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RECIPROCAL ACTIVITY OF THE CORNUA AND CERVIX UTERI OF THE GOAT.

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(*Received March* 5, 1934.)

In this paper are recorded a few experiments on smooth muscle taken from the pregnant uterus of the goat; they suggest a reciprocal activity which is nervous in origin on the part of the fundus and cervix uteri. It is not proposed to mention the history of this subject, except to say that no record has been found of any similar experiments having been made previously.

Method.

Strips of uterine muscle were suspended in a bath of oxygenated Dale-Ringer solution at 37° C., and their contractions recorded on a slow drum by means of a light lever and frontal writing point. The pregnant goats supplying the strips were the subjects of experiments by Prof. J. Barcroft [1933], involving removal of fœtuses through a uterine incision; the whole of these operations were performed under saline solution at 37° C., the goat, anæsthetized with urethane (4 c.c. of saturated solution per kg.) and chloroform-ether mixture as required, lying supine in a large bath. At the close of the experiment longitudinal strips were cut from each of the cornua (previously intact) and the whole cervix excised. These three pieces of tissue were placed in a specimen tube with cotton wool soaked in saline, the tube packed in ice and despatched from Cambridge to London. The strips from the cornua were trimmed, washed, and suspended in separate baths. The cervix was sliced transversely, the resulting rings opened, cleaned as well as possible, and suspended in further baths. This was about 3–3½ hours after their excision from the living uterus.

Results.

Specimens were obtained from six goats, respectively $13\frac{2}{7}$, $14\frac{5}{7}$, $15\frac{1}{7}$, $16\frac{2}{7}$, 18 and $19\frac{6}{7}$ weeks' pregnant (full term is about 21 weeks). Their serial numbers [Barcroft, 1933] were 9, 19, 11, 12, 14 and 15 respectively.

Cornua. The strips went into sustained tonic contraction in the bath, small spontaneous contractions being superimposed; these were larger and less frequent in the last goat, nearing full term, but the conditions of the experiments do not allow of definite significance being attached to this. 0·02 unit of *oxytocin* had a just perceptible effect in all cases, either in increasing the tonus, augmenting the contractions, or both. *Adrenaline* (final concentration 1 in 1 million) caused general relaxation, and slowing or stoppage of the spontaneous contractions. *Acetylcholine* (final concentration about 1 in 100 million) produced contraction and augmentation of the rhythm.

The goat has button placentæ, and although the majority of these are found in the body of the uterus, some are usually situated in one or other of the horns. No significant or consistent difference was noticed in any of the above particulars between the horn containing placentæ and that from which they were absent.

Cervix. This in all cases was plugged with a quantity, greater in the later animals, of extremely sticky mucus. It was almost impossible to free the circular strips from this without damaging them, so that a certain amount must always have been present in the bath. In the successive animals the cervix grew shorter and more spongy, so that in the protocol of the first experiment its consistency is described as "cartilaginous," and in that of the last experiment as "fairly soft."

In four experiments minute spontaneous contractions were observed; their absence in the other two probably has no significance.

Oxytocin had no effect on these strips, even in amounts up to 2 units. Owing to the unpromising nature of the strips and the uninteresting tracings which they provided, this would not have been remarkable except in view of the following findings. *Adrenaline* caused a contraction of the strips, as did *acetylcholine.* In one experiment the acetylcholine contraction was superimposed on that due to adrenaline. As can be seen from the figures, the effective power of contraction of the cervical strips is small, but these changes in length were quite obvious, and in view of the inactivity of oxytocin, striking.

With the possibility in mind that this might be an example of a general reaction of the circular muscle, one strip was cut from a horn in a

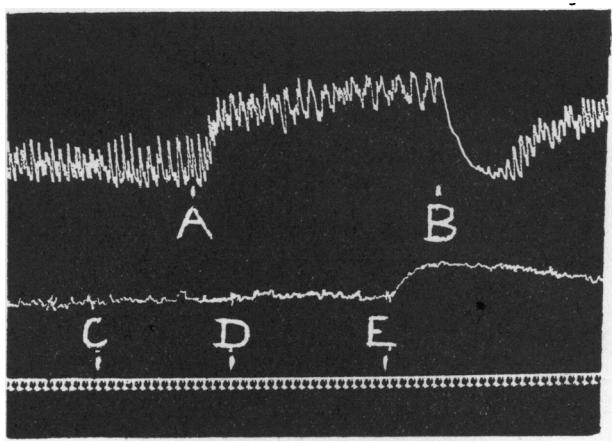

Fig. 1. Goat 11. 15 weeks' pregnant. *Upper tracing:* longitudinal strip of uterine horn in 50 c.c. bath. At A, 0·02 unit oxytocin; at B, 0·03 c.c. 0·1 p.c. adrenaline. *Lower tracing:* circular strip of cervix uteri in similar bath. At C, 0·02 unit oxytocin; at D, 2·0 units oxytocin; at E, 0·03 c.c. 0·1 p.c. adrenaline. Time tracing in minutes.

