

Effect of nedocromil sodium on allergen-induced airway responses and changes in the quantity of airway smooth muscle in rats

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Background: Allergen exposures induce growth of airway smooth muscle in the Brown Norway rat.

Objective: The purpose of the study was to examine the role of mediators associated with the early and late responses in the induction of airway smooth muscle growth.

Methods: Nedocromil sodium was administered to block early and late responses in ovalbumin-sensitized and ovalbumin-challenged rats undergoing single or multiple challenges (5 times at 5-day intervals) with ovalbumin. Airway smooth muscle was quantitated by morphometry on lungs removed 2 days after the final challenge.

Results: Nedocromil sodium administered before ovalbumin challenge blocked both the early and late responses. When administered 2 hours after ovalbumin challenge, it also blocked the late response. Rats undergoing challenge with aerosolized ovalbumin five times at 5-day intervals were also treated with nedocromil before ($n = 10$) or 2 hours after ($n = 10$) each ovalbumin inhalation, respectively. The quantity of airway smooth muscle standardized for size was greater after ovalbumin challenge (0.069 ± 0.005) compared with saline controls (0.033 ± 0.003 , $p < 0.005$). Nedocromil significantly reduced the airway smooth muscle (0.036 ± 0.003 , $p < 0.005$) when administered before ovalbumin. However, the airway smooth muscle in rats that received nedocromil 2 hours after ovalbumin challenge (0.046 ± 0.003), although lower than in ovalbumin-challenged rats ($p < 0.01$), was still significantly higher than in saline-treated rats ($p < 0.05$).

Conclusions: Allergen-induced early responses, late responses, and airway inflammation are antagonized by nedocromil. The mediators of both the early and late responses contribute to allergen-induced airway smooth muscle growth, a process that can be prevented by administration of nedocromil. (*J Allergy Clin Immunol* 1996;98:400-7.)

Key words: Ovalbumin, airway inflammation, bronchoalveolar lavage, airway smooth muscle, Brown Norway rat

Asthmatic airways show a number of characteristic histologic features, of which several have the potential to contribute to the airway hyperresponsiveness that is essential for the condition. In

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Abbreviations used

ASM:	Airway smooth muscle
BAL:	Bronchoalveolar lavage
BM:	Basement membrane
BN:	Brown Norway
ER:	Early response
LR:	Late response
LT:	Leukotriene
R _L :	Pulmonary resistance

postmortem asthmatic airways, both hypertrophy and hyperplasia of airway smooth muscle (ASM) have been described.^{1,2} ASM is often present in increased amounts throughout the entire airway

tree, although only the small airways are affected in nonfatal cases.³ The increase in the quantity of smooth muscle in the airway wall is a potential mechanism of airway hyperresponsiveness and may account for the chronicity of asthma and the infrequent occurrence of remission of this disease.

The mechanism of the increase in ASM in patients with asthma is unknown. Although the increase in muscle may have preceded the development of asthma, it seems more likely that it is an acquired characteristic. Recent evidence indicates a potentially important etiologic role for several of the bronchoconstrictive mediators of allergic asthma in the induction of muscle growth through hyperplasia.⁴⁻⁶ Panettieri et al.⁴ have shown that histamine can act as a mitogenic agent for canine tracheal smooth muscle cells in culture. Peptidoleukotrienes can also promote growth of cultured rabbit ASM.⁵ Endothelin, which is also expressed in asthmatic airways, causes ASM proliferation, which may act through phospholipase A₂ activation and thromboxane synthesis.⁶ It is also possible that hypertrophy of smooth muscle may occur in asthmatic airways, contributing to the increase in muscle mass.⁷

