Prostaglandins: Mediators of Inflammation?

The prostaglandins are a group of ubiquitous, hormonelike substances that participate in numerous processes in the human body. One focus of current investigations is their role in the body's defense mechanisms against injury and invasion by foreign matter, including bacteria and viruses. Although these normal defense mechanisms, the inflammatory response and the related immune response, are essential to health, they are potentially harmful in such disease states as rheumatoid arthritis and such allergic conditions as asthma. Prostaglandins are now implicated in the inflammatory and allergic reactions; however, there is conflicting evidence about the precise nature of their involvement.

Because of the complexity of the inflammatory process, its biochemistry is still not well understood. The essence of the problem is the identification of the chemical causes or mediators of the physiological events as they are provoked by different inflammatory stimuli. There is no lack of candidates; histamine, 5-hydroxytryptamine (also known as 5-HT and serotonin), the kinins, slow-reacting substance in anaphylaxis (SRS-A), immunoglobulins, serum complement, and, now, certain prostaglandins have all been implicated.

In the early phases of inflammation, the small blood vessels, especially the venules and capillaries, dilate and their permeability increases, so that the fluid and proteins leak into interstitial spaces and produce edema or swelling. As the vessels become more permeable, leukocytes—particularly the polymorphonuclear (PMN) leukocytes—migrate through the walls and accumulate locally, engulf the particles of dead tissues or bacteria, and digest them. Pain, reddening, and increased temperature are also characteristic of inflamed tissue. Allergic reactions are harmful manifestations of the immune response, with unpleasant, even dangerous, symptoms that are triggered by the interaction between antibodies and some foreign material. These symptoms often include all or part of the characteristics of inflammation. Moreover, many of the proposed mediators of inflammation may be involved in allergic responses.

At present, there are two apparently conflicting schools of thought regarding the specific role of the prostaglandins in inflammation and in allergy or hypersensitivity. Some investigators have presented evidence that certain prostaglandins can inhibit inflammation and hypersensitivity in both in vitro and in vivo models of these phenomena. In contrast, an accumulating body of data supports the hypothesis that prostaglandins are mediators of the inflammatory response.

In Vitro Studies

Gerald Weissmann of the New York University School of Medicine is using an in vitro system to study the type of inflammation found in rheumatoid arthritis. He exposes purified human PMN leukocytes to aggregates of immunoglobulin G and rheumatoid factor which belongs to the immunoglobulin M class and is a putative mediator of inflammation in rheumatoid arthritis. As the PMN leukocytes engulf these antibody aggregates, they selectively release potent hydrolytic enzymes from their lysosomes. The loss of lysosomal enzymes can be reduced, Weissmann finds, by treating the white cells with moderately high concentrations of PGE_1 and PGA_2, but not with PGE_2. (Prostaglandins are classified as E, F, A, or B on the basis of their structures.) Since the enzyme release is retarded by adenosine 3′,5′-monophosphate (cyclic AMP), and PGE_1 can cause increases in intracellular cyclic AMP concentrations, Weissmann believes that the prostaglandins may act by stimulating the enzyme adenylate cyclase to synthesize more of the nucleotide.

Weissmann has also tested the activity of PGE_1 in suppressing adjuvant arthritis, in the rat. Adjuvant arthritis is an artificially induced condition that results in persistent inflammation in the joints, similar to that of rheumatoid arthritis. Together with Robert Zurier and Franco Quagliata, he reported that massive doses of the prostaglandin did suppress the inflammation of adjuvant arthritis even in animals without adrenal glands. These experiments suggest that PGE_1 can produce antiinflammatory effects without the participation of adrenal steroids.

Lawrence Lichtenstein, at Johns Hopkins University School of Medicine, is studying the activity of the prostaglandins in two in vitro models of the allergic response, one of immediate and the other of delayed hypersensitivity. In the first system, human basophilic leukocytes (which constitute approximately 1 percent of the leukocyte preparation he uses) are obtained from allergic donors. Such basophils have immunoglobulin E (IgE) fixed to their surfaces; when challenged with the appropriate antigens they secrete histamine, a known mediator of allergic reactions. In Lichtenstein's experiments, PGE_1 and PGE_2, both in concentrations within the physiological range, significantly inhibited histamine release. The other prostaglandins were not as effective as the PGE's; $PGF_{1\alpha}$ and $PGF_{2\alpha}$ produced little inhibition. The prostaglandins also stimulated cyclic AMP synthesis by the total leukocyte population, with the same efficiencies that they displayed in the inhibition of histamine release. Several other drugs are known to both increase intracellular levels of cyclic AMP and decrease histamine secretion. Consequently, Lichtenstein believes that the concentration of cyclic AMP regulates histamine secretion and that the prostaglandins act indirectly through the nucleotide. Lichtenstein points out that this conclusion depends on the assumption that synthesis of cyclic AMP by the 1 percent of basophils is controlled in the same manner as its synthesis by the other leukocytes.

The other system that Lichtenstein uses is a model of delayed hypersensitivity or cellular immunity such as that occurring in graft and organ transplant rejections. It depends on the ability of sensitized spleen lymphocytes—obtained from mice that had been injected with mouse mastocytoma cells—to destroy the target cells in tissue culture. Again PGE_1 and PGE_2 increased the cyclic AMP content of the lymphocytes and inhibited lymphocyte-mediated cytolysis. Lichtenstein hypothesizes that the high content of cyclic AMP prevents the secretion of a cytolytic factor by the lymphocytes.

