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Pharmacological analysis of the responsiveness of guinea-pig lung parenchymal strip to dopamine

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1 Responses to dopamine were examined in the guinea-pig isolated lung parenchymal strip.

2 Complete cumulative concentration-response curves to dopamine exhibited a biphasic pattern with a small initial contraction at concentrations below 10^{-5} M followed by a dose-dependent relaxation at higher concentrations.

3 Phentolamine (10^{-5} M) completely abolished the contractile component and enhanced sensitivity and maximal relaxation to dopamine. In the presence of phentolamine, propranolol antagonized the dopamine-induced relaxation ($pA_2 = 8.54 \pm 0.07$). In the presence of propranolol (10^{-6} M), dopamine produced a dose-related contraction displaced to the right by phentolamine. Incubation with haloperidol (10^{-5} M) did not modify the characteristics of the concentration-response curve to dopamine.

4 Pretreatment with reserpine abolished the contraction to dopamine without affecting its relaxant response. Cocaine significantly increased the pD_2 value of dopamine in the presence of propranolol.

5 It is concluded that dopamine produced both relaxation of lung parenchymal strip due to direct activation of β-adrenoceptors and contraction mediated through direct and indirect (catecholamine release) actions at α-adrenoceptors. There is no evidence in favour of the existence of specific dopamine-receptors in this preparation.

Introduction

The pharmacological effects of sympathomimetic drugs upon the respiratory system have been studied extensively (Aviado & Micozzi, 1981) but while the action of α- or β-adrenoceptor agonists is reasonably characterized, the effects of dopamine on airway smooth muscle have received little attention compared with those on the cardiovascular system (Goldberg, 1972). However these effects could be important from a clinical as well as a pharmacological standpoint since patients receiving dopamine for haemodynamic reasons also may have airway disease and because dopamine is present in the lung (Eyre & Deline, 1971) and is released in anaphylaxis, at least in some animal species (Falck *et al.*, 1964).

Furthermore, results in the literature are contradictory. Thus Aviado & Sadavongvivad (1970) reported that dopamine has a bronchoconstrictor action in the dog, cat, rabbit and goat whereas Key *et al.* (1978) and Advenier *et al.* (1980) observed bronchodilation in the dog and guinea-pig respectively. Thomson & Patel (1978) failed to demonstrate any action in man. In isolated tracheal chains, dopamine elicits relaxation in the guinea-pig (Advenier *et al.*, 1980; Koga *et al.*, 1980; Michoud *et al.*, 1980) but contraction in dog and man (Michoud *et al.*, 1980). There is also controversy about the existence of specific dopamine receptors mediating bronchodilation in the airways as reported by Key *et al.* (1978) since this finding is negated by most researchers (Advenier *et al.*, 1980; Koga *et al.*, 1980; Michoud *et al.*, 1980).

The recent introduction by Lulich *et al.* (1976) of the lung parenchymal strip as an *in vitro* preparation of peripheral airways has prompted reevaluation of drug action at this level. The suggestion that contraction/relaxation of lung strip in part reflect contractile properties of tissue other than small airway smooth muscle (Evans & Adler, 1981) does not preclude the value of this preparation as a simple, convenient and less complex model of peripheral lung function. Again, while the effects of both direct α/β-adrenoceptor activators (Siegl *et al.*, 1979; Siegl & Orzechowski, 1981; Perpiñá *et al.*, 1981; Goldie *et al.*, 1982) and indirectly acting sympathomimetic

amines (Broadley *et al.*, 1981; Morcillo *et al.*, 1983) are well characterized, little information is available on the action of dopamine in this new preparation (Perpiñá *et al.*, 1981).

The present study deals with the pharmacological analysis of the responsiveness to dopamine of lung parenchymal strips obtained from guinea-pigs.

Methods

Randomly bred, male, adult guinea-pigs weighing 250–450 g were killed by a blow to the head and exsanguination and their lungs immediately removed and placed in oxygenated Krebs-Henseleit solution. A subpleural lung parenchymal strip was dissected from right and left lower lobes of each animal. The strips (20 × 3 × 3 mm) were mounted in different tissue baths containing a modified Krebs-Henseleit solution at 37°C. The composition of the physiological salt solution was (mM): NaCl 118.4, KCl 4.7, $NaHCO_3$ 25.0. $CaCl_2$ 2.5, $MgSO_4$ 0.6, KH_2PO_4 1.2, dextrose 11.1 and EDTA 0.04. This solution was aerated with 5% CO_2 in O_2 and had a pH of 7.3–7.4.

