Expression and regulation of intercellular adhesion molecule-1 on airway parasympathetic nerves

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Background: Eosinophils cluster along airway nerves in patients with asthma and release eosinophil major basic protein, an antagonist of inhibitory M2 muscarinic receptors on nerves. Blocking M2 function increases bronchoconstriction, leading to airway hyperreactivity. Intercellular adhesion molecule-1 (ICAM-1) mediates eosinophil adhesion to nerves.
Objective: We investigated mechanisms of ICAM-1 expression by parasympathetic nerves.
Methods: ICAM-1 expression was examined by immunocytochemistry of lung sections from ovalbumin-sensitized and challenged guinea pigs. ICAM-1 was measured in parasympathetic nerves isolated from subjects and guinea pigs and in human neuroblastoma cells by real-time RT-PCR, immunocytochemistry, and Western blot.
Results: ICAM-1 was not detected in control airway parasympatheric nerves *in vivo* or in cultured cells. ICAM-1 was expressed throughout antigen–challenged guinea pig lung tissue and was selectively decreased by dexamethasone only in nerves. ICAM-1 was induced in human and guinea pig parasympathetic nerves by TNF-α and IFN-γ and was inhibited by dexamethasone and by an inhibitor of nuclear factor-κB (NF-κB). In neuroblastoma cell lines TNF-α and IFN-γ–induced ICAM-1 was blocked by an inhibitor of NF-κB but not by inhibitors of mitogen-activated protein kinases. Dexamethasone did not inhibit ICAM-1 expression in neuroblastoma cells.
Conclusions: ICAM-1 induced in nerves by antigen challenge and proinflammatory cytokines is sensitive to dexamethasone. ICAM-1 expression is also sensitive to inhibitors of NF-κB. Neuroblastoma cells mimic many, but not all, characteristics of ICAM-1 expression in parasympathetic nerves.
Clinical implications: Dexamethasone and NF-κB inhibitors could prevent eosinophils from adhering to nerves by blocking ICAM-1 expression on parasympathetic nerves, thus protecting inhibitory M2 muscarinic receptors and making this pathway a potential target for asthma treatment. (J Allergy Clin Immunol 2007;119:1415-22.)

Key words: *Intercellular adhesion molecule 1, TNF-α, nuclear factor κB, dexamethasone, asthma, parasympathetic nerve, human, guinea pig*

Neuroimmune interactions in disease pathogenesis involve bidirectional communication between neurons and inflammatory cells. Neurotransmitters substantially affect leukocyte function.[1] For example, catecholamines stimulate $CD4^+$ lymphocytes to produce T_H2 cytokines after antigen exposure,[2] whereas acetylcholine suppresses endotoxin-induced TNF-α production by macrophages with a concomitant decrease in mortality.[3] Conversely, inflammatory cells, when recruited to nerves, profoundly affect neural function and neurotransmitter expression, as seen in neuropathies and other chronic inflammatory diseases.[4] Moreover, inflammatory cell proteins directly alter neurotransmitter release, as, for example, eosinophil major basic protein[5] blocking inhibitory M2 muscarinic receptors on nerves[6] and inducing acetylcholine release.

Eosinophils cluster along airway nerves in asthmatic patients and antigen-challenged animals.[7,8] Eosinophil-mediated blockade of M2 muscarinic receptors increases acetylcholine release, causing airway hyperreactivity in animal models of asthma[5,7,9,10] and might explain the M2 muscarinic receptor dysfunction that has been shown in human subjects with allergic asthma.[11] It is specifically eosinophil presence around airway nerves, rather than eosinophil number in lungs, that causes airway hyperreactivity. Redistributing eosinophils away from airway nerves by treating with either dexamethasone[12] or a CCR3 antagonist[13] prevents antigen-induced hyperreactivity and protects M2 receptor dysfunction. Airway nerves express eotaxin,[13] which signals through CCR3 to attract eosinophils. However, little is known about the signals mediating eosinophil adhesion to nerves.

Vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) are important in eosinophil migration. VCAM-1 interacts with very late activation antigen 4, whereas ICAM-1 interacts with CD11a/CD18 (LFA-1) and CD11b/CD18 (Mac-1) on eosinophils.[14,15] We have demonstrated that VCAM-1 is constitutively expressed in parasympathetic nerves but is not upregulated by proinflammatory cytokines and is not required for eosinophil adhesion to nerves.[16] In contrast, ICAM-1 plays a central role in eosinophil adhesion to parasympathetic nerves.[16] ICAM-1 is a 70-kd to 110-kd cell-surface glycoprotein with 5 extracellular immunoglobulin-like domains. Inappropriate ICAM-1 expression

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Supported by National Institutes of Health grants HL55543 (ADF), HL54659 (DBJ), and HL61013 (DBJ).
Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.
Received for publication January 11, 2007; revised February 9, 2007; accepted for publication March 2, 2007.
Available online April 6, 2007.
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0091-6749/$32.00

doi:10.1016/j.jaci.2007.03.005

Abbreviations used
c-JNK: c-Jun N-terminal kinase
ICAM-1: Intercellular adhesion molecule-1
MAP: Mitogen-activated protein
NF-κB: Nuclear factor-κB
VCAM-1: Vascular cell adhesion molecule 1

can contribute to clinical manifestations of allergic rhinitis,[17] eczema,[18] multiple sclerosis,[19] atherosclerosis,[20] and certain neurological disorders[21] by interfering with normal immune function.

