Br. J. Pharmac. (1987), **91**, 591–599

Dopamine released from nerve terminals activates prejunctional dopamine receptors in dog mesenteric arterial vessels

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1 The fractional release of dopamine and noradrenaline (NA) from the main trunk of the dog mesenteric artery and its proximal branches, when elicited by K^+ (52 mM), was measured by high pressure liquid chromatography with electrochemical detection.

2 K^+-induced depolarization released both dopamine and NA. For the main trunk of the mesenteric artery, the fractional release of dopamine and NA were of the same order of magnitude, whereas for the proximal branches dopamine fractional release was significantly lower than that of NA.

3 Phentolamine (0.2 μM) significantly increased dopamine and NA release in both segments of the mesenteric artery. However, for the proximal branches the effect of phentolamine on dopamine and NA release was greater than that observed in the main trunk.

4 Sulpiride (1 μM) significantly increased dopamine and NA release in the proximal branches of the mesenteric artery, whereas in the main trunk sulpiride did not increase amine release. In the proximal branches of the mesenteric artery, sulpiride significantly enhanced dopamine and NA fractional release even after it had been augmented by phentolamine.

5 Apomorphine (0.3 μM) significantly reduced dopamine and NA release in both segments of the mesenteric artery under study; this effect was abolished by sulpiride but not by phentolamine.

6 These results suggest that dopamine and NA released during depolarization by K^+ activate prejunctional dopamine and α-adrenoceptors, respectively, thereby playing a role in the control of transmitter release.

Introduction

Over the last few years, two distinct types of dopamine receptor have been identified in peripheral tissues: dopamine receptors on vascular smooth muscle cells (dopamine$_1$-receptors) and neuronal dopamine receptors (dopamine$_2$-receptors). The dopamine$_1$-receptor mediates active vasodilatation in several vascular beds. The dopamine$_2$-receptor occurs prejunctionally on sympathetic nerve terminals and its stimulation produces a reduction in the neuronal release of noradrenaline (NA), thereby inhibiting sympathetic tone. Functionally, this leads to a decrease in blood pressure and heart rate (Willems *et al.*, 1985).

While it has been shown that prejunctional α-adrenoceptors have a physiological role in providing a negative feedback regulation of NA release elicited during sympathetic nerve stimulation, it is not yet known what role, if any, prejunctional dopamine receptors have in modulating sympathetic neurotransmitter release (Langer, 1981: Lokhandwala & Barrett, 1982; Willems *et al.*, 1985). The physiological relevance of these prejunctional dopamine receptors is, however, dependent on the amount of endogenous dopamine available and on the cellular structure where the amine is localized. In the proximal branches of the mesenteric artery two main sources of dopamine have been described, namely as a precursor of NA and as a NA-independent non-precursor substance (Caramona & Soares-da-Silva, 1985; Soares-da-Silva & Davidson, 1985; Soares-da-Silva, 1986a). Also, it has been shown that dopamine and NA are probably stored in two different compartments inside sympathetic neurones supplying the proximal branches of the mesenteric artery; dopamine is released from a slowly-depleted pool, whereas NA is released from a rapidly-depleted pool (Soares-da-Silva, 1987a). However, the slowly-depleted dopamine pools, similar to the rapidly-depleted NA pools, reside in cellular compartments which are equally involved in transmitter turnover (Soares-da-Silva, 1987a). In contrast, the main trunk of the mesenteric artery is a blood vessel

where all of the dopamine is present as a precursor of NA (Soares-da-Siiva, 1986a) and both dopamine and NA are released from a common pool (Soares-da-Silva, 1987a).

The purpose of the present study was to determine the presence of prejunctional dopamine receptors in dog mesenteric arteries and to investigate a possible physiological role of prejunctional dopamine receptors in modulating sympathetic neurotransmission in this vascular area. A preliminary account of these findings has been presented previously (Soares-da-Silva, 1987b).

