Mast Cell Tryptase: A New Target for Therapeutic Intervention in Asthma

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Asthma is a chronic inflammatory disease characterized by reversible airway obstruction and increased airway responsiveness to exogenous and endogenous mediators [1]. Mast cells have been implicated in the pathogenesis of this disease, particularly in the acute response occurring immediately after exposure to allergen [2]. Tryptase, a mast cell serine protease, has also been implicated in the pathophysiology of allergic asthma [3-5], but formal evidence to support this hypothesis has been limited by the lack of specific inhibitors for use in vivo. Therefore, in this study we examined the effects of a novel inhibitor of tryptase, APC 366 [N-(1-hydroxy-2-naphthoyl)-Z-arginyl-L-prolinamide hydrochloride] on antigen-induced early and late responses, airway hyperresponsiveness as measured by carbachol provocation, microvascular permeability as measured by bronchoalveolar lavage (BAL) albumin concentrations, and accumulation of eosinophils in lung biopsies from allergic sheep. APC 366 and *Ascaris suum* antigen were administered by aerosol in all experiments. The allergic sheep used for these protocols develop both early and late airway responses after inhalation challenge with *A. suum* antigen [6]. Each animal served as its own control, with antigen challenges given on occasions at least 2 weeks apart.

Acute treatment with APC 366 (4.5 mg/3 ml H₂O given 0.5 h before, 4 and 24 h after antigen challenge) slightly reduced the peak early response and abolished the late response. Twenty-four hours after challenge, APC 366 completely blocked the antigen-induced airway hyperresponsiveness to inhaled carbachol. Protection against the late response and airway hyperresponsiveness was dose-dependent. At a 9 mg dose APC 366 also showed anti-inflammatory activity by significantly inhibiting post-antigen-induced increases in BAL albumin

and tissue eosinophilia when compared to control. Prophylactic administration of APC 366 (18 mg twice a day for 3 days plus 18 mg 0.5 h before antigen challenge) provided a significantly greater reduction in the early response as compared to the acute treatment. This multiple treatment regimen also blocked the late airway response and the post-challenge airway hyperresponsiveness.

The results of this study provide the first in vivo evidence to support the hypothesis that mast cell tryptase plays an

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important role in generating airway responses following antigen challenge. APC 366 blocked antigen-induced late responses, airway hyperresponsiveness, and airway inflammation in the sheep model of allergic asthma. The anti-inflammatory properties of APC 366 presumably account for the effectiveness of the drug at suppressing both the late bronchial response and airway hyperresponsiveness. The efficacy profile exhibited in sheep by APC 366 is similar to that shown by the antiasthmatic agents budesonide [7], cromolyn sodium [8], and nedocromil sodium [8,9] in this animal model. That is, all four compounds provided partial protection against the early response and blocked the late response. The development of airway hyperresponsiveness 24 h after antigen challenge was completely blocked by APC 366 and nedocromil [9] but only partially attenuated by budesonide [7]. Thus, tryptase inhibitors, exemplified by APC 366 (and more potent second-generation compounds), afford protection against antigen-induced airway responses and inflammation in the sheep model that equals or exceeds that provided by other antiasthmatic agents in clinical use such as budesonide and cromolyn.

The marked inhibition of the immediate bronchial response to antigen under conditions of prophylactic dosing

suggests that tryptase is not only released in conjunction with other preformed mast cell mediators but might also act to modulate the release and/or effectiveness of the other spasmogens. Thus, inhibition of tryptase could be important in regulating the severity of the allergic response. Although there are little in vivo data to suggest that tryptase causes mast cell degranulation, we have collected preliminary evidence that tryptase injected into the skin of sheep causes an immediate wheal; this response can be inhibited with APC 366 and/or antihistamines, thereby supporting a role for tryptase in modulating mediator release [Moliari et al., submitted]. Collectively, our results suggest that mast cell tryptase plays an important role in antigen-induced airway responses. The ability to suppress antigen-induced airway responses and inflammation by selectively targeting a single mediator, mast cell tryptase, offers the potentially significant advantage of treating asthma and other allergic diseases with drugs (including orally active compounds) that do not have the side effects associated with agents such as corticosteroids that affect multiple targets. Inhibition of this enzyme may represent a new target for therapeutic intervention in the treatment of asthma and other allergic diseases.

References

American Thoracic Society: Chronic bronchitis, asthma, and pulmonary emphysema. *Am Rev Respir Dis* 1987;136:224-225. Holgate ST, Hardy C, Robinson C, Agius RM, Howarth PH: The mast cell as a primary effector cell in the pathogenesis of asthma. *J Allergy Clin Immunol* 1986;77:274-282. Tarn EK, Caughey GH: Degradation of airway neuropeptides by human lung tryptase. *Am J Respir Cell Mol Biol* 1990;3:27-32. Sekizawa K, Caughey GH, Lazarus SC, Gold

WM, Nadel JA: Mast cell tryptase causes airway smooth muscle hyperresponsiveness in dogs. *J Clin Invest* 1989;83:175-179.

Lilly CM, Martins MA, Drazen JM: Peptidase modulation of vasoactive intestinal peptide pulmonary relaxation in tracheal superfused guinea pig lungs. *J Clin Invest* 1993;91:235-243.

Abraham WM, Delehunt JC, Yerger L, Marchette B: Characterization of a late phase pulmonary response following antigen challenge in allergic sheep. *Am Rev Respir Dis* 1983; 128: 839-844.

Abraham WM, Lanes S, Stevenson JS, Yerger L: Effect of an inhaled glucocorticosteroid (budesonide) on post-antigen induced increases in airway responsiveness. *Bull Eur Physiopathol Respir* 1986;22:387-392.

Abraham WM, Stevenson JS, Chapman GA, Tallent MW, Jackowski J: The effect of nedocromil sodium and cromolyn sodium on antigen-induced responses in allergic sheep in vivo and in vitro. *Chest* 1987;92:913-917.

Abraham WM, Stevenson JS, Eldridge M, Garrido R, Nieves L: Nedocromil sodium in allergen-induced bronchial responses and airway hyperresponsiveness in allergic sheep. *J Appl Physiol* 1988;65:1062-1068.