THE ACTION OF CERTAIN DRUGS AND IONS ON THE RAT'S UTERUS

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We have shown elsewhere (1) that the rate and facility of conduction in the rat's uterus varies with the oestrus cycle, being poor in dioestrus and good during oestrus and pregnancy. The following experiments were undertaken to analyse the action of adrenalin, pituitary extract, and certain ions upon the movements of the rat's uterus.

Experiments were made upon uteri in situ and isolated uteri. Rats were anaesthetised with sodium phenyl-ethyl barbiturate (sodium-luminal) 0.2 gram per kilogram body weight given subcutaneously. The abdomen was opened and filled with warm Locke's fluid, and the uterine movements were recorded in situ with a light lever. The Locke's fluid had the composition per cent. NaCl 0.9, KCl 0.042, $CaCl_2$ 0.024, $NaHCO_3$ 0.05, glucose 0.5.

The isolated uteri were suspended in oxygenated Locke's fluid of the above composition; in most cases the movements of the whole uterus were recorded, but in some cases the uterus was fixed by pins onto cork, and leads were taken from three or four points on the uterus, and attached to very light levers, and the movements of the levers were recorded optically on bromide paper. In this way the conduction of waves of contraction along the uterus could be measured.

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THE ACTION OF ADRENALIN

Adrenalin produces an extremely powerful depressant action on the rat's uterus both in situ and when isolated. This action is shown in figure 1. Intravenous injection of 0.0002 mgm.

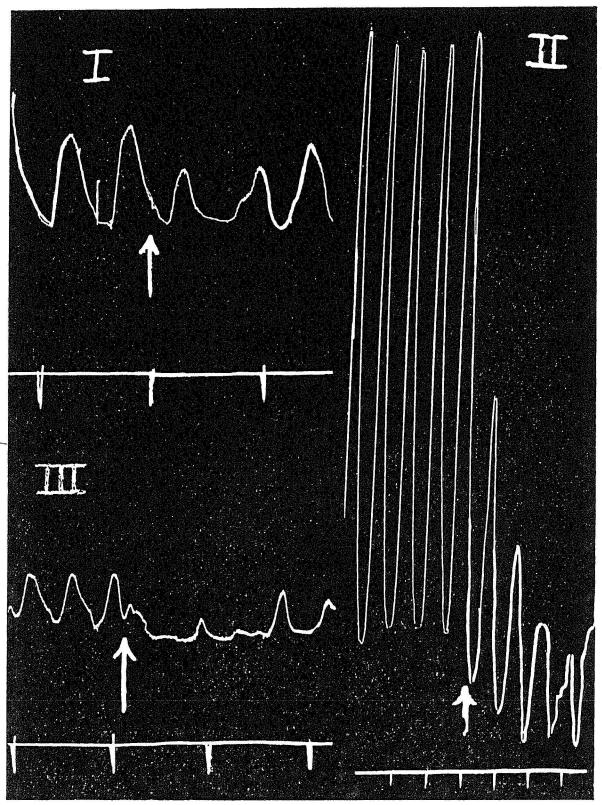

FIG. 1. THE ACTION OF ADRENALIN ON THE RAT'S UTERUS

I, rat An. Stage 5 (dioestrus). Uterus in situ. Adrenalin 0.0002 mgm. given intravenously.

II, rat An. Uterus isolated. Adrenalin 1 part in 2,000,000,000.

III, rat, eighteen days pregnant. Uterus in situ. Adrenalin 0.0002 mgm. given intravenously.

(In this and other figures the upstroke represents contraction and the tracing reads from left to right.)

regularly produced a well marked response, and a response after 0.00005 mgm. was sometimes detected. A dilution of one part of adrenalin in 2000 million regularly produced a response on the isolated uterus, and a dilution of one in 10,000 million sometimes

produced a response. These figures show that adrenalin produces a greater effect in vitro than in vivo since 0.0002 mgm. in 10 cc. of blood would produce a concentration of one part in 50 million, which is 40 times the minimal effective concentration in vitro.

Figure 1 shows that the uterus of a rat in the last stages of pregnancy is inhibited as powerfully by adrenalin as that of a virgin rat. No difference in sensitivity to adrenalin was detected between the uteri of rats in oestrus and dioestrus, or between virgin and parous rats.

