Results The development of HIE stage 3 was significantly lower in Anapyrexia group(8%) than in the Normothermia group(28%) (p=0.032; [RR]=0.285). Fifteen neonates in the anapyrexia group had normal outcome versus only 9 in the normothermia group(p=0.049,[RR]=0.5). The incidence of mortality(12% vs 16%,p=0.264,[RR]=0.75) complications and baseline characteristics were comparable.

Conclusions Anapyrexia if allowed to persist for 72 hours after birth, alleviates the ill effects of hypoxic ischemic insult and results in improved outcome in the neonates particularly the neurodevelopmental outcome at 6 months of age.

296 PHARMACOKINETICS, CLINICAL EFFICACY AND SAFETY OF LIDOCAINE IN ASPHYXIATED NEWBORNS TREATED WITH THERAPEUTIC HYPOTHERMIA

doi:10.1136/archdischild-2012-302724.0296

[1]MPH van den Broek, [1,2]CMA Rademaker, [3]ADR Huitema, [4]HLM van Straaten, [2]MC Toet, [2]LS de Vries, [1,5]ACG Egberts, [2]F Groenendaal. *[1]University Medical Centre Utrecht; [2]Wilhelmina Childrens' Hospital/UMCU, Utrecht; [3]Slotervaart Hospital/The Netherlands Cancer Institute, Amsterdam; [4]Isala Clinics, Zwolle; [5]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands*

Background and Aims Therapeutic moderate hypothermia for neuroprotection in asphyxiated newborns can influence pharmacokinetics and pharmacodynamics. Lidocaine is administered if seizures persist despite initial therapy. Because cardiotoxicity is a potential risk of lidocaine, dose adjustment under hypothermia might be necessary to prevent toxicity. The aim was to evaluate the effect of hypothermia on lidocaine pharmacokinetics and to evaluate the efficacy and safety under hypothermia.

Methods Hypothermic data were obtained from the SHIVER-study. Term born newborns with perinatal asphyxia and encephalopathy with lidocaine therapy were included. Therapeutic hypothermia (33.5°C, for 72 hours) was applied within 6 hours after birth. Lidocaine dosing under hypothermia was reduced; initial dose 2 mg/kg in 10 minutes, followed by an infusion of 4 mg/kg/h during 6 hours. Subsequently the infusion was reduced to 2 mg/kg/h during 12 hours, and then stopped.

Data from normothermic newborns were obtained from a previously published study (van den Broek *et al*., 2011). Pharmacokinetic modelling was performed using NONMEM.

Results 22 hypothermic newborns were included and were compared with 26 normothermic newborns. Based on a one-compartmental model with allometric relationships, lidocaine clearance was decreased by 24% under hypothermia, while relative metabolite formation was unchanged. During hypothermia no effect of lidocaine on heart frequency could be observed and the observed efficacy, i.e. decrease of seizure activity, was 78%.

Conclusion Hypothermia has a clinically relevant effect on lidocaine clearance. The dosing regimen needs to be adjusted under hypothermia in order to maintain efficacy and to prevent adverse events. This model is currently validated.

297 DUAL ACTION OF NO SYNTHASES ON BLOOD FLOW AND INFARCT VOLUME CONSECUTIVE TO NEONATAL FOCAL CEREBRAL ISCHEMIA

doi:10.1136/archdischild-2012-302724.0297

[1]P Bonnin, [2]PL Leger, [3]S Renolleau, [2]O Baud, [2]C Charriaut-Marlangue. *[1]Physiologie Clinique - Explorations-Fonctionnelles, APHMP; [2]U676, INSERM Unit 676; [3]APHP, Service de Réanimation Pédiatrique, Paris, France*

Research into neonatal ischemic brain damage is impeded by the lack of a complete understanding of the initial hemodynamic mechanisms resulting in a lesion, particularly that of NO-mediated vascular mechanisms. In a neonatal stroke rat model, we recently show that collateral recruitment contributes to infarct size variability.

