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Mechanism of Action of Isoprenaline, Isoxuprine, Terbutaline and Orciprenaline on Gravid Human Isolated Myometrium. Influence of the Neuronal Uptake Process

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ABSTRACT

The present report analyzes the relative potencies and the mechanism of action of isoprenaline (Iso), isoxsuprine (Isox), terbutaline (Terb) and orciprenaline (Orc) on gravid isolated human myometrium in either spontaneous or in K^+-induced contractions. Spontaneous activity was observed in 80% of the strips studied and the rate of contractions was 3.22 ± 0.21 per 15 min. Dose-dependent inhibition of spontaneous contractions was observed with all the agonists. Pre-incubation with cocaine, 10^{-5} M, shifted the inhibitory dose-response curves of Iso and Orc to the left, 16.6- and 23.3-fold respectively. The rank order of relative potencies was: Iso>> Isox> Terb> Orc in the absence and Iso>> Isox> Orc> Terb in the presence of cocaine. In the strips stimulated with K^+, 80 mM, Isox, Terb and Orc produced only 20–30% inhibition while Iso was without effect. The incubation with propranolol (10^{-8}–10^{-4} M) did not modify the inhibitory response produced by Isox, Terb and Orc, but produced a parallel shift to the right of the Iso dose-response curve. Dose-ratio experiments yielded a straight line, and a Schild plot showed a pA_2 value of 8.5 ± 0.26 (slope=2.76 ± 0.47). The results with Iso confirm the existence of β-adrenoreceptors in gravid human myometrium. On the other hand, in view of the low potency of Isox, Terb and Orc, and also the inability of propranolol to block their responses, it is suggested that the relaxant effects of these drugs are not mediated by β-adrenoreceptors.

INTRODUCTION

Selective β_2-adrenoceptor agonists such as isoxsuprine and terbutaline have been widely used to inhibit uterine contractions in cases of premature labor or fetal distress (for review see Caritis et al., 1979; Ingemarsson, 1979, 1982).

Evidence has also been accumulated in the recent years suggesting that the myometrium relaxation in pregnant women induced by either isoprenaline or terbutaline can be antagonized by the nonselective β-adrenoceptor blocker propanolol, but not by the selective β_1-adrenoceptor blockers practolol or metoprolol (Andersson et al., 1973, 1975a,b). Such results, obtained either in in vivo or in vitro conditions, favor the presence of β_2-adrenoceptors in this tissue.

Although most studies on human uterine pharmacology have been qualitative, one of the few quantitative analyses carried out in the pregnant human uterus (Lossuis and Neisheim, 1976), showed that propranolol shifted the dose-response curve of isoprenaline to the right, yielding a K_d around 10^{-8} M. Recently, Hayhashida et al. (1982) showed that dihydroalprenolol binds specifically and reversibly, with high affinity to β-adrenoceptors (K_d= 0, 5 nM) of pregnant human myometrium. It was also shown that zinterol (a β_2-specific adrenergic agonist) competed with dihydroalprenolol for this binding site, indicating the existence of β_2-adrenoceptors in gravid human myometrium.

The purpose of the present study was to analyze, by means of dose-response curves, the relative potencies and mechanism of action of isoprenaline, isoxsuprine, terbutaline and orciprenaline in inhibiting spontaneous or K^+-induced contractions of the gravid human isolated myometrium. The influence of the neuronal uptake process on the potencies of these agonists was also analyzed.

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MATERIALS AND METHODS

Uterine Strips

Myometrial tissues were obtained from 60 women aged 25.7 ± 0.75 yr, 30 being primiparous and 36 multiparous. The muscle strips were obtained from the lower uterine segment during caesarean section at or near term (36–40 wk). The tissue pieces were immediately transferred to Krebs' solution (see composition below) and transported to the laboratory, or were stored at 4°C overnight and tested on the following day. No difference in response was observed between preparations mounted on the day of operation and those analyzed the next day.

In general, 4–6 uterine strips from each muscle piece, approximately 2- to 3-mm wide, 1- to 2-mm thick and 15- to 20-mm long were suspended in 10-ml jacketed organ baths bubbled with 95% O_2 and 5% CO_2. The baths were maintained at 37°C and contained a solution of the following composition (mM): NaCl 118.0; KCl 4.4; $CaCl_2$ 2.5; $MgSO_4$ 1.1; $NaHCO_3$ 23.9; KH_2PO_4 1.1 and glucose 5.5, at pH 7.2–7.4, dissolved with double-distilled and demineralized water.

