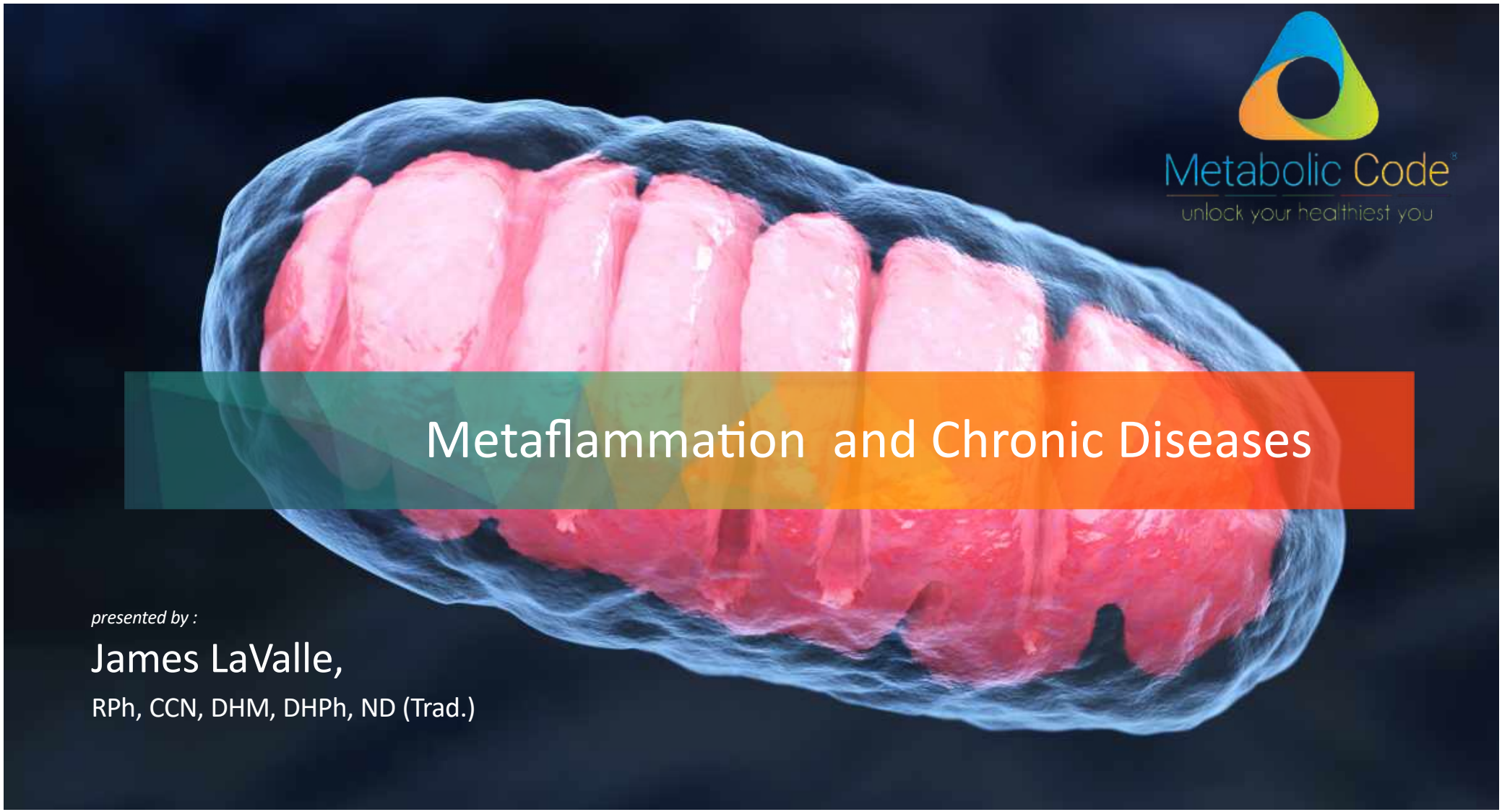

Metaflammation and Chronic Diseases

presented by :

James LaValle,

RPh, CCN, DHM, DHPh, ND (Trad.)

Metabolic Code®
unlock your healthiest you

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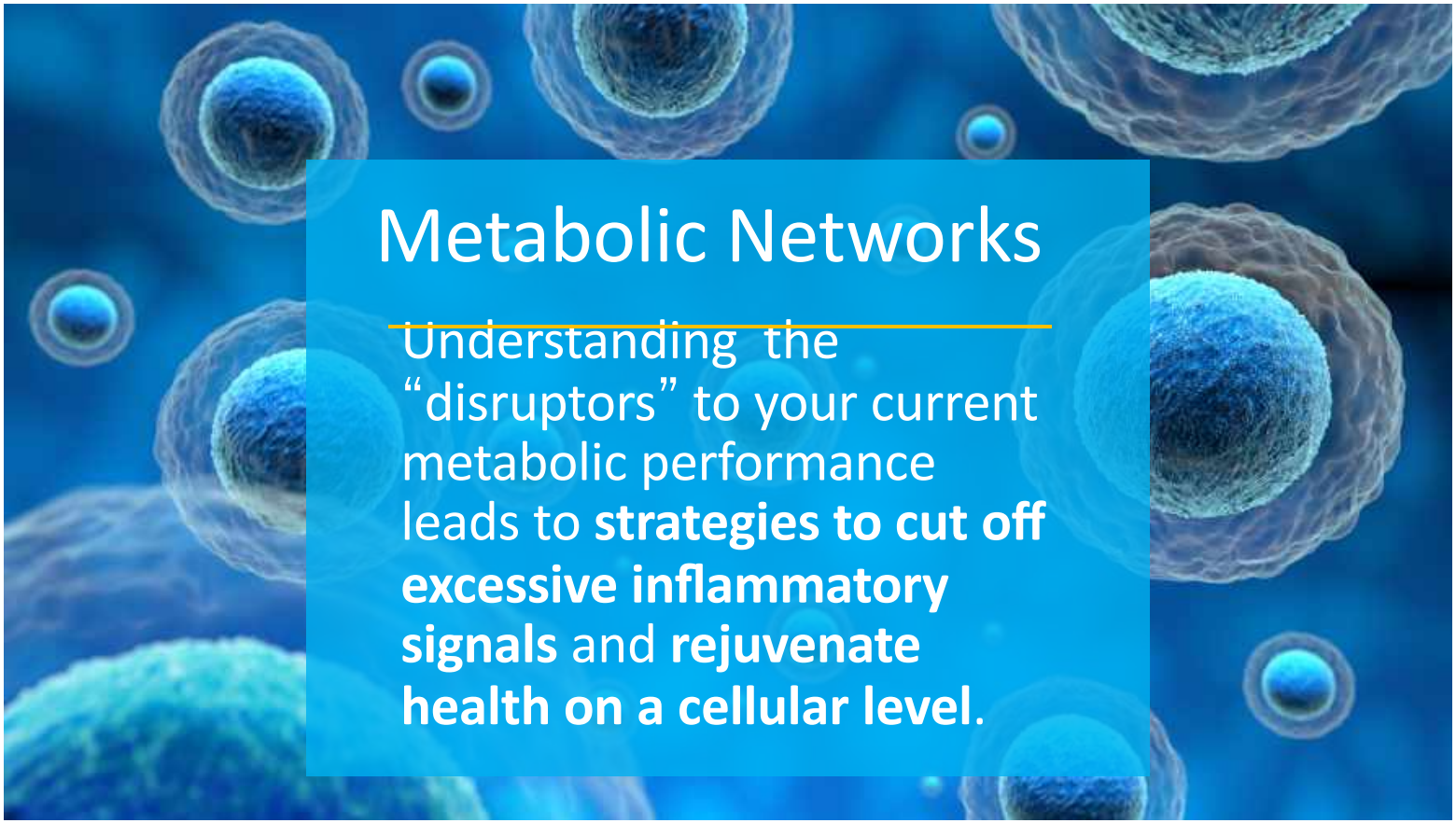
METABOLISM

The sum total of all the chemical reactions **driving how you feel today** and creating the chemistry **moving you toward future health**.

METABOLISM

Directly under the influence of Global Metabolic Inflammatory Signaling =

Metaflammation drives Metabolic Dysregulation


Metabolic Networks
Understanding the "disruptors" to your current metabolic performance leads to **strategies to cut off excessive inflammatory signals** and **rejuvenate health on a cellular level**.

Key Tenants of

Aging, Performance and Vitality

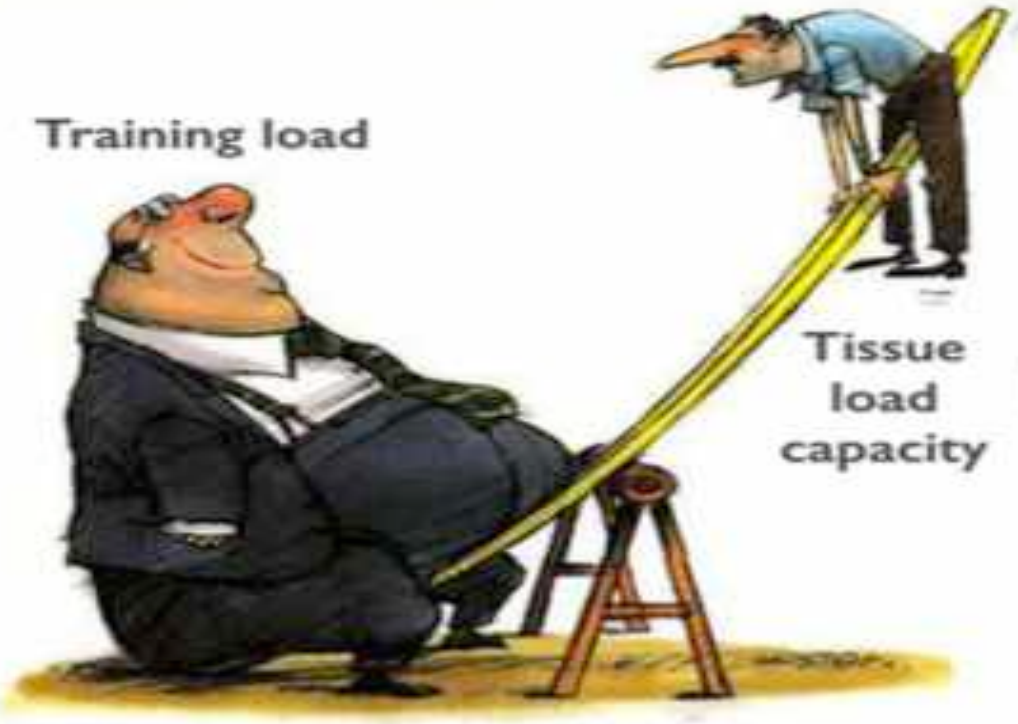
- Oxidative Stress / Inflammation
- Hormonal Balance
- Stress Hormones
- Glucose / Insulin Regulation
- GUT integrity and microbiome diversity
- Immune Balance
- Environmental Burden
- Individuality

FINDING THE BALANCE

Training

Volume
Intensity
Frequency
Type

Work
Habits
Etc.



Strength
Control
Flexibility
Tissue sensitivity
Biomechanics
Running gait
Previous injury
Etc.

RUNNINGPHYSIO

JANUARY 29, 2020

Scientists have identified the role of chronic inflammation as the cause of accelerated aging

by Lobachevsky University

Metaflammation

- Also know as “Inflammaging” and metabolism induced inflammation
- Chronic low-grade inflammatory sequela
- Increases aging processes and metabolic signaling issues
- Increased **peripheral and central** inflammation

Prattichizzo F, et al. Inflammageing and metaflammation: the yin and yang of type 2 diabetes. Ageing Res Rev. 2018;41:1-17.

Metaflammation

Results in co-morbid conditions:

- Altered methylation patterns
- Cardiovascular issues – lipid, vascular
- Hormonal imbalances
- Liver and kidney diseases
- Immune dysfunction
- Thyroid, fatigue
- Sleep problems
- Cognitive and mood problems
- Sarcopenia
- Osteoporosis
- Cancer

Prattichizzo F, et al. Inflammageing and metaflammation: the yin and yang of type 2 diabetes. Ageing Res Rev. 2018;41:1-17.

Metaflammation Contributors

- STRESS
- Caused by AND leads to “diabesity”:
  - Insulin resistance; type 2 diabetes
  - Obesity
  - Stress
  - Diet
  - LPS induced
  - Liver / kidney issues
- GUT microbiome issues - Leaky GUT

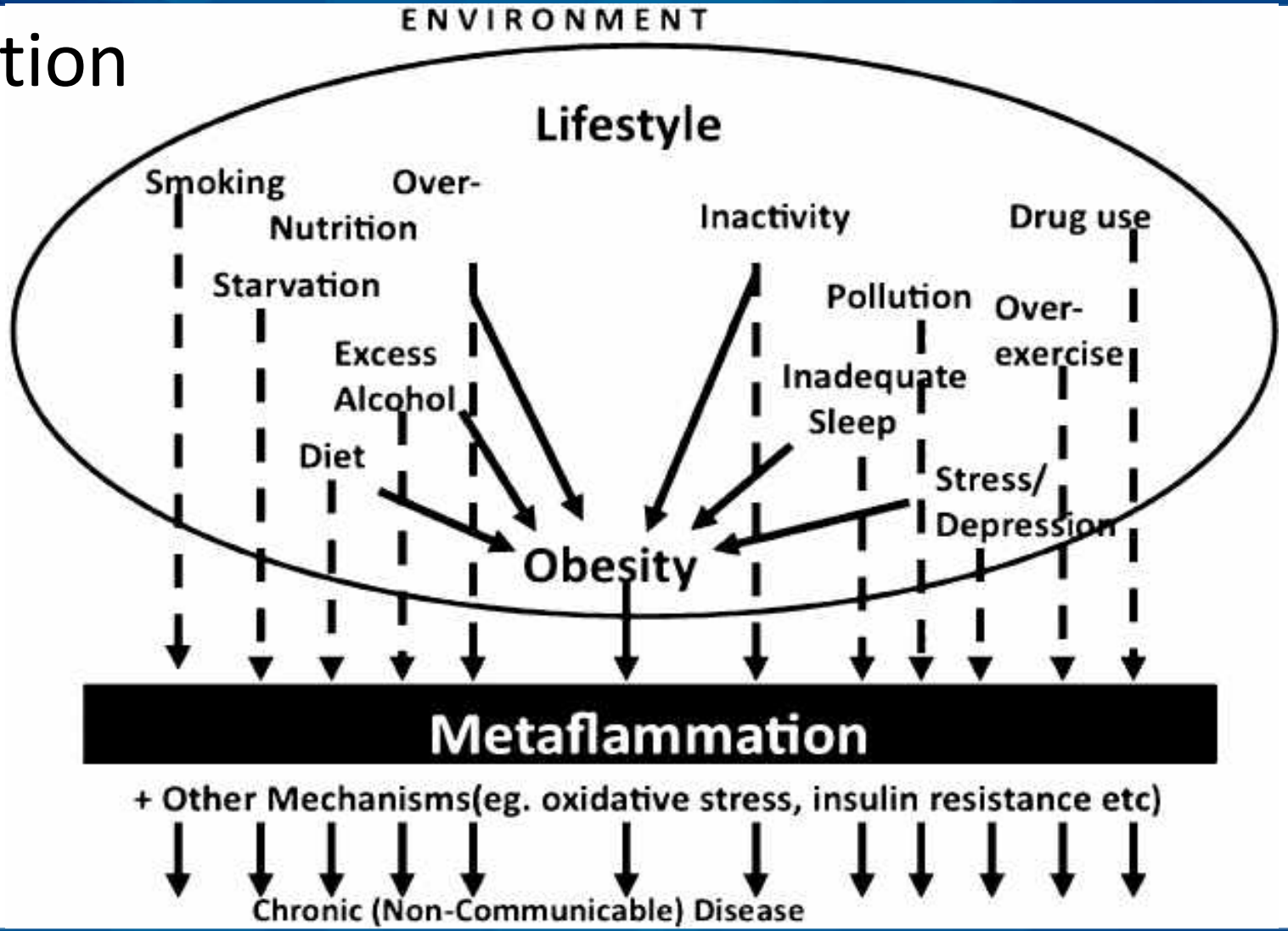
Prattichizzo F, et al. Inflammageing and metaflammation: the yin and yang of type 2 diabetes. Ageing Res Rev. 2018;41:1-17.

Metaflammation Contributors

- Chronic bacterial or viral infections
- Periodontitis/ gingivitis
- Cellular debris
- Misplaced self molecules
- Misfolded/oxidized proteins
- DIET
- Lifestyle – overexercise?
- SLEEP quality and quantity
- Environmental factors – metals, artificial food additives, sweeteners, POPs, others

Prattichizzo F, et al. Inflammageing and metaflammation: the yin and yang of type 2 diabetes. Ageing Res Rev. 2018;41:1-17.

Metaflammation Constructs



Egger G, et al. Obesity Reviews. 2008;10(2):237-49.