Methods

Mongrel dogs of either sex weighing 14–23 kg were anaesthetized with sodium pentobarbitone (30 mg kg^{-1} i.v., injected in the forelimb) and the main trunk of the anterior mesenteric artery and its proximal branches removed, stripped of their mesentery, rinsed free from blood and cut longitudinally. Each segment (about 4 cm long) weighed 40 mg in the case of proximal branches of the mesenteric artery or up to 100 mg for samples of the main trunk. The segments were incubated for 30 min in 5 ml of Krebs solution (37°C), gassed with 95% O_2 and 5% CO_2, in the presence of 55 μM hydrocortisone and 0.1 mM pargyline, in order to block extraneuronal uptake and monoamine oxidase, respectively. The Krebs solution had the following composition (mM): NaCl 118, KCl 4.7, $CaCl_2$ 2.4, $MgSO_4$ 1.2, $NaHCO_3$ 25, KH_2PO_4 1.2 and glucose 11. EDTA 0.04 mM was added to the Krebs solution in order to prevent oxidative destruction of catecholamines.

After the incubation period, segments of proximal branches and main trunk of the mesenteric artery were continously perfused for 90 min in a 1 ml organ bath; gassed (95% O_2 and 5% CO_2) and warm (37°C) Krebs solution (containing hydrocortisone, as above) was pumped through the bath by means of a Harvard Peristaltic Pump (model 1210) at a constant rate of 0.3 ml min^{-1}, and the overflow was collected. In all experiments cocaine (10 μM) and propranolol (1 μM) were added to the perfusion fluid from 0 min onwards. Tissues were perfused with a K^+-enriched Krebs solution from t = 60 to t = 90 min; 40% of the NaCl was replaced by KCl in the KCl-enriched medium giving final concentrations of NaCl and KCl of 71 and 52 mM, respectively. The spontaneous loss from t = 30 to t = 60 min was also measured and this value subtracted from the K^+-induced release to give the extra overflow as a result of catecholamines released during the depolarization period. On the assumption that dopamine and NA levels in the overflow during depolarization by K^+ do reflect their release from tissue stores, results are presented as fractional release calculated using the expression

$$(A_o/A_t) \times 10^4$$

where A_o is the concentration of the amines in the overflow and A_t the tissue amine content.

In some experiments phentolamine (0.2 μM), sulpiride (1 μM), phentolamine plus sulpiride, apomorphine (0.3 μM), apomorphine plus sulpiride or apomorphine plus phentolamine were added to the perfusion fluid from 0 min onwards. The fluid was collected in 10 ml cooled vials containing 0.8 ml 1.0 mM perchloric acid. At the end of the collection period 50 mg alumina was added and the pH of the sample immediately adjusted to pH 8.6. Mechanical shaking for 10 min was followed by centrifugation and the supernatant discarded. The adsorbed catecholamines were then eluted from the alumina with 150 μl 0.1 μM perchloric acid on Millipore microfilters (MF 1); 50 μl of the eluate was injected into a high pressure liquid chromatograph with electrochemical detection (BAS model 304 LC 4A) and the dopamine and noradrenaline measured. A 5 μM ODS column of 25 cm length was used. The mobile phase was degassed solution of monochloroacetic acid (0.15 mM), sodium octylsulphate (0.3 mM) and EDTA (2 mM), pH 3.0, pumped at a rate of 1.8 ml min^{-1}. A carbon paste electrode was used and the detector potential was + 0.65 V. Dihydroxybenzylamine was used as an internal standard. Peak height increased linearly with the concentration of NA and dopamine. The interassay coefficient of variation was less than 5%. Under our conditions, the lower limits of detection for noradrenaline and dopamine were 10 and 30 pg per sample, respectively.

After the depolarization period tissues were removed from the organ bath, blotted with filter paper, weighed, minced with fine scissors and homogenized with a Duall-Kontes homogenizer in 2.0 ml 0.1 mM perchloric acid. The homogenates were centrifuged (10,000 r.p.m., 15 min, 0°C) and the supernatant decanted. Aliquots of 1.5 ml supernatant were placed in 5 ml conical glass vials with 50 mg alumina and the pH adjusted to 8.6. Mechanical shaking for 10 min was followed by centrifugation, the supernatant discarded and subsequently treated like samples of bathing fluid.

Differences between two means were estimated by Student's *t* test for paired data; a probability of less than 0.05 was assumed to denote a significant difference.