Isotonic contractions were recorded on a kymograph using a light lever (magnification 6-fold) under a resting load of 1.0 g. Tissues were initially allowed to equilibrate during 2 h under a resting tension of 2 g before drug administration with the solution being changed every 20 min.

In another series of experiments, after the equilibration period, 80 mM of the NaCl of the nutrient solution was replaced by 80 mM of KCl. Isometric tension was recorded by means of force transducers F-60 (Narco- Byosystems) with tension of 1 g under the same experimental conditions as described previously (Calixto et al., 1983).

Estimation of Pharmacological Parameter

After stabilization of spontaneous or K^+-induced contractions, inhibitory cumulative dose-response curves were obtained with one of four agonists (isoprenaline, terbutaline, isoxsuprine or orciprenaline) according to Van Rossum (1963). In all experiments the organ bath concentration of the inhibitor was increased by a factor of 10 and the time lag between each concentration was about 30 min. Such procedures ensured that each dose was only added after the effects of the previous concentration reached a maximum and remained constant. Since, in general, 3–4 h were necessary for the construction of a cumulative dose-response curve, only one complete dose-response curve was obtained in each preparation. The maximal spontaneous or K^+-induced contractions obtained in each individual experiment were taken as 100%. The effects of all drugs analyzed were determined in relation to the maximal initial contraction of the preparation.

In order to inhibit the neuronal uptake of the employed drugs cocaine 10^{-5} M (an inhibitor of neuronal uptake of catecholamine) was incubated in the nutrient solution. Thus, the potency of each agonist was determined in the absence and in the presence of cocaine. The sensitivity to the drugs studied was expressed as the geometric mean ED_{50}s accompanied by their respective 95% confidence intervals.

In order to study the possible interaction of isoprenaline, terbutaline, isoxsuprine and orciprenaline, with the adrenergic receptors, propranolol (10^{-8}–10^{-4} M) was added to the nutrient solution 30 min before the construction of a dose-response curve for these agonists. The dissociation constant (K_d) of the competitive antagonist was determined by the method of Arunlakshana and Schild (1959), using isoprenaline as the agonist. A linear regression analysis was obtained for each dose-ratio plot (i.e., the ratio of concentration of agonist giving an equal response in the presence or absence of the competitive antagonist, measured at the ED_{50} level) by using different concentrations of propranolol. The intercept of the line with the abscissa is the pA_2, which is equal to $-\log K_d$ (under equilibrium conditions). One uterine strip was always exposed only to the agonist and thus used as the control. These experiments were performed in the presence of 10^{-5} M cocaine and either 3×10^{-5} M phenoxybenzamine or 10^{-6} M phentolamine, to prevent neuronal uptake and stimulation of α-adrenoceptors, respectively. In each preparation only one agonist and one concentration of propranolol were tested.

Drugs and Salts

The following drugs were used: isoprenaline hydrochloride; propranolol hydrochloride (Sigma Chemical Co., St. Louis, MO), phenoxybenzamine hydrochloride (Smith, Kline & French, Philadelphia, PA) terbutaline sulphate (usafarma, San Paulo, Brazil), orciprenaline sulphate (Boeheringer-Ingelheim, Rhein, W. Germany), isoxsuprine hydrochloride (Organon Int., West Orange, NJ) cocaine hydrochloride (Merck, Rahway, NJ) and phentolamine hydrochloride (Ciba-Geigy, Summit, NJ). The solutions of isoprenaline, terbutaline, isoxsuprine and orciprenaline were prepared in 0.9% NaCl in the presence of 10 μg/ml EDTA to retard oxidation. Cocaine, phenoxybenzamine or phentolamine were added directly to the nutrient solution just before starting the experimental measurements. All other drugs were administered directly to the organ bath to give the derived concentration.

Statistical Analysis

The data obtained, expressed as the mean ± SEM were analyzed by means of Student's t test for unpaired samples (Snedecor and Cochran, 1967). Differences below the 0.05 probability level ($P<0.05$) were considered statistically significant. Slope and correlation of Schild plots were obtained through linear regression analyses.

