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Increased Th2 Cytokine Secretion, Eosinophilic Airway Inflammation, and Airway Hyperresponsiveness in Neurturin-Deficient Mice

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Neurotrophins such as nerve growth factor and brain-derived neurotrophic factor have been described to be involved in the pathogenesis of asthma. Neurturin (NTN), another neurotrophin from the glial cell line-derived neurotrophic factor family, was shown to be produced by human immune cells: monocytes, B cells, and T cells. Furthermore, it was previously described that the secretion of inflammatory cytokines was dramatically stimulated in NTN knockout (NTN−/−) mice. NTN is structurally similar to TGF-β, a protective cytokine in airway inflammation. This study investigates the implication of NTN in a model of allergic airway inflammation using NTN−/− mice. The bronchial inflammatory response of OVA-sensitized NTN−/− mice was compared with wild-type mice. Airway inflammation, Th2 cytokines, and airway hyperresponsiveness (AHR) were examined. NTN−/− mice showed an increase of OVA-specific serum IgE and a pronounced worsening of inflammatory features. Eosinophil number and inflammation using NTN were rescued by OVA partially. NTN is a protective cytokine in airway inflammation. This study investigates the implication of NTN in a model of allergic airway inflammation and AHR in a murine model of asthma. The Journal of Immunology, 2011, 186: 6497–6504.

A llergic asthma is characterized by an inflammatory airway obstruction triggered by inhalation of specific allergens. A hallmark of allergic asthma is an inappropriate regulation of the Th1/Th2 balance in favor of a Th2 response. Asthmatic airways are characterized by infiltrates of eosinophils and T lymphocytes secreting Th2 cytokines: IL-4, IL-5, and IL-13 (1). The production of IL-5 results in maturation and enhancement of recruitment of eosinophils into airways mucosa. Asthma may result in acute life-threatening reactions but more commonly results in a chronic disabling disease. Many efforts have been spent in the last 10 years to characterize the regulatory events involved in the balance of Th1/Th2 cytokines, to identify significant therapeutic targets. An effective therapy for asthma would be to inhibit the development of such allergen-specific Th2 cells, but the factors responsible for the initial induction of the Th2-like response in vivo remain incompletely understood.

Neural regulation of the airways consists of cholinergic, adrenergic, and nonadrenergic noncholinergic nerves. The nonadrenergic noncholinergic nervous system, through the release of neuropeptides such as substance P, contributes to airway smooth muscle contraction and to airway hyperresponsiveness (AHR) and modulates neurotrophin synthesis (2). Neurotrophins are molecules originally described for their effects on neuronal cells. They control differentiation, development, and survival of neurons (3, 4). Factors with a neurotrophic activity can be divided into three structurally different families: 1) the nerve growth factor (NGF) family including NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3, and neurotrophin-4; 2) the ciliary neurotrophic factor/IL-6 family; and 3) the glial cell line-derived neurotrophic factor (GDNF) family, including GDNF, neurturin (NTN), artemin, and persephin. Neurotrophins such as NGF and BDNF are expressed in a variety of nonneural tissues, including the pulmonary system (5). Recent studies suggest that NGF and BDNF participate in the pathogenesis of many features and symptoms of asthma (2, 6–8).

Intensive research has focused on GDF, which is the prominent member of the neurotrophin family; however, several recent reports suggest that GDNF family members may also modulate airway inflammation. It was described that GDNF is expressed in mouse lung, in particular in airway smooth muscle cells. After allergen challenge in OVA-sensitized mice, the number of GDNF+ cells was shown to increase within the inflammatory infiltrate (9). Another member of this family, NTN, exerts its effects through a multi-component receptor system consisting of the GDNF family receptor α 2 (GFRα-2) and the proto-oncogene RET (10, 11). It was previously shown that NTN is produced by human immune cells: monocytes, B cells, and T cells (12). NTN is also structurally similar to TGF-β1, and it was demonstrated that TGF-β1 is a protective cytokine in airway inflammation (13). Furthermore, it was described that the production of inflammatory cytokines was dramatically stimulated in the corneal epithelia of the NTN knockout (NTN−/−) mice. These mice also have an immune
activation of the conjunctival epithelium and an abnormal gut motility caused by a reduction in substance P secretion by gut muscle cells (14, 15). In this study, we assessed the influence of NTN on lung function. NTN−/− mice were investigated for airway inflammation and for development of AHR after sensitization and challenge with OVA.

