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Vasodilator response to dopamine in the ferret pulmonary circulation

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1 The isolated perfused lung of the ferret was used to study the effects of dopamine receptor agonists and antagonists. Under constant flow, a fall in pulmonary artery pressure reflects a vasodilator response. Since tone is normally low, agonists were given during hypoxic pulmonary vasoconstriction to enable detection of dilator responses.

2 Vasodilator responses were produced by bolus doses of dopamine over the range 0.1 to 5.0 $\mu g\,kg^{-1}$, and by the selective DA_1 agonist SK&F 38393 (1-phenyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride).

3 The dopamine response was blocked by low doses of the selective DA_1-antagonist SCH23390 (R-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol maleate), and by sulpiride.

4 The vasodilator response to the relatively selective DA_2-agonist N,N-di-n-propyl dopamine occurred only at high dose and was incompletely blocked by the selective DA_2 antagonist domperidone at a cumulative dose of 10 $mg\,kg^{-1}$.

5 Thus dopamine receptors of the DA_1 type may mediate vasodilatation in the ferret pulmonary circulation, but no evidence was obtained for the existence of DA_2-receptors.

Introduction

Despite considerable progress in understanding the effects of dopamine on the systemic circulation, its actions on the pulmonary circulation remain unclear. An important unwanted effect of clinical dopamine administration is hypoxaemia (Marin *et al.*, 1979). Since local vasoconstriction in hypoxic lung regions helps to maintain an appropriate ventilation-perfusion balance and hence arterial blood oxygen tension, a vasodilator effect of dopamine in these regions might cause hypoxaemia. Vasodilatation mediated by dopamine DA_1-receptors has been established in the renal, mesenteric and coronary beds, and by DA_2-presynaptic receptors on sympathetic postganglionic axons (Lokhandwala & Barrett, 1982). However, attempts to clarify the actions of dopamine on the pulmonary vasculature in intact animals have been hampered by concurrent variations in cardiac output, metabolic changes, and neurogenic reflexes. In this study the effects of dopamine on the isolated perfused lung of the ferret were investigated to determine the vascular actions independently of these other variables, and to look for evidence of dopamine receptors of the DA_1 or DA_2-types (Goldberg & Kohli, 1979). A preliminary account of some of the data has been published (Gorman, 1986).

Methods

Male ferrets were anaesthetized with i.p. urethane (1 $g\,kg^{-1}$, dopamine dose-response studies), pentobarbitone (60 $mg\,kg^{-1}$, dopamine/SCH23390 studies) or inactin (100 $mg\,kg^{-1}$, other studies). Within any series, all animals were anaesthetized with the same agent. The three anaesthetics were used because of prevailing circumstances rather than differences in their pharmacological properties and there appeared to be no qualitative variation in experimental responses with the different anaesthetics.

Isolated lung preparations were perfused by use of a Watson Marlow roller pump with autologous blood at a constant flow rate of 100 $ml\,kg^{-1}\,min^{-1}$. Blood entered the pulmonary circulation through a cannula in the pulmonary artery, and returned to the perfusion circuit reservoir through a cannula in the

left atrium. The temperature was maintained at 37°C by immersing the circuit reservoir in a heated water bath. The volume of blood in the circuit reservoir was initially 25 ml kg^{-1}. The lungs were ventilated by a Starling Ideal pump with 5% CO_2 in air, or under hypoxic conditions with 2% O_2 and 5% CO_2 in 93% N_2. Arterial blood pH was corrected initially, if required, with sodium bicarbonate. Agonist drugs were injected into the perfusion circuit tubing in a volume of 0.1 ml or 0.2 ml, and antagonist drugs were added to the reservoir. Pulmonary artery pressure was measured just proximal to the pulmonary artery cannula and monitored continuously using an SE 6300 u.v. recorder and transducer system. The systolic/diastolic effects of the roller pump and ventilation were averaged electronically to an excursion of a few mmHg, and the mean pulmonary artery pressure (P_{PA}) was obtained by taking the arithmetic mean from the trace.

