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Preclinical Evaluation of Hypertonic Saline as Therapy for Cystic Fibrosis Lung Disease in Mice

Promotionsfach: Kinderheilkunde
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Dehydration of airway surfaces and reduced mucus clearance due to increased Na^+ absorption via the epithelial sodium channel (ENaC) plays an important role in the pathogenesis of CF lung disease in patients and causes CF lung disease in βENaC-overexpressing mice. Hypertonic saline (HS, NaCl 7%) improves airway surface hydration by inducing osmotic flux of water into the airway lumen. Previous clinical trials demonstrated that inhalation of HS improved mucus clearance and lung function and reduced pulmonary exacerbations in CF patients with chronic lung disease (28, 42), and recent pilot studies demonstrated that inhalation of HS is well tolerated by infants and young children with CF (23, 26). However, effects of HS therapy on other characteristic features of CF lung disease, i.e. airway mucus obstruction and airway inflammation, and the benefits of preventive HS treatment have not been studied. In the present study, we used βENaC-overexpressing mice as a model of CF lung disease, and examined the effects of preventive and late treatment with HS in different concentrations on mortality, airway mucus obstruction and airway inflammation. Newborn or 4-week-old βENaC-overexpressing mice and wild-type littermate controls were treated by intrapulmonary instillation of HS (NaCl 3% and 7%; 1µl/g bw) or vehicle ($_{dd}H_2O$) alone 3 times per day for a period of 2 weeks.

Preventive 3% HS therapy significantly improved survival and growth and reduced mucus obstruction in distal airways. Preventive therapy with 7% HS had an even stronger effect on airway mucus obstruction, reducing mucus content also in proximal airway regions compared to vehicle-treated βENaC-overexpressing neonates. Intervention therapy in adult βENaC-overexpressing mice with chronic lung disease with 3% HS failed to reduce airway mucus obstruction in adult βENaC-overexpressing mice whereas with 7% HS airway mucus content could be significantly reduced compared to vehicle treatment. Treatment effects of 7 % HS

could not be further improved by a combination of HS therapy with the long acting ENaC blocker P643.

In all studies we observed a pro-inflammatory effect of HS in wild-type littermates. It was also observed in βENaC-overexpressing neonates that received 7% HS treatment. The pro-inflammatory effect of HS in absence of airway inflammation reflected by an increase in neutrophils in BAL fluids seems to be triggered by hypertonic stress as similar pro-inflammatory effects were observed with mannitol as an alternative osmotic agent. In βENaC-overexpressing mice with chronic airway inflammation HS has no anti-inflammatory, but also no further pro-inflammatory effect.

Our preclinical studies indicate that both preventive and late 7% HS treatment provide an effective mucokinetic therapy for CF lung disease. However, HS promoted airway inflammation in neonates and had no therapeutic effect on airway inflammation in adult βENaC-overexpressing mice with established CF-like lung disease. In summary our results suggest that combined mucokinetic and anti-inflammatory therapeutic strategies may be necessary for the treatment of CF lung disease.