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Effect of some spasmolytic drugs on the isolated human myometrium

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Spasmolytic drugs possessing a musculotropic action appear to be the most effective in inhibiting the motility of the human myometrium *in vitro*. Substances whose action is mediated via a predominently β-receptor mechanism have relatively little or no effect on this preparation.

A NUMBER of substances which possess an excitatory action on the human uterus exist, but there is a paucity of drugs which can inhibit its spontaneous motility *in vivo*. Such drugs would be of potential importance in the management of certain obstetric and gynaecological problems such as dysmenorrhoea (Bygdeman & Eliasson, 1964), and premature labour (Hendricks, Cibils, Pose & Eskes, 1961), prematurity being a leading cause of perinatal mortality (Johnson, McGaughey, Scoggin, Wilson & Thornton, 1963).

The object of the work described here was threefold; firstly, to re-investigate the action of some drugs of known activity on the isolated human myometrium preparation; secondly, to establish if possible the type of activity required of a compound for it to inhibit the isolated human myometrium; and thirdly, to investigate the action of some drugs not previously tested on this preparation.

Experimental

Human uteri were obtained from patients aged 35–45 years, having undergone hysterectomy, usually for menorrhagia, and all uteri were postpartum. Each uterus was stored in a salt solution of the following composition: g/litre NaCl, 9·0; KCl, 0·4; $CaCl_2$, 0·24; $NaHCO_3$, 0·4; glucose, 0·1; at 4° for 12–24 hr before experiment. Segments were prepared as described by Chambers & Pickles (1958) and suspended in the aerated physiological solution in a 50 ml bath at 38°. Isotonic contractions were recorded with frontal writing lever, at a tension of 1 g and magnified ten times.

Drugs. Noradrenaline hydrochloride, adrenaline hydrochloride, phenylephrine hydrochloride, isoprenaline hydrochloride, papaverine hydrochloride, orciprenaline (Alupent), isoxsuprine, Efosin (Hoechst) [a mixture of 1-(3,3-diphenylpropyl) piperidine and αα-diethyl-1-piperidine butyramide], fencamfamin, (*m*-methoxy-α-methylphenethyl) (*m*-methoxyphenethyl)amine hydrochloride (AH.1101), 1-(3,4-dihydroxyphenyl)-2-hexylaminoethanol hydrochloride (AH.2139).

Results

The effects of noradrenaline, phenylephrine, adrenaline, isoprenaline, orciprenaline, isoxsuprine, papaverine, Efosin, fencamfamin, AH.2139 and AH.1101 on the isolated human myometrium preparation are summarised in Table 1.

The predominantly α-receptor stimulant sympathomimetic amines noradrenaline and phenylephrine and the αβ-receptor stimulant adrenaline all produce a contraction of the isolated human myometrium (Fig. 1).

TABLE 1. THE EFFECT OF SOME COMPOUNDS ON THE ISOLATED HUMAN MYOMETRIUM

Drug	Class	Dose μg/ml	Effect on human myometrium *in vitro*
Noradrenaline ..	α-predominant adrenergic stimulant	2·5 (3)	Marked rise in tone
Phenylephrine ..	,,	25·0 (1) 250·0 (2)	Rise in tone Rise in tone
Adrenaline ..	αβ-adrenergic stimulant	0·04 (2) 1·50 (2)	Rise in tone Rise in tone
Isoprenaline ..	β-predominant adrenergic stimulant	2·0 (1) 2·5 (1) 6·25 (1) 12·50 (1) 25·0 (4)	No effect No effect No effect No effect Variable effect: (*a*) No effect (*b*) Fall in tone (*c*) Slight rise followed by slight fall
Orciprenaline ..	β-predominant adrenergic stimulant	12·0 (1) 25·0 (1)	No effect Very slight fall in tone.
Isoxsuprine ..	β-adrenergic stimulant + musculotropic activity	50·0 (1) 100·0 (1)	No effect No reduction in tone but abolition of contractions Long duration of action
AH. 2139 ..	β-predominant adrenergic stimulant	25·0 (2)	No effect
Papaverine ..	Musculotropic spasmolytic	2·0 (1) 2·5 (3) 6·25 (1) 10·0 (2) 12·5 (1) 20·0 (1)	Fall in tone Fall in tone Very marked fall in tone Marked fall in tone Very marked fall in tone Very marked fall in tone
Fencamfamin ..	Musculotropic spasmolytic	25·0 (2)	Fall in tone
Efosin	Musculotropic spasmolytic	6·25 (2) 10·0 (1)	Fall to very marked fall in tone Marked fall in tone
AH.1101 ..	Musculotropic spasmolytic	6·25 (1) 15·0 (1) 18·8 (1)	Fall in tone Marked fall in tone Marked fall in tone

Figures in parentheses indicate the number of experiments.

