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The action of dopamine and vascular dopamine (DA_1) receptor agonists on human isolated subcutaneous and omental small arteries

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1 Human small arteries were obtained from surgical specimens and studied *in vitro* by use of a myograph technique. Following induction of tone with a potassium depolarizing solution, dopamine in the presence of β-adrenoceptor and catecholamine uptake blockade relaxed isolated omental and subcutaneous arteries. Preincubation of tissues with phentolamine increased the maximum relaxation in response to dopamine.

2 The selective vascular dopamine receptor agonists, fenoldopam and SKF 38393 also relaxed isolated subcutaneous and omental arteries in a concentration-dependent manner. The order of potency for agonists was dopamine > fenoldopam > SKF 38393.

3 Dopamine-induced relaxation was competitively antagonized by SCH 23390, (**R**)- and (**S**)-sulpiride, and fenoldopam induced relaxation by SCH 23390 and (+)- but not (−)-butaclamol.

4 These results indicate the presence of vascular dopamine receptors (DA_1 subtype) on human isolated resistance arteries from omental and subcutaneous sites.

Introduction

Considerable evidence exists in many species to suggest the existence of vascular dopamine (DA) receptors in mediating vasodilatation (Goldberg, 1972; 1984). These receptors have been classified by Goldberg & Kohli (1979) as DA_1 subtype to differentiate them from the peripheral dopamine receptors present presynaptically on sympathetic nerves (DA_2 receptors).

DA_1 receptors have been demonstrated *in vitro* in a variety of preparations in several species (Brodde, 1982), including man (Ueda *et al.*, 1982; Toda, 1983; Forster *et al.*, 1983). However, these *in vitro* studies have generally been conducted using arteries of a size unlikely to contribute substantially to peripheral resistance (Mulvany, 1987). Mulvany & Halpern (1977) recently developed a technique which allows small arteries with an internal diameter less than 200 μm to be studied *in vitro*. Arteries of this diameter make an important contribution to peripheral resistance (Mulvany, 1987; Bohlen *et al.*, 1987). Consequently, we have used this technique to study the effect of dopamine and some selective DA_1 receptor agonists on human small isolated arteries. Some of this work has previously been presented to the British Pharmacological Society (Hughes & Sever, 1988).

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Methods

Arteries were obtained from tissue removed at surgery from a total of 31 patients (14 male, age range 25–80 years). Tissue was collected in cold physiological saline (PSS) of composition (mM): NaCl 118, KCl 4.7, $MgCl_2$ 1.2, $NaHCO_3$ 21, glucose 20, NaH_2PO_4 1, $CaCl_2$ 2.5, Na_2EDTA 0.002. Arteries (approximate external diameter 100–200 μm) were dissected free from surrounding tissue and mounted on two 40 μm wires in a myograph to allow measurement of isometric tension (Mulvany & Halpern, 1977). The myograph chamber contained 10 ml PSS aerated with 95% O_2:5% CO_2 maintained at 37°C. Following equilibration for 30 min the vessels were set to a resting internal circumference Lo corresponding to 0.9 L100, where L100 equals the internal circumference producing a wall tension equivalent to that produced by a distending

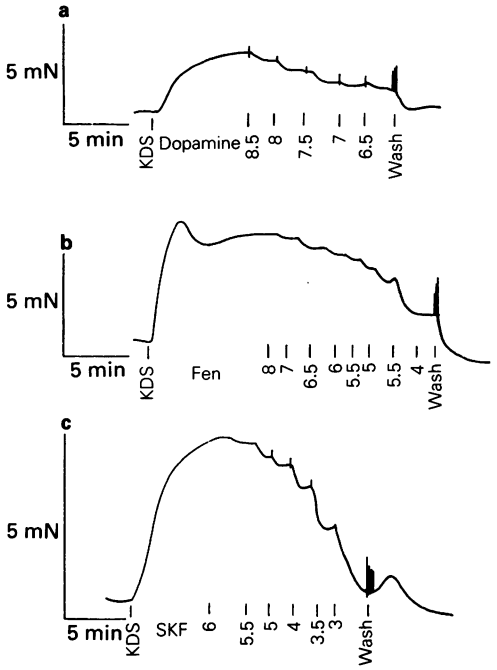

Figure 1 Representative traces showing the effect of dopamine and dopamine receptor agonists on isolated human arterioles: (a) omental arteriole internal diameter = 233 μm; (b) omental arteriole internal diameter = 485 μm; (c) omental arteriole internal diameter = 298 μm. Potassium depolarizing solution (KDS), dopamine, fenoldopam (Fen) or SKF 38393 (SKF) were added at the points shown, concentrations of drug are shown as $-\log$ [M].

