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P0556 **MULTI-ORGAN DAMAGE FOLLOWING PERINATAL ASPHYXIA IN RAT MODEL**

Tamas Lakat^{1,2}, Adam Hosszu^{1,2}, Agnes Molnar^{1,2}, Akos Roland Toth¹, Adar Saeed¹, Kornel Demeter³, Hanga Kelemen^{2,4}, Eva Miklos⁴, Attila Szabo^{2,5}, Adam Denes⁶, Andrea Fekete^{1,2}

¹MTA-SE, "Lendület" Diabetes Research Group, Budapest, Hungary, ²Semmelweis University, 1st Department of Pediatrics, Budapest, Hungary, ³MTA Institute of Experimental Medicine, Behavioral Studies Unit, Budapest, Hungary, ⁴MTA Institute of Experimental Medicine, Translational Behavioural Neuroscience, Budapest, Hungary, ⁵MTA-SE, Pediatrics and Nephrology Research Group, Budapest, Hungary and ⁶MTA Institute of Experimental Medicine, Neuroimmunology, Budapest, Hungary

Background and Aims: Perinatal asphyxia (PA) leads to the death of more than half a million mature newborns yearly. PA is associated with several serious complications, including hypoxic encephalopathy, renal, hepatic and cardiovascular injury, as well as respiratory distress. Basic research and clinical trials mainly focus on mitigating central nervous system damage by selective head or whole body cooling, which is currently the only routinely used treatment in clinical practice. However, the extent of PA-associated multi-organ damage is not clarified yet and effective therapies are lacking. The aim of the present study was to determine the acute renal, hepatic and cardiac impairment following PA and to identify pathways involved in the pathomechanism. In addition, we aimed to investigate long-term effects of PA on permanent organ damage and susceptibility to ischemia/reperfusion injury in adulthood.

Method: Postnatal 7-day-old male Wistar rat pups (n=5-10/group) were randomly grouped as follows: (i) Baseline, or separated from the dam and placed in a treatment chamber for 15 minutes (ii) Control: normal air; (iii) PA: 4% O₂, 20% CO₂ in N₂ gas mixture. Serum and tissue samples were collected after 4 (T4) and 24 (T24) hours respectively. In a second experiment 35 min bilateral renal ischemic insult was performed on control and PA rats aged 6 months (n=6-7/group). Serum and tissue samples were collected 24 (T24 IR) hours after reperfusion (Figure 1).

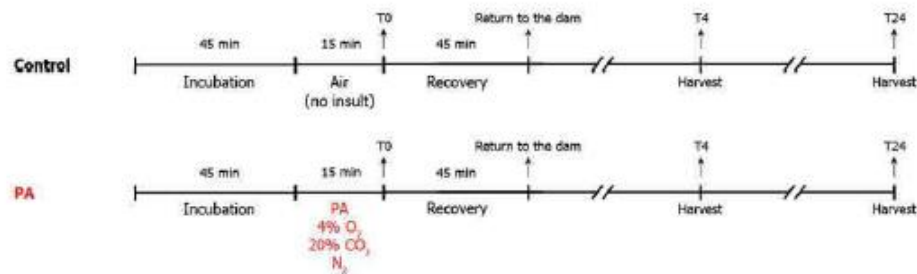
Serum levels of electrolytes, kidney and liver functional parameters, and myocardial ischemic protein Troponin I were determined. Highly selective tubular injury markers (Kim1, Ng2) were measured. Expressions of hypoxic (Hif1a, Hif2a) inflammatory (Il1 α , Il1 β , Il6, Tnf α , Mip1, Tlr2), apoptotic (Bax, Bcl-2) and angiogenic genes (Vegf, Epc) and heat shock proteins (Hsp27, Hsp72) were investigated. Periodic Acid Schiff staining and CD45 immunostaining on kidney tissue sections, and Hematoxylin & Eosin staining on liver tissue sections were performed.

Results: Blood urea nitrogen (BUN) and serum GPT were elevated at T4 following PA. Kim1, Ng2 and heat shock protein expressions were increased, inflammatory and angiogenic pathways were activated in the kidney after PA. CD45 staining showed increased leukocyte infiltration. In the liver hypoxic and apoptotic pathways were activated at T24 in controls and after asphyxia, but not in the Baseline group. Vacuolisation, cytoplasmic degradation, and the onset of necrosis were observed in the liver following PA. Serum Troponin I was elevated indicating myocardial damage, moreover inflammatory cytokines and heat shock proteins increased in the heart. In adult PA rats BUN levels were elevated, suggesting a long-term detrimental effect of PA on renal function. In addition, adult PA rats were more susceptible to renal ischemic insult, confirmed by higher serum creatinine and GPT levels, as well as increased expression of tubular injury, hypoxic and inflammatory markers compared to Control rats subjected to ischemia.

Conclusion: Acute renal, hepatic and myocardial impairment was observed after PA. These results may justify the need for clinical follow-up and novel treatment strategies for possible multi-organ damage. The molecular pathways described here are potential targets for therapeutic intervention. In addition, birth asphyxia may increase sensitivity to renal injury even in adulthood, which may be worth considering in clinical situations with potential renal impairment such as major surgeries.

7-day old Wistar rats

Baseline: not separated; terminated immediately



6 months-old Wistar rats

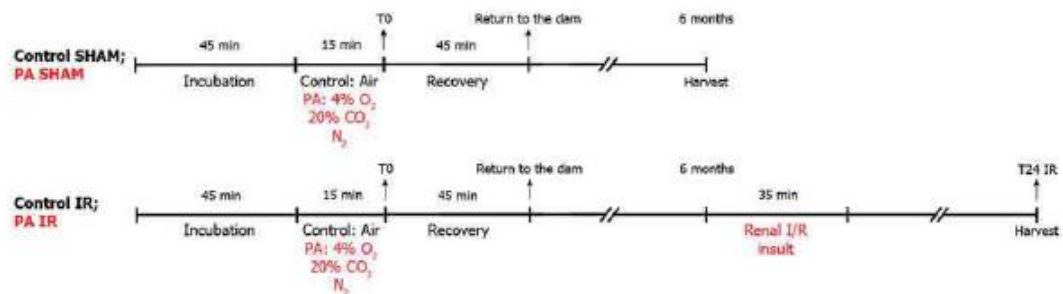


Figure 1: Experimental models. PA, Perinatal Asphyxia; I/R, ischemia-reperfusion.