In the ovalbumin-sensitized Brown Norway (BN) rat, an increase in the quantity of ASM has been reported after repeated allergen inhalations,^{8,9} making this animal a suitable model for the study of the regulation of ASM growth after allergic bronchoconstriction. The objectives of this study were several. First, we wished to test the efficacy of nedocromil sodium as an antagonist of the response of the sensitized BN rat to a single antigen challenge. To do this, we studied the effects of nedocromil on the early response (ER) and late response (LR) of the actively sensitized BN rat to ovalbumin. Further, we examined the relationship between the alteration in airway inflammation by nedocromil sodium and the LR by examining the bronchoalveolar lavage (BAL) of antigen-challenged rats. To test the effects of the timing of administration of nedocromil sodium on its ability to modify the LR, nedocromil sodium was administered both before and 2 hours after the antigen challenge. Second, we wished to evaluate the contribution of mediators released in association with both the early and late responses to the growth of ASM after multiple allergen challenges. To do this, we challenged rats with ovalbumin on five occasions, 5 days apart. Nedocromil was administered either before allergen challenge or 2 hours after each of the challenges, and ASM mass was quantitated by morphometry.

METHODS

Animals and sensitization

We studied BN rats of both sexes, (7 to 9 weeks old, ranging from 121 to 290 gm in body weight), which were purchased either from Charles River Laboratories, Inc. (St. Constant, Quebec, Canada) or Harlan Sprague Dawley, Inc. (Indianapolis, Ind.). Animals were actively sensitized by a single subcutaneous injection of 1 mg of ovalbumin and 200 mg of aluminum hydroxide in 1 ml of saline solution. Simultaneously, 1 ml of *Bordetella pertussis* vaccine, containing 6×10^9 heat-killed organisms, was given intraperitoneally as an adjuvant.

Drugs and chemicals

Ovalbumin (grade V) and urethane were purchased from Sigma Chemical Co. (St. Louis, Mo.), Pentobarbital sodium was obtained from Canada Packers Inc. (Mississauga, Ontario, Canada), aluminum hydroxide was from Anachemia Chemicals (Montreal, Quebec, Canada), and *Bordetella pertussis* was from Connaught Pharmaceuticals (Willowdale, Ontario, Canada). Nedocromil sodium was provided by Fisons Pharmaceuticals (Loughborough, Leicestershire, U.K.).

Study protocol

To evaluate the efficacy of nedocromil sodium against allergen-induced airway responses and airway inflammation, five groups of rats were studied. Thirteen sensitized rats were challenged with aerosols of saline solution. Thirty sensitized rats were challenged with aerosols of ovalbumin (50 mg/ml in saline solution) and are termed *control animals* throughout. Twenty-seven sensitized rats were divided into three groups and treated with nedocromil sodium. One group of rats ($n = 8$) received an aerosol of nedocromil (10 mg/ml in saline solution) 20 minutes before ovalbumin challenge. A second group ($n = 12$) received the same dose of nedocromil at 2 hours after ovalbumin challenge. A third group ($n = 7$) received a higher dose of nedocromil (50 mg/ml in saline solution) 20 minutes before aerosol challenge. All animals, except for the group that received 10 mg/ml nedocromil before ovalbumin challenge, underwent a BAL at the end of the 8-hour observation period.

To determine whether nedocromil sodium protected against allergen-induced ASM growth, we studied four groups of 10 rats each. The first group underwent five ovalbumin challenges at 5-day intervals (on days 16, 21, 26, 31, and 36 after sensitization). The second group was similarly exposed to ovalbumin but was pretreated with aerosolized nedocromil (10 mg/ml for 5 minutes) 20 minutes before each ovalbumin inhalation. The third group received aerosolized nedocromil (10 mg/ml for 5 minutes) at 2 hours after each ovalbumin exposure. The fourth group inhaled aerosolized saline solution according to a time course identical to that of the test animals and served as controls. Animals underwent BAL and were killed for morphometric studies 2 days after the

final exposure to either ovalbumin or saline solution (day 38 after sensitization).

