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The effects of posterior pituitary hormones on isometric tension and isotonic shortening of the pig myometrium

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Isotonic recording showed that uteri in the luteal stage of the oestrus cycle were more sensitive to oxytocin and vasopressin than those in the follicular stage. The uterine horn was more sensitive than the cervix. A comparison of isotonic and isometric recording revealed that the former exaggerated the response to oxytocin. Under isometric conditions there was no difference in sensitivity to oxytocin between progesterone-dominated and oestrogen-dominated uteri, but both were more sensitive than immature uteri. Tension developed in response to oxytocin was greatest in oestrogen-dominated, less in progesterone-dominated and least in immature uteri.

THE influence of the female sex hormones on the response of the uterus to the hormones of the posterior pituitary gland has been most clearly elucidated in the rabbit. In this species, oestrogens augment, and progesterone blocks the response of the myometrium to posterior pituitary hormones (Robson, 1933a, b; Csapo, 1955, 1956; Schofield, 1957). Complete "progesterone block" has not been demonstrated in any other species, where the uterus contracts in response to oxytocin at all stages of pregnancy; the evidence has been reviewed by Caldeyro-Barcia & Sereno (1961).

On the basis of *in vitro* experiments using isotonic levers, it has been shown that the uterus of the non-pregnant sow responds to oxytocin at all stages of the oestrus cycle and is apparently most sensitive during the luteal stage (Adams, 1940; Knifton, 1962). The present work was undertaken to study further this apparent anomaly, by measuring the responses of strips of sow and immature gilt uteri to synthetic preparations of the posterior pituitary hormones under isotonic and isometric conditions.

Experimental

METHODS

Uteri from freshly slaughtered non-pregnant pigs were collected from a nearby abbatoir and strips assembled for recording as previously described (Knifton, 1966). Krebs solution gassed with oxygen 95% and carbon dioxide 5% was used in all experiments.

Isotonic recording. Oxytocin (Syntocinon, Sandoz) was added to the 10 ml isolated tissue baths in increasing concentrations from 2×10^{-7} to 2×10^{-2} units, so that each uterus was tested with 6 concentrations of drug, each differing by the order of 10, and the sensitivity of each strip was assessed by the number of applications of drug which induced a change in the spontaneous motility (Knifton, 1962). After a resting period of 30 min, vasopressin (lysine-8-vasopressin, Sandoz) was added to the baths in concentrations increasing by the order of 10 from 2×10^{-6} to 2×10^{-1} units, in a similar sequence to that described for oxytocin. The load on the uteri was 2·0 g.

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Isometric recording. The response to varying the frequency of electrical stimulation (staircase effect, Knifton, 1966) was recorded and the strips rested for 1 hr, during which spontaneous contractions developed. (This effect was used in each experiment together with histological data, to determine whether the uterus was oestrogen- or progesterone-dominated.) Oxytocin was then added in increasing concentrations from 0·02 to 100·0 mU, so that each uterus was tested with 5 different concentrations of drug. The sensitivity of each uterus to oxytocin was assessed in the manner described for isotonic recording. In addition, responses were recorded, for each dose of drug, as the maximum tension developed during the period of drug contact.

In some cases the responses were also recorded with an isotonic lever on the same tissue, to compare the isometric tension and isotonic shortening of the uterus as a function of the dose of oxytocin.

Hormone dominance. The respective influence of the female sex hormones on the myometrium was assessed in each instance on the basis of histological data (Corner, 1921; Burger, 1952) and the type of staircase recorded (Knifton, 1966). This evidence enabled the uteri to be subsequently classified into immature, oestrogen-dominated and progesterone-dominated groups.

Results

Isotonic recording. The mean percentage responses to oxytocin of sow uteri and immature gilt uteri are summarized in Fig. 1. The sow uterus

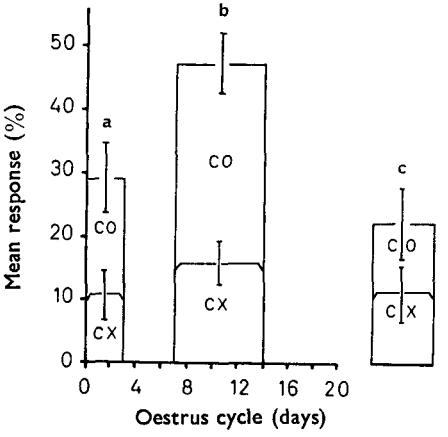

FIG. 1. The mean response (%) to six doses of oxytocin of the cervix (CX) and uterine horn (CO) of (a) 11 uteri from sows at oestrus stage, (b) 18 uteri from sows at luteal stage, (c) 9 uteri from immature gilts. The vertical bars indicate s.e. of the mean.