Despite the evidence that prosta-

glandins can suppress some manifestations of the immunological and inflammatory responses, other aspects are mediated by the same prostaglandins. John Vane and his colleagues at the Royal College of Surgeons of England have shown that prostaglandin release from many tissues could be provoked by physiological, pathological, or mechanical stimuli. Anthony Willis, currently a visiting scientist at Hoffmann-LaRoche in Nutley, New Jersey, identified PGE_2 in the exudate produced during the later stages of carrageenan-induced inflammation in the rat. (Carrageenan is an algal polysaccharide frequently used to elicit inflammation in vivo.) This later phase occurs even in the absence of mediators such as histamine, 5-HT, and the kinins, which are believed to be responsible for the initial burst of inflammation; its extent correlates with the prostaglandin concentration of the exudate. Moreover, the inflammation is alleviated by indomethacin, aspirin, and other antiinflammatory, nonsteroidal drugs. Many investigators consider the demonstration by Vane and, independently, by Willis that the antiinflammatory drugs inhibit the synthesis of PGE_2 and $PGF_{2\alpha}$ in a variety of tissues, including sites of carrageenan-induced inflammation, to be persuasive evidence that some prostaglandins do mediate inflammation.

Myles Glenn and Gordon White of the Upjohn Company, Kalamazoo, Michigan, have also been able to produce a significant, although diminished, inflammatory response by injecting carrageenan into rats, even after depleting the animals of several factors thought to be essential for inflammation. These included histamine, circulating white blood cells, and serum complement. Indomethacin and other inhibitors of prostaglandin synthesis still reduced the resultant edema. They concluded that the cells in the immediate environment of the inflammatory reaction are capable of producing enough prostaglandins to provoke inflammation in the absence of other known inflammatory mediators.

Prostaglandins are also capable of evoking the symptoms of inflammation. Gabor Kaley of the New York Medical College has shown that PGE_1 induces both vasodilation and increased permeability in the venules of the rat. The effects subside within 20 minutes, but the vessels remain unresponsive to vasoconstrictors like epinephrine and norepinephrine for much longer. Kaley does not think that PGE_1 acts through histamine release.

In addition, PGE_1 may have the ability to mediate the cellular phase of inflammation. Kaley reported that relatively high concentrations of PGE_1 stimulated the migration of rabbit PMN leukocytes through a Micropore filter, which separated the prostaglandin-containing medium from the leukocyte suspension. Thus a leukotactic stimulus could result from the synthesis and release of prostaglandins from damaged tissue during the development of inflammatory reactions. This result is supported by the observation of M. DiRosa and D. A. Willoughby at St. Bartholomew's Hospital in London that aspirin suppresses leukocyte emigration during carrageenan-induced inflammation in vivo.

The basis of the apparent disagreement about the role of the prostaglandins in inflammation and hypersensitivity no doubt resides, at least partially, in the complexity of the processes themselves. Several investigators have pointed out that it may not be possible to identify a single primary cause of the inflammatory response. Different agents that provoke inflammation may operate through one or more different mediators. Furthermore, the effects of prostaglandins vary, depending on the species, the cell, or the organ system studied. For example, $PGF_{2\alpha}$ produced little activity in Lichtenstein's in vitro models. According to Willis' work, its effects on vascular permeability are negligible, compared to those of PGE_1 and PGE_2, when it is injected into human or rat skin; it inhibits permeability increases induced by prostaglandins of the E type in the rat. Nevertheless, others have reported that $PGF_{2\alpha}$ exerts a delayed proinflammatory effect when injected into the knee joints of dogs.

Feedback Mechanism?

Several investigators have hypothesized that the prostaglandins could participate in the regulation of inflammation by feedback inhibition, if they are inflammatory at low concentrations and antiinflammatory at higher ones. Normal inflammation is transient; it subsides after a few hours or days at most. According to the feedback hypothesis, as prostaglandins from damaged cells and leukocytes accumulate, local concentrations may be sufficient to prohibit further release of inflammatory mediators, including prostaglandins. An analogous phenomenon has been observed in which histamine inhibits further secretion of histamine.

Although the elusive goal of delineating the precise involvement of the prostaglandins in the inflammatory and allergic reactions has not yet been attained, therapeutic applications are being explored. Aerosols containing the PGE's are being tested in Europe for the treatment of asthmatic patients. In addition to their inhibitory action on in vitro models of acute and delayed hypersensitivity, the PGE's are bronchodilators. Thus there are two modes by which they could alleviate asthmatic attacks.

According to the Arthritis Foundation, more than 5 million Americans are victims of rheumatoid arthritis, a potentially crippling disease characterized by persistent inflammation, usually of the joints. At present, treatment can only ameliorate the symptoms of rheumatoid arthritis but cannot cure it. This statement is true of aspirin, indomethacin, and the other antiinflammatory, nonsteroidal drugs commonly used in arthritis therapy and thought to inhibit prostaglandin synthesis.

The inability to identify the agent responsible for the transformation of acute to chronic inflammation is a major hindrance in the search for better drugs for the treatment of arthritis. In addition to looking for more efficient compounds to inhibit prostaglandin synthesis directly, some investigators, including Willis, think it may be possible to divert the synthetic processes from the synthesis of PGE_2 to that of the less inflammatory F-type prostaglandins or to depress prostaglandin formation by limiting the availability of its fatty acid precursors. These fatty acids, especially arachidonic acid, are formed by the hydrolysis of phospholipids by the enzyme phospholipase A. According to Willis, the lysosomes of the leukocytes that accumulate at the site of inflammation and those of other damaged cells in the areas are a major source of the phospholipase. Moreover, Weissmann has reported that lysosomal enzymes released in the joints can produce the lesions of rheumatoid arthritis by degrading the joint tissues. Thus, compounds that stabilize the lysosomes or prevent the release of their enzymes should inhibit inflammation. Although many investigators think that this research may ultimately result in the design of better therapeutic agents for the treatment of inflammation and allergy, numerous problems remain to be solved.—JEAN L. MARX