Metaflammation Pathophysiology

- Acute inflammation is a short-term defense response to injury
- Required for healing and tissue repair
- Resolution of acute inflammation should be terminated when no longer necessary to prevent tissue damage
- In a homeostatic model, pro-inflammatory response in balance with anti-inflammatory response
- Repeated stress, insult from dietary factors or injury to the body can lead to neuroendocrine dysregulation
- Results in prolong, chronic inflammation - metaflammation

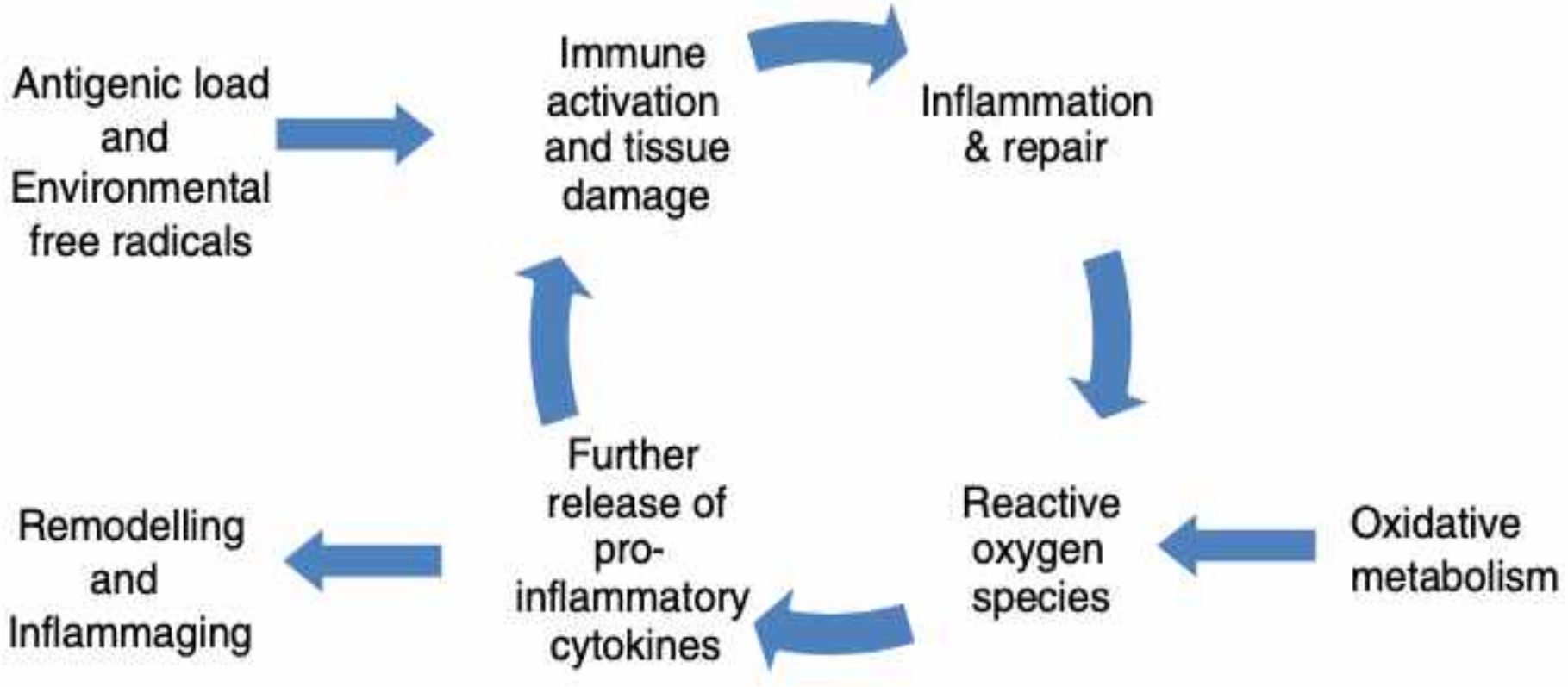
Miller ES, et al. Chronic stress induces persistent low-grade inflammation. Am J Surg. 2019;218:677-683.

Metaflammation Pathophysiology

- Chronic stress associated with persistent activation of HPA axis
- Leads to chronic release of stress hormones - glucocorticoids and catecholamines
- During chronic stress, activated polymorphonuclear cells (PMNs) release sIL-6Ra
- This combines with IL-6 to activate endothelial cells
- Monocyte chemotactic protein-1 (MCP-1) are produced
- Stimulates monocyte recruitment
- Transition of neutrophil to mononuclear cell infiltrate is hallmark trait of chronic inflammation vs. acute

Miller ES, et al. Chronic stress induces persistent low-grade inflammation. Am J Surg. 2019;218:677-683.

Cycles of Metaflammation



Baylis D, et al. Understanding how we age: insights into inflammaging. Long Healthspan. 2013;2(8):1-8

Hallmarks of Metaflammation

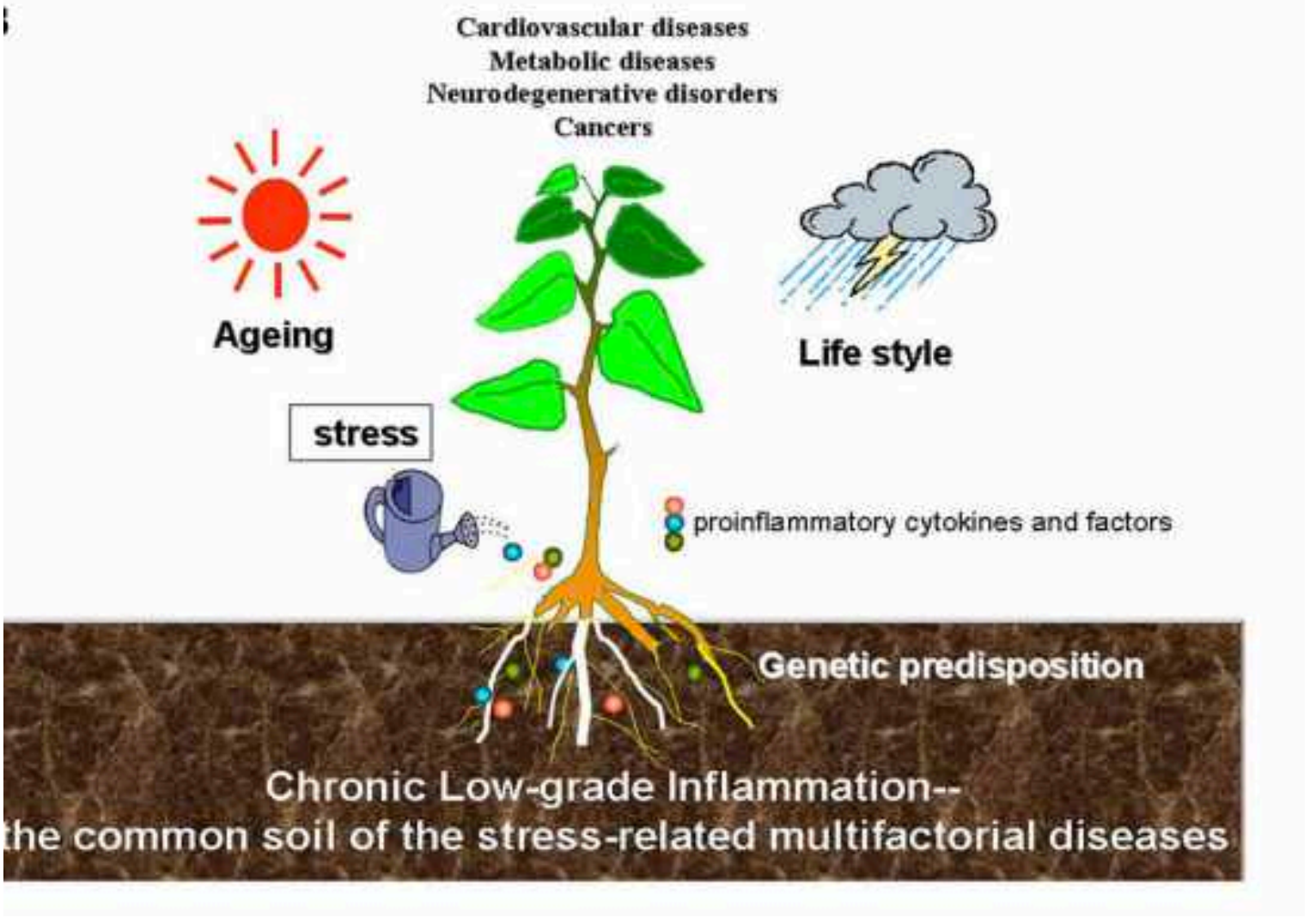
- Chronic STRESS = Immune Shifts = Disease progression

- Patients with chronic illness – including surgery recovery - frequently progress to a state of **persistent inflammation, immunosuppression and catabolism** (PICS)

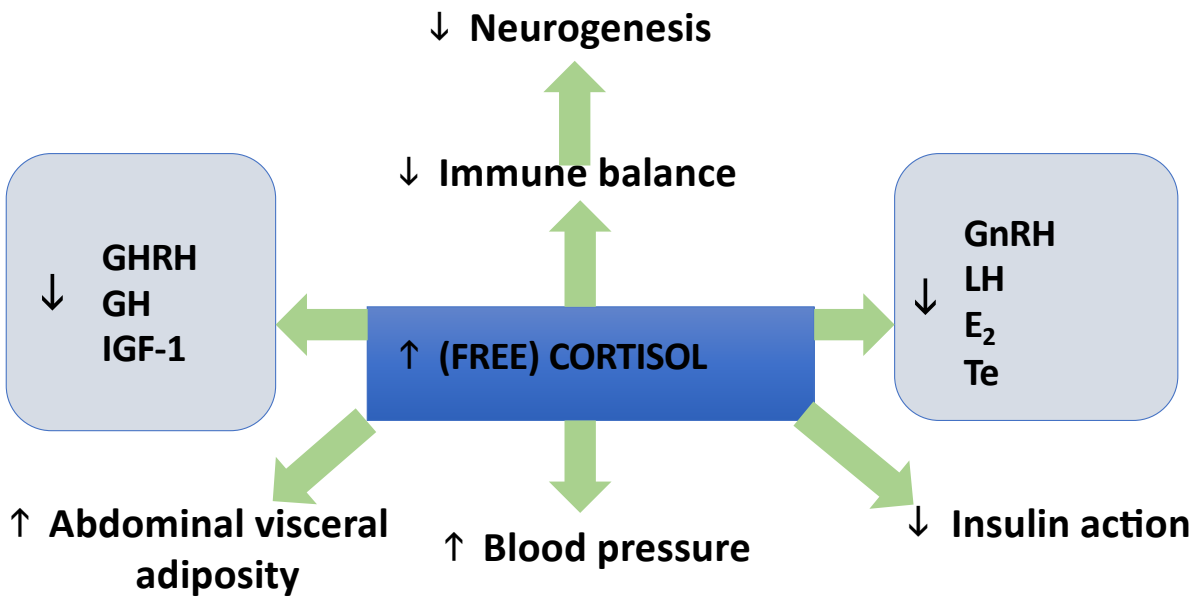
- PICS characterized by increased IL-6 and anemia

Miller ES, et al. Chronic stress induces persistent low-grade inflammation. Am J Surg. 2019;218:677-683.

Liu YZ, et al. Inflammation: the common pathway of stress-related diseases. Front Human Neurosci. 2017;2017:00316.



Clinical Effects of Excessive HPA axis Activation



OUTCOMES

(osteopenia, sarcopenia, syndrome X, cognitive decline, immunological compromise)
(*fractures*, frailty, cardiovascular disease, memory loss, infectious complications)

Adapted from: Endocrinology and Metabolism Clinics of North America, Elsevier Publishing, ed. Anne R. Cappola. June 2013, vol. 42, no. 2.

Stress - Metaflammation

- Stress activates Inflammation via
  - Overactivated Immunity
  - Increased Sympathetic tone
  - Reduced glucocorticoid responsiveness

- Stress – inflammation related diseases include:
  - Stress/Inflammation Metabolic – glucose/insulin, NAFLD
  - Stress/Inflammation CVD
  - Stress/Inflammation Depression
  - Stress/Inflammation Neurodegenerative diseases
  - Stress/Inflammation Cancer

Liu YZ, et al. Inflammation: the common pathway of stress-related diseases. Front Human Neurosci. 2017;2017:00316.

Stress - Metaflammation

Stress exposure (including psychological)

- Stress-related elevated proinflammatory cytokines
- Increases microglial activation
- Increases accumulation of peripherally-derived monocytes and macrophages in brain
- NLRP3 inflammasome activation – produce IL-1beta

Liu YZ, et al. Inflammation: the common pathway of stress-related diseases. Front Human Neurosci. 2017;2017:00316.

Diurnal Cortisol and Physical Performance in Aging Males

- Middle aged men (45-59) measured AM and night cortisol
- Tracked twenty years later (65-83)
- Outcome measures walking speed and balance time morning serum and 4 salivary samples for two consecutive days
- Worst Performance in people with poor morning cortisol response & less nocturnal decline.

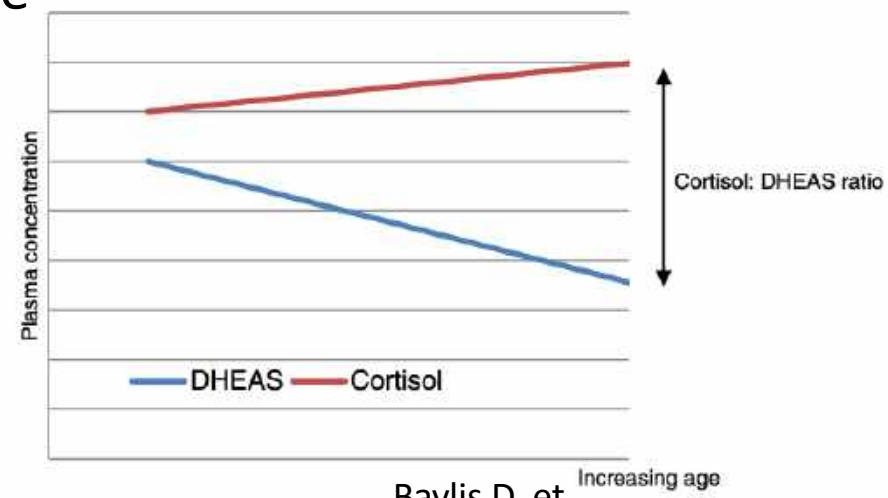
Outcome: HPA axis dysregulation is associated with worse physical performance later in life.

Diurinal cortisol patterns are associated with physical performance in Caerphilly Prospective Study
Gardner, MP,Lightman SL et al, Int J epidemiol 2011 dec;40(6):1693-702. doi: 10.1093/je/dyr113

Stress/Cortisol Gets the Metaflammation Ball Rolling

- Stress causes cravings, sleep disturbance and weight gain
- Cortisol – DHEA ratio
- Insulin resistance follows
- Weight gain leads to adiponectin alterations and loss of AMPK in the cell

. . . the inflammatory cycle begins . . .



Baylis D, et al. Understanding how we age: insights into inflammaging. Long Healthspan. 2013;2(8):1-8

ALLOSTASIS

Allostasis – The adaptive process of achieving stability, or Homeostasis, through physiological or behavioral change. The primary goal is to maintain a stable environment in the body.

More adaptability means greater ability to maintain Homeostasis

Familiar vs. Unfamiliar Stress

Unfamiliar stress causes greater stress response, greater resources to overcome stress, and greater recovery time

Familiar (reoccuring) stress causes less disruption over time because of adaptation

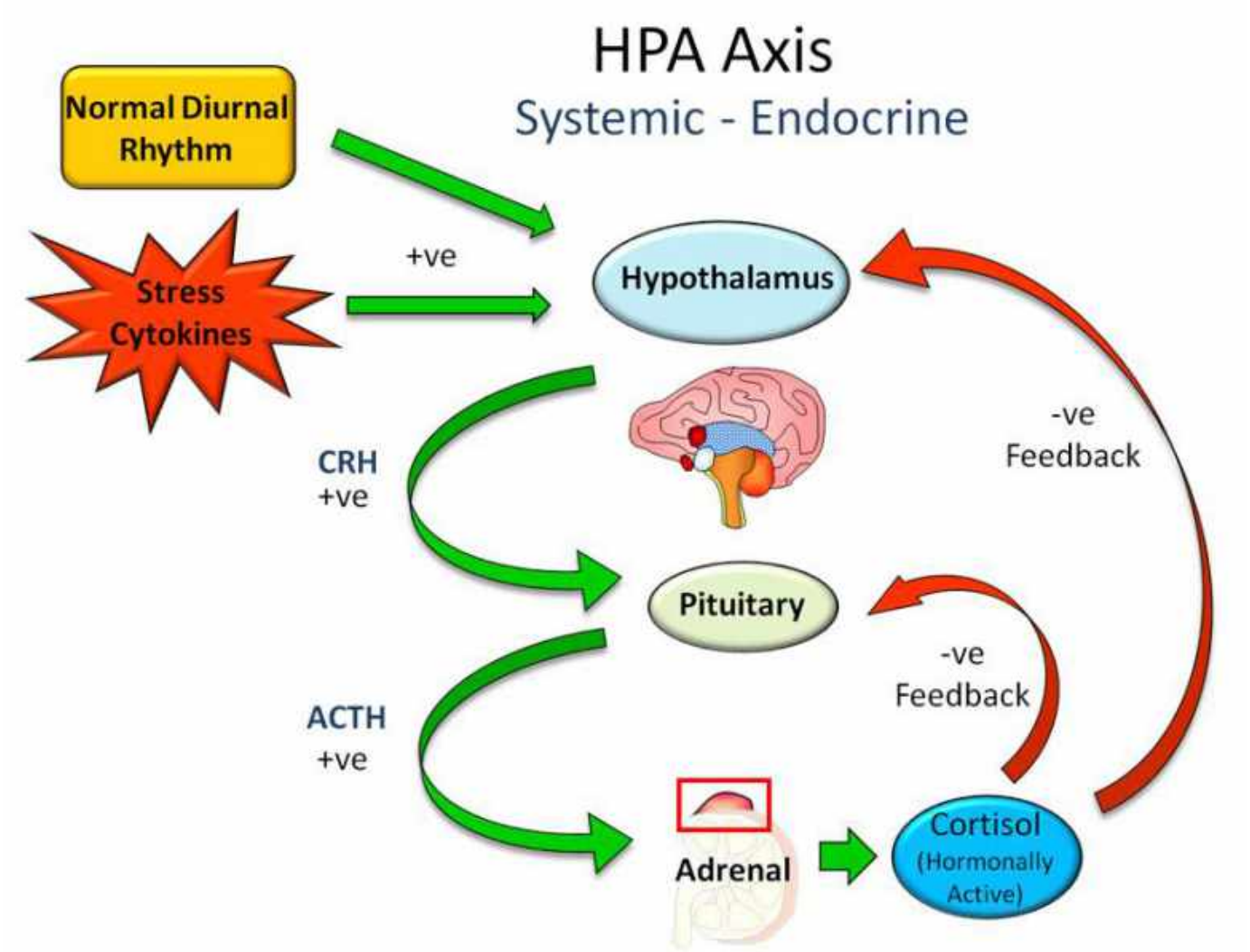
Effective handling of one stressor allows resources to be used for other stressors