ICAM-1 is increased in the lungs of sensitized animals compared with values in the lungs of nonsensitized animals.[22] A physiologic role for ICAM-1 in asthma is suggested because antibody to ICAM-1 inhibits bronchial hyperreactivity and reduces eosinophils in lungs of antigen-challenged monkeys.[23] ICAM-1 mediates eosinophil adhesion to parasympathetic nerves *in vitro*.[16] Eosinophil adhesion to ICAM-1 leads to degranulation,[24] and thus ICAM might be an important physiologic mechanism for eosinophil activation at airway nerves. Here we demonstrate that ICAM-1 is present *in vivo* in airway nerves of antigen-challenged guinea pigs and test whether proinflammatory cytokines, dexamethasone, and inhibitors of mitogen-activated protein (MAP) kinase and nuclear factor-κB (NF-κB) regulate ICAM-1 in neuroblastoma cells and in guinea pig and human parasympathetic neurons.

METHODS

Pathogen-free Dunkin-Hartley guinea pigs (300–350 g; Hilltop, Scottsdale, Pa) were kept in particulate-filtered air cages and handled as established by the National Institutes of Health guidelines. All protocols were approved by the Oregon Health and Science University Animal Care and Use Committee.

Guinea pigs were sensitized and challenged with ovalbumin, as previously described.[12] Twenty-one, 22, and 23 days later, dexamethasone (6 μg/kg administered intraperitoneally) or vehicle was given daily. One hour after the last dexamethasone dose, animals were exposed to aerosolized ovalbumin (5%) for 5 minutes, and airway tissues were harvested and fixed in formalin 24 hours later. Lung sections were dewaxed and treated with antigen-unmasking fluid at 90°C for 10 minutes, and sequential sections were incubated with either mouse mAb to PGP 9.5 diluted 1:1000 or ICAM-1 diluted 1:400 in 10% normal goat serum. Staining was visualized with biotinylated goat anti-mouse IgG or biotinylated goat anti-rabbit IgG (both from Vector Laboratories, Burlingame, Calif), both diluted 1:400, and streptavidin-linked horseradish peroxide substrate (Vector Laboratories) and DAB-Ni (Vector Laboratories). Omission of the primary antibody served as a negative control.

Parasympathetic neurons from guinea pig or human tracheas were isolated and maintained in serum free medium[13] in 4-chambered slides so that each culture had an internal control. Five days later, TNF-α (2 ng/mL) and IFN-γ (50 ng/mL) were added for 48 hours. In some experiments dexamethasone or Bay11-7082 was added 2 hours before cytokine stimulation. Nerves were fixed with methanol and acetone (1:1) for immunostaining.

The human neuroblastoma cell lines SK-N-SH (depleted of fibroblasts[25]), SH-SY-5Y, and Be-(2)-M17 (from ATCC) were cultured in minimum essential medium Eagle with 10% FBS, 100 U/mL penicillin, 0.1 mg/mL streptomycin, and 10 μg/mL gentamicin to 80% confluence before TNF-α (2 ng/mL) and/or IFN-γ (1000 U/mL) or IL-4 (1 ng/mL and 10 ng/mL) was added for 1 to 24 hours (for real-time PCR) or 48 hours (for Western blotting). In some experiments pharmacologic inhibitors of signaling pathways were added 90 minutes before application of TNF-α and IFN-γ.

ICAM-1 expression in parasympathetic nerves from guinea pig or human tracheas was identified by using species-appropriate anti-ICAM-1 antibodies diluted 1:50. Secondary antibodies were species specific, labeled with Alexa fluro 594, diluted 1:4000, and incubated for 60 minutes at 37°C. Normal serum (Vector Laboratories) replaced primary antibodies as a control. All slides were mounted in aqueous medium with 4′-6′diamino-2-phenylindole (DAPI, Vector Laboratories).

ICAM-1 expression was quantified in a blind fashion in guinea pig airway nerves by using Metamorph (Molecular Devices Corp., Downingtown, Pa). Each slide was photographed with the same exposure. ICAM-1–labeled neurites from TNF-α– and IFN-γ–treated and untreated cells were selected at random and outlined by hand. Nerve cells were difficult to distinguish individually and therefore were not included in the analysis. Average intensity was collected from 20 to 30 separate neurites from each group from each guinea pig, and the mean ± SE was calculated from the collected data.

Total RNA was isolated, reverse transcribed into cDNA, and subjected to real-time RT-PCR according to previous protocols.[13] Primer pairs for hICAM-1 were as follows: 5′-GGCTGGAGC TGTTTGAGAAC-3′ and 5′-ACTGTGGGGTTCAACCTCTG-3′. 18S ribosomal RNA was used as an internal control, and the primer pairs were as follows: 5′-GTAACCCGTTGAACCCCATT-3′ and 5′-CCATCCAATCGGTAGTAGCG-3′.

