Prostaglandins and Cancer

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ABSTRACT

This paper reviews the role of prostaglandins (PGs) in cancer. Specific topics of discussion include: (1) the potential use of PGs as tumor markers, (2) PG mediation of hypercalcemia of cancer, and (3) the use of PG synthesis inhibitors in cancer therapy.

Introduction

The prostaglandins (PGs) are a complex group of naturally occurring 20-carbon fatty acids that are synthesized from arachidonic acid. They have been detected in virtually all mammalian tissues examined to date and appear to play an important role in a wide variety of physiological processes and disease states.

Their synthesis is initiated by the release of arachidonic acid from membrane phospholipids (figure 1). The initial step, which is catalyzed by phospholipase, can be brought about by various types of stimuli including hormonal, nerve, inflammatory or immunological stimulation, and mechanical agitation. The free arachidonic acid can then be metabolized via the lipoxygenase pathway or can react with peroxidase and PG cyclooxygenase to form the endoperoxide intermediates, PGG2 and PGH2. These compounds are then converted to a variety of other biologically active products, the nature of which is determined by the specific tissue enzymes.

The PGs exhibit a diversity of pharmacological effects, all of which appear to be transient. At present, there is no concrete evidence to suggest that PGs are circulating hormones. They appear to act locally, affecting only the activity of the tissue in which they are formed. Although their precise mechanism of action is unclear, the available data suggest that their effects are mediated via calcium and/or the cyclic AMP-adenyl cyclase system.16

Characterization of their biological roles has been difficult because different PGs exhibit opposing effects on the same system. While some PGs are vasoconstrictors (PGF2α and TxA2) and platelet aggregators (TxA2), others are vasodilators (PGE2, PGD2, and PGI2) and inhibitors of platelet aggregation (PGI2). The opposing effects of different PGs are due, in large part, to small differences in structure (figure 2). Of particular importance are substitutions at C-9, the degree of unsaturation in the ring and side chain, and the configuration of the hydroxyl groups at C-11 and C-15.25
Figure 1. Arachidonic acid cascade. Prostaglandin synthesis is initiated by the release of arachidonic acid from membrane phospholipids. The free arachidonic acid is then metabolized via the lipoxygenase pathway or reacts with peroxidase and PG cyclooxygenase to form the endoperoxide intermediates, PGG₂ and PGH₂, which are then converted to a variety of biologically active compounds.

Despite a diversity of their biological effects, these compounds are structurally very similar and, as such, possess similar chemical and physical properties. These characteristics together with the very low endogenous levels of PGs make their detection and accurate measurement extremely difficult. A variety of methods has been used for the quantitation of PGs. Some of the early assays that were developed include biological, enzymatic, and radioimmunoassay techniques. The main advantages of these techniques were their sensitivity and rapid sample throughput. The main disadvantage was their lack of specificity. The chromatographic assays available include both gas and liquid chromatography. These techniques have the advantage of being able to separate and quantitate at the same time; however, they lack sensitivity and sometimes specificity, as some PGs co-elute. Gas chromatography-mass spectrometry (GC/MS) in combination with various separation techniques (high performance liquid chromatography, thin layer chromatography, or open column chromatography) offers both the sensitivity and selectivity needed for the measurement of PGs. The accuracy of the assay is enhanced by the use of deuterated PG analogs which are added to the biological sample and compensate for losses during the work-up procedure by acting as internal standards and as carriers for the small amounts of endogenous PGs present. At the present time, however, this type of assay requires large initial sample volumes and involves time consuming purifications prior to analysis, resulting in low sample throughput.

Prostaglandins appear to be involved in a variety of physiological processes and pathological states, some of which are listed in Table I. This brief review covers, primarily, the role of PGs in cancer, specifically in the following areas: (1) the potential use of PGs as tumor markers, (2) PG mediation of hypercalcemia of cancer, and (3) the use of PG synthesis inhibitors in cancer therapy. These topics have been more extensively discussed in several recent reviews.