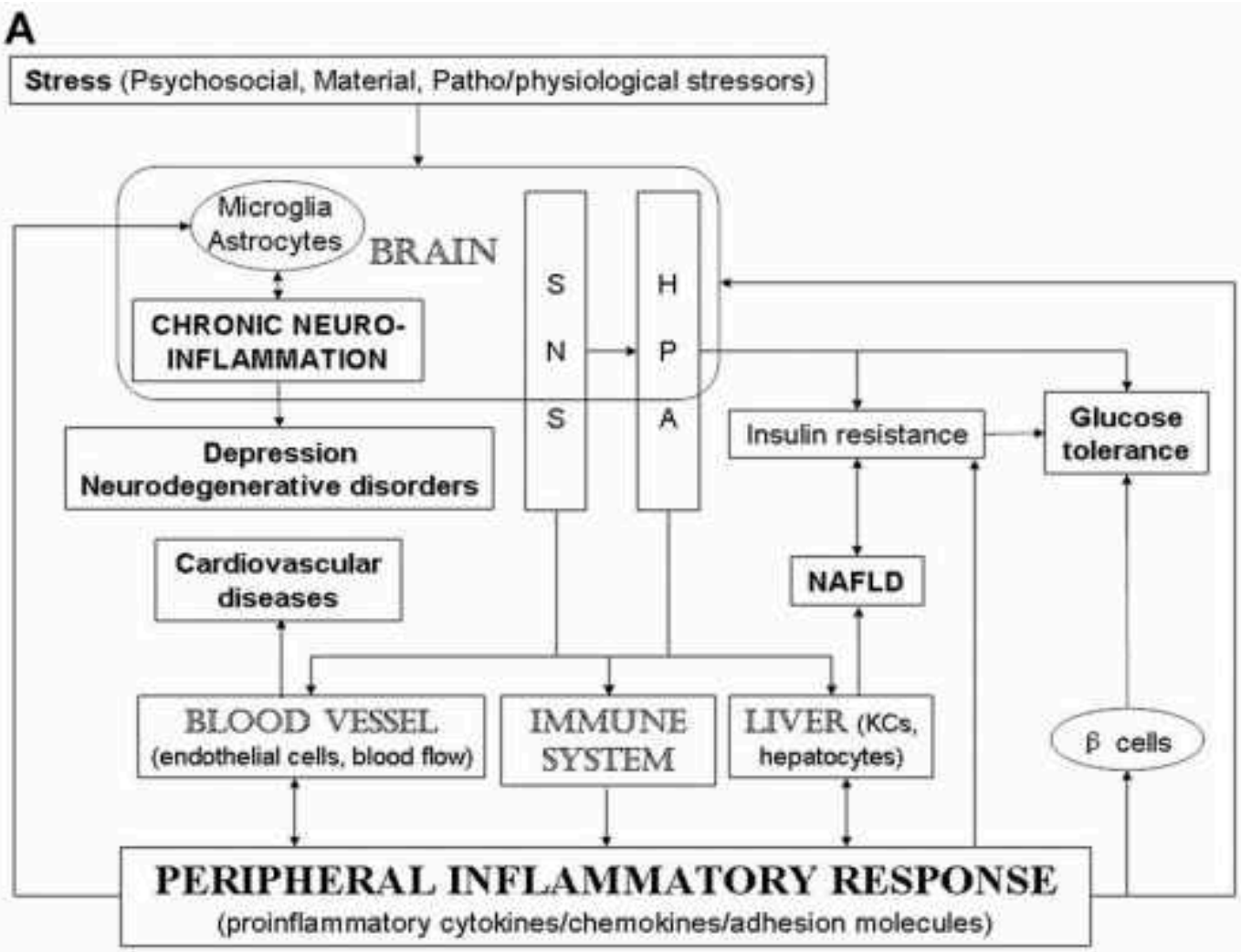
Allostatic Load

The wear and tear that the body experiences due to repeated cycles of Allostasis and/or inefficient regulation of the stress responses

Allostatic Load comes from many sources and they are all connected

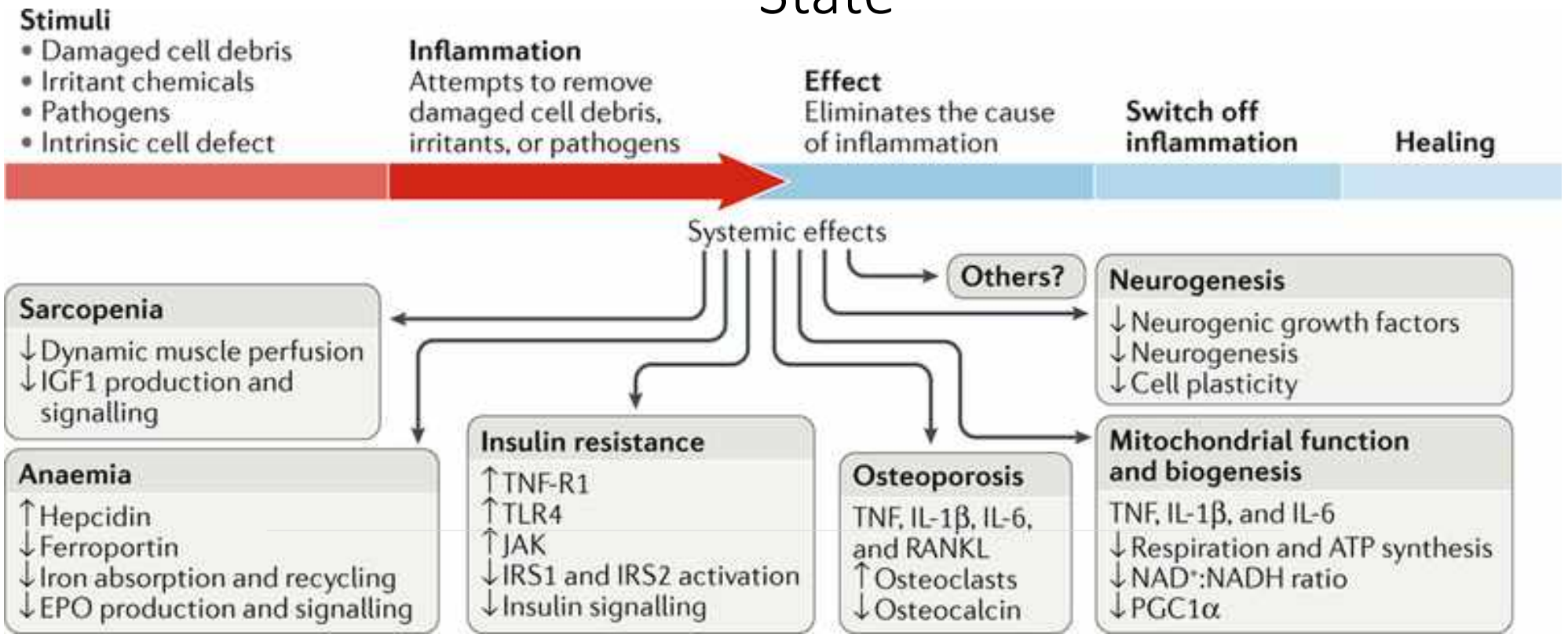
Stress is cumulative!


HPA Axis
Systemic - Endocrine
Normal Diurnal Rhythm
Stress Cytokines
+ve
Hypothalamus
CRH
+ve
-ve
Feedback
Pituitary
ACTH
+ve
-ve
Feedback
Adrenal
Cortisol
(Hormonally Active)



Liu YZ, et al. Inflammation the common pathway of stress-related diseases. Front Human Neurosci. 2017;2017:00316.

Metaflammation Induces Catabolic State



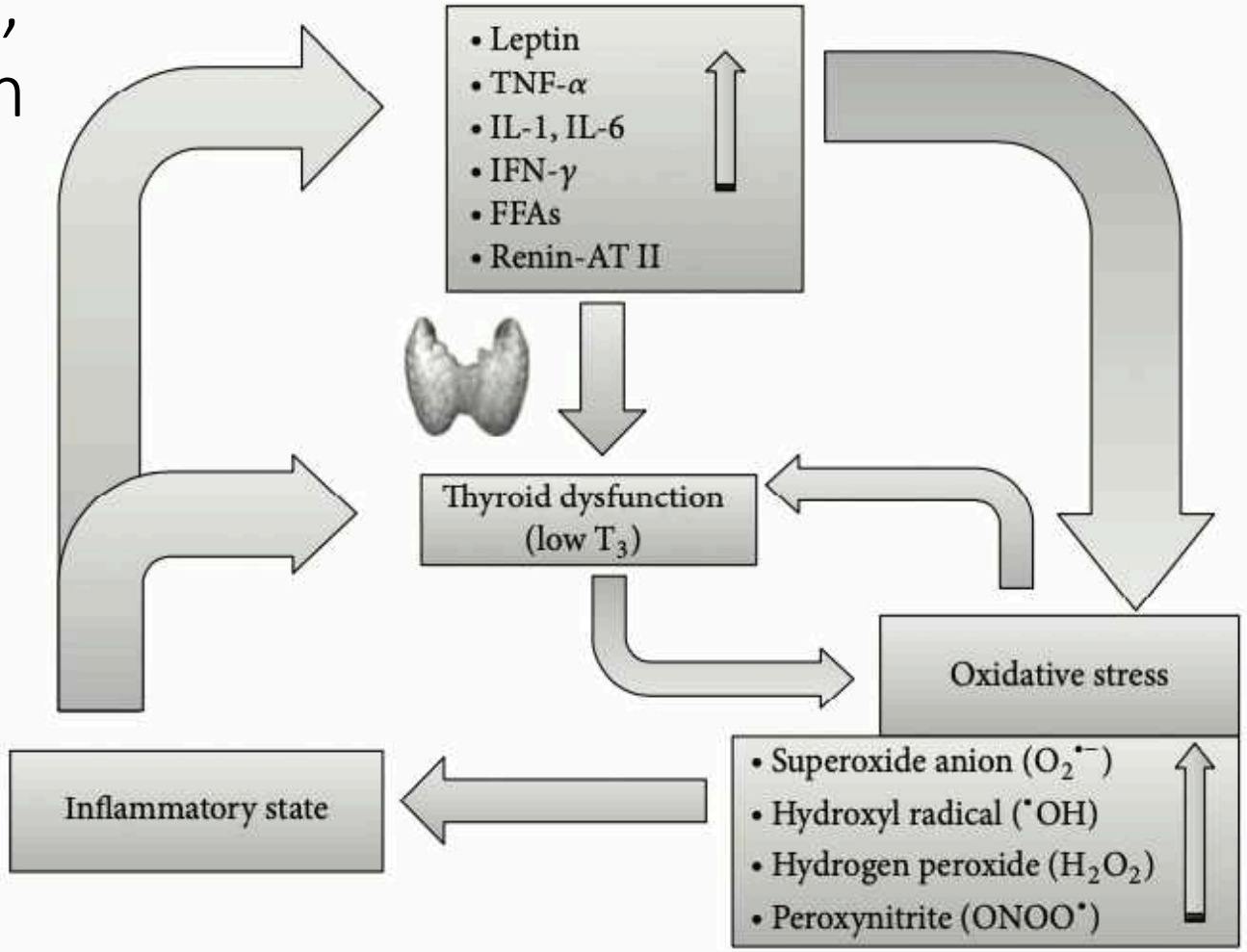
Ferruci L, et al. Inflammageing: chronic inflammation in ageing, cardiovascular disease and frailty. Nat Rev Cardiol. 2018;15(9):505-22.

Metaflammation - Thyroid

- 2016 study, n= 116 patients (72men, 44 women, ages 60-80) Hx stroke vs. control
- Purpose to investigate whether CRP is atherogenic factor in patients suffering from subclinical hypothyroidism
- RESULTS:
  - Increased levels of CRP in subclinical hypothyroid patients directly associated with increased risk of stroke vs. no hypothyroidism
  - Demonstrates important role of inflammation in the development of atherosclerosis in subclinical hypothyroid patients
  - Elevated TSH lead to endothelial dysfunction and increased atherogenesis
  - Increases IL-6, TNF-alpha, CRP

Bordean I, et al. Chronic inflammatory markers – factors favouring cerebrovascular disease in patients suffering from subclinical hypo- or hyperthyroidism. 2016;21(1):49-51.

Oxidative Stress, Metaflammation and Thyroid Dysfunction



Mancini A, et al. Thyroid hormones, oxidative stress and metaflammation. Mediator Inflamm. 2016; 6757154.

Inflammasomes

- Family of proteins in charge of the initiation of inflammatory process during innate immune response
- Major actors in metaflammation construct
- Signaling platforms associated with stress and damage
- No drug on the market targeting these proteins
- Most characterized = $NLRP_3$ nucleotide-binding domain leucine-rich repeat
- Controlling inflammasomes important

Zahid A, et al Pharmacological inhibitors of the NLRP3 inflammasome. Front Immunol. 2019;2019:02538

Sirtuins (SIRT) Crucial Role in Metaflammation

- Inflammation designed by nature for “defending and mending”
- Acute/chronic inflammations are linked to altered glycolysis and fatty acid oxidation through NAD+ dependent function of sirtuins
- SIRT targeting important in immune and inflammatory regulation
- Resveratrol potent SIRT-1 upregulation, **but…….**
- Thai ginseng’s (*Kaempferia parviflora*) root
  - 5,7 dimethoxyflavone reported 4-5x more potent at SIRT regulation than resveratrol
  - Most potent known SIRT1 activator in the plant kingdom

- Nakata A, et al. Potent SIRT1 enzyme-stimulating and anti-glycation activities of polymethoxyflavonoids from Kaempferia parviflora. Nat Prod Commun. 2014;9(9):1291-4.

Endothelial Metaflammation and Diabesity

- Cardiovascular disorders associated with diabesity = leading cause of morbidity and mortality in the Western world
- Endothelial cell dysfunction results from unbalanced production of endothelial-derived vascular mediators
- Presents at the earliest stages of insulin resistance and obesity
- May precede the clinical diagnosis of diabetes by several years
- Associated with metaflammation

Potenza MA, et al. Targeting endothelial metaflammation to counteract diabesity cardiovascular risk: current and perspective therapeutic options. Pharmacol Res. 2017;120:226-41.

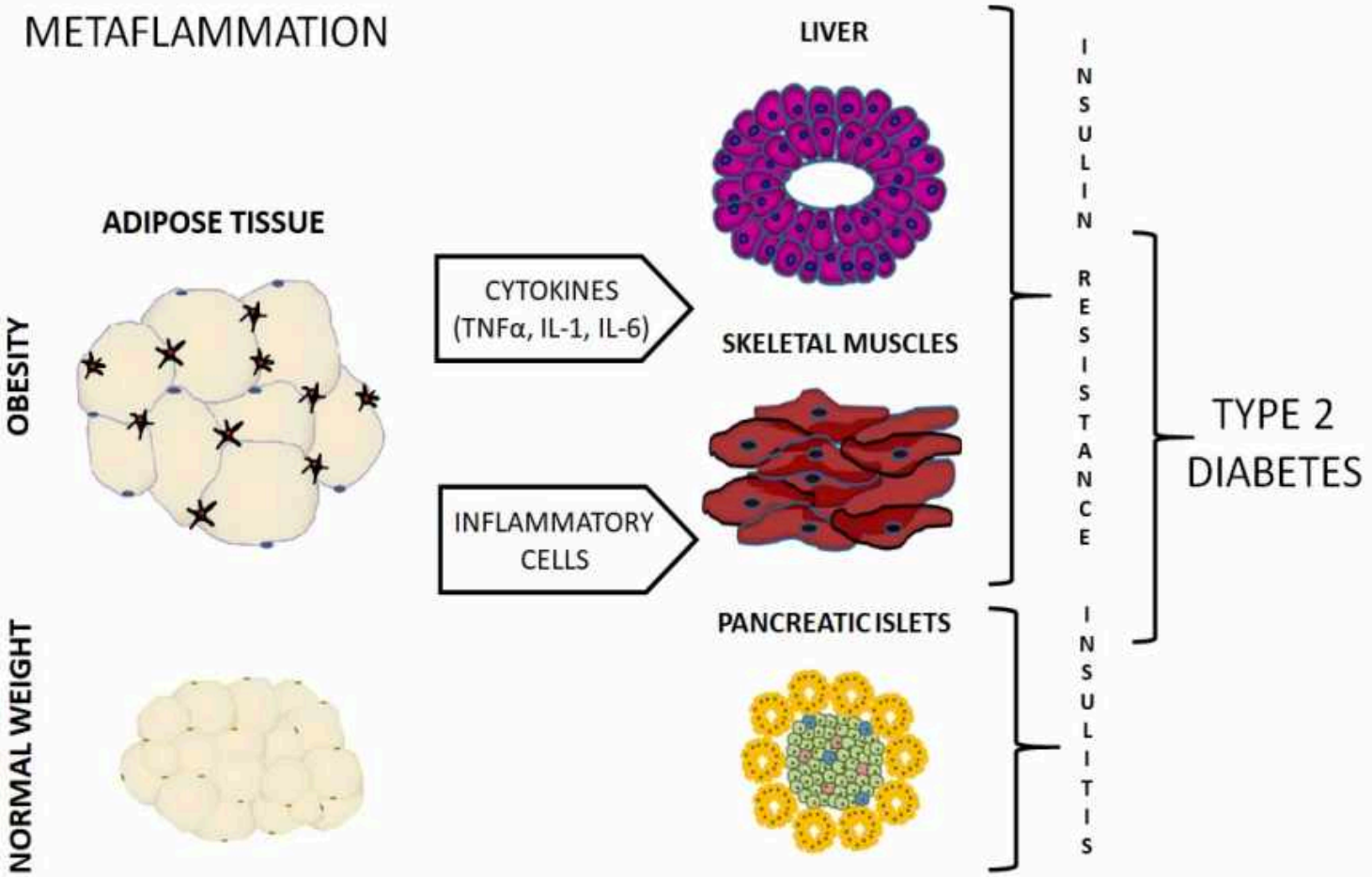


Figure 1. A schematic presentation of the concept of metaflammation.

