Short communications

The effect of histamine on the electrical activity of rat uterus

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Histamine produces a reduction in the spike frequency and the degree of depolarization which accompany spontaneous and induced contractions of rat uterus. Concentrations of 0·5 μg/ml can cause complete inhibition of both mechanical and electrical activity without producing any change in the resting membrane potential. Concentrations as high as 100 μg/ml cause no appreciable change in membrane potential.

The action of histamine on the rat uterus is interesting for two reasons. Firstly, histamine exerts an inhibitory effect on this tissue while it causes stimulation of most other mammalian uteri, and secondly, this effect resembles that of histamine on gastric secretion in being resistant to the antagonistic action of currently-available antihistamines. Indeed, there is evidence for a certain similarity between the receptors to histamine in the two tissues (Ash & Schild, 1966).

While the effect of histamine on both the spontaneous and induced mechanical activity of rat uterus has been reported (Guggenheim, 1912, Nishiyama & Chuma, 1955, Jensen & Sund, 1960) the effect on the electrical activity has not, as yet, been studied. The purpose of this study was to observe these effects by means of the sucrose-gap technique.

Methods.—The method used was a modification of that described by Bülbring & Burnstock (1960). One end of the preparation was immersed in potassium sulphate Ringer (Evans, Schild & Thesleff, 1958) while the other was immersed in a Krebs fluid of the following composition (mM): Na^+ 152·1; K^+ 5·4; Ca^{2+} 2·5; Mg^{2+} 0·57; Cl^- 134·1; HCO_3^- 24·7; $H_2PO_4^-$ 1·2; SO_4^- 0·57; glucose 11·1, at 37° C, and equilibrated with a mixture of 95% oxygen and 5% carbon dioxide. The isotonic sucrose solution (10% w/v) was prepared by dissolving sucrose (A.R.) in de-ionized water. The specific resistance of the solution was in excess of 2×10^6 ohm-cm.

Drugs were administered either by substituting a solution of the drug in Krebs solution for the normal Krebs solution, or by injection, in volumes of less than 0·05 ml, into the flow of Krebs solution between two flow-rate controlling taps.

The Ag/AgCl electrodes were attached to a Grass P17A high impedance probe, the output from which was recorded on one channel of a Devices M2 pen recorder. The frequency response of the recording system was such that a sine wave calibration signal of 60 Hz was reduced in amplitude by 50%. The end of the preparation in Krebs fluid was attached, by means of a thread, to a Devices isometric transducer type UFI. The signal from this transducer was recorded on the second channel of the recorder.

Uteri from virgin Wistar rats in natural oestrus were used. The body weight of the rats was about 160 grammes. One uterine horn was dissected to produce the linea uteri preparation (Melton & Saldivar, 1967). This is a bundle of closely-packed smooth muscle fibres which lies opposite the mesometrial attachment to the uterus.

Once set up in the apparatus, the tension on the tissue was adjusted to 1 g. Between 30 min and 1 h was normally required to allow the preparation to settle down and for steady recording of membrane potential to be obtained. All preparations showed spontaneous activity. The measured values of the resting membrane potential were of the order of 45–55 mV.

Results.—The inhibitory effect of histamine on mechanical activity of rat uterus was directly correlated with an inhibitory effect on the electrical activity associated with it. The effect on spontaneous electrical activity was to reduce the frequency of action potentials and the degree of depolarization achieved during the 'slow-wave' upon which the spikes are superimposed. This was demonstrated in one preparation by the reduction of a mean frequency of 3·7 spikes per second to one of 0·7 spikes per second by exposure to 1 μg/ml histamine.

Spike frequency was measured during the first continuous train of spikes of each contraction.

Concentrations of histamine as low as 0·5 μg/ml were shown to be capable of causing 100% inhibition of both mechanical and electrical activity. This inhibition took place without any change in the resting membrane potential. Exposures to histamine were normally of 20 min duration. Electrical and mechanical activity returned to their original levels within several minutes of returning to Krebs fluid containing no histamine. Even when the concentration of the first exposure of the tissue to histamine was raised to 100 μg/ml, the mean change in the resting membrane potential was only 0·69±0·17 mV (S.E.M., 10 preparations). In no case did histamine cause hyperpolarization.

