NOCICEPTIN/ORPHANINFQ (N/OFQ) COULD REPRESENT A NOVEL TARGET FOR THE TREATMENT OF ASTHMA

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Asthma is characterized by a triad of intermittent airway obstruction, bronchial hyperreactivity and chronic inflammation with structural changes in the airways. The ideal therapy should relieve symptoms, attenuate inflammation and prevent or even reverse remodelling (Brightling et al. 2012).

Airways allergic diseases, such as asthma, occur through activated mast cells, increased numbers of eosinophils, increased numbers of invariant natural killer T cells (NKT), T helper 2 (Th2) and T helper 17 lymphocytes (Th17), and neutrophils and increase in sensory neurogenic release (D'Agostino et al 2002). There is evidence supporting a role for the neuropeptide Nociceptin/OrphaninFQ (N/OFQ) receptor (NOP) and its endogenous ligand N/OFQ in the modulation of neurogenic inflammation, airway tone and calibre. We hypothesized that NOP activation has beneficial effects upon asthma immunopathology and airway hyperresponsiveness (AHR).

Our first study concerning the effects of NOP receptor activation in an animal model of gastroesophageal reflux, has demonstrated the ability of the N/OFQ to modulate bronchoconstriction and vascular permeability induced by the intraesophageal HCl infusion by inhibiting the release of tachykinins from airways sensory nerve. Afterwards we investigate the role of the N/OFQ-NOP receptor system in allergen sensitization. The obtained data have suggested, for the first time, an involvement of the endogenous nociceptin in the modulation of bronchoconstriction in sensitized mice, showing a role for the N/OFQ-NOP receptor pathway in the AHR induced by allergen, probably through a modulation of the immune response. In fact N/OFQ treatment, before or during sensitization, reduced airway constriction and immunocyte trafficking to the lung, in particular eosinophils. N/OFQ also reduced inflammatory mediators and mucin production. Moreover, in our recent study, we investigate the N/OFQ-NOP receptor pathway ability in the regulation of a Th2-like environment. These data have evidenced the reduction of IL-13 lung levels and IL-4+ CD4+ T cells in the mediastinic lymph node through a modification of the mature/active status of DCs into the lung of OVA-sensitized mice.

Finally, the expression and function of N/OFQ-NOP receptor pathway has been examined in healthy and asthmatic human airway tissues. We found that NOP receptors were expressed on a wide range of human immune and airway cells, in particular eosinophils expressed N/OFQ-precursor mRNA and their number correlated with N/OFQ concentration. In asthmatic human lungs N/OFQ immunoreactivity was elevated and NOP receptor activation inhibited migration of immunocytes.

These studies report for the first time a critical role for this system in asthma and describes a novel agent with combined anti-hyperresponsiveness and immunomodulatory properties.

This combination of beneficial effects is rarely observed and supports our assertion that this could open a completely new potential target/strategy in the treatment of asthma.

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