Prostaglandins as Tumor Markers

Abnormally high PG concentrations have been detected in both tumor tissue and blood from patients with a variety of endocrine and non-endocrine tumors (Table II). The increases were predominantly in prostaglandins of the E and F series. In gynecological and prostatic carcinomas, however, the primary PG produced appears to be prostacyclin, PGI₂ (measured as its stable non-enzymatic metabolite, 6-keto-PGF₁α).

In studies with human breast tissue, it was found that malignant tumors produced more PGE₂ in vitro than either benign tumors or normal breast tissue. It has also been reported that PG production was greatest in the early stages of cancer development. The highest rate...
of synthesis occurred in tumors associated with bone metastases and in those showing histological evidence of tumor spread (invasiveness).\textsuperscript{4,28} The amount of PG extracted from breast cancer tissue has also been shown to be inversely related to survival time after surgery.\textsuperscript{3} In one study which measured plasma concentrations of the PGE\textsubscript{2} metabolite (13,14-dihydro-15-keto-PGE\textsubscript{2}), there was no significant difference between the concentration in patients with either malignant or benign breast tumors, although in both groups the concentrations were higher than in the control group.\textsuperscript{22} That plasma PG levels were equally elevated in the group of patients with benign, as well as malignant, tumors limits their diagnostic use as markers of malignant disease. The fact that all patients with tumors exhibited higher levels than controls suggests that plasma PGs may be useful in the detection of developing breast tumors of any kind.

Elevated plasma PG concentrations have also been reported in patients with various types of gynecological tumors. Sanders et al\textsuperscript{29} found that plasma PGF concentrations in females with malignant tumors of the genital tract were three to

<table>
<thead>
<tr>
<th>Prostaglandin Involvement in Physiological Processes and Pathological States</th>
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<tbody>
<tr>
<td>Glucose homeostasis and diabetes mellitus</td>
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<tr>
<td>Hypersensitivity and inflammation</td>
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<tr>
<td>Renal function, vascular regulation and hypertension</td>
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<td>Reproductive processes</td>
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<tr>
<td>Hemostasis, thrombosis and thromboembolic disorders</td>
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<td>Pulmonary disease</td>
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<tr>
<td>Gastrointestinal secretion and motility and peptic ulcer disease</td>
</tr>
<tr>
<td>Host defense in cancer</td>
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<td>Hypercalcemia of cancer</td>
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TABLE II
Prostaglandins in Human Tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Prostaglandins</th>
<th>Tissue</th>
<th>Blood</th>
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<tbody>
<tr>
<td>Endocrine Tumors</td>
<td></td>
<td></td>
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<tr>
<td>Medullary carcinoma of thyroid</td>
<td>E₂, F₂</td>
<td></td>
<td>E₂, F₂</td>
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<tr>
<td>Anaplastic carcinoma of thyroid</td>
<td>F₂</td>
<td></td>
<td></td>
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<tr>
<td>Papillary carcinoma of thyroid</td>
<td>E₂, F₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>F₂, F₂₀</td>
<td></td>
<td>E₂</td>
</tr>
<tr>
<td>Phaeochromocytoma</td>
<td>F₂, F₂₀</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Islet cell tumor</td>
<td>F₂, F₂₀</td>
<td></td>
<td></td>
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<tr>
<td>Non-Endocrine Tumors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>E₂, F₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileal, jejunal and rectal carcinoma</td>
<td>E</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonic carcinoma</td>
<td>E, F</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>E, F₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung carcinoma</td>
<td>E, F₂</td>
<td></td>
<td></td>
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<tr>
<td>Breast carcinoma</td>
<td>E, E₂, F</td>
<td></td>
<td>E, E₂</td>
</tr>
<tr>
<td>Carcinoma of cervix, ovary and uterus</td>
<td>E₂</td>
<td></td>
<td></td>
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<tr>
<td>Prostatic carcinoma</td>
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</table>

*Based on data obtained from Karmali, Bennett et al., Malachi et al., Alam et al., Sanders et al., and Khan et al.*

Plasma levels of 6-keto-PGF₁α may also be of potential value for monitoring prostatic cancer. Concentrations of this PG were elevated in patients with M0 and M1 stage carcinomas in comparison to normal controls and patients with T0 carcinoma (table III). In patients with M1 carcinoma, plasma 6-keto-PGF₁α levels were actually found to be a more sensitive and accurate measure of disease status than tartrate labile acid phosphatase.

