Research Institute for Rheumatic Diseases, K. TRNAVSKÝ
Piešťany, Czechoslovakia.
February 9, 1965

References

Benitz, K. F. & Hall, L. M. (1963). *Arch. Int. Pharmacodyn.*, **144**, 185–195.
Büch, O. & Wagner-Jauregg, Th. (1962). *Arzneimitt.-Forsch.*, **12**, 639–640.
Horáková, Z. (1964). *International Symposium on Non-steroidal Anti-inflammatory Drugs*, Milan.
Houck, J. C. (1962). *Surgery*, **51**, 770–773.
Laden, C., Blackwell, R. Q. & Fosdick, L. S. (1958). *Amer. J. Physiol.*, **195**, 712–718.
Schneider, W. (1945). *J. biol. Chem.*, **161**, 293–301.
Stegemann, H. (1958). *Hoppe-Seyl. Z.*, **311**, 41–45.

The nature of the inhibition of the rat uterus by relaxin

SIR,—Wiqvist (1959) presented evidence that the inhibitory action of relaxin on the spontaneous contractions of the isolated uterus of the rat was not blocked either by phentolamine or by dihydroergotamine in concentrations which blocked the inhibition of the these contractions by adrenaline. He suggested that relaxin acted otherwise than by the adrenergic mechanism suggested by Miller & Murray (1959). However, a fuller investigation of these actions by Rudzik & Miller (1962a, b) added weight to their original contention that the mechanism was

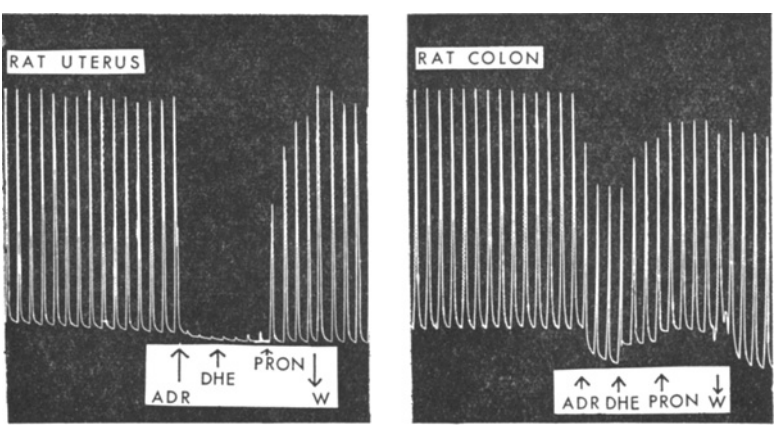

FIG. 1. Effects of pronethalol and dihydroergotamine on inhibitory actions of adrenaline. Isotonic contractions of the electrically stimulated rat uterus. At ADR 5×10^{-9} (-)-adrenaline, at DHE 5×10^{-7} dihydroergotamine and at PRON 5×10^{-7} pronethalol were added to the bath. The drugs were washed out at W. Isotonic contractions of the electrically stimulated rat colon. Legend as for uterus except for ADR, where 5×10^{-8} (-)-adrenaline was added to the bath.

adrenergic. The blocking drugs used by both groups, dihydroergotamine and phentolamine caused adrenergic block at α-receptors, but are now recognised to lack specificity (Ahlquist & Levy, 1961; Birmingham & Wilson, 1963). Also, the action of adrenaline on the rat uterus is known to be almost entirely at β-receptors (Levy & Tozzi, 1963; Levy, 1964). With the advent of a β-receptor blocking agent of high specificity, pronethalol (nethalide) (Black & Stephenson,

1962), the opportunity arose to investigate its action on the inhibition of the electrically stimulated rat uterus by adrenaline and by relaxin.

Isolated uterine horns from adult albino rats weighing 140 to 180 g were suspended at 37° in 75 ml Krebs solution gassed with 95% oxygen and 5% carbon dioxide. The preparation was mounted in a Perspex channel between two parallel platinum wires arranged along the length of the muscle. This allows electrical stimulation of the preparation in the way described for the guinea-pig vas deferens by Birmingham & Wilson (1963). The distance between the platinum wires was 4 mm so that the uterus could move unimpeded within the channel. The preparation was stimulated electrically with square wave impulses of 0·3 msec duration, 120 V at a frequency of 25 sec, for 10 sec every 2 min. No consideration will be given here to the identity of the structures which are being stimulated in the preparation, but preliminary experiments indicate that these are neuronal and cholinergic in nature. The contractions caused by the stimulation were recorded isotonically on a smoked drum with a frontal writing lever. The load on the preparation was 1g.