Changes in tone were recorded with a Hewlett-Packard FTA 100-1 (± 1 g) isometric force transducer connected to a Phillips PM-8222 pen recorder via an HP 8805B carrier amplifier. The strips were gently stretched up to 1 g of initial isometric force and a 60 min equilibration period was permitted before any drug addition. This initial tension of 1 g was found in preliminary experiments to allow near maximal responses to contractile and relaxant agonists. At the end of the equilibration period the length of the preparations were recorded. Agonists were added to the bath in a cumulative manner, at increments of 0.5 or 1 log units, to obtain concentration-response curves. Effective concentration 50% (EC_{50}) was calculated graphically from a plot of log concentration vs. % of the maximum response (E_{max}) produced by each agonist in individual experiments and then transformed into pD_2 (− log molar EC_{50}) values. Strips from the same animal were approximately equally responsive to the agonists; any pair which exhibited marked differences in sensitivity to agonists was discarded. If antagonists were not to be used, only one complete dose-response curve to a certain agonist was obtained in each strip. When using antagonists, after establishing the dose-response curve to one agonist on two strips from the same animal, a predetermined concentration of an antagonist was added to one of the tissues and after a 30 min incubation the dose-response curve was repeated on both strips, the second strip serving as control to monitor any time-related change in the sensitivity of the tissues to the agonists. The agonist dose-ratio, i.e. the ratio of equiactive concentrations of agonist in the absence and presence of antagonist was determined for a certain concentration of the antagonist (Gaddum *et al.*, 1955). The calculation of the pA_2 values was made from the dose-ratios for each of several (at least 3) concentrations of the antagonist according to the method of Arunlakshana & Schild (1959) using the least square regression analysis to determine the relationship between log (dose-ratio − 1) and log of the antagonist concentration. The results from test tissues were not corrected for spontaneous changes in sensitivity of control tissues but the results were used only from those experiments in which the control tissues showed less than 20% deviation from the initial concentration-response curves throughout the experiment.

A group of animals was treated with reserpine (5 mg kg^{-1} i.p.) 20 h before they were killed, in order to deplete endogenous stores of noradrenaline.

Immediately after completion of the pharmacomechanical studies the tissue was removed from the bath, blotted and weighed on a precision balance (± 0.1 mg). The changes in force resulting from the addition of drugs were directly determined from recordings and transformed into tension i.e. force ÷ unit cross-sectional area. The cross-sectional area of the preparations was determined by dividing the tissue wet weight by the tissue length.

Drug concentrations refer to the free base or acid and are expressed as a final bath concentration in

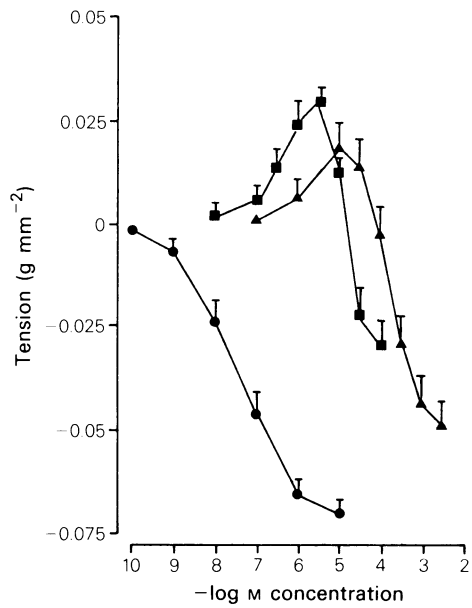

Figure 1 Concentration-response curves to dopamine (▲) ($n = 11$), noradrenaline (■) ($n = 6$) and isoprenaline (●) ($n = 6$) in lung parenchymal strips obtained from guinea-pig.

