Effects of Corticosteroids on Cytokine Generation and Expression of Activation Antigens by Monocytes in Bronchial Asthma

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Abstract

The capacity of corticosteroids to inhibit the secretion of cytokines and the expression of selective antigens on monocytes has been studied in corticosteroid-sensitive (CS) and corticosteroid-resistant (CR) asthmatic patients. Incubation of monocytes derived from CS subjects with hydrocortisone inhibited the production of the enhancing activity, whereas in CR subjects hydrocortisone at concentrations of up to 10^{-4} M did not suppress the release of enhancing activity. There was a rank order of potency for corticosteroid action: hydrocortisone < methylprednisolone < dexamethasone. The major activity was characterized as a heat-sensitive peptide of 3,000 daltons. The expression of CR1, CR3 and class II on asthmatic peripheral-blood mononuclear cells was increased relative to normal control donors. Culturing monocytes for 24 h in the presence of 10^{-4} M hydrocortisone inhibited the expression of CR1, CR3 and class II in CS subjects but not in CR individuals. These results suggest that monocytes of CR asthmatic patients can increase the inflammatory potential of neutrophils and that they are hyperactive, as indicated by increased cytokine production and enhanced expression of activation markers, despite the presence of corticosteroids.

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Introduction

The airflow obstruction of the majority of patients with chronic and severe bronchial asthma will improve after treatment with corticosteroids. However, there are some patients in whom systemic or inhaled treatment with corticosteroids, even when given in very large doses, does not lead to any increase in FEV_i. The asthma in such patients is usually severe and they are seriously disabled for long periods of time. Carmichael et al. [1] defined corticosteroid responsiveness in asthma as an increase in FEV_i of > 30% during a 7-day course of prednisolone treatment at 20 mg daily. Corticosteroid resistance in asthmatic subjects was defined as an improvement in the FEV_j of < 15% after a similar course of prednisolone. Comparison of corticosteroid-resistant (CR) and corticosteroid-sensitive (CS) asthmatic subjects revealed that the CR asthmatic individuals were older, with a longer history of asthma, and that their disease was frequently difficult to control.

In view of the suggestion that there may be a

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monocyte defect in CR asthmatic subjects [2], we have recently assessed the capacity of corticosteroids to inhibit the elaboration of activities from blood monocytes of asthmatic subjects which have the capacity to augment granulocyte function.

Cytokine Generation by Monocytes in Bronchial Asthma

Calcium-ionophore-activated neutrophils primed by supernatants of peripheral-blood monocytes from asthmatic subjects cultured in the absence of hydrocortisone generated approximately 3-fold more leu-kotriene B4 (LTB4) than neutrophils primed by supernatants derived from blood monocytes from normal individuals. Incubation of monocytes derived from CS subjects with hydrocortisone inhibited the production of the enhancing activity, whereas in CR subjects hydrocortisone at concentrations of up to 10^{-4} M did not suppress the release of enhancing activity [3]. There was a rank order of potency for corticosteroid action, and the concentration of hydrocortisone, methylprednisolone and dexamethasone which produced 50% suppression of enhancing activity from

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Table 1. Immunohistochemical analysis of class II, CR1 and CR3 in monocytes isolated from CS, CR and normal subjects

Subjects		Percentage of cells expressing					
class II		CR1		CR3			
-HC	+HC	-HC	+HC	-HC	+HC		
Normal		49.8 ± 3.4	41.7 ± 2.6	30.1 ± 4.2	23.5 ± 2.9	37.8 ± 4.5	25.3 ± 2.0
CS		58.0 ± 2.6	40.0 ± 3.5	48.3 ± 5.3	25.5 ± 1.3	53.2 ± 4.9	37.7 ± 3.7
CR		64.7 ± 3.7	68.0 ± 2.6	51.2 ± 3.9	51.7 ± 5.3	60.0 ± 2.8	58.5 ± 1.6

The values are means ± SEM in the absence (-HC) or presence (+HC) of 10^{-4} M hydrocortisone. monocytes of CS subjects was 6×10^{-7} , 7×10^{-8} and 5×10^{-10} M, respectively. The activity was characterized as a heat-sensitive peptide of 3,000 daltons, which enhanced LTB4 and superoxide anion generation by human neutrophils and LTC4 generation by eosinophils [3].

Immunohistochemical Analysis of the Monocytes from Asthmatic Subjects

Monocytes were purified by adherence to plastic plates and then cultured in monolayers for 24 h in the absence or presence of hydrocortisone at a concentration of 10^{-4} M. The plates were dried and then incubated, initially with specific antibodies to complement receptor type 1 (CR1), complement receptor type 3 (CR3), HLA-DR or Leu-M1. The plates were then developed, using a peroxidase-conjugated second antibody. The cells were counterstained with haematoxylin. Following purification, $84.6 \pm 2.7\%$ of the cells expressed Leu-M1, confirming that the majority of the cells were monocytes. There was no difference in the expression of Leu-M1 between normal and asthmatic subjects.

The expression of both the complement receptors CR1 ($46.6 \pm 4.8\%$ in asthmatics and $25.0 \pm 3.1\%$ in normal subjects; $n \approx 6$, $p < 0.01$) and CR3 ($60.0 \pm 2.1\%$ in asthmatics and $28.8 \pm 2.8\%$ in normal subjects; $n \approx 6$, $p < 0.01$) and of class II ($65.2 \pm 2.9\%$ in asthmatics and $52.0 \pm 4.5\%$ in normal subjects; $n \approx 6$, $p = 0.03$) was increased in asthmatic subjects relative to normal control donors. The effects of culturing monocytes for 24 h in the presence of 10^{-4} M hydro-cortisone are shown in table 1. In CS subjects, hydro-cortisone substantially suppressed the expression of CR1 ($p < 0.01$), CR3 ($p < 0.01$) and class II ($p < 0.01$), with the expression returning to normal levels. In contrast, in CR subjects, hydrocortisone failed to suppress significantly the enhanced expression of CR1 ($p = 0.88$), CR3 ($p = 0.82$) or class II ($p = 0.73$).

Conclusion

These results suggest that cells of the monocytic lineage within the lungs of CR asthmatic patients enhance the pro-inflammatory potential of infiltrating neutrophils and that they exist in hyperreactive state, as indicated by increased cytokine production and augmented expression of activation markers despite the presence of inhibitory concentrations of corti-costeroids.

References

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