Drugs

Drugs used were: apomorphine hydrochloride (Sigma, St. Louis, Mo, U.S.A.), cocaine hydrochloride (Uquipa, Lisboa, Portugal), dopamine hydrochloride (Sigma), ethylenediaminetetracetic acid disodium salt

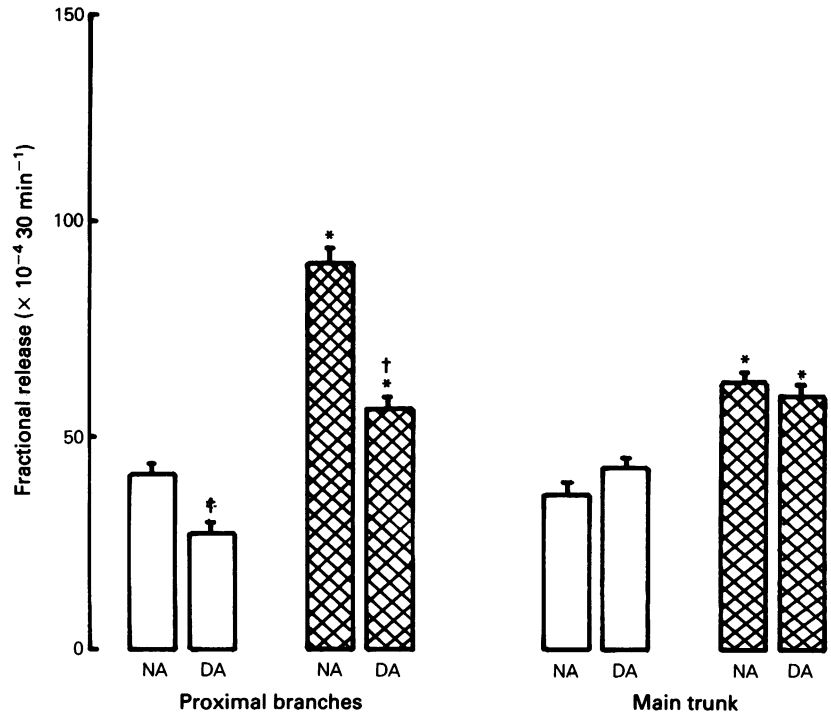

Figure 1 The effect of phentolamine (0.2 μM) on the release of noradrenaline (NA) and dopamine (DA) from the main trunk of the mesenteric artery and its proximal branches during depolarization by K^+ (52 mM). The release of NA and dopamine is expressed as a fraction of the tissue amine content. Each column represents the mean of five experiments per group; vertical lines show s.e.mean. Open columns, control; hatched columns, effect of phentolamine. * Significantly different from control values ($P < 0.01$). † Significantly different from corresponding NA values ($P < 0.01$).

(EDTA, Sigma), hydrocortisone phosphate (Sigma), (−)-noradrenaline bitartrate (Sigma), pargyline hydrochloride (Sigma), phentolamine hydrochloride (Regitin, Ciba, Switzerland), propranolol hydrochloride (Sigma) and RS-sulpiride (Sigma).

Results

In samples of the perfusion fluid obtained during spontaneous overflow only NA was detectable. The amounts were greatest after setting up the preparations and declined from t = 30 to t = 60 min to a lower steady value, namely 0.4 ± 0.04 ng 30 min^{-1} for the main trunk and 1.1 ± 0.09 ng 30 min^{-1} for the proximal branches. No drug used in the course of these experiments significantly altered the spontaneous overflow of NA from any vascular preparations used in this study.

The experiments where the main trunk of the mesenteric artery and its proximal branches were exposed to a K^+-enriched Krebs solution from t = 60 to t = 90 min showed that both dopamine and NA were released. Phentolamine increased the fractional release of both amines about two fold in the proximal branches of the mesenteric artery. However, for the main trunk from the same blood vessel the increase of dopamine and NA fractional release induced by phentolamine was only about 50 and 60%, respectively (Figure 1).

