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Vasomotor responses of cerebral arterioles *in situ* to putative dopamine receptor agonists

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1 The vasomotor responses of individual cerebral pial arterioles on the convexity of the cerebral cortex to subarachnoid perivascular micro-injections of dopamine and the putative dopamine receptor agonists, apomorphine, SKF 38393 and LY 141865, have been examined in 38 anaesthetized cats.

2 The perivascular microapplication of dopamine (10^{-9}–10^{-3} M) effected dose-dependent reductions in pial arteriolar calibre, with the maximum reductions in calibre (22 ± 2% from preinjection levels: mean ± s.e.) being observed at 10^{-3} M. The cerebrovascular constriction produced by dopamine (10^{-5} M) could be significantly attenuated by the concomitant perivascular administration of phentolamine (10^{-6} M) or methysergide (10^{-6} M).

3 The perivascular microapplication of apomorphine (10^{-8}–10^{-4} M) effected dose-dependent increases in arteriolar calibre, with the maximum increase (31 ± 6%) being observed with apomorphine (10^{-5} M).

4 The perivascular administration of the putative dopamine D_1-receptor agonist, SKF 38393 (10^{-9}–10^{-4} M) increased arteriolar calibre, with the maximum response (24 ± 3%) being observed with injection of 10^{-7} M. The putative dopamine D_2-receptor agonist, LY 141865, also increased cerebral arteriolar calibre, but only at high concentrations (maximum calibre increase 25 ± 6.1 with 10^{-4} M).

5 The cerebrovascular dilatations elicited by apomorphine and by SKF 38393 were markedly attenuated by the concomitant perivascular microapplication of the putative dopamine D_1-receptor antagonist, SCH 23390 (10^{-8} M). The perivascular administration of SCH 23390 (10^{-9}–10^{-5} M) *per se* did not alter arteriolar calibre nor the arteriolar dilatation provoked by microinjections of acidic cerebrospinal fluid.

6 These results point to the presence on cat cerebral arterioles of dopamine receptors (probably of D_1 subtype) mediating dilatation.

Introduction

The existence of dopamine receptors mediating relaxation has been demonstrated on cerebrovascular smooth muscle from various species (Toda, 1976; Edvinsson *et al.*, 1978; Oudart *et al.*, 1981; Forster *et al.*, 1983). Dopamine-mediated relaxation of cerebral arteries has only been demonstrable after the preconstriction of the cerebral arterial segments with prostaglandins or potassium) and the prior blockade of contractile receptors with high concentrations of phenoxybenzamine (Toda, 1976; Edvinsson *et al.*, 1978; Oudart *et al.*, 1981; Forster *et al.*, 1983). However, these previous investigations have been conducted *in vitro* using segments of major arteries of the circle of Willis, whereas, *in vivo*, it is the small arterioles and precapillary sphincters that determine the major fraction of vascular resistance (Folkow & Neil, 1971). In contrast, little information exists concerning the direct cerebrovascular effects of dopamine receptor agonists upon cerebral vessels *in vivo*, or in the absence of prior pharmacological manipulation. In the present paper we describe the vasomotor responses *in situ* of individual pial arterioles on the cortical surface to subarachnoid perivascular microapplication of dopamine and dopamine receptor agonists, and our attempts to characterize the dopamine receptors involved. The

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characterization of the dopamine receptor subtype which mediates cerebrovascular dilatation has been made possible by the recent development of SCH 23390, a putative selective antagonist of dopamine D_1-receptors (Cross *et al.*, 1983; Iorio *et al.*, 1983; O'Boyle & Waddington, 1984).

Methods

Preparation of animals

The experiments were performed on 38 cats, each weighing between 2 and 4.5 kg. The animals were anaesthetized initially with a mixture of alphaxolone (6.75 mg kg^{-1}) and alphadolone (2.25 mg kg^{-1}) administered intravenously. The animals were intubated and connected to an intermittent positive pressure pump delivering oxygen in open circuit. The right femoral artery and vein were cannulated to permit, respectively, the continuous measurement of arterial blood pressure and the administration of fluid or anaesthetic agents. Anaesthesia was maintained during the subsequent course of the experiments with α-chloralose (60 mg kg^{-1}, i.v.). Additional α-chloralose was administered, when necessary, to prevent the return of the corneal reflex. The animals were maintained normocapnic (arterial CO_2 tension, P_{CO_2}, close to 30 mmHg) throughout the course of the experiments. The end-tidal concentration of CO_2 was monitored continuously by means of an infra-red analyser, and samples of arterial blood were taken intermittently during the experiment for the estimation of P_{CO_2}, pH and arterial O_2 tension. In each cat, mean arterial blood pressure was greater than 90 mmHg. Rectal temperature was maintained at 38°C by means of a heating blanket.

