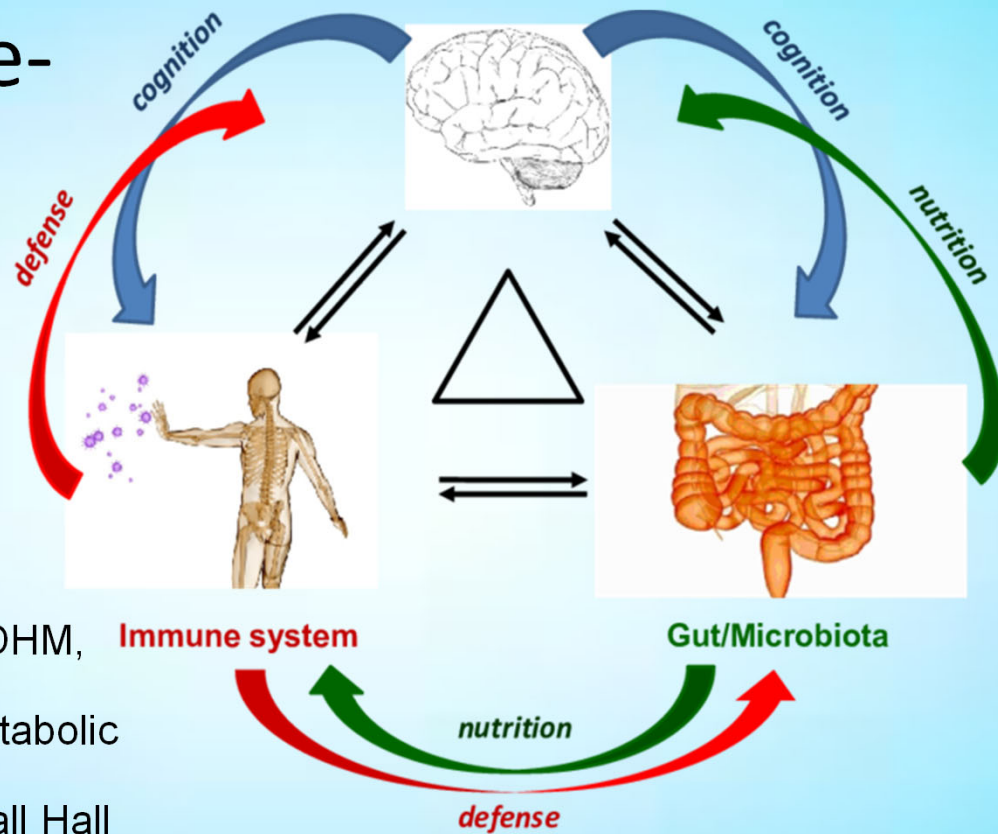


GUT-Immune- Brain Axis

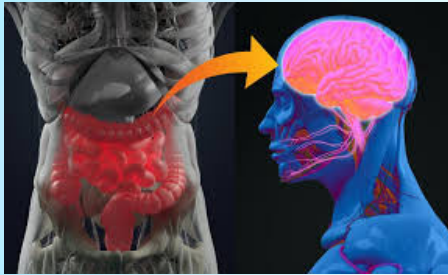


Jim LaValle, RPh, CCN, DHM,
DPh, N.D. (trad)
Founder and President, Metabolic
Code Enterprises
Clinical Director Pro Football Hall
of Fame Performance Health

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Gut-Immune-Brain



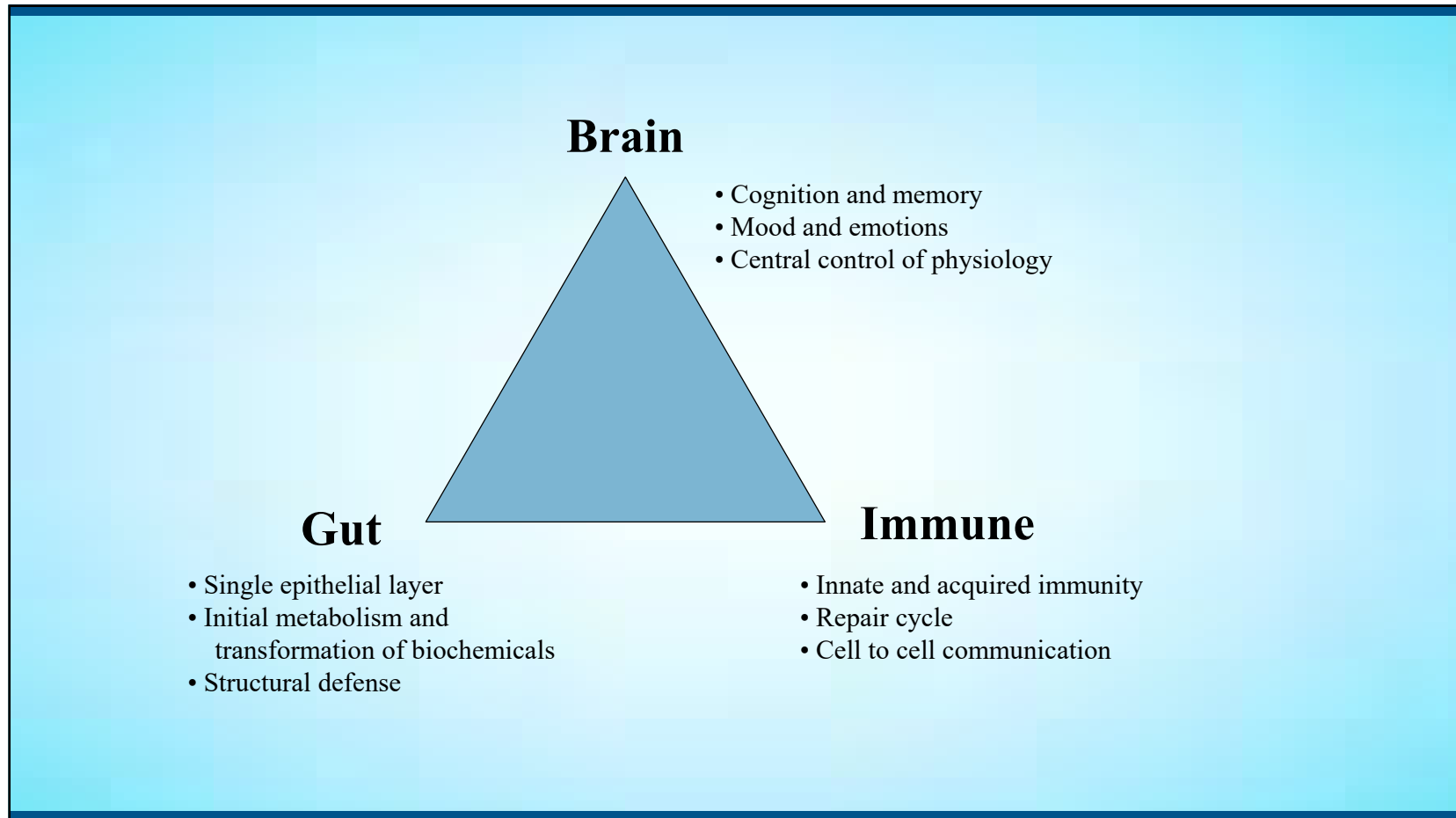
- Primary command and control
- Filtering, Defense and Repair
- Sleep regulation
- Memory
- Inflammatory responses
- Coordinates physical and emotional well-being
- Physiological Interfaces
- Normal: Organized – Secure
- Imbalanced: Disordered - Unpredictable

TRIAD 2 Characteristics

- Absorb and release appropriately
- Cellular intelligence
- Self knowing
- Calm borders
- Grounded
- Centered

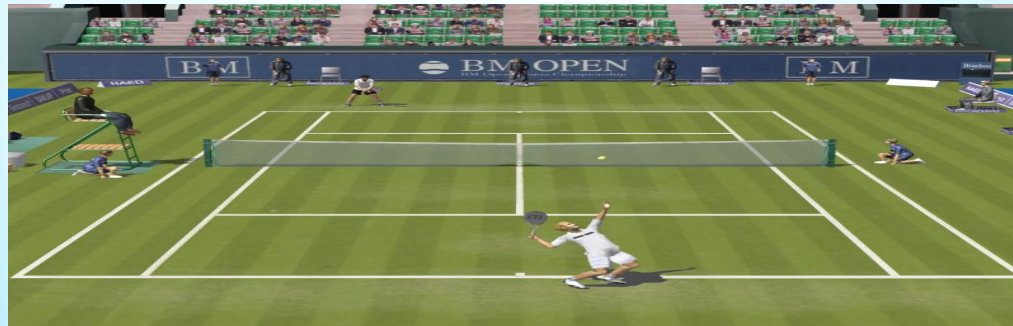
T2 Imbalances

- Weight gain
- Overeating due to food cravings
- Digestive complaints – belch, burp, full to ulcers/GERD, Inflammatory Bowel Diseases
- Allergies/food intolerances
- Sinus issues
- Colds/flu
- Memory problems
- Mood disturbances
- Sleep problems
- Fatigue
- Metaflammation
- Autoimmunity
- Nutrient absorption inadequate



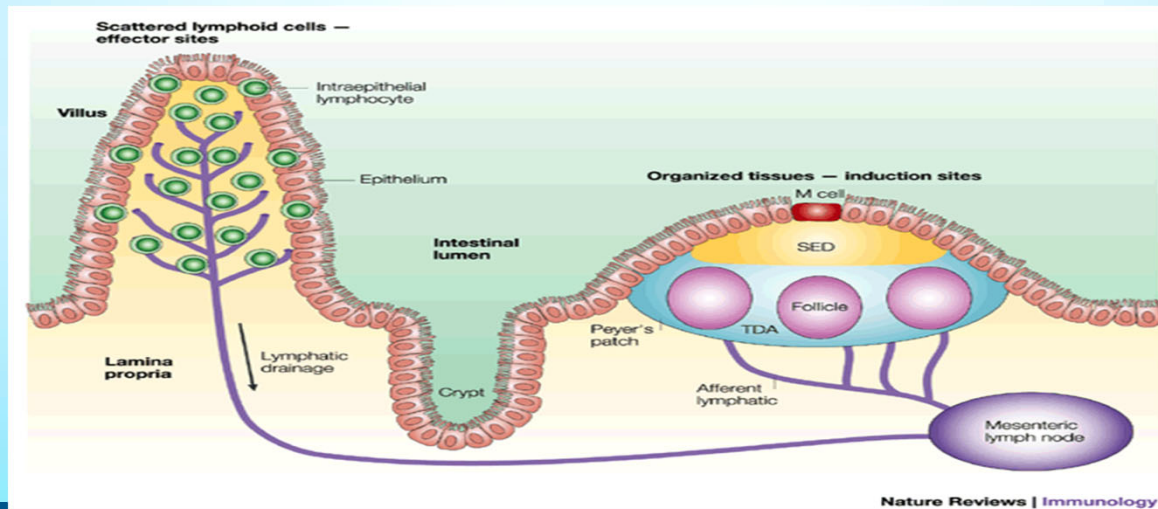
Intestine: Organ of Immune Tolerance

Intestinal mucosa: the largest area of the body in direct contact with exterior environment.
Expanded surface of the small intestine alone reaches roughly the size of a tennis court.

