Prostaglandins

The most recent work on the chemistry and physiology of prostaglandins, as well as their clinical applications, was presented at the third international conference on prostaglandins in New York City on 17 to 19 September 1970, under the auspices of the New York Academy of Sciences. The organizers and cochairmen of the meetings were two scientists prominent in prostaglandin research, Jane E. Shaw and Peter W. Ramwell.

The initial introductory lecture was given by Nobel laureate U. S. von Euler, the Swedish pioneer in the field. Von Euler, in 1935, gave the name prostaglandins to this class of biologically active lipids. Thirty-five years later, this misnomer is firmly entrenched as the generic name for a group of compounds that have ceased to be obscure, but are now of tremendous importance, including the possibility that prostaglandins may be a means of once-a-month birth control.

Chemistry

The first day of the conference was devoted to chemical and pharmacological progress reports. Several groups discussed different methods of total synthesis to obtain prostaglandins. E. J. Corey (Harvard) reported on various routes of synthesis, particularly an efficient 16-step process incorporating a resolution, leading in a stereoselective manner to $PGF_{2\alpha}$. It was estimated that, if this were scaled up, it could eventually produce prostaglandins at a cost of $10 per gram. J. Fried described the preparation of some 7-oxaprostaglandins of special interest as antagonists of the natural materials in various biological systems in vitro. The synthesis of biologically active prostaglandin analogs (3-oxa-15-methyl) at the Upjohn Company was described by G. L. Bundy. These analogs were designed as specially modified structures that would not be substrates for the various enzymes that metabolize prostanoic acids. Bundy also described the conversion of prostaglandins derived from the coral *Plexaura homomalla* to $PGF_{2\alpha}$ and PGE_2. Clearly, the chemical reports indicate that, over the next few years, prostaglandins will become relatively easily available, and that costs will be low enough to make their commercial production, if required, a viable operation. The Upjohn spokesmen also thought that the methods of synthesis which will eventually be used in large-scale operations have not yet been disclosed.

Factors controlling the biosynthesis of prostaglandins from unsaturated fatty acids were discussed. The substrate specificity of the cyclizing enzyme was studied by D. A. Van Dorp, who described the conversion of novel unsaturated fatty acids to biologically active prostaglandin (for example, Δ^2-prostaglandins). A particularly important paper on metabolism in rat, guinea pig, and man was given by B. Samuelsson; he also described a novel analytical technique combining gas chromatography, mass spectrometry, and reverse "isotope dilution" which would permit the detection of subnanogram amounts. Analysis of the metabolites in human urine led to the finding that about 100 μg of the E group of prostaglandins are made by the body each day, and the endogenous amounts of PGE_2 in the plasma of normal subjects was 700 pg/ml.

Using the standard, gerbil-colon bioassay, P. J. Piper reported that PGE_2 and $PGF_{2\alpha}$ were released after changes occurred in the cell membrane as a result of smooth-muscle contraction, anaphylaxis, or mechanical squeezing or stirring. It was suggested, therefore, that the amounts of prostaglandins in tissues under physiological conditions could be much lower than those reported.

Polyphloretin phosphate antagonizes the smooth muscle–stimulating actions of E and F prostaglandins. Kenneth Eakins demonstrated that this compound acts in vitro to block the effect of $PGF_{2\alpha}$ on the rabbit blood pressure and intraocular pressure. J. H. Sanner reported prostaglandin inhibition with a dibenzoxazepine hydrazine derivative and with morphine. The availability of antagonists should stimulate the use of these agents for physiologic experimentation. Information may be gained as to the role of endogenous prostaglandins by specific inhibition. Furthermore, prostaglandin antagonists may prove to have clinical value, for example, in the treatment of premature labor and glaucoma.

Physiology

On the second day of the meeting the physiologists took over. J. B. Lee reviewed his work on establishing the presence of PGA_1 and PGE_2 in the renal medulla and discussed his thesis that prostaglandins in the kidney participate in the regulation of blood pressure and sodium excretion. Infusion of PGA_1 into six patients with essential hypertension produced diuresis and naturiesis, and a subsequent decrease in blood pressure with a return of urine flow and electrolyte excretion toward control values. Thus there is an initial renal effect, leading to intravascular volume depletion which, associated with peripheral vasodilation, lowers the blood pressure. In three normal patients, PGA_1 infusion resulted in no change in renal venous concentration of renin, whereas in three patients with hypertension, renin went down in two and up in one.

One of the prominent features of prostaglandins is the ubiquitous nature of these fatty acid derivatives. J. E. Shaw presented evidence that not all cell types synthesize or metabolize prostaglandins; she further showed that prostaglandins are not required for the functioning of an adenyl cyclase system in the erythrocytes of the turkey, which has nucleated red blood cells. Ion movements and cyclic adenosine monophosphate (AMP) formation were not influenced by PGE_1.

