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LETTERS TO THE EDITOR

Salbutamol and inhibition of uterine contractions

Human premature labour is often managed symptomatically by attempting to reduce the force and frequency of uterine contractions (Turnbull & Anderson, 1971). One method used to suppress uterine contractions is the administration of drugs which are agonists at uterine β-adrenoceptors (for example, isoxsuprine, Hendricks, Cibils & others, 1961; orciprenaline, Baillie, Meehan & Tyack, 1970; ritodrine, Wesselius-De Casparis, Thiery & others, 1971). However, such drugs also act at β-adrenceptors in other tissues leading to unwanted effects including a pronounced maternal tachycardia and changes in blood pressure (Drug. Ther. Bull., 1973). Lands, Arnold & others (1967) originally classified β-adrenoceptors into two-groups, β_1 and β_2. In this scheme inhibition of uterine contractions and peripheral vasodilatation are β_2-adrenoceptor mediated actions while cardiac stimulation is designated β_1. Brittain, Farmer & others (1968) have described salbutamol as a selective agonist at β_2-adrenoceptors. In the present work we have examined in rats whether salbutamol shows a selective action in inhibiting uterine contractions in comparison with isoprenaline, a non-selective agonist at β-adrenoceptors.

In vitro experiments were carried out using ovariectomized Wistar rats, pre-treated with 17β-oestradiol, 5 μg kg^{-1}, daily for 7 days, and used 24 h after the last dose. Isolated uterine horns from these animals were mounted at 29° under a resting tension of 1 g in modified Krebs solution ($CaCl_2 \cdot 6H_2O$ 0·14, glucose 1 g litre^{-1}). A standard (EC 80) concentration of methacholine was applied to the tissue for 45 s every 5 min and the contractions recorded isometrically. Isoprenaline and salbutamol were added 2 min before the methacholine and the inhibition of the tension response to methacholine used as a measure of their effect.

In vivo experiments were performed in Wistar rats, 16 to 18 days pregnant, which were anaesthetized with urethane (1·05 g kg^{-1}) plus sodium pentobarbitone (28 mg kg^{-1}). They were continuously infused with oxytocin (50 mU kg^{-1} min^{-1}) via an external jugular vein, which was also used for the injection of other drugs. Blood pressure and intra-uterine pressure were measured by means of Statham pressure transducers from cannulae tied in a carotid artery and in one uterine horn and recorded on a Devices M4 recorder. Heart rate was measured with a Devices Instantaneous ratemeter triggered from the pulse pressure. Animals were given heparin (2000 units kg^{-1}, i.v.). Salbutamol and isoprenaline, doses calculated as free base, were injected intravenously alternately in ascending doses at 15 min intervals. Falls in diastolic blood pressure were expressed as percentages of the pre-drug diastolic blood pressure. Increases in heart rate were expressed absolutely in beats min^{-1}. Uterine contractions were measured as the integrated pressure above atmospheric pressure in two 3 min periods immediately before, and 0·5 to 3·5 min after drug injection. Inhibitions of uterine contractions were expressed as a percentage of the pre-drug uterine contractions.

In vitro, isoprenaline (EC50 = 28 pg ml^{-1}) and salbutamol (EC50 = 320 pg ml^{-1}) produced inhibition of methacholine-induced contractions with parallel log-concentration effect curves (15 experiments). Isoprenaline was 19 $\pm$ 6 (mean $\pm$ standard error) times more potent than salbutamol. In the presence of propranolol (100 ng ml^{-1}) the log-concentration effect curves to isoprenaline and salbutamol were shifted to the right (dose ratios of 3000 and 6500 respectively, means of 4 experiments).