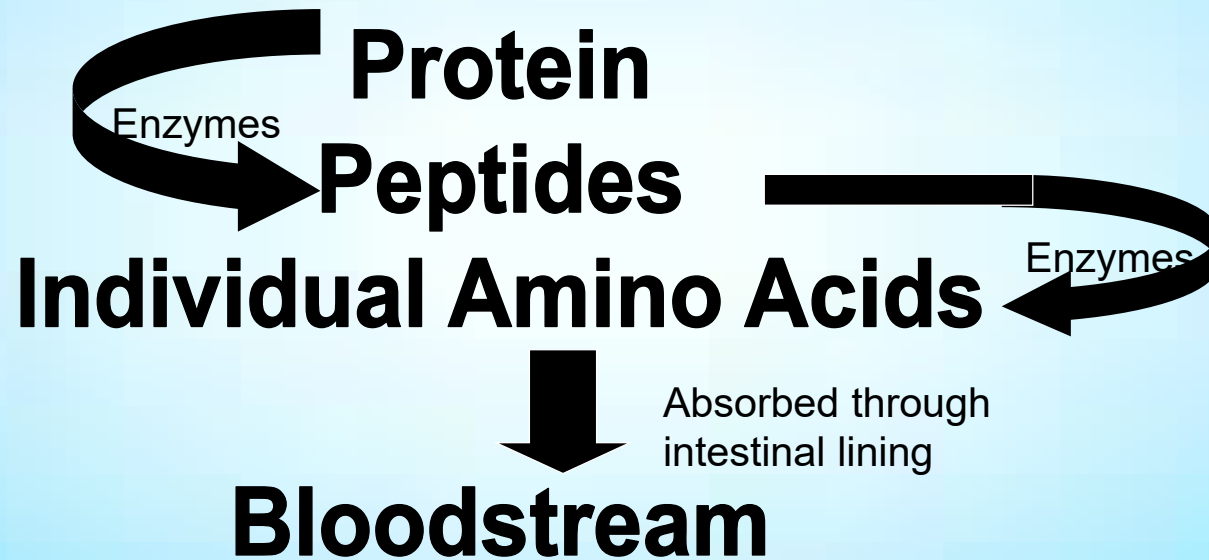


The Gut: Key Player in Immune Regulation

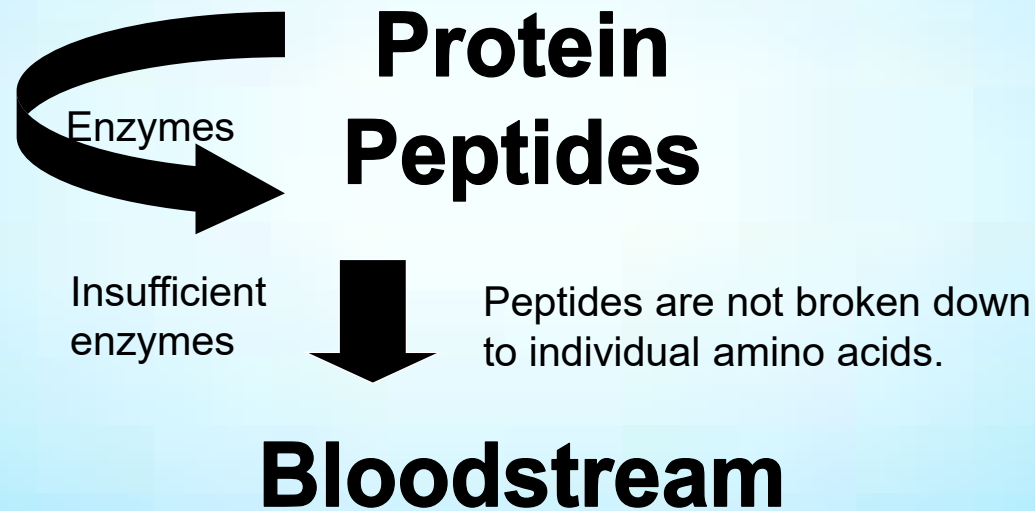
Intestinal mucosa contains diverse and large number of immune cells, mostly in the villi and lamina propria. Players in gut immune response include: Intraepithelial Lymphocytes, Gut-associated lymphoid-tissue (GALT), Peyer's patches (PP), isolated lymphoid follicles (ILFs), M cells and more.

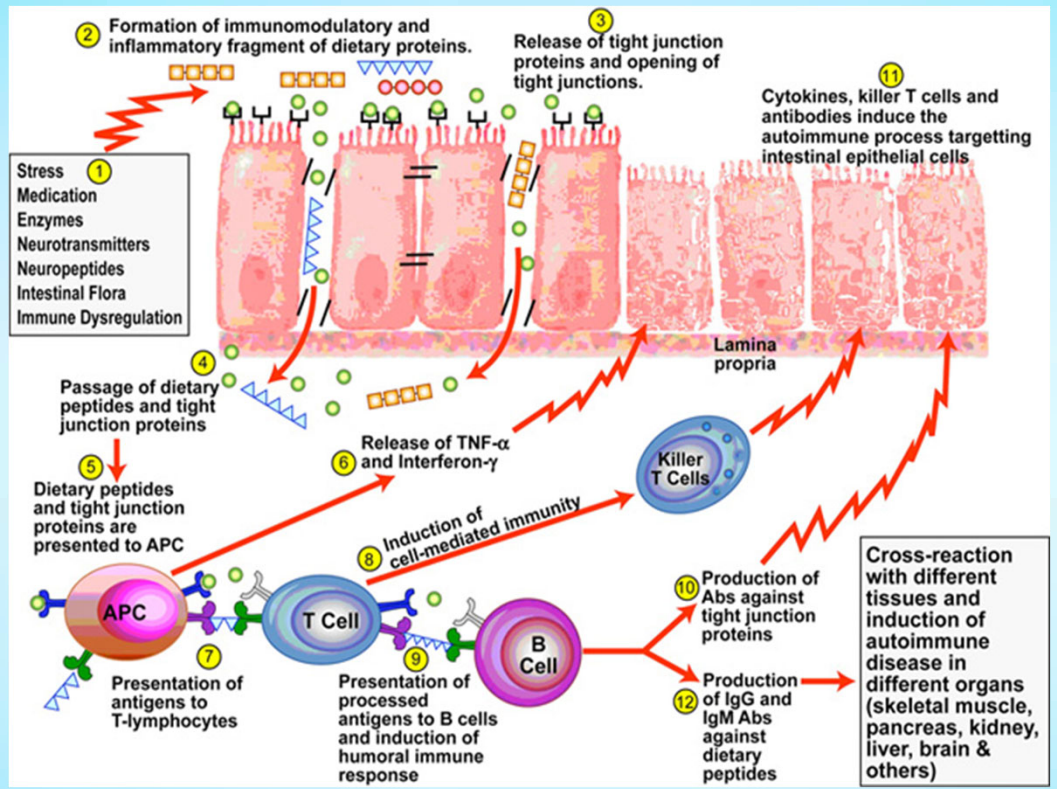


Normal Digestion



Abnormal Digestion



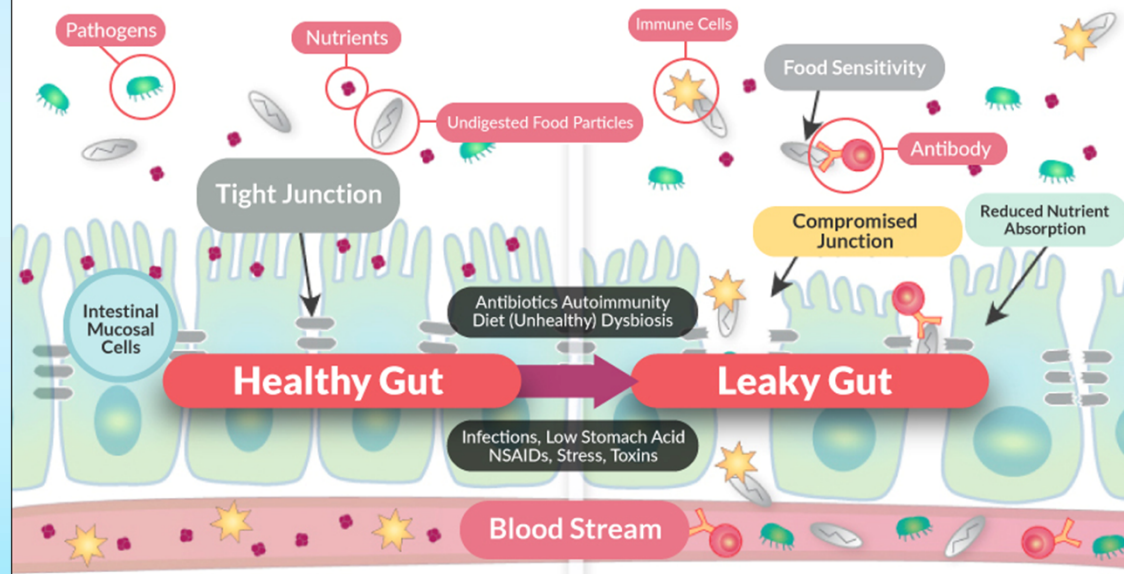


Gut as a Source of Inflammation

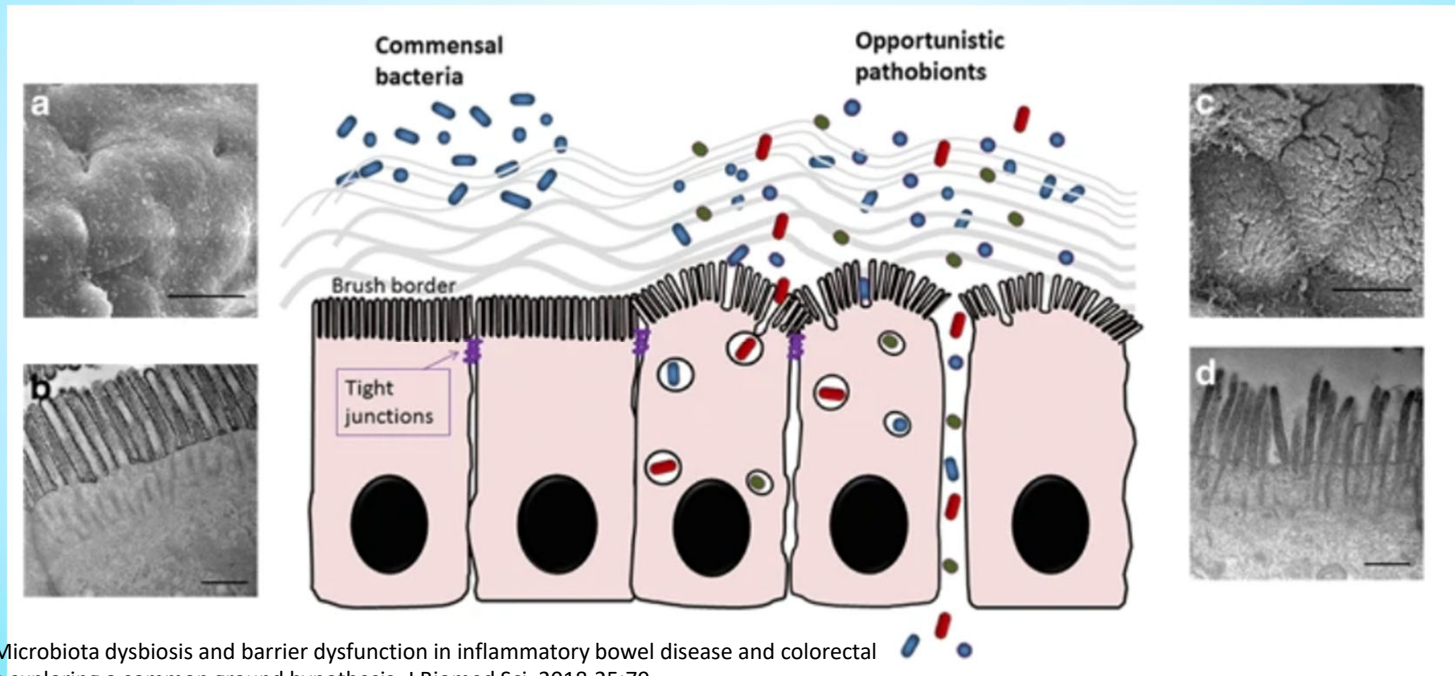
Over-activation of immunity in gut leads to increased production of inflammatory cytokines

Healthy Gut Versus Leaky Gut

A healthy gut works like a cheese cloth, allowing only nutrients through, but keeping larger food particles and pathogenic bacteria, yeast and parasites out. In a leaky gut, the tight junctions are loosened so undigested food particles and pathogens can get through and activate the immune system, causing inflammation and food sensitivities.

