Rapid loss of superoxide dismutase activity during antigen-induced asthmatic response
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Loss of superoxide dismutase activity occurs within minutes of an acute asthmatic response to segmental antigen instillation into the lung of individuals with atopic asthma. Decreased activity undoubtedly contributes to airway inflammation and injury through increased formation of reactive oxygen and nitrogen species, and suggests that enrichment of lung antioxidants is therapeutic for asthma.

Experimental antigen exposure can be used to mimic asthma attacks and investigate the mechanisms of episodic asthma. Bronchoscopic release of antigen into airways results in both a localised immediate asthmatic response occurring within minutes, and a similar but longlasting late asthmatic response that takes place after several hours. Mediators that contribute to the immediate and late asthmatic response include reactive oxygen species produced by epithelial cells and inflammatory cells recruited to the sites of antigen challenge. However, the effect of reactive oxygen species on airways will depend on the major extracellular enzymatic antioxidants are the Cu,Zn-superoxide dismutase and include both enzymatic and non-enzymatic systems. The antioxidant activity undoubtedly contributes to airway inflammation and injury through increased formation of reactive oxygen and nitrogen species, and suggests that enrichment of lung antioxidants is therapeutic for asthma.

To investigate antioxidant status in asthma attack, we used a segmental antigen challenge approach. Seven individuals with atopic asthma (three men; percentage predicted forced expiratory volume in 1 s 92% [SE 7]; age 37 years [3]) and five healthy non-atopic controls (three men; forced expiratory volume in 1 s 99% [6]; age 44 years [4]) were studied. Asthmatics had mild, stable asthma with no recent asthma attack, had not taken inhaled corticosteroid in the preceding 6 weeks, or systemic corticosteroids during the previous 6 months, and had had no change in medications for 6 weeks before the study. Bronchoscopy with bronchoalveolar lavage (BAL) was undertaken on all individuals to obtain baseline samples of epithelial lining fluid after instillation of normal saline into the lingula of the lung. Subsequently, antigen challenge was done in the middle lobe of the right lung with injection of a relevant antigen (grass or ragweed) diluted in normal saline. BAL was done in the right middle lobe after 10 min to sample epithelial lining fluid during the immediate asthmatic response. A second bronchoscopy was done 48 h later with BAL of the right middle lobe antigen-challenged segment, and BAL of the lingula saline-control contralateral segment. Antioxidant concentrations of SOD, glutathione peroxidases, and reduced and oxidised glutathione were measured in the acellular lavage fluid fraction as previously described. The amount of epithelial lining fluid recovered, calculated by the urea method, was similar between groups.

SOD activity was lower in asthmatic individuals than in controls (table). Strikingly, SOD activity fell in all asthmatic individuals immediately after segmental antigen challenge. Four of the asthmatic individuals had further decrease of SOD at 48 h. By contrast, SOD in the contralateral lingula segment at 48 h was similar to baseline (SOD activity: 55 U/mL [SE 20]; p=0.23). Antigen challenge had no effect on glutathione peroxidases activity in individuals with asthma (table). However, parallel to loss of SOD activity, reduced glutathione peroxidases declined immediately after antigen challenge in all individuals with asthma, whereas oxidised glutathione concentrations tended to increase indicating increased oxidative stress.

We have shown that immediate asthmatic responses are associated with a rapid and profound loss of specific antioxidant activity. Notably, our results show SOD inactivation occurs within minutes after antigen instillation but may persist for days. Importantly, loss of activity occurs in a specific fashion in the lung, since glutathione peroxidases activity is not affected. We have previously shown that airway epithelial cells of asthmatics have decreased intracellular SOD activity as a result of loss of enzyme-specific activity. SOD enzymes are highly sensitive to inactivation by oxidants.

Asthma attacks and experimental antigen challenge are both associated with increased release of reactive oxygen species, which may lead to inactivation of SOD. The rapid loss of reduced glutathione after antigen challenge verifies loss of reducing potential in the airway with acute asthma attack.

Because SOD is a first-line antioxidant essential to aerobic life, loss of SOD activity undoubtedly potentiates extracellular matrix damage and tissue injury through increased formation of reactive oxygen and nitrogen species. Small non-protein mimics of SOD are in development for use in human clinical inflammatory diseases since SOD mimics protect against tissue damage in models of inflammation and reduce production of cytokines, the immune regulators that fuel inflammation. These results validate a rationale to assess SOD mimics in the treatment of asthma.

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