Neuroblastoma cells were lysed with 1% NP-40, 0.5% Triton X-100, 10% glycerol, 0.15 M NaCl, 1 mM EDTA, and 0.05 M Tris in distilled H_2O and centrifuged. Thirty milligrams of supernatant protein was run per lane of a 10% SDS-PAGE gel, transferred to a nitrocellulose membrane, blocked with 10% milk in TTBS buffer (50 mM Tris-HCl, 150 mM NaCl, and 0.001% Tween 20, pH 7.4) and incubated with antibodies to ICAM-1 and actin (both 1:100 dilution). Labeled proteins were visualized by means of chemiluminescence of peroxidase-labeled secondary antibodies, as described by Amersham (Arlington Heights, Ill).

Reagents and drugs

Dexamethasone (D-2915), HP-CD (C-0926, the carrier for dexamethasone), human rTNF-α (T0157), human rIFN-γ (I3265), and Bay11-7082 were obtained from Sigma (St Louis, Mo). Mouse rTNF-α (315-01A) and mouse rIFN-γ (315-05) were obtained from Peprotech (RockyHill, NJ). Human IL-4 (IL004) was obtained from Chemicon (Temecula, Calif). Human cytokines were used in human nerves, and mouse cytokines were used in guinea pig nerves. The c-Jun N-terminal kinase (c-JNK) inhibitor (SP600125), MAP kinase kinase inhibitor (PD 98059), and p38 MAP kinase inhibitor (SB202190) were supplied by TOCRIS (Ellisville, Mo). Agents were dissolved as directed and diluted in prewarmed cell-culture medium when used.

Antibodies

Rabbit anti-mouse ICAM-1 (Sc-1511) was used in guinea pig tissues, and goat anti-human ICAM-1 (Sc-7891) was used in human tissues. These, along with mouse anti-actin antibody (Sc-8432), are all from Santa Cruz. Mouse mAb to PGP 9.5 is from Biogenesis (Sandown, NH).

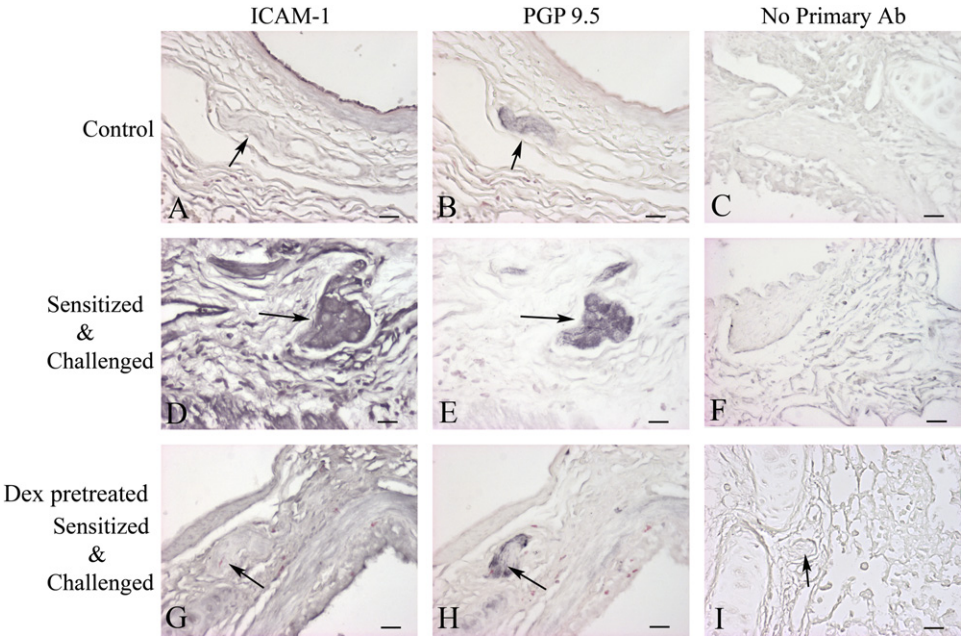

FIG 1. Lung sections from control **(A-C)**, sensitized and challenged **(D-F)**, and dexamethasone *(Dex)*–pretreated, sensitized, and challenged guinea pigs (**G** and **H**) are stained for ICAM-1 *(left column)*. Nerves *(arrows)* are labeled with PGP9.5 in sequential sections *(middle column)*. Negative controls are shown in the *right column*; absence of ICAM-1 (*C* and *F*) and absence of PGP9.5 **(I)** are also shown. Magnification bar, 50 μm.

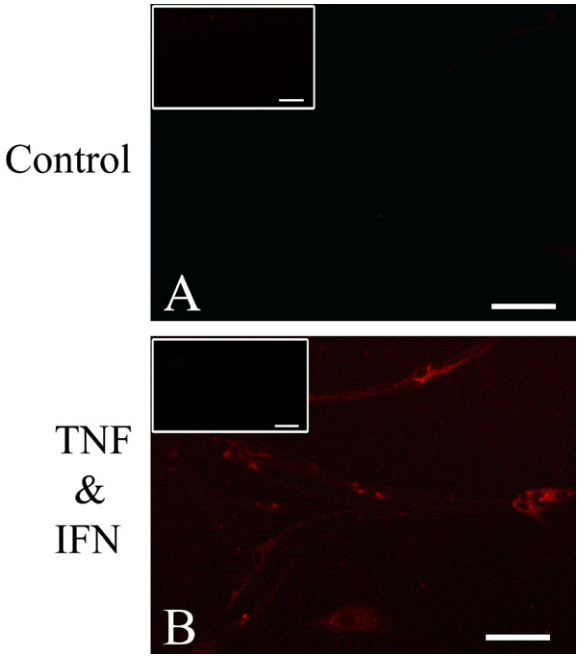

FIG 2. ICAM-1 is not normally found in guinea pig parasympathetic nerves **(A)** but is induced after 24 hours' exposure to TNF-α and IFN-γ **(B)**. Negative controls, in the absence of primary antibody, are shown in *insets*. Magnification bar, 50 μm.

