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Labetalol possesses β-adrenoceptor agonist action on the rat isolated uterus

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Labetalol has been described as an antagonist at α- and β-adrenoceptors (Brittain & Levy 1976), which has a lack of intrinsic sympathomimetic activity on β-adrenoceptors, (Farmer et al 1972). It is 6–10 times less potent than phentolamine in blocking α-adrenoceptors, 1·5–3 times less potent than propranolol in blocking β-adrenoceptors, and hence, 4–8 times more potent at β- than at α-adrenoceptors. This profile of labetalol is unique and has provided an agent which has been used successfully in clinical trials in the treatment of hypertension (Prichard & Boakes 1976), and recent observations on its use in the treatment of hypertension in pregnancy appear encouraging (Michael 1979; Lamming & Symonds 1979). Labetalol 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 labetalol may alter uterine function by interfering with these adrenoceptors. This study investigates the effect of labetalol on the in vitro uterus of the non-pregnant rat.

Virgin Sprague-Dawley rats, 200–250 g, in natural oestrus were used. The stage of the oestrous cycle was determined by microscopic examination of the vaginal smear. Whole uterine horns were mounted in a 20 ml organ bath containing Krebs solution at 37 °C bubbled with 5% CO_2 in oxygen. A resting tension of 0·5 g was applied to each tissue and isometric contractions recorded on a pen recorder. Under these conditions a spontaneously contracting uterus was obtained. The effect of labetalol on spontaneous activity was studied in the presence and absence of the β-adrenoceptor blocking agent (±)-propranolol. Labetalol was compared with isoprenaline.

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The drugs used were: labetalol hydrochloride (Glaxo-Allenburys Ltd), (−)-isoprenaline-(+)-bitartate (Sigma), (±)-propranolol hydrochloride (ICI).

Labetalol was found to produce dose-dependent reductions in spontaneous activity, the effect of $2·7 \times 10^{-7}$ M labetalol, which often produced near or complete inhibition, being shown in Fig. 1.

The reduction in uterine activity occurred gradually particularly with the lower doses of labetalol taking up to 10–15 min before a constant reduction was obtained. The effect of labetalol at all doses used was difficult to reverse by washing. When (±)-propranolol ($2·3 \times 10^{-7}$M) was added to the bath during near maximal inhibition by labetalol there was a partial reversal of the inhibitory effects with a return to spontaneous activity (Fig. 1). In contrast, this concentration of (±)-propranolol often produced a full reversal of the inhibitory effect produced by isoprenaline. In the presence of this concentration of (±)-propranolol full inhibition could now be obtained only with a much higher concentration of labetalol or isoprenaline.

Isoprenaline also produced dose-dependent reductions in uterine activity with maximal inhibition being obtained with $1·95 \times 10^{-8}$ M. In contrast to labetalol, all concentrations of isoprenaline produced a rapid

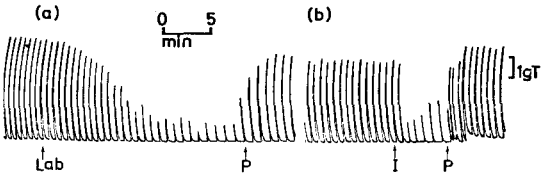

FIG. 1. Effect of (a) labetalol (L), $2·7 \times 10^{-7}$ M, and (b) isoprenaline (I), $0·95 \times 10^{-4}$ M on the spontaneously contracting rat isolated uterus. The effect of (±)-propranolol (P), $2·3 \times 10^{-7}$ M, after adding labetalol or isoprenaline is also shown.

reduction in uterine activity, and could be reversed by washing. As was expected (±)-propranolol ($2{\cdot}3 \times 10^{-7}$ M) reversed the uterine inhibitory effect of isoprenaline. Fig. 2 summarizes the effects of labetalol and isoprenaline in the presence and absence of (±)-propranolol. The mean amplitude multiplied by the frequency of response of a 5 min period after exposure to labetalol or isoprenaline were calculated during a period when the degree of inhibition was relatively constant. These values were compared with a control period and expressed as a percentage inhibition of spontaneous activity. It can be seen that labetalol is about 1000 times less potent than isoprenaline, and that propranolol produces a parallel rightward shift in the dose-response curve to both labetalol and isoprenaline.

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). 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). During late pregnancy and parturition there is an increase in the ratio of oestrogen to progesterone in the blood of the rat and since it has been suggested that the hormonal status varies the relative proportion of β- to α-adrenoceptors in the myometrium, then oestrogen dominance would result in a greater proportion of myometrial α- to β-adrenoceptors (Marshall 1969). If adrenaline is released from the adrenal medulla or activation of the adrenergic innervation of the uterus occurs during parturition then stimulation of the uterus would be expected via activation of α-adrenoceptors. β_2-Adrenoceptor blockade with (±)-propranolol augments uterine activity in vivo in pre-parturient rats (unpublished observations). Blockade of the α-adrenoceptors would be expected to inhibit uterine activity. The action of labetalol would be difficult to predict because of the relative difference in its α- and β-adrenoceptor blocking activities. It has been shown in conscious pregnant rats that labetalol prolongs gestation and prolongs parturition with a reduction in uterine activity duing parturition (Whalley 1977). This action could be explained by many mechanisms, the most likely at the myometrial level being preferential α-adrenoceptor blockade. However, the results from this study demonstrate that the inhibitory action of labetalol on the spontaneously contracting isolated rat uterus is blocked by (±)-propranolol, which suggests that labetalol possesses intrinsic sympathomimetic activity at β-adrenoceptors. Since it is β_2-adrenoceptors which mediate relaxation of the rat uterus (Lands et al 1967) it can be concluded that the intrinsic activity of labetalol is exerted at β_2-adrenoceptors. Labetalol was found to be 1000 times less potent than isoprenaline and the type of inhibitory response differed in that labetalol reduced uterine activity gradually, whereas the effect of isoprenaline was immediate. In addition, the inhibitory effect of labetalol at all doses was difficult to wash out, whereas that of isoprenaline was much more easily washed out.

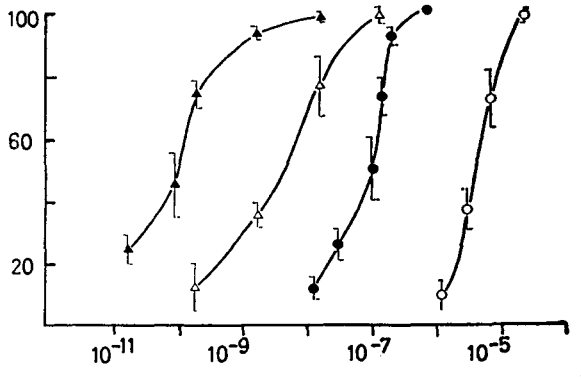

FIG. 2. The effect of isoprenaline, (▲—▲) and labetalol, (●—●) on spontaneous activity of the rat isolated uterus in the absence (closed symbols) and presence (open symbols) of (±)-propranolol ($2{\cdot}3 \times 10^{-7}$ M). Values are means (± s.e.m.) μg; n = 3–4. Ordinate: % reduction of spontaneous activity. Abscissa: molar concentration.

In conclusion, labetalol appears to possess β_2-agonist activity on the isolated spontaneously contracting rat uterus. This agonist activity possibly in association with the α-adrenoceptor blocking activity would be consistent with the marked prolongation of parturition associated with a reduction of uterine activity seen after labetalol given to parturient rats (Whalley 1977).

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