Dexamethasone and Cyclosporin A Suppress Mast Cell-Leukocyte Cytokine Cascades by Multiple Mechanisms

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Key Words

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Abstract

Based on in vitro findings with mouse mast cells and in vivo findings in mice, we report that dexamethasone or cyclosporin A can have at least three actions which interfere with the pathogenesis IgE-, mast-cell-, and cytokine-dependent inflammatory reactions: suppression of the IgE-dependent increase in tumor necrosis factor (TNF)- α mRNA by mast cells, inhibition of the IgE-dependent production of TNF- α protein by mast cells, and diminution of the responsiveness of target cells to TNF- α . Our findings in mice raise the possibility that similar actions of these agents in humans may account for some of the clinical efficacy of corticosteroids and cyclosporin A in allergic diseases.

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Many of the immediate consequences of IgE-dependent mast cell activation reflect the actions of mediators such as histamine, which are stored in the cytoplasmic granules and which are released within minutes of cell activation by exposure to specific antigen [1,2]. Yet the actions of these rapidly released mast-cell-granule-associated mediators cannot account for all of the pathology of chronic allergic diseases. For example, corticosteroids, which in clinically relevant concentrations have little or no ability to interfere with IgE-dependent mast cell activation and histamine release [1, 3], represent a mainstay of therapy for chronic allergic disorders, such as allergic asthma and atopic dermatitis [1]. Moreover, some patients with allergic asthma can benefit from treatment with the chemically unrelated immunosuppressive agent, cyclosporin A (CsA) [4, 5].

Both corticosteroids [1] and CsA [6, 7] can have several anti-inflammatory actions, including effects on basophil mediator release, which are independent of any effect on mast cells [1, 8]. Accordingly, it could be argued that the efficacy of these agents in chronic allergic diseases may be unrelated to any

action of these drugs on the mast cell. However, recent observations indicate that IgE-dependent activation induces mast cells to release tumor necrosis factor (TNF)- α and other cytokines, mediators that represent a potential link between mast cell activation and some of the more chronic manifestations of allergic diseases [2]. Corticosteroids or CsA can diminish cytokine production in lymphocytes and other cell types [1, 6], and CsA can reduce the production of certain cytokines by in vitro-derived mouse mast cells [9-11]. However, it was unclear whether corticosteroids or CsA ameliorate certain aspects of IgE-dependent responses through effects on mast cell cytokine production. We recently investigated this issue and found that either dexamethasone or CsA can inhibit production of TNF- α by

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in vitro-derived mouse mast cells (by diminishing Fc ϵ RI-dependent increases in both TNF- α mRNA and release of TNF- α bioactivity), and that these agents can also significantly suppress tissue swelling and leukocyte infiltration in two forms of TNF- α -associated inflammation in vivo: the entirely IgE- and mast-cell-dependent inflammation at sites of passive cutaneous anaphylaxis reactions [12] and the entirely TNF- α -dependent inflammation that is elicited by the direct intradermal injection of recombinant mouse TNF- α (rmTNF- α) [13]. The latter findings clearly demonstrated that one mechanism by which either dexamethasone or CsA can suppress IgE- and mast-cell-dependent inflammation (or inflammation due to TNF- α derived from sources other than the mast cell) is by diminishing the biological effects of any TNF- α which is released at these reaction sites [13].

Our findings of course do not rule out the possibility that the efficacy of corticosteroids or CsA in chronic allergic disorders importantly reflects multiple actions of these agents (including suppression of cytokine production) on cells other than the mast cell. It should also be noted that findings obtained in mice may not necessarily apply to humans. Nevertheless, our in vivo studies [13] employed doses of the drugs which are similar to those used in clinical settings [1, 7]. Accordingly, it does not seem unreasonable to speculate, on the basis of our findings [13], that some of the clinical benefit of corticosteroids or CsA in chronic allergic diseases or other disorders associated with mast cell activation may reflect the ability of these agents to interfere with mast cell cytokine production and other steps in the pathogenesis of mast cell-leukocyte cytokine cascades [2]. On the other hand, neither agent fully suppressed the leukocyte infiltration associated with the IgE-dependent cutaneous reactions, or that induced by intradermal rmTNF- α . These results indicate that some of the leukocyte recruitment associated with IgE-, mast-cell-, and/or TNF- α -dependent reactions in vivo occurs through the activation or recruitment of mediator pathways which are insensitive to inhibition by corticosteroids or CsA.

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324

Wershil/Furuta/Lavigne/Choudhury/ Wang/Galli

Pharmacological Inhibition of Mast-Cell-Dependent Inflammation