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Glucocorticoids inhibit the bradykinin B_2 receptor increase induced by interleukin-1β in human bronchial smooth muscle cells

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Abstract

We studied the effect of the glucocorticoids, dexamethasone and budesonide, on the interleukin-1β-induced increase of bradykinin B_2 receptors in cultured human bronchial smooth muscle cells, a cellular model of bronchial hyperreactivity. Both compounds prevented the increase of the bradykinin B_2 mRNA and the bradykinin-induced inositol phosphate accumulation. These results demonstrate a direct effect of glucocorticoids on airway smooth muscle hyperresponsiveness mediated through inhibition of the over-expression of receptors for contractile mediators induced by inflammatory mediators.

Keywords: Asthma; Hyperreactivity; Glucocorticoid

Bronchial hyperreactivity is one of the characteristics of asthma corresponding to the exaggerated contractile response to various stimuli (Lee, 1992). The most striking examples of such stimuli are bradykinin and adenosine which induce a potent bronchoconstriction in asthmatic patients but not in healthy subjects (Church and Holgate, 1986; Fuller et al., 1987). Glucocorticoids inhibit both the airways inflammation processes such as eosinophil infiltration (De Bie et al., 1996) and the bronchial hyperresponsiveness (Kraan et al., 1988), suggesting that the increased response of smooth muscle cells is a consequence of the inflammatory process. However, no experimental evidence has been provided to demonstrate that this hypothesis applies to smooth muscle cells. We have recently shown that interleukin-1β, a major mediator of inflammation in asthma, is able to induce the synthesis of bradykinin B_2 receptors in cultured human airway smooth muscle cells (Schmidlin et al., 1998). This increase is accompanied by the enhancement of inositol phosphate formation elicited by bradykinin, demonstrating its relevance to the contractile response of smooth muscle cells to bradykinin. Thus, human bronchial smooth muscle cells treated with interleukin-1β can be considered to be a model of airway hyperresponsiveness. We now show that glucocorticoids can prevent the interleukin-1β-induced increase of bradykinin B_2 receptors and the corresponding inositol phosphate formation.

Experiments were performed as previously described (Schmidlin et al., 1998). Briefly, primary human bronchial smooth muscle cells were incubated for 24 h in a serum-free medium, and then treated for 3 h with interleukin-1β in the presence of glucocorticoids (10^{-9} or 10^{-7} M). B_2 mRNA levels were evaluated by Northern blot analysis, using α-^{32}P-random primer-labeled B_2 receptor cDNA and GAPDH cDNA for normalization. The effect of bradykinin on the hydrolysis of inositol phosphate was assayed as previously described (Schmidlin et al., 1998). Dexamethasone, budesonide or cycloheximide was added 1 h before treatment with interleukin-1β for 6 h. In order to prevent degradation of inositol phosphate, bradykinin (10^{-6} M) stimulation was performed in the presence of LiCl 10 mM.

We showed that glucocorticoid pretreatment dose dependently prevented the increase of B_2 mRNA induced by interleukin-1β (10 U/ml) treatment (Fig. 1A). Budesonide was more potent than dexamethasone to prevent the increase in B_2 mRNA induced by interleukin-1β. Budesonide and dexamethasone also dose dependently inhibited the increase of inositol phosphate formation elicited by bradykinin (10^{-6} M) after a 6-h treatment with interleukin-1β (Fig. 1B). Cycloheximide fully prevented the increase of inositol phosphate formation elicited by bradykinin in interleukin-1β-treated cells.

