Metagenics Institute

Navigating the Gut-Brain Axis to Optimize Health Across the Lifespan

Integrative Healthcare Symposium
Pre-Conference Session

February 21, 2018

New York, NY

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Metagenics Institute

Heather Zwickey, PhD
Professor of Immunology

Gut Brain Axis

nunm
NATIONAL UNIVERSITY OF
Natural Medicine

Outcomes

- At the end of this lecture, participants should be able to:
  - Describe how the nervous system and immune system interact to connect the gut and brain
  - Report relationships between cytokines, neurotransmitters and microbes
  - List diagnoses that are known to have microbiota relationships
  - Suggest treatment possibilities based on system relationships

How are the Gut and Brain connected?

Gut

Brain

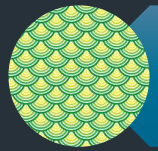
Historical

Present

Cytokines

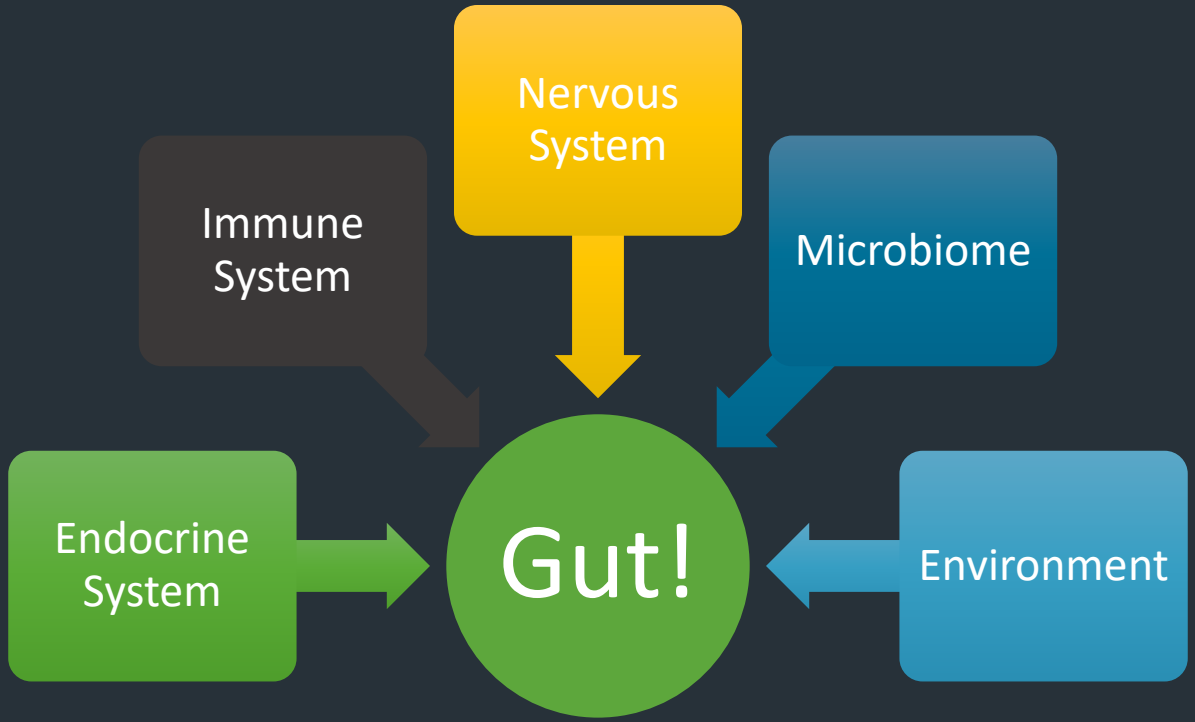
Neurotransmitters

Endorphins

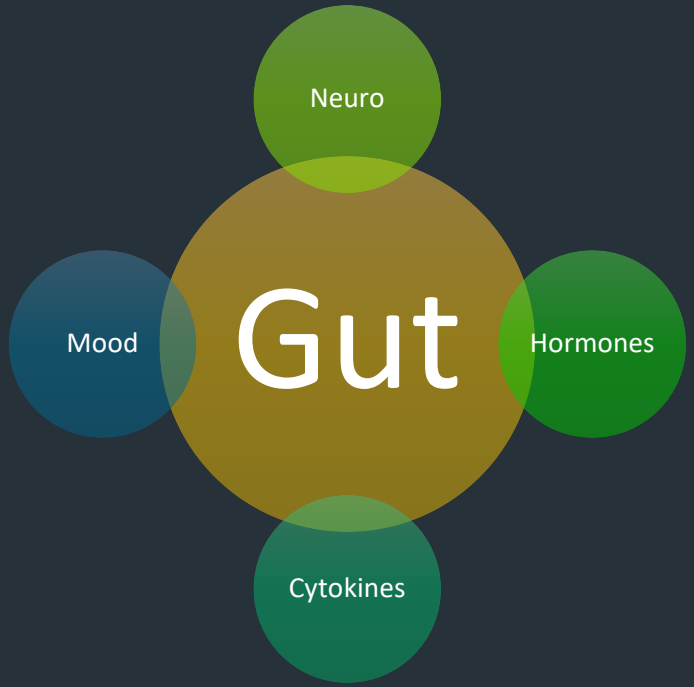


Endocannabinoids

It all converges at the gut!

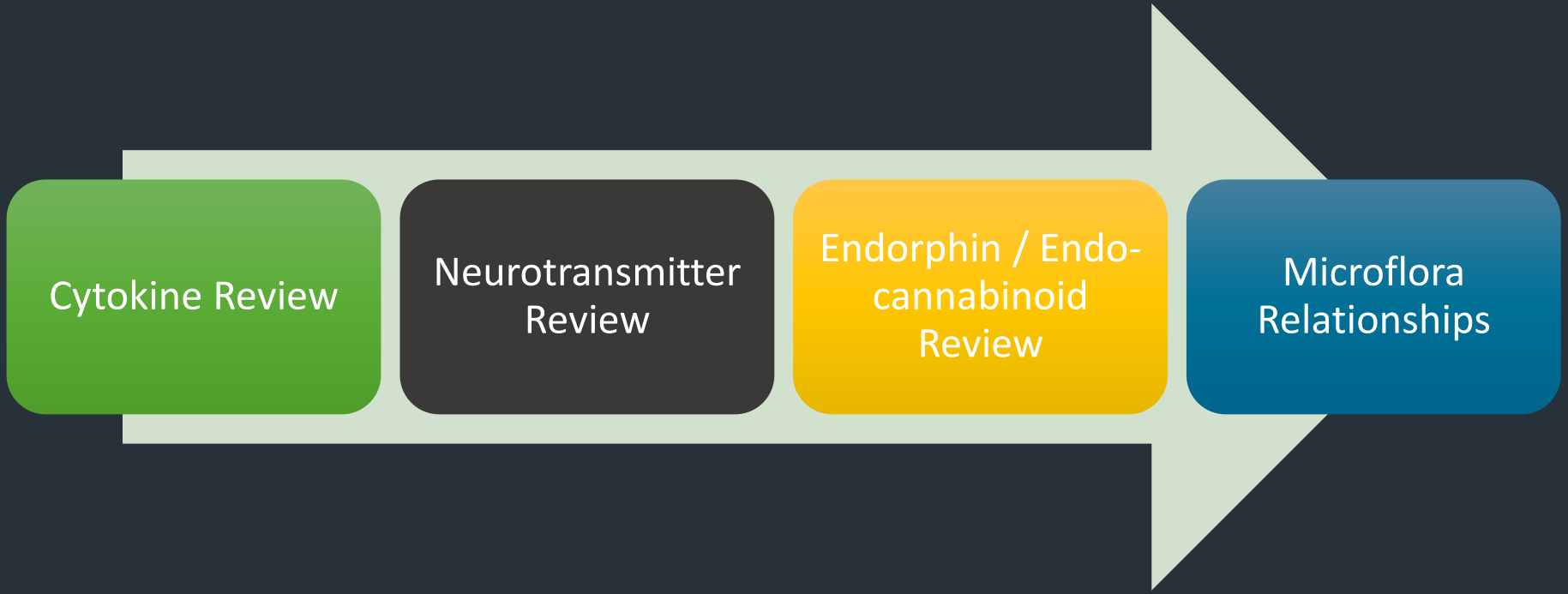


Gut – Center of the Universe?



- Gut is huge source of neurotransmitters and cytokines
- Microflora produce neurotransmitters (Dopamine, Serotonin, and GABA) and influence production of neurotransmitters
- Microflora can impact immune and brain outcomes

Today's Strategy



Cytokines

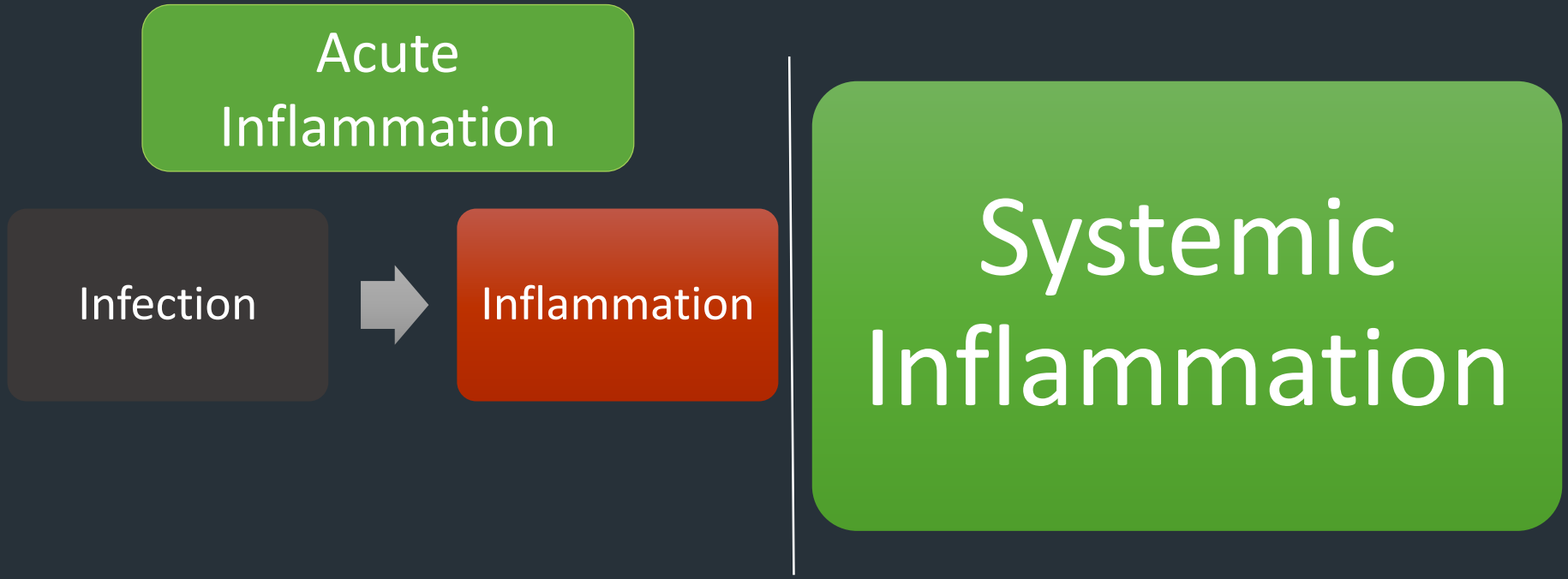
Innate Immunity

- Cytokines made by macrophages, DCs, and Neutrophils

Specific Immunity

- Cytokines made by CD4 T cells

Innate Immunity



Inflammation – Which cytokines are made?

Stress

Gum Disease

Obesity

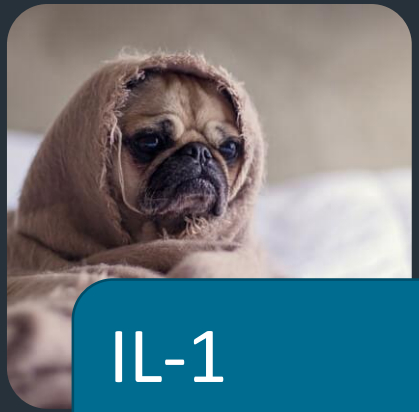
Fever

IL-1

IL-6

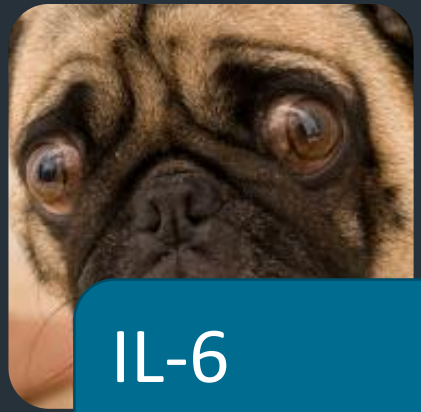
TNF

Inflammation – Neurological relationship



IL-1

- Depression



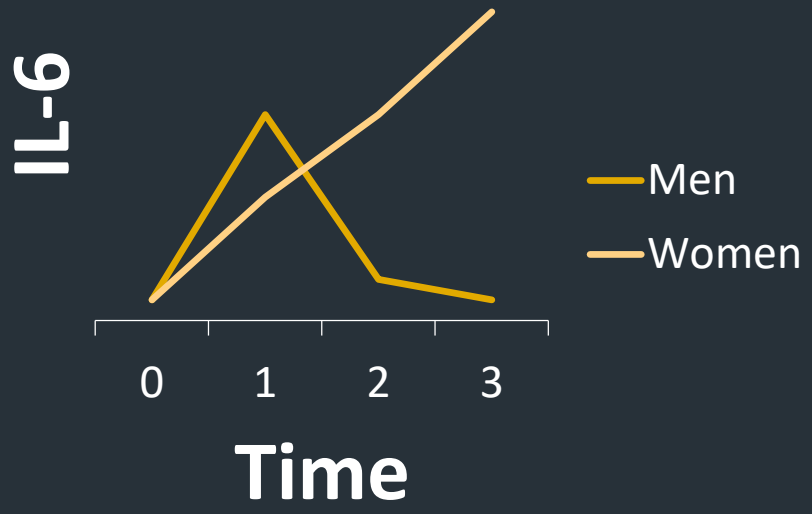
IL-6

- Anxiety

TNF

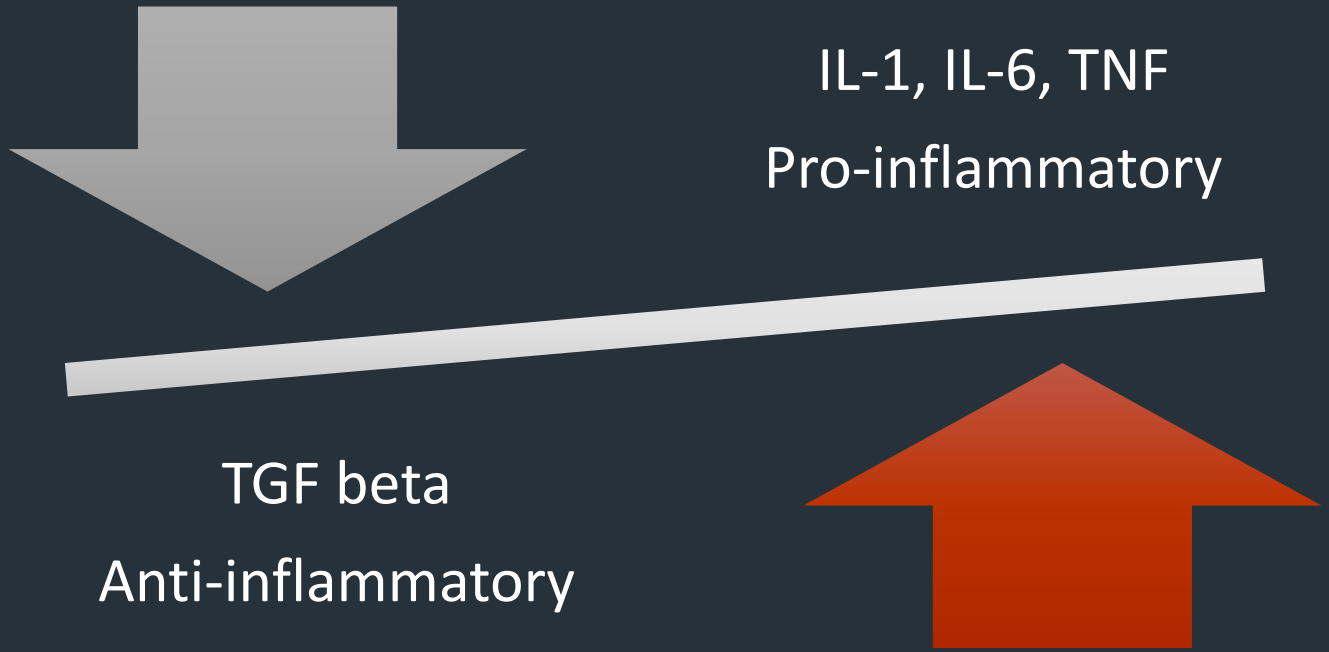
- Hostility

Catastrophizers

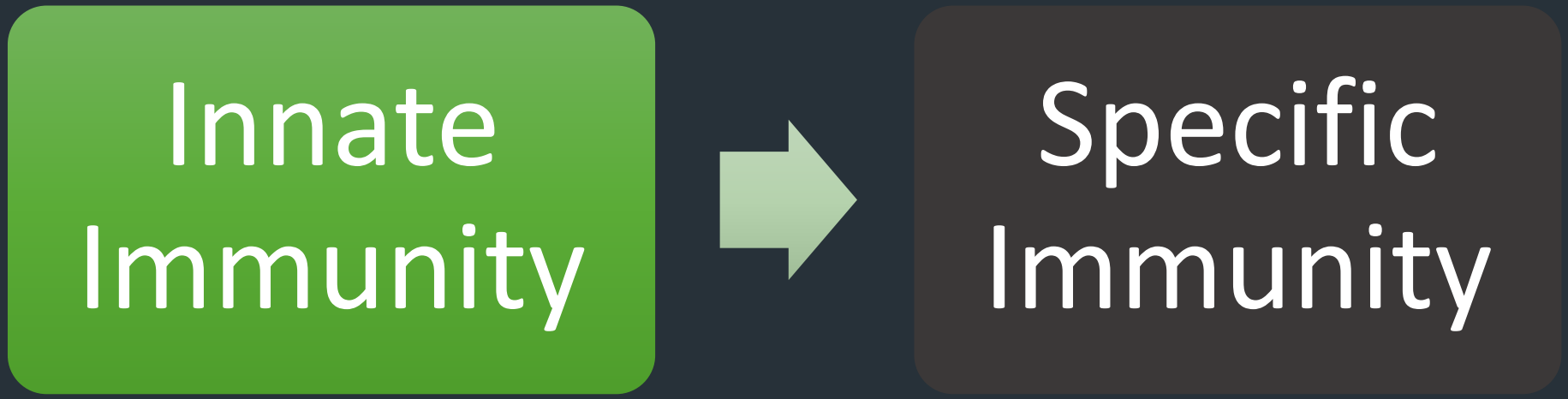


Gend Med. 2010 Jun;7(3):247-60. doi: 10.1016/j.genm.2010.06.003.

Balance



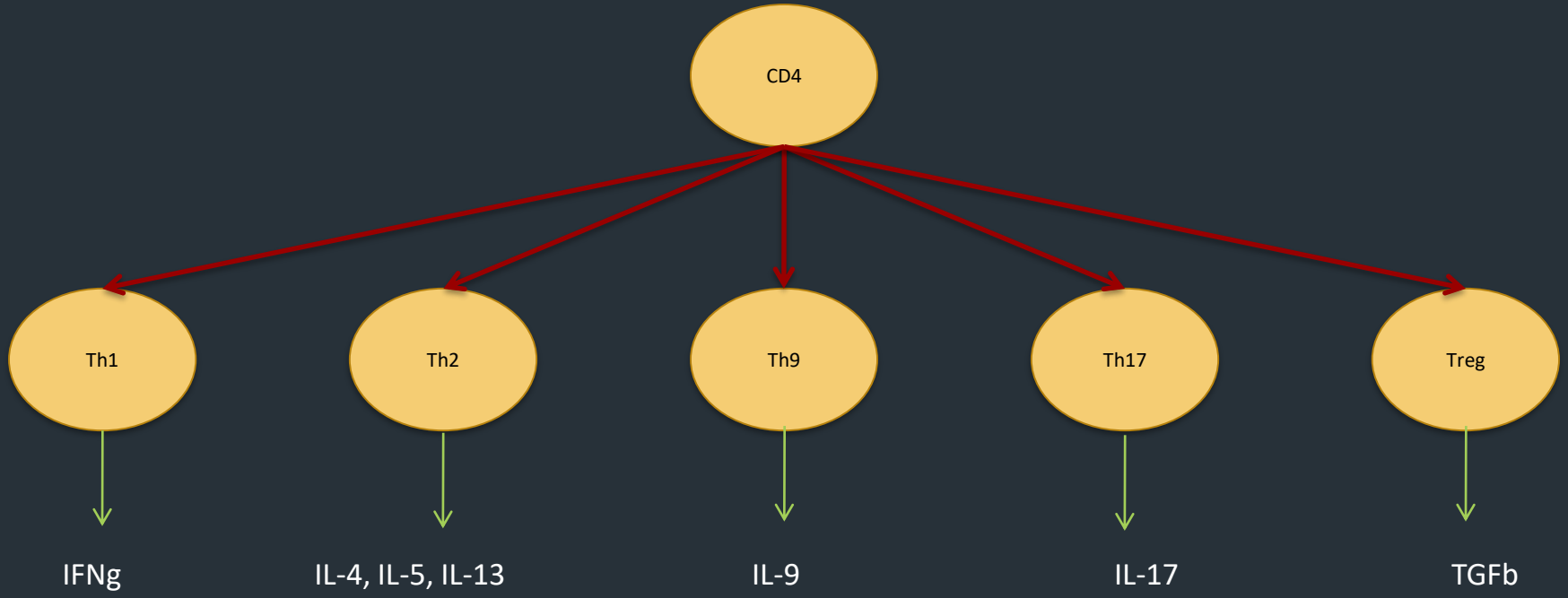
Specific Immunity



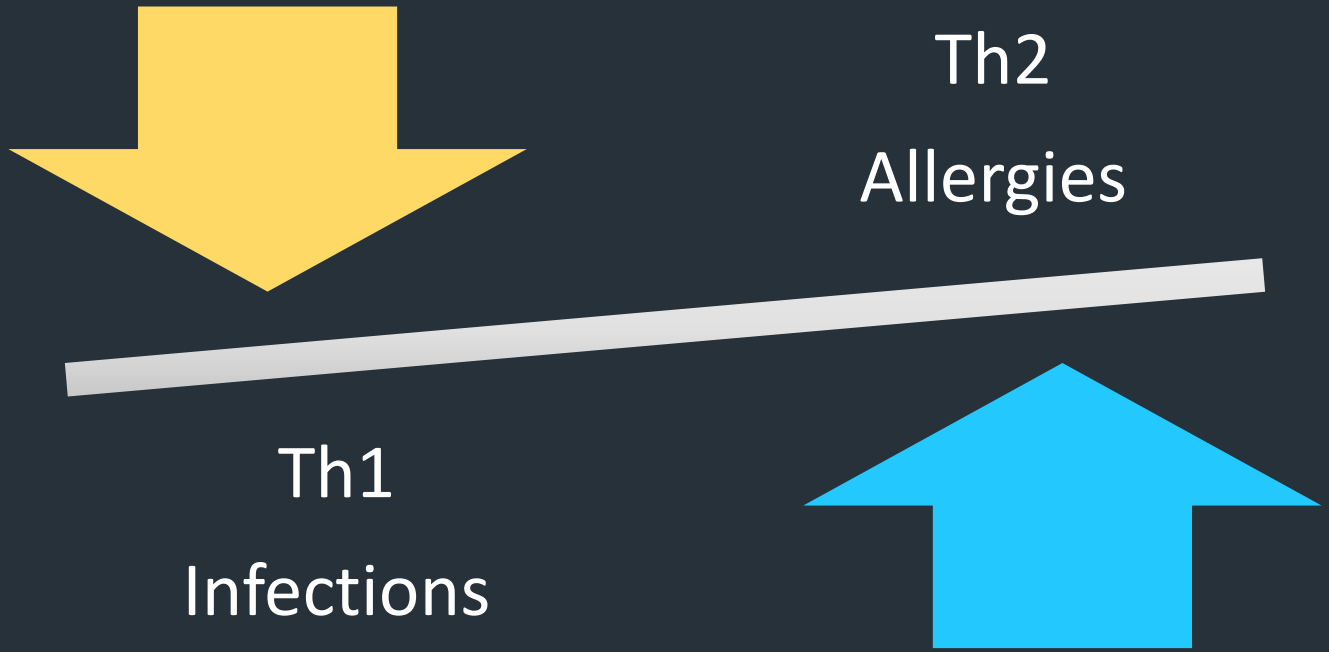
Specific Immunity overview

Reaction to:	T cell	Cytokine	Antibody
Bacteria and Virus	Th1	IFNgamma	IgG
Worms/Allergens	Th2	IL-4, IL-5, IL-13	IgE
Food	Th3/Treg	TGFbeta	IgA
Mold/Autoimmunity	Th17	IL-17	IgG

CD4 T cell Subtypes

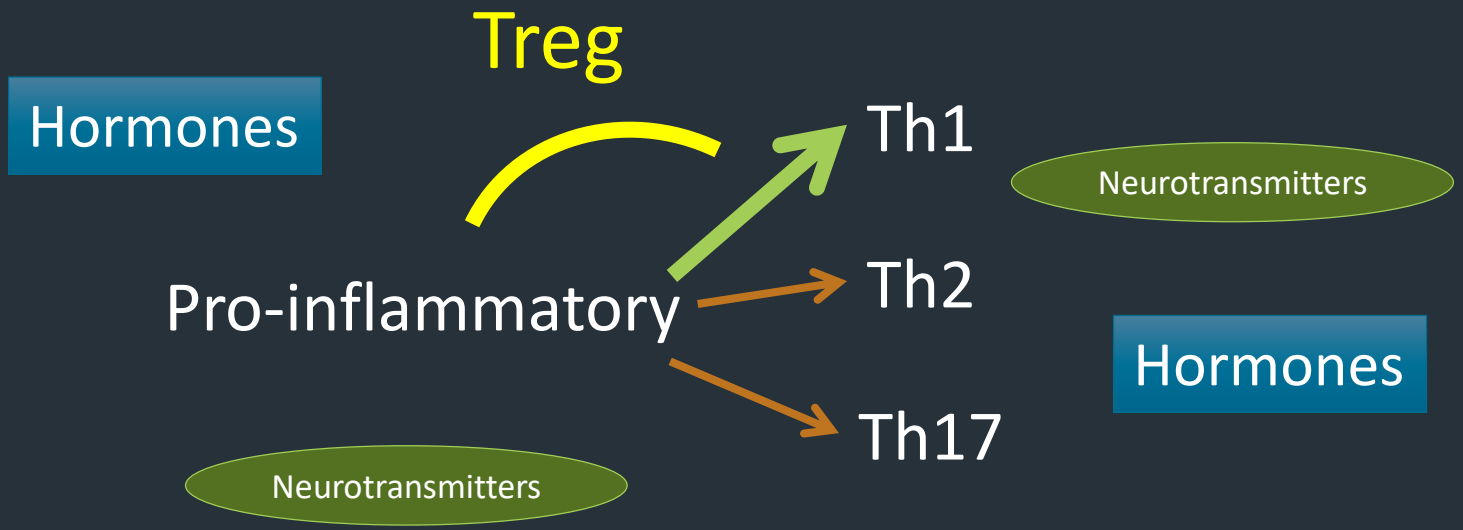


Balance

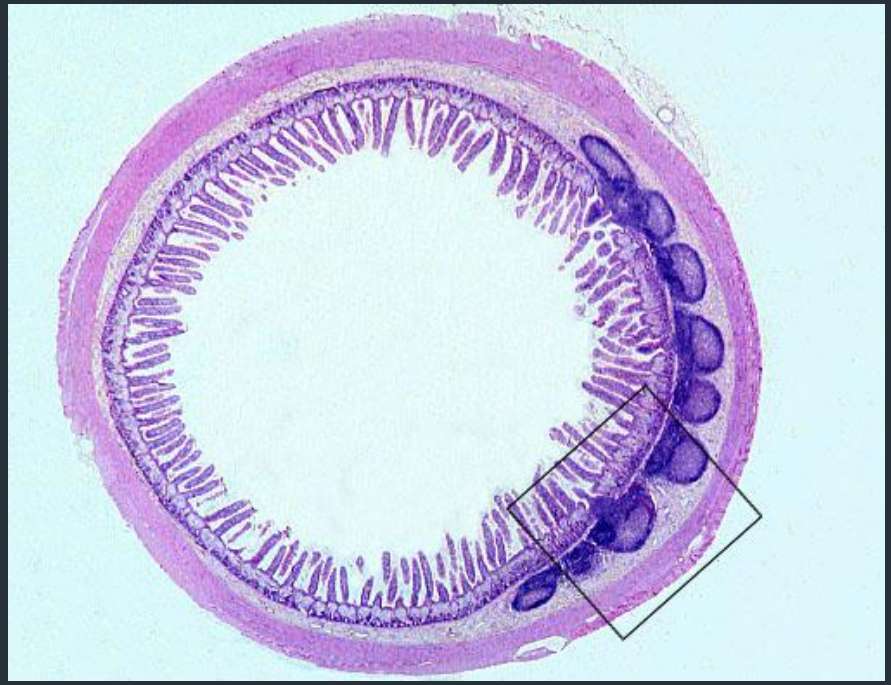


Balance

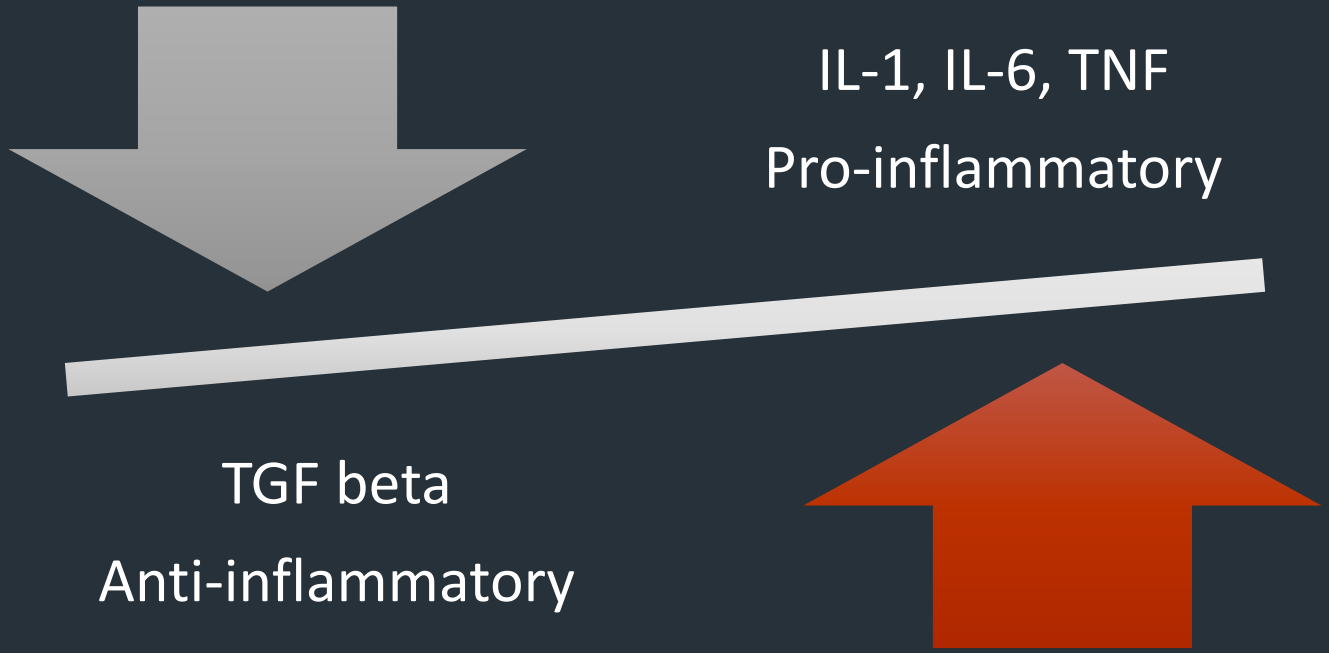
Balance


Treg
Hormones
Th1
Neurotransmitters
Pro-inflammatory
Th2
Hormones
Th17
Neurotransmitters

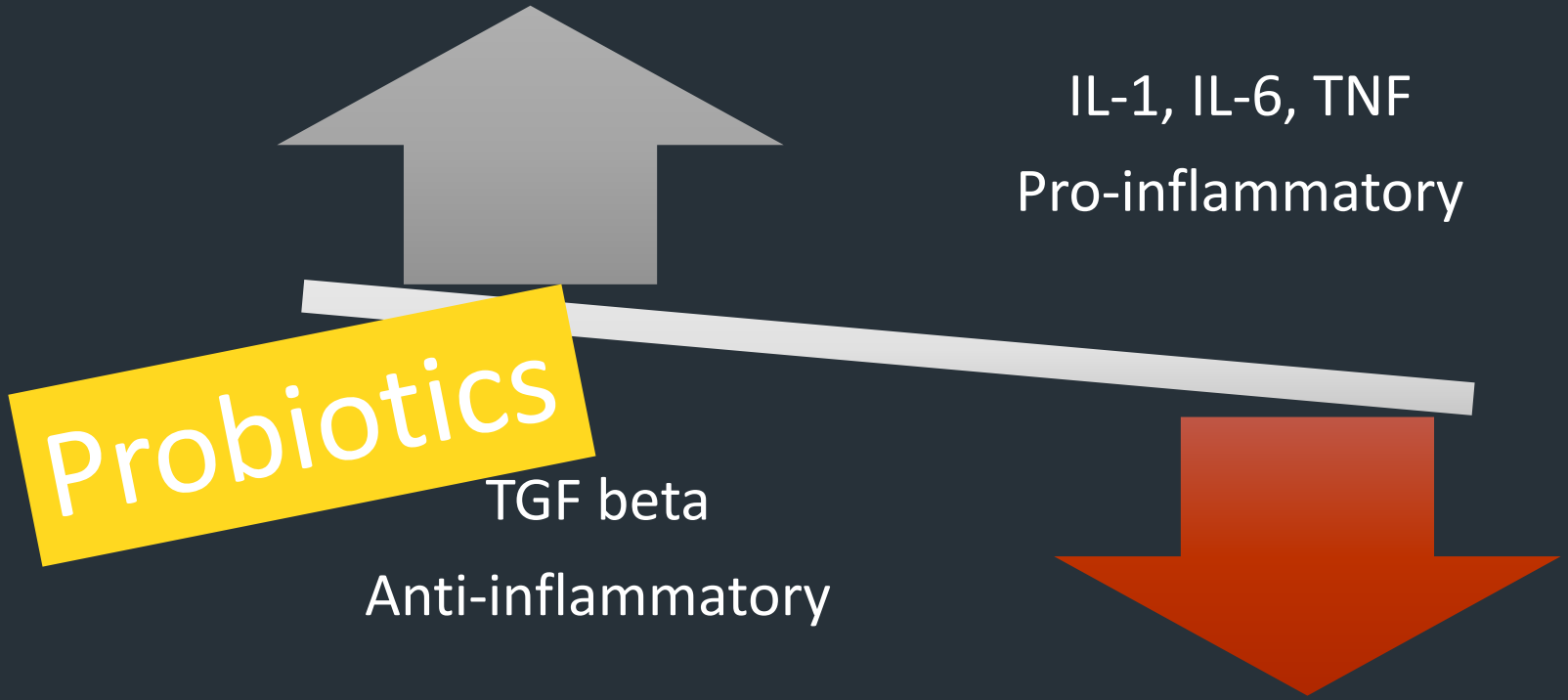
Immune System is in the Gut



Reduce inflammation? Treat the gut

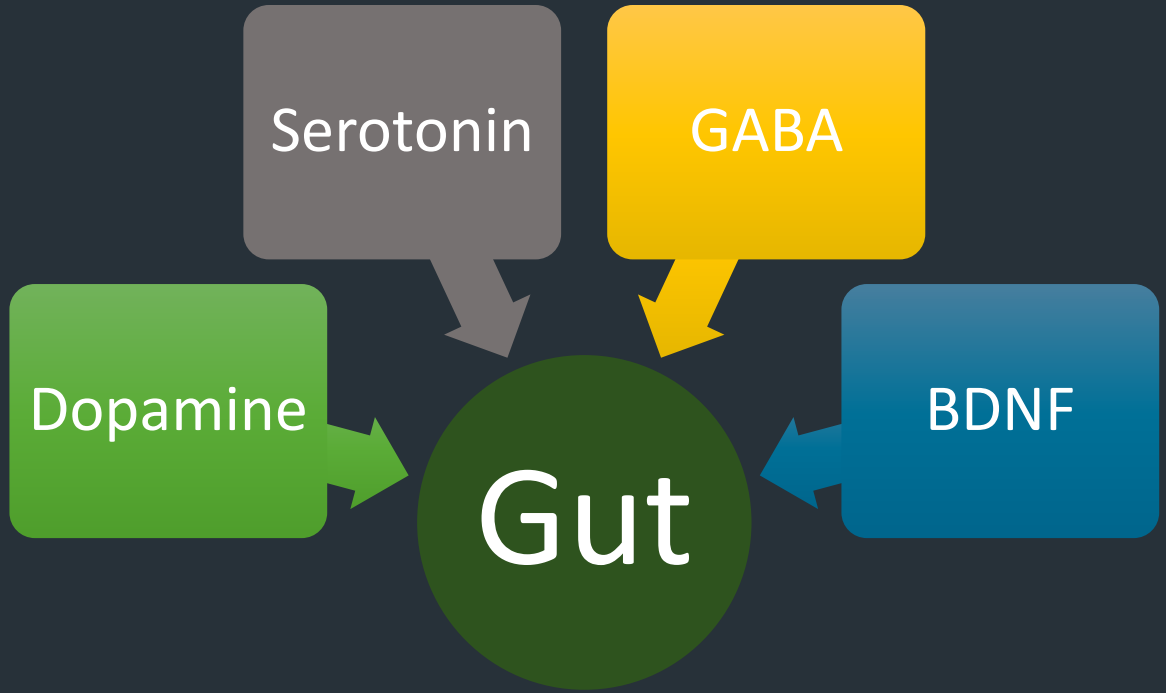


Reduce inflammation → Treat the gut



Hur, SJ, et al. Nutr Res. 2012 Nov;32(11):801-16. doi: 10.1016/j.nutres.2012.09.013. Epub 2012 Oct 30.

Neurotransmitters are also in the gut



Microbes in the gut make neurotransmitters

Dopamine

Serotonin

GABA

Neurotransmitters

Dopamine

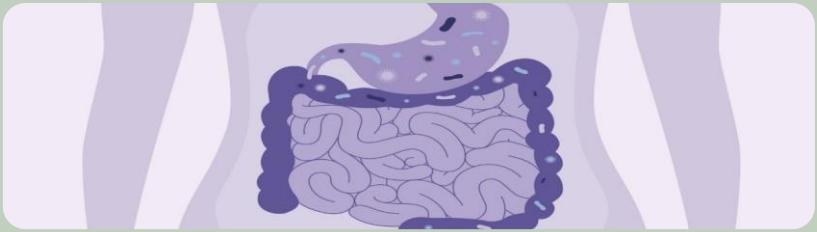
Reward

Positive Affect

Extraversion

Wacker J. Psychophysiology. 2017 Mar 17. doi: 10.1111/psyp.12727.

Dopamine



Psychological Effects

- Low – Depression, ADHD, Social Anxiety Disorder
- High – Schizophrenia, Mania

Gut Effects

- Contraction of the colon

Dopamine and Immunity

- T cells express 5 kinds of Dopamine receptors
- Stimulation of D1-D5 decreases IFNgamma (Th1) and increases IL-4 (Th2) in the blood
- Dopamine at certain concentrations drives Treg or Th17
- Evidence that dopamine is misregulated in autoimmune disease (MS, Lupus, IBD)

Huang Y, Qiu AW, Peng YP, Liu Y, Huang HW, Qiu YH. Neuro Endocrinol Lett. 2010;31(6):782-91.

Pacheco, Contreras, Zouali. Front Immunol. 2014 Mar 21;5:117. doi: 10.3389/fimmu.2014.00117. 2014.

Neurotransmitters

Happiness

Motivation

Calm

Serotonin

Ward R, Sreenivas S, Read J, Saunders KEA, Rogers RD. Psychopharmacology (Berl). 2017 Jul;234(14):2139-2147. doi: 10.1007/s00213-017-4619-4. Epub 2017 May 9

Serotonin

Psychological Effects

Low – Anxiety, Depression, Mood Impulse Disorders

High – Agitation, Restlessness

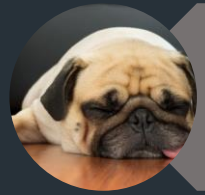
Gut Effects

- Regulates bowel function and appetite

Neurotransmitters

GABA
(inhibitory)

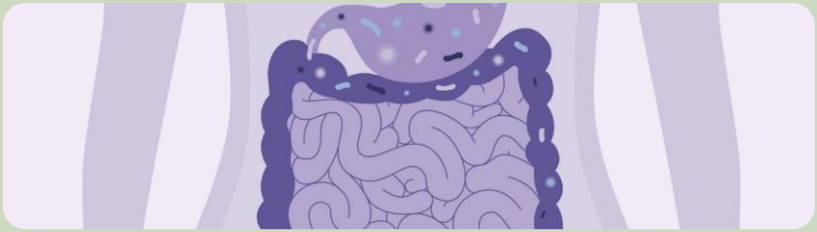
Relaxation



Sleep

Focus

GABA



Psychological Effects

- Low – Depression, mania, ADHD
- Relaxation – Xanax and Valium target GABA receptors

Gut Effects

- Intestinal motility,
- Relaxation
- Reduce sensation

Granger AJ, Wallace ML, Sabatini BL. Curr Opin Neurobiol. 2017 May 10;45:85-91. doi: 10.1016/j.conb.2017.04.007.

Neurotransmitter Summary

Neurotransmitter	Mood Effect	Gut Effect	Immune Effect
Dopamine	Pleasure/Depression	Colon contraction	Decreases Th1, Increases Th2 Could increase Treg or Th17
Serotonin	Happy/Anxiety	Bowel movements	IFNg decreases serotonin
GABA	Relaxation/Depression/Mania	Intestinal motility; Pain reduction	Decreases pro-inflammatory cytokines

Endorphins

Endogenous opioids are released during…


Exercise


Chocolate


Sex


Fear


Love


Music


Laughter

Does chocolate = sex?

Chocolate

Sex

- Chocolate
  - Endorphin is enkephalin
  - Also has magnesium which is calming
- Sex
  - Endorphin is beta-endorphin
  - Dopamine during sex (reward)
  - Serotonin at the end with sexual satiety

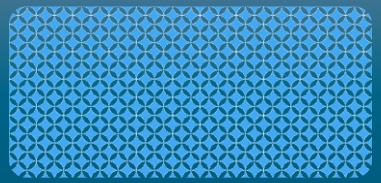
Music

Music

- Beta endorphin
- Rhythmic activity
- Social bonding

Tarr, B. et al.Front Psychol. 2014 Sep 30;5:1096. doi: 10.3389/fpsyg.2014.01096. eCollection 2014.

Natural Endorphins and Immunity



mu receptor

- Pro-inflammatory

delta receptor

- T cell proliferation

kappa receptor

- Anti-inflammatory

Taub, D. Cell Immunol. 2008; 252(1-2): 1–6. Published online 2008 Jul 10. doi: 10.1016/j.cellimm.2008.05.006

Chocolate, Sex, and Music

Met-enkephalin and Beta-endorphin

Don’t bind to classical opioid receptors

Increase IFNgamma (Increase Th1)

Finley, MJ, et al. Cell Immunol. 2008 Mar-Apr;252(1-2):146-54. doi: 10.1016/j.cellimm.2007.09.008. Epub 2008 Feb 14.

Opioids and Immunity

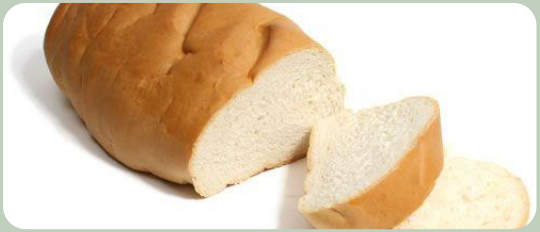
- Opioid abusers have higher incidence of infections
  - Impaired immunity
- Opioid treatment results in reactivation of latent viruses
  - *If you're placing a patient on opioids, consider this*
  - Slows clearance
  - Increases risk of secondary infections

- Influenza
  - Morphine impairs immunity in lungs
  - Opioids decrease NK cell activity
  - Opioids increases risk of pneumonia

Alireza Tahamtan,1 Masoumeh Tavakoli-Yaraki,2 Talat Mokhtari-Azad,1 Majid Teymoori-Rad,1 Louis Bont,3 Fazel Shokri,4 and Vahid Salimi1, "Opioids and Viral Infections: A Double-Edged Sword" Front Microbiol. 2016; 7: 970.*

Exorphins

Food derived peptides that bind to opioid receptors found in…



Bread

Milk

Corn

Front Hum Neurosci. 2016; 10: 130. Published online 2016 Mar 29. doi: 10.3389/fnhum.2016.00130

Journal of Biological Chemistry Vol. 254. No. 7, Issue Of April 10, pp. 2446-2449, 1979

Summary so far…

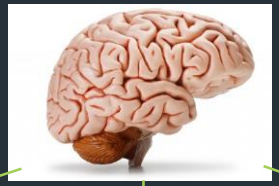
Nervous System

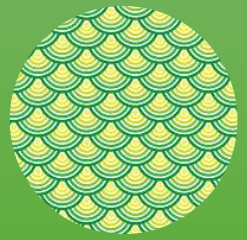
- Neurotransmitters
- Endorphins
- Exorphins

Immune System

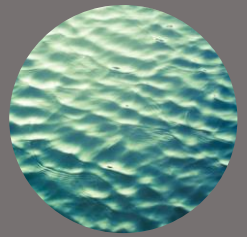
- Th1
- Th2
- Treg
- Pro-inflammatory

Gut Brain Axis





Neurotransmitters



Microflora

Cytokines

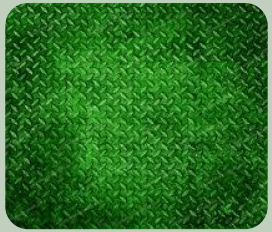
Neurotransmitters and Microbes

Neurotransmitter	Microbial Species
GABA	Lactobacillus & Bifidobacterium
Noradrenalin	Escherichia, Bacillus, and Saccharomyces
Serotonin	Candida, Streptococcus, and Escherichia, and Enterococcus
Dopamine	Bacillus
Acetylcholine	Lactobacillus

Carmen Cenit, M. et. Al., World J Gastroenterol. 2017 Aug 14; 23(30): 5486–5498.