The animal was placed in a stereotactic frame. A longitudinal incision was made in the scalp which was then retracted and ligated on to a metal ring in such a manner that it formed an intact pool (depth approximately 1.5 cm) over the calvarium. The left temporalis muscle was retracted. A craniotomy, measuring approximately 2.5 cm × 1.5 cm, was made over the left parietal region with a dental drill which was cooled with saline. The exposed dura was bathed by warmed mineral oil, maintained at 38°C. Thereafter, surgical manipulations were performed with the aid of a Bausch and Lomb stereomicroscope with a zoom lens (magnification range × 10 to × 70), the field being illuminated by Schott fibre optic systems. The dura was removed carefully, and any bleeding from the cut dural edges was sealed by use of bipolar diathermy.

Measurement of vascular calibre

Vascular calibre was measured by the method of Baez (1966) as described by us in detail previously (McCulloch & Edvinsson, 1980a). Individual pial vessels on the convexity of the brain were viewed through the microscope at a magnification of either × 40 or × 70. The image was passed through a Vickers image-splitting eyepiece to a closed circuit television camera and displayed on a television monitor. Vascular diameter was measured from the degree of shear applied to the image-splitter, which had been calibrated against wire and thread of known diameter.

Administration of drugs

The agents being examined (with the exception of SCH 23390) were dissolved, immediately before use, in artificial cerebrospinal fluid, the composition of which was (mM) Na^+ 145, K^+ 3, Ca^{2+} 2.5, HCO^-_3 11 and Cl^- 142. The pH of the mock CSF was then adjusted to 7.18 with aeration with CO_2. The solutions being examined were administered by means of glass micropipettes (tip diameter 8–10 μm) which were filled with the fluid under mineral oil. The micropipettes were positioned close to a superficial pial arteriole and, by use of a micromanipulator, were inserted through the arachnoid into the perivascular space surrounding the vessel. A small volume of artificial CSF (approximately 5 μl) was injected into the perivascular space over 15 s, and any resulting alterations in arteriolar calibre were monitored for periods of up to 3 min. Injections of drugs were made at a particular site on only one occasion.

The maximum alterations in arteriolar calibre, expressed as percentage changes from the diameter of the vessel before the injection, following the injection of mock CSF containing the agent being examined, were compared with the maximum alterations in arteriolar calibre following the microapplication of artificial CSF by Student's *t* test with the use of Bonferroni's inequality because of the multiple comparisons involved (Wallenstein *et al.*, 1980). Data are presented as mean values ± s.e.mean, derived from the responses of individual arterioles. Each drug solution was tested in at least two different cats. Drug-containing solutions were administered on one occasion only at each site of injection. Analysis of variance (factors: cats, individual arteriolar responses) for each drug solution demonstrated that the variance between arterioles within each cat is, almost invariably, greater than the variance between cats. Furthermore, no significant inter-animal difference in the arteriolar response to any concentration of any drug could be demonstrated.

Each day, SCH 23390 was dissolved initially in ethanol (5%), acetic acid (25%) solution to form a stock solution of 10^{-2} M. Serial dilutions in CSF were then performed to yield the desired injectate concentration. The ethanol/acetic acid solution was diluted in a similar manner to yield the appropriate vehicle for

comparison. Acidic artificial CSF (pH 6.8) was prepared by altering the HCO^-_3 (5 mM) and Cl^- (148 mM) concentrations of the standard artificial CSF solution.

The agents that were investigated, and their sources of supply, were as follows: apomorphine hydrochloride, atropine, propranolol hydrochloride (all Sigma), phentolamine (Ciba), methysergide bimaleate (Sandoz),2,3,4,5-tetrahydro-7-8-dihydroxy-1-phenyl-1H-3-benzazepine (SKF 38393, Smith, Kline and French), R-(+)-8-chloro 2,3,4,5,-tetrahydro-3 methyl-5-phenyl 1-H-3 benzazepine-7-ol (SCH 23390, Schering, U.S.A.) and *trans*-(+)-4,4a,5,6,7,8,8a,9-octa-hydro-5-propyl-2H-pyrazolo [3,4-g] quinoline hydrochloride (LY 141865, Lilly).

