Oxidant stress in asthma

Ryszard Dworski

Asthma is a chronic inflammatory disease of the respiratory tract of unknown aetiology. In severe asthma airway diathesis is profound, and thus apparent. Recently, however, evidence has indicated that specific inflammatory abnormalities exist even in the airways of subjects with mild disease. As inflammation is often associated with an increased generation of reactive oxygen species (ROS), and the biochemical environment in the asthmatic airways is favourable for free radical mediated reactions, it is rational to surmise that an oxidant stress could be mechanistically important in asthma.

Cellular and biochemical sources of ROS in asthma

The inflammatory cells recruited to the asthmatic airways have an exceptional capability for producing ROS. Activated eosinophils, neutrophils, monocytes, and macrophages can generate superoxide (O$_2^-$) via the membrane associated NADPH-dependent complex. Subsequently, dismutation of O$_2^-$ gives hydrogen peroxide (H$_2$O$_2$), O$_2$ and H$_2$O per se are moderate oxidants; however, both species are critical for the formation of potent cytotoxic radicals in biological systems through their interaction with other molecules. For example, hydroxyl radical (•OH), a powerful and indiscriminate oxidant, can be produced from O$_2^-$ and hypohalous acids (HOCI or HOBr). The latter component can be formed from H$_2$O$_2$ and a halide (Cl$^-$ or Br$^-$) in a reaction catalysed by myeloperoxidase (MPO) provided by neutrophils and monocytes, or eosinophil peroxidase (EPO) from eosinophils. MPO preferably utilises Cl$^-$ as a halide, whereas EPO uniquely prefers Br$^-$.

In principle an increase in the production of ROS is problematic because oxidation of proteins, DNA, and lipids may cause direct tissue injury or evoke a variety of cellular responses through the generation of secondary reactive species.

Antioxidants and asthma

Numerous disturbances of antioxidant defence mechanisms have been described in asthma. For example, the expression of the asthma phenotype has been linked to reduced selenium status, an essential element for the normal activity of glutathione peroxidase,22 23 numerous disturbances of antioxidant defence enzymes—for example, Mn-SOD and glutathione peroxidase—have potential stimuli or promoters of ROS production. In addition to endogenous sources, some environmental factors linked to asthma such as air pollutants (for example, ozone, diesel exhaust particles) may cause an extreme increase of ROS generation in the airways.

As in many other pathological conditions, the oxidant “burst” in asthma is presumably a self-propagating non-specific process initiated by the concurrent action of numerous inflammatory pathways. Several asthma mediators including lipid mediators,15 chemokines,16 17 adhesion molecules,18 and eosinophil granule proteins19 are potential stimuli or promoters of ROS production. In addition to ROS, other oxidant-free reactive species may cause direct tissue injury or evoke a variety of cellular responses through the generation of secondary reactive species.21
Could increased activity of ROS have a role in the pathogenesis of asthma?

The exposure of animals in vivo and human airway tissue in vitro to different oxidants has been shown to produce airway constriction and hyperresponsiveness. However, the relevance of these experiments to human asthma is uncertain. Of interest, however, are recent studies suggesting that ROS mediated reactions may alter or induce some inflammatory and immunological cellular responses—for example, through the generation of second messengers. It is important to emphasise that the consequences of oxidant stress may vary in normal lungs and in lungs with pre-existing allergic inflammation caused by a different biochemical and cellular environment. Nevertheless, some of the effects mediated by ROS with a feasible role in asthmatic inflammation and airway remodelling include activation of transcription factors such as STATs and NFKB, modulation of glucocorticoid dependent signal transduction, stimulation of phospholipase and eicosanoid synthesis, induction of growth factors, cytokines, and modification of cellular ion transport mechanisms. Specific studies will be necessary to establish which of these effects could be involved in asthma.

Evidence for oxidative stress in asthma

Much of the evidence for the activity of ROS in asthma is indirect or circumstantial because there are no reliable methods to assess oxidative stress in vivo. Thus, the measurement of increases in NO, HO_2, and pentane in exhaled gas or breath condensates, analysis of lipid peroxidation based on diene conjugate and thiobarbituric acid (TBA), and the assessment of substrate oxidisability (or spin trapping) of free radical adducts ex vivo all have low sensitivity and specificity. However, using these procedures, an augmented production of ROS has been found in adults and children with distinct asthma severity and acute exacerbations of asthma. The specific measurement of F_2-isoprostanes (F_2-Isop), stable prostaglandin-like arachidonate products formed on membrane phospholipids by the action of ROS, has recently been found to be a sensitive and reliable non-invasive method for assessing oxidant stress in vivo. Indeed, F_2-Isop production of 15-F_2t-Isop (8-iso-PGF_2α) and metabolite of F_2-Isop-M (8-iso-PGF_2α) provides a more reliable index of total systemic production of IsoPs because, unlike unmetabolised F_2-Isop, the metabolite cannot be produced in the kidney nor be generated artefactually by auto-oxidation of arachidonic acid during sample handling and storage. We have also found increased release of F_2-Isop and F_2-Isop-M into the urine of patients with aspirin induced asthma following challenge with inhaled lysine-aspirin (Dworski et al., unpublished observation).

If ROS are important in asthma, enhancement of the antioxidant defences would be expected to have beneficial effects in the disease. In this regard the available data in humans are unimpressive. Unfortunately, one of the major weaknesses of the studies to date is the lack of evidence that the chosen doses and mixtures of antioxidants were effective in vivo. We anticipate that measurement of the urinary excretion of F_2-Isop-M may provide a novel method to define the most effective dosages and combinations of antioxidants to suppress oxidant stress in patients with asthma, which will permit a reliable assessment of the effect of antioxidant treatment on the pathophysiology of the disease process.

Conclusion

There is evidence that oxidant stress occurs in asthma, which is not surprising considering the inflammatory nature of the disease. However, little is known about the role of ROS in the inflammatory and immunological cascade characteristic of asthma. This is a provocative question because some of the mechanisms may bypass the therapeutic effects of anti-inflammatory drugs, and antioxidant agents could prove useful adjuvant treatment for asthma.

This work was supported by NIH grant GM15431. The author thanks Tamara Lasakow for editorial assistance in preparing the manuscript.

Oxidant stress in asthma


