The Importance of The Nervous System – Digestive System in OFP

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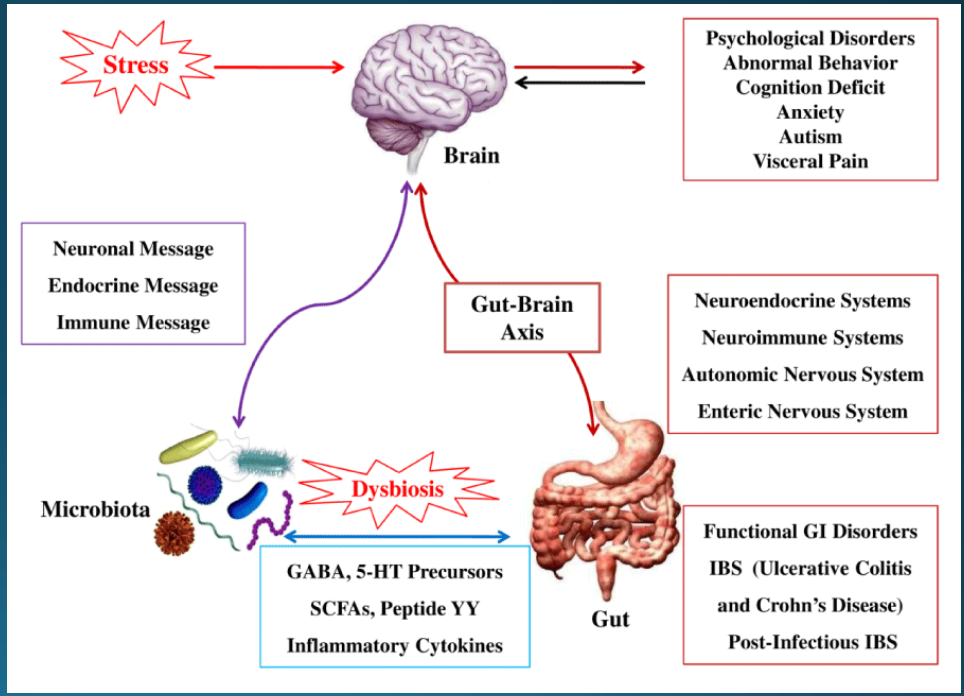

Disclosures

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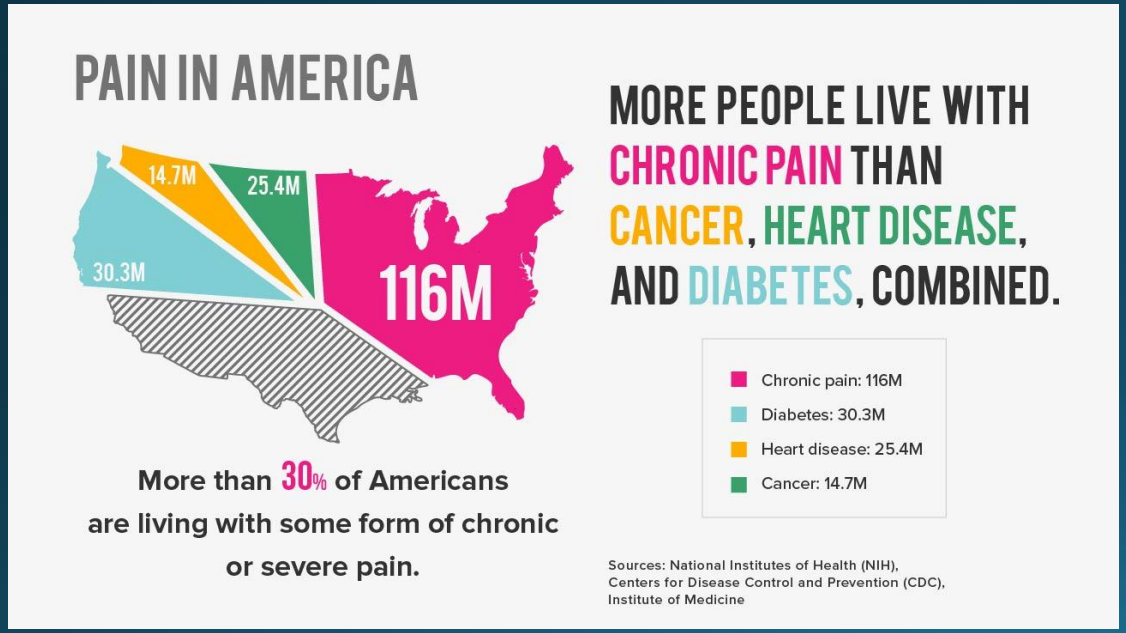
National Institutes of Health
electroCore
International Dehydrated Foods
CBD Life Sciences
Alder Bioharmaceuticals
Teva Pharmaceutical Industries

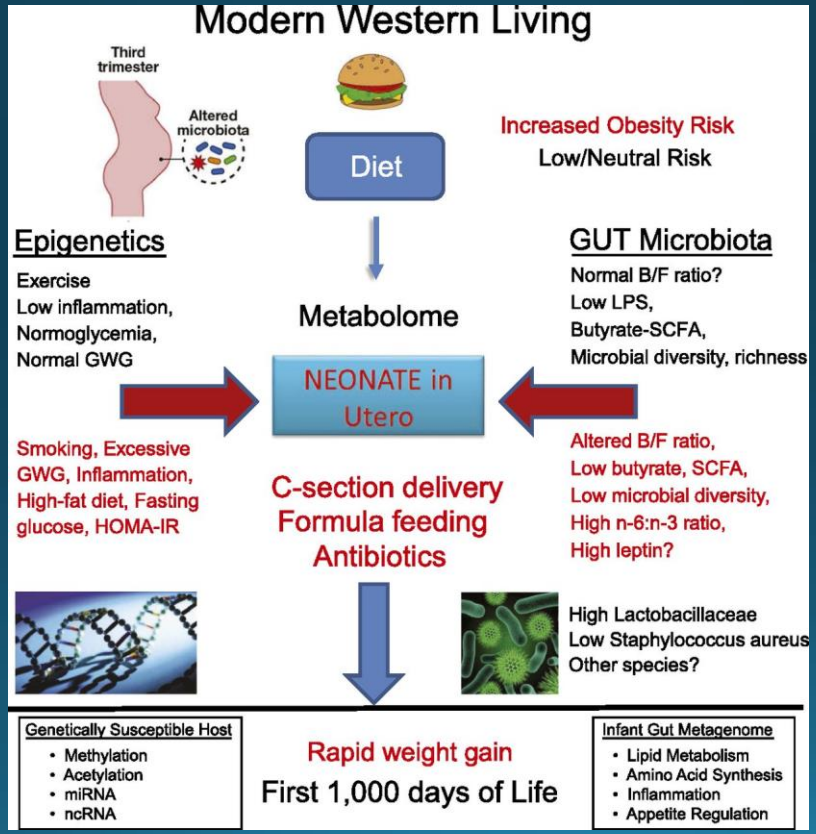
Chronic Pain – Significant Socioeconomic Burden



Standard American Diet or SAD – Recipe for Poor Health

When anxious, depressed, or sleep deprived we make poor dietary choices

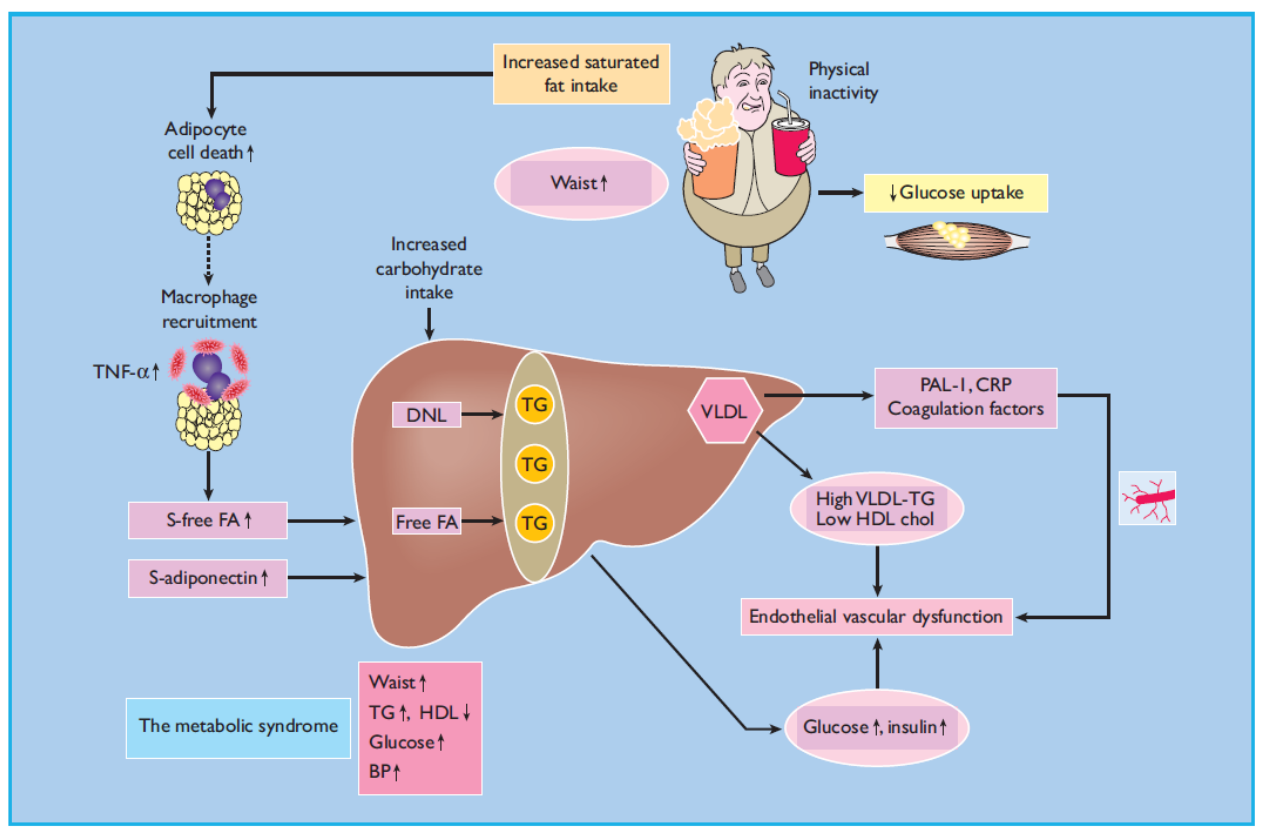
Crave – sugar, caffeine



Overeating may be result of our body's need for more nutritious foods

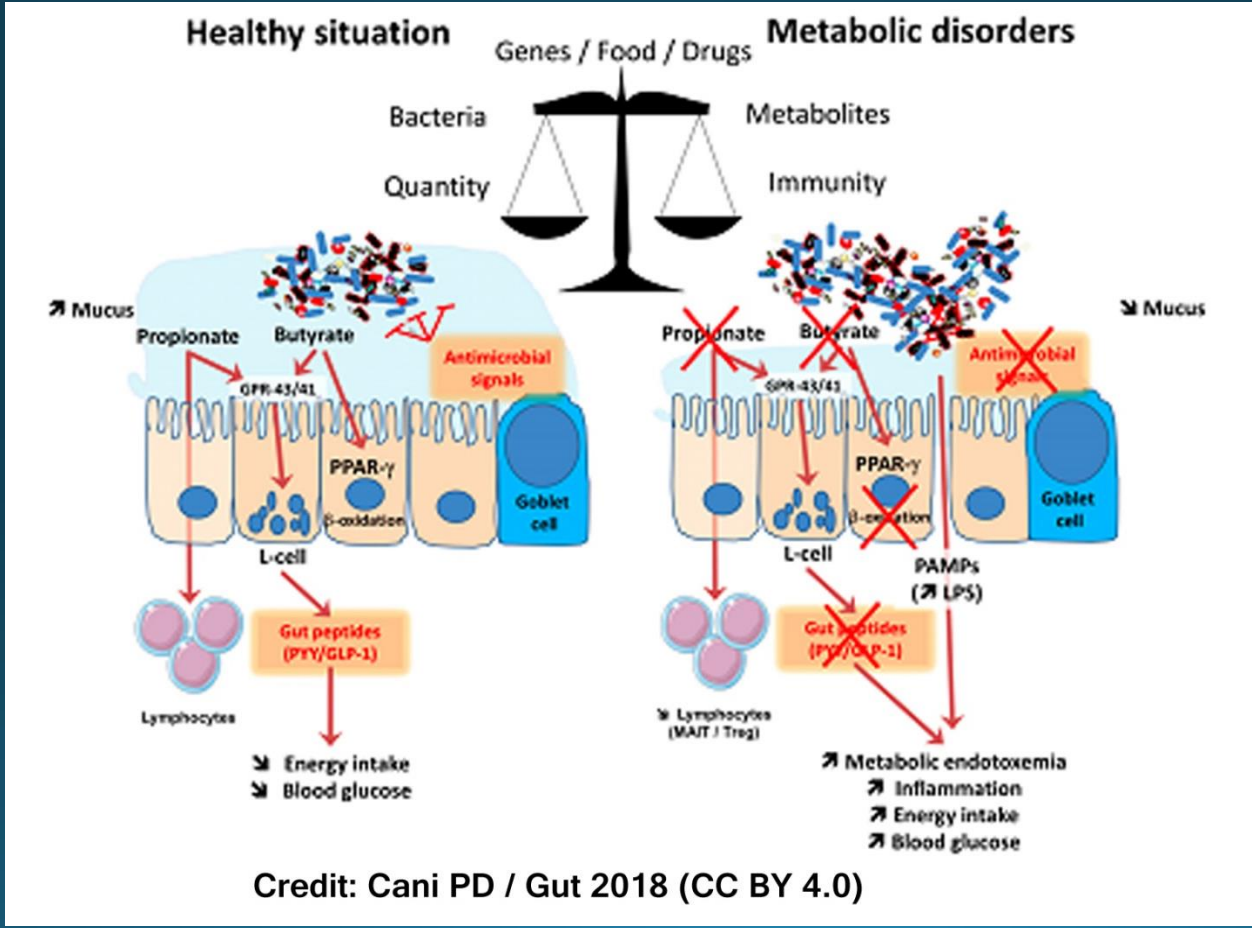
Why "junk" food does not satisfy our appetite

