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β-Adrenoceptor stimulating effects of phenylephrine and noradrenaline in the rat pulmonary vascular bed

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Abstract—The effects of phenylephrine and noradrenaline have been investigated on the perfusion pressure of the rat isolated lung. Both drugs (0·3–30 μg) produced a dose-dependent decrease in perfusion pressure elevated by 20 mM KCl, which was reversed to a dose-dependent increase after addition of propranolol (1×10^{-7} M) to the perfusion fluid. Increments due to both agonists in the presence of propranolol were antagonized by prazosin (1×10^{-6} M). Propranolol, but not prazosin, elevated the basal perfusion pressure. The results indicate that phenylephrine and noradrenaline are more effective in stimulating β-adrenoceptors than α-adrenoceptors in the rat pulmonary vascular bed and that β-adrenoceptors may regulate the vascular tone of the rat pulmonary circulation.

Phenylephrine is classically considered to be a prototype α-adrenoceptor agonist, however β-adrenergic stimulation by this agent has also been observed (Chahl & O'Donnell 1969; Lefèvre et al 1977; Cohen & Wiley 1978). Similarly, noradrenaline, another α-adrenoceptor agonist, has the ability to stimulate β-adrenoreceptors in some vascular tissues (Somlyo & Somlyo 1970; O'Donnell & Wanstall 1981). The present study was undertaken to examine whether phenylephrine and noradrenaline has any β-adrenoceptor stimulating effect in the rat pulmonary vascular bed.

Materials and methods

Male rats, 200–300 g, were lightly anaesthetized with ether. After sodium heparin (200 units/100 g i.v.) was administered, the lungs were isolated and perfused according to Bakhle et al (1969). Perfusion was carried out continuously through a cannula inserted into the pulmonary artery with oxygenated (95% O_2 and 5% CO_2 mixture) and warmed (37°C) Krebs Henseleit solution, using a Harward peristaltic pump (Model 1203 a) at a constant flow (8 mL min^{-1}). The composition of the Krebs Henseleit solution was as follows (mM): NaCl 118·1, KCl 4·7, $MgSO_4$ 1·2, $CaCl_2$ 2·5, KH_2PO_4 1·2, $NaHCO_3$ 25, glucose 11·1. Perfusion pressure was recorded on a Grass polygraph (Model 7B) by means of a pressure transducer (Statham P 23Ac) attached to a side arm above the pulmonary arterial cannula.

At the flow rate used, the perfusion pressure stabilized within 30 min at the level of 3–4 cm H_2O. Some preparations in which the initial perfusion pressure increased progressively were discarded. No tissue oedema occurred during the 3 h continuous perfusion period. Phenylephrine and noradrenaline were applied by single injections in a volume of 0·1 mL, through a rubber tubing segment distal to the pump. The amount of phenylephrine and noradrenaline mentioned in the text represents total amount (base) injected. Propranolol, prazosin and guanethidine were each added into the perfusion fluid. To evaluate the vasodilating effect of phenylephrine and noradrenaline perfusion pressure was elevated by increasing the KCl content of the solution to 20 mM. Maximum decreases in the perfusion pressure induced by the agonists were expressed as the percent of that induced by 0·2 mM papaverine. Responses to phenylephrine and noradrenaline were obtained before and after the addition of propranolol. Prazosin was then added to the same perfusion fluid and responses to both agonists were again tested. Guanethidine which prevents noradrenaline release was also tested under the same experimental conditions.

Drugs used: phenylephrine HCl (Sigma), noradrenaline bitartrate (Winthrop), propranolol HCl (Ayerst), prazosin HCl (Pfizer), guanethidine sulphate (Ciba), papaverine HCl (Sigma).

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Results

Single injections of phenylephrine (1–30 μg) and noradrenaline (0·3–3 μg) did not change the basal perfusion pressure. After vascular resistance was increased to the level of $13 \pm 2·0$ cm H_2O by infusing 20 mM KCl, both agonists decreased the perfusion pressure in a dose-dependent manner (Fig. 1). Control responses

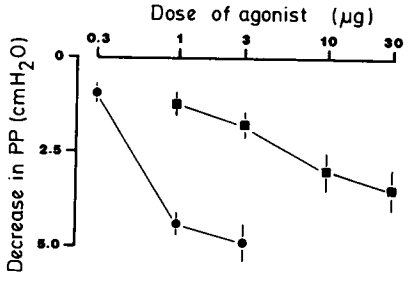

FIG. 1. The effects of noradrenaline (●) and phenylephrine (■) on the rat pulmonary perfusion pressure (PP) elevated by increasing the KCl content of the solution to 20 mM. Vertical lines indicate s.e.m. (n = 5).

to agonists were reproducible. Maximum decreases induced by phenylephrine and noradrenaline were $34·6 \pm 3·0$ and $47·6 \pm 3·4$%, respectively, of that induced by 0·2 mM papaverine. Guanethidine up to 1×10^{-4} M did not alter the vasodilation induced by both agonists. Propranolol (1×10^{-7} M) converted the vasodilation induced by phenylephrine and noradrenaline to the vasoconstrictor responses (Figs 2, 3). Propranolol itself

