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β_2-Adrenoceptor Agonists and Allergic Disease: The Enhancing Effect of β_2-Adrenoceptor Agonists on Cytokine-Induced TSLP Production by Human Lung Tissue Cells

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1. Introduction

1.1 β_2-adrenoceptor agonists and asthma

The adrenergic receptors (adrenoceptors) are a member of the G protein-coupled receptor superfamily of membrane proteins that are targets of the catecholamines, norepinephrine and epinephrine. To date, two main groups of adrenoceptors, α and β, with several subtypes have been identified. Many types of cells possess these receptors, and the binding of an agonist will generally cause a sympathetic response. Among them, β2-adrenoceptor agonists (β2-agonists) are widely used as bronchodilators in the treatment of bronchial asthma because of their potent bronchodilating effects on airway smooth muscle. In addition to being bronchodilators, they may also have anti-inflammatory properties, including inhibition of granulocyte functions (Yasui et.al., 2006). However, concerns have been raised regarding the use of β2-agonists on a regular daily basis rather than only as needed for rescue therapy. More specifically, continuous and repetitive β_2-agonist monotherapy has been considered to be associated with an increase in the degree of allergic inflammation (Cockcroft et.al., 1995), poor asthma outcomes (Paris et.al., 2008) and an increase in the risk of asthma death (Crane et.al., 1989; Nelson et.al., 2006). Although the precise molecular mechanisms underlying these undesirable effects of β_2-agonists are not fully understood, several studies have independently demonstrated that β_2-agonists have the potential to increase Th2 cytokine-mediated inflammation both *in vivo* and *in vitro*. For instance, Coqueret et.al. demonstrated that ovalbumin-sensitized mice treated with a daily injection of salbutamol showed increased anti-ovalbumin IgE levels in their serum, probably due to increased production of Th2 cytokines (Coqueret et.al., 1994). Panina-Bordignon et.al. demonstrated that β_2-agonists prevented Th1 development by selectively inhibiting IL-12 production (Panina-Bordignon et.al., 1997). More recently, Loza et.al. demonstrated that human Th2 cells express β_2-adrenergic receptor and that β_2-agonists augmented the accumulation of Th2 cells in human peripheral blood lymphocyte cultures subjected to bystander stimuli (Loza et.al., 2007). These findings suggest a mechanism by which β_2-agonist monotherapy may favor Th2 immune responses, which are believed to be involved in the pathogenesis of asthma.

1.2 TSLP and asthma

Thymic stromal lymphopoietin (TSLP) is an IL-7-like cytokine which was originally identified in the supernatant of a murine thymic stromal cell line (Friend et.al., 1994). Increasing evidence suggests that TSLP plays important roles in the pathogenesis of allergic diseases such as asthma and atopic dermatitis (Al-Shami te.al., 2005; Yoo et.al., 2005). The most clinically relevant role of TSLP is mediated by dendritic cells (DCs) through induction of OX40 ligand expression on DCs (Ito et.al., 2005; Liu, 2007a). Naïve T cells receiving antigen-presentation from TSLP-primed DCs develop into Th2 cells that produce IL-4, -5, -13 and TNF-α but not IL-10 (Ito et.al., 2005; Liu, 2007a; Soumelis et.al., 2002). These Th2 cells are now referred as to "inflammatory Th2 cells" in consideration of their potential for releasing the proinflammatory cytokine, TNF-α, in addition to Th2 cytokines (Orihara et.al.; 2008). Furthermore, mice with transgenic overexpression of TSLP in the lung develop severe airway inflammation, including massive infiltration by inflammatory cells, goblet cell hyperplasia and airway hyperresponsiveness (Zhou et.al., 2005). Mice with transgenic overexpression of TSLP in skin keratinocytes develop severe dermatitis with itching, which is similar to the clinical features of atopic dermatitis in humans (Yoo et.al., 2005). On the other hand, mice lacking the TSLP receptor exhibit strong Th1 responses and fail to develop an inflammatory lung response to antigens (Al-Shami te.al., 2005). Thus, TSLP is an important cytokine that is necessary and sufficient for initiation of allergic inflammation.

