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Mast Cell-Derived TNF-α Primes Sensory Nerve Endings in a Pulmonary Hypersensitivity Reaction

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TNF-α is a cytokine associated with inflammatory diseases, including asthma. Increased levels of TNF-α were found in the bronchoalveolar lavage fluid of mice undergoing a dinitrofluorobenzene (DNFB)-induced non-IgE-mediated pulmonary hypersensitivity reaction. We report in this work that TNF-α increases the susceptibility of sensory neurons to dinitrobenzene sulfonic acid (DNS) and capsaicin, leading to a tracheal vascular hyperpermeability response in DNFB-sensitized and DNS-challenged mice. mAb against TNF-α or the TNFR1 inhibited this hyperpermeability response in DNFB-sensitized and DNS-challenged mice. Furthermore, the hyperpermeability response after DNS challenge was abolished in DNFB-sensitized mast cell-deficient WBB6F1/W/W’ mice. These animals showed a remarked decrease of TNF-α bronchoalveolar lavage fluid levels after a single DNS challenge. The hyperpermeability response after DNS challenge was regained in mast cell-deficient mice after mast cell reconstitution. These findings indicate a prominent role for TNF-α and its TNFR1 in the DNFB-induced tracheal hyperpermeability response. We propose that a priming effect of mast cell-derived TNF-α on the sensory neurons could be the mechanism of action of TNF-α in the vascular hyperpermeability response in trachea of mice undergoing a pulmonary hypersensitivity reaction. The Journal of Immunology, 2002, 168: 5297–5302.

Formation of airway wall edema is one of the features observed in lungs from asthmatic patients (1, 2). Increased vascular permeability is related to edema formation and acts to bring plasma components into the extravascular space, which can constitute a defensive barrier (3). However, movement of extravascular plasma across the epithelium into the airway lumen can lead to shedding of the epithelium, impairment of mucociliary transport, and contribute to mucus plug formation. Furthermore, mediators derived from the kinin, complement, and coagulation system present in the extravasated plasma have the potential to cause bronchoconstriction and airway inflammation, and can activate sensory nerves (2, 3). Therefore, increased extravasation of plasma from vessels within the airways can represent a pathogenic mechanism in asthma.

TNF-α is a potent mediator associated with immunoregulation and inflammatory conditions such as asthma. In vivo application of TNF-α leads to bronchial hyperresponsiveness (4), neutrophilic inflammation in the airway (5), and increased pain perception in rats (6, 7). Furthermore, TNF-α is involved in alteration of the vascular permeability (8–10). In asthmatics, TNF-α levels are increased in sputum of symptomatic patients when compared with asymptomatic patients (11). The sources of TNF-α include various cell types, such as mast cells, macrophages, monocytes, and neutrophils (11–14). TNF-α acts through activation of two receptors: a 55-kDa (p55) form designated TNFR1 and a 75-kDa (p75) form designated TNFR2. Both TNFR1 and TNFR2 could be detected in human lung tissue (15, 16). TNFR1 is found mainly on alveolar macrophages, bronchioles, and small blood vessels, while TNFR2 was detectable only in alveolar macrophages (16). Also, on sensory neurons both TNFR1 and TNFR2 can be detected (17, 18).

Mice skin-sensitized with the low-m.w. hapten dinitrofluorobenzene (DNFB)2 and intra-airway-challenged with the water-soluble form of the hapten, dinitrobenzene sulfonic acid (DNS), develop a hypersensitivity reaction in the airways (19, 20). Features of the pulmonary hypersensitivity reaction in mice include acute bronchoconstriction, mast cell activation, tracheal hyperreactivity, leukocyte infiltration in the lungs, and increased mucosal exudation in the alveolar lumen 24–48 h after challenge (19, 20). Van Loveren and colleagues (21–23) originally described the pulmonary reaction as a delayed-type hypersensitivity. However, we have shown that mast cells are activated shortly after challenge (24).

