CHEMICAL SYNTHESIS OF EICOSANOIDS AS PART OF THE ADVANCE OF MEDICINAL SCIENCE

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Modern science and medicine derive from an optimistic philosophy which maintains that through deep thought, research, discovery, and the wise application of new knowledge, human life can be blessed by continuous good health through the elimination or control of disease almost to the end of the full lifespan. Many of the talented scientists who work in my field, the chemical synthesis of complex organic molecules, are dedicated to the long-term realization of this ideal. Their efforts combined with the research of specialists in such fields as biochemistry, molecular and cell biology, physiology, pharmacology, and clinical medicine are the means by which an ever deeper understanding of human health and disease and an increasingly more effective therapy will be achieved.

Organic chemistry and the development of new therapeutic agents

Historically organic chemistry has been intimately involved in the discovery and production of therapeutic agents. Starting in mid-century, the combined use of specific bioassays and large-scale screening of extracts from microorganisms and plants and also of synthetic compounds led an unprecedented outpouring of new and useful medicines, including antibiotics, antifungal agents, antitumor agents, antihistamines, and drugs acting on the cardiovascular and central nervous system. The majority of these therapeutic agents and most of the drugs which have been introduced recently, ranging from antibiotics to substances for treatment of asthma, arthritis, and heart disease, are synthetic. The trend toward synthetic medicinals will accelerate as the power of modern synthesis and the knowledge of disease mechanisms and biochemistry continue to increase.

What are eicosanoids and prostaglandins? Introduction

The eicosanoids (from the Greek word *eicosi*, twenty) are a large family of twenty-carbon, oxygenated molecules which are biosynthesized by many different cell types in the body from 20-carbon (C_{20}) polyunsaturated fatty acid precursors, principally arachidonic acid. They are produced in very small amounts (a few milligrams per day), act close to the site of biosynthesis, and suffer rapid inactivation byenzyme-induced chemical reaction. Eicosanoids serve as local signaling agents which are crucial to short-range cell-cell communication, environment-cell interaction, and regulation of cell secretion or function. The fatty acid for eicosanoid synthesis is liberated by a strictly regulated enzymatic cleavage of phospholipid molecules contained in cell membranes and is transformed into eicosanoids very soon thereafter.The eicosanoids are of paramount interest in biological science and now influence almost every aspect of clinical medicine.

The prostaglandins were the first of the known eicosanoids. Although recognized as bioactive materials more than fifty years ago, it was not until the pioneering work of Sune Bergrström and his group in Sweden during the 1950's and 1960's that the first pure samples of prostaglandins were isolated and their structures were determined. From the early biological studies of prostaglandins, it was learned that they act upon smooth muscle (as opposed to striated muscle) at very low concentration to produce either contraction or relaxation, dependent the particular prostaglandin tested.

By the year 1967 it had been established that there are three families of prostaglandins (PG_1's, PG_2's and PG_3's), differing in degree of unsaturation (one, two or three carbon-carbon double bonds) and originating from a different C_{20} fatty acid, and that there were at least five important members of each family. In addition the general outlines of the mode of biosynthesis from straight-chain C_{20} fatty acids could be discerned.

The chemical synthesis of prostaglandins

In late 1965 my group at Harvard started work on the chemical synthesis of prostaglandins. The major reasons for embarking on a synthesis were : (1) the prospect that only through synthesis could sufficient amounts of PG's be obtained to permit extensive biological investigation, (2) the conviction that such potent and novel mammalian substances might be very important in human health or disease, and (3) the thougt that an effective and flexible chemical synthesis could also provide structural analogs of the natural PG's which might be useful in medicine or in the fundamental study of the mechanisms by which PG's act in the body. In addition a totally new way of thinking about the design of chemical synthesis had just been developed by us which made the analysis of the problem of PG synthesis much easier and more interesting as a chemical exercise. This multistrategically guided, retrosynthetic approach to synthesis revolutionized the teaching of synthesis at Harvard and even allowed the first computerization of chemical synthetic analysis (E.J. Corey, *Science*, 1969 ; M. Ohno, *Kagaku no Ryoiki*, 1972). By coincidence, a definitive text on this approach to synthesis has just made its appearance (E.J. Corey and X. M. Cheng, *"The Logic of Chemical Synthesis"*, John Wiley, Publisher, April 1989). The first chemical synthesis of the major PG's in pure form was accomplished at Harvard in 1967. The initial publication (May 1968) triggered a deluge of requests for samples of PG's and information on their synthesis and chemistry, all of which made clear the enormous world-wide interest in these previously rare and esoteric compounds.

Ready access to pure synthetic prostaglandins in our laboratory set the stage for a second generation synthesis which was developed at Harvard in 1968-9 and reported in 1969. This synthesis, via an intermediate now commonly known as "Corey lactone", allowed for the first time the efficient production of all of the PG's and countless structural analogs on any scale, and it made these previously rare substances abundantly available.

More on the biological properties of prostaglandins

Subsequent to the availability of synthetic prostanoids (PG's and structurally related molecules) there was a spectacular efflorescence of biological research with PG's, which continues even at the present time. The field is now so vast that it is only possible to summarize a few of the salient developments.

