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AN *in vitro* COMPARISON OF β-ADRENOCEPTOR STIMULANTS ON POTASSIUM-DEPOLARIZED UTERINE PREPARATIONS FROM GUINEA-PIGS

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1 A comparison of six β-adrenoceptor stimulants has been carried out on *in vitro* preparations of guinea-pig uterus which were depolarized in K^+-Krebs solution. Results have also been obtained on uterine preparations in which contractions to acetylcholine were inhibited. The establishment of the conditions for the K^+-depolarized preparations are described.

2 There was no significant difference between potency values (mean neg log EC_{50} values) for any of the drugs on the two types of uterine preparation i.e. the preparations had the same sensitivity to the drugs.

3 There was a less than two-fold difference between the relative potency values for the β-adrenoceptor stimulants on the two types of uterine preparation. The relative potency values (isoprenaline = 100) on the K^+-depolarized preparation were fenoterol 74.1, salbutamol 15.1, rimiterol 13.5, terbutaline 8.2 and orciprenaline 5.6.

4 The relative potency values obtained on uterine preparations were less than three-fold different from those previously found for guinea-pig trachea (after inhibition of extraneuronal uptake).

5 The pA_2 value for propranolol on the K^+-depolarized uterine preparations was 9.13.

6 It is concluded that the K^+-depolarized guinea-pig uterine preparation can be used for quantitative studies on β-adrenoceptor stimulant drugs. It lacks spontaneous activity, drugs can be added cumulatively and several drugs can be compared on a single preparation. In addition, the results obtained support the classification of the β-adrenoceptors in guinea-pig uterus and trachea in the same sub-group (β_2).

Introduction

The uterus is a tissue which contains β-adrenoceptors and the uterine inhibitory action of selective β_2-adrenoceptor stimulants has been used clinically to delay premature labour e.g. Liggins & Vaughan (1973). There are experimental reports on the *in vitro* potency of individual drugs on the uterus e.g. salbutamol on rat uterus (Hollingsworth & Schnieden, 1973), hexoprenaline on guinea-pig uterus (O'Donnell & Wanstall, 1975) and terbutaline on human uterus (Andersson, Ingemarsson & Persson, 1973) but the clinically useful β-adrenoceptor stimulants have not previously been quantitatively compared in a single study in any species. In particular, uterine preparations from guinea-pigs have rarely been used in β-adrenoceptor studies despite much quantitative information comparing β-adrenoceptor stimulants on other tissues containing β-adrenoceptors from this species, e.g. O'Donnell & Wanstall (1974). One reason for this has been the difficulty in obtaining quantitative data on uterine preparations, particularly because of intermittent, spontaneous activity in the preparations. Thus the aims of the present study were to develop an *in vitro* preparation of guinea-pig uterus on which a comparative quantitative study of β-adrenoceptor stimulants could be made. A potassium (K^+)-depolarized preparation of guinea-pig uterus has been used, similar to that previously described for rat uterus (Evans, Schild & Thesleff, 1958; Edman & Schild, 1962; 1963; Schild, 1967). The use of this method allowed responses to cumulative addition of each β-adrenoceptor stimulant to be obtained and thus a number of drugs could be compared on each preparation. Results were also obtained for the same drugs on a preparation of guinea-pig uterus in which the relaxation responses of the β-adrenoceptor stimulants were used to inhibit standard contractions to acetylcholine (ACh) (O'Donnell & Wanstall, 1975).

