

EDITORIAL

Glucocorticoids 'on air'

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In the current issue of *Allergy*, Hostettler et al. (1) for the first time describe local glucocorticoid (GC) production in the lung, providing the basis for speculation about potential new therapeutic approaches to treat airway allergic diseases.

The anti-inflammatory potency of GC is well appreciated in the therapy of allergic diseases, including the current stepped-care approach to asthma treatment in which inhaled GC have a central place (2). Despite the persistently high prevalence of asthma worldwide, improved quality of care has led to recently observed favourable trends in Western countries with GC constituting the drug class that is thought to have the greatest effect for the achievement of well-controlled asthma (2, 3). Although the suppression of airway inflammation and asthma control is improved by increasing the dose of inhaled GC, such an approach will lead to a heightened risk of systemic absorption and adverse effects, and strategies that can achieve asthma control at reduced doses of inhaled GC are desirable (2). Deregulation of endogenous inflammation-regulating mechanisms often occurs in allergic diseases, and stimulation of such anti-inflammatory pathways may be a viable alternative to classical treatment approaches aiming at antagonizing pro-inflammatory mediators (4). Endogenous GC themselves represent potent anti-inflammatory mediators that are produced and released in the systemic circulation by the adrenal glands, in a process that is tightly regulated by the hypothalamic–pituitary–adrenal (HPA) axis. As an alternative to the topical treatment using exogenous inhaled and intranasal GC, finding ways to concentrate endogenous GC in the airways without also substantially increasing systemic GC levels or affecting the HPA axis, respectively, would be highly desirable from a therapeutic point of view.

While the adrenal glands are considered the major source of endogenous GC, there is an increasing evidence for extra-adrenal GC production. This was first shown in the murine thymic epithelium (5) and has since been reported for other tissues, including brain, skin, intestine and vascular endothelium (6). The most convincing *in vivo* evidence for a physiological role of local GC production comes from studies in murine intestine (7). Intriguingly, tumour necrosis factor α (TNF α), which is best known for its pro-inflammatory actions, clearly has anti-inflammatory effects in the intestinal mucosa where it potently induces extra-adrenal *de novo* GC synthesis from cholesterol during acute intestinal inflammation (8).

In the current issue of *Allergy*, Hostettler et al. (1) now present the first evidence for local GC production in the lung of mice. This study adds to the growing list of exciting animal model-based biomedical research papers, which were

published in *Allergy* recently (9–13). Hostettler et al. show that lung tissue expresses the complete enzymatic machinery needed for *de novo* GC synthesis. In contrast to the intestine, however, most enzymes are constitutively expressed with only the rate-limiting enzyme P450_{scc} (the Cyp11a1 gene product) being induced by inflammatory stimuli. *In situ* synthesis of corticosterone, the main GC in the mouse, is elegantly demonstrated in *ex vivo* cultured lung tissue, and bioactivity of locally produced GC is proven beyond doubt. Low GC levels could already be detected in the lungs of untreated mice; however, they significantly increased upon the pretreatment of animals with agonistic anti-CD3 antibodies or bacterial lipopolysaccharides. Accordingly, direct injection of TNF α induced very strong lung GC production. Interestingly, however, lung GC production was not diminished in mice lacking both TNF-receptors 1 and 2, indicating that cytokines other than TNF α can trigger the same response. In fact, cytokine receptors have been detected at all levels of the HPA axis (14), which, as a major component of the stress system, coordinates the adaptive responses of the organism to stressors and interacts mutually and extensively with the immune system (15). Effects of locally produced cytokines on HPA regulation have been observed decades ago, and the initially designated 'tissue corticotropin-releasing factor' later turned out as a mixture of cytokines and other inflammatory mediators that were thought to affect HPA axis regulation upon escape in the circulation (15). Interestingly, the results of Hostettler et al. (1) now suggest that local cytokines might have direct effects on lung tissue GC production, which would not require systemic HPA axis regulation.

Surprisingly, however, the authors observed that acute allergic airway inflammation, as assessed in an ovalbumin hypersensitization model, almost totally failed to induce lung GC production, despite the presence of strong neutrophilic and eosinophilic inflammation. It therefore seems that local GC production in the lung is favoured by a Th1-polarized inflammatory environment and not (or very weakly) induced by Th2 cytokines. In future studies, it would be interesting to test this hypothesis also in the animal models of chronic asthma, in which deregulation of endogenous inflammation-regulating mechanisms plays a critical role (4).