When contractions were induced by regular injections of acetylcholine (0·2–1·0 μg) or oxytocin (10 mU), exposure for several minutes to histamine again reduced spike frequency and the degree of depolarization. The duration of these induced contractions varied in different preparations between 16 and 60 seconds. Figure 1 shows the effect of two concentrations of histamine on the response to 10 mU oxytocin. In some cases, 100% inhibition of electrical activity was obtained while the mechanical activity was only partially inhibited. In general, higher concentrations of histamine were needed to cause inhibition of induced activity than were needed to inhibit spontaneous activity.

The degree of inhibition of spike frequency appeared to be dose-related. For example, in one experiment, the mean frequency of spikes induced by injection of 10 mU oxytocin was 3·5 spikes per second; during exposure to concentrations of histamine of 10, 20, 40 and 50 μg/ml, the mean frequencies were reduced to 3·1, 2·9, 2·3 and 2·0 spikes per second respectively.

Tachyphylaxis to the effect of histamine on both electrical and mechanical activity was often considerable, the effect of one concentration of histamine being less than that of a many times smaller concentration, to which the tissue had been previously exposed. In some cases, activity previously suppressed by histamine began to reappear while the preparation was still exposed to the drug.

Exposures of the tissue for 15 min to

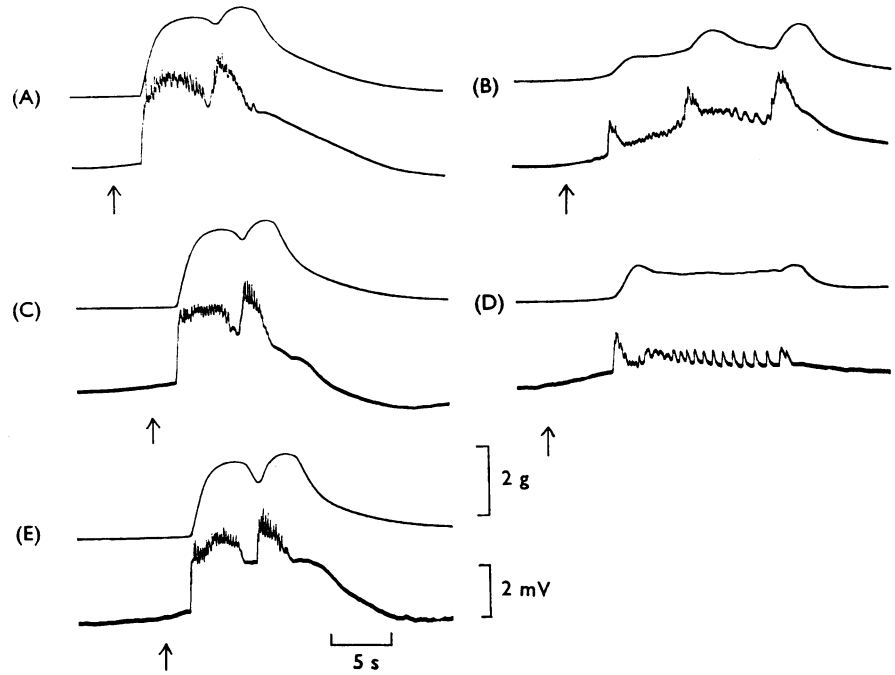

FIG. 1. Effect of histamine on mechanical activity (upper trace) and electrical activity (lower trace) of rat uterus induced with 10 mU oxytocin (injected at arrow). Increase in tension and decrease in membrane potential are represented by upward deflections of the respective traces. (A) response in normal Krebs solution, (C) and (E) responses after recovery from histamine inhibition, (B) response to 10 μg/ml histamine, (D) response to 40 μg/ml histamine.

the antihistamine drugs mepyramine (1 μg/ml), chlorcyclizine (1 μg/ml), chlorpheniramine (1 μg/ml), diphenhydramine (1 μg/ml) and promethazine (1 μg/ml) had no effect on the action of histamine on either the electrical or mechanical activity of the uterus.