Metabolic Syndrome – Global Health Epidemic Caused by Physical Inactivity and Poor Diet



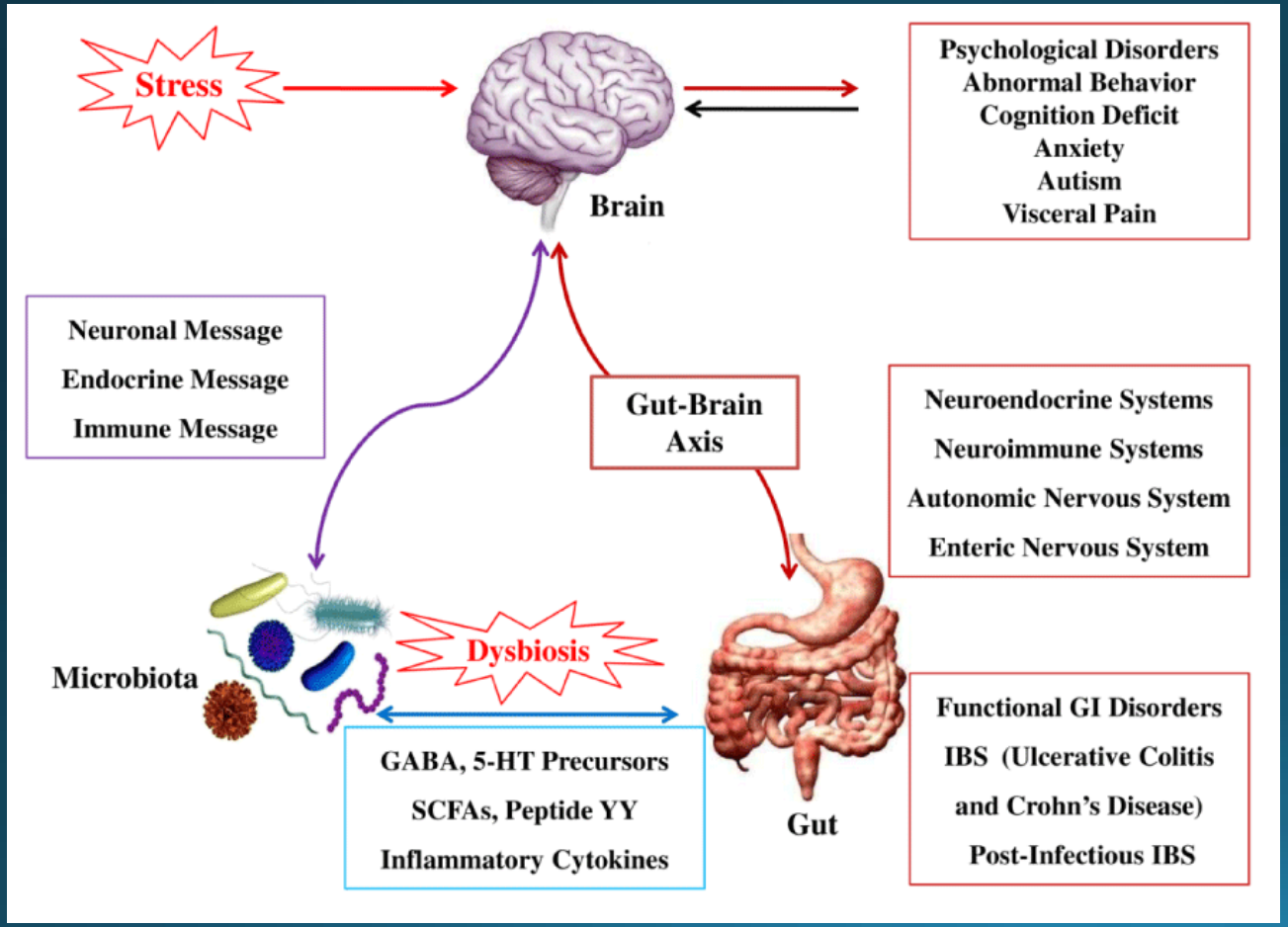
Obesity is an inflammatory disease

Metabolic Syndrome – Associated with Gut Dysbiosis



Credit: Cani PD / Gut 2018 (CC BY 4.0)

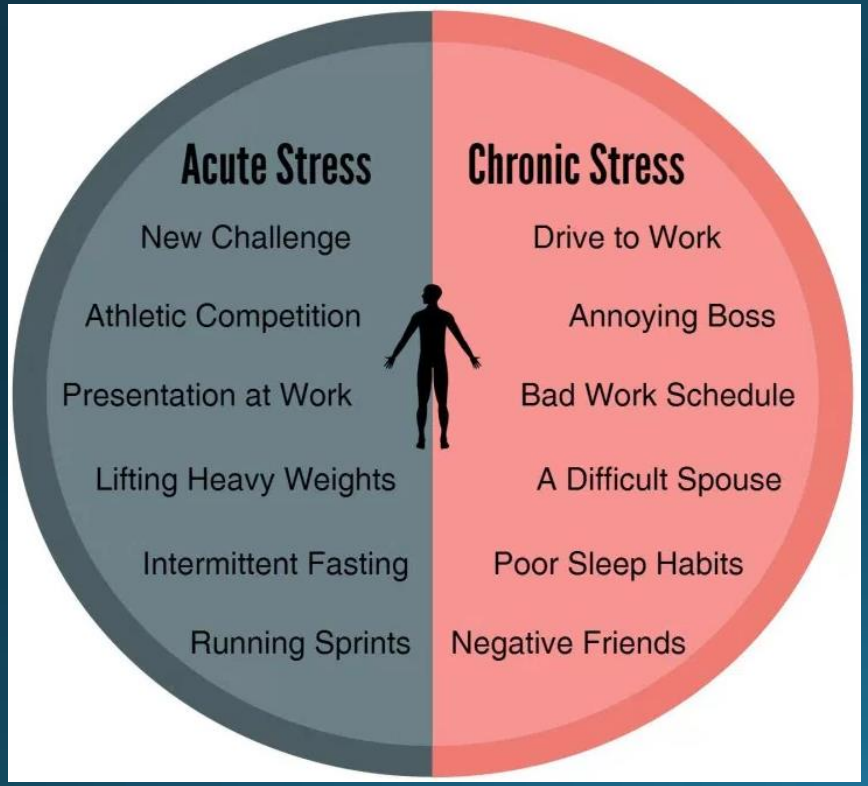
Gut-Brain Axis – Negatively Affected by Stress

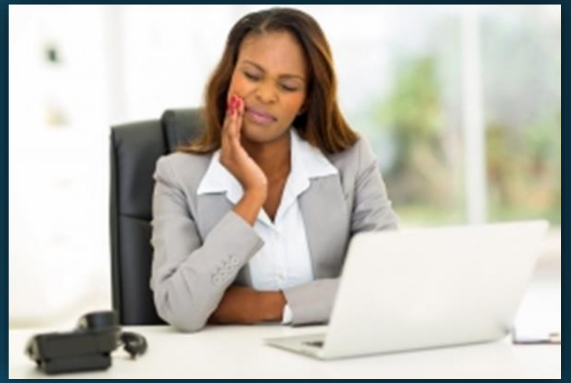


Unmanaged stress can cause dysbiosis and inflammation

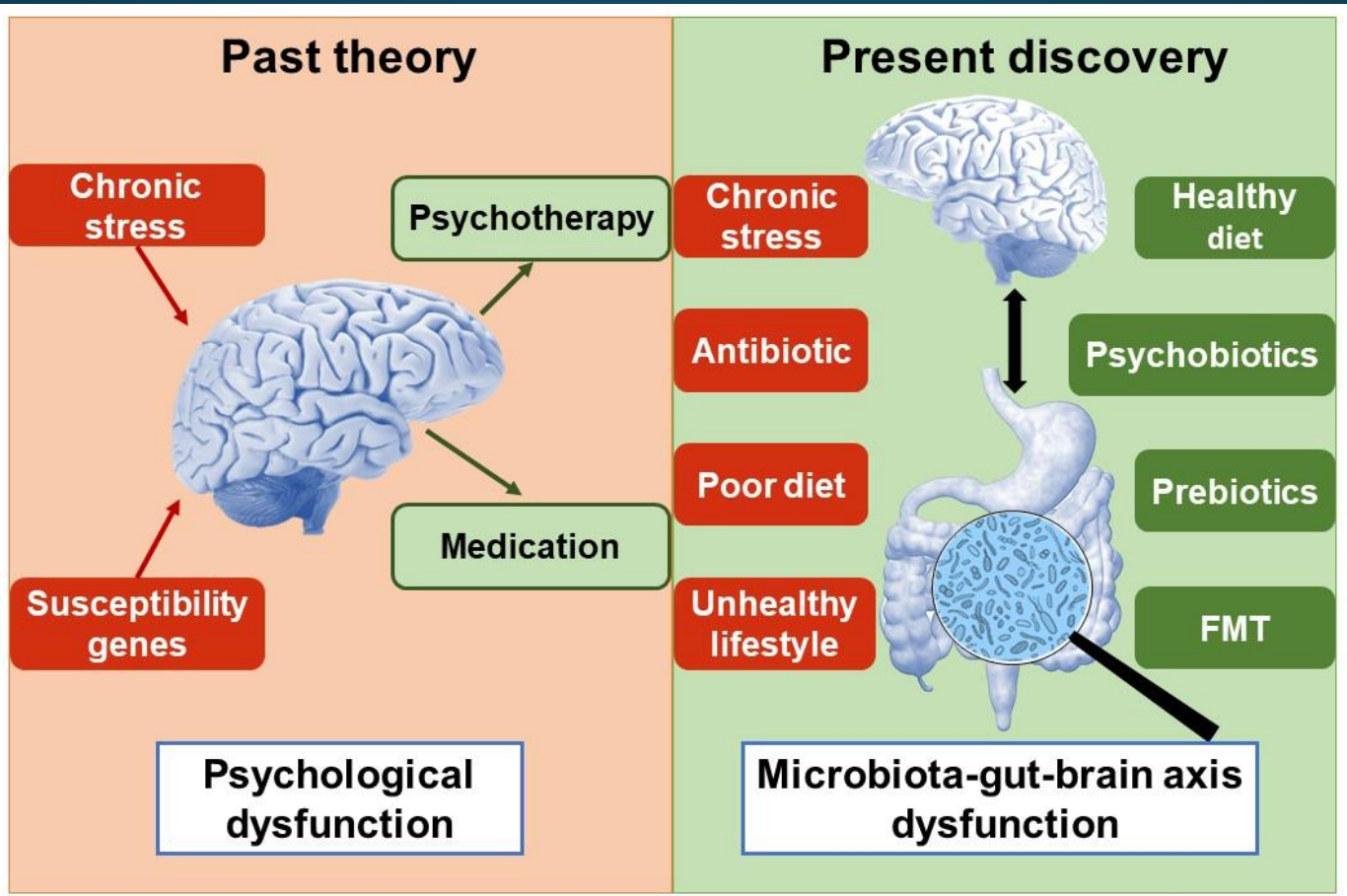
Altered production of key anti-inflammatory molecules and inhibitory neurotransmitters

