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# E-type prostanoid receptor 4 (EP4) in disease and therapy

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ABSTRACT

The large variety of biological functions governed by prostaglandin (PG) $E_2$ is mediated by signaling through four distinct E-type prostanoid (EP) receptors. The availability of mouse strains with genetic ablation of each EP receptor subtype and the development of selective EP agonists and antagonists have tremendously advanced our understanding of $PGE_2$ as a physiologically and clinically relevant mediator. Moreover, studies using disease models revealed numerous conditions in which distinct EP receptors might be exploited therapeutically. In this context, the EP4 receptor is currently emerging as most versatile and promising among $PGE_2$ receptors. Anti-inflammatory, anti-thrombotic and vasoprotective effects have been proposed for the EP4 receptor, along with its recently described unfavorable tumor-promoting and pro-angiogenic roles. A possible explanation for the diverse biological functions of EP4 might be the multiple signaling pathways switched on upon EP4 activation. The present review attempts to summarize the EP4 receptor-triggered signaling modules and the possible therapeutic applications of EP4-selective agonists and antagonists.



**Contents**

1. Introduction . . . 486
2. Prostaglandin $E_2$ and its four receptors . . . 486
3. E-type prostanoid receptor 4 structure, signaling and ligands . . . 487
4. Immune modulation by E-type prostanoid receptor 4 . . . 490
5. Airways . . . 491
6. Gastrointestinal tract . . . 492
7. Vasculature . . . 492
8. Kidney . . . 495
9. Bone and cartilage . . . 495
10. Cancer . . . 496
11. Miscellaneous . . . 497
12. Conclusion . . . 497
Conflict of interest . . . 497
Acknowledgment . . . 497
References . . . 498

*Abbreviations:* AMPK, AMP-activated protein kinase; cAMP, cyclic adenylyl monophosphate; CFTR, cystic fibrosis transmembrane conductance regulator; ClC, chloride channel; COX, cyclooxygenase; CREB, cAMP-response element-binding protein; DP, D-type prostanoid receptor; DSS, dextran sodium sulfate; EGFR, epidermal growth factor receptor; eNOS, endothelial nitric oxide synthase; EP, E-type prostanoid receptor; Epac, exchange protein activated by cAMP; EPRAP, EP4 receptor-associated protein; ERK, extracellular signal-regulated kinase; FEM1a, feminization 1 homolog a; FP, F-type prostanoid receptor; GRK, G protein-coupled receptor kinase; 5-HETE, 5-hydroxyeicosatetraenoic acid; ICER, inducible cAMP early repressor; ICAM-1, intercellular adhesion molecule-1; Ig, immunoglobulin; IL, interleukin; IFN, interferon; IP, I-type prostanoid receptor; LPS, lipopolysaccharide; MAP, mitogen-activated protein kinase; MCP, monocyte chemoattractant protein; MEK, MAP kinase kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NSAID, non-steroidal anti-inflammatory drug; PG, prostaglandin; PI3K, phosphatidyl insositol 3-kinase; PK, protein kinase; TP, T-type prostanoid receptor; TX, thromboxane receptor.

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## 1. Introduction

Prostaglandins (PGs) and thromboxane $A_2$ ($TXA_2$) are synthesized from arachidonic acid by cyclooxygenase (COX) and specific prostanoid synthases. Released in response to various physiological and pathological stimuli they play essential roles in maintaining body homeostasis. Prostaglandin $E_2$ ($PGE_2$) is involved in several biological processes such as pain, fever, regulation of vascular tone, renal function, mucosal integrity, inflammation, angiogenesis and tumor growth. $PGE_2$ often causes complex and divergent effects which can be attributed to its activation of four so-called E-type prostanoid receptors (EP1 to EP4). Studies conducted with EP receptor knock-out mice and the recent availability of highly selective pharmacological agonists and antagonists have allowed us to identify distinct — although sometimes overlapping — roles for EP receptor subtypes in $PGE_2$-regulated processes. In this review, we summarize the physiological roles of EP4, its molecular structure and intracellular signaling pathways, and how EP4 receptors might be targeted pharmacologically for the benefit of human disease, including vascular and renal diseases, inflammation, osteoporosis and cancer. Tables 1–3 provide an overview of currently described selective and non-selective agonists, and antagonists for EP4, respectively, and their affinity, dosing and biological effects.

## 2. Prostaglandin $E_2$ and its four receptors

Prostanoids are derived from arachidonic acid, a 20 carbon polyunsaturated fatty acid, which is usually found in phosphoglycerides of mammalian cell membranes (Fig. 1). Arachidonic acid is released by phospholipase $A_2$ from the cell membrane and is converted to $PGG_2$ and then reduced to $PGH_2$ by COX-1 or COX-2 (Smith & Dewitt, 1996; Park & Christman, 2006). In general COX-1 is constitutively active whose expression appears to be regulated developmentally, while COX-2 is usually absent from cells but its expression can be induced in response to different stimuli. However, COX-2 is also constitutively expressed in some tissues, such as the endothelium, kidney, gastrointestinal mucosa and brain (O'Banion, 1999; Grosser et al., 2006; Zidar et al., 2009). The endoperoxide intermediate $PGH_2$ is converted to the different prostanoids ($PGE_2$, $PGI_2$, $TXA_2$, $PGD_2$, $PGF_{2\alpha}$) by specific synthases. In general, the expression pattern of the prostanoid synthases is specific for different cells and determines which prostanoid they will be producing in abundance. $PGE_2$ is generated at large amounts in fibroblasts, monocytes, and epithelial and endothelial cells by three enzyme isoforms, i.e. inducible microsomal PGE synthase-1, and constitutively expressed microsomal PGE synthase-2 and cytosolic PGE synthase (Fig. 1) (Kudo & Murakami, 2005).