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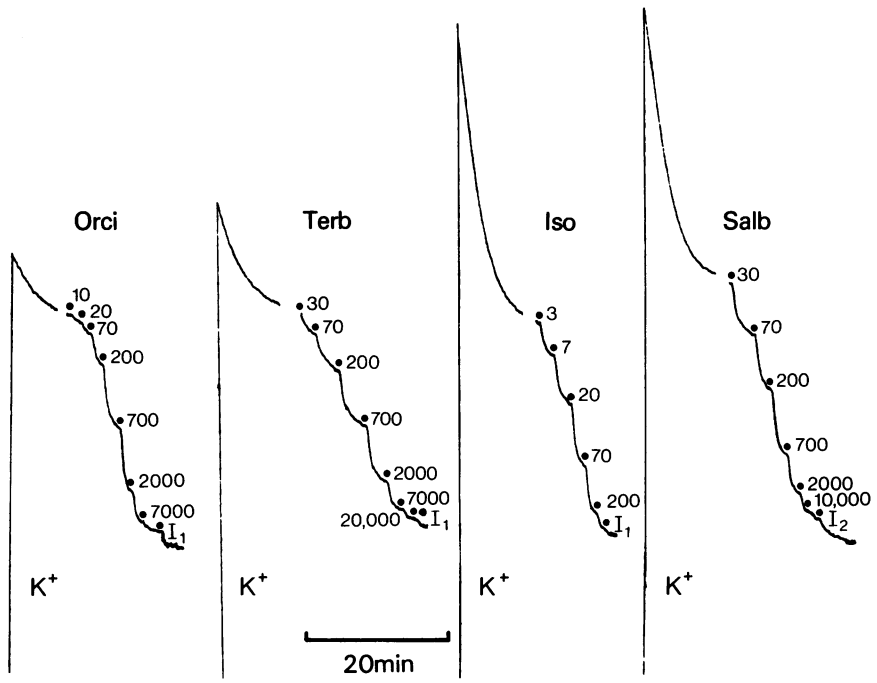

Figure 1 Responses to concentrations (in nM) of orciprenaline (Orci) terbutaline (Terb), isoprenaline (Iso) and salbutamol (Salb) added cumulatively to a longitudinal strip of guinea-pig uterus. At K^+, the preparation was immersed in K^+-Krebs solution. A supramaximal concentration of isoprenaline was added at the end of each cumulative line (I_1 = isoprenaline 10 μM; I_2 = isoprenaline 30 μM) after which the preparation was washed thoroughly with normal Krebs solution for 15 minutes.

Methods

Uterine horns were removed from guinea-pigs (300–500 g) which had been pretreated with reserpine (5 mg/kg, i.p., 24 h previously).

One series of experiments was carried out on uterine segments in de Jalon's solution at 27°C as described by O'Donnell & Wanstall (1975). On these preparations submaximal contractions to acetylcholine were inhibited by the β-adrenoceptor stimulants. One, or occasionally two, drugs could be compared with isoprenaline on each preparation and concentrations of drugs were given in a random order. Log concentration-response (% inhibition of the amplitude of the contractions) curves were plotted in order to obtain EC_{50} values for the β-adrenoceptor stimulant.

In all other experiments, longitudinal strips of uterus (approximately 20 mm long and 4 mm wide) were used. Each strip was mounted in an organ bath in aerated (95% O_2 and 5% CO_2) Krebs solution at 37°C. During the next 30 min the preparation was repeatedly washed and stretched to maintain a tension close to 200 mg; the tissues usually stabilized at a baseline tension of 100–150 mg. An increase in tension was then induced by exchanging the Krebs solution for one in which all the sodium ions were replaced by the equivalent amount of potassium ions (K^+-Krebs solution). This depolarization produced a contraction followed by a slow relaxation which equilibrated, usually within 10 to 15 min, at a tension that was higher than before depolarization. Relaxation responses to β-adrenoceptor stimulants, added in a cumulative fashion, could then be recorded (Figure 1). Each concentration of β-adrenoceptor stimulant was allowed to reach its maximum effect before addition of the next concentration. Responses were recorded isotonically with a modified Statham 10B strain gauge and pen recorder. In a series of experiments designed to compare the β-adrenoceptor stimulants, up to four different drugs could be compared on each K^+-depolarized preparation and drugs were examined in a random order. At the end of each cumulative concentration-response line to a β-adrenoceptor stimulant, a maximum response to isoprenaline was obtained. After each concentration-response line the drug was removed and the tissue repolarized by thoroughly washing the preparation in 3 changes of normal Krebs solution (containing Na^+) for 15 min before carrying out the next line. Log concentration β-adrenoceptor stimulant was plotted against %

maximum response to isoprenaline (obtained at the end of the cumulative concentration-response line to that β-adrenoceptor stimulant). Values for EC_{50} were interpolated.

Neg log EC_{50} values were used as a measure of potency and also in the calculation of relative potency values (isoprenaline = 100) for each drug on each preparation as follows:- log potency ratio = neg log EC_{50} compound − neg log EC_{50} isoprenaline. Relative potency (isoprenaline = 100) = 100 × (antilog mean log potency ratio).