Chronic Stress and Chronic Pain – A Vicious Cycle





A New Perspective on Gut-Brain Axis

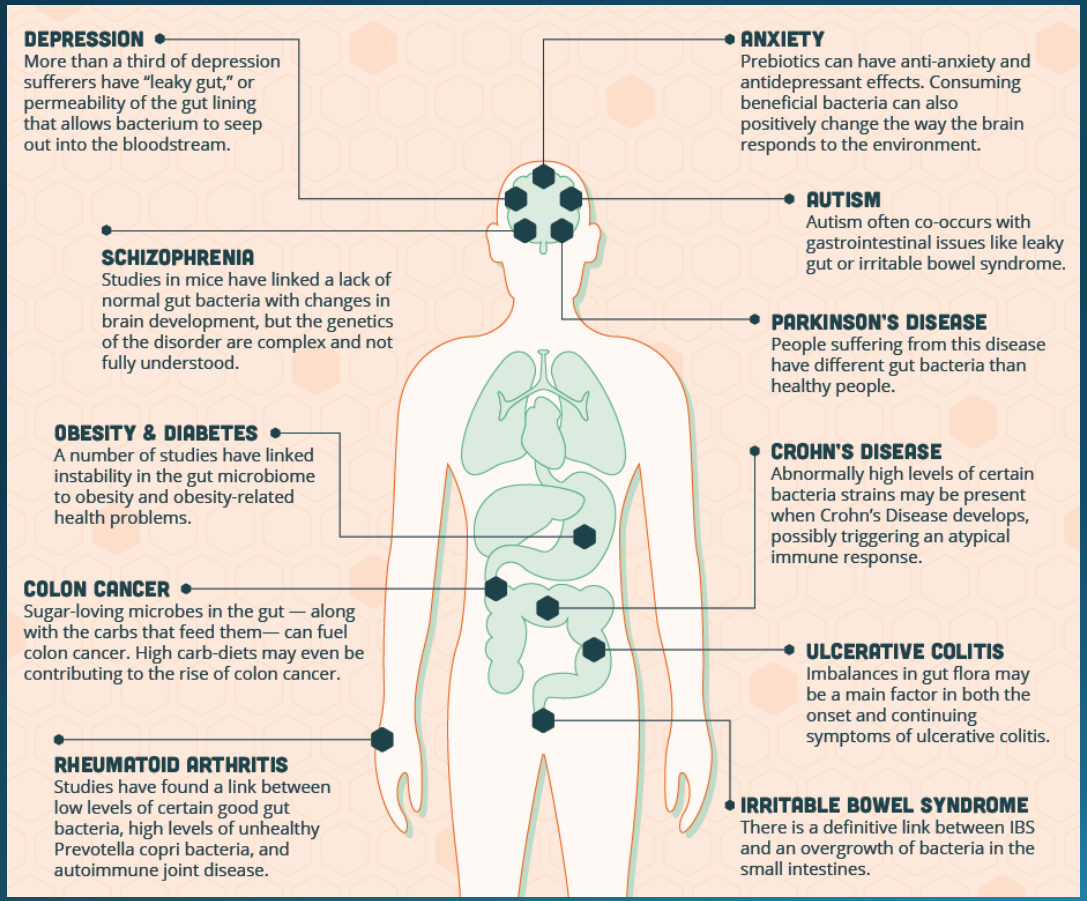


How Do You Fix HPA Axis Dysfunction?

Use the following tips to rebalance your HPA axis and support healing both your digestive and nervous systems

1. Clean Up Your Diet. Focus on balancing your blood sugar. ...
2. Avoid Caffeine. Caffeine mimics the stress response. ...
3. Engage in Stress Reduction. ... breathing exercises
4. Incorporate Movement and Regular Exercise. ... walking, yoga, tai chi
5. Get Regular Sun Exposure. ... most Americans are deficient in vitamin D
6. Support Your Sleep! ...
7. Can Supplements Help?
8. Often times OFP comorbid with IBS

Diseases Linked with Gut Microbiome Imbalance



Surprising number of neurological diseases associated with gut dysbiosis

Many chronic pain conditions also associated with gut dysbiosis

Commensal Bacteria Can Affect the Epigenetic Modification of Host Genes

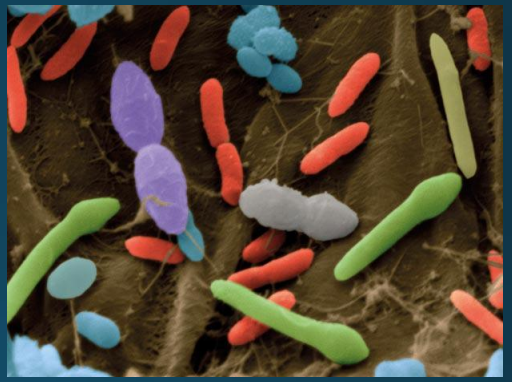
1. An overwhelming 100 trillion commensal bacteria live within the human gastrointestinal tract

2. In addition to diet, pollution, and infections, the intestinal microbiota are another factor affecting epigenetic gene modification

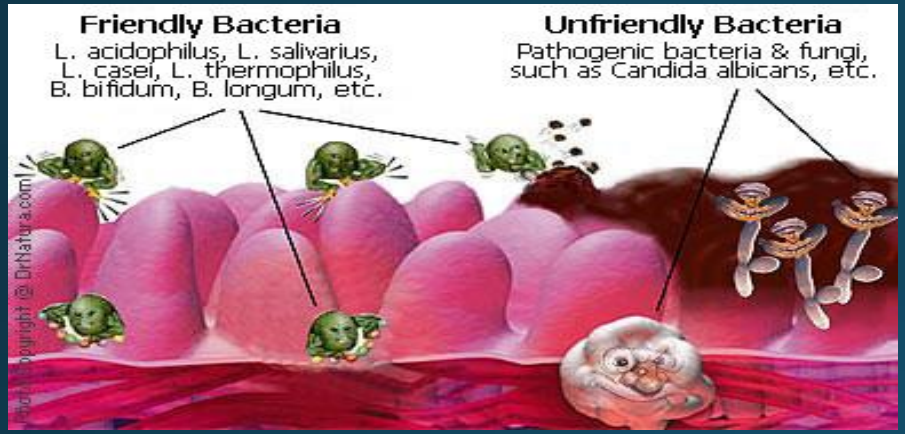
3. Maintenance of the symbiosis between the intestinal immune system and the commensals is required for intestinal homeostasis

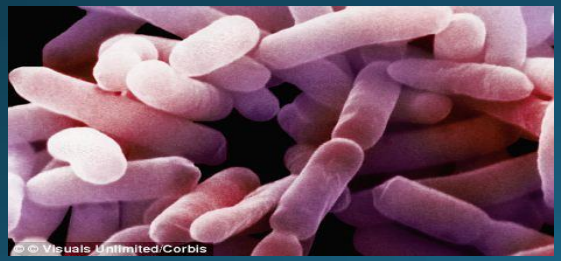
4. Disorders in this system lead to increased risk of onset or aggravated symptoms of various diseases, including allergy, inflammatory bowel disease, autoimmune disease, and metabolic syndrome

5. Many of these conditions involve excessive inflammation, indicating that regulation of inflammation is indispensable for the maintenance of the intestinal symbiotic system



Maintaining Your Commensal Bacteria – Key to Good Health

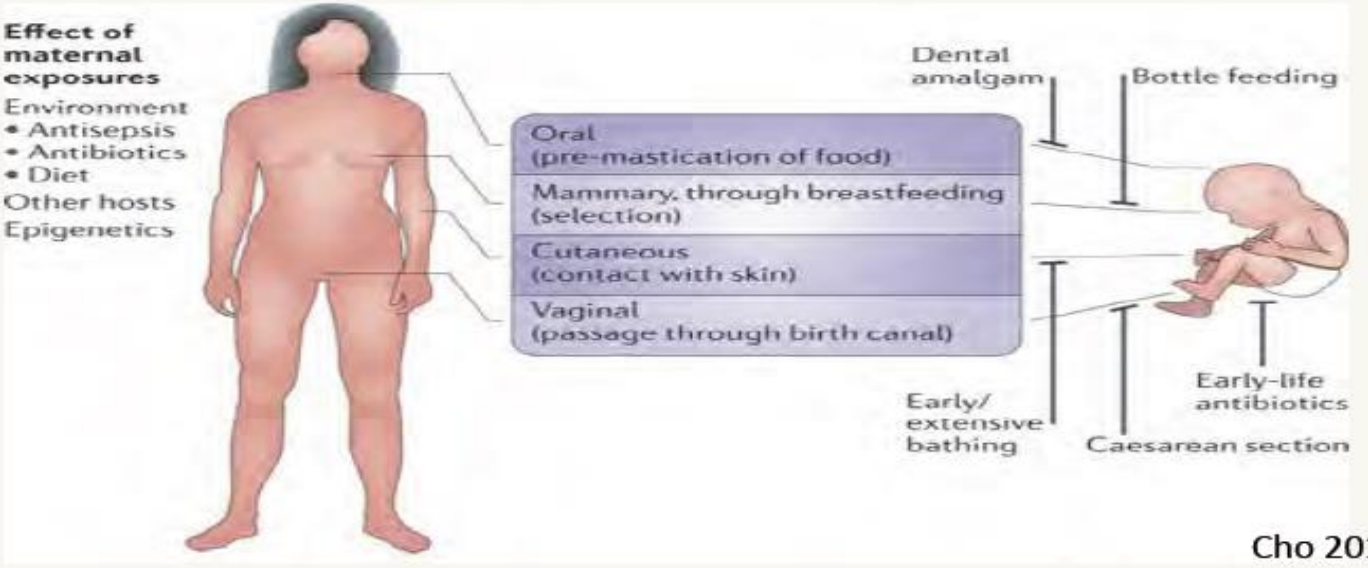




Thus, commensal bacteria play a novel role in the regulation of intestinal inflammation through their effect on epigenetic modification of the host gene, thereby providing a mechanism for the maintenance of the intestinal symbiotic system

How Do We Acquire Our Gut Microbiome?

- Different for C section vs. vaginal birth
- Initial colonization can be rapidly altered by diet, disease etc.
- Early microbiome programming influences HPA responsiveness
- Evolves to relative stability in adults, declines in elderly
- Evolves over lifespan like population succession in ecology



Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth

https://doi.org/10.1038/s41586-019-1560-1

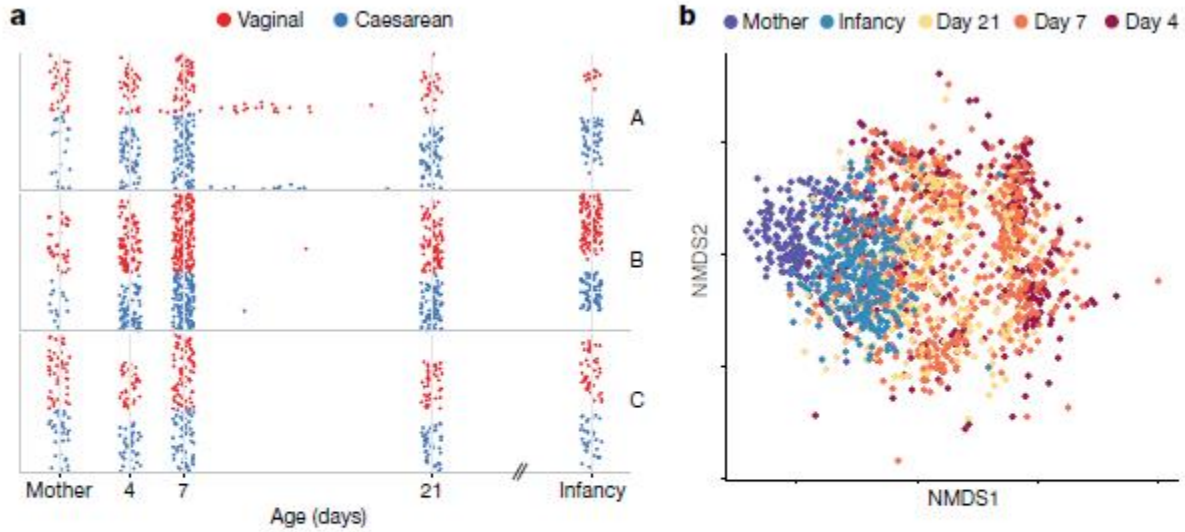


Fig. 1 | Developmental dynamics of the gut microbiota of newborn babies. a, Longitudinal metagenomic sampling of 1,679 gut microbiotas, from 771 BBS participants in 3 UK hospitals (labelled A, B and C). Each row corresponds to the time course of a subject. Five hundred and ninety-six babies were sampled during the neonatal period, primarily on day 4 ($n = 310$), day 7 ($n = 532$) and day 21 ($n = 325$), and in infancy (8.75 ± 1.98 months of age, $n = 302$), as well as 175 matched mothers. C-section, caesarean section. **b**, Nonmetric multidimensional scaling (NMDS) ordination of bacterial beta-diversities, measured by Bray–Curtis dissimilarity between species relative abundance profiles ($n = 1,679$ samples).

