Impact of vitamins & nutrients on neurological function

Choline, Vitamin E, and D

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Lecture Outline

• Clinical Trials & Alzheimer’s disease drug trial
• Choline Basics
• Neurodevelopment
• Neurodegeneration
• Questions
• BREAK
• Vitamin E and D
• Questions
Clinical Trial Basics

**Drug Research**
- Basic lab studies
- Testing potential drug compounds
- Medical device design
- New use for an approved drug
- Drug synthesis
- Drug delivery
- Animal testing

**Pre-clinical**
- Further animal testing
- Helps determine best dose of a drug for humans
- Pharmacodynamics (what the drug does to the body)
- Pharmacokinetics (what the body does to the drug)
- Bioavailability (amount of drug able to be used by the body)
- Toxicity (damage to tissue or body)

**Clinical Trials**
- Phase I
  - Small number of patients (20-100)
  - Is the treatment safe?
- Phase II
  - Hundreds of patients (100-500)
  - Does the treatment work?
- Phase III
  - Thousands of patients (1,000-10,000)
  - Large-scale safety and efficacy
  - Quality assurance (strength, quality, purity)

**Evaluation**
- Studies sent to FDA for approval
- Is the drug or device safe and effective?
- Do the benefits outweigh the risks?
- Product packaging and labeling
- Quality improvement
- Optimal use

**Phase IV Trials**
- Studies that continue after the drug is on the market
- Long-term safety
- Patient quality of life
- Cost effectiveness
- The quality of medical care increases for everyone!

**Public Impact**
- Doctors may use information from these studies to change their clinical practice
- Patients may receive a new drug, medical device, or treatment
Alzheimer’s disease overview

INCREASED LEVELS OF:
- amyloid beta protein
- tau
Alzheimer’s disease drug trial

• 3 phase three clinical trials of a drug
• Aducanumab: targets the buildup in the brain of beta-amyloid
• Why?
  • Independent experts
    • the trials had little hope of succeeding
Food sources of choline

- Food sources of choline are high in fats and cholesterol
- Only 20-25% of people get adequate levels of choline

Rich food sources of choline
(per 100 gram serving)

<table>
<thead>
<tr>
<th>Food</th>
<th>Choline (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef liver</td>
<td>350</td>
</tr>
<tr>
<td>Chicken liver</td>
<td>330</td>
</tr>
<tr>
<td>Egg, hard boiled</td>
<td>230</td>
</tr>
<tr>
<td>Salmon, smoked</td>
<td>220</td>
</tr>
<tr>
<td>Salmon, cooked</td>
<td>91</td>
</tr>
<tr>
<td>Soy protein powder</td>
<td>86</td>
</tr>
<tr>
<td>Tilapia</td>
<td>83</td>
</tr>
<tr>
<td>Chicken, roasted</td>
<td>79</td>
</tr>
<tr>
<td>Peanut butter</td>
<td>66</td>
</tr>
<tr>
<td>Almonds</td>
<td>52</td>
</tr>
<tr>
<td>Brussels sprouts</td>
<td>41</td>
</tr>
<tr>
<td>Broccoli</td>
<td>40</td>
</tr>
<tr>
<td>Cauliflower</td>
<td>39</td>
</tr>
</tbody>
</table>

Choline

- Essential Nutrient
- Involved in maintenance of DNA and chromosome stability
How choline affects DNA summary

- Choline
  - Methyl-tetrahydrofolate
    - S-adenosylmethionine
      - Epigenetic changes
        - Defective DNA repair
          - thymidylate
            - Uracil misincorporation
  - Folate
  - ROS

DNA strand breaks and mutations
Choline & Neurological Function

• Membrane formation
Neurotransmitter: acetylcholine

Choline + AcetylCoA → Acetylcholine
Choline & Neurological Function

- Makes Acetylcholine
  - Acetylcholine is involved in memory and motor function
Choline & Neurological Function

• Metabolism of Homocysteine
  • Reduces levels of homocysteine
  • Interacts with folates metabolism
Choline and Neurodevelopment

• Generally: involved in building of cellular membranes, DNA methylation and stores of choline in body

• Brain demands a lot of choline
  • Specially for cellular membranes
  • Neurotransmitter: acetylcholine

• Myelination
• Synapse formation
• Neural tube defects: preliminary animal studies
Choline in Aging and Neurodegeneration

- Significant cholinergic cell loss during aging
Choline in Aging and Neurodegeneration

• Possibly a result of a loss of nerve growth factor (NGF)
• NGF is neurotrophic factor
Neurotrophins

Nerve Growth Factors (shown in green) is required by neurons in order to survive. As they are a limited extracellular resource, some neurons (shown in blue) may uptake a disproportionate share of survival factors, leading to the eventual death of neighboring neurons (shown in red).
Choline in Aging and Neurodegeneration

