

Effect of nedocromil sodium on mediator release from mast cells

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Bronchial asthma is a complex inflammatory disorder that involves activation of, and mediator release by, a variety of cells including mast cells. Nedocromil sodium can inhibit the activity of a range of inflammatory cells including mast cells, as has been demonstrated in several studies. In human beings nedocromil sodium inhibited histamine secretion from mast cells obtained by bronchoalveolar lavage and from dispersed lung mast cells. Tachyphylaxis was noted with the latter cells only. Because the bronchoalveolar lavage mast cells would come into direct contact with inhaled drugs, these cells may be a major target for the action of nedocromil sodium. The inhibitory effects of nedocromil sodium on mast cell activation and secretion are one way the drug may be effective in controlling airway obstruction. (J ALLERGY CLIN IMMUNOL 1993;92:155-8.)

It is now recognized that human bronchial asthma is a highly complex inflammatory disorder involving the participation of a range of effector cells, including macrophages and mast cells, together with neutrophils, lymphocytes, and eosinophils, which characteristically infiltrate the airways of patients with the disease.^{1, 2} The release of mediators from these cells leads to local inflammatory processes and tissue damage. This then results in structural alterations to the airways, including desquamation of the surface respiratory epithelium, mucosal edema, mucus hypersecretion, thickening of the basement membrane, and smooth muscle hypertrophy. Ultimately these changes produce the characteristic nonspecific bronchial hyperreactivity that is the clinical hallmark of the disease. Nedocromil sodium is effective in the control of airway obstruction in a number of experimental and clinical situations, and is able to inhibit the activation of a range of inflammatory cells.³ This article describes the effect of the compound on mediator release from mast cells.

Mast cells are widely distributed throughout the human respiratory tract and are found in large

Abbreviations used

BAL: Bronchoalveolar lavage
IC₂₀: 20% inhibition concentration
IC₃₀: 30% inhibition concentration
IC₅₀: 50% inhibition concentration
PGD₂: Prostaglandin D₂

numbers in the walls of the alveoli and the airways. Two populations of these cells can be envisaged. One is situated beneath the basement membrane near blood vessels and fibrous stroma. The second population is located between the basement membrane and the epithelium and abutting onto the luminal surface. The latter cells may be recovered by BAL, whereas parenchymal mast cells may be obtained by enzymic dissociation of whole lung tissue.

In a continuing study these two types of pulmonary mast cells have been shown to exhibit subtle but distinct differences in their functional properties.⁴⁻⁸ Moreover, they might be expected to play different roles in the pathogenesis of asthma. The BAL cells, lying superficially within the airways, would come into immediate contact with inhaled allergens and might thus mediate the initial stages of the asthmatic response. With the development of the chronic disease, the opening of tight junctions and damage to the surface respiratory epithelium would allow increased penetration of aeroallergens and the progressive involvement of the parenchymal mast cells. The particular importance of the BAL cell may be evidenced by the observations that these cells increase strikingly in