Perturbed Composition of Neonatal Gut Associated with C-section Delivery

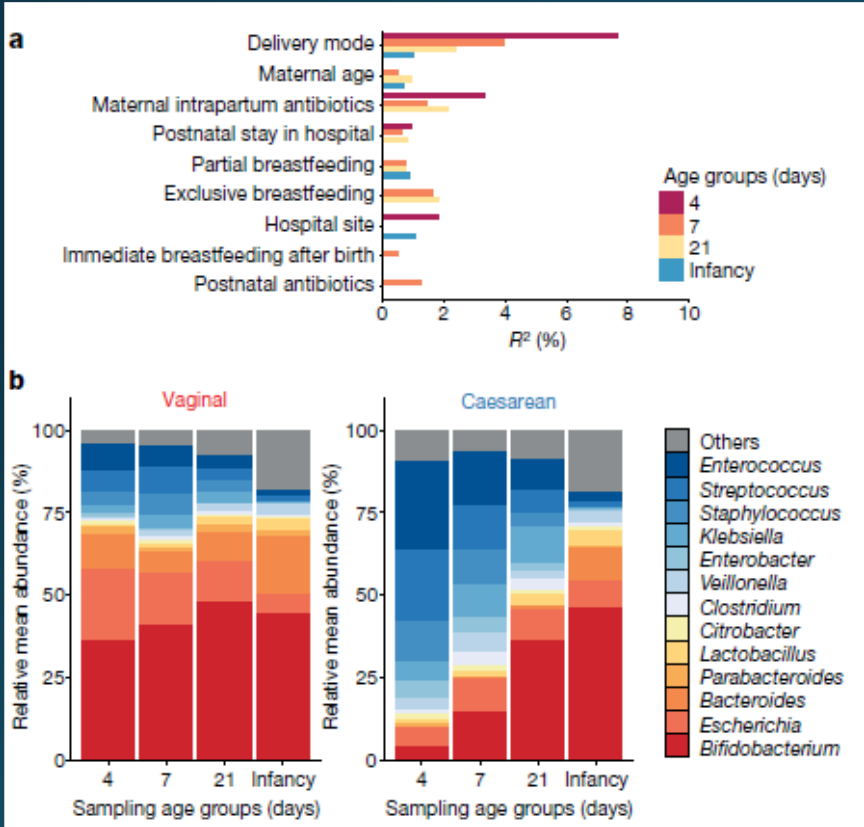


Fig. 2 | Perturbed composition and development of the neonatal gut microbiota associated with delivery by caesarean section. **a**, Bar plot illustrating the clinical covariates that are associated with variation in the neonatal gut microbiota on day 4 ($n = 310$ individuals), day 7 ($n = 532$ individuals), day 21 ($n = 325$ individuals) and in infancy ($n = 302$ individuals). Only significant associations in cross-sectional tests are shown. Covariates are ranked by the number of significant effects observed across sampling-age groups. The proportion of explained variance (R^2) and significance were determined by PERMANOVA on between-sample Bray–Curtis dissimilarity. **b**, Longitudinal changes in the mean relative abundance of genera of faecal bacteria, sampled on day 4, day 7, day 21 and in infancy, for genera with >1% mean relative abundance across all samples from the neonatal period. Vaginal deliveries, $n = 744$ samples from 310 babies; deliveries via caesarean section, $n = 725$ samples from 281 babies.

may predispose individuals to opportunistic infections. Our findings highlight the critical role of the local environment in establishing the gut microbiota in very early life, and identify colonization with antimicrobial-resistance-containing opportunistic pathogens as a previously underappreciated risk factor in hospital births.

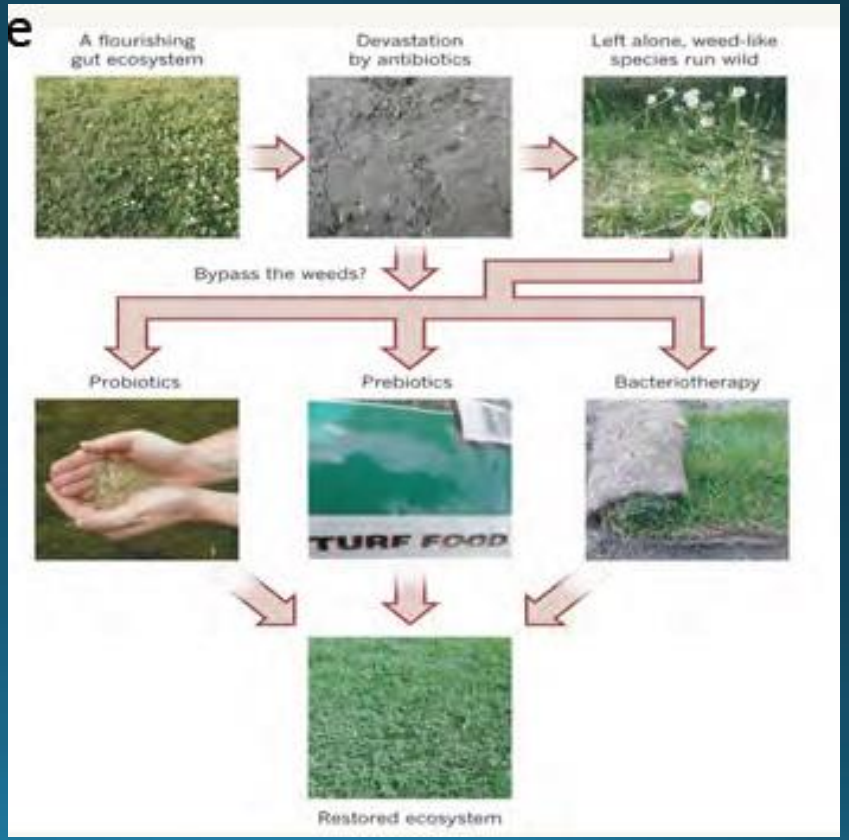
Environment and Lifestyle Choices: Implications for Maintaining a Healthy Gut Microbiome

- Antibiotics (therapeutic, subtherapeutic/diet)
- Dietary interventions (refined diet, formula feeding therapeutic diets)
- C-section birth
- Surgery
- Hygiene
- Pro, pre and synbiotic use
- Fecal transplants
- Effects of drugs: therapeutic and adverse effects
  - Traditional Chinese medicine, Olanzapine
- Stress
- Urbanization, small households: low exposure
- Geography

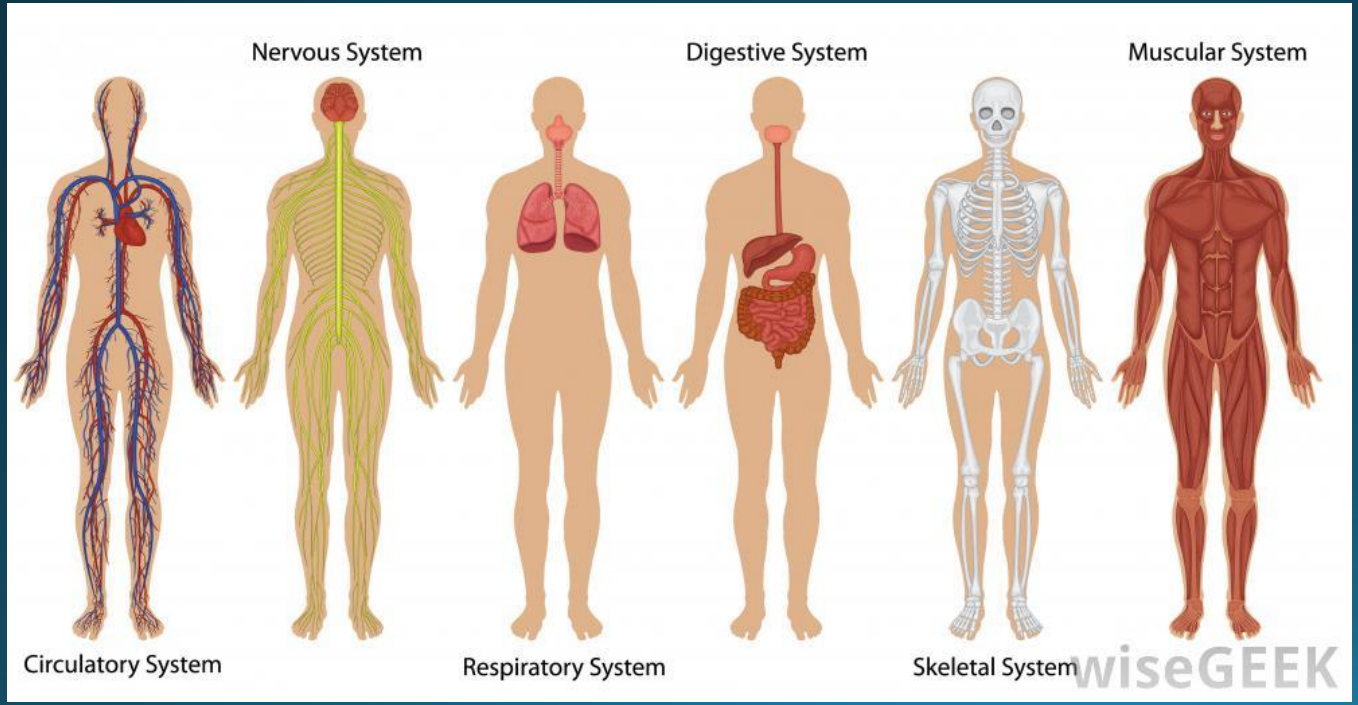
The Microbial Lawn – Maintaining Commensal Bacteria Population and Minimizing Invasive Species

- Reduction in antibiotic exposure
- Targeted antibiotics
- Diet (fermented foods)
- Probiotics
- Prebiotics
- Transplants
  - mixed flora
  - selective flora
- Role of viruses and fungi?

Lozupone 2012



“Let Food Be Thy Medicine” – Hippocrates

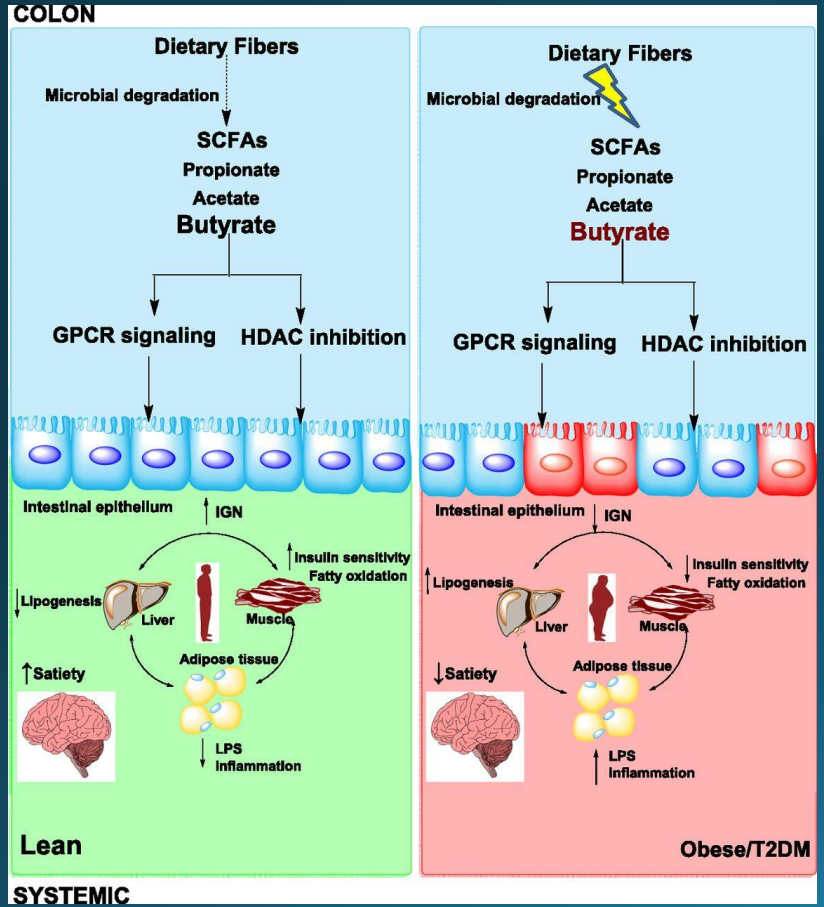


Good Nutrition Needed for Healthy Tissues and Cells -- and Gut Microbiota

Focus should be on nutrition and not just calories

Food for gut microbiota – natural fiber

Health Benefits of Dietary Fiber



Not only does it feed your gut bacteria, fermentable fiber also forms short-chain fatty acids, which nourish the colon wall

Soluble fiber may reduce your appetite, lower cholesterol levels and decrease the rise in blood sugar after high-carb meals

A Need for Better Treatments

- Need for novel TN – Migraine - TMD treatments
- Many currently used drugs exhibit adverse side effects
- Few FDA approved effective pharmacological treatments
- Most drugs used do not target underlying neuron-glia inflammatory cycle

- FDA Approved Drugs
  - Many patients don’t respond to these drugs and other common therapies
- Many patients have turned to alternative medicine because their prescription medications are not effective

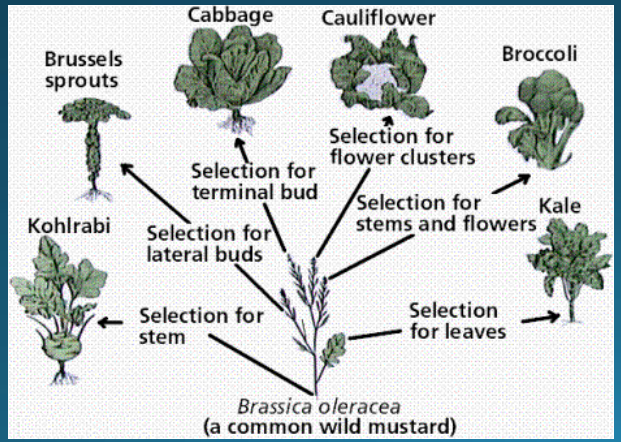
- Any compound that inhibits sensitization of trigeminal nociceptive neurons may be useful in managing TN - TMD – Migraine Pathology

