Nutrition and the Developing Brain

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Disclosure

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Michael K. Georgieff, MD

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Mead Johnson Nutrition – Brain Iron Deficiency

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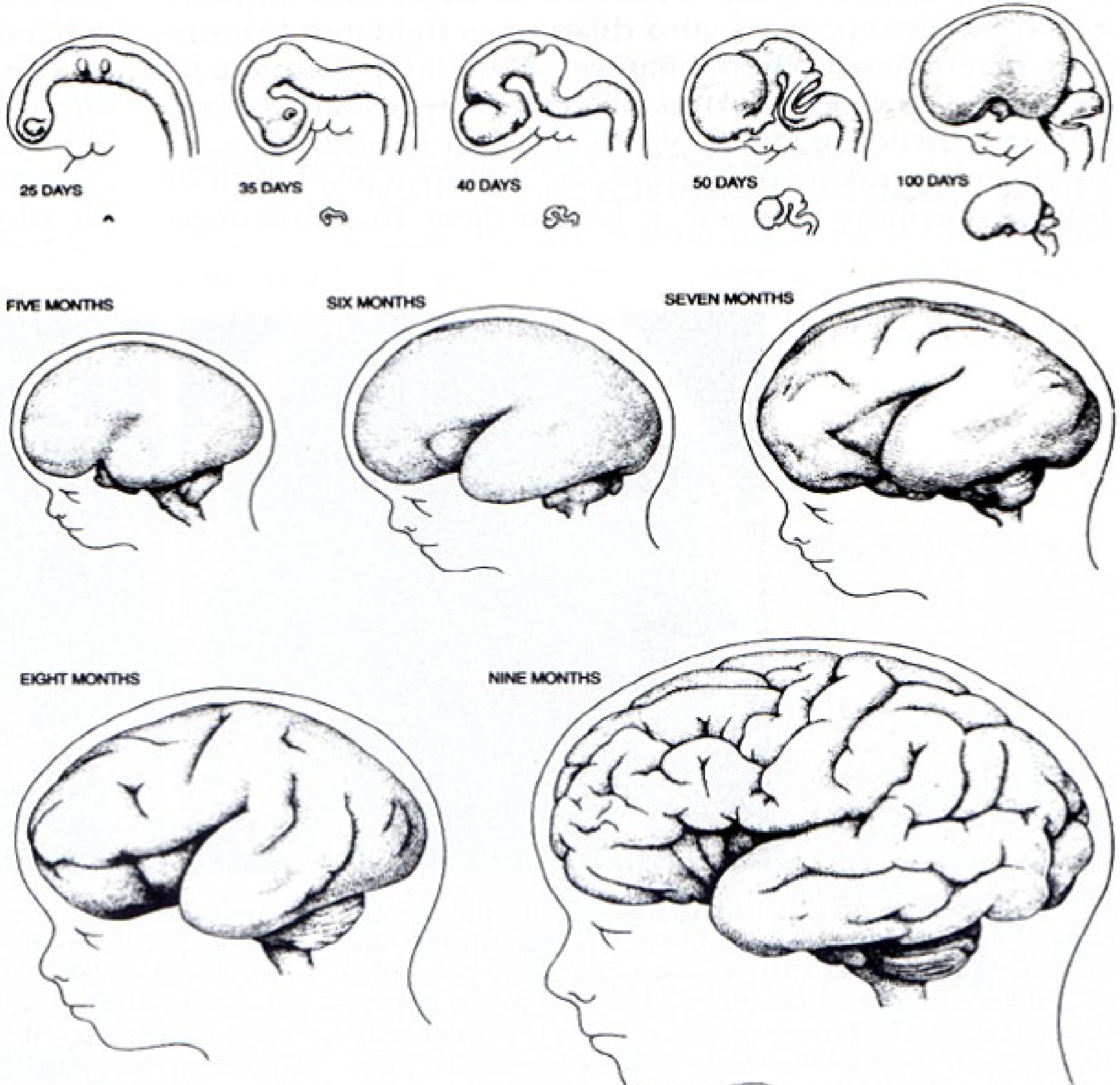

Cowan MW. The development of the brain. *Sci Am.* 1979.241, p.106. Reproduced with permission from *Scientific American*.