Microflora and Brain



Anxiety

Depression

Autism

Parkinson’s

Multiple Sclerosis

Alzheimer’s

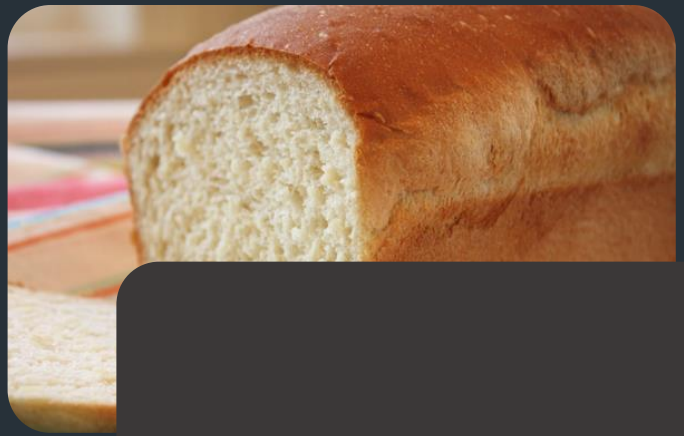
Neurotherapeutics. 2018 Jan 16. doi: 10.1007/s13311-017-0598-8.

Depression and Anxiety

Anxiety & Woe	• Forced swim test; Reduce woe with Lactobacillus • Lactobacillus increases GABA
Anxiety	• Campylobacter induces anxiety in rats • Bifidobacterium infantis reduces anxiety → Psychobiotic
Depression	• In humans, high Bacteroites (Alistipes) associated with depression • Restored with Lactobacillus, Bifidobacteria,

Menard, C. et al. Neuroscience. 2016 May 3; 321: 138–162.

Autism



Antibiotics & Diet

Gut dysbiosis

- Overgrowth of Clostridium genus and other commensals
- Overgrowth or depletion of Bacteroides

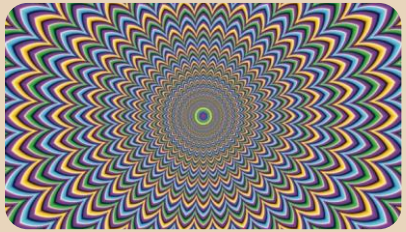
Mangiola, et al. World J Gastroenterol. 2016 Jan 7; 22(1): 361–368. Published online 2016 Jan 7. doi: 10.3748/wjg.v22.i1.361

Parkinson’s Disease

Reduced Provetellae

Increased Enterobacteriae

Postural instability and Gait difficulty

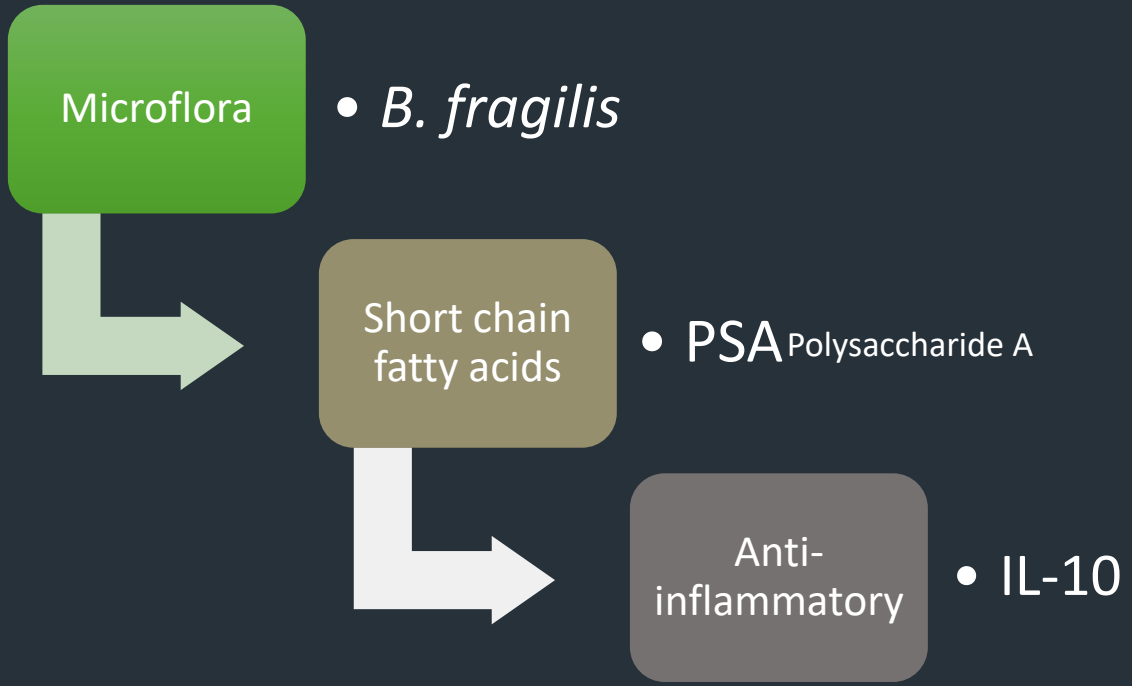


Dose dependent

Prebiotics

Sheperjans, F. et al. Mov Disord. 2015 Mar;30(3):350-8. doi: 10.1002/mds.26069. Epub 2014 Dec 5.

Multiple Sclerosis



Animal Studies

Ochoa-Reparaz, J. et al. Cold Spring Harb Perspect Med. 2018 Jan 8. pii: a029017. doi: 10.1101/cshperspect.a029017.

Alzheimer's Disease

GABA deficient

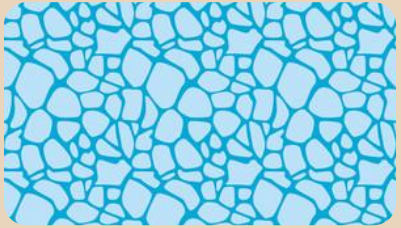
- AD has GABA deficiency

Lactobacillus and Bifidobacterium

- Metabolize glutamate to make GABA

BDNF

- BDNF repairs AD damage

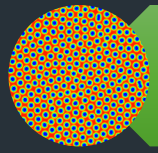


Short-chain fatty acids

- Histone deacetylation
- Butyrate

Carmen Cenit, M. et al. World J Gastroenterol. 2017 Aug 14; 23(30): 5486–5498.

Treat the Gut



Antibiotics

Probiotics

Diet/Prebiotics

Fecal Transplant

Summary

Nervous system and immune system interact

Gut is important source of neurotransmitters and cytokines

Neuroinflammation can be caused by microflora dysbiosis

Summary

Gut Brain Axis

- Controlled by microflora & mediated by cytokines, neurotransmitters, endorphins, and food

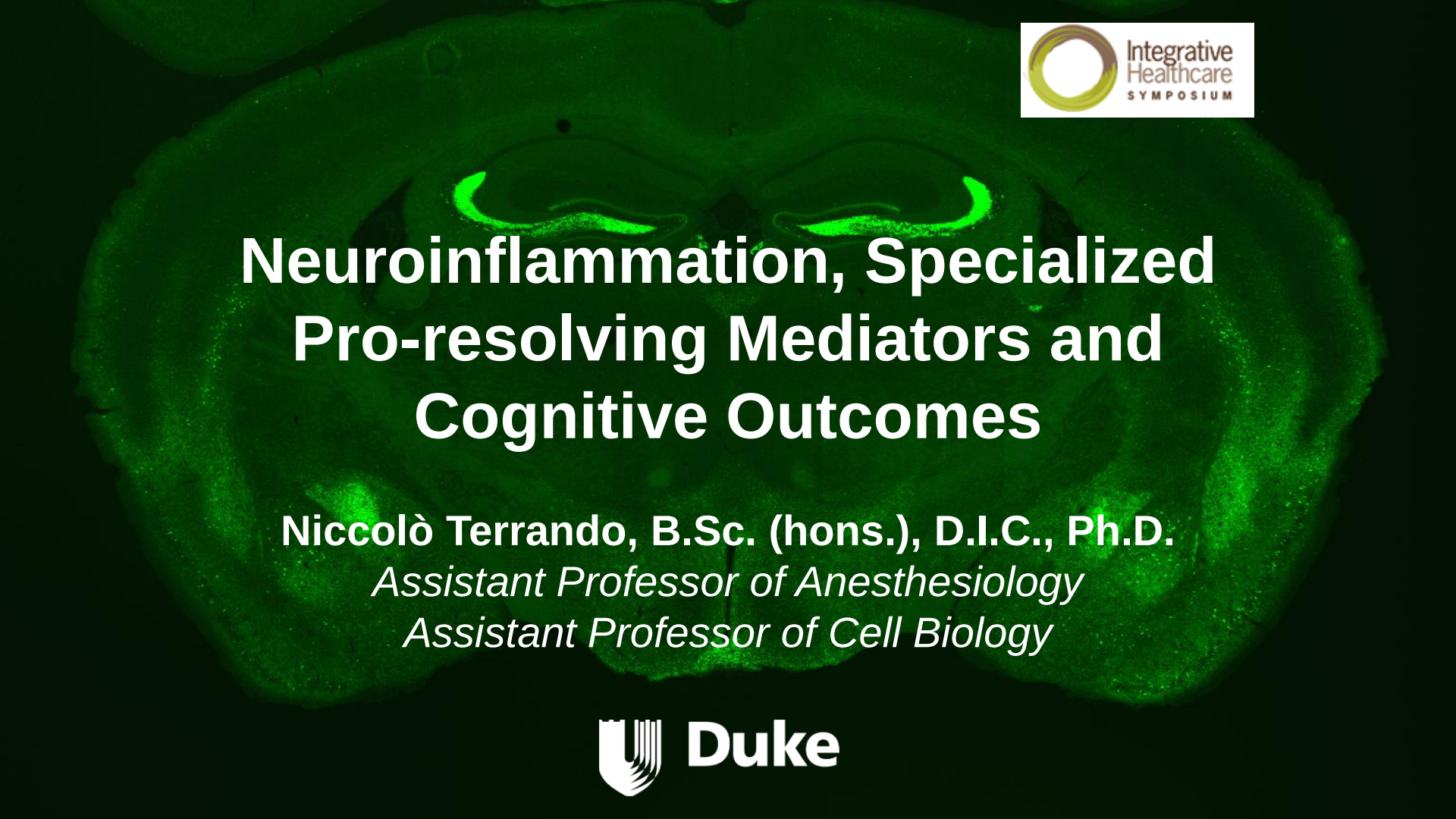
Thank you!!!

Thanks to

Metagenics Institute

Nutrition by Heather Zwickey


Metagenics Institute



Neuroinflammation, Specialized Pro-resolving Mediators and Cognitive Outcomes

Niccolò Terrando, B.Sc. (hons.), D.I.C., Ph.D.
Assistant Professor of Anesthesiology
Assistant Professor of Cell Biology

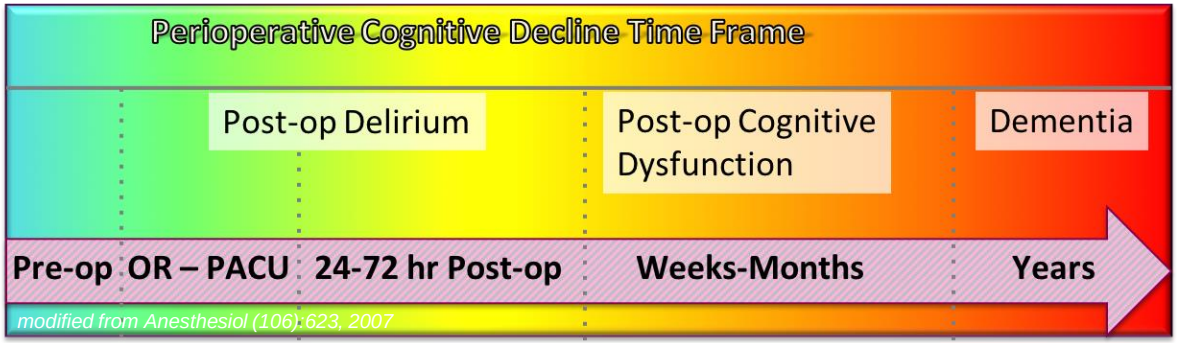
Integrative Healthcare SYMPOSIUM

Duke

Agenda

- Perioperative Neurocognitive Disorders
- Preclinical Models to study Postoperative Neuroinflammation
- Endogenous Strategies to modulate Neuroinflammation
  - Cholinergic reflex
  - SPMs

Periop Neurocognitive Disorders



- Deterioration of intellectual function reflected as memory and concentration impairment
- Separate entities, although many similarities
- New nomenclature in accordance with DSM-5 classification (*in press*)

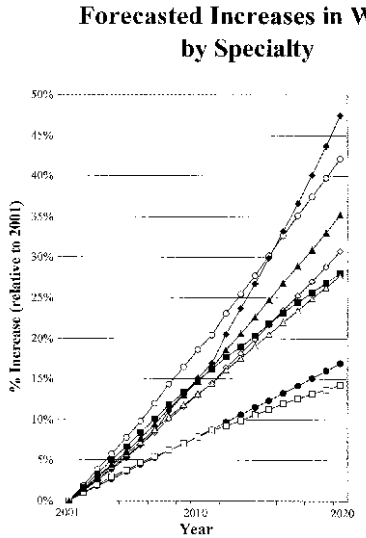
Why it matters?

PMID21474666

Table 3. Incidence of Postoperative Cognitive Dysfunction for Control, Coronary Angiography, Total Hip Joint Replacement Surgery, and Coronary Artery Bypass Graft Surgery Groups

	Control (*n* = 34)	CA (*n* = 168)	THJR (*n* = 164)	CABG (*n* = 312)	Total (*n* = 644)
Day 7	*n* = 34		*n* = 162	*n* = 281	*n* = 443
POCD	2 (6%) [1, 20]		28 (17%) [12, 24]	122 (43%) [38, 49]	150 (34%) [29, 38]
3 mo	*n* = 32	*n* = 167	*n* = 157	*n* = 312	*n* = 636
POCD	0 (0%) [0, 11]	35 (21%) [15, 28]	25 (16%) [11, 23]	51 (16%) [11, 23]	111 (17%) [15, 21]

Data are presented as *n* (%) [95% confidence interval] in percent.
POCD = postoperative cognitive dysfunction; CA = coronary angiography; THJR = total hip joint replacement surgery; CABG = coronary artery bypass graft surgery.



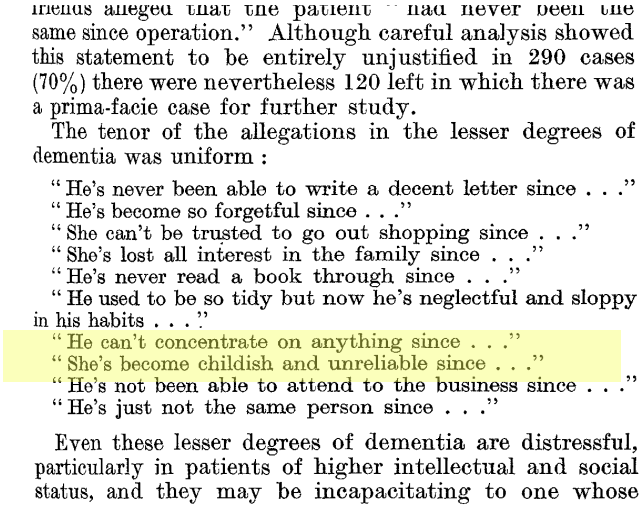
29%

PMC5370103

150 bn

PMC3415302

Age as a Predictor of cognitive dysfunction after major non-cardiac surgery



friends alleged that the patient had never been the same since operation." Although careful analysis showed this statement to be entirely unjustified in 290 cases (70%) there were nevertheless 120 left in which there was a prima-facie case for further study.

The tenor of the allegations in the lesser degrees of dementia was uniform:

"He's never been able to write a decent letter since . . ."
"He's become so forgetful since . . ."
"She can't be trusted to go out shopping since . . ."
"She's lost all interest in the family since . . ."
"He's never read a book through since . . ."
"He used to be so tidy but now he's neglectful and sloppy in his habits . . ."
"He can't concentrate on anything since . . ."
"She's become childish and unreliable since . . ."
"He's not been able to attend to the business since . . ."
"He's just not the same person since . . ."

Even these lesser degrees of dementia are distressful, particularly in patients of higher intellectual and social status, and they may be incapacitating to one whose

THE LANCET

Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study

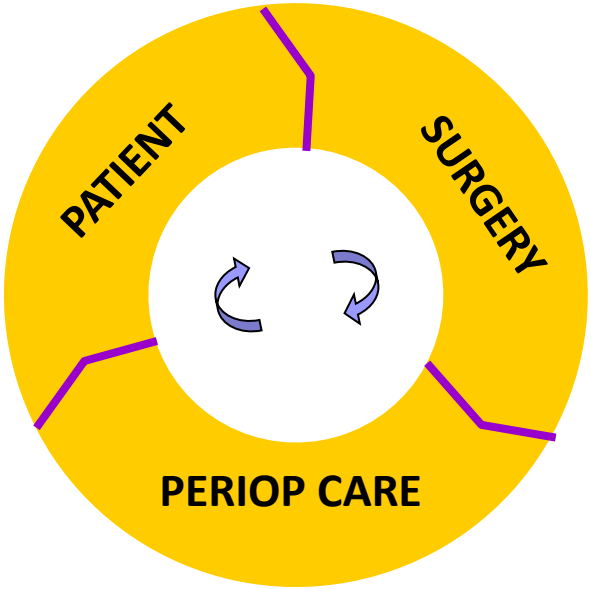
*J T Moller, P Cluitmans, L S Rasmussen, P Houx, H Rasmussen, J Canet, P Rabbitt, J Jolles, K Larsen, C D Hanning, O Langeron, T Johnson, P M Lauven, P A Kristensen, A Biedler, H van Beem, O Fraidakis, J H Silverstein, J E W Beneken, J S Gravenstein, for the ISPOCD investigators**

Monk, T.G. et al Anesthesiology 2008; 108(1):18-30

- 1064 patients undergoing major non-cardiac surgery with general anaesthesia
- 36.6% (18-39 yr), 30.4% (40-59 yr), 41.4% (>60 yr) patients had POCD at hospital discharge and 5.7%, 5.6% and 12.7% at 3 months postop respectively

Multifactorial Pathology

- Advanced age
- “cognitive reserve”
- Genes
- Dementia/MetaS

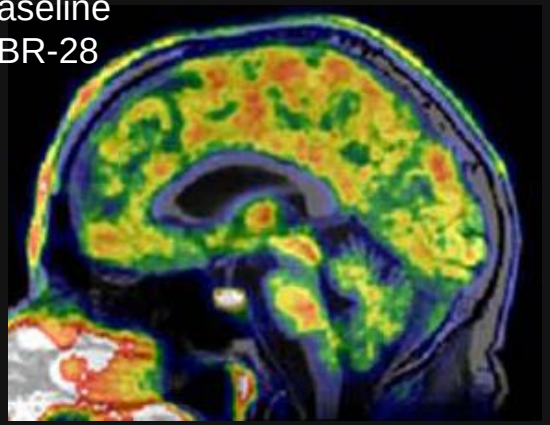


- Cardiac, orthopedic
- Postop complications (respiratory, infection)
- Multiple operations

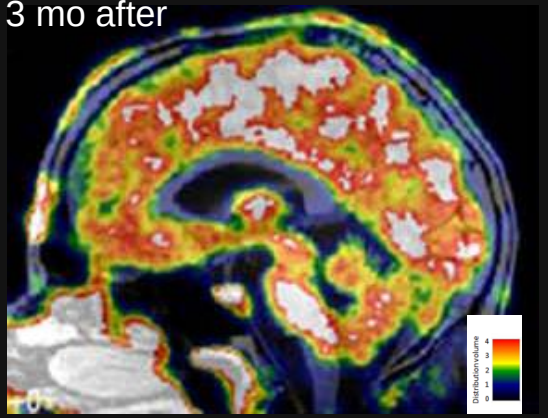
- Anesthesia
- Drugs

The brain after surgery
Neuroinflammation

Baseline
PBR-28



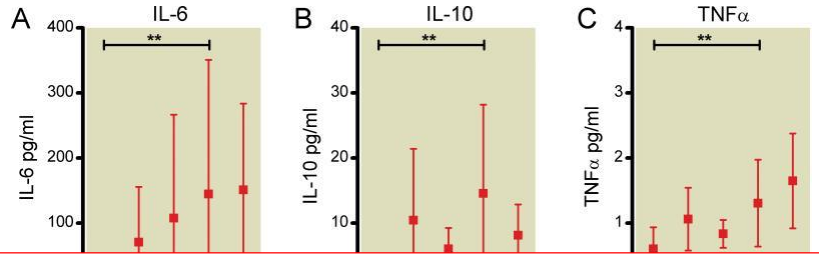
3 mo after



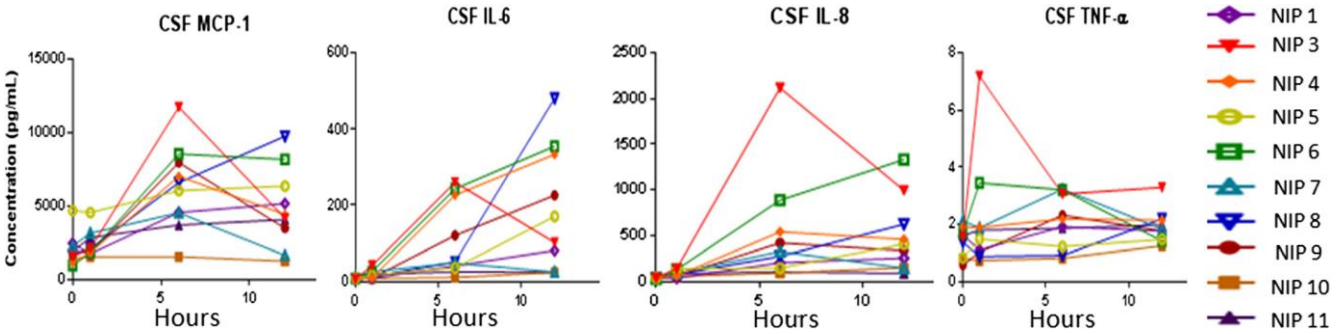
- Peripheral surgery (orthopedic, cardiac, abdominal…)
- Independent form the type of anesthesia

Forsberg et al, Ann Neurol 2017

Neuroinflammation – CSF biomarkers

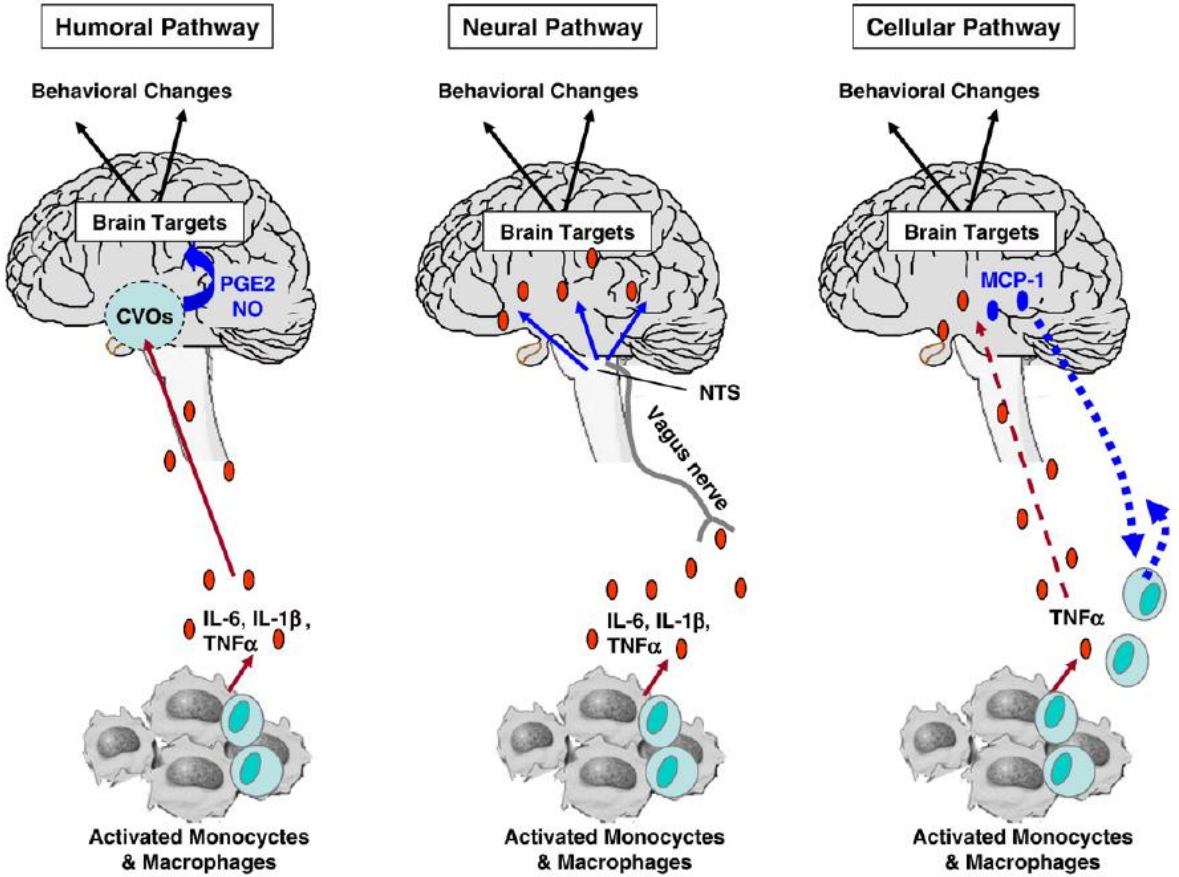


No *safe* therapeutics available!



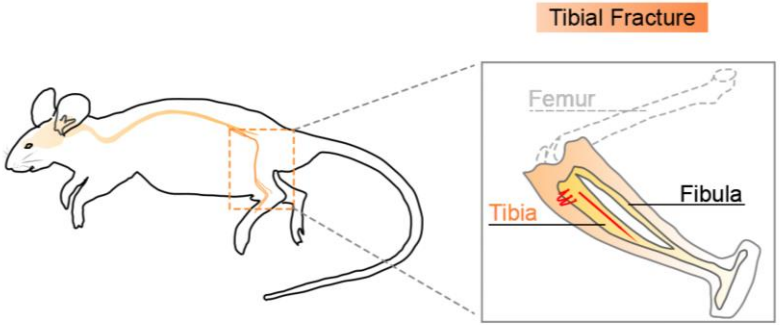
Tang et al, Anesthesiol 2011; Hirsh et al J Neuroinfl 2016

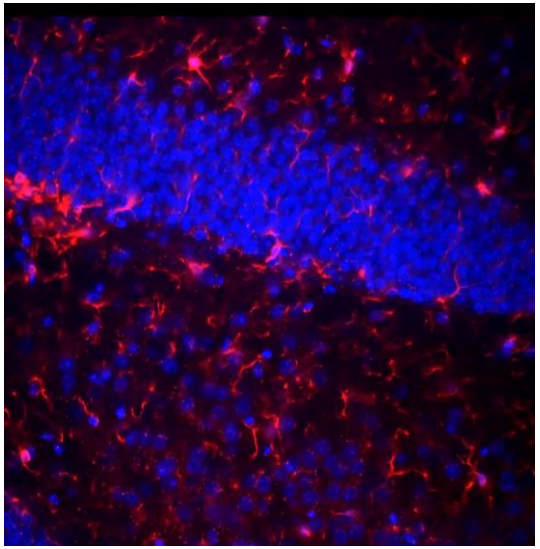
Immune-to-brain signaling

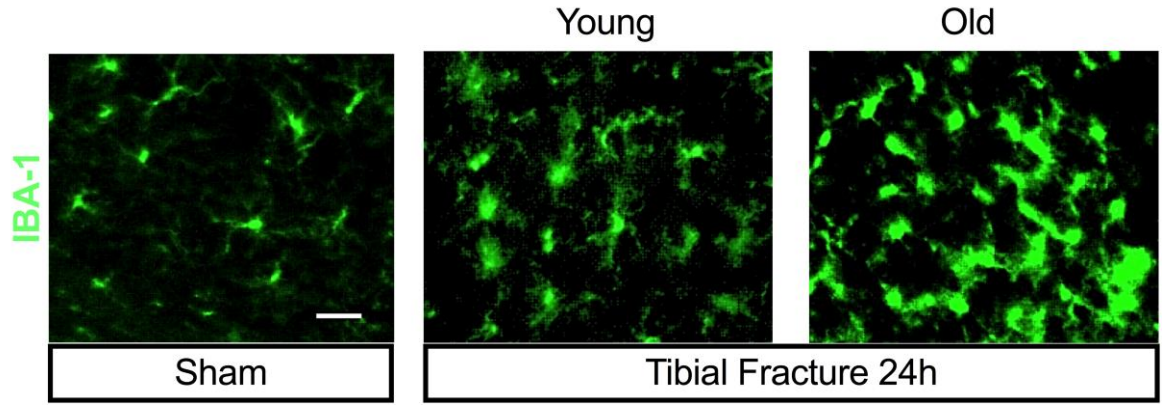


Capuron and Miller 2011

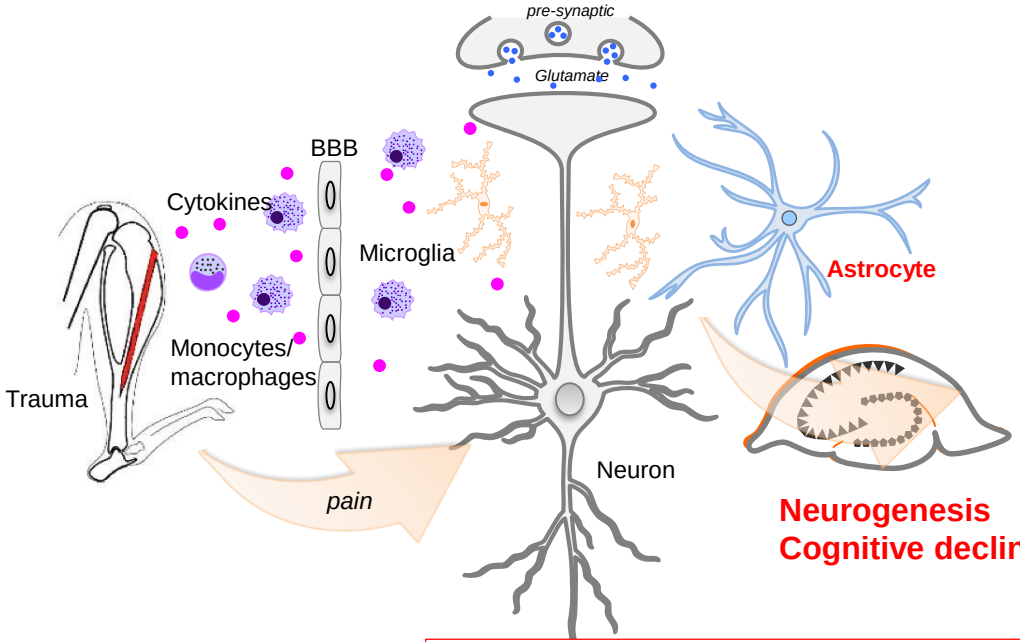
Orthopedic surgery model







Orthopedic model and MOA

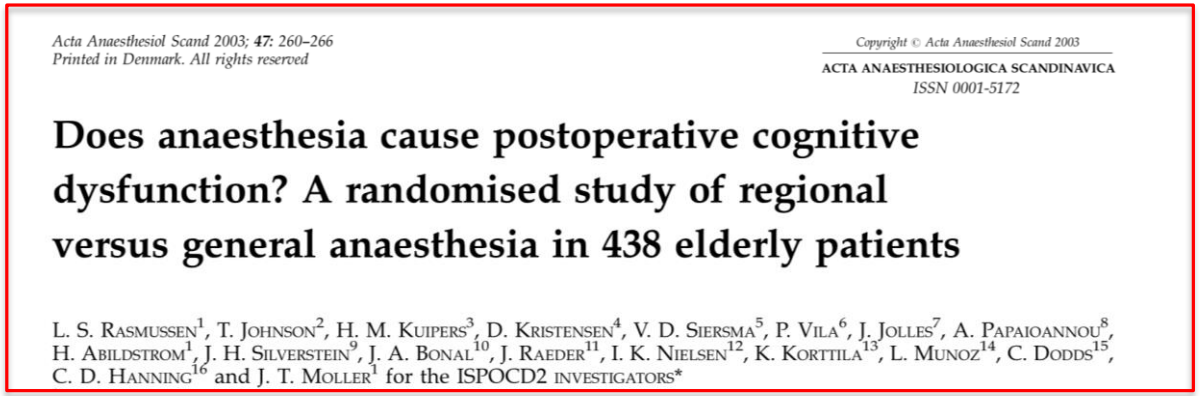


Key references:

- Terrando et al PNAS 2010
- Cibelli et al Ann Neurol 2010
- Terrando et al Ann Neurol 2011
- Terrando et al Mol Med 2015
- Terrando et al FASEB 2013
- Femenia et al J Neuro 2018
- Zhang et al PNAS 2016

SURGERY, NOT ANESTHESIA

Anesthesia and Cognition



Acta Anaesthesiol Scand 2003; 47: 260–266
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ACTA ANAESTHESIOLOGICA SCANDINAVICA
ISSN 0001-5172

Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients

L. S. RASMUSSEN[1], T. JOHNSON[2], H. M. KUIPERS[3], D. KRISTENSEN[4], V. D. SIERSMA[5], P. VILA[6], J. JOLLES[7], A. PAPAIOANNOU[8], H. ABILDSTROM[1], J. H. SILVERSTEIN[9], J. A. BONAL[10], J. RAEDER[11], I. K. NIELSEN[12], K. KORTTILA[13], L. MUNOZ[14], C. DODDS[15], C. D. HANNING[16] and J. T. MOLLER[1] for the ISPOCD2 INVESTIGATORS*

- No significant differences at 3 months
- RA lower mortality incidence
- Similar results when comparing GA with **Spinal Anesthesia** (*Silbert et al, BJA 2014*)
- Meta-analysis inconclusive for delirium, RA preferable for POCD (*Mason et al, JAD 2010*)

"As with other organs, like the heart and kidneys, so too with the brain: acute postoperative dysfunction is probably common and potentially preventable."

Avidan MS & Benzinger TL.
Anesthesiology. 2012 Mar;116(3):510-2

- Cholinergic anti-inflammatory pathway

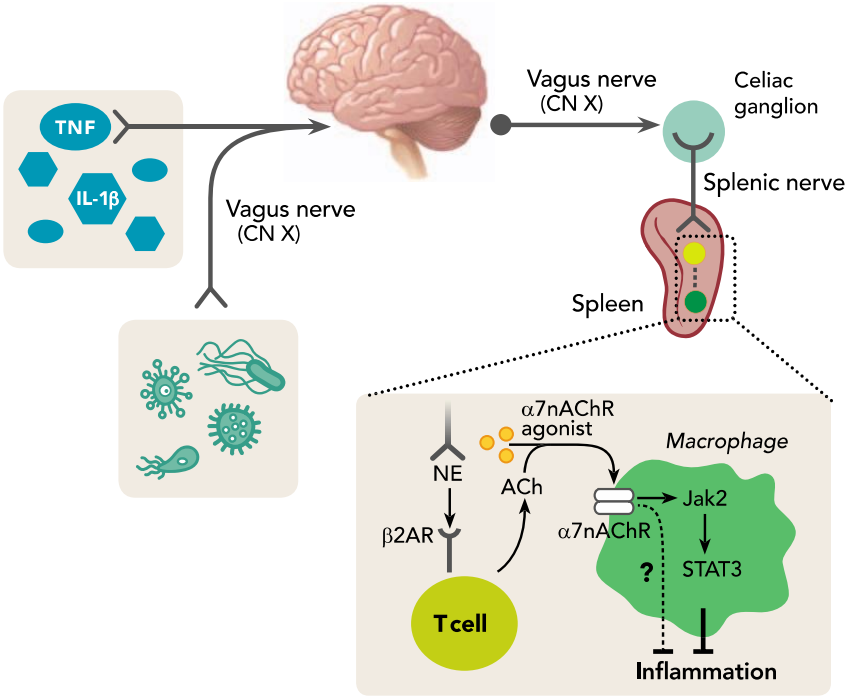
  α7 nAChR

- Specialized pro-resolving mediators

  AT-RvD1

  Annexin-A1

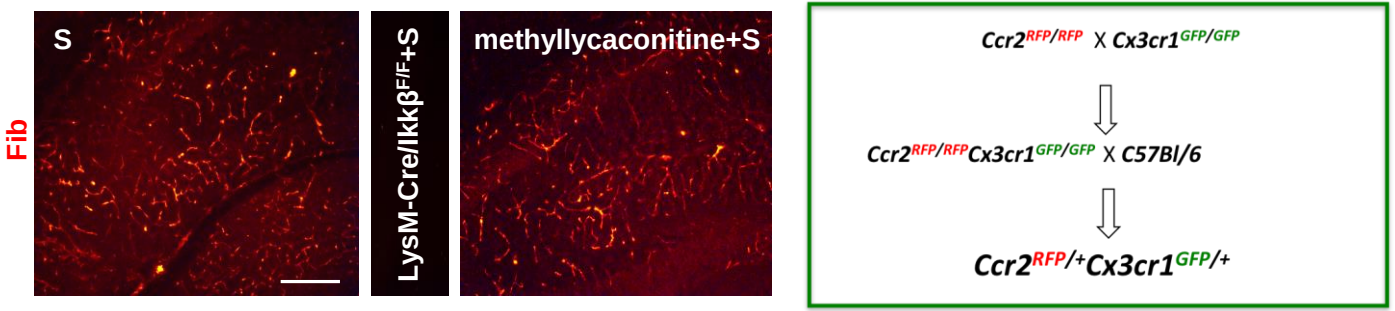
The vagus and the "anti-inflammatory reflex"

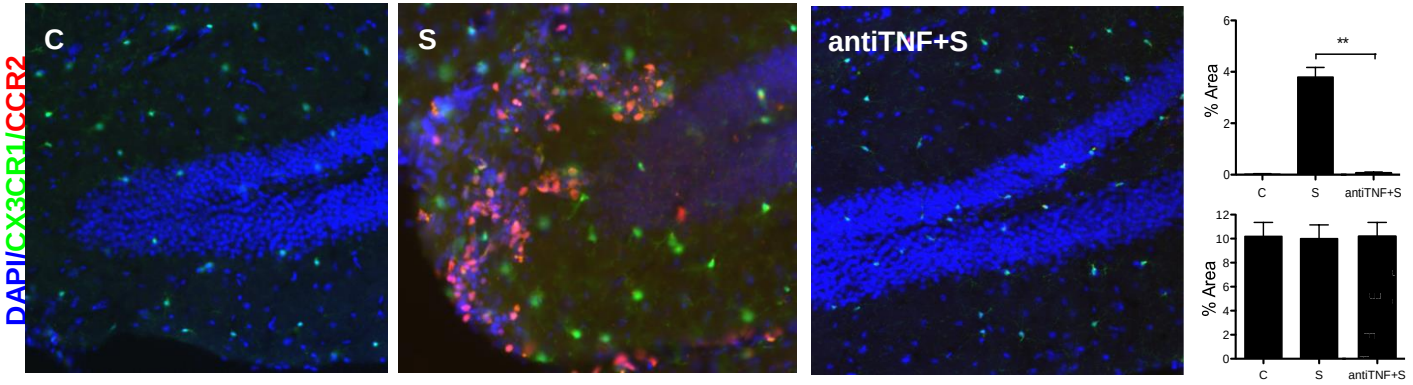


Biochemical
Pharmaceutical

Steinberg B et al Anesthesiol, 2016

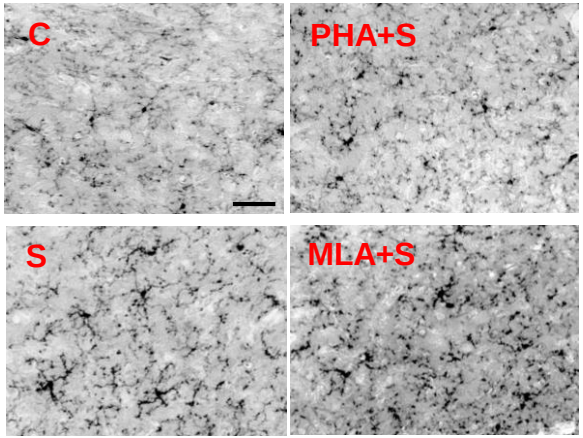
Surgery opens the blood-brain barrier causing macrophage infiltration

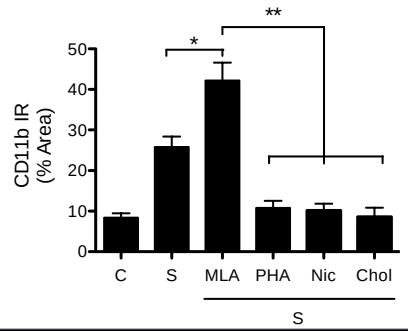


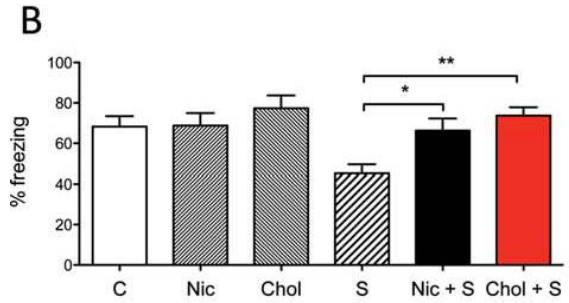


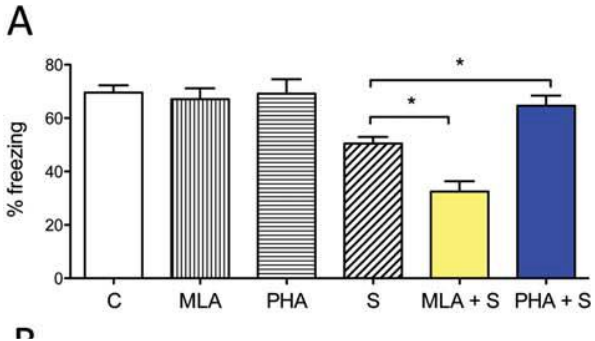
Terrando et al, Ann Neurol 2011

Cholinergic modulation of microglia activity and memory



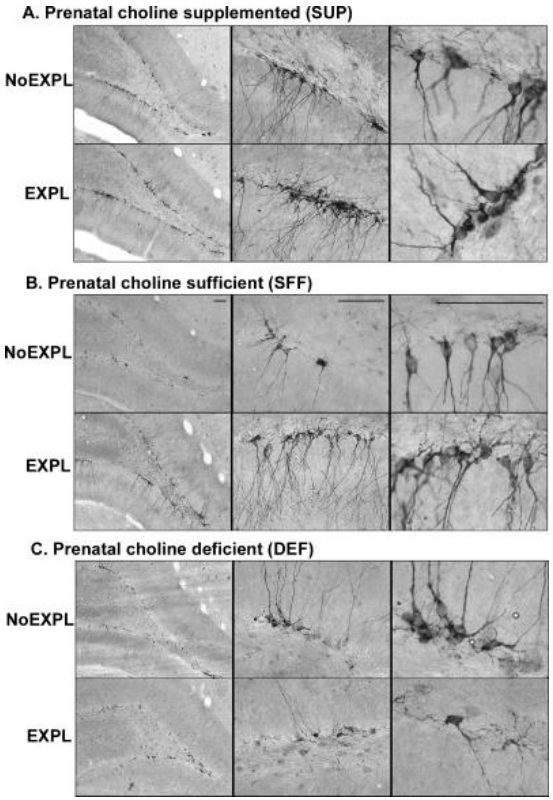


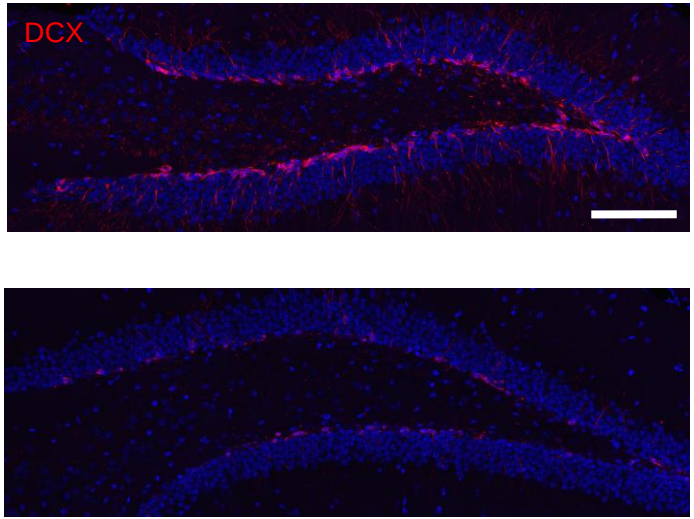




Terrando et al, Ann Neurol 2011

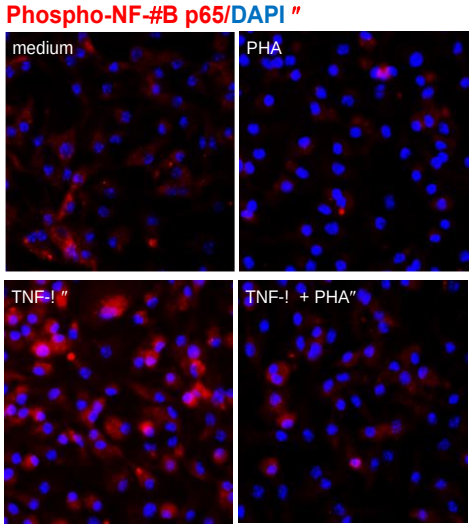
Choline supplementation and neurogenesis