Although in the proximal branches of the mesenteric artery sulpiride significantly increased both dopamine and NA fractional release, for the main trunk sulpiride did not change the dopamine and NA release due to depolarization by K^+ (Figure 2). When the proximal branches of the mesenteric artery where perfused with K^+-enriched Krebs solution containing sulpiride plus phentolamine, values for dopamine and NA fractional release were significantly greater than those of experiments with phentolamine alone (Figure 3). For the main trunk the effect of sulpiride plus phentolamine on dopamine and NA release was of

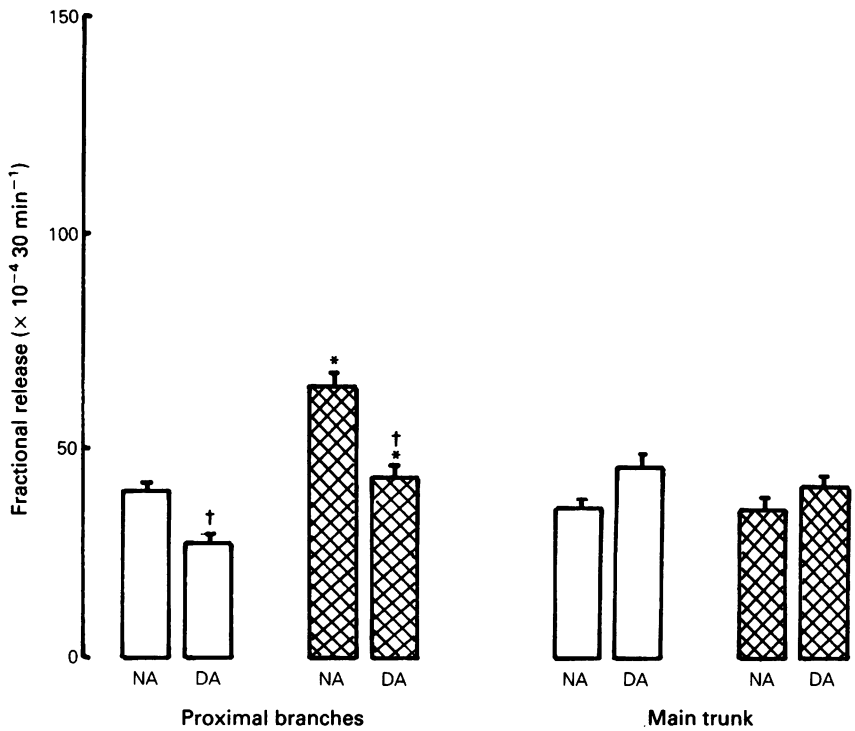

Figure 2 The effect of sulpiride (1 μM; hatched columns) on the release of noradrenaline (NA) and dopamine (DA) from the main trunk of the mesenteric artery and its proximal branches during depolarization by K^+ (52 mM). Open columns represent control release. The release of NA and dopamine is expressed as a fraction of the tissue amine content. Each column represents the mean of five experiments per group, vertical lines show s.e.mean. *Significantly different from control values ($P<0.01$). † Significantly different from corresponding NA values ($P<0.01$).

about the same order of magnitude as that produced by phentolamine alone (Figure 3).

Apomorphine significantly reduced dopamine and NA release in both segments of the mesenteric artery (Figure 4). This inhibitory effect of apomorphine was antagonized by sulpiride (Figure 5). As shown in Figure 6, the inhibitory effect of apomorphine on the dopamine and NA fractional release in the proximal branches and main trunk was still present when α-adrenoceptors were blocked by phentolamine.

Although for the main trunk of the mesenteric artery dopamine and NA release were of about the same order of magnitude in all experimental conditions, for the proximal branches dopamine fractional release was significantly lower than that of NA in both control conditions and when phentolamine, sulpiride or apomorphine was present. Only when the proximal branches were perfused with the solution containing phentolamine plus sulpiride were dopamine fractional release values similar to NA fractional release values.

Discussion

The present study shows that K^+-induced depolarization released both dopamine and NA from intramural nerve endings and that prejunctional dopamine receptors are located on sympathetic fibres supplying the main trunk of the mesenteric artery and its proximal branches. In fact, the dopamine receptor agonist apomorphine significantly decreased dopamine and NA release and its inhibitory effect was selectively abolished by sulpiride, in both segments of the mesenteric artery.

