluoride (NaF) on contractile responses to 30 mM potassium (presence indicated by open bar). The figure is representative of observations in six rats.

(Figure 5). The sensitivity for clonidine and its maximal potentiating effect did not differ significantly between mesenteric and renal preparations (Table 3). Following pretreatment of mesenteric and renal resistance vessels with pertussis toxin

Figure 3 Effects of forskolin in isolated mesenteric (□) and renal (●) resistance arteries that had been contracted with 30 mM potassium. The data are expressed as a percentage of the response to potassium in the absence of pharmacological agents and are shown as means (*n* = 12) with s.e.mean indicated by vertical bars.

Figure 4 Effects of dibutyryl cyclic AMP (db cyclic AMP) in isolated mesenteric (□) and renal (●) resistance arteries that had been contracted with 30 mM potassium. Data are expressed as a percentage of the active wall tension in the absence of the cyclic AMP-analogue and are shown as means (*n* = 6) with s.e.mean indicated by vertical bars.

Table 3 Effects of clonidine in mesenteric and renal resistance arteries*

Resistance artery	Maximal effect		Sensitivity ($-\log M ED_{50}$)	
	Mesenteric	Renal	Mesenteric	Renal
Resting (mN mm ⁻¹)	0.0	0.0	<5	<5
K ⁺ 30 mM (% change)				
Control	+104 ± 31	+51 ± 9	6.7 ± 0.5	6.9 ± 0.2
Prazosin 1 μ M	+34 ± 3	+36 ± 4	<5†	<5†
Yohimbine 1 μ M	+90 ± 8	+65 ± 7	6.6 ± 0.4	6.7 ± 0.3
PTX 1 μ g ml ⁻¹	+110 ± 52	+57 ± 13	5.5 ± 3†	5.2 ± 3†

* Data are shown as means $\pm$ s.e.mean ($n = 6$). When the maximal effect was apparently not reached at 10^{-5} M, the effect of this concentration is indicated. Prazosin and yohimbine were applied 30 min before clonidine; pertussis toxin (PTX) was applied during a 90 min pretreatment.

†: The difference from control observations is statistically significant.

1 μ g ml⁻¹, concentration-response curves for the potentiating effect of clonidine on contractile responses to 30 mM potassium, were shifted to higher concentrations (Table 3). Also prazosin (1 μ M), but not yohimbine (1 μ M) rendered resistance arteries less sensitive to the potentiating effect of clonidine (Table 3). In the presence of prazosin (1 μ M), clonidine (10 μ M) reduced the amplitude of relaxant responses to isoprenaline in mesenteric resistance arteries (Table 2). In renal resistance vessels, clonidine did not modify the absence of responses to isoprenaline but reduced the sensitivity to forskolin (Table 2).

Discussion

In contrast to isolated mesenteric resistance arteries, renal resistance arteries failed to relax in response to isoprenaline. Indirect observations suggest that this is primarily due to absence of β -adrenoceptors on renal resistance arterial smooth muscle cells or inappropriate coupling of these receptors to adenylate cyclase.

Effects of β -adrenoceptor agonists in various cell types including arterial smooth muscle cells, are mediated by cyclic AMP (Kukovetz *et al.*, 1981; Krall *et al.*, 1983). The binding of agonist to its receptor is transduced by stimulatory GTP-binding regulatory proteins (G_s proteins) to activation of the catalytic subunit of adenylate cyclase (Gilman, 1987). The enzyme catalyzes conversion of ATP into cyclic AMP. This cyclic nucleotide in turn activates certain protein kinases. In arterial smooth muscle this leads to relaxation. The cyclic AMP that is formed by adenylate cyclase can be degraded by phosphodiesterases, several types of which are present in arterial smooth muscle (Weishaar *et al.*, 1986). In several cell types, adenylate cyclase can not only be activated by β -adrenoceptor agonists, but also by dopamine, prostaglandin E_2 and prostacyclin (Goldberg, 1984; Gilman, 1987; Gry-

glewski *et al.*, 1988). Other pharmacological agents can inhibit adenylate cyclase. This has been documented for the α_2 -adrenoceptor agonist, clonidine (Pettinger *et al.*, 1987), the effect of which is mediated by pertussis toxin-sensitive GTP-binding regulatory proteins (G_i proteins; Limbird, 1988).

Whether these pathways and components are all operative in smooth muscle of arteries that are small enough to regulate total peripheral resistance and local blood flow, is unknown. Ideally this should be demonstrated by receptor-binding and other biochemical assays. Some of these have previously been performed in resistance arterial preparations (see Kwan *et al.*, 1987). They require pooling of large numbers of resistance arteries. This can be done for certain vascular beds such as the mesentery, but is virtually excluded for renal resistance arteries that are laborious to isolate. Haemodynamic data (for review see Bomzon, 1983) as well as preliminary observations in isolated resistance arteries (Boonen *et al.*, 1990) indicate, however, that the susceptibility of the resistance part of the circulation to cyclic AMP affecting agents is not uniform and could differ between vascular beds. We therefore used an indirect pharmacological approach to document the responsiveness of isolated mesenteric and renal resistance arteries to cyclic AMP affecting agents and to evaluate the mechanisms that could be involved in the regional differences. Since observations in large arteries following long term exposure to agonist, hypertension and ageing, indicated that every step in the receptor-cyclase-kinase chain could be subject to modulation (see Triner *et al.*, 1975; Cohen & Berkowitz, 1976; Bhalla *et al.*, 1978; Fleisch, 1980; Harden, 1983; Tsujimoto *et al.*, 1986; Asano *et al.*, 1988a,b), we evaluated effects of potential receptor-mediated and direct activators of adenylate cyclase as well as those of a degradation-resistant cyclic AMP-analogue. Taking into account that interventions such as depolarizing solution, isoprenaline, clonidine, and dopamine can affect arterial function not only through a direct action on smooth muscle but also by interferences with adrenergic neurotransmission (Vanhoutte *et al.*, 1981), the experiments were performed in resistance arteries that had been acutely sympathectomized.

