Pharmacological investigations of the vasodilator nerves supplying the duck's foot

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1 Vasodilator responses to electrical nerve stimulation and to various putative autonomic inhibitory neurotransmitters were studied in the Krebs-perfused foot of the domestic duck.

2 Electrical stimulation resulted in frequency-dependent vasoconstrictor responses which were abolished by the infusion of guanethidine. After abolition of the vasoconstriction, electrical stimulation produced a frequency-dependent vasodilatation.

3 The putative inhibitory transmitter substances tested were substance P, somatostatin, vasoactive intestinal polypeptide, adenosine triphosphate and dopamine. Of these only dopamine produced dilator responses similar in appearance to those following nerve stimulation.

4 Infusion of metoclopramide (170 µM) greatly reduced dilator responses to nerve stimulation and to dopamine but not those to glyceryl trinitrate.

5 These results suggest that the vasculature of the duck foot may be supplied by dopaminergic vasodilator nerves.

Introduction

The unfeathered portions of birds' feet are important areas for heat exchange with the environment. High blood flow through the numerous arteriovenous anastomoses of the feet may be essential not only for heat loss in order to prevent hyperthermia (Bernstein, 1974; Johansen & Millard, 1974; Baudinette et al., 1976), but also for local warming and prevention of tissue damage during exposure to cold substrates (Grant & Bland, 1931; Johansen & Millard, 1974; Murrish & Guard, 1977).

It is known that both vasoconstrictor and vasodilator nerves innervate the vasculature of the feet in a number of avian species: chicken (McGregor, 1979; Hillman et al., 1982), duck (McGregor, 1979) and giant petrel (Johansen & Millard, 1974; Murrish & Guard, 1977). The basis therefore exists for increasing thermoregulatory blood flow through the feet by active vasodilatation as well as by reducing vasoconstrictor neural tone. Moreover, it has been found that local anaesthesia or sectioning of the autonomic nerves supplying the foot vessels prevents the vasodilatation normally seen on immersion of the foot in ice-cold water (Johansen & Millard, 1974; Murrish & Guard, 1977).

The neurotransmitter responsible for mediating vasodilatation in the bird foot has not been identified, although studies by McGregor (1979) have shown that in duck and chicken the responses to nerve stimulation are not attenuated by antagonists of acetylcholine or histamine. In this paper, the possible involvement of a number of other substances, suggested to function as inhibitory autonomic neurotransmitters, has been examined with regard to the neurogenic vasodilator response in the foot of the domestic duck. The substances tested were substance P (Lembeck & Holzer, 1979) somatostatin (Campbell et al., 1982), vasoactive intestinal polypeptide (Lundberg et al., 1980) adenosine triphosphate (Burnstock, 1972) and dopamine (Bell, 1982). Some of these results were presented to the Australian Physiological and Pharmacological society in May, 1983 (Rome & Bell, 1983).

Methods

All experiments described here were performed over the summer months (December–February).

Perfusion experiments

Adult domestic ducks (*Anas platyrhynchos*) of either sex were killed by cervical dislocation under anaesthesia with carbon dioxide vapour. We used carbon
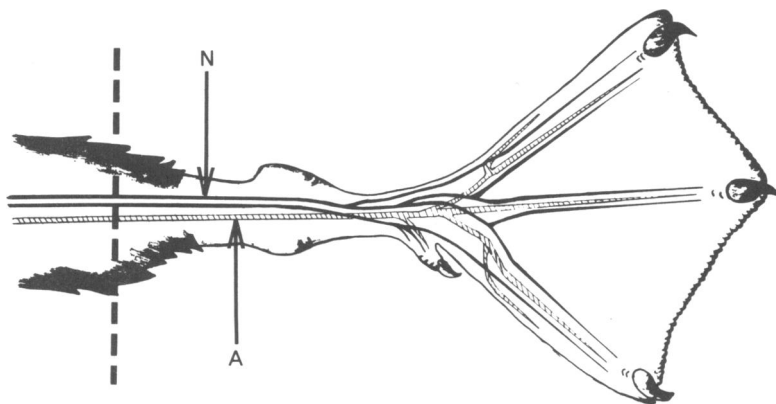
Figure 1 Diagrammatic representation of the duck foot, showing the distributions of the dorsal metatarsal nerves (N) and the anterior tibialis artery (A). The dashed line indicates the approximate level of arterial cannulation and nerve stimulation.

dioxide for anaesthesia because it produces less pre-induction excitement in birds than ether. The leg skin was cleared of feathers below the thigh joint and a longitudinal incision was made on the anterior surface of this region. The muscle was then parted to expose the dorsal pedal anterior tibialis artery and the adjacent, paired, dorsal metatarsal nerves (Figure 1). A polyethylene cannula (Boots PP160, bore 1.1 mm, external diameter 1.5 mm) was inserted into the dorsal artery above the tarsometatarsal-tibiotarsal joint and following this the leg was severed (Figure 1).