All statistical comparisons were made on neg log EC_{50} values or on log potency ratio values (Student's *t* test).

Drugs and solutions

The following drugs were used:- acetylcholine chloride (Sigma), fenoterol hydrobromide (Boehringer-Ingelheim), isoprenaline sulphate (Burroughs-Wellcome), metanephrine hydrochloride (Calbiochem), orciprenaline sulphate (Boehringer-Ingelheim), phentolamine methanesulphonate (ampoules Regitine, Ciba), propranolol hydrochloride (ICI), reserpine (ampoules Serpasil, Ciba), rimiterol hydrobromide (Riker), salbutamol sulphate (Allen & Hanburys) and terbutaline sulphate (Astra). All drugs were as pure powders (except where indicated) and we are grateful to those companies which donated the drugs.

The composition of the physiological solutions used were as follows:- Krebs solution (mM): NaCl 114, KCl 4.7, $CaCl_2$ 2.5, KH_2PO_4 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 25 and glucose 11.7; K^+- Krebs solution (mM): KCl 119, $CaCl_2$ 2.5, KH_2PO_4 1.2, $MgSO_4$ 1.2, $KHCO_3$ 25 and glucose 11.7; de Jalon's solution (mM): NaCl 154, KCl 5.6, $CaCl_2$ 0.54, $NaHCO_3$ 5.9 and glucose 2.8. All the solutions also contained ascorbic acid 200 mg/litre.

Results

Establishment of conditions for K^+-depolarized preparations

In the series of experiments in which the β-adrenoceptor stimulants inhibited contractions to ACh the preparations were set up in de Jalon's solution at 27°C, to reduce spontaneous activity. Spontaneous activity was not a problem in depolarized preparations so the Krebs solution was maintained at 37°C in order that the results could be compared with those obtained on other tissues, particularly trachea. It was established that, at 37°C, the neg log EC_{50} of isoprenaline obtained in a K^+-de Jalon's solution (7.30 and 7.74 in 2 experiments) was within the range of those obtained in K^+-Krebs solution (7.56 ± 0.10, $n = 11$, Table 1). Four experiments were carried out to compare the responses of depolarized preparations (K^+-Krebs solution) to isoprenaline at 25°C (the temperature used by Schild (1967) in rat experiments) with those obtained at 37°C. Preparations of guinea-pig uterus tended to be more sensitive to isoprenaline when maintained at 25°C than at 37°C (neg log EC_{50} isoprenaline:- 25°C, 8.41 ± 0.19; 37°C, 7.95 ± 0.29; $t = 5.26$, d.f. = 3, $0.05 > P > 0.01$; paired *t* test) but the secondary relaxation phase, after depolarization at 25°C, was so marked that further quantifiable relaxation responses to isoprenaline were not possible. Thus K^+-Krebs solution and a temperature of 37°C were used in all subsequent experiments.

All guinea-pigs received reserpine pretreatment but neither a neuronal uptake inhibitor drug nor an extraneuronal uptake inhibitor drug was included in the Krebs solution for reasons outlined in the discussion. Evidence was obtained that, in the presence of propranolol 1 μM or 10 μM, contractions of the K^+-depolarized uterine preparations occurred to noradrenaline but not to isoprenaline (in concentrations

Table 1 Potency (neg log EC_{50}) values for β-adrenoceptor stimulants on K^+-depolarized and non-depolarized (inhibition of acetylcholine (ACh) contractions) uterine preparations of the guinea-pig

Compound	*neg log EC_{50} K^+-depolarized*	*Inhibition of ACh contractions*
Isoprenaline	7.56 ± 0.10 (11)	7.68 ± 0.13 (17)
Fenoterol	7.36 ± 0.21 (5)	7.86 ± 0.35 (4)
Salbutamol	6.69 ± 0.16 (5)	6.32 ± 0.14 (5)
Rimiterol	6.62 ± 0.23 (5)	6.89 ± 0.16 (4)
Terbutaline	6.64 ± 0.05 (5)	6.71 ± 0.18 (5)
Orciprenaline	6.36 ± 0.20 (5)	6.49 ± 0.19 (5)

All values are mean values ± s.e. mean. The number of different tissue preparations is given in parentheses.

up to 2 mM). Since the comparative study would be using β-adrenoceptor stimulants with less α-adrenoceptor stimulant activity than isoprenaline, an α-adrenoceptor blocking drug was also not included. An experiment was carried out to confirm that inclusion of phentolamine (10 μM) had no effect on the location of isoprenaline log concentration-response lines either in the absence or in the presence of propranolol (1 μM). This dose of phentolamine was shown to antagonize the contractile responses to noradrenaline in the presence of propranolol (1 or 10 μM) on these preparations.

