

Adenosine-induced bronchoconstriction and its inhibition by nedocromil sodium

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The inhalation of adenosine or adenosine-5'-monophosphate (AMP) causes a reproducible and transient bronchoconstriction in both atopic and nonatopic asthmatic subjects that is not followed by a late-phase response. The response may be prevented by prophylactic treatment with histamine H₁-receptor antagonists, local anesthetics, and atropine, which suggests that both mast cell mediator release and neuronal reflexes are involved. Adenosine- and AMP-induced bronchoconstriction are both blocked by cromolyn sodium and nedocromil sodium, with the PD₂₀FEV₁ for the latter approximately four times lower than that of cromolyn sodium in atopic asthmatic patients and approximately 2.3 times lower than that of cromolyn sodium in nonatopic asthmatic patients. We suggest that AMP-induced bronchoconstriction, in combination with other indirect-acting provocants, may be used to determine the effectiveness and mechanism of action of antiasthmatic drugs. (J ALLERGY CLIN IMMUNOL 1993;92:190-4.)

The interaction of specific allergens with immunoglobulin E bound to the surface of mast cells within the bronchial lumen induces the release of chemical mediators that initiate the bronchoconstrictor events of the early asthmatic response. Among these mediators are histamine, prostaglandins, and leukotrienes. This response may be prevented by drugs that prevent mast cell mediator release, such as cromolyn sodium and nedocromil sodium,^{1, 2} and partially ameliorated by agents that antagonize the effects of histamine at H₁ receptors or prevent the generation of prostaglandins.³ However, in asthma, allergen is not the only agent that may provoke an episode of bronchoconstriction. Exposure to exercise, isocapnic hyperventilation, fog, sulfur dioxide, bradykinin, or adenosine may also induce bronchoconstriction. Interestingly, the effect of all of these agents can be blocked by nedocromil sodium or cromolyn sodium.⁴⁻¹⁰ In this review, we briefly assess what is known of the mechanism of action of adenosine in causing bronchoconstriction and how nedocromil sodium may prevent it.

EFFECT OF INHALED ADENOSINE IN ASTHMA

When inhaled by asthmatic subjects, adenosine causes a rapid and reproducible bronchoconstriction,

Abbreviations used

AMP: Adenosine-5'-monophosphate
PD₂₀: Dose of provicant calculated to induce 20% bronchoconstriction
FEV₁: Forced expiratory volume in 1 second

tion,¹¹ an event that is mimicked by adenosine-5'-monophosphate (AMP).¹² Because animal experiments have shown that exogenous AMP is rapidly metabolized to adenosine¹³ and because the characteristics of bronchoconstriction induced by the two agents are identical, it is probable that the AMP-induced bronchospasm followed its extracellular hydrolysis to adenosine.¹² The use of the more soluble AMP has allowed comparative studies in patients with and without asthma, the latter not being sensitive to the provicant.¹² Interestingly, allergic nonasthmatic subjects give a weak response to AMP, suggesting that unlike methacholine, which is an indicator of bronchial hyperresponsiveness, the presence of allergy may also be a determinant for the action of AMP.^{14, 15}

In contrast to allergen, AMP does not cause late responses, nor does it increase nonspecific bronchial hyperresponsiveness.¹⁶ However, repeated exposure to AMP does induce a state of tachyphylaxis¹⁷ and is cross-tachyphylactic to exercise but not to allergen challenge, which has an increased effect under these conditions.¹⁸

