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**Studies on  
neuroimmune interactions in allergic inflammation**  
with focus on neurotrophins

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## ABSTRACT

Allergic asthma is a chronic airway disease characterized by an eosinophilic inflammation, bronchoconstriction, increased mucus production and bronchial hyperreactivity. The disease involves several mediators and cell types and is associated with a Th2-mediated immune response.

Stress is a factor reported to deteriorate the allergic inflammation. Stress can influence the immune system by activating the HPA axis, resulting in release of glucocorticoids which could effects functions such as leukocyte trafficking and mediator release. These functions could be important for the course of the allergic inflammation.

NGF, BDNF and NT-3 are members of the neurotrophin family, and since they have important functions in both the nervous and immune systems they have been suggested to play a role as neuroimmune modulators. The neurotrophins are essential growth factors in the nervous system, and can also be produced by and activate inflammatory cells. Elevated neurotrophin levels have been found both in blood and locally in the airways of asthmatic subjects, and the levels have been shown to be elevated further following allergen exposure. The neurotrophins have also been linked to bronchial hyperreactivity. However, it is not completely established which cells in the airways that produce the elevated levels of neurotrophins. Further, the levels of NGF have been found to be elevated in healthy humans in response to stress, but it is unknown if stress affects other neurotrophins than NGF, such as BDNF, and whether the neurotrophins are regulated differently in allergic compared to healthy subjects in response to stress.

The first major focus of this thesis was to determine if bronchial smooth muscle cells (SMC) could be a source of the neurotrophins in the human airways, and how inflammatory cytokines might influence such production. This was studied by using an *in vitro* cell culture model. The second focus was to determine how stress could influence immune regulation, allergic inflammation and neurotrophin release, and the possible involvement of glucocorticoids in stress-evoked neuroimmune interaction. This was performed by utilizing both human and *in vivo* animal stress models.

It was shown that human bronchial SMC could produce NGF, BDNF and NT-3, and that the production was differentially regulated by inflammatory cytokines. In the human stress model, stress increased the proportion of regulatory T-cells in both allergic and healthy subjects, whereas a decrease in blood NK cell numbers and Th1/Th2 cytokine ratio was observed in allergic subjects only. Furthermore, PBMC from asthmatic subjects released more BDNF than PBMC from healthy controls. In response to stress, the release of BDNF from PBMC increased in healthy controls, but not in asthmatic subjects. However, the levels of BDNF from asthmatic subjects at the stress period correlated positively to the levels of IL-5. In the allergic animal model, stress aggravated airway eosinophilia. The stress-induced eosinophilia was reduced when glucocorticoid release was inhibited. In response to stress, the levels of NGF decreased in the airways of non-allergic animals, whereas higher levels of NGF were detected in the airways of allergic compared to non-allergic animals during stress. In contrast to the eosinophils, the NGF levels were elevated when glucocorticoid release was inhibited.

The results indicate that in inflammatory conditions, human bronchial SMC may be a source of neurotrophins. Also, PBMC may be a source of neurotrophins, especially in allergic inflammation. Further, atopic and non-atopic subjects shared some immune changes in response to stress. However, other stress-induced immune changes are unique to atopic individuals, indicating that some pathogenic mechanisms in atopics may be more strongly affected by stress than others. Data also supports an increased eosinophilic airway inflammation and increased neurotrophin production in response to stress, and an involvement of glucocorticoids in these responses. Altogether, it is suggested that stress could contribute to an aggravated allergic inflammation, and that neurotrophins may be suggested as messengers in this response.

**Keywords:** Allergic inflammation, neuroimmune interaction, neurotrophins, smooth muscle cells, stress

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