**Materials and Methods**

**Mice**

C57BL/6 mice were obtained from Harlan (Horst, The Netherlands). NTN−/− mice on C57BL/6 background were kindly provided by Prof. Jeffrey Milbrandt (Washington University School of Medicine, St. Louis, MO). Mice were kept under specific pathogen-free conditions and were used at 6–8 wk of age. All procedures respected current European regulations and were approved by the National Animal Research Authority.

**Sensitization and airway challenge**

Mice were sensitized with OVA (20 μg/injection; grade V; Sigma, Bornem, Belgium) emulsified in 2.25 mg aluminum hydroxide (Sigma) by i.p. injections in a total volume of 200 μl PBS on days 1, 14, and 21, followed by 1% OVA in 50 μl normal saline administered intranasally after a short anesthesia with halothane on days 27, 28, and 29. Control mice received i.p. injections of aluminum hydroxide in PBS and were challenged with normal saline intranasally. On day 30, AHR was measured as described later, followed by collection of samples for further analysis.

**Intranasal NTN treatment of mice**

After a short anesthesia with halothane, 50 μl (5 μg/ml) recombinant mouse NTN (R&D Systems, Abingdon, U.K.) diluted in PBS was administered intranasally 1 h before the OVA challenge on days 27, 28, and 29. Control mice received PBS 1 h before the OVA or PBS challenge on days 27, 28, and 29.

**Determination of airway responsiveness**

Airway function was assessed by measuring changes in lung resistance and dynamic compliance (Cdyn) in response to increasing doses of inhaled methacholine. Before testing, mice were anesthetized by s.c. injection of 80 mg/kg ketamine, 10 mg/kg xylazine, and 2.5 mg/kg midazolam. Then mice were tracheotomized, mechanically ventilated, and lung function was analyzed by Flexivent equipment (Emka Technologies, Paris, France).

**Bronchoalveolar lavage fluid, lung, and lymph node cell isolation and analysis**

Immediately after assessment of AHR, lungs were washed via a tracheal tube with PBS and 5% BSA (700 μl) followed by PBS (2 × 500 μl). Lung cells were isolated using collagenase digestion, followed by staining for FACS analysis. Lung draining lymph nodes (LNs) were excised from mice, and cells were isolated, adjusted to 5 × 10⁷ cells/ml, and cultured in 48-well plates in DMEM supplemented with 10% FBS, 100 U/ml penicillin/streptomycin, and IL-2 (1000 U/ml) for 1 or 3 d with or without OVA (200 μg/ml). Bronchoalveolar lavage fluid (BALF), lung, and lung draining LN supernatants were frozen at −80°C for later cytokine analysis. All cell culture reagents were purchased from Invitrogen (Paisley, U.K.).

**Measurement of OVA-specific Abs**

Before performing BALF, blood was removed from the heart of mice using a syringe for measurement of OVA-specific IgG1, IgG2a, and IgE. Serum levels of anti-OVA IgG1, IgG2a, and IgE were measured by ELISA. Ninety-six-well plates were coated with either OVA or purified anti-IgE (BD Biosciences, Erembodegem, Belgium). After addition of serum samples, IgE standard (BD Biosciences), biotin rat anti-mouse IgG Ab (BD Biosciences), goat anti-mouse IgG1 Ab, or goat anti–mouse IgG2a Ab (SEROTEC, Oxford, UK) was used as detecting Ab, and the reaction was developed using alkaline phosphatase. The OVA-specific Ab titer of the sample was related to pooled standards that were generated in the laboratory and expressed as ELISA units per milliliter. OVA-specific IgE concentrations were calculated by comparison with the defined IgE standards.

**Cytokine measurement**

The levels of IL-4, IL-5, IL-6, IL-13, IFN-γ, and TNF-α in BALF, lung, and lung draining LN culture supernatants were measured by Cytometric Bead Array (CBA; BD Biosciences), according to the manufacturer’s protocol.