Results

Dopamine

The injection of 5 μl of artificial CSF into the perivascular space surrounding individual pial arterioles (calibre range: 43–230 μm) had minimal effect upon pial arteriolar diameter relative to the calibre of the vessel before the injection (Table 1). The perivascular microinjection of artificial CSF containing dopamine resulted in dose-dependent constriction of the pial arterioles (Figure 1). The changes in calibre following the administration of CSF containing dopamine differed significantly from those observed with artificial CSF when the concentration of dopamine in the injectate exceeded 10^{-7} M (Table 1). No significant correlation could be demonstrated, with any concentration of dopamine, between the magnitude of the response of an individual arteriole and the calibre of the arterioles before the injection of dopamine.

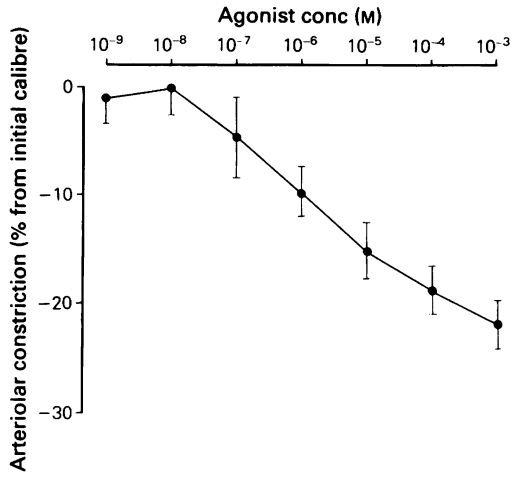

Figure 1 Alterations in pial arteriolar calibre following perivascular microapplication of dopamine (●). Significant reductions ($P < 0.05$) in calibre are observed with dopamine concentrations in excess of 10^{-7} M. Data are presented as mean (number of arterioles tested at each concentration, $n = 6–12$) with s.e.mean shown by vertical line. Each solution was tested in 2–6 cats.

The perivascular administration of phentolamine (10^{-6} M) was without significant effect on the 10 arterioles (calibre range: 62–212 μm) in which it was examined (mean response ± s.e.mean − 1.5 ± 3.6%). The addition of phentolamine (10^{-6} M) to the injectate significantly reduced ($P < 0.01$) the constriction of the pial arterioles associated with dopamine (10^{-5} M) administration (Figure 2). The perivascular microinjection of methysergide (10^{-6} M) did not alter significantly the calibre of the 10 arterioles (calibre range:

Table 1 Alterations in pial arteriolar calibre following subarachnoid perivascular microapplication of putative dopamine receptor agonists and of dopamine

Conc (M)	n	*Dopamine* Δ%	n	*Apomorphine* Δ%	n	*SKF 38393* Δ%	n	*LY 141865* Δ%
0	13	1.2 ± 1.8	12	1.1 ± 2.3	14	0.0 ± 2.1	13	0.2 ± 2.3
10^{-9}	6	− 1.0 ± 2.4	—	—	10	2.1 ± 2.9	—	—
10^{-8}	6	− 0.2 ± 2.4	7	2.5 ± 4.0	13	14.8 ± 3.9*	5	3.0 ± 2.5
10^{-7}	11	− 4.6 ± 3.6	11	8.3 ± 1.8	9	23.8 ± 3.0**	6	5.6 ± 1.6
10^{-6}	9	− 9.8 ± 2.2**	15	23.1 ± 4.1**	15	20.0 ± 5.8**	8	11.6 ± 5.7
10^{-5}	11	− 15.3 ± 2.7**	9	30.6 ± 5.8**	12	8.8 ± 3.0	8	18.1 ± 3.7**
10^{-4}	12	− 18.7 ± 2.2**	7	3.3 ± 3.8	9	4.1 ± 2.3	7	24.6 ± 6.1**
10^{-3}	9	− 21.9 ± 2.2**	—	—	—	—	—	—

Data are presented as mean response ± s.e.mean. n = number of arterioles examined. Each solution was tested in 2–6 cats.