**Prostaglandin Mediation of Hypercalcemia of Cancer**

Prostaglandin production by tumors is now a recognized cause of the hypercalcemia of cancer.

The first evidence that prostaglandins could induce bone resorption was published in 1970 by Klein and Raisz. They examined the mobilization of calcium from bones of rat fetuses, and reported that PGE₁ and PGE₂ were as effective in causing calcium release as was parathyroid hormone. Subsequently, Harris et al. demonstrated that extracts from benign dental cysts, which induced bone resorption in tissue culture, contained large amounts of prostaglandin-like material, most of which was PGE₂. Addition of prostaglandin synthesis inhibitors to cyst tissue culture medium reduced both the PG-like material released from the cyst and the bone resorbing activity.

five-fold higher than in healthy controls. After radiotherapy and surgical removal of the tumor, there was a decrease in plasma PGF levels in four out of the five women studied. In those patients who subsequently developed advanced disseminated disease, the PG concentrations were markedly elevated when compared to the concentrations at the time of tumor diagnosis. Alam and coworkers reported similar elevations in the PG₁₂ metabolite, 6-keto-PGF₁α, in female patients with both malignant and nonmalignant gynecological tumors. As with PGF, plasma concentrations of 6-keto-PGF₁α were a reflection of the patient’s response to therapy. In patients whose conditions were operable and who responded to therapy, plasma PG levels fell postoperatively and were even lower at follow-up six to 12 weeks later; however, in the inoperable, non-responder group, plasma PG levels remained elevated.

**TABLE III**

Plasma 6-keto-PGF₁α Levels in Patients with Carcinoma of the Prostate

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>6-keto-PGF₁α (pg per ml) Mean ± S.D.</th>
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<tbody>
<tr>
<td>Controls</td>
<td>98 ± 17</td>
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<tr>
<td>Stage To</td>
<td>129 ± 16</td>
</tr>
<tr>
<td>Stage Mo</td>
<td>224 ± 58</td>
</tr>
<tr>
<td>Stage M1</td>
<td>330 ± 18</td>
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</table>
To date, a number of clinical studies have been reported linking increased PGE$_2$ production with the hypercalcemia of cancer. Seyberth and co-workers$^{31}$ demonstrated increased urinary excretion of the PGE$_2$ metabolite (13,14-dihydro-15-keto-PGE$_2$) by nine out of 13 hypercalcemic patients with cancer. With one exception, hypercalcemic patients with primary hyperparathyroidism and normocalcemic cancer patients had normal metabolite levels. All of the patients, except those with hyperparathyroidism, had low or undetectable levels of parathyroid hormone (PTH). In the same study, the authors also examined the effect of prostaglandin synthetase inhibitors (PGSIs) on serum calcium concentrations in hypercalcemic cancer patients having elevated urinary PGE$_2$ metabolite levels either without or with bone metastases and in hypercalcemic cancer patients with normal metabolite levels. In patients without bone metastases, calcium levels returned to normal after treatment, whereas serum calcium levels in patients with bone metastases were only partially reduced. Prostaglandin synthetase inhibitors had no significant effect on the hypercalcemia in cancer patients with normal PGE$_2$ metabolite excretion.

Demers et al$^{10}$ measured circulating plasma levels of PGE in 79 patients with various types of malignancies. Thirteen patients were found to be hypercalcemic, and of these, 10 had elevations of plasma PGE well above the normal range.