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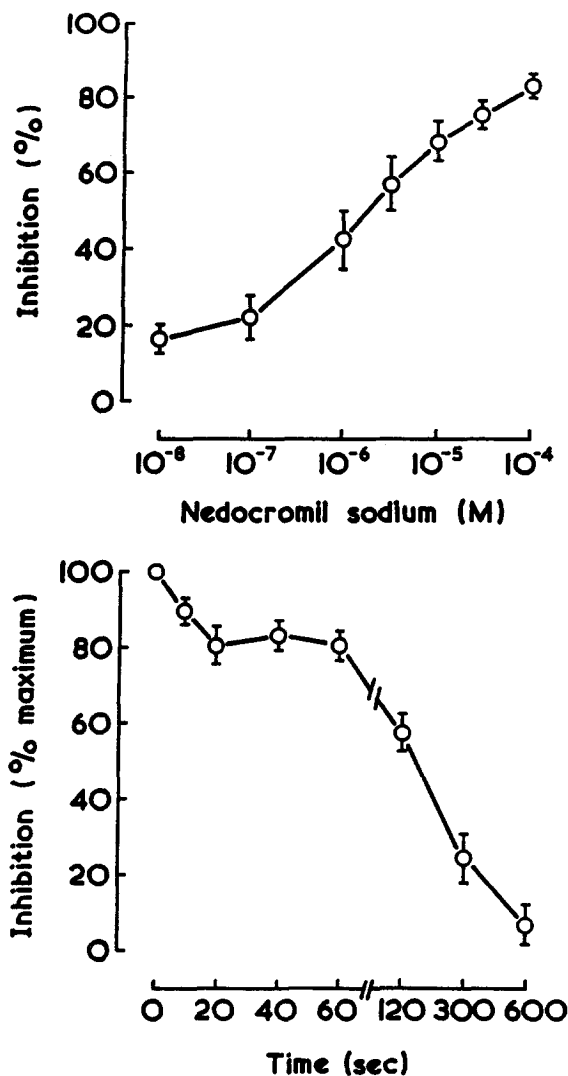


FIG. 1. Effect of nedocromil sodium on histamine release from rat peritoneal mast cells. Cells were obtained from actively sensitized animals and challenged with allergen from *Nippostrongylus brasiliensis*. *Upper panel*, Drug added simultaneously with secretory stimulus. *Lower panel*, Cells preincubated with drug (10 μ mol/L) for indicated times before challenge. Values expressed as mean $\pm$ SEM for four experiments. (From Pearce FL, Al-Laith M, Bosman L, et al. *Drugs* 1989;37[suppl 1]:38. Reproduced with permission of Adis Press Ltd., Auckland, New Zealand.)

number in the lavage fluid of asthmatic subjects and that this increase is significantly correlated to the severity of the disease as assessed by measured indexes of both airway obstruction and hyperreactivity. The cells recovered from asthma patients also appear to be inherently unstable and hyperresponsive to immunologic activation.⁶ In light of these observations, we sought to examine the effect of nedocromil sodium on various mast cells.

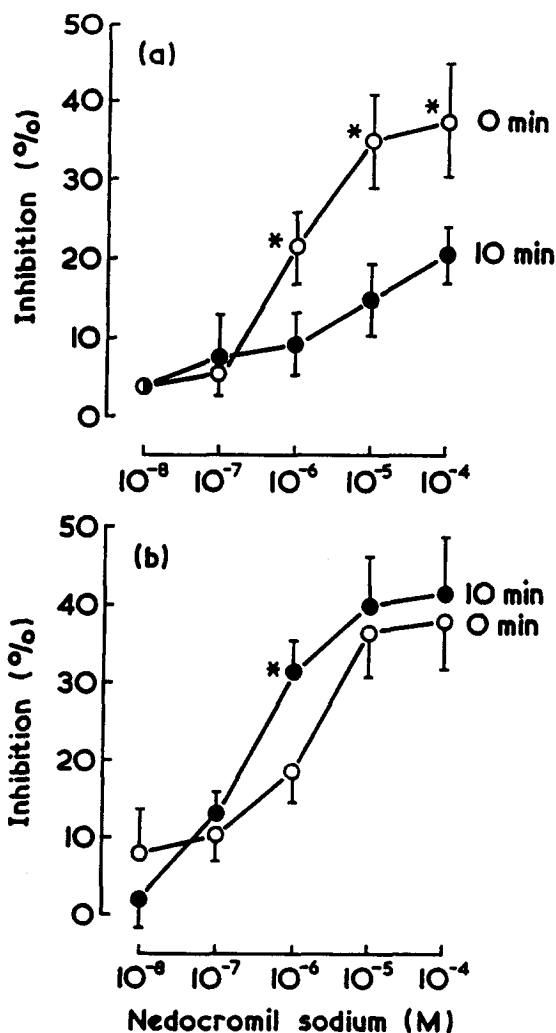


FIG. 2. Effect of nedocromil sodium on histamine release from dispersed human lung mast cells (a) and human BAL cells (b). Drug was added to cells simultaneously with secretory stimulus ($\circ$) or preincubated with cells for 10 minutes ($\bullet$) before challenge with antihuman immunoglobulin E. Values are means $\pm$ SEM for 10 (a) or 7 (b) experiments. Asterisks denote pairs of values that were significantly different ($p < 0.05$). (From Leung KBP, Flint KC, Brostoff J, et al. *Thorax* 1988;43:758-9.)

