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The role of prostaglandins in oviduct function: facts and fantasies *

Papel de las prostaglandinas en la función del oviducto: hechos y fantasías

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The classical prostaglandins as well as the more recently discovered arachodinate products have powerful effects on the smooth muscle of the human oviduct. There is a complex pattern of reactivity with differentiated responses in the various tubal segments (utero-tubal junction, ampullary-isthmic junction and the infundibulum) and in the separate muscle layers of each particular segment. Furthermore, the prostanoids may have different actions depending on the hormonal state prevailing.

There is evidence that prostanoids may have a messenger or modulator role in the control of ovum pick-up from the ovary and in the further regulation of tubal transport. These compounds may be involved also in tubal dysfunction due to pathological conditions such as endometriosis and pelvic inflammatory disease.

Recently it has been discovered that prostaglandins can be utilized for medical treatment of ectopic pregnancies, probably by contracting tubal smooth muscle and by constricting tubal blood vessels.

INTRODUCTION

The prostaglandins (PGs) and related compounds have been implicated in several events related to the function of the oviduct. Although the secretory cells of the tubal epithelium are responsible for the production of tubal fluid and thus the creation of a proper microenvironment for the process of fertilization, little is known about the biological role of prostanoids in this very context. Considerably more information is available concerning PGs and two other biological functions of the oviduct, *i.e.* ovum pick up and ovum/embryo transport.

PGs are of interest also in certain other contexts, *e.g.*: 1. mechanism of action of copper intrauterine devices; 2. pelvic inflammatory disease; 3. pelvic endometriosis; 4. treatment of ectopic pregnancy.

The term "prostanoids" encompasses prostaglandins and other products formed from the precursor compound, arachidonic acid by the action of the enzymes cyclooxygenase and lipoxygenase. These substances are synthesized by nearly every tissue in the body and are characterized by powerful actions close to the area of production. Hence they have been considered as locally active hormones. The following scheme illustrates the principal pathways in the metabolism of arachidonic acid, which in turn is derived from phospholipids (Fig. 1).

PGE2 and PGF2α belong to the "natural prostaglandins" and were discovered already in the 1950s, while during the last two decades an increasing number of products formed in the arachidonate "cascade" have been identified (1, 2).

This presentation, will focus on the *human* oviduct trying to distinguish concepts considered "facts" or commonly accepted views, from those which are pure speculation and therefore should be referred to as "fantasies".

Ovum pick up

The human preovulatory follicle contains high concentrations of prostaglandins and

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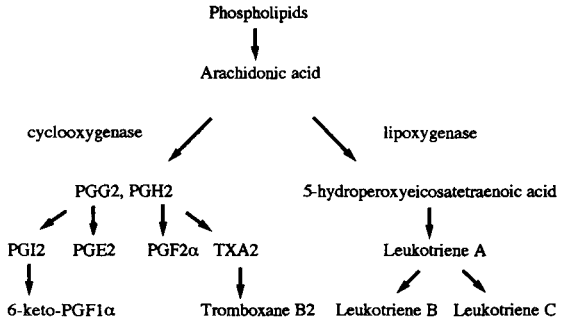

Fig. 1: Principal pathways in the biosynthesis of prostanoids. The prostaglandins and the tromboxanes are formed via the cyclooxygenase pathway, which can be inhibited by indomethacin and similar agents. The leukotrienes are formed via the lipoxygenase pathway.

volumes of up to 20 ml are showered over the surrounding structures at ovulation (3, 4). Crude follicular fluid and PGs found in the fluid induce contractile responses of the tubo-ovarian ligament and fimbriae when studied in *in vitro* models (5). In the rabbit, PGE_2 and $PGF_{2\alpha}$ concentrations in the fimbriae increases at ovulation (6). PGs also stimulate the contractile activity of the human mesosalpinx (7). These are the facts. Our fantasy is that PGs from the follicular fluid released at ovulation are involved in a chemotactic smooth muscle process which enables the tubal fimbriae to come in close contact with the ovarian surface and pick-up the ovum.

Ovum transport

Two factors are believed to influence ovum transport: muscular activity and ciliary activity, perhaps functioning in an integrated manner. The ciliary activity and the influence of PGs on ciliary beat are discussed elsewhere in this volume and it should only be recalled that both E- and F- prostaglandins have a stimulatory action on beat frequency.

Throughout life, the smooth muscle of the tube contracts intermittently. *In vivo* studies, using intraluminal pressure transducers, have shown an inhibitory effect of PGE_2, while $PGF_{2\alpha}$ is excitatory (8). However, these observations tell little about the role of endogenous PGs for ovum transport. *In vitro* studies have provided and insight into the complex arrangement of tubal smooth muscle in humans (9) and explored the differentiated actions of various prostanoids and of PG synthetase inhibitors (10). To briefly summarize the actions of various agents on different structures of the tube, the following table can be made.

