PROSTAGLANDINS AND THE REPRODUCTIVE SYSTEM

by

SISIR K. MAJUMDAR, B.Sc., M.B.B.S. (Cal.)

Introduction

Prostaglandins are a generic name for a family of closely related biologically active lipids. Chemically all are unsaturated hydroxy-carboxylic acids derived from the mother substance—prostanoic acid. The name—"prostaglandins" was given to a smooth muscle stimulating lipid of unknown structure, which was discovered in human seminal plasma by Euler (1935). Substances with similar biological activity were found in the seminal plasma of sheep and in extracts of prostate and vesicular glands (Euler, 1936).

Prostaglandin is a new letter is the alphabet of intrinsic biochemical system controlling the human body. Prostaglandins possess an astonishingly wide range of pharmacological as well as physiological activities in vanishingly small amounts. It is probably a neurotransmitter and a powerful stimulant of gastric secretion.

Resurrecting the prophetic comment of Sir Willium Boyd regarding the anti-hypertensive role of kidney, a new provocating hypothesis implicating a reno-medullary prostaglandin as that long-sought renal anti-hypertensive factor has been put forward recently by this author (Majumdar, 1971).

There are about 14 naturally occurring prostaglandins which are 20 carbon fatty acids containing a cyclopentane ring. However, in obstetrical practice PGE, PGE_1, PGE_2 and $PGF2\alpha$ are generally used. The prostaglandins are synthesized under the influence of prostaglandin synthetase from some of the essential fatty acids—arachidonic acid, linolenic acid and pentaenoic acid. It is present in brain, lung, thymus, pancreas, kidney and human seminal fluid is the richest source (100 ug/ml).

Action on Uterus

In 1930 Kurzok and Lieb of New York reported that strips of myometrium taken from fertile women relaxed in the presence of human semen but similar strips from infertile women contracted and the active principle concerned was a mixture of prostaglandins, since they have been isolated from human seminal plasma. Following normal coitus prostaglandins originating from seminal plasma are absorbed from the vagina in amounts sufficient to affect smooth muscle tone in the female reproductive tract. It may be concerned with either sperm transport or retention of the ovum within the fallopian tube until fertilisation has taken place. It may also be relevant that prostaglandin constricts placental vessels.

The uterine activity produced by prostaglandin infusion in pregnant women resembles that of normal spontaneous labour. Incidentally, PGE_2 and $PF2\alpha$ have been found to present in human amniotic fluid during labour and in the decidua; $PF2\alpha$ is released in maternal

Department of Pharmacology and Therapeutics, The National Medical College, Calcutta, India.

Received for Publication on 21-2-1972.

circulation during labour in close relation to each uterine contraction and PGE_2 is present in the venous blood of women during labour (Karim *et al*, 1970).

Cervix can exhibit independent contractility. Its largely collagenous structure precludes an ability to show significant contractility. Instillation of seminal fluid into the non-pregnant vagina causes contraction of the corpus, but relaxation of the cervix depending on the phase of menstrual cycle; it is likely to be due to high concentration of prostaglandins in the semen—PGE_2 causes marked relaxation of isolated non-pregnant cervix (Zeeba Nazak *et al*, 1970). Cervix may respond to prostaglandins in an opposite manner to the body of the uterus. Prostaglandins are especially successful in cases where cervix is extremely unfavourable and in some cases where oxytocin has failed.

The role of prostaglandins in parturition is not clear at present, but a possible mechanism in the initiation of labour and for termination of pregnancy by their oxytocic actions has been strongly envisaged, but in considering the total effect, action of prostaglandins on the cervix should be borne in mind. It has been suggested that the prostaglandins found in menstrual fluid may be responsible for the painful spasms of dysmenorrhoea.

Its Mode of Action

Oxytocics are drugs that stimulate the motility of uterus. According to Csapo, Ca++ is the myoplasmic activator and the neurohypophysial oxytocic hormone —oxytocin acts as a Ca++ carrier resulting in the release of Ca++ from the myometrial muscle membrane or it modifies the distribution of membrane Ca++ by a special affinity for some component of the muscle membrane (Csapo, 1961). Prostaglandins have been reported to potentiate and enhance the uterine action of oxytocin when used in combination (Guillespie, 1972). It has been further reported by the same author that prostaglandins stimulate the pituitary directly to secrete more oxytocin and plasma oxytocin levels were found to be higher after prostaglandin infusion (Guillespie *et al*, 1972). It is highly likely that both oxytocin and prostaglandins may have identical mechanism of action on myometrium, thereby making them complimentary to each other. The action of prostaglandin is mediated through 3' 5' cyclic adenosine monophosphate (Cyclic AMP) —the intracellular master molecule of hormonal and metabolic control (BMJ, Editorial, 1971). This cyclic AMP is likely to have a modulating and controlling role in the transport of Ca++ which is the final pathway of the uterotonic action of both prostaglandins and oxytocin.