Animal preparation and lung mechanics

For the evaluation of pulmonary responses to ovalbumin challenge, animals were studied between 14 to 18 days after sensitization. For the study of ER and LR, anesthesia was induced by intraperitoneal injection of urethane at a dose of 1.1 gm/kg body weight. Otherwise, rats were anesthetized with pentobarbital sodium (30 mg/kg intraperitoneally). Orotracheal intubation was performed with a 6 cm length of polyethylene tubing (PE 240). The tip of the tracheal tube was inserted into a small Plexiglas box (265 ml in volume). Pleural pressure changes were determined by using a water-filled esophageal catheter. Pulmonary resistance (R_L) was obtained from flow, transpulmonary pressure, and the integrated flow signal by fitting the equation of motion of the lung with multiple linear regression. The resistance of the endotracheal tube was measured as 0.11 cm H₂O/ml/sec. R_L is reported after subtraction of tube resistance.

Ovalbumin challenge and nedocromil sodium inhalation

Ovalbumin was diluted in saline solution immediately before each experiment (5% wt/vol). Test rats inhaled an aerosol of ovalbumin for 5 minutes, and control rats were challenged with saline solution. Nedocromil sodium was diluted in saline solution in a concentration of 10 mg/ml or 50 mg/ml and was administered either 20 minutes before or 2 hours after ovalbumin challenges. Aerosols were generated by a Hudson nebulizer (Hudson Respiratory Care, Inc., Temecula, Calif.) connected to a side port of the box and driven by compressed air to produce an output of 0.18 ml/min.

Tissue preparation, histology, and morphometric studies

Lungs were fixed with intrabronchial perfusion of 10% formalin at a constant pressure of 25 cm H₂O and at room temperature for 48 to 72 hours. The sections were taken from midsagittal and hilar regions of each lung. Five-micrometer sections were cut from paraffin-embedded tissue and stained with hematoxylin-phloxine-saffron.

Six rats were chosen randomly from each group for morphometric studies. For each animal, six to 10 airways representing small, medium, and large airways were analyzed at random. The airway sizes were determined by using different objectives, and sizes corresponded to internal perimeters of less than 1 mm (small), greater than 1 but less than 2 mm (medium), and greater than 2 mm (large). Airways for which the ratio of maximal to minimal internal diameter was larger than 2 were considered to be cut tangentially and were not further considered.

For each airway, images of the areas of interest were traced on paper by using a drawing tube attachment

(Leitz, Wetzlar, Germany) and measured by using a commercial digitizing program (Sigma Scan; Jandel Scientific, Corte Madera, Calif.). The following dimensions were determined: (1) length of the epithelial basement membrane (BM), (2) airway lumen defined by the BM, (3) external area of the airway defined by the outer boundary of the airway wall (Ae), (4) area of ASM. The area of the airway wall (Aw) was calculated as the difference between Ae and the airway lumen. The ASM was identified on the basis of its pink staining in contrast to connective tissue, which stains yellow when hematoxylin-phloxine-saffron is used.

BAL

Immediately before each animal was killed, lung lavage was performed with five aliquots of 5 ml of saline solution instilled into the trachea. Each instillation was followed by gentle suction. Retrieved BAL fluid was approximately 93% of the instilled saline solution. Total cell count was determined with a hemocytometer (Fisher Scientific, Montreal, Quebec, Canada). Differential white cell counts were performed on slides that were prepared by using a cytopsin (Cytospin II; Shandon, Cheshire, England). The slides were stained with Wright-Giemsa stain and counted under oil immersion (200 cells per slide).

Data analysis

To compare the magnitude of the ER among groups, the highest value of R_L within 1 hour of ovalbumin challenge was used. To compare the magnitudes of the LR among groups, we defined the LR as the area under the curve of R_L , referenced to the baseline value of R_L , from 75 to 480 minutes after challenge. There were differences in body weight between male and female rats so that baseline values of R_L varied within groups as a function of their composition. For this reason, data for each group are expressed as percent changes from the baseline values of R_L .