Non-specific and selective NO synthase (NOS) inhibition were evaluated on cerebral blood-flow changes and outcome in a P7 rat model of arterial occlusion (left middle cerebral artery electrocoagulation with 50 min occlusion of both common carotid arteries). Blood-flow changes were measured by using ultrasound imaging with sequential Doppler recordings in both internal carotid arteries and basilar trunk. Cortical perfusion was measured by using laser Doppler flowmetry. We showed that global NOS inhibition significantly reduced collateral support and cortical perfusion (collateral failure), and worsened the ischemic injury in both gender. Conversely, endothelial NOS inhibition increased blood-flows and aggravated volume lesion in males, whereas in females blood-flows did not change and infarct lesion was significantly reduced. These changes were associated with decreased phosphorylation of neuronal NOS at Ser^{847} in males and increased phosphorylation in females at 24 hours, respectively. Neuronal NOS inhibition also increased blood-flows in males but not in females, and did not significantly change infarct volumes compared to their respective PBS-treated controls.

In conclusion, both nNOS and eNOS appear to play a key role in modulating arterial blood flow during ischemia mainly in male pups with subsequent modifications in infarct lesion.

298 ANTENATAL TAURINE SUPPLEMENTATION REDUCES CEREBRAL CELL APOPTOSIS IN FETAL RATS WITH INTRAUTERINE GROWTH RESTRICTION

doi:10.1136/archdischild-2012-302724.0298

[1]J Liu, [1]XF Wang, [2]HY Teng, [1]N Yang, [1]XT Ren. *[1]Department of Neonatology and NICU, Bayi Children's Hospital Affiliated with General Hospital of Beijing Military Command; [2]Department of Pediatrics, The Second Artillery General Hospital, Beijing, China*

Intrauterine growth restriction (IUGR) is closely associated with neonatal and prenatal morbidity, mortality and even with adult diseases. Term infants with IUGR have a five- to seven-fold risk of developing cerebral palsy, compared with gestational age-matched infants with normal birth weights. Our previous study showed that antenatal supplementation of taurine can improve brain ultrastructure of fetal rats with IUGR, but the mechanism remains unclear. This paper was to explore the effect of antenatal taurine supplementation on cerebral apoptosis and glial cell line-derived neurotrophic factor (GDNF)-cysteinyl aspartate specific (caspase-3) in fetal rats with IUGR. Fifteen pregnant rats were randomly divided into 3 groups: control group, IUGR and IUGR+antenatal taurine supplements. Taurine was added to the diet of the taurine group at a dose of 300 mg/kg·d from 12 days after conception until natural delivery. Two fetal rats were chosen in every litter. brain cellular apoptosis was detected using TUNEL, and the changes in protein expression of GDNF and caspase-3 using immunohistochemistry. The results showed that (1)the counts of apoptotic brain cells in the control group, IUGR group and IUGR with antenatal taurine supplementation group were (0.28±0.57)%, (15.30±5.96)%, (9.36±3.92)%, respectively. (2) The expressions of GDNF in three groups respectively were (93.56±6.73), (120.36±6.23) and (139.56± 5.28) (F= 492.56). (3) The expressions of caspase-3 in three groups respectively were (7.51± 2.31), (151.33±24.41) and (37.29±11.27) (F=128.18. Antenatal taurine can significantly decrease brain apoptosis, the mechanism maybe through increasing the expression of GDNF and decreasing the expression of caspase-3. This work was supported by Natural Science Foundation of China (81170577).