The foot was placed on a cork platform in air (19–20°C) and perfused with an avian Krebs solution (McGregor, 1979) containing $100 \,\mu g \,ml^{-1}$ ascorbic acid, at $6 \,ml \,min^{-1}$ using a constant-rate roller pump (Cole-Parmer Masterflex). This rate of perfusion was sufficient to produce a resting perfusion pressure of between 30 and 50 mmHg, and substantial pressure changes in response to vasoconstrictor agents. The venous effluent was allowed to flow freely from the severed veins in the leg. Perfusion pressure was recorded via a Statham arterial pressure transducer as an index of vascular resistance. In order to study vasodilator responses, the resting vascular tone was raised by including guanethidine and in some preparations noradrenaline in the perfusion medium (see Results for details).

In preliminary experiments, we utilized Krebs at avian body temperature (42°C). However, in these preparations observation of dilator responses was often impossible because of spontaneous, periodic falls in perfusion pressure, followed by recovery over one to two minutes. During these episodes, the pressure falls were associated with visible spurting of perfusion fluid from the severed venous vessels. The variations in pressure were not affected by addition of 1% bovine serum albumin to the perfusate (2 experiments), but were eliminated by reducing the perfusate temperature to 32°C. Most of the data presented in this paper have, therefore, been obtained using the lower temperature, although there was no apparent qualitative difference in responses to either nerve stimulation or dilator agonists between preparations at 32°C and 42°C. All numerical data were obtained at 32°C.

The dorsal metatarsal nerves were freed from the neighbouring artery and threaded through a pair of shielded platinum ring electrodes. The electrodes were connected to a Grass S44 stimulator and the nerves were stimulated with trains of 1 ms square wave pulses at supramaximal voltage and frequencies of 1–20 Hz. For investigations of dilator responses to nerve stimulation, the trains used were 10 pulses in length, regardless of the frequency.

All drugs were made up in the avian Krebs solution and were freshly prepared each day. Dilator agents used were substance P (Sigma); somatostatin (Peninsula laboratories); vasoactive intestinal polypeptide (VIP, Peninsula laboratories); adenosine triphosphate (ATP, Sigma); dopamine hydrochloride (Sigma); glyceryl trinitrate (Anginine, Wellcome) and isoprenaline hydrochloride (Sigma). Antagonist drugs employed were guanethidine (Ismelin, Ciba-Greigy) and metoclopramide hydrochloride (Maxolon, Beecham).