Table 1 Maximal effect (E_{max}) and pD_2 values for dopamine and other agonists in the absence and presence of various antagonists in the guinea-pig lung parenchymal strip

Agonist	*Antagonist*	*Response*	n	E_{max} (g mm^{-2})	pD_2 values
Dopamine	—	Contraction	11	0.018 ± 0.004	5.65 ± 0.11
	—	Relaxation		0.050 ± 0.005	3.80 ± 0.10
Dopamine	Phentolamine 10^{-5} M	Relaxation	8	0.069 ± 0.003	4.85 ± 0.12
Dopamine	Propranolol 10^{-6} M	Contraction	4	0.059 ± 0.003	5.20 ± 0.15
Noradrenaline	—	Contraction	6	0.030 ± 0.004	6.41 ± 0.14
	—	Relaxation		0.031 ± 0.005	4.85 ± 0.13
Noradrenaline	Phentolamine 10^{-5} M	Relaxation	5	0.069 ± 0.003	5.81 ± 0.15
Noradrenaline	Propranolol 10^{-6} M	Contraction	5	0.053 ± 0.005	6.10 ± 0.10
Isoprenaline	—	Relaxation	6	0.071 ± 0.003	7.55 ± 0.12
Acetylcholine	—	Contraction	10	0.082 ± 0.009	5.60 ± 0.15

mol l^{-1}. All data are expressed as mean ± standard error of the mean (s.e.mean). Statistical analysis of the data was by Student's *t* test at a 5% significance level.

Drug sources were: acetylcholine chloride (Roche), cocaine hydrochloride (Abelló), dopamine hydrochloride (Sigma), haloperidol (Latino), indomethacin (Merck, Sharp & Dohme), (−)-isoprenaline hydrochloride (Sigma), methoxamine hydrochloride (Wellcome), methysergide bimaleate (Sandoz), (±)-noradrenaline bitartrate (Sigma), phentolamine mesylate (Ciba), propranolol hydrochloride (ICI), reserpine (Ciba).

Results

Complete cumulative concentration-response curves to dopamine exhibited a biphasic pattern with contraction at low concentrations (10^{-7} to 10^{-5} M) and reversal of contraction followed by reduction of the intrinsic tone of the preparation for concentrations of dopamine higher than 10^{-5} M (Figure 1, Table 1). The shape of the concentration-response curve to dopamine closely resembles that of noradrenaline which also exhibited a biphasic pattern while isoprenaline elicited a dose-related relaxation.

Maximal contraction to dopamine was significantly lower than that of noradrenaline (60% of noradrenaline-maximum) and represents only 22% of acetylcholine-maximum response. Maximal relaxation to dopamine and noradrenaline was significantly lower than that obtained with isoprenaline although this may be because high enough concentrations of dopamine and noradrenaline were not used.

The concentration-response curve to dopamine could be repeated at 60 min intervals attaining an identical maximal response and pD_2 values and therefore no tachyphylaxis was observed.

Blockade of α-adrenoceptors with phentolamine (10^{-5} M) completely abolished the contractile component of the concentration-response curve to dopamine and noradrenaline and enhanced both sensitivity and the maximally attained relaxant response without modification of the concentration-response curve to isoprenaline, (Figure 2, Table 1). A good parallelism was observed between the concentration-response curves to these three agonists. After incubation with phentolamine (10^{-5} M) maximal relaxant responses to dopamine and noradrenaline were equal to that of isoprenaline but dopamine was 8.75 times less potent than noradrenaline and 500 times less potent than isoprenaline. In the presence of phentolamine (10^{-5} M) β-adrenoceptor blockade with propranolol shifted the concentration-response curve for dopamine-induced relaxation to the right in a dose-dependent manner. The analysis of this dis-

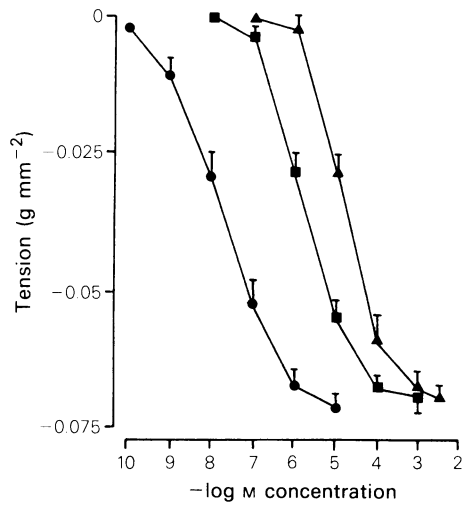

Figure 2 Concentration-response curves to dopamine (▲) (n = 8), noradrenaline (■) (n = 5) and isoprenaline (●) (n = 5) in the presence of phentolamine 10^{-5} M in guinea-pig lung parenchymal strips.