Propranolol antagonism of isoprenaline on K^+-depolarized preparations

Propranolol produced a parallel shift in the concentration-response line to isoprenaline to a higher concentration range. Analysis of the data by the method of Arunlakshana & Schild (1959) gave a regression line with a slope of 0.72 ± 0.10 (s.e. slope) from which the pA_2 value for propranolol (contact time 60 min) was 9.13 (Figure 2).

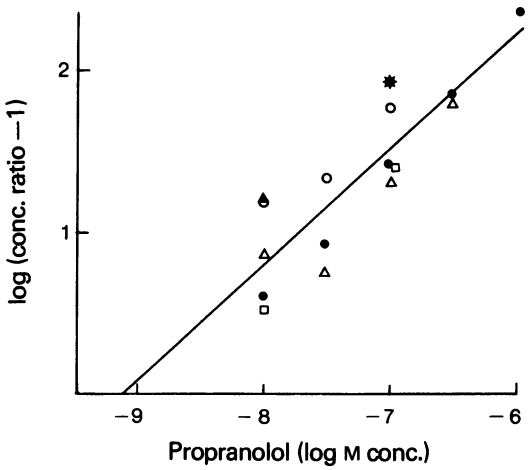

Figure 2 Arunlakshana & Schild (1959) plot for propranolol on guinea-pig uterus (K^+-depolarized) with isoprenaline as agonist and 60 min contact time with propranolol. The points represent values from 6 preparations from different animals, indicated by different symbols.

Comparison of β-adrenoceptor stimulants on K^+-depolarized and non-depolarized preparations

There was no significant difference between the K^+-depolarized and the non-depolarized preparations (i.e. inhibition of ACh contractions) in their sensitivity to the β-adrenoceptor stimulant drugs (Student's t test, $P > 0.05$ for comparison of mean neg log EC_{50} values, Table 1). Also, the potencies of the β-adrenoceptor stimulants, relative to isoprenaline, on K^+-depolarized preparations were not significantly different from those on the non-depolarized preparations (Student's t test, $P > 0.05$ for comparison of mean log potency ratio values, Table 2). Thus, the order of potencies of the β-adrenoceptor stimulants was the same on the two types of uterine preparation (see relative potency values, Table 3). This order was the same as that previously reported on tracheal chain preparations in which extraneuronal uptake was inhibited with phenoxybenzamine (O'Donnell & Wanstall, 1976). Also for each drug, there was a less than three-fold difference between the relative potency values obtained on either type of uterine preparation or on trachea (Table 3). On the uterus, fenoterol was the only β-adrenoceptor stimulant examined with a potency comparable with that of isoprenaline (Table 3).

Discussion

In the present study a number of clinically important β-adrenoceptor stimulant drugs have been compared on two types of *in vitro* preparation of guinea-pig uterus. The K^+-depolarized preparation had the fol-

Table 2 Log potency ratio values for β-adrenoceptor stimulant drugs on K^+-depolarized or non-depolarized (inhibition of acetylcholine (ACh)-induced contractions) uterine preparations

Compound	*Log potency ratio*†	
	K^+-depolarized	*ACh contractions*
Fenoterol	−0.13 ± 0.10 (5)	0.06 ± 0.06 (4)
Salbutamol	−0.82 ± 0.08 (5)	−0.80 ± 0.06 (5)
Rimiterol	−0.87 ± 0.16 (5)	−0.99 ± 0.07 (4)
Terbutaline	−1.09 ± 0.11 (5)	−1.31 ± 0.02 (5)
Orciprenaline	−1.25 ± 0.18 (5)	−1.46 ± 0.13 (5)

† Log potency ratio = neg log EC_{50} compound − neg log EC_{50} isoprenaline.
All values are mean values ± s.e. mean with number of different tissue preparations in parentheses.