**Lung histology**

After BALF, the lungs were collected, fixed in 4% paraformaldehyde, and embedded in paraffin. Lung tissue sections were stained with H&E or with periodic acid-Schiff (PAS) to assess the airway inflammation and goblet cell metaplasia, respectively. All slides were read by an observer who was blinded to the treatment groups. The extent of peribronchial inflammatory cell infiltration around the bronchi in the lung tissue was quantified on a 0–3 scale. The histology in untreated control mice was defined as 0, and maximum changes were given a score of 3 as previously described (16). Pictures were taken with a Leica microscope with a camera (model DMI 6000B).

**RT-PCR**

Total RNA was extracted from lung, brain, and lung draining LN tissues with the RNeasy mini kit (Qiagen, Venlo, The Netherlands). cDNA was

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**FIGURE 1.** Expression of GFRα-2 mRNA by RT-PCR. Tissues from WT brain, lung, and lung draining LN were prepared. The experiments were performed by using primers for GFRα-2 and GAPDH as a housekeeping gene. There were three mice in each group. B, brain; L, lung; W, water.

**FIGURE 2.** OVA-specific Abs in the serum. Serum titers for OVA-specific Ab in NTN−/− and WT mice were determined after sensitization and challenge. Data are derived from three mice per group of five independent experiments (n = 15). The results for each of the groups are expressed as means ± SEM. Significant differences (*p < 0.05, ***p < 0.001) between the WT OVA versus NTN−/− OVA and PBS versus OVA groups are observed. EU, ELISA units.
reverse transcribed from 1 μg total RNA by using Primerscript Reverse Transcriptase (TAKARA, Shiga, Japan), according to the manufacturer’s instructions. For the PCR experiment, the TAKARA Taq was used. Primers for GFRα-2 were as follows: forward, 5'-CTC TGG TGG GCT CCC AAG CTT GCC-3'; reverse, 5'-GAG TCC CCG GCC ACA GCC CCA TC-3'; size, 328 bp. Primers for GAPDH were as follows: forward, 5'-TGA GTA TGT CGT GGA GTC TAC-3'; reverse: 5'-AGT TGT CAT ATT TCT CGT GGT TC-3'; size, 200 bp. PCR synthesis was run for 35 cycles (2 min at 94˚C, 30 s at 94˚C, 30 s at 65˚C for GFRα-2 and 58˚C for GAPDH, 1 min at 72˚C) followed by a final extension at 72˚C for 7 min.

Flow cytometry

Anti-mouse Ab used for flow cytometry were as follows: CD19-FITC and Gr-1–PE (Immunotools, Friesoythe, Germany), CCR3-PE (R&D Systems), NK1.1-PECy7, CD11c-allophycocyanin, and CD3-allophycocyanin-Alexa 780 (eBioscience, San Diego, CA). The analysis was performed as described previously (17, 18).

Statistical analysis

The statistical significance of differences was determined by one-way ANOVA Newman–Keuls test. The values were expressed as means ± SEM from independent experiments. Any difference with a p value <0.05 was considered significant.

Results

NTN receptor GFRα-2 mRNA expression in lung and lung draining LNs

The presence of GFRα-2, the NTN receptor, has been observed in mouse lung by Northern blot analyses (19). We have corroborated
this observation by RT-PCR: the expected GFRα-2 transcripts were detected in lung tissue and in lung draining LNs (Fig. 1). This finding indicates that the gene of the NTN receptor is transcribed in tissues localized at the site of inflammation in our animal model.

**Ab responses to OVA sensitization and challenge**

To investigate the role of NTN in allergic airway inflammation, we used OVA-sensitized NTN<sup>−/−</sup> and wild-type (WT) mice. One hallmark of allergic asthma is the production of allergen-specific IgE. As shown in Fig. 2, in nonsensitized mice (PBS i.p.), anti-OVA Ab could not be detected in serum. After sensitization and challenge with OVA, the IgE levels were significantly higher in immunized NTN<sup>−/−</sup> mice compared with their WT counterparts. Furthermore, we observed significantly reduced IgG2a levels in OVA-sensitized NTN<sup>−/−</sup> mice.

