Part 1

- Nutrition & Brain Development
- Gut-Brain Axis
- Chronic Inflammation
- Neuroinflammation

Part 2

- Nutripsychiatry
- Depression
- Anxiety
- ADHD
- Autism
- Anti-Inflammatory Diet

Overview

First 1000 days

- Conception through 2 years of age

Goyal et al. 2015. PNAS. 112:14105.
## Nutrition & Brain Development

<table>
<thead>
<tr>
<th>Neurologic Process</th>
<th>Cell Type</th>
<th>Function</th>
<th>Nutrients/Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomy</td>
<td>Neuron</td>
<td>Neurogenesis, differentiation &amp;</td>
<td>Protein, carbohydrates, iron, copper, zinc, long chain polyunsaturated fatty acids, iodine, vitamin A, vitamin B6, vitamin D, vitamin C</td>
</tr>
<tr>
<td></td>
<td>Oligodendrocyte</td>
<td>Myelination</td>
<td>Protein, carbohydrates, iron, iodine, selenium, zinc, vitamin B6, vitamin B12</td>
</tr>
<tr>
<td>Chemistry</td>
<td>Neuron &amp; Astrocyte</td>
<td>Neurotransmitter synthesis, receptor,</td>
<td>Protein, iron, iodine, copper, zinc, selenium, choline, vitamin B6, vitamin D</td>
</tr>
<tr>
<td>Physiology</td>
<td>Neuron &amp; Oligodendrocyte</td>
<td>Electrical efficiency</td>
<td>Glucose, protein, iron, iodine, zinc, choline, copper</td>
</tr>
</tbody>
</table>

### Nutrition & Brain Development

- **Protein**
  - Restriction leads to smaller brains, fewer neurons, simpler neuron architecture and less neurotransmitters

- **Lipids**
  - Essential fatty acids are most important including:
    - Omega-3 DHA & omega-6 arachidonic acid
    - Required for neurogenesis, synaptogenesis & neurotransmitter synthesis
    - Eyes & prefrontal cortex are most likely to be targets of omega-3 supplementation

- **Iron**
  - Required for myelination & neurotransmitter synthesis
  - Bioavailability in utero is dependent on maternal stress levels, which control hepcidin concentration

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Goyal et al. 2015. PNAS. 112:14105.
Iron Transport

Hepcidin binds ferroportin, preventing iron from crossing basolateral membrane. Iron is stuck in the enterocyte.

Nutrition & Brain Development

Iron
- Deficiency:
  - Slower central nerve conduction, loss of cytochrome c oxidase activity in brain, impaired social-emotional behavior
  - Risks: short gestation, excessive zinc, timing of umbilical cord clamping, maternal factors, faster growth, breastfeeding
- Excess:
  - Cognitive impairment, oxidative stress
  - Risks: transfusion, inappropriate infant formulas, sex

Prevention of Iron Deficiency Anemia – Clinical Practice Guidelines

- Complete or partially breastfed infants
  - Supplemented at 4 months of age (1 mg/kg/day)
  - Supplementation continued until iron-containing foods introduced

- Complete or partially preterm breastfed infants
  - Supplemented at 1 month of age (2 mg/kg/day)
  - Supplementation continued until iron-containing foods introduced

- Formula-fed infants
  - No supplementation is necessary

- Toddlers not meeting intake
  - Liquid supplements until 3 years
  - Chewable multivitamins >3 years

RDAs
- 0-6 mo = 0.27 mg/d
- 6-12 mo = 11 mg/d
- 1-3 yr = 7 mg/d
Nutrition & Brain Development

**Iodine**
- Prenatal deficiency causes deficits in neurogenesis, neuronal migration, glutamatergic signaling, and brain weight
- Postnatal deficiency leads to impaired dendritogenesis, synaptogenesis, and myelination

**Zinc**
- Required for normal neurogenesis and migration, myelination, synaptogenesis, regulation of neurotransmitter release
- Early zinc deficiency leads to poorer learning, attention, memory and mood

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**Zinc Deficiency**

**Manifests as:**
- Altered immune function
- Increased cytokine production
- Increased intestinal permeability
- Villous atrophy
- Food allergy & eczema