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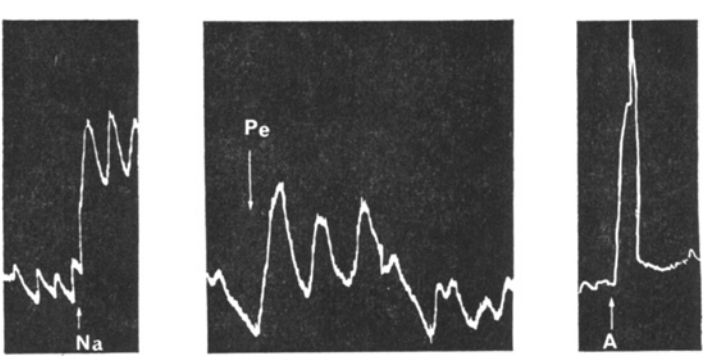

FIG. 1. Isolated human uterus. The effect of some sympathomimetic amines. A Na, noradrenaline, 2 μg/ml; Pe, phenylephrine, 200 μg/ml; A, adrenaline, 1 μg/ml

Phenylephrine showed less activity than either adrenaline or noradrenaline. The predominantly β-receptor stimulant isoprenaline had no effect on the preparation below the high concentration of 25 μg/ml. At this dose it gave variable effects; two administrations of the drug produced a fall in tone, one produced a very slight rise followed by an equally slight fall and a fourth administration had no effect at all. No effect was also obtained with the predominently β-receptor stimulant orciprenaline.

In contrast to these results, papaverine, at concentrations ranging from 2–20 μg/ml, consistently caused a decrease in tone and abolished the spontaneous contractions of this preparation (Fig. 2). A similar effect

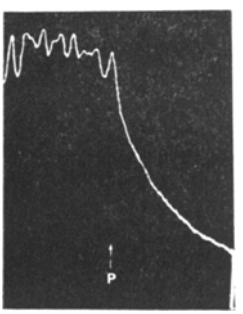

FIG. 2. Isolated human uterus. The effect of papaverine, a musculotropic spasmolytic drug. At P, 20 μg/ml papaverine was added to the organ bath.

was seen with fencamfamin or Efosin, both of which possess a predominently musculotropic action.

Isoxsuprine, which has a β-receptor excitor action (Lish, Dungan & Peters, 1960) and a papaverine-like action (Lish, Hillyard & Dungan, 1960), occupied an intermediate position in that although the drug was effective in inhibiting the motility of the human myometrium, the dose necessary was greater than that required for the other effective spasmolytics under test (Fig. 3).

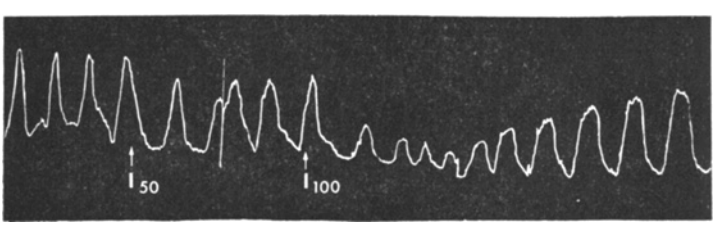

FIG. 3. Isolated human uterus. The effect of isoxsuprine, a drug possessing both β-stimulant sympathomimetic and musculotropic spasmolytic properties. At I_{50}, 50 μg/ml; I_{100}, 100 μg/ml of isoxsuprine was added to the organ bath.

During the evaluation of a number of new compounds, including two phenethylamines AH.2139 and AH.1101, it was found that AH.2139 possessed potent β-stimulant activity whilst AH.1101 was direct acting in the manner of papaverine. Of these two compounds, AH.1101 had marked spasmolytic activity on the isolated human uterus whilst AH.2139

was without effect. One experiment with AH.1101 is illustrated in Fig. 4.

