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DOPAMINE ACTS AT THE SAME RECEPTORS AS NORADRENALINE IN THE RAT ISOLATED VAS DEFERENS

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1 The proposal that dopamine activates a different population of receptors from those activated by noradrenaline and phenylephrine to cause contraction of the rat vas deferens has been investigated using a preparation of the epididymal half of this tissue.

2 In preparations preincubated in cocaine, oestradiol and propranolol, to block sites of amine loss and β-adrenoceptors, noradrenaline was the most, and dopamine the least, potent of the three agonists. Phentolamine competitively inhibited each of the agonists to a similar extent. Prazosin also inhibited the actions of the three agonists to a similar extent. These results indicate that the three agonists activate a single population of α_1-adrenoceptors to cause contraction in this preparation.

3 In experiments using the prostatic half of the rat vas deferens, in the presence of cocaine, oestradiol, propranolol and prazosin, noradrenaline was approximately 40 times more potent than dopamine in causing inhibition of twitches induced by electrical field stimulation. Yohimbine competitively antagonized the effects of the two agonists to a similar extent indicating that both act at the same population of α_2-adrenoceptors.

4 Taken together, these findings do not lend support to proposals that there are populations of specific dopamine receptors located pre- and postjunctionally in the rat vas deferens.

Introduction

Controversy has surrounded the existence of specific pre- and postjunctional dopamine receptors in the rat vas deferens. Simon & Van Maanen (1971, 1976) proposed that there are specific postjunctional dopamine receptors, since they found that pA_2 values, determined in the presence and absence of cocaine, for phentolamine with noradrenaline or phenylephrine, were different from that obtained with dopamine. These authors have also reported differences in pA_2 values for haloperidol with dopamine and with noradrenaline. In contrast, Patil, Burkman, Yamauchi & Hetey (1973) obtained no clear evidence for the existence of separate postjunctional receptors for dopamine in the rat vas deferens, since in their study both phentolamine and apomorphine were equieffective in antagonizing the effects of noradrenaline and dopamine.

Dopamine inhibits the stimulation-induced release of tritium from vasa deferentia preloaded with [^{3}H]-(−)-noradrenaline (Pennefather, Handberg, Shipley & Taylor, 1979). Tayo (1977, 1979a) has proposed the existence of specific prejunctional receptors, which dopamine activates to inhibit twitches in the field-stimulated rat vas deferens. This worker determined pA_2 values for antagonists, and found that yohimbine, a specific prejunctional α_2-adrenoceptor antagonist, was more potent against noradrenaline than against dopamine; while for pimozide, a specific dopamine antagonist, the reverse was true.

In 1972, Furchgott enumerated the experimental conditions which must be met in studies designed to determine, by the pA_2 method of Arunlakshana & Schild (1959), the nature of the receptors at which catecholamines act. These include the use of inhibitors of sites of amine loss; the use of specific antagonist drugs to block actions at receptor sites other than those under study; and the use of equilibrium conditions for the antagonist being used as a tool in the investigation. Furchgott also emphasized the importance of including a test of the competitive nature of the antagonism, by the antagonist, of the agonists under study. The more general importance of all these conditions, in receptor classification, has recently been emphasized in a series of papers by Kenakin (for a review see Kenakin, 1982).

In the studies of Simon & Van Maanen (1971, 1976), Tayo (1979b), and Badia, Bermejo & Jané (1982) from which it was concluded that dopamine activates a population of postjunctional receptors distinct from those activated by noradrenaline, the criteria outlined by Furchgott and by Kenakin were not met. The same criticism can, however, be directed to those studies from which it has been concluded that the two agonists activate the same

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population of postjunctional α-adrenoceptors (Van Rossum, 1965; Patil *et al.*, 1973). Similar criticisms can also be made of the studies of Tayo (1977, 1979a, 1981) and of Badia *et al.* (1982) of the actions of these two agonists at prejunctional receptors in the rat vas deferens. The present study in which the criteria outlined by Furchgott have been met, was therefore conducted to resolve the uncertainty which continues to persist as to the nature of the receptors activated by dopamine in the rat vas deferens. A preliminary account of the results of these experiments has been presented to the Annual Meeting of the Australian Society of Clinical and Experimental Pharmacologists (Leedham & Pennefather, 1982).