2. The enhancing effect of β_2-adrenoceptor agonists on cytokine-induced TSLP production by human lung tissue cells

2.1 Cytokine-induced production of TSLP by lung tissue cells

It is widely accepted that TSLP is expressed predominantly in epithelial cells of the lung, intestine and skin keratinocytes (Soumelis et.al., 2002; Liu et.al., 2007b). We confirmed an earlier report (kato et.al., 2007) that a combination of IL-4 and TNF-α synergistically induced TSLP production by normal human bronchial epithelial cells (NHBE) (Fig. 1A). Unlike NHBE, lung mesenchymal cells such as bronchial smooth muscle cells (BSMC) and normal human lung fibroblasts (NHLF) produced TSLP in response to TNF-α, but not IL-4 alone. However, like NHBE, those cells produced greater amounts of TSLP as a result of synergistic effects between IL-4 and TNF-α (Fig. 1B and 1C). Of note, these mesenchymal cells produce appreciable amounts of TSLP compared to NHBE, suggesting the possibility that lung mesenchymal cells are, like epithelial cells, important cellular sources of TSLP.

2.2 Effects of β_2-agonists on cytokine-induced TSLP production

We next examined the effects of β_2-agonists on the cytokine-induced TSLP production by the human lung tissue cells. Although β_2-agonists act mainly on airway smooth muscle as bronchodilators, they are also known to express anti-inflammatory effects on granulocytes (Yasui et.al., 2006), epithelial cells (Koyama et.al., 1999) and fibroblasts (Spoelstra et.al., 2002). As shown in Fig 2A, when NHBE were stimulated with a combination of IL-4 and TNF-α, simultaneous addition of various concentrations of two long-acting β_2-agonists, i.e., salmeterol and formoterol, and a short-acting β_2-agonist, salbutamol, showed significant enhancement of the cytokine-induced TSLP production. Optimal concentrations of these β_2-agonists were employed, and then the mRNA expression of TSLP in NHBE was measured by quantitative real-time PCR. TSLP mRNA expression was significantly enhanced by 10^{-10} M salmeterol, 10^{-10}

M formoterol and 10^{-8} M salbutamol (Fig. 2B), suggesting that the enhancing effects of β_2-agonists on TSLP production were transcriptionally-regulated. It should be noted that β_2-agonists enhanced TSLP production by airway smooth muscle cells and lung fibroblasts as well as bronchial epithelial cells (Fig. 2C and 2D). We suppose that the production of TSLP by these lung tissue cells is particularly important because dendritic cells have to migrate through these airway interstitial cells to lymphopoietic tissues in order to present antigen information to naïve T cells. Therefore, enhanced TSLP production by lung tissue cells in response to β_2-agonists may lead to exacerbation of allergic airway inflammation, and this may partly explain the undesirable clinical effects of continuous β_2-agonist monotherapy.

