A comparison of the β-adrenoreceptor stimulant properties of isoprenaline, with those of orciprenaline, salbutamol, soterenol and trimetoquinol on isolated atria and trachea of the guinea-pig

In a previous publication (Cullum, Farmer & others, 1969) the β-adrenoreceptor agonist activities of isoprenaline, orciprenaline and salbutamol on the force of contraction of isolated whole atria and on the tone of tracheal chain preparations of the guinea-pig were reported. We have now examined the activities of these drugs and those of soterenol and trimetoquinol on isolated right and left atria and on isolated whole trachea of the guinea-pig.

Guinea-pigs were killed by a blow on the head and the trachea and heart removed. The trachea was mounted on an apparatus which allowed the measurement of the changes in intraluminal pressure of the trachea in response to transmural electrical stimulation (Farmer & Coleman, 1969). Right atrial strips were prepared for the measurement of the rate of contraction according to the method of Black, Duncan & Shanks (1965). The strips were attached to an isometric strain gauge, the output of which was used to drive an instantaneous rate meter. The left atrium was prepared for measurement of isometric tension and was driven electrically by supramaxial square wave pulses of 0·5 ms duration, every second (Blinks, 1967). Cumulative dose response curves for the above drugs were determined on these three preparations and the results are illustrated in Fig. 1A–C. Activities shown are relative to isoprenaline. The maximum effect obtained with isoprenaline was taken as 100%.

Isoprenaline, salbutamol, soterenol and orciprenaline produced dose-dependent decreases in the response of the isolated trachea to electrical stimulation. The slope of the dose effect curve and maximum response achieved were similar for each drug. Trimetoquinol however produced a plateau effect at the 75% level of inhibition which is probably attributable to its β-adrenergic activity. With further and much larger increases in concentration, 100% inhibition was obtained. This latter effect may be due to a non-adrenergic spasmolytic action which would not be surprising in a drug which is chemically related to papaverine. The dose ratios for 50% inhibition were: isoprenaline 1, trimetoquinol 2, soterenol 5, salbutamol 6 and orciprenaline 144.

On the isolated atria preparations, only isoprenaline and orciprenaline had dose effect curves of similar slope and magnitude on both rate and force of contractions. Soterenol was a full agonist with respect to rate but a partial agonist with respect to force. Salbutamol and trimetoquinol were partial agonists with respect to both force and rate although salbutamol had fuller agonist activity on rate than trimetoquinol. The dose ratios with respect to rate (50% maximum) for these drugs were: isoprenaline 1, soterenol 3·3, orciprenaline 125, salbutamol 500. A dose ratio for trimetoquinol could not be calculated. The dose ratios with respect to force were: isoprenaline 1, orciprenaline 63, salbutamol 2500 and for soterenol and trimetoquinol $<10{,}000$.

Lands, Arnold & others (1967) showed that small modification of the chemical structure of isoprenaline at or near the nitrogen atom could produce compounds with high selectivity for cardiac or bronchial β-receptors. They postulated that the β-receptors in these tissues were different and classified those in heart muscle as β-1 type and those in the bronchial muscle as β-2 type. The activities of new β-receptor agonists which do not have catechol functions, e.g. salbutamol and soterenol, or which are not phenylethanolamines e.g. trimetoquinol show very clearly that these receptors are not the same. Salbutamol and trimetoquinol show selectivity for the β-2 type receptors in the trachea. Soterenol has high activity on β-2 type but also on β-1 type