**Eosinophil accumulation in BALF and lung**

Sensitization and challenge with OVA in NTN<sup>−/−</sup> and WT mice affected the composition of the cells recovered in BALF and lung tissue. In both groups of negative control mice, macrophages were the predominant cell type in BALF (Fig. 3A). However, after sensitization and challenge with OVA, the predominant cells in the BALF and in the lung were eosinophils in both NTN<sup>−/−</sup> and WT mice. In NTN<sup>−/−</sup> mice, a significantly higher eosinophil accumulation was observed in the BALF (43 ± 3.9% SEM) compared with WT mice (29 ± 3.6% SEM) (Fig. 3A). The cellular composition of lung tissues also showed a marked increase of...
eosinophils (Fig. 3B). Similar to the BALF, there was a significantly higher level of eosinophils in lung tissue of NTN−/− compared with WT mice (20.5 ± 2.3% SEM and 14 ± 2.3% SEM, respectively) (Fig. 3B).

Pulmonary inflammation

Lung histology was assessed 24 h after the last OVA challenge. In control groups, H&E staining revealed no airway inflammation (Fig. 4A, 4B). In contrast, a significant eosinophilic and monocellular cell infiltrate was apparent in both perivascular and peribronchial areas in OVA-sensitized WT mice (Fig. 4C, 4G). Under the same conditions, sections from NTN−/− lung tissue revealed that the level of infiltration of inflammatory cells into the peribronchial region was greater compared with those in WT mice (Fig. 4C, 4D). The peribronchial infiltration scores were increased significantly in NTN−/− mice after OVA sensitization and challenge compared with the score found in the WT mice (Fig. 4I). PAS staining of mucus was negative in control groups (Fig. 4E, 4F), whereas mucous-producing epithelium was present after OVA challenge in WT and NTN−/− mice (Fig. 4G, 4H). In contrast with data obtained for cell infiltration, the mucous secretion score was not higher in NTN−/− mice compared with that seen in WT mice (Fig. 4G–I). The percentage of blood eosinophils was determined at the time of tissue harvest. Eosinophil levels in immunized NTN−/− and WT mice were similar (n = 10, data not shown).

Cytokine levels in BALF and lung

To further investigate the effect of NTN on allergic inflammation, we measured cytokine production in the BALF and lung supernatants by CBA. To observe all parameters implicated in the inflammatory response, and the GFRα-2 receptor expression was detected in these organs. The ratio of CD4+ and CD8+ cells in the lung draining LNs did not differ between the OVA-sensitized WT and NTN−/− mice (data not shown). The lung draining LN cells were isolated and restimulated in vitro with OVA for 1 and 3 d to investigate cytokine production. The increase of IL-4, IL-5, and also IL-13 production by OVA immunization was significantly higher in NTN−/− mice compared with WT mice after 1 d (data not shown). This difference was even more pronounced after 3 d of culture (Fig. 5C). In contrast, there were no significant differences in TNF-α, IFN-γ, IL-6, and IL-17 production (data not shown).

The cytokine data from BALF, lung tissue, and lung draining LN of immunized animals demonstrate a consistent pattern of much higher Th2 cytokine levels (IL-4, IL-5, and IL-13) in NTN−/− compared with WT mice, whereas levels of the other types of cytokines (Th1 and Th17) were not significantly affected by the absence of functional NTN genes.

Airway responsiveness

We then investigated whether a deficiency of NTN could influence AHR. AHR was measured in response to methacholine, 1 d after the last intranasal challenge with OVA or PBS in WT and NTN−/− mice. OVA-immunized WT and NTN−/− mice showed significantly increased pulmonary resistance in response to methacholine challenge compared with control mice (Fig. 6A). Furthermore, OVA-immunized NTN−/− mice displayed a significantly reduced Cdyn compared with unimmunized NTN−/− mice, indicating the successful induction of AHR in immunized mice (Fig. 6B). The AHR data of the resistance in immunized NTN−/− mice were significantly higher in comparison with their WT counterparts, and the compliance data were significantly lower (Fig. 6A, 6B).