Studies by Forman *et al.* (11) suggest that the $PGF_{2\alpha}$ induced stimulation of contraction in the circular layer is dependent on potential -sensitive membrane channels for calcium. In electrophysiological studies, Lindblom & Wikland (12) showed that PGE_2 reduced the number of action potentials whereas $PGF_{2\alpha}$ had the opposite effect. Nozaki & Ito (13) found that PGE_2 and $PGF_{2\alpha}$ enhance the frequency of "slow waves", which in turn trigger muscle contraction.

The inner longitudinal layer of the isthmus is of specific interest for many reasons. Primarily, it is unique in that it is present only in the isthmic portion, which is considered to be "locked" for ova during the delay period, *i.e.* the first 3-4 days after ovulation. In contrast to the monkey, this layer is truly muscular in humans (9, 14). Secondly, this muscle exhibits a hormone-dependent response to PGE_2 with an excitatory ("locking"?) response under estrogen influence, *i.e.* during the periovulatory period when ova are retained in the tube. During the other phases of the cycle, an inhibitory effect is observed (14). This represents the facts from *in vitro* studies of small strips carefully dissected from the excised tube. Our fantasy is that the estrogen/progesterone ratio could be the superior control of the effector and that there is a direct hormonal influence on the PGE_2 receptors of the tubal smooth muscle cells.

Investigations of spontaneous tubal muscle activity *in vitro* also demonstrate an inhibitory influence of cyclooxygenase inhibitors like indomethacin. ETYA, a compound thought to inhibit both this enzyme and lipoxygenase has a similar influence (15, 16). After total inhibition of intrinsic activity by these compounds, contractile activity can be reestablished by addition of small amounts of $PGF_{2\alpha}$

TABLE 1

Evidence for a role of PGs in the regulation of contractile activity of various smooth muscle elements within the human oviduct

Function	Tissue	PG/PG inhibitor	Influence
Pick-up mechanism			
	Tubo-ovarian ligament	E_2, $F_2\alpha$, I_2	stimulation
		indomethacin	inhibition
	Fimbria	$F_2\alpha$	stimulation
		indomethacin	inhibition
	Mesosalpinx	E_2, $F_2\alpha$, I_2	stimulation
		indomethacin	inhibition
Ampullary function			
	Circular and longitudinal muscle layer	E_2	inhibition
		$F_2\alpha$, I_2	stimulation
		ETYA	inhibition
	In vivo intraluminal pressure (tubal wall)	E_2	inhibition
		$F_2\alpha$	stimulation
Isthmic function			
	Outer longitudinal muscle layer	E_2, $F_2\alpha$, I_2	stimulation
		ETYA, indomethacin	inhibition
	Circular layer	E_2, I_2	inhibition
		$F_2\alpha$	stimulation
		ETYA, indomethacin	inhibition
	Inner longitudinal layer	E_2	inhibition/ stimulation*
		$F_2\alpha$, I_2	stimulation

* Stimulation at the time of ovulation, inhibition in other cycle phases.

to the *in vitro* medium (Fig. 2). Our fantasy is that maintenance of normal tubal activity and ovum transport is dependent on an intact local formation of prostanoids.

At the time of ovulation, $PGF_{2\alpha}$ levels are elevated in the oviductal fluid of the pig (17) and in the local arterial blood of the same species, probably by a countercurrent exchange mechanism (18).

Little is known about the interplay between the fertilized ovum and the tubal mucosa in terms of PGs, but apparently there are animal data to suggest a role of PGE_2 produced by the fertilized egg on the surrounding structures, *e.g.* the smooth

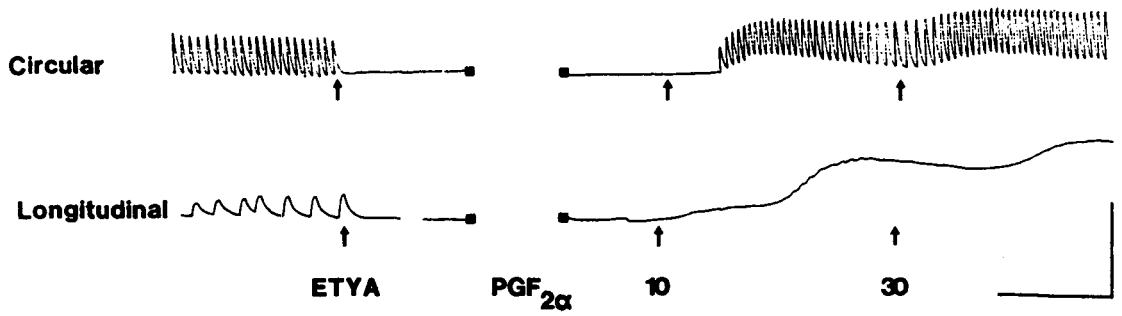

Fig. 2: In vitro experiment demonstrating the inhibitory action of eicosatetraynoic acid (ETYA) (30 µg/ml) on circular and longitudinal muscle activity of the human oviduct and the reestablishment of activity by addition of $PGF_{2\alpha}$ (10-30 ng/ml) to the medium. Vertical calibration 4 mN, horizontal calibration 3 min.

muscle cells close to the lumen.(19). The data thus represent evidence that the ovum may influence its own transport and that this influence could be exerted by local formation of PGs. Certainly, more information will be generated in the near future regarding this very interesting topic.