Results

Effects of nerve stimulation

Under control conditions, resting perfusion pressure of the foot was stable and had a value of
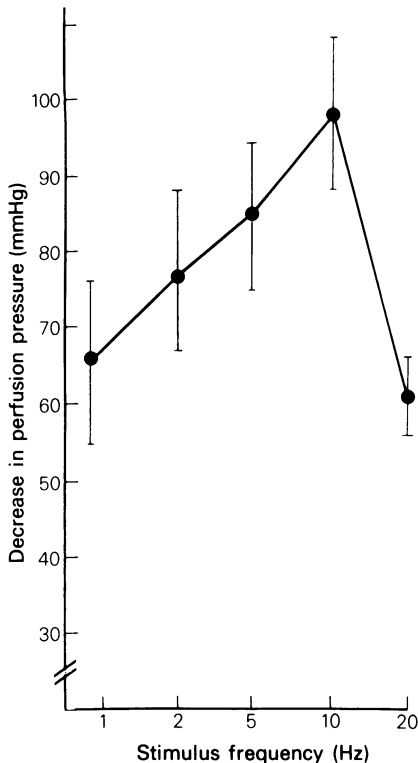
Figure 2 Frequency-response relationship of neural vasodilator responses to electrical stimulation with trains of ten 1 ms pulses at 1–20 Hz. Preparations treated with guanethidine (25 μM). The vertical bars represent s.e.mean.
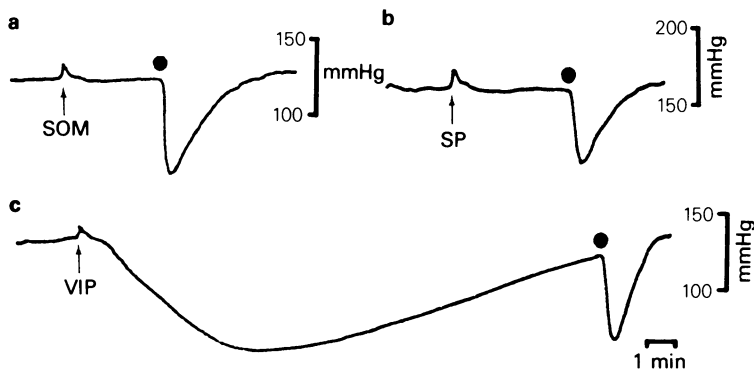
release of noradrenaline from intramural nerve endings (Gillespie, 1972). Where this did not naturally occur, an infusion of noradrenaline (250 nM) was used to provide a sustained elevation of pressure (McGregor, 1979). The final perfusion pressure after guanethidine or guanethidine plus noradrenaline was 201 ± 14.4 mmHg. Under these conditions, nerve stimulation produced a vasodilator response that was maximal at between 5 Hz and 10 Hz (Figure 2). The threshold frequency was generally about 1 Hz, though in some extremely responsive preparations 1 Hz stimulation elicited near-maximum responses. Electrically mediated vasodilatation with 5–10Hz would often reduce perfusion pressure to levels as low as those produced by large intraluminal doses of glyceryl trinitrate (1 nmol). Reproducible responses to many consecutive periods of similar stimulation could be obtained.

Effects of peptides

Bolus intraluminal injections of substance P (3.7 pmol–1 nmol) or somatostatin (0.3–6 nmol) produced no consistent changes in perfusion pressure in the 4 preparations examined (Figure 3). By contrast, VIP caused vasodilatation in doses as low as 17 pmol, and at doses of 0.34–3.4 nmol, the absolute falls in perfusion pressure produced were of the same order of magnitude as those produced by nerve stimulation (8 preparations). However, the time course of responses to VIP was invariably far more prolonged, by a factor of 5–20, than that of responses to nerve stimulation having similar amplitudes. (Figure 2).

Effect of ATP

As described previously by McGregor (1979), ATP was a potent dilator of the duck foot, and doses of

42 ± 4.3 mmHg (mean $\pm$ s.e.mean, $n = 20$). Electrical stimulation of the dorsal metatarsal nerves resulted in a frequency-dependent vasoconstriction which was abolished by infusion of guanethidine (25 μM). Guanethidine usually caused a gradual increase in perfusion pressure, presumably due to continuous

Figure 3 Vasodilator responses to nerve stimulation (2Hz, 10 pulses at the black dots) in three perfused feet, and responses in the same preparations to intraluminal injections of (a) somatostatin (SOM) 1 nmol, (b) substance P (SP) 1 nmol and (c) vasoactive intestinal polypeptide (VIP) 1 nmol. Preparations treated with guanethidine (25 μM).
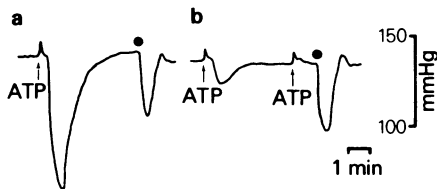
Figure 4 (a) Vasodilator responses to nerve stimulation (2Hz, 10 pulses, at the black dot) and to intraluminal adenosine triphosphate (ATP) 20 nmol. (b) Successive further injections of ATP (20 nmol) show profound tachyphylaxis, without attenuation of the nerve-mediated response. Preparation treated with guanethidine (25 μM) and noradrenaline (250 nM).

1.9–19 nmol produced falls in perfusion pressure comparable to those produced by nerve stimulation. Repeated applications of ATP several minutes apart led, in 4 preparations, to progressive tachyphylaxis of the dilator effect and in 2 cases, to reversal of this to a constrictor response. In contrast, there was no attenuation of the dilator response to nerve stimulation over the same period in any preparation (Figure 4, Table 1).