One of the criteria used to determine whether a prejunctional receptor mechanism plays a physiological role in inhibiting NA release is that, an increase in release of the transmitter and a larger effector organ response during sympathetic nerve stimulation after blockade of these receptors occurs (Starke, 1977; Langer, 1981). The increase in the K^+-evoked release of dopamine and NA after blockade of

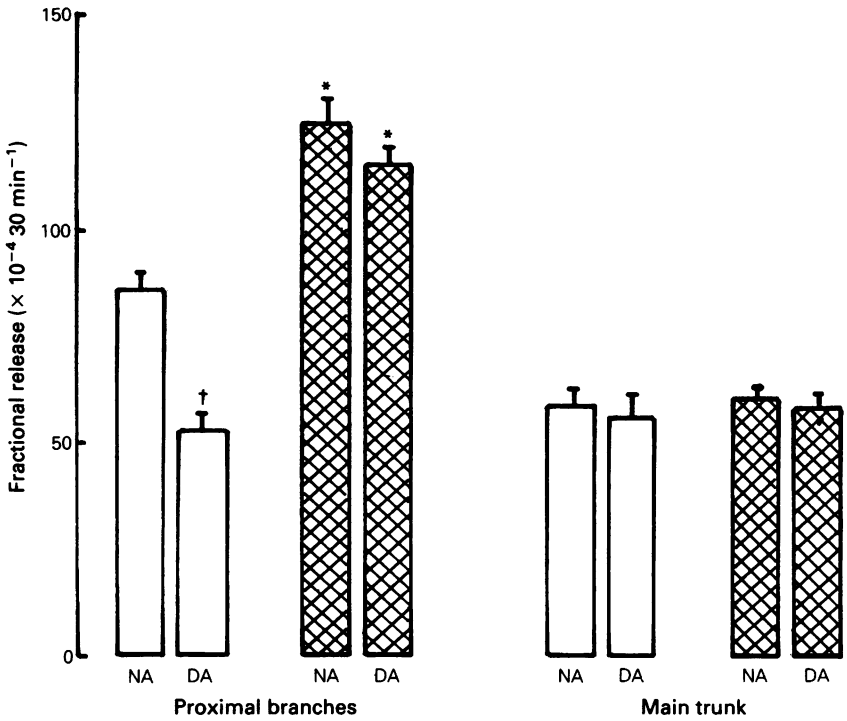

Figure 3 The effect of sulpiride (1 μM; hatched columns) on the release of noradrenaline (NA) and dopamine (DA) from the main trunk of the mesenteric artery and its proximal branches during depolarization by K^+ (52 mM) in phentolamine (0.2 μM) treated preparations. Open columns represent control phentolamine-treated preparations. The release of NA and dopamine is expressed as a fraction of the tissue amine content. Each column represents the mean of five experiments per group; vertical lines show s.e.mean. *Significantly different from control values ($P < 0.01$). † Significantly different from corresponding NA values ($P < 0.01$).

α-adrenoceptors by phentolamine is in agreement with a physiological role of prejunctional α-adrenoceptors on the negative feedback control of transmitter release. However, for most of the preparations examined, blockade of prejunctional inhibitory dopamine receptors did not *per se* increase the release of the transmitter during nerve stimulation, thus suggesting that prejunctional dopamine receptors do not play a physiological role in noradrenergic transmission (Langer, 1981; Lokhandwala & Barrett, 1982; Willems *et al*, 1985; Soares-da-Silva, 1987b).

The same result was obtained when the main trunk of the mesenteric artery was considered; sulpiride did not enhance the release of either amine. In contrast, sulpiride significantly increased both dopamine and NA release in the proximal branches of the mesenteric artery. Thus, it seems that in this blood vessel released dopamine may physiologically activate prejunctional inhibitory dopamine receptors. It should be noted that the proximal branches of the mesenteric artery are unusual blood vessels in that part of the existing dopamine has been found to be in the form of a NA-independent non-precursor pool (Soares-da-Silva & Davidson, 1985; Soares-da-Silva, 1986a) with a pattern of release different from that of NA (Soares-da-Silva, 1987a).