To judge from responses to pharmacological agents, all components of the pathway that was outlined above, seem to be present in mesenteric resistance arteries. These vessels relaxed in response to isoprenaline and dopamine, potential receptor-mediated activators of adenylate cyclase. Relaxant responses to isobutyl-methylxanthine and milrinone, also directly activate GTP-binding regulatory proteins (Sternweis & Gilman, 1982), the catalytic subunit of adenylate cyclase (Seamon & Daly, 1981) and cyclic AMP-dependent protein kinases, further strengthen the view that adenylate cyclase and protein kinase A are ultimately coupled to relaxation of the resistance arterial smooth muscle. As judged from relaxant responses to isobutyl-methylxanthine and milrinone, also phosphodiesterases are present in mesenteric resistance arteries and sufficient cyclic AMP would be generated under unstimulated conditions to cause relaxation when the phosphodiesterases are inhibited. Since in the presence of an

Figure 5 Effects of clonidine in isolated mesenteric (□) and renal (●) resistance arteries that had been contracted with 30 mM potassium. Data are expressed as a percentage of the active wall tension in the absence of α -adrenoceptor agonist and are shown as means ($n = 6$) with s.e.mean indicated by vertical bars.

α_1 -adrenoceptor antagonist, clonidine reduced relaxant responses to isoprenaline, α_2 -adrenoceptor inhibition of adenylate cyclase (Pettinger *et al.*, 1987; Limbird, 1988) could also be operative in mesenteric resistance arterial smooth muscle. This is also suggested by the biphasic nature of relaxing responses to NaF, which can activate both G_s - and G_i -proteins (Sternweis & Gilman, 1982).

The mesenteric resistance arteries are thus equipped with a pharmacologically modulatable adenylate cyclase system that can interfere with contractile reactivity. Observations with clonidine and pertussis toxin deviate, however, from the classical picture. The α_2 -adrenoceptor agonist on its own did not contract mesenteric resistance arteries. This indicates that in mesenteric as in renal resistance arteries (Edwards & Trizna, 1988), postjunctional α_2 -adrenoceptors are not directly coupled to a contractile mechanism. The potentiating effect was reduced by pertussis toxin, the bacterial toxin that irreversibly ADP-ribosylates GTP-binding proteins involved in receptor-mediated inhibition of adenylate cyclase (Limbird, 1988). In mesenteric resistance arteries, as in a variety of other systems (Limbird, 1988; Pettinger *et al.*, 1987) α_2 -adrenoceptor activation would thus inhibit adenylate cyclase. However, the potentiating effect of clonidine was also inhibited by prazosin and not affected by yohimbine. Clonidine thus displayed α_1 -adrenoceptor agonist properties. That clonidine lacked a direct contractile effect but increased responses to potassium in a prazosin-sensitive way indicates that the intrinsic activity of the partial α_1 -adrenoceptor agonism of clonidine can be increased by precontraction or depolarization. Interference of pertussis toxin with the potentiating effect of clonidine thus

can be due to both inactivation of G-proteins that are negatively coupled to adenylate cyclase and to the existence of pertussis toxin-sensitive components within excitation-contraction coupling during α_1 -adrenoceptor activation (Nichols *et al.*, 1989).

In addition to interfering with effects of clonidine, pretreatment with pertussis toxin decreased contractile responses to potassium in mesenteric resistance arteries and increased those in renal preparations. The mechanisms underlying these effects are at present unclear since the direct contractile effect of depolarization on smooth muscle is supposed to be due to an effect on sarcolemmal calcium channels without the involvement of G-proteins or enzymes. One possibility is that pertussis toxin interferes with endogenously released neuropeptides which (i) are abundantly present in perivascular nerves that resist chemical sympathectomy, (ii) can be released by depolarization and which (iii) can modulate contractile responses to exogenous stimuli (see Wharton & Gulbenkian, 1987; Kawasaki *et al.*, 1988). This however remains to be established.

Unlike mesenteric preparations, renal resistance arteries failed to relax in response to isoprenaline or dopamine. They relaxed, albeit to a lesser extent, in response to NaF and forskolin. Dibutyryl-cyclic AMP, on the other hand, affected mesenteric and renal resistance arteries similarly. These indirect pharmacological observations suggest that in renal resistance arteries, β -adrenoceptors and dopamine binding sites are absent or not coupled to adenylate cyclase, which in turn is present to a lesser extent than in mesenteric resistance arterial smooth muscle.

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