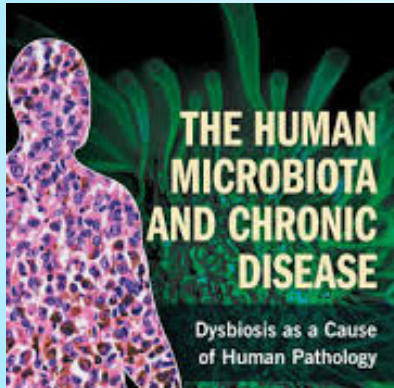


Electron Microscopy of GUT Epithelial Barrier Healthy vs. Non-Healthy



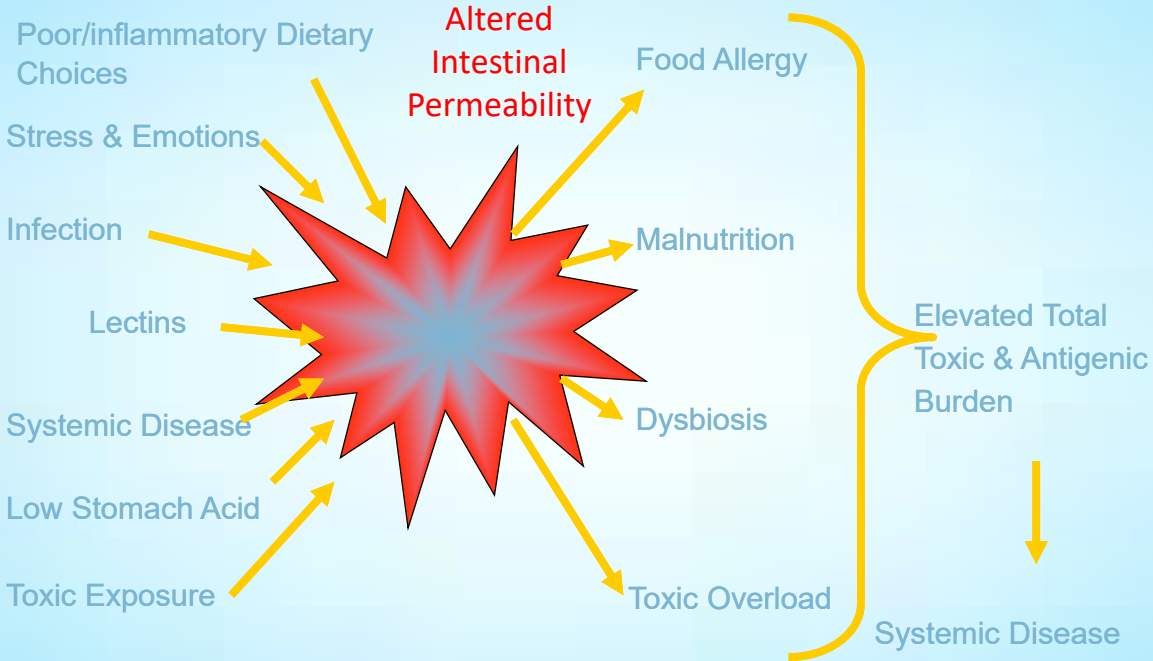
Yu, L.C. Microbiota dysbiosis and barrier dysfunction in inflammatory bowel disease and colorectal cancers: exploring a common ground hypothesis. *J Biomed Sci.* 2018;25:79.

Important Point:

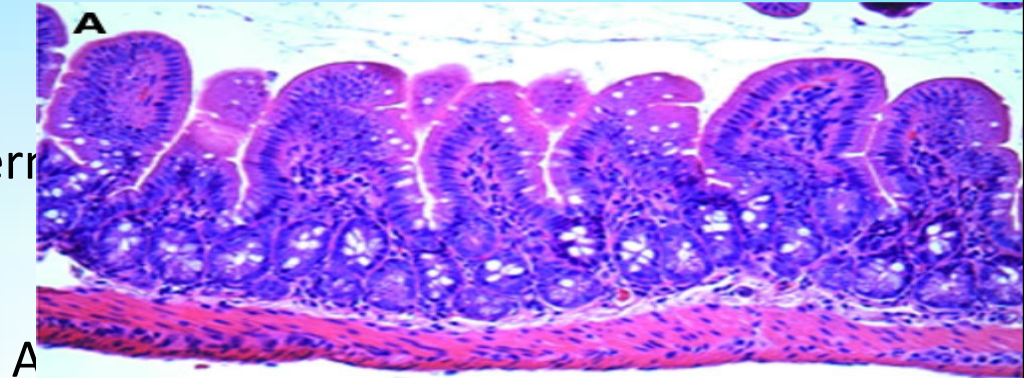


Most All Chronic Diseases
Are Reporting Dysbiosis -
Altered Microbiomes

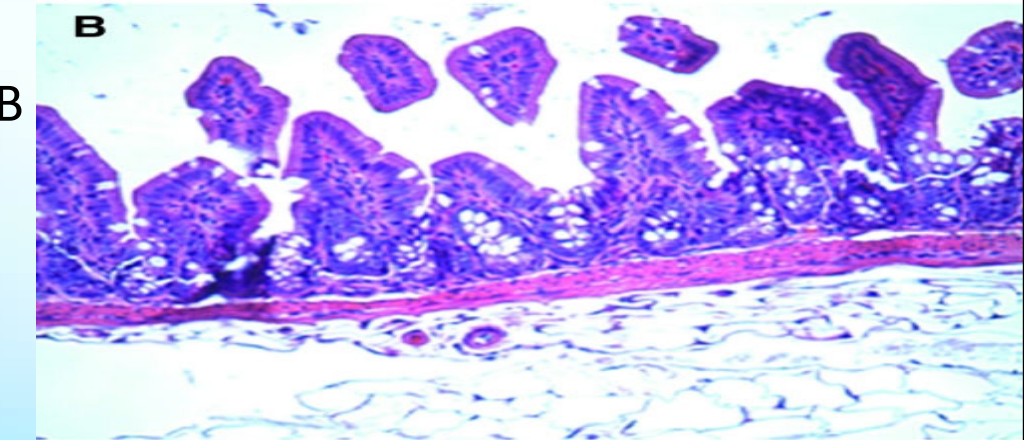
Leaky Gut - Pathophysiology



Terr

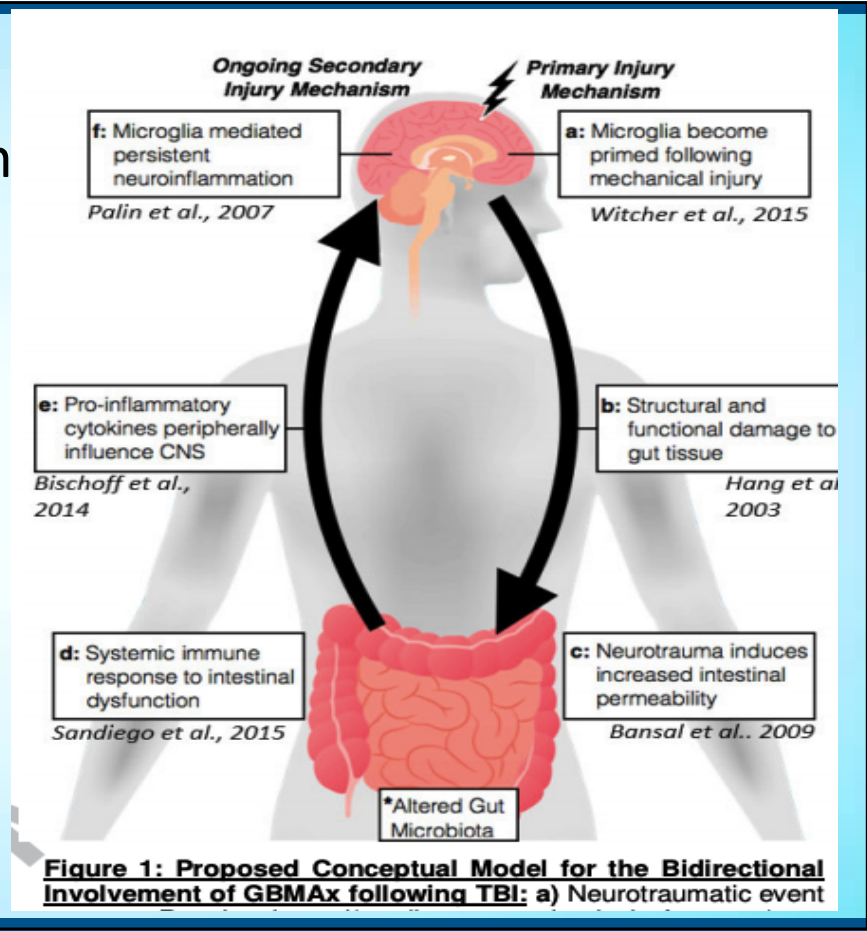


consis



Bansai V, et al. Traumatic brain injury and intestinal dysfunction: uncovering the neuro-enteric axis. *J Neurotrauma*. 2009;26(8):1353-59.

TBI and GUT-BRAIN Disruption



Zhu CS, et al. A review of traumatic brain injury and the gut microbiome: insight into novel mechanisms of secondary brain injury and promising targets for neuroprotection. Brain Sci. 2018 Jun; 8(6):113.

GUT as a Source of Metaflammation

- TBI leads to intestinal permeability
 - Via decreased expression of tight junction protein ZO-1 and occludin
- Over-activation of immunity in GUT leads to increased production of inflammatory cytokines
- Leaky gut allows bacterial and toxins to enter bloodstream
- Leads to peripheral and central inflammation

Viera M, et al. Translocation of a gut pathobiont drives autoimmunity in mice and humans. *Science*. 2018;359(6380):1156-61.

The facts on Irritable Bowel Syndrome

The facts

[IBS is a chronic gastrointestinal disorder of unknown cause]

IBS affects **35,000,000** people in the US

That's about **15%** of the population



1 in 7 Americans lives with IBS



2 out of every 3 IBS sufferers are women

Symptoms

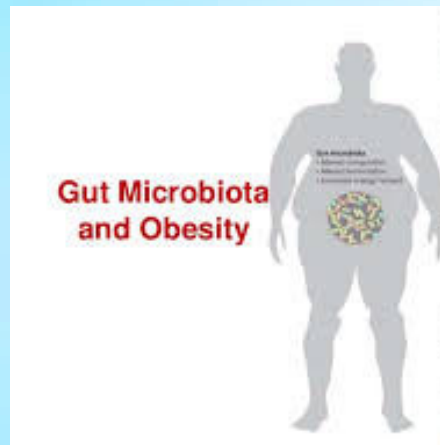
Abdominal pain or cramping
Diarrhea or constipation - often alternating
Gas (flatulence)



A bloated feeling
Feeling that a bowel movement is incomplete
Mucus in the stool

[To meet the definition of IBS, symptoms must occur at least **3 days** a month]

GUT Imbalances and Obesity



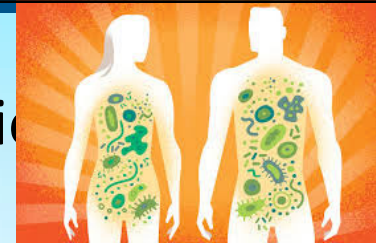
- Obesity characterized by low grade inflammation.
- Gut microflora imbalances linked to inflammatory conditions, obesity and type 2 diabetes
- Probiotics dampen inflammatory signaling
- Obese individuals commonly have imbalances in microflora
- GUT health important in metabolic homeostasis.
- Serotonin made in the gut.

