Nutrition and the Developing Brain

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Disclosure

In accordance with the Accreditation Council for Continuing Medical Education Standards, parallel documents from other accrediting bodies, and Annenberg Center for Health Sciences policy, the following disclosure has been made:

Michael K. Georgieff, MD
Research Support:
  Mead Johnson Nutrition – Brain Iron Deficiency
PRINCIPLES OF NUTRIENT-BRAIN INTERACTIONS
Early Nutrition and Brain Development: General Principles

• Nutrients regulate brain development during prenatal and postnatal life
• Rapidly growing brain in neonate
  – More vulnerable to damage
  – More amenable to repair

“Vulnerability outweighs plasticity”

(National Institutes of Health)
Early Nutrition and Brain Development: General Principles

Positive or negative nutrient effects on brain are based on:

**Timing, Dose and Duration of Exposure**

Kretchmer, Beard, Carlson

*(Am J Clin Nutr, 1996)*
Nutrients->Brain

• Brain is not a homogenous organ
  – Regions (cortex, hippocampus, striatum, cerebellum)
  – Processes (myelin, neurotransmitters)
• All have different developmental trajectories
• Vulnerability to a nutrient deficit is based on
  – When a nutrient deficit occurs
  – Region’s requirement for that nutrient at that time
Hippocampus

Human Brain Development

Neurogenesis in the Hippocampus

Experience-dependent synapse formation.

Synaptogenesis (3 months to 15-18 years?)

Adult Levels of synapses

Cell Migration (6-24 prenatal weeks)

Maturational (2 months to 3-10 years)

Receptive language (Broca's area)

Nervous system (caudate, amygdala)

Visual cortex (occipital cortex)

Auditory cortex

Sealing / hearing

Higher cognitive functions

Prefrontal cortex

Angular gyrus (Broca's area)

Production

Nutrients that Particularly Affect Early Brain Development and Later Adult Function

• Macronutrients
  – Protein\(^1,2\)
  – Fats (LC-PUFA)\(^1,2,3\)
  – Glucose\(^1,2\)

• Micronutrients
  – Iron\(^1,2,3\)
  – Zinc\(^1,2\)
  – Copper\(^1,2\)
  – Iodine (Thyroid)\(^1,2\)

• Vitamins/Cofactors
  – B vitamins (B6, B12\(^1\))
  – Vitamin A
  – Vitamin K
  – Folate\(^1,2,3\)
  – Choline\(^1,2,3\)

\(^1\)Exhibits critical/sensitive period for neurodevelopment
\(^2\)Early deficiency results in long-term dysfunction
\(^3\)Evidence for epigenetic mechanism
Nutrients and Brain Development: Processes Affected

• NEUROANATOMY
  – Neurons
    • Division (numbers)
    • Growth (size)
    • Development (complexity)
  – Supporting Cells
    • Oligos => Myelin
    • Astrocytes => Nutrient Delivery; Repair
    • Microglia => Trafficking

Nutrient examples: protein, fats, energy, iron, zinc, choline
Nutrients and Brain Development: Processes Affected

• NEUROCHEMISTRY (Neurotransmitters)
  • Concentration
  • Receptors
  • Reuptake
Nutrient examples: protein, iron, zinc, choline

• NEUROPHYSIOLOGY
  • Neuronal metabolism => Electrical activity of brain
Nutrient examples: glucose, protein, iron, zinc, choline
## Examples of Nutrients and Regional vs Global Perinatal Brain Effects

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Brain Requirement for Nutrient</th>
<th>Affected Areas</th>
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</thead>
<tbody>
<tr>
<td><strong>Protein-Energy</strong></td>
<td>Cell Proliferation&lt;br&gt;Cell Differentiation&lt;br&gt;Synaptogenesis&lt;br&gt;Growth Factors</td>
<td>Global Cortex&lt;br&gt;Hippocampus</td>
</tr>
<tr>
<td><strong>Iron</strong></td>
<td>Myelin&lt;br&gt;Dopamine&lt;br&gt;Energy</td>
<td>White Matter&lt;br&gt;Striatal-Frontal&lt;br&gt;Hippocampal-Frontal</td>
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<tr>
<td><strong>Zinc</strong></td>
<td>DNA&lt;br&gt;Neurotransmitter release</td>
<td>Autonomic NS&lt;br&gt;Hippocampus&lt;br&gt;Cerebellum</td>
</tr>
<tr>
<td><strong>LC-PUFAs</strong></td>
<td>Synaptogenesis&lt;br&gt;Myelin</td>
<td>Eye Cortex</td>
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</table>
DEVELOPMENTAL ORIGINS AND THE BRAIN
The Cost to Society

