DRIES VAN ELST

MECHANISMS OF ASTHMA ENDOTYPE ASSOCIATED WITH THE METABOLIC SYNDROME – THE EFFECTS OF HORMONE STIMULATION ON THE BRONCHIAL SMOOTH MUSCLE CELLS

or

BADANIA MECHANIZMÓW ENDOTYPU ASTMY ZWIĄZNEGO Z ZESPOŁEM METABOLICZNYM – WPŁYW HORMONÓW NA FUNKCJE KOMÓREK MIĘŚNI GŁADKICH OSKRZELI

Rozprawa doktorska

Abstract

Background: Asthma is a chronic, immune-mediated inflammatory disease of the respiratory system, affecting more than 300 million people worldwide. Asthma is a heterogenous disease and several clinical and immune phenotypes have been distinguished. One of them is obesity-associated asthma, characterized by neutrophilic infiltration of the airways, frequent exacerbations and poor response to therapy with inhaled corticosteroids. With steady increase in the prevalence of both diseases, obesity-associated asthma is a major socioeconomical burden.

Aim: We aimed to uncover the role of obesity hormones leptin and insulin in their capacity to influence the immune responses in asthma. We specifically focused on their impact on human bronchial smooth muscle cells (HBSMCs) as the determinants of long-term disease outcomes.

Material and methods: We exposed HBSMCs *in vitro* to a range of sub- and supraphysiological concentrations of leptin and insulin. Next, in order to mimic the pro-inflammatory environment present during allergic hypersensitivity reactions, we exposed HBSMCs to a combination of interleukin 4 (IL-4) or interferon γ (INF-γ) and an obesity hormone. We measured immune receptor expression via RT-PCR and adipokine and cytokine production using cytometric bead arrays.

Results and discussion: The expression of histamine receptor 1 (HR1), IL-13 receptor and glucocorticoid receptor NRC31 by HBSMCs decreased upon exposure to both leptin and insulin. Furthermore, exposure to insulin stimulated fibroblast growth factor-1 (FGFa) expression in a dose-dependent manner. Exposure to obesity hormones caused a transient reduction in production of IL-6 and IL-8. Exposure to IL-4 and IFN-γ caused an upregulation in IL-6, and downregulation in IL-8 production, regardless of additional insulin or leptin exposure.

Conclusion: Leptin and insulin affect the expression of immune receptors and cytokine production by HBSMCs. In physiological concentrations these hormones have an anti-inflammatory effect, which disappears at supraphysiological concentrations, as seen in obese patients.