NEONATAL PULMONARY RESEARCH

Prevention of hyperoxia-mediated pulmonary inflammation in neonatal rats by caffeine

Background

Aeration of the lungs of preterm human infant after birth can result in BPD. The rate of that hyperoxia-mediated chronic lung disease can be reduced by caffeine administration, especially during the first 3 days of life. It has been suggested, that caffeine improves respiratory muscle strength and reduces rates of apnoea, which lead to reduced ventilator-induced lung injury, however, the direct actions of caffeine on immature lungs are still unclear. In this study, the authors investigated the effect of administering caffeine in an established animal model, where early exposure to high oxygen concentration results in BPD-like lung disease by analysing the expression of pulmonary chemokines, proinflammatory cytokines and signs of tissue destruction.

6-day-old rats were exposed to:
1) normoxia (21% O2, room air)
2) normoxia and caffeine (10mg/kg body weight once at the beginning of hyperoxia)
3) hyperoxia (80% O2)
4) hyperoxia and caffeine (10mg/kg body weight once at the beginning of hyperoxia)
for 6h, 24h and 48h

Summary of results

The authors showed that caffeine abolishes any hyperoxia-mediated increase in chemokine (CINC-1, MIP-2, MCP-1) and pro-inflammatory cytokine (TNFa, IL-6) expression in the lung. Chemokines in turn cause leukocyte extravasation ($CD11b^+$, $ED\text{-}1^+$, MPO^+), which is also decreased by caffeine. In addition, caffeine reduces the tissue destruction caused by exposure to high oxygen for 24h or 48h. According to these results caffeine protects the neonatal lung, at least in part, by reduction of pulmonary inflammation.

Strength

Caffeine is used to treat apnoea of prematurity, but the direct pulmonary effect is unclear. This study showed that caffeine acts in the inflammatory pathway where it inhibits chemokine and cytokine expression. In contrast to most other publication, which shows the effects of hyperoxia after several days, the authors investigate the effect of high concentrations of oxygen with and without caffeine already in the first 48h of hypoxia.

Limitations

- Caffeine was given only once to the animals, while preterm human infants receive caffeine for many weeks and therefore the direct effect of repeated caffeine administration is still unclear.
- Caffeine decreases not only the CINC-1 and MCP-1 expression at 24h and 48h of hyeroxia but also at 24h and 48h of normoxia and caffeine administered to animals in room air also promoted septal thinning, which could be due to a maybe inappropriate caffeine concentration.
- Caffeine and its metabolites have nonlinear pharmacokinetics, what needs to be considered.

Practical conclusion

The data suggest that caffeine is a good therapeutic to prevent pulmonary inflammation after ventilation, thus reduces the development of BPD in preterm infants. However, such aspects like the best concentration of caffeine or the effect on cell development factors still need to be determinate. In addition, it would also be important to analyse the effects of caffeine in rat pups < 6days old, which are more similar to preterm infants.

Weichelt U et al., Prevention of hyperoxia-mediated pulmonary inflammation in neonatal rats by caffeine. Eur Respir J. 2013 Apr;41(4):966-73.

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