The Specific Role of Iron in Early Brain Development

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Why Worry About Iron Deficiency?

2 billion people world-wide are iron deficient (WHO)
- 30-50% of pregnant women

Every cell/organ system needs iron for proper development and subsequent function

Iron deficiency anemia is associated with clinical symptoms
- Due to tissue level ID
- Symptoms occur prior to anemia because iron is prioritized to red cells before the brain when iron supply does not meet iron demand (Georgieff et al, 1992; Petry et al, 1992)

- ANEMIA IS A POOR SCREEN FOR RISK OF BRAIN ID

Main reason to worry is the effect on the developing brain
- Cognitive and motor effects
- Some temporary (while ID), others long-term (after iron repletion)
Why Worry about Iron and Neurodevelopment?

3 pediatric populations are at high risk for ID:

1) Fetus and Newborn
2) Children 6 months --> 2.5 years
3) Teenage girls

All show a wide range of motor and cognitive deficits while ID

Unlike in adolescence, early-life ID results in neurodevelopmental alterations that persist despite iron repletion
Iron: A Critical Nutrient for the Developing Brain

• One of the most studied nutrients in brain development
• Iron is found in proteins involved in brain development and function
• Also directly regulates genes in the brain
Iron: A Critical Nutrient for the Developing Brain

- **Myelin** = fatty coating on nerves that mediates Speed of Processing
  - Critical period: 32 weeks gestation to 2 years

- **Energy** => complexity of brain structures, which in turn supports Learning and Memory
  - Critical period for hippocampus: 28 weeks gestation to 18 months

- **Dopamine** = mediates reward, affect, memory, motivation
  - Critical period: mid-gestation to 3 years
Concordant Studies of Short and Long-Term Effects on Myelin, Energy & Dopamine

**Human (>50 studies)**

- **Slower Speed of Processing**
  - While ID (Roncagliolo et al, 1998)

- **Reduced Learning and Memory**
  - While ID (Siddappa et al, 2004)
  - Long term (Riggins et al, 2009)

- **Hesitancy, wariness, poor social interaction**
  - While ID (Lozoff et al, 2008)
  - Long term (Lukowski et al, 2010)

- **Poorer motor coordination**
  (Lozoff et al, 2008)

**Animal (>250 studies)**

- **Abnormal myelin fat and long-term myelin gene expression**
  (Ortega et al, 2004; Clardy et al, 2006)

- **Abnormal long-term hippocampal structure, synaptic plasticity, gene expression**
  (Carlson et al, 2009; Tran et al, 2009)

- **Abnormal midbrain and frontal lobe monoamine regulation**
  - While ID (Beard & Connor, 2003)
  - Long term (Unger et al, 2013)
Nutrient->Brain->Behavior Relationships: Why Timing of ID is Important

- Brain regions have different developmental trajectories

- Vulnerability of a region to ID is based on
  - **Timing** of when ID is likely to occur during the lifespan
  - Brain region **requirement** for iron at that time

- Behavioral changes seen with ID map onto those brain regions
The Effect of Timing of ID on Brain Development

Defines likely period of ID
Neurobehavioral Sequelae of Early Life ID in Humans: The Differential Effect of Timing

• Prenatal ID: (Siddappa et al, 2004; Amin et al, 2010; Nelson et al, in press; Insel et al, 2010)
  – Learning and Memory
  – Speed of Processing
  – Long-term Organizational Skills
  – Hyperactivity/Attention Deficits
  – Higher risk of Schizophrenia in Adulthood

• ID in Infancy: (For Review, see Grantham-McGregor, 2001; Walker et al, 2007; 2011; Lozoff, 2008; Lukowski, 2010)
  – Speed of Processing
  – Paucity of Movement
  – Sleep Disorders
  – Hesitancy/Wariness
  – Higher risk of Depression in adulthood
Is it Really the Lack of Iron? The Classic Rat IDA Dietary Model

• Strengths
  – Backbone of ID modeling for over 40 years (eg, Youdim, Dallman, Beard)
  – Models “the human condition” of ID anemia

• Limitations (same as in human studies)
  – Not able to define specific role of iron in neuron development and function
  – Confounds (many are same as human):
    • Anemia => Tissue Hypoxia Effects
    • Brain toxicity from uptake of other divalent metals (Zn, Cu, Mn, Pb)
    • Activation of stress response
Isolating the Role of Iron: Non-Anemic, Neuron Specific ID Mice:

**DMT-1 KO**
- *slc11a2* KO (exons 6-8)
- E18.5
- Hippocampus-specific
Why is this Important?

- Non-anemic ID is 3x more common than ID anemia
- Non-anemic brain ID in newborn humans reduces recognition memory (Siddappa, 2004)
- Non-anemic ID in toddlers reduces motor and affective domain function (Lozoff, 2008)
Summary

• Iron plays a critical role in early neurodevelopment

• Multi-layer investigations demonstrate that the behavioral deficits are due specifically to the lack of iron

• Early iron deficiency without anemia affects brain function

• ID brain/behavior alterations persist into adulthood

• Early detection of at risk infants is crucial for brain health

• Need new tools to detect pre-anemic iron deficiency