Br. J. Pharmac. (1979), **67**, 13–15

β-ADRENOCEPTOR AGONIST ACTIVITY OF LABETOLOL ON THE ISOLATED UTERUS OF THE RAT

BERNADETTE CAREY & E.T. WHALLEY

Department of Pharmacology, Materia Medica & Therapeutics, Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT

Isoprenaline produced dose-dependent reductions of responses of the isolated uterus of the rat produced by an EC_{80} of acetylcholine. Propranolol acted as a competitive antagonist to isoprenaline. Labetolol also reduced the acetylcholine-induced contractions but was much less potent than isoprenaline. The greatest reduction was smaller than that produced by isoprenaline. Propranolol antagonized the lower doses of labetolol. It is suggested that labetolol possesses partial agonist activity at the β-adrenoceptors of the rat isolated uterus.

Introduction Labetolol has been described as an antagonist at α- and β-adrenoceptors (Brittain & Levy, 1976) which lacks intrinsic sympathomimetic activity (Farmer, Kennedy, Levy & Marshall, 1972; Brittain & Levy, 1976). Labetolol is 6 to 10 times less potent than phentolamine in blocking α-adrenoceptors and 1.5 to 3 times less potent than propranolol in blocking β-adrenoceptors (Brittain & Levy, 1976). This profile of labetolol has provided an agent which has been used successfully in clinical trials in the treatment of hypertension (Prichard & Boakes, 1976) and could also be indicated for hypertension in pregnancy. Labetolol given to normotensive late pregnant rats prolonged the duration of gestation and the parturient process (Whalley, 1977). Since the uterus contains both excitatory α-adrenoceptors and inhibitory β-adrenoceptors (Tothill, 1967) it is possible that labetolol may alter uterine function by interfering with these adrenoceptors. This preliminary study investigates the effect of labetolol on the *in vitro* uterus of the non-pregnant rat which is a useful preparation for evaluating the effect of sympathomimetic drugs and their antagonists (Brugger, 1975).

Methods Virgin Sprague-Dawley rats, 200 to 250 g, in natural oestrus were used. The stage of the oestrous cycle was determined by microscopic examination of the vaginal smear. Uterine horns were mounted in 20 ml organ baths containing de Jalon's solution at 32°C bubbled with 95% O_2 and 5% CO_2. A resting tension of 0.5 g was applied to each tissue and isometric contractions recorded on a single channel pen recorder. Dose-response curves to acetylcholine were produced and a mean ($n = 4$) EC_{80} (1.7×10^{-5} M) chosen. The acetylcholine EC_{80} was applied repeatedly in a 5 min cycle until constant responses were obtained. Labetolol was added to the bathing fluid and left to incubate for 10 min after which time the acetylcholine EC_{80} was added and the response compared to those observed in a concurrent control preparation. This was repeated for various doses of labetolol. Propranolol (3.2×10^{-7} M) was then added to the bathing fluid for the remainder of the experiment and the above procedure repeated.

A similar series of experiments was performed with isoprenaline instead of labetolol.

The composition of the DeJalon's solution (g/l) was NaCl 9, KCl 0.42, $CaCl_2.6H_2O$ 0.472, $MgSO_4.7H_2O$ 0.38, glucose 1.0 and $NaHCO_3$ 0.5.

Results Isoprenaline antagonized the acetylcholine-induced contractions of the uterus in a dose-dependent fashion with a maximum inhibition of 84.7 ± 3.2%. (±)-Propranolol (3.2×10^{-7} M) produced a parallel rightward shift of the isoprenaline concentration-response curve (Figure 1). In contrast, labetolol was found to be much less potent than isoprenaline and initially, produced only partial antagonism of the EC_{80} acetylcholine-induced contractions.

Between 2.7×10^{-6} M and 1.35×10^{-5} M of labetolol the inhibitory effect was constant; however, a second increase in the inhibitory activity of labetolol developed above 2.7×10^{-5} M. A concentration of about 10^{-4} M labetolol was found to be just below the limit of solubility for these experiments. (±)-Propranolol shifted the labetolol concentration-effect curve to the right, but at concentrations above 2.7×10^{-5} M labetolol there was a sharp increase in the response and the response to 1.04×10^{-4} M labetolol in the presence of (±)-propranolol was equivalent to that seen in the absence of (±)-propranolol.

