



Inhaled corticosteroids reduce asthma-associated airway hyperperfusion through genomic and nongenomic mechanisms

Gabor Horvath, Szilvia Vasas, Adam Wanner

► To cite this version:

Gabor Horvath, Szilvia Vasas, Adam Wanner. Inhaled corticosteroids reduce asthma-associated airway hyperperfusion through genomic and nongenomic mechanisms. *Pulmonary Pharmacology & Therapeutics*, 2006, 20 (2), pp.157. 10.1016/j.pupt.2006.03.009 . hal-00499130

HAL Id: hal-00499130

<https://hal.science/hal-00499130>

Submitted on 9 Jul 2010

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

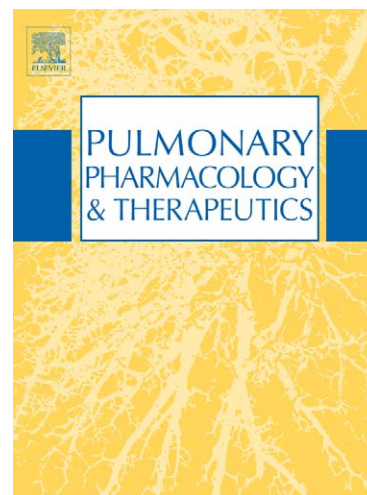
L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Author's Accepted Manuscript

Inhaled corticosteroids reduce asthma-associated airway hyperperfusion through genomic and nongenomic mechanisms

Gabor Horvath, Szilvia Vasas, Adam Wanner

PII: S1094-5539(06)00040-X
DOI: doi:10.1016/j.pupt.2006.03.009
Reference: YPUPT 672



www.elsevier.com/locate/ypupt

To appear in: *Pulmonary Pharmacology & Therapeutics*

Received date: 9 March 2006
Accepted date: 17 March 2006

Cite this article as: Gabor Horvath, Szilvia Vasas and Adam Wanner, Inhaled corticosteroids reduce asthma-associated airway hyperperfusion through genomic and nongenomic mechanisms, *Pulmonary Pharmacology & Therapeutics*, doi:[10.1016/j.pupt.2006.03.009](https://doi.org/10.1016/j.pupt.2006.03.009)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting galley proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Da Vinci Special Issue*Short Review***INHALED CORTICOSTEROIDS REDUCE ASTHMA-ASSOCIATED
AIRWAY HYPERPERFUSION THROUGH GENOMIC AND
NONGENOMIC MECHANISMS**

Gabor Horvath¹, Szilvia Vasas², and Adam Wanner³

¹Department of Respiratory Medicine, Semmelweis University, Budapest, Hungary

²Department of Respiratory Medicine, Budai MAV Hospital, Budapest, Hungary

³Division of Pulmonary and Critical Care Medicine, University of Miami School of
Medicine, Miami, Florida, USA

Corresponding Author:

Gabor Horvath, M.D.

Department of Respiratory Medicine
Semmelweis University School of Medicine
Diosarok 1/C, Budapest 1125, Hungary
Phone: +36 1 355-9733 Fax: +36 1 214-2493

E-mail: hg2000@freemail.hu

Pages: 16
Words: 3689
Tables: 3

Figures: 1

ABSTRACT

Inhaled corticosteroids have both genomic and nongenomic actions on the tracheobronchial (airway) vasculature in asthma. Genomic actions involve the activation or repression of target genes associated with inflammation, and reduce inflammatory hyperperfusion in the airway. In contrast, nongenomic actions are mediated by rapid cellular mechanisms, and induce transient vasoconstriction. This article reviews recent progress on the mechanisms by which inhaled corticosteroids reverse inflammatory blood flow changes in the airway in asthma.

KEYWORDS:

airway blood flow

airway vasculature

asthma

inhaled corticosteroids

nongenomic action

vasoconstriction

1. INTRODUCTION

Inhaled corticosteroids have prominent effects on inflammatory changes of the tracheobronchial (airway) vasculature in patients with bronchial asthma. These include the inhibition of hyperperfusion, microvascular hyperpermeability, mucosal oedema formation, inflammatory cell recruitment and the formation of new blood vessels (angiogenesis) [1, 2]. Inhaled corticosteroids are believed to exert most of their vascular effects indirectly by suppressing inflammation in the airway [3]. However, recent studies revealed interactions of inhaled corticosteroids and airway blood vessels by which vascular manifestations of inflammation can be rapidly reversed in patients with asthma. These recent advances in our understanding of the cellular mechanisms may open new avenues for additional interventions in the pharmacotherapy of asthma.