The mode of action of adrenalin was further analysed by recording the movements at three points on the isolated uterus simultaneously, and the results are shown in figure 2 and table 1.

These results show that adrenalin produces a great reduction in the rate of conduction through the uterus. The facility of conduction also is reduced and as a result the two ends of the uterus tend to contract independently after adrenalin.

THE ACTION OF PITUITARY EXTRACT ON THE UTERUS

The action of pituitary extract is shown in figures 2 and 3. In the case shown in figure 3 the intravenous injection of 0.025 mgm. of moist posterior lobe of the pituitary produced a doubtful action, whereas the injection of 0.1 mgm. produced a well marked action. When the same uterus was isolated the same preparation of pituitary produced no action at a dilution of one part in one million, but produced a well marked action at a dilution of one part in 250,000. Since 0.1 mgm. in 10 cc. of blood corresponds to a dilution of one part in 100,000, therefore pituitary extract produces its action in concentrations of the same order on the uterus in situ and when isolated. The mode of action of pituitary on the uterus is shown in figure 2 and table 1. The drug caused a great increase in the rate of conduction and in the facility of conduction through the uterus. The action of pituitary is most obvious in the uterus in dioestrus where conduction is poor, but no certain differences were observed between the sensitivity of the uterus to pituitary in oestrus, dioestrus and in pregnancy. It is possible that the uterus in the last stages of pregnancy may

become more sensitive to the drug, but sufficient observations have not yet been made on this point to warrant a conclusion.

THE ACTION OF ADRENALIN AND OF PITUITARY EXTRACT UPON THE CONDUCTION AND DURATION OF CONTRACTION

It is impossible to obtain accurate figures for the rate of conduction in the uterus, because it has no fixed length. A rat's

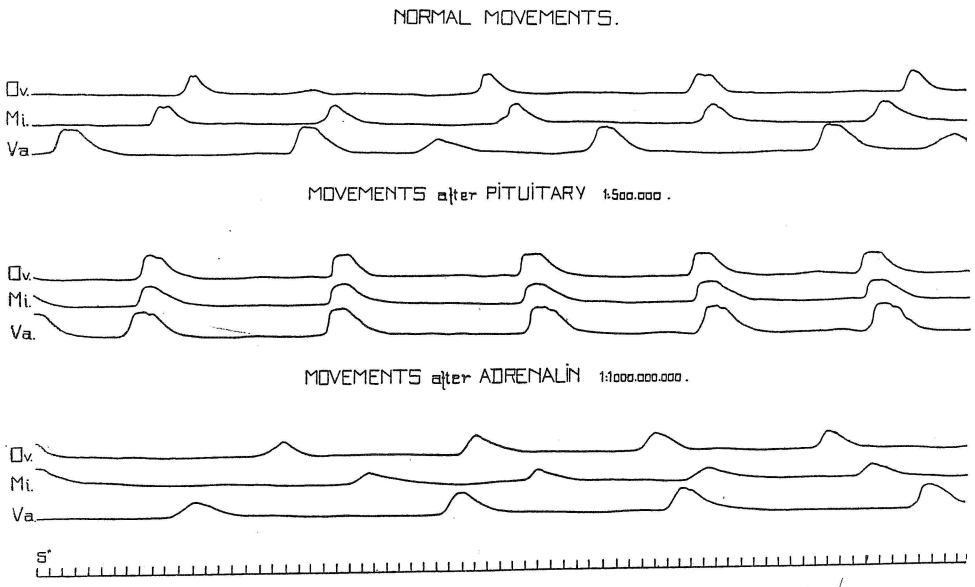

FIG. 2. THE ACTION OF ADRENALIN AND PITUITARY EXTRACT ON CONDUCTION IN THE RAT'S UTERUS

Isolated uterus of rat C4. Stage 5 (dioestrus).

The movements of the ovarian and, the middle, and the vaginal end of the uterus were recorded simultaneously.

The records were obtained on bromide paper and the figure is from a tracing made from these records.

uterus, which when fully relaxed measures 100 mm. can shorten during contraction to 40 mm., and any intermediate length can be obtained by varying the tension. The figures given below are therefore only rough approximations.