lowing advantages over the non-depolarized preparation:- spontaneous motility was suppressed, drugs could be added in a cumulative fashion and several drugs could be compared on a single preparation. Also the physiological solution (except for the high K^+) and the experimental temperature were the same as those used for tracheal experiments in which the relative potencies of β_2-selective adrenoceptor stimulants were obtained (O'Donnell & Wanstall, 1976). So that relative potency values would allow some conclusion regarding the sub-classification of the β-adrenoceptor in the uterus, the experimental conditions were designed to meet the criteria proposed by Furchgott (1972). All preparations were taken from animals pretreated with reserpine to avoid possible catecholamine release resulting from depolarization of sympathetic nerves in the tissue (Gibson & Pollock, 1973). Inhibition of neuronal uptake was considered to be unnecessary for a number of reasons e.g. cocaine had no effect on the responses of other tissues to the drugs being investigated (O'Donnell & Wanstall, 1974); Kulkarni, Wakade & Kirpekar (1976) found that cocaine did not potentiate responses to noradrenaline on guinea-pig uterus; and neuronal uptake in other tissues is inhibited when there is lack of Na^+ and high K^+ (Iversen, 1970). The necessity for inclusion of an extraneuronal uptake inhibitor drug was examined and preliminary experiments indicated that inclusion of metanephrine 50 μM did not potentiate responses to isoprenaline on either the depolarized or non-depolarized preparation. Thus extraneuronal uptake did not appear to affect responses of the uterus to isoprenaline and therefore an extraneuronal uptake inhibitor drug was not used.

Uterine tissue from most species contains not only β-(inhibitory) adrenoceptors but also α-(excitatory) adrenoceptors (Miller, 1967) and this includes guinea-pig (Davidson & Ikoku, 1966). Pennefather & Isaac (1967) demonstrated in guinea-pig uterus that, in the presence of propranolol, noradrenaline and adrenaline produced contractions. This was confirmed for noradrenaline in the present study and it was shown that these contractions were partially blocked by high concentrations of phentolamine (10 μM). However, the presence of this concentration of phentolamine was shown not to affect the EC_{50} values for isoprenaline, in the absence or in the presence of propranolol (1 μM). The use of higher concentrations of phentolamine was avoided because it may then block β-adrenoceptors (unpublished observations). Thus, an α-adrenoceptor blocking drug was not used. Although the relative dominance of α- and β-adrenoceptor activity in uterus is under hormonal control (Marshall, 1970), the hormonal state of the guinea-pigs used in the present study was not established nor controlled. However, the appearance of the uterus suggested that the majority of animals were not in oestrus. Oestrus in guinea-pigs is short lasting and occurs mainly at night (Wagner & Manning, 1976). Also, the sensitivity to isoprenaline of the uterus in rats (Abdel-Aziz, Ghazal & Daabees, 1974) and rabbits (Nesheim, 1974) was not affected by hormonal changes.

Since it could be argued that the effects of the β-adrenoceptor stimulants on the depolarized uterus were obtained under 'abnormal' conditions which may affect the receptor, the pA_2 value for propranolol (agonist isoprenaline) was obtained (9.13). No value was found on guinea-pig non-depolarized uterine preparations but comparison can be made with values quoted for propranolol on rat uterus (9.56, Wasserman & Levy, 1972; 8.5, Farmer & Levy, 1970) and on other guinea-pig tissues e.g. trachea (8.7, Furchgott, 1972); atria (8.8, Blinks, 1967). These values are fairly close and Furchgott (1972) suggested that, unless the pA_2 values for an antagonist were different by greater than 0.5 log units, there was no suggestion of the receptor being different. Schild (1967) has shown on the rat uterus preparation that the affinity (pA_2) of dichloroisoprenaline was the same on the depolarized and non-depolarized preparation. Retro-

Table 3 Relative potencies (isoprenaline = 100) of β-adrenoceptor stimulants on uterine preparations (as described in Table 2) and on tracheal chain preparations treated with phenoxybenzamine (50 μM) to inhibit extraneuronal uptake

	Relative potency (isoprenaline = 100)		
	Uterus		*Trachea**
	K^+-depolarized†	*ACh contractions*†	
Isoprenaline	100	100	100
Fenoterol	74.1	114.8	60.0
Salbutamol	15.1	15.8	14.5
Rimiterol	13.5	10.2	6.8
Terbutaline	8.2	4.9	3.8
Orciprenaline	5.6	3.5	1.9

