BEHAVIOR OF PULMONARY VAGAL SENSORY RECEPTORS WITH MYELINATED AFFERENTS DURING FREE RADICAL INDUCED AIRWAY HYPER-REACTIVITY AND ITS MODULATION BY ANTI-OXIDANTS IN GUINEA-PIGS

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ABSTRACT

The vagal sensory receptors provide sensory inputs to the central nervous system about the changes that take place in the airways and lungs in various pathophysiological conditions to produce appropriate reflex responses. These receptors are considered to play an important role in the respiratory symptoms associated with various inflammatory lung diseases such as asthma. However, there is scanty information on the involvement of free radicals in stimulation of vagal sensory receptors and eliciting the defense reflexes.

In this investigation, an attempt has been made to determine the behavior of vagal sensory receptors mainly rapidly adapting receptors (RARs) and slowly adapting receptors (SARs) during the oxidative stress induced airway hyperreactivity as observed in the case of asthma. Following the activation of RARs, there is a reflex cough, an increase in airway secretion and bronchoconstriction. Even though the main function of the SARs is to ‘regulate’ respiration, they get activated by conditions which promote airway constriction. However, unlike the RARs, their stimulation causes airway relaxation. An imbalance in the balance in their responses may precipitate the symptoms of asthma. Thus, modulation of their activities by dietary antioxidants such as vitamin C and vitamin E may be clinically useful and hence has been investigated.

For making these observations, a guinea pig model of asthma was successfully developed using ovalbumin as an allergen. The animals were divided into six Groups. In each animal, pulmonary mechanics was determined and vagal afferent activity originating from RARs and SARs was recorded. The changes in pulmonary mechanics and vagal afferent activity to histamine inhalation were observed. Finally, the study was repeated after intake of the antioxidants, vitamin C and vitamin E.

- Group 1 served as control.
- In Group 2, the animals were sensitized with ovalbumin. It was divided into two Groups- Group 2a and Group 2b.
- In Group 2a, twenty eight days after sensitization, ovalbumin challenge was given and the early asthmatic response was investigated.
In Group 2b, the animals were sensitized and challenged with ovalbumin and were utilized 24 hr after challenge to observe the response in late asthmatic phase.

The animals of both the groups were given normal diet.

In Group 3, the effect of in vivo generation of oxidants by xanthine xanthine oxidase inhalation was determined.

In Group 4a and Group 4b, the interventions were the same as in Group 2a and Group 2b respectively. Unlike in Groups 2a and 2b, in these Groups, the diets of the animals were supplemented with the antioxidants vitamin C (2 mg/kg body weight) and vitamin E (7 mg/kg body weight).

The salient observations of the present study are summarized below.

**Group 1**

- In this Group, saline inhalation did not produce any significant change either in pulmonary mechanics or afferent activity.
- Both the RARs and SARs were stimulated by histamine inhalation.
- Histology showed no gross lung pathology.

**Group 2a (Early Asthmatic Response Group)**

- The allergen challenge in the sensitized animals leads to widespread bronchoconstriction as evidenced by changes in pulmonary mechanics.
- There were increases in the receptor activity, oxidative stress and infiltration of inflammatory cells along with fluid flux and epithelial damage.
- Following allergen challenge, there was an increase in the sensitivity of airways and airway receptors to histamine.
- Between the RARs and SARs, the responses of RARs were greater.

**Group 2b (Late Asthmatic Response Group)**

- The bronchoconstriction and increased RAR activity continued in late asthmatic phase also.
- In this phase, there was an increase in the airway responsiveness to histamine.
- There was an increase in the response of RARs and SARs to histamine. However, the responses of RARs were greater.
• These increases in airway sensitivity and afferent activity were further associated with oxidative stress and other inflammatory changes such as infiltration of inflammatory cells along with fluid flux and epithelial damage.

Group 3 (In vivo Generation of ROS)

• The in vivo generation of oxidants led to bronchoconstriction as evidenced by changes in pulmonary mechanics.
• There were significant stimulations of both RARs and SARs.
• There was an increase in the airway responsiveness to histamine.
• The responses of RARs and SARs to histamine were increased.
• These changes in airway sensitivity and afferent activity were further associated with oxidative stress and mild infiltration of inflammatory cells along with mild fluid flux and epithelial damage.

Group 4a (Early Asthmatic Response Group with Antioxidants)

• There was a reduction in the responsiveness of the airways and the responses of airway sensory receptors to ovalbumin challenge following antioxidant supplementation.
• There was also partial reversal in the responsiveness of the airways and the responses of the sensory receptors to histamine following antioxidant supplementation thereby suggesting that part of these responses could be oxidative stress mediated.
• The partial reversal was also evident in oxidative stress parameters and pulmonary inflammation with a reduction in the infiltration of inflammatory cells, fluid flux and epithelial damage.

Group 4b (Late Asthmatic Response Group with Antioxidants)

• In this group also, there was partial reversal in the responsiveness of the airway and lung receptors to histamine following antioxidant supplementation thereby suggesting that part of these responses could be oxidative stress mediated.
• The partial reversal was also evident in oxidative stress parameters and pulmonary inflammation.
From the present study, it may be concluded that oxidative stress plays a significant role in inducing the airway hyperresponsiveness in asthma. Upon exposure to the allergen, there occurs widespread bronchoconstriction resulting in increases in tracheal pressure and airway resistance and decrease in dynamic compliance. All these changes lead to the stimulation of the vagal sensory receptors connected to myelinated afferents, the RARs and SARs. The RARs are more sensitive to the allergen challenge than the SARs. Exposure to an allergen increases the sensitivity of airways and lung receptors to lung autacoids such as histamine. Since an increase in tracheal tone has been reported following RAR stimulation, it is proposed that their activation would lead to further bronchoconstriction. Their stimulation increases mucus production and causes cough. All these symptoms worsen asthma. Though less sensitive, the SARs are also stimulated. The SARs may counteract the bronchoconstriction as their activation causes bronchodilation. During the late asthmatic response, there is an increase in the sensitivity of airways and vagal sensory receptors to lung autacoids. In both early and late asthmatic phases there is fluid flux and infiltration of inflammatory cells in the lungs. These changes are associated with increased oxidative stress parameters. All these changes stimulate the RARs. Thus, RAR activation may give rise to the dyspneic sensation associated with asthma and SAR stimulation may relieve it to some extent.

Upon supplementation with dietary antioxidants, there is a partial reversal in the airway hyperresponsiveness and inflammation. Also the sensitivity of these vagal sensory receptors to histamine is also reversed partially. These findings indicate that oxidative stress plays a significant role in inducing the airway hyperresponsiveness in asthma. The in vivo generation of oxidants by xanthine-xanthine oxidase inhalation causes bronchoconstriction and stimulation of these receptors. The study provides direct evidence that oxidants activate lung receptors. Even though the results are promising, since allergic disorders such as asthma are multifactorial, blocking oxidative stress alone is unlikely to lead to complete resolution of bronchoconstriction, inflammation and receptor activation but such an approach may prove to be a useful adjunct therapy.