The duration of contraction shown in figure 3 and table 1 depends partly on the rate of conduction and partly on the length of contraction of the individual cells.

The uterus was fixed so that the movements of about 10 mm.

TABLE 1

The action of drugs and ions on the rat's uterus

			Frequency of contractions		The distance along the uterus to which contractions are conducted from the ovarian end	Rate of conduction	Relative height of contraction		Duration in seconds of contraction and relaxation	
			Ovarian end	Vaginal end			Ovarian end	Vaginal end	Ovarian end	Vaginal end
						mm. per sec.				
Rat C_4. Stage 5. (Dioestrus)	1	Normal	60	48	To middle	1.5	9.5	11.2	20″	28.4″
	2	1–5′ after adrenalin 1 in 1,000,000,000	50	40	To middle	0.47	8.7	10.6	30″	30″
	3	1–5′ after 1 in 500,000 moist post-lobe pituitary	53	53	To vaginal end	5–7.7	11.5	14	22″	25″
Rat C_5. Stage 4. (End of oestrus)	4	Normal	60	60	To vaginal end	1.8–3.5	12	12	31″	34″
	5	1–5′ after adrenalin 1 in 1,000,000,000	34	20	To middle	0.55	5.7	10.5	35″	50″
Rat C_3. Stage 3. (Middle of oestrus)	6	Normal	60	60	To vaginal end	6.3	4	4.8	17.5″	10.5″
	7	1–5′ after 1 in 500,000 moist post-lobe pituitary	73	73	To vaginal end	7–20	4.2	5.7	18.1″	12.5″
Rat C_7. Pregnant 10 days	8	Normal	60	60	To vaginal end	5– 5.3	19.8	15.0	27.5″	22.3″
	9	1–5′ after 1 in 500,000 moist post-lobe pituitary	72	72	To vaginal end	5–9	24.8	11.6	32″	26.6″
Rat C_{10}. Stage 5. (Dioestrus)	10	Normal	87	67	To middle	3.3	6.3	10.6	30″	31.2″
	11	1–5′ after KCl increased to 0.084 per cent	120	120	To vaginal end	14	4.5	6.4	28″	26″
	12	Normal	88	72	To middle	2.5	7	12	27	31
	13	1–5′ after KCl free Locke's fluid	153	140	No certain conduction		3	4.5	20	22

of uterus were recorded by each lead, and therefore the duration of contraction measures the time from when the first cell in the segment started contracting until the moment when the last cells

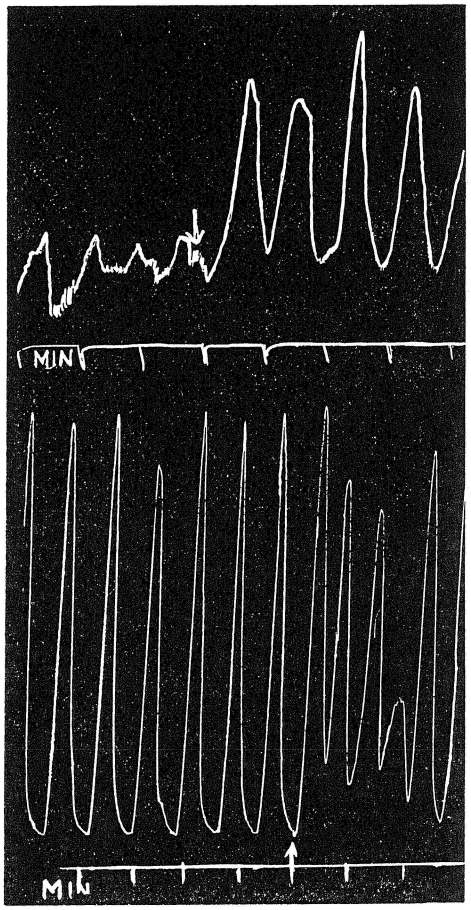

FIG. 3. THE ACTION OF PITUITARY EXTRACT ON THE RAT'S UTERUS

Rat Bi. Parous. Stage 5 (dioestrus).

Upper tracing: Uterus in situ. The action of an intravenous injection of 0.1 mgm. moist posterior lobe of pituitary.