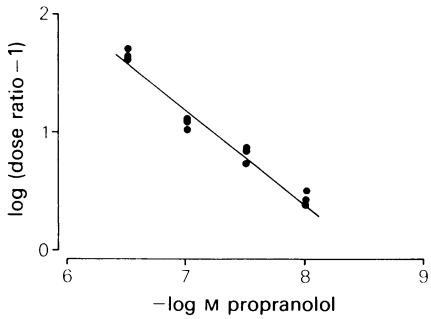

Figure 3 Dopamine dose-ratio as a function of propranolol concentration. Dopamine was added in the presence of phentolamine 10^{-5} M. The intercept on the abscissa of the regression lines for log (dose-ratio − 1) versus the negative log propranolol concentration gives a pA_2 value of 8.54 ± 0.07.

placement by use of the Arunlakshana-Schild plot is shown in Figure 3, and yielded a pA_2 value of 8.54 ± 0.07 but the result was atypical for competitive antagonism since the slope (0.77 ± 0.04) was significantly ($P < 0.05$) less than unity. Under these experimental conditions, the dose-ratio of dopamine in the presence of propranolol 10^{-7} M was not significantly different from that of isoprenaline with the same concentration of propranolol. The values were 13.4 ± 0.7 ($n = 3$) and 12.1 ± 1.1 ($n = 3$) respectively.

When lung parenchymal strips were incubated with propranolol 10^{-6} M, dopamine elicited only a contractile response as depicted in Figure 4 with a maximal response significantly higher than control but without modification of sensitivity (Table 1). In the presence of propranolol 10^{-6} M, phentolamine 10^{-5} M displaced the concentration-response curve to dopamine to the right in a parallel manner with a calculated dose-ratio of 52 ± 4 ($n = 3$). The dose-ratio for noradrenaline (plus propranolol 10^{-6} M) in the presence of phentolamine 10^{-5} M was 47 ± 6 ($n = 3$); not significantly different from that reported for dopamine in the same experimental conditions. In the presence of a lower concentration of propranolol, the biphasic pattern of the dopamine concentration-response curve is still apparent (Figure 4) demonstrating the functional opposing influences of α and β-adrenoceptors. Concentrations of propranolol greater than 10^{-6} M did not enhance the contractile effect of dopamine but produced a slight rightward displacement (dose-ratio 1.6 ± 0.5, $n = 3$, $P < 0.05$) probably reflecting the appearance of a weak α-blocking action of propranolol (Gulati *et al.*, 1969).

Incubation with haloperidol (10^{-5} M) did not modify the characteristics of the concentration-response curve to dopamine either in the absence or presence of phentolamine 10^{-5} M. At this bath concentration, haloperidol did not significantly alter either the

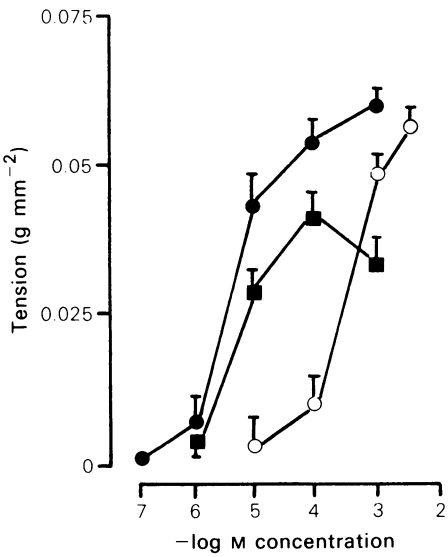

Figure 4 Concentration-response curves to dopamine in the presence of propranolol 10^{-7} M (■) ($n = 4$) and 10^{-6} M (●) ($n = 4$) and after propranolol 10^{-6} M plus phentolamine 10^{-5} M (○) ($n = 3$).