Corticosteroids are known to interrupt the development of inflammation and suppress ongoing inflammatory reactions through the activation or repression of target genes [4]. According to this transcriptional (genomic) model of action, the lipophilic corticosteroid molecules cross the cell membrane and bind to intracellular glucocorticoid receptors, which ultimately alter transcription through direct DNA binding (transactivation) [5] or by the inactivation of pro-inflammatory transcription factors (transrepression) [6] such as nuclear factor- κ B [7] and activating protein-1 [8]. Corticosteroids are the most effective drugs for suppressing asthma-associated airway inflammation mainly by downregulation of pro-inflammatory proteins. In addition to genomic actions, corticosteroids have also been shown to regulate mRNA stability and thus translation of many pro-inflammatory genes [9]. Since increased mRNA degradation leads to reduced production of pro-inflammatory proteins, the

post-transcriptional actions might also have significant implications in the pharmacotherapy of asthma [10].

Some corticosteroid effects are mediated by cellular mechanisms that are too rapid to involve gene expression [11, 12] and have been termed nongenomic actions. These rapid actions are initiated by actions on membrane-bound [13, 14] or cytoplasmic receptors [15, 16], or nonspecific interactions with the cell membrane [17]. The common features of nongenomic actions include rapid onset of action and recovery after drug removal, insensitivity to blockers of gene transcription (e.g. actinomycin D) and protein synthesis (e.g. cycloheximide), and retained activity of cell membrane impenetrable corticosteroid-protein conjugates.

In this article, we review genomic and nongenomic cellular mechanisms by which inhaled corticosteroids reverse inflammatory blood flow changes in patients with asthma.

2. Airway blood flow in asthma

Since the vasculature typically participates in the inflammatory responses at the tissue level, airway blood flow is expected to change in an inflammatory airway disease such as asthma. In animal models of airway inflammation such as *Ascaris suum* sensitized sheep, antigen challenge has been shown to cause an increase in airway blood flow [18, 19]. These findings have now been confirmed in human subjects using recently invented noninvasive methods for airway blood flow measurements [20-23]. By measuring the uptake of an inhaled, soluble inert gas (dimethyl-ether, DME) [24, 25], mean airway mucosal blood flow values (comprising about 70% of total airway blood flow) were 24% to 77% higher in patients with stable asthma than in healthy controls [20, 23]. Using acetylene rather than DME for

measurements, airway blood flow has been confirmed to be elevated in patients with mild persistent and moderate asthma compared with healthy subjects [26].

In the airway of asthmatics, increased blood flow is due to dilatation of resistance arteries and increased numbers of vessels in the bronchial mucosa. In animal models, most inflammatory mediators cause vasodilation [27]. Histamine has a triphasic effect with an initial vasodilation followed by vasoconstriction, and then a long-lasting vasodilation. Sensory neuropeptides released from afferent nerves are also strong vasodilators. A number of studies have also demonstrated increased vascularity (i.e. size and number of vessels, or cross-sectional vascular area) of the bronchial mucosa in patients with asthma compared with healthy controls [28, 29]. However, the contribution of increased hypervascularity to airway hyperperfusion needs to be explored.

3. Rapid effects on airway blood flow

Inhaled corticosteroids are known to exert their effects on the airway vasculature through genomic and nongenomic mechanisms in asthma (Fig. 1). Among these effects, corticosteroids acutely suppress airway hyperperfusion associated with asthma [21, 26, 30]. Inhaled fluticasone propionate has been shown to decrease airway mucosal blood flow with a maximal effect about 30 min after inhalation, and a return to baseline at 90 min [21]. The blood flow effect increased in a dose-dependent manner up to 880 µg of fluticasone propionate, with a significantly greater effect in asthmatics than in healthy controls. The vasoconstrictor action has also been demonstrated after inhalation of beclomethasone dipropionate and budesonide [31]. Since pretreatment with the selective α_1 -adrenoreceptor antagonist terazosin inhibited the effect of fluticasone propionate on blood flow [32], it is likely that

corticosteroids facilitate noradrenergic signal transmission to induce neurogenic vasoconstriction.

