Biochimica et Biophysica Acta 1851 (2015) 414–421

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbalip

Review

Prostaglandin E_2-induced inflammation: Relevance of prostaglandin E receptors ☆

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ARTICLE INFO

Article history:
Received 17 April 2014
Received in revised form 4 July 2014
Accepted 10 July 2014
Available online 17 July 2014

Keywords:
Prostanoid
Mast cell
Irritant contact dermatitis
Helper T cell
Multiple sclerosis

ABSTRACT

Prostaglandin E_2 (PGE_2) is one of the most typical lipid mediators produced from arachidonic acid (AA) by cyclooxygenase (COX) as the rate-limiting enzyme, and acts on four kinds of receptor subtypes (EP1–EP4) to elicit its diverse actions including pyrexia, pain sensation, and inflammation. Recently, the molecular mechanisms underlying the PGE_2 actions mediated by each EP subtype have been elucidated by studies using mice deficient in each EP subtype as well as several compounds highly selective to each EP subtype, and their findings now enable us to discuss how PGE_2 initiates and exacerbates inflammation at the molecular level. Here, we review the recent advances in PGE_2 receptor research by focusing on the activation of mast cells *via* the EP3 receptor and the control of helper T cells *via* the EP2/4 receptor, which are the molecular mechanisms involved in PGE_2-induced inflammation that had been unknown for many years. We also discuss the roles of PGE_2 in acute inflammation and inflammatory disorders, and the usefulness of anti-inflammatory therapies that target EP receptors. This article is part of a Special Issue entitled "Oxygenated metabolism of PUFA: analysis and biological relevance".

1. Introduction

Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the activity of COX by binding to its active site [1,2], and thereby inhibit the biosynthesis of prostanoids, resulting in antipyretic, analgesic, and anti-inflammatory effects. Since exogenously added PGE_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 EP subtype as well as EP-specific agonists/antagonists have revealed the physiological functions of PGE_2 *via* each EP receptor [3,4]. In this review, we summarize the molecular basis of prostanoid receptors and the recent advances in PGE_2 receptor research, by focusing on the molecular mechanism of PGE_2-induced inflammation, and discuss the pathophysiological roles of PGE_2-EP receptors as well as their usefulness as target proteins for drug design.

2. Molecular basis of prostanoid actions

2.1. Biosynthesis and structure of prostanoids

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 by the sequential actions of COX and the respective synthases from AA, which is released by phospholipase A_2 (PLA_2) from membrane phospholipids [1,2,5]. The COX protein contains two active sites: a cyclooxygenase site, where AA is converted into hydroperoxy endoperoxide PGG_2, and a peroxidase site, responsible for the reduction of PGG_2 to PGH_2 (Fig. 1A) [1,2]. To date, two COX isozymes are known: COX-1 and COX-2. PGs are molecules with a basic structure of prostanoic acid, which consists of a cyclopentane ring and two carbon chains, and are classified from A to J, according to the structure of their cyclopentane ring. On the other hand, the basic structure of TXs is thrombanoic acid, which contains two oxygens in a ring structure (Fig. 1B). Therefore, TXs should be strictly distinguished from PGs. However "PGs" in a broad sense refers to the products of COX that includes TXs, and in many cases the term is used as a synonym for prostanoids.

2.2. Prostanoid receptors

Receptors mediating the action of prostanoids were characterized first by pharmacological analysis, which indicated the presence of

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http://dx.doi.org/10.1016/j.bbalip.2014.07.008
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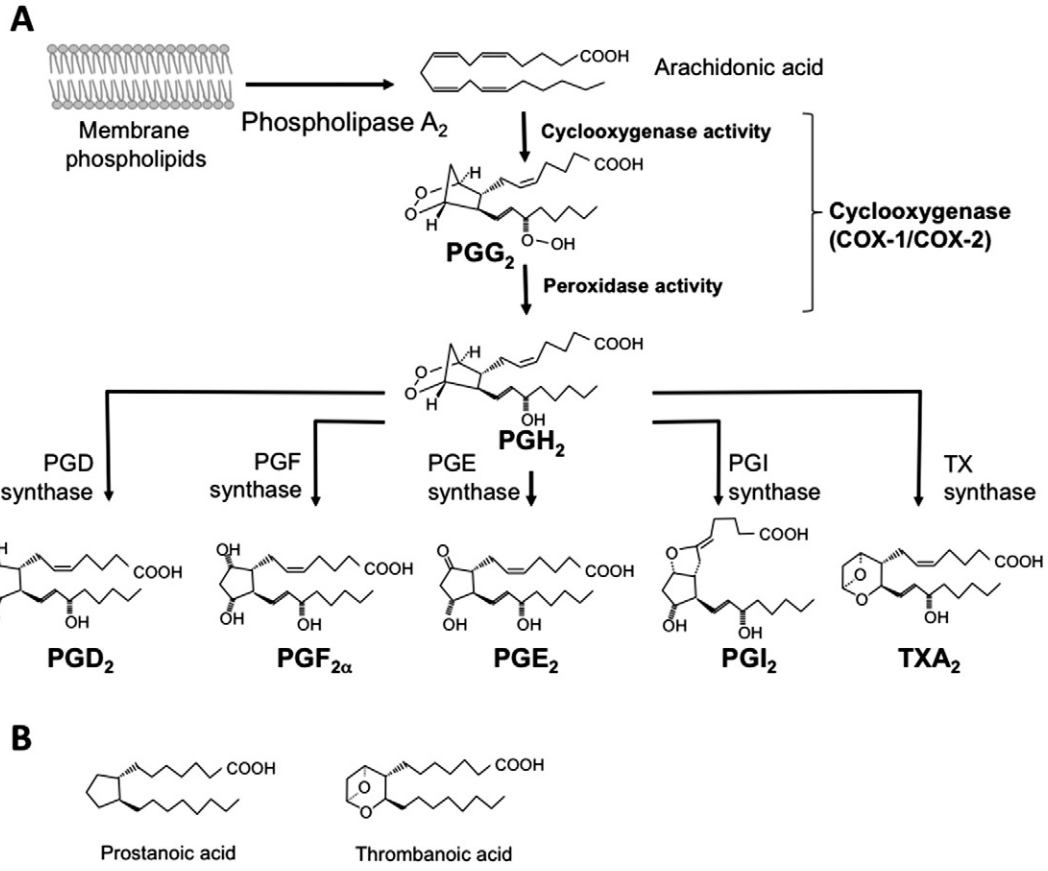