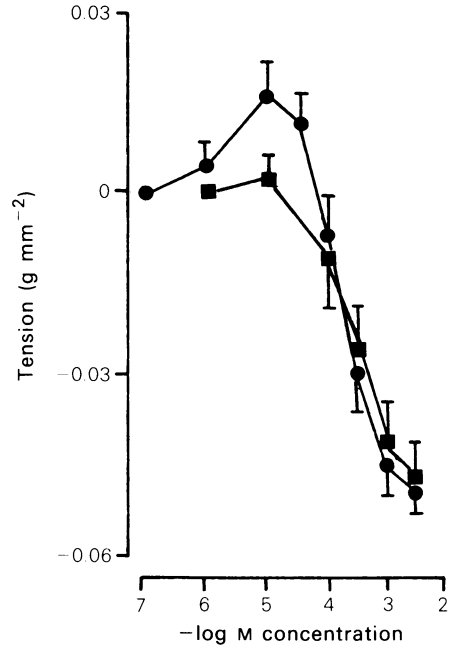

Figure 5 Concentration-response curves to dopamine in lung parenchymal strip obtained from control (●) ($n = 11$) and reserpine-treated (■) ($n = 3$) animals.

Table 2 Modification by cocaine (3×10^{-5} M) of pD_2 values of dopamine and noradrenaline

Agonist	*Preincubation*	n	*Control*	*Cocaine-treated*
Noradrenaline	Propranolol 10^{-6} M	5	5.96 ± 0.06	6.20 ± 0.05*
Dopamine	Propranolol 10^{-6} M	5	5.20 ± 0.04	5.50 ± 0.06*
Noradrenaline	Phentolamine 10^{-5} M	4	5.80 ± 0.05	6.00 ± 0.07
Dopamine	Phentolamine 10^{-5} M	4	4.85 ± 0.06	5.00 ± 0.07

*$P < 0.05$

concentration-response curves to methoxamine (α-mediated contraction) ($E_{max} = 0.10 \pm 0.007$ g mm^{-2}, $pD_2 = 4.4 \pm 0.2$, $n = 3$ versus $E_{max} = 0.09 \pm 0.008$ g mm^{-2}, $pD_2 = 24.1 \pm 0.3$, $n = 3$ in the absence and presence of haloperidol 10^{-5} M respectively) or isoprenaline (β-mediated relaxation) ($E_{max} = 0.078 \pm 0.01$ g mm^{-2}, $pD_2 = 7.4 \pm 0.3$, $n = 3$ versus $E_{max} = 0.072 \pm 0.008$ g mm^{-2}, $pD_2 = 7.6 \pm 0.2$, $n = 3$, in the absence and presence of haloperidol 10^{-5} M respectively).

Pretreatment with reserpine virtually abolished the contractile response to dopamine (Figure 5) without significant modification of the relaxant component of its concentration-response curve ($E_{max} = 0.051 \pm 0.006$ g mm^{-2}, $pD_2 = 3.6 \pm 0.1$, $n = 3$, not significantly different from control values). Relaxant response to isoprenaline was not altered by pretreatment with reserpine ($E_{max} = 0.074 \pm 0.011$ g mm^{-2}, $pD_2 = 7.6 \pm 0.3$, $n = 3$, $P > 0.05$ compared with values (Table 1) obtained in lung parenchymal strip from animals not treated with reserpine).

Cocaine significantly increased the pD_2 values of noradrenaline and dopamine in the presence of propranolol 10^{-6} M without affecting those obtained in the presence of phentolamine 10^{-5} M (Table 2).

Incubation with indomethacin 3×10^{-7} M did not modify either the contraction or relaxation induced by dopamine in this preparation.

Discussion

Exposure of lung parenchymal strip to dopamine resulted in a biphasic response consisting of an initial small contraction (22% of acetylcholine maximum) with concentrations below 10^{-5} M followed by a dose-dependent relaxation for higher concentrations. The shape of the concentration-response curve to dopamine closely resembles that of noradrenaline in the same preparation. This pattern of response is in contrast with that observed in the guinea-pig trachea where dopamine and noradrenaline produced only dose-related relaxations reaching the same maximal effect of isoprenaline although small contractions may appear occasionally with low concentrations of dopamine (Koga *et al.*, 1980).