Corticosteroids could increase sympathetic signal transmission and consequently vascular tone by inhibiting extraneuronal catecholamine uptake [33]. This nongenomic mechanism was demonstrated recently in dissociated rabbit aortic smooth muscle cells by showing that the inhibitory action on noradrenaline uptake occurred rapidly, was neither altered by protein synthesis nor transcription inhibitors, and could be reproduced with a corticosteroid made membrane-impermeant by conjugation to bovine serum albumin [34]. Furthermore, the impaired extraneuronal catecholamine uptake in atopy, which was demonstrated by comparing uptake by vascular smooth muscle cells isolated from ovalbumin-sensitized and control rabbits [35], might lead to increased vasoconstrictor responsiveness to inhaled corticosteroids as seen in asthmatic subjects *in vivo* [21].

In recent *in vitro* experiments, various clinically significant corticosteroids such as budesonide and methylprednisolone have been shown to inhibit the extraneuronal monoamine transporter-mediated uptake of norepinephrine by bronchial arterial smooth muscle cells [14, 34]. This rapid (< 5 min) effect could reduce the removal of noradrenaline released from airway sympathetic nerves and, therefore, may be responsible for the rapid vasoconstrictor actions of corticosteroids.

Alternatively, the acute vasoconstrictor effect may involve other nongenomic actions of corticosteroids on vascular smooth muscle cells (**Table 1**). In addition, corticosteroids could disrupt the inflammatory process through rapid inhibitory actions on cellular processes or mediators related to inflammation, which might reduce inflammatory hyperperfusion in the airway in asthma (**Table 2**).

4. Delayed effects on airway blood flow

In asthma, inhaled corticosteroids have been shown to counteract all the vascular manifestations of airway inflammation by inhibiting the release of vasoactive inflammatory mediators or by acting directly on vascular smooth muscle or the endothelium. Because disease severity seems to correlate with airway vascular changes, these genomic vascular actions of inhaled corticosteroids may be of therapeutic value and have received increased interest recently [36].

A number of studies have demonstrated that inhaled corticosteroid therapy decreases airway mucosal blood flow in patients with asthma. In a cross-sectional study, airway mucosal blood flow was higher by about 23% in corticosteroid-naïve compared with corticosteroid-treated asthmatics [20]. In interventional studies, inhaled fluticasone propionate (440 µg/day) therapy for 2 weeks reduced blood flow by about 12% and 21% in two different groups of asthma patients [22, 37], and additionally showed that airway blood flow returns to the pretreatment level 2 weeks after cessation of therapy.

Corticosteroids are believed to decrease blood flow in the airway mucosa largely by suppressing inflammation and the release of vasodilator mediators. This concept was supported by the fact that the effect of inhaled fluticasone propionate (440 µg/day for 2 weeks) was similar to that of the leukotriene modifier montelukast (10 mg/day) in decreasing airway blood flow in asthma patients [37]. Corticosteroids may also act directly on both vascular smooth muscle and endothelial cells (reviewed in [2]), thereby increasing vascular tone and reducing blood flow in the airway vasculature (**Table 3**).

Inhaled corticosteroids have a potential therapeutic role of reversing airway angiogenesis in asthma. In a cross-sectional study, therapy with high doses (≥ 800

$\mu\text{g/day}$) of beclomethasone dipropionate was associated with a reduced vascular area of the lamina propria [38]. In interventional studies, beclomethasone dipropionate ($800 \mu\text{g/day}$) therapy for 6 months reduced the number of blood vessels and the vascular area [39], whereas a 6-week treatment with fluticasone propionate was effective at $1000 \mu\text{g/day}$ inhaled dose in reducing the number of blood vessels and the vascular area [29].

5. Perspective

Since vascular hyperperfusion is a consistent feature of tissue inflammation, airway hyperperfusion has recently been proposed as a biomarker of asthma-associated inflammation. Thus, with the advent of a noninvasive method to measure airway blood flow [20, 25], airway blood flow changes might be assessed independent of lung function as an index of disease severity and to quantitate the response to anti-inflammatory therapy. Reported reduction of airway blood flow by anti-inflammatory therapy in asthmatics [22, 37] and a positive correlation between exhaled nitric oxide and airway blood flow levels [26] lend support to this concept.