† Obtained from values in Table 2.
Relative potency = 100 × antilog (mean log potency ratio).
* Data taken from O'Donnell & Wanstall (1976).

spectively, the lack of any significant difference between the potencies of the β-adrenoceptor stimulant drugs obtained on the guinea-pig depolarized and non-depolarized preparations, added further weight to the conclusion that the use of a depolarized preparation did not affect estimations on β-adrenoceptors. It was thus feasible to compare the relative potency values found on the uterus with those previously obtained on trachea. The relative potency values on uterine preparations were less than threefold different from those obtained on tracheal preparations. This observation could be considered (refer Furchgott, 1972) to provide some evidence for the classification of the β-adrenoceptors in the uterus of guinea-pig in the same sub-group as those in trachea i.e. β_2, as was concluded for rat uterus by Lands, Luduena & Buzzo (1967). In addition, the fact that the relative potency values on uterus were obtained without an extraneuronal uptake inhibitor drug whereas those on trachea were obtained after inhibition of extraneuronal uptake, might lend support to the earlier conclusion that extraneuronal uptake was not affecting responses to isoprenaline on guinea-pig uterus. It is not known whether the guinea-pig uterus accumulates isoprenaline extraneuronally or not. If it does, it may be inhibited by the conditions of the experiments. The latter possibility is feasible since lack of Na^+ and high K^+ (as was used in the depolarized preparations) and low temperature (the non-depolarized preparations were maintained at 27°C) have been shown to inhibit extraneuronal uptake in other tissues (Gillespie & Towart, 1973). Experiments to explore these possibilities, using fluorescence histochemistry, are in progress.

Fenoterol was the most potent of the drugs examined on the uterus and on trachea (O'Donnell & Wanstall, 1976). Since the relative potency values on uterus agreed well with those previously reported on trachea, the compounds which showed trachea-atria selectivity, i.e. fenoterol, rimiterol, salbutamol and terbutaline (O'Donnell, 1972; O'Donnell & Wanstall, 1974; O'Donnell & Wanstall, 1977), could also be expected to show comparable selectivity between uterus and atria and experiments are being carried out to quantify this selectivity.

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References

ABDEL-AZIZ, A., GHAZAL, A. & DAABEES, T. (1974). The effect of mestranol and lynoestrol on the sensitivity of the isolated rat uterus to the inhibitory action of sympathomimetic agents. *J. Reprod. Fertil.*, **40**, 463–466.

ANDERSSON, K-E., INGEMARSSON, J. & PERSSON, C.G.A., (1973). Relaxing effects of β-receptor stimulators in isolated gravid myometrium. *Life Sci.*, **13**, 335–344.

ARUNLAKSHANA, O. & SCHILD, H.O. (1959). Some quantitative uses of drug antagonists. *Br. J. Pharmac.*, **14**, 48–58.

BLINKS, J.R. (1967). Evaluation of the cardiac effects of several Beta adrenergic blocking agents. *Ann. N.Y. Acad. Sci.*, **139**, 673–685.

DAVIDSON, W.J. & IKOKU, C. (1966). The adrenergic receptors in the guinea-pig uterus. *Canad. J. Physiol. Pharmac.*, **44**, 491–493.

EDMAN, K.A.P. & SCHILD, H.O. (1962). The need for calcium in the contractile responses induced by acetylcholine and potassium in the rat uterus. *J. Physiol.*, **161**, 424–441.

EDMAN, K.A.P. & SCHILD, H.O. (1963). Calcium and the stimulant and inhibitory effects of adrenaline in depolarized smooth muscle. *J. Physiol.*, **169**, 404–411.

EVANS, D.H.L., SCHILD, H.O. & THESLEFF, S. (1958). Effects of drugs on depolarized plain muscle. *J. Physiol.*, **143**, 474–485.

FARMER, J.B. & LEVY, G.P. (1970). Differentiation of β-adrenoreceptors by the use of blocking agents. *J. Pharm. Pharmac.*, **22**, 145–146.

