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ORIGINAL ARTICLE

Beneficial effects of ursodeoxycholic acid via inhibition of airway remodelling, apoptosis of airway epithelial cells, and Th2 immune response in murine model of chronic asthma

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Abstract
Background and aims: In previous studies, anti-inflammatory, anti-apoptotic and immunomodulatory effects of ursodeoxycholic acid (UDCA) on liver diseases have been shown. In this study, we aimed to investigate the effects of UDCA on airway remodelling, epithelial apoptosis, and T Helper (Th)-2 derived cytokine levels in a murine model of chronic asthma.
Methods: Twenty-seven BALB/c mice were divided into five groups; PBS-Control, OVA-Placebo, OVA-50 mg/kg UDCA, OVA-150 mg/kg UDCA, OVA-Dexamethasone. Mice in groups OVA-50 mg/kg UDCA, OVA-150 mg/kg UDCA, OVA-Dexamethasone received the UDCA (50 mg/kg), UDCA (150 mg/kg), and dexamethasone, respectively. Epithelium thickness, sub-epithelial smooth muscle thickness, number of mast and goblet cells of samples isolated from the lung were measured. Immunohistochemical scorings of the lung tissue for matrix metalloproteinase-9 (MMP-9), vascular endothelial growth factor (VEG-F), transforming growth factor-beta (TGF-β), terminal deoxynucleotidyl transferase-mediated dUTP nick endlabeling (TUNEL) and cysteine-dependent aspartate-specific proteases (caspase)-3 were determined. IL-4, IL-5, IL-13, Nitric oxide, ovalbumin-specific immunoglobulin (Ig) E levels were quantified.
Results: The dose of 150 mg/kg UDCA treatment led to lower epithelial thickness, sub-epithelial smooth muscle thickness, goblet and mast cell numbers compared to placebo. Except for MMP-9 and TUNEL all immunohistochemical scores were similar in both UDCA treated groups and the placebo. All cytokine levels were significantly lower in group IV compared to the placebo.

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Conclusions: These findings suggested that the dose of 150 mg/kg UDCA improved all histopathological changes of airway remodelling and its beneficial effects might be related to modulating Th-2 derived cytokines and the inhibition of apoptosis of airway epithelial cells.
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Introduction

Asthma is a common chronic disorder of the airway that is characterised with the complex interaction of airway inflammation, airway remodelling, and bronchial hyperresponsiveness which lead to recurrent episodes of breathlessness, wheezing, chest tightness, and coughing.[1] The airway inflammation is typically eosinophilic and it is accompanied by the elevation of Th-2 cytokines such as IL-4, IL-5, IL-13. Airway remodelling consists of epithelial injury, goblet cell hyperplasia, airway smooth muscle hyperplasia, sub-epithelial layer thickening from increased deposition of extra cellular matrix proteins, and angiogenesis.[2] Extensive studies on airway remodelling in asthma focused on the determination of the implicated cytokines, growth factors, and chemokines. Several mediators of remodelling were identified, including IL-4, IL-9, IL-13, IL-17, VEGF, MMP-9 and TGF-β.[3,4]

Apoptosis has important and beneficial regulatory roles in the normal airway epithelium. However, airways of asthmatics exhibit an elevated rate of epithelial apoptosis and this is related with increased disease severity.[5] Apoptotic process includes the cleavage of a number of proteins, which can be observed by cysteine-dependent aspartate-specific proteases (caspase)-3 staining and DNA fragmentation that can be detected by terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL) staining.[5]

The presence of advanced airway remodelling is associated with a poorer clinical prognosis and is therefore considered as an important therapeutic target.[6] Unfortunately, current anti-inflammatory therapeutic strategies including inhaled corticosteroids are less successful in treating structural alterations in airway remodelling even though they are effective in reducing the inflammation.[7] Thus, novel therapeutic strategies which have a potent effect on the airway remodelling should be developed.

Ursodeoxycholic acid (UDCA) is a tertiary bile acid that has been used for centuries in the clinical treatment of gallstones, primary biliary cirrhosis, and primary sclerosing cholangitis.[8] Immunomodulatory properties of UDCA in liver diseases have been shown in previous studies.[9–12] UDCA also has immunomodulatory effects except in the gastrointestinal tract.[13] However, according to our knowledge, the effects of UDCA on airway remodelling, epithelial apoptosis, and TH2 immune response have been firstly investigated in the murine model of chronic asthma in our study in comparison with the conventional dexamethasone treatment.

Materials and methods

Animals, experimental protocol and study drugs

A total of twenty-seven, conventionally raised, 6–8-week-old male BALB/c mice weighing 18–20 g were used in the study. The animals were kept in hygienic macrolane cages in air-conditioned rooms on a 12-hour light/dark cycle. Mice were fed with commercial diet ad libitum for the experiment. All experimental procedures complied with the requirements of the Animal Care and Ethics Committee of the Dokuz Eylul University.

Mice were divided into five groups: PBS-Control; OVA-Placebo; OVA-50 mg/kg UDCA; OVA-150 mg/kg UDCA; and OVA-Dexamethasone. The PBS-Control group was exposed to saline only. Mice in the groups OVA-Placebo, OVA-50 mg/kg UDCA, OVA-150 mg/kg UDCA, OVA-Dexamethasone were sensitised by an intraperitoneal (IP) injection of ovalbumin (10 μg/0.1 ml, 2 weeks apart, i.e. Days 0 and 14) consisting of chicken egg albumin (ovalbumin, grade V, ≥98% pure, Sigma, St. Louis, MO, USA) with alum adjuvant as described by Temelkovski et al.[14] The mice in study OVA-Placebo, OVA-50 mg/kg UDCA, OVA-150 mg/kg UDCA, OVA-Dexamethasone were then exposed to aerosolised ovalbumin (5 ml, 2.5%) for 30 min per day (three days per week) for eight weeks, beginning from the 21st day of the study (Fig. 1). The mice in PBS-Control group were intraperitoneally administered with normal saline with alum on Days 0 and 14 of the experiment and exposed to aerosolised saline without alum for 30 min per day (three days per week) for eight weeks, beginning from the 21st day of the study. Exposures were carried out in a whole-body inhalation exposure system in a Plexiglas chamber measuring 40 × 60 × 120 designed for the placement of cages, in all groups. Temperature and relative humidity were maintained between 20–25 °C and 40–60%, respectively. A solution of 2.5% ovalbumin in normal saline was aerosolised by the delivery of compressed air to a sidestream jet nebuliser injected into a chamber with a flow rate of 6 L/min (Medicair, UK). The aerosol generated by this nebuliser comprised >80% particles with a diameter of <4 μm. Particle concentration was maintained in the range of 10–20 mg/mm^3 in the chamber. Thus, it was predicted that more than 90% of the particles would remain in the mouse airways, which would be enough for the development of the asthma model.[15] During the last five days of the challenge period, mice in group OVA-Placebo received saline, mice in group OVA-50 mg/kg UDCA received UDCA (Sigma Aldrich, St. Louis, MO, USA) at dose of 50 mg/kg, mice in group OVA-150 mg/kg UDCA received UDCA at dose of 150 mg/kg,

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