In vivo drug activity is known to depend on the drug's tissue bioavailability, which is the rate and extent to which the drug is absorbed and becomes available at the site of action [40]. Currently, the standard screening test to rank the relative anti-inflammatory potencies and tissue bioavailabilities of corticosteroids is the McKenzie "skin blanching" test [41]. This test is based on the ability of corticosteroids to cause vasoconstriction in the skin after topical application [42], a phenomenon that is similar to the observed rapid vasoconstriction in the human bronchial mucosa [21]. Airway blood flow responsiveness to inhaled corticosteroids seems to be ideal in assessing how these drugs gain access to their sites of actions in the bronchial wall [21, 31].

Thus, analysis of the rapid vasoconstrictor action can provide information on the airway tissue bioavailability of inhaled corticosteroids, which might also depend on the aerosolized drug's physicochemical characteristics and the aerosol-generating device.

The airway vasculature is known to occupy a significant portion of the inner bronchial wall [43]. Thus, the hypothesis that inflammatory changes of the vasculature increase mucosal thickness enough to influence airway resistance might seem reasonable. Theoretically, a small change in airway wall thickness caused by the increased size of the vascular compartment interior to the smooth muscle layer might potentiate airway narrowing when bronchial smooth muscle shortening occurs (airway hyperresponsiveness). Although airway blood and vascular engorgement have been proposed to contribute to airway narrowing and hyperresponsiveness in asthma, the reported data are conflicting [44, 45]. Despite the prominent effects of inhaled corticosteroids on airway blood flow, the immediate impact of inhaled corticosteroids on lung function appears to be marginal in patients with acute asthma [21, 46].

Since the airway circulation has an important role in the clearance of inhaled drugs (e.g. bronchodilators) from the respiratory tract, the inflammatory increase in airway blood flow is likely to have clinically undesirable effects in asthma [47]. With respect to airway disposal of inhaled drugs, the corticosteroid induced decrease in airway blood flow is likely to enhance the action of inhaled bronchodilators by diminishing their clearance from the airway. Thus, the rapid airway vasoconstriction induced by inhaled budesonide [31] might be responsible for enhancing the bronchodilator action of inhaled formoterol as seen in patients with chronic obstructive pulmonary disease [48]. Since the corticosteroid-induced vasoconstriction

peaks rapidly (within 30 min after drug inhalation), simultaneous administration of inhaled corticosteroids and bronchodilators is likely to be of clinical significance.

6. Conclusions

In recent years, attention has focused on vascular components of airway inflammation because of their correlations to asthma severity, including airflow limitation and bronchial hyperresponsiveness [36]. Inhaled corticosteroids seem to reverse both functional and structural abnormalities of the airway vasculature through genomic and nongenomic actions. Although the respective roles of these actions are still incompletely understood, the inhibitory effects on airway hyperperfusion, hyperpermeability, and angiogenesis are expected to have significant diagnostic and therapeutic implications in the management of asthma.

ACKNOWLEDGEMENT

G.H. is a recipient of the Bolyai Fellowship of the Hungarian Academy of Sciences, Budapest, Hungary.

REFERENCES

- [1] Charan NB, Baile EM, Pare PD. Bronchial vascular congestion and angiogenesis. *Eur Respir J* 1997; 10(5):1173-1180.
- [2] Horvath G, Wanner A. Inhaled corticosteroids: effects on the airway vasculature in bronchial asthma. *Eur Respir J* (in press)
- [3] McFadden ER, Jr. A century of asthma. *Am J Respir Crit Care Med* 2004; 170(3):215-221.
- [4] Adcock IM, Ito K, Barnes PJ. Glucocorticoid: effects on gene transcription. *Proc Am Thorac Soc* 2004; 1(3):247-254.
- [5] Hayashi R, Wada H, Ito K, Adcock IM. Effects of glucocorticoids on gene transcription. *Eur J Pharmacol* 2004; 500(1-3):51-62.
- [6] Karin M. New twists in gene regulation by glucocorticoid receptor: is DNA binding dispensable? *Cell* 1998; 93(4):487-490.
- [7] Barnes PJ, Karin M. Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases. *N Engl J Med* 1997; 336(15):1066-1071.
- [8] Nguyen C, Teo JL, Matsuda A, Eguchi M, Chi EY, Henderson WR, Jr., Kahn M. Chemogenomic identification of Ref-1/AP-1 as a therapeutic target for asthma. *Proc Natl Acad Sci U S A* 2003; 100(3):1169-1173.
- [9] Wilusz CJ, Wilusz J. Bringing the role of mRNA decay in the control of gene expression into focus. *Trends Genet* 2004; 20(10):491-497.
- [10] Stellato C. Post-transcriptional and nongenomic effects of glucocorticoids. *Proc Am Thorac Soc* 2004; 1(3):255-263.

