The Potential Role of Prostaglandins in Skeletal and Muscular Disorders

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ABSTRACT

Musculoskeletal diseases such as rheumatoid arthritis and polymyositis are characterized by chronic inflammation. There is evidence to suggest that prostaglandins participate in the production of the inflammatory response. In several tissues, the production of inflammation has been associated with the release of prostaglandins. The inhibitory effect of some anti-inflammatory agents on prostaglandin synthesis further suggests a prostaglandin role in inflammation. Reduction by prostaglandins of release from cells of mediators of inflammation has been described. Prostaglandin treatment also suppresses acute and chronic inflammation in several experimental models. Thus, prostaglandins may serve to regulate the inflammatory response.

Introduction

The first clue to the existence of prostaglandins emerged in 1930 when two New York City gynecologists observed that human myometrium exhibited rhythmic contractions and relaxation when incubated with fresh human semen. Goldblatt and von Euler independently confirmed this finding and identified the active principle as an acidic lipid which von Euler believed to be produced in the prostate gland and therefore named prostaglandin. Eliasson later demonstrated that prostaglandin in human semen is, in fact, derived from seminal vesicles. Bergstrom and Sjovall found the active substance to be not one but several closely related compounds. Using homogenates of sheep vesicular glands, these investigators isolated two of the substances in crystalline form and described their chemical structure.

Structure

The basic structure common to all prostaglandins is a prostanoic acid skeleton, a 20 carbon atom unsaturated hydroxy fatty acid with a cyclopentane ring at C⁸–C¹². In nature, the prostaglandins are produced from the corresponding polyunsaturated fatty acid by a microsomal synthetase system. They are unusual among highly active biological compounds in that they lack nitrogen, in which respect they resemble the steroid hormones. The prostaglandins are grouped according to the type of chemical functionality present. Thus, prostaglandins are divided into the E, F, A and B compounds by the nature of the five membered ring functions (figure 2). The two main series, prostaglandins E and F (PGE,
Figure 1. Prostanoic acid. The basic structure of a fully saturated C20 acid with C8 to C12 closed to form a 5-membered ring is designated prostanoic acid.

PGF) differ only in the presence of a ketone or hydroxyl function at C9. The subscript numeral after the letter indicates the degree of unsaturation in the alkyl and carboxylic side chains. Thus, whereas the numeral 1 indicates the presence of a double bond at C13-14 (PGE1), the numeral 2 marks the presence of an additional double bond at C5-6 (PGE2) and the numeral 3 denotes a third double bond at C17-18 (PGE3). Substituents on the same side of the ring as the carboxyl group are in the alpha position and those on the same side as the alkyl group are in the beta position. That is, below the plane of the ring is designated alpha and above is designated beta. In the presence of weak acid or alkali, the PGE compounds undergo dehydration within the ring resulting in formation of the PGA compounds. In the presence of stronger alkali the C10-11 double bond rearranges to the 8, 12 position, and PGB compounds are formed (figure 2). Thus, the six naturally occurring PGE and PGF compounds are designated as primary compounds since none is a precursor of any other in this group.

Physiological Role

The physiological role of the prostaglandins is not clear. They appear to be almost ubiquitous, having been identified in many tissues, each of which has the capacity for synthesizing prostaglandins from essential fatty acids. It therefore seems unlikely that the prostaglandins are part of a classical endocrine-target organ system. They may, however, serve as local regulators of cell functions. The prostaglandins possess a broad spectrum of pharmacological activities which, in several cases, appear to involve changes in cyclic adenosine 3',5'-monophosphate (cAMP) concentrations. The first of these changes to have been measured was in adipose tissue, where prostaglandins were found to decrease cAMP levels in isolated fat cells. A more usual effect of prostaglandins is to increase levels of cAMP by virtue of activating membrane adenyl cyclase in a manner common to the action of many hormones.