In order to describe the methods used in this study the results of preliminary experiments are important. Under conditions of constant flow, changes in pulmonary artery pressure reflect changes in pulmonary vascular resistance. In order to measure a dilator effect the tone, which is normally low in the pulmonary circulation, must initially be elevated. Hypoxic pulmonary vasoconstriction was used to achieve this. All measurements of the pulmonary vasodilator effects of dopamine agonists were carried out during ventilation hypoxia; each agonist challenge was followed by a recovery period of about 7 min on normoxic gas before the next period of hypoxia was started. Injection of a bolus dose of dopamine during ventilation hypoxia leads to a biphasic response, with an initial transient pressor phase followed by a greater and more prolonged depressor phase. A typical record is shown in Figure 1. An initial pressor phase, seen during normoxia but only becoming marked at higher doses during hypoxia, is due to α-adrenoceptor stimulation and is not discussed further in this paper. Due to variation in the pressure rise caused by hypoxic vasoconstriction between animals and during the course of the experiments, the responses obtained during different levels of hypoxic vasoconstriction were standardised. Thus the change in pulmonary artery pressure (dP_{DA}) due to dopamine (DA) at the minimum of the depressor phase is described as a percentage of the change in pressure (dP_{HPV}) due to hypoxic vasoconstriction.

Protocols

Prior to each administration of agonist, ventilation hypoxia was started and a stable level of hypoxic vasoconstriction reached. Following the agonist response, normoxic ventilation was reinstated and a recovery period of approximately 5 min allowed before the next hypoxic challenge.

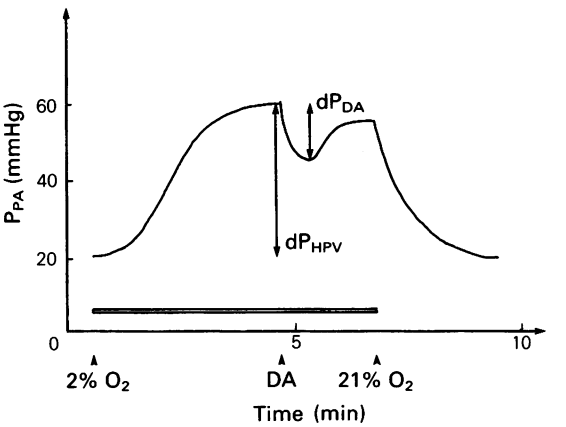

Figure 1 A typical record of mean pulmonary artery pressure (P_{PA}) with time, showing the pressor response to ventilation with 2% oxygen and biphasic response to dopamine (2 μg kg^{-1}). The maximum dilator response to dopamine (dP_{DA}) is subsequently described as a percentage of the rise in pressure (dP_{HPV}) due to hypoxic vasoconstriction.

Agonist dose-response studies (a) *Dopamine* Initial studies were carried out in 9 ferrets of body weight (b.wt.) 1367 ± 68 g. Adrenoceptor blockade was not used. Bolus doses of dopamine were given in random order.

(b) *SK&F 38393* was investigated in 9 ferrets (b. wt. 1122 ± 28 g), of which the active drug was tested in 6 and 0.9% saline was given in 3 control animals. In order to exclude any vascular effects due to adrenoceptor agonist action, α- and β-adrenoceptor blockade was provided by phentolamine (1 mg kg^{-1}) and propranolol (1 mg kg^{-1}) respectively and confirmed by an absence of response to adrenaline (1 μg kg^{-1}) during hypoxia. Preliminary studies had indicated that recovery from the effects of SK&F 38393 did not occur during the time course of the experiment, and the drug was given in successive doses increasing by a factor of 10.

(c) *N,N-di-n-propyl dopamine hydrobromide* was studied in 6 ferrets (b.wt. 1233 ± 105 g). Adrenoceptor blockade was not used since this would prevent recognition of vasodilatation by a presynaptic DA_2 mechanism (see Discussion). The order of administration of different doses in any given animal was randomised.

Antagonist studies When a bolus dose of dopamine was given several times in succession the vasodilator response tended to increase during the experiment. Allowance for this gradual change was therefore

made in the experimental protocols for the three antagonist studies. In each case the agonist was administered serially at the same dose in experimental and control groups, and antagonist or solvent given between agonist doses. It was assumed that the antagonists would accumulate in the perfusate with serial administration and they were given in increasing doses. The effect of the antagonist on the agonist response was studied by comparison with the control group.

(a) *Sulpiride* Repeated $2\,\mu g\,kg^{-1}$ doses of dopamine were administered. Phentolamine ($1\,mg\,kg^{-1}$) and propranolol ($1\,mg\,kg^{-1}$) were added and adrenoceptor blockade was confirmed by absence of response to adrenaline ($1\,\mu g\,kg^{-1}$) during hypoxia. Although the level of hypoxic vasoconstriction was reduced by adrenergic blockade, the dopamine response described as a percentage of dP_{HPV} was not altered. In 7 ferrets (b.wt. 1045 ± 27 g) sulpiride was added in increasing doses between the last five administrations of dopamine, and in 7 control animals (b.wt. 1028 ± 25 g) solvent was added instead.