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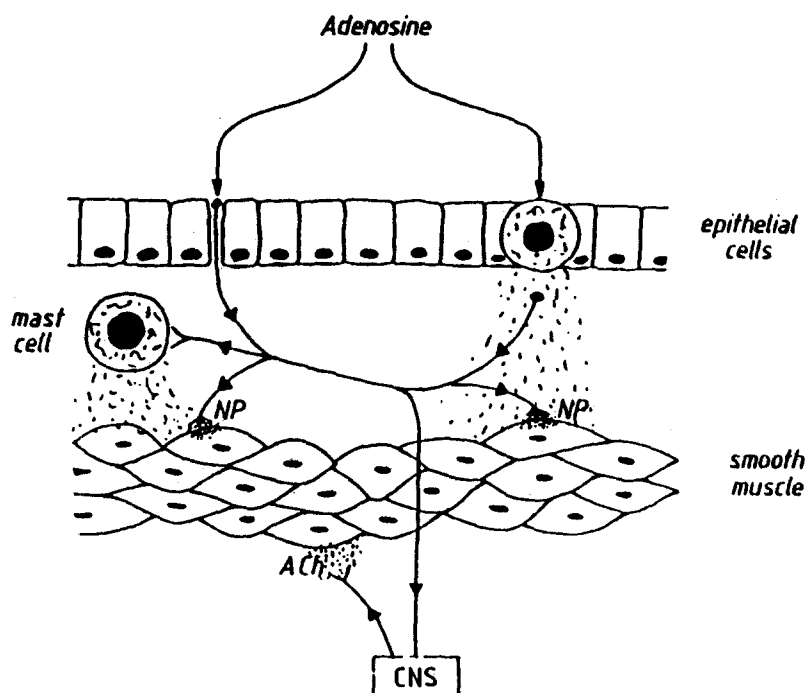


FIG. 1. Possible sites of action of adenosine at bronchial mucosa. Adenosine is indicated to be acting at two sites. The first is a direct action on the mast cell to release its bronchoconstrictor mediators that then act directly on bronchial smooth muscle to cause contraction and on sensory neurons to induce local release of neuropeptides (NP) by antidromic reflexes. The second is an initial action on sensory neurons in epidermis to stimulate antidromic reflexes and indirect release of mast cell mediators. Stimulation of other neuronal reflexes including C fibers may also occur.

POSSIBLE MECHANISMS OF ACTION OF ADENOSINE

Several possible mechanisms of action for adenosine in asthma have been proposed (Fig. 1). These include a direct constrictor effect on bronchial smooth muscle, an effect on luminal mast cells in the bronchi, and an effect on neuronal reflexes within the lung.

The ability of histamine H_1 -antagonists^{19, 20} and the antiasthma drugs cromolyn sodium and nedocromil sodium^{4,21-23} to block the bronchoconstrictor effects of AMP or adenosine suggests that a direct effect on bronchial smooth muscle is unlikely.

The report of Marquardt et al.²⁴ stimulated interest in the possible role of adenosine as a modulator of mast cell mediator release. According to these investigators, although adenosine did not directly stimulate histamine release, it was capable of augmenting immunologically stimulated histamine release from rodent mast cells.²⁴ This effect appears to be mediated by the interaction of adenosine with a novel purinoceptor.²⁵ Studies of adenosine-potentiated mediator re-

lease from human mast cells are less consistent than those that use rodent mast cells. However, small enhancements of release have been reported to occur under optimum conditions.²⁶ Clinical evidence of histamine release after adenosine challenge has been difficult to obtain; only small increases in plasma histamine levels have been observed after provocation.²⁷

Although a direct action of adenosine on mast cells is an attractive hypothesis, there is substantial evidence against it. First, studies by Peachell et al.²⁸ showed that the release of leukotriene C_4 is enhanced in parallel with histamine release. This finding does not fit with the almost total blockade of adenosine-induced bronchoconstriction afforded by histamine H_1 -antagonists.^{19, 20} Second, the purinoceptor antagonist theophylline, which specifically antagonizes adenosine-induced bronchoconstriction,²⁹ does not inhibit the enhancement of mediator release by adenosine in rodent mast cells.²⁵ Third, if adenosine acts by releasing histamine from luminal mast cells, then tachyphylaxis could be explained by the depletion of histamine from these cells.¹⁷ This finding is not

TABLE I. Comparison of cromolyn sodium and nedocromil sodium in preventing an AMP-induced fall in FEV₁ in atopic and nonatopic patients*

Atopic patients			Nonatopic patients	
Treatment	PD ₂₀ AMP	Dose ratio	PD ₂₀ AMP	Dose ratio
Placebo	4.9 (0.3-14)†	1	4.9 (0.3-40)	1
Cromolyn sodium	34.5 (4-133)	7.0 (2.7-21.9)	46.5 (2-560)	9.6 (1.5-41.6)
Nedocromil sodium	134 (12-560)	26.9 (6.9-95.8)	107.9 (6-560)	22.2 (3.7-89.1)

*Cromolyn sodium and nedocromil sodium were administered as 60 breaths of a 1% w/v nebulized solution in 0.9% sodium chloride.