Δ% Alteration in arteriolar calibre (expressed as percentage of calibre before injection). Negative values represent vasoconstriction; positive values represent vasodilatation.

* $P < 0.05$; ** $P < 0.01$ (derived from t statistic with use of Bonferroni's inequality).

58–175 μm) in which it was examined (mean calibre alteration, 0.5 ± 2.7%). The addition of methysergide (10^{-6} M) to the injectate significantly attenuated ($P < 0.01$) the constriction of pial arterioles following microapplication of dopamine (10^{-5} M) (Figure 2). Despite varying the concentrations of dopamine, phentolamine and methysergide in the injectate, we were unable to demonstrate consistent dilatation of pial arterioles with any concentration of dopamine.

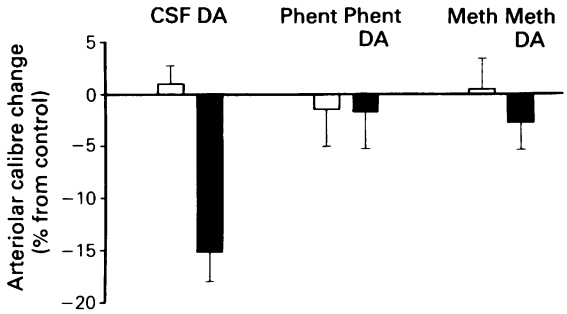

Figure 2 Alterations in pial arteriolar calibre following perivascular microapplication of cerebrospinal fluid (CSF) and dopamine (DA, 10^{-5} M). The vasoconstrictions elicited by dopamine are attenuated significantly ($P < 0.05$) by the concomitant perivascular microapplication of either phentolamine (Phent, 10^{-5} M) or methysergide (Meth, 10^{-6} M). Data are presented as mean (number of arterioles tested at each concentration, $n = 10$ or 11) with s.e.mean shown by vertical line. Each solution was tested in 2–3 cats.

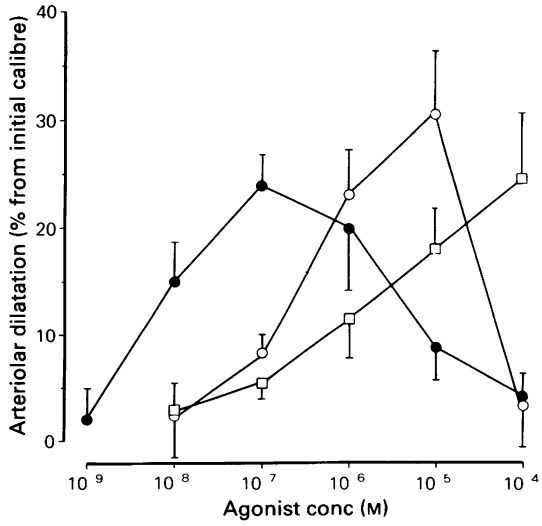

Figure 3 Alterations in arteriolar calibre following perivascular microapplication of apomorphine (○), SKF 38393 (●) and LY 141865 (□). Data are presented as mean (number of arterioles tested at each concentration, $n = 5–15$) with s.e. mean shown by vertical line (see Table 1 for details). Each solution was tested in 2–5 cats.

Dopamine receptor agonists

The perivascular microapplication of apomorphine, SKF 38393 and LY141865 effected a significant, dose-dependent dilatation of pial arterioles (Figure 3, Table 1). The magnitudes of the maximum responses provoked by these putative dopamine receptor agonists were not significantly different from each other. The rank order of potency (in respect of threshold and approximate EC_{50} values) was SKF 38393 > apomorphine > LY 141865 (Figure 3). At no concentration, with any of the three putative dopamine receptor agonists, could a significant correlation be demonstrated between the magnitude of the arteriolar response and the preinjection calibre of the vessel.