Fig. 1. Cyclooxygenase pathway and prostanoids. A, Arachidonic acid, which is released by phospholipase A_2 (PLA_2) from membrane phospholipids, is converted to PGG_2 and then to PGH_2 by cyclooxygenase (COX), and then each prostanoid is produced by the action of their specific synthases. B, Chemical structure of prostanoic acid and thrombanoic acid.

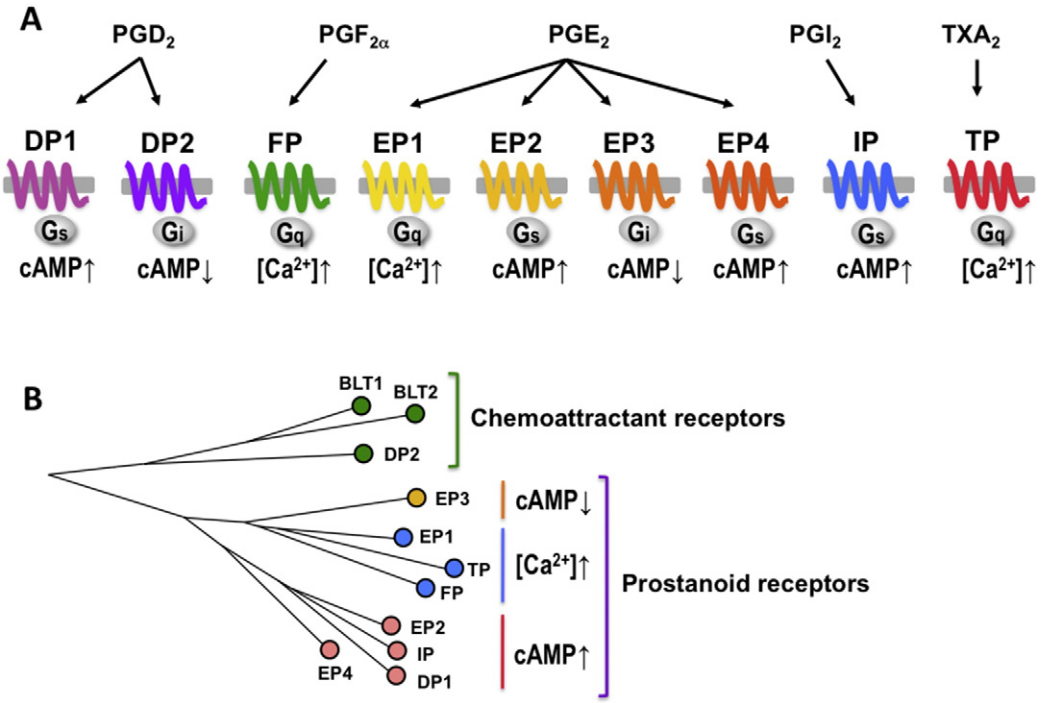

Fig. 2. Prostanoid receptors and their molecular (evolutionary) phylogenetic tree. A, Prostanoids exert various actions by acting on each specific receptor, which is coupled to a specific G protein. PGE_2 acts on four kinds of receptor subtypes (EP1–EP4), each of which has distinct signal transduction properties, and exerts diverse physiological functions. PGD_2 also acts on two different receptors, DP1 and DP2. B, Phylogenetic tree of the human prostanoid DP1, EP1, EP2, EP3, EP4, FP, IP, and TP receptors, together with the human DP2 receptor and leukotriene B_4 receptors BLT1 and BLT2. Each branch length indicates the phylogenetic distance. The eight prostanoid receptors form clusters not according to their ligand but according to the signal transduction pathway that they are coupled to. The DP2 receptor belongs to the chemoattractant receptor family that includes BLT1 and BLT2, rather than the prostanoid receptor family.