Characterization of Adrenoceptors in the Guinea-pig pulmonary Artery

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ABSTRACT

An investigation was carried out to determine the adrenoceptor types in isolated pieces of the guinea-pig pulmonary artery. The results indicated a predominance of α-adrenoceptors and the presence of a paucity of β-adrenoceptors in the tissue which may increase at the level of the pulmonary arterioles. The sympathomimetics used acted principally on the α-adrenoceptors to produce contraction of the preparation.

Keywords: Adrenoceptors, bronchdilators, pulmonary compliance, pulmonary circulation.

INTRODUCTION

The object of this paper is to attempt to characterize the adrenoceptors in isolated pieces of the guinea-pig pulmonary artery using certain sympathomimetics, cholinomimetics, histamine and some adrenoceptor blocking agents.

Bronchodilators (which are substances used in the treatment of bronchial asthma) are known to cause a simultaneous decrease in pulmonary resistance (an effect on β-adrenoceptors in conducting airways) in the guinea-pig (Daly & Thomas, 1). Airways (pulmonary) resistance is the change in driving pressure per unit in air flow, that is, the degree of obstruction offered by the conducting airways to air flow. Pulmonary compliance, on the other hand, involves the distensibility of the peripheral airways, that is, it is the change in lung volume per unit of pressure change. Although it is known that pulmonary vasodilatation accompanies an increase in pulmonary compliance (West, 2) the involvement of β-adrenoceptors in this process is not clearly understood.

MATERIALS AND METHODS

Guinea-pigs weighing about 300g were killed and used. About 1cm. length of pulmonary artery was taken and opened by making a longitudinal cut through it. Opened rings about 1.5mm in width were cut from the tissue and sewn end to end to form a chain. The preparation was suspended in a 10ml organ bath containing Krebs-Henseleit solution at a temperature of 37°C and gassed with a mixture containing 5% carbon dioxide in oxygen. A tension of 0.5g was applied to the tissue. Tension changes in the tissue were recorded using a Grass Model FTO3 strain gauge (without springs) coupled to a two-channel Grass Model 79 pen recorder. The tissue was allowed to equilibrate for one hour, after which the effects of carbachol, noradrenaline, phenylephrine, histamine, dopamine, isoprenaline, phentolamine and propranolol were investigated. Cumulative concentration response curves were determined for noradrenaline, phenylephrine, histamine and dopamine. pA_2 values were also determined for phentolamine against noradrenaline and phenylephrine.

RESULTS

Carbachol in concentrations ranging from 2.8×10^{-6} to 1.7×10^{-4} M had some, although very little, spasmogenic effect on the preparation. Noradrenaline, phenylephrine and histamine in concentrations from 1.2×10^{-7}, 1.2×10^{-7} and 3×10^{-7} M respectively caused contraction whereas

dopamine needed a much higher concentration ($4.2x10^{-6}$M) to produce contraction. The effects of noradrenaline, phenylphrine, hitamine and dopamine were dose-related. Figs 1 and 2 show the effect of noradrenaline and the cumulative concentration- response curves respectively for noradrenaline, phenylphrine, histamine and dopamine on the guinea-pig pulmonary artery preparation. Noradrenaline and phenylephrine have approximately equal dose ratios and they were both 3 and 75 times more potent than histamine and dopamine respectively at the $E_{max.50}$ level (Fig.2). Phentolamine 1.4×10^{-7} M caused a rightward shift of the concentration-response curves for noradrenaline and phenylamine. The calculated pA_2 values for phentolamine were 8.1 against noradrenaline and 8.2 against phenylephrine (n = 4).

