Effects of oestrogen, progesterone and betamethasone on the guinea-pig uterus

The effects of female sex hormones on the myometrium have been extensively studied, particularly in rabbits and rats (the evidence is reviewed by Abe, 1970). In the rabbit, the progesterone-dominated uterus, when compared with the oestrogen-dominated uterus, is insensitive to oxytocin, gives a different staircase effect in response to electrical stimulation (Schofield, 1954) and binds calcium more effectively.

However, studies in pregnant guinea-pigs (Schofield, 1964) gave equivocal results, particularly in the effects of progesterone on the calcium-depleted uterus. The object of the present work was to repeat these studies in non-pregnant, hormone pretreated guinea-pigs. Because of current interest in the role of foetal adrenal steroids in the initiation of parturition (Liggins, 1969), preliminary studies were also made of the effects of the synthetic glucocorticoid betamethasone on the myometrium.

Sexually mature virgin guinea-pigs, about 500 g, were injected with oestrogen or progesterone according to the stage of the oestrus cycle. Animals in pro-oestrus or oestrus were injected daily with 100 μg/kg stilboestrol intraperitoneally for 3 days and killed on the fourth day. A second group, in metoestrus or early dioestrus, received the same dose of stilboestrol plus 50 mg/kg progesterone daily for 3 successive days. Vaginal smears were again taken before killing the animals to confirm that the uteri were respectively oestrogen-dominated or progesterone-dominated. A third group were injected daily with 100 μg/kg stilboestrol and 200 μg/kg betamethasone for three successive days.

Animals were stunned, decapitated and a 2 cm length of uterine horn removed to a 10 ml tissue bath containing Dale's solution at 32° gassed with carbon dioxide in oxygen. The tissues were assembled for isometric recording and electrical stimulation as previously described (Knifton, 1966). After adjusting the tissue to resting length the threshold voltage and staircase effect were determined. Electrical stimulation of optimum voltage was then applied at 1 min intervals. When a steady state tension was reached the tissue was rinsed repeatedly in calcium-free Dale's solution and the time taken for the tension to decrease to 50% of the steady state tension (T50) was measured.

The mean threshold voltage/cm resting length in uteri from 11 oestrogen pre-treated animals was 0·47 $\pm$ 0·04 s.e. and 0·78 V/cm ($\pm$0·09) in 9 progesterone-dominated uteri; the difference between the groups is significant at the 1% level. Tension developed to optimum electrical stimulation was significantly greater in the oestrogen-treated group (6·1 g $\pm$ 0·43 s.e.) than in the progesterone-treated group (4·1 g $\pm$ 0·25 s.e.). These results are similar to earlier studies in the rabbit (Schofield, 1963) and are in accord with the concept of progesterone causing a "desensitisation" of the myometrium.

Varying the frequency of electrical stimulation did not reveal any characteristic differences in tension (staircase effect) between oestrogen- and progesterone-dominated uteri. This confirms studies made by Schofield (1964) in strips from pregnant guinea-pig uteri.

Calcium depletion progressively reduced the response to electrical stimulation in both oestrogen- and progesterone-dominated uteri (Fig. 1A). There is a significant ($P<0·01$) difference between the two groups in the time taken for tension to be reduced by 50% and since both were pre-treated with the same dose of oestrogen, it is concluded that progesterone increases the degree of calcium binding in the uterus. Electrophysiological studies (Abe, 1970) suggest that increasing the effectiveness of calcium binding in smooth muscle induces a relative refractoriness to stimulation.

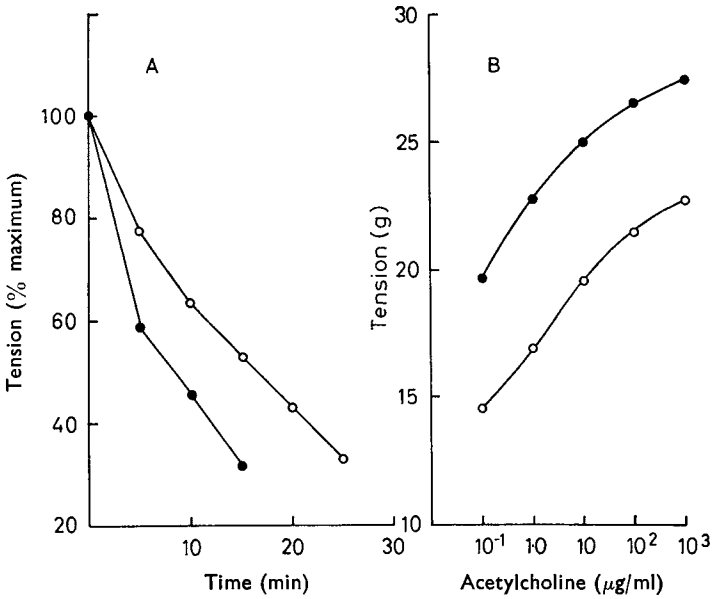

FIG. 1A. Decline of isometric response to electrical stimulation of uteri in Ca-free solution. The open circles represent mean tensions in 9 progesterone-dominated uteri and the closed circles in 11 oestrogen-dominated uteri.

B. Mean responses to μg doses of acetylcholine in 6 uteri from oestrogen pre-treated animals (closed circles) and 7 uteri from oestrogen plus betamethasone pre-treated animals (open circles).

However, the present results do not support studies by Schofield (1964) with pregnant guinea-pig uteri. In calcium-free solution the reduction in tension in response to electrical stimulation occurred more slowly at the end of pregnancy than in mid-pregnancy but the influence of progesterone on the myometrium was assumed to be less at the end of pregnancy.

Spontaneous and electrically-induced uterine contractions were enhanced by low concentrations of betamethasone and suppressed by higher doses; this confirms the results of Mossman & Conrad (1969) with other adrenal corticosteroids. The inhibitory effect of betamethasone was further demonstrated by measuring the response to acetylcholine in uteri from animals pretreated with oestrogen and others pretreated with oestrogen and betamethasone (Fig. 1B). The effect of betamethasone was to cause a parallel shift in the dose-response curve.

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REFERENCES

ABE, Y. (1970). In *Smooth Muscle*, pp. 396–417. Editors: Bülbring, E., Brading, A. F., Jones, A. W. & Tomita, T. Arnold: London.

KNIFTON, A. (1966). *J. Pharm. Pharmac.*, **18**, *Suppl.*, 151S–159S.

LIGGINS, G. C. (1969). *J. Endocr.*, **45**, 515–523.

MOSSMAN, R. G. & CONRAD, J. T. (1969). *Am. J. Obstet. Gynec.*, **105**, 897–908.

SCHOFIELD, B. M. (1954). *Endocrinology*, **55**, 142–147.

SCHOFIELD, B. M. (1963). In *Recent Advances in Physiology*, pp. 222–251. Editor: Creese, R., London: Churchill.

SCHOFIELD, B. M. (1964). In *Pharmacology of Smooth Muscle*, pp. 105–111. Editor: Bülbring, E. London: Pergamon.