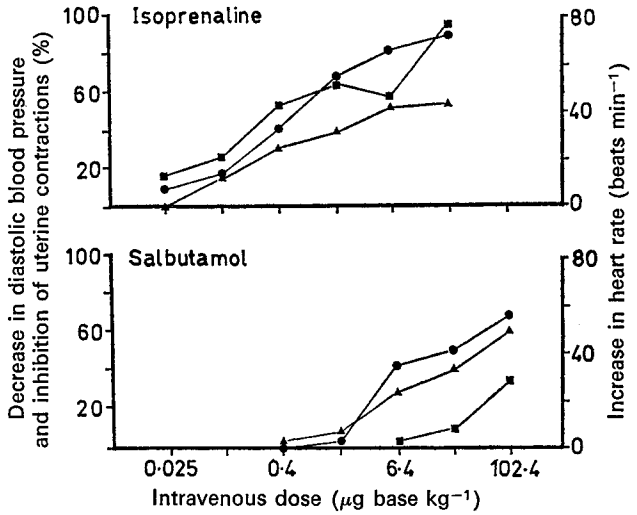

FIG. 1. Effect of isoprenaline and salbutamol on diastolic blood pressure (▲), heart rate (■) and uterine contractions (●) in anaesthetized, late pregnant rats. Each point is the mean of 6 to 9 experiments.

In 4 preliminary *in vivo* experiments using non-pregnant female rats, isoprenaline produced dose-related falls in diastolic blood pressure and increases in heart rate in doses from 0·025 to 25·6 μg kg^{-1}. Salbutamol had no significant effect on heart rate in doses up to 102·4 μg kg^{-1} but at this dose produced a 42% fall in diastolic blood pressure.

In vivo, in nine pregnant rats, isoprenaline caused a significant fall in diastolic blood pressure and increase in heart rate at all doses which produced significant inhibition of uterine contractions (Fig. 1). Isoprenaline was 20 times more potent in increasing heart rate than reducing diastolic blood pressure but had approximately equipotent chronotropic and uterine inhibitory effects (Table 1). Salbutamol was less potent than isoprenaline in causing a fall in diastolic blood pressure and inhibiting uterine contractions (5·3 and 24·5 times, respectively). However, salbutamol was even less potent in increasing heart rate (>235 times) than isoprenaline.

These results show that salbutamol was potent in inhibiting methacholine-induced contractions of rat uterus *in vitro* and oxytocin-induced uterine contractions in

Table 1. *Potencies of isoprenaline and salbutamol on diastolic blood pressure, heart rate and uterine contractions in late pregnant rats.*

Parameter	Isoprenaline	Salbutamol
Diastolic blood pressure (% fall, ED50)	8·1 μg kg^{-1} (3·3–45·0)	42·4 μg kg^{-1} (19·1–240)
Heart rate (Increase; 40 beats min^{-1})	0·43 μg kg^{-1} (0·22–1·17)	>102·4 μg kg^{-1}
Uterine contractions (% inhibition; ED50)	0·61 μg kg^{-1} (0·25–1·45)	14·9 μg kg^{-1} (5·2–48·9)

Mean values (of 6 to 9 experiments) from Fig. 1, with 95% confidence limits. ED50 = dose to produce 50% maximum effect. Heart rate increase of 40 beats min^{-1} was approximately half the maximum increase obtained with isoprenaline.

anaesthetized late pregnant rats. The mean potency of salbutamol relative to isoprenaline was similar *in vitro* and *in vivo* (19 and 24·5 times less potent, respectively). In pregnant rats salbutamol only caused a significant increase in heart rate at a dose (102·4 μg kg^{-1}) that produced a 70% inhibition of uterine contractions (Fig. 1). Also, these results confirm the high potency of salbutamol in reducing diastolic blood pressure as compared to the lower potency in increasing heart rate (Brittain, Farmer & others, 1968; Daly, Farmer & Levy, 1971). The potencies of isoprenaline and salbutamol on heart rate may be influenced by the high autonomic tone found under urethane anaesthesia (Barrett, 1971). However, there was a distinction between the two drugs as salbutamol, unlike isoprenaline, could produce inhibition of uterine contractions without tachycardia.

The β-adrenoceptor agonists at present used in the treatment of premature labour cause unwanted tachycardia at doses inhibiting uterine contractions; the changes in blood pressure produced are of less significance. One preliminary clinical trial with salbutamol has indicated that this drug is potentially useful in human premature labour (Liggins & Vaughan, 1973). The present results demonstrate that some separation can be obtained between inhibition of uterine contractions and cardiac effects with a β-adrenoceptor agonist.

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