STUDY

- clinical trial of nerve growth factor (NGF) gene therapy
- individuals with mild Alzheimer disease (AD) for 22 months
- No long-term adverse effects of NGF
- Delayed the rate of cognitive decline

Schliebs et al., 2010
Choline in Aging and Neurodegeneration

STUDY:
• Aged monkeys long-term NGF delivery
• cholinergic basal forebrain (subcortical structure)
• restored cholinergic neuronal markers to levels of young monkeys
• extended NGF support to neurons may reverse aging-related neuronal loss

Schliebs et al., 2010
Choline in Aging and Neurodegeneration

- Cognitive deficits in Parkinson's disease, Down-syndrome, progressive supranuclear palsy, Jakob–Creutzfeld disease, Korsakoff's syndrome, traumatic brain injury

- Significant degenerations of basal forebrain cholinergic cells have been observed
Choline in Aging and Neurodegeneration

Mild Cognitive Impairment
- Duration: 7 years
- Disease begins in Medial Temporal Lobe
- Symptoms: Short-term memory loss

Mild Alzheimer's
- Duration: 2 years
- Disease spreads to Lateral Temporal & Parietal Lobes
- Symptoms include: Reading problems, Poor object recognition, Poor direction sense

Moderate Alzheimer's
- Duration: 2 years
- Disease spreads to Frontal Lobe
- Symptoms include: Poor judgment, Impulsivity, Short attention

Severe Alzheimer's
- Duration: 3 years
- Disease spreads to Occipital Lobe
- Symptoms include: Visual problems
Choline in Aging and Neurodegeneration

• Late stage of Alzheimer’s disease, extensive cholinergic loss in cortex

• Early stages of Alzheimer’s disease and Mild Cognitive Impairment no loss of cholinergic cells
Alzheimer’s disease
Choline in Aging and Neurodegeneration

[Diagram showing the relationship between choline function, trophic responsiveness, and neurodegeneration stages such as MCI, early AD, AD, and advanced AD.]
Acetylcholine and Alzheimer's disease
Questions?
Break!
Vitamin E

• Found naturally in vegetables (green vegetables), nuts and nut oils, dairy products, meat and fish
• Gamma-tocopherol, most common form of Vitamin E found in North American diet
• Alpha-tocopherol biological active form of vitamin E, second most common form of Vitamin E in diet
• Association with vitamin E levels and cardiovascular disease
Vitamin E

• Plays a role as an antioxidant

• Antioxidants are man-made or natural substances that may prevent or delay some types of cell damage.

• Antioxidants are found in many foods, including fruits and vegetables. They are also available as dietary supplements.
Free Radicals

Free Radical is an uncharged molecule (typically highly reactive and short-lived) having an unpaired valence electron.
Free Radicals
Antioxidants

Antioxidants Doing their Job

Healthy Cell Membrane

Antioxidant neutralizing a free radical

HUMAN CELL

Damaging Free Radicals

NUCLEUS

Antioxidants have extra electrons that they can donate to free radicals

Free radical missing an electron in its outer shell
## Vitamin E Recommended Intake

<table>
<thead>
<tr>
<th>mg/day</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0 to 6 months</td>
</tr>
<tr>
<td>5</td>
<td>7 to 12 months</td>
</tr>
<tr>
<td>Children</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1 to 3 years</td>
</tr>
<tr>
<td>7</td>
<td>4 to 8 years</td>
</tr>
<tr>
<td>11</td>
<td>9 to 13 years</td>
</tr>
<tr>
<td>Adolescents and adults</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>14 and older</td>
</tr>
</tbody>
</table>
Vitamin E and neurological function

• The role of vitamin E and brain is not very clear

• Study in rats found....
  • Deprived of vitamin E over one year
  • Loss of vitamin E less rapid in neural tissue (e.g. brain, spinal cord and nerves) than in non-neural tissue (e.g. liver, blood)
  • Neural tissues conserve vitamin E
Vitamin E and Alzheimer's disease

• No current therapies will delay, prevent, or cure Alzheimer’s disease (AD)
• Current therapies: slow functional decline
• Study in 2014
• Made headlines: Vitamin E can cure AD
Vitamin E and Alzheimer's disease

- 613 patients aged 53 to 96 with diagnosis of possible or probable AD
- Memantine: a drug that targets glutamine neurons, prevents damage from glutamate
- Treatment Groups:
  - Vitamin E + Memantine Placebo
  - Memantine + vitamin E Placebo
  - Both vitamin E and Memantine
  - Two placebos
Vitamin E and Alzheimer's disease