(b) *SCH23390* Repeated $2\,\mu g\,kg^{-1}$ doses of dopamine were given. Adrenoceptor blockade with phentolamine ($1\,mg\,kg^{-1}$) and propranolol ($1\,mg\,kg^{-1}$) was confirmed by lack of response to adrenaline ($1\,\mu g\,kg^{-1}$). In 7 ferrets (b.wt. 1114 ± 74 g) increasing doses of SCH23390 were added between 6 successive dopamine administrations, and in 6 control animals (b.wt. 1117 ± 70 g) saline was added instead of the active drug.

(c) *Domperidone* DPDA was used in preference to dopamine as a DA_2-agonist because of its relative selectivity for the DA_2-receptor subtype. Repeated $20\,\mu g\,kg^{-1}$ doses of DPDA were administered. In 5 ferrets (b.wt. 1230 ± 77 g) increasing doses of domperidone were added between five consecutive agonist challenges, and in 5 control animals (b.wt. 1220 ± 102 g) solvent was added instead. The last administration of DPDA followed addition of $1\,\mu g\,kg^{-1}$ SCH23390 in both groups.

Drugs

The following drugs were used: dopamine hydrochloride (Sigma Chemical Company), N,N-di-n-propyl dopamine hydrobromide (DPDA, Glaxo), 1-phenyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (SK&F 38393, Smith Kline and French Laboratories), phentolamine (Rogitine, Ciba Laboratories), propranolol (Inderal, Imperial Chemical Industries), adrenaline (Antigen Ltd), domperidone (Motilium, Janssen Pharmaceutical Ltd), domperidone solvent (dextrose anhydrous, glacial acetic acid, and water for injections, Janssen Pharmaceutical Ltd), R-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol maleate (SCH23390, Schering Plough Corporation), racemic sulpiride (Delagrange International), prostaglandin $F_{2\alpha}$ (Upjohn Ltd), pentobarbitone sodium (Sagatal, May and Baker) and inactin (5-ethyl-5-(1-methylpropyl)-2-thiobarbitone sodium, BYK Gulden, Konstanz). Phentolamine, propranolol, adrenaline, pentobarbitone, domperidone and domperidone solvent were supplied in solution, and were administered as dilutions in 0.9% saline. Sulpiride was dissolved in saline containing a trace of hydrochloric acid. All other drugs were given as freshly prepared solutions in saline, the weight quoted being that of the anhydrous salt.

Statistics

Data were analysed by multivariate analysis, using the GLIM programme of the Royal Statistical Society on the Sheffield University computer. Linear analysis of variance models suitable for repeated measures data such as these (Armitage, 1971), and assuming Normal errors, were fitted to both the raw percentage data and to the data expressed as logarithms. The methods gave the same results, suggesting that the assumption of Normality had not distorted the results. Estimates obtained from fitting these models, and statistical results, have been expressed in terms of the mean $\pm$ the standard error (mean $\pm$ s.e.), and the number (n) in the group.

Results

Agonist studies

(a) *Dopamine* During initial studies a dose-related vasodilator response to dopamine was established (Figure 2), such that a mean dose of $0.73\,\mu g\,kg^{-1}$ caused a decrease in pulmonary artery pressure equivalent to half of the rise due to hypoxia ($dP_{DA} = 47.2 \pm 5.6\% dP_{HPV}$). When allowance was made for the gradual increase in response with time, a dose of $2\,\mu g\,kg^{-1}$ gave a large (dP_{DA} about 60% dP_{HPV}) but submaximal and repeatable response.

(b) *SK&F 38393* With this agonist a dose-related vasodilator response was again found (Figure 2). A $20\,\mu g\,kg^{-1}$ bolus dose of SK&F 38393 caused a reduction in P_{PA} of $58.2\% dP_{HPV}$, suggesting a potency approximately 10 times less than that of dopamine by weight, or 7 times less in molar terms. In the 3 control preparations normal saline was added instead of SK&F 38393, with no measurable effect on pulmonary artery pressure.