In previous experiments we have shown that a profound increase in tracheal vascular permeability can be detected after a second DNS challenge to DNFB-sensitized mice (25). Replacement of the second DNS challenge by capsaicin could mimic the tracheal vascular permeability response, indicating a possible role for sensory neurons and sensory neuropeptides in the tracheal hyperpermeability response in DNFB-sensitized mice (25). This finding was confirmed by tachykinin NK1 receptor blockade. The tachykinin NK1 receptor antagonist, RP67580, inhibited the tracheal vascular permeability response to a repeated DNS challenge in DNFB-sensitized mice (25).

It is known that TNF-α can modulate the susceptibility of neurons. In isolated human bronchial tissue, TNF-α increased the responsiveness to electric field stimulation (26). Moreover, in vitro incubation of rat sensory nerves with TNF-α enhanced the sensitivity of the neurons to capsaicin-induced excitation (27). Therefore, TNF-α could be involved in priming sensory nerve endings

1 Address correspondence and reprint requests to Dr. Anneke H. van Houwelingen, Department of Pharmacology and Pathophysiology, Utrecht University, P.O. Box 80082, 3508 TB Utrecht, The Netherlands. E-mail address: A.H.vanHouwelingen@pharm.uu.nl

2 Abbreviations used in this paper: DNFB, dinitrofluorobenzene; BMMC, bone marrow-derived mast cell; BAL, bronchoalveolar lavage; i.n., intranasal(ly); DNS, dinitrobenzene sulfonic acid.
in the DNFB-induced tracheal hyperpermeability response to repeated DNS challenge.

To establish the role of TNF-α in the pulmonary DNFB-induced hypersensitivity reaction, the amount of TNF-α present in the bronchoalveolar lavage (BAL) fluid of DNFB-sensitized mice was determined on different time points after DNS challenge and compared with vehicle-sensitized animals. To investigate the ability of TNF-α to prime sensory nerve endings we followed two approaches. First, the role of TNF-α and its receptors in the tracheal hyperpermeability response in DNFB-sensitized mice was examined by the use of a neutralizing mAb against TNF-α and two TNFR mAb. Second, we investigated whether exogenous TNF-α sensitizes sensory nerve endings in naive mice, thereby enhancing capsaicin-induced tracheal vascular permeability. To determine whether mast cells could be the source of TNF-α, mast cell-deficient WBB6F1-/- mice were used prior to and after reconstitution with bone marrow-derived mast cells (BMMCs) from WBB6F1-+/- mice.

Materials and Methods

Animals

Male BALB/c mice were supplied by the Central Animal Laboratory (GDL, Utrecht University, Utrecht, The Netherlands). Mast cell-deficient (WBB6F1-/-W/W) mice and the respective normal littermates (WBB6F1-+/-) were purchased from The Jackson Laboratory (Bar Harbor, ME). All mice were housed in a barrier facility with free access to water and chow food. Age-matched animals were used in all individual experiments. All experiments were conducted in accordance with the Animal Care Committee of Utrecht University.

Mast cell reconstitution

BMMCs were obtained and cultured from spleenocytes (20% v/v). Medium was refreshed once a week. Mast cell-depleted BMMCs were obtained and cultured in complete RPMI (RPMI 1640 medium, which contained 4 mM l-glutamine, 0.5 mM 2-ME, 1 mM sodium pyruvate, 100 U/ml penicillin, 100 mg/ml streptomycin, and 0.1 mM nonessential amino acids) supplemented with supernatant from a 7-day culture of PWM-stimulated splenocytes (200 ng/ml). Medium was refreshed once a week. Mast cell-depleted W/W mice were infused via the tail vein with 2.5 x 10^6 cultured BMMCs from +/+ mice, and the recipients were studied 20 wk later.

