

Prostanoids as anti-inflammatory therapy: separating the good from the bad

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Prostanoids are important endogenous signalling molecules that are produced locally both physiologically and in inflammatory diseases and have potent effects on a number of inflammatory processes. Endogenous prostaglandin production consists of several stages: conversion of membrane phospholipid to arachidonic acid via phospholipase A₂, conversion of arachidonic acid to PGG₂ by cyclo-oxygenase (COX), a peroxidase reaction to produce PGH₂ and then conversion of PGH₂ by specific synthases and isomerases to PGE₂, PGI₂, PGF_{2α} or PGD₂. COX is present in most cells, and it is the synthase/isomerase complement of the cell that determines the balance of prostanoids produced by a given cell type. Inflammatory cells tend to produce PGD₂ and PGF_{2α}, whereas airway structural cells such as smooth muscle (airway and vascular), fibroblasts, endothelial and epithelial cells produce an abundance of PGE₂ or PGI₂.¹

In contrast to PGD₂ and PGF_{2α}, which are predominantly pro-inflammatory, PGE₂ is predominantly anti-inflammatory.² PGE₂ inhibits acetylcholine release from parasympathetic nerve endings, mast cell mediator release and cellular responses in eosinophils, macrophages and T lymphocytes in vitro. Inhaled PGE₂ inhibits a number of bronchoconstrictor challenges in patients with asthma in vivo including metabisulphite, ultrasonically nebulised water, exercise and allergen. A role for endogenous PGE₂ has also been implicated in the refractory period, which occurs after bronchoconstrictor challenge in asthma. Everything PGE₂ does is not beneficial, however. Although it relaxes airway smooth muscle at low concentrations, it can cause contraction at higher concentrations in vitro.² When given to patients with asthma in vivo, it also causes a cough, which would limit its potential

usefulness as a therapeutic anti-inflammatory agent as does its relatively short half-life.

PGE₂ acts on four different G-protein-coupled receptors EP₁₋₄.³ Both EP₂ and EP₄ are coupled through adenylylate cyclase to increases in cAMP, suggesting that these receptors are likely candidates for the bronchoprotective effects of PGE₂. In contrast, EP₁ and EP₃ receptor activation is associated with mobilisation of intracellular calcium via phospholipase C β and/or Gi-mediated inhibition of adenylyl cyclase. There are PGE analogues in development, which selectively target different prostanoid receptor subtypes. In order to exploit the beneficial properties of PGE₂ therapeutically, a greater understanding of the pharmacology of prostanoid receptor subtypes is required in order to tease out the receptors responsible for the beneficial compared with the detrimental effects of PGE₂.

The study by Birrell *et al* in this issue of *Thorax*⁴ sets out to try and do this by using a range of cell-based assays and in vitro models to identify the EP receptor mediating the anti-inflammatory actions of PGE₂ in the lung. Previous work has suggested that the bronchodilator properties of PGE₂ in human airways are mediated via activation of the EP₄ receptor,⁵ whereas the undesirable triggering of airway sensory nerves appears to be mediated by the EP₃ receptor.⁶ An advantage of the study by Birrell *et al* is that they profiled the inflammatory status of the EP receptor knockout (KO) mice in an array of preclinical respiratory disease model systems: an endotoxin model to mimic innate immune responses, an allergen asthma model and a cigarette smoke chronic obstructive pulmonary disease model.

In the lipopolysaccharide and allergen models, inflammatory cell infiltration was significantly increased in the EP₄ receptor KO mice (with no change in EP₁₋₃ KO mice) compared with the wild-type control, suggesting a protective role for EP₄ receptor activation. Similar findings were seen with regard to inflammatory cell infiltration into the airway in the

cigarette smoke challenge model where absence of the EP₄ receptor enhanced the inflammatory response. Collectively these studies in a range of mouse model systems provide compelling evidence that EP₄ is the dominant anti-inflammatory EP receptor at least in the mouse.

In parallel with the studies in KO mouse models, they performed additional studies in vitro in mouse and human cell-based assays using cytokine production as a read-out and treating cells with a range of available EP receptor selective pharmacological agents and came to similar conclusions, namely that the EP₄ receptor was the dominant anti-inflammatory prostanoid receptor. As cAMP, the main intracellular second messenger associated with the EP₄ receptor, can stimulate different intracellular signalling proteins, the main two being protein kinase A (PKA) and exchange protein directly activated by cAMP (EPAC),⁷ Birrell's studies also explored which were involved in their cell systems downstream of cAMP elevation. They found that PKA but not EPAC were implicated in the EP₄ receptor effects.

It will be interesting to extend studies with selective prostanoid receptor agonists to man as these agents undergo further development. Unfortunately, things may be more complex in human lung diseases than in the mouse models. We have previously shown that pro-inflammatory stimuli such as interleukin-1β can downregulate EP₄ receptors in airway epithelial cells in vitro.⁸ If this occurs in these and other lung cell types that contribute to airway inflammatory diseases in vivo, it might potentially limit the effectiveness of EP₄-directed therapies. However, inflammation can also interfere with β₂ adrenoreceptor signaling,⁹ and this has not stopped these drugs been used widely and effectively to treat airways diseases. The study by Birrell *et al* is thus of major interest and may help direct prostanoid-based therapeutic approaches selectively targeting the EP₄ prostanoid receptor for lung diseases in the future.

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