Welcome

Terminology

- Potentiation defined
  - Enhancement of one agent by another so that the combined effect is greater than the sum of the effects of each one alone
  - "Phytopotentiation"
    - Complex formulas and chemically complex plants are better than isolated nutrients and/or isolated secondary plant metabolites
- Physiologic support
  - What we do
  - Physiologic compensation
    - What drugs do

A Systemic Approach

- Age
- Attitude
- Diet
- Enviornment
- Lifestyle
  - Exercise
  - Alcohol
  - Drug use
- Stress
  - Finances
  - Job
  - Relationship(s)
- Sleep
- Medications

Therapeutic approaches must be tailored to the specific person vs. a cluster of symptoms.

Adapted from: Principles and Practice of Phytotherapy, 2nd edition, Kerry Bone, 2013 pg. 137
Healthy Digestion

Chronic PPI Use in Adults

- Osteoporosis, bone fracture\(^1\)
- Hypomagnesemia, enteric infections, interstitial nephritis, and pneumonia\(^2\)
- Heart attacks\(^3\)
- Mortality in liver cirrhosis\(^4\)
- Cryptogenic liver abscess\(^5\)
- SIBO\(^6\), dysbiosis\(^7\)
- Hyperparathyroidism\(^8\), chronic kidney disease\(^9\)
- Anemia, iron and B12 deficiency\(^10\)
References for Previous Slide

2. Shih CJ, Chen YT, Ou SM et al. *Int J Cardiol* 2014; 177(1): 292-297

Things to Consider Regarding Supplementation

- B12 support should also take into consideration the intrinsic factor
- Iron support should provide synergistic factors for healthy RBC synthesis
- If on proton pump inhibitors or histamine blockers supplement should provide proteolytic enzymes that work in relatively high pH environment. Supplement should also provide enzyme support taking into account what we talked about earlier
- HCL supplement should provide synergistic factors along with support for endogenous HCL synthesis
- How about bitters for better digestion?

Bitter Receptors

- TAS2Rs are designated as bitter receptors
- Located throughout body, not just at back of tongue
  - Expressed in stomach and throughout GIT
    - Enteroendocrine cells in GIT sensitive to bitters
    - Goblet cells in GIT also sensitive to bitters
      - Issues with constipation
      - Mucosal layer needed for…

Bitter Receptors/Digestion

- Bitters in part work via the vagus nerve
  - HCl release
  - Bile release
  - Pancreatic exocrine secretions
    - as well as endocrine secretion (i.e., insulin) but through another mechanism which we will look at in a minute
  - Slows stomach emptying and GI motility
    - Increases nutrient availability and satiation
    - Tonic effect on GIT

Incretins

- Gut derived hormones that stimulate insulin secretion
  - Produced from enteroendocrine cells
    - Gastric inhibitory peptide (GIP)
      - GIP is secreted from enteroendocrine K cells mostly located in the duodenum and upper jejunum
    - Glucagon-like peptide 1 (GLP-1)
      - GLP-1 is secreted from enteroendocrine L cells found along the length of the intestinal tract, from duodenum to colon
  - This means that stimulation of insulin secretion in not only dependent upon sweet but also upon bitters

References:

GLP-1 and GIP

- Insulinotropic effect of GIP and GLP-1 combined, can account for up to 60% of the insulin secreted after a meal in healthy humans and plays a crucial role in postprandial glucose homeostasis
- Patients with long-standing T2DM and poor glycemic control have deficient GLP-1 secretion
- Why?

Chia CW, and Egan JM. Role and development of GLP-1 receptor agonists in the management of diabetes. Diabetes Metab Syndr Obes 2009; 2: 37

GLP-1 and GIP

- Delays gastric emptying and gut motility which in turns delays absorption of ingested nutrients and dampens postprandial glucose uptake (i.e., glucose spike)
- Increases the duration of postprandial satiety therefore suppressing appetite and decreasing food intake which eventually leads to weight loss

Chia CW, and Egan JM. Role and development of GLP-1 receptor agonists in the management of diabetes. Diabetes Metab Syndr Obes 2009; 2: 37

GLP-1

- Inhibits beta cell apoptosis
- Promotes beta-cell neogenesis
- Increases islet size and growth

2. Chia CW and Egan JM. Role and development of GLP-1 receptor agonists in the management of diabetes. Diabetes Metab Syndr Obes 2009; 2: 37
Bitter Herbs Stimulate GLP-1

- Berberine via TAS2R38 in vitro
- Gentian (Gentian scabra ) in vitro and in vivo
  - Side note: Gentian and Wormwood are two of the most bitter herbs
- Bitter melon (Momordica charantia) via its bitter triterpenoid glycosides in vitro


Bitter Receptors/Airways

- TAS2Rs (i.e., bitter receptors)
  - Also found in respiratory tract
  - Nasal epithelium (i.e., olfactory receptors)
  - Ciliated cells of lung epithelium
  - Smooth muscle in airway (bronchi and bronchioles)
    - Old days – bitter cigarettes for asthma

Bitter Receptors/Airways cont.