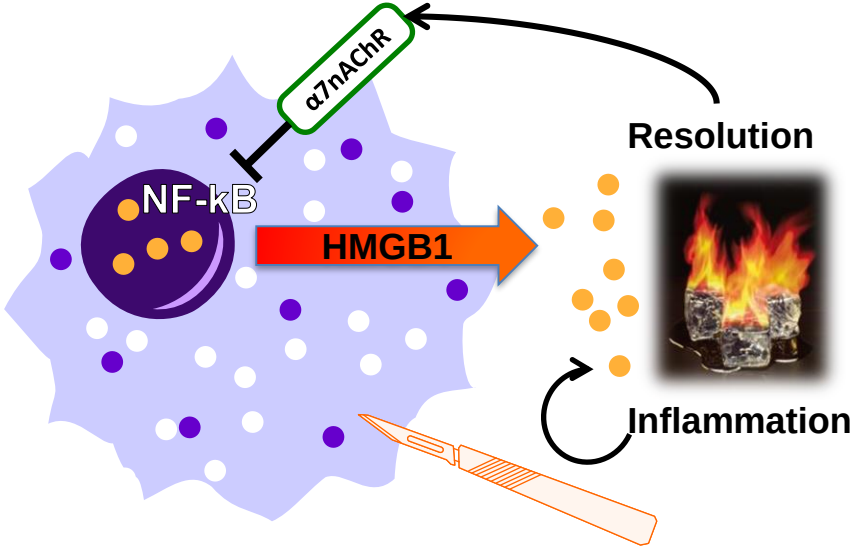


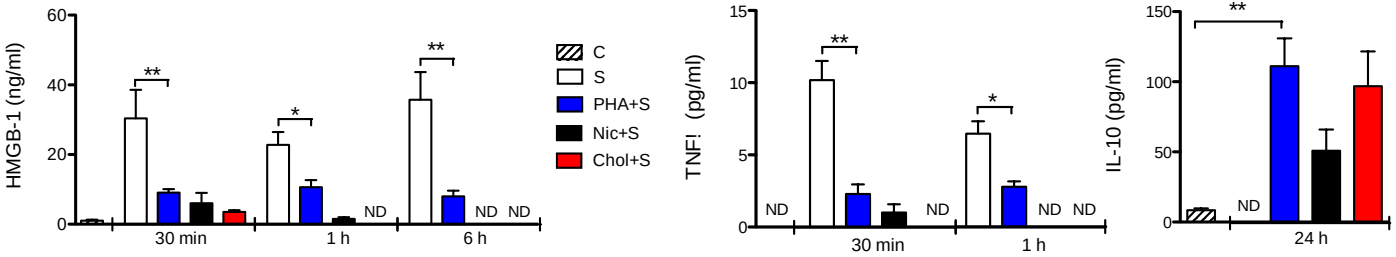


Glenn et al EJN 2007 and Zhang MD et al PNAS 2016

Cholinergic signaling dampens systemic inflammation through NF-κB and HMGB1

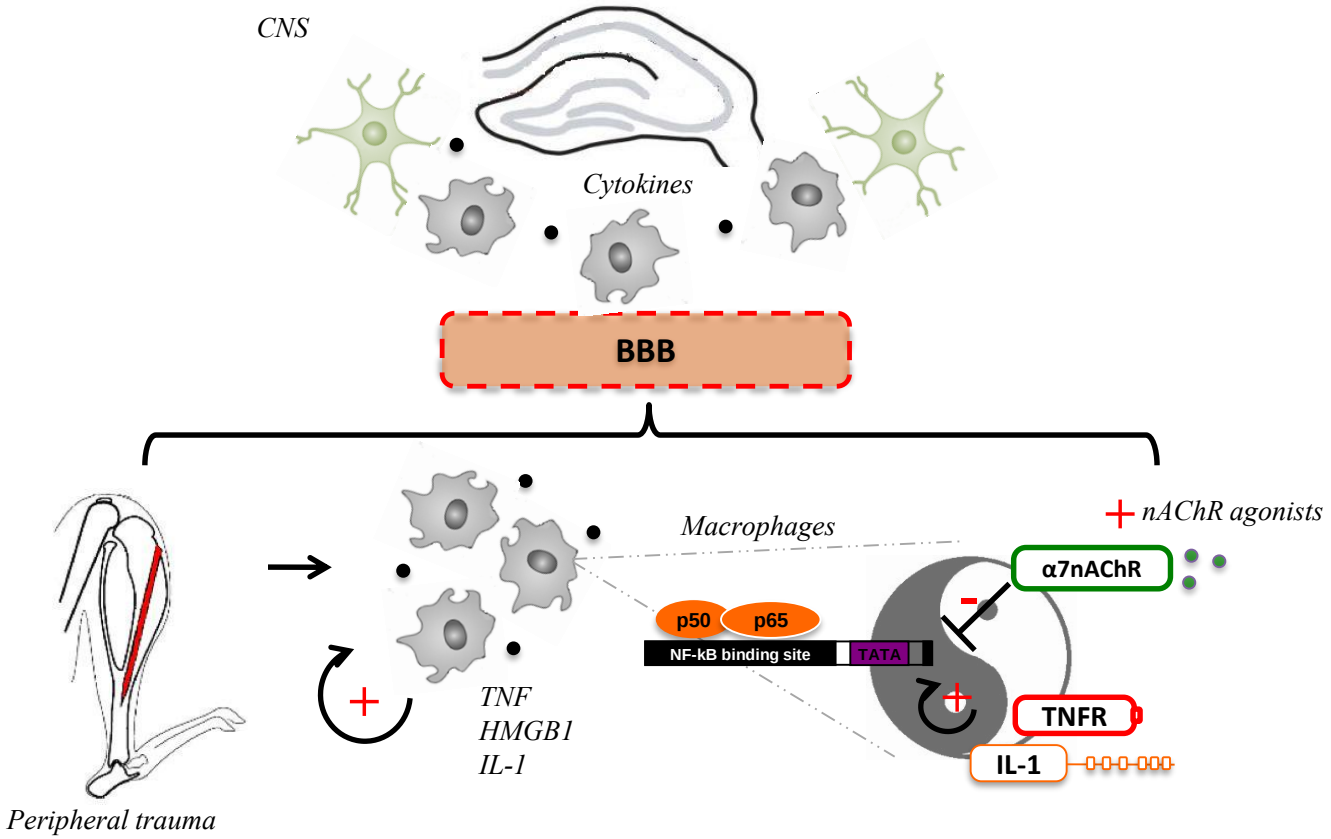






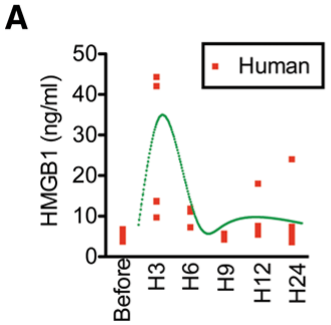
Terrando et al, Ann Neurol 2011

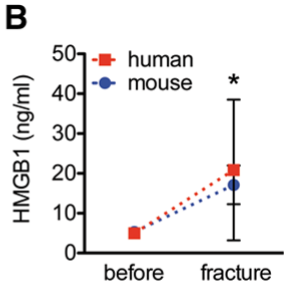
Proposed signaling mechanisms



Terrando et al, Ann Neurol 2011

Human relevance





Acta Anaesthesiol Scand 2014; **; **–**
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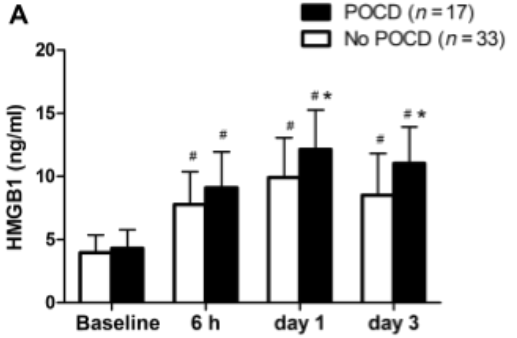
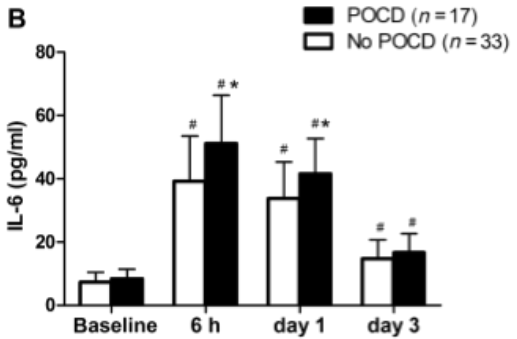
ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/aas.12320

Serum high-mobility group box 1 protein correlates with cognitive decline after gastrointestinal surgery

G.-X. Lin, T. Wang, M.-H. Chen, Z.-H. Hu and W. Ouyang
Department of Anesthesiology, The Third Xiangya Hospital of Central South University, Changsha, China

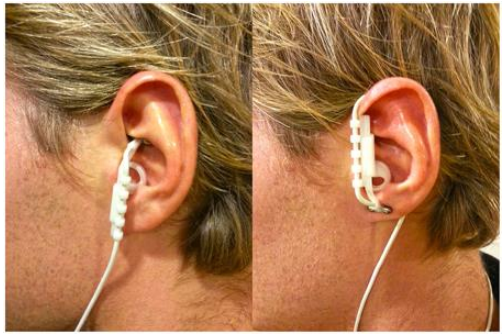




Degos et al, Anesthesiol 2013

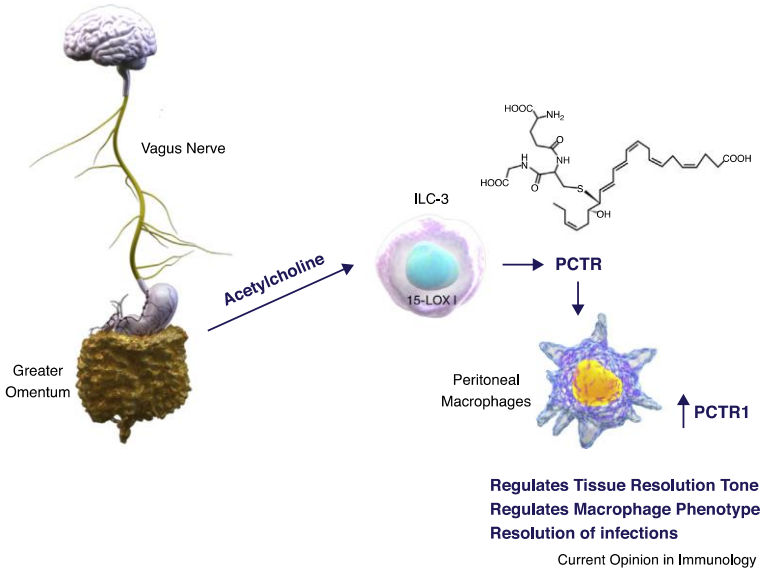
VNS for Postop Cognitive Disorders?

gammaCor
e



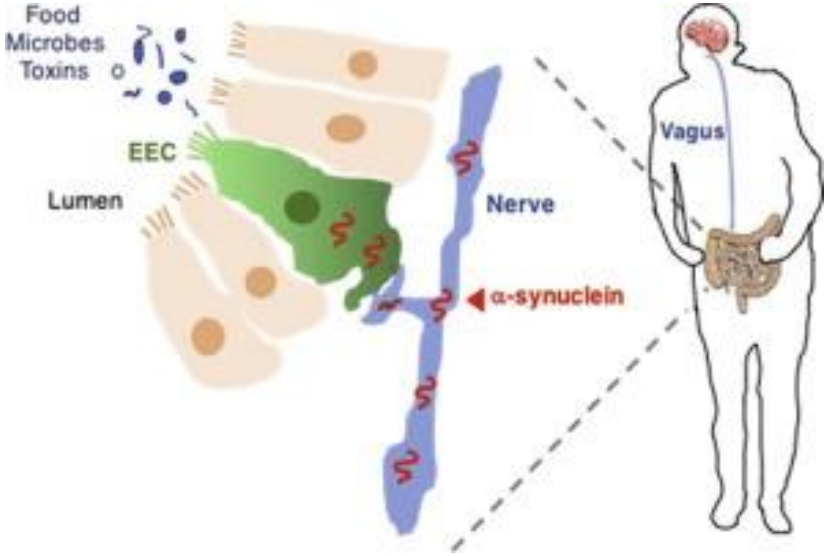
Leusden
(2015)

Mechanisms and appropriate mode of delivery?



Dalli and Serhan 2018

Vagus and Neurodegeneration



- Enteroendocrine cells express α-synuclein and could be a source of PD
- Cholinergic hypofunction during aging

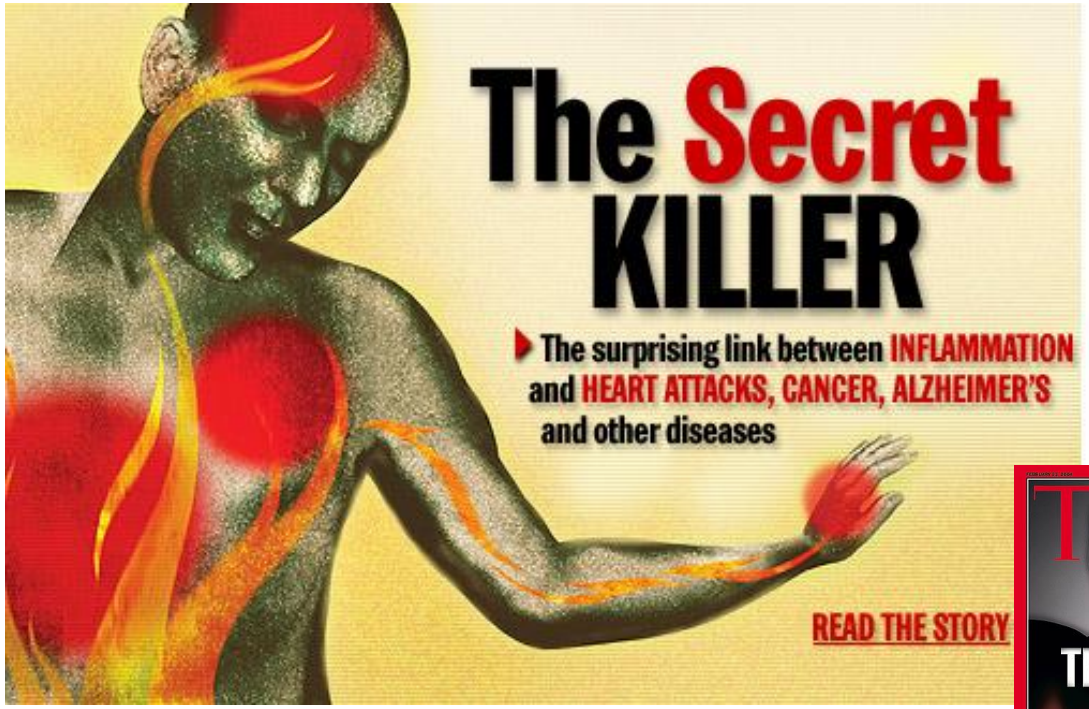
Summary

- Trauma and surgery activate the innate immune system to ultimately affect CNS function, causing neuroinflammation and cognitive decline

- Neuroinflammation after peripheral surgical trauma derives from BBB disruption and infiltration of peripheral macrophages into the hippocampus

- Stimulation of endogenous anti-inflammatory signaling improves surgery-induced systemic inflammation, neuroinflammation and cognitive decline

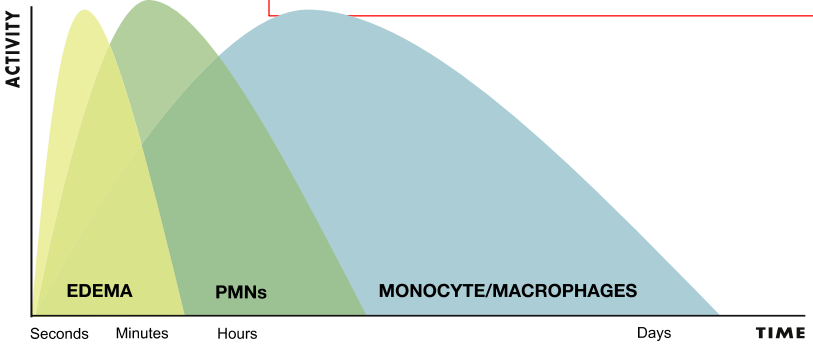
Inflammation – the fire within



Prof. Charles N. Serhan, Harvard

Complete resolution

the ideal outcome



Injury
Invasion
Surgery
→ Acute Inflammation

ACTIVE PROCESS | SELF-LIMITED

→ Resolution

Calor (heat)
Rubor (redness)
Tumor (swelling)
Dolor (pain)
Loss of Function

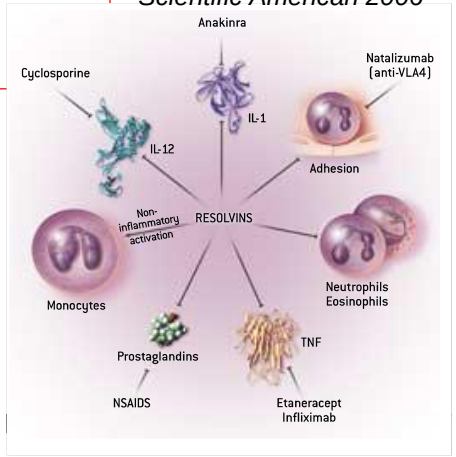
Cardinal Signs of inflammation

LIPOXINS
RESOLVINS E-SERIES D-SERIES
PROTECTINS MARESINS

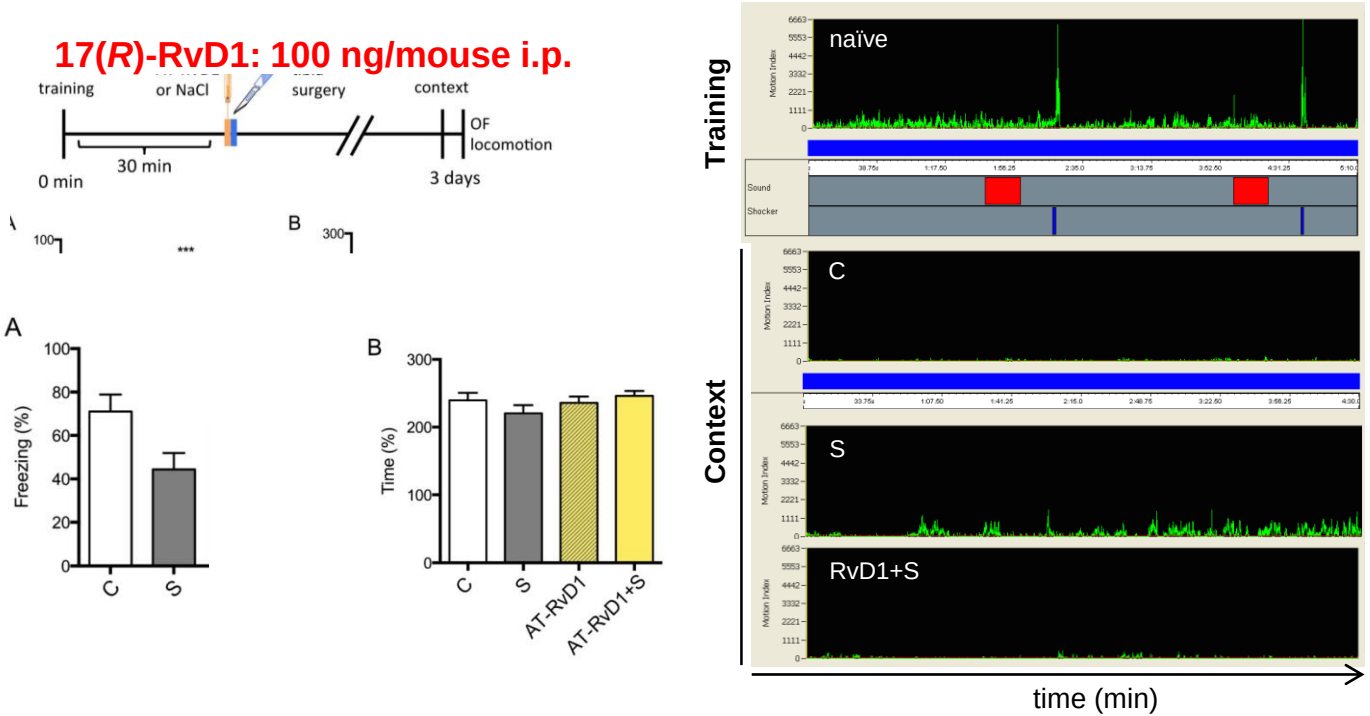
Sequestration and counter-regulation of pro-inflammatory cytokines (e.g. PAF, LT, PG)
PMN clearance from epithelial surfaces
Phagocytosis of apoptotic PMNs
Removal of inflammatory debris

Signs of resolution

Scientific American 2006

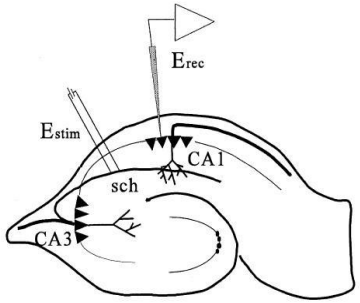


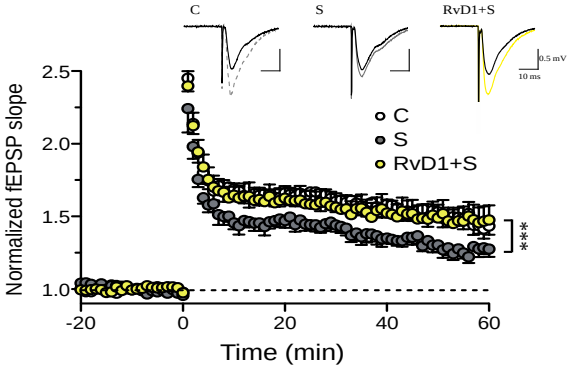
Do SPMs prevent POCD?

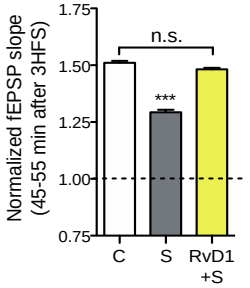


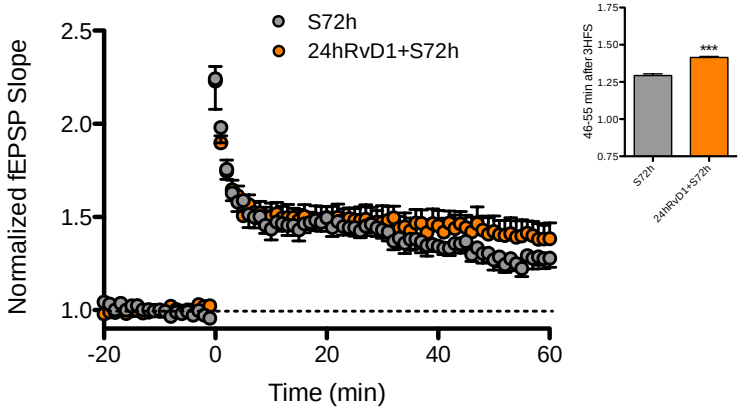
mean ± SD (n = 10/group). ***P < 0.001 analyzed with 1-way ANOVA with Bonferroni.

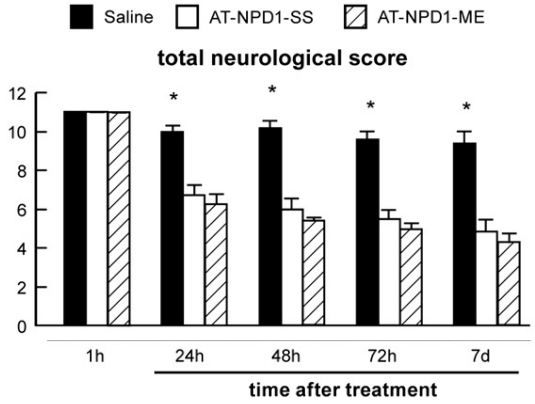
How RvD1 rescues memory decline?







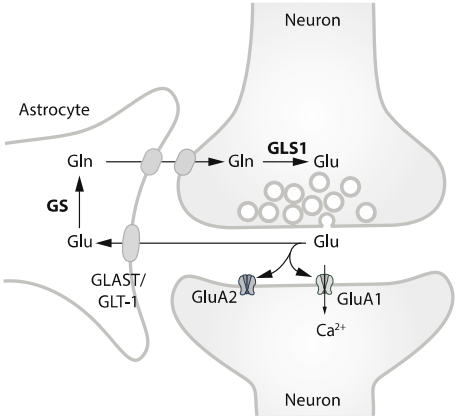


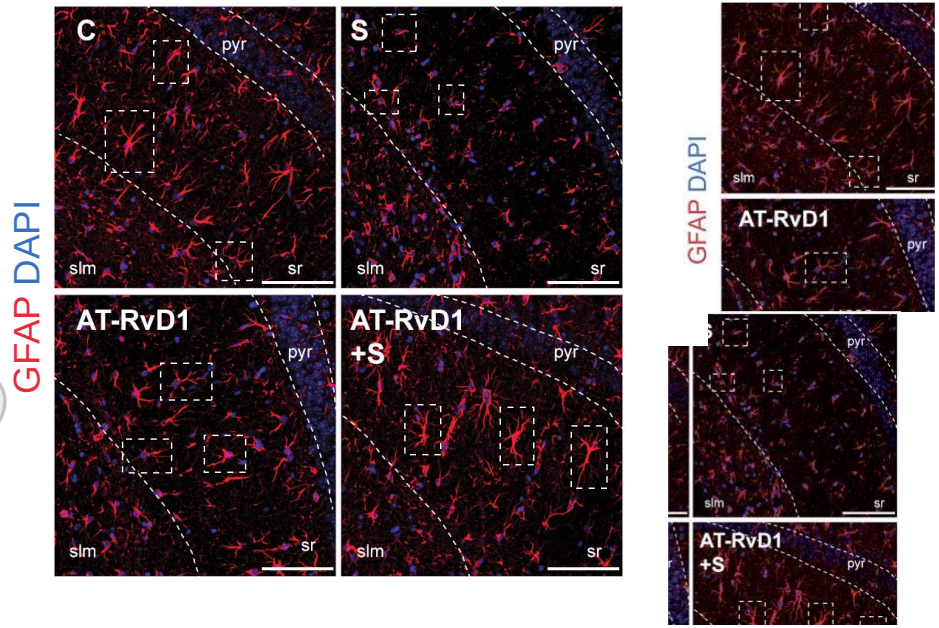


Bazan et al, Exp Neurol 2012

Terrando et al, Faseb J 2013

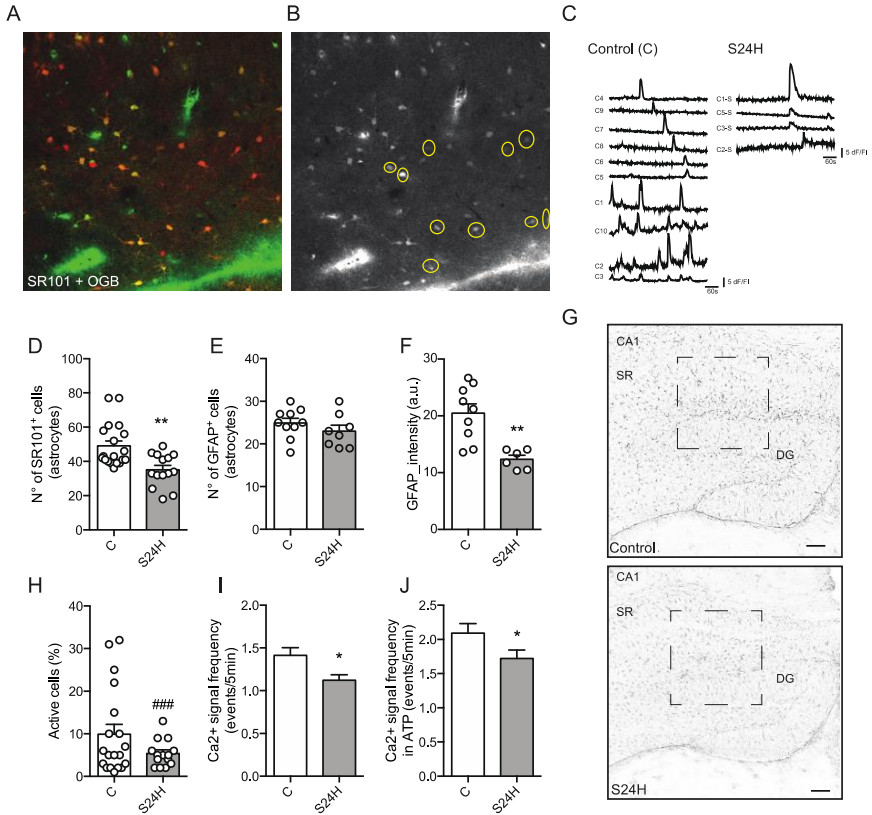
RvD1 prevents neuroinflammation





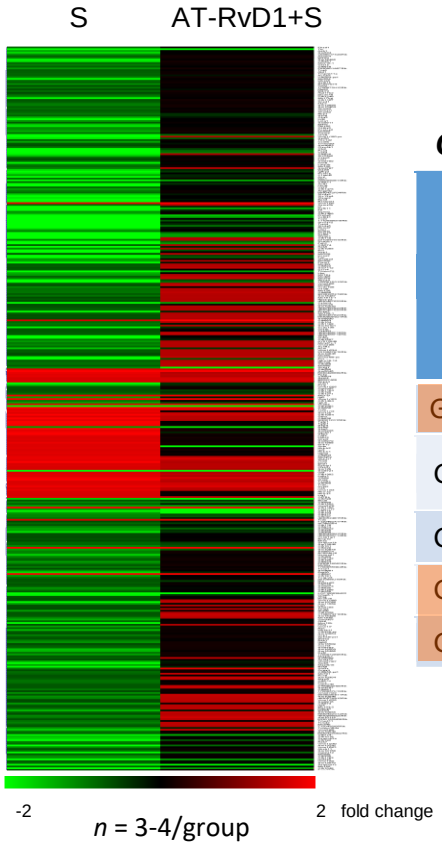
mean ± SD (*n* = 5/group). ***$P < 0.001$ analyzed with 1-way ANOVA with Bonferroni.

Neuro-glia effects after surgery



Femenia et al J Neurosci 2018

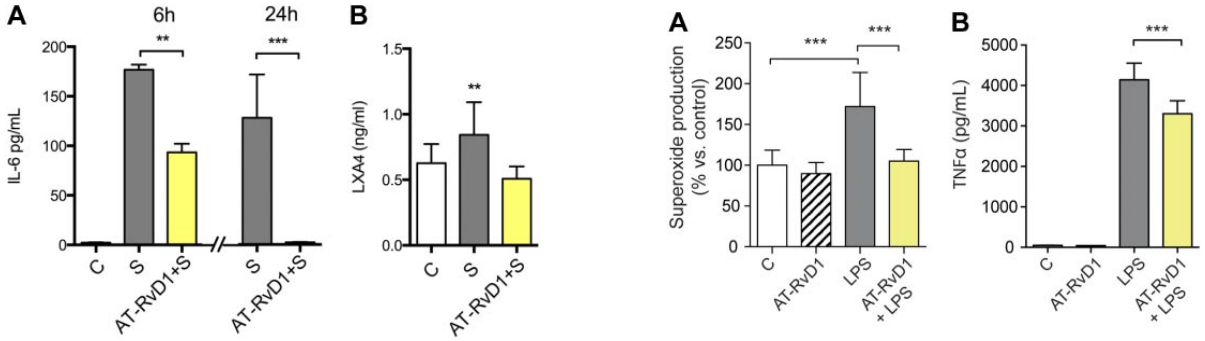
Hippocampal gene expression changes



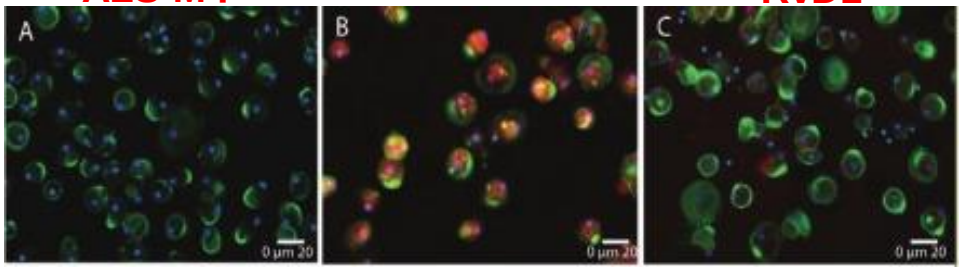
Gene Ontology (GO) groups downregulated

Category	GO term	Fold Enrichment (Surgery)
GOTERM_MF	olfactory receptor activity	3.3
GOTERM_BP	sensory perception of chemical stimulus	3.2
GOTERM_BP	sensory perception	2.9
GOTERM_BP	cognition	2.7
GOTERM_BP	neurological system process	2.4

Systemic anti-inflammatory effects



ALS MΦ **+ RvD1**



Liu et al, Am J Neurodegener Dis 2012

Summary

- SPMs affect systemic inflammation and oxidative stress response
- SPMs actively regulate neuro-glia interactions (humoral and neuronal)
- AT-RvD1 (and other SPMs) prevent postop memory dysfunction

Inflammation's STOP SIGNALS

Inflammation doesn't just peter out. The body actively shuts it down, using signals that researchers hope to transform into therapies *By* **Mitch Leslie**

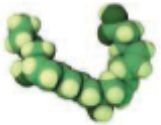
Players in the endgame

An assortment of molecules shut down inflammation and promote tissue healing by target

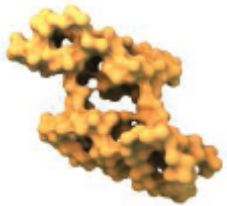
Lipoxins
Lipids whose jobs include stimulating macrophages and preventing neutrophils from slipping between endothelial cells to enter damaged tissue.

Resolvins
Family of lipids that block neutrophils' exit from the bloodstream and prod macrophages to eat cellular debris.

Maresins
Made by macrophages, lipids that spur tissue repair and act on nerves to ease pain.



Protectins
Lipids that curtail release of inflammation-promoting molecules and are protective in the nervous system.



Annexin A1
A protein released by dying neutrophils, its functions include preventing other neutrophils from entering the injured site.

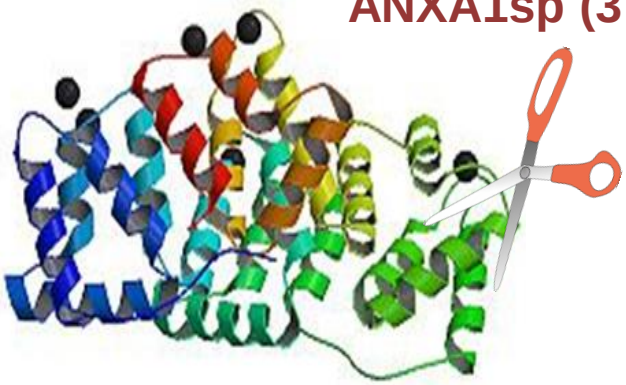
Hydrogen sulfide
Message-carrying gas that reduces pain and stimulates neutrophils to commit suicide.

SCIENCE sciencemag.org

Annexin A1

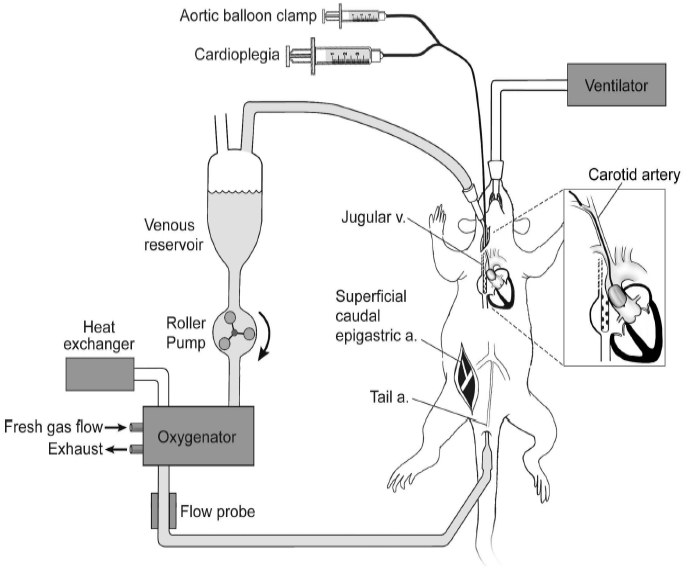
ANXA1 (346 AA)

ANXA1sp (3 AA)



N-terminal Domain

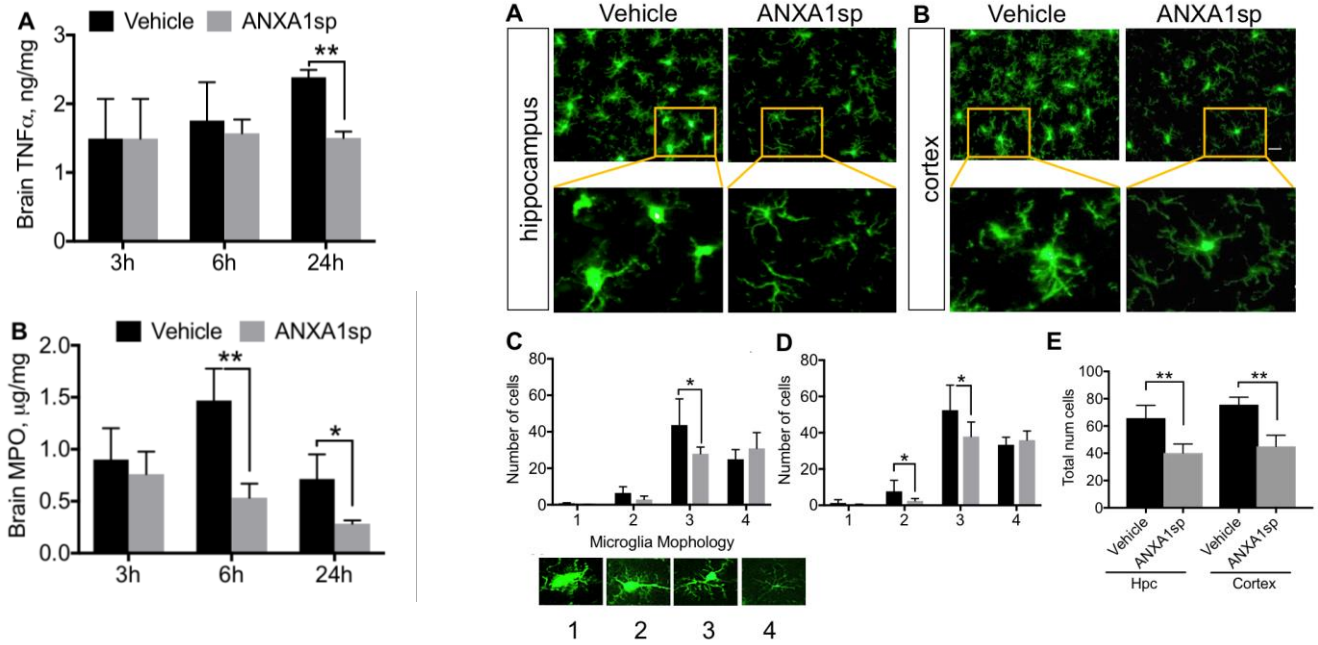
Rat model of CPB/DHCA



Grocott and Mackensen

- Sprague-Dawley rats (Charles River, age 14–16 weeks; weight ~400g)
- CPB followed by 60min DHCA
- ANXA1sp 1mg/kg iv 30min before surgery

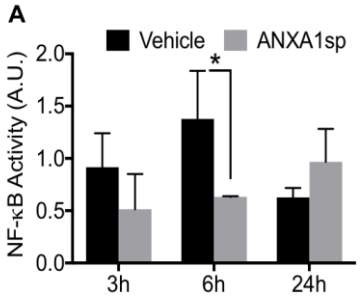
ANXA-1sp reduces neuroinflammation



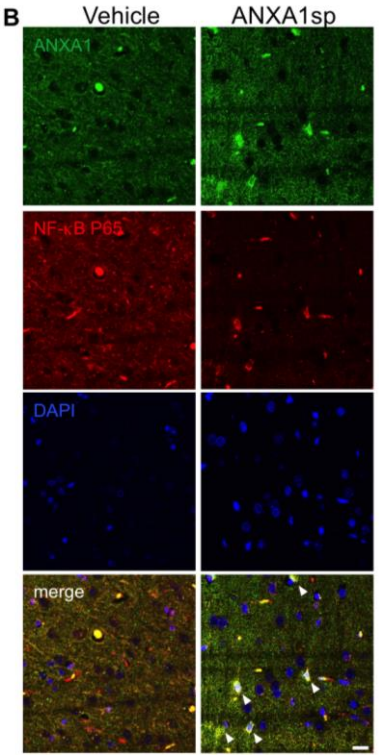
mean ± SD (n = 3–5 rats/group). *P < 0.05, **P < 0.01 compared to vehicle controls, analyzed with unpaired t test; microglia morphology analyzed with two-way ANOVA Sidak's multiple comparisons test.

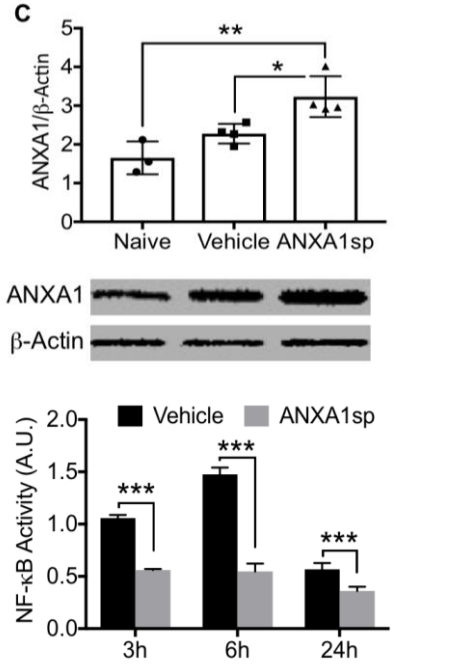
Zhang Z et al, Front Immunol 2017

Modulation of brain NF-kB after surgery



Mean ± SD (n = 3–5 rats/group). *P < 0.05, **P < 0.01 analyzed with unpaired t test or one-way ANOVA with Tukey's multiple comparisons test.





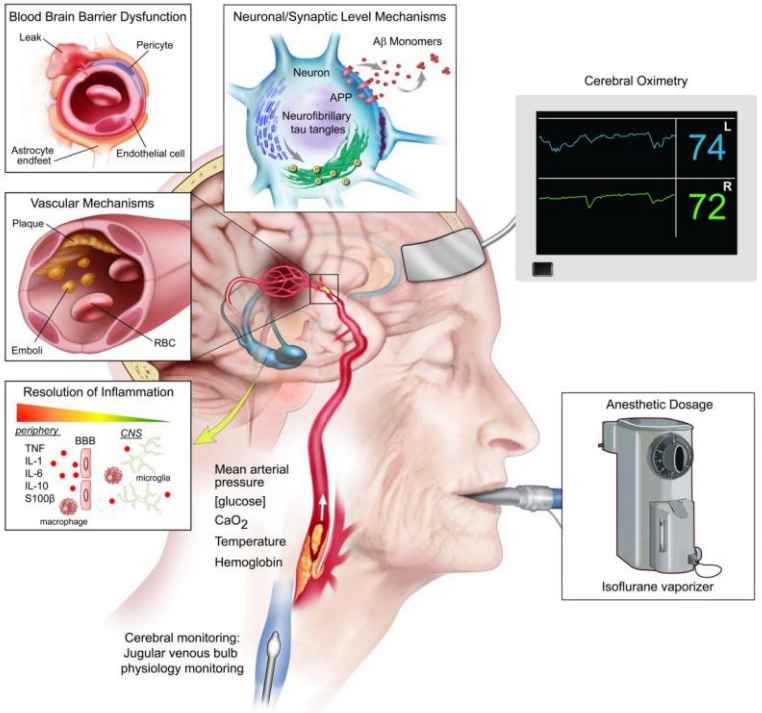
BV2 cells (n = 3 independent experiments) pretreated with 30 μM ANXA1sp.

Zhang Z et al, Front Immunol 2017

Summary

- Cardiac surgery elicits a strong inflammatory response
- ANXA-1sp modulates neuroinflammation after cardiac surgery
- ANXA-1sp prevents memory dysfunction and improves immune-metabolic signaling after surgery

A complex pathology…

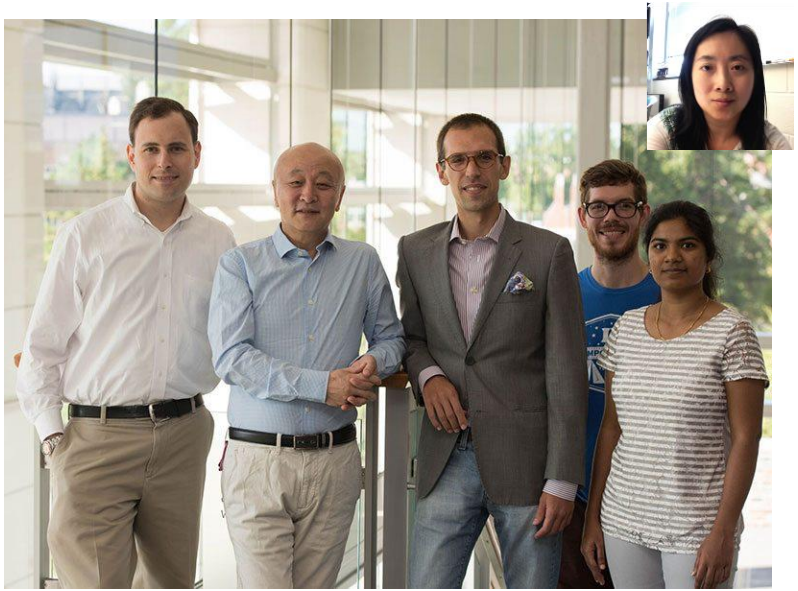


Future

- Molecular mechanisms to boost brain resilience to inform new clinical discoveries

- Interventions to boost Resolution Programs
  - *Immunonutrition*
  - Diet/SPMs

Acknowledgments



National Institute on Aging
R01AG057525 (NT)

Duke Institute for Brain Sciences

Duke Anesthesiology
Duke University School of Medicine

Terrando lab
- Zhiquan Zhang
- Saras Subramaniyan
- Chao Xiong
- Will Huffman
- Qing Ma
- Ping Wang
- Ting Yang (*Coffman lab*)

CTPM
- Ru-Rong Ji

Duke Anesthesiology
- Joseph Mathew
- Miles Berger

Karolinska Institute
- Tomas Hokfelt


Metagenics Institute

The Microbiome in Neuropsychiatry

The Role of the Gut-Brain Axis in Anxiety, Depression, and Cognitive Decline

Robert Kachko, ND, LAc
Inner Source Health
New York, NY

The Gut-Brain Axis

Clinically Relevant Research and Perspectives

What is a "gut feeling" anyway?

For Context

We are not alone…

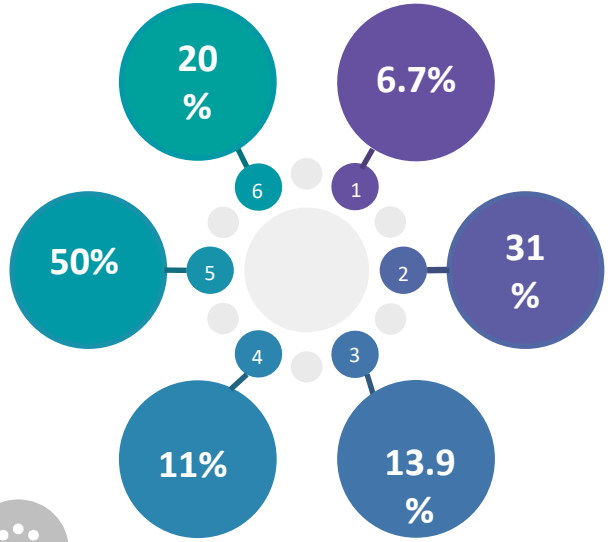
The collective genes within the microbiome outnumber genes in the human genome 100:1 (Ref: 1)

Gut microbiota is dominated by the phyla Firmicutes and Bacteroidetes.