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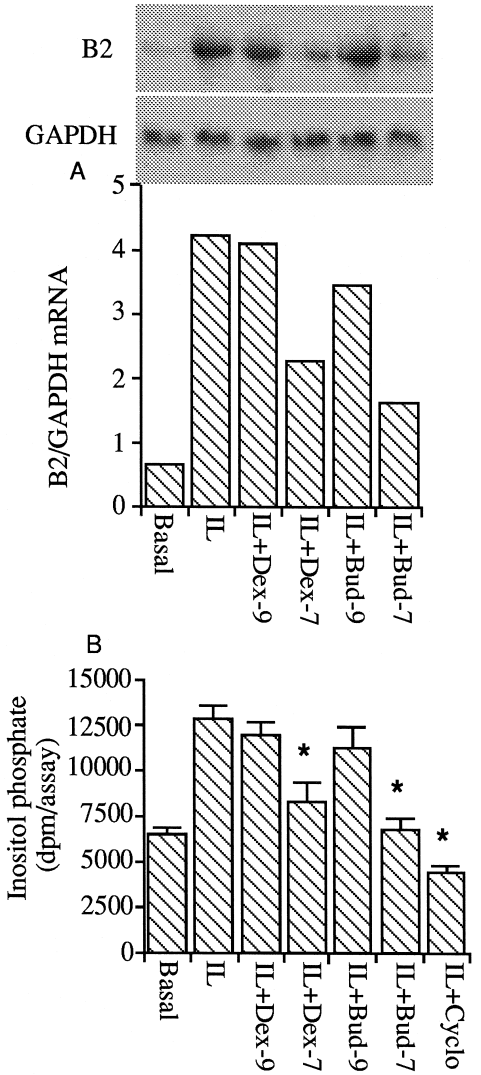

Fig. 1. Effect of glucocorticoids in human bronchial smooth muscle cells treated with interleukin-1β on B_2 receptor mRNA level (A) and on bradykinin-induced (10^{-6} M) inositol phosphate formation (B). Cells were treated with interleukin-1β (10 U/ml) for 3 h (A), or 6 h (B) in the presence of dexamethasone or budesonide (10^{-9} or 10^{-7} M) or cycloheximide (10^{-5} M). Northern blot (A) is representative of three experiments. Inositol phosphate values (B) are the means ± S.E.M. of four experiments. $*$ P values < 0.05 (paired Student's t-test).

The results provided strong experimental evidence that the airway hyperreactivity observed in asthmatic subjects is a consequence of the inflammatory process involving mediators such as interleukin-1β, able to induce the de novo synthesis of proteins. Among these proteins, the receptors of contractile mediators play a crucial role in the increased response of airway smooth muscle.

In cultured smooth muscle cells, two main types of action can be proposed for an effect of glucocorticoids on the synthesis of bradykinin receptors. One hypothesis is the direct repression, by glucocorticoids associated to their receptors, of the transcription of the bradykinin B_2 receptor gene through interaction with transcription factors activated by interleukin-1β. The second major effect of glucocorticoids is activation of the synthesis of mRNA coding for lipocortin 1, which inhibits phospholipase A_2 activity. Indeed, we recently have shown that the effect of interleukin-1β is mediated through the synthesis of prostanoids, thus involving the activation of phospholipase A_2 (Schmidlin et al., 1998).

Such inhibitory effects of corticoids on smooth muscle cells might counteract the effect of inflammatory mediators associated with the hyperreactive state of airway smooth muscle. The antiinflammatory beneficial properties of the glucocorticoids, as now used in the early stages of asthma, are most likely the lessening of cell migration and the decreased release of inflammatory mediators. The direct effect on smooth muscle cells to prevent hyperresponsiveness might be crucial for a full therapeutic benefit.

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References

Church, M.K., Holgate, S.T., 1986. Adenosine and asthma. Trends Pharmacol. Sci. 7, 49–50.

De Bie, J.J., Hessel, E.M., Van Ark, I., Van Esch, B., Hofman, G., Nijkamp, F.P., Van Oosterhout, A.J., 1996. Effect of dexamethasone and endogenous corticosterone on airway hyperresponsiveness and eosinophilia in the mouse. Br. J. Pharmacol. 119, 1484–1490.

Fuller, R.W., Dixon, C.M.S., Cuss, F.M.C., Barnes, P.J., 1987. Bradykinin induced bronchoconstriction in humans. Am. Rev. Respir. Dis. 135, 176–180.

Kraan, J., Koeter, G.H., Van Der Mark, T.H.W., Boorsma, M., Kukler, J., Sluiter, H.J., De Vries, K., 1988. Dosage and time effects of inhalated budesonide on bronchial hyperreactivity. Am. Rev. Respir. Dis. 137, 44–48.

Lee, T.H., 1992. Precipitating factors of asthma. Br. Med. Bull. 48, 169–178.

Schmidlin, F., Scherrer, D., Daeffler, L., Bertrand, C., Landry, Y., Gies, J.-P., 1998. Interleukin-1β induces bradykinin B2 receptor gene expression through a prostanoid cAMP-dependent pathway in human bronchial smooth muscle cells. Mol. Pharmacol. 53, 1009–1015.