MEETINGS

Prostaglandins

The prostaglandins (PG's) are a family of lipid acids, originally discovered in semen and seminal vesicles; they have since been shown to be associated with most mammalian tissues. Their physiological roles are not yet clearly defined, but it seems unlikely that they are hormones in the classical sense. Instead, they may be "local hormones," formed within tissues in response to some stimulus; they then exert their effects locally. Their potency and activity in many apparently unrelated biological systems, coupled with ready availability in research quantities, has resulted in much new information about these agents.

Schering AG, Berlin, sponsored an international conference on the prostaglandins in Vienna on 24 to 28 September 1972. Except for reports of analytical methods, the conference emphasized the biological and clinical aspects of the prostaglandins. Among nearly a hundred scheduled presentations and three round-table discussions, nearly every facet of the known activities of prostaglandins was considered.

Analytical methods suitable for determining prostaglandin in plasma or tissue must be sufficiently sensitive to detect a few nanograms. Until recently, only biological assays in which isolated smooth muscle was used were sufficiently sensitive. For some of the natural prostaglandins there are now radioimmunoassays and a chemical mass spectrometric method. Because of their simplicity, radioimmune methods are most suitable for general use, but are limited by specificity of the antibodies. The antibodies against $PGF_{2\alpha}$ are the most specific. The chemical method is specific but complex, requiring combined vapor phase chromatography and mass spectrometry, with the use of deuterated prostaglandins as internal standards and multiple-scanning techniques coupled with on-line computer control. Its greatest utility will probably be to check other analytical methods.

It was pointed out that the concentration of natural prostaglandins in plasma may not always be the most relevant value. Prostaglandins formed in tissues may be converted to a 15-keto metabolite before reaching the bloodstream. Indeed, amounts of this metabolite in the blood are much higher than those of the parent prostaglandin. Both mass spectrometric and radioimmunoassays for 15-keto $PGF_{2\alpha}$ were described.

Until the recent discovery of PGA_2 esters in the sea whip (*Plexaura homomalla*), prostaglandins have been reported only in association with vertebrates. A number of insects and marine invertebrates were surveyed for biosynthetic potential. The gills of carp and lobster were especially active in converting precursor unsaturated fatty acids to prostaglandins. If we assume that these enzymes function to form prostaglandins in the living animal, these findings suggest not only that prostaglandins may play a role in salt and water transport (as has been suggested for the mammalian kidney) but also that prostaglandins may have some fundamental physiological roles throughout the animal kingdom.

After ovulation, the corpus luteum forms in the ovary and produces the hormone progesterone. If the ovum is not fertilized, the corpus luteum then degenerates and another reproductive cycle follows.

There is much evidence that degeneration of the corpus luteum is brought about by a luteolytic factor produced in the uterus. Because $PGF_{2\alpha}$ is a powerful luteolytic agent in rodents, it has been postulated that it may be "the" luteolysin. Proof of such a role, among other things, demands demonstration of production in the uterus, in quantities sufficient to induce luteolysis (and a concomitant fall in progesterone), and also that production be temporally related to luteolysis. In sheep and some rodents, such a role now seems well established. However, in the human the evidence is conflicting. During the menstrual cycle, luteolytic activity may be evident only at certain times, and in any event is not so obvious as in sheep and rodents. During early pregnancy, progesterone from the corpus luteum is required to maintain pregnancy, but this sustained progesterone production continues only so long as pregnancy continues. A prostaglandin-induced fall in progesterone at this time may not necessarily be luteolysis, but may only reflect placental damage secondary to direct stimulant actions of prostaglandin on the uterine muscle.

Prostaglandins E_2 and $F_{2\alpha}$ have been tried for termination of pregnancy from postcoital contraception to induction of labor at term. With respect to inducing abortion, the majority opinion was that PGE_2 or $PGF_{2\alpha}$ would have advantages

over standard methods during the second trimester. Suction curettage is, at present, the favored method during the first trimester. Those investigators who had used both PGE_2 and $PGF_{2\alpha}$ thought that there were fewer side effects (vomiting and diarrhea) with PGE_2. However, if the prostaglandin were administered directly into the uterus, either into the amniotic fluid or into the space between the uterine wall and the fetal membranes, side effects could be reduced. Indeed, incidence of side effects parallels concentrations of prostaglandins in the blood. Simultaneous administration of PGE_2 or $PGF_{2\alpha}$ with oxytocin resulted in more than an additive response, enabling the usual abortifacient dose of prostaglandin to be reduced to about 20 percent and also avoiding side effects.

One of the problems attending suction curettage is adequate dilatation of the cervix. Preliminary studies indicated that dilatation was facilitated by administration of prostaglandin the day before. Suction curettage could then be performed easily as late as the 11th to 12th week of pregnancy. Whether this facilitation is due to relaxation of cervical muscle (as observed in vitro) or to contraction of the body of the uterus is not clear.