Proteobacteria, Actinobacteria, Fusobacteria, Cyanobacteria, and Verrucomicrobia also occur but in much less abundance

Plus a plethora of viruses, archaea, fungi and parasites

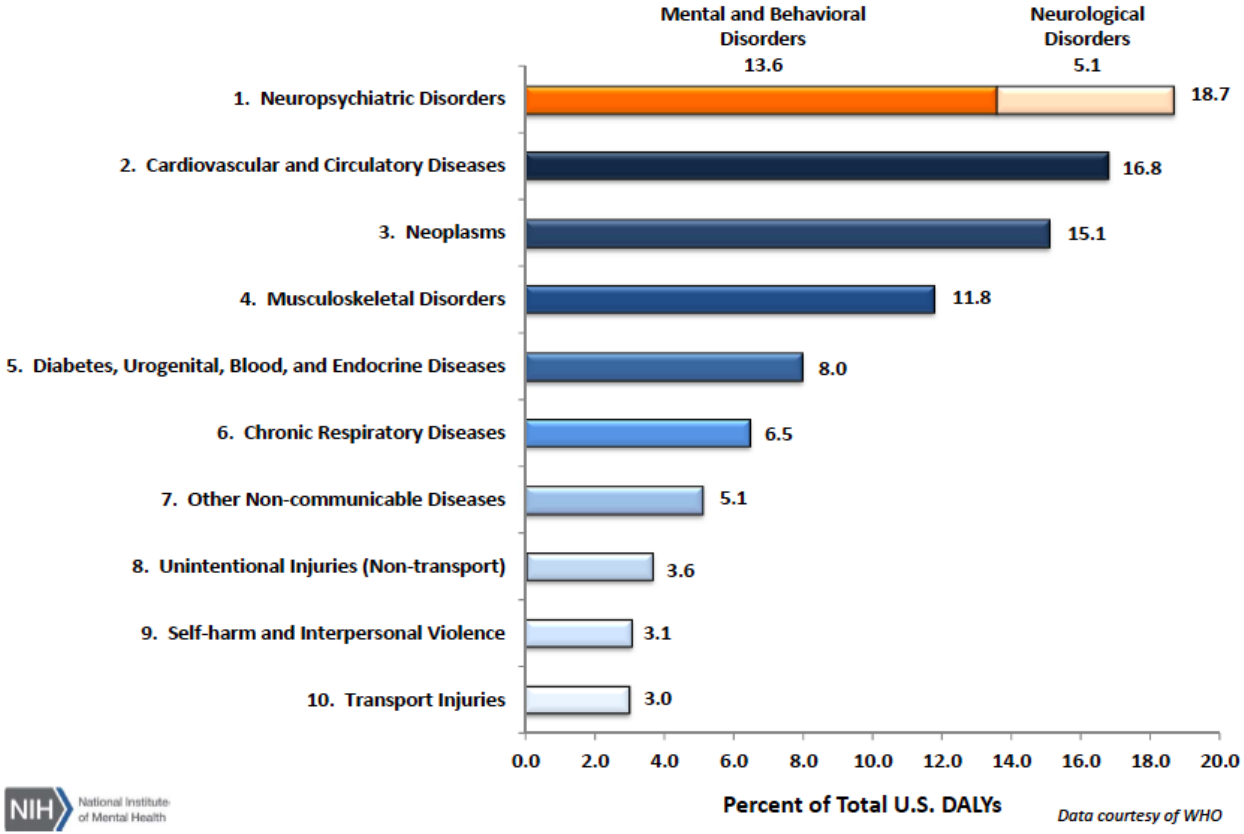
Gut-Brain Epidemiology



Neuropsychiatric disorders are strongly correlated with GI disease, and have major prevalence in the US

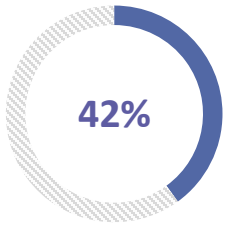
1. **Major *depressive* episodes among 6.7% of adults in past year in US** (2)
2. **Prevalence of any *anxiety* disorder among adults is 31% in US** (3)
3. **Prevalence of dementia in those 70 and older 13.9% in US** (4)
4. **Irritable Bowel Syndrome impacts 11% of the global population** (5)
5. **IBD prevalence in US has increased by 50% since 1999** (6)
6. **Prevalence of chronic constipation in US as high as 20%** (7)

Top 10 Leading Disease/Disorder Categories Contributing to U.S. DALYs (2010)

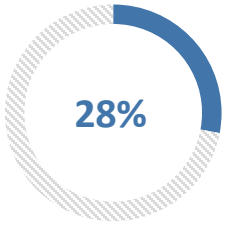


(Ref 8)

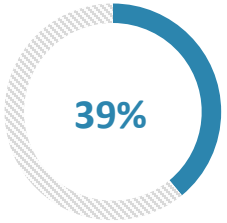
Dementia and Psychiatric Comorbidity



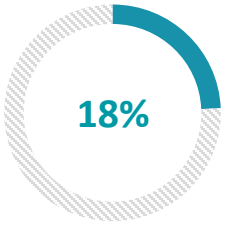
Up to 42% of people with Alzheimer's disease **suffer from significant depression**



28% higher likelihood of **conversion from MCI to dementia with comorbid depression**



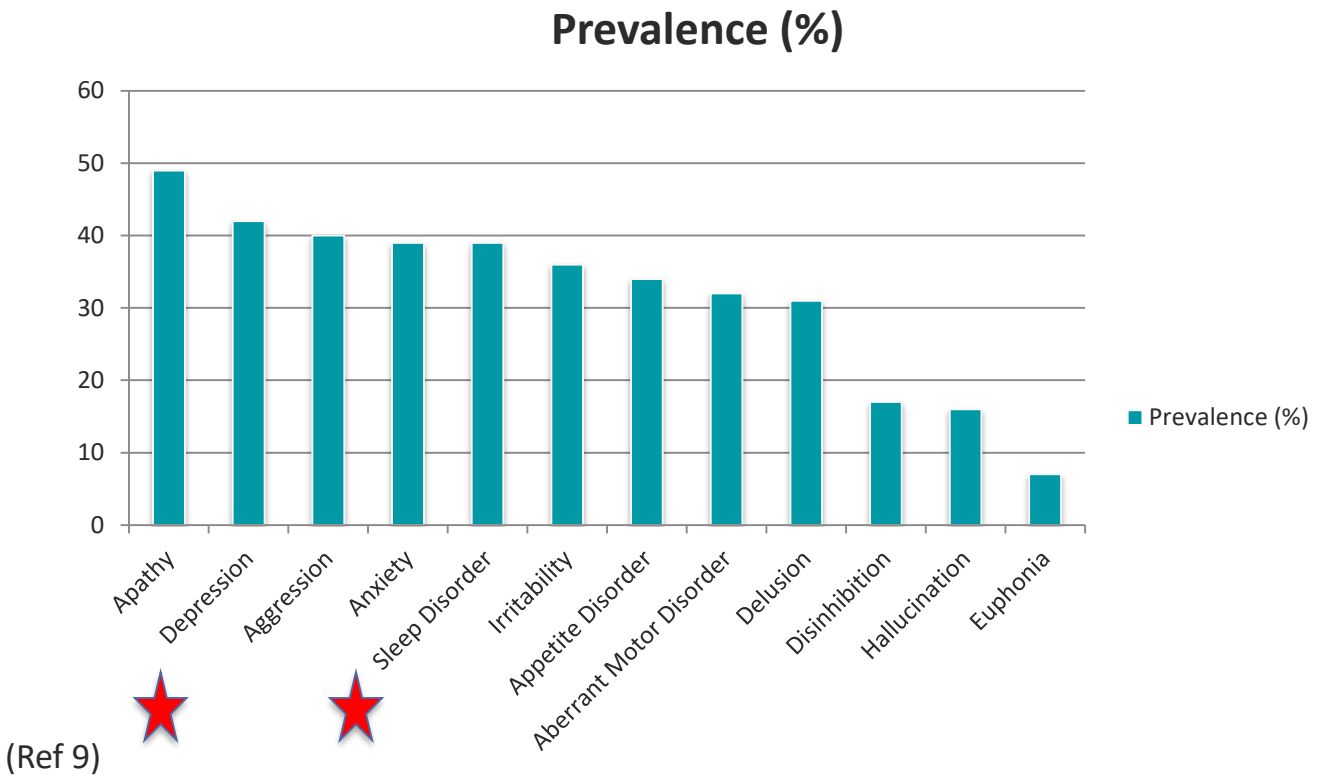
Up to 39% of people with Alzheimer's Disease **suffer from anxiety**



18% higher likelihood of **conversion from MCI to dementia with comorbid anxiety** (Ref 10)

(Ref 9)

The prevalence of neuropsychiatric symptoms in Alzheimer's Disease



(Ref 9)

Functional GI and Neuropsychiatric Disorder Risk

- "…the prevalence of anxiety (37%) and depression (24%) disorders in *constipated* patients is much higher than the general population" (11)
  - "Of patients undergoing psychological assessment for *intractable* constipation, three fifths had evidence of current, and two thirds a previous, affective disorder. " (12)
- "the interaction between psychiatric disorders including generalized anxiety disorder, panic disorder, major depressive disorder, bipolar disorder, and schizophrenia and IBS, which suggests that this association should not be ignored when developing strategies for screening and treatment." (13)
- "The risk ratios are highest for these disorders within 1 year of IBS diagnosis, but the risk remains statistically significant for more than 5 years. Clinicians should pay particular attention to psychiatric comorbidities in IBS patients." (14)
- "In the elderly, all measured psychiatric diagnoses are strongly associated with an increased prevalence of constipation." (15)

YET, THERE HAVE BEEN FEW MAJOR ADVANCES IN PSYCHOPHARMACOLOGY SINCE THE 1950S…

Gut-Brain Axis: Mechanisms

Bidirectional relationship

Neural – Vagus Nerve

Full truncal vagotomy for peptic ulcer shown to reduce risk of some neurological disorders, such as Parkinson's Disease. Effects from *Lactobacillus rhamnosus* eliminated post-vagotomy (16)

Immune/Inflammatory

Interleukin 1 and interleukin 6 activate the hypothalamic-pituitary-adrenal axis (HPA) and cause cortisol release (Infections and IBD cause neuropsychiatric sx) (21,22,23)

Metabolic

Short-chain fatty acids (SCFAs), which include butyrate, propionate, and Acetate may exert central effects through G protein–coupled receptors (20)

Neurotransmitter production

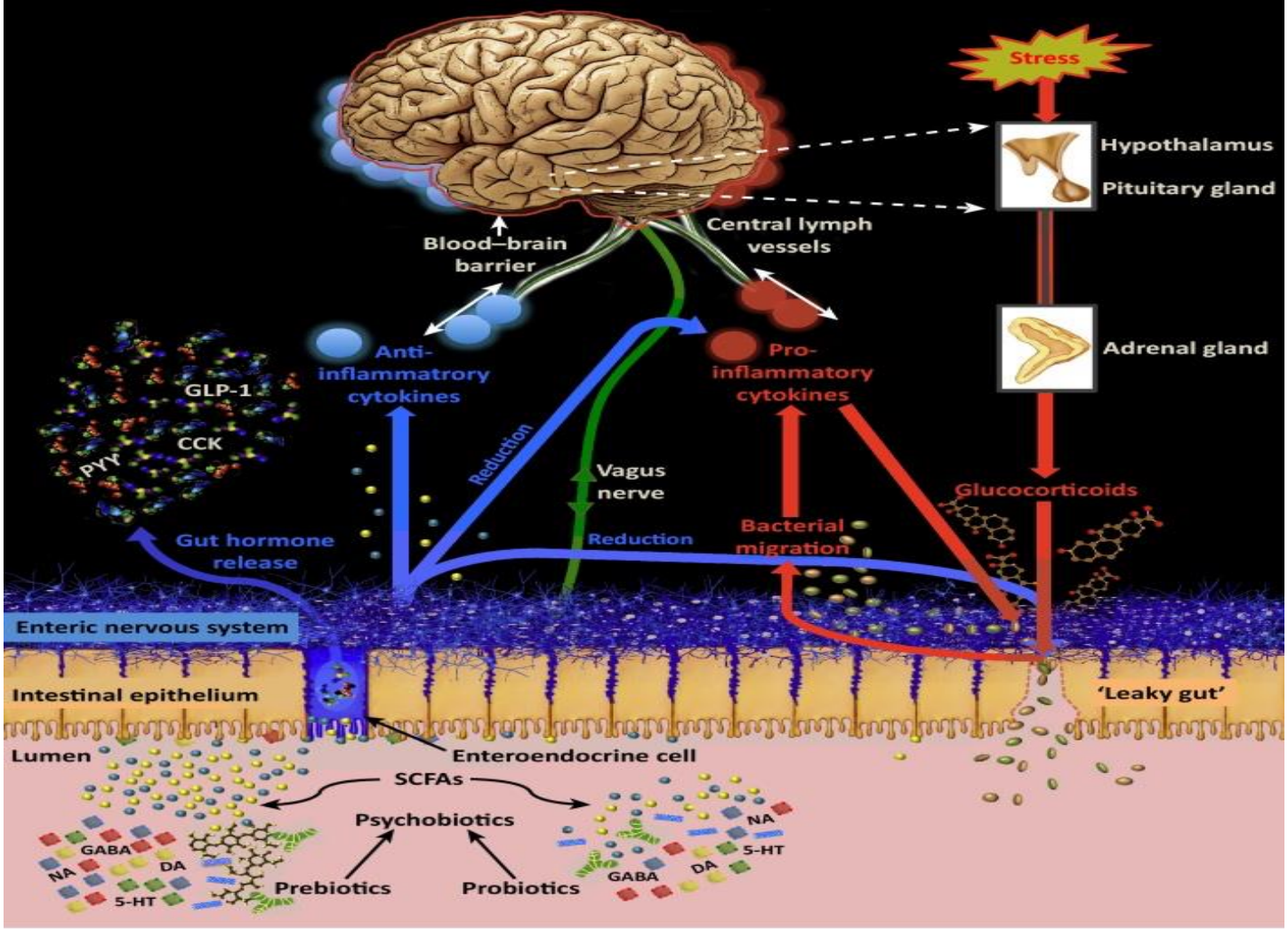
Bifidobacterium infantis has been demonstrated to elevate plasma tryptophan levels and thus influence central 5-HT (17)

In addition to producing precursors, many bacteria can synthesize and release neurotransmitters (18,19)

- Lactobacillus and Bifidobacterium species can produce γ-aminobutyric acid (GABA)
- Escheridia, Bacillus, and Saccharomyces species can produce norepinephrine
- Candida, Streptococcus, Escheridia, and Enterococcus species can produce 5-HT
- Bacillus can produce dopamine
- Lactobacillus can produce acetylcholine

Endocrine

- 5-HT is produced by enterochromaffin cells
- More than 20 signaling molecules, which are modulated by microbiota, released from specialized enteroendocrine cells (EECs) in the GI tract
    - significant endocrine and metabolic functions and are able to communicate with the brain (24)
    - *Includes neuropeptide Y, CRF, CCK, Ghrelin, GLP-1, Oxytocin and others*



Ref 47

Trends in Neurosciences

Bacteria–Enteric Nervous System Interactions

- There is evidence of direct, bacteria-induced modulation of the enteric nervous system:
  - Gut bacteria play a crucial role in the development and homeostasis of glial populations in the gut (25)
    - myenteric plexus of the jejunum and ileum of Germ Free mice show an unorganized lattice-like appearance, with fewer ganglia, and thinner nerve fibers (26)
  - Myenteric neurons exposed to *Bifidobacterium longum* NCC3001-fermented substances showed reduced generation of action potentials (27)
  - Dorsal root ganglion in the colon do not display hyperexcitability in response to noxious stimulation if they are treated with *Lactobacillus rhamnosus* (28,29)

Vagal Signaling

- The Vagus nerve has more afferent than efferent nerve fibers which have been shown to be modulated by stress, nutrition, exercise etc.
- Antidepressants and anxiolytics may work through vagal effects (30-32)
- Severing the vagus nerve (vagotomy) abolishes responses to psychobiotic administration
  - (at least partially, as this effect is not evident in all relevant trials) (33-35)

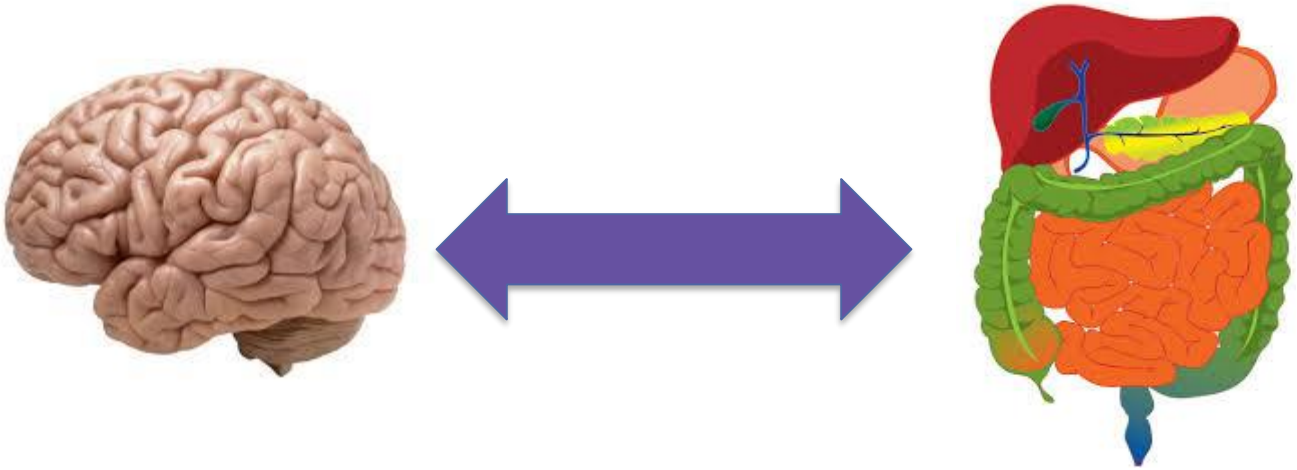
Short-Chain Fatty Acids, Gut Hormones, and Bacteria-Derived Blood Metabolites

- Sodium butyrate injections (200 mg/kg body weight) in rats produce (37):
  - Antidepressant effects
  - Increased central serotonin neurotransmission
  - BDNF expression Mechanism for SCFA likely via epigenetic rather than direct agonist effects (few central FFA receptors)
    - Through histone deacetylases
- SCFAs modulate secretion of gut peptides from enteroendocrine cells

Bacteria-Immune Interactions

- MAMPs (microbe-associated molecular pattern) of beneficial bacteria may increase secretion of anti-inflammatory cytokines such as interleukin-10 (37,38)
  - Specifically, *Bifidobacterium infantis* 35624 and *Lactobacillus GG*
  - Proposed Mechanism: competitive inhibition of pro-inflammatory MAMPs via TLR2 and TLR4
- Prebiotics may work by similar inhibition mechanisms (39,40)

A Bidirectional Relationship



The Central Nervous System can control the gut microbiota via adrenergic nerve signaling, primarily affecting:

- intestinal motility
- neurotransmitters activation of immune mediators that shape microbiota composition and function

Ref 41

Nature or Nurture?

Implications from Monozygotic Twin Studies

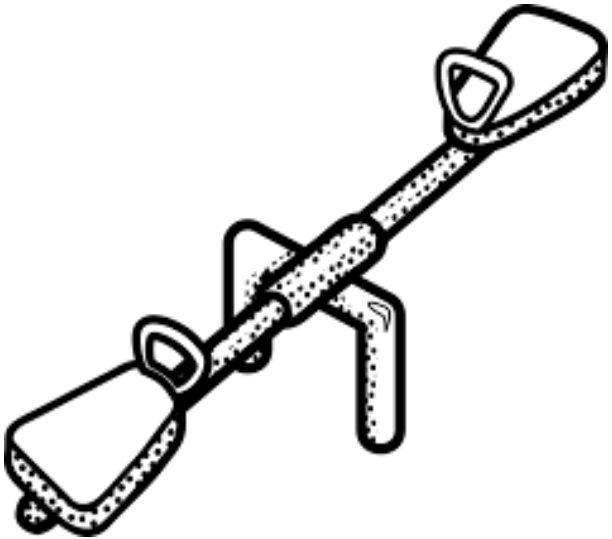
There is considerable discordance in the development of neuropsychiatric disorders among sets of monozygotic twins:

- *Indicates that non-genetic factors are also involved*
- *The microbiome is one such environmental factor (also more readily altered than the human genome)*
- *The microbiome is known to impact the epigenome via metabolites*

(Ref 42-44)

As we age…

1- Healthy aging correlates with a diverse microbiome



2- Reductions in microbial complexity correlate to decreases in neuronal complexity and increased risk of neurodegenerative disorders

(Ref 45-46)

What we learn from germ-free animals

The Pre-Clinical Evidence

- Germ-free mice have:
  - Impaired social behavior (48)
  - Higher anxiety (49)
  - Impaired stress response (50)
  - Trial: 40% greater plasma tryptophan concentrations than normal mice, but the normal mice had 2.8 times greater plasma serotonin levels than the germ-free mice (51)
- Implications
  - *Fecal* transplant has been shown to alter these behaviors (52)
  - Impaired microglial function mitigated by *oral* SCFA (53)
  - *Oral* probiotics in rats and mice improve anxiety and depression (54,55)

Depression

The Role of the Gut-Brain Axis

Animal Trials

- Increase in gut microbiota alpha diversity is associated with depression (57)
  - Alpha diversity (Intra) vs Beta Diversity (Inter)
- Experimentally elevated HPA axis responses and depression have been reversed in rats by administering a single bacterium, *Bifidobacterium infantis* (58)
- Two varieties of Bifidobacterium have been more effective than Lexapro (59)

Gut-Brain-Depression Axis

- Review of gut microbiomes of 1135 participants from a Dutch population cohort using deep sequencing showed correlation between gut microbiota diversity and depression (60)
- Increases in the genus Eggerthella, Holdemania, Gelria, Turicibacter, Paraprevotella and Anaerofilm
    - reductions in Prevotella and Dialister have been found in individuals with depression (61)
- Lower numbers of Bifidobacterium and Lactobacillus have been found in individuals with depression (62)
- A negative correlation between Faecalibacterium spp. and severity of depressive symptoms has been reported (61)
- Higher Firmicutes:Bacteroides ratio in IBS patients was correlated with clinically significant depression and anxiety (63)

Correlative Stool Samples

- 16S rRNA gene Illumina deep sequencing
  - Microbiome alterations and depression in humans by the analysis of fecal microbiota of 37 patients diagnosed with depressive disorder compared to 18 non-depressed
- The most pronounced result was a general underrepresentation of Bacteroidetes in those diagnosed with depression (64)
  - *Alistipes*, a genus in the phylum of Bacteroidetes was overrepresented in depressed patients
    - Correlates with chronic fatigue syndrome, IBS

Intervention: Probiotics

- Male and female participants (n = 124)
  - Consumed either a fermented milk drink containing *Lactobacillus casei* Shirota or a placebo for 3 weeks
  - Result: No overall changes in self-reported affect (65)
- **Subgroup analysis**: participants whose baseline mood scores fell in the lowest third of the total range:
  - Probiotic supplementation resulted in significantly more participants self-rating as happy rather than depressed, relative to placebo
  - Potential “ceiling” effects

Intervention: Probiotics

- Study performed by Mohammadi et al.
  - consuming a probiotic yogurt or a multispecies probiotic capsule for *6 weeks* had beneficial effects on the mental health biomarkers of petrochemical workers (66)
- Study performed by Akkasheh et al.
  - *8 weeks* of administration of probiotics to patients with major depressive disorder (MDD) had beneficial effects on Beck Depression Inventory scores (67)

Effect of Probiotics on Depression

- **Systematic Review and Meta-Analysis of Randomized Controlled Trials**
- (5 Trials examined)
  - One of the five - individuals with major depression
  - Remaining four studies examined non-depressed individuals
- **Conclusion**: probiotics were associated with a significant reduction in depression (68)
- *Of note:*
  - Subjects aged 60 and below, oral probiotics effective
  - Aged 65 and older (only 1 trial), no effect was observed

Anxiety

The Role of the Gut-Brain Axis

Intervention: Probiotics

- Double-blind, placebo controlled 30-day trial of a probiotic mixture containing *Lactobacillus helveticus* R0052 and *B. longum* R0175 (69)
- **Outcomes Measures:** Hopkins Symptom Checklist (HSCL-90), the Hospital Anxiety and Depression Scale (HADS), the Perceived Stress Scale, the Coping Checklist (CCL) and 24 h urinary free cortisol (UFC)
- **Results**: Improvements in
  - Anxiety
  - Depression
  - Reduced levels of cortisol

Intervention: Prebiotics

- Administered prebiotics (oligosaccharides) to healthy volunteers
- Forty-five healthy volunteers received one of two prebiotics (fructooligosaccharides, FOS, or Bimuno®-galactooligosaccharides, B-GOS) or a placebo (maltodextrin) daily for 3 weeks (70)
  - lower cortisol levels at awakening
  - improved attention to positive stimuli compared to negative stimuli in
    - an emotional categorization task
    - an emotional recognition task

* Effects similar to admin of selective serotonin reuptake inhibitor citalopram or the benzodiazepine diazepam in healthy individuals

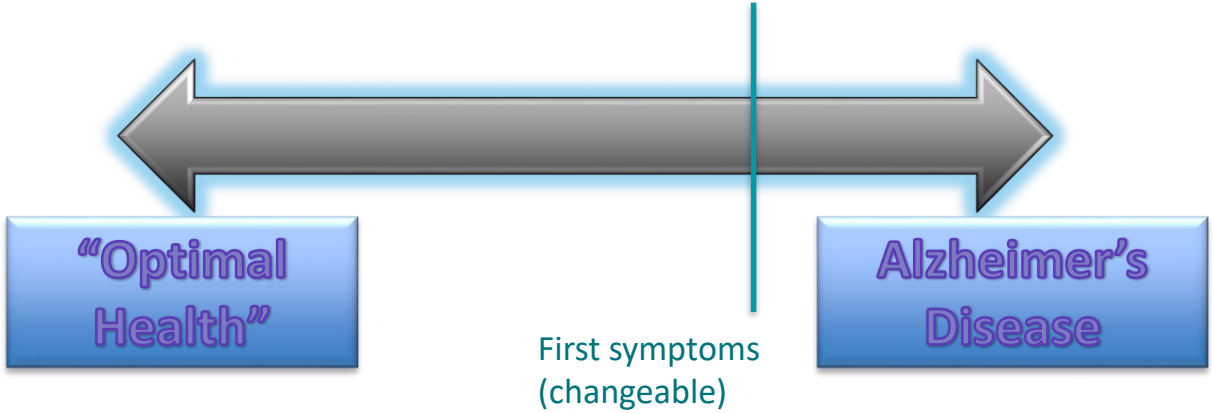
Intervention: Psychobiotic Formulation on Body Composition and Anxiety

- 45 subjects - 3 week intervention
  - 3 Groups: (1) Psychobiotics, (2) Hypocaloric Diet, (3) Combination
  - Primary outcomes: body composition (DXA and BIA)
  - Secondary outcomes: Hamilton Anxiety Scale
- Psychobiotic suspension:
  - Streptococcus thermophilus
  - Lactobacillus bulgaricus
  - Lactococcus lactis
  - Lactobacillus acidophilus
  - Streptococcus thermophiles
  - Lactobacillus plantarum
  - Bifidobacterium lactis
  - Lactobacillus reuteri
- Results (71)
  - Hypocaloric group had increased HAM-A scores, while Psychobiotic and Combined group had improvements (highest improvement in combined group)

Cognitive Decline

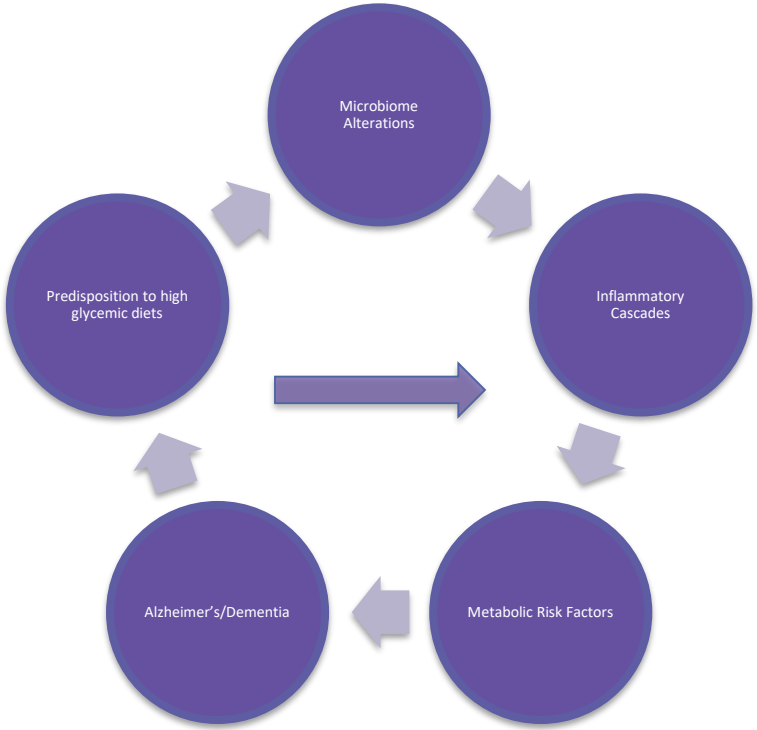
The Role of the Gut-Brain Axis

A Continuum



- Degeneration doesn't occur overnight (decades)
- Diseases of the brain are at their core systemic and multi-factorial
- The growth of new brain cells is normal
- If we don't look at it this way, what we can accomplish will be marginal

A Vicious Cycle



Risk factors for AD such as metabolic syndrome, type 2 diabetes and obesity are associated with gut microbiota alterations (72,73)

“Diabetes of the brain”

- Current Estimated lifetime risk of DM: 38%
  - HbA1c correlates with lower cognitive capacity and changes in hippocampal microstructure
- Risk of AD attributed to hyperinsulinemia: 40%
  - *50–100% increase in overall risk*
- T2DM *and* positive APOE e4: higher neuritic plaques and neurofibrillary tangles in the cortex and hippocampus
- High glucose: Changes in cognitive capacity and hippocampal microstructure even without DM2
- Autopsy studies: correlation between increased pancreatic amyloid deposition and the progression of AD

Ref 74-83

Insulin Resistance → Dementia

- Hallmark of pathology: impaired cerebral glucose *utilization*
  - Impairments in brain insulin/IGF signaling lead to increased expression of amyloid-β precursor protein (AβPP) and accumulation of AβPP-Aβ.
  - Mechanisms:
    1. Activated kinases which phosphorylate tau
    2. Higher APP expression
    3. Oxidative and ER stress
    4. Increased ROS and RNS = DNA, RNA, Lipid, Protein damage
    5. Direct mitochondrial dysfunction
    6. Increased pro-inflammatory and apoptotic cascades
    7. Down-regulation of genes which enhance cholinergic homeostasis

Ref 74-83

Microbiome Contributors to Metabolic Risk Factors

- Dysbiotic signatures in the gut microbiota associated with metabolic disease phenotypes include an increased ratio of Firmicutes to Bacteroidetes at phylum level (84)
- Other correlations:
  - expansion of Proteobacteria
  - reduced abundance of Akkermansia
- Insulin Resistance: proliferation of *Prevotella copri* and *Bacteroides vulgatus*
    - Specifically Insulin-resistant phenotypes with elevated circulating levels of branch chain amino acids
- Obesity predisposition: associated with augmented serum glutamate levels due to the reduced abundance of *Bacteroides thetaiotaomicron* that converts glutamate
- NAFLD: Increased abundance of *Proteobacteria* and *Escherichia coli* with a reduction in the population of Firmicutes
  - associated with advanced fibrosis in human non-alcoholic fatty liver disease (NAFLD)

Alzheimer's Disease and the Microbiome

Gut microbiota seems to be involved in the direct accumulation of amyloid plaques according to the results of a study using a mouse model of AD (85)

AD Microbiome changes parallel changes observed in other conditions linked to gut microbiome alterations, including obesity, diabetes, IBD, and Parkinson's disease (86-89)

Alzheimer's Disease and the Microbiome

- "the gut microbiome of AD participants has decreased microbial richness and diversity and a distinct composition compared to asymptomatic age- and sex-matched Control participants" (90)
- Correlations to CSF p-tau/ Aβ42, a composite measure of AD pathology. AD Patients have….
  - Reduction in phylum Firmicutes (also in T2DM and obesity) (88,91)
  - Increase in the phylum Bacteroidetes (also in T2DM and Parkinson's) (86, 88)
  - Increase in LPS exposure
  - Reduced Actinobacteria, specifically Bifidobacterium genus (longevity, anti-inflammatory properties, gut permeability) (92)

Bifidobacterium: Intervention Trial

- Randomized, double-blind controlled trial (93)
- A small study of probiotics that included *Bifidobacterium* demonstrated a change in Mini-Mental State Examination scores after a 12-week intervention among participants with severe dementia

A Fungal Etiology?

- “The present findings demonstrate that fungi can be detected in brain tissue from different regions of the AD CNS. In all eleven patients (plus three additional CP samples) described in this study, as well as in four patients previously analysed, there is clear evidence for fungal cells inside neurons or extracellularly. Therefore, 100% of the AD patients analysed thus far by our laboratory present fungal cells and fungal material in brain sections.” (94)
- Specific Brain regions:
  - External frontal cortex; Cerebellar hemisphere; Entorhinal cortex/hippocampus; Choroid plexus
- Increased chitinase levels are found in blood serum and cerebrospinal fluid from AD patients (95-98)

The Oral Microbiome and AD

- Retrospective cohort study using the National Health Insurance Research Database (NHIRD) of Taiwan (99)
- 9291 patients with Chronic Peridontitis (CP) compared to 18,672 matched controls without CP
- 10-year CP exposure was associated with a 1.707-fold increase in the risk of developing AD
  - Most likely mediated through activated pro-inflammatory cascades

Diet and Microbiome

Standard American Diet contributes to an altered/impaired Microbiome

An impaired microbiome impacts dietary response to specific foods

For more research see almost every other talk at IHS 2018 ☺

Probiotics in food

- Add Natto, Sauerkraut, kim chi, yogurt, miso etc.
- work to boost mood by generating gamma-aminobutyric acid (GABA) and enhance brain receptors for GABA

Russian microbiologist Ilya Ilyich Mechnikov
1845-1916

“When in doubt, treat the gut”

- Condition specific pre and probiotics (when research is available, and not contradictory)
- Approaches to address intestinal permeability and inflammation
- Liver support
- Digestive/Assimilation support
- Water goal: half body weight in pounds, in ounces
- Fiber: 25-35g/day
- Foot stool hygiene
- Mindful eating/cooking
  - Appropriate food combining
  - Appropriate meal timing
  - Proper mastication
  - Low-heat/intensity cooking methods
- Castor oil packs
- Symptom-Specific Botanicals

THE ALZHEIMER'S DEFENSE PLAN

HEAL YOUR BODY, SAVE YOUR MIND

DR. ROBERT KACHKO ND, LAC
DR. PETER BONGIORNO ND, LAC

References

References

1. Qin, J., R. Li, J. Raes, et al., A human gut microbial gene catalogue established by metagenomic sequencing. Nature, 2010. 464(7285): p. 59-65.
2. https://www.nimh.nih.gov/health/statistics/major-depression.shtml
3. https://www.nimh.nih.gov/health/statistics/any-anxiety-disorder.shtml
4. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of Dementia in the United States: The Aging, Demographics, and Memory Study. *Neuroepidemiology*. 2007;29(1-2):125-132. doi:10.1159/000109998.
5. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. *Clinical Epidemiology*. 2014;6:71-80. doi:10.2147/CLEP.S40245.
6. https://www.cdc.gov/ibd/data-statistics.htm
7. Harris LA, Hansel S, DiBaise J, Crowell MD. Irritable bowel syndrome and chronic constipation: Emerging drugs, devices, and surgical treatments. Curr Gastroenterol Rep. 2006;8:282–90.
8. US Burden of Disease Collaborators. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. JAMA, 310(6): 591-608, 2013.
9. Qing-Fei Zhao, Lan Tan, Hui-Fu Wang, Teng Jiang, Meng-Shan Tan, Lin Tan, Wei Xu, Jie-Qiong Li, Jun Wang, Te-Jen Lai, Jin-Tai Yu, The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis, Journal of Affective Disorders, Volume 190, 2016, Pages 264-271, ISSN 0165-0327, https://doi.org/10.1016/j.jad.2015.09.069.
10. Li X. The impact of anxiety on the progression of mild cognitive impairment to dementia in Chinese and English data bases: a systematic review and meta-analysis.. *International journal of geriatric psychiatry.* 2018-01;33:131-140.

References

11. Hosseinzadeh ST, Poorsaadati S, Radkani B, Forootan M. Psychological disorders in patients with chronic constipation. Gastroenterology and Hepatology From Bed to Bench. 2011;4(3):159-163.
12. Dykes S. Chronic idiopathic constipation: a psychological enquiry.. European journal of gastroenterology & hepatology. 2001-01;13:39-44.
13. Fadgyas-Stanculete M, Buga A-M, Popa-Wagner A, Dumitrascu DL. The relationship between irritable bowel syndrome and psychiatric disorders: from molecular changes to clinical manifestations. Journal of Molecular Psychiatry. 2014;2(1):4. doi:10.1186/2049-9256-2-4.
14. Lee Y-T, Hu L-Y, Shen C-C, et al. Risk of Psychiatric Disorders following Irritable Bowel Syndrome: A Nationwide Population-Based Cohort Study. Maher B, ed. PLoS ONE. 2015;10(7):e0133283. doi:10.1371/journal.pone.0133283.
15. Jessurun JG, van Harten PN, Egberts TCG, Pijl YJ, Wilting I, Tenback DE. The Relation between Psychiatric Diagnoses and Constipation in Hospitalized Patients: A Cross-Sectional Study. Psychiatry Journal. 2016;2016:2459693. doi:10.1155/2016/2459693.
16. Svensson E, Horvath-Puho E, Thomsen RW, Djurhuus JC, Pedersen L, Borghammer P, Sorensen HT. Vagotomy and subsequent risk of Parkinson's disease. Ann Neurol 2015;78:522–9.
17. Desbonnet L, Garrett L, Clarke G, Kiely B, Cryan JF, Dinan TG. Effects of the probiotic Bifidobacteriuminfantis in thematernal separationmodel of depression. Neuroscience 2010;170:1179–88.
18. LyteM.Microbial endocrinology in the microbiome-gut-brain axis: howbacterial production and utilization of neurochemicals influence behavior. PLoS Pathog 2013;9:e1003726.
19. Lyte M. Microbial endocrinology and the microbiota-gut-brain axis. Adv Exp Med Biol 2014;817:3–24.
20. Stilling RM, Dinan TG, Cryan JF. Microbial genes, brain & behaviour— epigenetic regulation of the gut-brain axis. Genes Brain Behav 2014;13:69–86.

References

21. El Aidy S, Dinan TG, Cryan JF. Immune modulation of the brain-gut-microbe axis. Front Microbiol 2014;5:146.
22. Capuron L, Hauser P, Hinze-Selch D, Miller AH, Neveu PJ. Treatment of cytokine-induced depression. Brain Behav Immun 2002;16:575–80.
23. Abautret-Daly Á, Dempsey E, Parra-Blanco A, Medina C, Harkin A. Gut-brain actions underlying comorbid anxiety and depression associated with inflammatory bowel disease. Acta Neuropsychiatr 2017:1–2.
24. Dockray GJ. Gastrointestinal hormones and the dialogue between gut and brain. J Physiol 2014;592:2927–2941.
25. Kabouridis P.S. Microbiota controls the homeostasis of glial cells in the gut lamina propria. Neuron. 2015;85:289–295.51 Ma X. Lactobacillus reuteri ingestion prevents hyperexcitability of colonic DRG neurons induced by noxious stimuli. Am. J. Physiol. Gastrointest. Liver Physiol. 2009;296:G868–G875.
26. Collins J. Intestinal microbiota influence the early postnatal development of the enteric nervous system.. Neurogastroenterology and motility. 2014-01;26:98-107.
27. Bercik P. The anxiolytic effect of Bifidobacterium longum NCC3001 involves vagal pathways for gut–brain communication. Neurogastroenterol. Motil. 2011;23:1132–1139
28. Cryan J.F., Dinan T.G. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat. Rev. Neurosci. 2012;13:701–712.
29. Ma X. Lactobacillus reuteri ingestion prevents hyperexcitability of colonic DRG neurons induced by noxious stimuli. Am. J. Physiol. Gastrointest. Liver Physiol. 2009;296:G868–G875.
30. Adinoff B. Vagal tone decreases following intravenous diazepam. Psychiatry Res. 1992;41:89–97.

References

31. Salam O.M.A. Fluoxetine and sertraline stimulate gastric acid secretion via a vagal pathway in anaesthetised rats. Pharmacol. Res. 2004;50:309–316.
32. Smith R. Increased association over time between regional frontal lobe BOLD change magnitude and cardiac vagal control with sertraline treatment for major depression. Psychiatry Res. Neuroimag. 2014;224:225–233.
33. Bravo J.A. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc. Natl. Acad. Sci. U.S.A. 2011;108:16050–16055.
34. Bercik P. The anxiolytic effect of Bifidobacterium longum NCC3001 involves vagal pathways for gut–brain communication. Neurogastroenterol. Motil. 2011;23:1132–1139.
35. De Lartigue G. Vagal afferent neurons in high fat diet-induced obesity; intestinal microflora, gut inflammation and cholecystokinin. Physiol. Behav. 2011;105:100–105.
36. Sun J. Antidepressant-like effects of sodium butyrate and its possible mechanisms of action in mice exposed to chronic unpredictable mild stress. Neurosci. Lett. 2016;618:159–166.
37. O'Mahony L. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. Gastroenterology. 2005;128:541–551.
38. Chu H., Mazmanian S.K. Innate immune recognition of the microbiota promotes host-microbial symbiosis. Nat. Immunol. 2013;14:668–675.
39. Bode L. Inhibition of monocyte, lymphocyte, and neutrophil adhesion to endothelial cells by human milk oligosaccharides. Thromb. Haemost. 2004;92:1402–1410.
40. Eiwegger T. Prebiotic oligosaccharides: in vitro evidence for gastrointestinal epithelial transfer and immunomodulatory properties. Pediatr. Allergy Immunol. 2010;21:1179–1188.

References

41. Collins, S.M., M. Surette, and P. Bercik, The interplay between the intestinal microbiota and the brain. Nature Rev Microbiol, 2012. 10(11): p. 735-742.
42. Cannon JR, Greenamyre JT. The role of environmental exposures in neurodegeneration and neurodegenerative diseases. Toxicol Sci 2011; 124: 225-250
43. van Loo KM, Martens GJ. Genetic and environmental factors in complex neurodevelopmental disorders. Curr Genomics 2007; 8:429-444
44. Majnik AV, Lane RH. The relationship between early-life environment, the epigenome and the microbiota. Epigenomics 2015; 7: 1173-1184
45. Biagi E, Franceschi C, Rampelli S, et al. Gut Microbiota and Extreme Longevity. Curr Biol 2016; 26: 1480-1485
46. Leung K, Thuret S. Gut Microbiota: A Modulator of Brain Plasticity and Cognitive Function in Ageing. Healthcare (Basel) 2015; 3: 898-916
47. Sarkar A, Lehto SM, Harty S, Dinan TG, Cryan JF, Burnet PWJ. Psychobiotics and the Manipulation of Bacteria–Gut–Brain Signals. Trends in Neurosciences. 2016;39(11):763-781. doi:10.1016/j.tins.2016.09.002
48. Sudo N, Chida Y, Aiba Y, et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. J Physiol 2004; 558: 263-275
49. Diaz Heijtz R, Wang S, Anuar F, et al. Normal gut microbiota modulates brain development and behavior. Proc Natl Acad Sci USA 2011; 108: 3047-3052
50. Neufeld KM, Kang N, Bienenstock J, Foster JA. Reduced anxietylike behavior and central neurochemical change in germ-free mice. Neurogastroenterol Motil 2011; 23: 255-264, e119

References

51. Wikoff W.R. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. Proc. Natl. Acad. Sci. U.S.A. 2009;106:3698–3703.
52. Collins SM, Kassam Z, Bercik P. The adoptive transfer of behavioral phenotype via the intestinal microbiota: experimental evidence and clinical implications. Curr Opin Microbiol 2013; 16: 240-245
53. Erny D, Hrabě de Angelis AL, Jaitin D, Wieghofer P, Staszewski
54. O, David E, Keren-Shaul H, Mahlakoiv T, et al. Host microbiota constantly control maturation and function of microglia in the CNS. Nat Neurosci 2015; 18: 965-977
55. Dinan TG, Stanton C, Cryan JF. Psychobiotics: a novel class of psychotropic. Biol Psychiatry 2013; 74: 720-726
56. Messaoudi M, Violle N, Bisson JF, et al. Beneficial psychological effects of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in healthy human volunteers. Gut Microbes 2011; 2: 256-261
57. Kelly JR, Borre Y, O' Brien C, et al. Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat. J Psychiatr Res 2016; 82: 109-118
58. Desbonnet L., Garrett L., Clarke G., Kiely B., Cryan J.F., Dinan T.G. Effects of the probiotic Bifidobacterium infantis in the maternal separation model of depression. Neuroscience. 2010;170:1179–1188.
59. Savignac H.M., Kiely B., Dinan T.G., Cryan J.F. Bifidobacteria exert strain-specific effects on stress-related behavior and physiology in BALB/c mice. Neurogastroenterol. Motil. 2014;26:1615–1627.
60. Zhernakova A, Kurilshikov A, Bonder MJ, et al.. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. Science 2016; 352: 565-569

References

61. Aizawa E, Tsuji H, Asahara T, et al. J Affect Disord 2016; 202: 254-257
62. Dinan TG, Cryan JF. Melancholic microbes: a link between gut microbiota and depression? Neurogastroenterol Motil 2013; 25:713-719
63. Jeffery I. An irritable bowel syndrome subtype defined by species-specific alterations in faecal microbiota.. Gut. 2012-07;61:997-1006.
64. Naseribafrouei A. Correlation between the human fecal microbiota and depression.. Neurogastroenterology and motility. 2014-08;26:1155-1162.
65. Benton, D. et al. (2007) Impact of consuming a milk drink con-taining a probiotic on mood and cognition. Eur. J. Clin. Nutr. 61, 355–361
66. Mohammadi A.A., Jazayeri S., Khosravi-Darani K., Solati Z., Mohammadpour N., Asemi Z., Adab Z., Djalali M., Tehrani-Doost M., Hosseini M., et al. The effects of probiotics on mental health and hypothalamic-pituitary-adrenal axis: A randomized, double-blind, placebo-controlled trial in petrochemical workers. Nutr. Neurosci. 2015 doi: 10.1179/1476830515Y.0000000023. [PubMed] [Cross Ref]
67. Akkasheh G., Kashani-Poor Z., Tajabadi-Ebrahimi M., Jafari P., Akbari H., Taghizadeh M., Memarzadeh M.R., Asemi Z., Esmaillzadeh A. Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. Nutrition. 2016;32:315–320. doi: 10.1016/j.nut.2015.09.003.
68. Huang R, Wang K, Hu J. Effect of Probiotics on Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2016;8(8):483. doi:10.3390/nu8080483.
69. Messaoudi M. Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects.. British journal of nutrition. 2011-03;105:755-764.
70. Schmidt K, Cowen PJ, Harmer CJ, Tzortzis G, Errington S, Burnet PWJ. Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers. Psychopharmacology. 2015;232(10):1793-1801.