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)

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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

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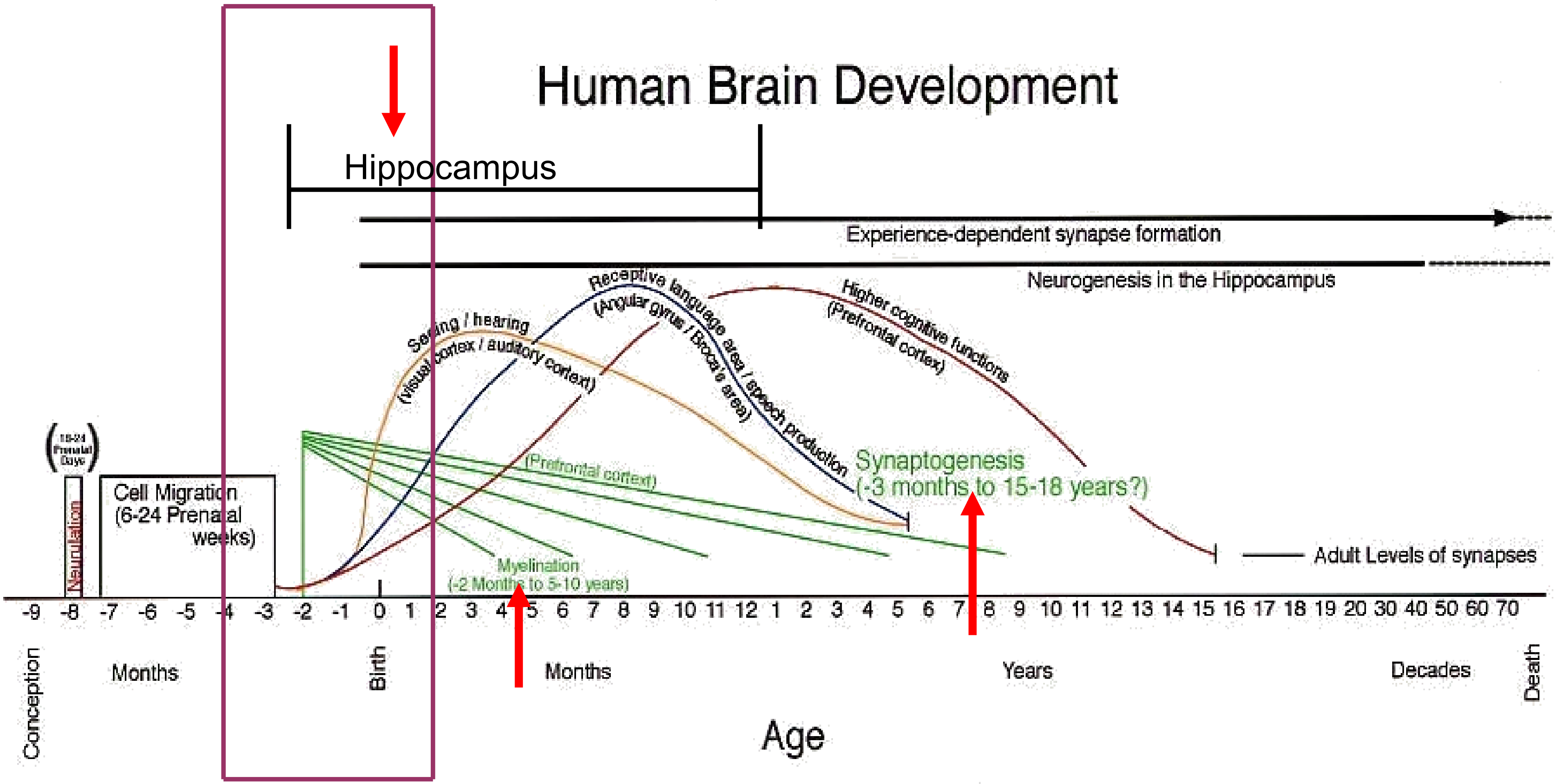

Thompson RA, Nelson CA. *Am Psychol.* 2001;56:5-15. Reproduced with permission from APA.