- [11] Losel R, Wehling M. Nongenomic actions of steroid hormones. *Nature Reviews Molecular Cell Biology* 2003; 4(1):46-56.
- [12] Norman AW, Mizwicki MT, Norman DP. Steroid-hormone rapid actions, membrane receptors and a conformational ensemble model. *Nat Rev Drug Discov* 2004; 3(1):27-41.
- [13] Johnson LR, Farb C, Morrison JH, McEwen BS, Ledoux JE. Localization of glucocorticoid receptors at postsynaptic membranes in the lateral amygdala. *Neuroscience* 2005; 136(1):289-299.
- [14] Horvath G, Sutto Z, Torbati A, Conner GE, Salathe M, Wanner A. Norepinephrine transport by the extraneuronal monoamine transporter in human bronchial arterial smooth muscle cells. *American Journal of Physiology - Lung Cellular & Molecular Physiology* 2003; 285(4):L829-837.
- [15] Tumlin JA, Lea JP, Swanson CE, Smith CL, Edge SS, Someren JS. Aldosterone and dexamethasone stimulate calcineurin activity through a transcription-independent mechanism involving steroid receptor-associated heat shock proteins. *J Clin Invest* 1997; 99(6):1217-1223.
- [16] Croxtall JD, Choudhury Q, Flower RJ. Glucocorticoids act within minutes to inhibit recruitment of signalling factors to activated EGF receptors through a receptor-dependent, transcription-independent mechanism. *Br J Pharmacol* 2000; 130(2):289-298.
- [17] Whiting KP, Restall CJ, Brain PF. Steroid hormone-induced effects on membrane fluidity and their potential roles in non-genomic mechanisms. *Life Sci* 2000; 67(7):743-757.

- [18] Long WM, Yerger LD, Martinez H, Codias E, Sprung CL, Abraham WM, Wanner A. Modification of bronchial blood flow during allergic airway responses. *J Appl Physiol* 1988; 65(1):272-282.
- [19] Wanner A. Circulation of the airway mucosa. *J Appl Physiol* 1989; 67(3):917-925.
- [20] Kumar SD, Emery MJ, Atkins ND, Danta I, Wanner A. Airway mucosal blood flow in bronchial asthma. *Am J Respir Crit Care Med* 1998; 158(1):153-156.
- [21] Kumar SD, Brieva JL, Danta I, Wanner A. Transient effect of inhaled fluticasone on airway mucosal blood flow in subjects with and without asthma. *Am J Respir Crit Care Med* 2000; 161(3 Pt 1):918-921.
- [22] Brieva JL, Danta I, Wanner A. Effect of an inhaled glucocorticosteroid on airway mucosal blood flow in mild asthma. *Am J Respir Crit Care Med* 2000; 161(1):293-296.
- [23] Brieva J, Wanner A. Adrenergic airway vascular smooth muscle responsiveness in healthy and asthmatic subjects. *J Appl Physiol* 2001; 90(2):665-669.
- [24] Onorato DJ, Demirozu MC, Breitenbucher A, Atkins ND, Chediak AD, Wanner A. Airway mucosal blood flow in humans. Response to adrenergic agonists. *Am J Respir Crit Care Med* 1994; 149(5):1132-1137.
- [25] Scuri M, McCaskill V, Chediak AD, Abraham WM, Wanner A. Measurement of airway mucosal blood flow with dimethylether: validation with microspheres. *J Appl Physiol* 1995; 79(4):1386-1390.
- [26] Paredi P, Kharitonov SA, Barnes PJ. Correlation of exhaled breath temperature with bronchial blood flow in asthma. *Respir Res* 2005; 6(14-16):15.