Strowski MZ, Wiedenmann B. Probiotic carbohydrates reduce intestinal permeability and inflammation in metabolic diseases.Gut. 2009 Aug;58(8):1044-5.

Cani PD, Delzenne NM. The role of the gut microbiota in energy metabolism and metabolic disease. Curr Pharm Des.2009;15(13):1546-58. Review.

Das UN. Obesity: Genes, brain, gut, and environment. Nutrition. 2009;Dec. 22, Ahead of Print.

What Are Beneficial Probiotics



- Probiotics are defined as “microorganisms that have a beneficial effect on the host intestinal microbial balance”
- They make up our microbiome skin, GUT, mouth
- Confer health benefits to the host – they produce vitamins and nutrients and also help metabolize hormones
- Probiotics support the GUT-Immune-Brain Axis

Probiotics



- Probiotic flora consists of over 400 species of bacteria
- Enhanced immunity
- Interact with mucosal cells of GUT to provide a barrier against pathogens
- Microfloral imbalances
 - Overtraining; intense physical exercise
 - Poor food choices – high sugar, pesticides, additives, preservatives, antibiotics, hormones, red meats
 - Chronic stress
 - Impure water
 - Drugs

Probiotics play an essential role in:

- Immune modulation
- Population control of pathogens
- Nutrient absorption and metabolism
- Allergies/Intolerances
- Hormonal Regulation
- Brain – mood cognition
- Cancer development and metastasis

Park C, et al. Probiotics for the treatment of depressive symptoms: An Antiinflammatory mechanism? Brain Behav Immun. 2018;[73:115-124.

GUT Microbiome Diversity



Helps control inflammatory responses

Immune modulation

GUT microbiome diversity important for chronic conditions

Obesity related to microbiome phylum changes and loss of functional diversity

Human GUT microbiome generally 4:1
(Bifidobacterium to Lactobacillus)

Functions of Beneficial Flora

- Make vitamin K and biotin via nutrient metabolism
- Functions in digestion of foods, absorption and use of nutrients
- Detoxify compounds from food or created in digestion process (probiotics have been found to decrease colon cancer risk)
- Helps metabolize estrogens in the body via inhibiting beta glucuronide.

Cani PD, Delzenne NM. The role of the gut microbiota in energy metabolism and metabolic disease. *Curr Pharm Des.* 2009;15(13):1546-58. Review.

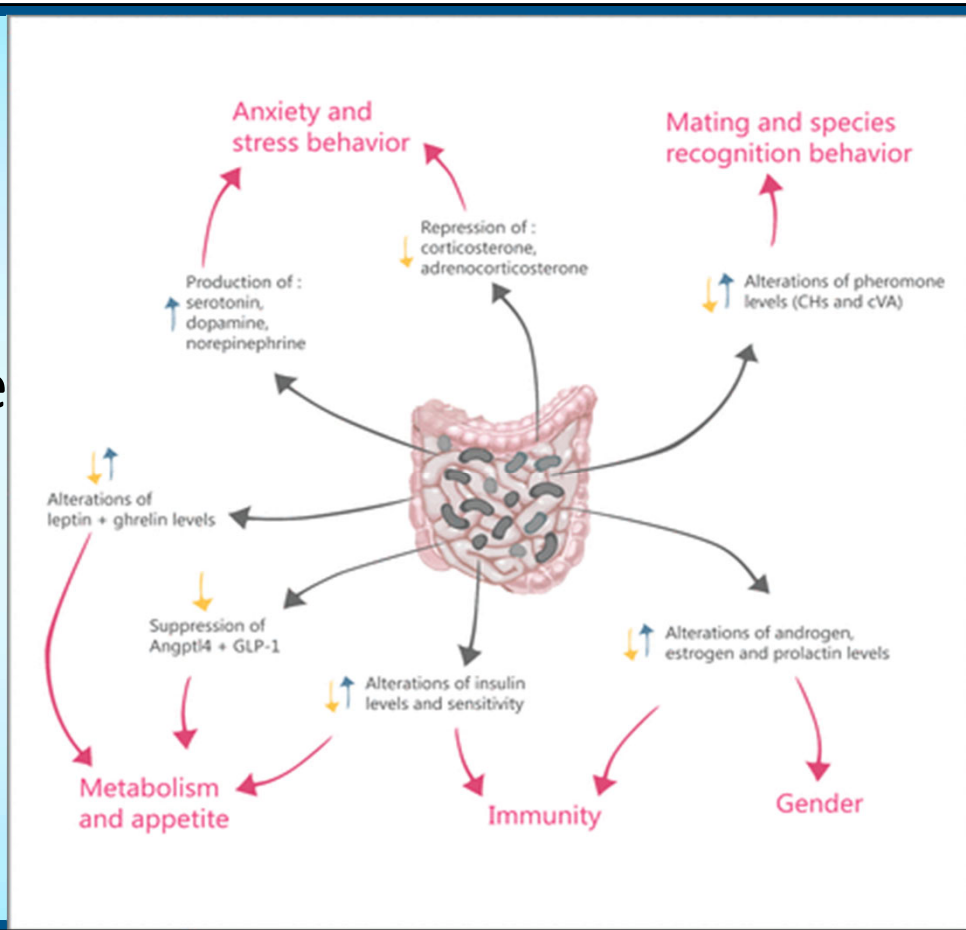
Functions of Probiotics

- Synthesize short chain fatty acids (SCFA)
- SCFA a primary source of fuel for intestinal epithelial cells, keeps them from flattening out.
- Butyrate - helps remove lipid soluble toxins
- Butyrate protects intestinal cells from abnormal growth, and may protect against colon cancer
- SCFA' s improve acidic environment in the intestines
- Acidic environment decreases pathogenic overgrowth

Cani PD, Delzenne NM. The role of the gut microbiota in energy metabolism and metabolic disease. *Curr Pharm Des.* 2009;15(13):1546-58. Review.

Effects of Microbiome on Host Hormones

Neuman H, et al.
Microbial endocrinology: the interplay between the microbiota and the endocrine system.
FEMS Microbiol Rev. 2015;39(4):509-21.



Factors Influencing Microflora

- DRUGS
- Sugar intake / diet
- Bactericidal chemicals in drinking water
- Food pesticide residues, food additives, preservatives, flavoring and manufacturing agents
- Alcohol
- Heavy metals
- *H. pylori*
- Gastrointestinal pH
- Stress
- Bowel transit time
- Allergies
- Intense Exercise

Microflora Disruption Can Lead To...

- Increased food allergies/intolerances
- Digestive problems like IBDs, IBS, Crohn's, colitis
- Increased sleep and mood disturbances
- Fatigue
- Increased time to recovery
- Increased joint and connective tissue issues
- Decreased performance and exercise ability
- Memory and cognitive decline
- Cancer
- Sex hormone issues – testosterone, estrogen
- Thyroid imbalance
- Nutrient deficiencies – vitamin D, B vits
- Food cravings
- Immune problems
- Cardiovascular problems
- Chronic Inflammation
- NAFLD non-alcoholic fatty liver
- Weight gain

Probiotic Supplement Use Meta-Analysis

- Meta- analysis 1970-2011
- 79 randomized, controlled trials in 10,351 patients comparing probiotic to placebo
- 11 probiotic strains
- The Question - Are probiotics beneficial in treating gastrointestinal diseases, including
 - Infectious diarrhea
 - IBS
 - *H. pylori* infections
 - *C. Difficile*
 - Antibiotic Associated Diarrhea
 - Traveler's Diarrhea
 - Necrotizing enterocolitis
 - Pouchitis
- The results: YES for all (statistically significant positive outcomes over placebo)

Ritchie ML, et al. A meta-analysis of probiotic efficacy for gastrointestinal diseases. PLoS One. 2012;7(4):e34938.

Probiotic Use Cochrane Database Review

- 2018 Cochrane Collaboration Overview of 14 Cochrane Database Systematic Reviews from 2006-2015
- Focused on probiotic supplementation and GI related medical conditions
- RESULTS:
 - Probiotic use does have a beneficial effect on diarrheal conditions and related GI symptoms

Parker EA, et al. Probiotics and gastrointestinal conditions: an overview of Evidence from the Cochrane Collaboration. *Nutrition*. 2018;45:125-34.

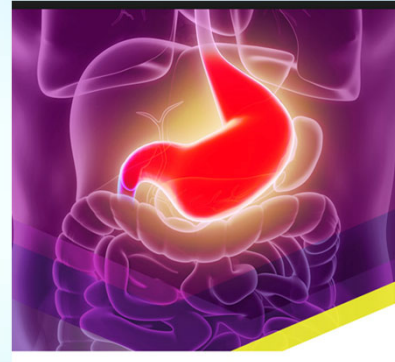
GUT Microbiome and Drugs

- Almost 60% of the population takes at least 1 prescription daily – leading to DIMD, DIND
- Study tested 1,100 drugs on 40 representative human GUT bacterial strains
- 25% of drugs affected bacterial growth
- Possible new source of antibiotic resistance
- Major source of TRIAD 2 imbalances that lead to chronic health conditions

Maier L, et al. Extensive impact of non-antibiotic drugs on human gut bacteria. Nature. 2018;555:623-28.

Drug Induced Microbiome Disruption (DIMD)

- Prescription and non-prescription drugs can alter the microbiome
- Potentially disrupting metabolic pathways
- Affects all facets of metabolism
 - Nutrient absorption
 - GUT-IMMUNE-BRAIN axis
 - Blood glucose balance/insulin resistance
 - Hormonal balance – sex / thyroid / appetite
 - Sleep
 - Detoxification



DIMD = Drug Induced Microbiome Disruption

- Study tested 1,100 drugs on 40 representative GUT bacterial strains
- 25% of drugs affected bacterial growth *in test tube studies*
- Almost 60% of the population takes at least 1 prescription daily
 - In 2014 it was 46.9%
 - In 1994 it was 39.1%
- Possible new source of antibiotic resistance
- DIMD = Drug Induced Microbiome Disruption

Bastard QL, et al. Systematic review: human gut dysbiosis induced by non-antibiotic prescription medications. *Aliment Pharmacol Ther.* 2018;47(3):332-45.

What Drugs Commonly Affect the Microbiome?

- Antibiotics
- NSAIDs
- Corticosteroids
- OCs/HRT
- PPIs / H2 blockers
- Metformin
- Statins
- Antipsychotics
- Opioids
- Others not tested?



Bastard QL, et al. Systematic review: human gut dysbiosis induced by non-antibiotic prescription medications. *Aliment Pharmacol Ther.* 2018;47(3):332-45.

STRESS

Effects on GUT-Immune-Brain TRIAD

- Immune issues
 - Chronic cytokine upregulation
 - DHEA ratio to cortisol ↓ = Th1/Th2 imbalances
 - ↑ illnesses and ↓ resilience
 - ↑ Autoimmunity
- BRAIN
 - Sleep pattern disruption
 - ↑ cognitive deficit
 - ↑ risk of neurodegenerative conditions
 - ↑ neuroinflammation
 - ↓ neurogenesis
 - ↑ mood disturbances – anxiety, depression, psychiatric complaints, cravings/addictions

Aging, Inflammation and Gut Permeability

IL-6 is unregulated with aging leading to disruption of the permeability of the gut.