**Diagnosed using:**
- Serum zinc concentration
- Dietary intake of zinc and phytate
- Stunting of growth

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**Nutrition & Brain Development**

**Methyl Donors**
- Folate, vitamin B6, vitamin B12, betaine, choline
- Prenatal deficiency exacerbates effect of stress on offspring behavior
- Deficiency leads to imbalance in hypothalamic-pituitary-adrenal (HPA) axis
<table>
<thead>
<tr>
<th>Phyla</th>
<th>Class</th>
<th>Genus Ex.</th>
<th>Species Ex.</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Firmicutes</td>
<td>Bacilli</td>
<td>B. acidophilus</td>
<td>L. acidophilus, L. delbrueckii, L. rhamnosus</td>
<td>Gram+, rod, obligate anaerobe, produce lactic acid, produce GABA &amp; acetylcholine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clostridium</td>
<td>C. perfringens, C. difficile</td>
<td>G-, rod, obligate anaerobe, produce toxin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ruminococcus</td>
<td>R. spp.</td>
<td>G+, cocci, obligate anaerobe, digest cellulose, glucose, &amp; xylose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Streptococcus</td>
<td>S. salivaris, S. intermedius</td>
<td>G+, spherical, facultative or obligate anaerobe, produce serotonin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Staphylococcus</td>
<td>S. Epidermidis</td>
<td>G+, clusters of cocci, facultative anaerobes</td>
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<tr>
<td></td>
<td></td>
<td>Bacteroidetes</td>
<td>Bacteroides</td>
<td>G-, rod, obligate anaerobe</td>
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<td>Bifidobacterium</td>
<td>B. Longum, B. breve, B. bifidum</td>
<td>G+, branched rods, obligate anaerobe, produce lactic acid, able to use plant fiber for energy, produce GABA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Propionibacterium</td>
<td>P. spp.</td>
<td>G+, rods, facultative anaerobes, ferment glucose into lactic, propionic or acetic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enterobacteriaceae</td>
<td>Enterococcus</td>
<td>G-, rods, facultative anaerobes, produce serotonin &amp; lipo polysaccharides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Akkermansia muciniphila</td>
<td>A. muciniphila</td>
<td>G-, rods, strict anaerobes, able to live off of mucin</td>
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**Gut Microbiome**

**Actinobacteria**

**Proteobacteria**

**Verrucomicrobiaceae**

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**Potentially Harmful Bacteria**

**Potentially Beneficial Bacteria**

Production of enterotoxins

Production of short-chain fatty acids

Production of serotonin

Potential tumor marker
Prenatal Stress & Fetal Programming

- Cortisol is **inactivated** by 11-β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) during pregnancy
- Maternal cortisol is **inversely** linked to fetal brain growth

Maternal anxiety, stress, diet, increased methylation of 11β-HSD2

Decreased expression of 11β-HSD2

Increased fetal cortisol

Maternal Dietary Stress

- Calorie restriction
- Low protein
- High fat
- High sugar
- Low magnesium
- Low choline
- Low folate

Can cause silencing of 11β-HSD2 and other epigenetic changes
In Utero Environmental Stress

- Depression during pregnancy
- Diabetes in pregnancy
- Pregnancy anemia
- Smoke exposure in utero

Chemical Mediators in Inflammation

- Cytokines: Small proteins
- Lipid-derived compounds: Prostaglandins, thromboxanes & leukotrienes produced from omega-6 fatty acid
- Reactive oxygen species (ROS): Important signaling compounds at low concentrations

Inflammatory Cytokines

- Chemokines: Mediate chemotaxis
- Interferons: Interfere with viruses
- Interleukins: Activate other immune cells
- Lymphokines: IL-1, IL-6
- Tumor necrosis factor: Secreted by lymphocytes
- Able to stimulate apoptosis
Inflammatory Lipids

- Arachidonic acid (20:4n-6)
- 2 series prostaglandins (PG)
  - Prostaglandins (PG)
  - Thromboxanes (TX)
- 4 series leukotrienes (LT)

Reactive Oxygen Species (ROS)

- Free radicals
  - Superoxide (O₂•⁻)
  - Hydroxyl radical (•OH)
- Nonradicals
  - Hydrogen peroxide (H₂O₂)
  - Singlet oxygen (¹O₂)

