CONTRACTION OF THE DEPOLARIZED UTERINE MUSCLE

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UDC 612.731:612.627

Strips of the depolarized myometrium of rats do not contract by action of noradrenalin and oxytocin. Acetylcholine causes weak contraction of strips of myometrium from castrated rats receiving estrodiol but has no action on the uterus of castrated rats receiving no other treatment or rats receiving progesterone after castration. Noradrenalin has a purely relaxing action on the depolarized myometrium whatever the hormonal state. Stretching does not affect contraction of the depolarized myometrium produced by acetylcholine, noradrenalin, and oxytocin.

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The uterine smooth muscle is under the constant control of the sex hormones and mediators [8]. Contraction of the muscle fiber is produced by changes in the electrical properties of the excitable membrane and by an increase in its permeability to certain ions [7, 11]. However, Evans and Schild [6] and Edman and Schild [4, 5] have shown that the myometrium can contract under the influence of certain substances even when in a depolarized state. The author's previous findings indicated that the magnitude of isometric tension developed by the myometrium under the influence of acetylcholine, noradrenalin, and oxytocin is dependent on the hormonal background and on the degree of stretching of the strips of myometrium.

The object of the present investigation was to determine the mechanism of action of these substances, i.e., to study whether they act only through the excitable membrane or whether they can also act directly on the contractile mechanisms of the cell.

EXPERIMENTAL METHOD

Experiments were carried out on castrated albino rats (30 rats, 219 preparations). The animals were divided into three groups: group 1, castrated rats not receiving hormones; group 2, castrated rats receiving 5 daily doses of 70 μg of an oily solution of estradiol benzoate; group 3, castrated rats receiving 5 daily doses of 5 mg of an oily solution of progesterone. Longitudinal strips 15 mm in length and 1 mm in width were cut from the uterine cornua of the rats and immersed in Krebs' solution at room temperature. Krebs' solution in which some of the NaCl was replaced by 108 mmoles K_2SO_4 was used as depolarizing agent. Acetylcholine (10^{-5} g/ml), noradrenalin (10^{-5} g/ml), and oxytocin (0.005 i.u./ml) were added to the Krebs' solution + K_2SO_4. The solutions were warmed to 37 ± 0.2°. The threads tied to the ends of the preparation were led out of the chamber to two manipulators, by means of which the strips were stretched from their length in situ (100%) to 110, 125, and 150% of the initial length. In the experiments using the 6MKh1S mechanotron the isometric contraction and relaxation developed by strips of uterus in response to the action of acetylcholine, noradrenalin, and oxytocin were recorded on a type N373 dc self-writing multirange milliampere-voltmeter.

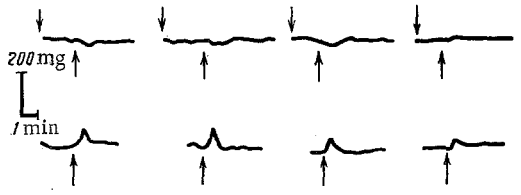

Fig. 1. Action of acetylcholine on depolarized strips of the body of the uterus. Top curve: isometric contraction of strips of uterus from castrated rats; bottom curve: contractions of strip of uterus from castrated rats receiving estradiol. Arrows pointing downward indicate beginning of recording after previous stretching; arrows pointing upward denote addition of acetylcholine (10^{-5} g/ml) for 20 sec.

EXPERIMENTAL RESULTS

None of the strips of depolarized myometrium contracted spontaneously. Under the influence of acetylcholine

Department of Normal Physiology, Sverdlovsk Medical Institute (Presented by Academician L. S. Persianinov, Academy of Medical Sciences of the USSR). Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 68, No. 7, pp. 8-11, July, 1969. Original article submitted July 30, 1968.

TABLE 1. Isometric Tension (in mg) Developed by Depolarized Strips of Rat Myometrium under the Influence of Acetylcholine, Noradrenalin, and Oxytocin against Different Hormonal Backgrounds

Hormonal backgrounds	Acting substance	Degree of stretching (in %)				
		100	110	125	150	number of measurements
Castration	Acetylcholine	No response				23
	Noradrenalin	7.6±2	10.8±3	11.6±4	0	24
	Oxytocin	No response				25
Castration + estrogen	Acetylcholine	60±4	70±4	60±4	60±4	26
	Noradrenalin	20±2	20±2	20±2	0	22
	Oxytocin	No response				26
Castration + progesterone	Acetylcholine	No response				26
	Noradrenalin	30±3	40±4	50±4	50±4	25
	Oxytocin	No response				22

(exposure 20 sec) the strips of uterus of castrated rats and castrated rats receiving progesterone did not contract whatever the degree of stretching (Table 1). Strips of uterus from rats receiving estrogen responded with slight contraction (Fig. 1). If their length was 100%, the strips developed isometric tension of 18% of that developed by strips of the body of the uterus in normal Krebs' solution, and for lengths of 110%, 125%, and 150 the tension developed was 20%, 30%, and 50%,respectively. This apparent increase in the amplitude of contraction in response to stretching was due to a sharper decrease in amplitude of contraction of the strips under the influence of stretching in normal Krebs' solution.

