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Molecular hydrogen affords neuroprotection in a translational piglet model of hypoxic-ischemic encephalopathy

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Abstract

Hypoxic-ischemic encephalopathy (HIE) is the major consequence of perinatal asphyxia (PA) in term neonates. Although the newborn piglet is an accepted large animal PA/HIE model, there is no consensus on PA-induction methodology to produce clinically relevant HIE. We aimed to create and to characterize a novel PA model faithfully reproducing all features of asphyxiation including severe hypercapnia resulting in HIE, and to test whether H_2 is neuroprotective in this model. Piglets were anaesthetised, artificially ventilated, and intensively monitored (electroencephalography, core temperature, O_2 saturation, arterial blood pressure and blood gases). Asphyxia (20 min) was induced by ventilation with a hypoxic-hypercapnic (6%O_2 - 20%CO_2) gas mixture. Asphyxia-induced changes in the cortical microcirculation were assessed with laser-speckle contrast imaging and analysis. Asphyxia was followed by reventilation with air or air containing hydrogen (2.1%H_2, 4 hours). After 24 hours survival, the brains were harvested for neuropathology. Our PA model was characterized by the development of severe hypoxia (pO2 = 27 ± 4 mmHg), and combined acidosis (pH = 6.76 ± 0.04; pCO_2 = 114 ± 11 mmHg; lactate = 12.12 ± 0.83 mmol/L), however, cortical ischemia did not develop during the stress. Severely depressed electroencephalography (EEG), and marked neuronal injury indicated the development of HIE. H_2 was neuroprotective shown both by the enhanced recovery of EEG and by the significant preservation of neurons in the cerebral cortex, hippocampus, basal ganglia, and the thalamus. H2 appeared to reduce oxidative stress shown by attenuation of 8-hydroxy-2'-deoxyguanosine immunostaining. In summary, this new PA piglet model is able to induce moderate/severe HIE, and the efficacy of hydrogen post-treatment to preserve neuronal activity/function in this PA/HIE model suggests the feasibility of this safe and inexpensive approach in the treatment of asphyxiated babies.

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