Sensitization and experimental procedure

Skin sensitization was accomplished by 0.5% DNFB (Sigma-Aldrich, St. Louis, MO) and paws (50 μl). On day 1, DNFB or vehicle was only applied onto the abdomen (50 μl). On day 3, the mice were anesthetized with pentobarbital sodium (100 mg/kg i.p. and intranasally (i.n.) challenged with DNS (25 μg per mouse). Thirty minutes after the i.n. administration of capsaicin, the animal was perfused via the right ventricle with 10 ml warm saline (37°C). Blood and perfusion fluid were expelled through an incision in the vena cava. Thereafter, the trachea was removed from the animal, dissected free of fat and connective tissue, and placed into formamide (250 μl). Evans blue dye was extracted from the tracheas overnight at 40°C. Trachea was dried for 3 days at 40°C and tracheal dry weight was determined. The amount of Evans blue in the plasma samples and formamide extracts was quantified by measuring the OD at a wavelength of 595 nm with a Benchmark microplate reader (Bio-Rad, Hercules, CA). The amount of Evans blue present in the trachea was calculated by dividing OD value of the formamide sample (corrected for the volume) by the OD value of the plasma sample. Changes in tracheal vascular permeability were expressed as microliters of leakage per milligram of tracheal dry weight.

Measurement of TNF-α levels in BAL fluid

In separate series of experiments, BAL fluid was taken from vehicle-sensitized or DNFB-sensitized animals on different time points after DNS challenge on day 5 and 30 min after the second challenge on day 6. At the time of the lavage, mice were killed and the chest cavity was exposed to allow expansion. The trachea was carefully intubated and the catheter was secured with ligatures. Warm saline (37°C, 1 ml) was slowly injected in the lungs and withdrawn. The concentration of TNF-α in BAL fluid was measured via a murine TNF-α ELISA kit (BioSource, Nivelles, Belgium).

Statistical analysis

The results are expressed as mean ± SEM. Differences between the groups were analyzed by a Student’s t test or ANOVA. If appropriate, the ANOVA was followed by the Bonferroni’s multiple comparison test (GraphPad Prism version 2.01; GraphPad, San Diego, CA). All p values <0.05 were considered to reflect a statistically significant difference.

Results

TNF-α levels in the BAL fluid of mice undergoing a DNFB-induced pulmonary hypersensitivity reaction

TNF-α was detectable in the BAL fluid of both vehicle- and DNFB-sensitized mice (Table 1). Thirty minutes after a challenge with DNS, the levels of TNF-α in the BAL fluid of DNFB-sensitized animals were increased when compared with vehicle-sensitized animals. The amount of TNF-α in DNFB-sensitized animals declined at 6 h to control level.

Effect of anti-TNF-α pretreatment on the vascular hyperpermeability found in mice undergoing a DNFB-induced pulmonary hypersensitivity reaction

Because the amount of TNF-α was increased dramatically after the first DNS challenge, anti-TNF-α mAb was administered before the first DNS challenge on day 5. A second challenge with DNS enhanced the tracheal vascular permeability in DNFB-sensitized and DNS-challenged mice treated with control Ab (Fig. 1A). This increased response to a second challenge with DNS could be inhibited with the anti-TNF-α mAb given 1 h before the first DNS challenge on day 5 (Fig. 1A). In addition, capsaicin exposure to DNFB-sensitized and single DNS-challenged mice increased the tracheal vascular permeability mice treated with control Ab (Fig.
TNF-α elicits its effects via binding to two TNFRs, TNFR1 and TNFR2. The effect of anti-TNF1R and anti-TNF2R mAb treatment on DNF-induced tracheal vascular hyperpermeability response after a repeated DNS challenge or DNS/capsaicin-challenge is also depicted in Fig. 1. Anti-TNF1R or anti-TNF2R itself had no influence on basal tracheal vascular permeability. Anti-TNF1R, but not anti-TNF2R pretreatment, inhibited the hyperpermeability response to a second DNS challenge (Fig. 1, C and D). Moreover, an i.n. application of capsaicin, instead of the second DNS challenge, enhanced the tracheal vascular permeability in DNF-sensitized and single DNS-challenged mice. This increased response to capsaicin could also be blocked by anti-TNF1R (Fig. 1E) but not with anti-TNF2R pretreatment (Fig. 1F).