Relation to Inflammation

Stimulation of cells and tissues, whether by mechanical, hormonal or neurologic means, results in the increased biosynthesis of prostaglandins. It has been suggested that one such stimulus is inflammation, in the course of which phospholipases are freed from the lysosomes of phagocytes, cells which often become the center of inflammatory lesions. For example, it has been demonstrated in patients with rheumatoid arthritis that synovial fluid leucocytes and synovial lining cells contain intracytoplasmic particulate complexes consisting of immunoglobulins and complement components. The accumulating evidence favors the idea that in the rheumatoid joint, antigen(s) combining with antibody(s) activates the complement sequence generating a variety of biologically active materials including some with potent chemotactic properties. These bring polymorphonuclear leucocytes (PMN) into the articular cavity where they are attracted to and ingest the immune complexes. After phagocytosis, the neutrophiles discharge, from their lysosomal granules, a variety of hydrolytic enzymes. It is these substances that appear to be the
direct cause of the proliferative and destructive changes characteristic of rheumatoid arthritis. Similarly, muscle wasting caused by a variety of factors is accompanied by an increased activity of lysosomal acid hydrolases, perhaps released from invading inflammatory cells. This occurs in muscular dystrophy and polymyositis.

Phagocytic cells release prostaglandins and it has been suggested that lysosomal phospholipases hydrolyze phospholipids of cell membranes to yield fatty acids. These are in turn presumably converted to prostaglandins by freely available enzymes (prostaglandin synthetase). There is evidence that prostaglandins do, in fact, participate in the development of the inflammatory response. It is, therefore, not surprising that such inflammatory diseases as rheumatoid arthritis and polymyositis have served as common interest to students both of musculoskeletal pathophysiology and the prostaglandins.

The prostaglandins are capable of inducing the four cardinal signs of inflammation: redness, swelling, heat and pain. In addition, PGE compounds increase pain sensitivity to other chemical mediators (bradykinin, histamine), and the injection of PGE1 or PGE2 into knee joints of dogs results in a severe disabling arthritis.

PGE1 is chemotactic for rabbit PMN suggesting that released prostaglandins might help perpetuate the inflammatory reaction by calling forth additional leukocytes. Explants of synovium obtained at surgery from patients with rheumatoid arthritis and maintained in organ culture, produce larger amounts of prostaglandin than synovium from patients with osteoarthritis. The prostaglandin-like substance associated with several experimental models of inflammation appear to be terminal mediators of the acute response and it has been suggested that the prostaglandins might be responsible, at least in part, for the transition from an acute to chronic inflammatory lesion. The presence of a substance in an inflammatory reaction does not, of course, permit conclusions to be drawn about its importance in the pathogenesis of the lesion. However, the prostaglandins clearly seem able to function as mediators of inflammation and anti-inflammatory compounds such as aspirin and indomethacin reduce prostaglandin synthesis in a dose-related manner.

Although there is strong experimental evidence that prostaglandins are local mediators of inflammation, effects on mediator release which suggest anti-phlogistic actions have also been described. Thus, PGE compounds, which increase levels of cAMP in human leucocytes, reduce extrusion of lysosomal enzymes from viable human leucocytes in vitro, prevent release of histamine and slow reacting substance of anaphylaxis (SRS-A) from basophiles and lung fragments and prevent lymphocyte-mediated cytotoxicity. PGE1 and E2 also suppress adjuvant-induced arthritis and cartilage destruction in rats and cAMP treatment suppresses acute and chronic inflammation in several experimental models. These data suggest that PGE compounds, perhaps acting via cAMP, may inhibit as well as mediate acute and chronic inflammation.