• Outcome measure was a AD questionnaire
  • Functional abilities to perform activities of daily living
• All participants got worse over the period of the study
• Subjects in vitamin E group had significantly slower decline
Vitamin E and stroke

• Supplementation with vitamin E
  • Increases risk of haemorrhagic stroke by 22 %
  • Decreases risk of ischaemic stroke by 10%

• More information: http://www.bmj.com/content/341/bmj.c5702.full
Vitamin E Summary Video
https://www.youtube.com/watch?v=N8ZJlEMQ2Qg
Vitamin D Metabolism

• Obtained from diet (e.g. dairy or fish) or environment (e.g. sun)
• Converted to active form in liver in order to participate in physiological function, for example:
  • Inhibition of growth of cancer cells
  • Protection against immune diseases
Vitamin D Recommended Intake

<table>
<thead>
<tr>
<th>Age group</th>
<th>RDA (IU/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants 0–6 months</td>
<td>400*</td>
</tr>
<tr>
<td>Infants 6–12 months</td>
<td>400*</td>
</tr>
<tr>
<td>1–70 years</td>
<td>600 (15 μg/day)</td>
</tr>
<tr>
<td>71+ years</td>
<td>800 (20 μg/day)</td>
</tr>
<tr>
<td>Pregnant/Lactating</td>
<td>600 (15 μg/day)</td>
</tr>
</tbody>
</table>
Vitamin D and Neurological Function

- Development of brain (neurogenesis)
- Neurotransmission (neurotransmitters: acetylcholine, dopamine, serotonin)
- Neuroprotection
  - after Ischemia (stroke)
  - Parkinson’s disease (anti-neurodegenerative)
Vitamin D and Neurological Function

• Neuroimmunodulation
  • Microglial cells
    • Type of glial cells
    • Immune cells in the brain
    • 10-15% of cells in the brain
Vitamin D and Neurological Function

- Neuroimmunodulation
  - Microglial cells
Vitamin D and Neurological Function

• Neurotrophic factors
  • Growth factors in the brain help neurons develop or maintenance of mature neurons

• Vitamin D involved in synthesis of:
  • Growth derived neurotrophic factor: GDNF
  • Neurotrophin-3: NT-3
Vitamin D and Neurological Function

- Neurotrophic factors

Nerve Growth Factors (shown in green) is required by neurons in order to survive. As they are a limited extracellular resource, some neurons (shown in blue) may uptake a disproportionate share of survival factors, leading to the eventual death of neighboring neurons (shown in red).
Vitamin D and Neurological Function

• Deficiency of Vitamin D associated with neurological and psychiatric disorders

• Hypovitaminosis D (too little vitamin D) associated with neuromuscular disorders, dementia and Parkinson’s disease
Causes of Alzheimer's disease

- Genetic/epigenetic modulation
- Environmental and metabolic risk factors
- Secondary trigger

Mechanisms:
- Oxidative stress
- Calcium imbalance
- Disturbed neurotrophin and NT homeostasis
- Neuronal hypometabolism
- Abnormal protein accumulation
- Mitochondrial dysfunction

Risk factors:
- Hyperhomocysteinemia
- Diabetes
- Metal stress
- Head injury
- Vitamin D deficiency
- Psychological stress
- Folate, B12 deficiency
- Vascular injury

Aging
Inflammation
Sedentary lifestyle

Neuronal degeneration and neuronal death
Multiple Sclerosis

demyelinating disease
environmental risk factors
autoimmune
Multiple Sclerosis & Vitamin D

• Vitamin D deficiency a risk factor for multiple sclerosis
• Vitamin D plays a role in regulation, proliferation, differentiation and immunomodulation in central nervous system
Basic Science and Multiple Sclerosis

• In laboratory animals....
• Vitamin D deficiency responsible for worsening of symptoms
• Supplementation with vitamin D made symptoms disappear

• Human Data not clear
Recent human study from McGill University.....

• Investigated the link between Vitamin D metabolism and risk of Multiple Sclerosis development

• European population
• Single nucleotide polymorphisms (SNPs) of enzymes involved in Vitamin D metabolism

Mokry et al., 2015
Single nucleotide polymorphism (SNPs)

is a variation in a single nucleotide which may occur at some specific position in the genome (DNA)
Vitamin D Metabolism

Study investigated genetic changes in enzymes involved in vitamin D metabolism.
Findings

- Genetically lowered levels of 25OHD associated with increased risk of Multiple Sclerosis in European population
Conclusion

• Choline
  • Nutrient
  • Importance of brain function

• Vitamin E
  • Antioxidant
  • Impact of brain function still unclear

• Vitamin D
  • Neuroimmunomodulation and neurotrophic factors
Next week: Impact of different diets on brain function
Questions ?