†Values in parentheses are the range of the experimental observations; results from Richards et al.²² and Phillips et al.²³

compatible with the enhancement of allergen-induced bronchoconstriction in the presence of adenosine tachyphylaxis. Fourth, the report that adenosine-induced bronchoconstriction may be reduced by atropine³⁰ is also not consistent with a direct effect on mast cells.

An alternative hypothesis is that adenosine induces bronchoconstriction by exciting sensory neurons or down-regulating inhibitory neurons in the bronchi. We would suggest that stimulation of an axon reflex to release sensory neuropeptides may subsequently induce the release of histamine from luminal mast cells. This hypothesis involving mucosal mast cells is attractive because it accommodates the majority of the experimental data, including the effects of local anesthetics,³⁰ atropine,³⁰ tachyphylaxis occurring at the neuronal rather than the mast cell level,¹⁶ H₁-antagonists,¹⁹⁻²⁰ and the antiasthma drugs nedocromil sodium and cromolyn sodium.^{4, 21-23}

EFFECTS OF NEDOCROMIL SODIUM ON ADENOSINE-INDUCED BRONCHOCONSTRICTION

Many studies have now demonstrated the effectiveness of cromolyn sodium and nedocromil sodium against adenosine- or AMP-induced bronchoconstriction.^{4, 21-23} Because this indirectly acting provicant is easy and safe to use, is effective in both allergic and nonallergic asthmatic subjects, and gives reproducible levels of bronchoconstriction, it represents an ideal agent with which to estimate the potency of inhibitory drugs in early-phase bronchoconstriction. In two recent studies (Table I) the potencies of nedocromil sodium and cromolyn sodium against AMP-induced bronchoconstriction in atopic²² and nonatopic²³ asthmatic subjects were compared. In both studies, subjects inhaled a 1% aerosol of drug or saline solution 60 times during a 6-minute period before a dose-response curve to AMP was constructed. Analysis of the FEV₁ data in atopic subjects

showed that cromolyn sodium displaced the concentration of AMP required to cause a 20% bronchoconstriction (PD₂₀) by sevenfold and nedocromil sodium caused a 27-fold shift in the dose of AMP required to cause a 20% drop in FEV₁. Similar data were obtained in nonatopic subjects, cromolyn sodium causing a 9.6-fold and nedocromil sodium a 22.2-fold shift in the PD₂₀FEV₁.

The mechanisms by which nedocromil sodium and cromolyn sodium prevent adenosine- and AMP-induced bronchoconstriction are not entirely clear. Because the drugs were given only 30 minutes before assessment of an acute bronchoconstrictor event, an effect on the inflammatory basis of asthma³¹⁻³⁴ is unlikely. Two major possibilities remain. One explanation is that the agents exert a direct effect in preventing increased release of mediators from mast cells associated with the bronchial mucosa. Such an effect would be consistent with the ability of histamine H₁-receptor antagonists to block AMP-induced bronchoconstriction by more than 80% in both atopic²¹ and nonatopic³⁵ subjects and with in vitro observations of the inhibitory effects of nedocromil sodium and cromolyn sodium on mast cell mediator release.¹ An alternative hypothesis is that inhibitory drugs modulate neuronal reflexes in the lung to prevent bronchoconstriction. Evidence that cromolyn sodium may have such effects is available,^{36, 37} and available data suggest that nedocromil sodium has similar effects.^{38, 39} The ability of nedocromil sodium to prevent bradykinin-induced bronchoconstriction⁴⁰ in which neuronal but no mast cell-mediated mechanism has been invoked⁷ also provides indirect evidence of its ability to modulate nervous reflexes in the lung.

CONCLUSIONS

The inhalation of adenosine or AMP causes bronchoconstriction in patients with atopic and

nonatopic asthma. This bronchoconstriction is reproducible, of short duration, and is not followed by a late-phase response. Its ability to be blocked by treatment with histamine H₁-antagonists, local anesthetics, and atropine suggests that both mast cell mediator release and neuronal reflexes are involved in its mediation. Cromolyn sodium and nedocromil sodium are both effective inhibitors of adenosine-induced bronchoconstriction. Statistically significant between-group differences were determined favoring nedocromil sodium over cromolyn sodium for challenges in both atopic and nonatopic asthmatic patients.

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