The antagonistic effects of phentolamine on noradrenaline and on phenylephrine are shown in Figs 3 and 4 respectively. Submaximal responses to noradrenaline, phenylephrine, histamine and dopamine were inhibited by phentolamine 1.4×10^{-8}M but not by propranolol 3.4×10^{-6}M. Noradrenaline responses were potentiated by cocaine 2.9×10^{-5}M. Isoprenaline $1.2x10^{-8}$M and $3.8x10^{-7}$M had little effect on the tissue but on preparations already contracted with any of the spasmogens, concentrations of about 9.4×10^{-8}M caused a slight mean approximate 25% relaxation followed by a secondary contraction as soon as concentrations of approximately 4.7×10^{-6}M were reached. This secondary contraction was blocked by phentolamine which produced only a slight relaxation of the tissue already contracted with histamine.

Isoprenaline did not produce full relaxation of the tissue in the presence of phentolamine $1.4 x10^{-6}$M; the maximum relaxant effect was about 30% of induced tone.

DISCUSSION

The powerful contractile effects by noradrenaline and phenylephrine of the isolated pulmonary artery, together with the blockade of this effect by phentolamine indicate the presence of α-adrenoceptors, in accordance with the findings of Okpako (3) and Lewis (4). Large concentrations of isoprenaline (such as 4.7×10^{-6}M) were capable of stimulating the -adrenoceptors as evidenced by the phentolamine-sensitive contractile effect. Okapko (3) also noted this effect. The transient relaxant effect of isoprenaline when tone was previously induced in the pulmonary artery suggests the presence in the tissue of a population of ß-adrenoceptors whose effects are masked by the predominantly α-adrenoceptor population. The indication of the presence of a small population of ß-adrenoceptors in the guinea-pig pulmonary artery does not accord with the findings of Okpako (3) and Lewis (4) who concluded that such receptors were absent. Weiner & Taylor (5), however, have reported a mixture of α - and ß-adrenoceptors in the pulmonary arterioles of man which mediate vasoconstriction and vasodilatation respectively.

The aim of this experiment was to determine whether there are any ß-adrenoceptors in the pulmonary artery. Although the mechanism by which pulmonary compliance is increased is not known, one possibility is that pulmonary vasodilatation is involved in the process. If the pulmonary vessels had an appreciable proportion of ß-adrenoceptors, then these receptors might mediate a vasodilation possibly responsible for the increase in pulmonary compliance. Although the experimental results indicate the presence of only a small proportion of ß-adrenoceptors in the guinea-pig pulmonary artery, the possibility of the presence of a much greater proportion of these receptors in the pulmonary arterioles cannot be ruled out. Different distributions of adrenoceptors in different types of blood vessels have been reported by several workers. Thus Fleisch et al. (6) reported an abundance of ß-adrenoceptors in the thoracic aorta of young rats and rabbits, but a paucity of these receptors in the abdominal aorta. A heterogeneity of drug receptors in different segments of the rabbit aorta has been observed by Altura & Altura (7). Similarly, small coronary arteries have been found to exhibit greater ß-receptor activity than larger coronary vessels (Bohr, 8).

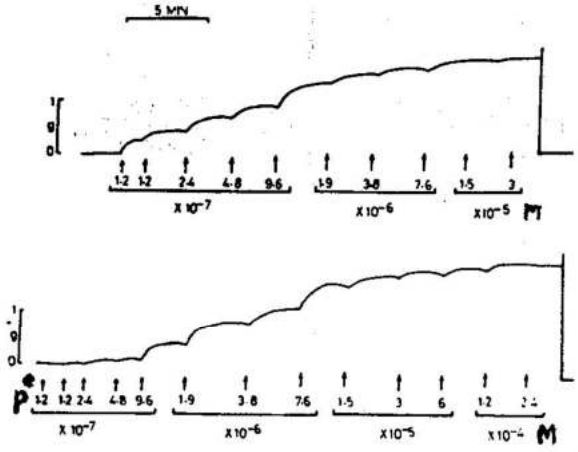

Fig. 1. Effects of Noradrenaline in the absence (upper trace) and in the presence (lower trace) of phentolamine on the guinea-pig pulmonary artery. The concentrations are molar. Phentolamine 1.4 x 10^{-7}M was added at P.