pressure of 100 mmHg calculated from the Laplace relationship as described by Mulvany & Halpern (1977). Under these conditions vessels generated contractile responses to potassium-induced depolarization that were near to maximal (unpublished data).

Following a further 30 min equilibration, vessels were exposed to potassium depolarizing solution (KDS) composed of PSS in which the NaCl was replaced by an equimolar quantity of KCl (118 mM). Arteries not generating a tension equivalent to 90 mmHg (calculated by Laplace's relationship) were not used for further studies. Only 2 out of 60 vessels studied failed to fulfil this criterion. Following washout and recovery, the vessels were exposed to PSS containing noradrenaline (10^{-5} M). The functional integrity of the endothelium was assessed by the addition of acetylcholine (10^{-6} M) once stable tone had been induced by noradrenaline; relaxation was taken as indicative of release of endothelium-derived relaxing factor and the presence of a functional endothelium (Furchgott, 1983). In some vessels the endothelium was disrupted by passing a third 40 μm wire through the lumen of the vessel; the effectiveness of this procedure was confirmed by the abolition of relaxation in response to acetylcholine.

Concentration-response curves to dopamine, fenoldopam and SKF 38393 were generated by cumulative addition of agonist. Stable tone was induced by KDS and responses were calculated as % relaxation of KDS-induced tone. Propranolol (4×10^{-6} M), cocaine (10^{-5} M) and 17β-oestradiol (10^{-5} M) were present in studies where dopamine was the agonist to block β-adrenoceptors and catecholamine uptake processes respectively. Phentolamine (10^{-5} M) was also included in some studies with dopamine to block any possible α-adrenoceptor agonist action of this agent.

Concentration-response data obtained from individual arteries were fitted to a logistic function by use of a computer programme (Barlow, 1983) and values for EC_{50}, namely the concentration of agonist producing 50% of the maximum response to the same agonist, and maximum responses derived. pA_2 values were similarly calculated from data derived from individual vessels; after contraction by KDS a concentration-response curve to an agonist was generated in the absence of an antagonist. Following washout, the tissue was equilibrated with the appropriate concentration of antagonist for 20 min, contracted by KDS containing the antagonist at the appropriate concentration and the agonist concentration-response curve was repeated. The tissue was then washed and the same sequence of contraction and agonist concentration was used for a higher concentration of antagonist. Concentration-ratios of EC_{50} values in the presence and absence of antagonist were calculated and pA_2 values obtained by the method of Arunlakshana & Schild (1959). Values for EC_{50} are geometric means (95% confidence limits) and maximum responses are expressed as mean $\pm$ s.e.mean. pA_2 values and slope of the regression line are presented as means $\pm$ s.e.mean; deviation of the slope of the regression line from unity was tested by analysis of variance; $P < 0.05$ was taken as indicating statistical significance. Concentration-response curves have been drawn by the horizontal averaging method advocated by Carpenter (1986).

Drugs

Acetylcholine HCl (Sigma), cocaine HCl (McCarthy's), (+)- and (−)-butaclamol HCl (Research Biochemicals Inc.), dopamine HCl (Sigma), fenoldopam methanesulphonate (a gift from SK&F Ltd.), noradrenaline bitartrate (Sigma), 17β-oestradiol (Sigma), phentolamine mesylate (Ciba Geigy),