Effect of dopamine

The catecholamine dopamine proved to be a potent dilator of the duck foot vasculature (Figures 5 and 6). The threshold dose causing dilatation was approximately 65 pmol, the dose producing 50% maximum response was 2.5 nmol (Figure 5). The amplitudes of the maximum responses elicited by dopamine were comparable to those elicited by nerve stimulation, sometimes with a reduction in perfusion pressure to levels approximating those existing before administration of guanethidine and noradrenaline.

The β-adrenoreceptor stimulant isoprenaline, when tested in 4 preparations, produced no vasodilatation with doses of up to 1.5 μmol (Figure 6). In order to test the possibility that responses to dopamine were mediated through specific dopamine
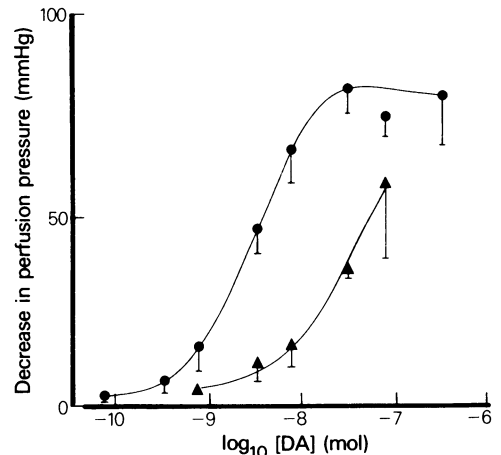
Figure 5 Dose-response relationship for the dilator effect of dopamine (DA) in a series of 7 perfused, guanethidine-treated duck feet under control conditions (●) and in the presence of metoclopramide 170 μM (▲). The vertical bars represent s.e.mean.

receptors rather than through β-adrenoreceptors, we studied the effects on the dopamine dose-response curve of the selective dopamine-receptor antagonist metoclopramide, infused into the arterial cannula at a
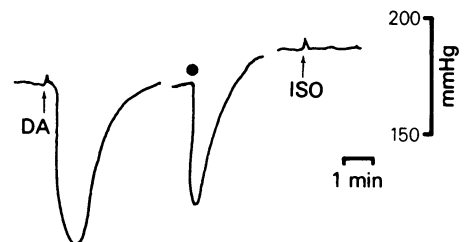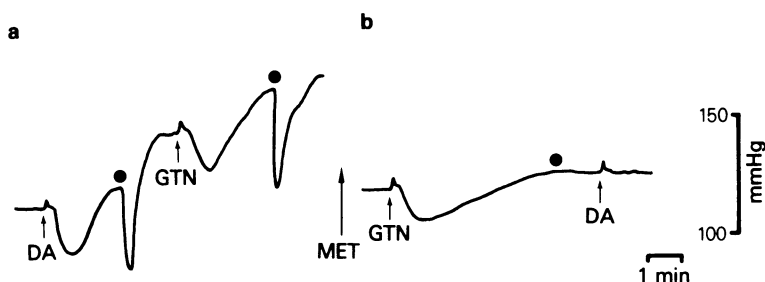

Figure 6 Vasodilator responses to nerve stimulation (5 Hz, 10 pulses, at the black dot) and to intraluminal dopamine (DA) 10 nmol. In the same preparation isoprenaline (ISO) 200 nmol produced no dilatation. Preparation treated with guanethidine (25 μM) and noradrenaline (250 nM).

Table 1 Effect of tachyphylaxis to adenosine triphosphate (ATP) on amplitudes of vasodilator responses to nerve stimulation, in 4 preparations treated with guanethidine (25 μM) and noradrenaline (250 μM)

Duck	Amplitude of vasodilator response (mmHg fall in perfusion pressure)			
	Initial nerve stim	Initial ATP	Post-tachyphylaxis ATP	Post-tachyphylaxis nerve stim
1	77	165	0	75
2	49	248	37	92
3	85	123	0	54
4	30	119	8	30
mean ± s.e.mean	60 ± 15	164 ± 30	11 ± 9	63 ± 13

Resting perfusion pressures did not change appreciably during the production of tachyphylaxis.

a

b

Figure 7   (a) Vasodilator responses to submaximal doses of dopamine (DA) 5 nmol and glyceryl trinitrate (GTN) 2 nmol, and to submaximal nerve stimulation (2 Hz, 10 pulses at black dots). (b) Following initiation of an infusion of metoclopramide (MET) 170 μM, there is some reduction in the resting perfusion pressure, and abolition of responses to nerve stimulation and to dopamine. The response to glyceryl trinitrate is not appreciably affected. Preparation treated with guanethidine (25 μM).