Primed effect of TNF-α on capsaicin- or DNS-induced tracheal vascular permeability changes

Twenty-four hours after the administration of TNF-α, an increased vascular permeability response to capsaicin (10^{-10} M per mouse) was observed in tracheas of naive mice (Fig. 2). This TNF-α-induced hyperpermeability response was dose dependent. Treatment with TNF-α or capsaicin alone had no influence on basal tracheal vascular permeability in naive mice. The influence of TNF-α on the tracheal vascular permeability induced by substance P is depicted in Table II. With increasing dosages, substance P itself induced an enhancement of the tracheal vascular permeability in a dose-dependent manner. No additive response to substance P could be found after TNF-α pretreatment.

To investigate whether TNF-α is responsible for the hyperpermeability response in DNF-sensitized mice, the first DNS challenge on day 5 was replaced by TNF-α or PBS. On day 6, these mice were challenged with DNS, capsaicin, or PBS. In DNF-sensitized mice, TNF-α elicted a tracheal hyperpermeability response to both DNS and capsaicin compared with DNF-sensitized TNF-α-treated and PBS-challenged mice (Fig. 3). TNF-α itself had no influence on the tracheal vascular permeability.

Effect of a second DNS challenge in DNF-sensitized mast cell-deficient mice

To investigate whether mast cells are involved in the tracheal vascular hyperpermeability response to a repeated DNS challenge, mast cell-deficient W/W^v and their congenic normal (+/+) mice were used. In DNF-sensitized +/+ mice, a second DNS challenge increased the tracheal vascular permeability, as depicted in Fig. 4. However, in mast cell-deficient W/W^v mice the hyperpermeability to a second DNS challenge was not observed (Fig. 4A). The tracheal hyperpermeability response to a repeated DNS challenge on day 5 was replaced by TNF-α or PBS. On day 6, these mice were challenged with DNS, capsaicin, or PBS. In DNF-sensitized mice, TNF-α elicited a tracheal hyperpermeability response to both DNS and capsaicin compared with DNF-sensitized TNF-α-treated and PBS-challenged mice (Fig. 3). TNF-α itself had no influence on the tracheal vascular permeability.

Effect of a second DNS challenge in DNF-sensitized mast cell-deficient mice

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Table I. Amount of TNF-α present in the BAL fluid of vehicle-sensitized or DNFB-sensitized BALB/c mice on different time points after the first DNS challenge on day 5

<table>
<thead>
<tr>
<th>Sensitization</th>
<th>Time After the Challenge (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>24</td>
</tr>
<tr>
<td>Vehicle</td>
<td>67.3 ± 14.3</td>
</tr>
<tr>
<td>DNBFB</td>
<td>91.0 ± 10.0</td>
</tr>
</tbody>
</table>

* Data (measured in picograms per milliliter) are expressed as mean ± SEM for n = 4-6 animals per group.

* p < 0.05 as compared with vehicle-sensitized animals at the same time point (unpaired t test).

* p < 0.001 as compared with PBS-challenged animals (ANOVA and Bonferroni test).
challenge was regained after mast cell reconstitution in DNFB-sensitized W/WV mice when compared with their age-matched +/+ mice (Fig. 4B).

**TNF-α levels in the BAL fluid of DNFB-sensitized mast cell-deficient mice after single DNS challenge**

Because TNF-α appears to increase directly upon the first DNS challenge (Table I) in DNFB-sensitized BALB/c mice, TNF-α BAL fluid levels were measured 30 min after a single DNS challenge in mast cell-deficient DNFB-sensitized W/WV mice and their congenic littermates (+/+). Increased TNF-α BAL fluid levels were found 30 min after the first DNS challenge in DNFB-sensitized BALB/c and DNFB-sensitized +/+ animals (Fig. 5) compared with vehicle-sensitized BALB/c or vehicle-sensitized +/+ mice. However, no difference in TNF-α levels in the BAL fluid was found after DNS challenge in DNFB-sensitized W/WV mice compared with vehicle-sensitized mice (Fig. 5).

