The relation between tracheorelaxant and fat mobilising action of some derivatives of noradrenaline and 2-amino-1-*p*-hydroxyphenylethanol

SIR,—Attempts to classify the fat mobilising action of sympathomimetic amines into Ahlquist's (1948, 1962) scheme of α- or β-adrenergic receptor functions has hitherto met with numerous difficulties. Fat mobilisation has been attributed to adrenergic actions of the α-type (Ariëns, Waelen, Sonneville & Simonis, 1963), β-type (Pilkington & others, 1962), both types (Steinberg, Vaughan & Margolis, 1960) and neither type (Wenke, Mühlbachová & Hynie, 1962; Love, Carr & Ashmore, 1963; Nickerson, 1965). We have now attempted a correlation of adrenergic fat mobilisation on the one hand and a typical β-adrenergic response, namely the relaxation of tracheal muscle, on the other.

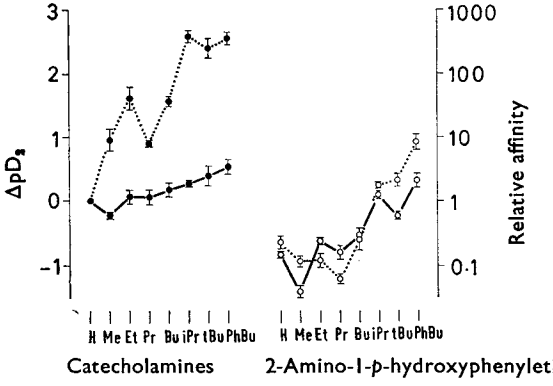

FIG. 1. ΔpD_2 values and relative affinities of the 2-amino-1-*p*-hydroxyphenylethanol and catecholamine derivatives to tracheal relaxation (●) and for fat mobilisation (○). (PhBu = phenyl-t-butyl).

Using the guinea-pig tracheal chain according to Castillo & de Beer (1947), a contraction provoked by histamine in a final concentration of $1{\cdot}1 \times 10^{-4}$M was antagonised by cumulative concentrations of sympathomimetic drugs and recorded isotonically. Homologous series of derivatives of noradrenaline and 2-amino-1-*p*-hydroxyphenylethanol substituted on the nitrogen atom were used. The derivatives were: methyl, ethyl, propyl, butyl, isopropyl, t-butyl and phenyl-t-butyl. The results were related to the effects of the same drugs on fat mobilisation from depot adipose tissue *in vitro* (Černohorský, Cepelík, Lincová & Wenke, 1966).

The affinity parameter pD_2 was derived from the dose-response curves according to van Rossum (1963). In the Figures, relative ΔpD_2 values are given ($\Delta pD_2 = pD_2x - pD_2$ noradrenaline); noradrenaline was used as the comparative standard on each occasion.

In Fig. 1, the relative affinity parameters of the two series of drugs are given for tracheal relaxation and fat mobilisation. The figures for fat mobilisation are those of Černhorský & others (1966). For the noradrenaline derivatives the affinities for tracheal relaxation show large differences from their affinities for fat mobilisation. With the 2-amino-*p*-hydroxyphenylethanol derivatives the relation between tracheorelaxant effect and fat mobilisation is closer.

The results may also be compared by following the influence of substitution by a particular radical in both parent compounds (Fig. 2). The linear correlation of the fat mobilising action of the two series of derivatives found by

Černhorský & others (1966) is again shown for comparison. In this instance, the clear linear relation of affinities differs markedly from the situation for the tracheal muscle. Here, a parabolic relation is evident. By lengthening the unbranched side-chain, the affinity of the noradrenaline derivatives rises, but the affinity of the 2-amino-1-*p*-hydroxyphenylethanol series decreases from the parent compound down to the propyl substituted compound.

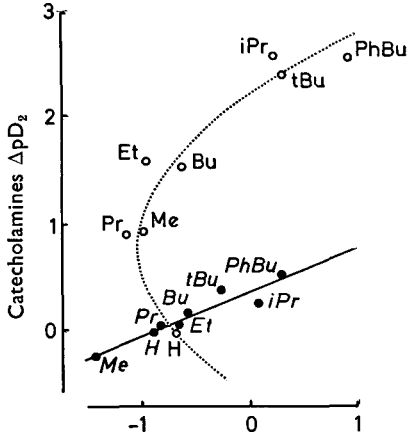

FIG. 2. Correlation of the ΔpD_2 values of both series of derivatives. Relative affinity parameters to fat mobilisation (—●—) and to tracheal relaxation (···○···) are given. (PhBu = phenyl-t-butyl).

We are well aware that it is not possible to evaluate directly all similarities and differences found by comparing the reactivity of such different material under widely different experimental conditions. In spite of this, some common features can be seen in the rising affinity in the direction of higher radicals and a marked enhancement of affinities of derivatives substituted by branched radicals compared with the unbranched ones containing the same number of carbon atoms. The pattern of response suggests that fat mobilisation, like tracheal relaxation, may be attributable to β-adrenergic activation.

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Innervation of domestic fowl and guinea-pig ventricles

SIR,—Marked changes in the force of contraction of driven ventricular strips occurred when the suprathreshold electrical stimulation used to drive the strips was increased tenfold.

A strip was cut from the wall of the right ventricle of a chick (domestic fowl) or guinea-pig heart, one end being anchored to bipolar platinum hook electrodes, and the other (apical) end to a transducer for isometric tension recording.

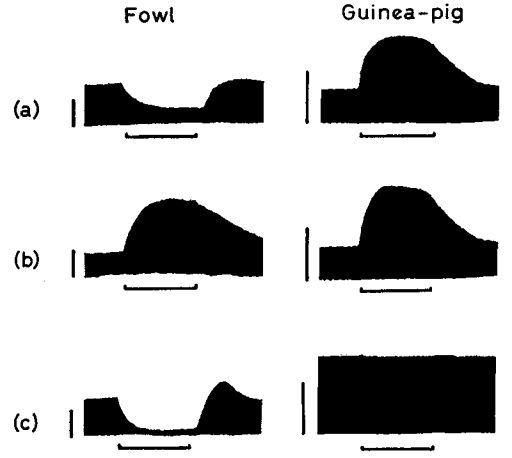

FIG. 1. Polygraph records of isometric tension of guinea-pig and chick ventricular strip preparations stimulated at constant rates. The stimulus strength was increased for periods of 2 min, indicated by the horizontal bars. Vertical calibrations 1 g. (*a*) Untreated preparations, (*b*) in the presence of 1 μg/ml atropine and (*c*) in the presence of 10 μg/ml guanethidine.

Strips were suspended in a solution of the following composition (g): NaCl 6·92, KCl 0·34, $CaCl_2$ 0·30, $MgCl_2$ 0·11, KH_2PO_4 0·16, $NaHCO_3$ 1·0, glucose 2·0, sucrose 4·5, water to 1 litre, and aerated vigorously with oxygen. The temperature was maintained at 41–42° for chick and 37–38° for guinea-pig ventricular strips, which were driven at constant rates of 4–6/sec with square wave pulses of 1–2 V and 5 msec duration.

Increasing the stimulation strength caused a decrease in the force of contraction of chick and an increase in the force of contraction of guinea-pig ventricular strips (Fig. 1a). Atropine, 1 μg/ml, had slight or no effect on the response of guinea-pig ventricular strips but in the chick the decrease was converted to a large increase in the force of contraction (Fig. 1b). Guanethidine, 2–10 μg/ml, abolished the increase in force of contraction in untreated guinea-pig strips but