- [27] Widdicombe JG, Webber SE. Neuroregulation and pharmacology of the tracheobronchial circulation. In: Butler J, ed. The bronchial circulation. Marcel Dekker, New York/Basel/Hong Kong, 1992; pp. 249-289.
- [28] Wilson J. The bronchial microcirculation in asthma. *Clinical & Experimental Allergy* 2000; 30 Suppl 1:51-53.
- [29] Chetta A, Zanini A, Foresi A, Del Donno M, Castagnaro A, D'Ippolito R, Baraldo S, Testi R, Saetta M, Olivieri D. Vascular component of airway remodeling in asthma is reduced by high dose of fluticasone. *Am J Respir Crit Care Med* 2003; 167(5):751-757.
- [30] Clarke GW, Rafferty GF, Ledbetter CL, Ketchell RI, Ratoff JR, Greenough A, O'Connor B J. The effects of inhaled spasmogens on airway mucosal blood flow in asthmatic subjects. *Am J Respir Crit Care Med* 2004; 169:A185.
- [31] Mendes ES, Pereira A, Danta I, Duncan RC, Wanner A. Comparative bronchial vasoconstrictive efficacy of inhaled glucocorticosteroids. *Eur Respir J* 2003; 21(6):989-993.
- [32] Wanner A, Horvath G, Brieva JL, Kumar SD, Mendes ES. Nongenomic actions of glucocorticosteroids on the airway vasculature in asthma. *Proc Am Thor Soc* 2004; 1(2):235-238.
- [33] Iversen LL, Salt PJ. Inhibition of catecholamine uptake-2 by steroids in the isolated rat heart. *Br J Pharmacol* 1970; 40(3):528-530.
- [34] Horvath G, Lieb T, Conner GE, Salathe M, Wanner A. Steroid sensitivity of norepinephrine uptake by human bronchial arterial and rabbit aortic smooth muscle cells. *Am J Respir Cell Mol Biol* 2001; 25(4):500-506.

- [35] Horvath G, Torbati A, Conner GE, Salathe M, Wanner A. Systemic ovalbumin sensitization downregulates norepinephrine uptake by rabbit aortic smooth muscle cells. *Am J Respir Cell Mol Biol* 2002; 27(6):746-751.
- [36] Busse W, Banks-Schlegel S, Noel P, Ortega H, Taggart V, Elias J, Group NW. Future research directions in asthma: an NHLBI Working Group report. *Am J Respir Crit Care Med* 2004; 170(6):683-690.
- [37] Mendes ES, Campos MA, Hurtado A, Wanner A. Effect of montelukast and fluticasone propionate on airway mucosal blood flow in asthma. *Am J Respir Crit Care Med* 2004; 169(10):1131-1134.
- [38] Orsida BE, Li X, Hickey B, Thien F, Wilson JW, Walters EH. Vascularity in asthmatic airways: relation to inhaled steroid dose. *Thorax* 1999; 54(4):289-295.
- [39] Hoshino M, Takahashi M, Takai Y, Sim J, Aoike N. Inhaled corticosteroids decrease vascularity of the bronchial mucosa in patients with asthma. *Clinical & Experimental Allergy* 2001; 31(5):722-730.
- [40] Hammond GL. Determinants of steroid hormone bioavailability. *Biochem Soc Trans* 1997; 25(2):577-582.
- [41] McKenzie AW, Stoughton RB. Method for comparing percutaneous absorption of steroids. *Arch Dermatol* 1962; 86:608-610.
- [42] Noon JP, Evans CE, Haynes WG, Webb DJ, Walker BR. A comparison of techniques to assess skin blanching following the topical application of glucocorticoids. *Br J Dermatol* 1996; 134(5):837-842.
- [43] Mariassy AT, Gazeroglu H, Wanner A. Morphometry of the subepithelial circulation in sheep airways. Effect of vascular congestion. *Am Rev Respir Dis* 1991; 143(1):162-166.

