COMMENTARY

At last, a truly selective EP₂ receptor antagonist

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Keywords

Prostanoids; prostanoid receptors; EP₂ antagonist

Received

12 May 2011

Accepted

12 May 2011

Ever since the discovery of prostaglandin E₂ (PGE₂), this lipid mediator has been the focus of intense research. The diverse biological effects of PGE₂ are due, at least in part, to the existence of four distinct receptors (EP₁₋₄). 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 EP₂ receptor-induced responses has been hampered by the lack of a selective EP₂ 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 EP₂ 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

EP₂, prostaglandin E₂ receptor-2; PGE₂, prostaglandin E₂

Ever since PGE₂ 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 PGE₂ is diverse and we now know that it can act, predominantly, on four different receptors [prostaglandin E₂ 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. EP₁₋₄ gene disrupted mice), much more has been learnt about the biological actions of PGE₂. For example, using these tools, we have compiled data to suggest that PGE₂ activates airway sensory nerves and can cause cough via the EP₃ receptor (Maher *et al.*, 2009). Further, using selective ligands we have recently shown that in human airways, PGE₂ relaxes smooth muscle tone via the EP₄ receptor (Buckley *et al.*, 2011). Indeed, there has recently been a plethora of publications describing the actions of PGE₂ (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 EP₂ receptor in responses mediated by PGE₂ have proved to be difficult due to the lack of a suitable EP₂ receptor antagonist. A recent publication in the *British Journal of Pharmacology* by af Forselles *et al.* (2011) describing in detail a new EP₂ 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 EP₂ receptor antagonist. Selectivity over the other EP (EP_{1, 3 and 4}) and prostanoid (DP₁, CRTH₂, 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 EP₂ receptor. Furthermore, the authors state that PF-04418948 does not have any activity itself in the EP₂ receptor assay without the presence of an agonist (suggesting it only has antagonist activity at the EP₂

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 EP₂ receptor. The authors have profiled PF-04418948 in EP₂ receptor-driven, isolated tissue preparations (agonist-induced relaxation of isolated human myometrium, dog bronchiole and mouse trachea) using PGE₂ and the partially selective EP₂ 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, EP₁₋₄ 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.

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