Docosahexaenoic acid (DHA) significantly reduces oxidative stress after hypoxia-ischemia in newborn piglets

Marianne Ullestad Huun¹, MD, PhD student

Håvard T. Garberg¹, Javier Escobar¹,², Max Vento²,
Ola Didrik Saugstad¹ & Rønnaug Solberg¹

¹Department of Pediatric Research, Institute of Surgical Research, Oslo University Hospital Rikshospitalet, Oslo, NORWAY;
²Neonatal Research Unit, Health Research Institute Hospital La Fé, Valencia, SPAIN;
Background

- Hypoxic ischemic encephalopathy (HIE) is a major cause of newborn death and long term complications.
- Worldwide, 10–60% of infants who develop HIE will die and at least 25% of the survivors will have long-term neurodevelopmental sequelae.
- Therapeutic hypothermia is the only established neuroprotective treatment, mostly effective in mild and moderate cases of HIE, to a lesser extent the severe.
- Search for adjuvant therapies.
Objective

• We wanted to assess the effect of docosahexaenoic acid on oxidative stress after hypoxia ischemia in newborn piglets through measuring degradation products of lipid peroxidation.

• Is there an augmented effect of hypothermia?
Docosahexaenoic acid (DHA)

- Long-chain ω-3 polyunsaturated fatty acid, C22:6 n-3
- Cold-water fish and marine foods
- Accumulates during pregnancy to meet the greater substrate need in the 3rd trimester corresponding to neuron growth.
DHA location

• Especially found in lipid bilayer membranes of brain grey matter and retinal membranes.
• Component of myelin.
• Modulator of lipid peroxidation, apoptosis and inflammation
Neuroprotective properties

- Exact mechanisms not known
- H/I: DHA → Neuroprotectin D1 which exerts neuroprotective effects in the cell.
- Our group has previously shown DHA to be neuroprotective in a piglet model of H/I.³

http://www.asbmb.org/asbmbtoday/asbmbtoday
Lipid peroxidation

• Gold standard of measuring oxidative stress

• The degradation products can be measured in urine, easy access.

• Types of lipid peroxidation:
  1. By free radical oxidation like the hydroxyl group
  2. Non-enzymatic oxidation like through ozone or singlet oxygen
  3. Enzymatic reaction through lipoxygenase or cyclooxygenase
Lipid peroxidation

Iso-Prostanes: Most reliable marker of oxidative damage in humans.
The Neuroprostanes and Neurofuranes are sensitive and specific markers of neuronal damage. \(^2,^4\)
Experimental method

1. Randomisation

2. Randomisation

DHA 5 mg/kg at 210 min

9.5 h stabilisation 21 % O2

Tissue harvesting

H

H + DHA

HHypoT

HHypoT + DHA

Control
No hypoxia N =6

SHAM

Surgery. 1h stabilization.

Hypoxia
BE<20, MABP>20mmHg

Hypoxia N=12

Hypoxia DHA N=12

Hypoxia Hypothermia N=12

Hypoxia Hypothermia DHA N=12

Urine harvested at 210 min and at end of study through bladder tap.
• Non-parametric statistics
• There were no significant differences between the groups at 210 minutes, \( p=0.24 \)
• Neuroprostanes were significantly downregulated in the DHA groups (\( p=0.018 \)) at end of study.
• No significant differences were found between groups in Isoprostanes, Isofuranes or Neurofuranes.
Conclusion

- DHA significantly reduces oxidative stress after hypoxia ischemia in newborn piglets measured by degradation products of lipid peroxidation in urine.
- DHA seems to significantly augment hypothermia in this piglet model.
References