The various biological effects of $PGE_2$ are mediated by four EP receptors, which show differential patterns of tissue distribution. EP1 mRNA is ubiquitously expressed in murine tissues, while EP3 receptor mRNA levels are high in adipose tissues, pancreas, kidney and vena cava. EP4 mRNA is mainly expressed in the gastrointestinal tract, uterus, hematopietic tissues and skin, whereas EP2 receptor

**Table 2**
EP2/EP4 receptor agonists.

| Name | Dose, concentration, affinity | Model, species | References |
|---|---|---|---|
| 11-Deoxy-$PGE_1$ | 100 nM–50 μM | Bone resorption, mouse | Sakuma et al., 2000 |
| γ-Lactam PGE analog 2a | 1.7 μg/kg | Bronchodilation, guinea pig | Xiao et al., 2008 |
| γ-Lactam PGE analog 4 | 30–300 μg/kg | Bone fracture healing, rat | Kambe et al., 2012 |

**Table 1**
EP4 receptor-selective agonists.

| Name | Dose, concentration, affinity | Model, species | References |
|---|---|---|---|
| AGN205203 | Ki = 81 nM | HEK-EP4, human | Jiang et al., 2007 |
| | 3 mg/kg | Colitis, mouse | |
| APS-999 Na | 50 μg/animal | Ovarian follicle growth, rat | El-Nefiawy et al., 2005 |
| Cay10598 (19a) | Ki = 1.2 nM | HEK-EP4, human | Billot et al., 2003 |
| CP-044,519-02 | 10 mg/kg/day | Acute and chronic kidney failure, rat | Vukicevic et al., 2006 |
| EP4RAG | 1–3 mg/kg | Myocardial dysfunction, rat | Hishikari et al., 2009 |
| | 10–50–100 nM | THP-1 monocyte migration | Hishikari et al., 2009 |
| L-902688 | 10 nM–10 μM | Bronchi, human | Benyahia et al., 2012 |
| | 10 nM–10 μM | Pulmonary vein, human | Foudi et al., (2008) |
| Lubiprostone | 50–500 nM | Short circuit current in tracheal epithelium and submucosal gland secretion, sheep | Cuthbert, 2011 |
| ONO-4819CD | 36 ng/kg | Ulcerative colitis, human | Nakase et al., 2010 |
| | 300 μg/kg | Cardiac ischemia, mouse | Maruyama et al., 2002 |
| | 1–30 μg/kg 3× a day | Inhibition of bone loss, de novo bone formation, rat | Yoshida et al., 2002 |
| ONO AE1-329 | 25–100 μg/kg | Colitis, mouse | Nitta et al., 2002 |
| | 10 nM–10 μM | Bronchi, human | Benyahia et al., 2012 |
| | 30 nM | Eosinophil inhibition, human | Konya et al., 2011 and Luschnig-Schratl et al., 2011 |
| | 100 nM | Aortic rings, mouse | Hristovska et al., 2007 |
| | 10 nM–10 μM | Pulmonary vein, human | Foudi et al., 2008 |
| | 1 μM | Ductus arteriosus smooth muscle cells, rat | Maruyama et al., 2002 and Yokoyama et al., 2006 |
| | 300 μg/kg | Cardiac ischemia, mouse | Maruyama et al., 2002 |
| | 30–100 μg/kg | Hepatic ischemia, mouse | Kuzumoto et al., 2005 |
| | 30–300 μg/kg | Cerebral ischemia, mouse | Liang et al., 2011 |
| | 30 nM | Human pulmonary endothelial barrier | Konya et al., 2013 |
| | 3–30 nM | Human platelet aggregation | Philipose et al., 2010 |
| | 800 nM/kg/day | Bone formation, mouse | Yoshida et al., 2002 |
| ONO AE1-734 | 0.1 mg/kg/day | Colitis, mouse | Kabashima et al., 2002 |
| $PGE_1$-OH | 10–1000 nM | Human dermal microvascular endothelial angiogenesis | Zhang and Daaka, 2011 |
| TCS 2510 | 1 μM | Renal epithelial cell proliferation, mouse | Liu et al., 2012 |
| | 10 μM | GLP-1 release, mouse GLUTag cells | Coskun et al., 2013 |
| γ-Lactam PGE analog 3 | 30–300 μg/kg | Bone fracture healing, rat | Kambe et al., 2012 |