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General Editors: J. TUOMISTO & M. K. PAASONEN

Volume 5

CLINICAL PHARMACOLOGY

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M. J. MATTILA

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Preface

The International Union of Pharmacology (IUPHAR) held the Sixth International Congress of Pharmacology in Helsinki, Finland on 20–25 July 1975. The scientific programme was organised with the help of the International and Scandinavian Advisory Boards and it consisted of 15 invited lectures, 20 symposia, 5 seminars on methods, and volunteer papers, some of them as poster demonstrations. Altogether 1580 communications were delivered by the 2 600 active participants attending the Congress.

The texts of the invited lectures and symposia have been included in the Proceedings of the Congress. It is readily noticeable that all the major areas of pharmacology, including clinical pharmacology and toxicology, are well represented. Special attention has been paid to several interdisciplinary areas which are on the frontiers of pharmacology and have connections with physiology, biochemistry and endocrinology. Many of the topics are of special interest to internists, psychiatrists, neurologists and anaesthesiologists. Chapters on the abuse of alcohol, new teaching methods and the conservation of wild animals reflect the wide scope of the Congress.

One can hardly imagine any other Congress Proceedings where more world-famous authors representing pharmacology and the related sciences have reported the most recent developments in their special fields. The invited lectures give a particularly clear introductions to the areas in question, even for those previously unfamiliar with them.

For the first time the Proceedings of an International Pharmacology Congress have been produced by the photo offset-litho process. This method was chosen in order to publish the volumes in the shortest possible time. It clearly demands the emphasis be placed upon the scientific content of the volumes, possibly at the expense of retaining some infelicities of style or presentation.

We are convinced that these Proceedings present a unique opportunity to keep abreast of the latest developments in pharmacology and related areas of research. Our sincere thanks are due to the authors, the members of the advisory boards and our colleagues of the Programme Committee for making the scientific programme of the Congress so successful and the publication of the Proceedings possible.

The Editors

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Invited lectures

PROSTAGLANDINS AND REPRODUCTION

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Introduction

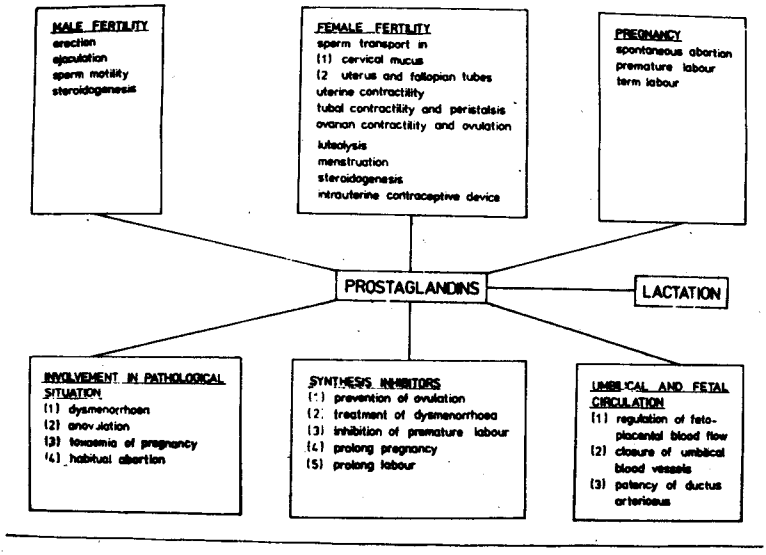
Although the involvement of prostaglandins extends to almost all branches of medicine, it is in the field of reproduction that they have evoked widest interest and have found practical applications.

Since their discovery in human seminal fluid in the 1930s prostaglandins have been shown to be present in many organs of the reproductive system and associated secretions. Consequently, various physiological roles, both in male and female reproductive processes, have been ascribed to these compounds. Deficiency or overproduction of prostaglandins have also been implicated in the disturbance of some reproductive functions. The pharmacological actions of prostaglandins on various aspects of reproduction have been extensively studied.

From the large number of studies reported so far it has become quite evident that prostaglandins hold a key position in the common pathway through which hormones and drugs exert control over different aspects of reproduction. However, there are gaps in our understanding of the precise role of prostaglandins in reproductive system and the basic mechanisms of their pharmacological action.

The task of the reviewer, in a field where the literature has expanded at an explosive rate, is a difficult one. The situation is further complicated by the fact that often different experimental models are used and there seems to be considerable inter-species variation. For these reasons the present review will be confined mainly to prostaglandins and human reproduction. References to animal studies will be made where relevant or in areas of particular interest where no human data are as yet available.