299 PRE-084, A SIGMA-1 RECEPTOR LIGAND, PROTECTS AGAINST EXCITOTOXIC PERINATAL BRAIN INJURY IN NEWBORN MICE

doi:10.1136/archdischild-2012-302724.0299

[1]E Griesmaier, [1]A Posod, [1]MJ Gross, [1]V Neubauer, [1]K Wegleiter, [2]M Hermann, [1]M Urbanek, [1,3]M Keller, [1]U KiechlKohlendorfer. *[1]Department of Paediatrics IV, Division of Neonatology; [2]Department of Anaesthesiology, Innsbruck Medical University, Innsbruck, Austria; [3]Department of Paediatrics, Children's Hospital Passau, Passau, Germany*

Background Excessive glutamate release followed by N-methyl-D-aspartate receptor (NMDAR) activation displays an important cascade in the pathophysiology of perinatal brain injury. We have previously shown that dextromethorphan, a low-affinity NMDAR antagonist, is neuroprotective in an animal model of neonatal excitotoxic brain injury. Of interest, dextromethorphan also shows agonistic properties at the sigma-1 receptor (σ1R). Sigma-1 agonists have given beneficial results in animal models of adult brain injury.
Aim of the study To evaluate the effect of the selective σ1R agonist 2-(4-morpholinethyl) 1-phenylcyclohexanecarboxylate (PRE-084) in neonatal excitotoxic brain injury.
Results A single intraperitoneal injection of 0.1 μg/g (low dose) or 10 μg/g (high dose) bodyweight (bw) PRE-084, given 1 h after the excitotoxic insult, significantly reduced lesion size in cortical gray matter 24 h and 120 h after the insult. Repetitive injections of 0.1 μg/g PRE-084 proved to be equally effective. PRE-084 treatment resulted in a decrease in cell death indicated by reduced TUNEL positivity and caspase-3 activation. PRE-084 reduced the number of isolectin B4-positive, activated microglial cells. Quantitative real-time PCR analysis showed no effect on σ1R gene expression at 1, 4, 8, 12, 24 and 48 h after intracranial ibotenate injection compared to healthy controls. *In vitro* PRE-084 protected against glutamate-induced morphological and functional changes in primary hippocampal neurons.
Conclusion We demonstrate that systemic treatment with the highly selective σ1R agonist PRE-084 protects against NMDAR-mediated excitotoxic brain damage.

300 CIRCULATING PROGENITOR CELLS IN PRETERM NEONATES WITH CNS INJURY - A PRELIMINARY REPORT

doi:10.1136/archdischild-2012-302724.0300

[1]N Efstathiou, [2]G Kyriazis, [3]D Bougiouklis, [1]V Drossou, [1]V Soumbasi. *[1]1st Neonatal Department, Ippokratio General Hospital; [2]Immunology Department, Papanikolaou General Hospital, Aristotele University of Thessaloniki; [3]Biologist, Specialist in Flow Cytometry, Thessaloníki, Greece*

Background and Aims The assumption that the circulating progenitor cells participate in a chemotactic way in the endogenous regeneration effort after damage of body tissues is controversial and the exact type of the cells involved remains unknown, especially when referring to damages of the Central Nervous System (CNS). We assume that preterm neonates who undergo CNS injury respond in a similar way, and we investigate the progenitor cell populations that might be related to the devastating event.
Methods 23 preterm newborns were enrolled (gestation age ≤32weeks). 10 of them undergo severe perinatal stress with metabolic acidosis and developed CNS injury (IVH III or higher, PVL or infarct), whereas 13 of them were assumed as controls with no obvious CNS injury. Peripheral blood was collected at days 1, 3, 9, 18 and 45 after birth and analyzed using flow cytometry. Cell populations of interest were EPCs (Endothelial progenitor cells, CD34+/CD133+/CD184+), HSCs (Hematopoietic stem cells, CD34+/CD184+/CD45+) and VSELs (Very Small Embryonic-Like SCs, CD34+/CD184+/CD45-).
Results EPCs were significantly increased in the group with CNS injury at days 1.9 and 18 and VSELs were marginally increased at day 1 and significantly at day 9. HSCs showed no specific variation.
Conclusion Circulating progenitor cells seem to play a role in the endogenous regeneration effort. Enhancing this effort might prove to be a good therapeutic practice in the future, whereas delineation of the timeframe of this effort would be essential. Larger studies are needed, as well as correlation with chemoattractants and longterm outcome is necessary.