Age Associated modifications of intestinal permeability and innate immunity in human small intestine, Man, A., Bertelli, E., et al; Clinical Science Jul 03, 2015 129 (7) 515-527; DOI 10.1042/CS20150046

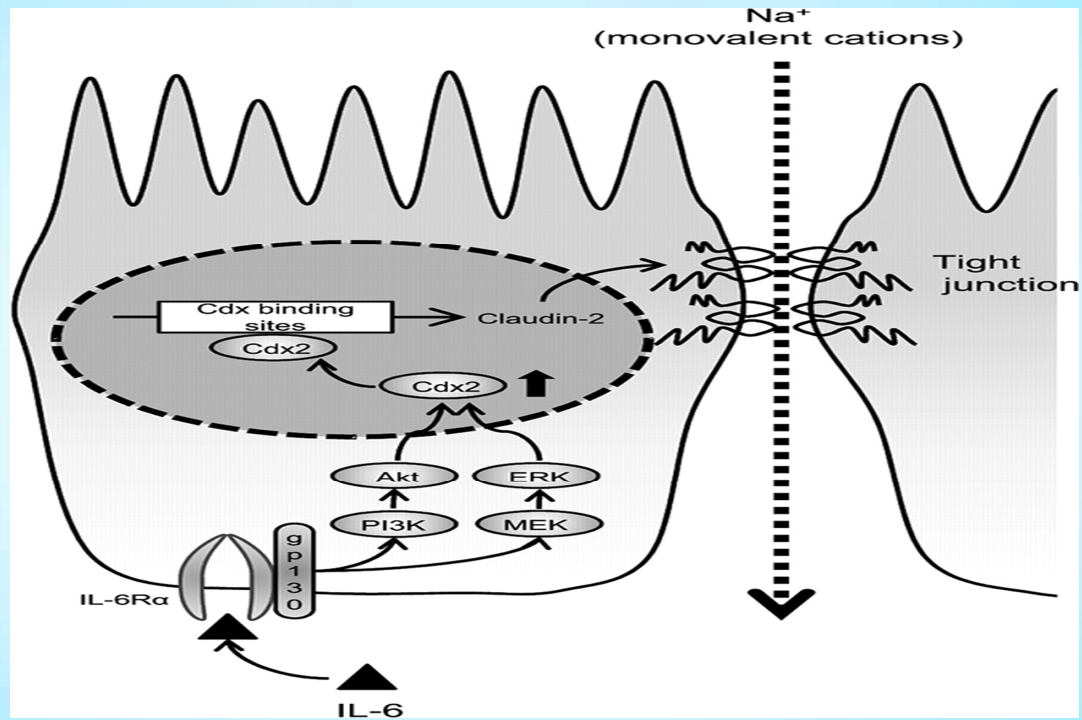
IL-6 regulates Claudin 2 Expression of Tight Junction Permeability in Intestinal Epithelium

-

- Key immune cytokine in chronic inflammation
- Induced by chronic hypercortisolism and flattening of cortisol curve
- Induced in overtraining in athletes
- Markedly induces expression of Claudin-2
- Disrupts tight junction structure (TJ) multi-protein structure (disrupts protein scaffold cytoskeleton)

Susuki, Takuya, Yoshinaga N., Tanabe, Soichi; IL-6 regulates expression of Tight Junction Permeability in the Epithelium; September 9, 2011 The Journal of Biological Chemistry, 286, 31263--31271

Schematic representation showing the mechanism for the IL-6-mediated increase in the TJ permeability in intestinal epithelium cells.

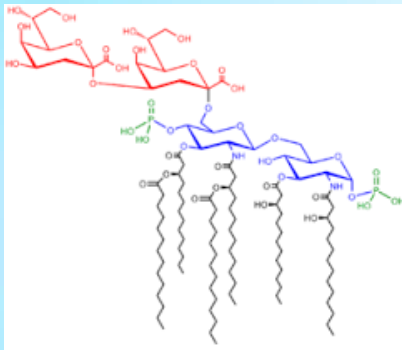


Takuya Suzuki et al. J. Biol. Chem. 2011;286:31263-31271

©2011 by American Society for Biochemistry and Molecular Biology

jbc

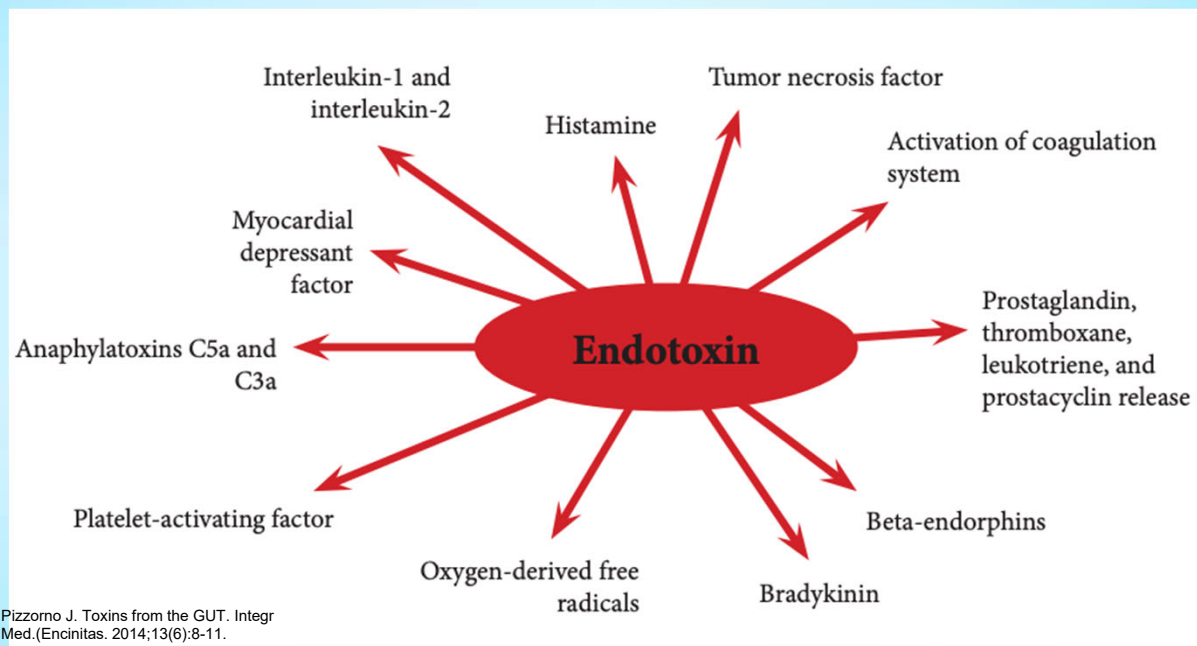
Endotoxin Production



- LPS represent 80% of the cell-wall mass of Gram-negative gut bacteria.
- Disturbances in microbiome can release endotoxin
- Long Duration Exercise induces Endotoxemia due to plasma **↑** Lipopolysaccharide (LPS) levels
 - LPS leads to: **↑**cytokine release **↑**oxidative stress and alterations in gut function
 - Vitamin C reduced nitrate and LPS serum levels
- Ketogenic Diets induce endotoxin production

Guy JH, et al. Nutrition and Supplementation Considerations to Limit Endotoxemia When Exercising in the Heat. Sports (Basel). 2018;6(1):12.

Metabolic Effects of Endotoxin



LPS Effects

↑ inflammatory response
(TNF α and Il-6)