Although for the main trunk of the mesenteric artery dopamine and NA release values were of the same order of magnitude, in the proximal branches K^+-evoked release of dopamine was significantly lower than that of NA. These results suggest that in the proximal branches of the mesenteric artery dopamine and NA are not equally available for release by depolarization. This could be due to the presence in sympathetic neurones of two different compartments; one more accessible to depolarization, containing mainly NA, and the other less accessible to depolarization and containing a higher proportion of dopamine (Soares-da-Silva, 1987a). When the proximal branches were perfused with a solution containing phen-

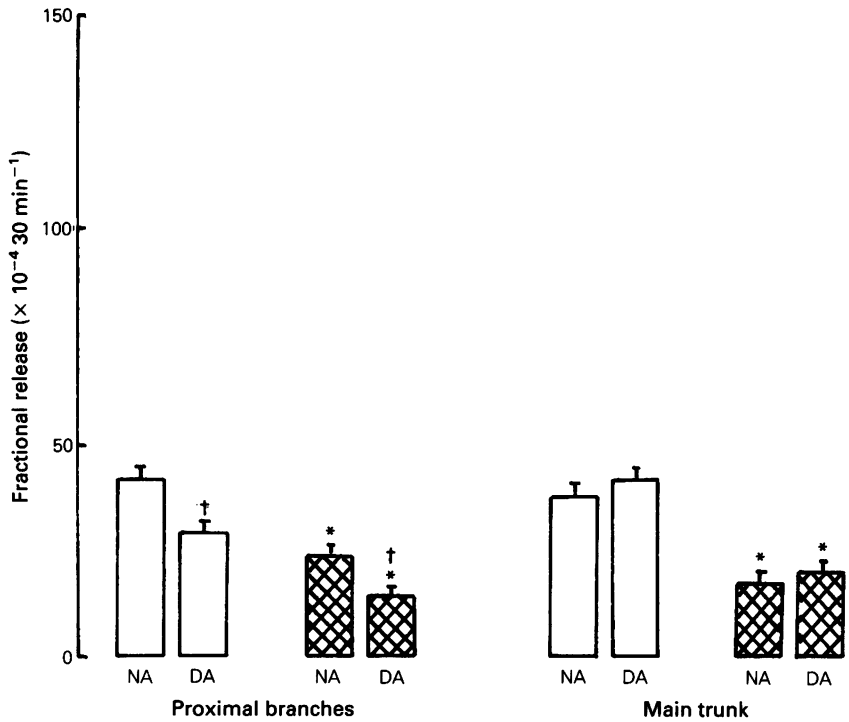

Figure 4 The effect of apomorphine (0.3 μM; hatched columns) on the release of noradrenaline (NA) and dopamine (DA) from the main trunk of the mesenteric artery and its proximal branches during depolarization by K^+ (52 mM). Open columns represent control release. The release of NA and dopamine is expressed as a fraction of the tissue amine content. Each column represents the mean of five experiments per group; vertical lines show s.e.mean. *Significantly different from control values ($P < 0.01$). †Significantly different from corresponding NA values ($P < 0.01$).

tolamine plus sulpiride, dopamine and NA release values were virtually the same; this result suggests that, in this particular situation, the exocytotic process of amine release became so facilitated that both amines participate equally in transmitter outflow.

Another point which deserves further attention concerns the effects of phentolamine and sulpiride on the dopamine and NA release in the proximal branches. As previously mentioned, phentolamine increased the release of dopamine and NA similarly, both during electrical nerve stimulation and K^+-induced depolarization; this was interpreted as the result of the release of both amines from the same sympathetic neurone (Soares-da-Silva, 1987a). In fact, in a dopaminergic nerve terminal there would be no NA release to activate the α-adrenoceptor mediated feedback system. The results presented in this study regarding the effect of phentolamine on dopamine and NA fraction release confirm those previously demonstrated. Furthermore, if the released dopamine was derived from independent dopaminergic neurones, sulpiride would probably not induce a parallel increase in dopamine and NA release. Thus, it is highly unlikely that dopamine comes from independent dopaminergic neurones but almost certain that both dopamine and NA are released from the same sympathetic neurone.