Pharmacological Basis of Therapeutics

The clinical use of prostaglandins as oxytocics is now well established. During the past two years over 500 inductions of labour at term have been carried out with prostaglandins PGE_2 and $PF2\alpha$, the drugs being administered by continuous intravenous infusion.

But after oral administration, PGE_2 and $PGF2\alpha$ are absorbed into the circulation and produce a stimulant effect on the pregnant human uterus. Prostaglandins E_2 and $F2\alpha$ administered orally were used to induce labour in 100 patients between 35 and 44 weeks' of gestation; the usual effective dose of PGE_2 was 0.5 mg and $PF2\alpha$ 5 mg repeated every two hours until labour was established; induction was successful in 79 out of 80 women treated with oral prostaglandins E_2 and in 16 out of 20 women treated with $F2\alpha$ (Karim and Sharma, 1971).

PGE_2 and $PGF2\alpha$ administered by in-

trauterine instillation have been successfully used as abortifacients in 14 patients without any untoward effect (Embrey and Hillier, 1971). It seems likely that prostaglandin-antagonists would prevent spontaneous labour or abortion but selective prostaglandin-antagonists for human use are not yet available.

The intravenous continuous infusion is the widely used method of administration of prostaglandins to induce labour. But subcutaneous, intramuscular or single intravenous injection is unsuitable owing to the very short duration of action. Intravenous infusion of both PGE an F series of prostaglandins cause stimulation of myometrial contractility—in late pregnancy and at term the response was characterized by an increase in the frequency and amplitude of contractions without any appreciable increase in tone. In early months of pregnancy, hypertonus was a feature of the response (Embrey, 1969).

Intravenous continuous infusion of PGE_2 (0.5 ug/min.) successfully induced labour in 50 women at or near term; the uterine activity produced by prostaglandins infusion resembled that of normal spontaneous labour without any unphysiological increase in uterine tonus; the average infusion time was 5.5 hours and the average infusion—delivery interval was 10 hours (Karim *et al*, 1970). Labour was also successfully induced with continuous infusion of 0.05 ug/kg/min. of PGF2α in 29 out of 35 women at or near term without any increase in the resting tone (Karim *et al*, 1969). It has been further reported that intravenous infusion of PGE_2 (effective range—10.2-14.0 ug/kg/min) successfully induced vaginal delivery in 37 out of 40 patients between 29 and 42 weeks gestation without any foetal, maternal cardiovascular or alimentary complications; transient uterine hypertonus was found when infused with 40 ug/kg/min. (Beazley *et al*, 1970).

Traditional oxytocic drug is the neurohypophysial polypeptide hormone-oxytocin. A double-blind trial of oxytocin (Syntocinon) and PGE_2 in the induction of labour in 300 patients resulted in equal success rates for both drugs (Beazley and Gillespie, 1971).

Whether prostaglandin infusion leads to uterine hypertonicity or not is not yet settled beyond doubt. PGE_2 may cause unphysiological elevation of tonus. Roberts and Turnbull reported occurrence of hypertonus in 4 out of 18 cases induced with PGE_2 but labour was successfully induced at or near term in 34 out of 35 cases by combined amniotomy and intravenous infusion of either PGF2α, PGF_2 or PGE_1 (Roberts and Turnbull, 1971). Prostaglandin metabolites or derivatives may give even better results than the compounds available at present. In cases of late pregnancy, reliable measurement of amniotic fluid pressure needs to be carefully monitored to detect any abnormal rise in uterine tone. Allergic reaction to prostaglandins has not yet been reported; being a chemical substance, the likelihood of their being haptens in certain individuals cannot be ruled out. It needs to be kept in mind while using this new drug.

Prostaglandins have also been successfully used in the management of missed abortion, missed labour and hydatidiform mole. Treatment of six cases of missed abortion, one case of hydatidiform mole with intravenous infusion of PGE_2 resulted in complete abortion in all cases and in 14 cases out of 15 patients with missed labour (Karim, 1970).

The pharmacological phenomena of enhancement and potentiation of uterine response occurs respectively when combination of some prostaglandins and oxy-

tocin are given serially and simultaneously to the patient. The clinical application of this phenomena allows small doses of the drugs to achieve the same effects as a large dose given alone. In a pilot study of the use of prostaglandins E or F for the induction of midtrimester abortion seven of nine women were aborted within 48 hours without any side-effect (Gillespie, loc. cit.). A physiological role for the prostaglandins in parturition, whereby these substances cause the uterus to contract by enhancing the myometrial response to circulating endogenous oxytocin can at present be an interesting hypothesis; however, estimation of plasma oxytocin and prostaglandins during labour needs to be done (Gillespie, loc. cit.).