Dopamine receptor antagonists

Microinjection of SCH 23390 (10^{-9}–10^{-5} M) around individual pial arterioles did not significantly alter arteriolar diameter (Figure 4). The concomitant administration of SCH 23390 did reduce significantly the arteriolar dilatation elicited either by apomorphine (10^{-6} M) or by SKF 38393 (10^{-7} M). With both agonists, the IC_{50} value for SCH 23390 was between 10^{-9} and 10^{-8} M (Figure 5). SCH 23390, even at very high concentrations (10^{-7} M), did not modify the pial arteriolar dilatation elicited by microinjections of acidic CSF (pH 6.8) (calibre increase provoked by acidic CSF alone: 32.9 ± 4.2%. $n = 9$, compared to 31.1 ± 4.3%, $n = 8$ with acidic CSF with SCH 23390, 10^{-7} M). Moreover, the pial arteriolar dilatation provoked by apomorphine, 10^{-6} M (calibre increase

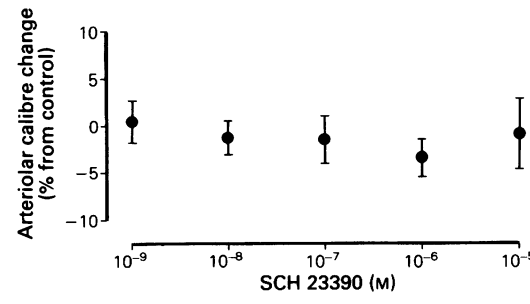

Figure 4 Alterations in arteriolar calibre following perivascular microapplication of SCH 23390. There are no significant alterations in arteriolar calibre. Data are presented as mean (number of arterioles tested at each concentration, $n = 6–8$) with s.e.mean shown by vertical lines. Each solution was tested in 2–3 cats.

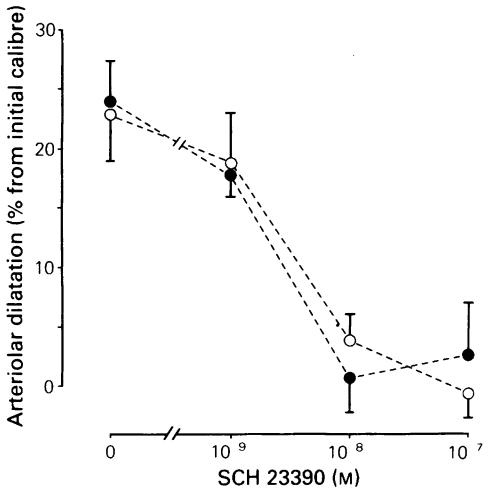

Figure 5 Attenuation by SCH 23390 of the pial arteriolar dilatation provoked by apomorphine, 10^{-6}M(○) or SKF 38393 10^{-7}M (●). The response to both agonists is reduced significantly ($P<0.05$) by the presence of SCH 23390 (10^{-8}M and 10^{-7}M) in the injectate. Data are presented as mean (number of arterioles tested at each concentration, $n = 6-15$) with s.e.mean shown by vertical line. Each solution was tested in 2–3 cats.

$23.1 \pm 4.1\%$, $n = 15$) was not influenced by the presence of propranolol, 10^{-6}M (calibre increase $24.2 \pm 4.8\%$, $n = 10$) or atropine (calibre increase $21.8 \pm 5.3\%$, $n = 10$). Neither propranolol, 10^{-6}M, nor atropine, 10^{-5}M, when administered alone, altered pial arteriolar calibre (mean alterations, $-0.3 \pm 1.5\%$, $n = 10$, and $0.7 \pm 2.2\%$, $n = 10$, respectively).

Discussion

The present data, with synthetic putative dopamine receptor agonists, point to the presence on cerebral pial arterioles of specific dopamine receptors whose activation, without any prior pharmacological manipulation, results in pronounced vasodilatation. These data are in excellent accord with the more extensive *in vitro* studies on major cerebral arteries (such as the middle cerebral artery or basilar artery) in which dopamine-mediated relaxation could be demonstrated (Toda, 1976; Edvinsson *et al.*, 1978; Oudart *et al.*, 1981; Forster *et al.*, 1983) but, in addition, extend the finding to small precapillary arterioles (the diameter of which determines blood flow), investigated *in situ* in their normal mileu and, crucially, without the pharmacological manipulations required *in vitro*. The necessity of prior treatment with high concentrations of phenoxybenzamine and contraction by prostaglandins or potassium to unmask dopamine receptors on cerebral vessels *in vitro* could suggest that these receptors might be unimportant in the cerebral circulatory changes resulting from the systemic administration of dopamine receptor agonists to the whole animal (McCulloch & Harper, 1977; McCulloch & Edvinsson, 1980b; McCulloch *et al.*, 1982), quite apart from the problems created for detailed receptor characterization (see below). However, the present demonstration of dopamine receptor mechanisms mediating changes in calibre of resistance vessels may suggest that these receptors have physiological as well as pharmacological significance. The direct apposition of dopamine-containing dendritic processes to small arterioles has been demonstrated within the substantia nigra (Felten & Crutcher, 1979). Dopamine constitutes about 50% of the catecholamine content of microvessels isolated from bovine or rat brain (Head *et al.*, 1980), whereas in peripheral blood vessels, where dopamine is considered to be present only as a precursor for noradrenaline, dopamine constitutes only 2–4% of the total catecholamine content (Bell & Gillespie, 1981; Berkowitz, 1983). Thus, there is a body of evidence, albeit circumstantial, suggestive of the presence of dopamine-containing nerve fibres around cerebral blood vessels. Whether endogenous neuronally released dopamine would provoke cerebral vasoconstriction or vasodilatation remains unresolved. Vasodilatation via the specific dopamine receptor would appear to be possible only if vessels in regions which are innervated by dopamine-containing nerve fibres, such as the caudate nucleus, did not possess the vasoconstrictor receptors with which dopamine interacts.