RESULTS

Spontaneous activity was observed in approximately 80% of the strips studied. The rate of contraction was very regular with a mean frequency of 3.22 ± 0.21 over 15 min (Fig. 1). Muscle strips from the same myometrium showed a very similar rate of contraction. A dose-dependent inhibition of spontaneous contractions was observed when isoprenaline (10^{-11} to 10^{-7} M), isoxsuprine (10^{-7} to 3×10^{-4} M), terbutaline (10^{-8} to 10^{-2} M) and

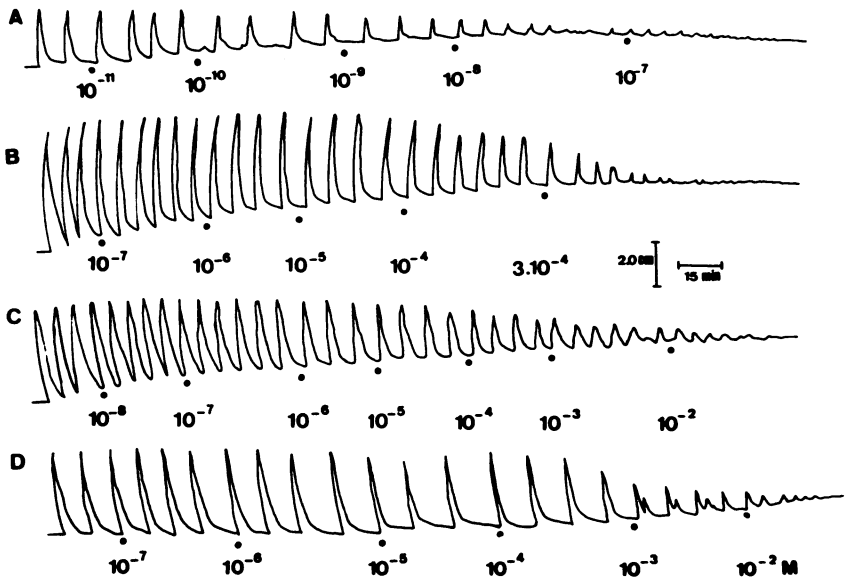

FIG. 1. Typical isotonic record of the spontaneous contractions of strips from gravid human myometrium before and after the addition of cumulative doses of isoprenaline (*A*), isoxsuprine (*B*), terbutaline (*C*) and orciprenaline (*D*). All experiments were conducted in the presence of 10^{-5} M cocaine.

orciprenaline (10^{-7} to 10^{-2} M) were administered to the preparations (Fig. 1). However, when higher concentrations of these agonists were administered, an increase in the tonus of the preparations was also observed. Fig. 2 (A, B and C) shows that orciprenaline, isoxsuprine and terbutaline inhibited in a dose-dependent fashion the spontaneous myometrium contractions. In experiments performed in the absence of cocaine, isoprenaline was approximately 21,600-, 208,300- and 716,600-fold more potent than isoxsuprine, terbutaline and orciprenaline, respectively (Table 1). Thus, isoxsuprine was significantly more potent than terbutaline and orciprenaline, 10- and 23-fold, respectively ($P<0.05$).

When preparations were preincubated with 10^{-5} M cocaine, the inhibitory dose-response

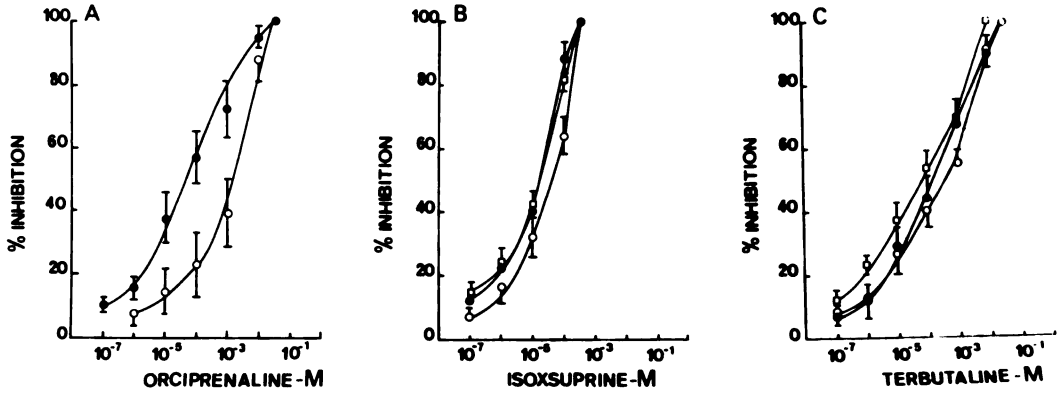

FIG. 2. Mean inhibitory dose-response curves of orciprenaline (*A*), isoxsuprine (*B*) and terbutaline (*C*) on the spontaneous contractions of the gravid human isolated myometrium in the absence (○—○) and presence of cocaine 10^{-5} M (●—●), and also in the presence of cocaine plus propranolol (□—□). The curve of the association of cocaine with propranolol was omitted in *A* in order to show better the potentiating action of cocaine. See typical record in Fig. 4. *Vertical bars* represent the SEM. Each point is the mean of 8 to 14 experiments.