In recent years the existence of independent dopaminergic neurones in some well-defined areas has been proposed (Bell, 1982a; Relja & Neff, 1983). Some of the criteria used to suggest the existence of independent dopaminergic neurones are the presence of high levels of dopamine and a high dopamine/NA ratio (Bell & Gillespie, 1981), histochemical visualization of catecholamines after administration of 6-hydroxydopamine (6-OHDA) and guanethidine (Bell *et al.*, 1978a,b; Commissiong *et al.*, 1978; Dinerstein *et al.*, 1979; Lackovic & Neff, 1980), the dopamine-mediated vasodilatation after nerve stimulation of some peripheral sympathetic nerves (Bell, 1982b; Clark, 1985)

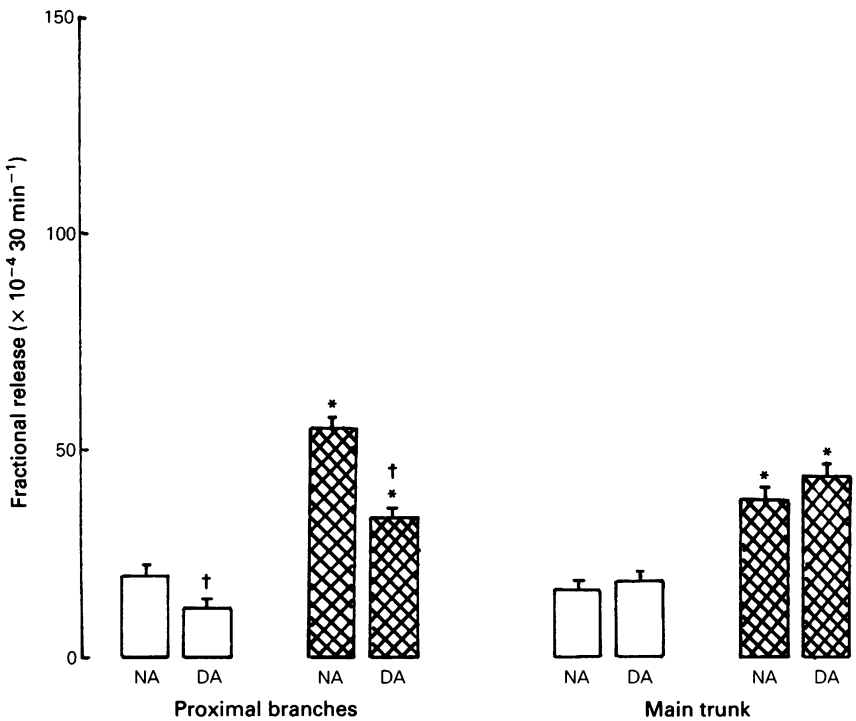

Figure 5 The effect of sulpiride (1 μM; hatched columns) on the release of noradrenaline (NA) and dopamine (DA) from the main trunk of the mesenteric artery and its proximal branches during depolarization by K^+ (52 mM) in apomorphine (0.3 μM) treated preparations. Open columns represent control apomorphine-treated preparations. The release of NA and dopamine is expressed as a fraction of the tissue amine content. Each column represents the mean of five experiments per group; vertical lines show s.e.mean. *Significantly different from control values ($P < 0.01$). † Significantly different from corresponding NA values ($P < 0.01$).

and the well-documented existence of specific receptors for dopamine (Goldberg, 1972; Lokhandwala & Barrett, 1982; Willems *et al.*, 1985). However, evidence in favour of a widely distributed peripheral dopaminergic system (Lackovic & Relja, 1983) has not found much support, at least if one thinks of that system as being formed by dopaminergic neurones (Bell, 1987). Thus, before one admits the possibility of independent dopaminergic neurones in tissues where dopamine has been found to exist as a noradrenaline-independent non-precursor substance, it seems reasonable to discuss the possibility that dopamine and NA may coexist in the same sympathetic neurone in two different compartments. As far as the proximal branches of the mesenteric artery are concerned, this seems to be the most likely explanation, since the 6-OHDA-insensitive dopamine pool which has been found to occur in that particular tissue can be explained either by differences in dopamine β-hydroxylase activity (Soares-da-Silva, 1986a) or by substrate compartmentation (Soares-da-Silva, 1987a). Since the existence of a specific receptor is not a self-evident prerequisite for a substance to be located in an independent neurone, though it could be for a substance to act as a transmitter or co-transmitter, it can be speculated that in those areas where dopamine was ascribed to non-noradrenergic neurones the amine could exist as a transmitter, or co-transmitter, in sympathetic neurones and not necessarily in 'independent' dopaminergic neurones. One particular exception seems to be the nervous supply to the canine paw pads where substantial evidence has been presented in favour of the existence of an independent dopaminergic innervation (Bell & Lang, 1974; 1979; Bell *et al.*, 1975; 1978a; Bell, 1982b).

