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Mini-review

Prostanoid receptors and acute inflammation in skin

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ABSTRACT

Prostanoids such as prostaglandins (PGs) and thromboxanes exert a wide variety of actions via nine types of G protein-coupled receptors, including four PGE_2 receptors (EPs) and two PGD_2 receptors (DPs). Recent studies have revealed that prostanoids trigger or modulate acute inflammation in the skin via multiple mechanisms involving distinct receptors and molecules; PGE_2 elicits vascular permeability and edema formation via EP3 receptor on mast cells, and PGE_2 increases blood flow by eliciting vasodilatation via EP2/EP4 receptors on smooth muscle cells. PGD_2-DP1 signaling plays a role in mast cell maturation and mast cell-mediated inflammation. Therefore, the local inhibition of specific prostanoid receptor signaling is expected to be an effective strategy for the prevention and treatment of acute inflammation.

1. Introduction

Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the activity of cyclooxygenase (COX) by inactivating its active center [1,2], and thereby inhibit the biosynthesis of prostanoids, resulting in antipyretic, analgesic, and anti-inflammatory effects. Since exogenously added prostaglandin (PG) E_2 elicits actions such as pyrexia, pain sensation, and inflammation, it was thought that the action of NSAIDs is mainly based on the inhibition of PGE_2 production. Recently, studies on mice deficient in each prostanoid receptor as well as receptor-specific agonists/antagonists have revealed the physiological functions of prostanoids via each receptor [3,4]. In this mini-review, we summarize the molecular basis of prostanoid receptors and the recent advances in prostanoid receptor research, by focusing on the molecular mechanisms of prostanoid-induced acute inflammation, and discuss the pathophysiological roles of prostanoid receptors as well as their usefulness as therapeutic targets.

2. Biosynthesis of prostanoids and prostanoid receptors

Prostanoids are a group of eicosanoids consisting of four kinds of prostaglandins (PGs) and thromboxanes (TXs): PGE_2, PGD_2, PGF_2, PGI_2, and TXA_2. Prostanoids are produced from arachidonic acid (AA) that is released by phospholipase A_2 (PLA_2) from membrane phospholipids, by the sequential actions of COX (COX-1 or COX-2) and the respective synthases [5] (Fig. 1). Prostanoids are then quickly released from the cells and act as local hormones in the vicinity of their production sites to maintain local homeostasis. Prostanoids exert a wide variety of actions in the body, which are mediated by specific receptors on plasma membranes [6]. Prostanoid receptors were initially characterized pharmacologically in several bioassay systems, including contraction-relaxation assays on various smooth muscles and the aggregation of platelets [7,8]. These receptors are classified into five basic types, termed DP (type D Prostanoid receptor), EP, FP, IP, and TP, on the basis of their sensitivity to the five primary prostanoids, PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and TXA_2, respectively. Furthermore, EP is subdivided into four subtypes, EP1, EP2, EP3, and EP4, on the basis of their responses to various agonists and antagonists. Molecular identification of these receptors was achieved by their cDNA cloning, which revealed that the prostanoid receptors are G-protein-coupled receptors (GPCRs) and that there is indeed a family of eight GPCRs that correspond to the pharmacologically defined receptors [3,6]. A second type of PGD_2 receptor, CRTH2 (chemoattractant receptor homologous molecule expressed by T helper 2 cells) was identified by molecular analysis as belonging to the chemoattractant receptor family [9]. CRTH2 is also called DP2, in reference to its endogenous ligand and the initially identified DP receptor, which is designated as DP1 [4] (Fig. 1). Among the prostanoids, PGE_2 is most widely found in animal species, and exhibits the most versatile actions. Since each EP subtype has distinct signal transduction properties, PGE_2 is able to