After blockade of α-adrenoceptors with phentolamine, dopamine produced only dose-dependent relaxations reaching a maximal effect equivalent to that produced by noradrenaline (in the presence of phentolamine) and isoprenaline although dopamine was about 9 times less potent than noradrenaline and 500 times less potent than isoprenaline. This low potency of dopamine with respect to other catecholamines is in reasonable agreement with previous studies in guinea-pig trachea (Advenier *et al.*, 1980; Koga *et al.*, 1980) or canine femoral bed (McNay & Goldberg, 1966).

It has previously been demonstrated that β-adrenoceptors in the guinea-pig lung parenchymal strip mediate the relaxation elicited by noradrenaline (in the presence of α-blockade) and isoprenaline (Siegl *et al.*, 1979; Perpiñá *et al.*, 1981; Siegl & Orzechowski, 1981). The relaxant response to dopamine (in the presence of phentolamine) found in this study was antagonized, in a dose-related manner, by the β-blocking agent, propranolol. The parallelism of the concentration-response curves of dopamine and isoprenaline and the similar pA_2 values for propranolol as an antagonist of these two agonists suggest interaction with the same type of receptor. The Schild plot did not show simple competitive antagonism of dopamine-induced relaxation of guinea-pig lung parenchymal strip by propranolol since its slope was less than 1 but a similar result has been reported for isoprenaline in this preparation (Siegl *et al.*, 1979) and for several β-adrenoceptor blocking agents in other preparations (Schild, 1973). The experiments were carried out in the absence of uptake blocking agents and this factor probably explains the low slope of the Schild plot (Furchgott, 1972).

The possibility of the contribution to the dopamine-induced relaxation of specific dopamine-receptors (Goldberg *et al.*, 1978) has been explored by using a selective antagonist, haloperidol, which did not modify the responses (either contraction or relaxation) elicited by dopamine. In addition, neither reserpine nor cocaine pretreatment altered the relaxant response to dopamine. The absence of supersensitivity to dopamine-induced relaxation in reserpine-treated animals agrees with a similar observation for isoprenaline in this preparation (Broadley & Hawthorn, 1981).

Our results, therefore, indicate that dopamine-induced relaxation of guinea-pig lung parenchymal strip is mediated exclusively through direct activation of β-adrenoceptors and do not support the existence of specific dopamine-receptors or the contribution of an indirect (catecholamine-release) mechanism to this response.

On the other hand, dopamine is able to produce a small contraction at concentrations below 10^{-5} M. The maximum of this contraction was significantly enhanced by propranolol although sensitivity remains identical and, in the presence of β-blockade, phentolamine produced a parallel rightward displacement of similar magnitude to that produced for noradrenaline (plus propranolol) therefore suggesting the involvement of an α-adrenoceptor-mediated mechanism. Pretreatment with reserpine virtually abolished the contraction to dopamine (control) and incubation with cocaine increased the EC_{50} of dopamine (in the presence of propranolol) to produce this contraction without affecting the maximum attainable response. Thus the contractile effects of dopamine are mediated partly directly and partly indirectly, through release of endogenous catecholamines, although their source is not known.

The possibility that prostaglandins mediate part of the response to dopamine as suggested in other tissues (Takenaka & Morishita, 1976) was partially examined in this study by using a cyclo-oxygenase inhibitor, indomethacin (Vane, 1971) which did not modify either the contraction or the relaxation induced by dopamine. Arachidonic acid produces a dose-related contraction in this preparation with a maximum similar to that of acetylcholine (Perpiñá, 1981). These results argue against a prostaglandin link in the action of dopamine in the guinea-pig lung parenchymal strip.

In conclusion, the predominant effect of dopamine in the guinea-pig lung parenchymal strip is a dose-dependent relaxation due to direct activation of β-adrenoceptors with no pharmacological evidence in support of the existence of specific dopamine-receptors in this preparation. A low concentration of dopamine produced a small contraction mediated through direct and indirect actions at α-adrenoceptors.

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