References

71. Colica C, Avolio E, Bollero P, et al. Evidences of a New Psychobiotic Formulation on Body Composition and Anxiety. *Mediators of Inflammation*. 2017;2017:5650627. doi:10.1155/2017/5650627.
72. van Dijk G, van Heijningen S, Reijne AC, et al. . Integrative neurobiology of metabolic diseases, neuroinflammation, and neurodegeneration. Front Neurosci 2015; 9: 173 [PMID: 26041981 DOI: 10.3389/fnins.2015.00173]
73. Festi D, Schiumerini R, Eusebi LH, et al.. Gut microbiota and metabolic syndrome. World J Gastroenterol 2014; 20: 16079-16094 [PMID: 25473159 DOI: 10.3748/wjg.v20.i43.16079]
74. Sandoval DA, Obici S, Seeley RJ. Targeting the CNS to treat type 2 diabetes.Nat Rev Drug Discov 2009;8(May (5)):386–98.
75. Meneilly GS, Hill A. Alterations in glucose metabolism in patients withAlzheimer's disease. J Am Geriatr Soc 1993;41(July (7)):710–4.
76. Luchsinger, JA, Tang, M-X, Shea, S, & Mayeux R. Hyperinsulinemia and risk of Alzheimer disease. Neurology 2004; 63(October): 1187-1192.
77. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P (2006) Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 5: 64–74.
78. Kopf D, Frolich L (2009) Risk of incident Alzheimer's disease in diabetic patients: a systematic review of prospective trials. J Alzheimers Dis 16: 677–685.
79. Whitmer, RA. Type 2 diabetes and risk of cognitive impairment and dementia. Curr Neurol Neurosci Rep 2007; 7:373-380.
80. Park CR. Cognitive effects of insulin in the central nervous system. Neurosci Biobehav Rev 2001;25:311-323.

References

81. Kerti L, Witte AV, Winkler A, Grittner U, Rujescu D, Floel A. Higher glucose levels associated with lower memory and reduced hippocampal microstructure.Neurology 2013;81(November (20)):1746–52.
82. M. Fujishima, Y. Kiyohara, Changes in incidence and mortality of stroke and risk factors in a Japanese general population: the Hisayama study. International Congress Series 2004; 1262: 344-347.
83. De la Monte SM. Contributions of Brain Insulin Resistance and Deficiency in Amyloid-Related Neurodegeneration in Alzheimer's Disease. Drugs. 2012;72(1):49-66.
84. Li X. Gut Microbiota Dysbiosis Drives and Implies Novel Therapeutic Strategies for Diabetes Mellitus and Related Metabolic Diseases.. *Frontiers in immunology.* 2017;8:1882.
85. Harach T, Jammes F, Muller C, et al. Administrations of human adult ischemia-tolerant mesenchymal stem cells and factors reduce amyloid beta pathology in a mouse model of Alzheimer's disease. Neurobiol Aging 2017; 51: 83-96
86. Keshavarzian, A. et al. Colonic bacterial composition in Parkinson's disease. Mov. Disord. 30, 1351–1360 (2015).
87. Turnbaugh, P. J. et al. A core gut microbiome in obese and lean twins. Nature 457, 480–484 (2009).
88. Larsen, N. et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS ONE 5, 1–10 (2010).
89. Dicksved, J. et al. Molecular analysis of the gut microbiota of identical twins with Crohn's disease. ISME J. 2, 716–727 (2008).
90. Vogt NM, Kerby RL, Dill-McFarland KA, et al. Gut microbiome alterations in Alzheimer's disease. Scientific Reports. 2017;7:13537.

References

91. Schwiertz, A. et al. Microbiota and SCFA in lean and overweight healthy subjects. Obesity 18, 190–195 (2009).
92. Underwood, M. A., German, J. B., Lebrilla, C. B. & Mills, D. Bifidobacterium longum subspecies infantis: champion colonizer of the infant gut. Pediatr. Res. 77, 229–235 (2015).
93. Akbari, E. et al. Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. Front. Aging. Neurosci. 8, 1–8 (2016).
94. Pisa D, Alonso R, Rábano A, Rodal I, Carrasco L. Different Brain Regions are Infected with Fungi in Alzheimer's Disease. Scientific Reports. 2015;5:15015.
95. Choi, J., Lee, H. W. & Suk, K. Plasma level of chitinase 3-like 1 protein increases in patients with early Alzheimer's disease. J Neurol 258, 2181–2185 (2011).
96. Rosen, C. et al. Increased Levels of Chitotriosidase and YKL-40 in Cerebrospinal Fluid from Patients with Alzheimer's Disease. Dement Geriatr Cogn Dis Extra 4, 297–304 (2014).
97. Watabe-Rudolph, M. et al. Chitinase enzyme activity in CSF is a powerful biomarker of Alzheimer disease. Neurology 78, 569–577 (2012).
98. Wildsmith, K. R. et al. Identification of longitudinally dynamic biomarkers in Alzheimer's disease cerebrospinal fluid by targeted proteomics. Mol Neurodegener 9, 22 (2014).
99. Chen, C.-K., Wu, Y.-T., and Chang, Y.-C. (2017). Association between chronic periodontitis and the risk of Alzheimer's disease: a retrospective, populationbased, matched-cohort study. Alzheimers Res. Ther. 9:56.


Metagenics Institute

Nutritional Tools to Improve Cognitive Health from Infancy through Young Adulthood

Jennifer Stagg, ND
Medical Director
Whole Health Wellness Center
Avon, CT

Learning Objectives

- ***Understand the nutritional needs for support of cognitive health in infants, young children and adolescents***
- ***Review implementation of nutritional support in case study format***

Nutrition and Cognitive Health

Preconception through adolescence

Number of Children with Autism in the US (Per 1000)

2011/13: 12.5
2014: 22.4
2016: 27.6

Credit: Nigel Hawtin Spectrum

‘Pre-pregnant’ women are giving up vices before conception

By Anna Davies

July 17, 2017

NEW YORK POST

We once thought our genes were our destiny, but now we know what we eat, our activity level, our exposures to toxic chemicals in our lives and even stress all affect how our DNA gets expressed — and gets passed down to our children,” explains Jennifer Stagg, ND, an integrative medical practitioner and author of “Unzip Your Genes: 5 Choices To Reveal A Radically Radiant You.” “Stress, in particular, has a direct impact on DNA expression … both in terms of conception and in terms of optimal DNA health once [the baby is] conceived,” she says

Credit: https://nypost.com/2017/07/17/pre-pregnant-women-are-giving-up-vices-before-conception/

Preconception Nutrition

- **Prenatal vitamins (3 months prior) reduce risk of autism, especially in genetically susceptible individuals—maternal MTHFR 677 TT, CBS rs234715 GT + TT, and child COMT 472 AA genotypes (1)**
- **“Maternal exposure to folic acid and multivitamin supplements before and during pregnancy is associated with a reduced risk of ASD in the offspring compared with the offspring of mothers without such exposure.” (2)**

1. *Prenatal Vitamins, One-carbon Metabolism Gene Variants, and Risk for Autism. Schmidt, Rebecca et.al. Epidemiology: July 2011 - Volume 22 - Issue 4 - p 476-485*
2. *Association of Maternal Use of Folic Acid and Multivitamin Supplements in the Periods Before and During Pregnancy With the Risk of Autism Spectrum Disorder in Offspring. Stephen Z. Levine, PhD et.al. JAMA Psychiatry. Published online January 3, 2018.*

Prenatal Nutrition

Lower seafood intake during pregnancy resulted in:

- **lower IQ at age 8**
- **suboptimal behavior at age seven**
- **lower levels of social, fine motor and language development at six, 18, 30, and 42 months of age**

Hibbeln J. R., Davis J. M., Steer C., Emmett P., Rogers I., Williams C., et al. (2007). Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. Lancet 369, 578–585

Omega-3 Fatty Acids

- neuronal membranes-60% of brain's dry weight is lipids of which 20% are DHA and AA
- modulate membrane fluidity- receptor and enzyme activities, ion channels
- regulate gene expression in the brain
- neuronal and dendritic spine growth and synaptic membrane synthesis

Prenatal Nutrition

Women in third trimester given choline supplements:

- **tested infant information processing speed and visuospatial memory at 4, 7, 10 and 13 months of age (correlates with higher IQ)**
- **higher intake of choline improved scores**
- **infants demonstrating fast processing speeds typically continue to be fast as they get older**

Maternal choline supplementation during the third trimester of pregnancy improves infant information processing speed: a randomized, double-blind, controlled feeding study. Marie A. Caudill et.al.FASEB J. 32, 000–000 (2018)

Choline

- cell membrane structure and function
- DNA methylation and gene expression
- precursor to the neurotransmitter acetylcholine

Prenatal Nutrition

Vitamin B12 deficiency in vegetarian/vegan mothers:

- **48 case studies of infants with vitamin B12 deficiencies**
- **showed hypotonic muscles, involuntary muscle movements, apathy, cerebral atrophy, and demyelination of nerve cells**
- **rapid improvement in neurological symptoms was reported when treated with B12, but many "remained seriously delayed in cognitive and language development in the longer term"**

Dror D. K., Allen L. H. (2008). Effect of vitamin B12 deficiency on neurodevelopment in infants: current knowledge and possible mechanisms. Nutr. Rev. 66, 250–255

Vitamin B12

- axon myelination
- synthesis of different cytokines, growth factors and oxidative energy metabolites
- homocysteine-methionine-S-adenosylmethionine pathway

“Babies Who Get More Cuddles Have Their Genetics Changed for Years”

David Nield, November 29, 2017

Credit: sciencealert.com

Nutrition in Infancy

Mild but persistent malnutrition during the first 2 years of life negatively influences:

- **learning and reasoning**
- **visuospatial functions**
- **IQ and academic achievement**
- **language development**
- **attention**

Supplementation with food can improve cognitive performance.

Laus M. (2011). Early postnatal protein-calorie malnutrition and cognition: a review of human and animal studies. Int. J. Environ. Res. Public Health 8, 590–612

Nutrition in Infancy

Breast feeding and comparison of 3 different formulas

- **breastfed children had increased general, verbal, and non-verbal cognitive abilities compared to children exclusively formula-fed**
- **“significant developmental differences depending on formula composition received and that, in particular, long-chain fatty acids, iron, choline, sphingomyelin and folic acid are significantly associated with early myelination trajectories”**
- **effects persist into childhood- groups were matched for socioeconomic status and demographics**

Deoni S. et.al.. (2011). Early nutrition influences developmental myelination and cognition in infants and young children. Neuroimage. 2017 Dec 19. pii: S1053-8119(17)31080-7

Nutrition in Infancy

- **Higher IQ found at 4 years of age in children who consumed higher amounts of fruit, vegetables and food prepared at home between 6 and 12 months**

Gale C. R., Martyn C. N., Marriott L. D., Limond J., Crozier S., Inskip H. M., et al. (2009). Dietary patterns in infancy and cognitive and neuropsychological function in childhood. J. Child Psychol. Psychiatry 50, 816–823

Childhood Nutrition

- levels of lutein/zeaxanthin found in breast milk
- β-Carotene, carotene and lutein/zeaxanthin intake in adolescent girls (mean age 12) was inversely associated with development of benign breast disease (BBD)
- BBD is an independent risk factor for breast cancer

Boecke et. al. Adolescent carotenoid intake and benign breast disease. Pediatrics. 2014 May;133(5):e1292-8

Lutein and Zeaxanthin

- development of nervous system
- visual development
- development of retina, energy metabolism and brain electrical activity

Childhood Nutrition

- double-blind cross-over study, 21 children aged 7-10 years consumed placebo or blueberry drinks containing 15 or 30g freeze-dried wild blueberry powder
- cognitive performance improved across all measures (verbal memory, word recognition, response interference, response inhibition and levels of processing)
- results consistent with dose-response

Whyte AR et. al. Cognitive effects following acute wild blueberry supplementation in 7- to 10-year-old children. Eur J Nutr. 2016 Sep;55(6):2151-62

Anthocyanins

- flavonoids found to improve executive function (EF)-linked to processes like (e.g., rumination) that maintain low mood and improve positive affect
- free-radical scavenging pathway, cyclooxygenase pathway, inflammatory cytokines signaling

Khalis S. Effects of Acute Blueberry Flavonoids on Mood in Children and Young Adults. Nutrients. 2017 Feb 20;9(2)

Childhood Nutrition

- children (aged 6 years and older) with anemia who were treated with ***iron*** demonstrated increased IQ
- iron supplementation did not improve IQ in non-anaemic children

Falkingham M., Abdelhamid A., Curtis P., Fairweather-Tait S., Dye L., Hooper L. (2010). The effects of oral iron supplementation on cognition in older children and adults: a systematic review and meta-analysis. Nutr. J. 9:4

Iron

- cytochrome c oxidase enzyme system in energy production
- DA receptor synthesis
- delta-9- desaturase for myelination and fatty acid synthesis
- brain growth regulation

Childhood Nutrition

- iodine supplementation trials of mildly iodine deficient 10–13 year old children improved matrix reasoning, fine motor skills and visual problem solving
- meta- analysis of 18 studies found a difference of 13.5 points in IQ between iodine sufficient and iodine deficient children

Zimmermann MB et. al. Am J Clin Nutr. 2006 Jan;83(1):108-14
Qian M et. al. Asia Pac J Clin Nutr. 2005;14(1):32-42.

Iodine

Thyroid hormones (T3 and T4):

- **neuronal cell differentiation, maturation and migration**
- **neurotransmission and synaptic plasticity**
- **myelination**

Nutrition in Clinical Practice

Case Studies

Case Study #1
Birth-3
ASD with Developmental Language Delay

- 29 month old boy
- Problem list: recent diagnosis mild ASD with language delay, constipation and bloating, sleeping problems
- Rx: None
- Supplements: None
- Additional treatments: Birth-3 services
- PMHx: born at 36 weeks, feeding difficulties and reflux—elemental formula, took proton pump inhibitor
- FHx: Father – depression, metabolic syndrome. Sibling- anxiety

Diet

- Breakfast – cereal with milk and orange juice
- Lunch – Mac and cheese, carrots
- Dinner – chicken strips, pasta

Assessment

- Microbiome: dysbiosis, low SCFA
- Labs: double heterozygous MTHFR, low B12

Case Study #1
Birth-3
ASD and Speech Delay

Treatment:

- **Diet: GFDF, phytonutrient rich dietary intervention**
- **Supplements:**
  - **Fish oil (mixed in blueberry juice in AM)**
  - **Phytonutrient blend**
  - **Vitamin B12, L-5-MTHF**
  - **Probiotics, Digestive enzymes**

Case Study #1
Birth-3
ASD and Speech Delay

3 month follow-up

- **Subjective: Parent reports significant improvements in disruptive behavior, some gains in speech, BMs more regular, eating more variety of foods**
- **Objective: Normal vitamin B12 levels, reduced abdominal distension**

1 year follow-up

- **Subjective: Therapist impressed with speech development (classified as only mild delay), sleep and behavior improved**
- **Objective: improved GI effects profile, SCFA levels close to normal range**

Case Study #2
Early Childhood
ADHD

- 8 year old girl
- Problem list: ADHD, anxiety with repetitive behaviors, mild asthma and allergies
- Rx: Rescue inhaler
- Supplements: OTC Chocolate Calm—l-theanine, magnesium, chamomile, oat
- FHx: Mother – anxiety, PMS. Maternal uncle- anxiety. Cousin- ADHD
- Assessment:
  - COMT AA, MTHFR homozygous c677t
  - Food Sensitivity testing- whey

Treatment

- Diet: Modified Feingold Elimination Diet with Protein Phytonutrient Smoothie in AM
- Guided Meditation- Calm App
- Supplements:
  - Fish oil
  - Multivitamin with phytonutrients
  - Magnesium glycinate, Taurine, B6
  - L-5-MTHF
  - Probiotic

Case Study #2
Early Childhood
ADHD

3 month follow-up

Parents report improved behavior at home—more responsive to parents, noted improvements in school, less disruptive to class

6 mo follow-up

Improved academic performance in school, getting along better with peers, less nail biting. Also noted reduced need for rescue inhaler

Case Study #3
Adolescence
Concussion

- 14 year old girl
- Problem list: Grade 1 post-concussion syndrome—1mo ago hit in head with field hockey ball at practice
- Symptoms: fatigue, headaches, limited school attendance, reading and learning impairments, depression
- Rx: None
- Supplements: Vitamin D

Nutritional Interventions

- Magnesium-L-threonate
- Fish oil—4000mg EPA-DHA/day
- Curcumin

Additional treatments

Acupuncture

1 month follow-up

Improved fatigue, attention and mood, reduced HAs, increased attendance at school

3 month follow-up

Energy levels back to normal, regular school schedule

Summary

- Nutritional interventions can be an effective way to address cognitive conditions in children
- Nutrition in pre-conception, pre-natal period and childhood affects cognitive health, critical nutrients include:
  - Omega-3 fatty acids
  - Lutein and zeaxanthin
  - Choline
  - Anthocynanins
  - Iron, Iodine and Vitamin B12


Metagenics Institute

HEALTHY AGING, HEALTHY BRAIN

Susan Blum, MD, MPH
Founder and Director
Blum Center for Health
Blumcenterforhealth.com
Blumhealthmd.com

Affiliations

- Assistant Clinical Professor, Department of Preventive Medicine, Icahn School of Medicine at Mount Sinai, NYC
- Integrative Medicine, Greenwich Hospital, CT.
- Medical Advisory Board, Dr Oz Show
- Senior Teaching Faculty, Center for Mind Body Medicine, Washington
- Advisory Board, Institute for Integrative Nutrition
- Council of Directors, GLiMMER/True Health Coalition
- Certified Practitioner, Institute for Functional Medicine
- Board Certified in Preventive Medicine

Healing Arthritis

Author of *The Immune System Recovery Plan*

The 3-Step Guide to Conquering Arthritis Naturally

- Treat Rheumatoid Arthritis, Osteoarthritis and more
- Heal your gut to heal your joints
- Reduce inflammation without medication

Susan Blum

M.D., M.P.H.

with Michele Bender

Foreword by Mark Hyman, M.D.

Oxidative Stress

- **Normal process: low levels of oxidative stress**
  - Balance between free radicals (also called Reactive Oxygen Species or ROS) from every day biochemistry and immune activity, and the antioxidants we eat in our diet
- **Runaway oxidative stress**
  - Imbalance between too many free radicals and not enough antioxidant activity
- **Tissue damage**
  - Brain
    - Cognition and aging
    - Chronic degenerative/neuroinflammatory conditions
  - Blood vessels: CVD
  - Joints: Arthritis
  - All tissue, cells and mitochondria

Brain and Oxidative Stress

- Alzheimer's disease
  - Zhou Y, et al. **Protective effects of microRNA-330 on amyloid β-protein production, oxidative stress and mitochondrial dysfunction in Alzheimer's disease by targeting VAV1 via the MAPK signaling pathway.** J Cell Biochem 2018 Jan 25. doi: 10.1002/jcb.26700. [Epub ahead of print]
  - superoxide dismutase (SOD) and malondialdehyde (MDA)
- Parkinson's disease
  - Gill EL, et al. **L-Carnitine Inhibits Lipopolysaccharide-Induced Nitric Oxide Production of SIM-A9 Microglia Cells**. ACS Chem Neurosci. 2018 Jan 25. doi: 10.1021/acschemneuro.7b00468. [Epub ahead of print]
- Cognitive function
  - Li Q, et al. **The Protective Effect of Antarctic Krill Oil on Cognitive Function by Inhibiting Oxidative Stress in the Brain of Senescence-Accelerated Prone Mouse Strain 8 (SAMP8) Mice**. J Food Sci. 2018 Jan 19. doi: 10.1111/1750-3841.14044. [Epub ahead of print]
  - superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px)
- Oxidative stress drives aging and disease in the brain, just like it does in the rest of the body!

Oxidative Stress

- Essential Hypertension:
  - Oxidative stress and neuroinflammation in brainstem cardiovascular centers and other brain regions
    - Haspula D, Clark MA. **Neuroinflammation and sympathetic overactivity: Mechanisms and implications in hypertension**. Auton Neurosci. 2018 Jan 12. pii: S1566-0702(17)30250-3. doi: 10.1016/j.autneu.2018.01.002. [Epub ahead of print]
- Arthritis
  - RA
    - Mateen S, Moin S, Khan AQ, Zafar A, Fatima N (2016) **Increased Reactive Oxygen Species Formation and Oxidative Stress in Rheumatoid Arthritis**. PLoS ONE 11(4): e0152925. doi:10.1371/ journal.pone.0152925
    - Quiñonez-Flores CM, González-Chávez SA, Del Río Nájera D, Pacheco-Tena C. **Oxidative Stress Relevance in the Pathogenesis of the Rheumatoid Arthritis**: A Systematic Review. BioMed Research International. 2016;2016:6097417. doi:10.1155/2016/6097417
    - Lipid peroxides, OxLDL, 8-OHDG
  - OA:
    - Loeser RF, et al. **Ageing and the pathogenesis of osteoarthritis.** Nat Rev Rheumatol. 2016;12(7):412-20.

Brain and Inflammation

- **Obesity-associated systemic inflammation** leads to inflammation within the brain
- Circulating cytokines, free fatty acids and immune cells initiate local inflammation, including microglial proliferation
  - Disruption to cognitive function in hippocampus, amygdala, and reward-processing centers.
- Central inflammation is also likely to affect these regions directly and to produce negative outcomes on cognition.

- Alyson A. Miller, Sarah J. Spencer. **Obesity and neuroinflammation: A pathway to cognitive impairment.** Brain, Behavior, and Immunity, Volume 42, 2014, Pages 10-21.

Brain and Inflammation

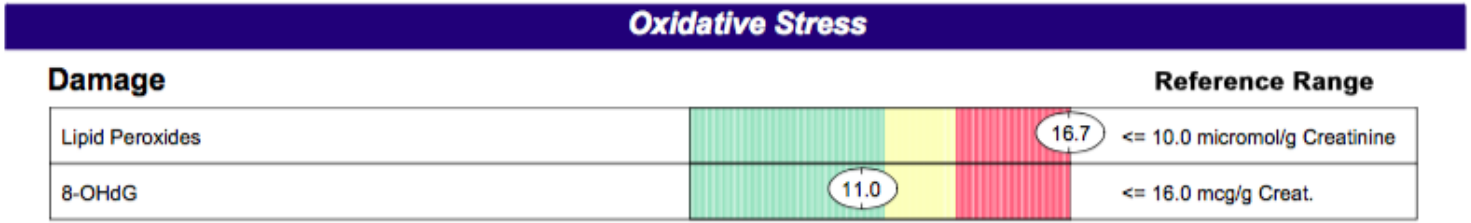
- **Obesity**
  - Associated with a high prevalence of mood symptoms and cognitive dysfunctions and low grade systemic inflammation
  - Excessive production of proinflammatory cytokines and the resulting activation of the brain tryptophan catabolizing enzyme indoleamine 2,3-dioxygenase (IDO)

- Caroline André, et al. **Diet-induced obesity progressively alters cognition, anxiety-like behavior and lipopolysaccharide-induced depressive-like behavior: Focus on brain indoleamine 2,3-dioxygenase activation.** Brain, Behavior, and Immunity, Volume 41, 2014, Pages 10-21.

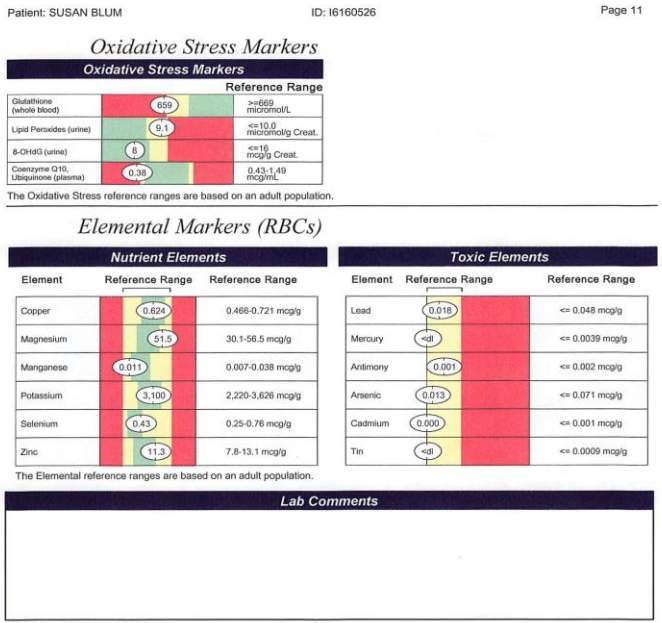
Measuring Oxidative Stress

- **Urine organic acids**
  - Lipid peroxides (can also be measured in blood)
  - 8-OHDG: urine organic acids
- Blood tests from routine or advanced cardiovascular testing companies:
  - F2-Isoprostane
  - Oxidized LDL
  - LpPLA2
- Other oxidative stress testing:
  - Glutathione, SOD

Oxidative Stress Testing: Urine



Oxidative Stress panel in Nutreval



Patient: SUSAN BLUM ID: I6160526 Page 11

Oxidative Stress Markers

Oxidative Stress Markers

	Reference Range
Glutathione (whole blood) 659	>=669 micromol/L
Lipid Peroxides (urine) 9.1	<=10.0 micromol/g Creat.
8-OHdG (urine) 8	<=16 mcg/g Creat.
Coenzyme Q10, Ubiquinone (plasma) 0.38	0.43-1.49 mcg/mL

The Oxidative Stress reference ranges are based on an adult population.

Elemental Markers (RBCs)

Nutrient Elements

Element	Reference Range	Reference Range
Copper 0.624		0.466-0.721 mcg/g
Magnesium 51.5		30.1-56.5 mcg/g
Manganese 0.011		0.007-0.038 mcg/g
Potassium 3,100		2,220-3,626 mcg/g
Selenium 0.43		0.25-0.76 mcg/g
Zinc 11.3		7.8-13.1 mcg/g

Toxic Elements

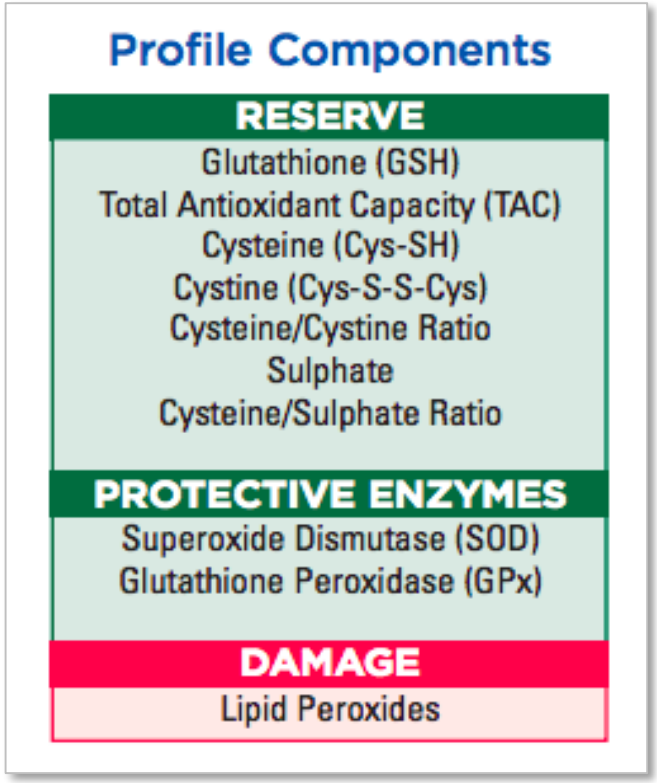
Element	Reference Range	Reference Range
Lead 0.018		<= 0.048 mcg/g
Mercury <dl		<= 0.0039 mcg/g
Antimony 0.001		<= 0.002 mcg/g
Arsenic 0.013		<= 0.071 mcg/g
Cadmium 0.000		<= 0.001 mcg/g
Tin <dl		<= 0.0009 mcg/g

The Elemental reference ranges are based on an adult population.

Lab Comments

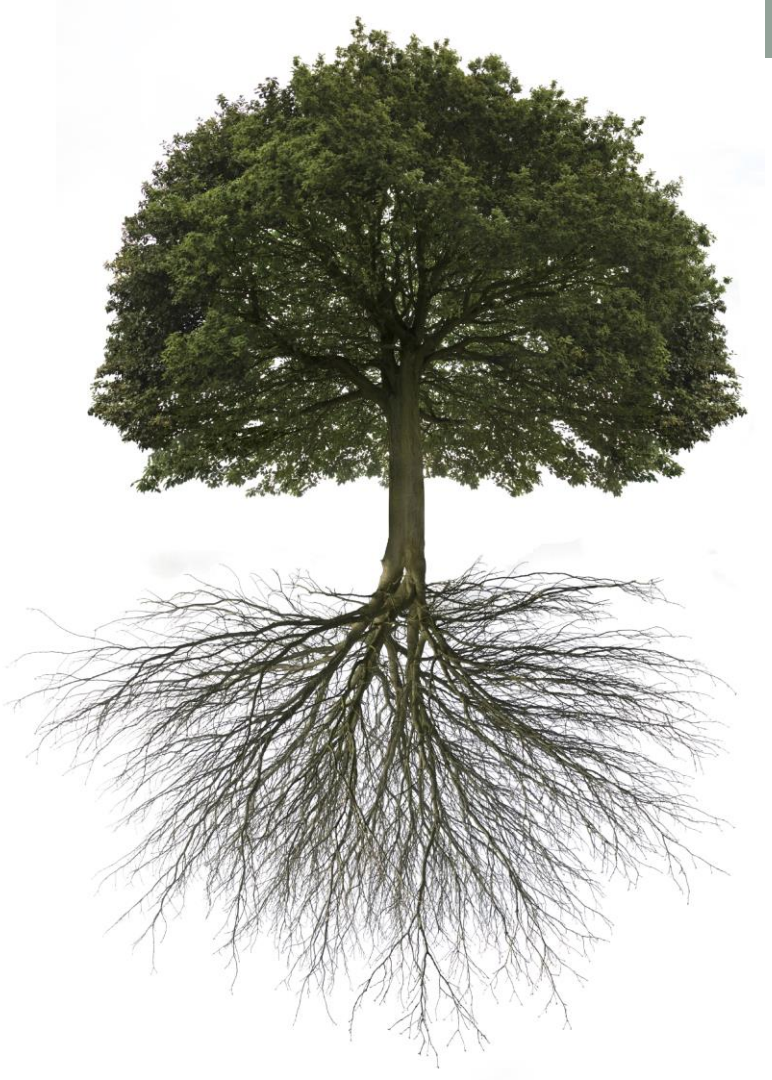
The performance characteristics of all assays have been verified by Genova Diagnostics, Inc. Unless otherwise noted with ♦, the assay has not been cleared by the U.S. Food and Drug Administration.

Oxidative Stress Analysis 2.0



Treating Oxidative Stress and Inflammation

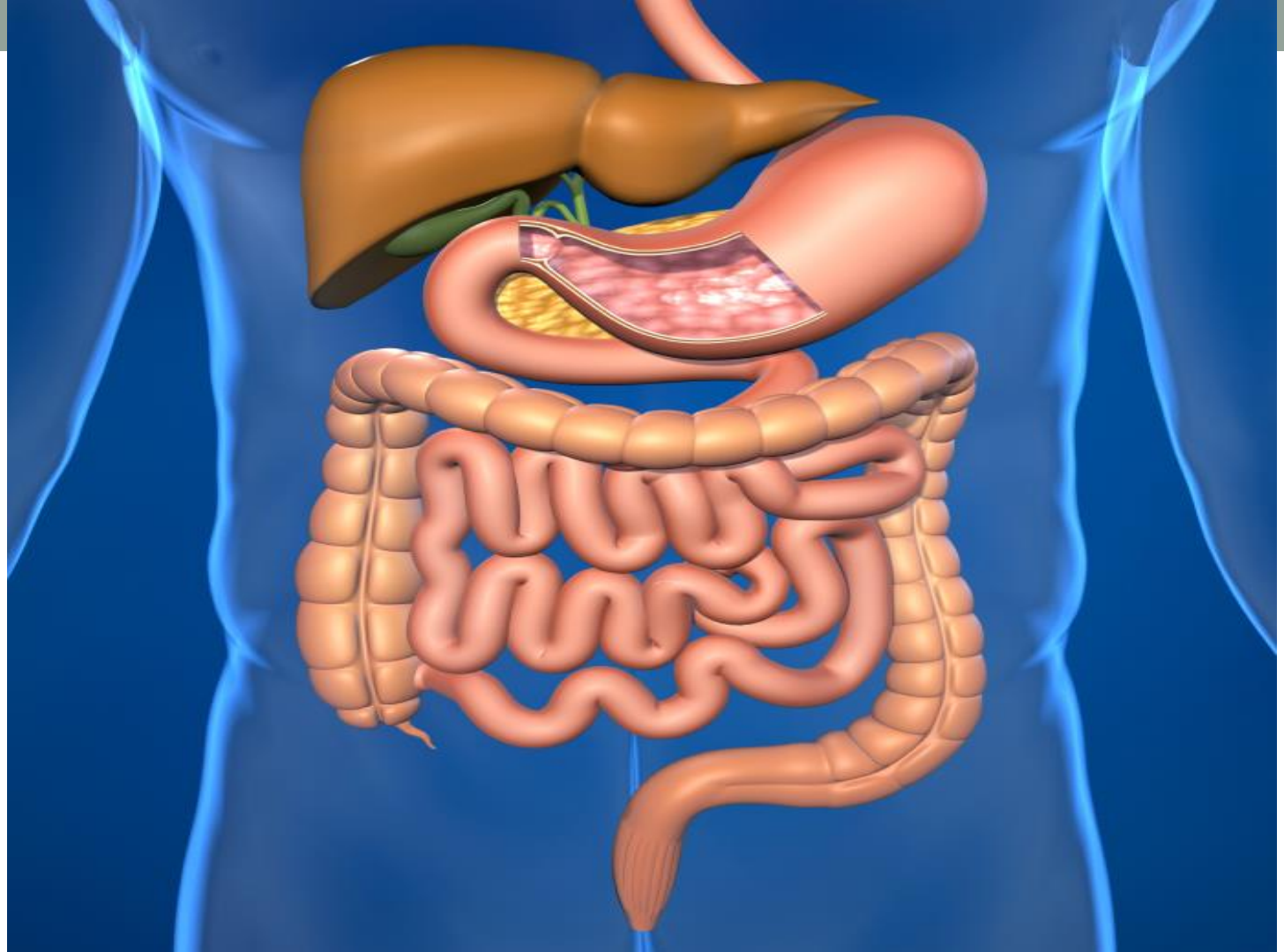
- **Find and treat the root cause(s):**
  - Impaired gut health: the gut microbiome
    - Key focus in autoimmune arthritis
  - Environmental exposures
    - Heavy metals, pesticides/herbicides, smoking
  - Diet: especially low levels of antioxidants
  - Obesity: key focus in Osteoarthritis
  - Stress and trauma
  - Infections
- **Support antioxidant needs**
  - Food focus
  - Supplements



HEALTHY GUT MICROBIOME

Foundation for immune system

Imbalance can trigger autoimmunity, inflammation and oxidative stress



Gut Microbiome

- 100 trillion microbes, 1000 species
- 100 species make up 99% of the population
- Small bowel: 10% of microbiome, mostly aerobic
- Colon: 90% of microbiome, mostly anaerobic
- Feces 60% bacteria
- 99% anaerobes
- Food #1 determines composition of gut flora
  - Animal eaters vs Vegetarians
  - Microbiome switches within 24 hours if swap
- Short chain fatty acids: health supportive molecules produced by gut flora when you eat fiber

- *Andoh A.. Digestion 2016; 93:176-181****Physiological Role of Gut Microbiota for Maintaining Human Health***

Benefits of Good Flora

- SCFAs
- Vitamins: each species has a unique niche
- Support the immune system
  - Antibacterial action against pathogens
  - **Stimulate immune cells to make IgA**: reduces inflammation in the gut and binds to harmful microbes. Helps prevent leaky gut. Prevents dysbiosis and bacterial overgrowth
  - Intestinal barrier
  - Directs functioning of antigen presenting cells with modulation of T cell responses
  - Interact with enteric nervous system which affects immune system

- *Suzuki, K and Nakajima A.* ***New aspects of IgA synthesis in the gut****. International Immunology 2014; Vol. 26, No. 9, pp. 489-494.*

Dysbiosis

- Altered state of gut bacteria
- Not enough good or overgrowth of harmful bacteria
- Also can be yeast or parasites in the gut
- Dysbiosis can damage tight junctions and cause leaky gut
- You can have dysbiosis without having any digestive symptoms and this is common
  - Stress, PPIs, antibiotics, gut infections, diet, chronic constipation

- *Stephan C Bischoff et al.* ***Intestinal Permeability – A New Target for Disease Prevention and Therapy****. BMC Gastroenterol. 2014;14(189)*

Microbiota and the Brain

- Microbes produce neurotransmitters like serotonin and GABA
- SCFA: Butyrate, proprionate, acetate influence functioning of the central and peripheral nervous system
- Changes in gut microbiota can alter brain functioning

- Bienenstock J, et al. **Microbiota and the gut-brain axis**. Nutr Rev. 2015 Aug;73 Suppl 1:28-31. doi: 10.1093/nutrit/nuv019.

Leaky Gut and Inflammation

- **Tight junctions**:
  - Zonulin opens the gates and increases intestinal permeability
  - Gut microbiome is important for regulating zonulin and tight junctions
- **Leaky gut**:
  - Gut lumen antigens (including bacterial cell wall proteins) get into the body and trigger an immune and inflammatory response
  - Increases oxidative stress and inflammation
  - Must fix leaky gut to stop this process
  - Leaky Gut, Leaky Blood Brain Barrier

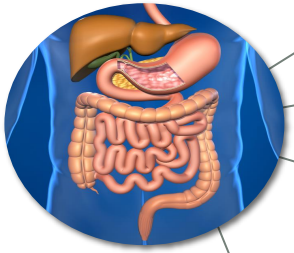
- Fasano A. **Zonulin and Its Regulation of Intestinal Barrier Function: The Biological Door to Inflammation, Autoimmunity, and Cancer**. 2011. Physiol Rev 91: 151-175
- Fasano, Alessio**. Leaky Gut and Autoimmune Diseases**.Clinic Rev Allerg Immunol (2012)42:71-78
- Pulukool SANDHYA, Debashish DANDA, Disha SHARMA and Vinod SCARIA. **Does the buck stop with the bugs?: an overview of microbial dysbiosis in rheumatoid arthritis**. International Journal of Rheumatic Diseases 2015

Gut-Brain Barrier

- Increased permeability of intestine and blood-brain barrier induced by gut microbiota disturbance will increase the incidence of neurodegeneration disorders
  - Hu X, et al. **Alzheimer's disease and gut microbiota**. Sci China Life Sci. 2016 Oct;59(10): 1006-1023**.**

- And neuropsychiatric disorders
  - Maes, M, et al. **The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leakygut) plays a role in the inflammatory pathophysiology of depression**. Neuro Endocrinol Lett 2008 Feb;29(1): 117-24**.**

Factors Influencing the Gut Ecosystem



- **Childhood**
  - Breast vs formula
  - C-section
  - Excessive Hygiene
- **Lifestyle**
  - Chronic stress
  - Poor sleep
  - Physical inactivity
- **Food**
  - Processed diet
  - Insufficient fiber and phytonutrients
- **Environment**
  - Exposure to toxins
  - Medication
  - Alcohol
  - Infections

Gut Testing

- **Functional testing by specialty labs**
  - Stool testing is currently best way to check the bacteria
    - Many kinds of tests
  - LPS and anti-LPS can show the immune reaction and marker for leaky gut
  - Intestinal permeability testing
  - Zonulin testing
  - Food sensitivity testing
    - IGG vs mediator testing

Gut Treatment Protocol

- Treat Dysbiosis: 1-2 months depends on diagnosis and results of testing
  - Herbal blend: berberine, black walnut, uva ursi, oregano
- Digestive enzymes: 1-2 with each meal
  - Plant based vs Pancreatin
  - Ox Bile
  - Betaine
- Probiotic: multi strain formula
  - Saccharomyces boulardii

Heal The Lining

- Repair the lining with food: permanent
  - Ghee (butyrate)
  - Coconut oil and medium chain triglycerides
  - Glutamine: found in all animal protein, beans, cabbage, beets, spinach, and parsley
  - Turmeric and cinnamon
- Supplementation: 1 year minimum
  - Glutamine: loose powder is best
  - Powder blends with aloe, licorice, zinc carnosine, NAG

- Jin, CJ et al. **Supplementation of sodium butyrate protects mice from the development of non-alcoholic steatohepatitis** (NASH). Br J Nutr 2015 Dec;114(11):1745-55
- *Rapin JR, Wiernsperger N.* ***Possible links between intestinal permeability and food processing: a potential therapeutic niche for glutamine****. Clinics. 2010;65(6):635-43*

Do Herbs Treat Dysbiosis?

- Look at SIBO as example that is well studied
- The response rate for normalizing breath hydrogen testing in patients with SIBO was 46% for herbal therapies vs 34% for Rifaximin
- Study herbs: mixture of >20 herbs in 4 different supplements given at the same time
- Herbal treatment as effective as Rifaximin
- Advantages: cost, does not promote yeast, well tolerated

- *Chedid, V, et al.* ***Herbal therapy is equivalent to rifaximin for the treatment of small intestinal bacterial overgrowth****. Glob Adv Health Med 2014 May;3(3):16-24*

Herbal Antibiotics

- Herbal treatment of dysbiosis
  - Recommend for 2 months initially, often repeating treatment 6 months later
  - Combination formulas
- Berberine
  - *Joshi PV, Shirkhedkar AA, Prakash K, Maheshwari VL.* ***Antidiarrheal activity, chemical and toxicity profile of Berberis aristata****. Pharm Biol. 2011;49(1):94–100*
  - Han, Junling et al. **Modulating gut microbiota as an anti-diabetic mechanism of berberine.** Med Sci Monit, 2011; 17(7): RA164-167
  - Chedid, V, et al. **Herbal therapy is equivalent to rifaximin for the treatment of small intestinal bacterial overgrowth**. Glob Adv Health Med 2014 May;3(3):16-24
- Artemesia
  - *Juteau F, Jerkovic I, Masotti V., et al.* ***Composition and antimicrobial activity of the essential oil of Artemisia absinthium from Croatia and France****. Planta Med. 2003;69(2):158–61*

Herbal Antibiotics Cont'd

- Uva Ursi
  - *Tolmacheva, Anna A, et al.* ***Antibacterial and quorum sensing regulatory activities of some traditional Eastern-European medicinal plants****. Acta Pharmaceutica. Volume 64, Issue 2 (June 2014*
- Black Walnut and Sea Buckthorn
  - *Abidi, SH, et al.* ***Synergy between antibiotics and natural agents results in increased antimicrobial activity against Staphylococcus epidermidis.*** *J Infect Dev Ctries. 2015 Sep 27;9(9):925-9*.
- Grapefruit seed extract
  - *Heggars, JP et al.* ***The effectiveness of processed grapefruit-seed extract as an antibacterial agent: II. Mechanism of action and in vitro toxicity****. J Altern Com[lement Med 2002 Jun;8(3):333-40*
- Oregano:
  - *Saeed S, Tariq P.* ***Antibacterial activity of oregano (Origanum vulgare Linn.) against gram positive bacteria****. Pak J Pharm Sci. 2009;22(4):421–4*

Long Term: Probiotics?

- Probiotics are influencers that
  - lower inflammation and
  - support gut lining integrity
  - prevent harmful microbes from sticking
- Long term: prefer food
  - Cultured non-dairy yogurt and kefir
  - Fermented vegetables: beets, kimchi, sauerkraut
- Low dose probiotics: 25-30 billion CFU
  - Stay on probiotics until all inflammatory, autoimmune or oxidative stress markers are resolved
  - Then discontinue and use intermittently if needed

REDUCE TOXIN LOAD

Toxins increase oxidative stress and inflammation

Toxins and Oxidative Stress

- Toxins are anything your immune system thinks is bad
  - Heavy metals or other environmental exposure
  - Reaction to foods
  - Food toxins
  - Infections also release toxic compounds
- Oxidative stress
  - Chronic persistent activation of the immune system
  - Direct damage to tissues from toxins

Toxins and Inflammation

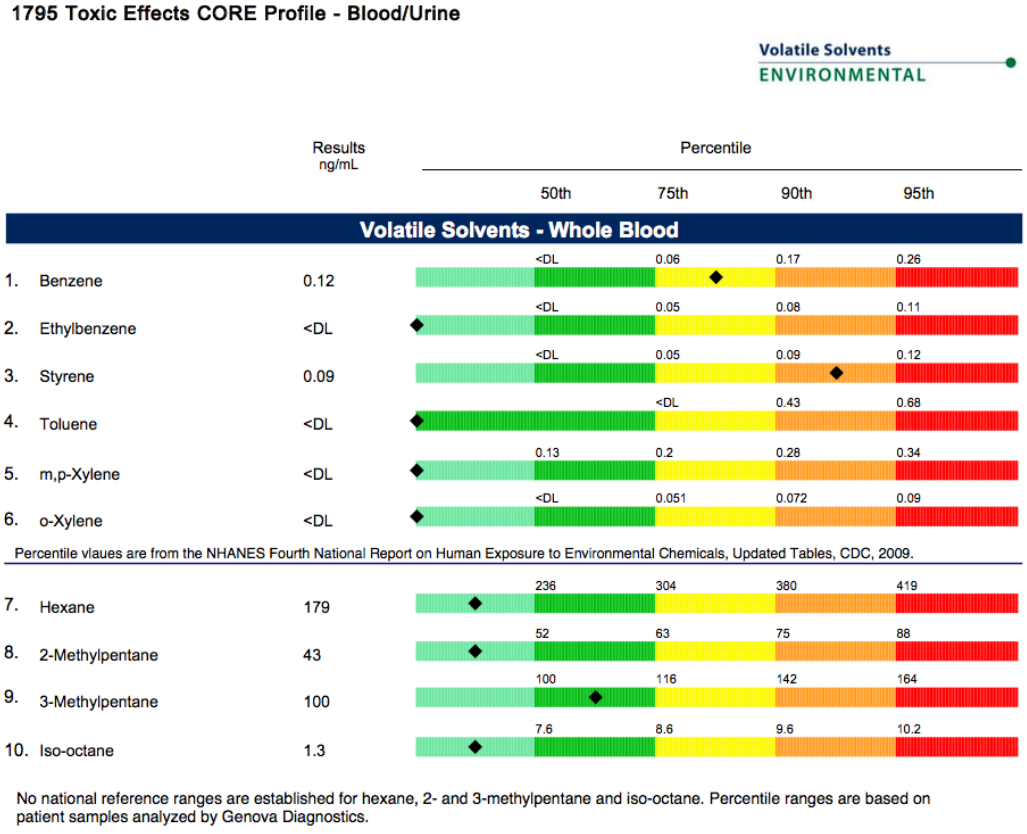
- Huge global human exposure:
  - Persistent chlorinated organics and POPs
  - Heavy metals and pesticides/herbicides
  - Phthalates, flame retardants
  - Electronic waste and airborne pollutants
- Toxins induce inflammation and related chronic diseases
- Diets enriched with bioactive foods can prevent/treat
  - Polyphenols and omega-3s
  - High levels of antioxidant and anti-inflammatory compounds

- Hennig B, et al. **The role of nutrition in influencing mechanisms involved in environmentally mediated diseases**. Rev Environ Health. 2018 Jan 30. E pub DOI: 10.1515/reveh-2017-0038

Measuring Toxin Load

- Environmental toxins
  - Pesticides and herbicides like PCB's, DDT and it's cousins
  - Volatile solvents like xylene, toluene, styrene
  - Bisphenol A
  - Phthalates and parabens
  - Routine labs have low sensitivity for picking these up
- Heavy metals
  - Mercury
  - Lead
  - Arsenic, aluminum, cadmium and more
  - Option to use a provoking agent like DMSA for the urine testing
  - Pros and cons of testing whole blood

Toxic Effects Core Test: Genova



1795 Toxic Effects CORE Profile - Blood/Urine

Volatile Solvents
ENVIRONMENTAL

		Results ng/mL	Percentile 50th	75th	90th	95th
Volatile Solvents - Whole Blood						
1.	Benzene	0.12	<DL	0.06	0.17	0.26
2.	Ethylbenzene	<DL	<DL	0.05	0.08	0.11
3.	Styrene	0.09	<DL	0.05	0.09	0.12
4.	Toluene	<DL		<DL	0.43	0.68
5.	m,p-Xylene	<DL	0.13	0.2	0.28	0.34
6.	o-Xylene	<DL	<DL	0.051	0.072	0.09

Percentile vlaues are from the NHANES Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, CDC, 2009.