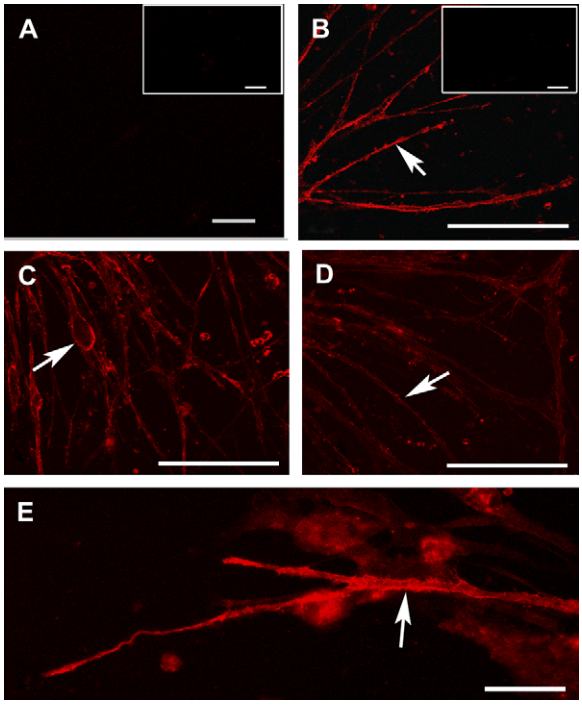

FIG 3. ICAM-1 is not normally expressed in human parasympathetic nerves **(A)** but is induced after 24 hours' exposure to TNF-α and IFN-γ **(B-E)** on both nerve cell bodies (*arrow*; *C*) and neurites (*arrows*; *B*, *D*, and *E*). Negative controls are shown in *insets* in *A* and *B*. Magnification bar, 50 μm.

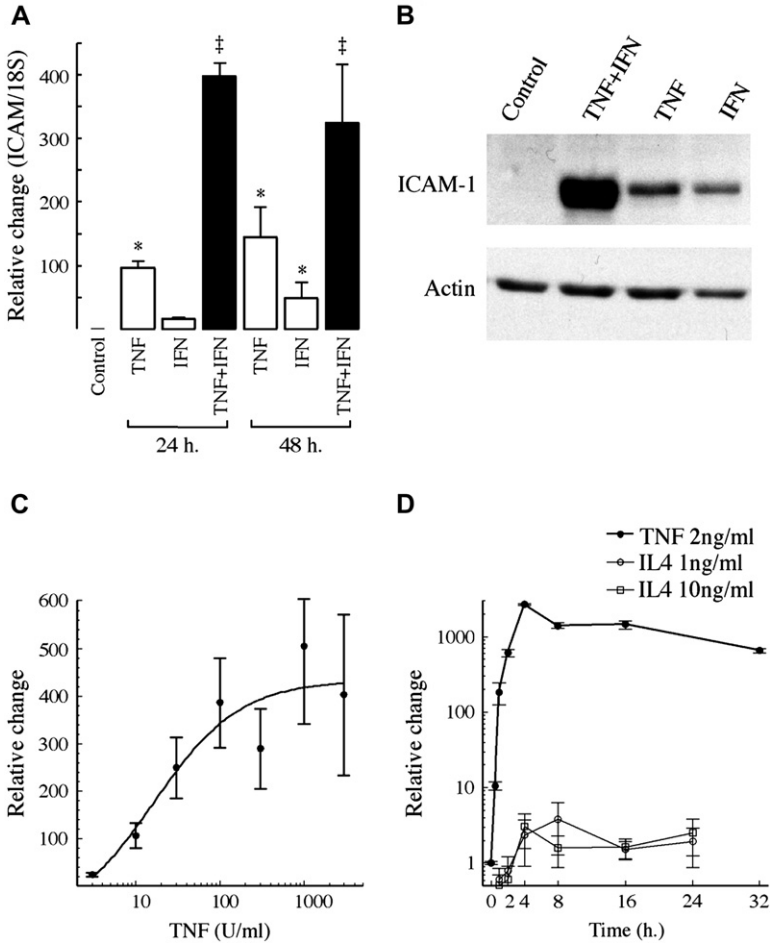

FIG 4. TNF-α and IFN-γ induce ICAM-1 mRNA **(A)** and protein **(B)** in SK-N-SH cells. ICAM-1 expression is dose dependent (**C**: ED_{50} = 16 U/mL; 4 hours' incubation) and time dependent **(D)**. IL-4 did not increase ICAM (*D*). *Significantly different from control; ‡significantly different from TNF-α and IFN-γ by using the unpaired 2-tailed Student *t* tests (mean ± SE, n = 3). Western blot (*B*) is representative of 3 experiments.