Dopamine receptors associated with the vasculature are not confined to the cerebral circulation, but have a widespread distribution throughout the body (Goldberg *et al.*, 1978). A population of dopamine receptors in peripheral vessels is localized presynaptically on sympathetic nerve terminals, and the activation of these receptors can modify the release of noradrenaline (Goldberg *et al.*, 1978; Steinsland & Hieble, 1978). It is unlikely that prejunctional inhibition of noradrenaline release plays any role in the cerebrovascular vasodilatation observed in the present study, as there is no evidence that the resting tone of pial arterioles in the present conditions has any sympathetic component (see also the lack of efficacy of phentolamine in the present study in altering arteriolar calibre) (Kuschinsky & Wahl, 1975). A second population of dopamine receptors is present in vascular smooth muscle in a number of vascular beds (for example, renal, coronary, femoral, mesenteric and splenic arteries), and after blockade of the contractile

receptor mechanisms (most commonly with phenoxybenzamine) the actions of dopamine and dopamine receptor agonists cause relaxation of these peripheral arteries (Goldberg & Toda, 1975; Goldberg *et al.*, 1978; Hilditch & Drew, 1981; Toda, 1983). The cerebrovascular dilatation mediated via dopamine receptor activation, noted in the present *in situ* study and in previous *in vitro* studies (Toda, 1976; Edvinsson *et al.*, 1978; Oudart *et al.*, 1981; Forster *et al.*, 1983), are comparable, at least in general terms, with these peripheral dopamine receptors mediating vascular smooth muscle relaxation.

Although dopamine receptor agonists have been shown, in the present study, to produce dilatation of pial arterioles without any prior pharmacological manipulation, dopamine itself provoked only pial vasoconstriction mediated, on the basis of its attenuation by phentolamine and methysergide, via α-adrenoceptors and 5-hydroxytryptamine receptors. These data are entirely consistent with our earlier, more detailed characterization of dopamine-induced cerebral vasoconstriction conducted *in vitro* (Edvinsson *et al.*, 1978). In a brief investigation on rat pial arterioles *in situ*, Altura *et al.* (1980) described the almost identical constriction of cerebral vessels in response to dopamine in concentrations similar to those in the present study (e.g., 20% reduction in calibre at approximately 10^{-3} M). However, at low concentrations (10^{-10}–10^{-8} M) dopamine was reported to produce small increases in arteriolar calibre (Altura *et al.*, 1980), whereas no alteration in arteriolar calibre was produced by dopamine microinjections at these concentrations in our study. It should be pointed out, however, that a major methodological difference exists between these two apparently similar cranial window techniques for investigating pial vessels *in situ*. In our approach, agents are administered as microinjections close to an individual vessel to avoid possible disturbances of cerebral metabolic activity and, consequently, indirect alterations in cerebral blood flow, whereas Altura and his associates (1980) administered dopamine as a superfusion over the entire exposed cortex, allowing the access of the amine to both cerebral tissue and to cerebral vessels (for detailed discussion of this problem, see McCulloch & Edvinsson, 1984). As it is well recognized that activation of dopamine receptors in cerebral tissue results in increased cortical glucose utilization (McCulloch *et al.*, 1979) with concomitant cerebrovascular dilatation (McCulloch *et al.*, 1982), it is far from certain that the increases in arteriolar calibre produced by low concentrations of dopamine (Altura *et al.*, 1980) represent a direct effect of the amine on the vessel rather than an indirect change in calibre as the result of an increased cortical metabolism.

