H_2S prevents bronchial hyper-responsiveness development in a murine model of allergic asthma

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Sulfurous thermal waters have been recognised since Ancient Roman times as useful in relief and cure of chronic upper respiratory diseases. Recently, hydrogen sulphide (H_2S) has been identified as the third gaseous neurotransmitter, along with nitric oxide (NO) and carbon monoxide (CO). It is synthesized in the mammalian tissues starting from L-cysteine through different pathways catalyzed by the action of cystathionine γ-lyase (CSE), cystathionine β-synthase (CBS) or 3-mercaptyopyruvate sulfotransferase (MPST). H_2S is involved in a wide range of physiological effects but its role in respiratory system is yet to be clarified. Recently, it is emerging that in various subtypes of chronic respiratory diseases an altered metabolism and functions of endogenous H_2S occur.
The aim of this study is to assess the effects of H_2S in an animal model of asthma. We set up an experimental model where mice sensitized to ovalbumin (OVA) were exposed to an exogenous H_2S donor (NaHS) through aerosolized.
Mice received subcutaneous injection of OVA (100μg) at day 0 and 7 and were sacrificed at day 21. Isolated bronchi harvested from OVA-sensitized mice showed an increased concentration-dependent contraction to carbachol compared to vehicle-treated mice. Exposure to NaHS (aerosol, 0.1 mM) from day 7 to 14 prior to the experimental procedure prevented the airway hyper-reactivity *in vitro*. In a separate set of experiments we tested changes in the lung function by evaluating total lung resistances (R_L). R_L to carbachol were measured in anesthetized, tracheostomized and ventilated mice using a whole-body in OVA-sensitized animals. NaHS prevented airway hyper-responsiveness to carbachol. Interestingly, in OVA-sensitized mice exposed to NaHS during sensitization there was an increased response to salbutamol *in vitro*. Therefore, H_2S i) reduces bronchial contractility to muscarinic agonists and ii) ameliorates the response to adrenergic agents. In order to further clarify the molecular mechanisms underlying H_2S effects, flow cytometry analyses were performed on lungs. OVA-sensitized mice showed a significant increase of the percentage of mast cells, identified as CD11c+cKit+ cells, whose recruitment was repealed by NaHS. Increase in IL-13 and FGF-2 further supported a key role for mast cells and confirmed a modulatory role for the L-Cysteine/H_2S pathway since NaHS aerosol inhibited the production of these mediators. A final proof on the involvement of mast cells was obtained by using a mast cell-dependent murine model of asthma where NaHS aerosol prevented the development of bronchial hyper-responsiveness *in vitro*.
In conclusion our data demonstrate that H_2S plays a critical protective role in the development of airway hyper-reactivity and offers new therapeutic potential for asthma.