The involvement of prostaglandins in various physiological and pathological processes associated with human reproduction is illustrated in Fig. 1. Development of clinical application is based on either mimicing these effects by exogenous prostaglandins or, in pathological situations, by preventing their synthesis.



PROSTAGLANDINS AND THEIR INHIBITORS: MODULATION AND MEDIATION OF REPRODUCTIVE PROCESSES

Male Reproduction

It is almost forty years since prostaglandin were first discovered in the human seminal fluid. However, physiological significance of their presence in the seminal fluid is still far from established. Prostaglandins in the male have been implicated in theprocesses of erection, ejaculation, sperm motility and morphology, testicular and penile contraction and in steroidogenesis. Being potent inhibitors of lipolysis they may also play an important role in the stabilization of cell membranes.

Human seminal fluid is rich in prostaglandins belonging to four groups - PGA, PGB, PGE and PGF (1). Although seminal vesicles have been shown to be the major source of prostaglandins the possibility that other glandular systems may also contribute towards the seminal fluid prostaglandins cannot be ruled out.

Recent studies have thrown some doubt on the presence of 19-OH PGA and 19-OH PGB compounds in human seminal fluid. Taylor and Kelly (2) have shown that the main 19-hydroxy prostaglandins of the semen are of the E series - 19-OH PGE_1 and 19-OH PGE_2 (average total concentration of 100 µg/ml). Kelly and Taylor (3) have also shown that 19-hydroxylated

compounds are absent in the semen of the bull, ram, boar, stallion and rabbit - but are present in the semen of chimpanzee. The biological significance of these findings is not clear.

Seminal Prostaglandin and Male Fertility

There does not appear to be a correlation between prostaglandin content of the seminal fluid and the number or degree of motility of spermatozoa. Similarly addition of pure prostaglandin to spermatozoa does not affect spermatozoal activity. However, there seems to be a correlation between deficiency of E prostaglandins in seminal fluid and male infertility. Semen samples from men in infertile marriages contain less PGE compounds than semen samples from men with recently documented fertility (1). Since prostaglandins do not seem to affect sperm motility or morphology the infertility associated with prostaglandin deficiency could be due to their diminished effects on (a) cervical mucus (see later) or (b) sperm transport through the cervix by an action on uterine and tubal motility.

It is possible to reduce the content of prostaglandins in the seminal fluid by aspirin. Aspirin given in therapeutic doses reduced both PGE and PGF in the semen of healthy males (4, 5). Whether reduced levels of prostaglandins had any effect on the number of sperms and motility or on erection and ejaculation was not reported.

Erection and Ejaculation

Because of their smooth muscle stimulating and vasodilator actions Goldblatt (6) and Euler (7) suggested that prostaglandins may be involved in the emptying of the genital glands and the maintenance of peristalsis involved in ejaculation. However, up till now the role of prostaglandins in the process of erection and ejaculation has remained unexplored. Virtually nothing is known of their effect on the smooth muscle of the human seminal vesicle, testicular capsule and other parts of the male reproductive system. Prostaglandins are present in rat and rabbit testicular tissue (8). It has been suggested that they participate in regulating capsular motility and may also be responsible for contractility of the seminiferous tubules. While PGE_1 decreases the resting tone and frequency of spontaneous rhythmic contractions of the rabbit testicular capsule, $PGF_{1\alpha}$ increases the tone and frequency of contraction (9, 10).

Recently in vitro effects of prostaglandin on corpus cavernosa muscle from the human penis have been studied (11). Prostaglandin E_1 added to spontaneously contracting strips of cavernosa muscle caused a reduction in frequency of spontaneous contractions and resting tone. PGE_2 had a similar effect at low doses. In contrast prostaglandins A_1, A_2, B_1, B_2 and $F_{2\alpha}$ increased the tone and frequency of contractions of the penile muscle. PGA_2 was found to be most potent. In view of its known potent vasodilator action

it is possible that PGA_2 could play a role in erection and ejaculation. The resting tone and spontaneous activity of the human penis in vitro are also likely to be due to prostaglandin produced by the tissue since both are abolished by prostaglandin synthesis inhibitors.

