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Inhibitory effect of *p*-hydroxyphenylisopropylarterenol on the isolated human myometrium

There is a need for drugs to suppress excessive uterine activity of premature labour. Compounds with β-adrenergic receptor stimulating properties have been synthesized and tested for this action *in vitro* and *in vivo*. One of the most active seems to be *p*-hydroxyphenylisopropylarterenol (Cc 25; Philips-Duphar). In this paper two characteristics not previously described are presented*.

Myometrial strips from patients undergoing hysterectomy, legal abortion or Caesarean section, were mounted in an isolated organ bath and the motility recorded on a smoked drum (Bygdeman & Eliasson, 1963). The drug was dissolved in normal saline and fresh solutions were prepared immediately before use because at neutral pH there was a rapid auto-oxidation.

Myometrial strips (n = 50) at late proliferatory phase from 16 non-pregnant patients showed a clear inhibition (50% or more) of the amplitude or frequency of the contractions, or both, with the drug at $1–2{\cdot}5 \times 10^{-7}$ g/ml. When the spontaneous activity had been restored after washing, the myometrium was always completely refractory to a second dose, even if this was 10 times larger than the first (Fig. 1). A subsequent dose of PGE_1 always inhibited the motility indicating a normal reactivity to other inhibitors.

Myometrial strips (n = 16) from four patients in the 12th to 20th week of gestation responded qualitatively in the same way as those from the non-pregnant patients but the sensitivity was 100–1000 times higher, i.e. a clear inhibition could be obtained with $0{\cdot}1–1 \times 10^{-9}$ g/ml. The tachyphylaxis was not as complete as for the non-pregnant myometrium (Fig. 2).

Myometrial strips from patients at term were less sensitive to the drug than those from non-pregnant women. In one experiment (three strips from one patient) a clear inhibition was obtained with $0{\cdot}1 \times 10^{-6}$ g/ml, while in two experiments (five strips) no effect was noted with $0{\cdot}25–0{\cdot}75 \times 10^{-6}$ g/ml. Doses up to 1×10^{-5} g/ml were tested, but were always without effect. Whether this arose from primary insensitivity or tachyphylaxis could not be ascertained.

Propranolol (10^{-5} g/ml) completely blocked the effect of the drug.

The effects of the drug on the human uterus *in vitro* have also been described by

* Presented at an International Symposium on Uterine Physiology and Pharmacology, June 20–22, 1968, New York.

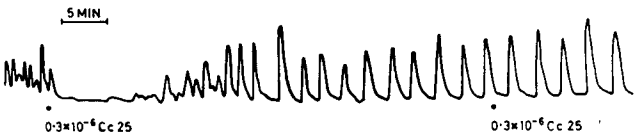

FIG. 1. Inhibitory effect of the drug (0·3 μg/ml) on the spontaneous motility of the isolated human non-pregnant myometrium. Note the lack of effect of the second dose.

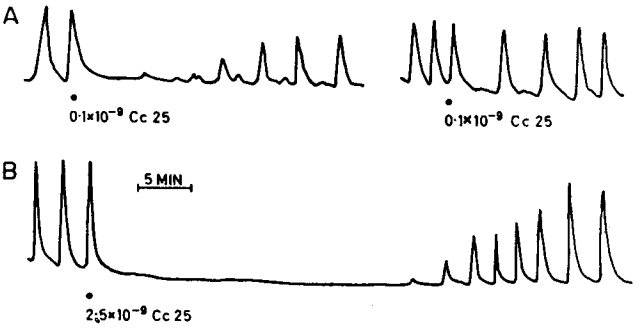

FIG. 2. Inhibitory effect of the drug (0·1 and 2·5 ng/ml) on two strips of myometrium from a woman in the third month of pregnancy. The experimental conditions as in Fig. 1.

Nakanishi, McLean & others (1969) but my results are at some variance with theirs, since they noted that the pregnant myometrium at term was more sensitive than the non-pregnant myometrium. The sensitivity of the non-pregnant uterus was the same in both studies.

Despite the marked tachyphylaxis *in vitro* there seems to be no escape phenomenon when the drug was given intravenously to suppress the uterine activity (Stolte, Eskes & others, 1965; Wansbrough, Nakanishi & Wood, 1968).

The reason for the significant increase in sensitivity during the early stage of pregnancy is not clear, but it could be related to the change in adrenergic innervation of the uterus that takes place during pregnancy (Sjöberg, 1967).

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