ckj OXFORD era edta

Clinical Kidney Journal, 2019, vol. 12, no. 6, 861–870

doi: 10.1093/ckj/sfz106
Advance Access Publication Date: 18 September 2019
CKJ Review

CKJ REVIEW

A journey from microenvironment to macroenvironment: the role of metaflammation and epigenetic changes in cardiorenal disease

Mehmet Kanbay [1], Aslihan Yerlikaya[2], Alan A. Sag[3], Alberto Ortiz[4], Masanari Kuwabara[5], Adrian Covic[6], Andrzej Wiecek[7], Peter Stenvinkel[8] and Baris Afsar[9]

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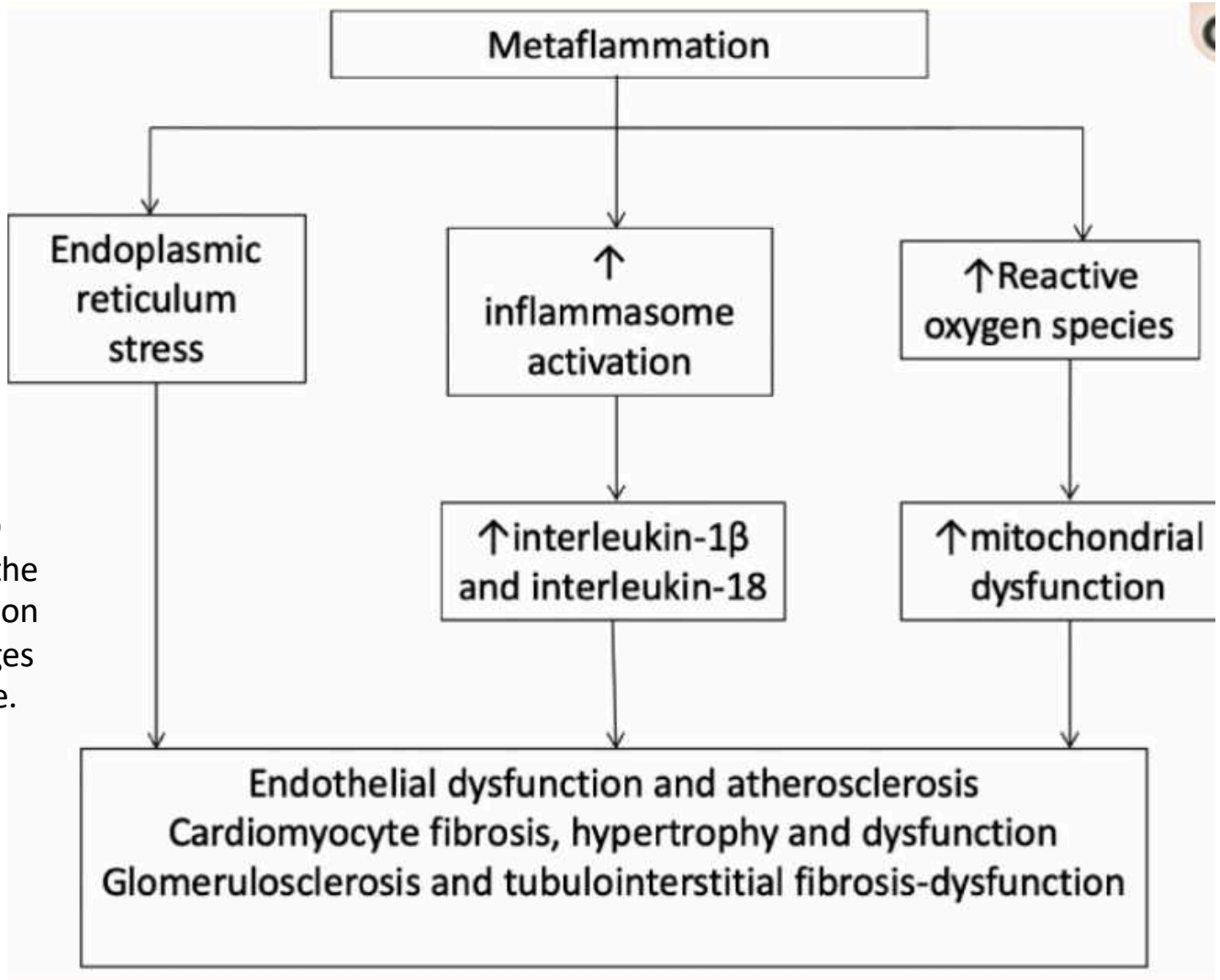


Kanbay M, et al. A journey from microenvironment to macroenvironment: the role of metaflammation and epigenetic changes in cardiorenal disease. Clin Kidney J. 2019;12(6):861-70.

Metaflammation and Obesity

- Altered homeostasis of nutritionally overloaded cells in obesity
- Elevated expression of pro-inflammatory cytokines from M1 macrophages in white adipose tissue – TNFalpha, IL-6, CRP, IL-1b etc…
- Decrease in anti-inflammatory cytokines from M2 macrophages – IL-10, IL-Ra, adiponectin, etc..
- Macrophage-like Kupffer cells increase pro-inflammatory cytokines
  - In response to transducer signals produced by white adipose
  - Leads to necroinflammation
  - “Cycle” of inflammation leading to tissue and cell death

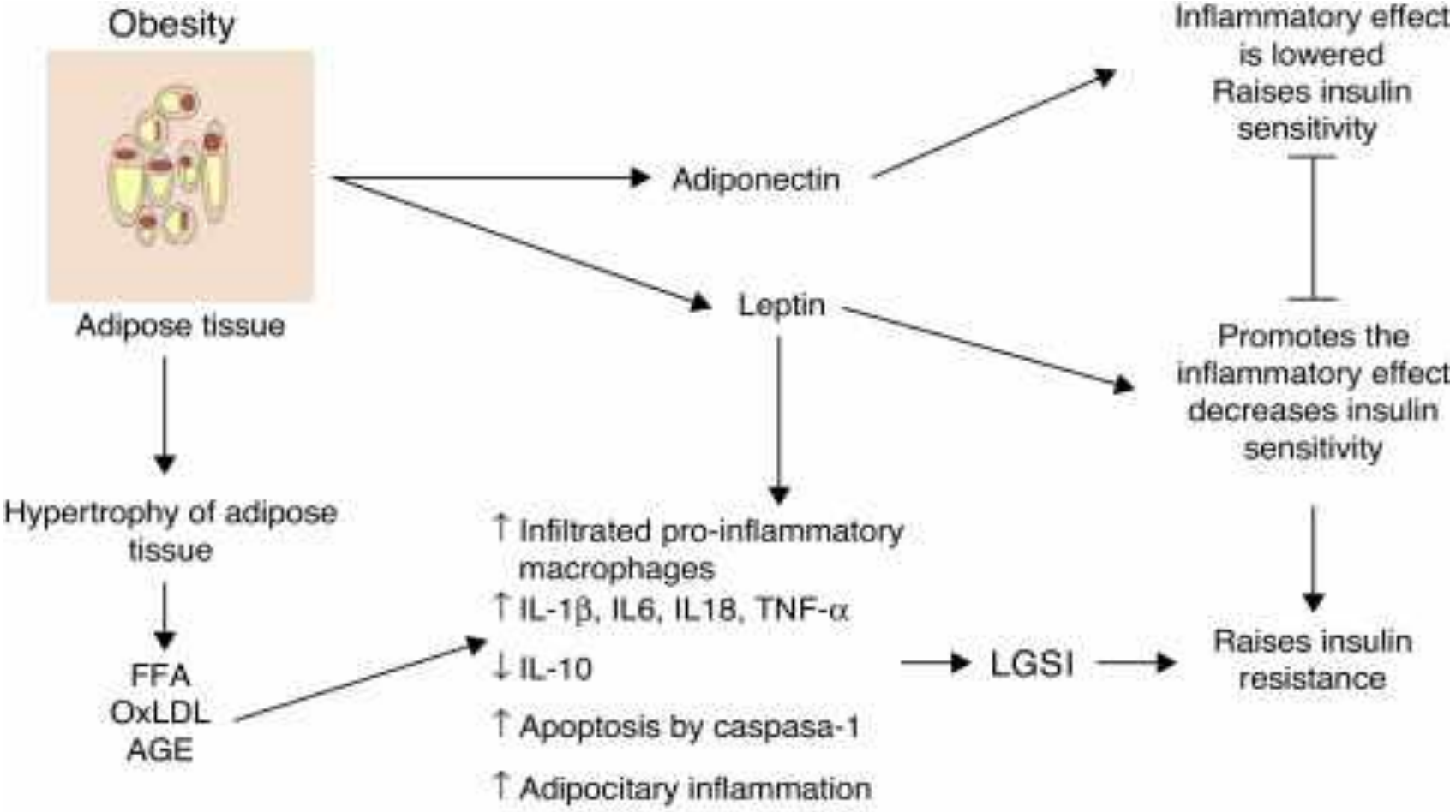
Debnath M, et al. Obesity induced metaflammation: pathophysiology and mitigation. J Cytokine Biol. 2016;1:1.

Metaflammation and Obesity

- Adipose tissue over-expression of chemoattractant CCL2 leads to macrophage infiltration, IR and hepatosteatosis
- Adipocytes under stress activate mTOR pathway
- Downregulation of AMP-activated protein kinase (AMPK) and SIRT pathways
- Muscle fibers suffer from decreased glycogen synthesis
- HPA axis dysregulation
- Insulin signaling issues

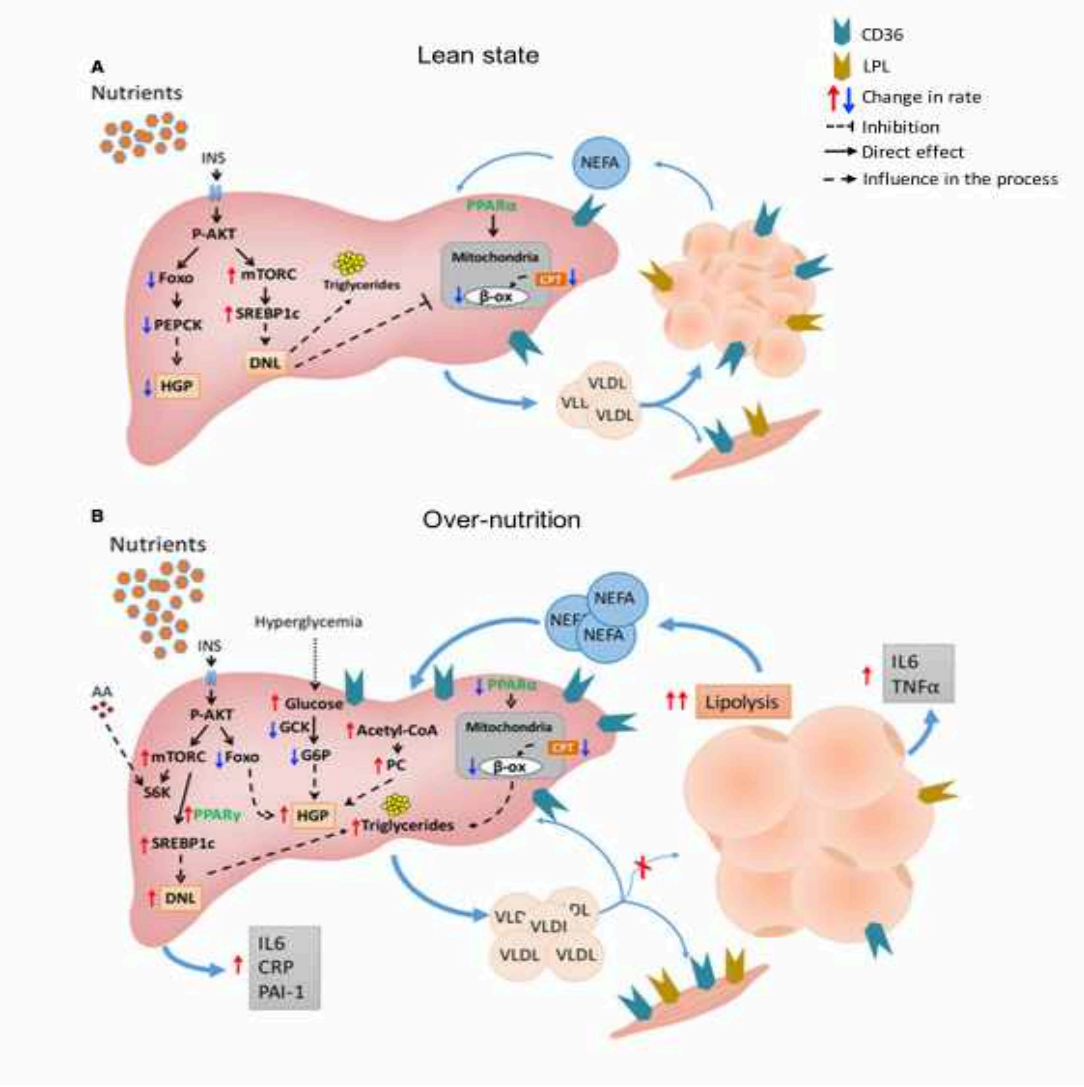
- Debnath M, et al. Obesity induced metaflammation: pathophysiology and mitigation. J Cytokine Biol. 2016;1:1.
- Li et. . Suppression of the mTORC1/STAT3/Notch1 pathway by activated AMPK prevents hepatic insulin resistance induced by excess amino acids. Am. J. Physiol. Endocrinol. Metab. 2014;306:E197–E209. (2014)

Metaflammation of Visceral Adipose Tissue



Leon-Pedroza JI, et al. Cirguria y Cirujanos. 2015;83(6): 543-551.

Liver-Adipose CrossTalk in Lean and Over-Fed states



Caputo T, et al. From chronic overnutrition to metaflammation and insulin resistance: adipose tissue and liver contributions. FEBS Letters. 2017;2017:3061-88.

Gut as a Source of Metaflammation

- Over-activation of immunity in GUT leads to increased production of inflammatory cytokines
- Leaky guy allows bacterial and toxins to enter bloodstream
- Leads to peripheral and central inflammation

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

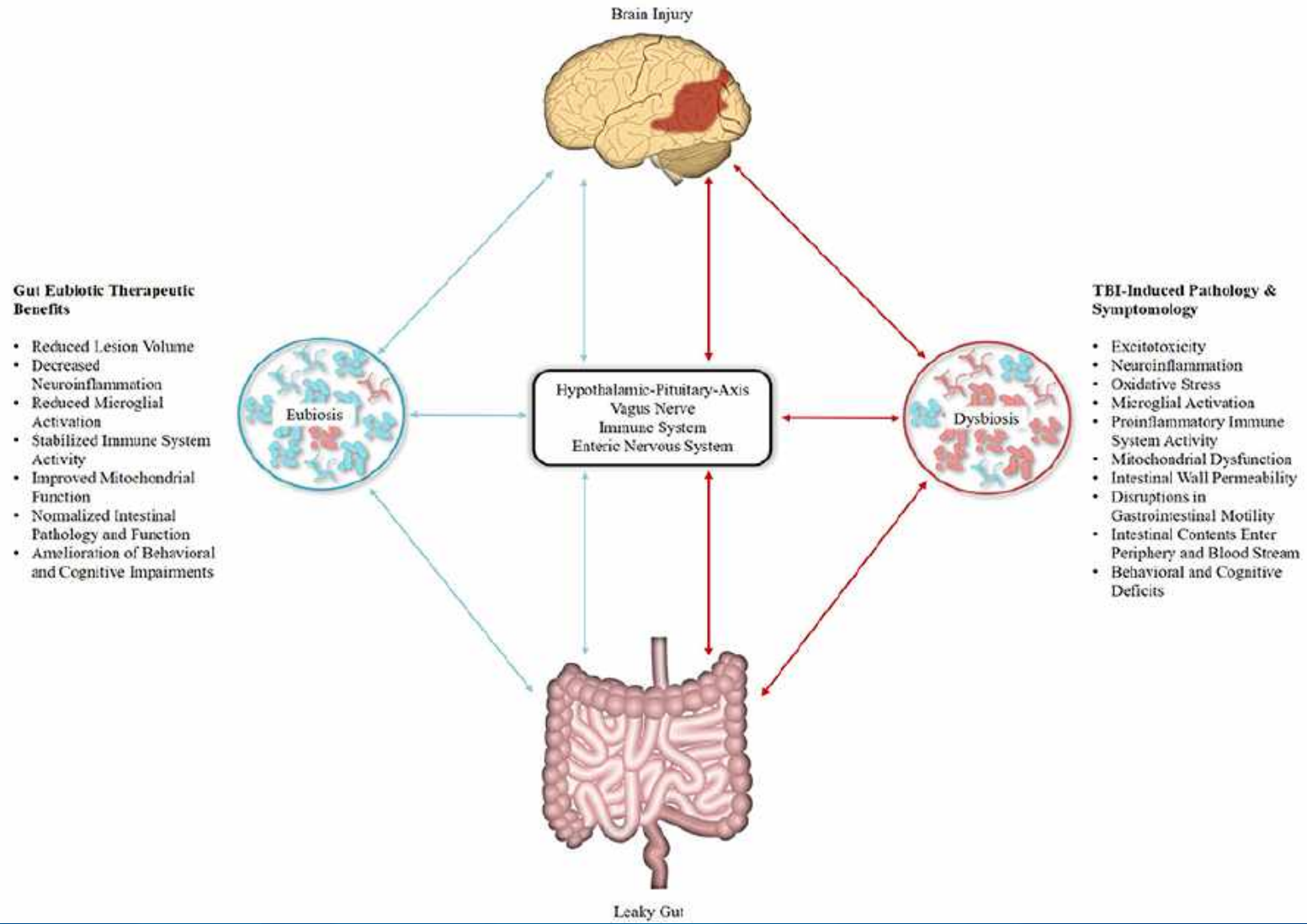
Gut as a Source of Inflammation

- Recent study reports 75% with new onset RA (rheumatoid arthritis) have microbiome problems

- Presence of *Prevotella copri in GUT* correlates with RA in US
  - Other countries reported different microbiome disturbances in RA
  - Japan and US = *Prevotella*

Maeda Y, et al. Role of gut microbiotic in rheumatoid arthritis. J clin Med. 2017;6(6):60.