Plant Products – A Recipe for Good Health

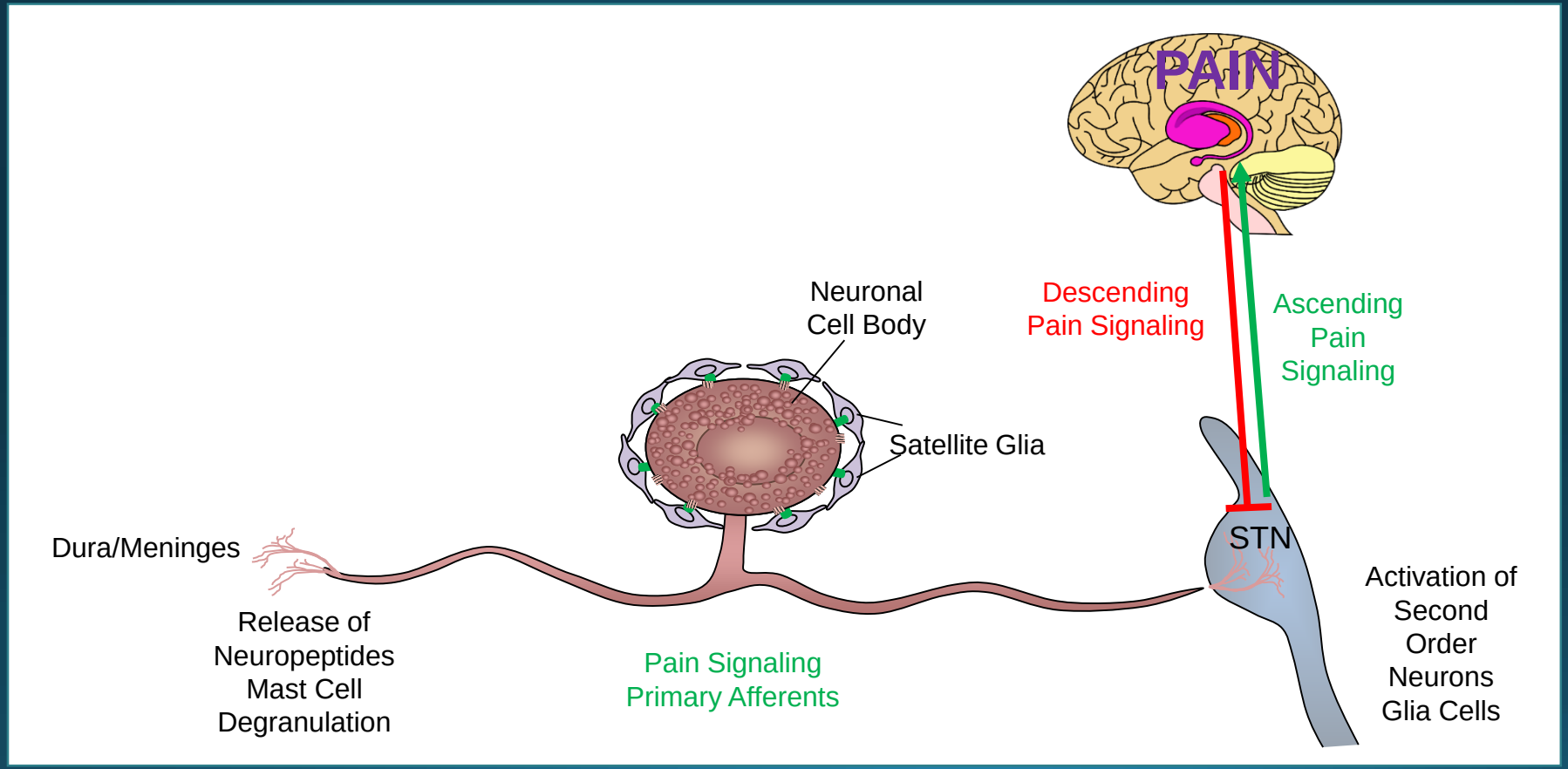
25% of modern prescription drugs contain compounds derived from plants

Only 5-15% of plants have been investigated for the presence of bioactive compounds

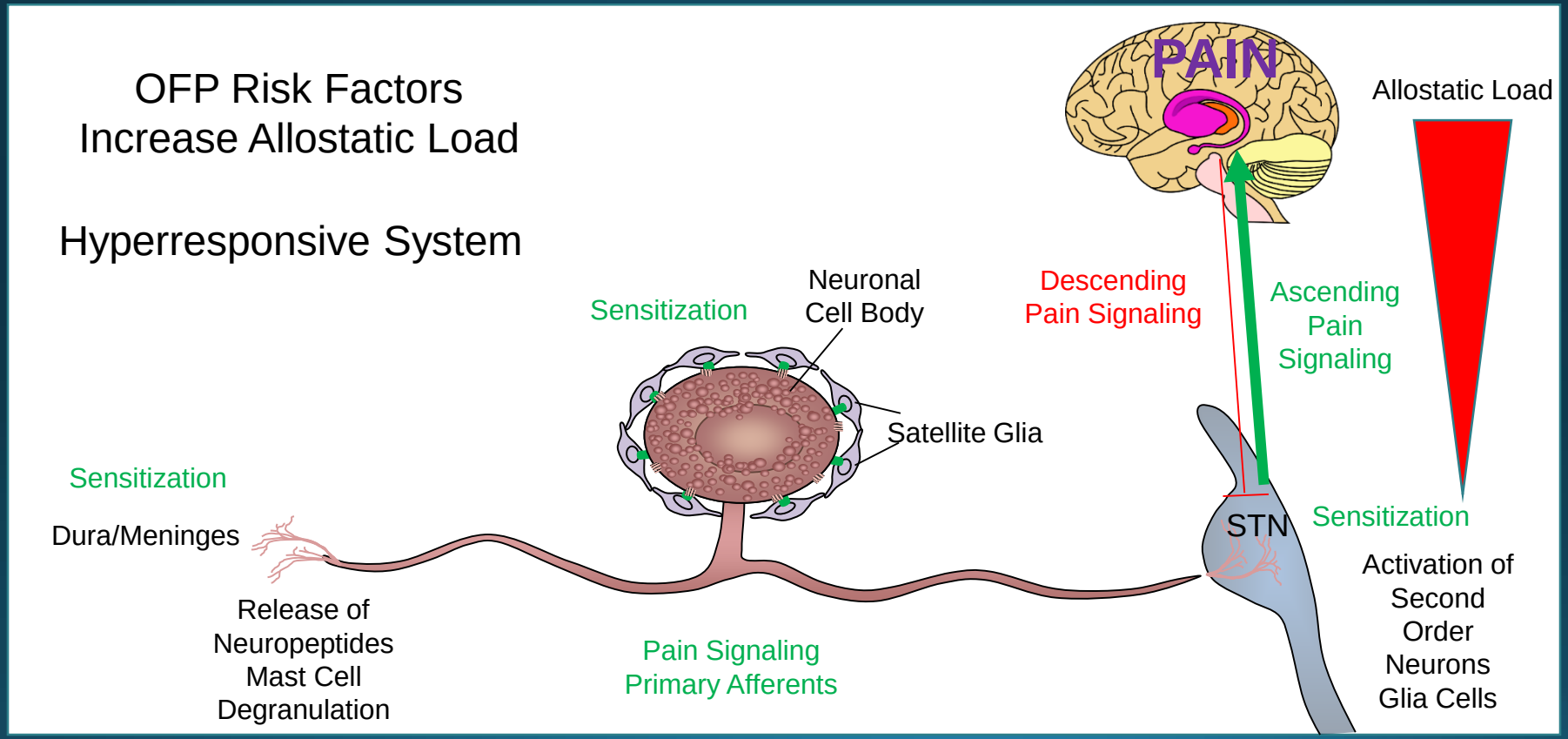
Plants represent an unparalleled reservoir of molecular diversity for drug discovery and development



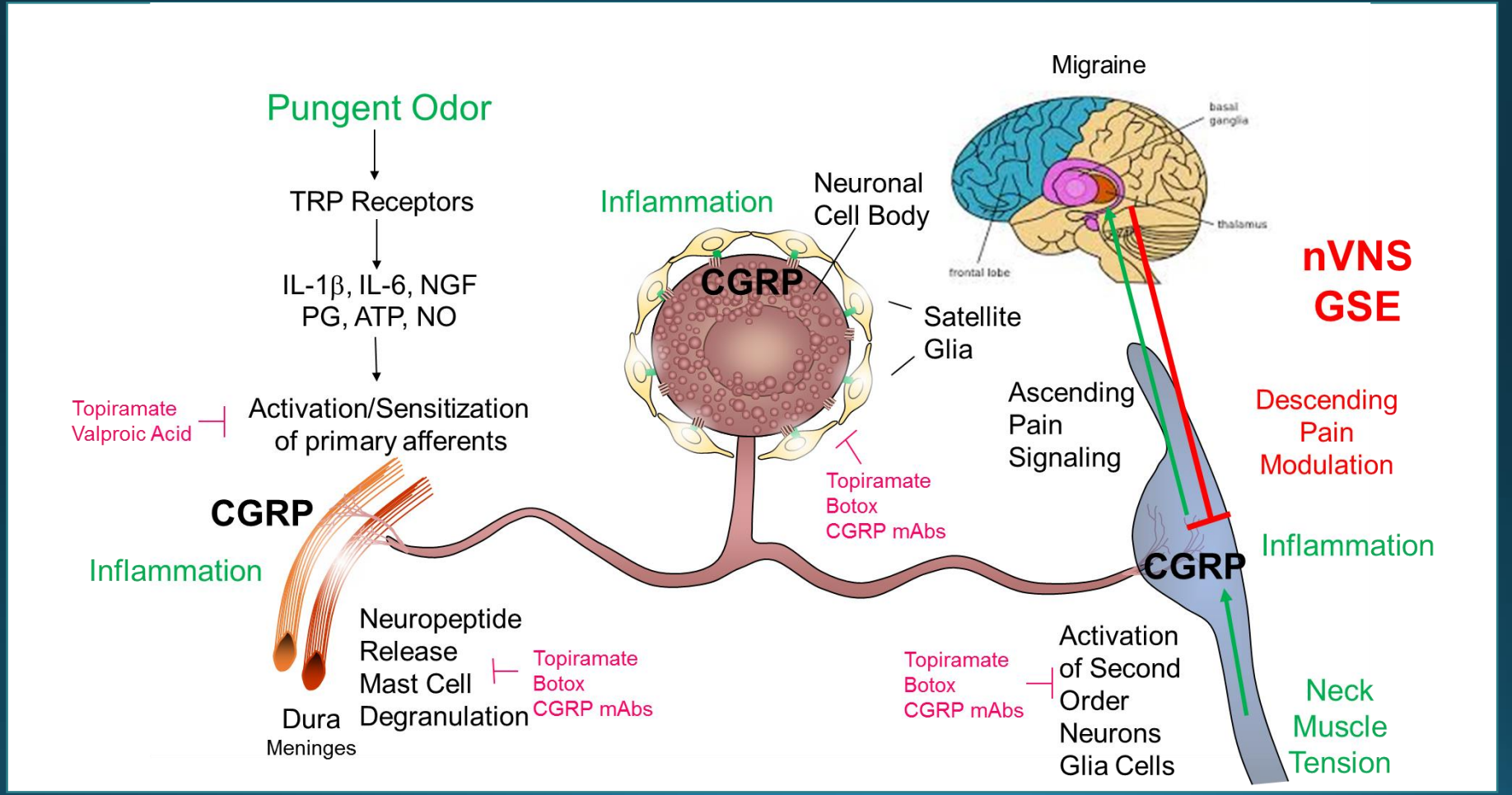
Homeostasis – Role of Ascending and Descending Pain Modulation to Balance Allostatic Load



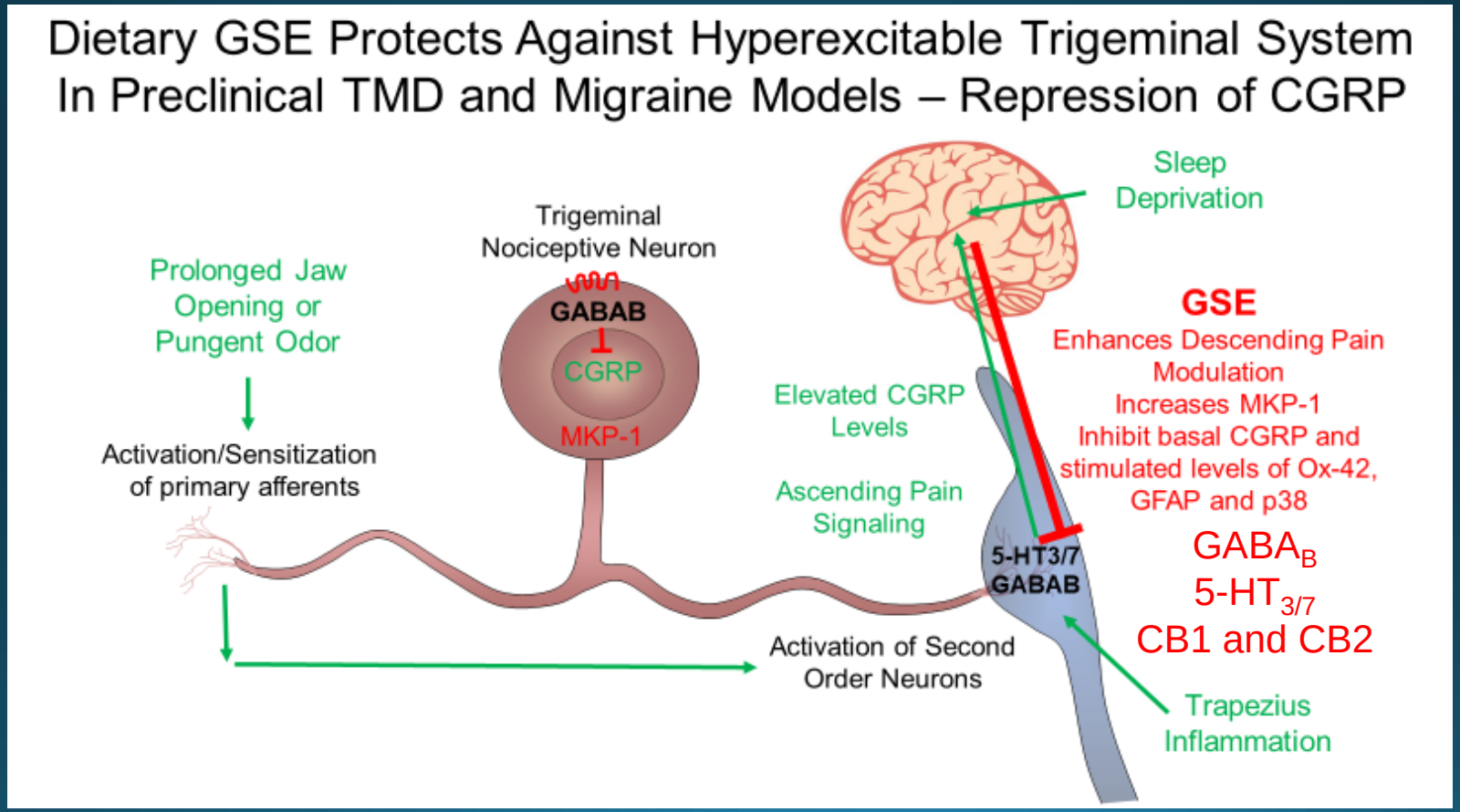
Orofacial Pain – Enhanced Ascending Pain Signaling and Diminished Descending Pain Modulation