A promising improvement in prostaglandin-induced abortions lies in intra-amniotic injection of an analog. With the natural prostaglandins, multiple injections during several hours are usually necessary. The human placenta is especially rich in a prostaglandin-metabolizing enzyme, prostaglandin 15-hydroxy dehydrogenase. The (15*S*)-15-methyl- analogs of $PGF_{2\alpha}$ or PGE_2 methyl ester have, at carbon-15, a methyl group in addition to a hydroxyl. These analogs have been reported not to be substrates for the dehydrogenase enzyme. When such an analog was injected into the amniotic fluid, abortion time was shortened, and usually only a single injection was needed. The side effects were no more than those with the natural prostaglandins.

The parenteral administration of PGE_1, PGE_2, or PGA_1 inhibits gastric secretion in man, dogs, and rats. This inhibition seems to be on the secretory process itself, and seems not to be due to secondary changes in gastric blood flow. In dogs, two synthetic prostaglandins, (15*S*)-15-methyl-PGE_2 methyl ester and 16,16-dimethyl-PGE_2 methyl ester, were found to be many times more potent and longer acting than natural PGE_2. Furthermore, the latter

analog was orally effective in dogs. An unscheduled presentation confirmed that the (15*S*)-15-methyl-PGE_2 methyl ester was orally effective in man. All prostaglandins thus far described from vertebrate sources have an asymmetric carbon atom at position 15 at which there is a hydroxyl group with the *S* configuration (sometimes, less accurately, described as "alpha"). Among many other naturally occurring optically active compounds, the so-called unnatural isomers often have much less biological activity. Such was the case with the depressor activity of (15*R*)-PGA_2, isolated from certain strains of the sea whip. It was, therefore, very surprising to learn that (15*R*)-15-methyl-PGE_2 methyl ester was also an orally effective gastric antisecretory agent in man. The (15*S*) isomer was more potent, but was associated with vomiting and diarrhea. However, at larger but fully effective doses the (15*R*) isomer was without side effects. These data suggest that the gastric antisecretory action of prostaglandins may now have practical application.

Several years ago the principal acute vasodepressor lipid from the medullary portion of the kidney was identified as PGE_2. An antihypertensive role of the kidney, which seems to be associated with the renal medulla, has also been proposed for many years. Since PGE_2 is not only a vasodepressor substance but also has potent natriuretic and diuretic actions, a physiological role for renal prostaglandins has been postulated. Evidence in favor of this hypothesis continues to accumulate.

A pure culture of rabbit renal medullary interstitial cells synthesized prostaglandins. This culture was obtained free from fibroblast contamination by a novel method. Medullary tissue from one kidney was first grown as an autotransplant in the donor rabbit and then used later to establish the cultured cell line.

Histochemical techniques localized prostaglandin synthetase activity in the renal medulla of several rodents, mainly along the collecting ducts and papillae. Prostaglandins E_1, E_2, and $F_{2\alpha}$ were found in human urine, but it is not clear whether these were derived directly from the blood or from biosynthetic processes in the kidney.

An active vasodilator role for renal PGE_2 was suggested by studies on renal autoregulation. In such studies, blood pressure and flow to a dog kidney is controlled. If the pressure of the blood

is reduced, the flow at first diminishes, but then recovers spontaneously toward the initial value by dilatation of the blood vessels in the kidney. In parallel with this autoregulatory dilatation, a PGE_2-like vasodilator appeared in the renal venous blood. Both autoregulation and the appearance of PGE_2 were blocked by indomethacin, an inhibitor of prostaglandin synthesis.

Prostaglandins of the A series are $\Delta^{10, 11}$-prostaglandins formed by dehydration of E series prostaglandins. Prostaglandin A_1 has relatively little smooth muscle stimulating activity, and so would not be detected by the usual biological assay methods used for prostaglandins. This fact may explain why little has been published concerning the presence and possible physiological roles of this prostaglandin. Published studies have primarily dealt with the renal and overall cardiovascular actions of PGA_1, which, at least superficially, resemble PGE_1 and PGE_2. Evidence for a physiological role independent of the kidney was presented. Subdepressor infusions of PGA_1 in man strikingly increased plasma aldosterone, a salt-retaining steroid hormone from the adrenal cortex. This effect was independent of changes in renin, adrenocorticotropic hormone, or serum electrolytes. Support for the concept that PGA_1-controlled secretion of aldosterone came in a participant's comment that a radioimmunoassay has now been developed and that, in rats and in human volunteers, a low-sodium diet increased and high-sodium diet decreased the concentrations of PGA_1 in the plasma.

Convincing evidence that prostaglandins may be one of several mediators of the inflammatory response has been reported, and it has been proposed that nonsteroidal anti-inflammatory agents (for example, aspirin and indomethacin) owe their activity to inhibition of prostaglandin synthetase. This conference added evidence that prostaglandins were associated with the writhing reaction in mice following interperitoneal injection of irritants, were present in the aqueous humor of rabbit experimental uveitis, and were formed by the skin after scalding injury. In contrast, anti-inflammatory actions have also been attributed to prostaglandins. Subcutaneous treatment twice daily of rats with PGE_1, PGE_2, PGA_2, and $PGF_{2\alpha}$ inhibited adjuvant-induced arthritis.

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