**Discussion**

In this study, we demonstrate that TNF-α is able to increase the susceptibility of the sensory nerve endings for excitatory stimuli, such as capsaicin, in a non-IgE-mediated pulmonary hypersensitivity reaction. The enhanced susceptibility leads to a tracheal vascular hyperpermeability response as a result of a repeated DNS challenge in DNFB-sensitized mice. This effect of TNF-α on the sensory nerves is mast cell dependent and TNFR1 mediated.

TNF-α is believed to play a role in the pathogenesis of asthma in humans and in animal models for asthma (33–35). In the present study, we have found increased amounts of TNF-α in the BAL fluid of DNFB-sensitized mice after a first challenge with DNS. In vehicle-sensitized mice, a small increase in TNF-α BAL levels was also observed 6 h after the first DNS challenge when compared with nonchallenged animals. This was probably due to the irritant effect of DNS.

TNF-α can be released from several cell types, including activated mast cells (13), macrophages (36), and monocytes (14). Appearance of TNF-α in the BAL fluid directly after the first challenge suggests that TNF-α is released by cells that contain prestored TNF-α. This includes tissue-resident inflammatory cells like mast cells and macrophages in the hyperpermeability response in DNFB-sensitized animals. DNFB-sensitized W/WV mice showed no increase in TNF-α levels in their BAL fluid 30 min after the first DNS challenge compared with their congenic littermates (+/+ ) or BALB/c mice. Furthermore, in DNFB-sensitized mast cell-deficient W/WV mice the hyperpermeability response to a repeated DNS challenge was absent while reconstitution of mast cells regained this response. Altogether, mast cells play a key role in the release of TNF-α in mice undergoing a pulmonary hypersensitivity reaction.

The biological effects of TNF-α are elicited by two distinct TNFRs. TNFR1 has been associated with inflammation (37), neutrophil infiltration (38), and apoptosis (39). TNFR2 seems to play a

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**Table II. Changes in tracheal vascular permeability in BALB/c mice induced by i.n. application of different dosages of substance P or PBS 24 h after intranasal pretreatment with TNF-α (25 pg/mouse) or PBS**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage (moles per mouse)</th>
<th>PBS</th>
<th>TNF-α</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBS</td>
<td></td>
<td>0.49 ± 0.08</td>
<td>0.51 ± 0.09</td>
</tr>
<tr>
<td>Substance P</td>
<td>$10^{-12}$</td>
<td>0.56 ± 0.08</td>
<td>0.46 ± 0.05</td>
</tr>
<tr>
<td>Substance P</td>
<td>$10^{-11}$</td>
<td>0.80 ± 0.07*</td>
<td>0.88 ± 0.04*</td>
</tr>
<tr>
<td>Substance P</td>
<td>$10^{-10}$</td>
<td>1.20 ± 0.16*</td>
<td>1.13 ± 0.14*</td>
</tr>
</tbody>
</table>

* Data are expressed as mean ± SEM for n = 6–8 animals per group. *p < 0.05 as compared with PBS-treated mice.

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**FIGURE 2.** Changes in tracheal vascular permeability in BALB/c mice induced by i.n. applied capsaicin ($10^{-10}$ M per mouse) or PBS 24 h after i.n. pretreatment with different dosages of TNF-α or PBS. Data are expressed as mean ± SEM for n = 6–8 animals per group. *, p < 0.005 as compared with PBS-treated animals, unpaired t test.

**FIGURE 3.** Changes in tracheal vascular permeability induced by i.n. applied DNS (filled bar), capsaicin ($10^{-10}$ M per mouse), or PBS on day 6. All BALB/c mice were DNFB sensitized and treated i.n. with either TNF-α (25 pg/mouse) or PBS on day 5. Thus, the first DNS challenge was replaced by the i.n. pretreatment with either PBS or TNF-α. Data are expressed as mean ± SEM for n = 6–8 animals per group. *, p < 0.005 as compared with PBS-treated animals, unpaired t test.