Methods

Male Long Evans Hooded rats (180–250 g) were killed by a blow to the head and each vas deferens was removed. Each tissue was bisected transversely and the prostatic and epididymal segments were set up in separate 30 ml organ baths. The prostatic segments were field-stimulated at 0.05 Hz, 1 ms and 60 V, as described previously (Pennefather, Vardolov & Heath, 1974; Leedham, Handberg, Ishac & Pennefather, 1981). The epididymal segments were not stimulated. The bathing solution had the following composition (mmol/l): NaCl 118.05, KCl 4.69, $MgSO_4 7H_2O$ 0.45, KH_2PO_4 1.18, $NaHCO_3$ 25.00, glucose 11.66 and $CaCl_2$ 2.52 and was bubbled with 5% CO_2 in O_2 at 37°C.

The prostatic segment was used to determine log concentration-response curves for noradrenaline and dopamine, both of which cause reduction of twitch height in this portion of the vas deferens via activation of prejunctional receptors to decrease the release of transmitter (Vardolov & Pennefather, 1976; Pennefather *et al.*, 1979). The epididymal segment was used to determine log concentration-response curves for noradrenaline, phenylephrine and dopamine, which cause contraction of the smooth muscle in this portion of the tissue via activation of postjunctional receptors (Vardolov & Pennefather, 1976).

In all of the experiments the following drugs were added to the bathing solution: cocaine (10 μmol/l), to block neuronal uptake; oestradiol (10 μmol/l), to block extraneuronal uptake; and propranolol (1 μmol/l), to block β-adrenoceptors. Prazosin (50 nmol/l) was also added to the bathing solution in experiments using prostatic segments of the vas deferens, to block postjunctional α_1-adrenoceptors.

After a preliminary equilibration period of 60 min, cumulative concentration-response curves for the agonists were obtained in both the epididymal and prostatic segments of tissues from each rat, with dose progression ratios of three and two respectively. Each dose was added when the response to the previous dose had reached a plateau. On completion of each concentration-response curve, tissues were washed with four to six times the bath volume of bathing solution. Two curves were obtained, with an interval of 20–30 min between them, before the addition of the α-adrenoceptor antagonists. The latter were allowed to equilibrate with the tissue for 30 or 60 min before concentration-response determinations for the agonists were repeated. Three different doses of each of the antagonists (phentolamine 0.1–5.0 μmol/l; prazosin 2.0–100 nmol/l; and yohimbine 10–300 nmol/l) were employed. The potencies of dopamine and noradrenaline, and the pA_2 vlues for the antagonists with either of the agonists were determined using paired preparations from any one animal. Studies with phenylephrine were conducted using tissues from a separate group of rats.

The potencies of agonists were expressed as pD_2 values which are the negative log molar concentrations producing 50% of the maximum effect. Comparisons of differences between mean values were made by means of either paired or unpaired Student's *t* tests.

Dose-ratios were determined from the concentrations causing either 50% of the maximum inhibition of the twitch response or 50% of the maximum contraction obtained in the prostatic and epididymal segments respectively, at each dose of antagonist. The pooled log (dose-ratio − 1) values thus obtained in each experiment were plotted against log antagonist concentration in the form of a Schild plot (Arunlakshana & Schild, 1959). From these pooled data a mean slope and its 95% confidence limits were obtained. The x-intercepts, and their 95% confidence limits, from these Schild plots were determined and were called pA_2 values only if the slopes of the regression lines were not significantly different from unity.

Drugs

The following drugs were used: (−)-noradrenaline-D-bitartrate (Sigma); dopamine hydrochloride (3-hydroxytyramine, Sigma); (−)-phenylephrine hydrochloride (Koch-Light Laboratories); phentolamine hydrochloride (Ciba-Geigy): prazosin (Pfizer); yohimbine hydrochloride (Sigma); cocaine hydrochloride (MacFarlan-Smith); β-oestradiol (Sigma); propranolol hydrochloride (I.C.I., Australia).

Noradrenaline, dopamine and phenylephrine were dissolved in a catecholamine diluent of the following composition (mmol/l); NaCl 154, NaH_2PO_4 1.2, ascorbic acid 0.23. Dopamine was made fresh daily and

Table 1 Mean pD_2 values for agonists at postjunctional receptors in epididymal segments in the presence of cocaine (10 μmol/l), oestradiol (10 μmol/l) and propranolol (1 μmol/l)

Agonists	*pD_2* mean ± s.e.mean (*n*)
Noradrenaline (NA)	7.03 ± 0.06 (22)
Dopamine	4.94 ± 0.11 (18)*
Phenylephrine	6.53 ± 0.04 (16)*

n = number of experiments.
*Significantly different from corresponding value for NA ($P < 0.05$, non-paired *t* tests).

noradrenaline and phenylephrine were frozen overnight and kept for no longer than 3 days. Cocaine, yohimbine, phentolamine and propranolol were dissolved in distilled water and oestradiol was dissolved in ethanol. Solutions were prepared daily. A stock solution of prazosin was prepared by suspending an amount of prazosin in glycerol and after standing in the dark for 20 min, a 5% w/v dextrose solution was added slowly whilst swirling vigorously. The stock solution was stored at 4°C.