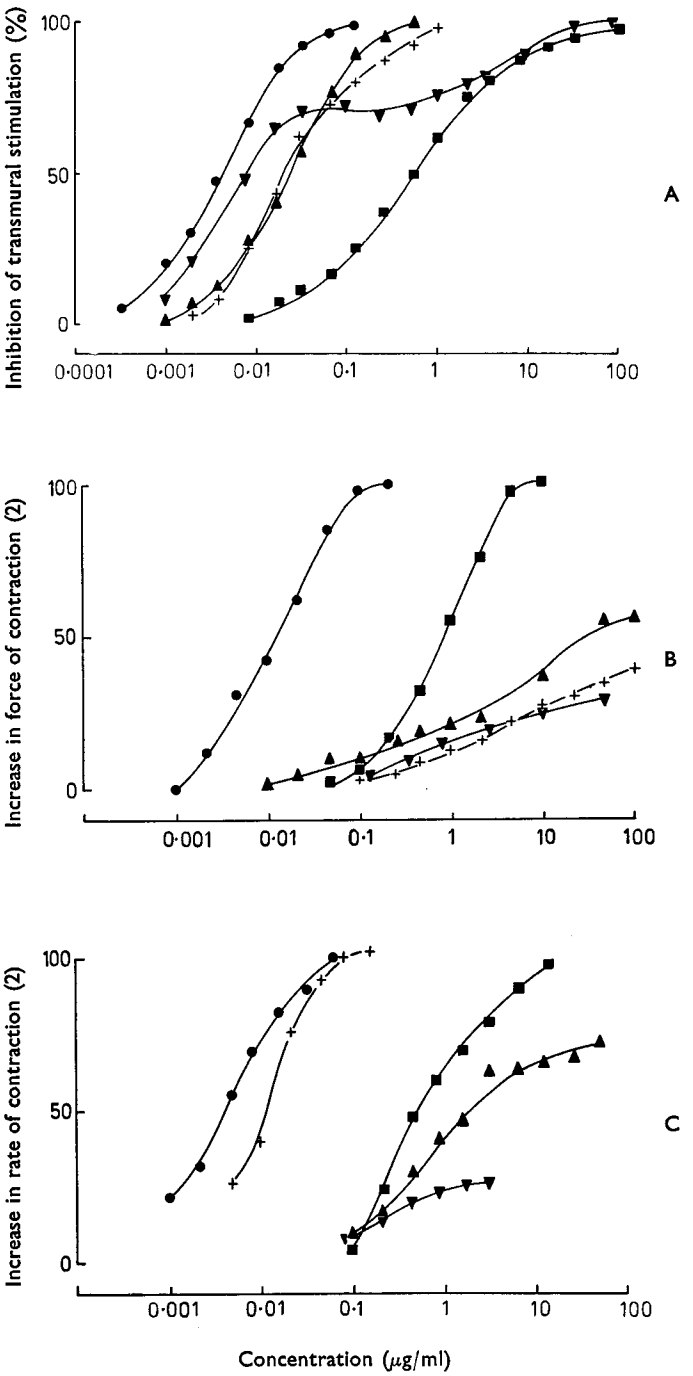

FIG. 1. Dose-response curves for isoprenaline (●), salbutamol (▲), soterenol (+), orciprenaline (■) and trimetoquinol (▼) A, in inhibiting increases in intraluminal pressure induced by transmural electrical stimulation of isolated guinea-pig trachea; B, on the force of contraction of the electrically driven isolated left atrium of the guinea-pig; C, on the rate of contraction of the spontaneously beating right atrial strip of the guinea-pig.

(rate) but not β-1 type (force) of the atria. This result suggests that β-1 type receptors are not homogeneous. Orciprenaline is not selective and has equal but low activity on β-1 and β-2 type receptors. The activities described for these new compounds further substantiate the classification proposed by Lands and co-workers (1967) for β-receptors in cardiac and bronchial muscle.

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The absence of a significant histamine receptor reserve in vascular smooth muscle

The existence of a receptor reserve was first postulated by Nickerson (1956) on the basis of the parallel shift in the dose response curve for histamine, produced by partial blockade with GD-131, an irreversible antagonist of the β-haloalkylamine class. This phenomenon, which was observed in the guinea-pig ileum preparation, can readily be explained by supposing that only a small fraction of the total number of available receptors need to interact with the agonist in order to elicit the maximum response. Such a receptor reserve has been observed in cholinergic systems (Ariens, van Rossum & Koopman, 1960) but appears to be absent or insignificant in adrenergic systems (Moran, May & others, 1967a, 1967b; Moran, Triggle & Triggle, 1969).

To determine whether this parallel shift of the dose-response curve after partial blockade with a β-haloalkylamine is a characteristic of other histamine receptor systems, the nature of the progressive blockade of the histamine-induced contractions of rabbit aortic strips has been observed, using phenoxybenzamine as the irreversible antagonist.

Rabbit aortic strips prepared as described by Furchgott & Bhadrakom (1953) were suspended in organ baths of 15 ml working volume and allowed to equilibrate at 37° for 3 h in Krebs bicarbonate solution containing 0·05 M glucose. The resting tension was maintained at 1 g. A cumulative dose response curve to histamine was then obtained; contractions were recorded by means of a force-displacement transducer (Grass FT03) connected to a Grass model 5P1 polygraph. The preparations were then washed with Krebs bicarbonate solution at frequent intervals until they had returned to the resting tension. Phenoxybenzamine hydrochloride was dissolved in normal saline containing 0·01 M hydrochloric acid and, after this solution had been kept at room temperature for 10 min, aliquots were added to the organ baths to achieve the required concentration. After 5 min exposure to phenoxybenzamine the tissues were washed twice and washed thereafter at 15 min intervals for 2½ h. A further cumulative dose-response curve to histamine was then obtained. Since this preparation is known to increase in sensitivity with time, the experiment was repeated