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ORIGINAL ARTICLE

Oxidized vitamin E and glutathione as markers of clinical status in asthma☆

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Summary
Background & aims: Antioxidant status is disturbed in asthma. Measurement of both oxidized and reduced forms of antioxidants provides important information regarding the oxidant/antioxidant balance. The aim of this study was to investigate the clinical relevance of key antioxidants (α-tocopherol and glutathione) in asthma, by measuring the oxidized and reduced forms, in the airways (induced sputum) and systemically (peripheral blood).
Methods: This cross-sectional study examines stable asthmatics ($n = 44$) and healthy controls ($n = 31$) recruited through John Hunter Hospital, NSW, Australia. We collected peripheral blood and induced sputum during hypertonic saline challenge. α-tocopherol and α-tocopherol quinone were measured by HPLC. Total glutathione and glutathione disulfide were determined by a colorimetric assay.
Results: Plasma α-tocopherol was low in asthma versus controls. Subjects with asthma had higher levels of whole blood α-tocopherol quinone and %α-tocopherol quinone than controls and %α-tocopherol quinone correlated with asthma control ($p = 0.009$). Sputum supernatant levels of total, reduced and oxidized glutathione were elevated in asthma versus controls. Oxidized glutathione in sputum supernatant negatively correlated with $FEV_1/FVC\%$ ($p = 0.029$).

☆ Conference presentation: Parts of this work have been presented at the Thoracic Society of Australia & New Zealand Annual Conference, Sydney, 2004, and the Nutrition Society of Australia Annual Scientific Meeting, Melbourne, November 2005.

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Conclusions: In asthma, both systemic and airway antioxidant defences are disturbed. Oxidized forms of α-tocopherol and glutathione are associated with clinical asthma outcomes, and should be further investigated as a tool for monitoring asthma.
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Introduction

Antioxidants are crucial to host antioxidant defence against oxidative stress.[1] In asthma there is enhanced oxidative stress, demonstrated by elevated levels of various biomarkers including 8-isoprostane,[2] malondialdehyde[3–7] and breath ethane.[8] Asthma is also characterised by disturbed antioxidant defences, including deficiencies in vitamin C,[4,5,9–11] vitamin E,[4,5,11,12] β-carotene,[4,13] lycopene,[13] α-carotene,[13] lutein[13] and β-cryptoxanthin.[13] However, interpretation and assessment of antioxidant defences in asthma has been limited by two key issues. Firstly, when measuring antioxidant levels, it is important to differentiate between the reduced and oxidized forms, as these molecules can only act as antioxidants in the reduced state. Secondly, investigation of oxidative stress in airway disease should incorporate analysis of airway lining fluid. Most analysis of antioxidant defences in asthma has been carried out in peripheral blood. However, blood markers may not accurately represent conditions at the airway surface,[11] the site of oxidative damage. Thus, reliable tools need to be developed for directly assessing antioxidant airway defences. We have sought to address these issues in this study.

We have examined two antioxidants that exist in a relatively stable, quantifiable form in both the reduced and oxidized states, and we have assessed these in the airway and in circulation. An important dietary antioxidant is vitamin E. The term vitamin E describes a group of eight structurally related molecules, including four tocopherols and four tocotrienols. The most abundant form of vitamin E, both in the diet and in biological systems is α-tocopherol. This exogenous antioxidant is oxidized to form α-tocopherol quinone. Both α-tocopherol and α-tocopherol quinone can be measured using HPLC. While altered α-tocopherol levels have been observed in asthma,[4,5,11,12] to our knowledge, α-tocopherol quinone levels have not been reported in asthma to date. Comparison of the relative amounts of oxidized and reduced α-tocopherol in asthma is important in understanding the role of α-tocopherol in protecting against oxidative stress and affecting clinical asthma outcomes.

Another key antioxidant is reduced glutathione. This endogenous antioxidant plays a prominent role in the respiratory tract due its ability to scavenge free radicals, as well as act as a cosubstrate in the glutathione peroxidase-catalysed reduction of H_2O_2 and lipid hydroperoxides.[14] Both the reduced form (GSHr) and the oxidized form, glutathione disulfide (GSSG), are quantifiable using a colorimetric assay. While altered levels of (GSHt) have been reported in asthma in BAL[15] and sputum,[16] these studies did not elucidate what form of the antioxidant was driving this increase. Another study found increased GSSG levels in asthma,[11] but did not report GSHt and GSHr remained unchanged. Another small study found no changes in GSHt or GSSG.[17] Since glutathione is widely recognised as a key antioxidant in the respiratory tract, a comprehensive examination is warranted.

In order to examine antioxidant defences in the airways, we have investigated these antioxidants in induced sputum samples. Induced sputum has been used extensively to investigate airway inflammation in stable asthma[18] and in acute exacerbations of asthma[19] and has been shown to be a safe,[20] effective and reproducible method.[21] Inflammatory markers that have been measured in induced sputum in asthma include: IL-8,[19,22] IL-2,[19] eosinophil cationic protein (ECP),[19,22] IL-2,[19] neutrophil elastase,[22] myeloperoxidase[22] and IL-5.[22] Induced sputum has also been found to contain biomarkers useful for studying oxidative stress in the lower respiratory tract[2] and may provide a useful means of monitoring airway antioxidant defences. This is important as we seek to understand the relevance of antioxidant status to clinical outcomes in asthma.

This study therefore aims to investigate the clinical relevance of two key antioxidants (α-tocopherol and glutathione) in asthma, by determining the relative concentrations of the oxidized and reduced forms in the airways (induced sputum) and systemically (peripheral blood).

Materials and methods

Subjects

Adults (over 18 years) with current diagnosis of asthma were recruited from specialist clinics at John Hunter Hospital, Newcastle. Controls were recruited by advertisement and asthma was excluded on the basis of history, normal spirometry and airway responsiveness, together with data review by a respiratory physician. Current smokers were excluded. Atopy was assessed by skin allergy testing. Plasma, whole blood and induced sputum were collected. In cases where the sample volume collected from a subject was insufficient for analysis of all biomarkers, this is indicated [Tables 3 and 4]. All participants gave informed written consent and the study was approved by the Hunter Area Research and University of Newcastle Ethics Committees.

Clinical classification of asthma

Asthma was diagnosed based upon a history of current (past 12 months) episodic respiratory symptoms, a prior doctor's diagnosis of asthma (ever), current (past 12 months) use of inhaled asthma therapy and airway hyperresponsiveness to hypertonic saline. Subjects were considered to be unstable, and thus excluded from the study, if their asthma had worsened such that they had needed

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