There is a multiplicity of schemes (and subschemes) for the classification of dopamine receptor subtypes. Of the many classifications available, the simplest system, based essentially on adenylate cyclase, holds the greatest sway at the present time for the mammalian central nervous system (Kebabian & Calne, 1979; Creese *et al.*, 1983). In this system, D_1-receptors mediate adenylate cyclase stimulation, and there is abundant evidence that SKF 38393 and SCH 23390, are, respectively, selective agonists and antagonists at D_1-receptors (Setler *et al.*, 1978; Stoof & Kebabian, 1981; Cross *et al.*, 1983; Iorio *et al.*, 1983; O'Boyle & Waddington, 1984); in contrast, D_2-receptor activation has either no effect or inhibits adenylate cyclase, and there is evidence that the compound LY 141865 is a selective agonist at this receptor site (Tsuruta *et al.*, 1981; Stoof & Kebabian, 1981; Scatton, 1982). All previous attempts to determine *in vitro* which dopamine receptor subtype mediates cerebrovascular dilatation (Edvinsson *et al.*, 1978; Oudart *et al.*, 1981; Forster *et al.*, 1983) have been complicated by the necessity to pretreat the cerebral arteries with phenoxybenzamine (10^{-5} M, or more) to reveal relaxation with dopamine administration. Phenoxybenzamine is a potent dopamine D_1-receptor antagonist producing half maximal inhibition of dopamine-stimulated adenylate cyclase at a concentration of 3×10^{-6} M (Walton *et al.*, 1978), as well as being a potent irreversible blocker of dopamine D_2 ligand binding sites in striatal membranes (Hamblin & Creese, 1982).

The hierarchy of agonist potency (SKF 39393, apomorphine and LY 141865) in producing cerebrovascular dilatation is indicative of D_1-receptors. However, the most compelling evidence that D_1-receptors are involved results from the use of the novel D_1-receptor antagonist, SCH 23390, which has recently been developed (Cross *et al.*, 1983; Iorio *et al.*, 1983; O'Boyle & Waddington, 1984). The pial arteriolar dilatations provoked by apomorphine or SKF 38393 were attenuated by SCH 23390 at low concentrations, whereas even at high concentrations this agent did not modify the dilatations elicited by acidic CSF. Cerebral vessels appear to be similar to the peripheral vasculature where there is growing evidence that the dopamine receptor located on the vascular smooth muscle is of the D_1 type (see Hilditch *et al.*, 1984). The relative responses of pial arterioles to apomorphine and SKF 38393 (in respect of relative potencies and maximum response, and the shape of the concentration-response curves) are almost identical to those of striatal adenylate cyclase to these two agents (Setler *et al.*, 1978). The view that a population of D_1-receptors exists associated with cerebral vessels receives support from the reported presence of dopamine-sensitive adenylate cyclase in homogenates of cerebral arteries or cerebral microvessels (Baca & Palmer, 1978; Amenta *et al.*, 1984), although there is no evidence linking this generation of cyclic AMP to any functional response such as cerebrovasodilatation. The

precise mechanism underlying the cerebrovascular dilatation noted with the putative D_2 agonist, LY 141865, at very high concentrations, may be unrelated to its actions on dopamine receptors. This compound, at high concentrations, displays agonist activity at histamine H_2-receptors (Armstrong *et al.*, 1983; Ruffolo & Shaar, 1983), and activation of these receptors does result in increases in pial arteriolar calibre (Wahl & Kuschinsky, 1979).

The alterations in cerebral blood flow which result from the administration of dopamine receptor agonists have been extensively investigated over the last decade (for review, see McCulloch *et al.*, 1982). The primary mechanism by which the changes in cerebral blood flow are initiated has been attributed to alterations in tissue metabolic activity. These function-related alterations in cerebral oxidative metabolism are mediated predominantly via dopamine D_2-receptors (Sharkey & McCulloch, unpublished observations), and the present detailed characterization of the cerebrovascular dopamine receptor as D_1-receptors provides a potential mechanism by which specific dopamine agonists and antagonists may modify cerebral blood flow *in vivo* in normal and pathological states without alteration in cerebral metabolic activity.

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