Brenner et al$^7$ reported that 10 out of 31 hypercalcemic cancer patients studied had elevated plasma concentrations of PGE. Indomethacin treatment in 14 of these patients caused a significant reduction of serum calcium in three patients, but had no effect on the concentration in the remaining 11 patients. Many of the patients in this study also had inappropriately high levels of parathyroid hormone which complicates the interpretation of these results. The results of these studies$^7,10,31$ nonetheless strongly implicate PGs, particularly PCE, as mediators of the hypercalcemia of cancer, and suggests that inhibitors of prostaglandin synthesis may prove to be valuable tools in treating this particular complication of the disease.

**Prostaglandin Synthesis Inhibitors in Cancer Therapy**

Because significant elevations of certain PGs have been noted in a variety of cancers, the concept that PGSIs might act as anti-cancer agents has become increasingly popular. At the present time, however, the findings are controversial.

The strongest argument for the use of PGSIs as anti-cancer agents is based on clinical studies in which indomethacin, a potent inhibitor of PG synthesis, reduced or completely eliminated the hypercalcemia in the majority of cancer patients with elevated plasma or urine concentrations of PGE and low or undetectable PTH levels.$^7,31$

There are studies, however, in which PGSIs were ineffective in treating hypercalcemic cancer patients.$^7,9,34$ One possible explanation for these results may be the use of a PGI$\mathbin{\text{S}}$ dose that was insufficient to counter an extremely high PG production by large tumors. It is also possible that the hypercalcemia was unrelated to PG production.

In animal studies, PGSIs have been reported to be effective in reducing the rate of tumor growth.$^1,13,16,20$ In mice, indomethacin or aspirin was found to reduce the growth of HSDM$^{35}$ and transplantable methy cholanthrene-induced fibrosarcomas,$^{21,23}$ Maloney sarcoma virus-induced tumors,$^{32}$ transplanted mast-cell ascites tumors,$^{20}$ and Lewis lung carcinomas.$^{20}$ These two PGSIs were also effective in inhibiting the bone destruction.
induced by Maloney sarcoma virus-induced mice tumors, preventing bone metastasis of the Walker carcinosarcoma in rats, and prolonging survival time of mice bearing a transplantable methylocthanthrene-induced fibrosarcoma.

Of greater potential perhaps is the use of PGSIs in combination with conventional anti-cancer therapy. Flurbiprofen, a non-steroidal anti-inflammatory drug and PGSI, enhanced the effects of chemotherapy and radiotherapy on tumor growth in mice. Additionally, flurbiprofen in combination with methotrexate and melphalan prolonged survival and reduced the incidence of local recurrence in mice following removal of the primary tumor.

In sharp contrast to these studies are experiments with the B-16 melanoma cell line in which the opposite effects of PGSIs were observed. In B-16 melanoma tumors, in which the major prostaglandin produced is PGD2 rather than PGE, administration of indomethacin to mice bearing these tumors either had no effect or depressed the immune response even further, resulting in accelerated tumor development.

In view of the conflicting data presented here, it is difficult to reach a simple conclusion as to the role of PGSIs in the treatment of cancer. Since it appears that both human and experimental tumors react to these agents in similar fashion, one could predict that PGSIs will be effective in treating only certain types of cancer, with the response to this type of treatment depending perhaps on the particular prostaglandin produced.

Summary

That certain PGs are markedly elevated in various types of cancer indicates that these hormones may have potential value as sensitive tumor markers for assessing tumor growth and spread and patient response to therapy. An important limiting factor in the use of PGs as tumor markers, however, will most certainly be the development of rapid and simple, yet specific and sensitive, methodology for measuring these compounds.

The results of animal and tissue culture experiments indicate that PGE2 is a potent stimulator of bone resorption. In clinical studies, marked elevations of this PG were noted in conjunction with high serum calcium levels in many cancer patients. Treatment with PGSIs reduced or completely normalized calcium levels, indicating that PGs are important mediators of the hypercalcemia of cancer. Finally, the fact that PGSIs have also been found to reduce tumor growth, prevent bone metastases, and prolong survival time in mice with various types of tumors suggests that they may prove to be valuable therapeutic agents in the treatment of human cancer as well.

References

7. BRENNER, D. E., HARVEY, H. A., LIPTON, A., and