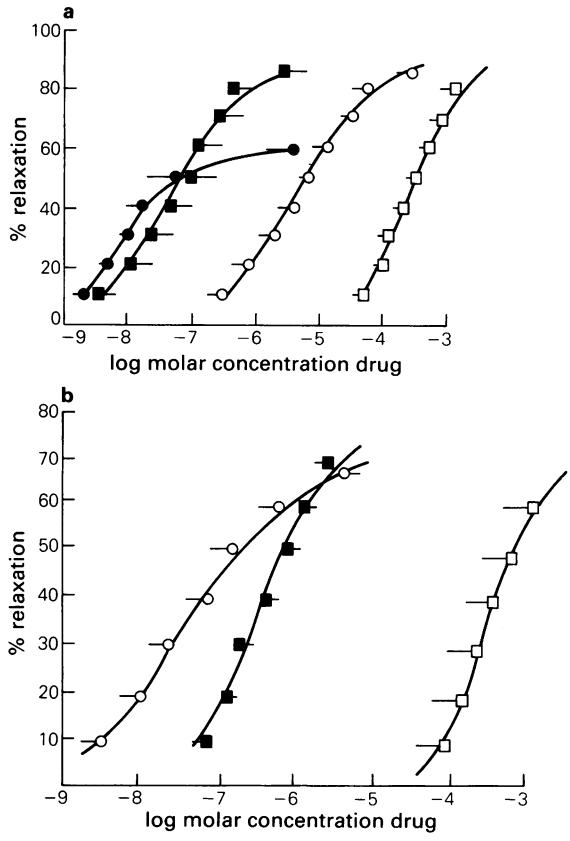

Figure 2 Concentration-response curves for dopamine and DA_1 receptor agonists: (a) in isolated omental arterioles, (●) dopamine ($n = 5$); (■) dopamine + phentolamine 10^{-5} M ($n = 15$); (○) fenoldopam ($n = 17$) and (□) SKF 38393 ($n = 5$). (b) In isolated subcutaneous arterioles, (○) dopamine + phentolamine 10^{-5} M ($n = 7$); (■) fenoldopam ($n = 4$); (□) SKF 38393 ($n = 3$). Points represent mean percentage relaxation of KDS-induced tone; s.e.means are indicated by horizontal bars.

(±)-propranolol HCl (Sigma), SCH 23390 ((R)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5,-tetrahydro-1H-3-benzazepine maleate, a gift from Schering Corp.), (R)- and (S)-sulpiride (gifts from Ravizza SpA), SKF 38393 HCl (1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol HCl, Research Biochemicals Inc.). (+)- and (−)-butaclamol, SCH 23390, and (R)- and (S)-sulpiride were made up freshly as 10^{-3} M stock solutions in methanol and 17β-oestradiol was made up as a 10^{-2} M stock solution in polyethylene glycol; these were then diluted appropriately in distilled water. Other drugs were made up in distilled water.

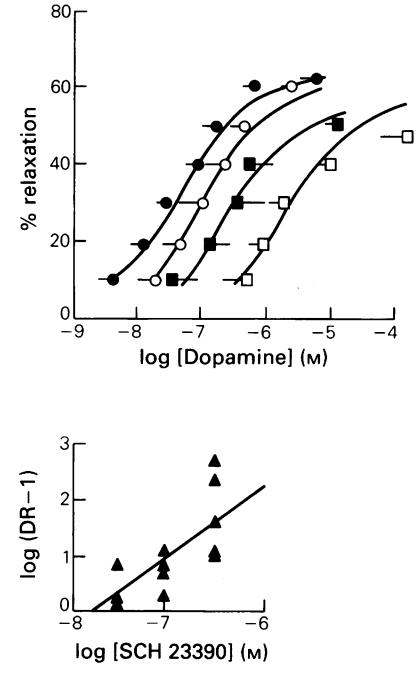

Figure 3 The effect of SCH 23390 on dopamine-induced relaxation of isolated subcutaneous arterioles: (●) dopamine alone ($n = 6$); (○) SCH 23390 3×10^{-8} M ($n = 3$); (■) SCH 23390 10^{-7} M ($n = 4$); (□) SCH 23390 3×10^{-7} M ($n = 5$); Points represent mean percentage relaxation of KDS-induced tone, s.e.means are indicated by horizontal bars. Schild analysis of the data is shown as an inset.