0007-1188/79/090013-03 $01.00

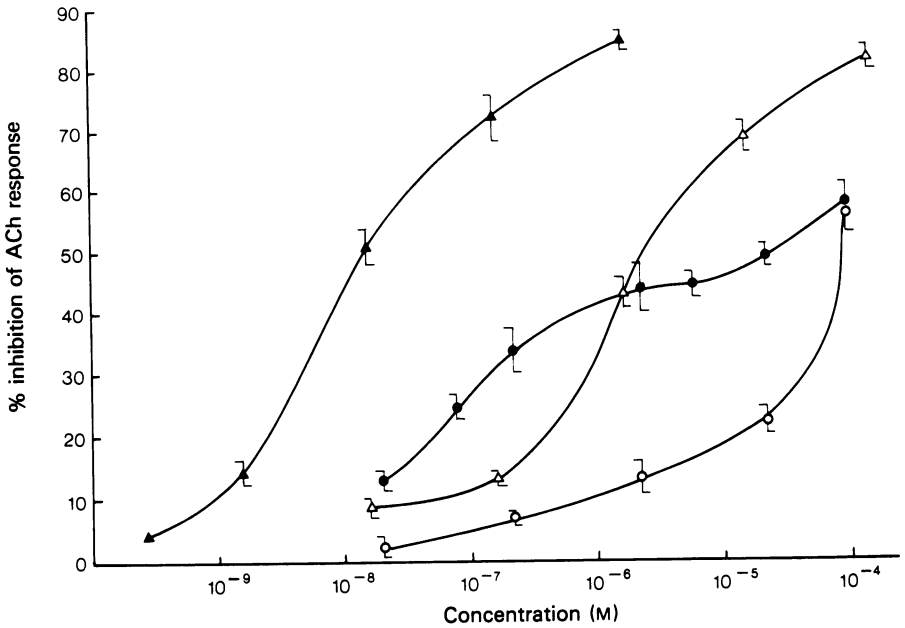

Figure 1 The effects of isoprenaline (▲) and labetolol (●) in the absence (closed symbols) and presence (open symbols) of (±)-propranolol (3.2×10^{-7} M) on the response of the rat isolated uterus to a standard EC_{80} (1.7×10^{-5} M) of acetylcholine (ACh). Results are expressed as percentage inhibition of the acetylcholine response. Vertical bars represent s.e. mean. $n = 4$ or 5.

Discussion The existence of inhibitory β-adrenoceptors in the rat uterus has been reported by many workers (Ahlquist, 1948; Rudzik & Miller, 1962; Levy & Tozzi, 1963; Butterworth & Randall, 1970) and it is known that it is β_2-adrenoceptors which mediate the relaxation of the uterus (Lands, Arnold, McAuliff, Luduena & Brown, 1967).

Excitatory α-adrenoceptors have been shown to exist only under certain conditions such as after oestrogen treatment (Tothill, 1967), during natural oestrus (Butterworth & Randall, 1970) and in late pregnancy (Tothill, 1967). It has been suggested that the hormonal status varies the relative proportion of β-adrenoceptors to α-adrenoceptors in the myometrium, oestrogen favouring α-adrenoceptors (Marshall, 1969). During late pregnancy and parturition there is a relatively high oestrogen to progesterone ratio. The effect of α- or β-adrenoceptor blockers on uterine activity at term would depend upon the degree of sympathetic activation at this time. β-Adrenoceptor blockade with propranolol does augment uterine activity in conscious pre-parturient rats (unpublished observations). α-Blockade would be expected to inhibit uterine activity, but the action of labetolol would be difficult to predict.