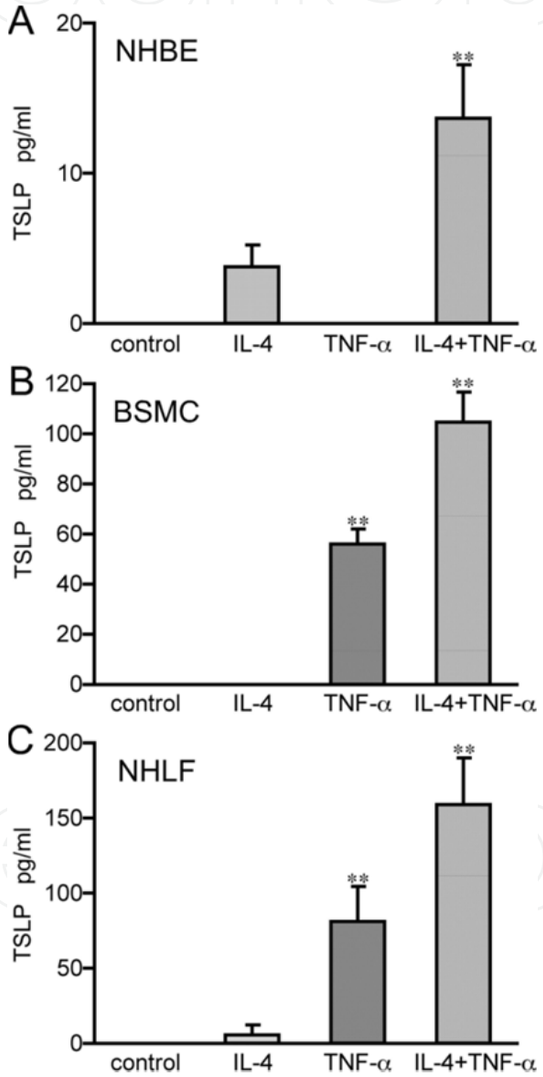


Fig. 1. Cytokines induce production of TSLP by lung tissue cells. NHBE (**A**), BSMC (**B**) and NHLF (**C**) were treated with 10 ng/ml IL-4 alone, 10 ng/ml TNF-α alone and a combination of both for 48 h. TSLP concentrations in the culture supernatants were quantified by ELISA. Data are shown as the mean ± SD of quadruplicate samples and are representative of at least three separate experiments. ** $p < .01$ compared with unstimulated control. Reprinted from Futamura et. Al., 2010.