In conclusion, the present results show that inhibitory dopamine prejunctional receptors are located on sympathetic nerve terminals supplying both segments of the mesenteric artery and suggest that dopamine and NA released from the proximal branches act on different prejunctional receptors

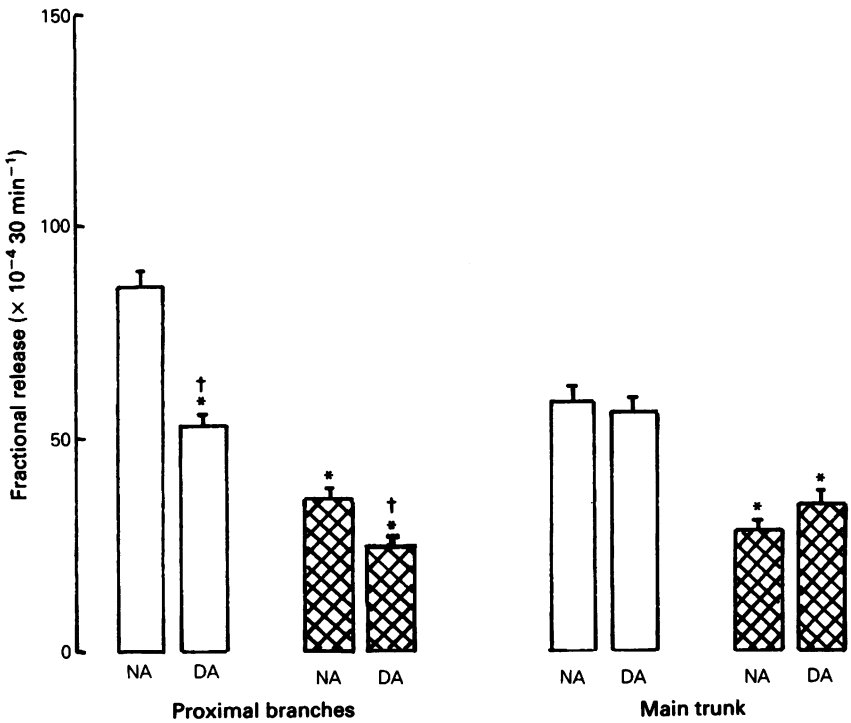

Figure 6 The effect of apomorphine (0.3 μM) on the release of noradrenaline (NA) and dopamine (DA) from the main trunk of the mesenteric artery and its proximal branches during depolarization by K^+ (52 mM) in phentolamine (0.2 μM)-treated preparations. Open columns, phentolamine-treated preparations; hatched columns, phentolamine + apomorphine-treated preparations. The release of NA and dopamine is expressed as a fraction of the tissue amine content. Each column represents the mean of five experiments per group; vertical lines show s.e.mean. *Significantly different from control values ($P < 0.01$). † Significantly different from corresponding NA values ($P < 0.01$).

(dopamine receptors and α-adrenoceptors), which have a role in controlling transmitter release. The results presented here, together with other findings previously reported on this subject (i.e. those concerning the different pattern of dopamine and NA release), also suggest that dopamine in the proximal branches of the dog mesenteric artery could be present as a co-transmitter.

The author is indebted to Professor Walter Osswald for his comments and helpful suggestions. The skilful technical assistance of Misses Prazeres Cleto and Manuela Moura is gratefully acknowledged. This work was supported by Instituto Nacional de Investigação Científica (FM P-1) (Portugal).

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Received November 18, 1986.
Revised March 17, 1987.
Accepted March 24, 1987.)