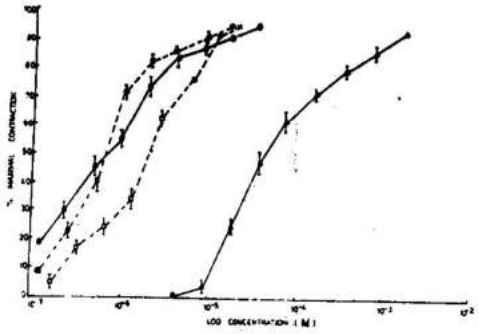

Fig. 2. Guinea Pig pulmonary artery. Cumulative concentration-respnse curves for noradrenaline (●) phenylephrine (■), histamine (□), and dopamine (▲). Each point is the Mean ± s.e. of 4 observations.

If the pulmonary vessels have a predominantly α-adrenoceptor population, the sympathomimetic bronchodilator drugs would either be without effect or have a vasoconstrictor effect on the pulmonary compliance since pulmonary vasoconstriction results in overall lung compliance.

The presence of an overwhelming proportion of α-adrenoceptors in the pulmonary vessels would be inconsistent with the mechanism by which symptho-mimetic bronchodilators increase pulmonary compliance if pulmonary vascular pressure is involved (which is not unlikely) in alterations of lung compliance. Species differences may also be a contributory factor

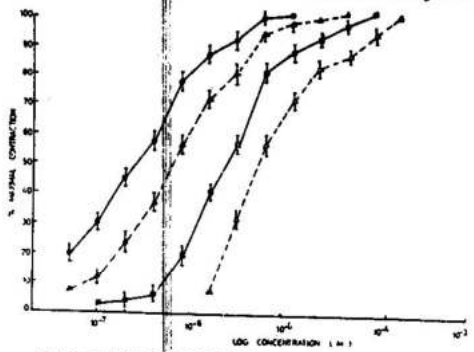

Fig. 3. Guinea-Pig pulmonary artery. Cumulative log concentration-response curves for noradrenaline in the absence (●) and in the presence of phentolamine 1.4 x 10^{-8}M (▲). 1.4 x 10^{-7}M (■), and 1,4 x 10^{-6}M (▲). Each point is the Mean ± s.e. of 4 observations.

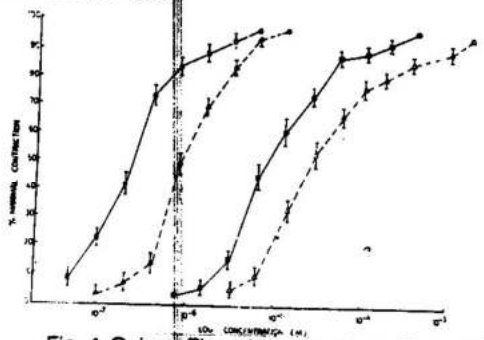

Fig. 4. Guinea-Pig pulmonary artery. Cumulative log concentration-response curves for phenylephrine in the absence (●) and in the presence of phentolamine 1.4 x 10^{-8}M (▲). 1.4 x 10^{-7}M (■), and 1,4 x 10^{-6}M (▲). Each point is the Mean ± s.e. of 4 observations.

in the distribution of adrenoceptors in the pulmonary blood vesels. For example, the pA_2 value for phentolamine against noradrenaline in this experiment was quite high [8.10] compared with the pA_2 value for the same agonist-antagonist pair, 6.18, on the rabbit pulmonary artery [Starke et al., 9].

Published evidence suggests that the pulmonary circulation in most intact animals behaves as though it is devoid of β-adrenoceptor sites (Rudolph & Scarpelli, 10; Stühlinger, Turnheim, Kraupp & Raberger, 11; Turnheim, Stühlinger & Kraupp, 12).

However, Somlyo & Woo (13) observed a ß-adrenoceptor mediated auto-inhibition of the effects of noradrenaline in avian pulmonary artery.

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