final concentration of 170 μM. As shown in Figure 5, metoclopramide produced a substantial shift to the right of the dose-response curve. Therefore, we compared the effects of the same concentration of metaclopramide on dilator responses to sub-maximal doses of dopamine (1–10 nmol), glyceryl trinitrate (0.1–5 nmol) and sub-maximal nerve stimulation (10 pulses, 1–5 Hz). The absolute doses of dilator agonists and the stimulation frequencies selected were adjusted for each preparation in order to produce comparable falls in perfusion pressure with each type of response. A representative record is shown in Figure 7. During infusion of metoclopramide there was reduction or abolition of the responses to both dopamine and nerve stimulation. Although metoclopramide also caused some reduction in the resting perfusion pressure, this could not account for the abolition of dopamine- and nerve-mediated responses, as the dilator effect of glyceryl trinitrate was not markedly affected. This pattern of effect of metoclopramide was seen in 8 out of 10 experiments performed: in the remaining 2 preparations metoclopramide had little effect on either dopamine or nerve-mediated responses. Following cessation of metoclopramide infusion, partial or complete recovery of responses to dopamine and to nerve stimulation occurred within 30 min in 4 preparations, but in the remaining 4 experiments the responses showed little or no recovery over this time. It was not clear whether this reflected persistence of the effect of the drug, or deterioration of vasodilator function due to

some other cause. However, responses to glyceryl trinitrate were not reduced. The pooled data for all experiments using metoclopramide are shown in Table 2.

Discussion

It is well documented that thermal stress induces large increases in blood flow in the feet of various birds. These increases are thought to represent increases in arteriovenous shunt flow rather than changes in capillary perfusion (Grant & Bland 1931; Johansen & Millard, 1973; 1974; Bernstein, 1974; Murrish & Guard, 1977). At least in some instances, the abolition of thermoregulatory hyperaemia by section or anaesthesia of the nerve supply to the foot has indicated that the response is due to active neurogenic dilatation, rather than being due simply to passive dilatation following the withdrawal of vasoconstrictor tone (Johansen & Millard, 1974; Murrish & Guard, 1977).

Hillman et al. (1982) showed that stimulation of the neural input to the chicken foot caused dilatation of arteriovenous anastomoses without a concomitant increase in capillary flow. In the present study, we found that although the amplitude of the dilator response to nerve stimulation was frequency-dependent, this dependence was not marked, and near-maximal falls in perfusion pressure could often be elicited by stimulation at 1–2 Hz. This pattern of

Table 2   Effect of metoclopramide infusion (170 μM) on submaximal vasodilator responses to dopamine and glyceryl trinitrate, and to electrical nerve stimulation

	Control	Metoclopramide	30 min wash
Dopamine	68 ± 15 (n = 9)	33 ± 14* (n = 9)	38 ± 18 (n = 7)
Glyceryl trinitrate	63 ± 17 (n = 10)	79 ± 18 (n = 10)	63 ± 16 (n = 8)
Nerve stimulation	56 ± 14 (n = 10)	27 ± 12** (n = 10)	35 ± 12 (n = 8)

Values represent mean ± s.e.mean, in mmHg. Preparations treated with guanethidine (25 μM).
Significant reduction: *$P < 0.05$; **$P < 0.02$.

response is one that would be anticipated for an effect selectively on shunt vessels, which are either fully shut or fully open, rather than on the pre-capillary arteriolar vessels that are capable of graded resistance changes, and in which there is a considerable increase in the effects on blood flow over the frequency range 1–10 Hz for both vasoconstrictor and vasodilator responses (Mellander, 1960; Hughes & Vane, 1967; Bell, 1968; Marshall, 1982). Thus it seems probable that the neural dilatation that we have examined is identical to that implicated by previous workers in thermoregulatory hyperaemia.

Previous work by McGregor (1979) has shown that in the duck foot, neurally induced dilatation is not attenuated by anti-muscarinic drugs or by metiamide in doses that abolish dilator responses to acetylcholine and histamine; suggesting that the neurotransmitter involved is neither of these substances. These negative results provided the stimulus for our present examination of other transmitters as possible candidates.

