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**Institutet för miljömedicin
Experimentell Astma- och Allergiforskning**

PROSTAGLANDIN E₂ AS MEDIATOR AND MODULATOR OF AIRWAY SMOOTH MUSCLE RESPONSES

AKADEMISK AVHANDLING

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ABSTRAKT

Prostaglandin E₂ (PGE₂) is a lipid mediator produced by virtually every cell of the human body. Because common non-steroidal anti-inflammatory drugs (NSAIDs) inhibit its biosynthesis, PGE₂ is usually considered to be a 'pro-inflammatory' mediator. The role of PGE₂ in the lung and airways has however always been unclear. In particular, the airway responses caused by activation of its four different EP receptors have been debated. Research on the mechanisms involved in the actions of PGE₂ has previously been limited by the low potency and selectivity of available pharmacological tools.

Recently, a number of potent receptor antagonists and enzyme inhibitors have become available. The aim of this thesis was therefore to characterise airway responses to PGE₂ in greater detail, focusing on the role of its receptors on baseline smooth muscle function and during antigen-induced contractions. Alongside investigating PGE₂ responses, the newly discovered relaxant effects of bitter tasting substances acting at their respective receptors (TAS2Rs) were examined.

The project mainly involved analysis of isometric contractions and relaxations in isolated airways from guinea pigs and humans in organ baths. In addition, mRNA expression of receptors and enzymes was analysed by PCR and prostanoïd release was measured by chemical or immunological methods.

It was found that all four EP receptors, the two cyclooxygenases (COX-1 and COX-2) and three PGE synthases were expressed in the guinea pig trachea and lung. Exogenous PGE₂ induced a bell-shaped concentration-response curve, causing contraction at lower concentrations mediated by the EP₁ receptor and relaxation mediated by the EP₂ receptor at higher concentrations. The spontaneous airway tone was maintained by biosynthesis of endogenous PGE₂, mainly catalysed by COX-2 in the airway epithelium. The level of tone in the preparation was determined by the balance between activation of EP₁ and EP₂ receptors. The EP₁ receptor, but not the EP₂ receptor, displayed homologous desensitisation to endogenous PGE₂.

When the antigen-induced contractions of the guinea pig trachea were studied, it was found that the primary effect of PGE₂ was again to maintain the spontaneous airway tone. When this effect was blocked by EP₁ and EP₂ receptor antagonists, it was revealed that a component of the antigen-response was mediated by prostaglandin D₂ and thromboxane A₂, acting at the thromboxane TP receptor.

In human small airways, PGE₂ induced relaxations mediated by EP₄ receptors at low concentrations and contractions through TP receptors at higher concentrations. In addition, it was discovered that the IgE-dependent contraction of human bronchi could be abolished by the action of exogenous PGE₂ at the EP₂ receptor, an effect presumably involving inhibition of mast cell mediator release.

The bitter tasting substances chloroquine, denatonium, thiamine, and noscapine caused relaxations of human and guinea pig airways with a greater efficacy than beta-adrenergic bronchodilators. TAS2R3, TAS2R4 and TAS2R10 were expressed in the guinea pig trachea. The EP receptor-mediated tone could be relaxed by chloroquine and noscapine, but not by denatonium and thiamine. Although the mechanisms underlying these powerful relaxations remain unknown, the data support the involvement of several different pathways.

In summary, PGE₂ causes contractions and relaxations of guinea pig and human airways, but the receptors involved differ between the two species. Furthermore, the data gathered suggest that EP, TP and TAS2R receptors may be potential targets for the development of drugs to treat asthma and other forms of airway obstruction.

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