EP₄ receptor agonists: the most promising novel bronchodilator for several decades

James Buckley¹, Mark Birrell¹, Sarah Maher¹, Anthony Nials², Deborah Clarke¹, Maria Belvisi¹

¹Respiratory Pharmacology, Imperial College London, London, SW7 2AZ, United Kingdom,
²GlaxoSmithKline Research and Development, Medicines Research Centre, Stevenage, SG1 2NY, United Kingdom

Due to recent safety concerns with beta 2 adrenoceptor agonists (e.g. salbutamol), there has been an ongoing attempt to identify novel bronchodilator agents for use in asthma and COPD. Due to its beneficial action on airway calibre, prostaglandin E₂ (PGE₂) was previously investigated as a potential therapy, however in addition to bronchodilator activity, in clinical studies PGE₂ also produced tussive effects and bronchial irritancy. As PGE₂ mediates its actions via a number of different prostanoid receptors, it was hoped that by selectively targeting individual receptors, the beneficial actions could be selected. In a previous study (Nials et al 1993), the EP₂ receptor was identified as mediating PGE₂-induced relaxation however when tested clinically, an EP₂ agonist (AH13205) produced disappointing results.

To investigate the receptor involved in PGE₂-induced airway smooth muscle relaxation, isolated tracheal tissue from a number of species (guinea pig, mouse, rat, Cyno monkey, human) was sutured to force-displacement transducers (Grass Instruments, U.S.A.) in 10ml organ baths containing 10µM indomethacin-treated Kreb’s Henseleit solution heated to 37°C and bubbled with 95% O₂/5% CO₂. Contractile tone was induced using 1µM carbachol and selective prostanoid receptor agonists and antagonists were evaluated. In addition, the relaxation to PGE₂ was investigated in tracheal segments from prostanoid receptor deficient mice.

The data produced showed that in guinea pig, mouse and Cyno monkey tracheal tissue, PGE₂-induced relaxation is mediated by EP₂ receptors. However in rat and human tissue, the EP₄ receptor appears to mediate PGE₂-induced relaxation. The two EP₂ agonists tested failed to relax human airway samples and 10µM AH6809 (an EP₁/EP₂/DP selective antagonist) failed to inhibit PGE₂-induced relaxation. Conversely, the EP₄ agonist ONO-AE1-329 produced substantial relaxation (61.1% max) and two structurally different EP₄ antagonists GW627368X and ONO-AE3-208 (both 1µM) both inhibited PGE₂-induced relaxation.

These results therefore offer a potential explanation for the poor efficacy of the EP₂ agonist (AH13205) in human subjects. In contrast to guinea pig tissue (where AH13205 produced the expected relaxant response), the EP₄ receptor mediates PGE₂-induced relaxation in human airways. Furthermore, as we have recently (Maher et al 2009) identified the EP₃ receptor as mediating the tussive actions of PGE₂, it appears possible that an EP₄ agonist could potentially produce the beneficial actions of PGE₂ in the absence of bronchial irritation or tussive effects. If this data is paralleled in clinical studies, targeting the EP₄ receptor could produce the most promising novel bronchodilator for several decades.