Rice MW, et al. GUT microbiota as a therapeutic target to ameliorate the biochemical neuroanatomical and behavioral effects of traumatic brain injuries. Front Neurol. 2019; https://doi.org/10.3389/fneur.2019.00875



Results of Dysbiotic GUT

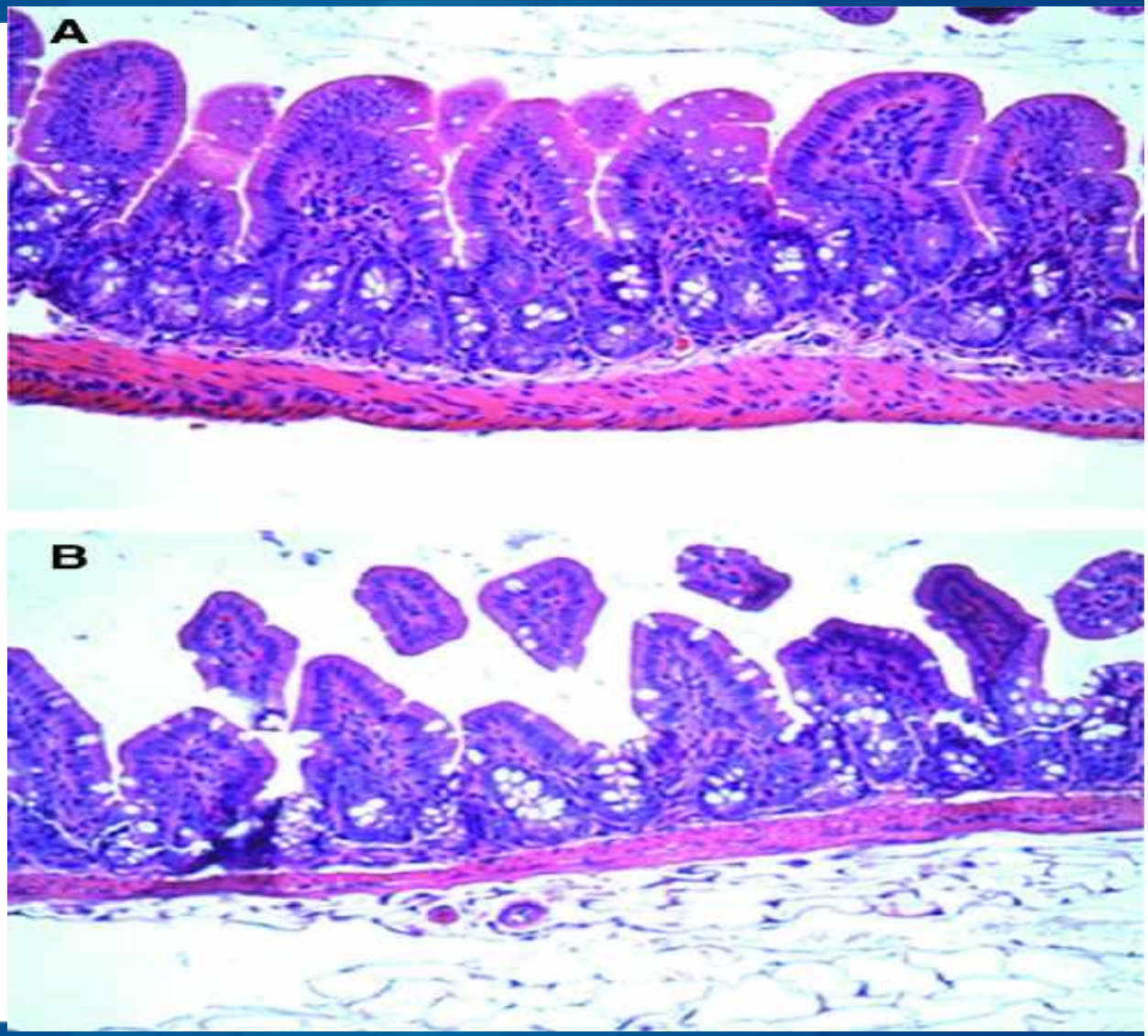
- METAFLAMMATION
- Increased food allergies/intolerances
- Digestive problems like IBDs, IBS, Crohn's, colitis
- Increased sleep and mood disturbances
- Fatigue
- Increased time to recovery
- Increased joint and connective tissue issues
- Decreased performance and exercise ability
- Memory and cognitive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

DeGruttola AK, et al. Current understanding of dysbiosis in disease in human and animal models. Inflamm Bowel Dis. 2016;22(5):1137-50.

Terminal ileum 6 hr post-TBI

A –normal villi consistent villous height

B – post-TBI villi



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

Autonomic Dysfunction Post mild TBI

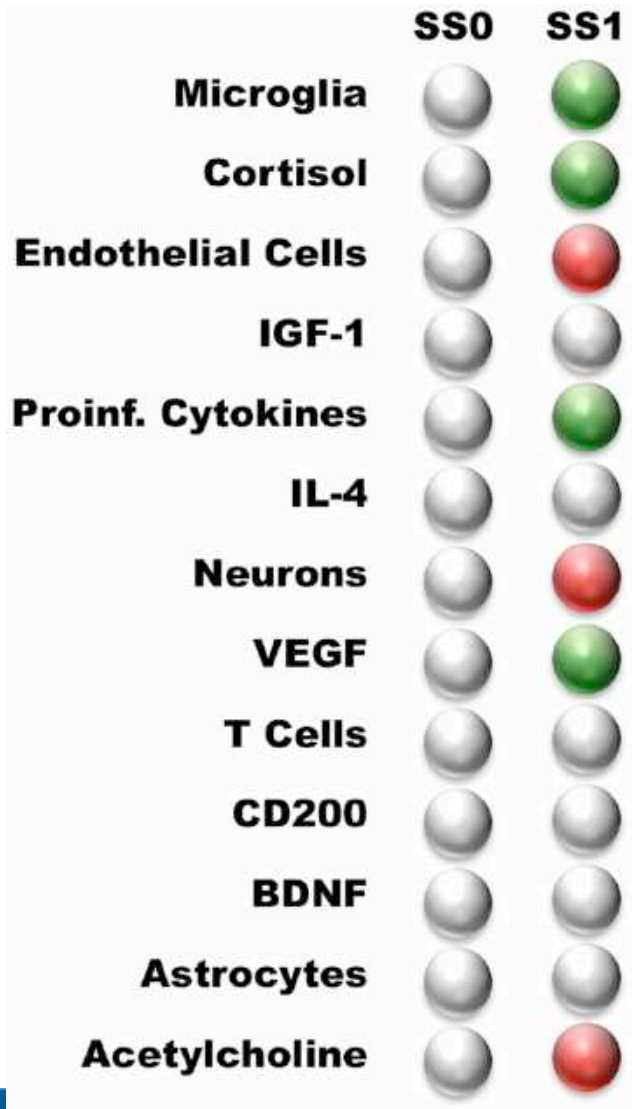
- Dysfunction of the autonomic nervous system (ANS) = Dysautonomia
  - Induces abnormalities in organ systems throughout the body
  - May contribute to cardiovascular dysregulation
  - Increased mortality
- Major contributor for symptomology of **mild** – moderate - severe TBIs
- Altered HRV changes, pupillary dynamics, eye pressure, arterial pulse wave
- Commonly persistent post mild-TBI
- Impacts performance and health of TBI victim

Esterov D, et al. Autonomic dysfunction after mild traumatic brain injury. Brain Sci. 2017;7(8):100.

Altered NeuroImmune Signaling

- There are 2 persistent homeostatic behaviors of neuroimmune signaling
- SSO – first persistent behavior
- SSI - alternate steady state characterized by
  - High levels of the stress hormone cortisol
  - High levels of pro-inflammatory cytokines IL-1β, IL-6, TNFα
  - High levels of growth factor VEGF
  - Microglia activation
  - Depressed levels of acetylcholine
  - Reduced neuron function
  - Increased BBB permeability

Craddock TJA, et al. A logic model of neuronal-glial interaction suggests altered homeostatic regulation in the perpetuation of neuroinflammation. Front Cell Neurosci. 2018;12:336.



Inflammation Brain Volume

- 2017 prospective cohort study. N= 1633 patients
- Assessed systemic inflammatory markers = fibrinogen, albumin, WBC, von Willebrand factor and Factor VIII
- inflammation composite score was created for each participant
- 24 years later, SD increase in midlife inflammation composite score associated with:
  - Lower regional brain volume
  - Reduced episodic memory
  - Subhects with elevations in a larger number of 5 inflammatory markers during midlife were reported to have lower regional brain volumes and reduced episodic memory in late life in a dose–response manner.
  - For several brain regions, including the hippocampus, the effect of a 1 SD increase in midlife inflammation composite score was comparable to that of possessing a single *APOE* ε4 allele during late life

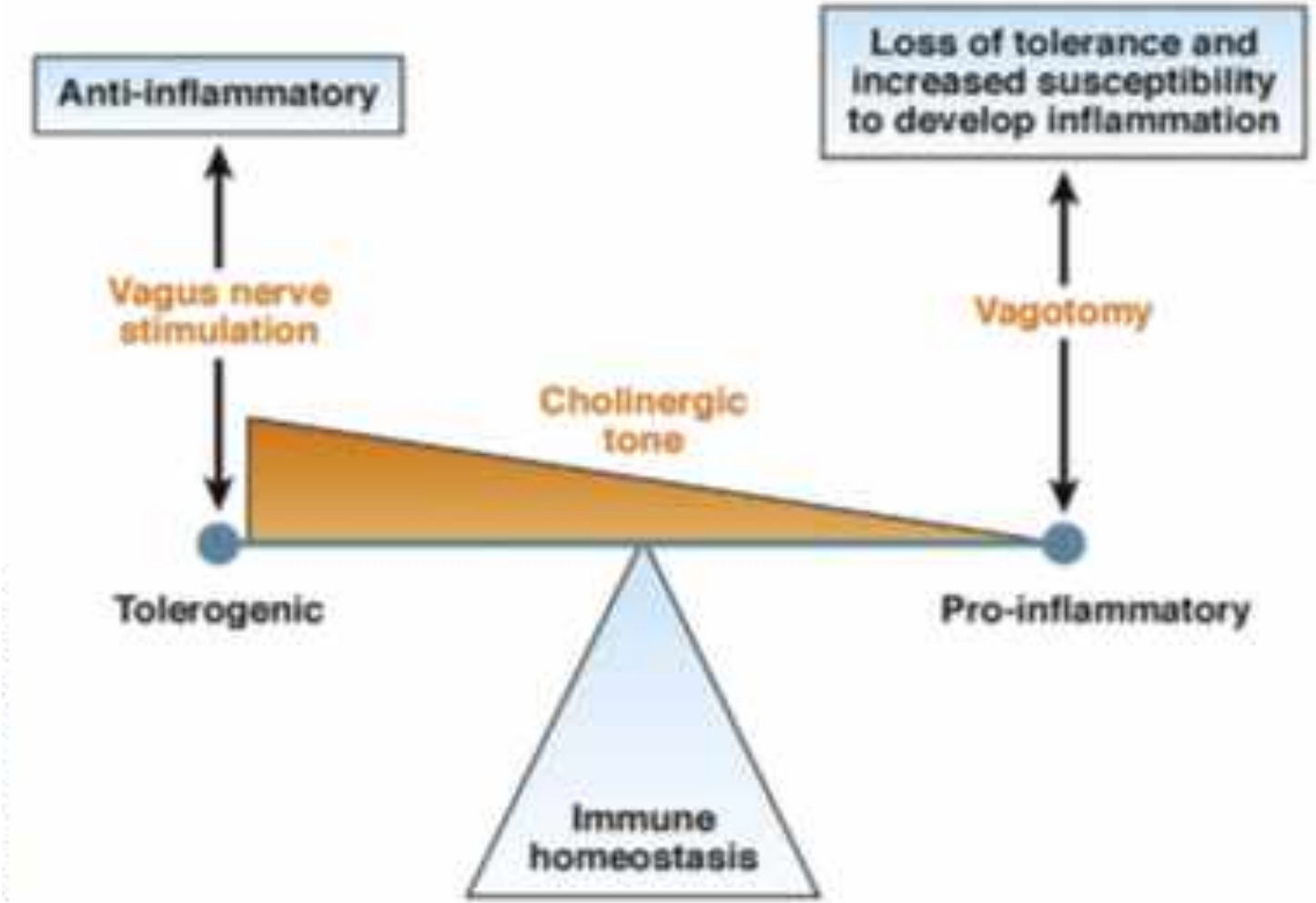
Walker KA, et al. Midlife systemic inflammatory markers are associated with late-life brain volume: The ARIC study.

Inflammation Brain Volume

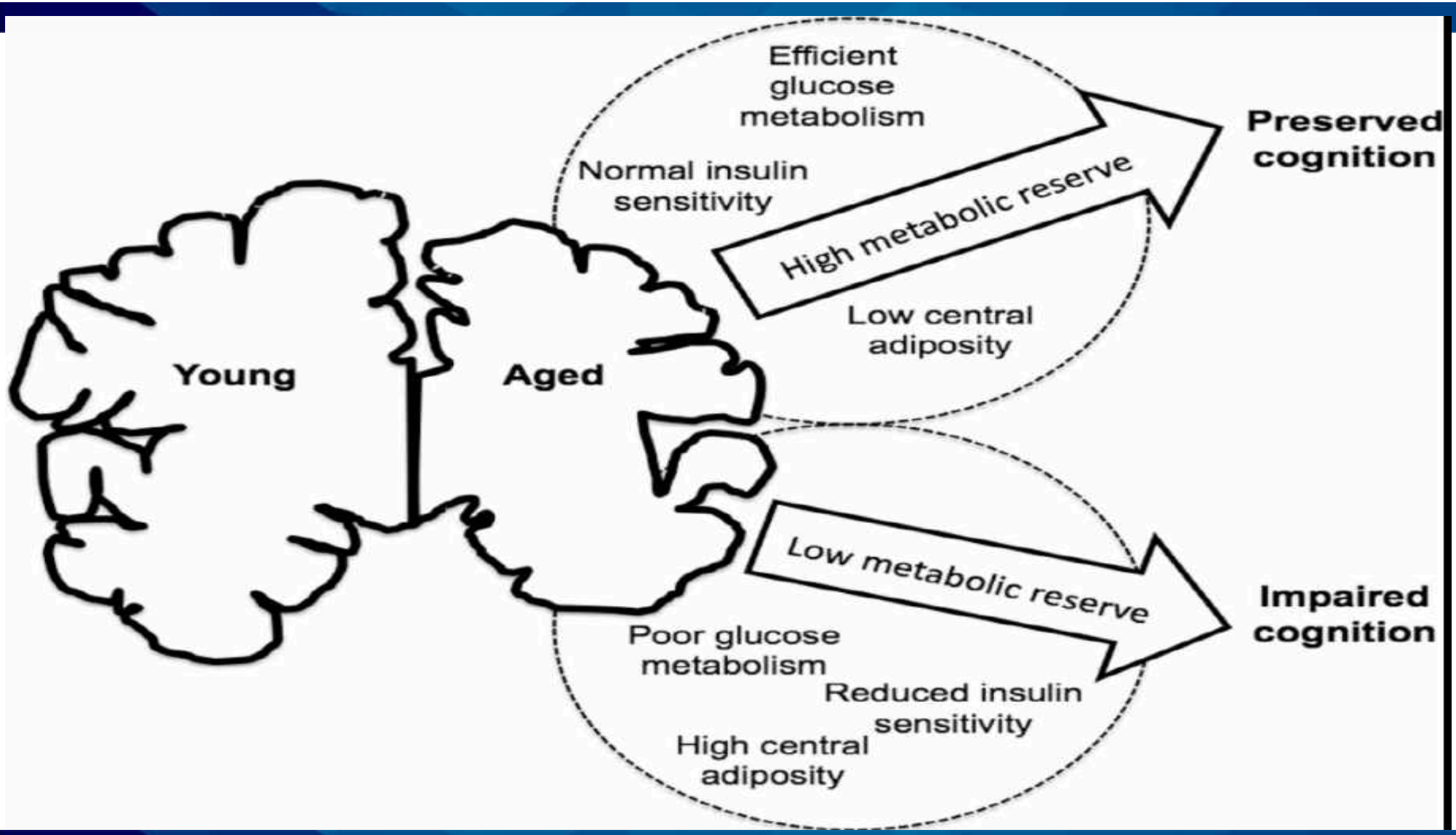
- Compared to participants with no elevated (4th quartile) midlife inflammatory markers - participants with elevations in 3 or more markers had, on average, 5% smaller hippocampal region volumes

- **Authors conclude:**
  - Systemic inflammation is a major contributor to neurodegeneration and cognitive aging

Walker KA, et al. Midlife systemic inflammatory markers are associated with late-life brain volume: The ARIC study.



Browning, et al. Gastroenterology. 2016; pii: S0016-5085(16)35487-7.