Later phases of induced inflammation are associated with increments in the concentration of prostaglandin E2 in the inflammatory exudate. It is possible that as their concentration increases to approach "pharmacologic" levels locally, prostaglandins may retard inflammation. A regulatory effect of prostaglandins is not without precedent in other systems. For example, although it is known that the prostaglandins are anti-lipolytic, the lipolytic hormones will increase prostaglandin formation in adipose tissue of certain species, suggesting that the endogenous prostaglandins may serve to attenuate hormonal stimulation of lipolysis. Such effects appear to be mediated by cAMP. A similar example of autoregulation is provided by the studies of
Hedqvist\textsuperscript{11} who has shown that PGE\textsubscript{1} and E\textsubscript{2} inhibit the release of noradrenalin from the spleen in response to sympathetic nerve stimulation. PGE\textsubscript{2} is released by the spleen when it contracts in response to nerve stimulation. Thus, by a feedback mechanism, the contracting smooth muscle can reduce the stimulus which is leading to the contraction. Prostaglandin release may, therefore, be a defense mechanism\textsuperscript{9} aimed at minimizing potential injury. Pertinent to a view of prostaglandins as local regulators of the inflammatory response is the observation\textsuperscript{16} that whereas large amounts of cAMP (500 mg per kg daily $\times$ 5 days) reduce the size of preformed granulomata, smaller amounts of cAMP (1 or 10 mg per kg daily $\times$ 5 days) increase the size of granulomata in rats. In addition, whereas the capacity of PGE\textsubscript{1} to suppress IgE dependent antigen-induced release of histamine from human lung tissue appears owing to enhancement by PGE\textsubscript{1} of cellular cAMP, low concentrations of PGE\textsubscript{1}, which decrease cAMP levels, enhance histamine release.\textsuperscript{31} Treatment of rats with PGE\textsubscript{1} and PGE\textsubscript{2} also inhibits the IgE mediated release of SRS-A in a dose response fashion.\textsuperscript{18} PGE\textsubscript{1} inhibits lymphocyte-mediated destruction of allogeneic cells \textit{in vitro},\textsuperscript{12} suggesting an effect on T-lymphocytes. However, it is also capable of reducing the humoral antibody response\textsuperscript{27} and appears to prolong homograft survival through an effect on B-cells.\textsuperscript{24} Moreover, there is experimental evidence that PGE\textsubscript{1} inhibits release of antibodies from splenic cells.\textsuperscript{21} Consequently, it is not clear whether PGE compounds act as "immunosuppressants" of T or B cells (or both) or whether, in pharmacologic concentrations, they inhibit release of several cell products such as mediators of inflammation and/or antibodies.

Alternatively, or additionally, the prostaglandins may serve to restrain the inflammatory response, not by means of a feedback mechanism but through a prescribed balance in local concentrations of E and F compounds. For example, PGF\textsubscript{2a} inhibits the increases in vascular permeability induced in skin by PGE\textsubscript{1} and E\textsubscript{2}.\textsuperscript{6} The formation of both compounds follows a common pathway until the final stage of biosynthesis and there is no evidence for interconversion between E and F prostaglandins. Local control of inflammation might therefore result from the preferential biosynthesis of one or another of the prostaglandins.

Conclusions

The mere presence of a substance does not necessarily denote a physiological role, but the ubiquitous nature of the prostaglandins and their remarkable potency suggest they have an important function. There is evidence they participate in the development and possibly the modulation of inflammation in man. Inflammation and tissue damage may result from immune (hypersensitivity) reactions. That pharmacologic doses of prostaglandins influence the immune response again suggests a possible regulatory function. It does not seem unreasonable to consider that either prostaglandin analogues or prostaglandin antagonists or specific combinations of both types of compounds may become important adjuncts to treatment of immune-inflammatory musculoskeletal diseases. Indeed, aspirin and indomethacin, both inhibitors of prostaglandin synthesis, have long been mainstays in the management of patients with inflammatory joint disease. The effects of prostaglandins on the immunological and inflammatory responses are varied, but further studies of their synthesis, metabolism and effects should make their functions, if not completely clear, then at least harmoniously confused.

References

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