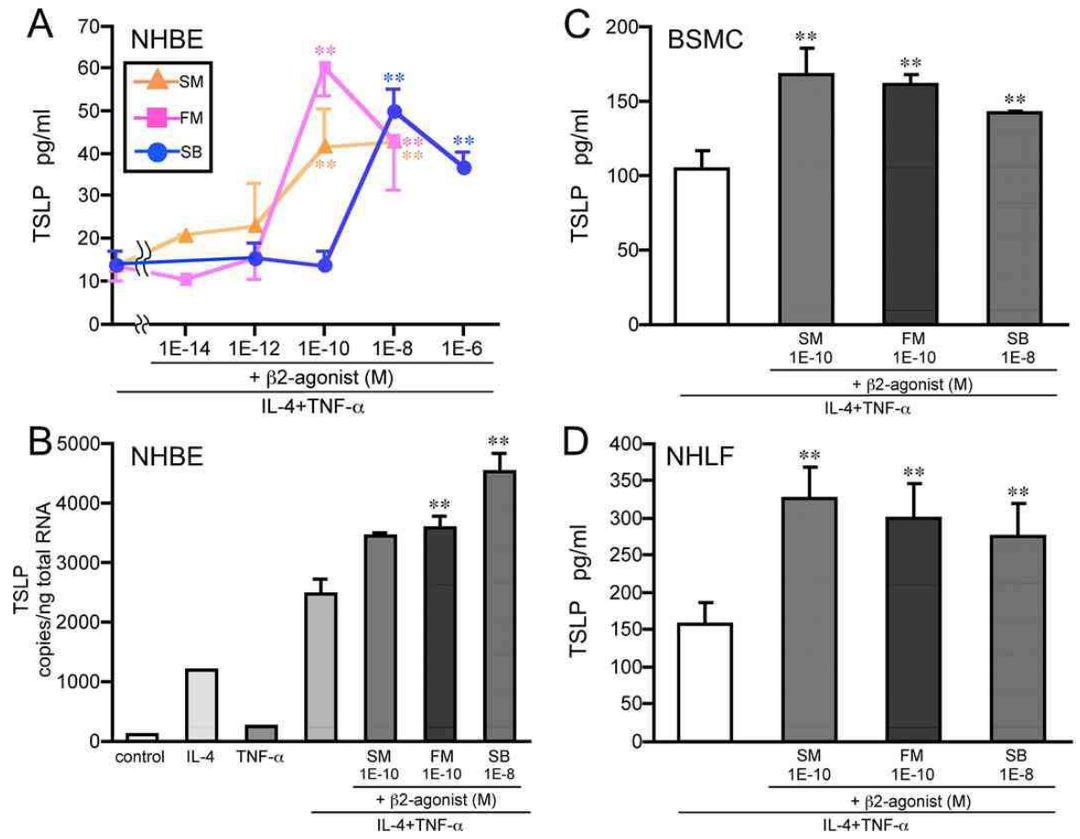


Fig. 2. β_2-agonists enhance cytokine-induced TSLP production by lung tissue cells. (**A**) NHBE were treated with different concentrations of two long-acting β_2-agonists, salmeterol (SM) and formoterol (FM), or a short-acting β_2-agonist, salbutamol (SB), in the presence of 10 ng/ml IL-4 and 10 ng/ml TNF-α for 48 h. TSLP concentrations in the culture supernatants were quantified by ELISA. (**B**) NHBE were treated with cytokines at 10 ng/ml in the presence and absence of the indicated concentrations of each β_2-agonist (SM, FM, SB) for 6 h. The copy numbers of TSLP mRNA are shown. BSMC (**C**) and NHLF (**D**) were treated with the indicated concentrations of each β_2-agonist (SM, FM, SB) in the presence of 10 ng/ml IL-4 and 10 ng/ml TNF-α for 48 h. TSLP concentrations in the culture supernatants were quantified by ELISA. All data are shown as the mean ± SD of quadruplicate samples and are representative of at least three separate experiments. ** $p < .01$ compared with IL-4 plus TNF-α. Reprinted from Futamura et. Al., 2010.

2.3 Effects of cAMP-elevating agents on cytokine-induced TSLP production

It is well known that binding of β_2-agonists to β_2-adrenoceptors activates adenylate cyclase, resulting in generation of intracellular cAMP. We therefore examined the role of intracellular cAMP in the enhancement of TSLP production. The cells were stimulated with three cAMP-elevating agents, i.e., 8-bromoadenosine cyclic monophosphate, dibutyryl adenosine cyclic monophosphate (hereinafter referred to as 8-Br cAMP and db cAMP, respectively) and forskolin (an adenylate cyclase activator). All three agents caused significant enhancement of cytokine-induced TSLP production by the lung tissue cells (Fig. 3). These results suggest that the enhancing effects of β_2-agonists on TSLP production were mediated via upregulation of intracellular cAMP in these cells.

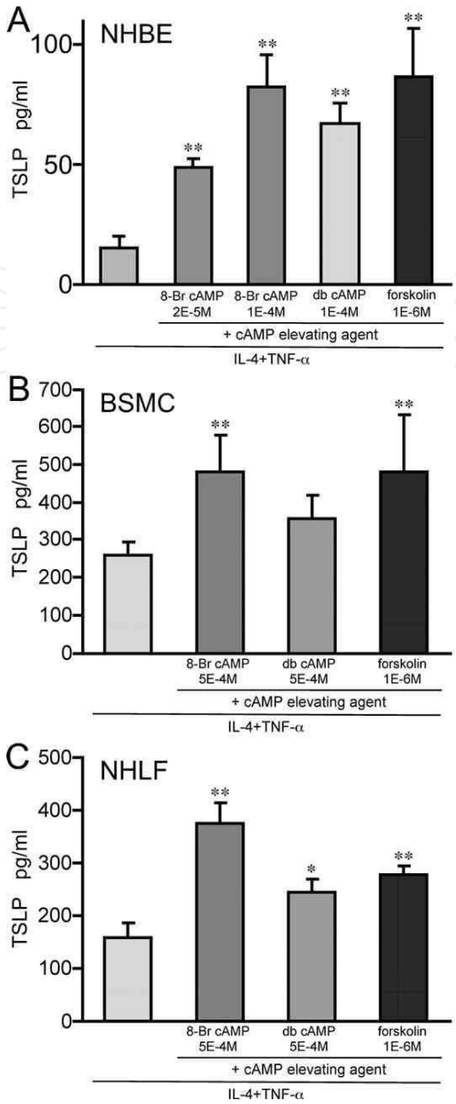


Fig. 3. Intracellular cAMP-elevating agents enhance cytokine-induced TSLP production by lung tissue cells. NHBE (**A**), BSMC (**B**) and NHLF (**C**) were treated with 10 ng/ml IL-4 and 10 ng/ml TNF-α in the presence and absence of the indicated concentrations of each cAMP-elevating agent (8-Br cAMP, db cAMP, forskolin) for 48 h. TSLP concentrations in the culture supernatants were quantified by ELISA. Data are shown as the mean ± SD of quadruplicate samples and are representative of at least three separate experiments. * $p < .05$ and ** $p < .01$ compared with IL-4 plus TNF-α. Reprinted from Futamura et. Al., 2010.