It has been shown in conscious pregnant rats that labetolol prolongs gestation and parturition, and reduces uterine activity during parturition (Whalley, 1977). This action would be consistent with a preferential α-blocking effect of labetolol on the uterus if sympathetic activation of uterus occurs during parturition, and this would reveal sympathetic activity at the inhibitory β_2-adrenoceptors. However, labetolol has been shown to block β_2-adrenoceptors in lung and peripheral vasculations of the anaesthetized dog (Brittain & Levy, 1976). This study suggests that labetolol possesses partial agonist activity at β_2-adrenoceptors on the *in vitro* uterus of the oestrous rat as indicated by the antagonism of acetylcholine contractions, the antagonism being much less than that produced by isoprenaline. In addition, (±)-propranolol antagonized the effects of labetolol, but clearly a second action of labetolol supervenes at concentrations above 2.7×10^{-5} M, independent of whether (±)-propranolol is present or absent. This was characterized by a sharp rise in the antagonism of the

acetylcholine-induced contractions with these high doses of labetolol. This could possibly be a manifestation of membrane stabilizing activity of labetolol at these concentrations, a property shared by several other β-adrenoceptor antagonists (Fitzgerald, 1969).

In conclusion, this study suggests that labetolol, which has been described as an antagonist at α and β-adrenoceptors, possesses intrinsic activity at β_2-adrenoceptors of the isolated uterus of the rat in oestrus.

References

AHLQUIST, R.P. (1948). A study of the adrenotropic receptors. *Am. J. Physiol.*, **153**, 586–600.

BRITTAIN, R.T. & LEVY, G.P. (1976). A review of the animal pharmacology of labetolol, a combined alpha and beta adrenoceptor blocking drug. *Br. J. clin. Pharmac.*, **3**, 681–694.

BRUGGER, A.J. (1975). The mechanism of the utero-inhibitory effect of β-sympathomimetics. *Pharmac. Ther. B.*, **1**, 277–296.

BUTTERWORTH, K.R. & RANDALL, M.J. (1970). The effects of α- and β-adrenoceptor blocking agents on the responses of the rat uterus to catecholamines throughout the oestrus cycle. *Br. J. Pharmac.*, **40**, 160P–161P.

FARMER, J.B., KENNEDY, I., LEVY, G.P. & MARSHALL, R.J. (1972). Pharmacology of AH 5158, a drug which blocks both α- and β-adrenoceptors. *Br. J. Pharmac.*, **45**, 660–675.

FITZGERALD, J.D. (1969). Perspectives in adrenergic beta-receptor blockade. *Clin. Pharmac. Ther.*, **10**, 292–306.

LANDS, A.M., ARNOLD, A., MCAULIFF, J.P., LUDUENA, F.P. & BROWN, T.G. Jr. (1967). Differentiation of receptor systems activated by sympathomimetic amines. *Nature*, **214**, 597–598.

LEVY, B. & TOZZI, S. (1963). The adrenergic receptive mechanism of the rat uterus. *J. Pharmac. exp. Ther.*, **142**, 178–184.

MARSHALL, J.M. (1969). The effects of ovarian hormones on the uterine response to adrenergic nerve stimulation and to adrenergic amines. In *Progesterone: its Regulatory Effect on the Myometrium.* Ciba Foundation Study Group No. 34. ed. Wolstenholme, G. E. W. & Knight, J. pp. 89–101. London: Churchill.

PRICHARD, B.N.C. & BOAKES, A.J. (1976). Labetolol in long-term treatment of hypertension. *Br. J. clin. Pharmac.*, **3**, 743–750.

RUDZIK, A.D. & MILLER, J.W. (1962). The mechanism of uterine inhibitory action of relaxin-containing ovarian extracts. *J. Pharmac. exp. Ther.*, **138**, 82–87.

TOTHILL, A. (1967). Investigation of adrenaline reversal in the rat uterus by the induction of resistance to isoprenaline. *Br. J. Pharmac. Chemother.*, **29**, 291–301.

WHALLEY, E.T. (1977). The cardiovascular and uterine effects of labetolol in conscious normotensive pregnant rats. *Br. J. Pharmac.*, **61**, 505–506P.

(*Received April 30, 1979.*)