Effects of NTN administration on cells and Th2 cytokine levels

To demonstrate directly the implication of NTN in eosinophil recruitment and Th2 cytokine secretion after allergen challenge, we pretreated mice with NTN or PBS before the OVA challenge. We focused on cells and cytokines that had significantly different levels between immunized NTN−/− and WT mice. The levels of eosinophils, IL-4, IL-5, and IL-13 were analyzed in BALF, lung tissue, and lung draining LNs (Fig. 7A, 7B). When NTN was administered before the OVA challenge, the percentage of eosinophils was significantly lower in BALF of WT and NTN−/− mice compared.

![FIGURE 6. AHR. Lung resistance (RL) (A) and pulmonary Cdyn (B) in sensitized and challenged mice. RL and Cdyn were obtained in response to increasing concentrations of methacholine (0, 6.25, 12.5, 25, and 50 mg/ml). Data are derived from three mice per group of three independent experiments (n = 9). The results for each group are expressed as means ± SEM. Significant differences (∗p < 0.05, ***p < 0.001) between PBS groups versus OVA groups are observed. Significant differences (∗∗∗p < 0.001) between the groups WT OVA versus NTN−/− OVA are observed.](http://www.jimmunol.org/Downloadedfrom)
with mice receiving only OVA challenge. The same tendency was observed in the lung (Fig. 7A). Furthermore, the level of IL-4 was significantly lower in BALF of WT mice and NTN^{-/-} mice after NTN administration (Fig. 7A). The same phenomenon was observed for the level of IL-4 in WT lung tissue. Adding NTN induced a slight decrease of IL-5 in BALF of OVA-sensitized WT and NTN^{-/-} mice, and a significantly weaker level of IL-5 was observed in WT lung tissues (Fig. 7A). The levels of IL-4 and IL-5 in lung draining LNs in presence or absence of NTN did not vary a lot, although the tendency was a decrease of IL-5 level when NTN was administrated (Fig. 7B). Lastly, IL-13 was also significantly lower in lung draining LNs from NTN^{-/-} mice challenged with OVA and NTN compared with NTN^{-/-} mice only challenged with OVA. These results demonstrated that adding NTN in our mouse model of airway inflammation partially rescues the NTN^{-/-} phenotype. Our data identify the importance of NTN as an anti-inflammatory molecule in the development of allergic airway inflammation.

Discussion

Asthmatic airway inflammation and AHR development are orchestrated by different cell types and mediators. Eosinophil accumulation and activation in bronchial tissues contribute to airway remodeling in chronic asthma (22). By using NTN^{-/-} mice, we clearly showed that the absence of NTN is linked to a significant increase in eosinophilic infiltration in BALF and lung tissue. Histological analyses confirm that the absence of NTN increases the peribronchial inflammatory cell infiltration in the lung tissue. NTN apparently has no influence on mucus development. According to our data, the increase of eosinophils in the peribronchial regions, BALF, and lung tissues in NTN^{-/-} mice was not correlated to an increase of blood eosinophils.

The Th2 cytokines IL-4, IL-5, and IL-13 are known to be increased in asthmatic BALF, lungs, and lung draining LN cells, and play major roles in the development and maintenance of the asthmatic IgE-driven conditions (23–25). In our study, the lack of NTN expression in OVA-sensitized mice led to strikingly increased levels of IL-4, IL-5, and IL-13. The increased Th2 cytokine levels were accompanied by significantly increased amounts of OVA-specific IgE Ab. TNF-α and IL-17, which are implicated in the recruitment of neutrophils (20), were not affected in NTN^{-/-} mice compared with WT mice. At the same time, the level of neutrophils also did not differ between NTN^{-/-} and WT mice. IFN-γ, which is thought to counterbalance Th2 cytokine effects

FIGURE 7. Effects of NTN administration. Mice were sensitized and challenged as described in Materials and Methods. Data are derived from three mice per group of two independent experiments (n = 6). A, Eosinophil, IL-4, and IL-5 levels in BALF and lung tissues. Results for each group are expressed as means ± SEM. Significant differences (*p < 0.05, **p < 0.01, ***p < 0.001) between OVA groups versus OVA+NTN groups are observed. B, IL-4, IL-5, and IL-13 cytokine levels in lung draining LNs were measured in supernatants. The lung draining LN cells were restimulated in vitro with IL-2 or OVA for 3 d. Results for each group are expressed as means ± SEM. Significant differences (*p < 0.05) between OVA groups versus OVA+NTN groups are observed.
(21), was not significantly decreased. These data demonstrate a Th2 shift in NTN−/− mice and show that, in our model, Th1 and Th17 pathways were not affected by NTN.