2.4 Effects of corticosteroid on cytokine-induced TSLP production

According to the recently updated guidelines for asthma management, the preferred treatment regimen for patients with intermittent asthma is an inhaled short-acting β_2-agonist, and the next step regimen is additional treatment with an inhaled corticosteroid. Therefore, we examined the effects of a corticosteroid, fluticasone, on the β_2-agonist-induced increase in TSLP production. Simultaneous addition of various concentrations of fluticasone caused dose-dependent, significant inhibition of both cytokine-induced (closed squares) and salmeterol-

enhanced (closed triangles) TSLP production by NHBE (Fig. 4A, upper graph). Similar results were obtained in experiments using NHLF (Fig. 4A, lower graph) and BSMC (data not

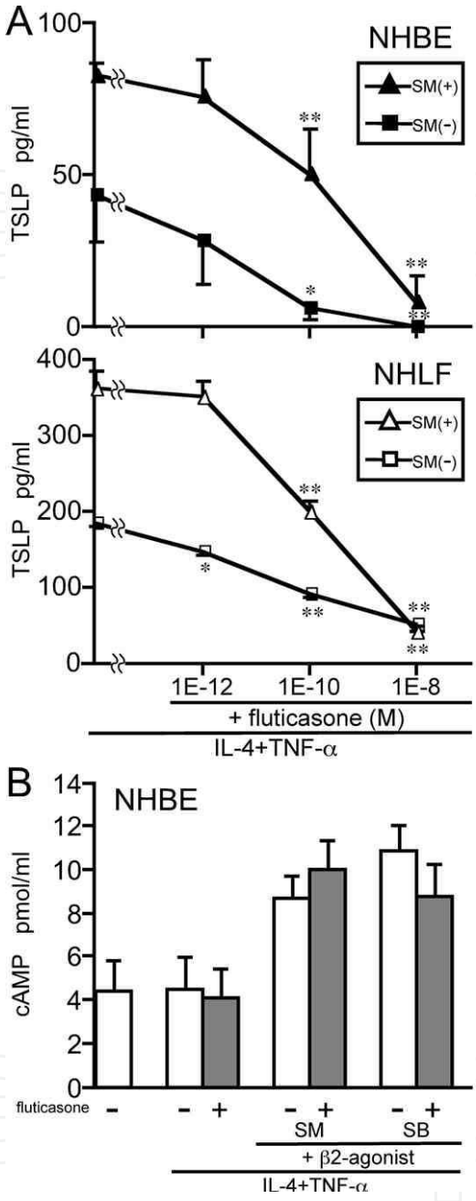


Fig. 4. Fluticasone inhibits TSLP production without affecting the intracellular cAMP level. (**A**) NHBE (upper graph) and NHLF (lower graph) were treated with 10 ng/ml IL-4 and 10 ng/ml TNF-α with and without 10^{-10} M salmeterol (SM) for 48 h. The effects of simultaneous addition of the indicated concentrations of fluticasone on the TSLP production are shown. Data are shown as the mean ± SD of quadruplicate samples and are representative of at least three separate experiments. * $p < .05$ and ** $p < .01$ compared to without fluticasone. (**B**) NHBE were treated with 10 ng/ml IL-4 and 10 ng/ml TNF-α with and without a β_2-agonist (10^{-10} M SM, 10^{-8} M SB) for 5 min. The effects of simultaneous addition of 10^{-8} M fluticasone on the intracellular cAMP levels are shown. Data are shown as the mean ± SD of triplicate samples and are representative of three separate experiments. Reprinted from Futamura et. al., 2010.

shown). Importantly, simultaneous treatment at the highest concentration of fluticasone (10^{-8} M), which can still considered to be clinically feasible, almost completely abrogated not only the cytokine-induced TSLP production but also the enhancement by the β_2-agonists.