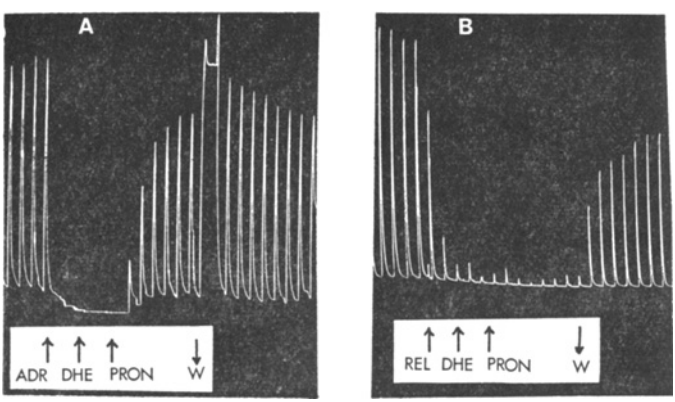

FIG. 2. Effects of pronethalol and dihydroergotamine on the inhibitory actions of adrenaline and relaxin on isotonic contractions of the electrically stimulated rat uterus. The two preparations were from the same animal and set up in identical conditions. (A) At ADR 2×10^{-8} (-)-adrenaline, at DHE 10^{-6} dihydroergotamine and at PRON. 10^{-6} pronethalol were added to the bath. The drugs were washed out at W. (B) Legend as for 2 (A) except that at REL 5×10^{-7} relaxin was added to the bath.

Experiments were also made with 3 cm lengths of rat colon prepared in the same way as for the uterus and stimulated electrically using the same parameters of stimulation. Drugs used were (–)-adrenaline bitartrate, dihydroergotamine methanesulphonate, pronethalol hydrochloride, and relaxin (Releasin). Except for relaxin the concentrations of drugs are expressed in terms of final bath concentration of the base. The concentration of relaxin is in terms of w/v of Warner-Chilcott Relaxin Standard.

Fig. 1 shows the inhibition of contractions of the rat uterus and colon by adrenaline. In the uterus the inhibition is seen to be reversed by pronethalol (5×10^{-7}) but not by dihydroergotamine (5×10^{-7}). This concentration of dihydroergotamine does, however, reverse the inhibition by adrenaline of the contractions of the rat colon. Similar results were obtained when the agonist-antagonist sequence was reversed, so that the antagonists were given 5 min before the adrenaline. The interpretations from these experiments, that adrenaline acts

at β-receptors in the rat uterus, are in agreement with the conclusions drawn by Levy & Tozzi (1963). When the antagonists were tested in the same way on the uterus against relaxin (Fig. 2), the inhibition caused by relaxin was not affected, whereas on a second horn from the same rat the action of adrenaline was reversed. Exposure of the uterus to pronethalol 10^{-6} for 5 min blocked the inhibition by adrenaline, but not that of relaxin. Contractions of the colon were not inhibited by concentrations of relaxin up to 5×10^{-6}.

These experiments do not support the hypothesis that relaxin inhibits contractions of the rat uterus by releasing adrenaline.

Department of Pharmacology,
King's College,
Strand, London, W.C.2.
March 4, 1965

GAVIN PATERSON

References

Ahlquist, R. P. & Levy, B. (1961). *J. Pharmacol.*, **133**, 202–210.
Birmingham, A. T. & Wilson, A. B. (1963). *Brit. J. Pharmacol.*, **21**, 569–580.
Black, J. W. & Stephenson, J. S. (1962). *Lancet*, **2**, 311–314.
Levy, B. (1964). *J. Pharmacol.*, **146**, 129–138.
Levy, B. & Tozzi, S. (1963). *Ibid.*, **142**, 178–184.
Miller, J. W. & Murray, W. J. (1959). *Fed. Proc.*, **18**, 423.
Rudzik, A. D. & Miller, J. W. (1962a). *J. Pharmacol.*, **138**, 82–87.
Rudzik, A. D. & Miller, J. W. (1962b). *Ibid.*, **138**, 88–95.
Wiqvist, N. (1959). *Acta endocrinol. Kbh.*, **32** *Suppl.*, 46, 3–14.