Efficient glucose metabolism
Normal insulin sensitivity
High metabolic reserve
Low central adiposity
Preserved cognition
Young
Aged
Low metabolic reserve
Poor glucose metabolism
Reduced insulin sensitivity
High central adiposity
Impaired cognition

Overreaching and Overtraining Effects on Autonomic Nervous System

- Clinical study; 43 athletes and 35 sedentary individuals
- Analyzed ANS function using Autonomic Balance Test and HRV
- Results lower HRV and lower vagal influence along with increased sympathetic cardiovascular control in athletes with nonfunctional overreaching
  (NFO) and particularly in over trained (OTS) athletes
- Total Autonomic Dystonia reported in 67% of those with OTS

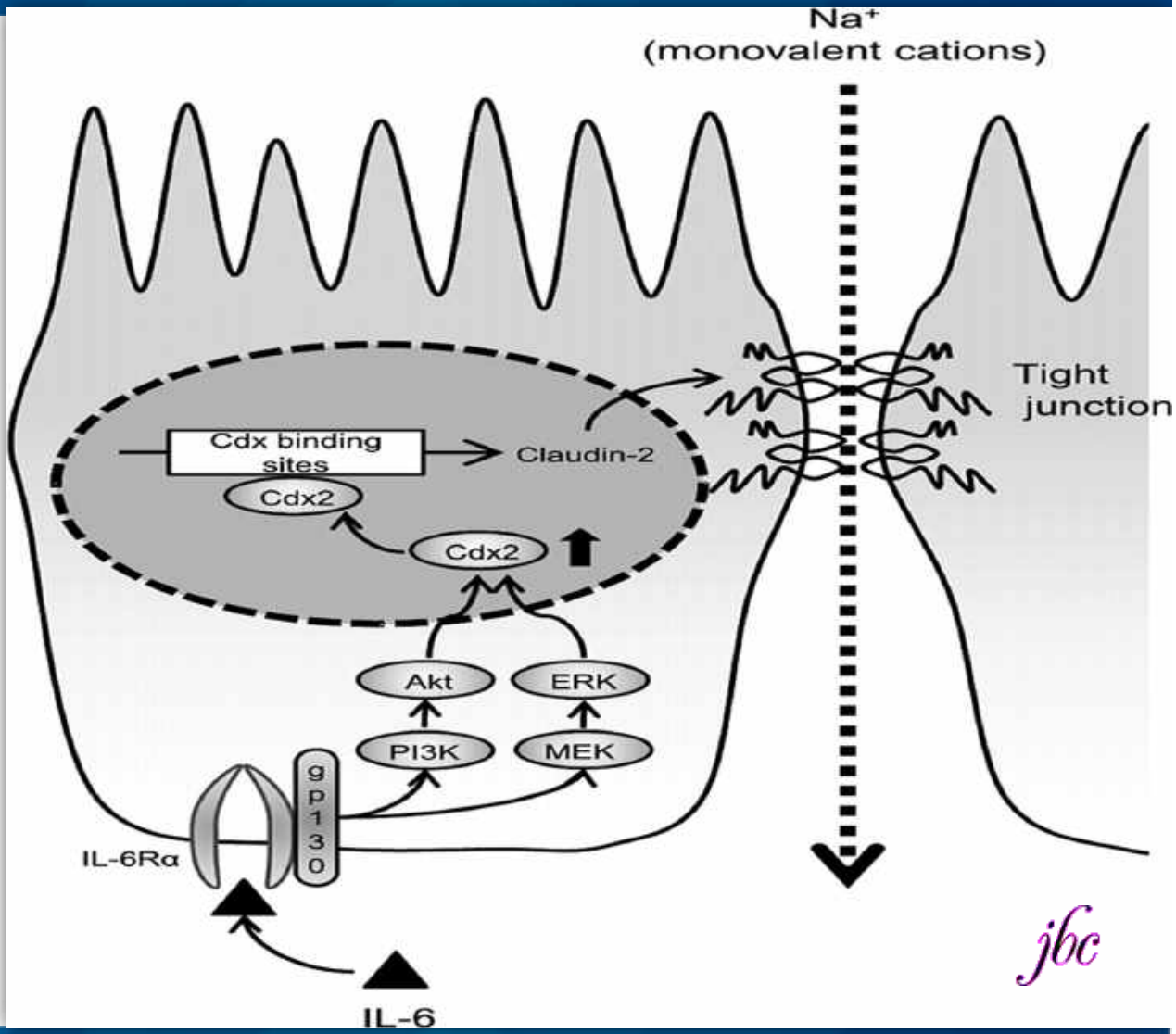
Kajala T, et al. The effects of non-funcitonal overreaching and overtraining on autonoic nervous system function in hightly trained athletes. Georgian Med News. 2017;(264):97-103.

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

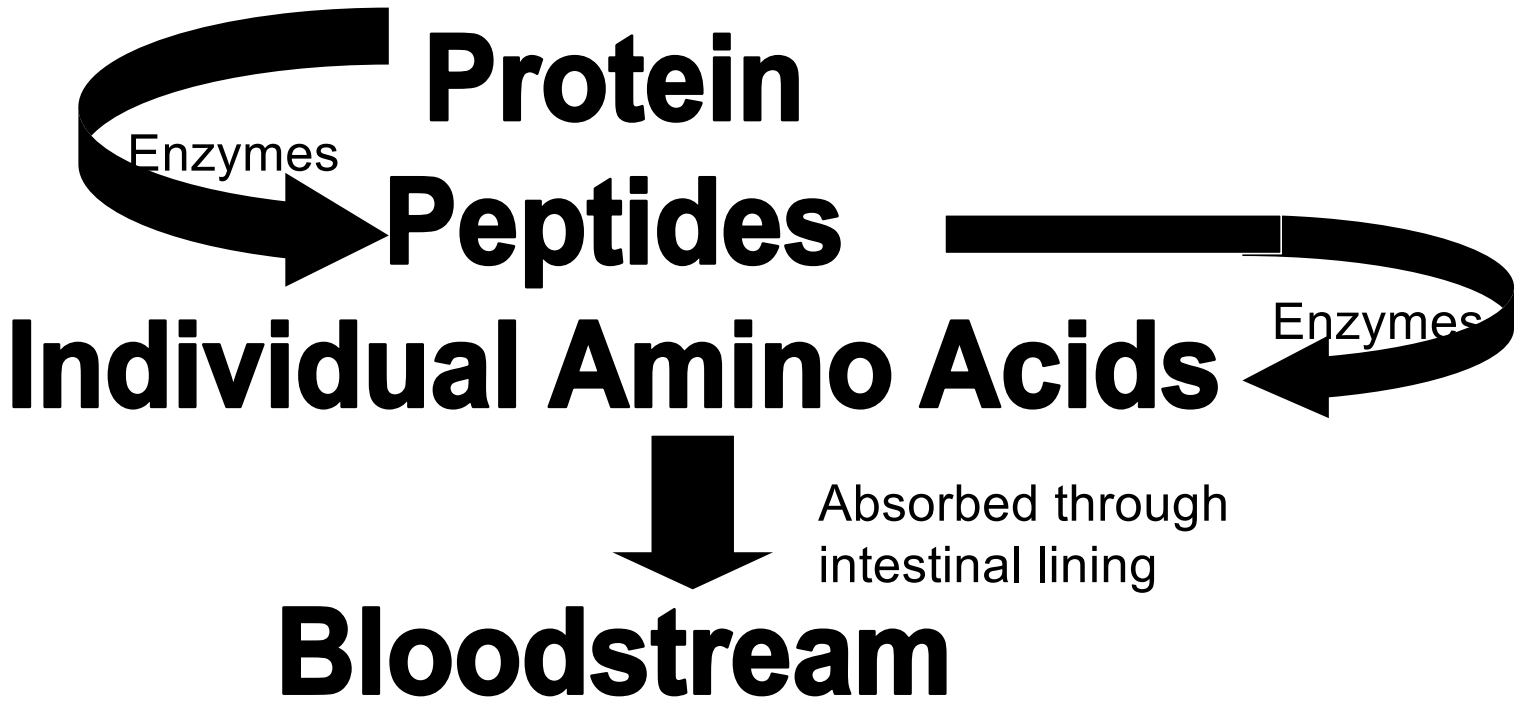
- Key immune cytokine in chronic inflammation
- Induced by chronic hypercortisolism and flattening of cortisol curve
- Induced in overtraining in athletes
- Markedly induces expression of Claudin-2
- Disrupts tight junction structure (TJ) multi-protein structure (disrupts protein scaffold cytoskeleton)

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

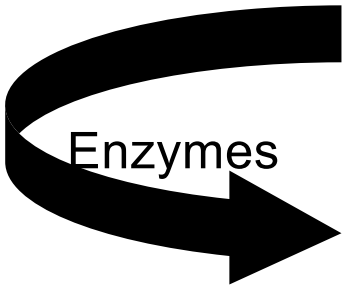
- IL-6-mediated increase in the Tight Junction permeability - intestinal epithelium cells



Normal Digestion



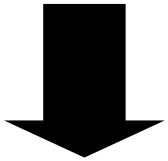
Abnormal Digestion



Protein

Peptides

Insufficient enzymes

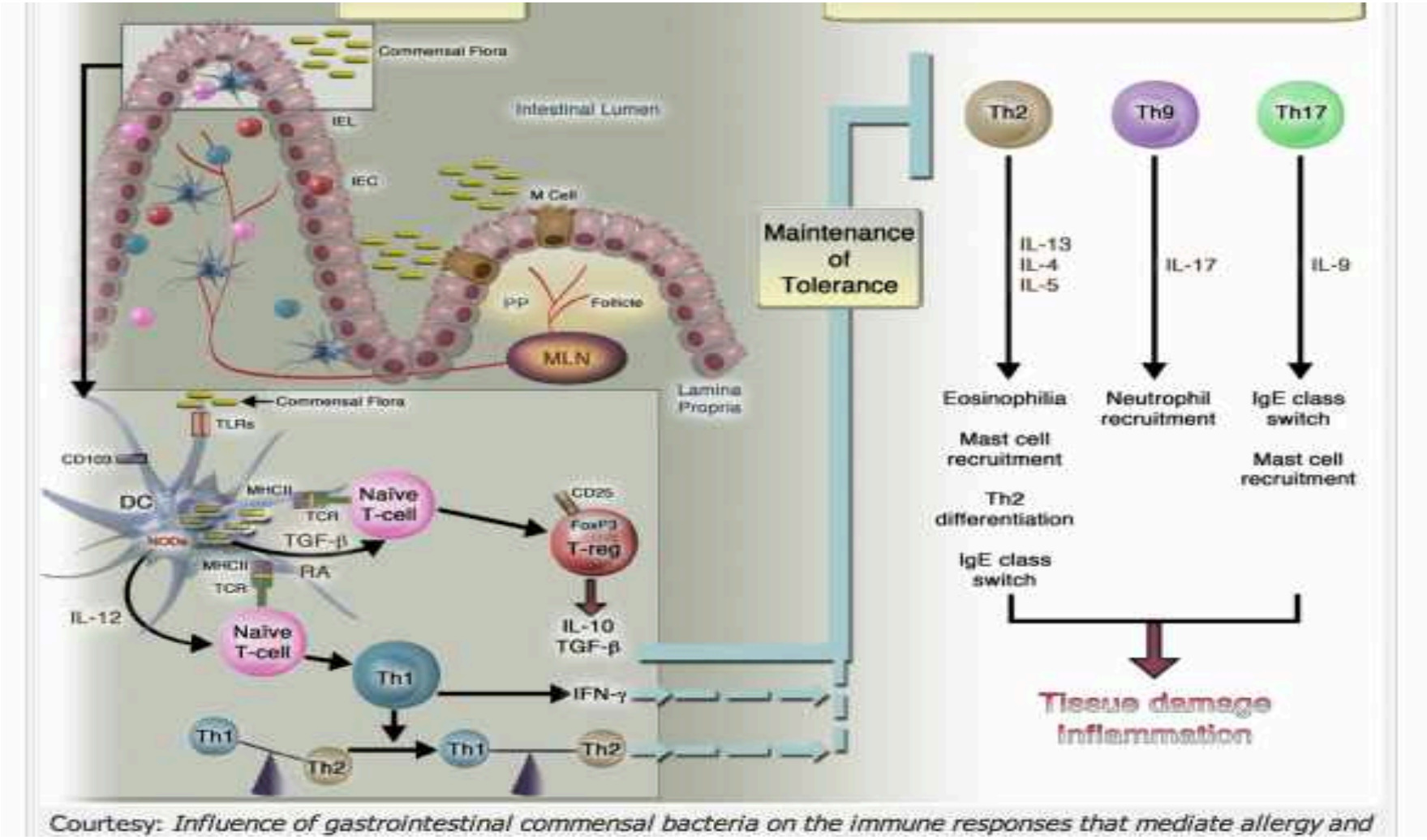


Peptides are not broken down to individual amino acids.

Bloodstream

Intestine

Effector T-helper cells in Allergy



Courtesy: *Influence of gastrointestinal commensal bacteria on the immune responses that mediate allergy and*

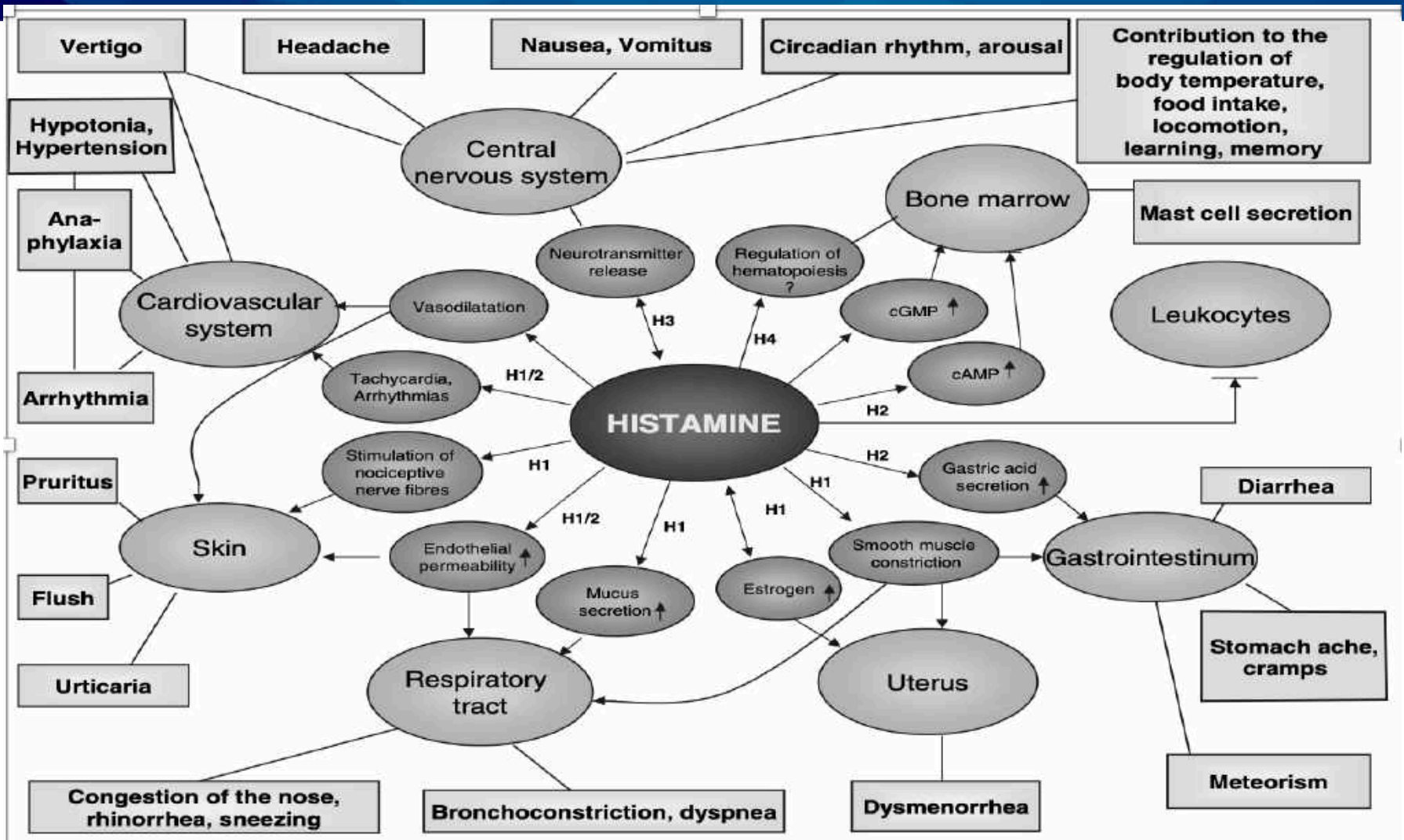
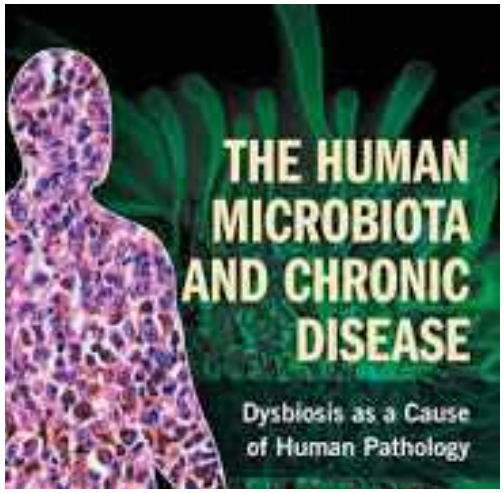