After morphometric measurements were obtained, airways were grouped into three categories on the basis of the length of the BM: small (0 to 0.99 mm), medium (1.0 to 1.99 mm), and large (2.0 to 3.99 mm) airways. Each size category from each animal had two to four airways. Because large-sized membranous airways (BM > 4.0 mm) were not always present in all of the lung sections, the occasional airway that had a BM in excess of 4 mm was excluded from analysis. Data for individual airways were standardized for airway size by dividing each measured area by the ideal lumen area, which is the airway lumen calculated from the BM length, assuming that the lumen of the unconstricted airway is a perfect circle. All morphometric measurements were performed by an observer blinded to the group status.

Comparisons among group means were made by analysis of variance, and the significance of differences between pairs of means was established by Newman-Keuls test for multiple comparisons. When data were

not normally distributed, statistical tests were performed after log transformation.

A *p* value less than 0.05 was considered significant. Data are expressed as means $\pm$ SEM throughout.

RESULTS

Effects of nedocromil on airway responses

The magnitude of the ER in the control group ($226\% \pm 24\%$, percent baseline R_L), which also included the data of the ER of the 12 rats that received nedocromil at 2 hours, was significantly greater than the ER in the two groups of rats that received nedocromil before ovalbumin challenge ($110\% \pm 5\%$, 10 mg/ml nedocromil and $144\% \pm 5\%$, 50 mg/ml nedocromil, $p < 0.05$, respectively). The peak values of R_L after ovalbumin challenge were not significantly different between the two groups pretreated with nedocromil before ovalbumin challenge.

Nedocromil also had a significant effect on the LR as determined by the area under the curve of R_L against time. The LR of the control group (29.5 ± 12.5) was substantially greater than in the saline-challenged animals (5.3 ± 2.0 ; $p < 0.05$). Nedocromil reduced the LR significantly in all three treatment groups: 2.3 ± 0.75 nedocromil, 10 mg/ml, before ovalbumin challenge ($p < 0.05$); 0.17 ± 0.06 nedocromil, 50 mg/ml, before ovalbumin challenge ($p < 0.01$); and 1.4 ± 0.5 nedocromil after ovalbumin challenge ($p < 0.01$).

Effects of nedocromil on BAL leukocytes after a single allergen challenge

The total number of cells recovered in BAL from the control group ($4.46 \pm 0.5 \times 10^6$) was significantly larger than in the saline group ($2.9 \pm 0.48 \times 10^6$, $p < 0.05$), the group treated with nedocromil (10 mg/ml) at 2 hours after ovalbumin challenge ($0.8 \pm 0.1 \times 10^6$, $p < 0.01$), and the group receiving 50 mg/ml nedocromil before ovalbumin challenge ($1.4 \pm 0.15 \times 10^6$, $p < 0.005$) (Fig. 1). The number of alveolar macrophages recovered by BAL was reduced by nedocromil both before ($p < 0.005$) and after challenge ($p < 0.005$). Likewise, the numbers of lymphocytes and neutrophils were lower in both nedocromil-treated groups. No significant differences were found in the numbers of eosinophils retrieved.

Morphometric measurements

There was an approximately twofold increase in the standardized ASM (0.069 ± 0.005) of ovalbumin-challenged rats compared with saline-challenged controls (0.033 ± 0.003 , $p < 0.005$). For