• Altered nutrient status in fetal and neonatal life can affect organ structure and function
  – Only during deficiency => Acute dysfunction
  – Beyond time of deficiency => Altered development & adult dysfunction

• The cost to society is from the long-term effects
  – Eradicating the iron, zinc and iodine deficiency would increase the world’s IQ by 10 points (Morris et al, *Lancet*, 2008)
Evidence for Long-Lasting Effects of Early Nutritional Status on Brain in Humans

• Outcomes of IUGRs (Strauss and Dietz, 1998)
  – Lower IQ
  – Poorer verbal ability
  – Worse visual recognition memory
  – 15% with “mild” neurodevelopmental abnormalities
  – 30% increased risk of schizophrenia (Eide et al, 2013)

• Fetal/postnatal iron deficiency and risk of
  – Schizophrenia (Insel et al, 2008)
  – Autism (Schmidt et al, 2014)
  – Depression/Anxiety (Lozoff et al, 2000)
  – Poorer executive function (Lukowski et al, 2010)
Two Major Theories Accounting for Long-Term Loss of Synaptic Plasticity

1. Residual structural deficits
   - Nutrient deficiencies during critical periods of development result in permanent structural change (Hensch, 2004; Carlson et al, 2009; Fretham et al, 2012; Callahan et al, 2013)
   - Neurobehavioral deficits relate to disordered neuronal structure (Jorgenson et al, 2005; Pisansky et al, 2013)
Two Major Theories Accounting for Long-Term Loss of Synaptic Plasticity

2. Altered regulation of synaptic plasticity genes through epigenetic modification of chromatin

Several fetal/neonatal nutritional conditions associated with brain epigenetic modifications in rodents

- **IUGR** (Ke et al, 2014; reviewed by Grissom & Reyes, 2013; Ke et al, 2010)
  - Generalized fetal malnutrition
    - Specific nutrients that are responsible have not been isolated
    - Disruption of hippocampal H4K20 me(1) (Ke et al, 2014)
  - Activation of GCRC (stress model) (Ke et al, 2010)
    - Stress alters BDNF DNA methylation

- **LC-PUFA status** (Tyagi et al, 2015)
  - DNA methylation of BDNF

- Methyl donors and DNA methylation
  - **Choline** (Reviewed by Zeisel, 2010, 2012)
  - **Folate** (Cho et al, 2013; Barua et al, 2014; Langie et al, 2013)

- **Iron deficiency** (Blegen et al, 2013; Tran et al, 2015)
  - Iron, anemia (hypoxia), or both
MACRONUTRIENTS

Why does the brain need protein and energy?

Effects of early protein-energy malnutrition
What the Brain Does with Protein

• DNA, RNA synthesis and maintenance
• Neurotransmitter production (synaptic efficacy)
• Growth factor synthesis
• Structural proteins
  – Neurite extension (axons, dendrites)
  – Synapse formation (connectivity)
IUGR: Experimental Evidence from Clinical Studies

• IUGR => Poor developmental outcome
  – verbal outcome
  – visual recognition memory
  – 6.8 point IQ deficit at 7 years (Strauss & Dietz, 1998)
  – dose responsive based on degree of IUGR
  – 15% with mild neurodevelopmental abnormalities

• Compounded by postnatal growth failure (prenatal + postnatal malnutrition) (Casey et al, 2006)
LONG CHAIN POLYUNSATURATED FATTY ACIDS

AKA “Fish Oils”
Docosohexaenoic Acid (DHA)
LC-PUFAs and Visual Development: Summary

• LC-PUFAs promote early visual development in **preterm infants** up to but not beyond that of human milk-fed infant (deficit repletion); no apparent long-term effect
  – Probably repleting lack of intrauterine accretion

• In **term infants**, sporadic findings or transient positive effects of supplementation on the visual system; little evidence for long-term effect
LC-PUFAs and Mental Development

• More consistent effect seen in preterms compared to terms
• Outcome measurements are short-term, general (MDI), and not generally predictive of later function
• Long-term studies - early acceleration may result in
  – No long-term advantage
  – Permanent advantage
• Studies are ongoing but are underpowered to draw conclusions about long-term efficacy
MICRONUTRIENTS AND EARLY BRAIN DEVELOPMENT
Worldwide Impact of Micronutrient Deficiencies

• Iron
  – 2 billion people (1/3 of world’s population) are iron deficient
  – Also causes low thyroid hormone state

• Zinc
  – 1.8 billion people are zinc-deficient
  – Usually comorbid with protein deficiency

