NOCICEPTIN/ORPHANINFQ (N/OFQ) COULD REPRESENT A NOVEL TARGET FOR AIRWAY INFLAMMATION TREATMENT

BD. BRUNO D'AGOSTINO, DEPT OF EXPERIMENTAL MEDICINE UNIVERSITY OF CAMPANIA "LUIGI VANVITELLI", NAPLES ITALY
GS. GIUSEPPE SPAZIANO, DEPT OF EXPERIMENTAL MEDICINE UNIVERSITY OF CAMPANIA "LUIGI VANVITELLI", NAPLES ITALY
FR. FRANCESCO ROSSI, DEPT OF EXPERIMENTAL MEDICINE UNIVERSITY OF CAMPANIA "LUIGI VANVITELLI", NAPLES ITALY

Inflammation normally is closely related by a response of the immune system to injury which is beneficial to the host under normal circumstances. An aberrant immune response to non-pathogenic stimuli in the asthmatic airway leads to a chronic inflammatory response relevant to the pathogenesis of the disease. 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 inflammatory 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 the N/OFQ-NOP receptor system could play a role in the pathogenesis of airway inflammation, one of the hallmarks of asthma.

In a well established animal model of asthma, for the first time, we documented an involvement of the endogenous N/OFQ in the modulation of bronchoconstriction in sensitized mice, showing a role for the N/OFQ-NOP receptor pathway in the airway hyperresponsiveness (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 levels of inflammatory mediators such as IL-4, IL-5, IL-12 and IL-13, Th2 cytokines linked to inflammation and IgE in BAL fluid.

Moreover, N/OFQ is able to regulate IL-4+ CD4+ T cells in LNs of a Th2-like environment in OVA-sensitized mice. In support of these data in the lung tissues, we found a modulation of the levels of IL-13, a cytokine closely related to IL-4, able to bind to IL-4 receptor α and also expressed by Th2 cells from patients with asthma. Moreover, this study showed that N/OFQ treatment facilitated the recruitment of DCs which were in their active phenotype (CD80+ cells).

Finally, the expression and function of N/OFQ-NOP receptor pathway has been examined in healthy and asthmatic human airway tissues. 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 inflammation 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 airway inflammatory desease such as asthma.

1. Brightling C et al. (2012). Clin Exp Allergy. 42:638–49.

2. D'Agostino B et al (2002). Clin Exp Allergy. 32:472–9.