Steroidogenesis

Very little information is available on the effect of prostaglandins on steroidogenesis in the male. Eik-Nes (12) showed that PGE_2 infused into the spermatic artery caused a gradual increase in testosterone secretion. In the rat however, administration of prostaglandins E_1, E_2, $F_{1\alpha}$, $F_{2\alpha}$, A_1 and A_2 significantly decreased serum testosterone levels (13). Prostaglandin $F_{2\alpha}$ also decreased plasma testosterone levels in mice (14).

Female Reproduction

More work has been carried out to evaluate the physiological involvement of prostaglandins in various aspects of female reproduction than in any other area. Similarly the pharmacology of the female genital tract in relation to prostaglandins has been extensively studied. As a direct result of this (a) substantial evidence has accumulated to implicate prostaglandins in several aspects of female reproduction (b) clinical uses of prostaglandins and their synthesis inhibitors have been developed.

Sperm transport in cervical mucus

It has been suggested that prostaglandins in the seminal fluid and in the female genital tract may have an influence on the passage of sperms through the cervical mucus. Eskin et al (15) studied the effect of $PGF_{2\alpha}$ and PGE_2 on sperm motility, sperm penetration and spermatozoa drive through cervical mucus obtained from normally cycling women. All three parameters increased significantly when $PGF_{2\alpha}$ (250 ng/ml) was added to the mucus specimen before incubation with spermatozoa. PGE_2 had very little effect. From these results the authors suggest a potential use of prostaglandins ($PGF_{2\alpha}$) in the treatment of infertility.

The modulation of sperm transport through cervical mucus by prostaglandins raises some interesting questions. Do other naturally occurring prostaglandins have the same effect as $PGF_{2\alpha}$? Does cervical mucus contain prostaglandin metabolizing enzymes? Are female infertility and the mechanism of action of oral contraceptives due to an alteration in the concentration of these enzymes? Is the relationship between deficiency of seminal prostaglandins and male infertility due to a lack of or reduced effect of prostaglandins on sperm penetration?

Ovulation

Evidence for the role of prostaglandins in ovulation is mainly derived from animal sutdies. These findings have aroused considerable interest because of important implication in the area of fertility control.

It has been known for sometime that prostaglandin-like material is present in the ovarian tissue (16, 17). However, their precise distribution with respect to various ovarian compartments (corpus luteum, follicle and interstitium) is still not known.

There is sufficient experimental evidence to support the hypothesis that ovarian prostaglandins are involved in the rupture of the follicles in rabbits, rats, swine and rhesus monkey.

1. In all these species F prostaglandins increase several-fold during the pre-ovulatory period, reaching a maximum level shortly before ovulation (18, 19).
2. In rabbits and rats the increase in PGF can be induced by exogenous luteinizing hormone (LH) (18).
3. Ovulation can be blocked by intrafollicular injection of either indomethacin or prostaglandin antiserum (20).
4. Indomethacin blocks ovulation even when administered after the LH surge (21, 22, 23).
5. Follicles in which ovulation is blocked by indomethacin go through luteinization without impairment of their hormonal pattern (21, 24).
6. Administration of $PGF_{2\alpha}$ to rabbits increases the frequency and amplitude of ovarian contraction and the ovary is more responsive to prostaglandin prior to ovulation.
7. $PGF_{2\alpha}$ also produces contractions of human ovary in vivo (25, 26).
8. Intrafollicular injection of $PGF_{2\alpha}$ in rabbits cause release of ova (18).

These results collectively implicate $PGF_{2\alpha}$ in the rupture of the follicle and release of ovum.

Tubel Contractility - Egg Transport

The suggestion that prostaglandins have a possible role in tubal motility comes from experiments carried out in human, monkey, sheep and rabbit. Essentially two different experimental approaches have been used.

1. Effect of prostaglandins on tubal motility both in vivo and in vitro.
2. Effect of prostaglandins on the transport of eggs through the fallopian tubes.

Human fallopian tubes contain both $PGF_{2\alpha}$ and PGE_1 (27) which are localized in the oviductal mucosal surface before ovulation but in the oviductal

lamina propria after ovulation. No $PGF_{2\alpha}$ was found in the postpartum or postmenopausal oviduct (28).

The mediation by prostaglandins of the in vitro spontaneous activity of the human fallopian tubes was reported by Myatt et al (29). Their results suggest that motility of the medial and lateral halves of the tube, at different phase of the menstrual cycle is dependent on the generation of prostaglandins.