Lower tracing: Isolated uterus. Action of 1 part in 250,000 of moist posterior lobe of pituitary.

ceased contracting. The duration of contraction measures therefore the sum of the time required for the wave of contraction to be conducted over 10 mm. of uterus and the duration of contraction of the last cells to be stimulated in the segment. The

duration of conduction can be calculated, and by deducting this figure from the duration of contraction recorded we obtain a figure indicating the true duration of contraction of individual cells.

The figures obtained are shown in table 2. This table shows that adrenalin shortens and pituitary extract increases the duration of contraction.

The length of the wave of contraction in millimeters equals the rate of conduction (in millimeters per second) multiplied by the duration of contraction (in seconds).

Adrenalin diminishes and pituitary increases both these figures, and therefore adrenalin causes a short wave of contraction

TABLE 2

	NORMAL UTERUS	UTERUS AFTER ADRENALIN (1 IN 1,000,000,000)	UTERUS AFTER PITUTIARY EXTRACT (1 IN 500,000)
Time for conduction of wave of contraction over 10 mm	7.3″	25″	1.3″
Duration of contraction of whole of segment of uterus	20″	30″	21″
Duration of contraction at any particular point in segment	12.7″	5″	19.7″

to travel slowly down the uterus, while pituitary causes a long wave of contraction to travel rapidly down the uterus.

In the case under discussion adrenalin reduced the length of the wave of contraction from the normal figure of $12.7 \times 1.5 = 19$ mm. to $5 \times 0.5 = 2.5$ mm. This explains the marked contrast in the effects of adrenalin shown in figures 1 and 2. In figure 2 the movements of only a short portion of the uterus were registered and adrenalin did not produce a very great reduction in the height of contraction, whereas in figure 1 one-half the former concentration of adrenalin reduced the height of contraction to one seventh of normal. In the latter case the movements of the whole uterus were recorded and therefore the reduction in the length of the wave of contraction produced a great effect on the amplitude of contraction registered, because only a small

portion of the uterus was contracting simultaneously. Adrenalin appears to have a much stronger action in depressing the conduction from cell to cell than in depressing the force of contraction of the individual cells.

Pituitary extract on the other hand increases the length of the wave of contraction to a figure considerably greater than the length of the uterus, which means that the whole uterus contracts simultaneously. The figures given in table 1 show that pituitary has a much more marked action in increasing the rate of conduction in the uterus than in increasing the force of contraction of the individual portions.

THE ACTION OF HORMONES ON THE RAT'S UTERUS

A visible inhibition is usually produced upon the rat's uterus by the intravenous injection of about 0.0005, mgm. per kilogram body weight of adrenalin. This quantity is similar to that required to produce a visible rise of blood pressure in cats (3 and 4) and rabbits (2). About half this amount is sufficient to produce a fall of blood pressure in a cat (3).

The adrenalin content of the rat's suprarenals has been found by various observers using Folin's method (5, 6, 7) to be about 0.09 mgm. (0.4 mgm. per kilogram). We obtained a similar value in one case, using the rat's uterus as a test. The corresponding figures for larger animals vary from 0.03 to 0.1 mgm. per kilogram (8).

The rat therefore has a proportionally larger adrenalin store than the cat, and yet its uterus is inhibited by concentrations of adrenalin as low as the minimal concentrations which produce a rise of blood pressure in the cat. Moreover the rat's uterus is inhibited by adrenalin at all stages of pregnancy.

The liberation of about one five-hundredth of the adrenalin present in its suprarenals would be sufficient to produce an inhibitory effect on the rats uterus.

The rat's uterus is relatively insensitive to the pituitary hormone, since about one part in one million of fresh posterior lobe is usually needed to produce a visible effect on the isolated uterus

whereas the guinea pig's uterus responds to about one tenth this concentration.