Under the influence of oxytocin (exposure 20 sec) strips from the body of the uterus of castrated rats, both receiving and not receiving estrogen and progesterone, did not contract whatever the degree of stretching.

Addition of noradrenalin to the depolarizing solution for 20 sec caused relaxation of the strips of uterus against all hormonal backgrounds (Fig. 2). Noradrenalin had only a relaxing action on strips of myometrium of castrated rats whether in Krebs' solution or in depolarizing solution. Changes in the degree of relaxation of the depolarized myometrium with different degrees of stretching were not statistically significant. After treatment of the animals with estrogen, the depolarized strips of uterus relaxed equally (20 ± 2 mg) during stretching from 100 to 125%, while further stretching to 150% suppressed the action of noradrenalin. Relaxation of the progesterone-treated myometrium under the influence of noradrenalin was dependent on the degree of stretching (Table 1). The amplitude of this relaxation was 100, 100, 50, and 60% respectively of the amplitude of relaxation arising under the influence of the substance in Krebs' solution at lengths of 100, 110, 125, and 150%. The relaxant action of noradrenalin on the depolarized myometrium of rats receiving estrogen and progesterone persisted, whereas in normal Krebs' solution the addition of noradrenalin produced a biphasic effect (initial contraction followed by relaxation).

The results of these experiments showed that depolarization of the excitable membrane of cells completely suppressed the contractile response of the myometrial fibers under the influence of oxytocin and noradrenalin. Under the influence of acetylcholine, the amplitude of isometric contraction developed by strips of myometrium from rats receiving estradiol was considerably reduced, while in the case of castrated animals and castrated animals receiving progesterone, contractions were absent altogether. The mechanism of action of oxytocin, acetylcholine, and noradrenalin on the strips of myometrium is evidently different. Since oxytocin did not cause contraction of the depolarizing strips of uterus, it can be postulated that it acts purely by depolarizing the cell membrane of smooth-muscle fibers, in agreement with results described by Jung and Marshall [8, 10].

Acetylcholine did not stimulate the depolarized myometrium only from castrated rats and castrated rats receiving progesterone. However, after treatment with estradiol, the strips of uterus developed a small isometric contraction. Acetylcholine is known to cause contraction of myometrial cells by depolarizing the membrane, increasing its permeability to ions [3], including calcium ions. Ability to develop weak and

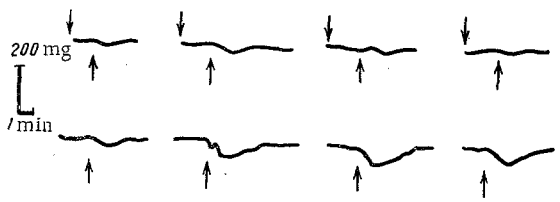

Fig. 2. Action of noradrenalin on depolarized strips of uterine body of rats. Top curve: isometric relaxation of strips of uterus from castrated rat; bottom curve: isometric relaxation of strips of uterus from castrated rat receiving progesterone. Arrows pointing downward denoted beginning of recording after previous stretching; arrows pointing upward denote addition of noradrenalin (10^{-5} g/ml) for 20 sec.

isometric contractions after saturation of the body with estradiol is evidently attributable to the greater resistance of the cell membranes of these strips to the depolarizing action of potassium sulfate or to the greater nonspecific permeability of the cell membranes of the myometrium after treatment with estrogen to ions compared with that of smooth-muscle cells of castrated animals and of castrated animals receiving progesterone. The results obtained by Evans, Edman, and Schild relative to the stimulating action of acetylcholine on the depolarizing myometrium do not conflict with the results now described, because these workers used the myometrium of animals in a normal hormonal state, i.e., against a background of saturation of the body with estrogens.

Noradrenalin led to least relaxation of strips of myometrium from castrated rats, slightly more of strips of myometrium from rats receiving estradiol. The greatest relaxation occurred in strips of myometrium from rats receiving progesterone. Stretching had no effect on the relaxant action of noradrenalin in the myometrium of castrated rats receiving estrogen.

The results obtained suggest that the excitatory action of noradrenalin is due to its direct action on the excitable membrane of the smooth-muscle cells of the uterus, and perhaps also to its binding with the α-receptors located in the membrane [3]. The relaxant action of noradrenalin can evidently be explained by its interaction with the β-receptors of the cells or, in accordance with Bülbring's hypothesis [2], by the primary action of noradrenalin on metabolic processes in muscle fibers.

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