Eosinophils in childhood asthma
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Summary

In this thesis several aspects of the contribution of the eosinophil to the pathophysiology of childhood asthma have been studied and described.

In the 1st chapter the pathophysiology of asthma is discussed, with special emphasis on the contribution of the eosinophil.

In the 2nd chapter we describe a possible relationship between age and both IgE and the number of eosinophils in childhood asthma. From previous clinical observations we hypothesized that IgE would increase and the number of eosinophils would decrease with age. In a retrospective study design we found that IgE increased and the number of eosinophils decreased with age in the population of 182 newly admitted children with asthma. This age-dependency of IgE and the number of eosinophils was less pronounced than we expected. This difference in results can possibly be due to selection of a group of children with considerable heterogeneity in the presence of atopy. Another explanation could be a difference in the severity of asthma of the population studied. Thirdly, we used a regression analysis to analyze the data, whereas other investigators compared mean values of IgE and eosinophils between artificially-created age-categories. The small effect of age on IgE and eosinophils in our population of asthmatic children is not easily explained by the concept of an imbalance in Th1/Th2-cell produced cytokines as a fundamental mechanism for the pathophysiology of atopic asthma.

In the 3rd chapter we describe the cytokine pattern produced by mononuclear cells in peripheral blood of 22 children with asthma compared with 17 healthy non-atopic controls. Consistent with findings reported in studies performed in asthmatic adults, we expected to find a Th2-cell pattern of cytokines in asthmatic children. The concentrations of Interleukin-4 (IL-4), Interferon-γ (IFN-γ) and Interleukin-5 were measured in serum and supernatants of cultures of peripheral blood mononuclear cells (PBMC). Production of IFN-γ in supernatants of cultures of stimulated PBMC’s lower and the ratio of IL-4/IFN-γ higher in the asthmatic children compared with the controls (all differences were significant). The number of eosinophils were related to the concentration of IL-4 and IL-5 in supernatants of cultures of stimulated PBMC’s. Lung function (FEV₁) and IgE were inversely related to IFN-γ in supernatants of cultures of stimulated PBMC. We concluded that the pattern of cytokines produced by PBMC of children with moderate stable
activity, resulting in a dominance of Th2-cell activity. The findings in this study indicate the importance of IFN-γ with respect to the pathophysiology of childhood asthma. The cytokine pattern found suggests the existence of insufficient Th1-cell activity in children with asthma, which could be compatible with a Th2-cell dominance.

In the 4th chapter we describe the degree of in vivo 'priming' of the eosinophils in the peripheral blood, measured as the percentage of hypodense eosinophils, which was increased in asthmatic children compared with healthy non-atopic controls. In asthmatic adults it was found that the sedimentation procedure (by which the leukocytes are separated from the erythrocytes) induced an increase in in vitro percentage of hypodense eosinophils in the peripheral blood. We determined a density profile of eosinophils in 18 children with allergic asthma and in 15 healthy non-atopic controls. Density was determined using two different procedures: erythrocytes were removed by isotone lysis in the first procedure (the direct method) and by the use of dextran sedimentation in the second procedure (dextran method). Results showed an increase in the in vitro percentage of hypodense eosinophils only if the dextran method was used to remove the erythrocytes. The in vitro percentage of hypodense eosinophils was significantly related with the number of eosinophils and with lung function when the direct method was used. We concluded that an increased percentage of hypodense eosinophils can be generated in vitro by dextran sedimentation, which suggests a 'primed' state of eosinophils in vivo in patients with asthma.

In the 5th chapter we describe the value of serum ECP and EDN (as in vitro parameters of eosinophil activation) and urinary EDN (EDN\textsubscript{o}) in the diagnosis of pediatric asthma. We determined the number of eosinophils, serum ECP and EDN and EDN\textsubscript{o} in 22 children with stable allergic moderate asthma, aged 4 to 14 years, and in 17 non-atopic healthy controls. Lung function tests (FEV\textsubscript{1} and PC\textsubscript{20}) were measured in children older than 8 years of age. Children younger than 8 years of age recorded symptoms and peak flow (PEFR) values during 1 week. At the time of the study the asthmatic children were free of symptoms. No significant difference in PEFR values was found between the asthmatic children and controls. The FEV\textsubscript{1} was significantly lower in asthmatic children compared with controls. The number of eosinophils, serum ECP and EDN and EDN\textsubscript{o} were signi-
Summary

Significantly higher in the asthmatic children compared with the controls. Serum ECP, and EDN and EDN$_u$ were related with the number of eosinophils. The number of eosinophils and EDN$_u$ were significantly related to the nocturnal PEFR and to the FEV$_1$. In conclusion, our results suggest that the determination of the serum and urine concentrations of eosinophil derived proteins can be determined in stead of the number of eosinophils to diagnose asthma in children. Especially urinary concentration of EDN$_u$ might be an important alternative and non-invasive tool in young asthmatic children.

In the 6th chapter we describe the effect of treatment with FP on several parameters of mast cell and on in vitro parameters of eosinophil activation in the the study design as described in chapter 7. Because FP is een anti-inflammatory drug, we expected to see a change in inflammatory parameters during treatment with FP. As a parameter of mast cell activation N$\text{\textdegree}$-methyl-histamine and as in vitro parameters of eosinophil activation serum ECP and EDN and urinary EDN (EDN$_u$) were determined. In the FP group, we observed a significant decrease in symptoms and bronchial hyperreactivity. (Chapter 7) We found no difference between the two treatment groups in any of the parameters measured during treatment. Also, we also did not find a significant change in any of the laboratory parameters within the FP group. The only parameter that tended to decrease was EDN$_u$, with a p-value < 0.07. We conclude that treatment of children with stable, moderate asthma with FP 100µg bd has a local rather than a systemic anti-inflammatory effect. Our results warrant further investigation of EDN$_u$ as a possible parameter to monitor inflammation.

In the 7th chapter we describe effects and side-effects of treatment with a recently developed inhaled corticosteroid, fluticasone propionate (FP), in 35 children with stable, moderate asthma, in a double blind placebo-controlled trial. After the treatment period there was a follow-up period of 4 weeks during which only bronchodilators were allowed. At home symptoms of asthma, the use of $\beta_2$-mimetics and peak expiratory flow (PEFR) were registered in a diary twice daily. Each month, lung function, bronchial hyperresponsiveness (PC$_{20}$-histamine) and reversibility to $\beta_2$-mimetics were determined. We found that during treatment wheezing decreased and all PEFR values increased in the FP group. FEV$_1$ increased, PC$_{20}$-histamine and reversibility decreased in the FP group. All the observed changes were significant, with exception of the change in nocturnal PEFR. The effect of FP on symptoms and lung function were transient, since
four weeks after cessation of FP, all parameters had returned to pre-treatment values. Side-effects regarding influence of FP on the hypothalamus-pituitary-adrenal axis (HPA-axis) were measured as serum and urinary cortisol concentration under fasting conditions. During treatment serum cortisol did not change and urinary cortisol significantly decreased in the FP group, only when the decrease was compared with an unexplained increase in the placebo group. We conclude that FP 100 μg bd is effective in children with moderate stable asthma. With respect to side effects, additional studies are necessary to exclude suppression of the HPA-axis during treatment with FP 100 μg bd.

In the 8th chapter we discuss the contribution of the studies presented in this thesis to the pathophysiology of asthma and possible issues for future research, emerging from this thesis.