RESULTS

ICAM-1 expression on airway nerves in antigen-challenged animals

ICAM-1 was not detected histologically in control lungs (Fig 1, *A*). However, in sensitized and challenged animals ICAM-1 was present throughout the lung, including airway nerves, which were identified by antibody PGP9.5 in sequential sections (Fig 1). There was no staining in the absence of primary antibodies in control (Fig 1, *C* and *I*) or sensitized and challenged animals (Fig 1, *F*).

TNF-α and IFN-γ induce ICAM-1 in parasympathetic neurons

Similar to parasympathetic nerves in lungs of control guinea pigs, ICAM-1 was not expressed in isolated parasympathetic nerves from guinea pig (Fig 2) or human (Fig 3) tracheas. TNF-α and IFN-γ induced ICAM-1 in parasympathetic nerves from guinea pigs (Fig 2, *B*). The average intensity per pixel was 112 ± 10 above threshold and significantly different from the control value ($P < .001$), as determined by using the paired 2-tailed Student *t* test. Similarly, TNF-α and IFN-γ induced ICAM-1 expression in human parasympathetic neurons, as demonstrated by means of immunofluorescence (Fig 3, *B-E*). ICAM-1 expression was visible on nerve cell bodies and neurites (Fig 3, *B-E*). The pattern of staining suggests that ICAM-1 is expressed on cell membranes (Fig 3, *B-E*, arrows). Neither TNF-α nor IFN-γ alone induced ICAM-1 expression in guinea pig parasympathetic neurons (data not shown).

TNF-α, IFN-γ, or both induce ICAM-1 in SK-N-SH neuroblastoma cells

Similar to parasympathetic nerves, neuroblastoma cells did not normally express ICAM-1, as measured with Western blotting (Fig 4, *A* and *B*). Both TNF-α (2 ng/mL) and IFN-γ (1000 U/mL) alone and in combination induced ICAM-1 (Fig 4, *A* and *B*). TNF-α induction of ICAM-1 was dose dependent, with a median effective dose that

produces 50% maximum response (ED_{50}) of 16 U/mL (0.16 ng/mL; Fig 4, *C*), and time dependent (Fig 4, *D*). IL-4 did not increase ICAM-1 levels (Fig 4, *D*). Thus ICAM-1 was induced in neuroblastoma cells by either of the proinflammatory cytokines IFN-γ or TNF-α.

TNF-α–induced ICAM-1 in nerves is NF-κB dependent

Bay11-7082, an IκB-α phosphorylation inhibitor that prevents NF-κB activation, significantly decreased TNF-α–induced ICAM-1 mRNA in SK-N-SH cells (Fig 5, *A*). Bay11-7082 inhibition of ICAM-1 was dose dependent between 1 and 5 μM; higher doses were cytotoxic. In the absence of TNF-α, Bay11-7082 itself did not change ICAM-1 mRNA. MAP kinase inhibitors (PD98059, a MAP kinase kinase inhibitor; SB202190, a p38 inhibitor; or SP600125, a c-JNK inhibitor) alone or in combination did not inhibit TNF-α–induced ICAM-1 mRNA (Fig 5, *B*). In human parasympathetic neurons Bay11-7082 also reduced TNF-α/IFN-γ–induced ICAM-1 mRNA (Fig 6, *A*), confirming the role of NF-κB in induction of ICAM-1.

Dexamethasone prevented ICAM-1 induction in airway nerves of antigen-challenged guinea pigs (Fig 1, *G*) and in human and guinea pig parasympathetic nerves treated with TNF-α and IFN-γ (Fig 6, *B* and *C*). However, in SK-N-SK cells dexamethasone did not reduce ICAM-1 expression at either the mRNA (Fig 7, *A*) or protein (Fig 7, *B*) level. In 2 additional neuroblastoma cell lines TNF-α and IFN-γ also independently induced ICAM-1 (Fig 7, *C*). However, although TNF-α had the dominant effect in SK-N-SH cells, IFN-γ had the dominant effect in SH-SY-5Y and Be(2)-M17 neuroblastoma cells. Thus, different neuroblastoma cell lines respond differently to TNF-α and IFN-γ. It is possible that no neuroblastoma cell line accurately represents parasympathetic nerves, including their response to dexamethasone.

DISCUSSION

Here we show that ICAM-1 expression was induced in airway nerves *in vivo* by means of antigen challenge (Fig 1). Neuronal ICAM-1 was induced by TNF-α and IFN-γ, mediated by NF-κB, and suppressed by dexamethasone. ICAM-1 was not expressed in nerves of control guinea pigs (Figs 1 and 2) or nonasthmatic human subjects (Fig 3). However, it was induced in cultured guinea pig[16] (Fig 2) and human (Fig 3) parasympathetic nerves after incubation with proinflammatory cytokines. ICAM-1 induction in primary nerve cells required both TNF-α and IFN-γ. Neither cytokine alone induced ICAM-1 (data not shown). However, ICAM-1 in human neuroblastoma cells was induced by either TNF-α or IFN-γ. The effects were additive at 4 hours (Fig 7, *C*) and synergistic at 24 hours (Fig 4, *A*).

