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Antagonism of protease activated receptor-2 leads to amelioration of airway reactivity and inflammation via dual oxidase-2 inhibition in a mouse model of allergic asthma

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Airway Epithelial Cells (AECs) are involved in allergic airway responses through modulation of a variety of receptors, which sense danger signals from various inhaled aeroallergens/pathogens. Proteinase-Activated Receptor 2 (PAR-2) is one such receptor expressed on innate/adaptive immune cells and is activated by cockroach allergens which have intrinsic serine proteinase activity. Recently, different signaling pathways have been shown to be involved in airway inflammation in response to toll-like receptor activation on innate immune cells. However, the contribution of DUOX-2 signaling in the modulation of airway reactivity, and inflammation after PAR-2 activation/antagonism on AECs has not explored earlier. Therefore, this study specifically focused on AECs isolated from murine trachea to delineate PAR-2 mediated signaling. For this purpose, mice were sensitized intraperitoneally with intact Cockroach allergen Extract (CE) followed by intranasal (i.n.) challenge with CE. The mice were then assessed for airway reactivity, inflammation, and DUOX-2 related oxidative stress (reactive oxygen species, inducible nitric oxide synthase, nitrite, nitrotyrosine and protein carbonyls) and apoptosis (Bax, Bcl-2, caspase-3) in AECs of allergic mice. Challenge with CE led to upregulation of DUOX-2 in AECs with concomitant increases in airway reactivity/inflammation, and parameters of oxidative stress/apoptosis. Intransal administration of ENMD-1068, a small molecule antagonist of PAR-2 before CE challenge led to improvement of allergic airway reactivity/inflammation through inhibition of DUOX-2 mediated signaling. The data from this study suggest that PAR-2 blockade through inhalation could be utilized as a therapeutic strategy to ameliorate airway reactivity and inflammation in allergic asthma.

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Potential effect of the extract of *Zataria Multiflora* and its constituent, carvacrol, on lung pathology, total and differential WBC, histamine, ige and eosinophil peroxidase levels in sensitized guinea pigs

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The effect of Zataria multiflora (Z. multiflora) and its main constituents, carvacrol (a phenolic compound), on lung inflammation of sensitized guinea pigs was examined. Sensitized guinea pigs to ovalbumin (OA) were given drinking water alone (group S), drinking water containing three concentrations of the extract (0.2, 0.4 and 0.8 mg/mL), three concentrations of carvacrol and dexamethasone (50 µg/mL), (n=6, for all groups). Lung pathology, total and differential white blood cell (WBC), serum levels of IgE and eosinophil peroxidase (EPO) were evaluated. All pathological indices, serum IgE and EPO levels and total and differential WBC except lymphocytes in group S showed significant increase but lymphocyte was decreased compared to the control group ($p<0.05$ to $p<0.001$). Dexamethasone, all concentrations of the extract and carvacrol treatment caused significant improvement in all parameters compared to group S ($p<0.05$ to $p<0.001$). The effect of a high concentration of the extract and carvacrol was higher compared to dexamethasone in most parameters ($p<0.05$ to 0.001). These results showed a preventive effect of the extract of Z. multiflora and its constituent, carvacrol, on lung inflammation of sensitized guinea pigs. The effect of the plant is perhaps due to its constituent, carvacrol.

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