↑ WBC's

↑ MCP-1

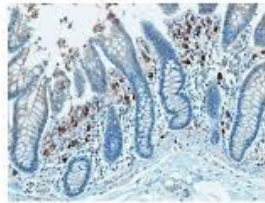
↑ Transient HR

↑ Cortisol

↑ Autoimmune

↑ Resistin

↑ Adipocyte inflammation



↓ Insulin sensitivity

↓ Glucose transport in skeletal muscle

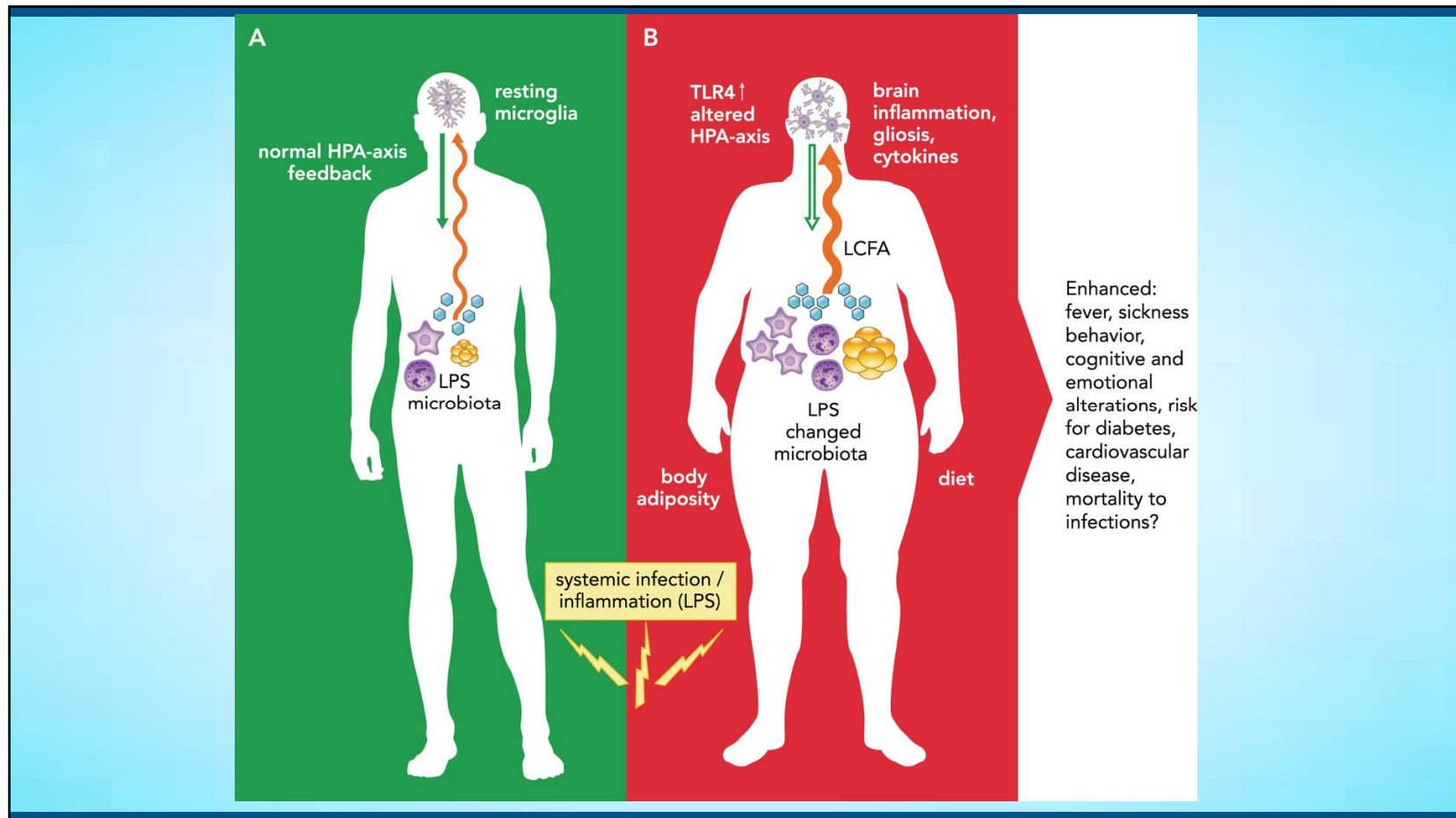
↓ Thyroid function

↓ Alters tryptophan metabolism and increase quinolinic acid and kynurenine

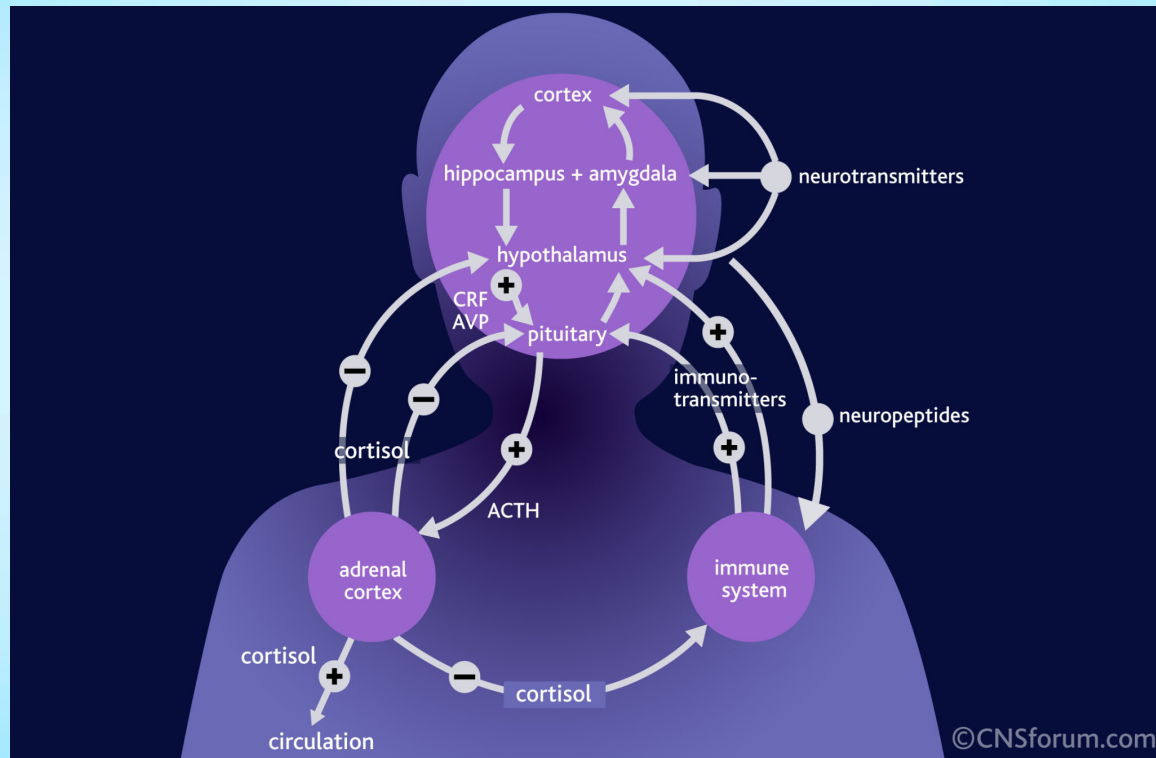
↓ Melatonin

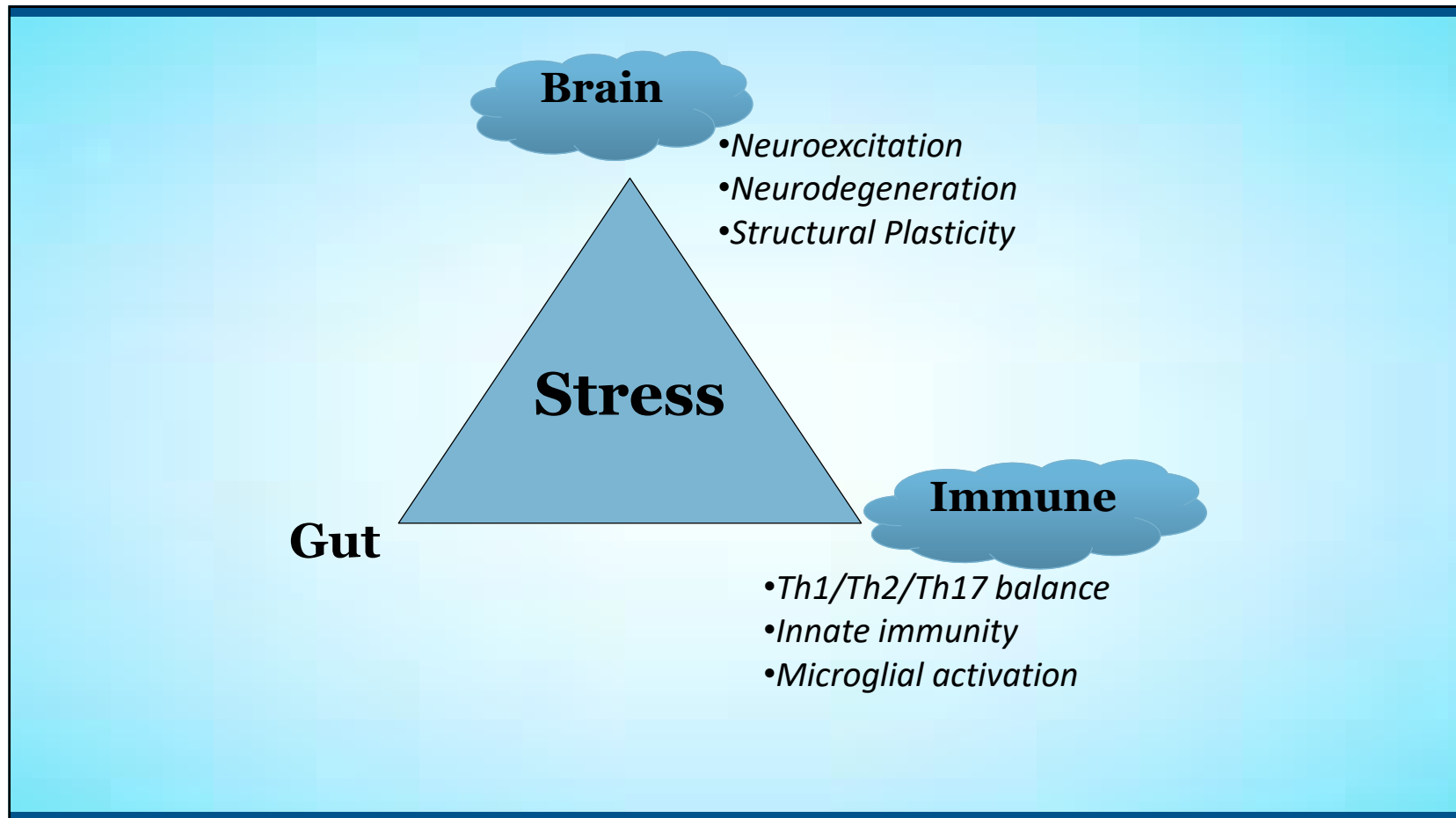
↓ Glutathione pool via increased ROS

Lipopolysaccharides in Food Food Supplements and Probiotics: Should we be worried? Eur J Microbiol Immunon(Bp). 2018;8(3):63-69.



The HPA Axis and Immunity





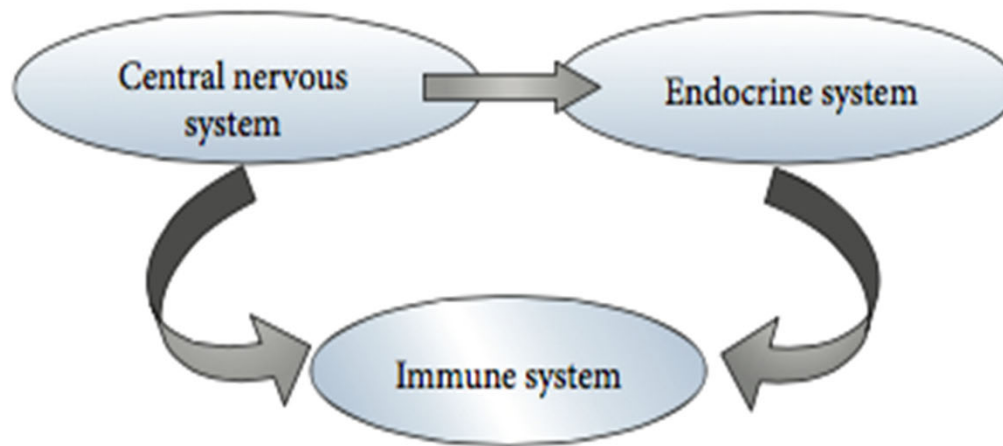
Immunity and Hormonal Shifts



- Immunity regulated by many factors
- Interconnected via signaling molecules (cytokines, hormones, neurotransmitters, peptides)
- Hormones
 - Sex hormones
 - Cortisol
 - GH / IGF-1
 - Inflammatory markers – TNF-a, IL-6

A. Bouman, M. J. Heineman, and M. M. Faas, "Sex hormones and the immune response in humans," *Human Reproduction Update*, vol. 11, no. 4, pp. 411–423, 2005.

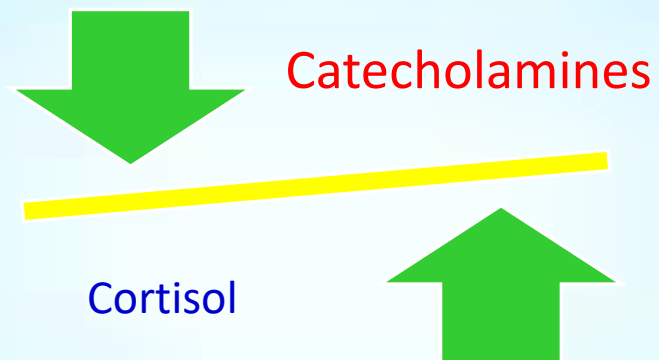
Immunity and Hormonal Shifts



Immune System Dysfunction

- Inadequate immune cell trafficking
- Inability to defend against pathogens
- Inadequate leukocyte trafficking
- Elevations of immune mediators (esp. hypocortisol states)
 - Interleukins (IL-6 and 10) and TNF α
 - Prostaglandins
 - Lymphocytes
 - Natural killer cells
 - ANA antibodies
 - Thyroid antibodies

SNS Hyperactivity and Stress



- Loss of negative feedback from cortisol results in a rise in catecholamine production and sympathetic overdrive
- RHR (resting heart rate) increases
- Palpitations

Central Nervous System

- Prolonged hypercortisolism leads to degeneration of the:
 - Hippocampus – memory
 - Hypothalamus – CFS, FM, Depression, PTSD
 - Pre-Frontal Cortex – executive decision making
 - Amygdala – emotional stability
- fMRI Pathologic changes seen, some irreversible despite treatment
- Effects remain after hypocortisolism has developed

Cardioendocrine System

- Accelerated progression of atherosclerosis, risk of MI and CHF
- Elevated inflammatory markers
 - PAI-1
 - Fibrinogen
 - HS-CRP
- Endothelial dysfunction and hypertension
- Enhancement of insulin resistance and hyperglycemia

Cortisol and the Hippocampus

- Repeated stress affects brain function, especially hippocampus.
- High concentrations of cortisol and NMDA receptors.
- Participates in verbal memory and memory context
- Impairment decreases the reliability and accuracy of contextual memories.
- Damage may exacerbate stress by preventing access to the information needed to decide that a situation is not a threat
- Regulates the stress response and acts to inhibit the response of the HPA axis to stress

Bruce S. McEwen, Ph.D. Protective and Damaging Effects of Stress Mediators. NEJM. Jan 2008: Volume 338:171-179

Cortisol and Cognitive Dysfunction



- Elevated HPA axis leads to Hippocampal degeneration
 - Bao AM, et al. The stress system in depression and neurodegeneration: focus on the human hypothalamus. *Brain Res Rev.* 2008;57(2):531-53.
- High plasma Cortisol associated with rapidly increasing dementia and Alzheimer's
 - Oanes S, et al. High cortisol and the risk of dementia and Alzheimer's Disease: A review of the literature. *Front Aging Neurosci.* 2019;11:43.