It has previously been shown that cytokines regulate ICAM-1 expression in a cell-specific manner.[14] Thus it is important to understand which signaling pathways regulate ICAM-1 in cells of neuronal origin. In airway epithelium and smooth muscle, ICAM-1 is mediated by MAP kinases[26] and NF-κB.[27-29] However, we found that in neuroblastoma cells inhibitors of 3 different MAP kinases did not block TNF-α–induced ICAM-1 expression either alone or in combination (Fig 5).

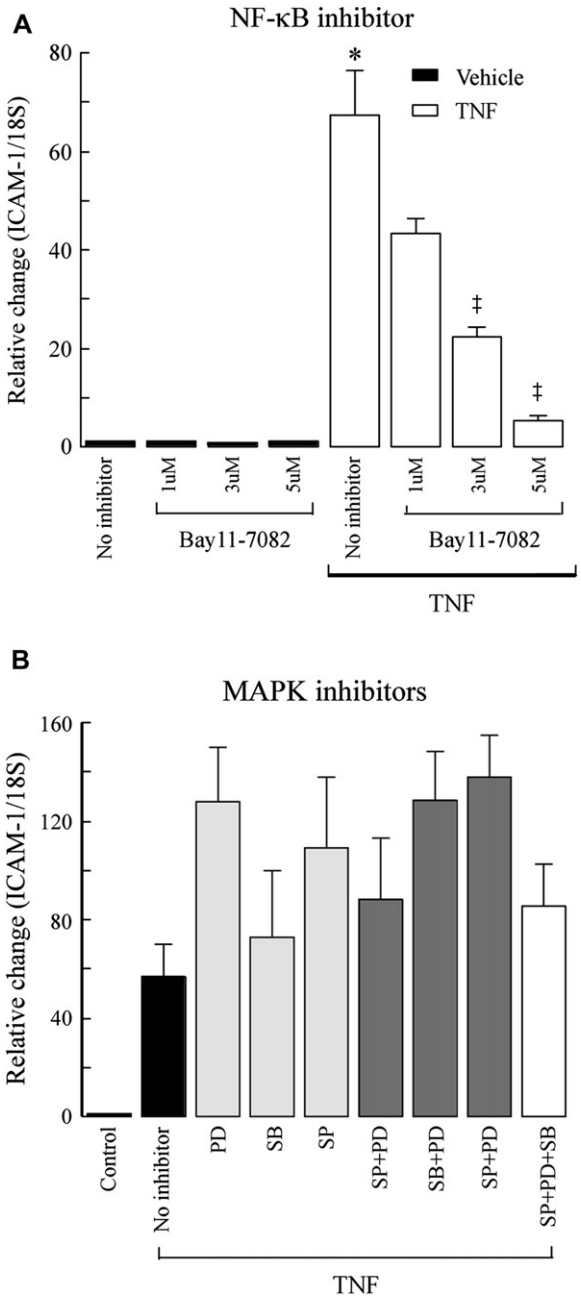

FIG 5. Bay11-7082, an IκBα kinase inhibitor, administered 90 minutes before 2 ng/mL TNF-α, blocked ICAM-1 induction in SK-N-SH neuroblastoma cells measured with real-time RT-PCR **(A)**. Neither PD98059 *(PD)*, a MAP kinase kinase inhibitor; SB202190 *(SB)*, a p38 inhibitor; nor SP600125 *(SP)*, a c-JNK inhibitor, blocked ICAM-1 **(B)**. *Significantly different from untreated; ‡significantly different from TNF-α by using the unpaired 2-tailed Student *t* tests (mean ± SE, n = 3).

