HYDROGEN IS NEUROPROTECTIVE AND PRESERVES NEUROVASCULAR REACTIVITY FOLLOWING ASPHYXIA IN NEWBORN PIGS

By

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PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS

I. Domoki F, **Olah O**, Zimmermann A, Nemeth I, Toth-Szuki V, Hugyecz M, Temesvári P and Bari F (2010) Hydrogen is neuroprotective and preserves cerebrovascular reactivity in asphyxiated newborn pigs. Pediatr Res 68: 387-392.

IF: 2,803

II. **Olah O**, Nemeth I, Toth-Szuki V, Bari F and Domoki F (2012) Regional Differences in the Neuronal Expression of Cyclooxygenase-2 (COX-2) in the Newborn Pig Brain. Acta Histochem Cytochem 45: 187-192.

IF: 1,48

III. Domoki F, Zolei D, **Olah O**, Toth-Szuki V, Hopp B, Bari F and Smausz T (2012) Evaluation of laser-speckle contrast image analysis techniques in the cortical microcirculation of piglets. Microvasc Res 83: 311-317.

IF: 2,929

IV. **Olah O**, Toth-Szuki V, Temesvari P, Bari F and Domoki F (2013) Delayed neurovascular dysfunction is alleviated by hydrogen in asphyxiated newborn pigs. Neonatology 104:79-86.

IF: 2,573

Summary

Perinatal asphyxia can elicit mortality or severe disability in the survivors called hypoxic-ischemic encephalopathy (HIE) in term infants. HIE yearly affects around one million babies worldwide. In contrast to the severe impact of HIE on the society and on the health care budget, the first effective neuroprotective therapy, mild whole-body hypothermia, has only recently been introduced into broader clinical practice. The resuscitation efforts in asphyxiated infants start invariably with adequate mechanical ventilation. The gas mixture used for artificial ventilation could be used to deliver possibly neuroprotective gases to reduce CNS damage, and to perhaps augment the efficacy of hypothermia. For instance, molecular hydrogen could be an ideal therapeutic agent, as it has recently been shown to exert selective antioxidant properties against hydroxyl and peroxynitrite radicals.

There are several animal models to study HIE pathology.. In our Szeged laboratory, a widely-used gyrencephalic large animal model of HIE, the newborn piglet has been utilized. Dysfunction of the so-called neurovascular unit – that is responsible for meeting the metabolic demands of neurons – may play an important role in the pathomechanism of HIE. Therefore, to assess the putative neuroprotective effects of molecular hydrogen, beside neuropathology we also determined CR to stimuli indicating neurovascular unit integrity both in the acute (1-4 h, n=31) and the subacute (24 h, n=27) phase of survival after asphyxia. We would like to highlight the novel observation from our results that after an initial recovery at the end of the acute period, a second delayed neurovascular unit dysfunction develops in the subacute phase. The molecular hydrogen gas *per se* did not affect CR or cortical perfusion, but preserved neurovascular unit function and diminished neuronal damage in the CNS after asphyxia.

Our results are in accordance with the antioxidant mechanism of molecular hydrogen actions, since neurovascular unit dysfunction has been previously shown to be triggered by elevated levels of reactive oxygen species during reoxygenation. Our data suggest that molecular hydrogen administered in the early reoxygenation can alleviate not only the acute but also the delayed phase of neurovascular dysfunction demanding further preclinical research. The importance of further research on molecular hydrogen is also substantiated by its other appealing features concerning its medical use: it is inexpensive, simple to produce and to administer, and has ideal pharmacokinetics.