A characteristic feature of chronic asthma is AHR. Mediators secreted during inflammation contribute to the development of AHR. IL-4, IL-5, and IL-13 have the capacity to influence airway smooth muscle contraction and to induce AHR (26, 27). In addition, IgE-mediated cytokine production by mast cells may contribute to AHR (28). Our data show that the lack of NTN significantly increases the OVA-induced AHR to inhaled methacholine. This may be associated with the increase in Th2 cytokine production, airway eosinophilia, and specific IgE levels. Indeed, the absence of NTN significantly increased these parameters in OVA-immunized mice.

When NTN was administered in our mouse model of inflammation, we partially rescued the NTN−/− inflammatory phenotype. Eosinophil and Th2 cytokine levels were significantly decreased in the presence of NTN. This neurotrophin was able to act directly on the lung tissue as an anti-inflammatory molecule. Taken together, these results suggest that NTN significantly reduces allergen-induced airway inflammation in our murine asthma model. These observations are supported by the fact that NTN is a member of the TGF-β family, TGF-β1 is an anti-inflammatory cytokine, and it was shown by Scherf et al. (13) that OVA-immunized TGF-β1−/− mice present strikingly increased levels of Th2 cytokines IL-4, IL-5, and IL-13, accompanied by an increased inflammatory response in the lung similar to NTN−/− mice. Furthermore, our data are in accordance with results described in NTN−/− mice by Song et al. (15). They also found an increase of inflammatory proteins and cytokines produced by corneal epithelia in NTN−/− mice compared with WT mice. We were able to detect NTN receptor in lung and lung draining LN tissues, although the cells producing NTN were not identified in this report. Further investigations need to be done in mice to detail the mechanisms responsible for the worsening of inflammatory features in NTN−/− mice and to explain the anti-inflammatory action of NTN when it was administrated to the airways.

NTN may orchestrate inflammatory changes by linking the immune system with the nervous system. Neurons and activated structural cells are capable of influencing the immune response through the release of cytokines and soluble mediators. One hypothesis could be a link with the production of substance P. This molecule plays a role in smooth muscle contraction, is elevated in the BALF of asthmatics (29, 30), and downregulates the IgE receptor expression on mast cells (31). Furthermore, the induction of substance P in allergic asthma is dependant on another neurotrophin, Nerve Growth Factor (NGF) (32). It was shown that in NTN−/− mice, gut motility was reduced because of a low level of substance P in these mice compared with the WT animals (14). To investigate whether the deficiency of NTN might influence substance P in the lung, we tested the level of substance P by ELISA in our mouse model of inflammation (data not shown). A higher quantity of substance P was detected in BALF and lung supernatant of NTN−/− and WT mice after sensitization and challenge with OVA compared with negative control. Nevertheless, the level was similar in the immunized NTN−/− and WT mice. At this stage of our experiments we were not able to find a link between substance P and the anti-inflammatory role of NTN. Other neuropeptide and cytokine production could be dependant on NTN and influence the inflammatory response like IL-1, capsaicin, or calcitonin gene-related peptide (33).

NTN was also shown to be produced by human immune cells (monocytes, B cells, and T cells) (12). Another hypothesis could be that NTN is expressed by immune cells and delivers an anti-inflammatory message that reduces migration or survival of eosinophils. Indeed, NTN is a molecule that influences cell proliferation and differentiation in the case of neurons (34). In conclusion, our findings provide good evidence that allergic airway inflammation is regulated, at least in part, by NTN. These observations suggest that NTN and its receptor could become potential therapeutic targets in asthma.

Disclosures
The authors have no financial conflicts of interest.

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