Effect of exogenous prostaglandins on tubal motility have been studied by several investigators. Sandberg et al (30) showed that the response of the human fallopian tube in vitro to prostaglandins was dependent on the type of prostaglandin used and the anatomical position of the tube studied. Prostaglandins E caused a contraction of the proximal quarter of the fallopian tube but relaxed the strips from the distal three quarters of the tube. On the other hand $PGF_{2\alpha}$ contracted all sections of the tube. The authors have postulated that the predominance of E prostaglandins in the semen may result in contraction of the proximal section and relaxation of the rest of the tube. Such an effect could result in suction allowing the entrance of the ovum into the tube and its retention in the middle part of the oviduct until fertilisation. The relaxant effect of E prostaglandins and stimulant effect of F prostaglandins on the fallopian tube in vivo has been confirmed (26).

The effect of prostaglandins on the transport of ovum through the fallopian tube have been carried out mainly in laboratory animals. Results are often contradictory. Subcutaneous administration of $PGF_{2\alpha}$ to rabbits severely disturbed egg transport. An autopsy, two days after ovulatory dose of hCG either no eggs could be found or they were found in the uterus or vagina whereas in control rabbits they were confined to the fallopian tubes. PGE_2 had no effect (31). In the hamster on the other hand prostaglandins have no effect on egg transport (32).

Luteolysis and Menstruation

Prostaglandins E_2 and $F_{2\alpha}$ are present in human menstrual fluid and in endometrial curettings obtained during the proliferative and secretory phase of the menstrual cycle. Prostaglandin-like activity in peripheral blood obtained during menstruation has also been reported (17). Attempts have been made to correlate the levels of prostaglandins in the endometrium and in peripheral circulation with luteolysis and onset of menstruation. Endometrial prostaglandins E_2 and $F_{2\alpha}$ increase progressively in the luteal phase of the cycle and reach a peak at the time of menstruation (33). This coincides with the declining phase of progesterone level. Two possibilities exist. In presence of declining progesterone level prior to the onset of menstruation prostaglandins produce a marked in crease in uterine activity causing disintegration of the endometrium and onset of menstruation or alternately the increasing levels of prostaglandins during the late luteal phase produce a regression of the corpus luteum and consequently onset of menstruation.

Measurements of plasma prostaglandin levels in relation to menstrual cycle have so far given inconsistent results. This may partly be due to technical difficulties involved in measuring plasma levels of prostaglandins (34).

The importance of corpus luteum in the normal menstrual cycle and in the maintenance of early pregnancy is well established. In the human its life span during normal menstrual cycle is 12-14 days after which it regresses. However, if conception occurs the life span of the corpus luteum is extended and it continues to actively secrete progesterone which is essential for the maintenance of pregnancy for the first 8 weeks.

In several animal species including the sheep, guinea pig, rat, hamster and cow regression of the corpus luteum is controlled by the uterus. Removal of the uterus in these species results in prolongation of life span of the corpus luteum. In the sheep, rabbit and the guinea pig there is considerable evidence to show that prostaglandin $F_{2\alpha}$ is the natural luteolysin. Exogenous $PGF_{2\alpha}$ in all these species causes premature regression of the corpus luteum (for reference see 35, 36).

In primates however, the natural luteolysin does not seem to originate from the uterus since hysterectomy is without effect on the life span of the corpus luteum (see 37 for references). However it is still possible that prostaglandin is natural luteolysin in these species since :

1. They are found in the ovary of the monkey and in human corpora lutea (36, 38).
2. Administration of $PGF_{2\alpha}$ directly into human corpus luteum produces a marked fall in plasma progesterone (39).

Earlier attempts to induce luteolysis in non-pregnant sub-primates were disappointing (40). However, Shaikh and Klaiber (41) have recently shown that oestradiol and prostaglandins given sequentially shortened menstrual cycle length in monkeys.

Several attempts have been made to demonstrate a luteolytic action of $PGF_{2\alpha}$ in non-pregnant cycling women. In these studies prostaglandins have been administered by the intravenous, intrauterine and intravaginal routes (for reference see 34). Overall results have been equivocal and if given by these routes prostaglandins are not luteolytic in the non-pregnant cycle. Possible reasons for this could be that (1) since naturally occurring prostaglandins are rapidly metabolised and inactivated sufficient amount does not reach the corpus luteum. (2) since the sensitivity of the corpus luteum to prostaglandins varies during the luteal phase, the time of administration of prostaglandins may be important. In contrast to the non-pregnant cycle, a marked depression in progesterone level is observed when prostaglandins are administered during early pregnancy in human and monkeys (for reference see 34, 42). Since functional corpus luteum is essential in early pregnancy and it is also the major source of progesterone at this stage