Results

Addition of dopamine usually had no effect on the tone of resting arteries, although occasionally a small contraction was observed in some vessels at concentrations greater than 10^{-6} M. Following contraction with KDS, addition of dopamine (10^{-9}–10^{-5} M) caused concentration-dependent relaxation of both omental and subcutaneous arteries (Figure 1, Figure 2). Preincubation with phentolamine (10^{-5} M) increased the maximum response to dopamine in omental arteries from 58 ± 16% ($n = 4$) to 86 ± 5% ($n = 15$) without causing much alteration in the EC_{50} for dopamine-induced relaxation, 2.19 (0.56–8.5) × 10^{-8} M in the absence of phentolamine and 3.8 (1.1–13.7) × 10^{-8} M in the presence of phentolamine (Figure 2a). No artery failed to relax in response to dopamine. Relaxation in response to dopamine was not dependent on a functional endothelium: EC_{50} and maximum response to dopamine was 3.8 (0.1–15) × 10^{-8} M and 74 ± 7% ($n = 5$) in arteries relaxing in response to acetylcholine compared with 3.2

(0.9–10.8) $\times 10^{-8}$ M and 67 ± 12% ($n = 5$) in those relaxing less than 10% to acetylcholine.

The selective DA_1 receptor agonists, fenoldopam and SKF 38393, both relaxed isolated omental and subcutaneous arteries in a concentration-dependent manner as can be seen in Figure 2a and b.

Responses to dopamine in the presence of phentolamine (10^{-5} M) were competitively antagonized by SCH 23390 (3×10^{-8}–3×10^{-7} M) in subcutaneous arteries. Schild analysis of these data gave a pA_2 value of 7.8 ± 0.2 with a slope of 1.3 ± 0.5 which was not significantly different from unity (Figure 3). (R) and (S)-sulpiride also antagonized dopamine-induced relaxation in omental arteries in the presence of phentolamine (10^{-5} M) ($pA_2 = 4.9 \pm 0.1$, slope = 1.3 ± 0.3 (NS), and $pA_2 = 4.7 \pm 0.1$, slope = 1.5 ± 0.4 (NS) respectively).

Fenoldopam-induced relaxation of isolated omental arteries was also competitively antagonized by SCH 23390 (3×10^{-8}–3×10^{-7} M) ($pA_2 = 7.6 \pm 0.1$, slope = 1.1 ± 0.2 (NS) (Figure 4) and by (+)-butaclamol (10^{-7}–10^{-6} M) ($pA_2 = 7.7 \pm 0.1$, slope = 1.2 ± 0.4 (NS)) (Figure 5) but not by (−)-butaclamol (10^{-6} M); the concentration-ratio for fenoldopam in the absence and the presence of (−)-butaclamol was 1.0 ± 0.1 ($n = 4$).

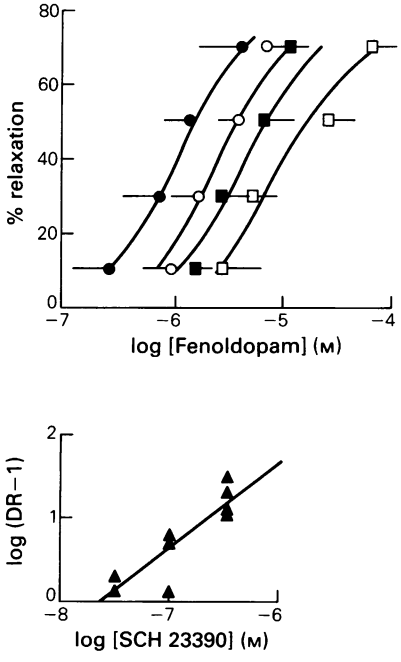

Figure 4 The effect of SCH 23390 on fenoldopam-induced relaxation in omental arterioles: (●) fenoldopam alone ($n = 5$); (○) SCH 23390 3×10^{-8} M ($n = 3$); (■) SCH 23390 10^{-7} M ($n = 3$); (□) SCH 23390 (3×10^{-7} M ($n = 4$). Points represent mean percentage relaxation of KDS-induced tone, s.e.means are indicated by horizontal lines. Schild analysis of the data is shown as an inset.