Hippocampal Changes in Chronic Stress

- Hippocampus alterations in both structure and function have been identified in long term stress
- Volume loss demonstrated in PTSD, depression, cushing' s syndrome
- Functional changes include reduction in hippocampal excitability, long-term potentiation and memory.



Dendritic Retraction of Hippocampus

- Induce shrinkage of the apical dendrites of the CA3 and CA1 pyramidal cells and dentate granule cells
- Changes of neuronal morphology likely to contribute to cognitive deficits
- A functional outcome of dendritic retraction is a disturbance of HPA axis regulation, leading to unregulated glucocorticoid release.
- Increased oxidative stress, neuroexcitation, loss of counter-regulatory control

NMDA Receptors

Neurons need to protect themselves from the excitotoxic effect of glutamate by reducing their input surface area.

How To Protect the Brain





ELSEVIER

www.elsevier.com/locate/euroneuro



REVIEW

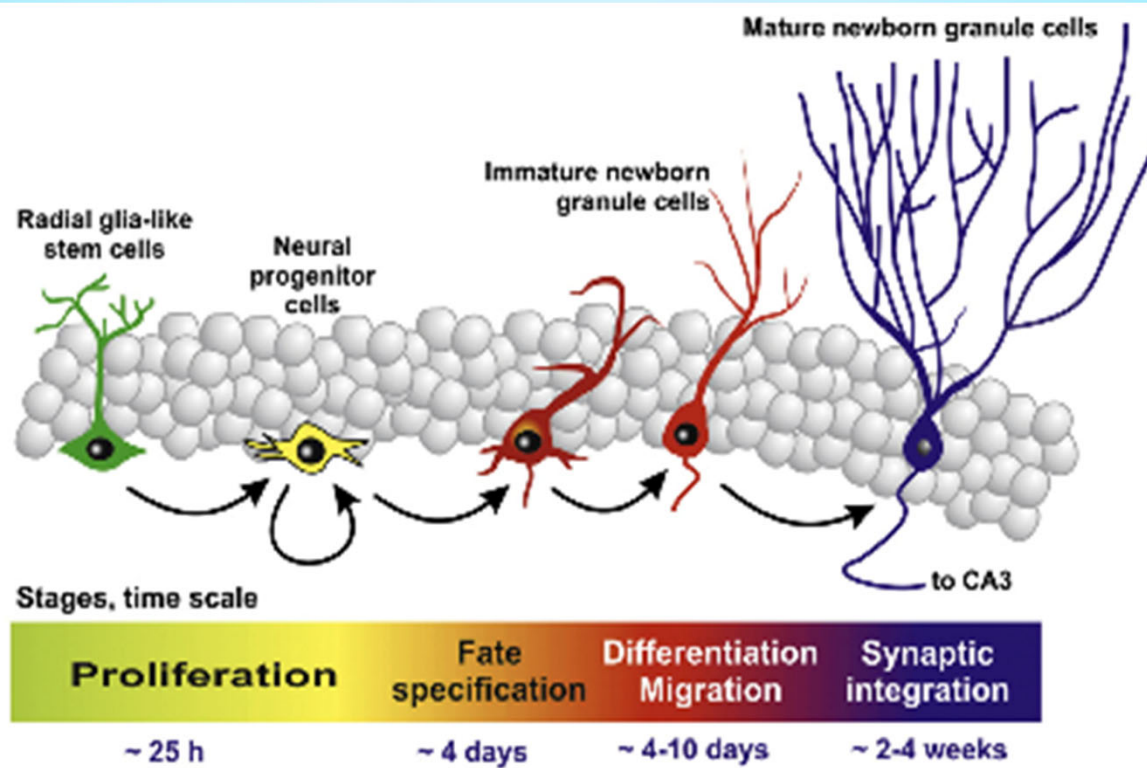
Regulation of adult neurogenesis by stress, sleep disruption, exercise and inflammation: Implications for depression and antidepressant action[☆]

P.J. Lucassen^{a,*}, P. Meerlo^b, A.S. Naylor^{c,d}, A.M. van Dam^e, A.G. Dayer^f,
E. Fuchs^{g,h}, C.A. Oomen^a, B. Czéh^{g,i}

Adult Neurogenesis

- Adult neurogenesis refers to the production of new neurons in an adult brain
- Follows a similar complex multi-step process that starts with the proliferation of progenitor cells, followed by their morphological and physiological maturation.
- Ends with a fully functional neuron that is integrated into the pre-existing hippocampal network

Adult Neurogenesis



Mediators of Adult Neurogenesis

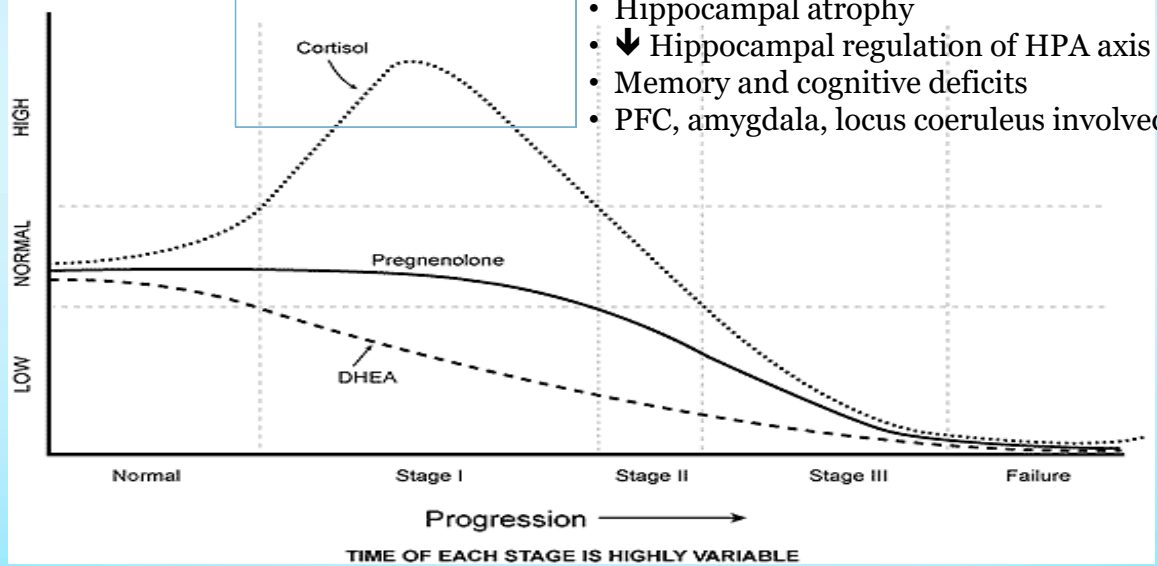


- Stress and sleep disruption suppress adult neurogenesis
- Stress interferes with all stages of neuronal renewal and inhibits both proliferation and survival.
- **Glucocorticoid** and **NMDA** receptors have been identified on progenitor cells.
- *Lasting inhibition of AN* occurs after an initial stressor, despite later normalization of cortisol.

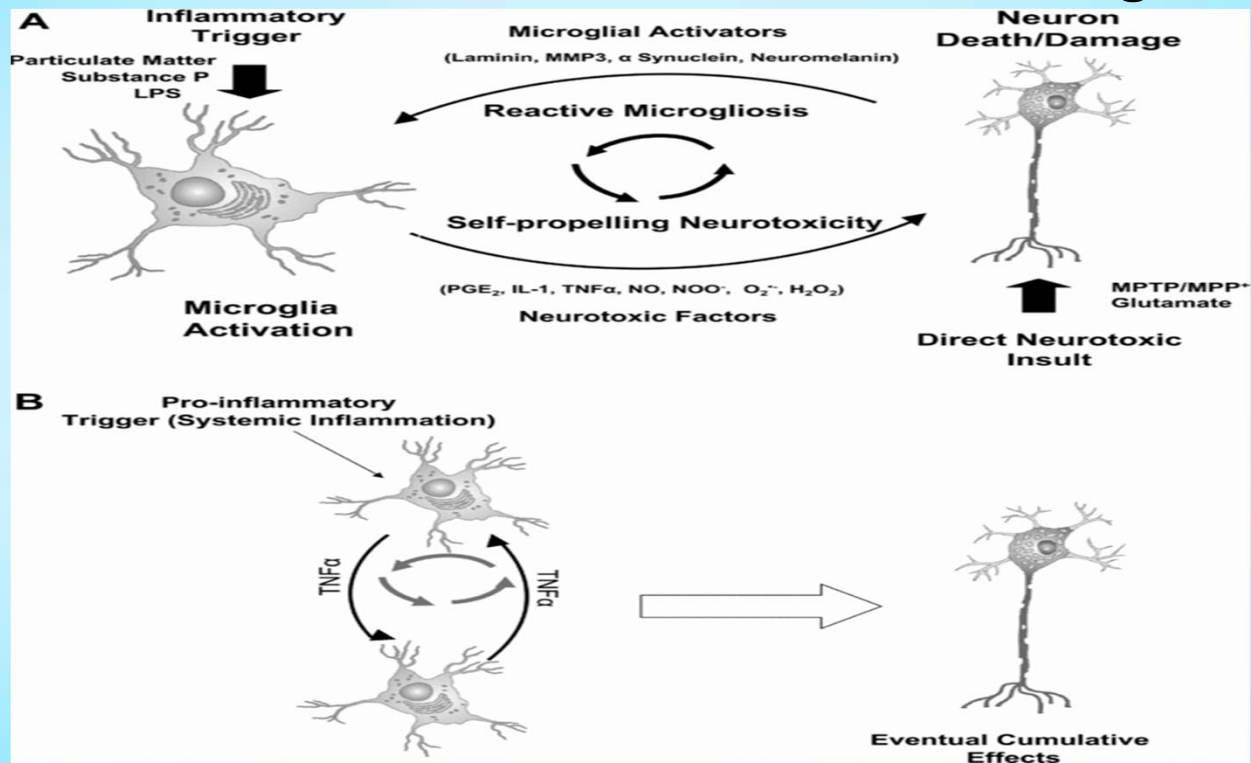
↑ Neurodegeneration

↓ Adult Neurogenesis

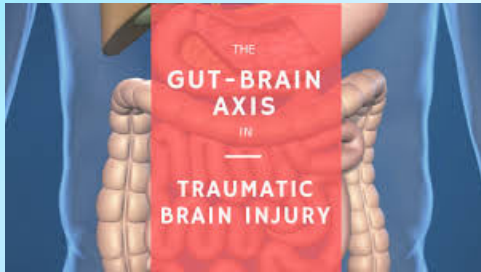
Progression of Stages of Adrenal Exhaustion