Discussion.—The results show that hyperpolarization does not result from exposure of the rat uterus to histamine. This indicates some difference between the mechanisms of action of histamine and adrenaline since in the postpartum rat uterus, adrenaline causes an increase in membrane potential (Marshall, 1959, Kuriyama, 1961, Csapo & Kuriyama, 1963). Hyperpolarization, however, is not a prerequisite of the action of adrenaline on the uterus although it is usually seen when concentrations above 0·1 μg/ml are used (Diamond & Marshall, 1969a). Adrenaline seems to exert its effect primarily by reducing the frequency of pacemaker discharge (Diamond & Marshall, 1969b). Similar observations have been made with the guinea-pig taenia coli preparation (Burnstock, 1958, Bülbring & Kuriyama, 1963, Bülbring & Tomita, 1969a & b).

Other inhibitors of spontaneous activity in rat uterus such as tetracaine, papaverine and nitroglycerine, have been shown to inhibit motility completely without causing any significant change in resting membrane potential (Diamond & Marshall, 1969a). Although these drugs reduce spontaneous pacemaker discharge, part of their action is independent of effects on the electrical activity of the membrane (Diamond & Marshall, 1969b). Since histamine still exerts its inhibitory effect on a KCl-depolarized uterus (unpublished observations), it is possible that the mechanisms of action of these drugs are in some way similar.

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REFERENCES

ASH, A. S. H. & SCHILD, H. O. (1966). Receptors mediating some actions of histamine. *Br. J. Pharmac. Chemother.*, **27**, 427–439.

BÜLBRING, E. & BURNSTOCK, G. (1960). Membrane potential changes associated with tachyphylaxis and potentiation of the response to stimulating drugs in smooth muscle. *Br. J. Pharmac. Chemother.*, **15**, 611–624.

BÜLBRING, E. & KURIYAMA, H. (1963). Effects of changes in ionic environment on the action of acetylcholine and adrenaline on the smooth muscle cells of guinea-pig taenia coli. *J. Physiol., Lond.*, **166**, 59–74.

BÜLBRING, E. & TOMITA, T. (1969a). Increase of membrane conductance by adrenaline in the smooth muscle of guinea-pig taenia coli. *Proc. R. Soc. B.*, **172**, 89–102.

BÜLBRING, E. & TOMITA, T. (1969b). Suppression of spontaneous spike generation by catecholamines in the smooth muscle of the guinea-pig taenia coli. *Proc. R. Soc. B.*, **172**, 103–119.

BURNSTOCK, G. (1958). The action of adrenaline on excitability and membrane potential in the taenia coli of the guinea-pig and the effect of DNP on this action and on the action of acetylcholine. *J. Physiol., Lond.*, **143**, 183–194.

CSAPO, A. & KURIYAMA, H. (1963). Effects of ions and drugs on cell membrane activity and tension in the postpartum rat myometrium. *J. Physiol., Lond.*, **165**, 575–592.

DIAMOND, J. & MARSHALL, J. M. (1969a). Smooth muscle relaxants: dissociation between resting membrane potential and resting tension in rat myometrium. *J. Pharmac. exp. Ther.*, **168**, 13–20.

DIAMOND, J. & MARSHALL, J. M. (1969b). A comparison of the effects of various smooth muscle relaxants on the electrical and mechanical activity of the rat uterus. *J. Pharmac. exp. Ther.*, **168**, 21–30.

EVANS, D. H. L., SCHILD, H. O. & THESLEFF, S. (1958). Effect of drugs on depolarized plain muscle. *J. Physiol., Lond.*, **143**, 474–485.

GUGGENHEIM, M. (1912). Zur kenntnis der wirkung des *p*-oxyphenyläthylamins. *Therap. monatsh.*, **26**, 795–798.

JENSEN, K. B. & SUND, R. B. (1960). The inhibitory action of histamine on the isolated rat uterus. *Acta pharmacol. (Kbh)*, **17**, 161–172.

KURIYAMA, H. (1961). Recent studies on the electrophysiology of the uterus. In: Ciba Foundation Study Group, No. 9, Progesterone and the defence mechanism of pregnancy., p. 65. London: Churchill.

MARSHALL, J. M. (1959). Effects of oestrogen and progesterone on single uterine muscle fibres in the rat. *Am. J. Physiol.*, **197**, 935–942.

MELTON, C. E. & SALDIVAR, J. T. (1967). The linea uteri, a conduction pathway in rat myometrium. *Life Sci.*, **6**, No. 3, 297–304.

NISHIYAMA, Y. & CHUMA, S. (1955). Pharmacological studies on the uterine movement of albino rat *in vitro* and *in vivo*. *Osaka City Med. J.*, **2**, 1–6.

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