British Journal of Pharmacology

DOI:10.1111/j.1476-5381.2011.01494.x
www.brjpharmacol.org

COMMENTARY

# At last, a truly selective $EP_2$ receptor antagonist

Mark A Birrell[1] and Anthony T Nials[2]

[1]*Respiratory Pharmacology, Pharmacology & Toxicology Section, Imperial College London, Faculty of Medicine, National Heart and Lung Institute, London, UK, and* [2]*Refractory Respiratory Inflammation Discovery Performance Unit, GlaxoSmithKline Research and Development, Medicines Research Centre, Stevenage, Hertfordshire, UK*

**Correspondence**
Dr Mark Birrell, Respiratory Pharmacology, Pharmacology & Toxicology Section, Imperial College London, Faculty of Medicine, National Heart and Lung Institute, Sir Alexander Fleming Building, London SW7 2AZ, UK. E-mail: m.birrell@imperial.ac.uk

**Keywords**
Prostanoids; prostanoid receptors; $EP_2$ antagonist

**Received**
12 May 2011
**Accepted**
12 May 2011

Ever since the discovery of prostaglandin $E_2$ ($PGE_2$), this lipid mediator has been the focus of intense research. The diverse biological effects of $PGE_2$ are due, at least in part, to the existence of four distinct receptors ($EP_{1–4}$). This can complicate the analysis of the biological effects produced by PGE2. While there are currently selective pharmacological tools to explore the roles of the $EP_{1,3,4}$ receptors in cellular and tissue responses, analysis of $EP_2$ receptor-induced responses has been hampered by the lack of a selective $EP_2$ receptor antagonist. The recent publication in this journal by af Forselles *et al.* suggests that such a tool compound is now available. In their manuscript, the authors describe a series of experiments that show PF-04418948 to be a potent and selective $EP_2$ receptor antagonist. The discovery of this tool compound will interest many scientists and through collaborations with Pfizer they may have access to PF-04418948 to facilitate further investigation of the biology of this fascinating lipid mediator.

## LINKED ARTICLE

This article is a commentary on af Forselles *et al.*, pp. 1847–1856 of this issue. To view this paper visit http://dx.doi.org/10.1111/j.1476-5381.2011.01495.x

## Abbreviations

$EP_2$, prostaglandin $E_2$ receptor-2; $PGE_2$, prostaglandin $E_2$

Ever since $PGE_2$ was first discovered in 1930 by Kurzrok and Leib (1930), this lipid mediator has been the focus of intense research. Yet despite this research effort, we are still learning much about this interesting molecule. The biology of $PGE_2$ is diverse and we now know that it can act, predominantly, on four different receptors [prostaglandin $E_2$ receptor $(EP)_{1–4}$] (Coleman *et al.*, 1984; Narumiya *et al.*, 1999). Recently, aided by the development of more selective pharmacological tools and the use of genetically modified animals (i.e. $EP_{1–4}$ gene disrupted mice), much more has been learnt about the biological actions of $PGE_2$. For example, using these tools, we have compiled data to suggest that $PGE_2$ activates airway sensory nerves and can cause cough via the $EP_3$ receptor (Maher *et al.*, 2009). Further, using selective ligands we have recently shown that in human airways, $PGE_2$ relaxes smooth muscle tone via the $EP_4$ receptor (Buckley *et al.*, 2011). Indeed, there has recently been a plethora of publications describing the actions of $PGE_2$ (Narumiya, 2009; Esaki *et al.*, 2010; Mizuguchi *et al.*, 2010; Aoki *et al.*, 2011; Hosono *et al.*, 2011)., thanks mainly to the excellent tools developed by Ono Pharma and the genetically modified mice produced by Professor Narumiya.