(horn and cervix) responds to oxytocin during both the follicular and luteal stages of the oestrus cycle. There is no difference in the sensitivity of cervical strips at different stages of the cycle, but the sensitivity of cornual strips during the luteal stage is greater ($P < 0{\cdot}01$) than during the follicular stage.

During both stages of the cycle the cornual strips are significantly more sensitive ($P < 0{\cdot}01$) to oxytocin than the cervical strips. There is no difference in sensitivity between gilt cornual and cervical strips.

The mean percentage responses of the uteri to vasopressin are summarized in Fig. 2, and the differences in sensitivity between the groups are the same as described for oxytocin.

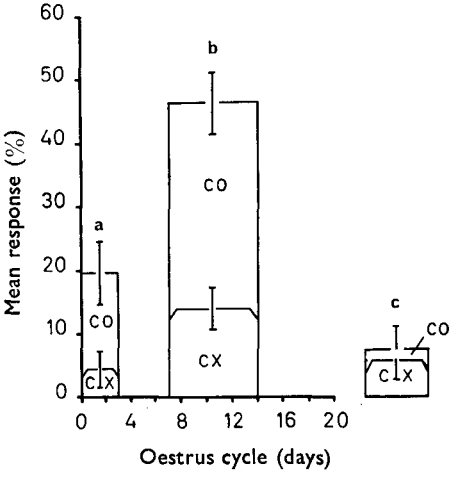

FIG. 2. The mean response (%) to six doses of vasopressin of the cervix (CX) and the uterine horn (CO) of (a) 11 uteri from sows at oestrus stage, (b) 18 uteri from sows at luteal stage, (c) 9 uteri from immature gilts. The vertical bars indicate s.e. of the mean.

Isometric recording. The results of these experiments in which the response to oxytocin was measured isometrically and then isotonically on the same strips revealed that a better dose-response effect was obtained with isometric levers. In some instances, the strips showed maximal isotonic shortening, but the same dose of oxytocin caused no detectable isometric response.

The results of recording isometrically the responses to oxytocin of uterine strips under the predominating influence of different female sex hormones are summarized in Fig. 3. The sow uteri developed significantly greater tension ($P < 0{\cdot}01$) in response to the doses of oxytocin of 2·0 to 100·0 mU than the immature gilt uteri, and the responses of the oestrogen-dominated sow uteri were significantly greater ($P < 0{\cdot}01$) than those of the progesterone-dominated group. These results correlate well with the results of measurements of tension developed during spontaneous contractions of the different groups of uteri. For each uterine strip, the greatest tension developed in spontaneous motility before the addition of oxytocin was measured, and the mean value for each group of uteri is shown in Table 1. The tension in the oestrogen-dominated group is significantly greater ($P < 0{\cdot}01$) than the tension in the progesterone-dominated group and the difference in tension between the oestrogen-dominated sow uteri and the

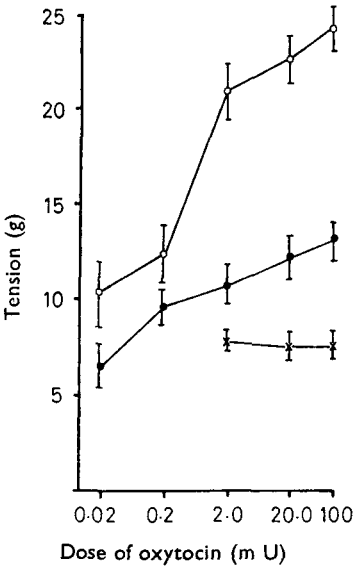

FIG. 3. The isometric response to oxytocin of cornual strips from immature gilts (×), progesterone-dominated (●) and oestrogen-dominated (○) sow uteri. Each point represents the mean response of 8 immature gilt uteri, 14 progesterone-dominated and 14 oestrogen-dominated sow uteri. The vertical bars indicate s.e. of the mean.

TABLE 1. MAXIMUM TENSION OF UTERINE STRIPS DURING SPONTANEOUS MOTILITY

	Oestrogen-dominated	Progesterone-dominated	Immature gilts
Mean tension (g)	19·1	6·4	7·4
s.e.	1·7	0·6	0·5
No. of uteri	14	14	8

gilt uteri is also highly significant. There is no significant difference however between the maximum spontaneous tension of the progesterone-dominated sow uteri and the gilt uteri.