- [44] Csete ME, Abraham WM, Wanner A. Vasomotion influences airflow in peripheral airways. *Am Rev Respir Dis* 1990; 141(6):1409-1413.
- [45] Wagner EM, Mitzner W. Effects of bronchial vascular engorgement on airway dimensions. *J Appl Physiol* 1996; 81(1):293-301.
- [46] Rodrigo GJ, Rodrigo C, Hall JB. Acute asthma in adults: a review. *Chest* 2004; 125(3):1081-1102.
- [47] Wanner A. Clinical perspectives: role of the airway circulation in drug therapy. *J Aerosol Med* 1996; 9(1):19-23.
- [48] Cazzola M, Santus P, Di Marco F, Carlucci P, Mondoni M, Matera MG, Centanni S. Onset of action of formoterol/budesonide in single inhaler vs. formoterol in patients with COPD. *Pulm Pharmacol Ther* 2004; 17(3):121-125.
- [49] Muto S, Ebata S, Okada K, Saito T, Asano Y. Glucocorticoid modulates Na^+/H^+ exchange activity in vascular smooth muscle cells by nongenomic and genomic mechanisms. *Kidney Int* 2000; 57(6):2319-2333.
- [50] Wehling M, Neylon CB, Fullerton M, Bobik A, Funder JW. Nongenomic effects of aldosterone on intracellular Ca^{2+} in vascular smooth-muscle cells. *Circ Res* 1995; 76(6):973-979.
- [51] Steiner A, Locher R, Sachinidis A, Vetter W. Cortisol-stimulated phosphoinositide metabolism in vascular smooth muscle cells: a role for glucocorticoids in blood pressure control? *J Hypertens* 1989; 7(6):S140-141.
- [52] Liu L, Wang YX, Zhou J, Long F, Sun HW, Liu Y, Chen YZ, Jiang CL. Rapid non-genomic inhibitory effects of glucocorticoids on human neutrophil degranulation. *Inflamm Res* 2005; 54(1):37-41.

- [53] Schmid D, Burmester GR, Tripmacher R, Kuhnke A, Buttgereit F. Bioenergetics of human peripheral blood mononuclear cell metabolism in quiescent, activated, and glucocorticoid-treated states. *Biosci Rep* 2000; 20(4):289-302.
- [54] Baccan GC, Oliveira RDR, Mantovani B. Stress and immunological phagocytosis: possible nongenomic action of corticosterone. *Life Sci* 2004; 75(11):1357-1368.
- [55] Long F, Wang YX, Liu L, Zhou J, Cui RY, Jiang CL. Rapid nongenomic inhibitory effects of glucocorticoids on phagocytosis and superoxide anion production by macrophages. *Steroids* 2005; 70(1):55-61.
- [56] Pitzalis C, Pipitone N, Perretti M. Regulation of leukocyte-endothelial interactions by glucocorticoids. *Ann N Y Acad Sci* 2002; 966:108-118.

TABLES

Table 1. Rapid nongenomic actions of corticosteroids in vascular smooth muscle cells

Tissue used	Rapid action	Antihormon	Sensitivity	Ref.
Rabbit aorta, human bronchial artery	Inhibition of the cell membrane catecholamine transporter	RU486	No effect	[14, 34]
Rat aorta	Activation of the cell membrane Na^+/H^+ transporter	RU486	Inhibition	[49]
Rat aorta	Intracellular Ca^{2+} mobilization		Not tested	[50]
Rat aorta	Stimulation of phosphoinositide breakdown to increase inositol-1,4,5-triphosphate levels	RU486	Inhibition	[51]

Table 2. Rapid nongenomic actions by which corticosteroids could interrupt the development of inflammation and suppress ongoing inflammatory reactions

Cell type	Rapid action	Ref.
Neutrophils	Inhibition of degranulation	[52]
Lymphocytes	Inhibition of membrane cation cycling and respiration	[53]
Macrophages	Inhibition of phagocytosis	[54]
Macrophages	Inhibition of superoxide anion production	[55]
Leukocytes	Inhibition of endothelial adhesion	[56]
Lung	Inhibition of phospholipase A ₂ activity and arachidonic acid release	[16]

Table 3. Corticosteroid-sensitive, potentially vasoactive genes in vascular smooth muscle and endothelial cells

Vascular smooth muscle cells	Endothelial cells
$\alpha_{1\beta}$ -adrenergic receptor	Endothelial nitric oxide synthase
Angiotensin II type 1 receptor	Angiotensin-converting enzyme
Vasopressin V _{1A} receptor	Cationic amino acid transporter-1
Natriuretic peptide receptor	Phospholipase A ₂
Angiotensin-converting enzyme	Cyclooxygenase type 2
Preproendothelin-1	
Na ⁺ -K ⁺ -ATPase	
Na ⁺ -Ca ²⁺ -ATPase	
Ca ²⁺ -activated K ⁺ channel	

LEGENDS

Figure 1. Genomic and nongenomic actions of inhaled corticosteroids in the airway vasculature in patients with asthma

Accepted manuscript

Figure 1. Genomic and nongenomic actions of inhaled corticosteroids in the airway vasculature in patients with asthma