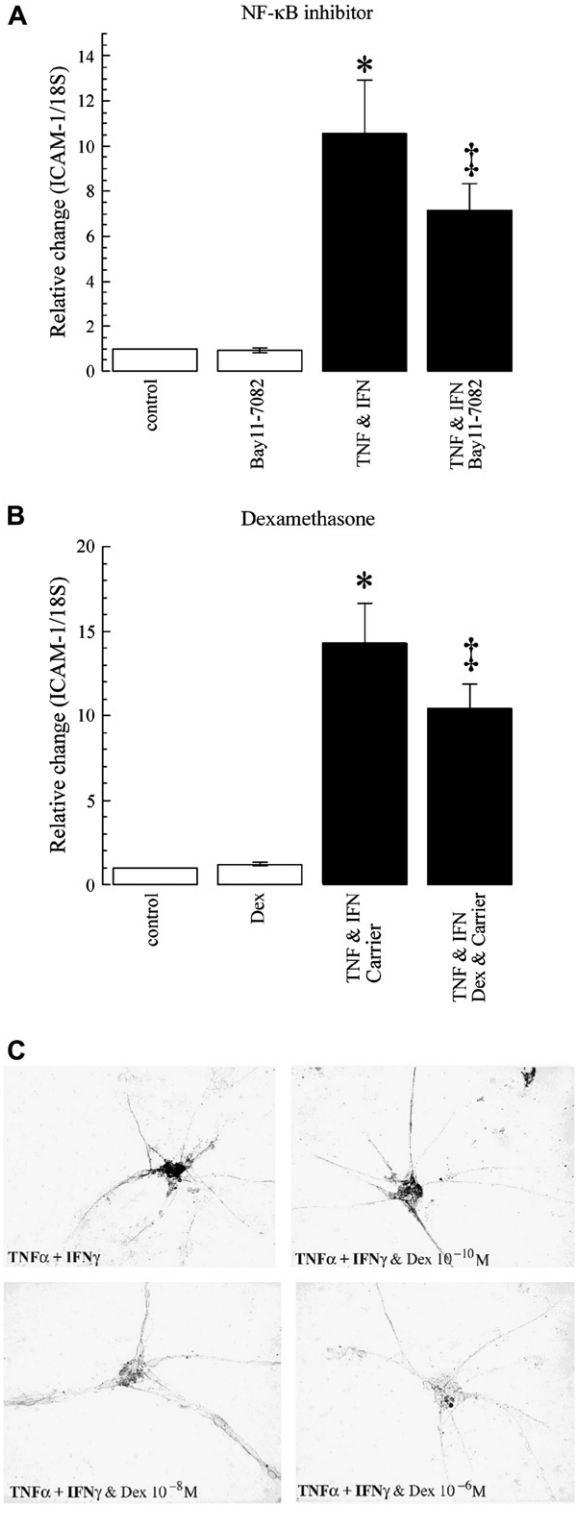

FIG 6. In human parasympathetic nerves 2 hours' preincubation with 5 μM of the IκB-α kinase inhibitor Bay 11-7082 **(A)** or 10^{-5} M dexamethasone (*Dex*; **B**) inhibited TNF-α/IFN-γ–induced ICAM-1 expression measured 24 hours later by means of RT-PCR. *Significantly different from untreated; ‡significantly different from TNF-α/IFN-γ alone; unpaired 2-tailed Student *t* tests (mean ± SE, n = 3). Dexamethasone decreased ICAM-1 staining of guinea pig parasympathetic nerves **(C)**.

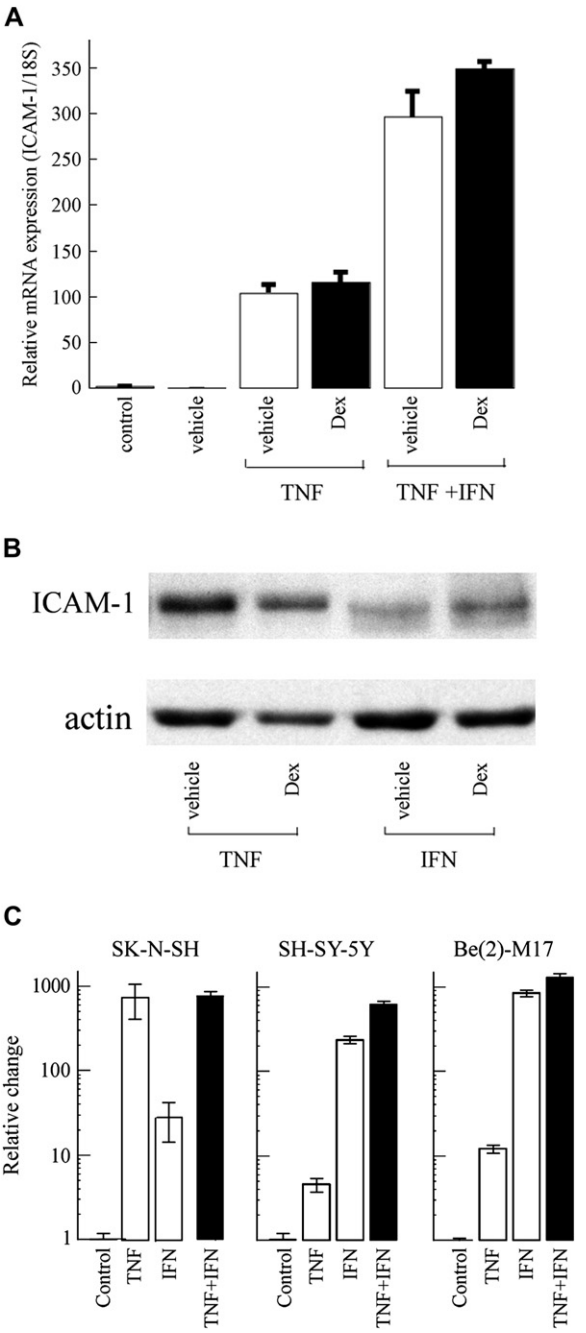

FIG 7. Dexamethasone *(Dex)* did not reduce TNF-α or TNF-α/IFN-γ–mediated ICAM-1 expression in neuroblastoma cells, as shown by means of real-time RT-PCR **(A)** and Western blotting **(B)**. Different cell lines responded differently to TNF-α and IFN-γ, as shown by different patterns of ICAM-1 mRNA expression **(C)**. Data shown are means ± SE of 3 experiments. The Western blot (Fig 7, *B*) is representative of 4 experiments.