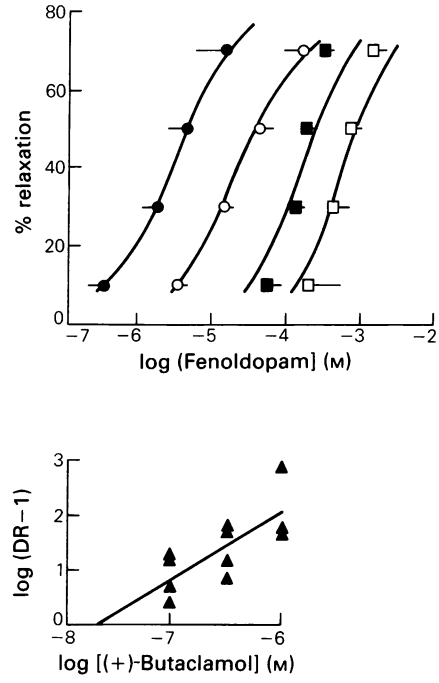

Figure 5 The effect of (+)-butaclamol on fenoldopam-induced relaxation in omental arterioles: (●) fenoldopam alone ($n = 6$); (○) (+)-butaclamol 10^{-7} M ($n = 4$); (■) (+)-butaclamol 3×10^{-7} M ($n = 4$); (□) (+)-butaclamol 10^{-6} M ($n = 4$). Points represent mean percentage relaxation of KDS-induced tone, s.e.means are indicated by horizontal lines. Schild analysis of the data is shown as an inset.

Analysis of the relationship between normalised internal diameter and both maximum response and EC_{50} for dopamine (in the presence of phentolamine) did not indicate any significant correlation between these variables, in contrast to results obtained with other agonists (Aalkjaer *et al.*, 1987; Nielsen *et al.*, 1987). Neither was there any correlation between the age or sex of the patient from whom tissue was obtained and the maximum response to or potency of dopamine or fenoldopam in these studies.

Discussion

These results indicate that dopamine and the selective dopamine receptor agonists, fenoldopam and

SKF 38393, relax human isolated omental and subcutaneous arteries. The relaxant effect of dopamine and fenoldopam observed in this study was competitively antagonized by the selective DA_1 receptor antagonists SCH 23390, (+)- but not (−)-butaclamol and weakly by (R)- and (S)-sulpiride. These findings suggest that the relaxant effect of dopamine and the selective dopamine agonists in this preparation are mediated by DA_1 receptors.

Comparison of these data with other studies of DA_1 receptors in man and other species show some differences. The finding that dopamine is a more potent agonist than SKF 38393 is similar to the report of Forster and colleagues (1983) in their study of human basilar arteries. Fenoldopam was not studied by these workers but we have found it to be a full agonist in human isolated cerebral arteries (unpublished data). In contrast, (Hilditch & Drew, 1981; 1985b) found both fenoldopam and SKF 38393 to be inactive or weak partial agonists in isolated splenic artery of the rabbit, whereas Ohlstein and others (1984) found fenoldopam to be a full agonist in this preparation. Brodde (1982) found SKF 38393 to be a partial agonist but more potent than dopamine in rabbit isolated mesenteric artery and Edwards (1986) found fenoldopam and dopamine to have similar potencies in rabbit renal arterioles *in vitro*. Using the perfused rat kidney *in situ*, Schmidt's group (Schmidt, *et al.*, 1982; 1985) have reported an agonist potency series of fenoldopam > SKF 38393 ≫ dopamine and in the cat Edvinsson and coworkers (1985) also reported that SKF 38393 was more potent than dopamine as a relaxant of cerebral arterioles *in situ*.