G. W. G. Sharp paid tribute to those who have spent a lifetime studying the toad bladder and reviewed the effects of prostaglandins on this animal model. The stimulatory effect of PGE_1 on sodium transport across the toad bladder is mediated by cyclic AMP. On the other hand, PGE_1 inhibits water flow induced by antidiuretic hormone and theophylline, apparently by inhibiting adenyl cyclase. Perhaps these studies indicate that two adenyl cyclases exist in toad bladder, one for water flow and one for sodium transport.

F. Coceani and G. R. Siggins reviewed their work with prostaglandins in the spinal cord of the central nervous system. Coceani showed that PGE_1 and $PGF_{1\alpha}$ are released in increased amounts when the lateral column fibers of the frog spinal cord are stimulated but that stimulation of dorsal roots did not alter the basal output of PGE_1 although it raised the rate of $PGF_{1\alpha}$ release.

PGE_1 and PGE_2 reversibly block Purkinje cell responses to norepineph-

rine in the cerebellum of the rat and rabbit. Siggins reported on the histochemical localization of prostaglandin dehydrogenase activity in the brain. The heaviest staining was found in the cerebellar cortex, particularly in molecular and Purkinje cell layers where norepinephrine fibers are most prevalent. Siggins suggested that Purkinje cells may utilize endogenous prostaglandins to modulate postsynaptic responsiveness to particular chemical synaptic inputs.

The paradox of the luteolytic effect of $PGF_{2\alpha}$ in vivo as compared to the steroidogenic effects of prostaglandins in vitro was not resolved. J. M. Marsh demonstrated that PGE_1 and PGE_2 stimulate the adenyl cyclase enzyme of homogenates of bovine corpora lutea to about the same degree as luteinizing hormone (LH). Among the prostaglandins tested, $PGF_{2\alpha}$ was least effective but still stimulatory. The stimulatory effect of LH was additive to that of PGE_2, an indication that prostaglandins are not mediators of LH stimulation, evidence contrary to that of Kuehl's work with antagonists [*Science* **169**, 883 (1970)].

Despite this stimulatory effect of prostaglandins in vitro, the luteolytic effect of $PGF_{2\alpha}$ is fairly well established. Indeed, E. W. Horton presented evidence that $PGF_{2\alpha}$ may be the uterine luteolysin active in the guinea pig. An assay utilizing a combination of gas chromatography and mass spectrometry identified $PGF_{2\alpha}$ in uterine venous blood after in vitro distension of the uterus or with estrogen treatment in vivo; both experimental conditions are known to have luteolytic effect.

H. R. Behrman could produce an acute decrease in progesterone secretion with $PGF_{2\alpha}$ both in unoperated and hypophysectomized rats, an effect which could be overcome by LH only in unoperated animals, suggesting an antagonistic action between $PGF_{2\alpha}$ and LH. Behrman did not find any changes in ovarian venous blood flow, a subject which was discussed the next day.

Reproduction

The final clinical session appropriately was introduced by Sune Bergstrom (Karolinska Institute) who has played a key role in bringing prostaglandins from relative obscurity to their present level of interest. He emphasized the importance of cooperation between academic centers throughout the world and industry and gave recognition to the Upjohn Company, whose efforts have enabled the study of prostaglandins to reach a stage where practical medical results are a realistic possibility.

Bruce B. Pharriss, the first investigator to demonstrate the luteolytic effect of $PGF_{2\alpha}$ in vivo, reviewed the evidence favoring $PGF_{2\alpha}$ as the long-sought-for uterine luteolysin and presented data which suggested that the mechanism of action is a reduction of blood flow through the ovary. Pharriss also showed that the luteolytic effect of $PGF_{2\alpha}$ could be overcome by LH or human chorionic gonadotropin (HCG). J. A. McCracken presented work in sheep whose ovaries had been autotransplanted to the neck. Radioactive $PGF_{2\alpha}$ injected into the uterine vein was found to concentrate several-fold in the ovarian artery, indicating a selective cross-current concentration of $PGF_{2\alpha}$. Furthermore, infusion of $PGF_{2\alpha}$ reduced progesterone secretion with a decrease in ovarian blood flow. As noted, Behrman did not find blood flow changes in the rat, and this possible mechanism of action requires more investigative work.

Pertinent to this need for more research was the paper by K. T. Kirton on a series of successful abortions in rhesus monkeys by means of PGE_2 and $PGF_{2\alpha}$ intravenously, subcutaneously, and intravaginally. In addition, $PGF_{2\alpha}$ lowers the plasma progesterone levels in the monkey when given late in the cycle. As measured by continuous recording of intrauterine pressure, PGE_2 was ten times as potent as $PGF_{2\alpha}$, a finding similar to results obtained in humans. These studies indicate that the rhesus monkey is a suitable animal for basic research.