(c) *DPDA* DPDA also produced a dose-dependent vasodilator response (Figure 2). Thus a $50\,\mu g\,kg^{-1}$ dose gave a reduction in pulmonary artery pressure

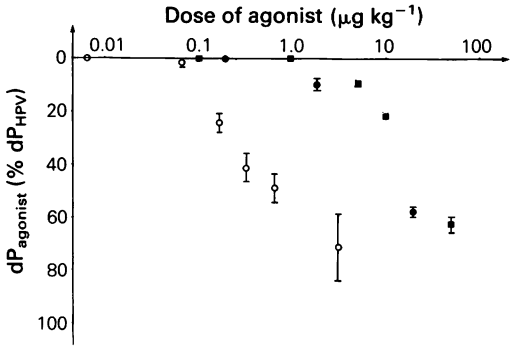

Figure 2 The pulmonary dilator effects of bolus doses of dopamine receptor agonists in the hypoxic ferret isolated perfused lung, where the maximum dilator response to an agonist ($dP_{agonist}$) is described as a percentage of the rise in pressure (dP_{HPV}) due to hypoxic vasoconstriction. Points represent mean ± s.e. In the preliminary dopamine dose-response studies, only, dopamine doses were calculated in μg rather than $\mu g\,kg^{-1}$; points were plotted according to the mean weight in the group. (○) dopamine; $2 < n < 7$ during studies in random order in 9 ferrets. (●) SK&F 38393 (1-phenyl-7,8-dihydroxy- 2,3,4,5-tetrahydro- 1H-3-benzazepine hydrochloride) given in increasing doses after initial α- and β-adrenoceptor blockade. $n = 6$ (■) DPDA (N,N-di-n-propyldopamine) in random order. $n = 6$. Some error bars omitted for clarity.

of 62.8 ± 3.5% of the rise due to hypoxia. Like dopamine, DPDA gave biphasic responses and the dilator phases were repeatable allowing for the gradual increase in response with time. However, it was a much less potent vasodilator agent, $50\,\mu g\,kg^{-1}$ DPDA having an equivalent effect to $2\,\mu g\,kg^{-1}$ dopamine, suggesting a molar potency ratio of the order of 15.

Antagonist studies

(a) *Sulpiride* The 'raw' data subsequent to α- and β-blockade are summarised in Table 1. There was a gradual increase in the dopamine dilator response in the control group. In the sulpiride-treated group there was dose-dependent blockade of the dopamine response, with almost complete abolition after the $1500\,\mu g\,kg^{-1}$ dose of sulpiride. The analysis of variance showed that the effect was highly significant ($P < 0.001$). Following 10, 90, 400, and $1500\,\mu g\,kg^{-1}$ doses of sulpiride the respective estimated mean reduction in dP_{DA} was 3.3, 24.1, 55.2, and 70.1% dP_{HPV} with s.e. = 4.6 in each case. The estimated results for the antagonist effect are slightly greater than the difference between the control and experimental groups after each dose of sulpiride, differences being clearer in the calculated results due to removal of sources of variation other than the antagonist action.

(b) *SCH23390* There was a dose-related decrease in dopamine vasodilator response with abolition after the $10\,\mu g\,kg^{-1}$ dose of SCH23390 in the experimental group, but a tendency to increase in the controls (Table 1). Analysis of variance again showed a highly significant effect ($P < 0.001$), and the respective estimated reductions in dP_{DA} obtained for 0.01, 0.1, 0.3, 1.0, and $10\,\mu g\,kg^{-1}$ were 1.1 ± 6.7, 10.0 ± 6.7, 36.4 ± 6.7, 54.7 ± 6.9, and 55.5 ± 6.7%dP_{HPV}. Again the calculated results for the drug effect are slightly bigger than the differences between control and experimental groups in the 'raw' data in Table 1.

(c) *Domperidone* The agonist responses tended to increase in control animals during these experiments, and particularly after the solvent dose corresponding to $7000\,\mu g\,kg^{-1}$ domperidone (Table 1). The experimental preparations and controls responded similarly to the agonist, with analysis of variance not showing a significant drug effect ($P > 0.1$) when the response to the last dose of domperidone was excluded. However, when the data were reanalysed including the effect of the last dose of domperidone the analysis of variance became significant ($P < 0.01$). Domperidone at this dose also reduced the hypoxic pressor response and had α-adrenoceptor blocking properties as confirmed by severe attenuation of the pulmonary pressor response to adrenaline $1\,\mu g\,kg^{-1}$ in experimental compared to control preparations. The estimated reductions in dP_{DPDA} due to the antagonist for the 100, 900, 1000, and $7000\,\mu g\,kg^{-1}$ doses respectively were 4.39, 6.5, 9.9, and 27.4 (±5.9 in each case) %dP_{HPV}. After the SCH23390 in the experimental group, the vasodilator response was almost abolished and in the controls the response became pressor.