Bay11-7082, an NF-κB inhibitor, did block TNF-α–induced ICAM-1 expression. Similarly, in parasympathetic neurons from human subjects, the NF-κB inhibitor decreased ICAM-1 induction. NF-κB inhibition was less effective in parasympathetic nerves than in neuroblastoma cells. This might be because parasympathetic nerves had

to be stimulated with both TNF-α and IFN-γ (which might signal through Janus kinases/signal transducers and activators of transcription[30]) because neither alone had any effect. Thus, ICAM-1 expression in nerves is regulated through NF-κB. Because NF-κB is common to ICAM-1 expression in airway epithelium,[29,31] airway smooth muscle,[27,32] and airway nerves (Figs 5 and 6), blockade of NF-κB might decrease ICAM-1 expression throughout the lungs.

Glucocorticoids are widely used for treatment of asthma. Dexamethasone suppressed ICAM-1 expression in airway nerves in guinea pigs *in vivo* (Fig 1) and in human parasympathetic nerves in culture (Fig 6). We previously showed that dexamethasone completely inhibits airway hyperreactivity in antigen-challenged guinea pigs[12] by selectively preventing eosinophil recruitment to airway nerves without affecting eosinophil numbers in whole lungs. Here we show that dexamethasone selectively inhibited ICAM-1 expression in nerves while not affecting ICAM-1 expression in other airway tissues (Fig 1). This agrees with data showing that dexamethasone only partially and transiently inhibits TNF-α–induced ICAM-1 expression in human airway smooth muscle.[27] Selective inhibition of eosinophil recruitment to nerves might explain the ability of dexamethasone to prevent airway hyperreactivity,[12] although it does not inhibit cytokines or eosinophils in bronchoalveolar lavage fluid.[33]

In contrast to *in vivo* data (Fig 1) and to parasympathetic neurons in cell culture (Fig 6, *B* and *C*), dexamethasone did not inhibit TNF-α–induced ICAM-1 expression in SK-N-SH cells (Fig 7). Although it is known that SK-N-SH cells have glucocorticoid receptors, stimulation of these cells with dexamethasone did not suppress NF-κB activation.[34] Thus, it is not surprising that dexamethasone did not inhibit TNF-α–induced ICAM-1 expression in neuroblastoma cells (Fig 7), which was NF-κB dependent (Fig 5, *A*).

Neuroblastoma cells are not predictive of parasympathetic neurons in other ways. For example, both TNF-α and IFN-γ were required to induce ICAM-1 expression in human and guinea pig parasympathetic nerves, whereas either TNF-α or IFN-γ alone induced ICAM-1 expression in 3 neuroblastoma cell lines (Fig 7). There was also no agreement between the neuroblastoma lines. TNF-α was more potent in SK-N-SH cells, whereas IFN-γ was more potent in the SH-SY-5Y and Be(2)-M17 neuroblastoma cell lines (Fig 7, *C*). Thus, it is necessary to confirm data obtained from cell lines in neurons of interest.

It is known that eosinophil adhesion to ICAM-1 leads to degranulation[24] and potentiates cytokine-induced degranulation *in vitro*.[35] We have previously demonstrated that eosinophil recruitment to nerves is mediated by CCR3 agonists[13] and is inhibited by dexamethasone,[12] which selectively blocks ICAM-1 expression in nerves (Fig 1). However, eosinophil recruitment to nerves is independent of eosinophil activation.[10] Once eosinophils are associated with nerves, they can be activated by subsequent challenges, including antigen challenge,[36] viral infection,[10] or ozone inhalation.[37] This results in M2 muscarinic receptor dysfunction and airway hyperreactivity that is mediated by major basic protein.[5,38] Thus ICAM-1 might facilitate the interaction of eosinophils with nerves by anchoring eosinophils or by increasing release of eosinophil proteins onto neuronal M2 receptors.

We have shown here that TNF-α is an important mediator for induction of ICAM-1 expression in neuroblastoma cells and parasympathetic neurons. TNF-α expression, TNF-α receptor 1, and TNF-α–converting enzyme levels are increased in lavage specimens from asthmatic subjects compared with those from healthy subjects.[39-41] Etanercept (a TNF-α receptor-Fc fusion protein) was effective in treating patients with severe asthma.[41] TNF-α upregulates ICAM-1 on airway epithelium and smooth muscle.[42] Additionally, TNF-α and TNF-α–converting enzyme have been detected in immune-mediated inflammatory demyelinating disorders of the peripheral nervous system.[43] Our data indicate that TNF-α also increases ICAM-1 expression on parasympathetic nerves and thus might induce or perpetuate neural inflammation and airway hyperreactivity.

Association of eosinophils with nerves is not limited to the airways but is characteristic of many diseases, including eczema,[44] inflammatory bowel disease,[45] and chronic pancreatitis,[46] and is found along the optic nerves in a model of multiple sclerosis.[47] Neural expression of chemokines and adhesion molecule expression is central to recruitment and activation of inflammatory cells. Thus, neuronal expression of ICAM-1 might be important in an array of inflammatory and immune disorders, and abnormal ICAM-1 induction might contribute to the clinical manifestations of a variety of diseases. Our data suggest that interfering with ICAM-1 expression could be an attractive strategy to prevent eosinophil migration to nerves.

We thank the Pacific Northwest Transplant Bank, Portland, Ore, for procuring and supplying tracheas from human organ donors. We thank Jesse Lorton and Barathy Kumaravel for technical assistance.

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