Beta-2-Adrenoceptor Agonists Up-Regulate the in vitro FcEpsilon Receptor II/CD23 Expression on, and Release from, the Promonocytic Cell Line U937 and Human Blood Monocytes

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Abstract

The possible regulatory role of β_2 -adrenoceptor agonists in the modulation of CD23 on the human promonocytic cell line U937 and on human monocytes was investigated. Incubation for 48 h in the presence of interleukin-4 (IL-4; 30 U/ml) induced optimal expression and release of CD23 on both U937 cells and human monocytes. When a β_2 -adrenoceptor agonist, either salbutamol or fenoterol, was added to U937 cells or monocytes both the IL-4-induced CD23 expression and release were markedly **up-regulated**. This effect was dose-dependent, starting at 10 nM and reaching a maximum at 1 μ M final concentration of either salbutamol or fenoterol. The potentiating effect of salbutamol and fenoterol on CD23 expression and release was not observed when a β -adrenoceptor antagonist, either D,L-propranolol (1 μ M) or butoxamine (1 μ M), was added to the incubation medium. The α -adrenoceptor agonist norepinephrine (1 μ M) was ineffective in enhancing the IL-4-induced expression and release of CD23 from U937 cells or human monocytes, demonstrating the specificity of the β_2 -**adrenoceptor-mediated** effect. In the absence of IL-4, a moderate but significant increase in the CD23 expression on U937 cells and human monocytes by these drugs was observed, as compared to the basal values. These results indicate that, besides their bronchodilator effect, β_2 -adrenoceptor agonists may regulate **IgE-dependent** processes.

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A role for the low-affinity receptor for IgE, CD23, and its soluble form (sCD23) in allergic diseases, including asthma, has been proposed [1]. Indeed, CD23 is expressed on several cell types involved in allergic diseases – particularly monocytes/macrophages – and is implicated in the regulation of B lymphocyte activation and IgE production [2, 3]. Since β -adrenoceptor agonists are widely used as bronchodilators in asthma [4], the aim of the present study was to analyze their possible influence on the spontaneous and in-terleukin (IL-4)-induced expression and release of CD23 from a model human promonocytic cell line and from normal, freshly isolated human monocytes.

Incubation of U937 cells for 48 h in the presence of salbutamol or fenoterol induced a dose-related increase in the expression of CD23. This effect was observed at concentrations above 1

nM and reached a maximum at 1 μ M of either drug (table 1). Kinetics studies performed with the concentration of 1 μ M salbutamol or fenoterol, or 30 U/ml IL-4, demonstrated that the maximal expression was reached by 48 h and declined thereafter. This effect of salbutamol and fenoterol was not related to blockade of cell proliferation. Indeed, U937 cells incubated in the presence of either drug (1 μ M) for 48 h demonstrated a similar proliferative rate as compared to untreated cells, however, a decrease in cell proliferation was observed after 72 h. The specificity of the β 2-adrenoceptor stimulation-mediated enhancement of CD23 expression on U937 cells was confirmed since the effect of salbutamol and fenoterol was blocked in the presence of a β -adrenoceptor antagonist, D,L-propranolol (1 μ M) or butoxamine (1 μ M), but the α -adrenoceptor agonist norepinephrine (10 μ M) was ineffective. In contrast, D,L-propranolol (1 μ M) or butoxamine (1 μ M) did not affect the IL-4 (30 U/ml)-induced expression of CD23 on U937 cells. Besides increasing the expression of CD23 on U937 cells, salbutamol and fenoterol

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Table 1. Effect of β 2-adrenoceptor agonists on CD23 expression on U937 cells and freshly isolated human monocytes

Challenge	Treatment	Percent CD23+cells	
U937 monocytes			
Medium	medium	9 ± 2	< 5
Medium	salbutamol	18 ± 3	9 ± 4
Medium	fenoterol	21 ± 5	10 ± 5
IL-4	medium	34 ± 4	25 ± 2
IL-4	salbutamol	57 ± 4	40 ± 6
IL-4	fenoterol	62 ± 8	41 ± 2

U937 cells and human monocytes were incubated for 48 h at 37 °C in the presence or absence of IL-4 (30 U/ml) and with or without salbutamol and fenoterol (1 μ M). The expression of CD23 was determined by indirect fluorescence analysis. The data represent the mean $\pm$ SEM of 4 different experiments.

(1 μ M) induced a significant ($p < 0.001$, Student's t test) release of sCD23 in the culture supernatants. Moreover, when salbutamol (1 μ M) or fenoterol (1 μ M) was added to U937 cells the IL-4-induced CD23 expression (table 1) and release were markedly enhanced after a 48-hour incubation period (table 1).

A similar increase in the expression and release of CD23 was observed when β 2-adrenoceptor agonists were added for 48 h to freshly isolated human monocytes, this effect being, however, of limited extent (table 1). The IL-4-induced expression (table 1) and release of CD23 on normal human monocytes were markedly potentiated when the cultures were performed for 48 h in the presence of salbutamol (1 μ M) or fenoterol (1 μ M).

β 2-Adrenoceptor agonists are widely used in the treatment of asthma [4]. However, clinical studies have reported that a prolonged use of these compounds leads to unresponsiveness to further β 2-adren-ergic medication. This phenomenon is attributed to a decrease in the response of pulmonary β 2-adrenoceptors due to desensitization and/or down-regulation. Moreover, inhaled β 2-adrenoceptor agonists have been shown to increase bronchial hyperresponsiveness in humans. Recently, Sanjar et al. [5] reported that, in guinea pigs treated with daily high doses of the β 2-adrenoceptor agonist salbutamol, bronchial hyperresponsiveness was not reduced

and lethality was even more increased following antigen exposure. This deleterious effect of β 2-adrenoceptor agonists may indeed be explained by a better penetration of the antigen in the airways, contributing to an increase in the pulmonary inflammatory reaction. The present findings indicate that β 2-adrenoceptor agonists may also affect local immune processes by altering the expression and release of CD23, possibly leading to increased IgE-dependent responses and modulating the production of this immunoglobulin isotype. Therefore, the consequence of the alteration of CD23 expression and release from alveolar macrophages and blood monocytes from experimental animals and allergic patients, treated or not with β 2-adrenoceptor agonists, deserves precise investigation.

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