The three peptides that were tested for dilator properties have all been suggested as inhibitory neurotransmitters in other situations. Substance P has been implicated in the vasodilator response to sensory nerve stimulation (Lembeck & Holzer, 1979) and as a transmitter in the gut (Franco et al 1979); somatostatin as a cardio-inhibitory vagal transmitter in the amphibian atrium (Campbell et al., 1982); and VIP as a vasodilator transmitter in exocrine glands (Lundberg et al., 1980). Our results suggest that none of these peptides is likely to be the substance responsible for vasodilator transmission in the duck foot. Substance P and somatostatin were devoid of dilator activity over a range of doses in excess of those that have marked inhibitory effects in other systems (somatostatin: 1 nM, Campbell et al., 1982; substance P: 15 pmol, Pernow & Rosell, 1975). Although VIP did cause dilatation, the response produced had a much greater time course than that due to nerve stimulation. However, some involvement of VIP cannot be absolutely excluded on these grounds, as it is not certain that application of exogenous VIP to the receptors on the outside of the vascular wall, where neurally-released transmitter acts, would have had a similarly prolonged effect.

ATP has been suggested as a possible inhibitory autonomic neurotransmitter in a number of situations, notably within the gut (Burnstock, 1972;) and has been shown to cause selective dilatation of arteriovenous shunts in the foot of the chicken (Hillman et al, 1982) as well as dilatation in the duck foot (McGregor, 1979). We have confirmed that ATP is a potent dilator agent in this preparation. On the other hand, our results argue strongly against a role for ATP in vasodilator transmission here, as the response to ATP showed profound tachyphylaxis during repeated applications while that to nerve stimulation was unaffected. It is not certain that tachyphylaxis to intraluminal ATP would have affected similarly responses to ATP applied from the extraluminal side of the vessels. Nevertheless, it seems unlikely that such extraluminal receptors would be so different that they would not exhibit tachyphylaxis to locally-applied ATP; and during repeated periods of nerve stimulation we never observed a progressive reduction of the nerve-mediated dilatation, which would be predicted to occur should extraluminal tachphylaxis have developed.

The catecholamine dopamine is another substance which is presently under consideration as an inhibitory autonomic neurotransmitter (see Bell, 1982). The present results show that the vasculature of the duck foot is highly responsive to dopamine, profound reductions of vascular tone being produced by quite small amounts of dopamine in the absence of pharmacological procedures for inactivation of α-adrenoceptors. By contrast, in the mammalian foot dopamine-induced dilatation is not pronounced unless the concomitant constrictor effect of dopamine on α-adrenoceptors is first abolished with an appropriate drug (Bell & Stubbs, 1978). We observed no dilator effect of isoprenaline in doses as high as 1.2 μmol, suggesting the absence of appreciable numbers of β-adrenoceptors in the foot. This is in agreement with observations made by Johansen & Millard (1974) and McGregor (1979), although Bolton & Bowman (1969) described a weak dilator effect of isoprenaline at high doses. In view of the paucity of β-adrenoceptors, the dilatation produced by dopamine must be due to an action on specific dopamine receptors. This was confirmed by our observation that responses to dopamine were reversibly attenuated or abolished by infusion of metoclopramide, a selective antagonist of dopamine at these receptors (Day & Blower, 1975; Kohli et al., 1978; Woodman et al., 1980).

Metoclopramide not only reduced dilator responses to exogenous dopamine but also reduced responses to dilator nerve stimulation by a similar extent. These effects were not due to non-selective depressant effects on the vasculature, as dilator responses of a similar amplitude elicited with glyceryl trinitrate were not reduced. Thus our results are compatible with the involvement of neurally-released dopamine in production of the dilator response to nerve stimulation. There is biochemical, morphological and pharmacological evidence for dopaminergic vasodilator innervation of the arteriovenous shunts within the dog foot (Bell & Lang 1979; Bell, 1982). Transmitter storage in and release from these nerves is resistant to guanethidine in doses that deplete noradrenaline stores in noradrenergic nerves and abolish the release of noradrenaline in

response to nerve stimulation (Bell, 1982). Thus it seems likely that the dilator responses in the duck foot are mediated by a similar population of dopaminergic neurones. However, some dopamine is also released from noradrenergic nerve endings following electrical stimulation, and the characteristics of the release reaction suggest that the dopamine and noradrenaline originate primarily from different storage pools (Bell *et al.*, 1984). The possibility exists that guanethidine might preferentially reduce the binding and release of the amine in the noradrenaline pool, and leave dopamine release unaffected. Resolution of these alternatives will require biochemical investigation of neurones supplying the duck foot.

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