Discussion

The ferret has a strong hypoxic pressor response which develops and resolves rapidly and is repeatable. Hypoxic pulmonary vasoconstriction (HPV) provided a convenient background of increased pulmonary pressure against which to measure a dilator response. Prostaglandin $F_{2\alpha}$ has been used for this purpose in the investigation of vasodilator responses in systemic arteries (Toda & Goldberg, 1975), but in preliminary experiments in the ferret isolated lung its pressor action was found to be subject to tachyphylaxis. The dopamine antagonists sulpiride and SCH23390 had little effect on the hypoxic response and the action of dopamine was qualitatively similar when other pressor agents such as 5-

Table 1 Vasodilator responses to repeated administration of a given dose of dopamine receptor agonist following increasing doses of antagonist

(a) *Sulpiride*	*Vasodilator response to dopamine* ($2\,\mu g\,kg^{-1}$) (dP_{DA} as $\%dP_{HPV}$)				
Sulpiride dose ($\mu g\,kg^{-1}$)	pre	10	90	400	1500
Controls	55.2	58.9	61.7	62.4	66.5
$n = 7$	(4.3)	(4.9)	(4.3)	(5.2)	(4.5)
Treated group	58.6	60.8	42.8	12.4	1.6
$n = 7$	(4.7)	(4.0)	(3.8)	(1.8)	(0.7)

(b) *SCH23390*	*Vasodilator response to dopamine* ($2\,\mu g\,kg^{-1}$) (dP_{DA} as $\%dP_{HPV}$)					
SCH23390 dose ($\mu g\,kg^{-1}$)	pre	0.01	0.1	0.3	1.0	10
Controls	44.6	51.0	53.1	54.8	55.4	54.0
$n = 6$	(4.0)	(4.0)	(3.3)	(5.8)	(6.0)	(5.3)
Treated group	46.4	51.4	44.6	19.9	3.6*	0
$n = 7$	(6.0)	(6.2)	(6.7)	(5.7)	(1.9)	(0)

(c) *Domperidone*	*Vasodilator response to DPDA* ($20\,\mu g\,kg^{-1}$) (dP_{DPDA} as $\%dP_{HPV}$)					
Domperidone dose ($\mu g\,kg^{-1}$)	pre	100	900	2000	7000	SCH23390 1
Controls	30.9	40.1	39.8	40.1	57.4	−9.4
$n = 5$	(4.0)	(2.6)	(1.9)	(1.5)	(4.7)	(0.6)
Treated group	32.3	41.5	39.1	35.9	35.7	1.9
$n = 5$	(3.6)	(3.3)	(4.0)	(3.8)	(5.6)	(1.3)

Values are mean (± s.e.) of observed data.
* $n = 6$.
Antagonist doses quoted are not cumulative. Sulpiride and SCH23390 studies: all preparations were pretreated with propranolol and phentolamine.

hydroxytryptamine or almitrine bimesylate were used. The dilator effect of dopamine is therefore unlikely to be due to a specific interaction with the mechanism of hypoxic vasoconstriction. Reports on the effect of α-adrenoceptor blockade on HPV have not been consistent; thus HPV was reduced by phentolamine in perfused lobes of cats (Barer & McCurrie, 1969) and dogs (Howard *et al.*, 1975) but there was no decrease in intact calves (Silove & Grover, 1968). In this study, phentolamine reduced HPV without affecting the percentage dilator response to dopamine. High doses of domperidone also decreased HPV, perhaps due to its α-blocking properties at these doses (Ennis & Cox, 1980).

Because of the slow increase in dopamine dilator response during the experiment, and the advantages of keeping the duration of the experiment to a minimum, the experimental protocol for antagonist studies was based on repeated administration of a given dose of agonist with subsequent multivariate analysis to remove the effect of the drift in response with time. This protocol is essentially semi-quantitative and does not support a formal quantitative assessment of antagonist pharmacokinetics such as that obtained with a Schild plot (Arunlakshana & Schild, 1959).