FURCHGOTT, R.F. (1972). The classification of adrenoceptors (adrenergic receptors). An evaluation from the standpoint of receptor theory. In *Handbook of Experimental Pharmacology, Catecholamines*, Vol. 33, ed. Blaschko, H. & Muscholl, E. pp 283–335. Berlin, Heidelberg & New York: Springer-Verlag.

GIBSON, A. & POLLOCK, D. (1973). The effects of drugs on the sensitivity of the rat anococcygeous muscle to agonists. *Br. J. Pharmac.*, **49**, 506–513.

GILLESPIE, J.S. & TOWART, R. (1973). Uptake kinetics and ion requirements for extraneuronal uptake of noradrenaline by arterial smooth muscle and collagen. *Br. J. Pharmac.*, **47**, 556–567.

HOLLINGSWORTH, M. & SCHNIEDEN, H. (1973). Salbutamol and inhibition of uterine contractions. *J. Pharm. Pharmac.*, **25**, 996–998.

IVERSEN, L.L. (1970). Neuronal uptake processes for amines and amino acids. In *Biochemistry of Simple Neuronal Models.*, ed. Costa, E. & Giacobini, F. pp. 109–132. New York: Raven Press.

KULKARNI, P.S., WAKADE, A.R. & KIRPEKAR, S.M. (1976). Sympathetic innervation of guinea-pig uterus and ovary. *Amer. J. Physiol.*, **230**, 1400–1405.

LANDS, A.M., LUDUENA, F.P. & BUZZO, H.J. (1967). Differentiation of receptors responsive to isoproterenol. *Life Sci.*, **6**, 2241–2249.

LIGGINS, G.C. & VAUGHAN, G.S. (1973). Intravenous infusion of salbutamol in the management of premature labour. *J. Obst. Gynaec. Br. Cwlth.*, **80**, 29–32.

MARSHALL, J.M. (1970). Adrenergic innervation of the female reproductive tract. *Revs Physiol.*, **62.** 6–67.

MILLER, J.W. (1967). Adrenergic receptors in the myometrium. *Ann. N.Y. Acad. Sci.*, **139.** 788–798.

NESHEIM, B-J. (1974). Comparison of α- and β-receptor stimulation in the circular and longitudinal muscle of the oestrogen and progesterone dominated rabbit uterus. *Acta pharmac. tox.*, **34.** 295–304.

O'DONNELL, S.R. (1972). An examination of some β-adrenoreceptor stimulants for selectivity using the isolated trachea and atria of the guinea-pig. *Eur. J. Pharmac.*, **19.** 371–379.

O'DONNELL, S.R. & WANSTALL, J.C. (1974). Potency and selectivity *in vitro* of compounds related to isoprenaline and orciprenaline on β-adrenoceptors in the guinea-pig. *Br. J. Pharmac.*, **52,** 407–417.

O'DONNELL, S.R. & WANSTALL, J.C. (1975). Hexoprenaline: β-adrenoreceptor selectivity in isolated tissues from the guinea-pig. *Clin. exp. Pharmac. Physiol.*, **2,** 541–547.

O'DONNELL, S.R. & WANSTALL, J.C. (1976). The contribution of extraneuronal uptake to the trachea-blood vessel selectivity of β-adrenoceptor stimulants *in vitro* in guinea-pigs. *Br. J. Pharmac.*, **57,** 369–373.

O'DONNELL, S.R. & WANSTALL, J.C. (1977). Some aspects of the trachea-heart selectivity of Rimiterol *in vitro* and *in vivo* in guinea-pig. *Arch. int. Pharmacodyn.*, **226,** 214–223.

PENNEFATHER, J.N. & ISAAC, P.F. (1967). The response of the isolated uterus of the guinea-pig to stimulation of the ovarian nerves during the oestrous cycle. *Aust. J. exp. Biol. med. Sci.*, **45.** 229–244.

SCHILD, H.O. (1967). The action of isoprenaline in the depolarized rat uterus. *Br. J. Pharmac. Chemother.*, **31.** 578–592.

WAGNER, J.E. & MANNING, P.J. (1976). *The Biology of the Guinea-Pig.* pp. 79–80. New York: Academic Press.

WASSERMAN, M.A. & LEVY, B. (1972). Selective beta adrenergic receptor blockade in the rat. *J. Pharmac. exp. Ther.*, **182.** 256–263.

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