In the case of the antagonist studies, there are also some anomalous results with reference to the literature. In our study sulpiride was a weak antagonist of the DA_1 receptor and showed little enantiomeric selectivity. This finding contrasts with the enantiomeric selectivity of sulpiride ((S)- > (R)-) at DA_2 receptors and is similar to a previous report on this drug as a DA_1 antagonist (Schmidt *et al.*, 1983). Similarly, most studies but not all (see Hilditch & Drew 1985b; Brodde, 1982) find racemic sulpiride to be a weak DA_1 receptor antagonist. The pA_2 value for (+)-butaclamol obtained in these studies (7.7) is around ten fold higher than reported by Brodde (1982) in rabbit isolated mesenteric artery but around ten fold lower than that obtained by Schmidt & Imbs (1980) in the *in situ* perfused rat kidney and by Drew in isolated rabbit splenic artery (cited in Brodde, 1982). The pA_2 value calculated for SCH 23390 in these studies is also lower than that reported in most other studies; $pA_2 = 10.65$ in rabbit splenic artery (Hilditch & Drew 1985a), $pA_2 = 9.7$ in rat perfused kidney (Schmidt *et al.*, 1987), $K_i = 10^{-9}$ M in cultured smooth muscle cells obtained from rat mesenteric artery (Balmforth *et al.*, 1988), IC_{50} between 10^{-9} M and 10^{-8} M in cat cerebral arteries *in situ* (Edvinsson *et al.*, 1985). The reasons for these discrepancies are unclear. Inter-species variation cannot be excluded. It is also possible that some differences relate to the contractile agonist used or the use of phenoxybenzamine, an irreversible α-adrenoceptor antagonist with weak dopamine receptor antagonist properties (Walton *et al.*, 1978) in many of these studies. In this context, Berkowitz & Ohlstein (1984) have reported that the K_B value for SKF 83566, a DA_1 receptor antagonist, structurally related to SCH 23390 differs by almost 1000 fold when calculated using dopamine as an agonist in splenic arterial rings treated with phenoxybenzamine and compared with the value obtained with fenoldopam in untreated rings. Alternatively, the possibility of the existence of different subtypes or affinity states of the DA_1 receptor as previously suggested by Hilditch & Drew (1987), and by other workers on the basis of ligand binding studies of the central D_1 receptor (Andersen & Braestrup 1986; Bzowej *et al.*, 1988) cannot be ruled out. Further work is necessary to clarify these issues.

No evidence was found in these studies to indicate an involvement of the endothelium in the response to DA_1 agonists. However, since endothelium-dependent relaxation is usually difficult to demonstrate using potassium-induced tone (Furchgott 1983) this does not necessarily exclude any role for the endothelium in mediating responses to dopamine. Nevertheless, it seems likely that the effects observed in this study represent action of these agonists solely on DA_1 receptors located on vascular smooth muscle.

These studies were conducted on isolated arteries small enough to contribute significantly to peripheral resistance (Mulvany, 1987). In contrast to previous studies in larger arteries (Ueda *et al.*, 1982; Forster *et al.*, 1983), dopamine-induced relaxation was seen in the absence of α-adrenoceptor blockade and relaxant responses to dopamine and dopamine agonists were consistently found in all the vessels studied. Furthermore, dopamine was found to be more potent in these studies of resistance arteries than has been found in previous work on larger arteries (Ueda *et al.*, 1982; Forster *et al.*, 1983). It is interesting that Edwards (1985) also found that dopamine was a considerably more potent relaxant of renal afferent and efferent arterioles than interlobular arteries in the rabbit. These findings may therefore suggest that the concentration of dopamine necessary *in vivo* to produce vasodilatation of resistance arteries may be less than has been inferred from previous studies of large arteries and while the concentrations of dopamine found to relax isolated resistance arteries in this study considerably exceed

plasma levels of free dopamine, the levels of dopamine occurring in the vicinity of dopaminergic nerves such as those identified by Bell and colleagues in the dog kidney (Bell *et al.*, 1978) and paw pad (Bell & Lang, 1979) could well be sufficient to activate DA_1 receptors in the vasculature.

At present the physiological role of DA_1 receptors in the vasculature is not understood. However, in view of the marked vasodilator and hypotensive effects of DA_1 agonists *in vivo* (Stote *et al.*, 1983; Hughes *et al.*, 1987) an important role for DA_1 receptors in cardiovascular physiology cannot be excluded.

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