NOCICEPTIN REDUCES THE INFLAMMATORY IMMUNE MICROENVIRONMENT IN A CONVENTIONAL MURINE MODEL OF AIRWAY HYPERRESPONSIVENESS

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Asthma is a disease characterized by chronic inflammation which is at the basis of mucus overproduction and airway-wall 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 (Buc et al 2009) and increase in sensory neurogenic release (D'Agostino et al 2002). Th2 cells (IL-4, IL-5 and IL-13) and type 2 innate lymphoid cells (ILCs) (IL-5 and IL-13) produce Th2-like cytokines. Furthermore, in this context, dendritic cells (DCs) and professional antigen-presenting cells (APCs) are essential for the induction and priming of the Th2- like response during asthmatic desease (Hammad et al.2008).

Our studies, previously conducted, showed that the neuropeptide Nociceptin/Orphanin FQ (N/OFQ), an endogenous heptadecapeptide (Meunier et al. 1995) that selectively binds a G protein-coupled receptor (GPCR) named NOP receptor, is involved in airway hyperresponsiveness (AHR) (Sullo et al. 2013), suggesting its potential involvement in the regulation of the inflammatory response into the lung. However, the role of Nociceptin at modulating the inflammatory immune microenvironment in asthma is still unclear.

To analyze the role of N/OFQ in the regulation of a Th2-like environment, we used a conventional murine model of AHR. Methods Balb/c and CD1 mice were sensitized to ovalbumin (OVA) and treated with saline solution or N/OFQ, at days 0 and 7. A group of Balb/c mice were killed at 7 and 14 days from the first sensitization for the inflammatory profile evaluation while a group of Balb/ c and CD1 mice were aerosol-challenged from day 21 to 23 with OVA and killed 24 h later for functional evaluations. Results In OVA-sensitized mice, N/OFQ significantly reduced IL-4+ CD4+ T cells in lymph nodes (LN) and IL-13 in the lungs, while it induced IFN-gamma increase in the lung. The efflux of dendritic cells (DCs) to the mediastinic LN and into the lung of OVA-sensitized mice was reduced in N/OFQ-treated mice. N/OFQ reduced the expression of CD80 on DCs, indicating its ability to modulate the activation of DCs. In a less prone Th2-like environment mice strain, such as CD1 mice, N/OFQ did not modify lung resistances as observed in BALB/c mice. Finally, spectroscopic data showed the N/OFQ was able to interact onto the membrane of DCs obtained from Balb/c rather than CD1 mice, indicating its ability to modulate AHR in a Th2-like environment with a direct activity on DCs.

Our data confirmed the capability of N/OFQ to modulate the immune microenvironment in the lung of Th2-biased, OVA-sensitized Balb/c mice, suggesting N/OFQ-NOP axis as a novel pharmacological tool to modulate the inflammatory immune microenvironment in asthma.

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