7.	Hexane	179	236	304	380	419
8.	2-Methylpentane	43	52	63	75	88
9.	3-Methylpentane	100	100	116	142	164
10.	Iso-octane	1.3	7.6	8.6	9.6	10.2

No national reference ranges are established for hexane, 2- and 3-methylpentane and iso-octane. Percentile ranges are based on patient samples analyzed by Genova Diagnostics.

Organophosphates - Urine

			<DL	1.8	5.2	15.7	30.4
29.	Dimethylthiophosphate (DMTP)	<DL					
30.	Dimethyldithiophosphate (DMDTP)	<DL	<DL	0.5	2.14	5.27	
31.	Diethylthiophosphate (DETP)	<DL	<DL	0.7	1.47	2.62	
32.	Diethyldithiophosphate (DEDTP)	13.73			<DL	0.41	
33.	Atrazine	<DL				<DL	
34.	Atrazine Mercapturate	<DL			<DL	0.072	

Percentile values for organophosphates are from the NHANES Fourth National Report on Human Exposure to Environmental Chemicals, CDC, 2009.

No national reference ranges are established for atrazine or atrazine mercapturate. Percentile ranges are based on patient samples analyzed by Genova Diagnostics.

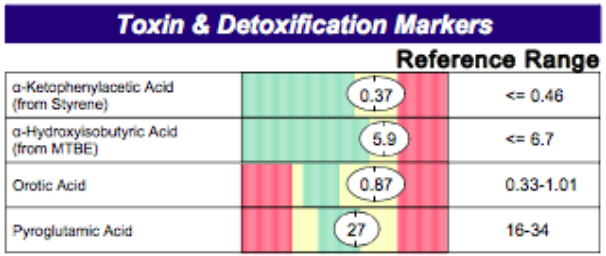
Bisphenol A
ENVIRONMENTAL

		Results mcg/gm creatinine	Percentile 50th	75th	90th	95th
Bisphenol A (BPA) - Urine						
35.	4-Nonylphenol	<DL		<DL	1.11	4.69
36.	Bisphenol A	<DL	1.95	3.45	6.09	10
37.	Triclosan	<DL	12	50	233	443

Testing for Metals, Detox and Oxidative Stress

Toxin & Detoxification Markers

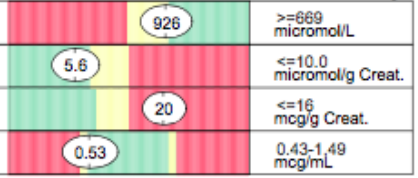
	Reference Range
α-Ketophenylacetic Acid (from Styrene)	<= 0.46
α-Hydroxyisobutyric Acid (from MTBE)	<= 6.7
Orotic Acid	0.33-1.01
Pyroglutamic Acid	16-34



Oxidative Stress Markers

Oxidative Stress Markers

	Reference Range
Glutathione (whole blood)	>=669 micromol/L
Lipid Peroxides (urine)	<=10.0 micromol/g Creat.
8-OHdG (urine)	<=16 mcg/g Creat.
Coenzyme Q10, Ubiquinone (plasma)	0.43-1.49 mcg/mL



The Oxidative Stress reference ranges are based on an adult population.

Toxic Elements

Element	Reference Range	Reference Range
Lead	0.059	<= 0.048 mcg/g
Mercury	0.0088	<= 0.0039 mcg/g
Antimony	0.001	<= 0.002 mcg/g
Arsenic	0.039	<= 0.071 mcg/g
Cadmium	0.001	<= 0.001 mcg/g
Tin	<dl	<= 0.0009 mcg/g

Metals and Inflammation

- SLE (systemic lupus erythematosus), RA and SS patients
  - Increased frequency of metal delayed-type hypersensitivity (DTH) (Type IV allergy).
  - Nickel, mercury, gold, palladium, titanium, and chromium
- Metals in these patients will induce an inflammatory response
- Hypothesized that metal-specific T cell reactivity can act as an etiological agent in the propagation and chronification of rheumatic inflammation

- Geir Bjørklund, Maryam Dadar, Jan Aaseth, **Delayed-type hypersensitivity to metals in connective tissue diseases and fibromyalgia**, Environmental Research,Volume 161,2018,Pages 573-579.

Mercury

- Fish
- Cosmetics
- Pesticides
- Some vaccines
- Pollutant released into air from factories, especially coal burning
- Air – soil and bottom of oceans, lakes, rivers
- Gets into our food and fish, converted to methyl

Total Toxin Load

- Strategy to address lowering total toxin load
- Can’t always know which toxin is responsible, doesn’t always matter
- An overloaded system can’t handle even simple things like alcohol
- Plan:
  - Test for heavy metals because there is something we can do specifically for metals
  - Otherwise, targeting metabolic detoxification pathways with nutraceuticals is a good strategy

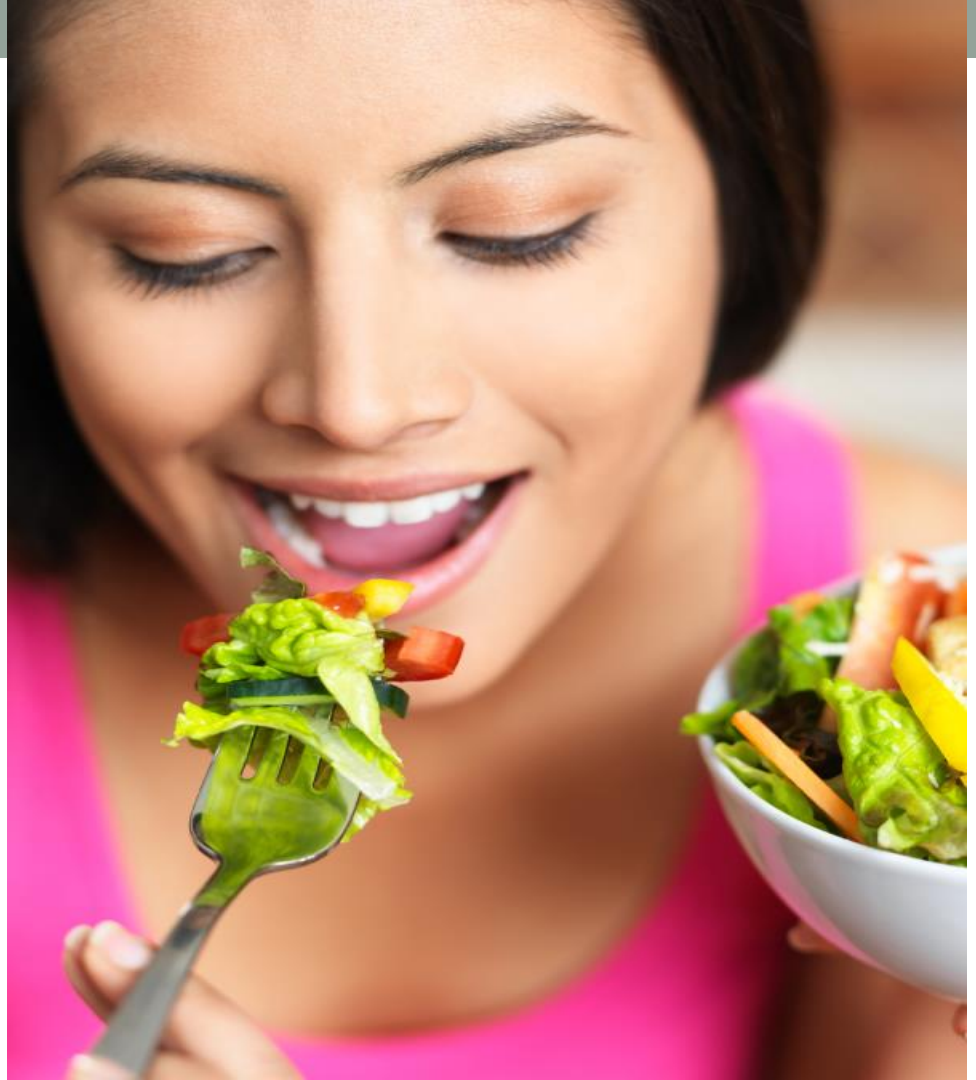
21 Day Detox Program

- Elimination/Challenge diet
- Supplements
  - Protein shake with additional ingredients to boost metabolic detoxification
  - Additional antioxidants and support for glutathione

Take Home Lessons:

- Always evaluate toxin load: history, MSQ, heavy metal testing
- Always work to clean up their environment and their food
  - Eating for enhancing liver function
- Always do basic detox program
  - Annually for most patients as an anti-aging, anti-inflammation prevention strategy
  - **As a foundation for treating all chronic illness, and decide how long they need it based on**
    - Toxic load assessment
    - How they respond or don’t respond
    - Sometimes 3 months or longer

USING FOOD AS MEDICINE



General Strategy

- Eat foods that support:
  - Detox and metabolic detoxification
  - Gut microbiome and overall gut health
  - Antioxidants to combat oxidative stress
  - Anti-inflammatory pathways
- Eliminate pro-inflammatory and pro-oxidant foods

Liver and Gut Loving Food

- Organic, non-GMO foods
- Remember, everything you eat is the sum total of what the plants and animals were fed
- If the animals were treated with antibiotics, those drugs get in your body and could damage your gut
- If the plants were treated with pesticides/herbicides, they can alter your flora and damage your intestinal lining, causing leaky gut, which in turn causes inflammation in your joints
- GMO foods can damage the gut lining, too, and eating them will work against the repair work we are doing to treat your arthritis

Liver-loving Food

- Greens rich in antioxidants:
  - Dark leafy greens like Kale, Collard, Turnip greens, Swiss chard, Spinach, Mustard greens, Red, green and romaine lettuce
- Cruciferous veggies:
  - Arugula, Bok Coy, Brussels Sprouts, Broccoli, Cabbage, Cauliflower, Chinese cabbage, Daikon, Kohlrabi, Collard greens, Kale, Mustard greens, Rutabaga, Radish, Turnip

- Razis A, et al. **Isothiocyanates and Xenobiotic Detoxification.** Molecular Nutrition & Food Research (2017). https://doi.org/10.1002/mnfr.201700916

Polyphenols: Antioxidants

- Fruit: Apples, pears, all berries (especially dark red and blue), grapes, pomegranate, oranges, peaches, bananas, lemons, limes, grapefruit, plums, apricots
- Vegetables: red and green onions, artichoke, snap peas, and okra
- Herbs and spices: cloves, parsley, dill, thyme, capers, cacao, oregano, sage, rosemary
- Beans: black, kidney, fava pinto
- Beverages: fresh pressed juices, black, red and green tea
- Nuts and seeds: walnuts, pecans, pistachio, cashew, flax

- See references next slide

Polyphenol References

Detox and gut supporting!

- Huang J Chen L Xue B Liu Q Ou S Wang Y Peng X. **Different Flavonoids Can Shape Unique Gut Microbiota Profile In Vitro**. Journal of Food Science Vol. 81, Nr. 9, 2016.
- Ozdal T, Sela D, Xiao J, Boyacioglu D, Chen F, Capanoglu E. **The reciprocal interactions between polyphenols and gut microbiota and effects on bioaccessibility**. Nutrients2016,8, 78; doi:10.3390/nu8020078
- Bjorklund G, et al. **Flavonoids as detoxifying and pro-survival agents: What's new?** Food and Chemical Toxicology. 2017 vol: 110 pp: 240-250

Polyphenols and Microbes

- In rodents
  - **Pomegranate** extract and apple juice increased Bifido
  - **Apple and red beet juice** increased Lactobacillus
  - **Cocoa powder** reduced Bacteroidetes, Staphylococcus, and Clostridium
- In healthy adults
  - **Grape seed extract** and **cocoa** increased Bifidobacterium, Lactobacillus, and inhibited the growth of harmful bacteria
  - **Red wine** consumption over a period of 20 days increased Firmicutes, Bacteroidetes, Bifidobacterium, and Prevotella
  - **Blueberry drink** for six weeks increased Bifidobacterium
  - Shinohara K, Ohashi Y, Kawasumi K, et. al. **Effect of apple intake on fecal microbiota and metabolites in humans.** Anaerobe 16 (2010) 510-515.
  - Mosele J Macià A Motilva M. **Metabolic and microbial modulation of the large intestine ecosystem by non-absorbed diet phenolic compounds: A review**. Molecules 2015, 20 , 17429-17468;

Flavonoids and Brain Health

- **Flavonoids** are a subclass of polyphenols
  - Studied EGCG, luteolin (most fruits and vegetables), anthocyanins (blueberries), hesperidin and hesperetin (citrus), and kaempferol (apple, strawberry, broccoli, beans)
  - Act as a potent anti-oxidant and anti-inflammatory
  - Alter signaling pathways and inhibit specific enzymes involved in phosphorylation of tau proteins
  - Neural rehabilitation and lost cognitive performance recovery

- Bakhtiari M, et al**. Protective effects of flavonoids against Alzheimer's disease-related neural dysfunctions**. Biomedicine et Pharmacotherapy. 2017 vol: 93 pp: 218-229

Diet and Gut Health

- Best for gut:
  - **Mediterranean diet**: increases SCFAs
  - Fiber and polyphenol rich diet: increases SCFA and reduces amounts of Enterobacteria

- **High protein, low carb diets**:
  - Reduced good, SCFA-producing bacteria and increased compounds that thought to promote colon cancer
  - Another study: reduced Bifido bacteria and SCFA
- Studies consistently show that low carb diets do not support bacteria

- Maukonen J, and Saarela M. **Human gut microbiota: does diet matter**? Proceedings of the Nutrition Society (2015), 74, 23–36

The Anti-inflammatory Diet

- Anti-oxidative stress diet!
- Basic principles:
  - Mediterranean diet as the foundation:
    - Focus on colorful vegetables, fruit, EVOO, nuts/seeds, fish, red wine, limited dairy and meat. Whole foods.
    - Anti-inflammatory and rich in antioxidants:
      - Omega 3s, polyphenols, alkaline, high fiber
    - Naturally alkaline: more veggies and less animal
  - Combine with elimination (leaky gut) diet to determine food sensitivities:
    - Remove gluten, dairy, soy, corn, eggs, peanuts, sugar for 3 weeks minimum before reintroduction/challenge
- Mark Houston, Deanna Minich, et al. (2018): **Recent Science and Clinical Application of Nutrition to Coronary Heart Disease**, Journal of the American College of Nutrition. https://doi.org/10.1080/07315724.2017.1381053

Supplements for Oxidative Stress

- Multi with antioxidants and minerals (Cu, Zinc, Mn for SOD)
- High Orac green or red powder
- Omega oils including Omega 3 and the Omega 6 - GLA
- NAC
- Sulforaphane
- Vitamin E
- Selenium
- Lipoic acid
- Green tea
- Curcumin

Supplements to Lower Inflammation

- Resolvins: new category of anti-inflammatory
- Fish oil/Omega 3's
- GLA: evening primrose or borage oil
- Vitamin D3
- Turmeric

BALANCING HORMONES AND STRESS

Stress and Cognition

- Perceived Stress Scale scores associated with reduced cognitive function
- Executive, memory and language areas in non-demented older adults

- Jiang JM, et al. **Positively worded subscale score of the Perceived Stress Scale is associated with cognitive domain function**. J Behav Brain Sci. 2017 Jul;7(7):311-324. doi: 10.4236/jbbs.2017.77023. Epub 2017 Jul 24.

Stress and Neuroinflammation

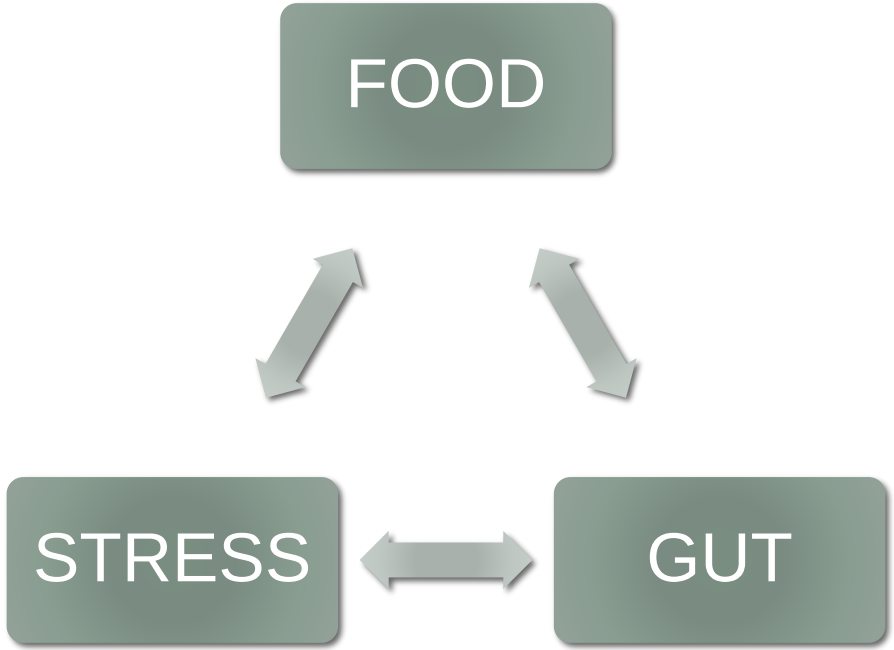
- Stress exposure alters immune system
- **Activates** an innate inflammatory/immune response
- Mechanism for neuroinflammation via Toll-like receptors

- Garate I, et al. Stress-induced neuroinflammation: role of the Toll-like receptor-4 pathway. Biol Psychiatry. 2013 Jan 1;73(1):32-43.

Stress-Gut-Immune

- Stress is the biggest influence on the gut microbiome, second to food.
- **Chronic stress causes alteration in the gut flora**
- Stress may or may not cause digestive symptoms
- Direct action in the gut wall, but also via:
  - Altering stomach acid and digestion
  - Cortisol drops IgA
  - Increased risk of Dysbiosis

- **Stress = Gut microbiome changes = oxidative stress and inflammation = systemic including brain**


FOOD
STRESS
GUT

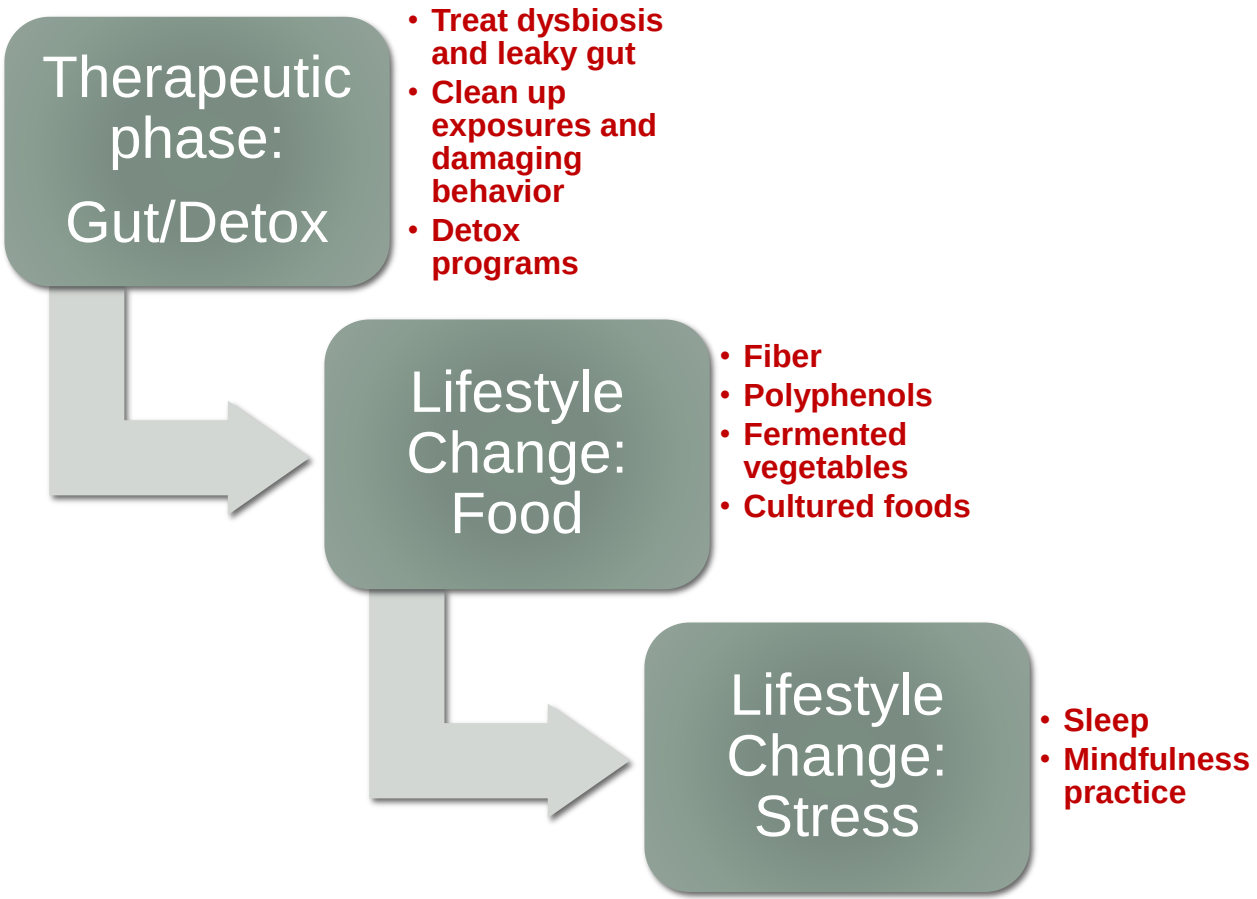
Testing and Treatment

- Adrenal saliva testing, Testosterone, DHEA-S
- Dutch urine hormone testing
- Lifestyle Health Coaching
  - Sleep, meditation, scheduling
- Adrenal supplements:
  - Rhodiola, Cordyceps, Ginseng
  - Glandular. When to use.

Goal: Resiliency and Balance

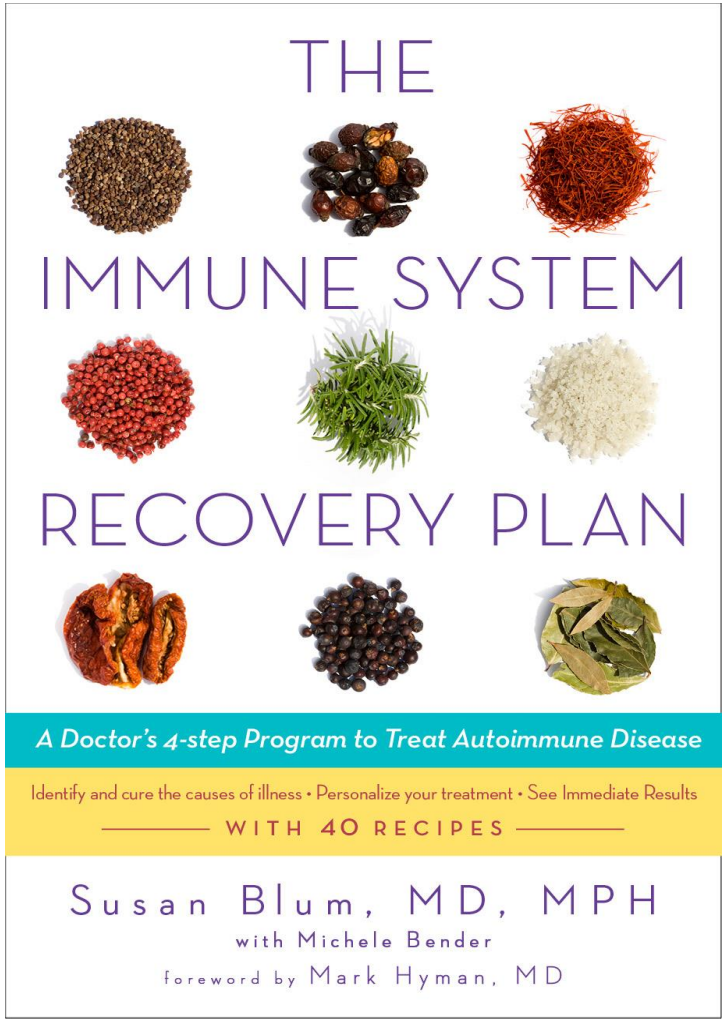
- Engage Parasympathetic nervous system to bring balance to the system
- All mind body techniques like meditation, breathing, yoga, engage the parasympathetic and bring balance to the system
- Must make this part of everyone’s treatment program
- This will build resiliency in the gland and prevent hormone depletion


Breathe


Therapeutic phase:
Gut/Detox
• Treat dysbiosis and leaky gut
• Clean up exposures and damaging behavior
• Detox programs
Lifestyle Change: Food
• Fiber
• Polyphenols
• Fermented vegetables
• Cultured foods
Lifestyle Change: Stress
• Sleep
• Mindfulness practice

4 Step Functional Medicine Program to Treat Autoimmune Disease:

1. Using Food As Medicine
2. Balancing Stress Hormones
3. Healing the Gut
4. Supporting the Liver



Resources

- *Healing Arthritis*
  - https://blumhealthmd.com/healing-arthritis-book/
- *The Immune System Recovery Plan*
  - https://blumhealthmd.com/the-immune-system-recovery-plan/
- HealMyGut Program
  - https://blumhealthmd.com/program-page/
- Simply Detox Program
  - https://blumhealthmd.com/product/21-day-simply-detox-kit/


Metagenics Institute

Links between physical fitness and brain health

Dr. Robert Silverman

Dc, DACBN, MS, CNS, CCN, CSCS, CIISN, CKTP, CES, DCBCN, HKC, FAKTR

Dr. Robert Silverman, White Plains


@drrobsilverman

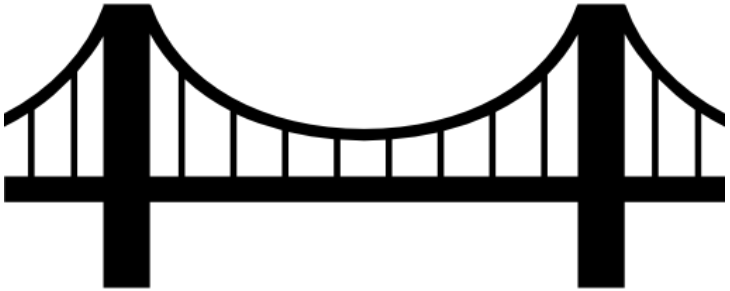

@drrobertsilverman

What you do to your **body**

You do to your **brain**

OBJECTIVE

Science



Reebok survey:

- 25,915 days in a person's lifetime
- 9 countries revealed:
  - Average human spend 0.69% of their life exercising
  - 41% spent engaging with technology
  - 29.75% of our lives spent sitting down

Lifestyle markers predict cognitive function

Conclusion: Modifiable biomarkers that impact cognitive performance favorably:

- Greater aerobic fitness and strength
- Lowering blood sugar levels
- Avoidance of tobacco
- Decreasing alcohol intake

Masley SC, Roetzheim R. *J Am Coll Nutr.* 2017;36(8):617-623

Brain health and physical activity

Study:

- 93 adults with at least one parent with Alzheimer's disease
- Had at least one gene linked to Alzheimer's or both
- Spending at least 68 minutes a day doing moderate physical activity had better glucose metabolism – signals a healthy brain
- Those who exercised had greater brain volume (areas of reasoning and executive functioning)

Dougherty RJ, Schultz SA, Kirby TK, et al. *J Alzheimers Dis.* 2017;58(4):1089-1097

Brain health and physical activity

- Older adults who score high on CRF tests display more brain activity while learning and perform better on memory tests than their less physically fit counterparts

Cortex Journal, Jan. 13, 2017

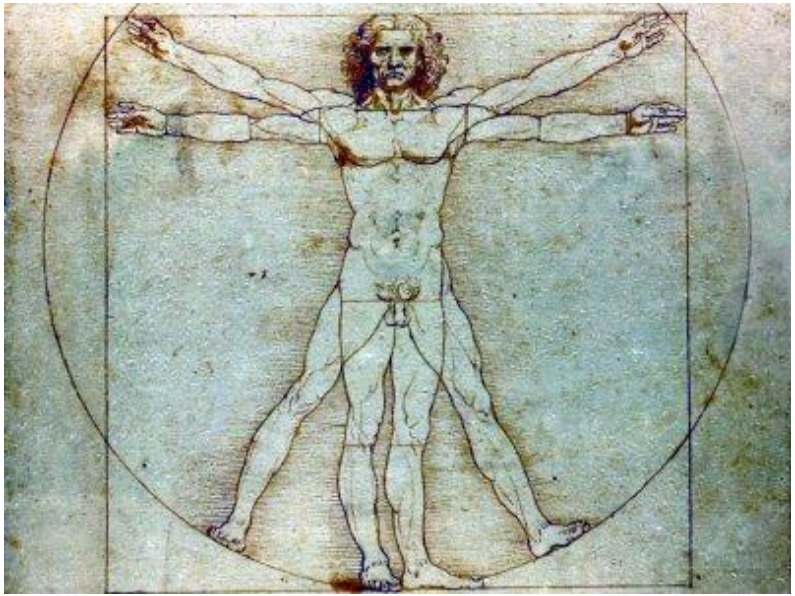
Brain health and physical activity

Summary

- Increased blood flow
- Release of BDNF
- Improved glucose and lipid metabolism
- Increased size of hippocampus
- Improves microstructures of white matter

https://www.health.harvard.edu/blog/regular-exercise-changes-brain-improve-memory-thinking-skills-201404097110 Accessed Feb 9, 2018

MENS
SANA IN
CORPORE
SANO

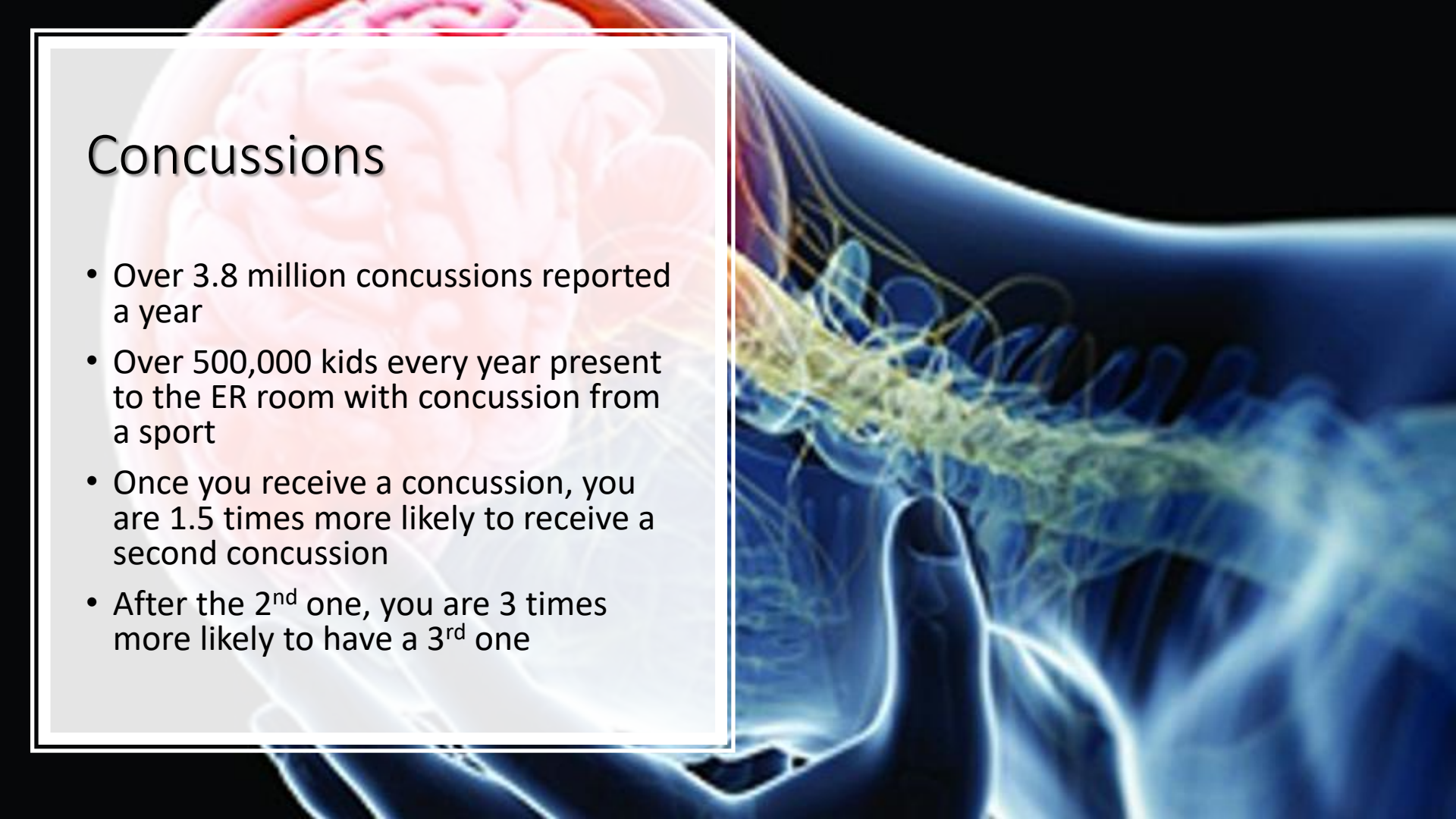


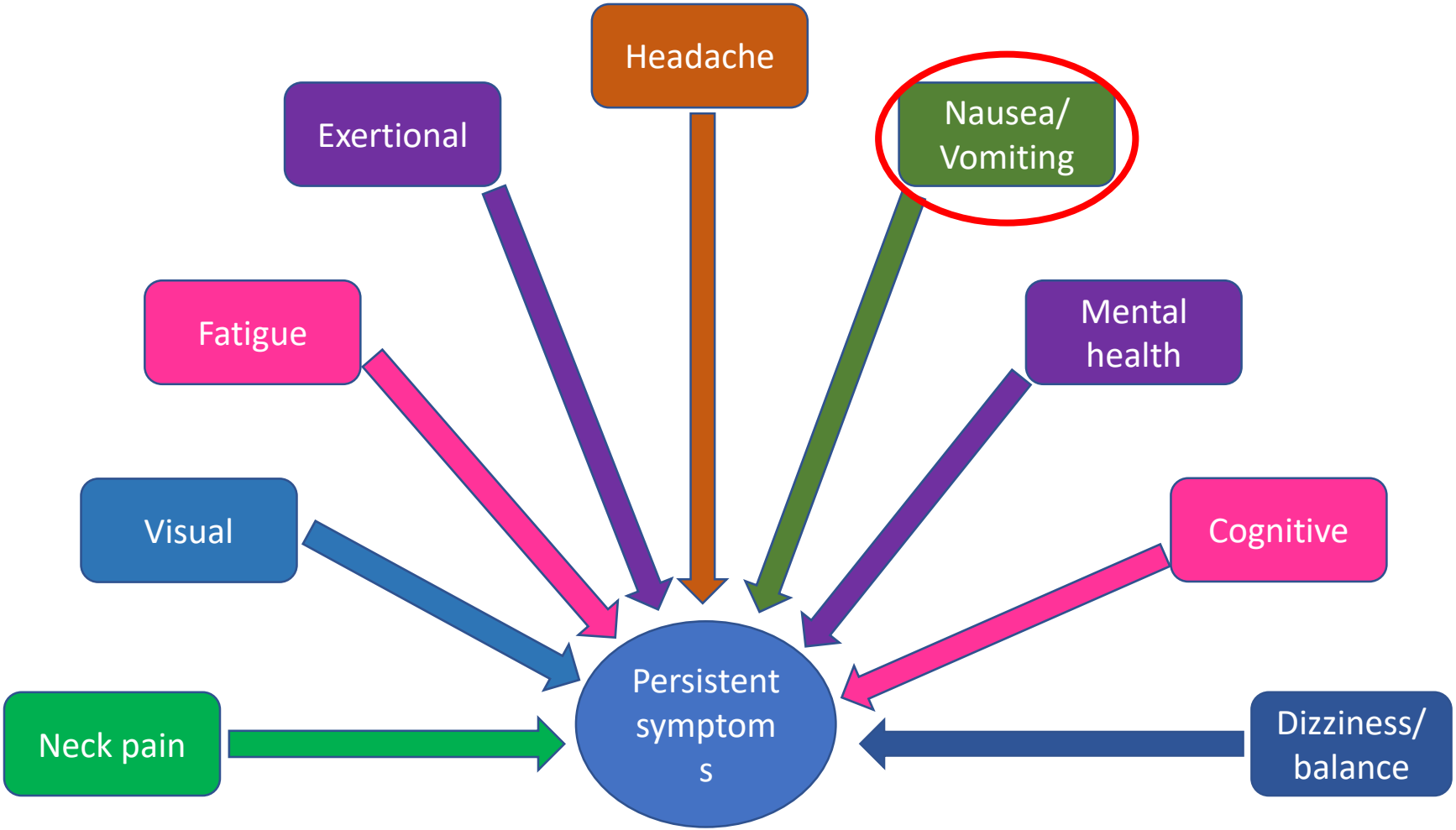
Your Brain

The Brain
is the most
nutrient
dependent,
energy
dependent and
toxin and **stress**
vulnerable organ

Concussions

- Over 3.8 million concussions reported a year
- Over 500,000 kids every year present to the ER room with concussion from a sport
- Once you receive a concussion, you are 1.5 times more likely to receive a second concussion
- After the 2nd one, you are 3 times more likely to have a 3rd one





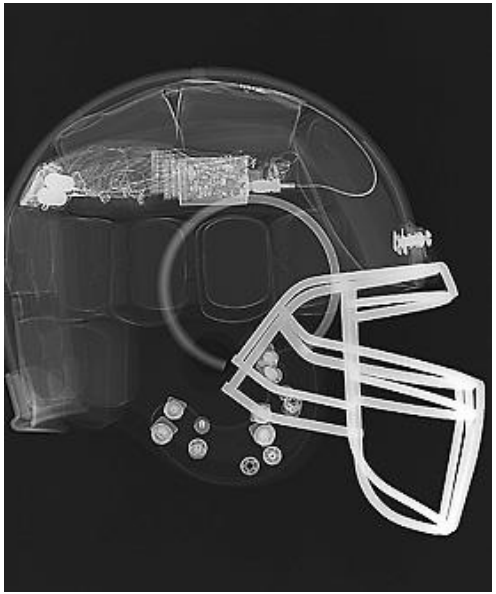
Commonly reported persistent symptoms following concussion

Concussion testing

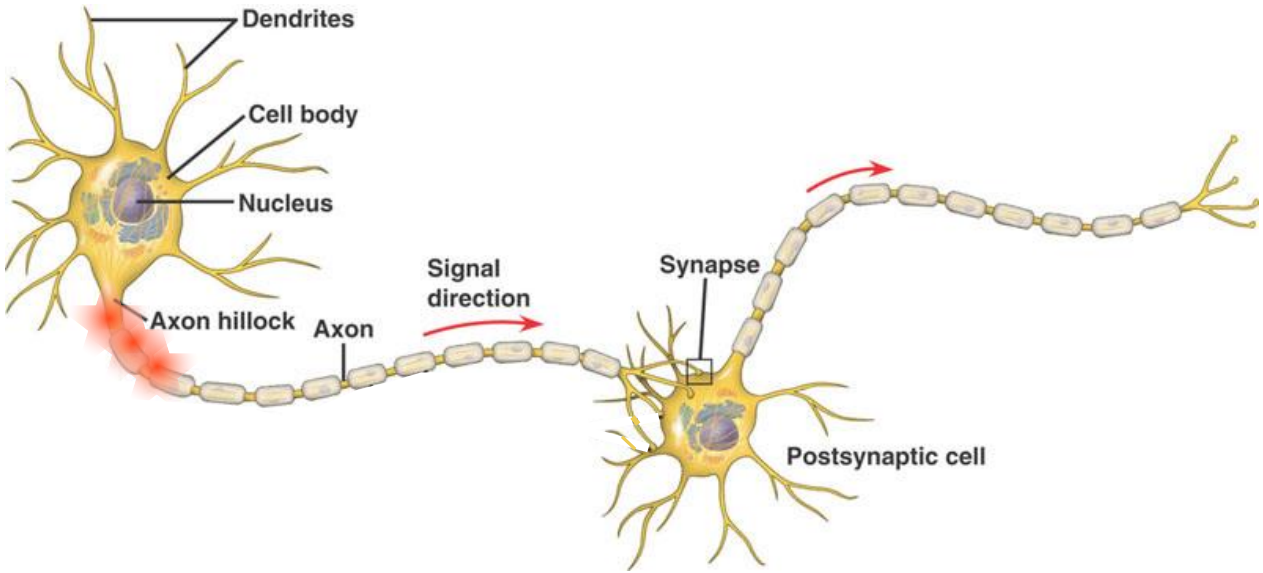
- Impact/impact pediatric
- Oculomotor nerve function may aid in concussion diagnosis *Neurology*, 2015
- King-Devick test – Mayo Clinic:
  - Accurate and objective
  - Remove-from-play sideline concussion screening test:
    - Speed of rapid number naming
    - Reading aloud – single digit
    - Detects impairments of eye movements, attention, language and overall brain function
- SCAT 3/5

Impact

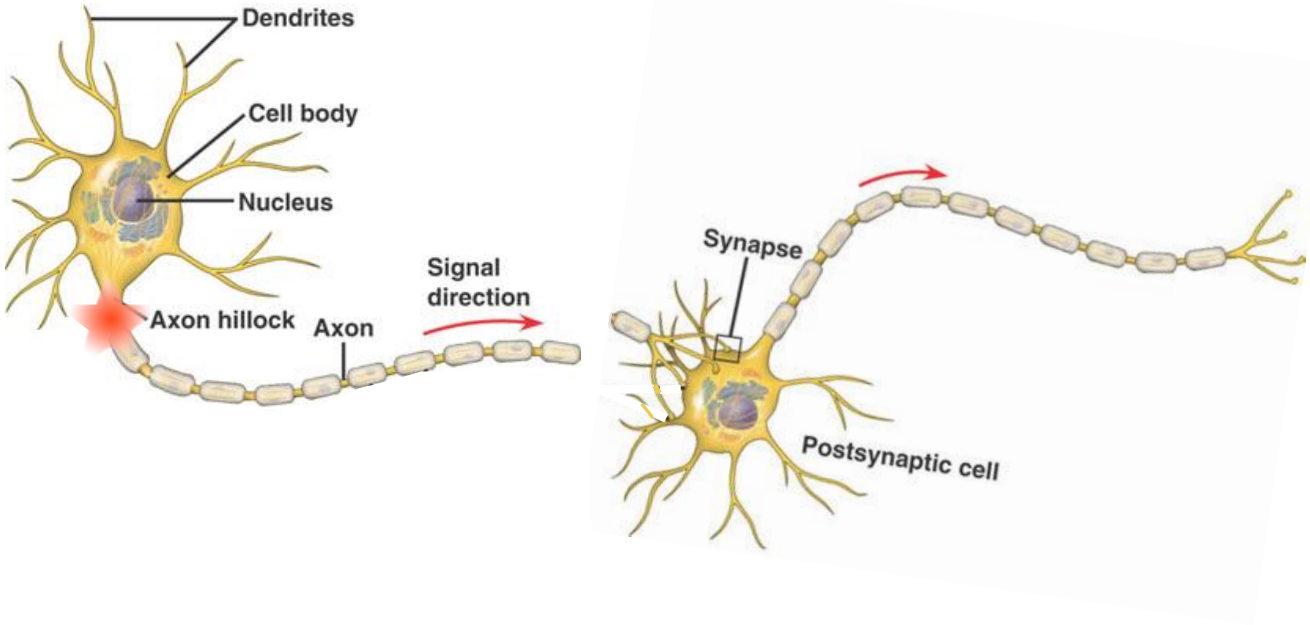
- Helmet sensors impact revealed:
  - Average HS football player takes 650 impacts, with max of more than 2,000 per football season
  - Concussion occurs at roughly 90 to 100 g-force (92 is average)
  - Equates to smashing your skull against a wall at 20 mph