An analysis of the responses to oxytocin made by calculating the mean percentage response of each group of uteri to the series of doses of oxytocin gives a comparison of the sensitivity of the different groups to the hormone (Knifton, 1962). When the present results are analysed in this way (Table 2), both the oestrogen and progesterone-dominated groups of sow

TABLE 2. MEAN PERCENTAGE RESPONSE OF UTERINE STRIPS TO 5 DOSES OF OXYTOCIN
Responses recorded with isometric levers

	Oestrogen-dominated	Progesterone-dominated	Immature gilts
Mean response (%) ..	71·4	81·4	57·5
s.e.	12·1	10·4	17·5
No. of uteri	14	14	8

uteri are more sensitive to oxytocin than the immature gilt uteri ($P = 0{\cdot}05$), but there is no difference in sensitivity between the two groups of sow uteri.

Discussion

In an earlier study of the response of the pig uterus to oxytocin (Knifton, 1962), Dale's solution was used in the tissue baths and the response to Pitocin (Parke-Davis) was measured isotonically. The results of the isotonic measurements in the present study do not differ from the earlier results despite the use of Krebs solution and synthetic oxytocin. The most significant feature of these results is that the uteri in the luteal stage of the oestrus cycle are more sensitive to oxytocin than those in the follicular stage; the predominating female sex hormones during these stages of the cycle are progesterone and oestrogen respectively (Knifton, 1966).

The isometric recordings produced a different result however, in that there was no difference in sensitivity to oxytocin between the oestrogen and progesterone-dominated sow uteri, but both were more sensitive than the immature uteri. This finding confirms that of other work, where it was shown that there was no difference in sensitivity to electrical stimulation of oestrogen and progesterone-dominated sow uteri (Knifton, 1966). The present study has also shown that the uterus can respond isotonically to doses of oxytocin which fail to elicit an isometric response.

It has been shown that in the rabbit, the membrane potential of the progesterone-dominated myometrium is greater than that of the oestrogen-dominated myometrium (Goto & Csapo, 1959; Kuriyama & Csapo, 1961; Marshall & Csapo, 1961). This is in accord with the evidence that in this species progesterone blocks the depolarizing, and hence contractile, effect of oxytocin (Schofield, 1963). In the rat, however, Jung (1964) found no difference in membrane potential between oestrogen and progesterone-dominated uteri. This accords with the evidence that progesterone does not appear to affect the sensitivity of the rat myometrium to posterior pituitary hormones (Reynolds, 1949). Oestrogens however do increase the sensitivity of the rat myometrium (Follett & Bentley, 1964). Similar findings with progesterone have been reported in the guinea-pig (Bell & Robson, 1937), cat (Robson & Schild, 1938) and woman (Moir, 1944; Bickers & Woods, 1949). The present results are thus in accord with those in several other species.

When the response of the uterus to oxytocin is assessed by the tension developed to different doses, however, the present study reveals marked differences between the immature, the oestrogen-dominated and the progesterone-dominated uterus. It has been shown that oestrogens regulate the concentration of contractile protein in the myometrium (Csapo, 1950; Needham & Cawkwell, 1957). Thus the more marked response of the mature uterus when compared with the immature uterus is presumably due to a greater concentration of actomyosin in the former. Csapo (cited by Reynolds, 1951) found no difference in the concentration of actomyosin in the sow myometrium at different stages of the oestrus cycle. In the present study however, the tension developed in response to oxytocin in the progesterone-dominated uteri was significantly less than the tension in the oestrogen-dominated uteri and it is concluded that this is due to progesterone "block", despite the fact that progesterone does

not appear to reduce the sensitivity (i.e. threshold dose) of the pig uterus to oxytocin. It has been shown, however, that progesterone affects the myometrium by various mechanisms (Daniel, 1964). The present studies with oxytocin also substantiate the conclusions drawn from experiments in which the tension developed in the pig uterus in response to electrical stimulation was measured (Knifton, 1966). It has also been shown that oestrogens produce a greater response to posterior pituitary hormones of the bovine uterus *in vivo* when compared with the response of the uterus in the luteal stage of the cycle (Fitzpatrick, 1960).

A further feature of the results is the relative insensitivity to posterior pituitary hormones of the cervix. This agrees with similar findings in the goat (Newton, 1934), rat, guinea-pig (Newton, 1937) and the rabbit (Bonnycastle & Ferguson, 1941).

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