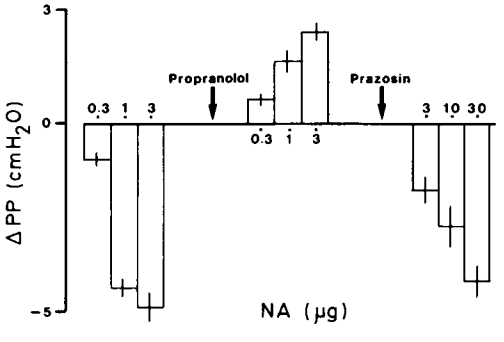

FIG. 2. The effect of noradrenaline on the perfusion pressure (PP) elevated by 20 mM K^+ in the absence and presence of propranolol (1×10^{-7} M) and subsequent prazosin (1×10^{-6} M) in the rat isolated lung. Vertical lines indicate s.e.m. (n = 4).

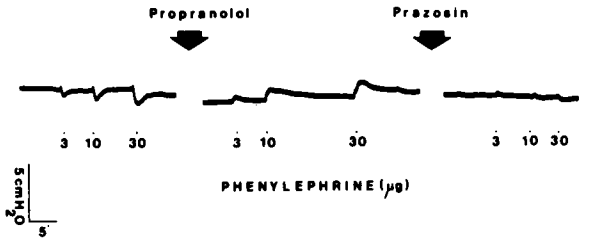

FIG. 3. The effect of phenylephrine on the perfusion pressure elevated by 20 mM K^+ in the absence and presence of propranolol (1×10^{-7} M) and subsequent prazosin (1×10^{-6} M) in the rat isolated lung.

caused a rise in perfusion pressure by $1{\cdot}2 \pm 0{\cdot}2$ cm H_2O. Vasoconstriction produced by two agonists in the presence of propranolol was dose-dependent and abolished by prazosin (1×10^{-6} M). Following pretreatment with propranolol, the maximum increases in the perfusion pressure induced by phenylephrine and noradrenaline were $2{\cdot}6 \pm 0{\cdot}2$ and $2{\cdot}4 \pm 0{\cdot}3$ cm H_2O, respectively. After administration of prazosin in addition to propranolol, larger doses of both agonists were necessary to elicit similar magnitude of vasodilatory responses.

Discussion

In most blood vessels, phenylephrine produces a contraction which is antagonized by conventional α_1-adrenoceptor blockers. However, the β-adrenoceptor stimulating property of this agent has also been shown in guinea-pig trachea (Chahl & O'Donnell 1969), in rat jugular vein (Cohen & Wiley 1978), and on the aortic pressure responses of cat, dog and rat (Lefèvre et al 1977). In our experiments, phenylephrine also produced a concentration-dependent relaxation that was antagonized by propranolol, providing evidence for the possibility of β-adrenoceptor stimulation by phenylephrine in the rat pulmonary vascular bed. Such a response to phenylephrine in this vascular bed is not restricted to this α-adrenoceptor agonist drug. Noradrenaline also exerted a predominant vasodilatory effect that was inhibited by propranolol. It is unlikely that the responses to phenylephrine and noradrenaline occur via liberation of noradrenaline from adrenergic nerve endings since agonist-induced decreases in perfusion pressure are unaffected by guanethidine.

It has been reported that noradrenaline decreases the vascular resistance only after the blockade of α-adrenoceptors in the cat pulmonary vascular bed (Hyman et al 1981). Similarly, phenylephrine-induced vasodilatory responses have been observed in the presence of α-adrenoceptor antagonists in dogs, cats and rats (Lefèvre et al 1977). However the relaxation of rat jugular vein by phenylephrine has been found to be independent of the blockade of α-adrenoceptors (Cohen & Wiley 1978). β-Adrenoceptor activation by phenylephrine and noradrenaline occurs in the rat pulmonary vascular bed without previous blockade of the α-adrenoceptors. On the contrary, pressor responses to these agents which are mediated by the stimulation of α_1-adrenoceptors, were observed only after the β-adrenoceptors had been blocked. For this reason, there may be more β-adrenoceptors than α-adrenoceptors in this vascular bed. However, phenylephrine and noradrenaline produced contractions that are antagonized by prazosin in the rat pulmonary artery rings (Uma et al 1987). In our previous experiments, we observed no relaxation by phenylephrine and noradrenaline in the pulmonary artery rings precontracted with K^+ (unpublished observations). It appears that the predominating adrenoceptors are α in the conductance vessels and β in the resistance vessels, i.e. arterioles in the rat pulmonary vascular bed. Furthermore, the enhanced vascular resistance elicited by propranolol alone in rat perfused lung suggest the presence of a vasodilator tone occurring via β-adrenoceptors, which may be induced by noradrenaline leaking from the adrenergic nerve endings.

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