Results

Postjunctional receptors

Dopamine, noradrenaline and phenylephrine produced concentration-dependent contractions of epididymal segments of the rat vas deferens. Each agonist produced similar maximal responses. The mean pD_2 values are shown in Table 1: the order of potency of these agonists was noradrenaline > phenylephrine > dopamine. The pA_2 values and slopes of Schild plots for the antagonists phentolamine and prazosin are shown in Tables 2 and 3. The slopes of Schild plots for prazosin with all three agonists, and for phentolamine with phenylephrine exceeded unity when the period of incubation with the antagonist was 30 min. Therefore only x-intercept values are given in Table 2. Slopes of Schild plots for phentolamine with noradrenaline and dopamine after 30 min equilibration, and with phenylephrine after 60 min equilibration (Table 3), did not differ significantly from unity ($P > 0.05$), and similar pA_2 values were obtained with all three agonists.

Further experiments were conducted in which three different concentrations of prazosin were each incubated with tissues for 60 min before repetition of noradrenaline and dopamine concentration-response curves. The results are shown in Table 3. Under these conditions, with noradrenaline as the agonist, the slopes of Schild plots did not differ significantly from unity ($P > 0.05$) and the resultant mean pA_2 estimate exceeded that obtained with the shorter incubation period. With dopamine, however, the mean slope of the Schild plot was still significantly greater than unity.

Table 2 Mean pA_2 (or x-intercept[1]) values and slopes with 95% confidence limits from Schild plots for antagonists at postjunctional adrenoceptors in epididymal segments, after a 30 min incubation in presence of cocaine (10 μmol/l), oestradiol (10 μmol/l) and propranolol (1 μmol/l)

	Antagonists			
	Phentolamine		*Prazosin*	
Agonists	*Slope*	*pA_2* ([1]x-intercept)	*Slope*	*[1]x-intercept*
Noradrenaline	−0.90 (0.72–1.08)	7.72 (7.42–8.17)	−1.39 (1.12–1.65)	[1]8.49 (8.31–8.76)
Dopamine	−0.88 (0.51–1.26)	7.90 (7.54–8.71)	−1.66 (1.30–2.03)	[1]8.43 (8.27–8.64)
Phenylephrine	−1.20 (1.05–1.36)	[1]7.77 (7.61–7.97)	−1.45 (1.22–1.67)	[1]8.50 (8.34–8.71)

The number of animals used was 7 for phentolamine and 5 for prazosin, and the number of data points were 21 and 15 respectively.
[1]x-intercept values are quoted when the 95% confidence limits for mean slope do not include 1.

Table 3 Mean pA_2 values (or x-intercept[1]) and slopes with 95% confidence limits from Schild plots for antagonists at postjunctional adrenoceptors in epididymal segments, after a 60 min incubation in presence of cocaine (10 μmol/l), oestradiol (10 μmol/l) and propranolol (1 μmol/l)

	Antagonists			
	Phentolamine		*Prazosin*	
Agonist	*Slope*	*pA_2*	*Slope*	*pA_2* ([1]x-intercept)
Noradrenaline	−1.09 (0.67–1.50)	7.71 (7.35–8.48)	−1.05 (0.86–1.23)	9.13* (8.88–9.49)
Phenylephrine	−1.16 (0.70–1.61)	7.65 (7.30–8.42)	—	—
Dopamine	—	—	−1.49 (1.35–1.63)	[1]8.77 (8.70–8.86)

Number of animals was 4 for phentolamine and 3 for prazosin and the number of data points was 12 and 18 respectively.
*Significantly different from corresponding value with 30 min incubation ($P < 0.05$, non-paired t test).
[1]x-intercept values are quoted when 95% confidence limits for mean slopes do not include 1.

Prejunctional receptors

Dopamine and noradrenaline produced concentration-dependent inhibition of field stimulation-induced contractions of prostatic segments of the rat vas deferens (Figure 1). The mean pD_2 values are shown in Table 4; noradrenaline was approximately 40 times more potent than dopamine.