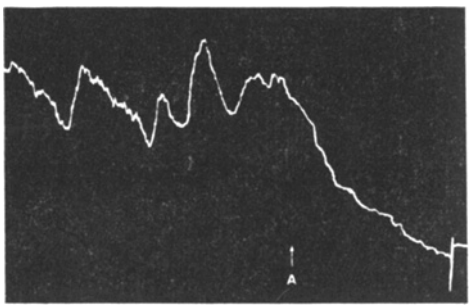

FIG. 4. Isolated human uterus. The effect of AH.1101, a musculotropic spasmolytic. At A, 20 μg/ml AH.1101 was added to the organ bath.

Discussion

Neurotropic agents such as atropine (Quadros & Sinha, 1960; Sandberg, Ingelman-Sundberg, Lindgren & Ryden, 1961) and hyoscine *N*-butyl bromide (Quadros & Sinha, 1960) are relatively ineffective in relaxing the isolated human myometrium preparation. Isoprenaline, which is a predominantly β-receptor activator has been reported to be inactive in relaxing the isolated human uterus and has, in fact, been shown to stimulate this preparation at high dosage (Quadros & Sinha, 1960). The action of adrenaline has been shown (Adair, 1935) to stimulate the excised human uterus, and this occurs on both gravid and non-gravid uteri. *In vivo*, however, adrenaline may either relax or contract the uterus depending on the contractile state, and on whether the uterus is in the pregnant or non-pregnant state (Garrett, 1959). Noradrenaline stimulates the human uterus under all these conditions (Bourne & Burn, 1927; Kaiser, 1950; Alvarez & Caldeyro-Barcia, 1954; Garrett, 1954, 1955). Rudzik & Miller (1962) have stated the activity of relaxin to be mediated by the release of catecholamines, in particular adrenaline, but relaxin was found not to affect the motility of the isolated human uterus.

With those substances whose action is mediated through a musculotropic papaverine-like activity, there is evidence which suggests that the motility of the human uterus is always inhibited. Jung (1962) showed that the musculotropic spasmolytic drugs Efosin, Erantin (α-2-dimethylamino-1-methylethyl)-α-phenylphenethyl propionate) and AD.205 [(2-benziloyloxyethyl)dimethyl octylammonium bromide] markedly inhibited the spontaneous contractility of the isolated human uterus preparation. The high antispasmodic effect of Efosin had been reported earlier by Quadros & Sinha (1960). Additional drugs of this category which have been shown to possess relaxant activity on the isolated human uterus preparation include papaverine and Monzal [1-(3,4-dimethoxyphenyl)-4-phenylbutyldimethylamine] (Wagner & Kessler, 1958) and papaverine and Spasmaverine [ethyldi(3-phenylpropyl)amine] (Sandberg, Ingelman-Sundberg, Lindgren & Ryden, 1961).

Bygdeman & Eliasson (1964) have shown that isoxsuprine has a spasmolytic action on the *in vivo* human uterus, and Lish & others (1960) reported it to have a direct musculotropic action in addition to activating β-receptors. It seems that the former mechanism is the more important. Recently bradykinin has been reported as having a powerful spasmolytic activity on the human uterus *in vitro* (Landesman, Campbell & Wilson, 1963), and once again this seems to be a direct action since Khairallah & Page (1961) have shown bradykinin to act directly on intestinal smooth muscle.

There is therefore some evidence to suggest that compounds likely to relax the isolated human myometrium preparation must possess a predominently musculotropic spasmolytic activity. Additional support to this evidence is given in this paper. Substances whose effects are mediated through a predominantly α-receptor mechanism, such as phenylephrine and noradrenaline, and an α- and β-receptor mechanism such as adrenaline, cause an increase in tone of the isolated human myometrium preparation. Substances like isoprenaline, orciprenaline and AH.2139, whose actions are mediated through a predominantly β-receptor mechanism, have no effect on this preparation unless very high concentrations are used, when a fall in tone may occasionally be observed, but these effects could not be reliably repeated. On the other hand, papaverine and drugs under investigation which possessed a predominantly musculotropic action consistently produced a marked fall in tone of the isolated human uterus preparation and abolished its spontaneous motility.

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