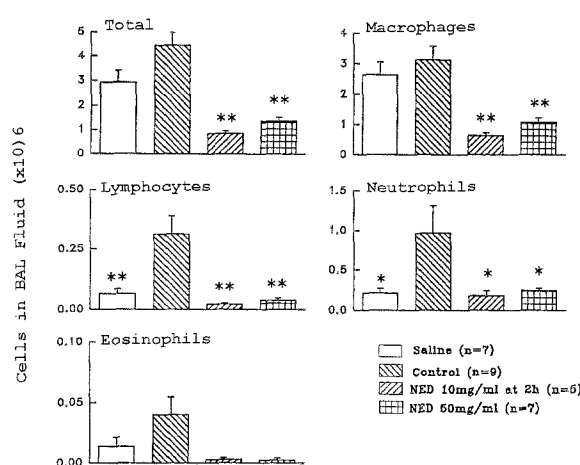


FIG. 1. Total cell yield from BAL is significantly reduced in both groups of animals in which LR was significantly inhibited by nedocromil. Numbers of alveolar macrophages, lymphocytes, and neutrophils are also significantly reduced by both concentrations of nedocromil. Eosinophils are not statistically significant in the nedocromil-treated animals. Asterisks indicate the significance level of the difference between ovalbumin-challenged controls and other groups. * $p < 0.05$; ** $p < 0.01$. NED, Nedocromil sodium.

animals pretreated with nedocromil before ovalbumin challenges, the quantity of ASM was significantly lower (0.036 ± 0.003 , $p < 0.005$) than that of the ovalbumin-challenged rats and was not significantly different from saline-challenged controls. Treatment with nedocromil at 2 hours after ovalbumin challenges also reduced ASM (0.046 ± 0.003 , $p < 0.01$) but less than when administered before challenge. In these animals the quantity of ASM was significantly higher than that in saline-challenged controls ($p < 0.01$) but significantly lower than that in ovalbumin-challenged rats ($p < 0.05$, Fig. 2).

When the airways were divided into three categories on the basis of size, the quantity of ASM in ovalbumin-challenged rats was significantly greater than that in controls in all categories. For animals treated with nedocromil before challenge, the quantity of ASM in all categories was similar to that in saline-challenged controls. However, for the animals that were treated with nedocromil after ovalbumin challenge, the amount of ASM was significantly greater only in the small airways, compared with saline-challenged rats (Fig. 3, $p < 0.05$). The trend was similar for medium-sized airways, but the difference was not significant.

Despite the increase in ASM, the repeated challenges with ovalbumin did not cause any statistically significant change in the airway wall area

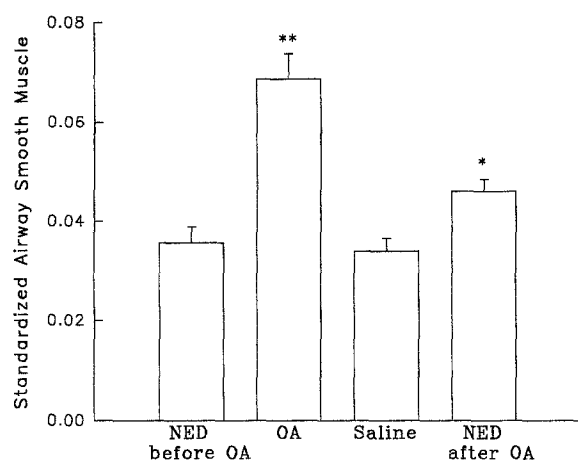


FIG. 2. ASM standardized to the ideal area of airway lumen. ASM of ovalbumin-challenged rats is significantly higher than that of saline-challenged rats (** $p < 0.005$). For nedocromil sodium-pretreated rats, ASM is not significantly different from that of saline controls. Treatment with nedocromil at 2 hours after ovalbumin challenges also reduces growth of ASM (* $p < 0.01$), but less than when administered before challenge. *NED*, Nedocromil sodium; *OA*, ovalbumin challenge.

compared with that of saline-challenged controls. The airways of rats pretreated with nedocromil before ovalbumin challenge were also not significantly altered. However, the walls of small and medium airways in rats that were treated with nedocromil at 2 hours after ovalbumin challenge were significantly thicker than those in the other groups (Fig. 4, $p < 0.05$).