The pA_2 values and slopes of Schild plots for yohimbine with these agonists are also shown in Table 4. The mean slopes of Schild plots were not significantly different from unity and the pA_2 values obtained with each agonist did not differ significantly from one another ($P > 0.05$).

Discussion

The results of the present study do not lend support to the proposal of Simon & Van Maanen (1976) that dopamine activates a specific population of postjunctional dopamine receptors to cause contraction of the rat was deferens, nor to that of Tayo (1979a) that this catecholamine activates a specific population of dopamine receptors, prejunctionally, to inhibit field stimulation-induced twitches in this tissue.

The proposal of Simon & Van Maanen (1976) that dopamine activates a population of postjunctional receptors which differs from that activated by noradrenaline and phenylephrine, was based in part upon their observation that the pA_2 estimate they obtained for phentolamine with dopamine as the agonist was higher than the corresponding estimates with either noradrenaline or phenylephrine as the agonist. In the majority of experiments Simon & Van Maanen omitted to add drugs which block sites of catecholamine loss and β-adrenoceptors to the bathing medium, and in addition, they incubated antagonist drugs for only 10 min. In contrast, we have studied the antagonism by phentolamine of dopamine, noradrenaline and phenylephrine using preparations which were preincubated for 60 min with propranolol, oestradiol, and cocaine to block β-adrenoceptors and sites of catecholamine loss, and in which phentolamine was allowed to equilibrate with the tissues for either 30 or 60 min. Under the latter conditions estimates of the potency of an antagonist can be expected to reflect more accurately its affinity for the receptors activated by the agonists employed (Furchgott, 1972; Kenakin, 1980b). Our finding that, after 60 min incubation, phentolamine was equipotent in antagonizing competitively the effects of all three agonists used, indicates that each of these agonists activates the same homogeneous population of postjunctional receptors.

The pA_2 estimates for phentolamine we obtained exceed those determined by Simon & Van Maanen (1976) but are similar to those reported by Furchgott (1980) for the antagonism by phentolamine of phenylephrine on strips of rabbit aorta ($pA_2 = 7.8$) and by Doxey, Smith & Walker (1977) for the antagonism of noradrenaline on the anococcygeus muscle of the rat ($pA_2 = 7.7$). The pA_2 estimates we have obtained for phentolamine with all three agonists, together with the relative order of potency of the agonists, which was noradrenaline > phenylephrine > dopamine, indicate that all three agonists activate α-adrenoceptors.

Although the slopes of the Arunlakshana-Schild plots exceed unity when the selective α_1-

Table 4 Mean pD_2 values for agonists, pA_2 values and slopes from Schild plots for yohimbine at prejunctional adrenoceptors in prostatic segments after a 30 min incubation in presence of cocaine (10 μmol/l), oestradiol (10 μmol/l), propranolol (1 μmol/l) and prazosin (50 nmol/l)

Agonist	pD_2 mean ± s.e.mean (*n*)	*Yohimbine* mean (95% confidence limits) *Slope*	pA_2
Noradrenaline	8.12 ± 0.17 (5)	−1.33 (0.80–1.86)	8.38 (8.07–9.05)
Dopamine	6.54 ± 0.23 (5)*	−0.98 (0.77–1.19)	8.43 (8.24–8.71)

n = number of animals. The number of data points for each pA_2 determination was 15.
*Significantly different from corresponding value for noradrenaline ($P < 0.05$, paired *t* test).

adrenoceptor antagonist prazosin was used, this antagonist was also found, after 30 min incubation, to be equipotent in inhibiting responses to each of the agonists, indicating that these act at α_1-adrenoceptors. In recent studies. Kenakin (1980b) has demonstrated that the slopes of Schild plots with several antagonists most closely approach unity when sufficiently long periods of incubation of the tissue with these antagonists are employed. When the period of incubation of prazosin with the vas deferens was increased from 30 to 60 min, an increase in the potency of this antagonist, coupled with a decrease in the slopes of Arunlakshana-Schild plots with both noradrenaline and dopamine was observed; although with the latter agonist the slope still differed from unity. It may be that an incubation period even longer than 60 min is required for complete equilibration when this antagonist is used.