TABLE 1. Inhibitory effects produced by isoprenaline, isoxsuprine, terbutaline and orciprenaline on the spontaneous contractions of gravid human isolated myometrium in absence or in presence of cocaine, 10^{-5} M.

Agonists	ED_{50}, molar concentration: Cocaine (10^{-5} M) Absent	Present	DR[a]	Potency[b]
Isoprenaline	1.2×10^{-9} (0.4–3.3)[c]	7.2×10^{-11} (1.9–27.0)	16.6*	1.0
Isoxsuprine	2.6×10^{-5} (0.8–8.1)	1.0×10^{-5} (0.2–4.3)	2.6	4.6×10^{-5}
Terbutaline	2.5×10^{-4} (0.4–12.8)	1.8×10^{-4} (0.3–9.6)	1.4	4.8×10^{-6}
Orciprenaline	8.6×10^{-4} (1.1–17.3)	3.7×10^{-5} (0.3–25.7)	23.4*	1.4×10^{-6}

[a]Dose-ratio calculated as ED_{50} in absence/ED_{50} in presence of cocaine.

[b]Experiments done in absence of cocaine.

[c]Confidence limits of 95%. Each group consisted of 8 to 14 experiments.

*Significantly different from experiments done in absence of cocaine ($P<0.05$).

curves for isoprenaline and orciprenaline were significantly shifted to the left, 16.6- and 23.2-fold, respectively ($P<0.05$; Table 1). On the other hand, the effects produced by terbutaline and isoxsuprine were not significantly affected (see Figs. 2 and 5 and Table 1).

In strips stimulated by K^+ 80 mM, the administration of terbutaline, isoxsuprine and orciprenaline (10^{-9} to 10^{-3} M) produced only about 20–30% of inhibition of maximal tonic response (Fig. 3). However, the maximal inhibitory effect did not differ among the agonists. In the same experimental conditions similar results were observed to isoprenaline.

The inhibitory dose-response curves obtained for terbutaline, isoxsuprine and orciprenaline in uterine strips contracting spontaneously were not significantly displaced when these preparations were incubated with propranolol (10^{-8} to 3×10^{-5} M) (Figs. 2 and 4). A further increase in the concentration of propranolol in the nutrient solution to 10^{-4} M also did not modify the inhibitory effects of the three agonists. On the other hand, the relaxant effect produced by isoprenaline in human myometrium was shifted to the right, in a parallel form, in the presence of propranolol (10^{-8}–10^{-7} M) (Fig. 5). Schild plots from these data showed pA_2 values of 8.51 ± 0.26, and linear regression of 0.99. The slope, however, differed significantly from unity (−2.76 ± 0.47; Fig. 6).

DISCUSSION

The present results show that isoprenaline, isoxsuprine, terbutaline and orciprenaline inhibited in a dose-dependent fashion the spontaneous contractions of gravid human isolated myometrium. The last three agonists were

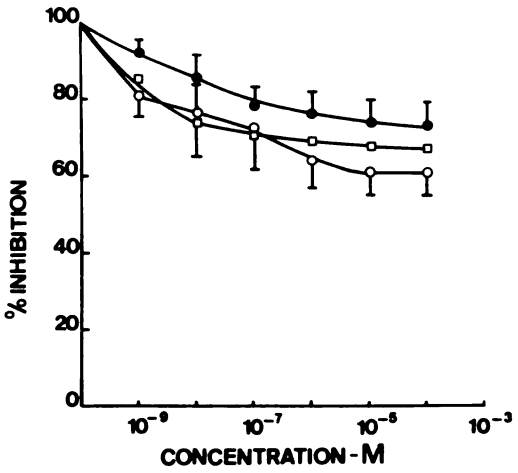

FIG. 3. Mean inhibitory dose-response curves of orciprenaline (○—○), terbutaline (●—●) and isoxsuprine (□—□) on gravid human isolated myometrium after tonic contraction induced by K^+ 80 mM. All experiments were conducted in the presence of 10^{-5} M cocaine. *Vertical bars* represent the SEM. Each point is the mean of 7 to 9 experiments.