Formation of Reactive Oxygen Species (ROS)

- Respiratory burst of WBC
- Leaking of electron transport chain
- Phase I detox enzymes (cytochrome P450s)
- NADPH oxidases
- Reperfusion injury

Mittal et al. 2014. Antioxidants & Redox Signaling. 20:1126.
Lipopolysaccharides (LPS) Bind Toll-like receptor 4 (TLR4) Activate NF-κB
Stimulate production of inflammatory cytokines Produce ROS

Pathway amplification

Stimulate production of inflammatory cytokines

Produce ROS

Th1
Th17
Th2
Tregs
B cells

Cytokines
IgAs

Altered gut microbes

HPA Axis
Endocrine pathway
Immune pathway

Altered gut functions

Th1
Th17
Th2
Tregs
B cells

APC
Microbial-derived products
SCFA, ATP, LPS

Endocrine pathway
Neural pathway
Immune education

Chronic Inflammation

Estimated that 30% of a patient's baseline level of inflammation is due to cytokines produced by adipocytes

More adipocytes = more inflammation

Gut inflammation precedes weight gain & adipocyte inflammation

M2 macrophage
M1 macrophage
'M2 means heal'
'M1 means kill'

Macrophage functions:
- Pro-inflammatory
- Antimicrobial
- Tumoroidal
- TH-1 response
- Antigen presentation capacity
- Killer of intracellular pathogens
- Tissue damage, etc.

Natural modulators:
- Lupeol: olive, mango, strawberry, grapes,
cucumber, tomato
- Resveratrol: berries, peanuts, grapes
- Quercetin: widely distributed in plants
- Curcumin: turmeric
- Naringenin: grapefruit
- Apigenin: widely distributed
- Procyanidins: cinnamon, cocoa beans, grapes
- Terpenes: forskolin, tea tree oil

Chronic Inflammation Summary
Diet/Stress: Causes change in gut microbiome
Gut changes:
- Inflammation
- Increased LPS absorption

Immune cell activation: Systemic inflammation

Biomarkers of Systemic Inflammation
- C-reactive protein (CRP)
  - Hepatic acute phase protein
  - Low inflammation: <1 mg/L
  - Average: 1-3 mg/L
  - High inflammation: >3 mg/L
- IL-6
  - Used as biomarker for bacterial or viral infections & some cancers
- Fibrinogen
  - Increased during pregnancy
  - Non-pregnant = <3 g/L
  - Pregnant = 4.5 g/L

Summary

Diet, Stress, Infection
- Gut changes
- Immune cell activation
- Fetal Inflammation
- Neurodevelopmental changes

Pregnancy Stress & Neurodevelopment
- Maternal cytokine production is associated with fetal neuroinflammation
  - IL-6 as an indicator of systemic inflammation
  - Maternal IL-6 concentrations alter parts of the brain associated with working memory
  - Abnormal network connections were formed in fetal brains
  - Brain lesions due to excessive activation of pro-inflammatory microglia

Neuroinflammation
- Microglia
  - Macrophages of brain & spinal cord
  - Make up 10-15% of all cells in brain
  - Necessary for synaptic plasticity, pruning & clearance of debris
  - Development:
    - Progenitor -> embryonic phase one -> embryonic phase two -> adult
    - Number of microglia peak around postnatal day 14

**Neuroinflammation**

**Microglia**
- Become activated via inflammatory cytokines and LPS
- Activated microglia bind and sequester iron
- When inflammatory subset is activated, they secrete:
  - Inflammatory cytokines: IL-1, TNF
  - Reactive oxygen species (ROS)
  - Proteases: matrix metalloproteinases (MMP-1, 2, 3 & 9), elastase
  - Amyloid precursor protein

**Neuroinflammation**

**Microglia**
- Anti-inflammatory cytokines (IL-4, IL-10, IL-13) and glucocorticoids drive the formation of deactivated phenotypes
- Increasing oxidative metabolism in microglia drives a pro-regenerative phenotype
- Sirtuins (SIRT1) prevents excessive microglia activation through deacetylation of NF-κB
  - Activators of SIRT1 are found in berries

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