ACTION ON PILOCARPINE ON THE GUINEA-PIG TRACHEAL CHAIN

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ABSTRACT

The muscarinic drugs carbachol and pilocarpine were used as tone-inducing agents on the guinea-pig tracheal chain preparation in an attempt to evaluate bronchodilator activity on the tissue. Whereas carbachol produced contraction of the tissue in all the doses used, pilocarpine had an unpredictable action in that it caused contraction of some tissues while producing an initial relaxation of others in the dose range used. The β-adrenoceptor drugs isoprenaline and rimiterol were found to be more potent in relaxing pilocarpine than carbachol-induced tone.

Keywords: Tracheal chain, bronchodilator, muscarinic agonists, relaxation.

INTRODUCTION

In the evaluation of bronchodilator substances on the guinea-pig trachea, a tracheal chain preparation was set up. Since the preparation has a very low tone, carbachol and pilocarpine in suitable doses were used to induce tone in order to study the effects of the sympathomimetic bronchodilators isoprenaline and rimiterol on the contracted tissue.

MATERIALS AND METHODS

Guinea-pigs of either sex weighing about 300g. were used. The guinea-pigs were killed by a blow on the head and the trachea was removed. A length of the trachea, measuring about 2.5cm, was opened by making a longitudinal cut through it at a point diametrically opposite to the strip of smooth muscle. Opened rings of about 2mm. in width were cut and sewn end to end, each preparation having about six such rings. Each set of tracheal chain was suspended in a 10ml organ bath in Krebs-Henseleit solution gassed with a mixture containing 5% carbon dioxide in oxygen and kept at a temperature of 37^0C. Tensions ranging from (2×10^{-3} to 5×10^{-3}N (i.e. approximately 0.2 to 0.5g)) were applied to the tissue. The open ring tracheal chain preparation of the guinea-pig was a modification of the method of Castillo and de Beer (1). Tension changes in the tissue were recorded using a Grass Model FT03 strain gauge (without springs) coupled to a two-channel Grass Model 79 pen recorder. The tissues were allowed to equilibrate for an hour.

Cumulative concentration -response tracings were obtained for carbachol and pilocarpine. Submaximal equi-effective doses of the spasmogens which gave about 80% of the maximal responses (carbachol 1.2×10^{-7}M, pilocarpine 1.0×10^{-6}M) were a added to the tissue and at a constant level of tone, isoprenaline and rimiterol were added separately in cumulative concentrations until complete relaxation of the tissue was obtained. The experiment was performed on four preparations using the relevant drugs against each spasmogen. Concentration-response curves for isoprenaline and rimiterol were plotted using each response as a percentage of the maximal relaxation and, from the mean curves, the ED_{50} doses of isoprenaline and rimiterol on the carbachol and pilocarpine-induced tone were determined.

RESULTS

While carbachol produced contraction with all the doses used which ranged from 1.6×10^{-8} to 9.3×10^{-6}M, pilocarpine had and unpredictable action in that it caused contraction of some tissues while it produced (in about 1 in 5 cases) an initial relaxation of others in the dose range used, that was 1.8×10^{-7} to 1×10^{-5}M. The lower tracing in Fig. 1 illustrates the unpredictability of the action of pilocarpine on the guinea-pig trachea. Fig. 2 shows the

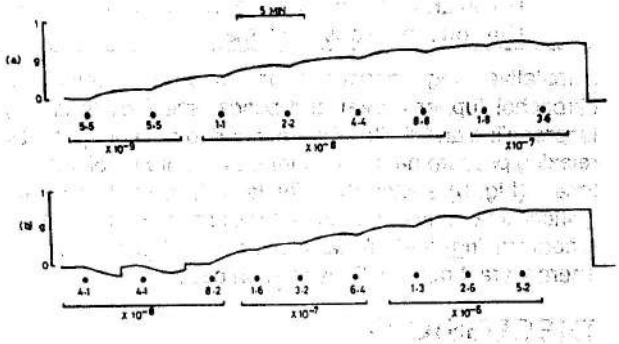

Fig. 1: The Effects of Carbachal (Upper Trace) and Pilocarpine (Lower Trace) on the Guinea-Pig Tracheal chain preparation. The concentrations are Molar.