2.5 Corticosteroid inhibition of TSLP production is not due to direct inhibition of cAMP signaling

In order to clarify how corticosteroids might inhibit TSLP production, we examined the effects of fluticasone and β_2-agonists on the intracellular cAMP level in NHBE. Addition of salmeterol or salbutamol significantly increased the cAMP level after 5 minutes of incubation. Addition of 10^{-8} M fluticasone showed no effect on the intracellular cAMP level whether in the presence or absence of a β_2-agonist (Fig. 4B), indicating that corticosteroid inhibition of TSLP production is not due to direct inhibition of cAMP signaling. These results also suggest that corticosteroids inhibit TSLP synthesis by acting on the downstream signaling pathway of cAMP.

To date, several mechanisms have been proposed to explain the synergistic action between corticosteroids and β_2-agonists: induction and protection of β_2-adrenoceptors by corticosteroids (Barnes, 2002), enhancement of translocation of glucocorticoid receptors into the nucleus by β_2-agonists (Usami et.al., 2005) and post-transcriptional regulation to suppress expression of inflammatory genes (Kaur et.al., 2008). Our results may shed new light on the mechanisms by which combination therapy using an inhaled β_2-agonist and an inhaled corticosteroid shows synergistic clinical efficacy in patients with asthma.

3. Future challenges

It remains to be clarified whether the enhancing effect of β_2-agonists on cytokine production is specific to TSLP or not. Koyama et. al. demonstrated that TNF-α-induced production of granulocyte-macrophage colony-stimulating factor (GM-CSF), CCL5 and IL-8 by a human bronchial epithelial cell line, BEAS-2B, was significantly inhibited by procaterol, a β_2-agonist (Koyama et. al., 1999). We confirmed that the cytokine-induced production of GM-CSF and CCL5, but not IL-8, by NHBE was significantly suppressed by β_2-agonist treatment (data not shown). On the other hand, it was reported that rhinovirus-induced IL-6 production by NHBE was increased by salmeterol (Edwards et. Al., 2007), and we also found that the cytokine-induced production of IL-6 as well as TSLP by NHBE was significantly enhanced by simultaneous treatment with β_2-agonists (data not shown). Thus, β_2-agonists are able to crucially modulate the production of various inflammatory mediators through mechanisms that need to be further elucidated.

4. Conclusion

In this study, we focused on the effects of β_2-agonists on the *in vitro* synthesis of TSLP, which is a key cytokine in the development of allergic diseases. We found that β_2-agonists significantly enhanced cytokine-induced TSLP production by cultured primary human lung tissue cells. This enhancement may be partly responsible for the undesirable clinical effects of continuous β_2-agonist monotherapy, and our other findings suggest that combination therapy with a corticosteroid might effectively inhibit TSLP-mediated allergic inflammation.

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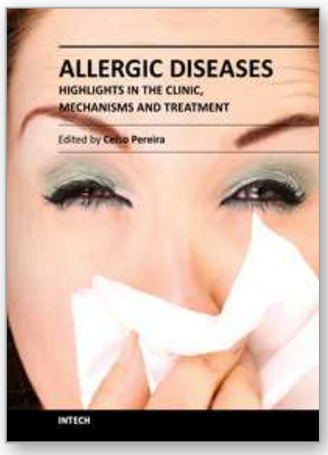
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Allergic Diseases - Highlights in the Clinic, Mechanisms and Treatment

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The present Edition "Allergic diseases - highlights in the clinic, mechanisms and treatment" aims to present some recent aspects related to one of the most prevalent daily clinical expression disease. The effort of a group of outstanding experts from many countries reflects a set of scientific studies very promising for a better clinical care and also to the treatment and control of the allergy. This book provides a valuable reference text in several topics of the clinical allergy and basic issues related to the immune system response. The inflammatory reaction understanding in allergic disease is clearly evidenced, as well as new strategies for further researches.

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