Neuroinflammation: Microglial Cells



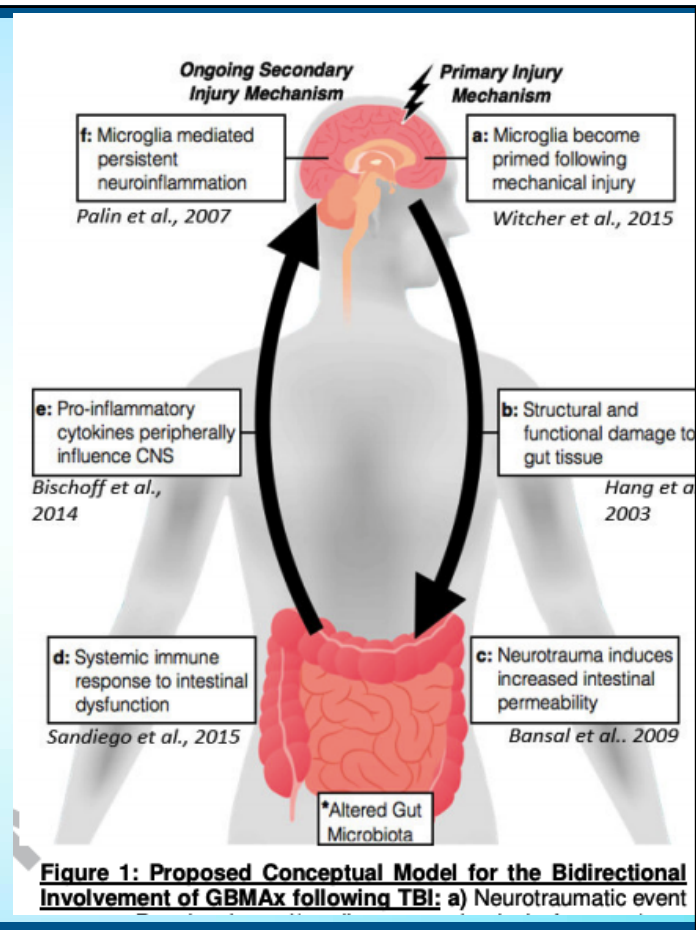
TBI and GUT-BRAIN Disruption



- ↓ intestinal absorption and contractility
- Microbiome disruption
- ↑ defective tight junctions and intestinal permeability
- ↑ GUT issues – Crohn's, Celiac disease
- ↑ Insulin dysregulation
- ↑ Immune dysregulation
- ↑ Brain issues – sleep, cognition, mood disturbances, anxiety and psychiatric disorders

TBI and GUT-BRAIN Disruption

Zhu CS, et al. A review of traumatic brain injury and the gut microbiome: insight into novel mechanisms of secondary brain injury and promising targets for neuroprotection. Brain Sci. 2018 Jun; 8(6):113.



Sleep



National Sleep Foundation. www.sleepfoundation.com.
Ohayon MM. Epidemiology of insomnia: what we know and
what we still need to learn. Sleep Med
Rev. 2002;6(2):97-111.

- Most individuals should obtain at least 7-9 hours of quality sleep a night
 - (Centers for Disease Control, CDC, 2011).
Centers for Disease Control (CDC).
www.cdc.gov.
- 67% of Americans experience frequent problems sleeping
- 43% say lack of sleep interferes with their daily activities.
- Between 9-12% of the population are clinically diagnosed with insomnia.

Insomnia or Disrupted Sleep

- Alters Growth Hormone release
- Increases TNF alpha, IL-6
- Increases insulin resistance
- Contributes to weight gain
- Increases TBG

Sleep Deprivation & Weight Gain Linked

- Subjects that avg. 4 hr. sleep/night:
 - ↓ Leptin (18%), ↑ Ghrelin (28%)
 - ↑ reported hunger (24%), ↑ carb cravings, especially sweets, salty, and starchy high calorie snacks
 - (Ann Intern Med, 2004, vol. 141, pp. 846—850)
- > 1,000 volunteers: those that avg. , 5 hr sleep had ↓ leptin (15.5%), ↑ ghrelin (14.9%), ↑ BMI (3.6%). Results were regardless of the subjects diet and exercise habits (Mignot et al, Stanford School of Medicine Dec. 2004)

Sleep Deprivation & Weight Gain Linked

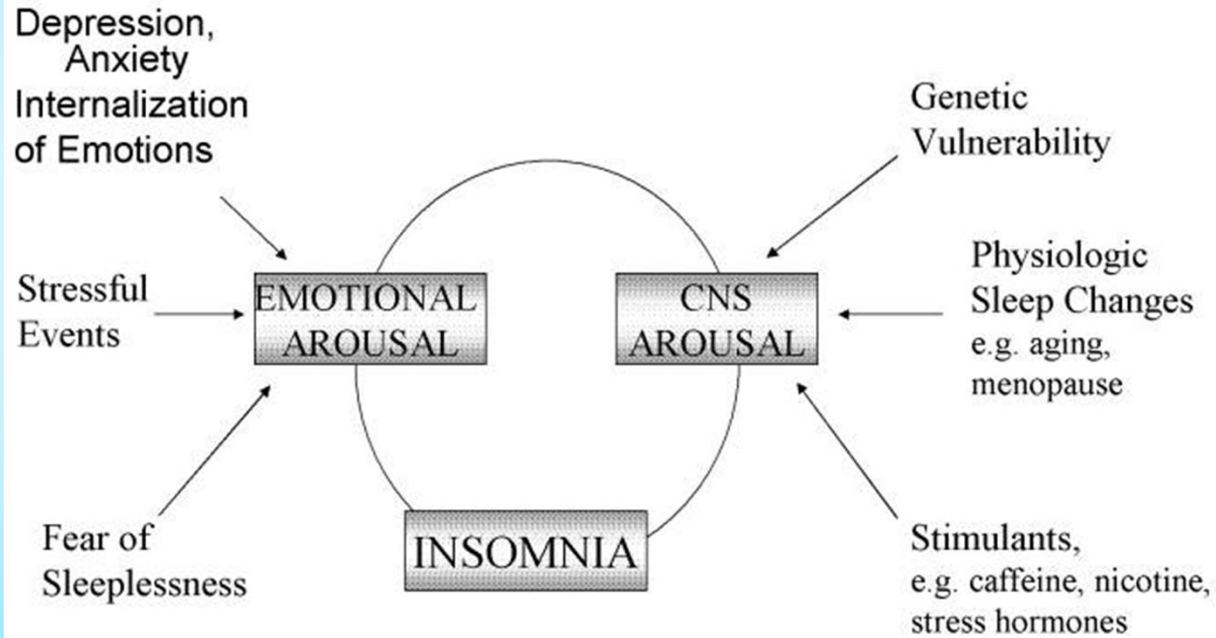
- Heymsfield and Gangwisch analyzed NHANES I data: Found that subjects with avg. 5hr./night sleep had 73% increased likelihood of obesity over those who slept 7-9 hr/night. (Findings reported at the annual scientific meeting of the North American Society for the Study of Obesity. Nov, 2004)
- Study showed a linear relationship: reduced amounts of sleep are associated with overweight and obesity (Arch. Intern Med, 2005;165:25-30)

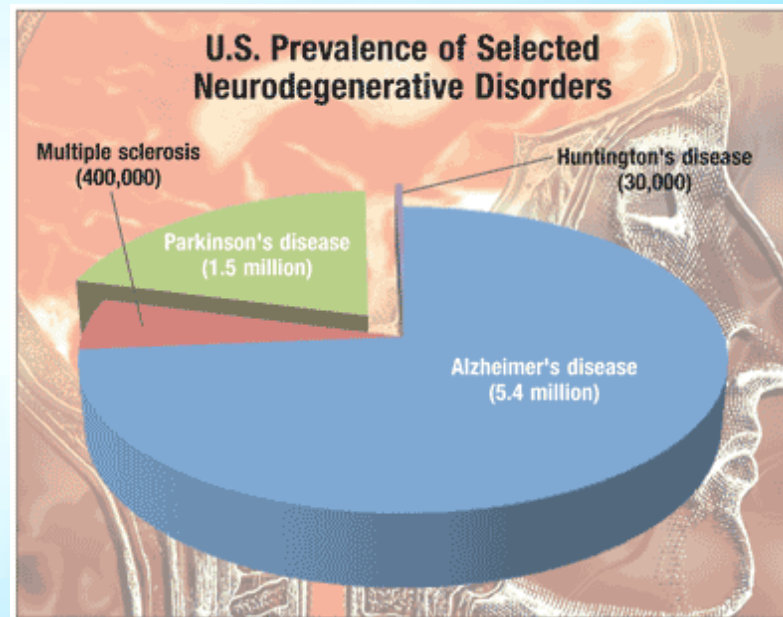
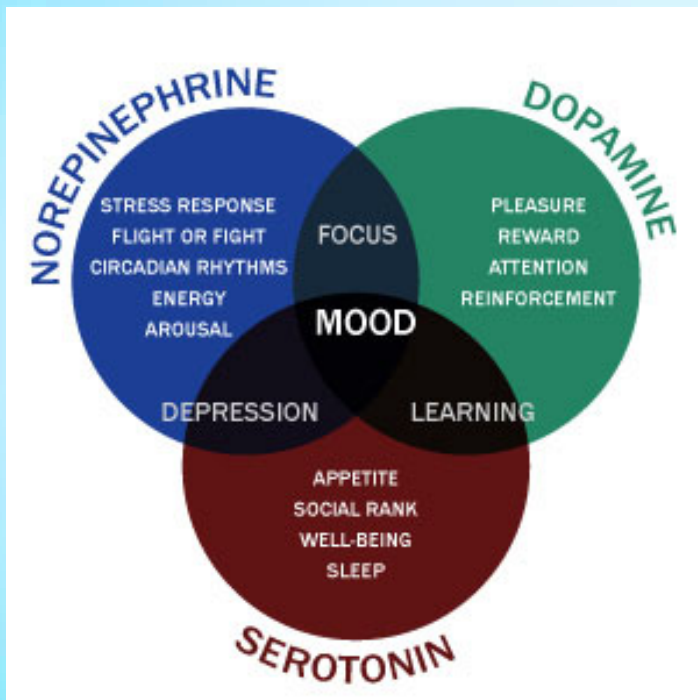
Daytime Sleepiness for Insomniacs

- Most chronic insomniacs do not complain of daytime sleepiness in fact they show increased alertness versus controls leading to the 24 hour hyperarousal.

Stepanski AJ, Glovinsky PB. Daytime alertness patterns in patients with chronic insomnia compared to asymptomatic control subjects
Sleep 1988;11(1):54-60

Hyperarousal Hypothesis (Emotional and Physiological)





Supplement Support for GUT-IMMUNE-BRAIN Axes

- Support the GUT – Brain – Immune Axis
- Improve gastrointestinal function, digestion and microfloral balance
- Improve neurotransmitter synthesis and function
- Support Dopamine reward
- Support circadian sleep cycles / improved sleep
- Support immune balance – Th1/Th2
- Support memory and cognition

Re-Populate the Microbiome

- Use a mixture of berberine and Cat's Claw + grapefruit seed extract
- Helps support gastrointestinal health
- Antimicrobial/antifungal
- Microbiome support – decreases *Candida* overgrowth
- Decreases inflammatory signaling in GUT
- Supports healthy gastrointestinal barrier
- Improves GUT-Brain-Immune signaling
- 1 capsule (200mg berberine, 500 mg std. 3% oxindole cat's claw, 100mg grapefruit seed USA) , 3 times daily
- If long term therapy, best to rotate w/ another GI antifungal w/ berberine

Sandoval-Chacon M, Thompson JH, Zhang XJ, et al. Antiinflammatory actions of cat's claw: the role of NF-kappaB. *Aliment Pharmacol Ther.* 1998;12(12):1279-89.

Li N, Gu L, Qu L, et al. Berberine attenuates pro-inflammatory cytokine-induced tight junction disruption in an in vitro model of intestinal epithelial cells. *Eur J Pharm Sci.* 2010;40(1):1-8.