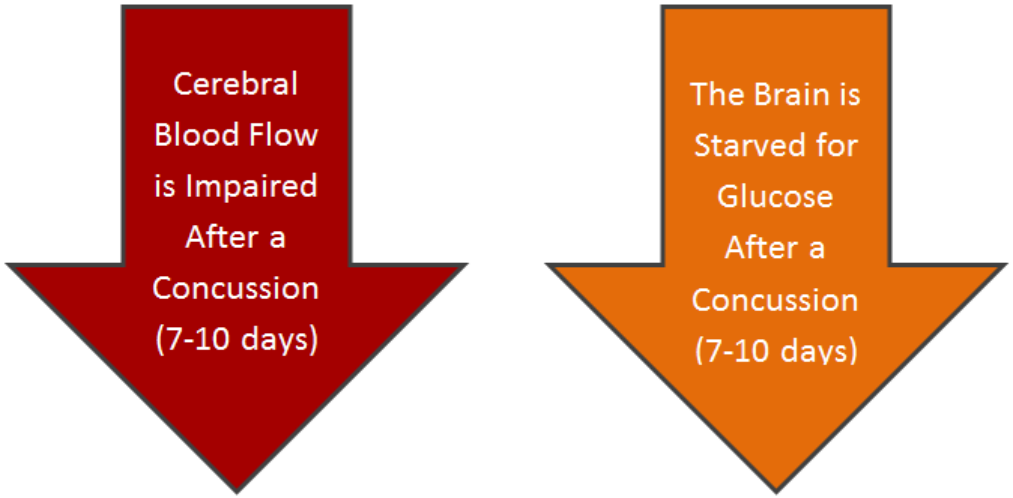
Normal Communication Between Neurons



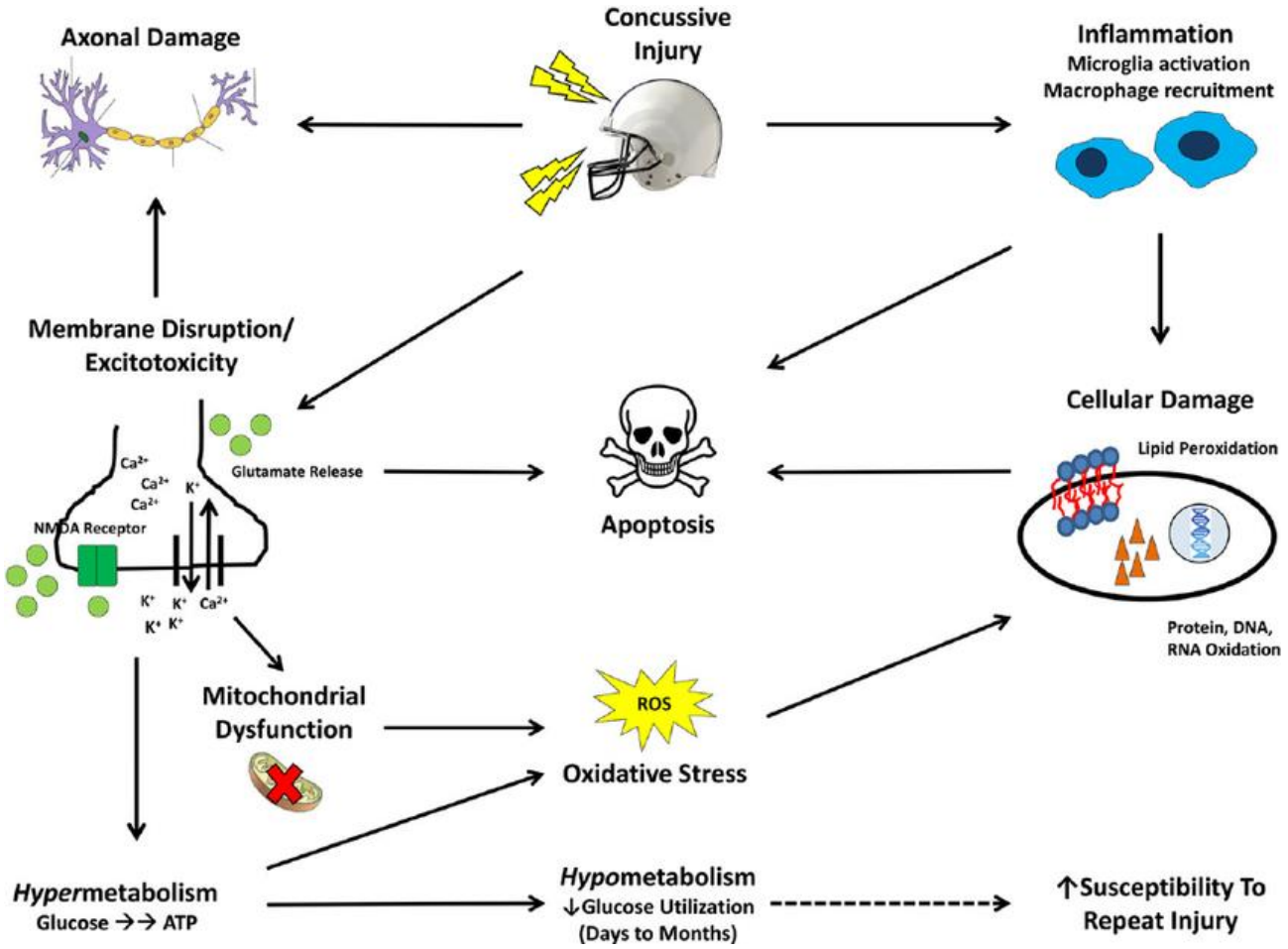
Concussion injury causes shearing (tearing) of neurons and disrupts communication



Concussion Neurometabolic Cascade



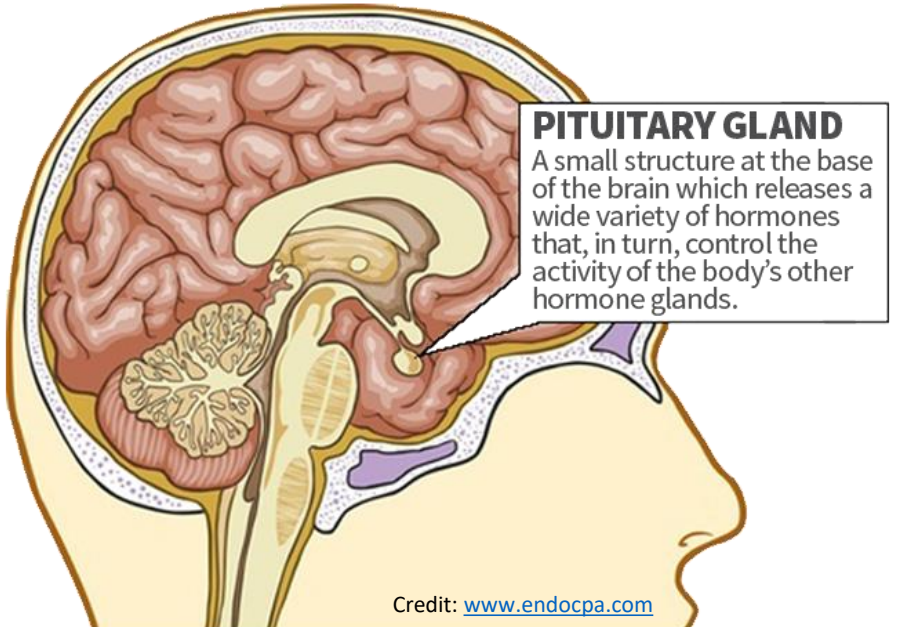
Molecular cascade of events after a mild traumatic brain injury



Barrett EC, McBurney MI. *Adv Nutr.* 2014;5(3):268-277

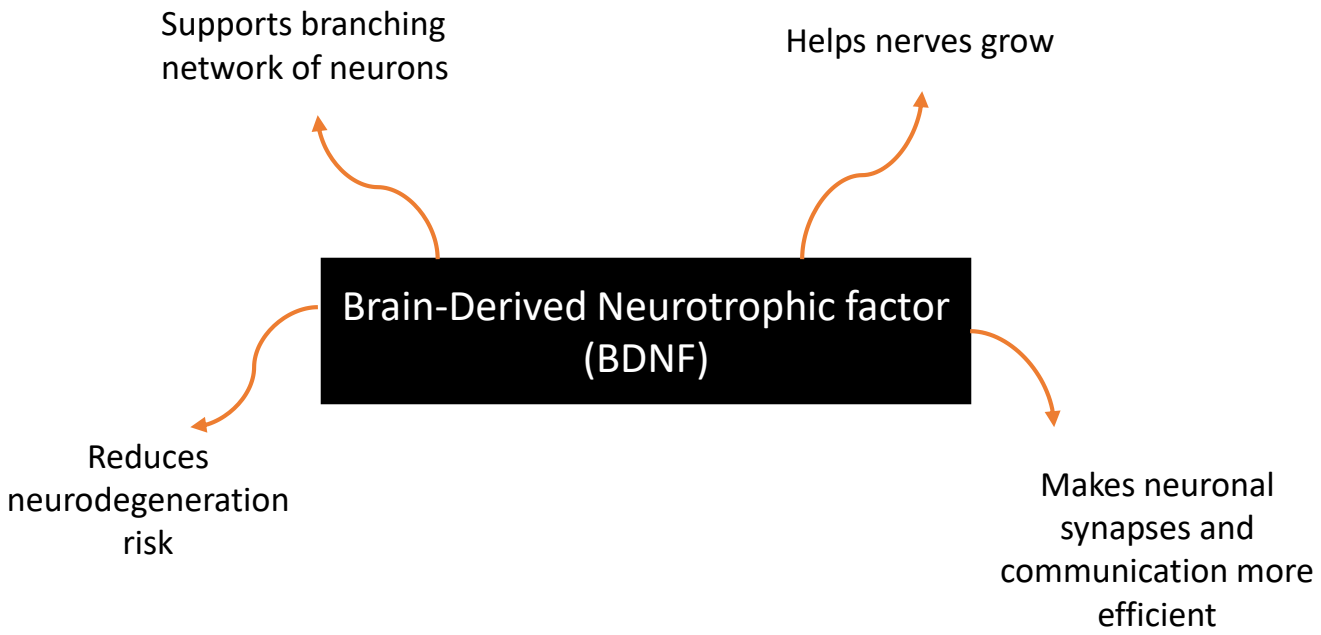
Pituitary dysfunction after concussion

- % of pituitary varies with type of concussion
- GH is most common hormone lost
- Then ACTH, Fsh and LH then TSH
- Genetic predisposition and autoimmunity have a role



Credit: www.endocpa.com

Tanriverdi F, Schneider HJ, Aimaretti G, et al. Pituitary dysfunction after traumatic brain injury: a clinical and pathophysiological approach. *Endocr Rev* 2015;36:305–42



Exercise positively impacts BDNF

Nokia MS, Lensu S, Ahtiainen JP, et al. *J Physiol.* 2016;594(7):1855-1873

Dr. Rob's Concussion Protocol

Concussion rehab

Multisystem approach:

- Musculoskeletal system
- Balance
- Gaze Stabilization
- Laser
- Nutrition support

Lifestyle recommendations – post-concussion

- Refrain from substances e.g. caffeine, alcohol, nicotine – more effects on brain than they did prior to injury
- Practice good sleep habits
- Ketogenic and/or low-carb diet
- Stay well-hydrated
- Choose healthy fats/quality proteins
- Avoid all fried foods and partially hydrogenated fats
- Avoid sugar and HFCS
- Eat gluten-free

Why post-concussion nutrition?

- Rest is not the answer
- Reduce inflammation
- Decrease chemical changes
- Affect neuronal function/provide neuroprotection
- Blood vessel and tissue repair
- Speed up recovery
- Prevent further damage

Photo credit: www.theodysseyonline.com

Ketogenic diet for concussion

- Brain craves carbohydrates
- Brain uses them for energy before breaking down fats and before breaking down protein
- Carbs aren't available
- Brain then breaks down fat instead of converting triglycerides into FA and ketone bodies
- Ketone bodies used for ATP and fuel the brain cells
- More efficient energy than glucose?

Maalouf M, Rho JM, Mattson MP. The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies. *Brain Res. Rev*. 2009;59:293–315

Samoilova, M., M. Weisspapir, P. Abdelmalik, A. A. Velumian, and P. L. Carlen. 2010. Chronic in vitro ketosis is neuroprotective but not anti-convulsant. *Journal of Neurochemistry* 113(4):826–835

Ketogenic diet for concussion (cont'd)

- Ketones found to prevent neuron cell death
- Helps ATP depletion, reactive oxygen species production and inflammation
- More effective in children since younger brains are better at transporting and utilizing ketone bodies
- A lot of fat decreases the level of triglycerides and LDL while increasing HDL

Maalouf M, Rho JM, Mattson MP. The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies. *Brain Res. Rev*. 2009;59:293–315

Samoilova, M., M. Weisspapir, P. Abdelmalik, A. A. Velumian, and P. L. Carlen. 2010. Chronic in vitro ketosis is neuroprotective but not anti-convulsant. *Journal of Neurochemistry* 113(4):826–835

Concussion Nutrition Protocol

Feed the concussion

1) **Protein:** helps heal the injury. Take 1g/kg of body weight
2) **Creatine:** gives the brain an intense/immediate energy to heal cells
3) **Reduce inflammatory damage** to brain DHA, boswellia, quercetin, ginger, turmeric, resveratrol, grapeseed extract
4) **Antioxidants:** alpha-lipoic acid
5) **Specialized Pro-Resolving Mediators (SPMs):** resolution of inflammation
6) **Choline:** critical for brain development

Slutsky I, et al. Enhancement of learning and memory by elevating brain magnesium. *Neuron*, 2010 Jan 28;65(2):165-77
Duguid IC, Smart TG. Presynaptic NMDA Receptors. In: Van Dongen AM, editor. Biology of the NMDA Receptor. Boca Raton (FL): CRC Press/Taylor & Francis; 2009. Chapter 14. Available from: https://www.ncbi.nlm.nih.gov/books/NBK5275/
Gomez-Pinilla F. The effects of nutrients or brain function. *Nat Rev Neuroscience*, 2008 Jul;9(7):568-78. doi: 10.1038/nrn2421

Concussion Nutrition Protocol (cont'd)

Feed the concussion

7) **Vitamin D:** neuroprotective
8) **Zinc:** enzyme for CNS
9) **Sulforaphane:** inhibits MMP-9 and activates NRF2
10) **Magnesium:** great weapon against delayed brain injury
11) **Acetyl-L-carnitine:** energizes the brain
12) **Glutathione:** body's #1 intracellular antioxidant
13) **Coffee fruit extract:** increases BDNF

Slutsky I, et al. Enhancement of learning and memory by elevating brain magnesium. *Neuron*, 2010 Jan 28;65(2):165-77
Duguid IC, Smart TG. Presynaptic NMDA Receptors. In: Van Dongen AM, editor. Biology of the NMDA Receptor. Boca Raton (FL): CRC Press/Taylor & Francis; 2009. Chapter 14. Available from: https://www.ncbi.nlm.nih.gov/books/NBK5275/
Gomez-Pinilla F. The effects of nutrients or brain function. *Nat Rev Neuroscience*, 2008 Jul;9(7):568-78. doi: 10.1038/nrn2421

Creatine

- Maintain function of the mitochondria
- Improves blood flow in the brain improves both short and long term symptoms
- Short term:
  - Post TBI – concussion – creatine shown to reduce the duration of post-concussion amnesia

Rubenstein C. *Nutritional Perspectives: Journal of the Council on Nutrition of the American Chiropractic Association.* 2016;39(3):21-22

Long-chain omega-3 fatty acids (LC-n3-FA) improve brain function and structure in older adults

- LC-n3-FA exert positive effects on brain functions
- They exerted beneficial effects on:
  - White matter integrity
  - Grey matter volume in frontal temporal, parietal and limbic areas
  - Increased BDNF
  - Decreased peripheral fasting insulin

Witte AV, Kerti L, Hermmannstadter HM, et al. *Cereb Cortex.* 2014;24(11):3059-3068

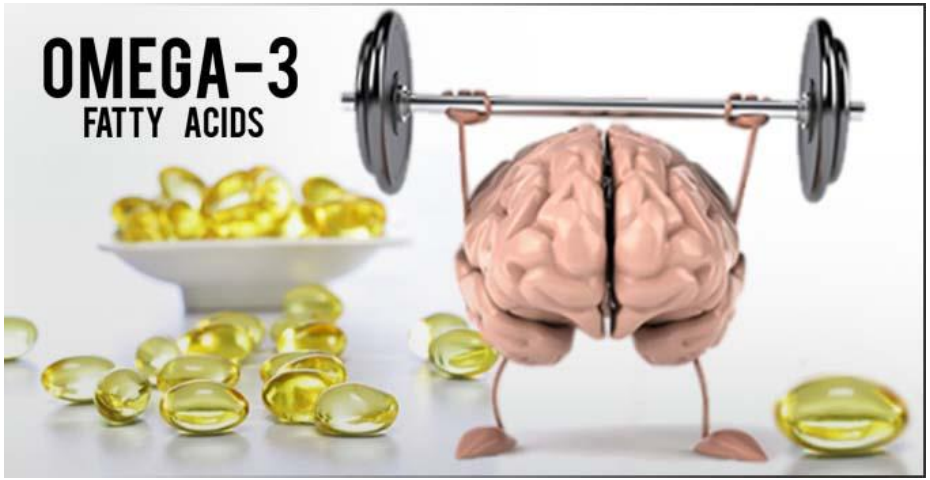
DHA for TBI

- Ten published preclinical trials
- DHA supplementation reduces:
  - Axonal and neuronal damage
  - Inflammation
  - Apoptosis
  - Oxidative stress
  - Cognitive impairment
  - Neurotransmitter decline

ClinicalTrials.gov NCT01903525

High levels of omega-3 for concussion

- Aggressive intake of omega-3 fatty acids benefit TBI, concussion, and post-concussion syndrome patients



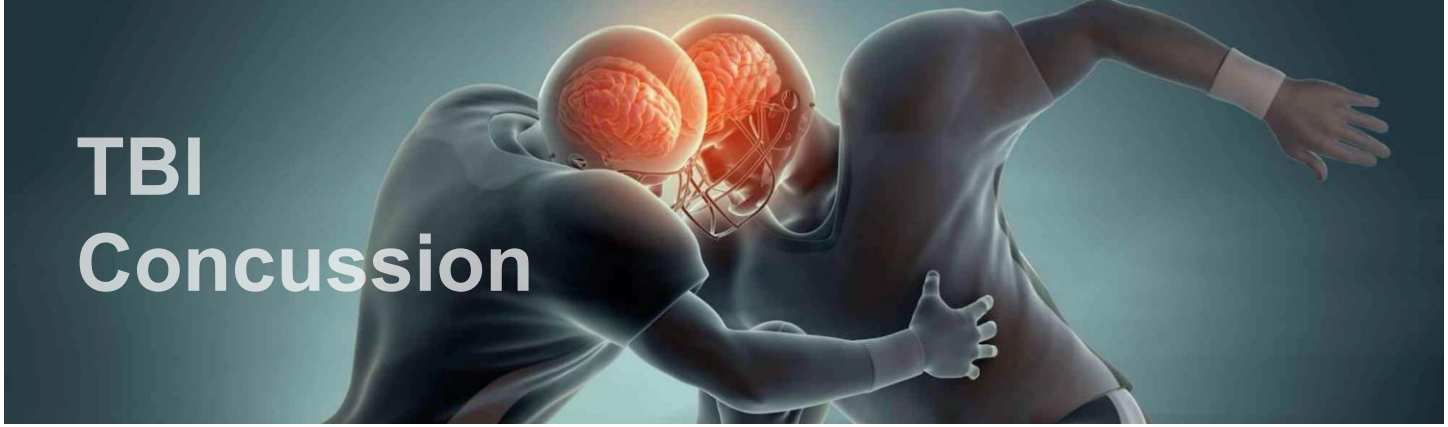
Michael DL. Concussions of brain injury – can omega-3 intake aid in brain health recovery. *J of the Am Col of Nutri*, 2016;35(5):469-75

Reversing brain damage in former NFL players

- Fish oil – 5.6 g. per day
- High potency multi-vitamin
- Nutrients for blood flow:
  - Ginkgo, acetyl-L-carnitine
  - Antioxidants (NAC + alpha lipoic acid)
- 6-month trial
- Results: Increased brain perfusion – prefrontal cortex, parietal occipital lobes and cerebellum

Conclusion: Study demonstrates that cognitive and cerebral blood flow possible

Amen DG, Wu JC, et al. *J Psychoactive Drugs*, 2011 Jan-Mar;43(1):1-5



High EPA & DHA blood levels could reduce the oxidative stress developed in brain due to TBI/concussion

The role of Omega-3s in the neuronal growth and maintenance is well documented. Omega-3 intake could lessen the secondary effects of the trauma in brain. Omega-3 fatty acids (FAs) could reduce the oxidative stress developed in brain due to TBI. The inclusion of omega-3 FA in diet could normalize the levels of brain-derived neurotrophic factor (BDNF), and thus, it could restore the survival of neuronal cells.

Kumar et al. Journal of Traditional & Complementry Med. 2014 Apr-Jun; 4(2): 89–92.

Increased DHA levels inhibit neuronal cell death and is an important neuroprotective agent

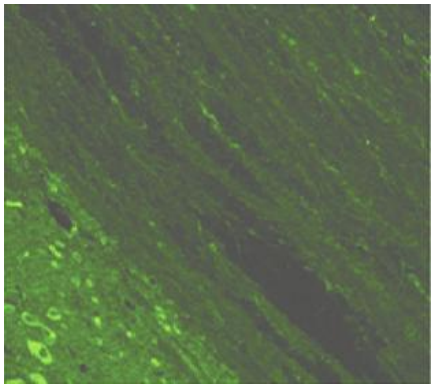
DHA is incorporated into the phospholipids in neuronal membranes, which in turn can influence not only the membrane chemical and physical properties but also the cell signaling involved in neuronal survival. Our studies have indicated that DHA supplementation inhibits neuronal cell death under challenged conditions, supporting a notion that DHA is an important neuroprotective agent.

Prostaglandins Leukot Essent Fatty Acids. 2010 Apr-Jun; 82(4-6): 165–172.

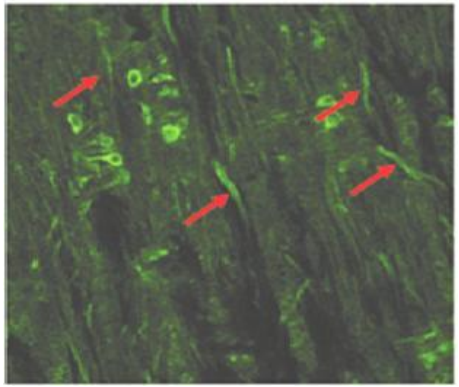
Photo credit: urbanhealthmedia.org

Fish Oil and TBI

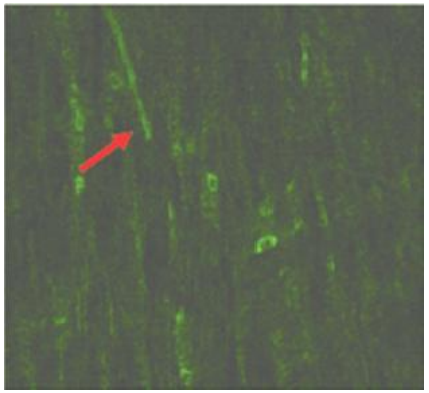
- Studies in rats have shown that supplementation with DHA for 30 days before or after TBI reduced damaged brain cells to levels seen in uninjured animals [17,18]



Brain pre-injury



Brain 30 days post-injury with no DHA supplement



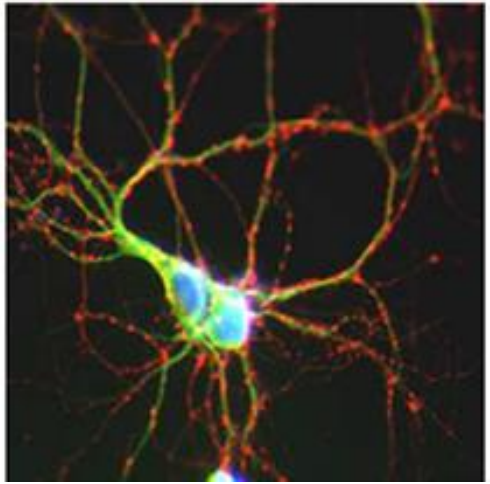
Brain 30 days post-injury with DHA supplement

→ Damaged areas

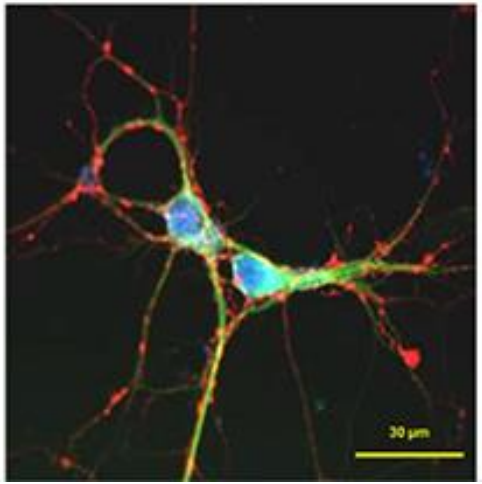
Neuro-Resilience: Increased connections between neurons can improve function despite injury

(The more connections, the more resilient)

Omega-3s are required for production of BDNF (Brain Derived Neurotrophic Factor), which supports the survival of existing neurons and encourages the growth of new neurons and synapses

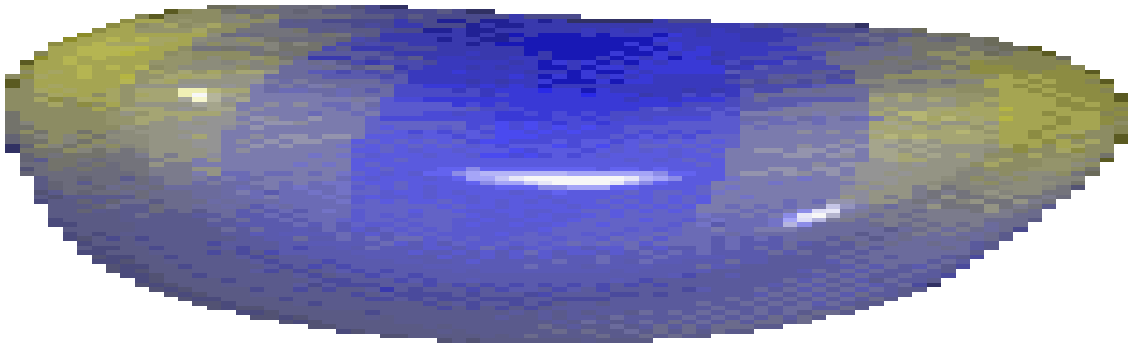


Optimal Omega-3 Index

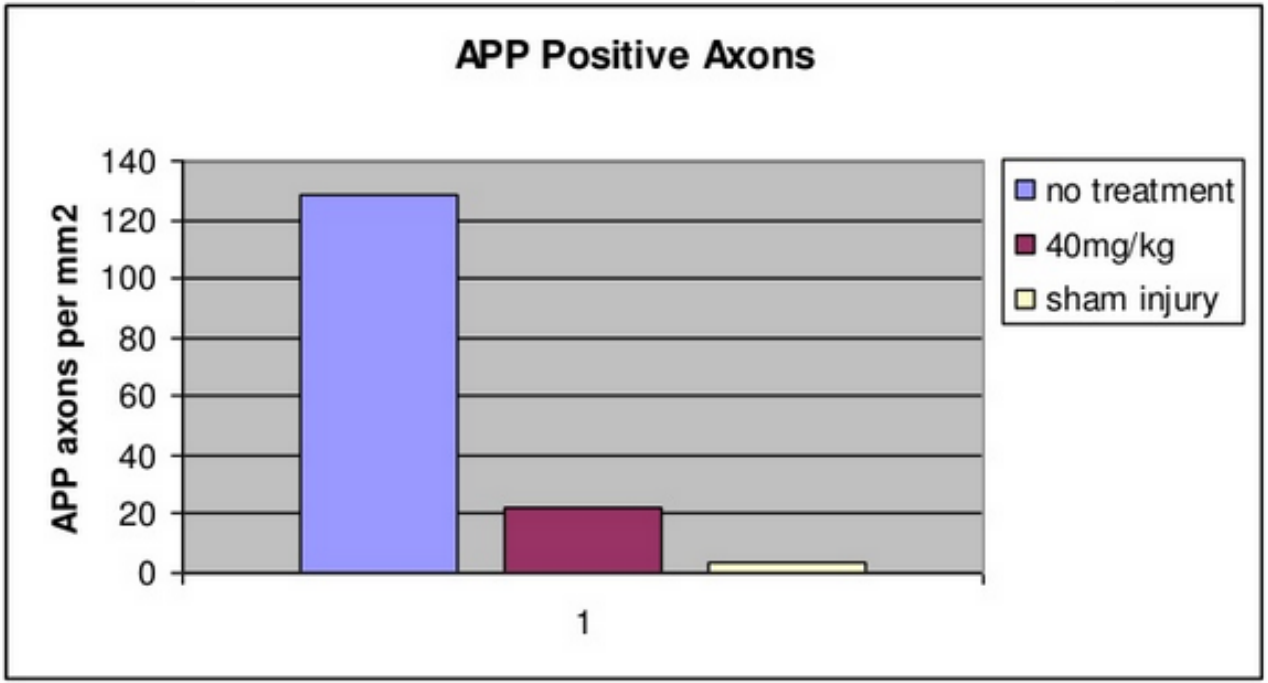


Deficient Omega-3 Index

Lipids provide the softness and elasticity of cells, which confers a more functional membrane, and a cell that is more resilient to blast/physical trauma

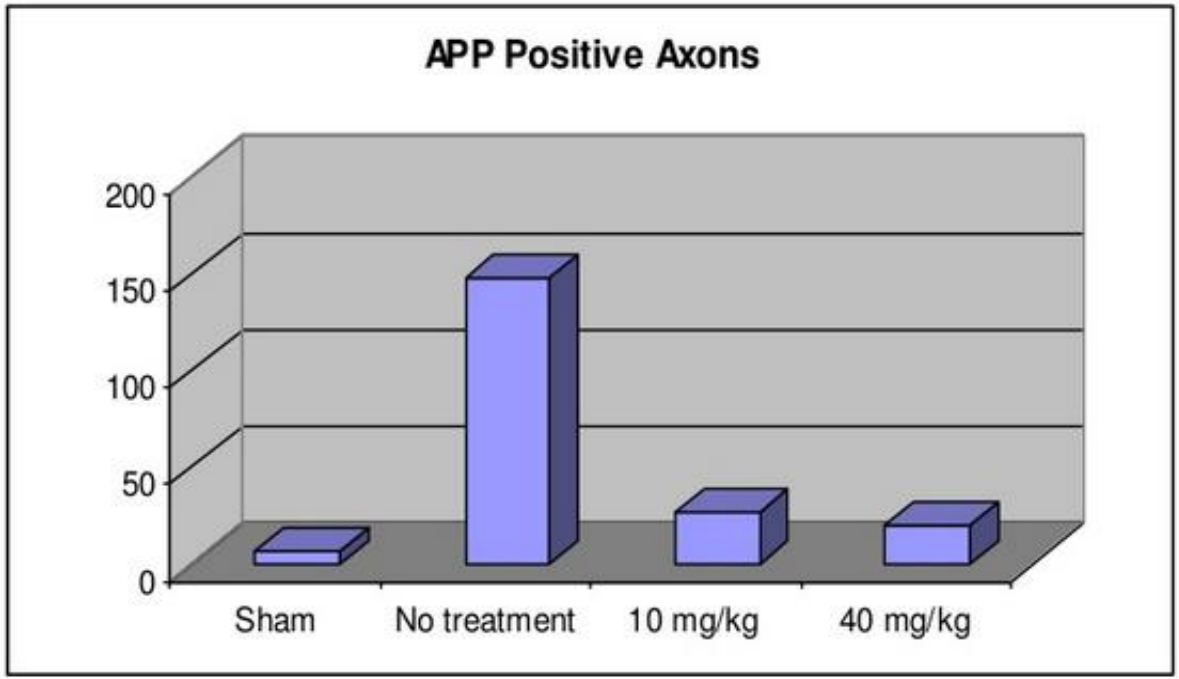


DHA Pre-Injury Treatment



Damaged axons measured after injury with omega-3 EPA/DHA.
Pre-injury greatly reduces concussion effects

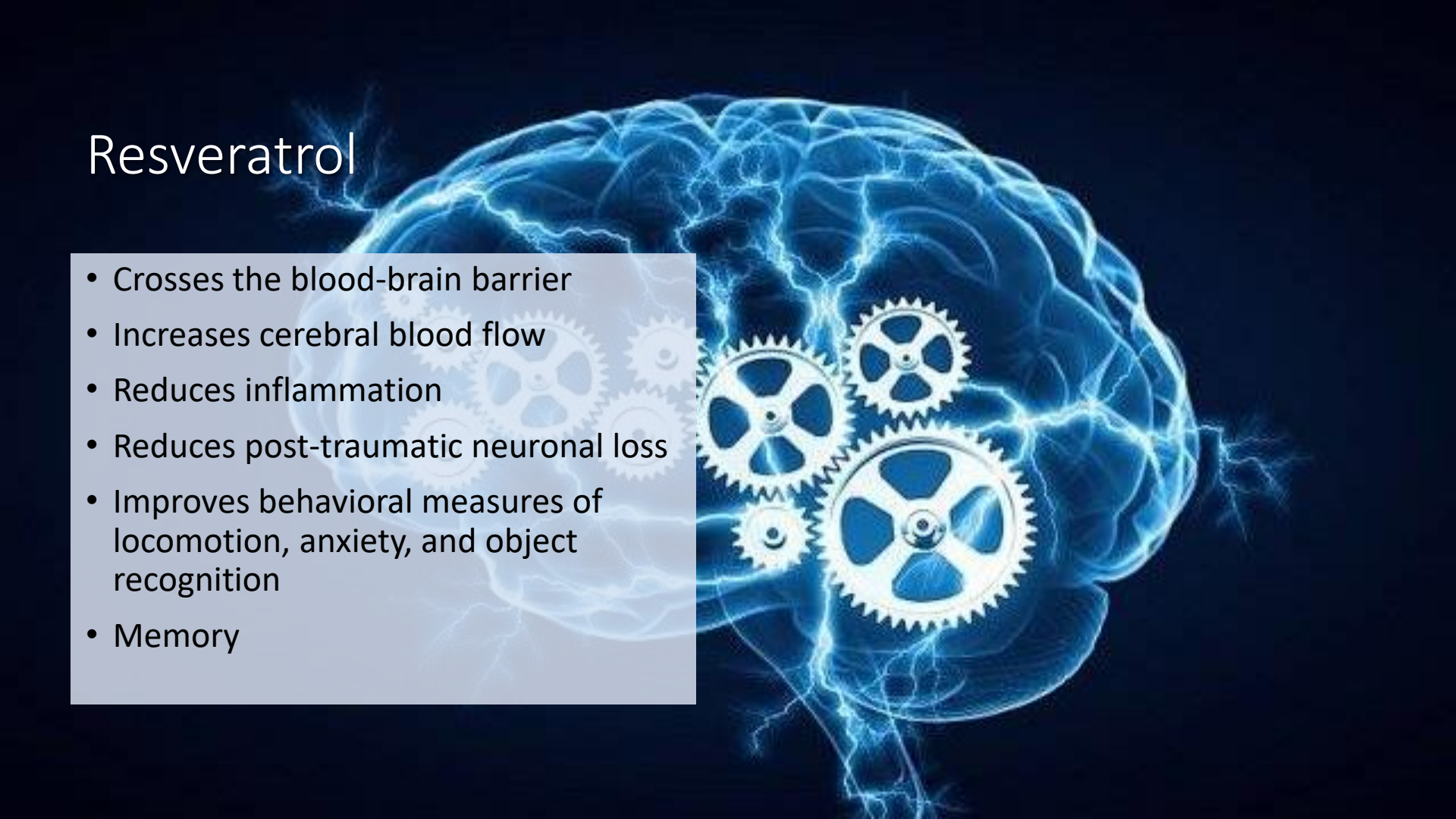
DHA Post-Injury Treatment



Damaged axons measured after injury with omega-3 EPA/DHA POST-injury:
also reduces concussion effects but less so

Resveratrol

- Crosses the blood-brain barrier
- Increases cerebral blood flow
- Reduces inflammation
- Reduces post-traumatic neuronal loss
- Improves behavioral measures of locomotion, anxiety, and object recognition
- Memory



Boswellia

- Objectives: To establish whether Boswellia serrata (BS) could improve outcome of patients who have diffuse axonal injury (DAI)
- 38 patients with pure DAI enrolled in this 12-week, double-blind, randomized, cross-over study
- Both group experienced close-to-significant increase in cognitive function during periods on BS

Conclusion: Enhances cognitive outcome of patients with DAI

Moein P, Abbasi Fard S, Asnaashari A, et al. *Brain Inj.* 2013;27(12):1454-1460

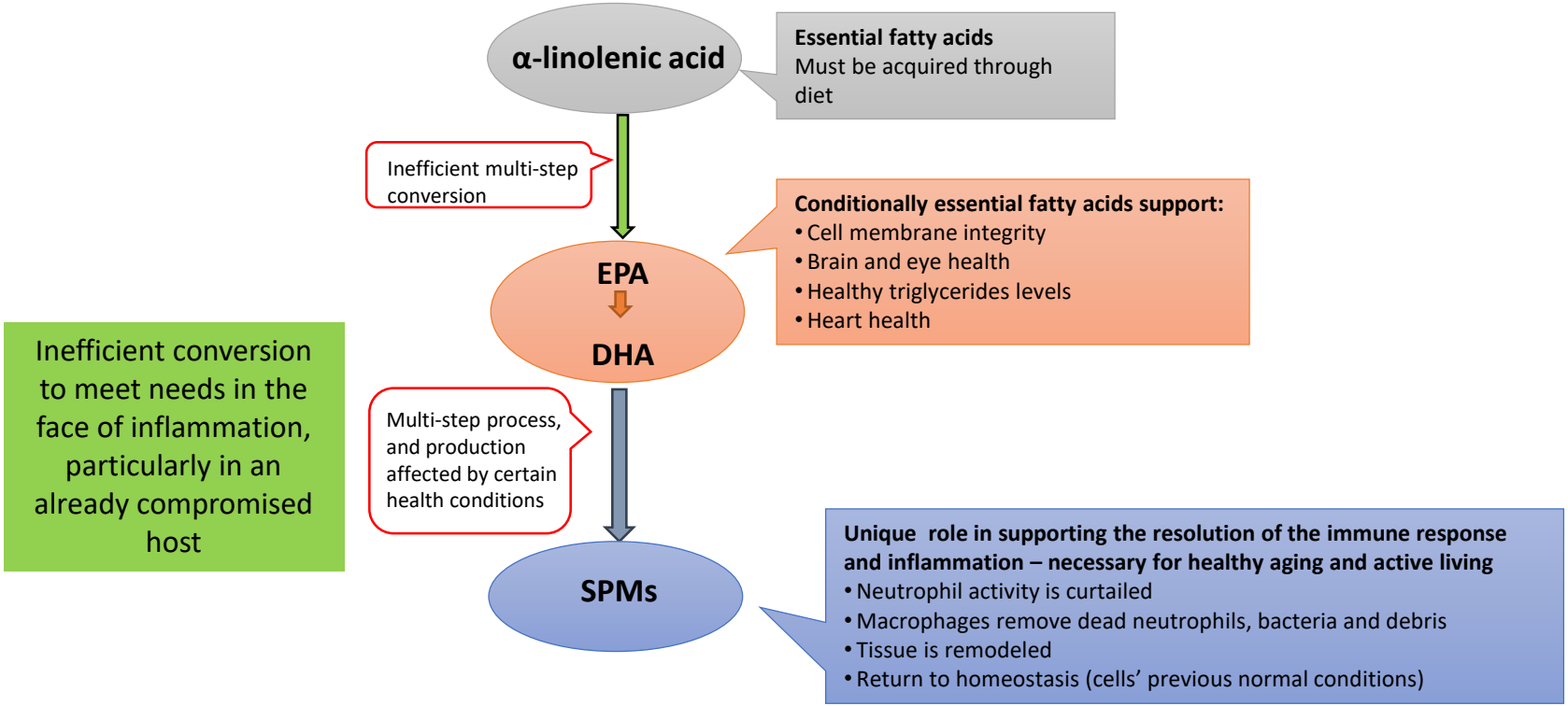
Curcumin

- Systemic anti-inflammatory and raises BDNF
- Treats central nervous system injury and inflammation and subarachnoid hemorrhage and TBI
- Improves patient outcome by reducing acute activation of microglia/macrophages and neuronal apoptosis Adapted from *Journal of Neuroinflammation*, 2014
- Study presented in the *Experimental Neurology Journal* 2016 revealed that curcumin counteracted the outcome of traumatic brain on oxidative stress, synaptic simplicity and cognition

Alpha lipoic acid

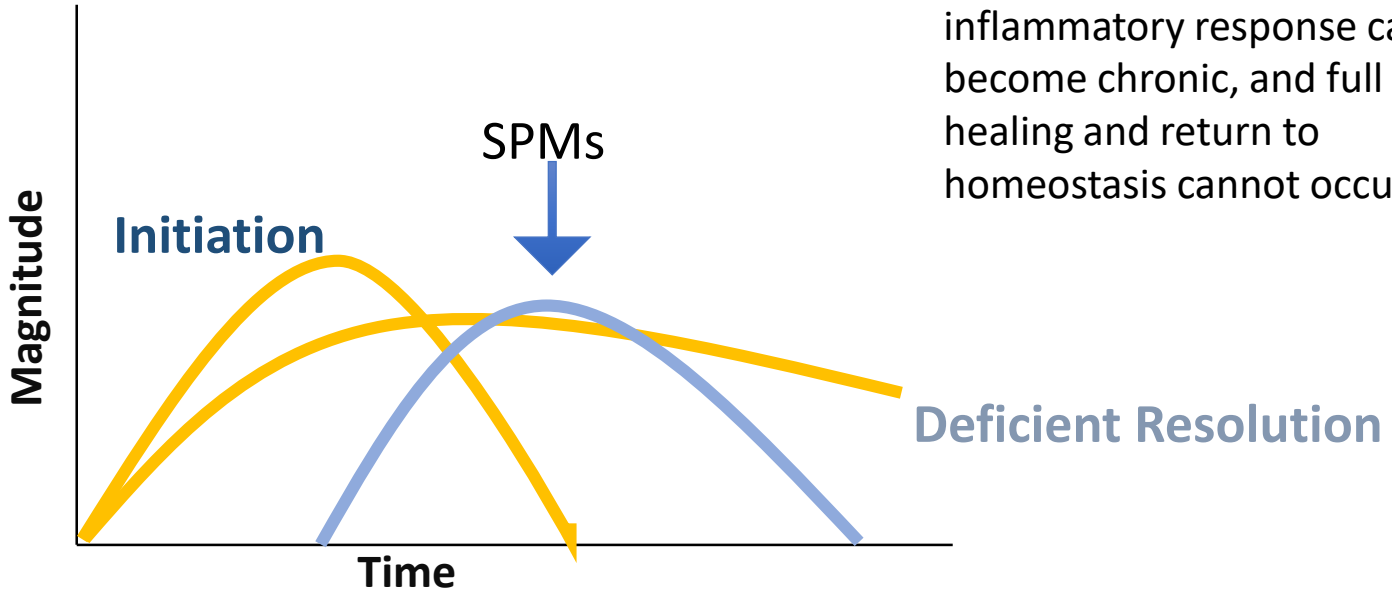
- Lowers oxidative stress at the BBB
- Protects against free radical damage
- Improves insulin sensitivity and lowers blood sugar
- Chelates metals
- Improved endothelial function
- Lowers blood pressure
- Decreased dementia risk
- Improves the lipid profile
- Activates AMPK, Nrf2, and SIRT1 while inhibiting NF-KB/

Specialized Pro-Resolving Mediators (SPMs)



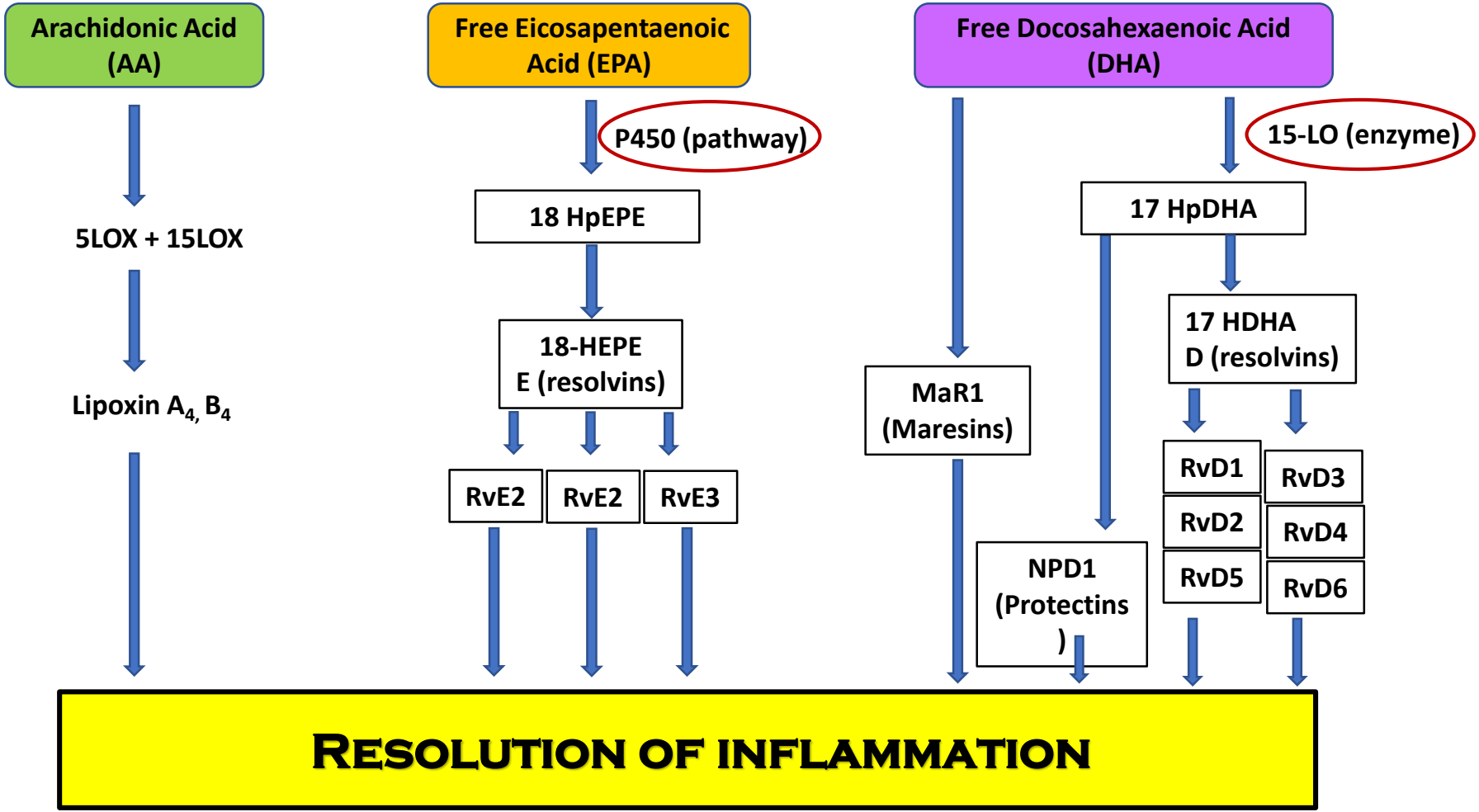
Serhan CN. *Nature*. 2014;510(7503):92-101

SPMs act to *resolve* inflammation. Without resolution, even a reduced inflammatory response can become chronic, and full healing and return to homeostasis cannot occur



Balance between **initiation** and **resolution** is critical

Serhan CN. *Nature*. 2014;510(7503):92-101
Spite M, Claria J, Serhan CN. *Cell Metab.* 2014 Jan 7;19(1):21-36


Arachidonic Acid (AA)
5LOX + 15LOX
Lipoxin A_4, B_4
Free Eicosapentaenoic Acid (EPA)
P450 (pathway)
18 HpEPE
18-HEPE
E (resolvins)
RvE2
RvE2
RvE3
Free Docosahexaenoic Acid (DHA)
15-LO (enzyme)
17 HpDHA
17 HDHA
D (resolvins)
MaR1 (Maresins)
NPD1 (Protectins)
RvD1
RvD2
RvD3
RvD4
RvD5
RvD6
RESOLUTION OF INFLAMMATION