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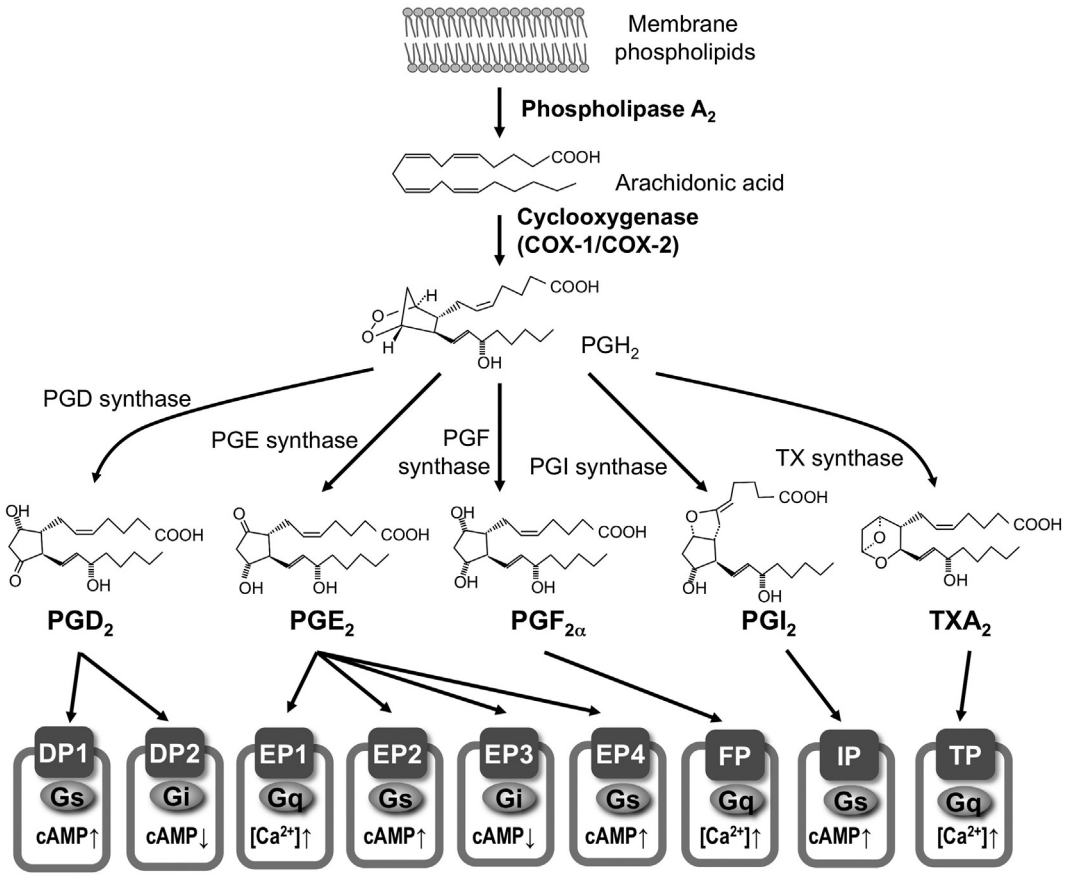

Fig. 1. Synthesis of prostanoids and prostanoid receptors. Arachidonic acid is released from membrane phospholipids by the action of phospholipase A_2. AA is then converted to PGH_2 by cyclooxygenase (COX-1 or COX-2), and then each prostanoid is produced by the action of their specific synthases. Immediately after synthesis, each prostanoid is released from the cells, and acts on specific receptors on various kinds of neighboring cells, which are coupled to a specific G proteins. PGE_2 acts on four kinds of receptor subtypes (EP1-EP4), each of which has distinct signal transduction properties, and exerts diverse physiological functions. PGD_2 also acts on two different receptors, DP1 and DP2.

exert diverse actions; EP1 is coupled to intracellular Ca^{2+} mobilization via G_q, EP2 and EP4 are coupled to the stimulation of adenylyl cyclase via G_s, and EP3 is mainly coupled to the inhibition of adenylyl cyclase via G_i. EP2 and EP4 receptors also elicit the activation of phosphoinositide 3-kinase (PI3K) via the β-arrestin pathway [10–12].

3. Traditional view of the progression of acute inflammation, and PGE_2 action therein

Tissue injury and the invasion of foreign organisms trigger acute inflammation, which is characterized by four clinical features: red flare, heat, swelling, and pain. The flare and heat reactions are elicited by an increase in local blood flow as a result of vasodilatation, and the swelling results from an increase in vascular permeability and resultant neutrophil recruitment. Invasion of exogenous organisms is detected by Toll-like receptors (TLRs) in epithelial and immune cells. TLRs trigger the inflammatory process by activating local cytokine and chemokine systems, which in turn affect vascular permeability and neutrophil recruitment [13,14]. In addition, chemical mediators such as bradykinin, histamine, proteases, and growth factors have been shown to elicit acute inflammation [15]. In the 1970's, Williams and Morley proposed the 'two mediator hypothesis' [16], which describes that the magnitude of inflammatory swelling depends on two factors: the degree of vasodilatation, which is regulated by PGE_2, and the extent of endothelial cell permeability, which is driven by various kinds of permeabilizing substances, including bradykinin and histamine. Moreover, according to this hypothesis, when both factors are present, they synergize to produce a greater net inflammatory swelling response. Of course this hypothesis was proposed long before the discovery of TLR molecules, but the basic notion underlying this hypothesis is still believed to date [15,17–19]. However, until recently, it was unknown as to which EP receptors mediate PGE_2-induced vasodilatation and whether PGs contribute to acute inflammation in a manner different from vasodilatory action.

4. EP receptors involved in acute inflammation

Recently, using an ultraviolet-induced skin inflammation model, EP2 and EP4 receptors were shown to be involved in edema formation, mainly by eliciting vasodilatation and the subsequent increase in local blood flow [20]. Since EP2 and EP4 receptors are widely expressed in vascular smooth muscle cells [21,22], such vasodilatory effects of PGE_2 may also take place in various tissues other than the skin. Therefore, vasodilatation and an increase in blood flow, which have long been regarded as the main actions of PGE_2 in acute inflammation, are at least partly mediated by EP2 and EP4 receptors on smooth muscle cells (Fig. 2).

In addition to its vasodilatory action, PGE_2 triggers mast cell (MC) activation via the EP3 receptor. In an AA-induced dermatitis