Summary of Possible Therapeutic Mechanisms



Inhibitory Effects of Grape Seed Extract



Early Life Stress – Major Risk Factor for Developing Depressive Disorders and Migraine

Early life stress, such as childhood abuse, neglect and loss, is a well established major risk factor for developing depressive disorders later in life. Also risk factor for migraine (Tietjen GE, Headache, 2012)

Table 2 Stress-induced transgenerational inheritance of pathologies

Stress exposure	Pathology	Reference
Maternal separation and stress	Social anxiety and recognition and stress resilience	Franklin *et al.* 2011 [43]
Traumatic paternal stress (odorant)	Behavioral and neural metabolic responses	Dias *et al.* 2014 [44]
Gestational restraint and forced swimming	Preterm birth and prenatal growth and behavior	Yao *et al.* 2014 [1]

Minimizing Early Stress – Long-term Benefits

- Reducing prenatal and postnatal stress may help reduce the cost of treating adult diseases
- Ideally, intervention and prevention should be achieved before pregnancy begins
- Psychosocial interventions in early life can affect brain development and thereby benefit children at risk
- Other perinatal adversities such as perinatal infection, nutritional disorders, and toxin exposures must be cautiously avoided and treated

Primary Traumatic Stress

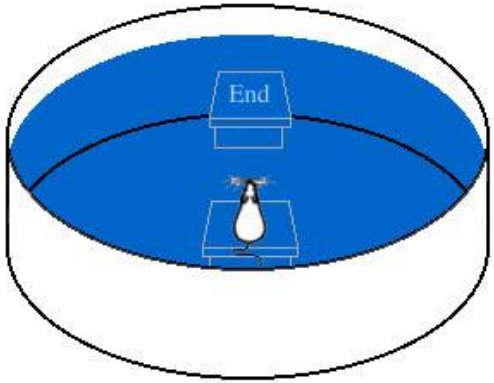
Individual is directly exposed to a stressor.

Secondary Traumatic Stress

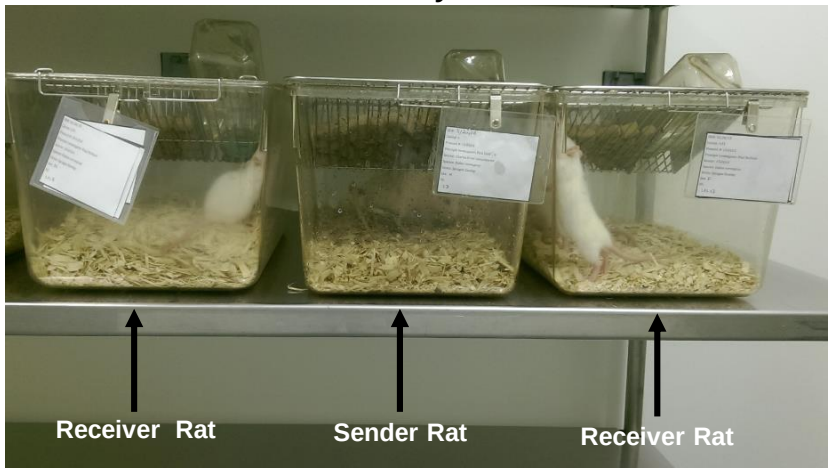
Individual hears about a traumatic experience or is around someone that has gone through a traumatic experience.

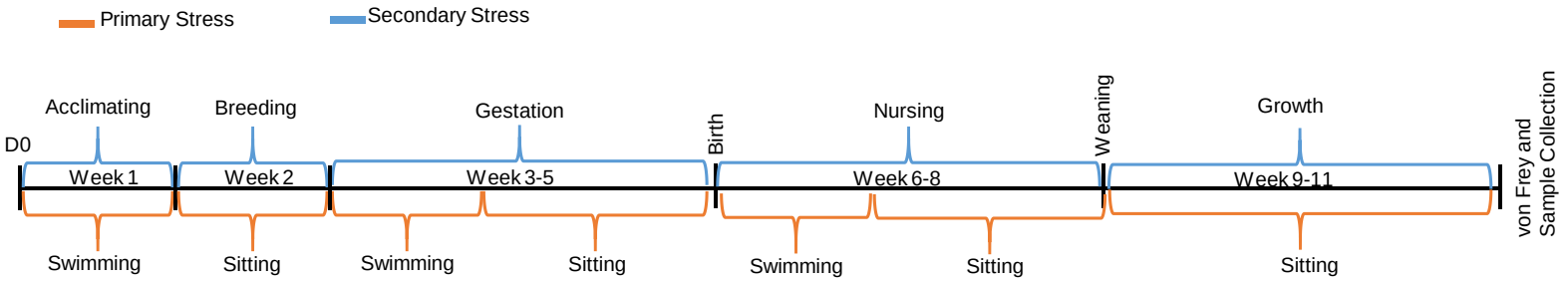
Model for Studying Secondary Traumatic Stress

Primary Stress



Secondary Stress





Hawkins, Moore, Miley, Durham. Brain Research 2018 May 15;1687:162-172

Early Life Stress – Risk Factor for Trigeminal Activation Episodic Migraine Model

Peripheral Sensitization

Pungent Odor - CBL

Primary Nociceptors

Neuronal Cell Body

Satellite Glia

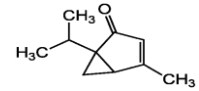
Trigeminal Ganglion

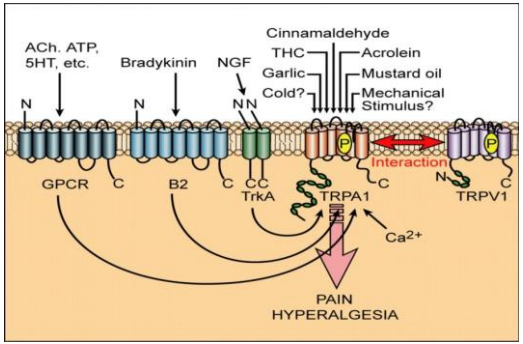
Early Life Stress

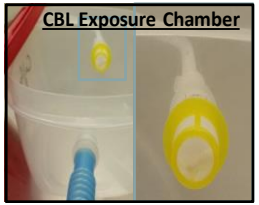
Central Sensitization

Sensitization of Second Order Neurons and Glia

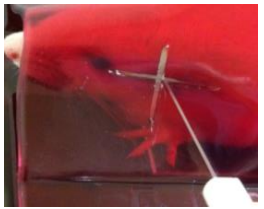
STN





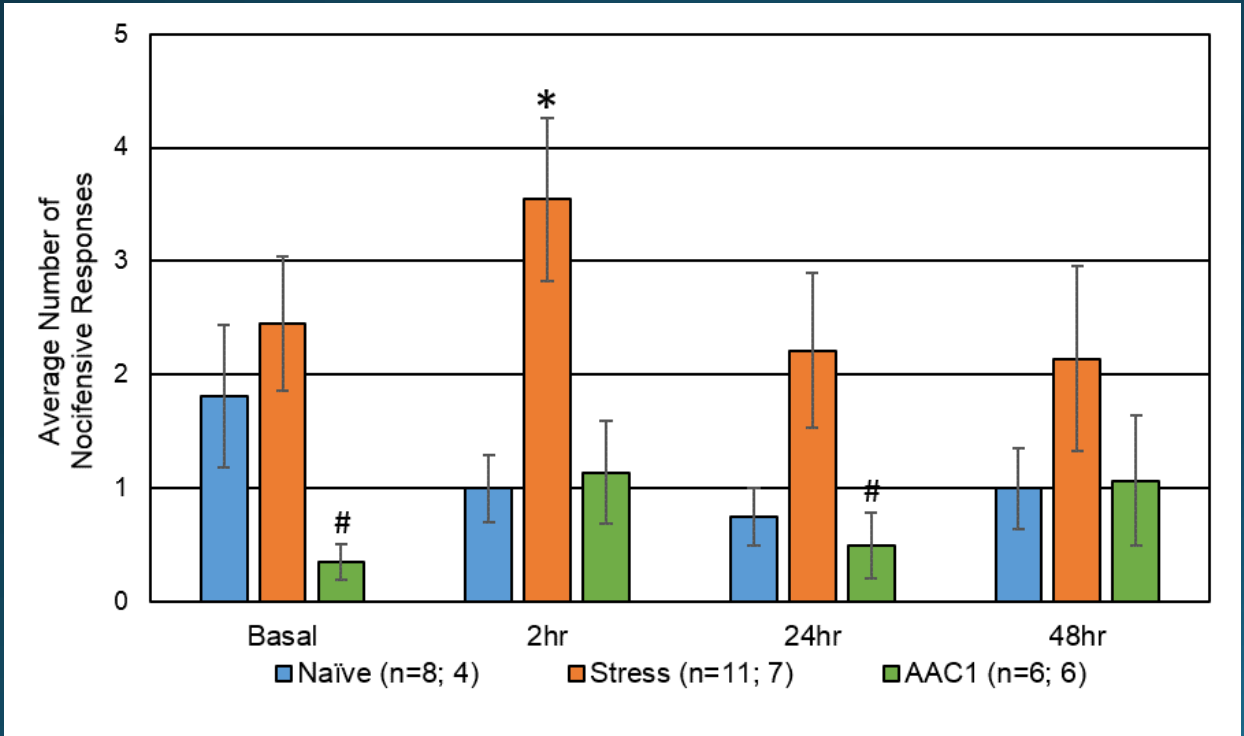


Testing mechanical sensitivity - von Frey filament



Hawkins, Moore, Miley, Durham. Brain Research 2018 May 15;1687:162-172

Dietary Supplementation with ECBB Inhibits Nociceptive Responses Induced by Odor Trigger in Female Offspring Exposed to Early Life Stress



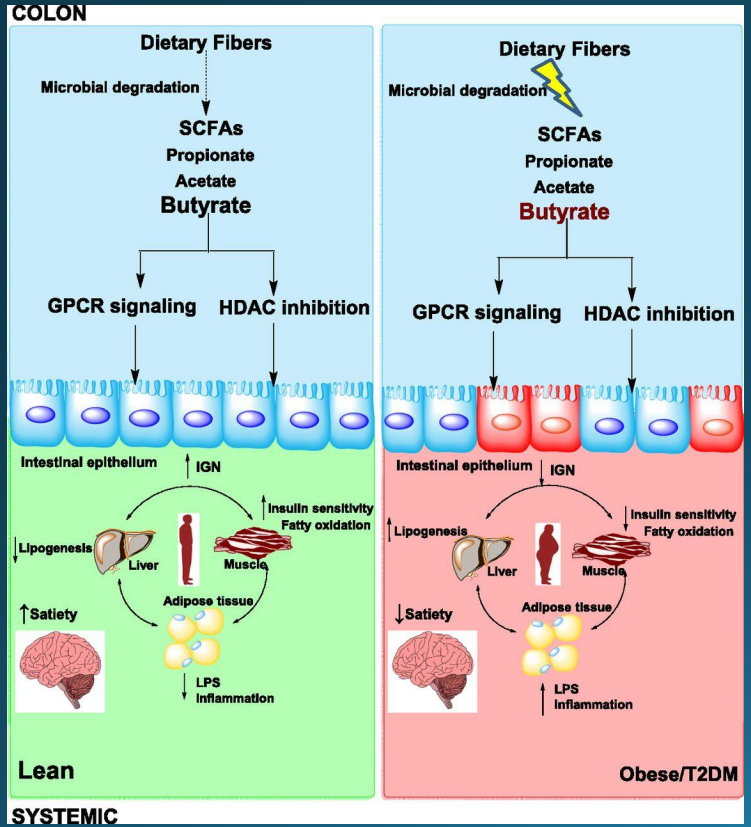
AAC1 = enriched chicken bone broth (ancient broth)