Lipid mediators of inflammation in neurological injury: Shifting the balance toward resolution

- Pathophysiology of TBI includes arachidonic acid derived lipid mediators driving inflammation conditions that promote activation of microglia and infiltration of neutrophils through BBB
- Specialized Pro-Resolving Mediators (SPMs) represent shift from inflammation-driving to inflammation-resolving conditions in CNS via repairing the BBB

Harrison JL, Rowe RK. *Neural Regen Res.* 2016;11(1):77-78

Specialized Pro-Resolving Mediators (SPMs)

- Resolvin D3 multi-level pro-resolving actions are most protective during infection
- D3 mediators produced by resolving exudates stimulates clearance of neutrophils and leukocyte attenuates pro-inflammatory signals
- RVD3 was identified in self resolving exudates during active E.coli infection
- Additionally – reduction of cytokines, chemokines, MMP2 and **MMP9**

Norris PC, Arnardottir H, et al. *Prostaglandins Leukot Essent Fatty Acids*. Jan 22, 2016 pii: S0952-3278(15)30052-1. doi: 10.1016/j.plefa.2016.01.001

Glycerophosphocholine (GPS)

- A form of choline shown to protect and repair damaged brain cells
- **Study revealed:** 23 patients who suffered concussions were given GPC for 3 month period. 26 percent of patients' mental faculties significantly improved

PM Kidd. GPC (GlyceroPhosphoCholine), *Ortho-Nutraceutical For Active Living and Healthy Aging* January 2004

Mandat T, et al. A preliminary evaluation of risk and efficacy of early choline alphoscerate treatment in craniocerebral injury. *NeurolNeurochir Pol*; 2003;37:1231-1238

Concussion – Vitamin D

- Down regulates inflammatory cytokines (NF-kB)
- Promotes production of heat shock protein (HSP)
- HSP:
  - Helps maintain integrity of neurons
  - Has anti-inflammatory effects
  - Decreases cerebral edema
  - Supports brain cell survival after brain injury

Hua F, Reiss JI, Tang H, et al. Progesterone and low-dose vitamin D hormone treatment enhances sparing of memory following traumatic brain injury. *Horm Behav* 2012 Apr;61(4):642-51

Zinc

- Needed for over 300 enzymes and aids in DNA synthesis, cell division and protein synthesis for tissue regeneration and repair
- Deficiency = poor wound healing and increased oxidative stress
- Increases resilience to TBI

Elevate Brain Magnesium (L-threonate)

- L-threonate **drives magnesium into the cerebrospinal fluid and then into neurons.** This leads to multiple changes, including **enhanced synaptic density and plasticity**, as supported by human clinical study
- These effects are unique to L-threonate, as other common Mg(2+) forms failed to have the same results
- Improvement shown in spatial memory and orientation

Sun Q, Weinger JG, et al. Regulation of structural and functional synapse density by L-threonate through modulation of intraneuronal magnesium concentration. *Neuropharmacology,* 2016 Sep;108:426-39

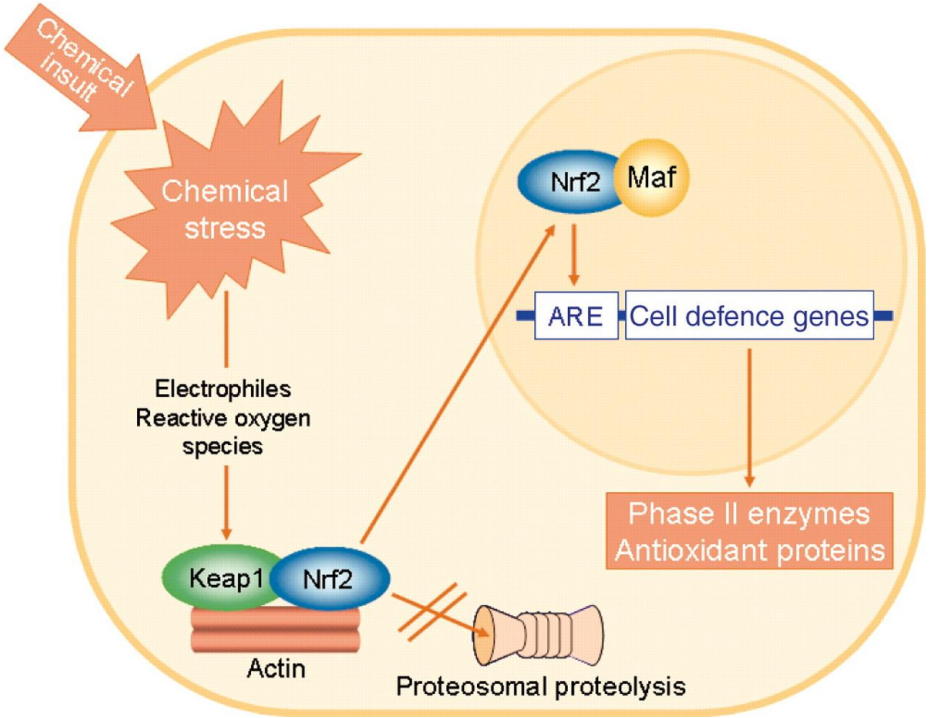
Mg L-Threonate (cont'd)

Alzheimer's Disease

- Prevents loss of synapses and decline of memory
- Helps prevent and clear accumulation of toxic beta amyloid plaques
- Supplementation suppressed the expression of the enzyme responsible for amyloid deposits by 80%

Li W, Yu J, Liu Y, et al. *Mol Brain*, 2014 Sep 13;7:65
Yu X, Guan PP, Guo JW, et al. *FASEB J*. 2015 Dec;29(12):5044-58

NRF2 on Cellular Antioxidants and Detoxification



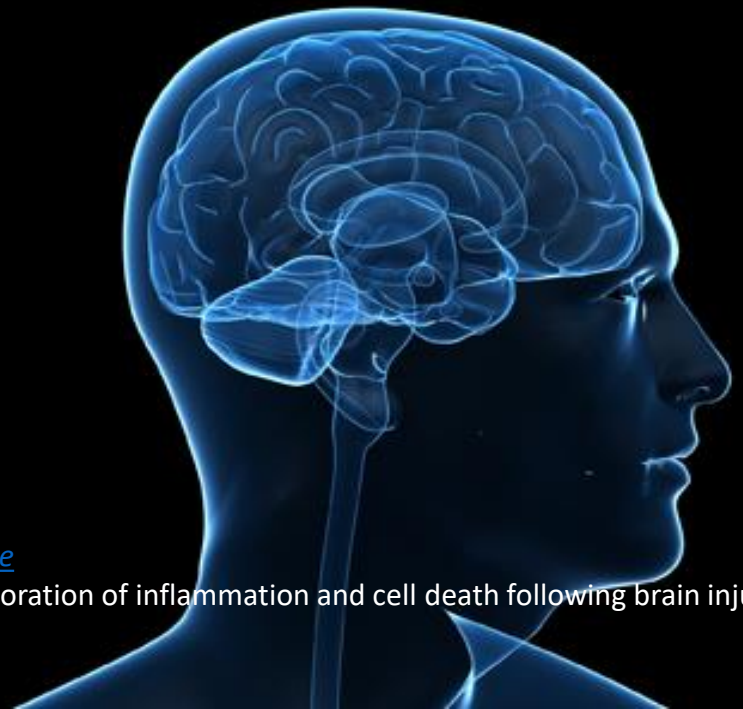
There are no drugs that up-regulate NRF2 but there are several natural ingredients which do

Photo credit:
http://jeb.biologists.org/content/209/12/2337

Acetyl L-carnitine

- Energizes the brain
- Increases levels of important neurotransmitter chemicals needed for memory, focus, and learning
- Repairs the damage done to brain cells caused by stress and poor nutrition
- Relieves depression
- Speeds stroke recovery
- Slows Alzheimer’s
- Helps damaged nerves and diabetic neuropathy

Using glutathione reduced brain tissue damage by an average of 70%



https://www.si.com/2014/04/17/mouse-concussions-nfl-cte

Theodore LR, Debasis N, Tatjana A, et al. Transcranial amelioration of inflammation and cell death following brain injury. *Nature.* 2014 Jan 9;505(7482):223-28

New kid on the block

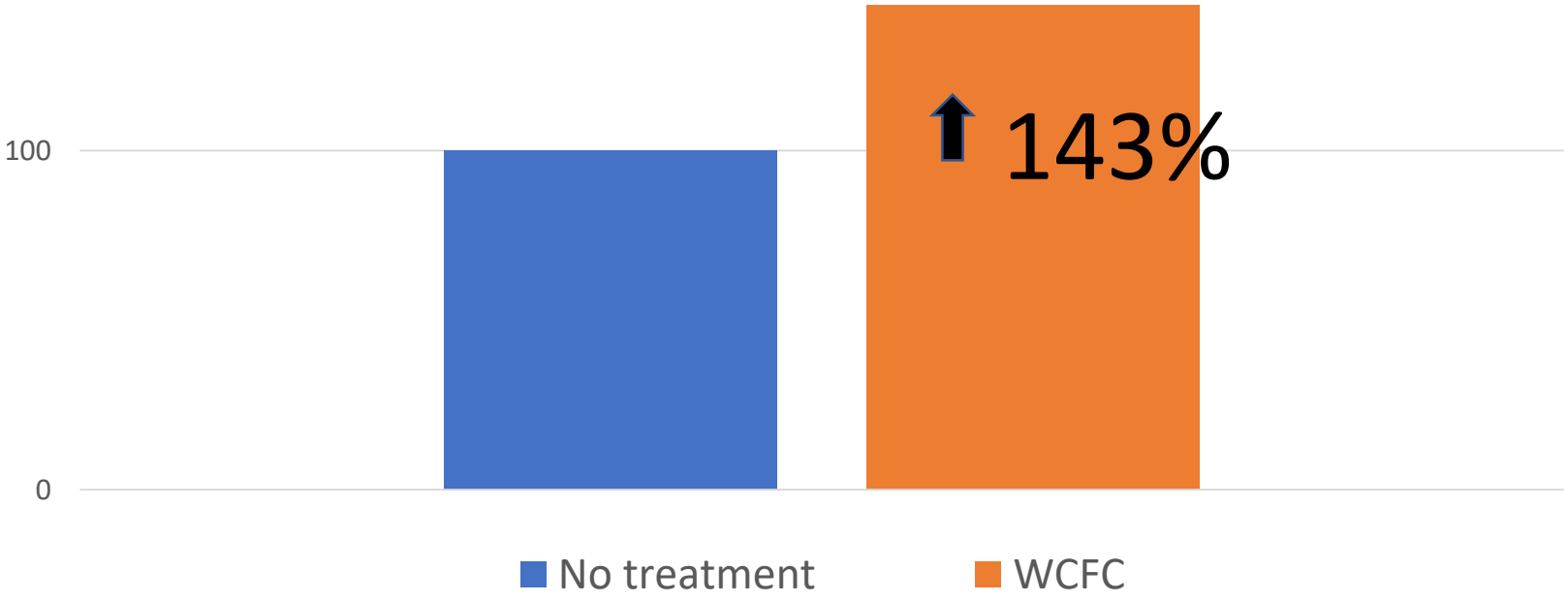
- Coffee fruit extract:
  - Contains very little caffeine
  - Increases BDNF

Modulatory effect of coffee fruit extract on plasma levels of brain-derived neurotropic factor in healthy subjects

- 25 randomized subjects
- No treatment, placebo (silica dioxide), grape seed extract, green coffee bean extract or whole coffee fruit extract (100 mg)
- BDNF time 0, then every 30 mins for 120 mins

Reyes-Izquierdo T, NemzerB, Shu C, et al. *Br J Nutri*. 2013 Aug 28;110(3):420-25

BDNF (% change over initial) at 120 min



Reyes-Izquierdo T, NemzerB, Shu C, et al. *Br J Nutri*. 2013 Aug 28;110(3):420-5

What enhances BDNF

- Exercise
- Turmeric
- Whole coffee extract
- DHA
- Alpha-lipoic acid
- Lactobacillus brevis, Bifidobacterium longum
- Ketones
- Prebiotics

Women's Brains May Have Tougher Time Recovering From Concussion

- Female athletes suffer concussions at higher rate than male athletes playing similar sports
- Women have weaker muscles in the neck – a factor in how head injuries affect them
- "Withdrawal hypothesis": If woman suffers a concussion in the premenstrual phase when progesterone levels are naturally high, an abrupt drop in progesterone after injury produces a kind of withdrawal – either contributes to or worsens post concussive symptoms like headache, nausea, dizziness and trouble concentrating

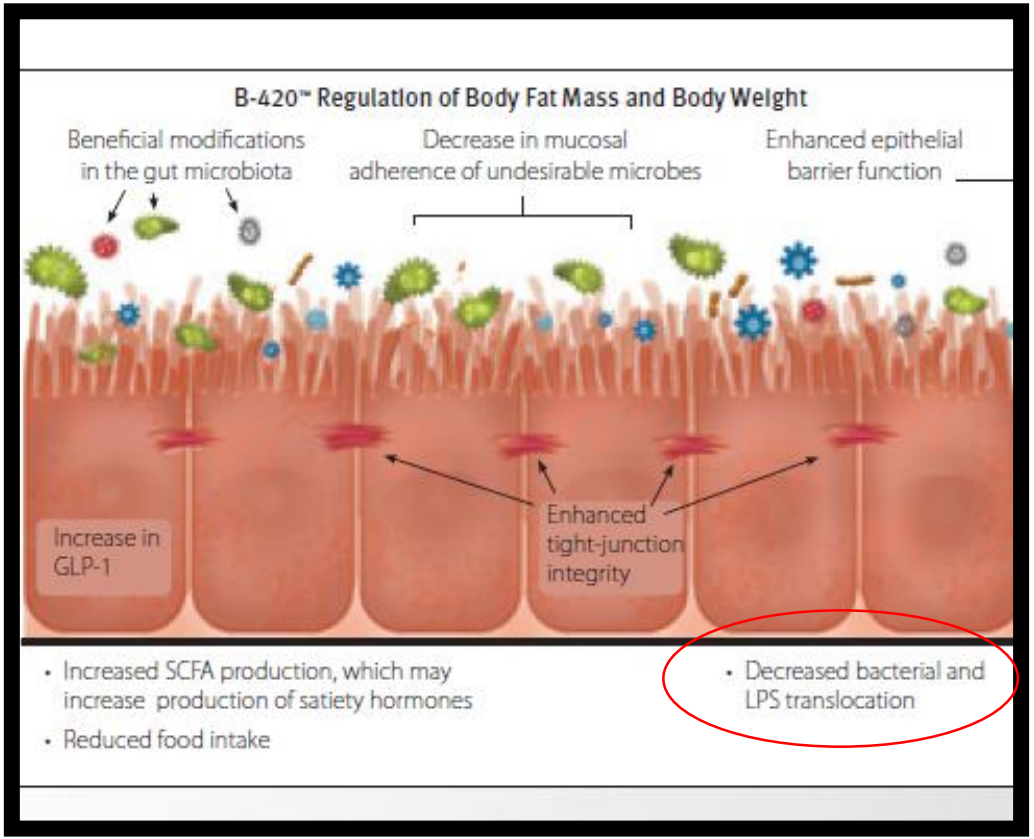
Adapted: Broglio S, Ellemberg D. Apr 28, 2015, *Radiology* online
Journal of Head Trauma Rehabilitation Dec. 2010, p.2255-60, *J of Head Trauma Rehab* Nov. 13, 2013

Acute concussion protocols (2 weeks)

- **Quality diet:** If on keto/low-carb diet – continue. No gluten/diary
  - **Exogenous ketone salts (BHB):** 11.7 g.
  - **Keto meal replacement/MCT oil**
- **Creatine:** 20 g. for 14 days
- **Omega-3 FA:** 6 g. TID for 1 week; 3 g. BID for week 2
- **Alpha-lipoic acid:** 1200 mg daily
- **Specialized Pro-Solving Mediators (SPMs)**
- **Vitamin D3:** 10,000 IU daily
- **Mag L-threonate:** 2 g. daily
- **Turmeric:** 1,000 mg daily

Acute Concussion Start 6R program

- **Berberine**
- **Bifidobacterium animalis ssp lactis 420**
- **Sulforaphane**

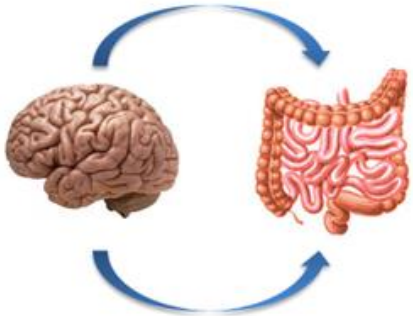


On-going concussion – Week 3 onwards

- **Omega-3 FA:** continued 6 g. for 2 weeks; 3 g. after first month
- **Mag L-threonate:** 2 g. daily
- **Herbs: turmeric, boswellia, quercetin, ginger, grapeseed**
- **Specialized Pro-Solving Mediators (SPMs)**
- **Vitamin D:** 5,000 IU
- **Glutathione:** 500 mg. Daily
- **Alpha-lipoic acid:** 600 mg

6R program

- **Powdered nutritional support** for inflammation and GI support
- **Bifidobacterium animalis ssp lactis 420**



Chronic long-lasting – 6 months onwards

- **Mag L-threonate:** 2 g. daily
- **Herbs: curcumin, hops, ginger formula:** support amyloid plaque removal and neural brain inflammation reduction
- **Multivitamin/mineral with phytonutrients:** supports neuron synapse growth and repaid
- **EPA/DHA:** 2,400 mg up to TID
- **Specialized Pro-Solving Mediators (SPMs)**
- **Alpha-lipoic-acid:** 600 mg daily

6R program: 1 “R” at a time

Decrease incidence of concussion

Super 5:

- Multivitamin/mineral with phytonutrients
- Omega-3 FA
- Vitamin D
- Probiotic
- Mag L-threonate

Detox: Fall and Spring cleaning

Diminished Brain Resilience Syndrome

- **Modern environment:** Toxicant exposure, nutrient-deficient foods, unhealthy omega 3:6 ratio in diet
- **Altered physiology:** Disruption of gut flora/liver function/CYP enzymes
- **Diminished brain resilience:** Nutrient functional deficiencies, reduced protection against impact damage
- **Neurological pathology:** Increased susceptibility to concussion, reduced ability to heal spontaneously from uncomplicated single concussion

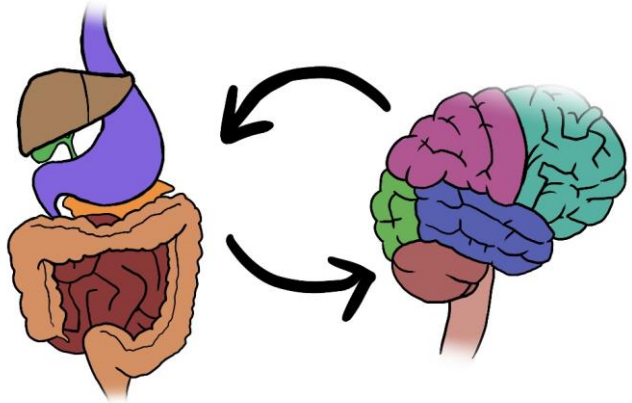
Morley WA, Seneff S. *Surg Neurol Int.* 2014;5:97

Food for Thought

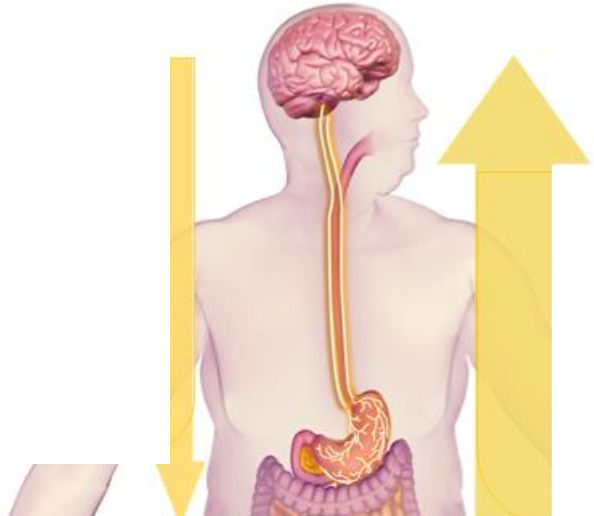
Traumatic brain injury leads to intestinal dysfunction and breakdown.

Why? The surprising answer:

The vagus nerve – the great wanderer

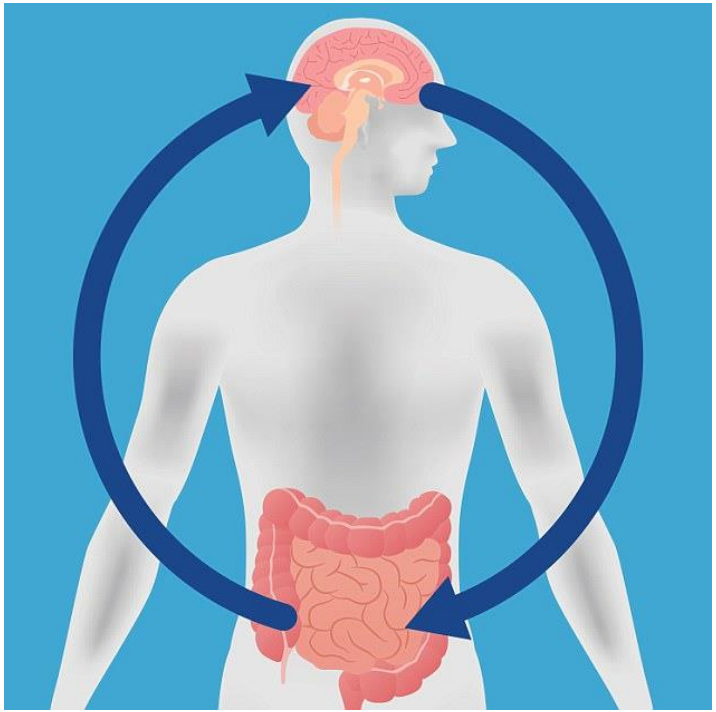


THE GUT-BRAIN CONNECTION



Head injury profoundly affects gut microbiota homeostasis

- Majority of HI patients develop infectious complications
- Head injury profoundly modified gut microbiota composition
- Gut dysbiosis could contribute to infection in head trauma patients



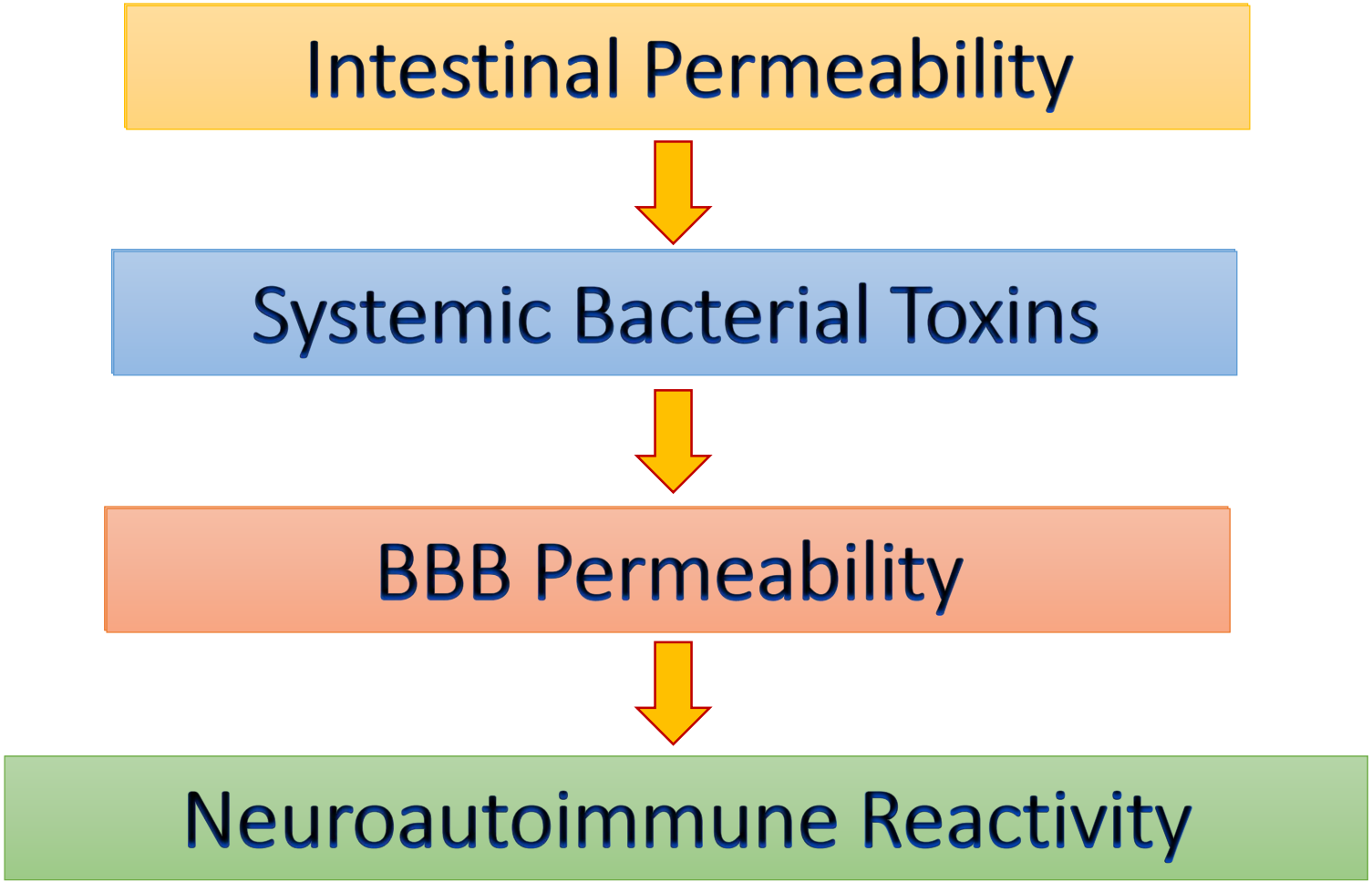
Waligora-Dupriet AJ, Lafleur S, Charrueau C, et al. *Nutrition.* 2018;45:104-107

Traumatic brain injury and intestinal dysfunction: Uncovering the neuro-enteric-axis

- Researchers from Brown University showed – irreversible damage occurs in brain cells about 6 hours after trauma
  Eyal BK, Mark TS, et al. *Scientific Reports*, 2016;6:30550

- An increase in intestinal permeability and marked changes in intestinal histology 6 hr. following TBI (Zonulin and occludin)
  Journal of Neurotrauma, 28:1353-1359, Aug 2009

- TBI can induce significant damages of gut structure and barrier function with 3 hours following brain injury (LPS)
  Chun HH, Ji XS, at al. *World J Gastroenterology* 2003 Dec 15;9(12):2276-81


Intestinal Permeability
Systemic Bacterial Toxins
BBB Permeability
Neuroautoimmune Reactivity

Spit test helps reveal concussion severity

- Researchers measured levels of microRNAs in saliva of concussion patients
- Presence of certain MRNAs in saliva able to better *identify* concussions and more *accurately* predict length of concussion symptoms
- MicroRNAs able to predict whether symptoms would last beyond 4 weeks with 85% accuracy
- SCAT-3 – 64% accurate
- Patient's report of symptoms – 55% accurate

William PM III, Rebekah M. *JAMA Pediatr.* 2018;172(1):14-15

FDA clears first blood test to aid in concussion diagnosis

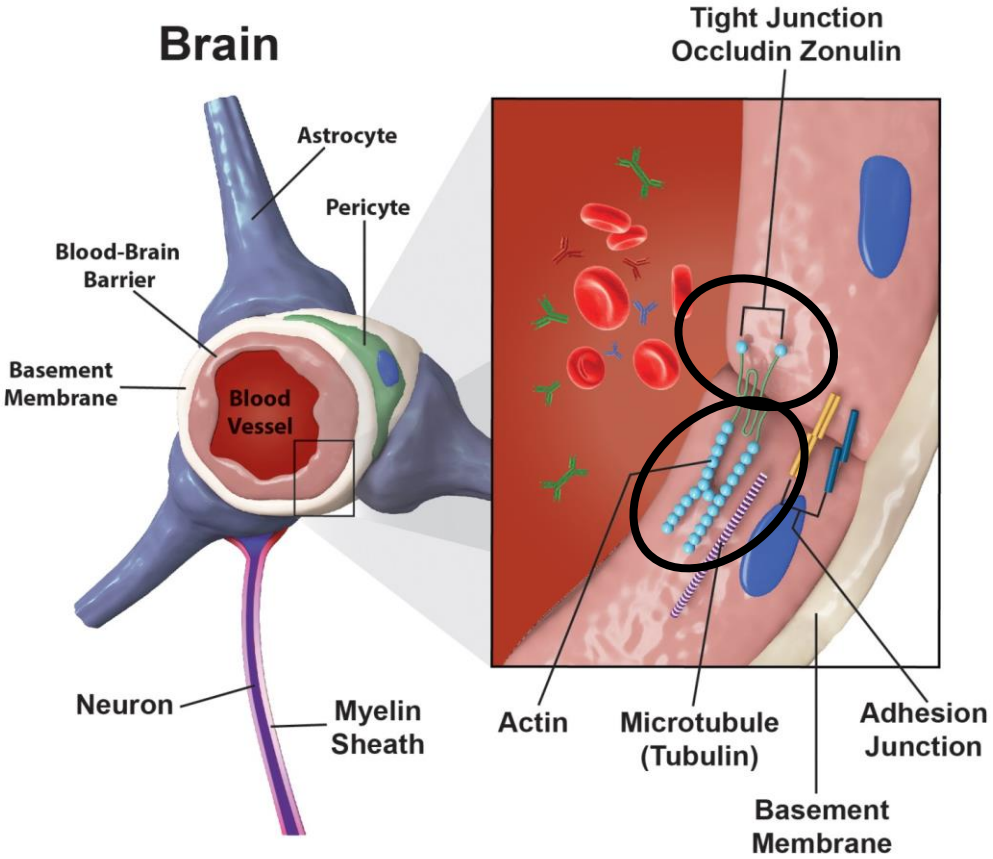
- Banyan *Brain Trauma Indicator* measures:
  - Ubiquitin C-terminal hydrolase
  - Glial fibrillary acidic protein
- Proteins released from brain into blood and measured within 12 hours of head injury
- Blood test 97.5% predict presence of intracranial lesions on CT scan
- Identified 99.6% absence of lesions
- 1947 individuals sampled

MedScape. Feb 14, 2018

Cleveland Clinic – biomarkers – brain damage

- Professional fighters brain health study:
  - Increase in protein tau showed a 7% decrease in thalamus size
  - Neurofilament light (NFL) chain proved to be 40% higher in active fighters compared with retired
  - Both are released into blood stream when nerve fibers in brain suffer damage

Charles Bernick, MD, from the Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Nevada, presented the study in a poster session July 14 at the American Academy of Neurology (AAN) 2017 Sports Concussion Conference in Jacksonville, Florida.



- Autoantibodies made against gut barrier proteins can also attack BBB proteins
- BBB Proteins:
  - IgG + IgA
  - IgM

BBB Functional

TEST	RESULT			
Array 20 - Blood Brain Barrier Permeability Screen	**IN RANGE (Normal)**	**EQUIVOCAL***	**OUT OF RANGE**	**REFERENCE** (ELISA Index)
Blood Brain Barrier Protein IgG+IgA	0.71			0.3-2.2
Blood Brain Barrier Protein IgM	0.97			0.3-2.2

Recent Onset BBB Damage

TEST	RESULT			
Array 20 - Blood Brain Barrier Permeability Screen	**IN RANGE (Normal)**	**EQUIVOCAL***	**OUT OF RANGE**	**REFERENCE** (ELISA Index)
Blood Brain Barrier Protein IgG+IgA	1.45			0.3-2.2
Blood Brain Barrier Protein IgM			2.36	0.3-2.2

On-Going BBB Damage

TEST	RESULT			
Array 20 - Blood Brain Barrier Permeability Screen	**IN RANGE (Normal)**	**EQUIVOCAL***	**OUT OF RANGE**	**REFERENCE** (ELISA Index)
Blood Brain Barrier Protein IgG+IgA			2.26	0.3-2.2
Blood Brain Barrier Protein IgM	0.91			0.3-2.2

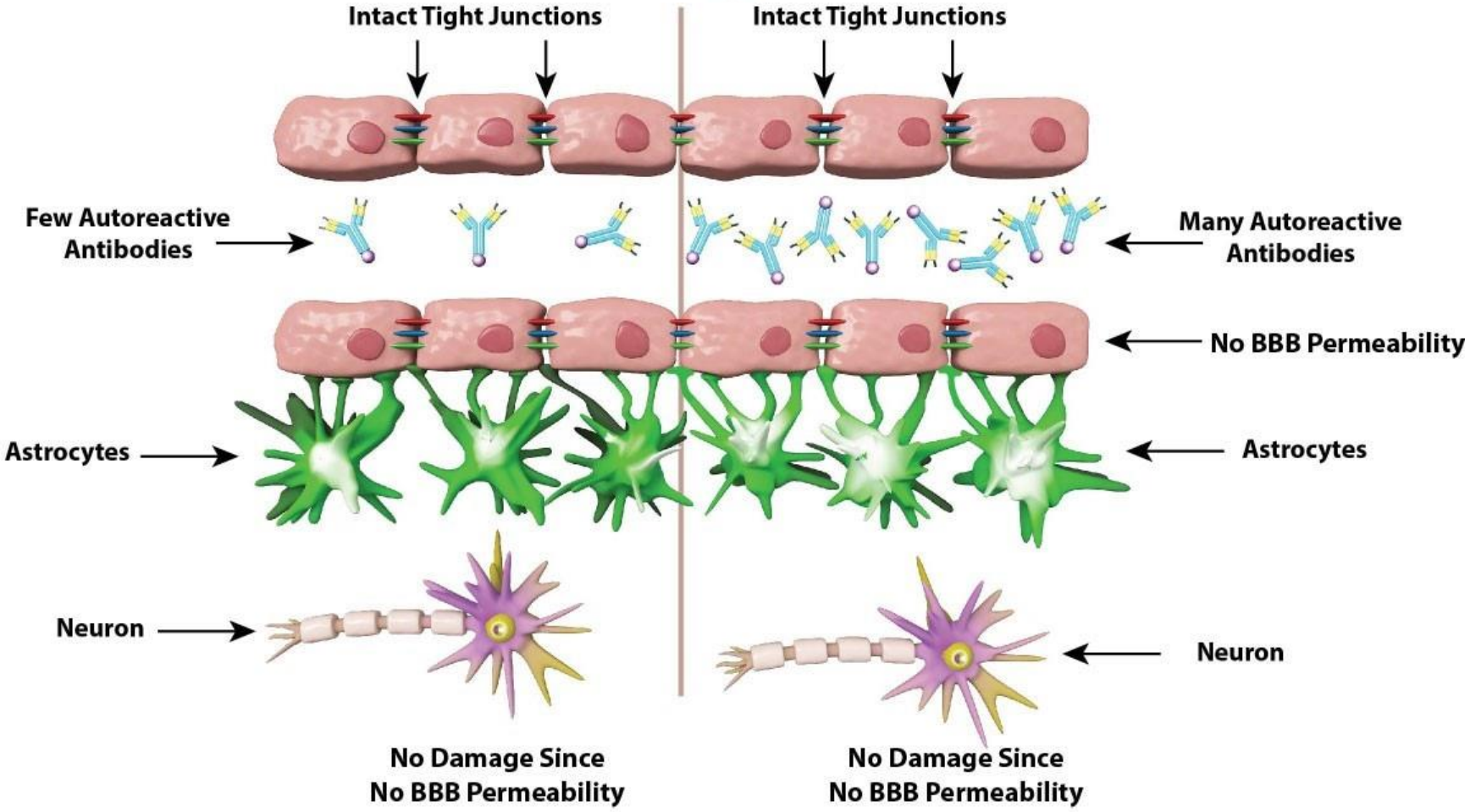


Photo credit: www.360neurohealth.com/whats-happening/the-blood-brain-barrier-function-and-assessment

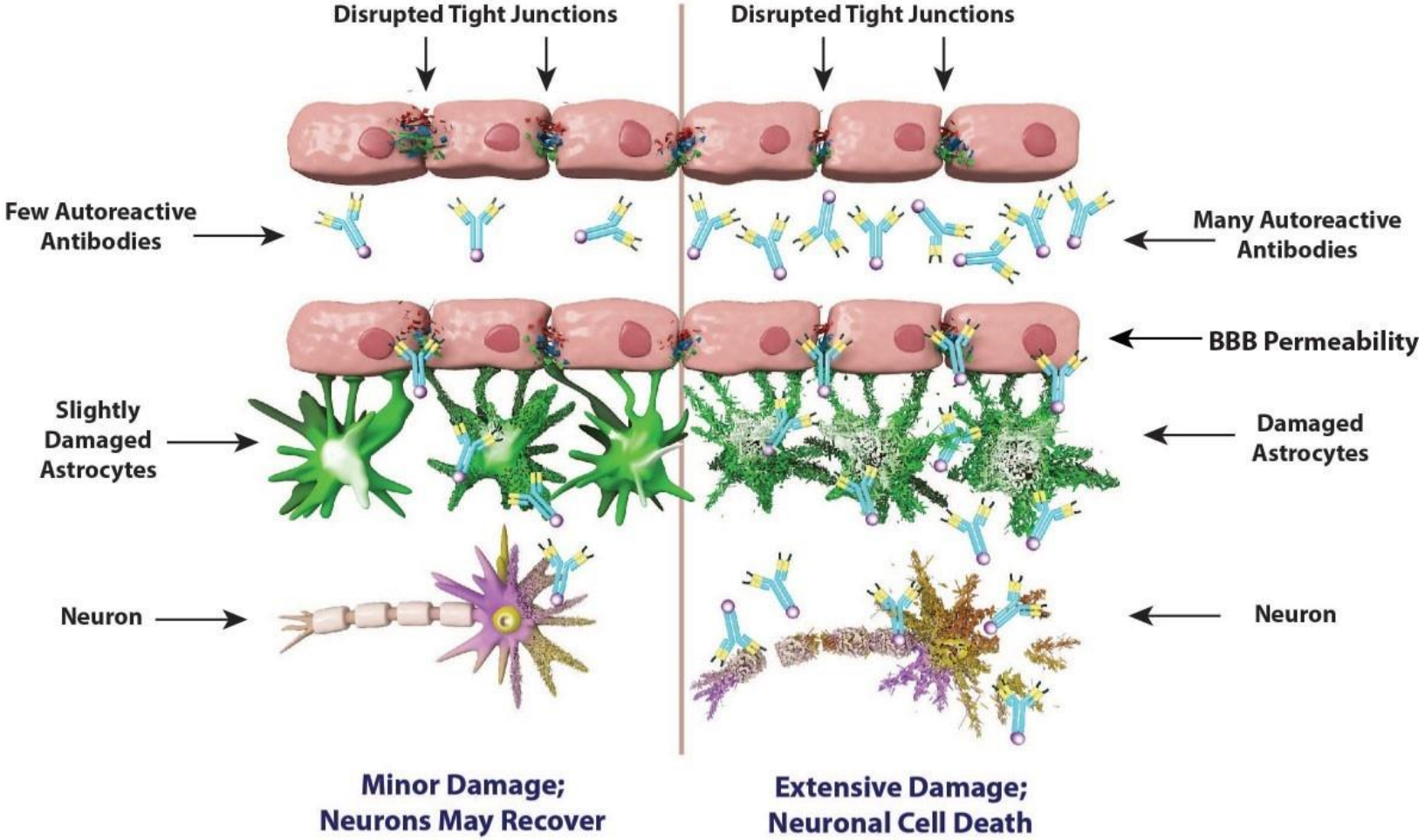
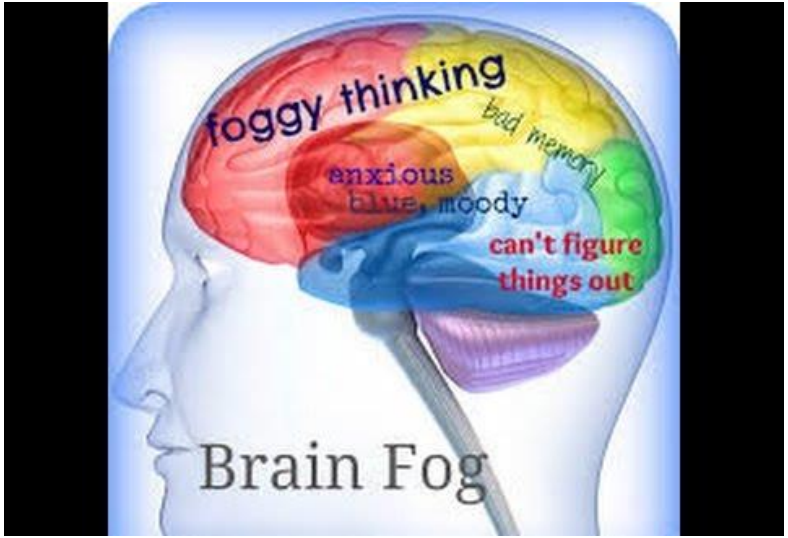


Photo credit: www.360neurohealth.com/whats-happening/the-blood-brain-barrier-function-and-assessment

Chronic Brain Inflammation

- Brain cells including microglial cells can produce TNF alpha, IL1b and IL6
- Inflammation – continue to damage brain cells
- Brain injury and disruption of BBB – lead to chronic ongoing brain inflammation and ongoing brain damage from leaky BBB
- **If you take care of patients with head injury you must assess and treat the BBB**



New advice to move after a concussion

- Instead of “cocooning”
- Most athletes should be active within a day or two after injury
- Brain benefits from movement and exercise, including after a concussion

McCrory P, Meeuwisse W, Dvořák J*, et al.* Consensus statement on concussion in sport—the 5th international conference on concussion in sport held in Berlin, October 2016. *Br J Sports Med* 2017;51:838-847

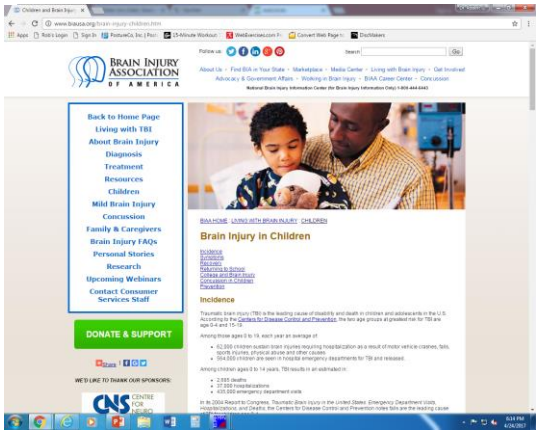
Sara PDC, Frederick PR. *JAMA.* 2016;316(23):2491-2492

Laura M, Francesca G, Laura S, et al. *Brain Plasticity*. 28 March 2017;2(2):127-52

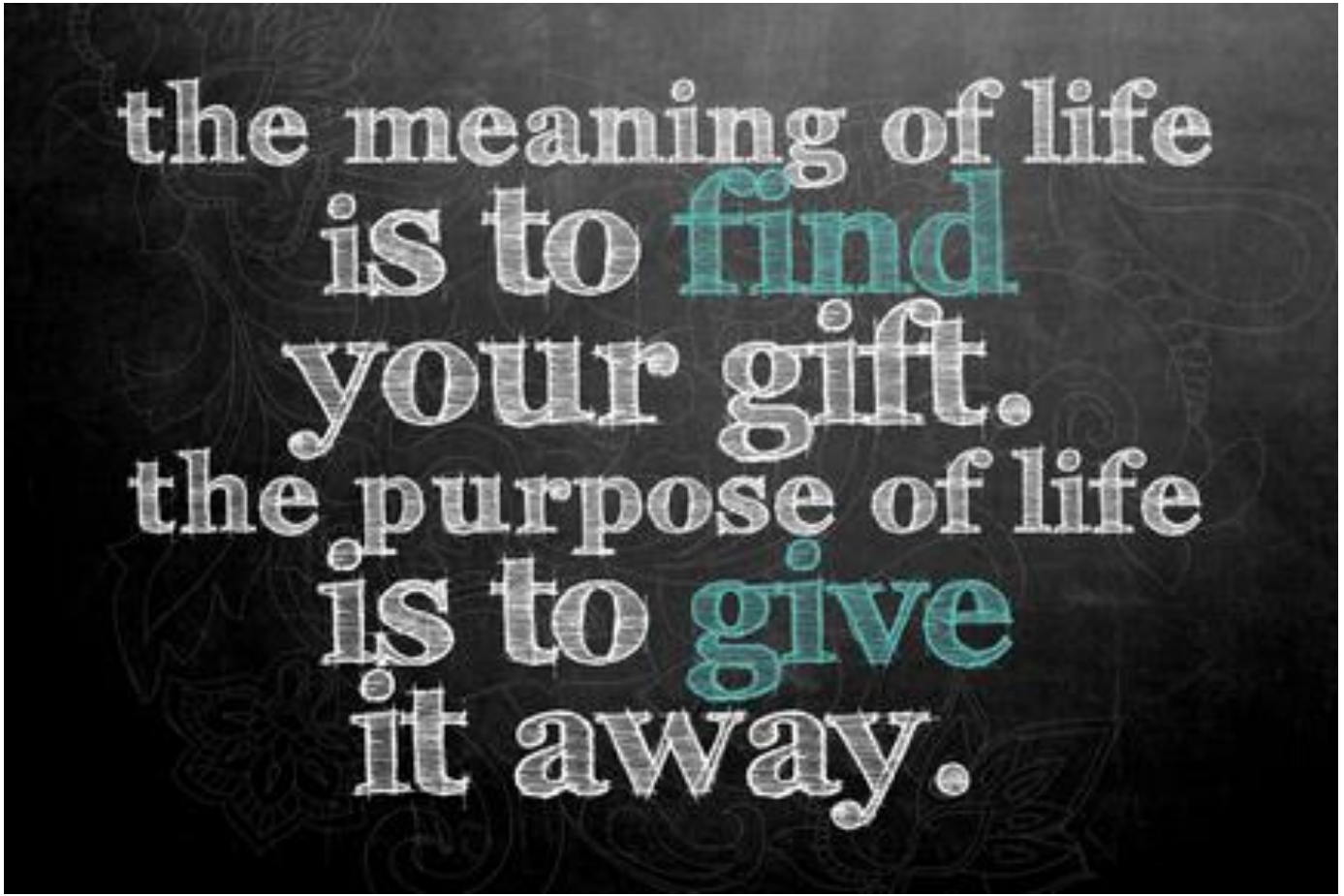
Suit up

Study up

Speak up



http://www.biausa.org/brain-injury-children.htm Accessed Feb 9, 2018


the meaning of life
is to find
your gift.
the purpose of life
is to give
it away.

Thank You

Metagenics Institute

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Navigating the Gut-Brain Axis to Optimize Health Across the Lifespan

Integrative Healthcare Symposium
Pre-Conference Session

February 21, 2018

New York, NY