**FIGURE 4.** Effect of a DNS challenge or PBS challenge in DNFB-sensitized and single DNS challenge WBB6F, W/WV and WBB6F, +/+ mice before (A) and after (B) reconstitution with cultured BMMCs. Data are expressed as mean ± SEM for n = 6–8 animals per group. *, p < 0.01 as compared with PBS-challenged animals; †, p < 0.01 as compared with control Ab-treated mice (ANOVA and Bonferroni test).
role in cell proliferation (40) and initiation of cutaneous immune response (41). We have found that anti-TNFRI mAb treatment administered 1 h before the first DNS challenge inhibited hyperpermeability responses in the trachea of DNFB-sensitized and repeatedly DNS-challenged mice. This finding is in accordance with studies on inflammatory conditions such as hyperalgesia and skin necrosis (30, 42). Besides an anti-TNF-α receptor Ab treatment, the influence of both receptors on the hyperpermeability response could be examined by TNFR1 and/or TNFR2 knockout mice. However, this will not give a definite answer on the TNFR1 involvement in this study, because both receptors are already involved in the sensitization phase of a hypersensitivity reaction (41, 43). Although both receptor types are widely expressed (including different cell lines and lung tissues), not much is known about the presence of TNFR1 and TNFR2 on sensory nerve endings. A recent study showed that dorsal root ganglion contains both TNFR1 and TNFR2 (17, 18). The expression of both receptor subtypes was enhanced after exogenous TNF-α or chronic constriction injury of the nerve, which is a model for inflammatory neuropathy (17).

It is known that TNF-α is able to modulate the sensory nerve endings in vivo. The responses of TNF-α associated with inflammation included an enhanced sensitivity to painful stimuli, a condition known as hyperalgesia. Administered systemically or intradermally, TNF-α induces a hyperalgesic state, presumably by an action at the peripheral terminals, leading to decreased thresholds required for stimulation of C-fibers (6, 7). Similar findings have been observed in the airways, where TNF-α facilitated the capsaicin-induced calcium gene-related peptide release in rat tracheas (44). Our findings also demonstrate that TNF-α is able to increase the sensitivity of sensory neurons to neurogenic stimuli in DNFB-sensitized mice. In naive mice, TNF-α only enhanced the capsaicin-induced permeability in contrast to substance P-induced permeability response. This leads to the conclusion that TNF-α acts specifically on the sensory nerve ending and not at the tachykinin receptor level.

This finding of an increased susceptibility to excitatory agents after TNF-α application is also demonstrated in cell cultures (44). Pretreatment with TNF-α not only increased the number of cobalt-labeled neurons in rat dorsal root ganglia cultures but also enhanced the peak amplitude of the capsaicin-evoked inward current (27). Furthermore, in single nociceptive primary afferent fibers of anesthetized rats application of low concentrations of TNF-α increased the axonal activity of the fibers (45).

The precise mechanism by which TNF-α influences the susceptibility of the sensory nerves for excitatory stimuli is unknown. It is possible that TNF-α increase the susceptibility directly by binding to its TNFR1 on the sensory neuron. This will result in mitogen-activated protein kinase and c-Jun N-terminal kinase and mobilization of calcium ions from intracellular stores (18). It is possible that the enhanced mobilization of calcium is linked to the sensitivity of the neuron for neurogenic stimuli. TNF-α can also be taken up by the nerve and transported to the ganglion, where it may modify protein and neuropeptide expression in the sensory neuron (17). A third mechanism for the increased sensitivity of the sensory neuron by TNF-α is via the production of other inflammatory mediators, such as nerve growth factor or PGs via binding and activation of the TNFR1. In fibroblasts, TNF-α stimulated the production of nerve growth factor via the TNFR1 (46). During peripheral inflammation, nerve growth factor increased the sensitivity of dorsal root ganglia (47). In addition, PGs are able to increase the susceptibility of sensory neurons to capsaicin (27, 48).

In summary, we propose that mast cells of DNFB-sensitized mice will release TNF-α upon the DNS challenge. This process will then increase the sensitivity of sensory nerve ending at the time of the second challenge, resulting in a tracheal hyperpermeability response. It can be concluded that mast cell-derived TNF-α and its TNFR1 play a prominent role in priming of the sensory nerve endings in airways of mice undergoing a hypersensitivity reaction.

Acknowledgments

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References