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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

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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

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Examples of Nutrients and Regional vs Global Perinatal Brain Effects

Nutrient	Brain Requirement for Nutrient	Affected Areas
Protein-Energy	Cell Proliferation Cell Differentiation Synaptogenesis Growth Factors	Global Cortex Hippocampus
Iron	Myelin Dopamine Energy	White Matter Striatal-Frontal Hippocampal-Frontal
Zinc	DNA Neurotransmitter release	Autonomic NS Hippocampus Cerebellum
LC-PUFAs	Synaptogenesis Myelin	Eye Cortex

DEVELOPMENTAL ORIGINS AND THE BRAIN

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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**
  - Intrauterine growth restriction increases adult cardiovascular risk by 25% and reduces IQ by 7 points (Curhan et al, *Circulation*. 1996; Strauss & Dietz, *J Pediatr.* 1998)
  - Eradicating the iron, zinc and iodine deficiency would increase the world's IQ by 10 points (Morris et al, *Lancet*, 2008)

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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)

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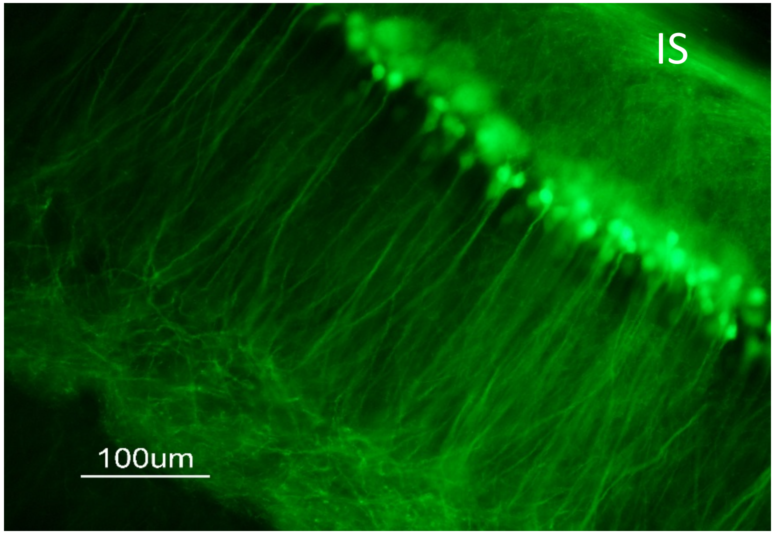
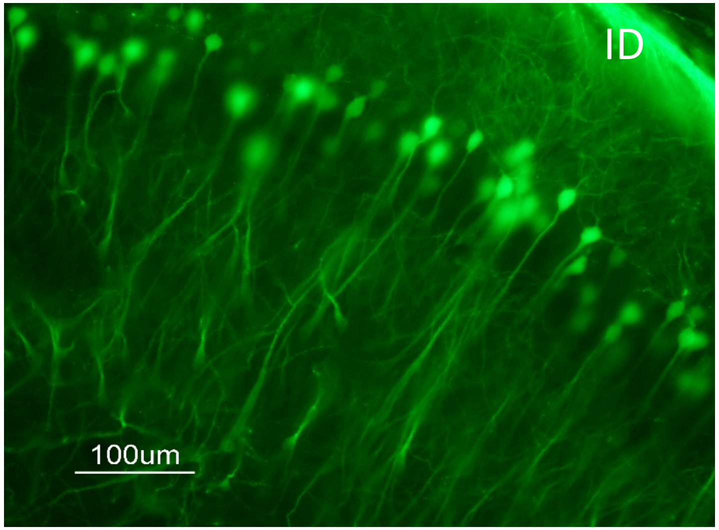
Two Major Theories Accounting for Long-Term Loss of Synaptic Plasticity

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)





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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)

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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

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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)

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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)

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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

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IODINE DEFICIENCY

Why does the brain need iodine?
Effects of perinatal iodine deficiency

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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

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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

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Nutritional Strategies to Protect the Developing Brain

- Preconception
  - Weight management in women of child-bearing 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

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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

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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

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