The prostaglandins show at astonishing range of biological effects on a wide array of cells and tissues. Certain PG's (e.g. PGE_1) cause relaxation of smooth muscle while others (PGF_{2a}) cause contraction. Muscles of the blood vessels, lungs, and uterus are very sensitive to PG's. Thus, PGF_{2a} plays an important role in the uterine contractions of labor and PGE_1 strongly reduces blood pressure. Prostaglandins are involved in inflammation, a normal process of the immune response which goes awry in inflammatory diseases such as arthritis. Prostaglandin E_2 is an important mediator of pain, fever, and arousal from sleep. John Vane showed in 1971 that aspirin and similar antiinflammatory drugs act by blocking the enzyme PGH synthase which converts unsaturated fatty acid precursors to PG's. These same drugs block the aggregation of blood platelets and thereby the clotting of blood, another important action of PG's. Prostaglandins strongly affect the various cells involved in the immune response and are thus vital to the immune defense system. The widespread action of PG's in the body is further indicated by their involvement in the functioning of brain, kidney, lung, heart, stomach, and intestines.

The discovery of the newer prostanoid

Bengt Samuelsson, a student of Bergström's, isolated an unstable intermediate in the biosynthesis of PG's from arachidonic acid, the endoperoxide PGH_2, and shows that it was coverted to a very potent but short-lived platelet aggregator, thromboxane A_2. Since damaged blood vessels activate platelets to produce thromboxane A_2, this mediator clearly can play a role in the clotting process which initiates the repair of blood vessels. An enzyme present in healthy endothelial cells which line the blood vessels converts the same endoperoxide to a different prostaglandin, PGI_2 (prostacycline, Vane, 1976), which is a powerful inhibitor of platelet aggregation. It is the function of PGI_2 to prevent the aggregation of blood platelets in normal undamaged blood vessels. The synthesis of PGI_2 from $PGF_{2\alpha}$ was achieved independently in our laboratory and at the Upjohn Co. (1977).

The PG endoperoxide, PGH_2, and thromboxane A_2 are both very unstable in neutral aqueous solution at body temperature, a factor which complicates the study of their biological properties. Fortunately, stable, biologically active structural analogs of these molecules which are useful research tools have been synthesized. The availability of these substances has greatly accelerated research on PG receptors and signal transmission.

The outstanding investigations of synthetic prostaglandins which have been carried out worldwide in the pharmaceutical industry have produced a number of important applications, although progress in this field has been difficult due to the universal action of PG's on most body tissues and cells the difficult problem of drug delivery to specific cells of the body. Synthetic $PGF_{2\alpha}$ and various potent analogs are used to induce labor at childbirth or to induce abortion during the first or second trimester. The combination of a progesterone anatagonist with a synthetic PG analog is the most effective known method for interrupting development of a newly fertilized ovum. Prostaglandin E_2 is used along with surgery as a life-saving treatment for "blue babies", infants born with congenital defects of the heart. Various synthetic analogs of PGE_2 (for example, enprostil) taken orally are highly effective in the treatment of gastric ulcers and in preventing ulcer formation in arthritic patients who take antiinflammatory agents. This application depends on the local action of PGE_2 in the stomach to inhibit the secretion of gastric hydrochloric acid simultaneously to enhance the secretion of cytoprotective mucous.

The leukotrienes, latecomers to the eicosanoid class

As was the case with the prostaglandins, the biologically active substances now described as members of the leukotriene group were detected (1938) as bioactive factors long before their chemical nature was known. The identification of these substances, termed slow reacting substances (SRS), as arachidonate derived eicosanoids was the result of contributions from Bengt Samuelsson's group at the Karolinska Institure in Sweden (*Science*, 1983) and our own group at Harvard (*Experientia*, 1982). A C_{20} epoxy acid, now called leukotriene-A_4 or LTA_4, couples with the tripeptide glutathione to form leukotriene-C_4 (LTC_4), the primary SRS. Enzymatic peptide cleavage of LTC_4 converts it successively to two other SRS's, LTD_4 and LTE_4. Enzymatic hydrolysis of LTA_4 produces LTB_4. All of these leukotrienes were made by our group by total synthesis, which not only was important to rigorous and complete determination of structure, but which also made these very unstable and rare substances available in ample amounts for scientific study across a broad range of biology and medicine.

Leukotrienes play a significant role in the normal immune response, in the process of

tissue repair, in inflammation, and in allergic and hypersensitivity reactions. The peptidic leukotrienes, LTC_4, LTD_4 and LTE_4, are potent spasmogens and show a contractile effect on smooth muscle of the airways, utcrus, heart, gut, and blood vessels. A pathophysiologic role of the peptidic leukotrienes in asthma and bronchial hyperirritability has been demonstrated experimentally. LTB_4 also has important biological effects. It is a potent inflammatory agent. Even at concentrations of 10^{-9}M it causes chemotactic migration of leukocytes as well as neutrophil activation with concommittant generation of proteolytic enzymes and superoxide anion (O_2^{-*}), and adhesion of leukocytes to endothelial cells.

The medical implications of these various effects of the leukotrienes are far reaching and consequently it is not surprising that many research laboratories are pursuing research based upon this new knowledge. New chemical compounds which can serve to inhibit leukotriene biosynthesis and also to block the action of leukotrienes at their receptors have been discovered in our laboratories and those of others. Useful new therapeutic agents can be expected to emerge from such studies.