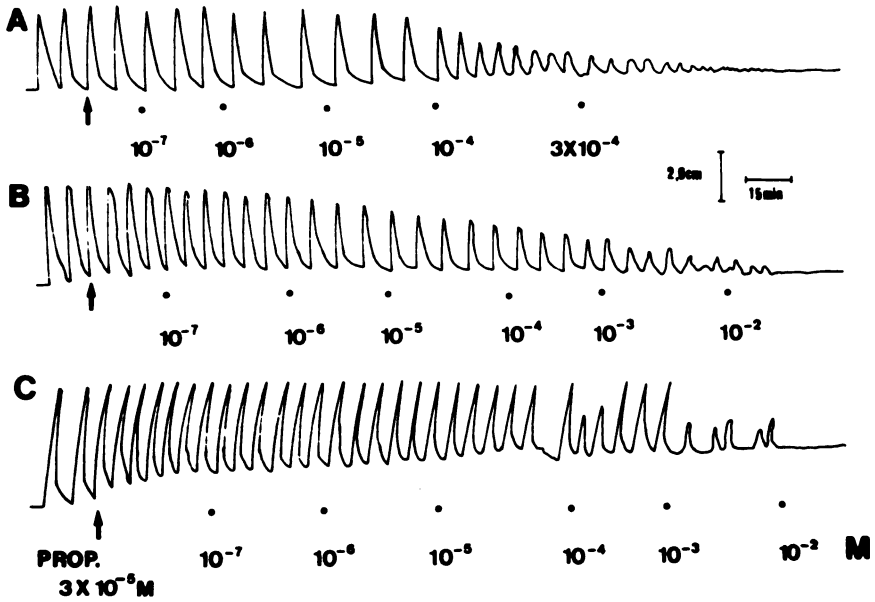

FIG. 4. Typical isotonic record of spontaneous contractions of strips from gravid human myometrium before and after addition of cumulative doses of isoxsuprine (*A*), terbutaline (*B*) and orciprenaline (*C*) in the presence of propranolol 3×10^{-5} M. All experiments were conducted in the presence of cocaine 10^{-5} M.

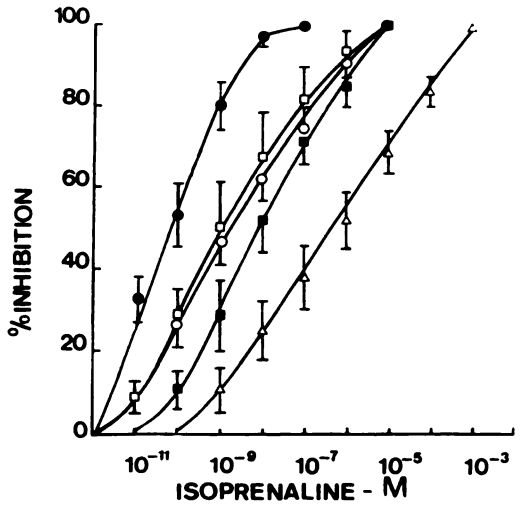

FIG. 5. Mean inhibitory dose-response curves of isoprenaline on the spontaneous contractions of the gravid human isolated myometrium in the absence (○—○) and in the presence of cocaine 10^{-5} M (●—●), or propranolol: 10^{-8} M (□—□), 3×10^{-8} M (■—■), 10^{-7} M (Δ—Δ). All experiments with propranolol were conducted in the presence of cocaine 10^{-5} M. The *vertical bars* represent the SEM. Each point is the mean of 7 to 8 experiments.

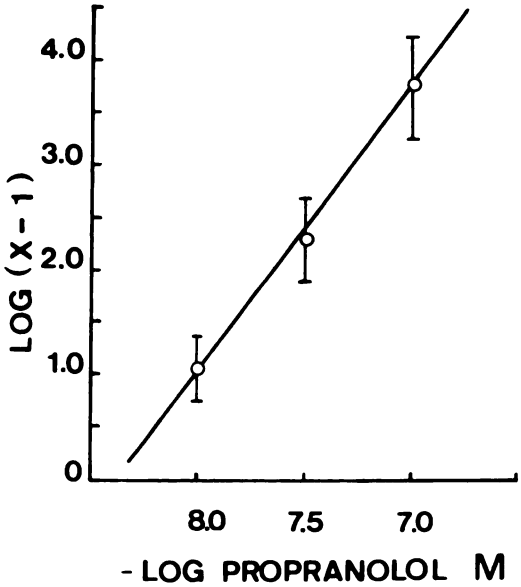

FIG. 6. Schild plot for the interaction of propranolol with isoprenaline on gravid human isolated myometrium. Linear regression analysis yielded a pA_2 value of 8.51 ± 0.26, a slope of −2.76 ± 0.47 and regression line (*r*) of 0.99. *Vertical bars* represent the SEM. Each point is the mean of 7 to 8 experiments. *X*=Indicates the ratio of the ED_{50} obtained in the presence of propranolol and the ED_{50} obtained in the absence of the drug.

