Letter

Reduction in airway epithelial chloride transport in septicaemia related pulmonary oedema reversible by beta agonist application

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Manocha and colleagues [1] found in a retrospective study on the association of beta-agonist use and lung injury a shorter duration and less severity of lung injury in patients on aerosolized beta-agonists. In their discussion of possible causes they and the investigators of the beta-agonist lung injury trial [2] did not comment on the effect of beta-agonist treatment on pulmonary chloride transport as an important independent determinant of pulmonary fluid clearance. It was first noted in experiments by Fang and colleagues [3] that mice with inhibited or defective cystic fibrosis transmembrane conductance regulator (CFTR) chloride channels (delta F508 homozygous) have a reduced cAMP dependent and CFTR mediated pulmonary fluid clearance and more severe pulmonary oedema in the fluid overload pulmonary oedema model. This group then established that CFTR is present in alveolar epithelial cells and contributes independently to cAMP dependent fluid transport [4]. Other groups found that chloride channels in respiratory epithelial cells can be activated by beta agonists via an increase in intracellular cAMP [5]. We measured the nasal potential difference and the amiloride (ENaC blocker) response of the nasal respiratory epithelium, which both represent upper airway epithelial sodium transport, and the response of the nasal respiratory epithelium to a low chloride solution (CFTR stimulation), which represents chloride channel function in the upper airway of children with meningococcal septicaemia related pulmonary oedema [6]. We found that nasal potential difference and amiloride response were not different between children with and without meningococcal septicaemia related pulmonary oedema. Response of the upper airway epithelium to a low chloride solution was, however, absent in children with septicaemia related pulmonary oedema and this was significantly different to children ventilated for other forms of critical illness without pulmonary oedema. This indicated that the systemic reduction of epithelial chloride transport we found in the children with septicaemia induced pulmonary oedema, which was also reflected in increased sweat and saliva chloride levels, extended to the respiratory tract. The reduction in chloride transport seemed to be more closely related to pulmonary oedema and its severity than features of sodium transport. Topical stimulation of chloride channels in the nasal airway of the children with pulmonary oedema with the beta agonist isoprenaline resulted in activation of chloride transport. Future trials and laboratory research related to treatment of pulmonary oedema needs to take into account parameters reflecting pulmonary epithelial chloride transport as important additional explanatory outcomes.

Authors' response

Anthony C Gordon and James A Russell

We thank Dr Eisenhut for his comments about our recent publication that demonstrated an association between inhaled beta-agonist use and improvement in acute lung injury (ALI) [1]. Dr Eisenhut and colleagues' recent work studying children with meningococcal septicemia found that reduced epithelial chloride transport was associated with pulmonary edema in this condition [6]. Interestingly, although only reported in two children, the inactivation of the chloride channel was reversed when the airway epithelium was perfused with the beta-agonist isoprenaline.

Unfortunately, the nature of our retrospective study means we can only report the association of beta-agonist use and improvement of ALI, without providing definitive answers to

ALI = acute lung injury; CFTR = cystic fibrosis transmembrane conductance regulator.

explain the mechanism of this effect. As discussed, possible mechanisms include improved respiratory mechanics, reduced inflammation and improved edema clearance. If the finding of reversibly impaired chloride transport is seen in lung injury due to other infectious and non-infectious etiologies then this is another potential mechanism by which beta-agonists might improve fluid clearance and thus support the findings of our study [1] and the beta-agonist lung injury trial [2].

Hopefully future studies will include randomized controlled trials to demonstrate if beta-agonists are an effective treatment in ALI and also mechanistic experiments to explain any therapeutic effect.

Competing interests

The authors declare that they have no competing interests.

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