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Minireview

Prostaglandin E receptors as inflammatory therapeutic targets for atherosclerosis

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ABSTRACT

Prostaglandin E receptors (EPs) are the G-protein-coupled receptors (GPCRs) that respond to type E_2 prostaglandin (PGE_2). Data has shown that PGE_2 may function as an endogenous anti-inflammatory mediator by suppressing the production of cytokines. However, other studies have demonstrated that PGE_2, a pro-inflammatory mediator produced by various cell types within the wounded vascular wall, plays a crucial role in early atherosclerotic development. These contradictory results may be due to the versatility of EPs. Experimental data suggest an individual role for each PGE_2 receptor, such as EP_1, EP_2, EP_3 and EP_4, in atherosclerosis. In this review, the roles of EPs in atherosclerosis are summarized, and the value of EPs as new therapeutic targets for atherosclerosis is explored.

Contents

Introduction

Atherosclerosis is characterized by the accumulation of lipids and fibrous elements in the large arteries and is a progressive disease of the arterial wall. It underlies the most frequent causes of cardiovascular mortality, such as myocardial infarction, peripheral vascular disease and cerebrovascular disease. According to the American Heart Association 2010 Heart and Stroke Statistical Update, atherosclerosis accounts for more than 50% of all deaths from cardiovascular disease. Atherosclerosis is now considered to be initiated by endothelial dysfunction, which is induced by chemical, mechanical or immunological insults (Libby et al., 2009). During atherosclerosis, endothelial dysfunction has a permissible effect on the entry of lipids and inflammatory cells into the artery wall and triggers a cascade of inflammatory reactions, in which monocytes, macrophages, T lymphocytes and vascular smooth muscle cells participate (Kaperonis et al., 2006; Libby et al., 2009). Atherosclerosis is currently considered to be a chronic inflammatory disease (Libby et al., 2009). Many kinds of pro-inflammatory cytokines, including leukocyte adhesion molecules, growth factors and matrix metalloproteinase (MMP), participate in all stages of atherogenesis (Kaperonis et al., 2006). For instance, the pro-inflammatory cytokines released from macrophages can infiltrate the vascular wall and instigate the activation of vascular smooth muscle cells from a contractile/quiescent to a secretory/proliferative phenotype. This is now considered to be one of the critical steps in atherosclerosis (Lusis, 2000; Orr et al., 2010). The activation of vascular smooth muscle cells often leads to an enhanced production of prostaglandin E_2 (PGE_2), which can potentiate the pro-inflammatory cytokine-related effects (Panzer and Uguccioni, 2004). Research has consistently indicated that the blockage of PGE_2 by its

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selective antagonist significantly attenuated the production of pro-inflammatory cytokines (Strong et al., 2000). These findings reveal the important immunoregulating role of PGE_2 in the pathophysiological process of atherosclerosis.

PGE_2 is the most common prostanoid with a variety of bioactivities and has been implicated in various pathologies. PGE_2 is the product of sequential reactions catalyzed by cyclooxygenase (COX) and PGE synthase (PGES) (Cipollone et al., 2008). PGES presents as three isoforms, one cytosolic PGES (cPGES) and two membrane-associated PGES (mPGES-1 and mPGES-2). cPGES is constitutively expressed and preferentially coupled to the constitutive COX-1 enzyme. mPGES-1 is induced by pro-inflammatory stimuli and is predominantly linked to the inducible COX-2 enzyme (Cipollone et al., 2008). COX-2 and mPGES-1 have been implicated in the PGE_2-dependent MMP biosynthesis (Cipollone et al., 2001) that is associated with the rupture of atherosclerotic plaques and subsequent acute coronary syndromes (Kunz, 2007). It seems that PGE_2 may function as a pro-inflammatory mediator, which is evidenced by the ability to augment the expression of the proteolytic enzymes, MMP-2 and MMP-9, in macrophages through a cyclic adenosine monophosphate (cAMP)-dependent pathway after synthesis (Jones et al., 2003). PGE_2 also plays a crucial role in early atherosclerotic development by relaying and/or amplifying the effect of cytokines on the de-differentiation of smooth muscle cells (Clément et al., 2006). However, other studies have demonstrated that through cAMP-dependent pathway, PGE_2 reduced inflammatory activation of human macrophages by suppressing the expression of cytokines and chemokines implicated in leukocyte recruitment to atheromata, including tumor necrosis factor (TNF)-α, interferon (IFN)-β and macrophage inflammatory protein-1_β (Xu et al., 2008; Takayama et al., 2002). PGE_2 can also inhibit smooth muscle cell proliferation induced by interleukin (IL)-1 (Norel, 2007). Thus, PGE_2 may also function as an endogenous anti-inflammatory mediator.