EFFECT ON ANIMAL MAST CELLS

Nedocromil sodium produced a marked, dose-dependent inhibition of histamine release from rat peritoneal mast cells.⁴ The IC_{50} value was 2 μ mol/L nedocromil sodium, and the maximum inhibition observed was greater than 80% (Fig. 1, *upper panel*). The compound exhibited a sharp tachyphylaxis, and activity was rapidly lost on preincubation with the cells before immunologic challenge (Fig. 1, *lower panel*). Such tachyphylaxis is also seen in this system with cromolyn sodium.⁹

The effect of nedocromil sodium was highly species and site specific. The drug produced a

comparable inhibition of immunologic histamine release from rat peritoneal and pleural mast cells, showed reduced activity against peritoneal cells from the hamster, and was completely ineffective against the latter cells from the mouse. The compound was also inactive against tissue mast cells of the guinea pig and mucosal mast cells from the gastrointestinal tract of the rat.⁴

EFFECT ON HUMAN PULMONARY MAST CELLS

Nedocromil sodium produced a dose-dependent inhibition of histamine release from both dispersed lung and human BAL mast cells (Fig. 2). However, the characteristics of the inhibition were different for the two cell types. Thus the activity of the drug decreased on preincubation with the dispersed lung cells but was unaffected or even increased after preincubation with the BAL cells. In 10 experiments⁸ in which carefully matched levels of secretion were used the IC_{30} values for the BAL and parenchymal cells were 0.52 ± 0.11 and 5.7 ± 1.4 $\mu\text{mol/L}$, respectively ($p < 0.01$).

Another important characteristic of the inhibition produced by nedocromil sodium was that the apparent potency of the drug varied markedly and inversely with the magnitude of the secretory response. That is, high levels of induced histamine release were much less effectively inhibited than low levels of secretion. This effect was apparent for both BAL and dispersed lung cells (Fig. 3).

In addition to its action on cells from normal persons, nedocromil sodium also inhibited histamine release from BAL cells of subjects with pulmonary sarcoidosis and, more relevantly, with intrinsic asthma.⁸ The drug was somewhat less potent under these conditions, but this may simply reflect the hyperreactivity of the mast cells from such patients and the corresponding increase in the levels of induced histamine secretion.

On immunologic activation human lung mast cells release not only the preformed mediator, histamine, but also generate newly synthesized products of the oxidative metabolism of arachidonic acid, principally PGD_2 and leukotriene C_4 .⁶ In preliminary experiments, nedocromil sodium effectively inhibited the release of these eicosanoids from dispersed lung mast cells, with the BAL cells still to be tested. Moreover, the drug was more effective in preventing the liberation of the prostanoid than of histamine; the IC_{20} values in parallel experiments were approximately 0.1 $\mu\text{mol/L}$ for PGD_2 and 5 $\mu\text{mol/L}$ for histamine release, respectively (unpublished data).