301 HYPERACTIVITY AND DISTURBED MOTOR COORDINATION IN ADOLESCENT MICE AFTER NEONATAL EXPSOURE TO HYPEROXIA

doi:10.1136/archdischild-2012-302724.0301

[1]T Schmitz, [1]S Endesfelder, [2]MC Reinert, [3]S Müller, [2]D Liebetanz, [1]C Bührer. *[1]Department of Neonatology, Charité Universitätsmedizin Berlin, Berlin; [2]Neurophysiology, Georg-August-Universität, Göttingen; [3]Berlin Center for Stroke Research, Charité Universitätsmedizin Berlin, Berlin, Germany*

Objective A small fraction of children born very preterm have overt cerebral palsy but many of them display subtle deficits in motor coordination, balance, and attention-deficit/hyperactivity disorder-like behavior. In the immature brain, the sudden increase of oxygen tension after birth amounts to hyperoxia, and experimental hyperoxia causes wide-ranging cerebral changes in neonatal rodents.
Methods Newborn mice were exposed to 48 h of hyperoxia (80% O_2) from P6 to P8, and motor activity in running wheels was tested starting at adolescent age P30. Thereafter, from P44 to P53, regular wheels were replaced by complex wheels with variable crossbar positions to assess motor coordination. To determine white matter diffusivity, MRI with diffusion tensor imaging was performed in the corpus callosum in mice after hyperoxia at ages P30 and P53 in comparison to control animals always kept in room air.
Results Mice after neonatal hyperoxia had significantly higher values for maximum velocity and mean velocity in regular wheels than did control animals ($P<0.05$). In contrast, the motor challenge of the complex running wheels caused a greated decrease of maximum velocity in mice previously exposed to hyperoxia than in controls ($P<0.05$). Lower fractional anisotropy and higher radial diffusivity were observed in the corpus callosum of P30 and P53 mice after neonatal hyperoxia compared to control mice.
Interpretation Newborn mice exposed to hyperoxia display hyperactivity, motor coordination deficits, and impaired white matter diffusivity at adolescent and young adult ages.

302 SEIZURE BURDEN AND NEUROBEHAVIORAL SCORES AFTER THERAPEUTIC HYPOTHERMIA IN THE NEWBORN PIGLET

doi:10.1136/archdischild-2012-302724.0302

[1]X Fan, [2]C Peeters-Scholte, [1]N Ward, [1]PB Colditz, [1]ST Bjorkman. *[1]Perinatal Research Centre, UQ Centre for Clinical Research, The University of Queensland, Brisbane, QLD, Australia; [2]Neurophyxia B.V, Den Bosch, The Netherlands*

Background Therapeutic hypothermia (TH) is standard of care in newborns with hypoxic-ischemic encephalopathy (HIE). Although the predictive value of amplitude-integrated EEG (aEEG) after HIE has been studied, the predictive value of aEEG during TH remains to be established.
Aim To study aEEG characteristics and timing of recovery of neurobehavior in a newborn piglet model of HIE following TH.
Methods Newborn piglets (N=14) were subjected to 30 min hypoxia-ischemia and survived to 72h. Animals were randomly assigned to hypothermia (N=8) or normothermia for 24h after hypoxia-ischemia (N=6). aEEG was continuously recorded until ~40h post-insult and at 48 and 72h post-insult. Background pattern aEEG and presence of seizures were analysed. Neurobehavior was scored from 40 until 72h post-insult.
Results In hypothermic piglets aEEG background pattern recovered to continuous low voltage (CLV) within 2h post-insult until 36h post-insult. Normothermic piglets recovered within 2h post-insult to continuous normal voltage (CNV) until 36h, where there was a decrease in background pattern to CLV. aEEG recovered to CNV in both groups by 72h post-insult. Seizures were recorded in