Fertility and Prostaglandins

The possibility that prostaglandins help the fertilization process is a more disputed one. It is known, however, that prostaglandins from the seminal fluid are absorbed from the vagina after coitus and it may be that sufficient quantities are taken up to affect the motility of the reproductive tract, promoting the transport of spermatozoa into the tubes or holding the ovum in a favourable position for fertilization. There is some slight evidence that male infertility may sometimes be attributable to deficiency of seminal prostaglandin.

Although their physiological role in the reproductive system may be to assist pregnancy and labour, the prostaglandins (particularly PGE_2 and $PGF2\alpha$) have antifertility effects when administered in pharmacologically active doses. In experimental animals they delay implantation, reduce the number of implantation sites, promote resorption of successfully implanted sites and cause an accelerated regression of the corpus luteum—(Crossland, 1971). It seems likely that these prostaglandins have a potential future as contraceptive agents.

Conclusion

It seems highly likely that prostaglandins have some positive correlation with the fundamental process of initiation of labour at the molecular level; its role in fertility and in contraception holds out a new promise for tomorrow. What actually triggers off the end of term in pregnancy is still a riddle wrapped in mystery—prostaglandins may hold the signal-key in unravelling this eternal riddle. Thoughts of today may be facts of tomorrow. Various prostaglandins elaborated so far are craving for specific physiological assignments in the complex human system as the roaming actors searching for a role in Nobel Laurate Italian dramatist Pirandello's—"Six characters in search of an Author."

Acknowledgements

Grateful thanks are due to my teacher Dr. N. N. Roy Chowdhury M.B.B.S., D.G.O., Ph.D. (Cal.), M.R.C.O.G. (Lond.). F.R.C.S. (Edin.), Reader of the Department of Gynaecology and Obstetrics, R. G. Kar Medical College, Calcutta and also to my colleague Dr. Ajoy K. Ghose, M.B.B.S., D.G.O., M.O. (Cal.), M.R.C.O.G. (Lond.), Assistant Professor of Gynaecology and Obstetrics, Calcutta National Medical College for valuable suggestions.

References

1. Beazley, J. M., Dew Hurst, C. J. and Gillespie, A.: J. Obst. & Gynec. Brit. Cwlth. **77: 193, 1970.**
2. Beazley, M. J. and Gillespie, A.: Lancet, **1: 152, 1971.**
3. Crossland, J.: The Practitioner. **207: 567, 1971.**
4. Csapo, A.: "Oxytocin", eds. Heller,

H. and Caldeyro Barcia, R. London, 1961, Pergamon.
5. Editorial (Nobel Prize): Brit. Med. J. 4: 188, 1971.
6. Embrey, M. P. and Hillier, Keith: Brit. Med. J. 1: 588, 1971.
7. Embrey, M. P.: J. Obst. & Gynec. Brit. Cwlth. 76: 783, 1969.
8. Euler, U. S. Von: J. Physiol. (Lond.), 88: 213, 1936.
9. Euler, U. S. Von: Klin, Wachr. 14: 1182, 1935.
10. Gillespie, A.: Brit. Med. J., 1: 150, 1972.
11. Gillespie, A., Hilary, C., Brummer, T. and Chard: Brit. Med. J., 1: 543, 1972.
12. Karim, S. M. M.: Brit. Med. J. 3: 196, 1970.
13. Karim, S. M. M., Hillier, K., Trussell, R. R., Patel, R. C. and Tamusange, S.: J. Obst. & Gynec. Brit. Cwlth. 77: 200, 1970.
14. Karim, S. M. M. and Sharma, S. D.: Brit. Med. J. 1: 260, 1971.
15. Karim, S. M. M. and Hillier, K.: J. Obst. & Gynec. Brit. Cwlth. 77: 837, 1970.
16. Karim, S. M. M., Trussell, R. R., Hillier, K. and Patel, R. C.: J. Obst. & Gynec. Brit. Cwlth. 76: 769, 1969.
17. Kurzok, R. and Leib, C. C.: Proc. Soc. Exp. Biol. Med. 28: 268, 1930.
18. Majumdar, S. K.: (Editorial) J. Indian. Med. Assoc. 57: 105, 1971.
19. Roberts, G. and Turnbull, A. C.: Med. J. 1: 702, 1971.
20. Zeeba Najak, Keith Hillier and Karim, S. M. M.: J. Obst. & Gynec. Brit. Cwlth. 77: 701, 1970.