Our studies of the actions of noradrenaline and dopamine in inhibiting twitches evoked by field stimulation, and of the ability of yohimbine to block these actions, have yielded results which differ from those of Tayo (1979a). Tayo obtained pA_2 estimates for yohimbine with dopamine, on the undivided vas deferens, which were significantly lower than those obtained for yohimbine with chlonidine and with noradrenaline; however, sites of agonist loss and β-adrenoceptors were not blocked. Moreover, al-

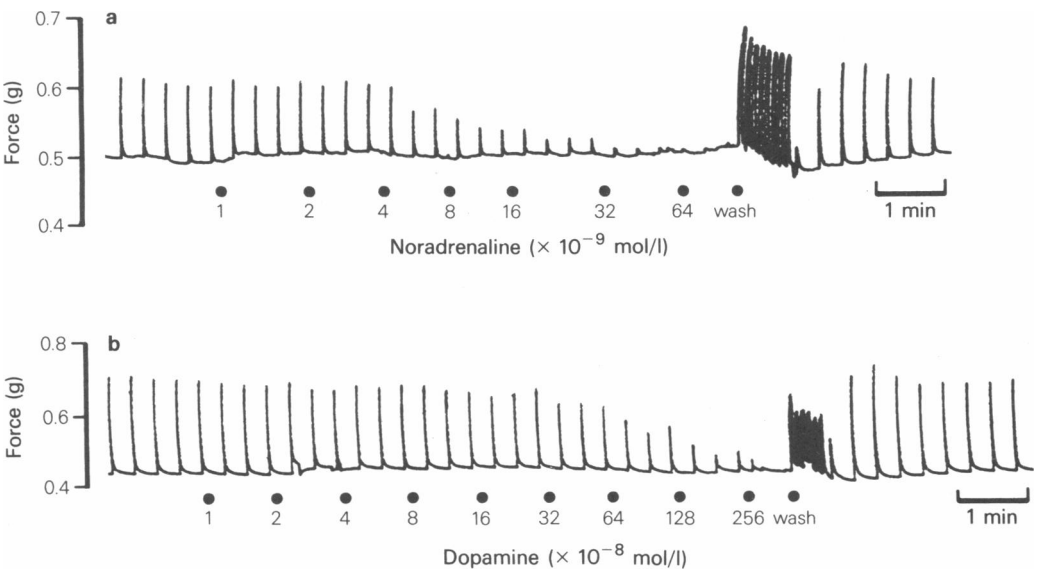

Figure 1 Typical cumulative concentration-response curves for (a) noradrenaline, and (b) dopamine in the field stimulated prostatic segment of the isolated vas deferens of the rat. Stimulation parameters were 0.05 Hz, 1 ms, and a supramaximal voltage (60 V). Drug additions are indicated by (●).

though dopamine and noradrenaline, like clonidine, reduce the stimulation-induced efflux of tritium from preparations of vasa deferentia pre-incubated in [^{3}H]-noradrenaline, indicating action at a prejunctional site (Vizi, Somogyi, Hadházy & Knoll, 1973; Pennefather *et al.*, 1979) these agonists, unlike clonidine, cause contraction of the undivided vas deferens in the dose range used by Tayo (1979a). Our use of the prostatic half of the tissue, in which the excitatory efficacy of noradrenaline and adrenaline is low (Vardolov & Pennefather, 1976; Kasuya & Suzuki, 1979; Brown, McGrath & Summers, 1979); together with the inclusion of prazosin in the bathing medium, eliminated these contractions. Sites of catecholamine loss and β-adrenoceptors were also blocked in our experiments.

Under the conditions outlined above, noradrenaline was found to be 40 times more potent than dopamine in inhibiting twitches induced by field stimulation. Furthermore, the pA_2 values for yohimbine with noradrenaline were found to be similar to those with dopamine, and to those reported by Doxey, Smith & Walker (1977) and by Kapur & Mottram (1978), using the selective α_2-adrenoceptor agonist, clonidine, in this tissue.

These results show, as previously emphasized by Furchgott (1972) and, more recently, by Kenakin (1980a, b), that misleading estimates of agonist potencies and of pA_2 values can result when neither saturable uptake mechanisms reducing the concentration of agonists in the biophase, nor activation by agonists of other receptor sites are blocked; and when antagonists are in contact with tissues for periods too short to allow complete equilibration with receptor sites. In consequence, apparent differences in the nature of receptors activated by agonists may emerge where no real differences exist. These factors have apparently influenced the results of Tayo (1979 a, b) and of Simon & van Maanen (1976) in their studies using phentolamine and yohimbine which have led them to propose the existence of distinct populations of pre- and postjunctional dopamine receptors in the rat vas deferens.

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