Two week supplementation in drinking water

* = $p < 0.05$

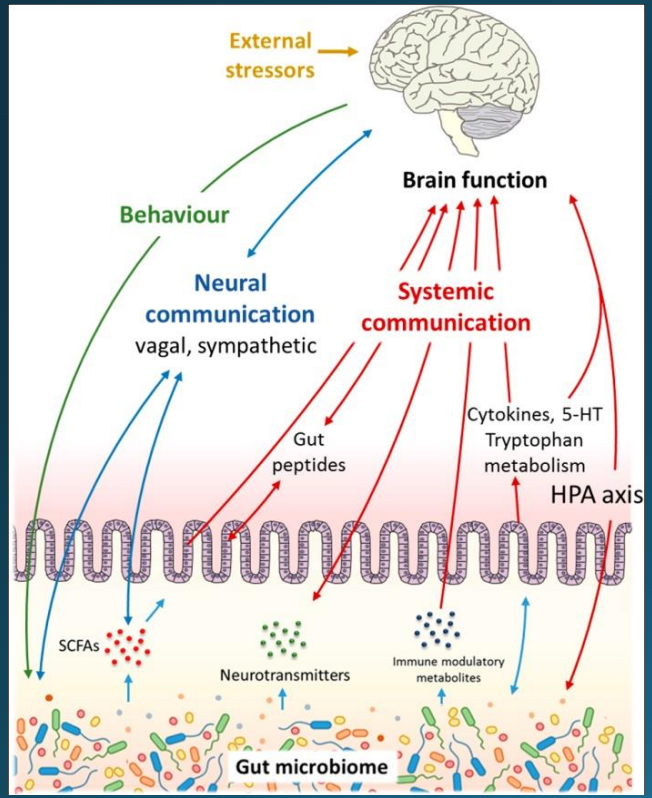
Peterson OJ, Cornelison LE, Durham PL. Neuroprotective Effect of Enriched Chicken Bone Broth as a Dietary Supplement in a Model of Migraine Mediated by Early Life Stress. J Med Food. 2020;23(12):1259-1265.

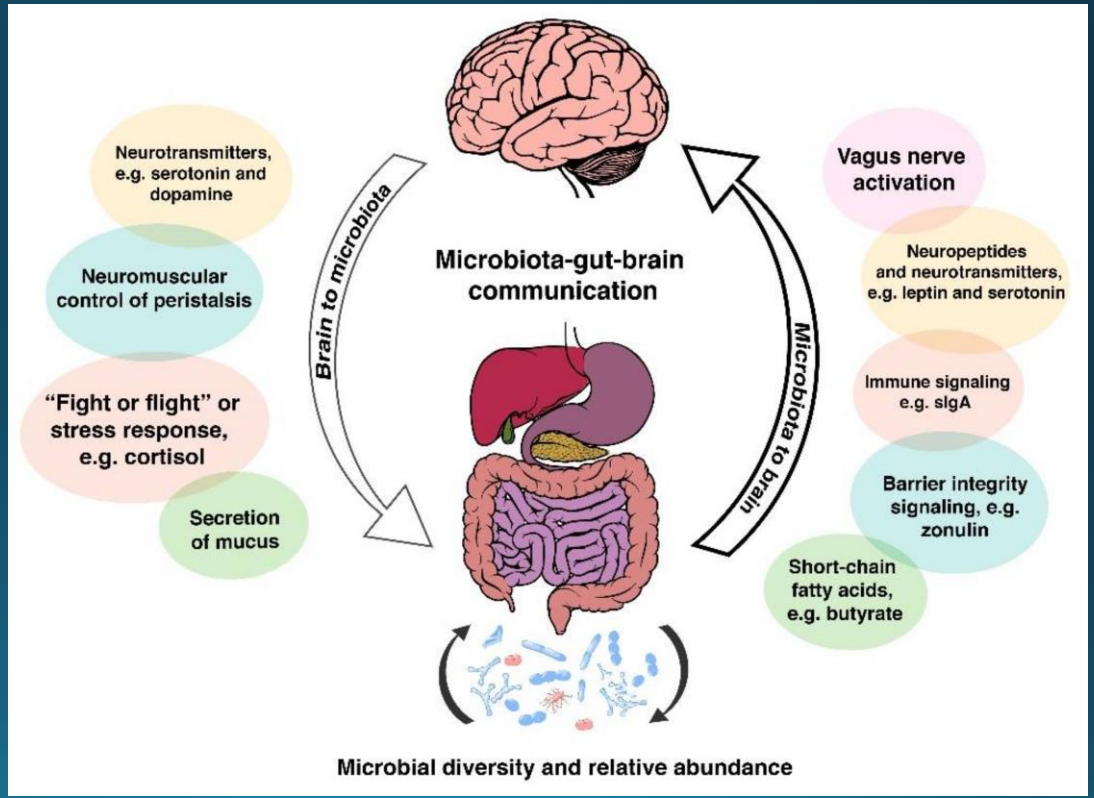
Inhibitory Effects of Enriched Bone Broth -- Dietary Fibers - Food for the Gut Microbiota



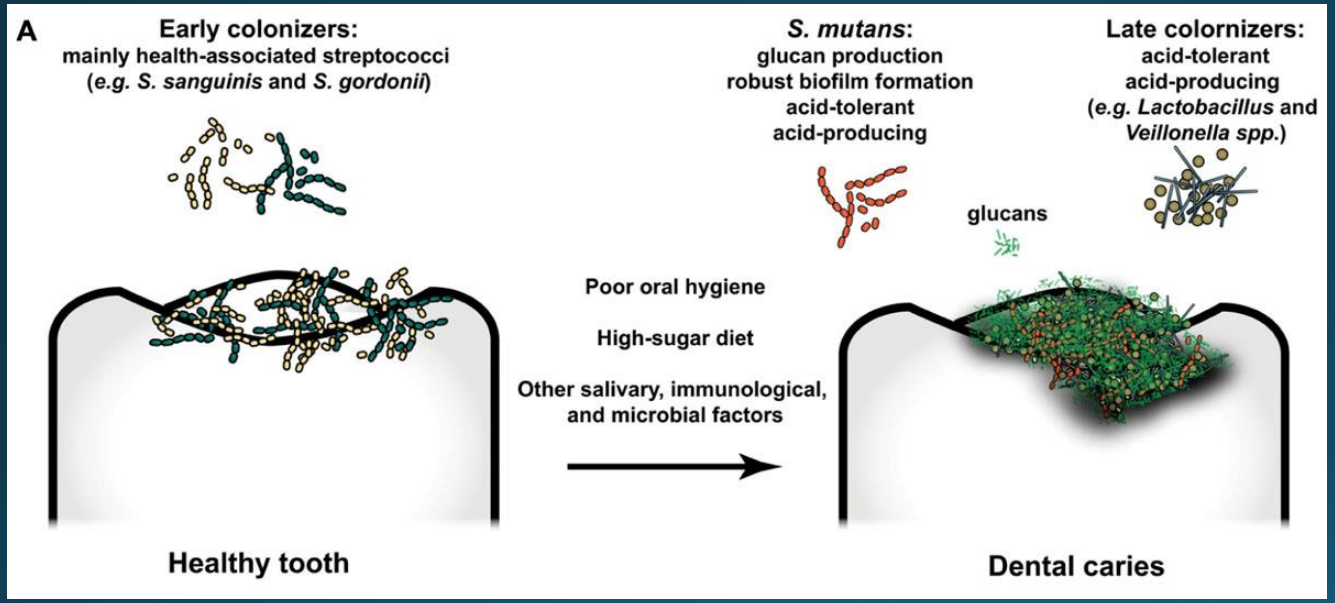
https://www.naturalfoodseries.com/21-best-foods-gut-health/

Dietary Supplements Act as Prebiotics to Maintain Healthy Gut Microbiota and Healthy Nervous System





Shift in Oral Microbiome Associated with Tooth Decay



Bacteria exists in your mouth on every surface including teeth, the area around tooth surfaces, tongue, hard palate as well as the area above and below the gums.

Front. Microbiol., 11 January 2019| https://doi.org/10.3389/fmicb.2018.03323

What Causes Shift in Oral Microbiome?

Signs of imbalance between the different species of oral bacteria are bad breath, bleeding gums, and tooth decay

- A diet high in refined carbohydrates and sugar.
- A diet low in fiber.
- A low pH in the mouth.
- Harmful oral-care products such as detergent-based toothpaste and mouthwashes containing alcohol.
- Vitamin D deficiency.
- Low levels of folate.
- Stress.
- A decrease in salivary flow.
- Mouth breathing leading to dry mouth.
- Acidic foods and drinks: soda, coffee, alcohol, and energy drinks.

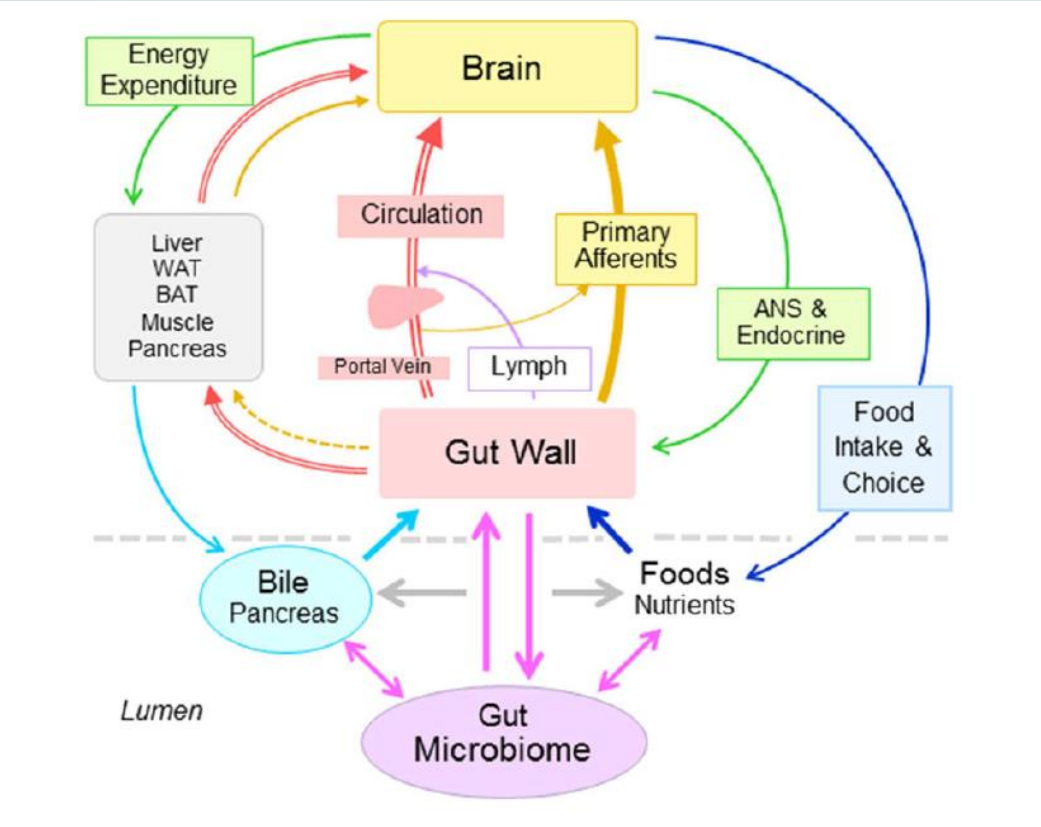
Important is to keep a healthy equilibrium of bacteria in our oral cavity to avoid progressive oral health issues

How To Maintain a Healthy Oral Microbiome

- Eat whole, nutrient-dense food with an abundance of colourful vegetables, high-quality protein, essential fatty acids, complex carbohydrates, and fermented foods.
- Increase green leafy vegetable intake.
- Eat a diverse selection of fiber.
- Eat and drink fermented foods on a regular basis like sauerkraut, kimchi, and kefir.
- Make sure you're getting enough fat-soluble vitamins including vitamins A, D, E, and K2.
- Make sure you're getting enough minerals, especially calcium, magnesium, and phosphorus.
- Optimise vitamin D levels. Essential for calcium absorption from diet.
- Get better relaxation (increase your sleep and reduce stress levels).
- Make time for regular exercise.
- Consume enough water.
- Avoid antibiotics.
- Avoid artificial sweeteners.

