Early-life iron excess causes iron overload and enhances purine degradation via activation of xanthine oxidase in developing hippocampus in a nursing piglet model

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INTRODUCTION & HYPOTHESIS

- In many developed countries, prophylactic iron (supplements and fortified formula) is commonly given to infants older than 4–6 months without a screening test for iron status.
- Recent study showed that iron regulatory mechanism (hepcidin – ferroportin axis) is not functionally mature in suckling mouse pups (Frazer et al., 2017).
- There is a growing concern over the neurological effects of dietary iron overexposure in iron-replete infants (Hare et al., 2018).
- Nursing piglet is a promising preclinical model to investigate the impact of iron overload on neurodevelopment and cognitive function in infants.
- We hypothesize that iron over-supplementation causes iron overload, alters hippocampal metabolome and affects sociability in nursing piglets.

MATERIALS & METHODS

- EXPERIMENTAL DESIGN:
  - Twenty-four newborn piglets were randomly assigned to treatments from postnatal day 2 to 21. Piglets were nursed by sow throughout the study.
  - Treatments:
    - CON: I.m. injection iron dextran on PD2 (100 mg iron)
    - NON: No iron (saline solution)
    - MOD: Moderate iron, 10 mg/kg BW-d
    - HIG: High iron, 50 mg/kg BW-d

ANALYSES

- Tissue iron: Atomic absorption spectrometry
- Non-targeted metabolomics (HIG vs. NON): GC-TOF MS for primary metabolites (West Coast Metabolomics Center, NIH)
- Gene and protein expression: RT-qPCR and western blot
- Activity of xanthine oxidase: ELISA (Cayman Chemical)
- Behavioral analysis: EthoVision XT (Noldus)

RESULTS

- Excess iron resulted in iron overload in the liver and hippocampus.
- The hippocampal iron content positively correlated with the hepatic iron.
- Excess iron diminished socialization with novel conspecifics.
- Excess iron increased purine degradation and enhanced mRNA and activity of xanthine oxidase in the hippocampus (q < 0.2).

CONCLUSIONS

- Dietary Iron overexposure caused iron overload in the liver and hippocampus in a nursing pig model.
- Duodenal ferroportin expression was unresponsive to the increase of hepcidin.
- Hippocampal iron overload shifted purine flux towards degradation via activation of xanthine oxidase, which may contribute to the increased lipid peroxidation.
- Iron overload impaired myelination in the hippocampus and diminished interaction with social novelty.