- Research has shown that bitter tastants reduced IgE-dependent mast cell activation
- Amarogentin from Gentian histamine and TNF-alpha from human mast cells


Bitter Receptors Everywhere

- Thymus
- Kidney
- Epidermis
- Thyroid
- Vascular smooth muscle and heart
- Urinary Tract
- Bone Marrow and Immune Cells
- Testes
- Olfactory cells
- Lungs

Keep in mind this list is not all inclusive and implications of bitter receptors in all areas is not known.

References Previous Slide

Bitter Herbal Formula Advantages

• Cover multiple areas with one product
• Consider for hypersensitivities (A)
• Poor appetite
• Role in maintaining healthy microbiota and healthy colonic structure
• Possible role in toning lower esophageal sphincter
• Weight management

Contraindicated
• Gastric and duodenal ulcer
• True hyperacidity

Examples of Bitters

• Gentian root from *Gentiana lutea* root
• Ginger rhizome from *Zingiber officinale* rhizome
• Tangerine (Citrus reticulata) fruit peel oil
• Tangerine fruit peel from *Citrus reticulata* fruit peel
• Wormwood herb extract from *Artemisia absinthium* herb

No Two People Are The Same

• When recommending nutritional and/or herbal support one needs to look at the global picture regarding each unique individual that presents themselves to us.
• 13% of American take an antidepressant.\(^1\)
• Approximately 50-70 million US adults have sleep or wakefulness disorder\(^2\)
• Parkinson’s disease is on the rise\(^3\)
• Alzheimer’s is on the rise\(^4\)
• 10% of Americans of those age 45-64 use five or more medications\(^5\)

5. “Medication Overload” Wall Street Journal 11 October 2016 D1

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Why Your Brain May Be in Pain

Systemic inflammation leading to neuro-inflammation

Direct neuro-inflammation

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Some drivers of systemic inflammation

- Insulin resistance
- Overweight
- Chronic infections
- Advanced glycation end-products
- Dysbiosis
- Leaky gut
- Fatty liver
- Trauma
- Trans fats
- Toxins
- Alcohol
- Chronic inflammatory conditions
- Acute inflammation

Systemic inflammation can affect the brain.
Brain Strategies

If you think that lifestyle does not affect the brain, look up Single Photon Emission Computed Tomography (i.e., SPECT scan) and you can see how what you put in the body affects the brain.

Alzheimer’s On The Rise

Causes of Death

Some Risk Factors

Adverse Risk Factors

<table>
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<tr>
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<th>AD</th>
<th>CVD</th>
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<tr>
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<td>✓</td>
<td>✓</td>
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<tr>
<td>Homocysteine</td>
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</tbody>
</table>

CVD = cardiovascular disease


Additional Risk/Causal Factors

- Air pollution
- Chemicals in food, cosmetics, carpets, etc.
- Herbicides/pesticides
- By products of normal cellular metabolism
  - E.g., ROS, Singlet oxygen
- Ischemia
- AGE’s
- Stealth pathogens
- Utero exposure to toxins
- Being overweight
- Systemic inflammation
- Mitochondrial dysfunction
- Fatty acid peroxidation
- Para-inflammation (i.e., neuroinflammation)
- Botanical and nutritional deficiencies

According to the medical model we know what is causing the symptoms, however they do nothing regarding prevention and/or stopping the progression of the formation of the beta-amyloid protein and neurofibrillary tangles.
I will take the AO’s and all will be fine. This is based on the assumption that the AO’s will...

- Get through digestive system intact
- Pass through the gut lining
- Pass through the BBB
- Be utilized when needed
- Get inside the cells
- Be regenerated

This is a non-specific, non-targeted and wishful approach.

The current approach.

Give the cells what they need so they can synthesize enzymatic antioxidants targeted at ROS excess.

- Catalase
- Super oxide dismutase (SOD)
- Glutathione peroxidases
- Glutathione reductase
- Glutathione transferase
- NADPH-quionone oxidoreductase (NQO1)
- Thioredoxin and
- Thioredoxin reductase
- Along with HSP70

How do we do this?

The new approach.

Keap1-Nrf2/ARE

Keap1-Nrf2/ARE is not only found in the brain

The Keap1-Nrf2/ARE pathway is the major regulator of cytoprotective responses to oxidative and electrophilic stress.
Technically it is called the Keap1-Nrf2/ARE Pathway, many simply call it "Nrf2/ARE. Here is how it works in a very simple yet effective explanation.