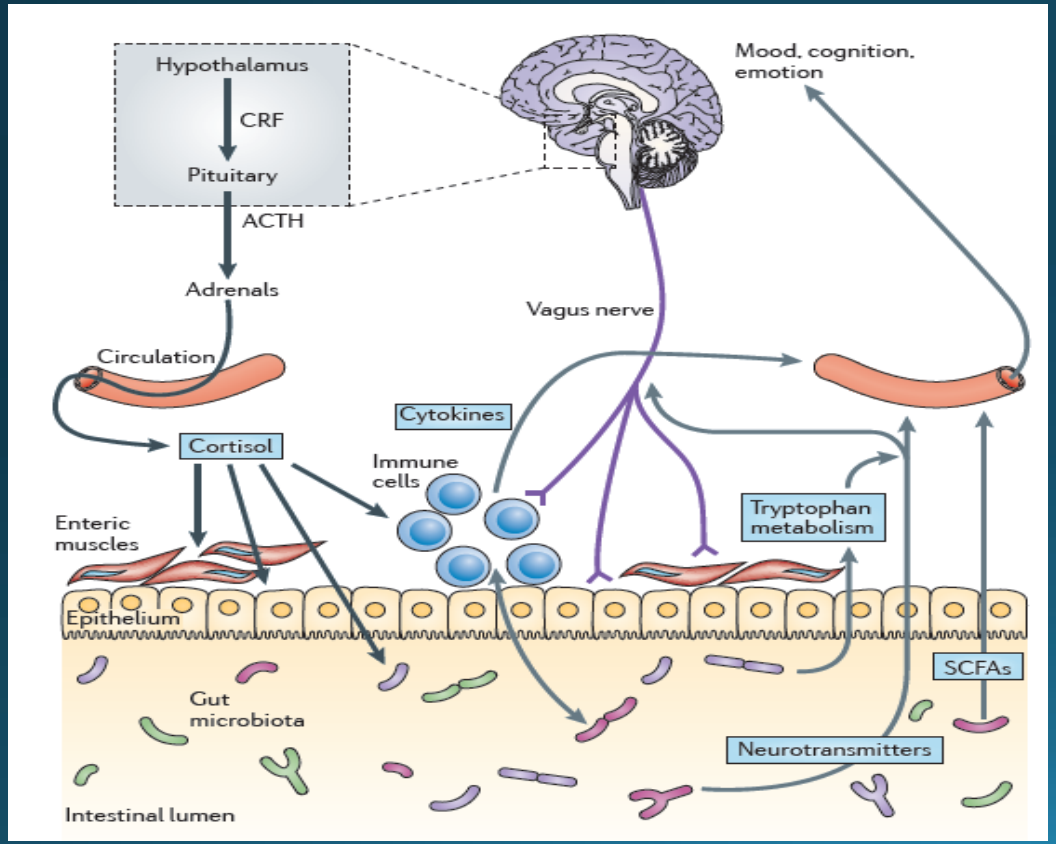
A healthy, balanced diet is more likely to deliver a variety of healing nutrients, help build enamel, prevent cavities, nourish the oral mucosa, promote saliva production, etc.

Dietary Maintenance of a Healthy Gut Microbiome Key to Human Mental and Physical Well-Being



Key Open Questions
1. Does intestinal dysbiosis impair mental health, and/or do mental health conditions disrupt intestinal microbiota?
2. Which microbes have the capacity to drive disease, and which are merely ancillary?
3. What are the mechanisms whereby altered microbiota disrupt brain function?
4. Can fecal samples adequately reflect intestinal microbiota across proximal-distal and luminal-mucosal axes?
5. Under what conditions are microbiome-based therapeutics (FMT, probiotics, and/or prebiotics) beneficial for mental health?

Healthy Brain = Healthy Gut
Key Role of HPA Axis

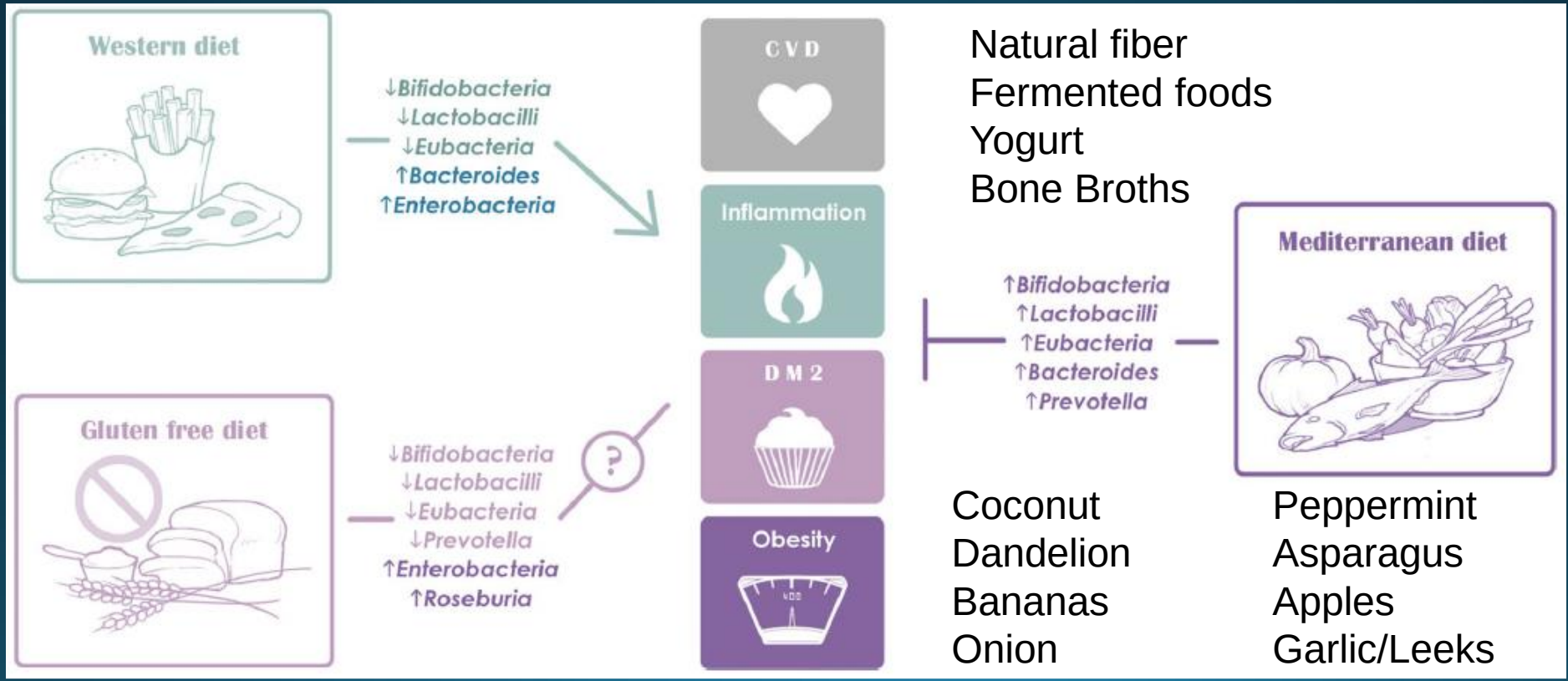


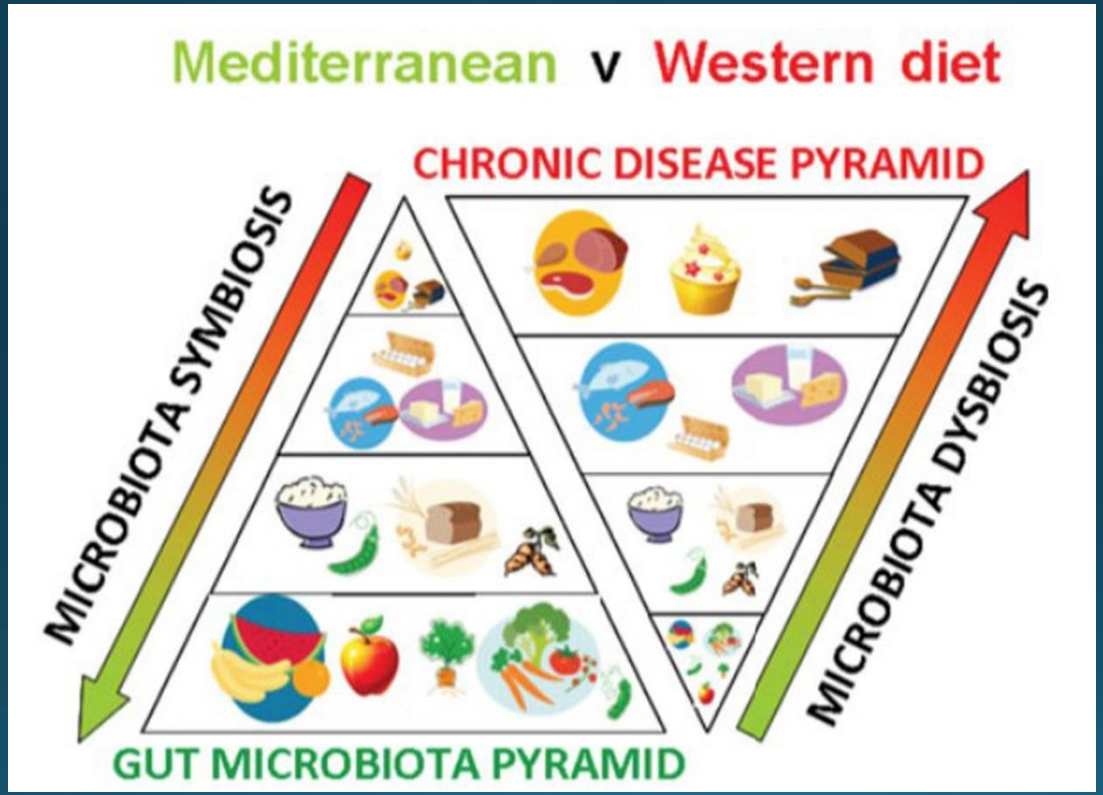
Chronic stress alters HPA axis

Changes expression of neurotransmitters that maintain brain and gut health

Need to “treat” both systems to restore homeostasis – stress management and diet

Impact of Popular Diets on Gut Microbiome and Human Health




Mediterranean v Western diet
CHRONIC DISEASE PYRAMID
MICROBIOTA SYMBIOSIS
MICROBIOTA DYSBIOSIS
GUT MICROBIOTA PYRAMID

Precision Nutrition and the Microbiome, Part I: Current State of the Science

nutrients

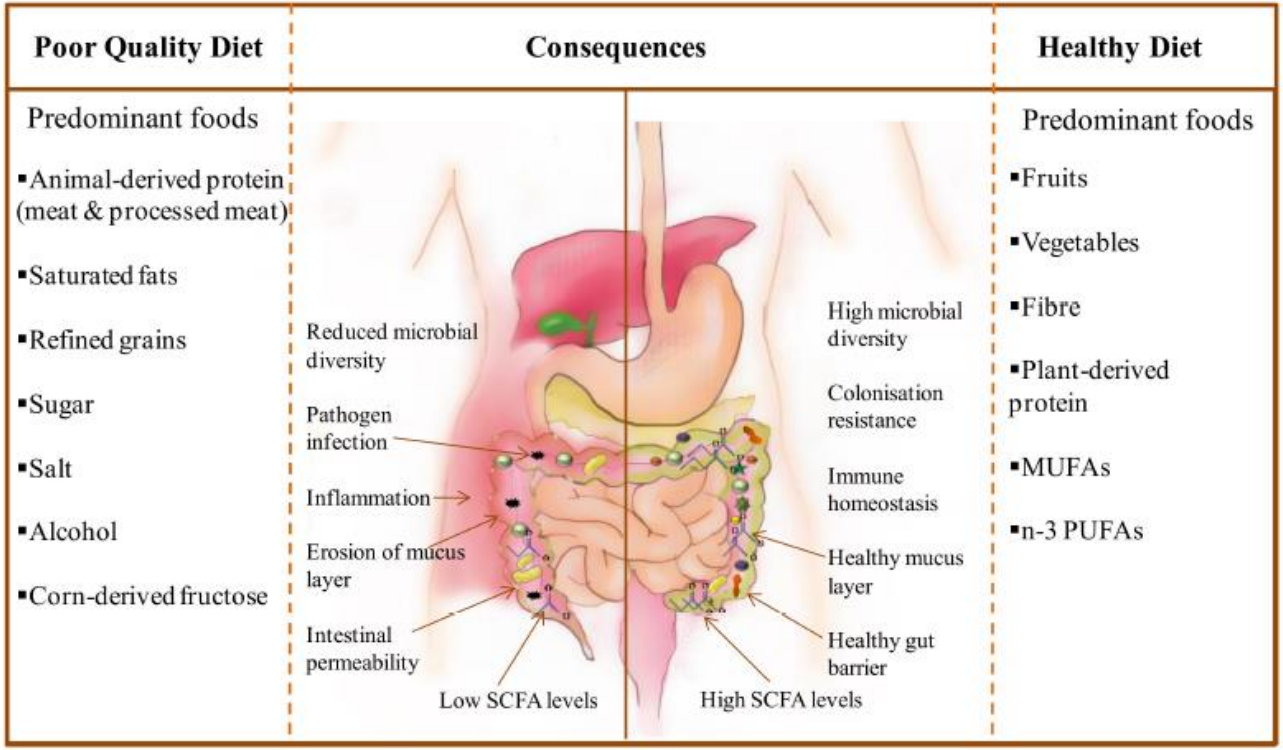


Figure 1. Comparison of consequences of poor-quality diet versus a healthy diet on the gut and gut microbiota (MUFAs = monounsaturated fatty acids; PUFAs = polyunsaturated fatty acids).

Inukshuk

"You are on the right path"

Goal of Health Care Professional:
Guide Patients Along Path to Good Health

SMILE

Regular Exercise

S
L
E
E
P

Good Relationships

D
I
E
T

Proper
Breathing

CBLS

Center for Biomedical
& Life Sciences