Coupling of cerebral phosphoethanolamine and nucleotide triphosphate levels and mitochondrial-respiration modulation during perinatal "secondary energy failure"

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Objective. Phosphoethanolamine concentration ([PE]) is enigmatically high in fetal and neonatal brain (1,2): [PE] declines during postnatal maturation (2). In addition to constituting a phospholipid precursor, PE also modulates mitochondrial respiration (3). After cerebral hypoxia-ischaemia (HI) phosphorus magnetic resonance spectroscopy (31P MRS) often reveals resolution of the acute energy-deficit: however, phosphocreatine (PCr) and nucleotide triphosphate (NTP; mainly adenosine triphosphate (ATP)) later fall again and inorganic phosphate (Pi) increases - an unfavourable phenomenon termed "secondary energy failure" (SEF) (4). We aimed to further elucidate the metabolic role of PE during perinatal SEF.

Methods. Thirty-three healthy normothermic piglets aged <24 hr were studied: 27 endured HI (bilateral common-carotid occlusion & inspired oxygen fraction 0.12 for ~1 hr); 6 were controls. Insulted piglets were assigned to mild, moderate, or severe SEF according to the minimum NTP level during SEF (5). 31P MRS used: a 7-Tesla Biospec Avance (Bruker, Germany); a 25-mm surface coil on the intact scalp; single-pulse acquire; 10 s repetition time; 384 free induction decays summed. Results were compared by Mann-Whitney U test with Bonferroni correction.

Results. Spectra were of quality adequate to resolve PE and phosphocholine (PCh; Fig. 1). Severe-SEF [PE]/[EPP] (EPP = exchangeable phosphate = Pi + PCr + 3NTP) fell below controls 21-41 hr after HI (lowest p 0.006) but then recovered (Fig. 2): however, [PE]/[NTP] remained almost constant despite ~45% [NTP]/[EPP] decline (Fig. 3).

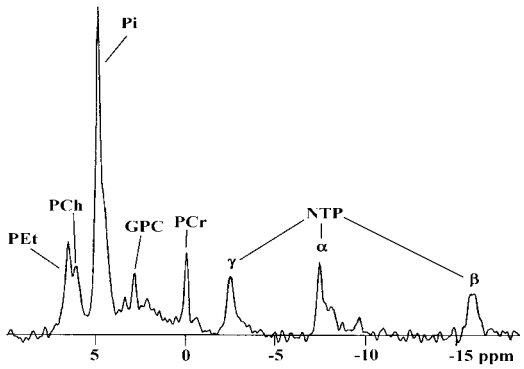

Fig. 1. A severe-SEF spectrum 41 hr after HI displays good resolution between PE and PCh.

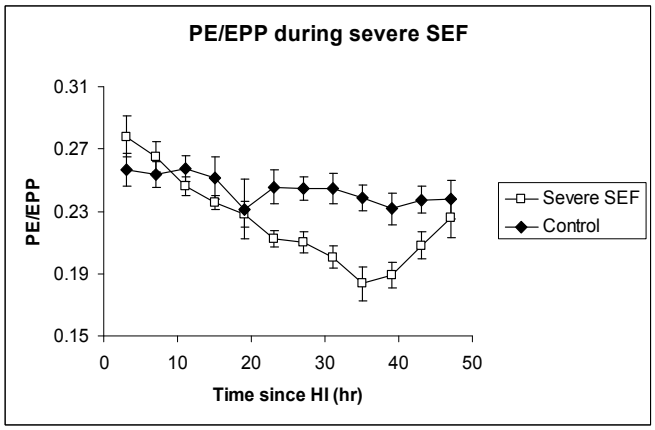

Fig. 2. Between 21 hr and 45 hr after HI severe-SEF [PE]/[EPP] (mean ±SEM) was less than control.

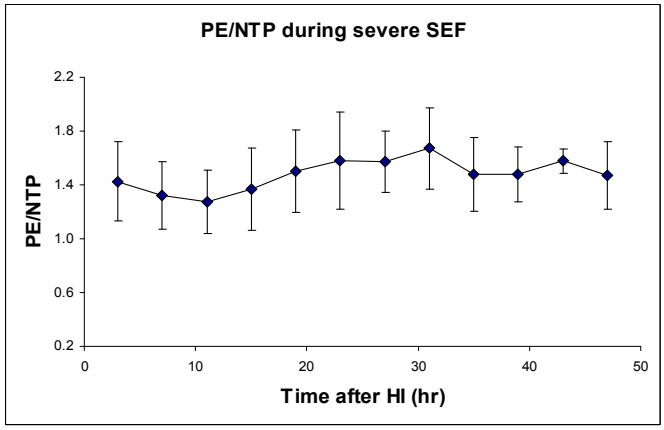

Fig. 3. [PE]/[NTP] (±SD) after HI in severe-SEF piglets. Despite [NTP]/[EPP] falling to ~55% of baseline, [PE]/[NTP] was almost constant suggesting coupling between [PE] & [NTP].

References.
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Conclusions. The [PE]/[NTP] constancy despite [NTP]/[EPP] decline suggested strong coupling between PE and NTP during SEF. In immature rat brain [PE] fell 14-72 hr after HI (6): timing similar to that in our piglets. Rat-liver [PE] reduction increases mitochondrial respiration (3): reduced ATP in cells stressed during SEF would inhibit ethanolamine phosphokinase activity resulting in [PE] reduction and mitochondrial stimulation. Hence, reduced [PE] after HI may constitute a servo mechanism stimulating respiration of, and ATP generation by, surviving mitochondria. High neonatal [PE] may be an intrinsic factor evolved to counter mammalian cerebral birth trauma.