J. Pharm. Pharmacol. 1982, 34: 262–263
Communicated January 11, 1982

0022–3573/82/040262–002 $02.50/0
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Synthesis of prostaglandins by the human uterine cervix in vitro during passive mechanical stretch

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Arachidonic acid and prostaglandins (PGs) have a variety of effects on the human uterine cervix. In vitro, these include alterations in motility (Najak et al 1970) and the biochemical modification of the cervix matrix proteins (Hillier & Wallis 1981; Norstrom et al 1981; Wilhelmsson et al 1981). In vivo, PGs may cause a beneficial softening of the cervix at term in humans (Mackenzie 1981) and laboratory animals (Stys et al 1981) thus aiding the processes of labour.

The human cervix synthesizes PGs in vitro (Ellwood et al 1980; Hillier & Wallis 1981) and if this occurs in vivo it may help remodel the cervical tissue structure at term. Because uterine contractility stretches the cervix and contractions not felt by the pregnant mother can occur well before the clinically identifiable onset of labour (Anderson & Turnbull 1969) we investigated the effect of passive mechanical stretching on PG synthesis by human isolated uterine cervix.

Materials and methods

Cervix tissue was obtained from pre-menopausal, non-pregnant women following hysterectomy for benign gynaecological disease which did not involve the cervix. Note was taken of the date of the last menstrual period and regularity of cycles but no further assessment of the phase of menstrual cycle was made. Tissue was taken from the inner fibrous region at the proximity of the internal os. The outer tissue containing muscle fibres was not used. The tissue was placed immediately in ice-cold Krebs solution of the following composition mM (NaCl 112·54, KCl 4·75, KH_2PO_4 1·19, $MgSO_47H_2O$ 1·19, $NaHCO_3$ 25·0, $CaCl_2$ 2·57, glucose 11·54), gassed with 95% O_2 and 5% CO_2 and maintained at this temperature (4 °C) during preparation.

Strips of cervix about 1·5 cm × 1 mm were cut longitudinally. A cotton thread was tied at both ends and the strips were weighed and suspended in 10 ml Krebs solution at 37 °C gassed with 95% O_2 and 5% CO_2. Tissues were used in sets of three preparations excised from a closely related position within the cervix and incubated in separate tissue baths. After 15 min the bath fluid was replaced with fresh Krebs solution. One strip was not stretched, the second was stretched with a 2 g weight and the third with a 9 g weight. The load was applied after the 15 min pre-incubation. One hour later the Krebs solution was removed, snap frozen in liquid nitrogen and stored at −20 °C. Small samples of incubation medium (0·05–0·2 ml) were assayed within 2 weeks following appropriate dilution. Immunoreactivity resembling prostaglandin E_2 (PGE_2) and $F_{2\alpha}$ ($PGF_{2\alpha}$) was measured as described by Hillier & Templeton (1982). The coefficients of variation of the PGE_2 and $PGF_{2\alpha}$ concentrations of a sample within an assay were 5·4 and 4·8% respectively (n = 6) and 15·5 and 13·1% respectively in 6 separate assays. The cross-reactivity of PGE_2 antibody was 52·5% with PGE_1, 3·0% with PGD_2 and less than 1% with $F_{2\alpha}$ and other tested metabolites. The cross-reactivity of $PGF_{2\alpha}$ antibody was 3·8% with $PGF_{1\alpha}$, 6·7% with PGD_2 and less than 0·1% with other tested metabolites.

Results

Sixteen sets of anatomically matched longitudinal strips from the essentially fibrous region of the internal os area of the human, non-pregnant cervix were examined. PG measurements on the Krebs solution from any one set of tissues was always made in the same assay. Assessment of the stage of the menstrual cycle was not made histologically. Because of this, differences in PG production between follicular and luteal phase could not be categorically documented. However, using the patient's date of last menstrual period no obvious menstrual phase differences were noted.

Table 1 shows the amount and range of PG released. Stretching the tissue with a 2 g weight increased PGE_2 and $PGF_{2\alpha}$ synthesis ($P < 0·01$). With a 9 g load PGE_2 release was greater than controls but tended to be less than with 2 g. Similarly, release of $PGF_{2\alpha}$-like material tended to be greater with a 2 g stretch than with 0 or 9 g stretch. PGs released by 2 g and 9 g stretch were not significantly different ($P > 0·05$).

Discussion

Many tissues increase PG synthesis in response to stretch. For example, Kloeck & Jung (1973) showed that loads of 2 and 9 g when applied to strips of human pregnant myometrium increased synthesis of PGE_2-like material. However, $PGF_{2\alpha}$ synthesis decreased compared with controls; no separate analysis of the effect of low or high loads was made. No paper has previously described PG synthesis in response to stretch of the fibrous area of the uterine cervix.

We have found that passive stretch with 2 g more than doubled PG release but the 9 g load did not increase this further and the output actually tended to be less than with 2 g. Whether this represents diversion of substrate metabolism is the subject of continuing investigation.

Increased cervical PG synthesis in response to stretch may have an important bearing on the essential modifica-

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Table 1. Release of prostaglandin E_2 and $F_{2\alpha}$-like material by the human non-pregnant uterine cervix when exposed to passive mechanical stretch.

Load (g)	0	2	9
PGE_2	3·9 ± 1·4	11·6 ± 2·9**	7·8 ± 3·5*
Range	(0·08–10)	(0·20–20)	(0·15–35)
$PGF_{2\alpha}$	9·9 ± 2·4	23·0 ± 5·7**	16·3 ± 4·4
Range	(0·5–17)	(1·28–61)	(0·5–36)
Weight (mg)	56 ± 3·9	60 ± 2·4	71 ± 3·2

Values are ng/100 mg wet weight tissue h^{-1} ± s.e.m. The range of observations is shown in parentheses (n = 16 each group).
*$P < 0.05$, **$P < 0.001$ when compared with control (zero stretch) using Wilcoxon's paired rank sum test.

tions of its matrix structure at term which result in a rigid tissue becoming elastic and distensible for childbirth. As with tissue from non-pregnant women, the pregnant human cervix synthesizes PGs in vitro (Ellwood et al 1980) and we suggest that it would probably respond to stretch in a similar manner qualitatively to that shown in this study.

Anderson & Turnbull (1969) showed that women exhibit subclinical uterine contractility well before the clinically identifiable onset of labour. These unfelt contractions might stretch the cervix and release mediators including arachidonic acid and PGs which help the softening process.

PGs can affect the matrix proteins. For example, with non-pregnant isolated cervix from the luteal phase PGE_2 and $F_{2\alpha}$ can increase collagen synthesis while a decrease occurs in the follicular phase (Norstrom et al 1981). With human isolated cervix and rat cervix in vivo arachidonic acid can increase collagen dissolution (Hillier & Wallis 1981; Wallis 1981). Also, PGs given therapeutically will soften the cervix at term and before abortion (MacKenzie 1981), although it is not known if this effect is direct or results from PG induced uterine contractility distending the cervix.

Additional evidence that tension will alter matrix proteins derives from the work of Reeds et al (1980) who showed that mechanical stretch of non-reproductive tissues enhanced protein synthesis. Perhaps similar events occur in the human uterine cervix.

We thank the staff of the Department of Obstetrics and Gynaecology, Southampton General Hospital for their help, the Upjohn Co. Ltd for PGs, May & Baker Ltd for supplies of PGE_2 antibody, the Lalor Foundation for financial support to K. H. and Richard Jewell for expert technical assistance.

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