• Iodine
  – 600 million people worldwide are deficient
  – I Deficiency => thyroid hormone deficiency => cretinism (global delays)
Neurodevelopmental Sequelae of Perinatal ID

• Term infants
  – GENERAL: Low neonatal iron stores (<76mcg/L) => poorer school age neurodevelopment (Tamura et al, 2002)
  – HIPPOCAMPUS: Cord ferritin <40 mcg/L => impaired recognition memory (Siddappa et al, 2004)
  – DOPAMINE: Iron deficient infants born to IDA mothers => altered temperament (Wachs et al, 2005)

• Preterm infants
  – GENERAL: Early iron supplementation => higher mental processing composite score at 5.3 years (Steinmacher et al, 2007)
  – MYELIN; SYNAPTOGENESIS: Ferritin <76 mcg/L at discharge => abnormal reflexes (Armony-Sivan et al, 2004)
  – MYELIN: Cord ferritin <76 mcg/L => slower central nerve conduction speeds (Amin et al, 2010)
Zinc Deficiency: Neurobehavioral Effects on Late Fetal Brain

• Fetuses of zinc deficient mothers demonstrate:
  – Decreased movement
  – Decreased heart rate variability
  – Altered Autonomic Nervous System stability

• Postnatally, fetal zinc deficiency causes:
  – Decreased preferential looking behavior (more random looks and equal looking times)
  – No difference in Bayley Scales of Infant Development

Suggests fetal ANS, cerebellar and hippocampal effects

No studies of neurodevelopmental outcomes of preterm infants as a function of Zn status
IODINE DEFICIENCY

Why does the brain need iodine?
Effects of perinatal iodine deficiency
Iodine Deficiency and Brain Biology

- Iodine’s primary role is in thyroid hormone
- Low iodine levels lead to hypothyroidism
  - No direct role of I in brain development
- Lower brain weight and brain DNA
- Thyroid sensitive promoter regions
- Reduced dendritic arborization
- Reduced myelination (fatty acid synthesis effect)
- Reduced synaptic counts
Iodine Deficiency: Behavioral Effects

- Timing of deficiency is critical
- Fetal effects are much more profound
  - Greatest effect is I deficiency during first 12 weeks
  - Reduced head size
  - Global mental deficits/not reversible
- Mostly during childhood due to lack of iodine in diet
  - Reduced verbal IQ=> global effect on cell division?
  - Decreased reaction time (motor effect)=> due to delayed myelination or reduced synaptogenesis?
  - Older children=> effects reversible, suggests metabolic effect (slower processing) rather than anatomic effect
Nutritional Strategies to Protect the Developing Brain

• Preconception
  – Weight management in women of childbearing age
    • Reduction of obesity
  – Nutrient sufficiency
    • Not just macronutrients, but micronutrients
    • 25-40% of women of CBA are iron deficient
      – Not just a developing world problem
Nutritional Strategies to Protect the Developing Brain

- **Gestation**
  - **Blood pressure control**
    - 75% of IUGR in USA is due to maternal hypertension or preeclampsia during pregnancy
    - 10% of population suffered IUGR
      - 50% are iron deficient at birth; all have protein malnutrition
  - **Blood sugar control**
    - 10% of pregnancies complicated by maternal diabetes (pregestational or gestational)
    - 65% of infants of diabetic mothers are iron deficient at birth
  - **Stress reduction**
    - Maternal stress -> fetal stress -> abnormal fetal brain development (and iron deficiency)
  - **Weight management**
    - Reduction of obesity
  - **Nutrient sufficiency**
    - Prenatal vitamins including iron
    - LC-PUFA (DHA) supplementation
Clinical Implications

• Postnatal (especially 0-3 years)
  – Nutrition
    • BREAST MILK
      – Breastfed babies are smarter, have less obesity, less infections
    • LC-PUFA (DHA) supplementation of formula-fed babies
    • Maintain iron and zinc sufficiency
    • Screen for thyroid status
      – In China, this means iodine and selenium nutritional status
  – Avoidance/reduction of toxic stress
    • Toxic stress alters brain development
    • Toxic stress alters how critical nutrients are accreted
  – Reduce infectious burden
    • Infection and inflammation alter brain development during critical periods of growth
Summary

• Certain nutrients have high impact on early brain development
  – Protein, fats, iron, zinc, iodine, vitamins A, folate
  – More impact in fetal and neonatal time period

• Nutrient effects depend on timing, dose and duration
  – Timing in terms of brain development process
  – Timing in terms of prevalence of nutrient deficit in population
  – Earlier identification and correction is essential!
    • Don’t wait to start TPN, iron, etc!

• Little evidence currently for enhancement of brain development in typically developing humans