BAL after multiple allergen challenges

The total leukocyte counts in BAL fluid of all ovalbumin-challenged rats were significantly higher than in saline-challenged rats (Fig. 5). Nedocromil treatment did not prevent the increase in cells, and indeed, in the rats that were treated with nedocromil after ovalbumin challenge, cell numbers were the highest of any group. Differential cell counts showed that the neutrophils in ovalbumin-challenged rats, including nedocromil sodium-treated rats, were similar and were significantly higher than in saline-challenged rats. Although there was a slightly higher percentage of eosinophils in BAL of ovalbumin-challenged rats, it did not reach statistical significance. Macrophages were also highest in the rats that received nedocromil 8 hours after ovalbumin challenge.

DISCUSSION

The administration of nedocromil sodium inhibited both early and late pulmonary responses of

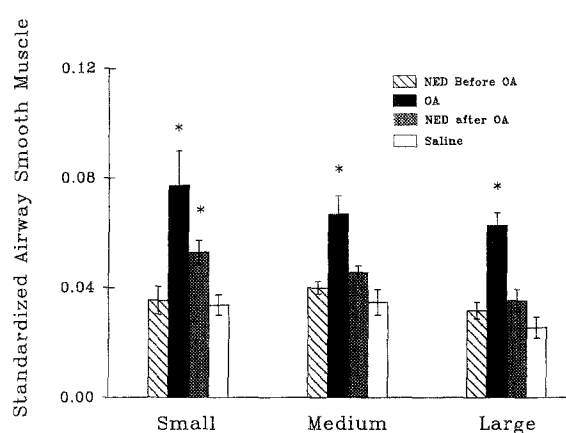


FIG. 3. ASM standardized to the ideal area of airway lumen in small-, medium-, and large-sized airways. ASM of ovalbumin-challenged rats is significantly higher than that of controls in all airway categories (* $p < 0.05$). For nedocromil-pretreated rats, ASM is similar to that of saline-challenged rats. For animals that were treated with nedocromil after ovalbumin challenge, ASM was significantly greater in the small airways compared with that of saline-challenged rats. *NED*, Nedocromil sodium; *OA*, ovalbumin challenge.

sensitized BN rats to antigen challenge. The LR was inhibited by nedocromil administered before antigen challenge and also when nedocromil was given 2 hours after ovalbumin challenge, indicating efficacy against the LR, independent of actions on the ER. The results of this study also demonstrated that structural remodelling of the airways in the form of an increased amount of ASM occurred in sensitized BN rats after repeated allergen administration, confirming previous observations.⁸ Inhaled nedocromil sodium, particularly when given before allergen challenge, prevented allergen-induced ASM growth. However, nedocromil sodium administered after ovalbumin challenge was less effective in preventing these changes.

Nedocromil sodium is a drug that has antiallergic and antiinflammatory actions.¹⁰⁻¹² Passive cutaneous anaphylaxis and the acute increase in lung resistance caused by administration of antigen systemically to passively sensitized rats are inhibited by nedocromil.¹¹ Immediate hypersensitivity reactions to inhaled *Ascaris* antigen are inhibited in the sensitized monkey,¹³ as is allergen-induced bronchoconstriction in patients with asthma.^{14, 15} Nedocromil sodium has also been reported to inhibit exercise-induced asthma.^{16, 17} These observations are consistent with the demonstration that nedocromil in vitro can prevent antigen-triggered mediator release from mast cells,^{18, 19} which pre-