Another surprising result was obtained upon adrenalectomy, which completely abolished *in situ* GC production in the lung, strongly suggesting that lung GC synthesis depends on adrenal factors. It was subsequently found that the reactivation of serum-derived, inactive 11-dehydrocorticosterone into active corticosterone by the enzyme 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) is predominant in the lung. Based on these results, it can be concluded that the lung produces

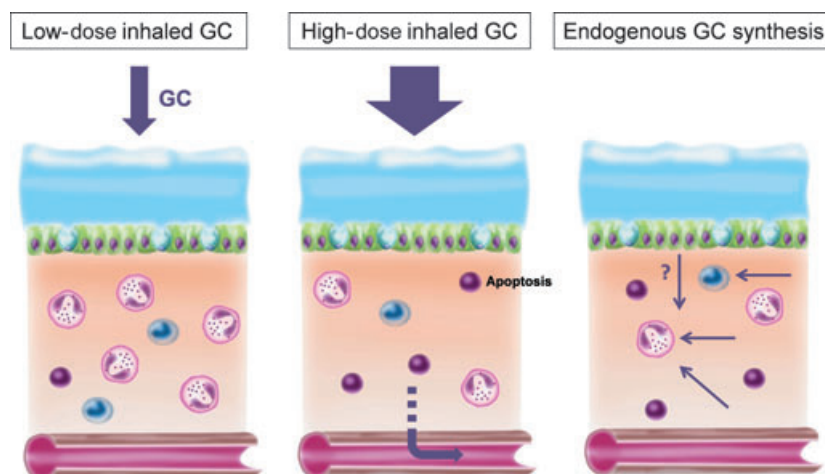


Figure 1 Proposed local anti-asthmatic effects by induction of endogenous tissue glucocorticoid (GC) synthesis. High-dose inhaled GC treatment has proven anti-inflammatory effects by mechanisms that include the inhibition of immune effector cells and their clearance by apoptosis. Because the dose–systemic absorption curve

appears to be linear, novel strategies to increase local GC, but not systemic GC levels, would be desirable. Induction of tissue GC synthesis may have potent local para- and autocrine effects on adjacent immune cells even at low concentrations. Illustration by Aldona von Gunten.

increased corticosterone levels after immune cell stimulation and that, in contrast to the intestine, this production occurs mainly via 11β -HSD1-mediated conversion of dehydrocorticosterone rather than by *de novo* synthesis.

Despite the clear evidence for local GC production in the murine lung tissue upon inflammation in a Th1-polarized environment, the question of the importance of *de novo* GC synthesis in the lung remains. Even though the entire enzymatic machinery for *de novo* GC synthesis is present, the major source of local GC is produced by the reactivation of serum-derived dehydrocorticosterone. Analysis of 11β -HSD1 gene-deficient mice (16) could help to better understand the relative contributions to the local immunosuppression of GC reactivation *vs de novo* GC synthesis in the lung. Another interesting aspect is the yet unknown identity of the GC-producing cell type(s) in the lung. In the intestinal mucosa, crypt cells seem to be the major site of *de novo* GC synthesis (7). A similar role could be attributed to lung type II alveolar epithelial cells, but this remains to be demonstrated. It is also conceivable that *de novo* GC synthesis and reactivation of dehydrocorticosterone do not necessarily have to take place in the same cell type.

Overall, the data by Hostettler et al. strongly point towards the ability of the lung to sense inflammatory responses and to react with *in situ* GC reactivation to resolve inflammatory processes and to limit tissue damage through the well-known effects of GC to suppress immune effector

functions and to repress genes encoding pro-inflammatory mediators by inhibiting the transcription factors AP-1 and NF- κ B in immune cells (17). Furthermore, the ability of GC to directly induce apoptosis in eosinophils (18) and T lymphocytes (19) could further aid in limiting immune responses and collateral tissue damage. The authors show that in their model of airway hypersensitivity lung GC synthesis is defective and suggest that local GC production may be similarly absent in asthma which could contribute to the pathogenesis or persistence of the disease. Future studies that include asthma patients are required to confirm this assumption. Specific local induction of GC *de novo* synthesis or 11β -HSD1 and subsequent conversion of dehydrocorticosterone may represent a novel strategy to topically treat inflammatory allergic disorders in the lung (Fig. 1).

Conflict of interest

The authors declare no conflict of interest.

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