Investigations of the role of the $EP_2$ receptor in responses mediated by $PGE_2$ have proved to be difficult due to the lack of a suitable $EP_2$ receptor antagonist. A recent publication in the *British Journal of Pharmacology* by af Forselles *et al.* (2011) describing in detail a new $EP_2$ receptor antagonist would suggest that there is now a complete set of EP receptor ligands. In their article, the authors provide the results from a series of experiments, demonstrating that PF-04418948 is a potent and selective $EP_2$ receptor antagonist. Selectivity over the other EP ($EP_{1,\ 3\ and\ 4}$) and prostanoid ($DP_1$, $CRTH_2$, IP, FP and TP) receptors is demonstrated in a range of cell-based assays, from which they calculate PF-04418948 to be over 2000-fold selective for the $EP_2$ receptor. Furthermore, the authors state that PF-04418948 does not have any activity itself in the $EP_2$ receptor assay without the presence of an agonist (suggesting it only has antagonist activity at the $EP_2$

receptor) and they show the compound to have little activity against a diverse panel of GPCRs and ion channels at concentrations greatly in excess of that needed to act on the $EP_2$ receptor. The authors have profiled PF-04418948 in $EP_2$ receptor-driven, isolated tissue preparations (agonist-induced relaxation of isolated human myometrium, dog bronchiole and mouse trachea) using $PGE_2$ and the partially selective $EP_2$ agonist butaprost. They then go on to show that their compound has *in vivo* activity in the rat after oral administration. This last feature of this compound is extremely useful as many of the currently selective EP receptor ligands have questionable or unknown *in vivo* activity which makes translation between *in vitro* and *in vivo* model systems difficult.

While we feel there is a need for further characterization of this molecule, for instance in functional, $EP_{1-4}$ receptor-driven, isolated tissue-based assays and *in vivo* modelling systems, the discovery of this compound will be of great interest to many scientists around the world. We thank and commend Pfizer, and its scientists, for all the hard work that led to the discovery of PF-04418948. Hopefully, through collaborations with Pfizer and, eventually, commercial sources, research groups will be able to access PF-04418948 to facilitate research with this fascinating lipid mediator.

## Conflicts of interest

Neither author has any conflicts of interest with this commentary.

## References

Aoki T, Nishimura M, Matsuoka T, Yamamoto K, Furuyashiki T, Kataoka H *et al.* (2011). $PGE_2$ -$EP_2$ receptor signaling in endothelium is activated by haemodynamic stress and induces cerebral aneurysm through an amplifying loop via NF-κB. Br J Pharmacol 163: 1237–1249.

Buckley J, Birrell MA, Maher SA, Nials AT, Clarke DL, Belvisi MG (2011). $EP_4$ receptor as a new target for bronchodilator therapy. Thorax [Epub ahead of print 23 May 2011].

Coleman RA, Kennedy I, Humphrey PPA, Lumley P (1984). Prostanoid receptors – the development of a working classification. Trends Pharmacol Sci 5: 303–306.

Esaki Y, Li Y, Sakata D, Yao C, Segi-Nishida E, Matsuoka T *et al.* (2010). Dual roles of $PGE_2$-$EP_4$ signaling in mouse experimental autoimmune encephalomyelitis. Proc Natl Acad Sci USA 107: 12233–12238.

af Forselles K, Root J, Clarke T, Davey D, Aughton K, Dack K *et al.* (2011). In vitro and in vivo characterisation of PF-04418948, a novel, potent and selective prostaglandin $EP_2$ receptor antagonist. Br J Pharmacol 164: 1847–1856.

Hosono K, Suzuki T, Tamaki H, Sakagami H, Hayashi I, Narumiya S *et al.* (2011). Roles of prostaglandin $E_2$-$EP_3$/$EP_4$ receptor signaling in the enhancement of lymphangiogenesis during fibroblast growth factor-2-induced granulation formation. Arterioscler Thromb Vasc Biol 31: 1049–1058.

Kurzrok R, Leib C (1930). Biochemical studies of human semen: the actions of semen on the human uterus. Proc Soc Exp Biol Med 28: 268–272.

Maher SA, Birrell MA, Belvisi MG (2009). Prostaglandin $E_2$ mediates cough via the $EP_3$ receptor: implications for future disease therapy. Am J Respir Crit Care Med 180: 923–928.

Mizuguchi S, Ohno T, Hattori Y, Ae T, Minamino T, Satoh T *et al.* (2010). Roles of prostaglandin $E_2$-$EP_1$ receptor signaling in regulation of gastric motor activity and emptying. Am J Physiol Gastrointest Liver Physiol 299: G1078–G1086.

Narumiya S (2009). Prostanoids and inflammation: a new concept arising from receptor knockout mice. J Mol Med 87: 1015–1022.

Narumiya S, Sugimoto Y, Ushikubi F (1999). Prostanoid receptors: 23 structures, properties, and functions. Physiol Rev 79: 1193–1226.