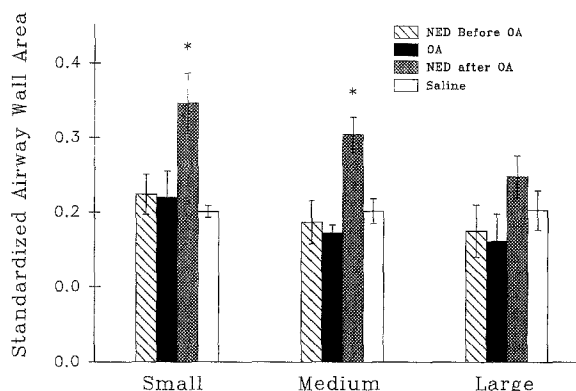


FIG. 4. Airway wall areas standardized to the ideal area of the airway. There are no significant changes in the airway wall areas of ovalbumin-challenged rats except for airway walls in rats treated with nedocromil at 2 hours after ovalbumin challenge. Small and medium airways of these animals are significantly thicker than those in the other groups. * $p < 0.05$. NED, Nedocromil sodium; OA, ovalbumin challenge.

sumably accounts for the effects of nedocromil sodium on the ER of the rat to antigen challenge.

Nedocromil was also effective in blocking the LR to antigen. Interestingly, the administration of nedocromil at 2 hours after ovalbumin challenge also inhibited the LR. These results indicate that nedocromil can act on the LR through mechanisms that are independent of the ER. This action therefore does not depend on the prevention of the early activation of mast cells by IgE cross-bridging. We cannot exclude the possibility that nedocromil affects the LR by inhibiting the mast cell because the role of this cell as a direct participant in the LR is uncertain. However, we believe that nedocromil acts rather by modifying the behavior of inflammatory cells (such as the eosinophil, neutrophil, basophil, or macrophage), which are recruited and activated after the ER. Recently, *in vitro* studies have shown that nedocromil sodium can inhibit the activation of eosinophils and neutrophils,^{20,21} the plasma leakage induced by histamine, leukocyte-dependent plasma extravasation,²² and neutrophil chemotaxis.²³ When human and rat macrophages and platelets are stimulated *in vitro* by specific antigen, they can release inflammatory mediators; and nedocromil sodium inhibits this process.^{24,25} Nedocromil not only inhibits histamine release from lung fragments but also the release of cysteinyl-leukotrienes¹⁹ and 15-hydroxy-eicosatetraenoic acid from bronchial epithelial cells.²⁶

The mediator of the LR in BN rats is leukotriene (LT) D_4 .²⁷ The source of the LTD $_4$ has not

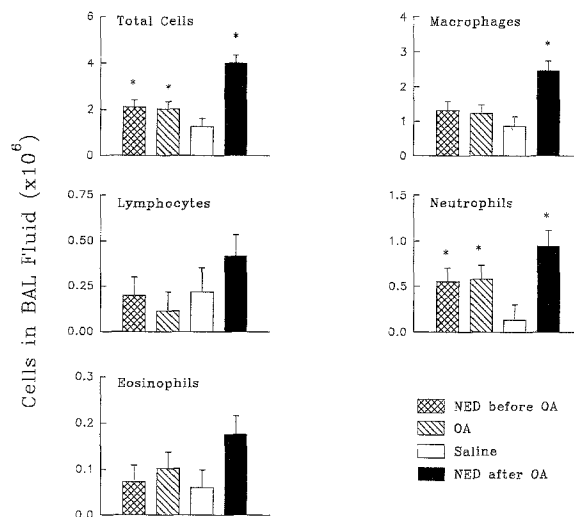


FIG. 5. Total leukocyte counts in BAL fluid of all ovalbumin-challenged rats are significantly higher than those of saline-challenged rats. Differential cell counts show that neutrophils are higher in all ovalbumin-challenged rats than in saline controls. Macrophages are also higher in rats treated with nedocromil 2 hours after ovalbumin challenge. * $p < 0.05$. NED, Nedocromil sodium; OA, ovalbumin challenge.

been identified, but mast cells and macrophages exposed to the products released by activated mast cells are potential sources of LTC $_4$ ^{28,29} available for conversion to LTD $_4$. Therefore it is reasonable to postulate that nedocromil inhibited the synthesis of LTC $_4$ by one or more of these cells. It is also possible that nedocromil acted by preventing the influx of cells, attenuating the inflammatory reaction and the release of associated mediators. This hypothesis seems likely in view of the marked reduction in the cellular return in the BAL of nedocromil-treated animals, as also reported in the guinea pig.³⁰