significantly less potent than isoprenaline either in the absence or in the presence of cocaine. The rank order of relative potencies was: isoprenaline>> isoxsuprine> terbutaline> orciprenaline, in absence of cocaine, and isoprenaline>> isoxsuprine> orciprenaline> terbutaline, in presence of cocaine. Furthermore, we have obtained some results indicating that the inhibitory effect produced by orciprenaline, a β-mimetic drug employed to inhibit premature labor (Poseiro et al., 1969; Delard et al., 1969; Baillie et al., 1979; Zillianti and Aller, 1971), was potentiated by cocaine, suggesting that its low potency may be due at least in part to its greater susceptibility to neuronal uptake. This fact seems to have some relevance and could explain the more intense maternal and fetal cardiovascular side effects of orciprenaline (Poseiro et al., 1968). In addition, these findings indicate an important physiological role of the neuronal uptake process to terminate the action of some adrenergic compounds in the human myometrium.

The much smaller inhibitory effects promoted by isoxsuprine, terbutaline, orciprenaline and isoprenaline in the preparations stimulated by K^+ 80 mM support the hypothesis that the pharmacological action of the drugs on human myometrium depends on the electrical integrity of the cellular membrane (Sullivan and Marshall, 1970). However, Andersson et al. (1973) showed that both isoprenaline and terbutaline inhibited in a dose-dependent manner the K^+-induced contraction for the isolated gravid human myometrium and that the relaxant effect induced by these agonists varied in functions of the tension and between the preparations. These discrepancies may be due in part to a difference in the methodology employed. Recently, we have demonstrated (Calixto and Aucélio, 1982) that both isoprenaline and adrenaline produced a dose-dependent relaxation of prepuberal isolated dog uteri stimulated by K^+ 127 mM in solution containing a low calcium concentration (0.2 mM). This relaxant effect was no longer observed when the calcium concentration was increased to 2.0 mM, a result which is in accordance with our present observations with the human myometrium immersed in a 2.5 mM Ca^{2+} solution.

In the presence of propranol, the dose-response curve for isoprenaline was shifted to the right in a parallel form, indicating a competitive antagonism and confirming the existance of β-adrenoceptors in gravid human myometrium as already reported by Lossius and Neisheim (1976). The pA_2 value obtained in the present study for propranolol (8.5) is similar to the values observed in other smooth muscle preparations, including the myometrium (Farmer and Levy, 1970; Kenakin, 1982; Larsen et al., 1979; Johnson et al., 1980; Patersson et al., 1983). However the slope of Schild regression differed from unity. This fact may be due to an increase in the tonus of the preparations when high concentrations of isoprenaline were administered. Furthermore, radioligand studies indicated that at least 87% of the β-adrenergic receptors present in the human gravid myometrium are of the β_2-type (Hayashida et al., 1982).

Although our results suggest a role of β-adrenoceptors in inhibiting pregnant myometrium activity, the low affinity of isoxsuprine, terbutaline and orciprenaline, and the fact that propranolol, even at an extremely high concentration (10^{-4} M), failed to antagonize their effects, support the hypothesis that these compounds induce inhibition of human myometrial activity by a mechanism which does not involve activation of β-adrenoceptors. Further support for this view derives from the fact that these agonists are effective inhibitors of contraction in either nonpregnant or pregnant strips, while isoprenaline is only effective in the latter preparations (Lossius and Nesheim, 1976; Berg-Johnsen and Nesheim, 1976; Sullivan and Marshall, 1970).

These effects are probably due to a non-specific action, as indicated by either in vivo or in vitro studies using isoxsuprine in human myometrium (Lish et al., 1960; Berg-Johnsen and Neisheim, 1976; Brazy et al., 1981). The low potency supports the clinical observation that long and repeated infusion is required in order to obtain successful results with these drugs. The increase in uterine and placental blood flow associated with the use of β-mimetic compounds may also, at least in part, account for their beneficial effect in treatment of premature labor.

These findings, therefore indicate that additional studies are necessary to understand the mechanism of action of these drugs and their relative potencies on human myometrium.

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