Acting in an autocrine/paracrine manner, PGE_2 modulates inflammatory responses via a family of four related receptors, termed EP_1, EP_2, EP_3, and EP_4, which are all G-protein coupled (Sugimoto and Narumiya, 2007; Nagai, 2008). However, it has been suggested that these four EP receptors are structurally and functionally distinct and have limited amino acid identity (Sugimoto and Narumiya, 2007). For example, the amino acid identity of EP_1 to EP_2, EP_3, and EP_4 is 30%, 33%, and 28%, respectively (Nagai, 2008). This divergence may be due to the different structures, because the EP subtypes exhibit differences in signal transduction, tissue localization, and regulation of expression (Sugimoto and Narumiya, 2007). The EP_1 receptor mediates Ca^{2+} mobilization and induces the contraction of smooth muscle (Funk et al., 1993). Activation of the EP_3 receptor attenuates the relaxation of smooth muscle by inhibiting adenylate cyclase that subsequently leads to a decrease in cAMP concentration (Kotani et al., 1995). In contrast, the activation of EP_2 and EP_4 causes increases in intracellular cAMP concentration and induces smooth muscle relaxation (Regan et al., 1994). In spite of structural and functional differences, the expression of the four subtypes of EPs is increased in the inflammatory region of carotid atherosclerotic plaques in the peripheral blood mononuclear cells (PBMC) of patients with carotid atherosclerosis (Gómez-Hernández et al., 2006a, 2006b). This finding is consistent with other studies that suggest EPs play an important role in the pathogenesis of atherosclerosis (Takayama et al., 2002; Kennedy et al., 1999; Pavlovic et al., 2006; Takayama et al., 2006). In this review, we will focus on the relationships between the four EPs subtypes and atherosclerosis and discuss the potential for atherosclerosis therapy using EPs.

EP_1 and atherosclerosis

No direct evidence revealing the relationship between the EP_1 receptor and atherosclerosis has been available thus far. However, EP_1 expression seems to be upregulated in atherosclerosis (Gómez-Hernández et al., 2006a, 2006b). By immunohistochemistry and immunofluorescence, the expression of EP_1 was enhanced in the inflammatory region of human atherosclerotic plaques (Gómez-Hernández et al., 2006a). Some currently available drugs, which benefit the therapy of atherosclerosis, statins for example, were observed to downregulate EP_1 expression in plaques and PBMC of patients with carotid atherosclerosis partially because of the inhibition of nuclear factor $_\kappa$B (NF-$_\kappa$B) (Gómez-Hernández et al., 2006b). Therefore, the possible role that the EP_1 receptor plays in the development of atherosclerosis cannot be excluded.

EP_2 and atherosclerosis

The expression of EP_2 was also significantly enhanced in the inflammatory region of human atherosclerotic plaques (Gómez-Hernández et al., 2006a). Meanwhile, Li et al. (2006) recently demonstrated that, by activating the EP_2 receptor and subsequently elevating cAMP levels, the oxidized phospholipid, 1-palmitoyl-2-epoxyisoprostane-sn-glycero-3-phospho-rylcholine (PEIPC), accumulates in atherosclerotic lesions and induces monocyte adhesion to the endothelial cells, which is a key step in atherogenesis. Leitinger (2006) found that the initiation of monocytic vascular inflammation can occur via the activation of EP_2 through the formation of the oxidized phospholipid PEIPC, even in the absence of COX-derived PGE_2. However, in a more advanced stage of atherogenesis, where monocytes/macrophages accumulate in the subendothelial space, activation of the EP_2 receptor may not only occur by PEIPC but also by COX-derived PGE_2 (Leitinger, 2006). Therefore, the PEIPC-EP_2 interactions and the subsequent activation of cAMP-dependent pathways may provide new insights into the mechanisms by which monocytes are selectively recruited to chronically inflamed tissues. More importantly, the EP_2 receptor may turn out to be an attractive pharmacological target for the treatment of atherosclerosis and other inflammatory diseases.

EP_3 and atherosclerosis

Platelets play a pivotal role in atherothrombosis and therefore are considered to be primary targets of antithrombotic therapy (Jennings, 2009). The regulatory role of EP_3 in atherosclerosis is suggested to be achieved by regulating platelet aggregation. It has been demonstrated that PGE_2 promoted platelet aggregation in mice via the activation of EP_3 receptors and the subsequent decrease in cAMP levels (Fabre et al., 2001). Again, acting via the EP_3 receptor, PGE_2 produced by atherosclerotic plaques in mice can facilitate the initiation of arterial thrombosis and subsequently contribute to atherothrombosis (Gross et al., 2007). More direct evidence was provided by Ma et al. (2001) by using EP_3 knock-out ($EP_3^{-/-}$) mice. In $EP_3^{-/-}$ mice, the potentiating effect of PGE_2 on platelet aggregation was absent and was associated with a significantly prolonged bleeding time (Ma et al., 2001). Also in the $EP_3^{-/-}$ mice model, the decreased thrombosis was photographed in the carotid by using a visualization technique (Gross et al., 2007). The activation of EP_3 by PGE_2 is also involved in the regulation of other steps in atherogenesis. For instance, the PGE_2-dependent potentiation of the effects of IL-1_β on smooth muscle cell de-differentiation, which contributed to atheroma plaque development, was achieved through the regulatory effects of the EP_3 receptor on adenylate cyclases isoform 8 (Clément et al., 2006). The important role of the EP_3 receptor in atherogenesis is further supported by the development of some selective EP_3 receptor antagonists. DG-041, a recently evaluated specific EP_3 antagonist, was recently found to inhibit the pro-aggregatory effect via PGE_2-EP_3 stimulation, but potentiate the anti-aggregatory effects of PGE_2 on platelets via the activation of other receptors, such as the P_2Y_{12} receptor (Heptinstall et al., 2008). Like the P_2Y_{12} receptor, the EP_3 receptor couples to the inhibitory G_i protein to