An increased quantity of ASM is one of the important pathologic alterations in the airways of patients with asthma¹⁻³ and is potentially an important cause of airway hyperresponsiveness. We previously demonstrated that in sensitized BN rats, the quantity of ASM increased after repeated allergen challenges,⁸ mimicking one of the airway histologic changes of asthma. There is, of course, uncertainty concerning the exact comparability of the changes observed in the quantity of ASM in the rat after allergen challenge and the asthmatic airway. To date, there have been no studies of the relative contributions of hyperplasia and hypertrophy to the changes observed in the rat. Furthermore, the extent to which the induction of muscle growth is specific to the allergic response or re-

flects a more nonspecific response to the bronchoconstrictive mediators is also uncertain. Despite the uncertainties concerning the mechanism of the increase in muscle, several *in vitro* studies suggest that mediators released from inflammatory cells have the potential to induce both ASM hypertrophy and hyperplasia.⁴ Therefore it is not entirely surprising that in doses sufficient to inhibit the allergic airway response in the rat, nedocromil was able to prevent allergen-induced ASM growth.

The quantity of ASM was least in the rats treated with nedocromil before allergen challenge. Because nedocromil administered in this way prevents both ERs and LR, it suggests that the mediators of both responses are involved as ASM growth factors. These results are consistent with the previous observations that LTD₄ seems to account for much of the increase in ASM after allergen challenge⁹ because cysteinyl-leukotrienes are synthesized in association with both early and late responses.²⁷ Whether serotonin, the important biogenic amine involved in the early airway response in the rat,³¹ is mitogenic for rat ASM *in vivo* has not been studied.

Pretreatment with nedocromil after ovalbumin inhalation did not inhibit ASM growth in small airways. The explanation for this finding is uncertain but could be related to the delivery of the drug. Perhaps less nedocromil reached the small airways after the development of the airway narrowing, perhaps because of mucus secretion during and after the ER. Interestingly, the rats that were treated with nedocromil after ovalbumin inhalation had the highest total cell yield in the BAL of all of the ovalbumin-challenged rats and also had thicker small and medium airways. The factors leading to the increase in airway wall thickness are presumably different from those causing the increase in muscle because this lesion developed despite protection against muscle growth and was not evident in animals that were not treated with nedocromil.

The total cellular yields in BAL were significantly higher in all animals undergoing multiple ovalbumin challenges than in the saline-challenged control rats. The cellular differential counts were similar in these animals. These findings are in contrast to the effects of nedocromil on the inflammatory response to a single challenge in which it potentially prevented the influx of inflammatory cells at 8 hours after challenge. Perhaps nedocromil administered near the time of allergen challenge delays but does not inhibit airway inflammation.

In allergic sheep, pretreatment with nedocromil

sodium blocks antigen-induced ERs and LR and also prevents the influx of eosinophils into the airways during the LR.³²⁻³⁴ Aerosolized nedocromil sodium administered before repeated exposure to allergen can also inhibit both airway eosinophilia and hyperresponsiveness to acetylcholine in allergen-sensitized guinea pigs.³⁵ Eosinophils were not significantly elevated in rats 2 days after repeated antigen challenge; therefore, we could not evaluate possible efficacy in preventing eosinophilia.

In conclusion, nedocromil sodium antagonizes both ERs and LR in the BN rat. With this drug it has been possible to demonstrate that the mediators of both the early and late allergic airway responses play an important role in ASM growth. Nedocromil, which blocks airway responses, also protects against allergen-induced ASM growth. However, inhalation of nedocromil before allergen challenges is more effective in preventing ASM growth than administration after the resolution of the ER. The timing of administration of the drug may be important in that other airway lesions may be induced when nedocromil is administered after the ER has resolved.

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