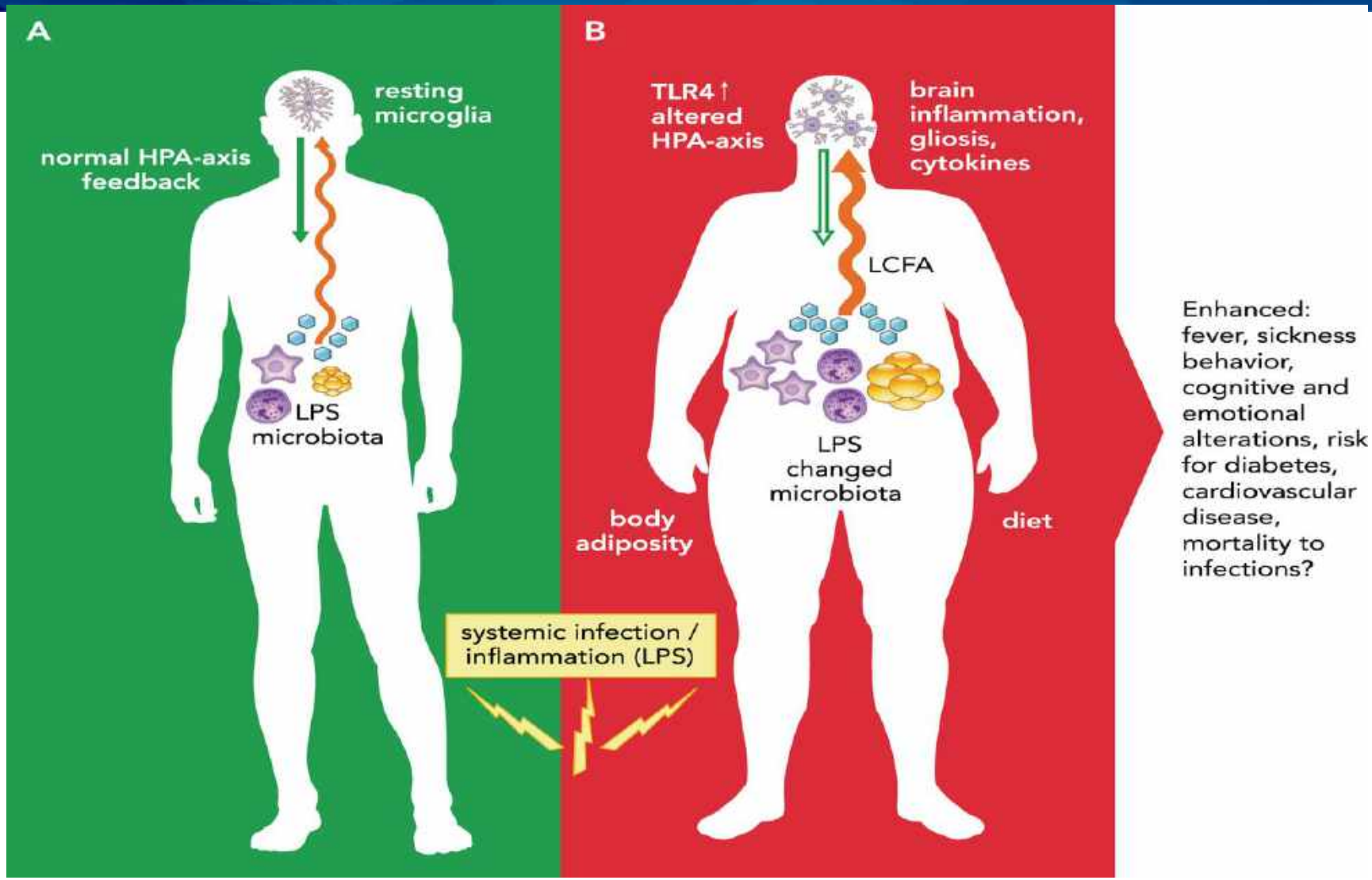
FIGURE 1. Summary of histamine-mediated symptoms. Adapted with permission from Maintz L et al. Dtsch Artzebl 2006;103:A3477-83.

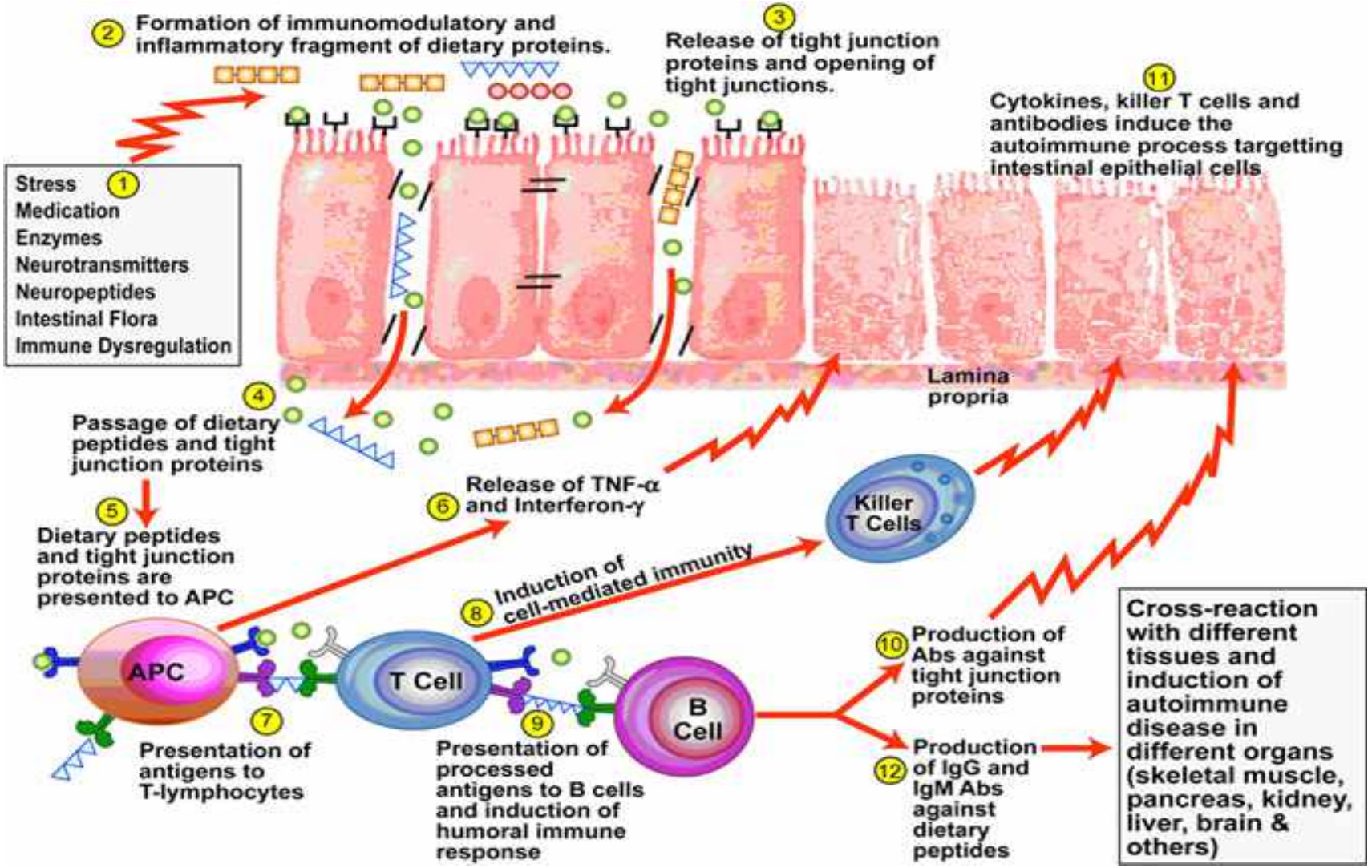


Most All Chronic Diseases Are Reporting Dysbiosis - Altered Microbiomes

Results of Dysbiotic GUT

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


A
resting microglia
normal HPA-axis feedback
LPS microbiota
B
TLR4 ↑ altered HPA-axis
brain inflammation, gliosis, cytokines
LCFA
LPS changed microbiota
body adiposity
diet
systemic infection / inflammation (LPS)
Enhanced: fever, sickness behavior, cognitive and emotional alterations, risk for diabetes, cardiovascular disease, mortality to infections?


2 Formation of immunomodulatory and inflammatory fragment of dietary proteins.
3 Release of tight junction proteins and opening of tight junctions.
11 Cytokines, killer T cells and antibodies induce the autoimmune process targetting intestinal epithelial cells
Stress
Medication
Enzymes
Neurotransmitters
Neuropeptides
Intestinal Flora
Immune Dysregulation
1
Lamina propria
4 Passage of dietary peptides and tight junction proteins
5 Dietary peptides and tight junction proteins are presented to APC
6 Release of TNF-α and Interferon-γ
Killer T Cells
8 Induction of cell-mediated immunity
APC
T Cell
B Cell
7 Presentation of antigens to T-lymphocytes
9 Presentation of processed antigens to B cells and induction of humoral immune response
10 Production of Abs against tight junction proteins
12 Production of IgG and IgM Abs against dietary peptides
Cross-reaction with different tissues and induction of autoimmune disease in different organs (skeletal muscle, pancreas, kidney, liver, brain & others)

Drug Induced Microbioime Disruption (DIMD)

- Prescription and non-prescription drugs can alter the microbiome
- Potentially disrupting metabolic Pathways
- DIMD can lead to metaflammation if not corrected
- Affects all facets of metabolism
  - Nutrient absorption
  - GUT-IMMUNE-BRAIN axis
  - Blood glucose balance/insulin resistance
  - Hormonal balance – sex / thyroid / appetite
  - Sleep
  - Detoxification

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

What Drugs Commonly Affect the Microbiome

- Antibiotics
- NSAIDs
- Corticosteroids
- OCs/HRT
- PPIs / H2 blockers
- Metformin
- Statins
- Antisychotics
- Opioids
- OTHERS not studied??

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

Metaflammation and Chronic Heart Disease

- Increased CRP directly interferes with NO formation by increasing endothelin-1
  - Increased endothelial dysfunction
  - Increased atherogenesis

- TNF and IL-1β downregulate Ca^{+2}-related gene expression, including sarcoplasmic reticulum Ca^{+2} ATPase and Ca^{+2} release channels

- Impairs the efficiency of gap junction mechanisms

- Leads to dysregulated electrical conduction and unsynchronized contraction

Kanbay M, et al. A journey from microenvironment to macroenvironment: the role of metaflammation and epigenetic changes in cardiorenal disease. Clin Kidney J. 2019;12(6):861-70.

Metaflammation and Chronic Heart Disease

- Negative inotropic effect on myocytes,
- Eccentric cardiomyocyte hypertrophy, myocardial fibrosis, ventricular dilation and ultimate CHF
- CKD-driven Klotho deficiency also contributes to cardiomyopathy
- GUT microbiota alterations also links metaflammation and CHD/CKD

Kanbay M, et al. A journey from microenvironment to macroenvironment: the role of metaflammation and epigenetic changes in cardiorenal disease. Clin Kidney J. 2019;12(6):861-70.

Lymphatic – Metaflammation Interplay

- Lymphatic vessels are routes for leukocyte migration and fluid drainage
- Also active role in immune regulation
- Tissue inflammation rapidly induces lymphatic endothelial cell proliferation and chemokine production
- Results in lymphangiogenesis
- Lymphatic endothelial cells induce T cell tolerance

Shin K, et al. Interplay between inflammatory responses and lymphatic vessels. Immune Network. 2014;14(4):182-86.

Assessing Metaflammation- LABS

- Cortisol serum
- CRP-hs
- MPV
- Vitamin D total
- IL-6
- Monocytes/Basophils/Eosinophil %
- WBC's
- Platelets
- Fibrinogen
- 8-OHdG
- F2 isoprostane
- Iron total
- Ferritin
- % saturation
- TIBC

8-OHdG

- Urinary 8-OHdG = 8-hydroxy-2'-deoxyguanosine
- Marker of oxidative stress level and DNA damage
- Factor of initiation and promotion of cancer
- Increased levels reported to induce transversion of DNA bases guanine to thymine
  - This mutation commonly reported in cancers
- Elevated indicates high level of oxidative stress
  - Correlates with poor DNA and mitochondrial health

Pliger A, et al. Int J Occup Environ Health. 2006;80(1):1-15.
Valavanidis A, et al . J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 2009;27(2):120-39.

8-OHdG

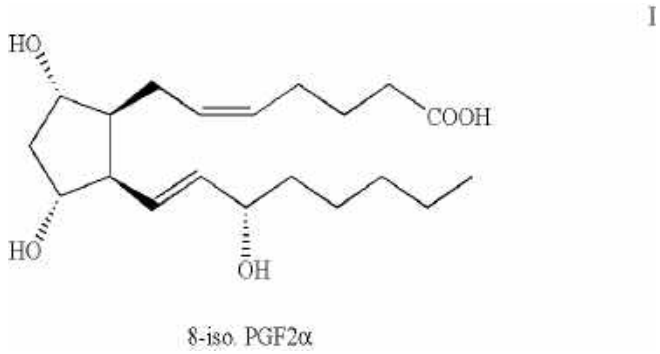
- Urinary level
  - < 8.2 optimal ng/mg creatinine

DNA/RNA Oxidative Damage Assay; Urine

	RESULT / UNIT	REFERENCE INTERVAL	LOW MODERATE HIGH
8-hydroxy-2'-deoxyguanosine* (8-OHdG)	**10.4ng/mg creat**	< 8.2	
			PERCENTILE 2.5th 16th 50th 84th 97.5th
Creatinine	**226 mg/dL**	35- 240	

- Support levels with antioxidant supplements and nutrients

F2 isoprostanes



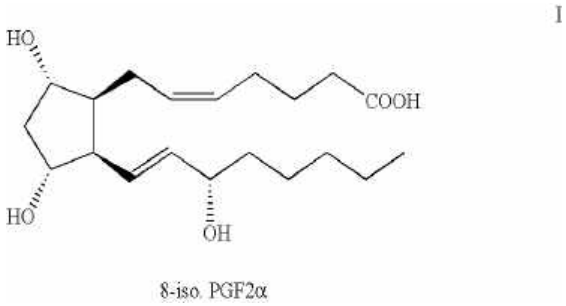
8-iso PGF2α

- F2 isoprostanes
- Formed by peroxidation of arachidonic acid
- High levels = high lipid peroxidation
  - High oxidative stress burden
  - Poor mitochondrial membrane health
- Urinary range ≤ 1.0 ng/mg creatinine

Milne GL, et al. F2-isoprostances as markers of oxidative stress in vivo: an overview. Biomarkers. 2005;10 Suppl 1:S10-S23.

F2 isoprostanes

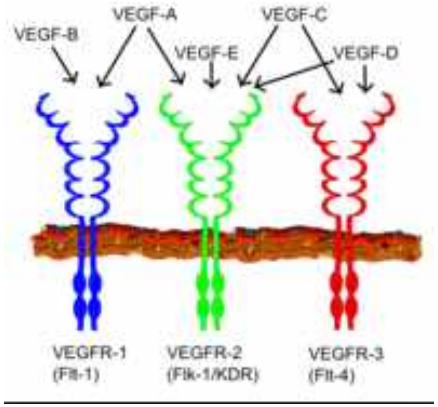
- 2009 Shanghai Women's Health Study
- 74,942 Chinese women ages 40-70
- Urinary F2 isoprostane levels
- In women with BMI > 29, high levels of F2 isoprostane associated with increased breast cancer



8-iso. PGF2α

Dai Q, et al. Oxidative sterss, obesity, and breast cancer risk: results from the Shanghai Women's Health Study. J Clin Oncol. 2009;27(15):2482-8.

VEGF



- Vascular endothelial growth factor VEGF
- 45 kDalton glycoprotein
- Bind to receptors exhibiting tyrosine-kinase activity (RTK)
- Marker of tumor angiogenesis
- Increases vascular permeability
- Reported to undergo autocrine and paracrine stimulation in tumoral angiogenesis
- Elevated levels correlate with increased cancer metastasis

Shinkaruk S, et al. Vascular endothelial cell growth factor (VEGF), an emerging target for cancer chemotherapy. Curr Med Chem Anticancer Agents. 2003;3(2):95-117.

VEGF

- Range 31 – 86 pg/mL (Quest) serum
- 61 - 86 trending high
- Lower VEGF levels associated with neurodegeneration

Devos D, et al. Low levels of the vascular endothelial growth factor in CSF from early ALS patients. Neurology. 2004;62(11):2127-9.

VEGF Support

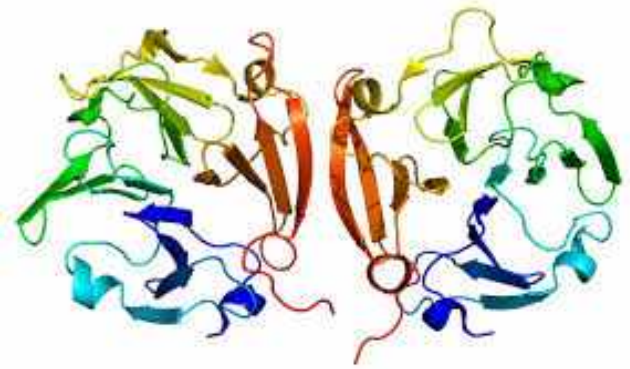
- Provide antioxidant support
  - Zeaxanthin
  - Lutein
  - Flavonoids and vitamin E reported to reduce release of VEGF from human tumor cells
  - N-acetyl cysteine reported to down regulate VEGF
- Fermented Wheat Germ Extract - antiangiogenic

Schindler R, et al. Flavonoids and vitamin E reduce the release of the angiogenic peptide vascular endothelial growth factor from human tumor cells. J Nutr. 2006;136(6):1477-1482.

Imit NG, et al. Mechanism of the antiangiogenic effect of Avemar on tumor cells. Oncol Lett. 2018;15(2):2673-78.

MMP-9

- Matrix metalloproteinase-9
- Zinc dependent end peptidases
- Marker of oxidative stress ; inflammation
- Levels elevated in:
  - Cancer
  - Autoimmune / RA, MS
  - CAD
  - COPD
  - Asthma
  - Gingivitis/periodontal disease



Cathcart J, et al. Targeting matrix metalloproteinases in cancer: bringing new life to old ides. Genes Dis. 2015;2(1):26-34.