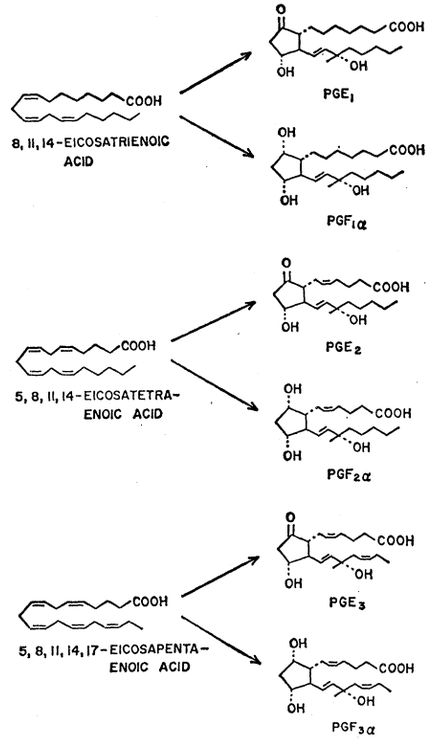

Fig. 1. The six primary prostaglandins and their fatty acid precursors. Each letter corresponds to a particular ring structure. The numeral in the subscript position indicates the degree of unsaturation in the side chains. Substituents below the plane of the ring are in the alpha position. The PGF_β isomers have not been found in nature.

The highlight of the meeting, at least to the assembled press corps, centered about the results in human clinical studies presented by S. M. M. Karim of Uganda, M. Bygdeman and N. Wiqvist of the Karolinska Institute, and G. G. Anderson of Yale.

Bygdeman presented a series of therapeutic abortion attempts, in 69 women, with the intravenous infusion of $PGF_{2\alpha}$. Patients who were less than 8 weeks pregnant aborted about 90 percent of the time after a 7-hour infusion (25 to 100 μg/min); while patients in the 9th to 16th week of pregnancy aborted completely or partially in only 20 percent of the cases after 13 hours of infusion. As in other series, gastrointestinal side effects were prominent. Therefore, other delivery systems were investigated that would produce high concentrations of prostaglandins in the uterus, without high concentrations in the peripheral blood and without side effects. A series of 12 patients was presented in whom a fine catheter was inserted transcervically to a position between the fetal membranes and the uterus. Injections of $PGF_{2\alpha}$ every 2 hours, with the total dose being about one-tenth of the intravenous dose, resulted in complete or partial abortion in all cases. Bygdeman also reported early work involving routine periodic infusions of $PGF_{2\alpha}$ in a group of women who were late with their menstrual periods. This technique apparently provides an early abortifacient form of birth control.

Karim, who has the widest clinical experience in the field, having used prostaglandins for various purposes in over 1000 women, has decided that PGE_2 rather than $PGF_{2\alpha}$ is the drug of choice in both induction of labor and therapeutic abortions. Indeed, prostaglandin infusions are no longer research projects at Makerere University in Uganda, but rather they have become standard clinical techniques.

Karim reported a double-blind study

in 300 women at term whose labors were induced with infusions of PGE_2, $PGF_{2\alpha}$, and oxytocin. The failures with each group were 4, 33, and 44, respectively. Karim then startled the audience by announcing excellent results in inducing labor with the use of relatively large amounts of oral prostaglandins. This route of administration was previously thought to be ineffective. The amount of oral prostaglandins necessary to produce therapeutic abortions, however, was found to be poorly tolerated, and his group, therefore, used the vaginal route. A series of successful abortions in 45 women was presented with vaginal applications of PGE_2 (20 mg) or $PGF_{2\alpha}$ (50 mg) every 2½ hours until abortion took place. The vaginal-tablet method was also used to bring about menses in 11 of 12 women who were 2 to 7 days past their expected menstrual date.

The Yale report concerned the induction of labor in 42 women in a double-blind study with PGE_2, $PGF_{2\alpha}$, and oxytocin. The results of the study were encouraging but far less spectacular than the results of others. It was emphasized that clinical efficacy trials must be carefully controlled, and several types of discrepancies in other series were pointed out. A need for a objective appraisal of results was stressed.

By popular demand, an extra afternoon session was added as a question and answer forum which served to clarify some issues and to allow more investigators to present some results. It was agreed that the definition of "success" in the clinical abortion studies was being used rather loosely, making comparison between various reports difficult.

The meeting was extremely productive and should do much to stimulate research on this important topic throughout the world. Certainly the possibility has been raised that prostaglandins may be a method of self-administered fertility control with an effect limited to the corpus luteum. However, Raymond L. Vande Wiele, co-chairman of the session on reproduction, rightfully raised a note of caution, urging quality in research rather than quantity, with a close look in the near future at side effects.

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