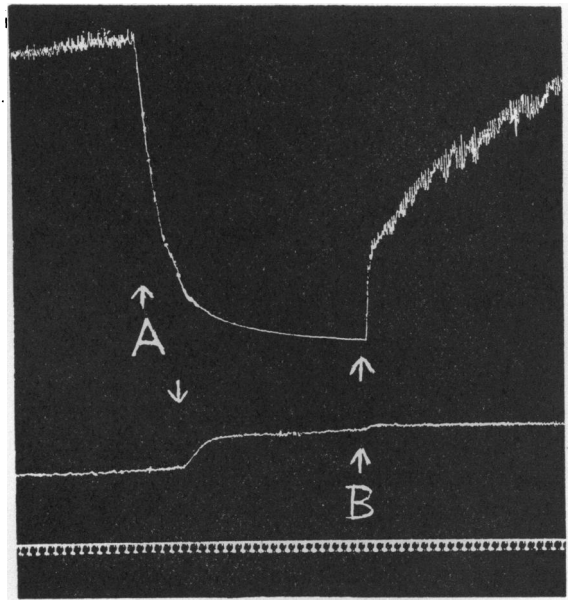

Fig. 2. Goat 14. 18 weeks' pregnant. *Upper tracing:* longitudinal strip of uterine horn in 50 c.c. bath. *Lower tracing:* circular strip of cervix in similar bath. At A, to both strips, 0·04 c.c. 0·1 p.c. adrenaline. At B, to both strips, (about) 0·5γ acetylcholine in 0·1 c.c. saline. Time tracing in minutes.

circular direction. Adrenaline did not cause relaxation of this strip, but abolished all rhythmic contractions. This provides no evidence for associating the circular muscle of the cervix with that of the remainder of the uterus.

These experiments were arranged so that at one time or another adrenaline, acetylcholine and oxytocin were each allowed to act on previously untreated strips. Whether or not the strips were untreated, the action of these substances remained constant.

Discussion.

Owing to the interval elapsing between the excision of the muscle and its mounting in the bath, it is not permissible to draw any conclusions from differences in spontaneous activity observed in the strips from the various goats. In view of the findings of Robson [1933*a*, *b*] and others in more careful experiments than these, it is proposed to ignore also the quantitative aspect of the reaction of the horns to oxytocin with advancing pregnancy. Since no parasympathetic nervous supply to the uterus has been described, the experiments with acetylcholine merely demonstrate at present that contraction can be produced in the cervical strips by other means than the administration of adrenaline.

We are left, therefore, with two constant findings which are well marked, and unlikely to have been influenced qualitatively by the experimental conditions. The first of these is that whereas the cornua contract with a small dose of oxytocin, the cervix appears insensitive even to amounts which are almost ridiculously large. The second is that adrenaline causes a relaxation of the horns and contraction of the cervix.

It is surprising that the cervix should be insensitive to oxytocin; the reaction of the strips to adrenaline and acetylcholine shows that the smooth muscle in the preparation was sufficient to produce a registrable contraction. The low threshold of the cornual muscle discounts any general hormonal depressant, and we are faced with two alternatives. Either the circular cervical muscle is specifically insensitive to oxytocin during pregnancy, or there is some obscure factor in the preparation which prevents the oxytocin from acting. It has previously been shown that the presence of œstrin in the bath has the latter effect [Marrian and Newton, 1932], and it is just possible that the traces of mucus adherent to the cervix act in the same way. The most likely explanation is the first, however, since Macdonald [1925, 1933] has shown that by

no means all smooth muscle contracts when submitted to the action of posterior pituitary extracts. In a large series of experiments [1933] he showed that 75 p.c. of renal arterial rings from various animals were inactive when exposed to even higher concentrations of the extract than those used in this work, although they could easily be made to contract or relax by other means.

Previous workers have shown that adrenaline and hypogastric stimulation act differently on the uterus in different animals, and sometimes in the same animal in different reproductive phases [summary by Gunn and Gunn, 1914]. Ergot will sometimes "reverse" the motor action, the inference being that the result of sympathetic stimulation at any one time is due to an algebraical summation of excitation and inhibition. It is therefore of interest to find, even in one animal, adrenaline causing at one and the same time contraction of one part of the uterus and relaxation of another. Fellner [1906] and Whitehouse and Featherstone [1923] differentiated between the fundus and cervix of the uterus, and came to different conclusions regarding the coordination of circular and longitudinal muscle in each of the parts, and between the two parts themselves. The latter authors state that in the rabbit hypogastric stimulation, or anæsthetization of the lumbar cord, produces contraction of the circular muscle in both parts of the organ, while stimulation of the lumbar cord causes contraction of all longitudinal muscle. They therefore postulate a sympathetic and parasympathetic innervation, there being little or no other evidence for the latter. Fleming [key reference, 1932] from physiological and careful histological investigation inclines to the view that there may be an intrinsic nervous system, of ultimate sympathetic origin, but located in the myometrium and accounting for such coordinated uterine movements as "normal" labour in the excised organ.

The present experiments show a functional coordination between the horns and the cervix, but not whether its control is vested in extra- or intra-uterine nerve cells. If labour is due to the action of an oxytocic substance, the advantages of insensitivity to such bodies on the part of the circular cervical muscle are obvious. Similarly contraction of the cervix with relaxation of the rest of the uterus would be a coordinated protective movement on the part of the organ, its initiation by adrenaline suggesting for it a sympathetic nervous origin. The question which remains unanswered is whether during pregnancy activity of the uterus is regulated by a balance between chemical and nervous mechanisms, or whether we are to look further for a nervous mechanism the opposite of

that described. If so, it will not necessarily be found in the parasympathetic, for others have shown that adrenaline may act on the same part of the uterus in different ways at different times.

SUMMARY.

Whereas the cornua of the pregnant goat uterus are sensitive *in vitro* to a normal dose of oxytocin, the cervix is insensitive to very large doses. Adrenaline, *in vitro*, relaxes the cornua and causes the cervix to contract. The relation of these findings to the function of the uterus and to the work of other observers is discussed.

I wish to express my deep indebtedness to Prof. J. Barcroft for providing the material for these experiments, and my further thanks to him and his assistants at the Physiological Laboratory, Cambridge, for its careful selection and transmission. The remaining expenses of this research were defrayed by a grant from the Medical Research Council.

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