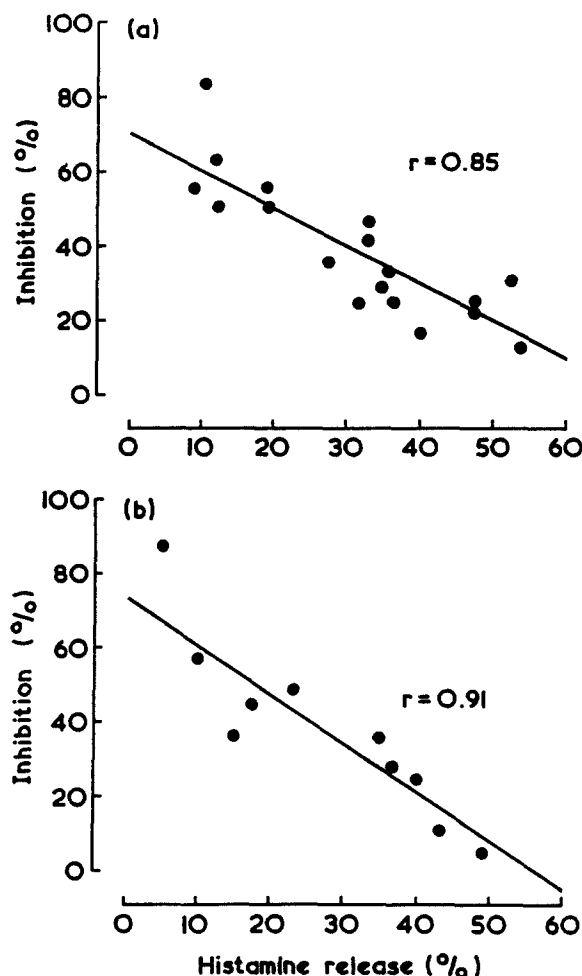


FIG. 3. Apparent variation in potency of nedocromil sodium against BAL (a) and dispersed lung mast cells (b) according to magnitude of secretory response. Scattergrams show inverse relationship in individual donors between degree of inhibition produced by fixed concentration of drug (a, 10 $\mu\text{mol/L}$; b, 100 $\mu\text{mol/L}$) and absolute level of histamine release produced by antihuman immunoglobulin E. (From Pearce FL, Al-Laith M, Bosman L, et al. *Drugs* 1989;37[suppl 1]:42. Reproduced with permission of Adis Press Ltd., Auckland, New Zealand.)

EFFECT ON OTHER HUMAN HISTAMINOCYTES

Nedocromil sodium inhibited histamine secretion from isolated mast cells from human colonic mucosa and colonic submucosa and muscle, albeit rather less effectively than human lung, but was completely inactive against human cutaneous mast cells and basophil leukocytes.^{10, 11}

DISCUSSION

Nedocromil sodium was a potent inhibitor of histamine release from rat peritoneal cells but showed a high degree of specificity in its effects on mast cells from other animal sources. The

origin of this selectivity is unclear, but these data clearly illustrate the problems involved in using animal models for the screening of mast cell-stabilizing compounds and emphasize the necessity of conducting such studies on human preparations.

Nedocromil sodium inhibited histamine secretion from both human BAL and dispersed lung mast cells and was approximately one order of magnitude more active against the former cell type. Moreover, tachyphylaxis was observed with the parenchymal cell but not the BAL cell. These findings may be of clinical significance. The luminal BAL cell would come into direct contact with inhaled drugs, and given that tachyphylaxis to the compound is not seen in clinical use, these cells may thus be a major target for the action of nedocromil sodium. A further important point in assessing the potency of the drug is the observation that its apparent activity varied markedly and inversely with the strength of the secretory stimulus. For purely practical reasons of measurement, studies in vitro necessarily use induced releases of histamine much greater than those likely to occur in even the most severe asthma attack in vivo. Under these conditions the potency of nedocromil sodium is likely to be considerably higher than that determined in the laboratory.

Nedocromil sodium also inhibited the release of PGD₂ from human lung mast cells. The drug was more potent in preventing liberation of the prostanoid than in blocking histamine secretion. PGD₂ is the major cyclooxygenase product of arachidonic acid metabolism in pulmonary mast cells and is a potent bronchoconstrictor. It also increases mucus production and may amplify the effect of other inflammatory mediators. The ability of nedocromil sodium to inhibit the liberation of this agent may thus be of considerable clinical importance.

Finally, nedocromil sodium prevented histamine secretion from human colonic, but not cutaneous, mast cells.

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