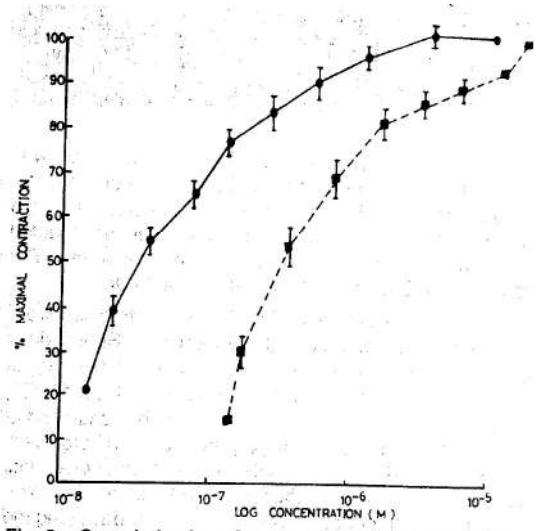

Fig. 2: Cumulative Log Concentration-Response Curve for Carbachol ( ) and Pilocarpine ( ) on the Guinea-Pig Tracheal chain preparation. Each point is the mean + s.e. of 4 observations.

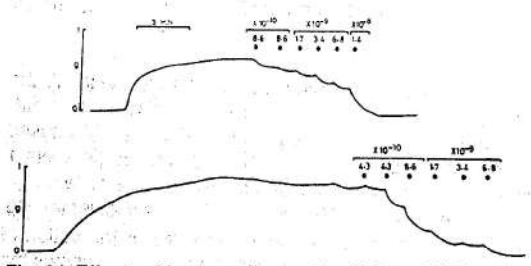

Fig. 3: Effects of Isoprenaline on the Guinea-Pig Trachea contracted with carbachol, 1.2×10^{-7}m (Upper Trace) and Pilocarpine 1.0×10^{-6}m (Lower Trace). The concentrations are Molar

cumulative log concentration-response curves for carbachol (upper curve) and pilocarpine (Lower curve). Isoprenaline and rimiterol were found to be more potent in relaxing pilocarpine-induced tone than carbachol-induced tone. (Fig. 3) shows the effects of isoprenaline on the guinea-pig trachea contracted with carbachol 1.2×10^{-7}M (upper tracing) and pilocarpine 1×10^{-6}M (lower tracing). There were 4 observations in each case.

DISCUSSION

Carbachol and pilocarpine, being two muscarinic agonists resistant to cholinesterase, might be expected to have similar modes of action on the smooth muscle of the guinea-pig trachea. Insofar as ionic fluxes are concerned, the actions of pilocarpine and acetylcholine appear to be similar on the guinea-pig ileum (Hurwitz, 2; Weiss, Coalson & Hurwitz, 3; Chujyo & Holland, 4). However, pilocarpine has been reported to act as a partial agonist on intestinal preparations from the rabbit (Busquet, 5) and the rat (Van Rossum, de Groot & Hurkmans, 6). Although there was not evidence of partial agonist activity of pilocarpine in these experiments on the guinea-pig trachealis muscle, there was evidence that in some preparations the drug possessed a relaxant action which was evident at low concentrations. It is possible that the relaxant action was present in all concentrations in all preparations but then it was masked, especially by high concentrations, through activation of the contractile mechanism mediated by muscarinic receptors. The experiment provided no evidence as to the mechanism underlying the weak relaxant action of pilocarpine. One possibility is that it causes the release of catecholamines from the preparation. Evidence of a smooth muscle relaxant action of pilocarpine has been demonstrated in other tissues. Thus Cushy (7) found that in the cat in vivo, the drug produces relaxation of the non-pregnant uterus, but contraction of the pregnant uterus. This relaxant effect in vivo may not, however, have been due to a direct action on the uterus. The smooth muscle relaxant action of pilocarpine shown in this experiment is in agreement with the observation of Cushy (7).

At ED_{50}, isoprenaline was 3.2 ± 1.2 times more potent on the pilocarpine-induced tone than on the carbachol-induced tone while rimiterol was 2.2 ± 1.6 times more potent on the pilocarpine-induced tone than on the carbachol-induced tone.

The greater ability of the sympathomimetic amines to oppose the contractions of the trachealis muscle, produced by pilocarpine than those produced by carbachol may be explained by a masked relaxant action of pilocarpine summating with that of the bronchodilators. This raises the question as to whether pilocarpine is a suitable tracheal tone-inducing agent for experiments on bronchodilators, since it may make the latter drugs appear more potent than is the case and thus give the appearance of a better selectivity compared with the heart. The results of this experiment are at variance with the observations of Persson & Olsson (8) who, in using pilocarpine as a tone-inducing agent in the evaluation of bronchodilator substances, did not report its relaxant effect on the preparation.

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