The action of dopamine on the pulmonary circulation remains unclear, largely because of the difficulty in measuring pulmonary vascular effects independent of other circulatory responses, variation in responses with physiological context and perhaps species variability. Dopamine has been reported to depress HPV in the intact canine pulmonary circulation (Marin *et al.*, 1979) and ferret isolated perfused lung (Bee *et al.*, 1981). However, its effect was pressor in intact neonatal lambs when α-blockade did not abolish the pressor response (Williams & Drummond, 1983), and in the canine left lower lobe preparation, due to α-adrenoceptor stimulation (Mentzer *et al.*, 1976). Drummond *et al.* (1983) obtained evidence for a DA_1-mediated dopaminergic vasoconstrictor mechanism in neonatal lambs, but specific vasodilator dopamine receptors have not been demonstrated in the pulmonary circulation.

In this study dopamine was shown to cause a dose-dependent vasodilator response in the ferret isolated perfused lung when administered during hypoxia. Since the effect persisted in the presence of α- and β-adrenoceptor blockade, an adrenergic mechanism was excluded. A dopaminergic mechanism was suggested by the antagonism of the dopamine dilator effect by sulpiride, a dopamine receptor antagonist (O'Connor & Brown, 1982). At high dose, sulpiride may also block α-adrenoceptors and 5-hydroxytryptamine receptors (Kohli & Cripe, 1979), but these actions are unlikely to be relevant in the presence of α-blockade and at the doses used in this study. Since racemic sulpiride blocks both DA_1- and DA_2-receptors (Glock, Kohli and Goldberg, 1981), further studies were carried out with more selective agents.

SK&F 38393 is a selective DA_1-agonist (Roby & Orzechowski, 1979), which is less potent than dopamine and has been shown to be a partial agonist in some studies (Hahn, 1984). The current investigation showed a vasodilator potency about 7 times less than that of dopamine, which is in reasonable agreement with the relative potency of 0.1 found at the canine renal DA_1-receptor (Weinstock *et al.*, 1983). The highly selective DA_1-antagonist SCH23390 (Goldberg *et al.*, 1984) blocked the vasodilator response to dopamine at low dose; a cumulative dose of $1.4\,\mu g\,kg^{-1}$ almost completely abolished the response. Thus agonist and antagonist studies suggest that the dopamine vasodilator response is mediated by DA_1-receptors.

It should be noted that extrinsic innervation of the pulmonary circulation is destroyed in setting up the isolated perfused lung preparation. Presynaptic DA_2-receptors which mediate a vasodilator response by reducing noradrenaline release from sympathetic nerves would not then be expected to participate in the response to circulating dopamine. However, since postsynaptic receptors of similar pharmacological profile might be present, and since intrinsic innervation has not been excluded, DA_2- as well as DA_1-agonists and antagonists were studied.

Although dopamine also stimulates DA_2-receptors, DPDA was used as the DA_2-agonist because of its greater selectivity for this dopamine receptor subtype. DPDA has been widely used as a preferential DA_2-agonist, although it is also a weak agonist at α-adrenoceptor and DA_1-receptors (Kohli *et al.*, 1978; 1980). In this study its effects were qualitatively similar to those of dopamine, but with a vasodilator potency 15 times less. Kohli *et al.* (1978) found a similar potency ratio for DPDA (15 to 30 times less than that of dopamine) as an agonist at canine renal DA_1-receptors. Since in addition the DPDA vasodilator response was blocked by SCH23390 it seems likely that DPDA is producing the vasodilator response through DA_1- rather than DA_2-receptors. Domperidone, a highly selective DA_2-antagonist in the periphery (Kohli *et al.*, 1983), failed to block the DPDA response until a cumulative dose of $10\,mg\,kg^{-1}$ had been given. The difference between the controls and experimental group at this dose appeared to be an increase in the responses in the controls rather than a decrease in the domperidone-treated animals and may have been related to the effect of the large dose of the domperidone solvent given alone. In contrast domperidone blocks DA_2-receptors at low dose. Kohli *et al.* (1983) found a dose-related antagonism of DPDA-induced femoral vasodilatation in the canine femoral circulation over the dose range 0.5 to $5\,\mu g\,kg^{-1}$. Thus the effect of domperidone on the DPD response appears to be due to some mechanism other than DA_2 antagonism. The pressor response to DPDA after SCH23390 administration in the control animals was probably due to unopposed α-adrenoceptor activity as a result of the dopamine receptor blockade.

In conclusion, evidence was obtained for a dopaminergic vasodilator mechanism in the ferret pulmonary circulation. Selective agonist and antagonist studies suggest DA_1-mediation. No evidence was gained for a DA_2-mechanism, although this cannot be excluded without studies with intact sympathetic innervation. Further studies are indicated to investigate the existence of this phenomenon in other animals, and its physiological relevance.

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