In the intact rat about 0.16 mgm. per kilogram body weight of fresh gland given intravenously is needed to produce a demonstrable effect on the uterus, whereas one of us (H. H. K.) found that in the cat a dose of 0.005 mgm. per kilogram of fresh gland produced a response on the uterus. This represents a twenty fold difference in sensitivity. There is however no corresponding difference in the sizes of the posterior lobe of the pituitary gland in these animals. In the cat the posterior lobe of the pituitary weighs about 5 mgm. (9) (i.e., about 2.5 mgm. per kilogram). The rat's posterior pituitary lobe weighs about (10) 1.0 mgm. (i.e., about 5 mgm. per kilogram). We found that the activity of the pituitary of a rat, when tested on a rat's uterus corresponded to between 0.5 mgm. and 1.0 mgm. of moist posterior pituitary lobe of the ox. The secretion therefore of about one five-hundredth of the active principle contained in the cat's pituitary would suffice to affect the cat's uterus, whereas in the rat the secretion of at least one fiftieth of its pituitary store would be needed to produce an effect. The latter figure seems impossibly high. There is however the possibility that during actual delivery the response of the rat's uterus to pituitary may be modified, and it is hoped to study this point further.

THE INFLUENCE OF POTASSIUM ON THE UTERUS

A two or three fold increase of the potassium chloride content of Locke's fluid produces an effect almost indentical with that produced by pituitary extract.

These effects are shown in table 1. Excess of potassium chloride causes an increase in the frequency of contraction in the rate and facility of conduction, in the length of the wave of contraction, and in the duration of the contraction at any point.

The removal of potassium chloride from Locke's fluid causes an increase in the tonus of the uterus. Table 1 shows a further analysis of the action of lack of potassium. The outstanding

change is the great increase in the frequency of the contractions of the uterus, and this is associated with a diminution in the rate of conduction, and in the force and length of contraction.

Engelmann (12) showed that increase in the frequency of the contractions of the ureter caused a diminution in the rate of conduction, and in the rat's uterus we have observed that increase in frequency usually is followed by a decrease in the force and length of the contractions. The primary effect of lack of potassium on the rat's uterus appears therefore to be an increase in the frequency of contractions.

THE INFLUENCE OF CALCIUM ON THE UTERUS

Removal of calcium from the Locke's fluid caused rapid arrest of the uterus in relaxation, with a preliminary stage in which the frequency and force of the contractions were diminished. A fourfold increase in the calcium chloride content of Locke's fluid, has been shown (11) to cause a diminution in the tonus of the rat's uterus. We found that the frequency and force of the contractions was diminished but that the action on the rate of conduction was uncertain.

It has previously been shown (11) that the antagonism between calcium and potassium is not nearly so well marked in the isolated uterus as it is in the heart, and these observations confirm this conclusion.

THE MODE OF CONDUCTION IN THE UTERUS

Since the uterus contains a plexus of post-ganglionic nerve fibres connecting plain muscle cells, conduction of excitation might occur in three ways: (1) through the nerve net; (2) through the muscle cells; or (3) through muscle and nerve alternately. The last condition would occur if the excitation was transmitted to a muscle cell from one nerve, excited the muscle cell, and then passed out into another nerve.

Potassium and pituitary are both believed to act directly on muscle cells, and since these substances increase the rate of conduction of the wave of excitation this is strong evidence

against this conduction passing entirely through the nerve plexus. The wave of contraction must therefore be conducted partly or entirely through the muscle cells.

CONCLUSIONS

1. Adrenalin causes inhibition of the rat's uterus in situ as well as when isolated, but the concentration required to produce an effect in situ is from 40 to 100 times that which acts on the isolated uterus. The uterus in a late stage of pregnancy is inhibited as readily as the virgin uterus.

2. Adrenalin diminishes the force, and frequency of contractions, and also decreases the rate and facility of conduction, and the length of the wave of contraction.

3. The minimal dose per kilo body weight of adrenalin which inhibits the rat's uterus in situ is about 0.0005 mgm., which is similar to the amount required to produce a visible rise of blood pressure in larger animals.

4. Pituitary extract and potassium excess cause similar effects, which are the opposite of those produced by adrenalin. The force and frequency of contractions, and the rate and facility of conduction of contractions are increased, and the length of the wave of contraction is increased.

5. The dose of fresh posterior pituitary lobe needed to produce a demonstrable effect on the uterus in situ is about 0.16 mgm. per kilo body weight. This is much greater than the amount needed to stimulate the cat's uterus, and the dose per rat is as high as one fiftieth of the active principle present in a rat's pituitary.

6. Variations in the calcium content of Locke's fluid do not produce in the isolate uterus of the rat's effects the opposite of those produced by similar variations in the potassium content.

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