Some stressor causes Nrf2 to separate from Keap1 in the cell cytoplasm. For our discussion let’s just keep it that Keap1 is a protein hooked to Nrf2. Once Nrf2 is set free it migrates to the cell’s DNA and attaches to an area called ARE (Antioxidant Response Element). The ARE then results in specific antioxidant synthesis or the activation of detoxification enzymes in an organ such as the liver. Obviously there is much more to this but if you get the concept then you understand more than most in the field.
**Functions Nrf2 Pathway Activation**

- Catalase
- Superoxide dismutase (SOD)
- Glutathione peroxidases
- Glutathione reductase
- Glutathione transferase
- NADPH-quione oxidoreductase (NQ01)
- Thioredoxin and Thioredoxin reducatase
- HSP70

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**Functions Nrf2 Pathway Activation**

- Phase II support
  - Enhancement of key phase II enzymes such as UDP-Glucuronosyltransferase (glucuronidation), N-acetyltransferase (acetylation), sulfotransferases (sulfation), and Glutathione transferase (glutathione conj.)
  - Upregulates phase III transporter proteins (removes toxins and damaged cellular components)

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**Functions Nrf2 Pathway Activation**

- Upregulation HO-1; highly cytoprotective; with nitric oxide which allow vasodilation in ischemic tissues
- Under homeostatic conditions: supports mitochondrial function by ↑ mitochondrial membrane potential, fatty acid oxidation and ATP synthesis
Functions Nrf2 Pathway Activation

• Under cellular stress: ↓ increased ROS in mitochondria and ↑ mitochondrial biogenesis (e.g., ↑ PGC-1α)

Nucleus


Nrf2 Pathway

• Expressed in many tissues but expressed highly in the:
  - Brain
  - Heart
  - Lungs
  - Liver
  - Kidneys
  - Skeletal muscles


Nrf2 Pathway

• Expressed in many tissues but expressed highly in the:
  - Brain
  - Arteries
  - Heart
  - Lungs
  - Liver
  - Kidneys
  - Skeletal muscles


Health Implications NrF2

• Research: important involvements of the Nrf2/ARE pathway in maintaining health and preventing disease:
  - Healthy aging and longevity
  - Protection against pathologenic development
  - Protection against radiation
  - Benefits in diseases involving oxidative damage and inflammation – including lung, liver, kidney diseases, arteries
  - Benefits in diseases resulting from accumulated toxins, even heavy metals

Health Implications NrF2

- Beneficial effects of NrF2/ARE priming in neurodegeneration and neuroinflammation:¹
  - Diabetic neuropathy²
  - Alzheimer’s disease³,⁴
  - Parkinson’s disease (PD)⁵
  - Age-related macular degeneration (AMD)⁶
- HO-1: a known neuroprotective HSP/enzyme that, for example, protects against ischaemia-reperfusion injury (as in a stroke)⁷

References for Previous Slide

References for previous slide

NrF2/ARE Primers

1. Cruciferous veg./sulforaphane
2. Turmeric/curcumin
3. Rosemary oil/ carnosol, carnosic acid
4. Green tea/EGCG
5. Polygonum/resveratrol
6. Garlic/sulfur
7. Ginkgo/terpanoids
8. N-acetylcysteine or whey protein
9. Zinc (NrF2), induces Metal responsive transcription factor-1 (MTF-1)
10. Co-factors: C, E, and selenium (support GSH synthesis)

There is strong evidence that these plant botanicals do affect the NrF2/ARE pathway. We just don't have the time to review the studies. The references are on the next slide for your review.
Nrf2/Primers References


Nrf2/Primers References cont.


   b. Two studies that showed ECGC, Curcumin, Carnosol, Garlic, Ginkgo, isothiocyanates, and Resveratrol primed the Nrf2/ARE pathway:


How much is this worth to you?
Optimizing Brain Health

- Goals
  - Address brain (i.e., NI) directly
    - NrF2/ARE - key cytoprotective pathway
    - NrF2/ARE - natural intracellular AO defense pathways
    - NrF2/ARE - support healthy mitochondrial function
  - Support healthy micro-circulation

Optimizing Brain Health cont.

- Goals
  - Address brain (i.e., NI) indirectly
    - Reduce toxic load systemically
    - Support Detox. Pathways - Phase I, II, and III
      - Glutathione conj.
      - Methylation
      - AA conjugation
      - Sulfation
      - Glucoronic acid conjugation
  - Address insulin resistance
  - Remove trans fats, AGE’s
  - Reduce toxic exposure (alcohol, food additives, etc)
  - Dysbiosis and bacterial translocation (leaky gut)
  - Stealth pathogens, chronic infections, AI issues

Optimizing Brain Health cont.

- Must also look at...
  - Stress and dysregulated HPA axis function
### Optimizing Brain Health

- Broccoli - sulforaphane
- Turmeric - curcumin
- Rosemary oil - carnosol, carnosic acid
- Green tea - EGCG
- Polygonum - resveratrol
- Ginkgo biloba
- Beet Juice: 1 cup/day
- Garlic - Hydrogen sulfide
- N-Acetyl cysteine
- Gotu Kola
- Omega 3 fatty acids
- Address systemic causes of inflammation such as obesity, dysglycemia,