Besides their effects on tubal smooth muscle, prostaglandins also possess clearcut and differentiated effects on tubal blood vessels. Both PGE_2 and $PGF_{2\alpha}$ induce vasoconstriction, the latter being more powerful in action. PGI_2 causes vasodilatation and counteracts the effects of PGE_2 and $PGE_{2\alpha}$ at equimolar concentrations (20). These effects are so reproducible that the tubal artery in combination with strips from the circular muscle can be utilized for bioassay purposes (20).

Pelvic inflammatory disease

Since a stimulation of PG production is part of the inflammatory response, it is reasonable to assume that PGs have a role in the patophysiology of pelvic inflammatory disease. Heinonen *et al.* (21) measured concentrations of leukotriene B4 (LTB_4) and PGE_2 in peritoneal fluid of women with acute salpingitis. Mean levels of LTB_4 in these cases were 505 pg/ml vs 44 pg/ml in healthy controls. Mean PGE_2 levels in acute salpingitis were 378 pg/ml vs 11 pg/ml in the control group. The authors suggested that these chemical mediators may have a role in scarring and peritubal adhesion formation after acute salpingitis. If this is the case, treatment with anti-inflammatory drugs could be a worthwhile complement to antibiotic therapy in *acute* salpingitis. Conversely, Alber *et al.* (22) found no increase in concentrations of 6-keto $PGF_{1\alpha}$, TxB_2, PGE_2 or $PGF_{2\alpha}$ in cases with *chronic* salpingitis.

Copper IUD

There is certain evidence that PGs play a role in the contraceptive mechanism of copper-bearing intra-uterine devices via an influence on tubal contractility (23). Thus, the response of the tubal muscle to copper ions *in vitro* is almost identical to the effect of $PGF_{2\alpha}$ and the effects of copper can be blocked by indomethacin. Furthermore, after maximal stimulation induced by exogenous $PGF_{2\alpha}$, copper becomes ineffective as a stimulant, whereas other agents may induce further stimulation despite prior "loading" of the tissue with $PGF_{2\alpha}$. The fantasy is that copper ions released from a copper intrauterine contraceptive device increase tubal motility and disturb ovum transport (and/or the process of fertilization?) by an action on endogenous synthesis of prostaglandins, predominantly $PGF_{2\alpha}$.

Endometriosis

Endometriosis is defined as the presence of tissue outside the uterus which possesses the histological structure and function of the uterine mucosa. The resulting local inflammation may cause acute and/or chronic pelvic pain, dysmenorrhea and dyspareunia and is often associated with female infertility. The etiology of the disease is far from clear, although increasing evidence suggests a role of retrograde menstruation, perhaps in conjunction with autoimmunological mechanisms. Prostaglandins and related compounds have been implicated in the patophysiology of this condition. Considerable amounts of PGs are produced by the endometrium of both normal and dysmenorrheic patients (24, 25) and it is reasonable to assume that also ectopic endometrium may have the same capacity. Drake and collaborators (26, 27) demonstrated an increase of 6-keto $PGF_{1\alpha}$ and TxB_2 in the peritoneal fluid of patients with endometriosis and Badawy and coworkers (28, 29) found an increase of PGF metabolites in cases with endometriosis or unexplained infertility as compared to controls. Similar results were obtained by Alber *et al* (22). One can hypothesize that the increased PG production could interfere with tubal motility, hereby disturbing ovum transport and reducing fertility.

Trials with PG synthetase inhibitors for treatment of secondary dysmenorrhea

(which is a common expression of endometriosis) have given contradictory results (30, 31) and the question is far from clarified. So far, selective inhibitors of $PGF_{2\alpha}$ production - which would be of specific interest in this context - are not yet available.

Ectopic pregnancy

Because of its powerful excitatory action on tubal smooth muscle and its vasoconstrictor effect on tubal arteries, $PGF_{2\alpha}$ was considered a suitable compound when the first trials with local injection therapy in tubal pregnancy were conducted (32). In addition to these actions, $PGF_{2\alpha}$ also has an antigonadotropic (luteolytic?) influence on the corpus luteum (33). This action may enhance the "mechanical" effect on tubal wall and the blood vessels especially in pregnancies with active trophoblast and, hence, a well-functioning corpus luteum. This regimen has been proven to be approximately 90% effective for treatment of tubal pregnancies when serum hCG levels are below 1,000-2,000 IU/L (32, 34, 35, 36, 37). Thus, our fantasy is that the combined influence on the different effector systems underlies the therapeutic effect. Certainly, more work is to be done to clarify the mechanism of action, the clinical efficacy as well as the long term results in terms of fertility in women subjected to this new treatment.

Concluding remarks

To conclude, prostanoids possess powerful actions on tubal contractility, which in turn appear to be crucial for normal ovum transport. The ultimate proof for a critical role of PGs in the control of human ovum transport is still lacking, although accumulating evidence suggest that inhibition of PG biosynthesis will abolish or disturb tubal motility. If specific inhibitors of different PGs will become available, this may certainly promote a more detailed exploration of the role of PGs in the biology - and the patophysiology - of the oviduct.

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