MMP-9

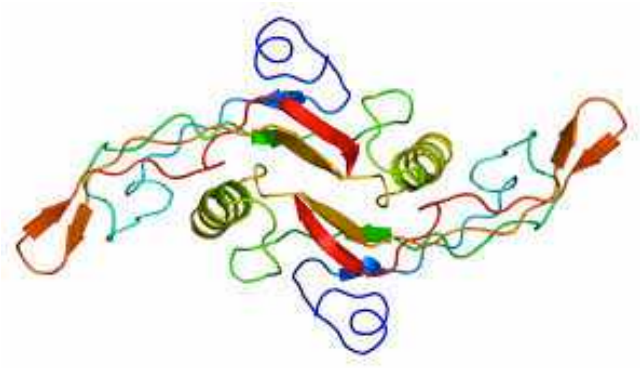
- Expression in cancer tied to tumor aggressiveness, stage and patient prognosis
- MMPs influence tumor environment
  - Promotes angiogenesis
  - Increased tumor growth
  - Increased metastasis
- Also important in synaptic plasticity
  - Low levels impair
- < 901 ng/mL optimal ; serum

Cathcart J, et al. Targeting matrix metalloproteinases in cancer: bringing new life to old ides. Genes Dis. 2015;2(1):26-34.

Kacmarek L. MMP-9 in control of synaptic plasticity: a subjective account. OMP. 2016;2(2):103-111.

TGF-beta 1

- Transforming growth-factor beta 1
- Polypeptide cytokine
- Marker of cellular :
  - Proliferation
  - Growth
  - Differentiation
  - Apoptosis
- Involved in cancer growth and progression
- Quest range 344-2372 pg/mL



Jakowlew SB. Transforming growth factor-beta in cancer and metastosis. Cancer Metastasis Rev. 2006;25(3):435-57.

TGF-beta 1 Breast Cancer

- 2003 study
- TGF-beta 1 levels in n=44 breast cancer patients vs. healthy donors n= 36
- Plasma TGF-beta 1 significantly elevated in metastatic patients vs. healthy
- Especially elevated in newly diagnosed + patients
- Similar results in other cancer-type studies

Ivanovic V,e t al. Elevated plasma levels of transforming growth factor-beta 1 (TGF-beta 1) in patients with advanced breast cancer: association with disease progression. Eur J Cancer. 2003;39(4):454-61.

MPV – Mean Platelet Volume

- Platelet size demonstrated to reflect platelet activity
- Useful predictive and prognostic biomarker of cardiovascular events
- Associated with prothrombotic and proinflammatory events
- Changes in MPV reported to be important biomarker for inflammatory processes
- Also neoplastic diseases

Korniluk A, et al. Mean platelet volume (MPV): New perspectives for an old marker in the course and prognosis of inflammatory conditions. Mediat Inflamm. 2019;2019:9213074/

Midlife systemic inflammatory markers are associated with late-life brain volume

The ARIC study

Keenan A. Walker, PhD
Ron C. Hoogeveen, PhD
Aaron R. Folsom, MD, MPH
Christie M. Ballantyne, MD
David S. Knopman, MD
B. Gwen Windham, MD, MHS
Clifford R. Jack, Jr., MD
Rebecca F. Gottesman, MD, PhD

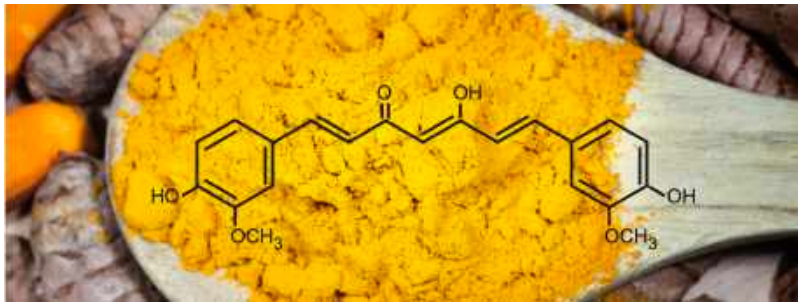
ABSTRACT

Objective: To clarify the temporal relationship between systemic inflammation and neurodegeneration, we examined whether a higher level of circulating inflammatory markers during midlife was associated with smaller brain volumes in late life using a large biracial prospective cohort study.

Methods: Plasma levels of systemic inflammatory markers (fibrinogen, albumin, white blood cell count, von Willebrand factor, and Factor VIII) were assessed at baseline in 1,633 participants (mean age 53 [5] years, 60% female, 27% African American) enrolled in the Atherosclerosis Risk in Communities Study. Using all 5 inflammatory markers, an inflammation composite score was created for each participant. We assessed episodic memory and regional brain volumes, using 3T MRI, 24 years later.

Results: Each SD increase in midlife inflammation composite score was associated with 1,788 mm^3 greater ventricular ($p = 0.013$), 110 mm^3 smaller hippocampal ($p = 0.013$), 519 mm^3 smaller occipital ($p = 0.009$), and 532 mm^3 smaller Alzheimer disease signature region

Metaflammation Nutritional Support



Metaflammation Support – Aged Garlic Extract

- Proprietary Fermented garlic - “Black garlic”
- Supports cardiovascular health
- Over 750 clinical studies supporting uses
- Clinically lowers blood pressure – 16%
- Supports blood vessel integrity
- Antiglycation, diabetes supportive

Reid K, Frank OR, Stocks NP. Aged garlic extract lowers blood pressure in patients with treated but uncontrolled hypertension: a randomised controlled trial. Maturitas. 2010;67(2):144-50.

Metaflammation Support – Aged Garlic Extract

- Supports immunity
- Supports healthy blood lipid levels – LDL, HDL, LDL-P
- Decreases metaflammation
- Decreases coronary artery calcification
- Improves microbiome
- Neuroprotective
- Lowers homocysteine, CRP

Reid K, Frank OR, Stocks NP. Aged garlic extract lowers blood pressure in patients with treated but uncontrolled hypertension: a randomised controlled trial. Maturitas. 2010;67(2):144-50.

New Research
Aged Garlic Extract (AGE) and Reducing Chronic Inflammation

- 2019 double-blind, placebo controlled randomized clinical study
- n= 51 healthy but obese adults
- 3.6gm AGE daily in divided doses x 6wk
- IL-6 and TNF-alpha significantly lower in AGE vs. placebo
- Increased gamma-delta T cells – modulated immunity
- Significant reduction in LDL cholesterol

Xu C, et al. Aged garlic extract supplementation modifies inflammation and immunity of adults with obesity: A randomized, double-blind, placebo-controlled clinical trial. Clin Nutr ESPEN. 2018;24:148-55.

Aged Garlic Extract Dosage

- Improves gingival health – decreases inflammation and bleeding
- 1-2 caps 2 times daily (600-1,200mg)
- Does NOT interact with anticoagulants unlike other garlic preparations
- No odor or taste

Zini A, et al. The efficacy of aged garlic extract on gingivitis – a randomized clinical trial. J Clin Dent. 2018;29(2):5-56.

Thai Ginseng (*Kaempferia parviflora*) root

- aka Black Ginger - in the ginger family
- Contains high level of antioxidant polymethoxyflavones specifically 5,7 dimethoxyflavone
- Improves mitochondrial biogenesis – increased energy
- SIRT-1 upregulation - 3-4x that of resveratrol
- Sirtuins involved in metaflammation
- **Sirtuins are evolutionarily viral restriction factors - antiviral**

Koynucu E, et al. Sirtuins are evolutionary conserved viral restriction factors. mBio. 2014;5(6):e02249-14.

Thai Ginseng (*Kaempferia parviflora*) root

- Reported to inhibit viral proteases
- Reported strong activity vs. pathogenic H5N1 avian influenza virus
- Upregulates of TNF-α and IFN-β mRNA expressions
- Inhibition of virus replication
- Active against cytokine response to virus infection – cytokine "storm"

Sookkongwaree K, et al. Inhibition of viral proteases by Zingiberaceae extracts and flavones isolated from Kaempferia parviflora.
Sompet B, et al. Antiviral activity of five Asian medicinal plant crude extracts against highly pathogenic H5N1 avian influenza virus. Asian Pac J Trop Med. 2017;10(9):871-76.

Thai Ginseng root

- Improves weight management
  - Potent SIRT1 and PPAR gamma regulating
  - Increases whole-body energy expenditure (EE)
  - Improves brown adipose tissue (BAT) production
- PDE5 inhibitor - improves nitric oxide utilization ; not as pronounced effects as PDE5 pharmaceuticals
- Traditionally used in erectile dysfunction

- Yoshino S, Kim M, Awa R, Kuwahara H, Kano Y, Kawada T. 2014. Kaempferia parviflora extract increases energy consumption through activation of BAT in mice. Food Sci Nutr 2: 634–637.
- Promthep K, et al. Effect of Kaempferia parviflora extract on physical fitness of soccer players: A randomized double blind placebo controlled trial. Med Sci Monit Basic Res. 2015;21:100-108.

Thai Ginseng Studies

- Reported to improve athletic performance based on stress response and cardiorespiratory performance

- A 2012 clinical study (n=45, healthy elderly individuals)
  - KP extract, 25 or 90mg daily for 8 weeks
  - 18 Subjects reported improved physical performance (30-second chair stand test and 6 min walk test)
  - Decreased malondialdehyde (MDA) levels (indicating decreased oxidative stress)

Wattanathorn J, Muchimapura S, Tong-Un T, et al. Positive modulation effect of 8-week consumption of Kaempferia parviflora on health-related physical fitness and oxidative status in healthy elderly volunteers. Evid Based Complement Alternat Med. 2012;2012:73816.

Thai Ginseng Studies

- 2015 double blind, placebo-controlled clinical study (n=60)
- 180mg KP standardized extract daily or placebo for 12 weeks in the physical fitness of soccer players using cardiorespiratory fitness testing.
- Right hand grip strength significantly improved in KP group vs. placebo

Promthep K, Eungpinichpong W, Sripanidkulchai B, et al. Effect of Kaempferia parviflora extract on physical fitness of soccer players: a randomized double-blind placebo-controlled trial. Med Sci Monit Basic Res. 2015;21:100-8.

Thai Ginseng Studies

- 2015 clinical study n=20 healthy males ages 21-29
- KP extract 100mg 4% 5,7 DMF single oral acute dose
- Improved whole body energy expenditure
- Increased brown fat (BAT)

Matsushita M, et al. Kaempferia parviflora extract increases whole-body expenditure in humans: roles of brown adipose tissue. J Nutr Sci Vitaminol. 2015;61:79-83

2018 Lab Study

J Med Food. 2018 Jan;21(1):30-38. doi: 10.1089/jmf.2017.3989. Epub 2017 Nov 10.

Standardized Kaempferia parviflora Extract Enhances Exercise Performance Through Activation of Mitochondrial Biogenesis.

Kim MB[1], Kim T[1], Kim C[1], Hwang JK[1].

⊕ Author information

Abstract

Exercise enhances mitochondrial biogenesis in skeletal muscle. Increased mitochondrial function and content can contribute to the improvement in skeletal muscle function and the benefits of exercise by increasing the response to energy demands. The effect of standardized Kaempferia parviflora extract (KPE) on exercise performance was accessed in L6 myotubes and C57BL/6J mice. KPE significantly activated peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) and increased mitochondrial density in L6 myotubes. KPE also upregulated the expression of transcription factors for mitochondrial biogenesis (estrogen-related receptor-α [ERRα], nuclear respiratory factor-1 [NRF-1], and mitochondrial transcription factor A [Tfam]) through activation of PGC-1α in L6 myotubes. In vivo models including normal diet mice and high-fat diet obese mice showed that KPE effectively enhanced running endurance and increased the skeletal muscle weight/body weight ratio. Furthermore, these observations were associated with a significant upregulation of mitochondrial biogenesis regulatory genes in skeletal muscle tissue. KPE enhanced the protein expression of the sirtuin 1 (SIRT1)/adenosine monophosphate (AMP)-activated protein kinase (AMPK)/PGC-1α/peroxisome proliferator-activated receptor-δ (PPARδ) signaling pathway components in vitro and in vivo, acting as an exercise metabolism regulator. These results suggest that KPE has the potential to enhance exercise performance through mitochondrial biogenesis and the SIRT1/AMPK/PGC-1α/PPARδ signaling pathways.

Thai ginseng 2018 human study

- Randomized, double-blind placebo controlled
- N= 76 BMI > 24, but < 30
- 150mg thai ginseng standardized daily for 12 weeks
- Significant reduction in visceral fat area – CT scan
- Significant reduction in triglycerides
- No difference in total cholesterol, LDL, BP and HR

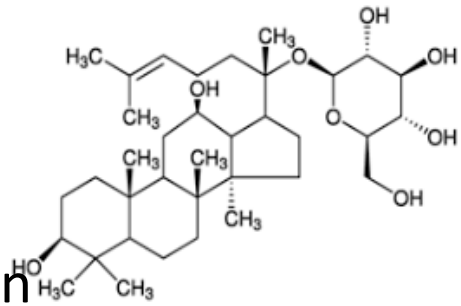
Yoshino S, et al. Diabetes Metab Syndr Obes. 2018;11:447-58.

Thai Ginseng Dosage

- 100mg AM daily std. to 4% 5,7 dimethoxyflavone
- Use with caution if patient taking prescribed PDE5 inhibitors
- 5,7-DMF markedly decreases expression of CYP3A11 and CYP3A25 in the liver – no evidence of real herb/drug interactions
  - Midazolam levels increased in lab studies – no human data
- There is no evidence of use in pregnancy – use caution

Ochiai W, et al. Effects of active ingredient of Kaempferia parviflora 5,7 dimethoxyflavone on the pharmacokinetics of midazolam. J Nat Med. 2018;72(3):607-14.
Nakata A, et al. Potent SIRT1 enzyme-stimulating and anti0glycation activities of polymethoxyflavonoids from Klaempferia parviflora. Nat Prod Commun. 2014;9(9):1291-4.

Compound K Metaflammation



- New to US market in 2020
- Compound K is a product of ginseng fermentation – either in manufacturing using bacterial fermentation or by human GUT microflora
- Compound K is the ginsenoside component that exerts biological activity in vivo
- The STEM cell of ginsenosides
- Other ginsenosides metabolized to Compound K
- Chinese developing pharmaceuticals using CK for
  - Epilepsy
  - Rheumatoid arthritis

Yang XD, et al. A review of biotransformation and pharmacology of ginsenoside compound K. Fitoterapia. 2014;209-17.

Compound K ginsenoside - Lab and Human Studies

- Gut/microbiome supportive
- Antiinflammatory/antioxidant
  - regulation of iNOS, PGs, cytokines, COX-2
- Anti-aging
  - photoprotective, increases Type 1 procollagen, increase hyaluronan production
- Neuroprotection/neurogenesis
  - inhibits microglial inflammation
  - Regulates $GABA_A$ transmission and suppresses NMDA excitotoxicity

Wang HY, Qi LW, Wang CZ, Li P. Bioactivity enhancement of herbal supplements by intestinal microbiota focusing on ginsenosides. Am J Chin Med 2011;39:1103e15.

Compound K ginsenoside

- Cognitive support – improves learning
- Immune supportive – Th1/Th2; antiviral
- Anticancer – increases apoptosis, decreases angiogenesis, decreases proliferation and motility of cancer cell lines
- Cardiovascular – increased nitric oxide, improves lipids
- Hepatoprotective

Wang HY, Qi LW, Wang CZ, Li P. Bioactivity enhancement of herbal supplements by intestinal microbiota focusing on ginsenosides. Am J Chin Med 2011;39:1103e15.

Compound K ginsenoside

- Blood glucose/insulin regulation
  - In vivo and in vitro comparable to Metformin antidiabetic activity
  - Enhances insulin secretion
  - Improved glucose tolerance – increases glucose uptake
  - Up regulates glucose transporter
  - Inhibits lipogenesis
  - PPAR gamma stimulation
  - Improved glucose uptake in adipocytes
  - Stimulates GLP-1 release in hepatic cells via bile acid receptor activation

- Yoon SH, et al. Antidiabetic effects of compound K versus metformin versus compound K-metformin combination therapy in diabetic db/db mice. Biol Pharm Bull. 2007;30(110:2196-200.
- Yuan HD, et al. Ginseng and diabetes: the evidences from invitro animal and human studies. J Ginseng Res. 2012;36(1):27-39.

Compound K - Antiviral Activity

- Modulates Th1/Th2 antibody responses
- Direct antiviral activity against influenza subtypes (H1N1
- Ginseng inhibits biofilm formation
- Induces the dispersion and dissolution of mature biofilms
- Improves viral clearance

Alipour M. Ginseng aqueous extract attenuates the production of virulence factor, stimulates twitching and adhesion and eradicates biofilms of Psuedomonas aeroginosa. Can J Physiol Pharmacol. 2011;89(6):419-27.

Kim DH. Gut microbiota-medicated pharmacokinetics of ginseng saponins. J Ginseg Res. 2018;42:255-63.

Compound K

- Dosage = 150mg BID
  - Standardized to 5% CK
  - Take on empty stomach if possible

- Reported safe in recommend doses

- Ginsenosides reported to decrease platelet aggregation
  Monitor patients appropriately

Zhou CL, et al. Single and multiple dose trials to determine the pharmacokinetics, safety, tolerability and sex effect of oral ginsenoside Compound K in healthy Chinese volunteers. Front Pharmacol. 2016;8:965.

Curcumin

- From turmeric (*Curcuma longa)* root/rhizome

- Traditionally for dyspeptic conditions

- Curcuminoids reported:
  - Antiinflammatory
  - Decreases inflammasome signaling
  - Supports musculoskeletal system
  - Joints/connective tissue support
  - Helps improve flexibility and mobility

Curcumin - Metaflammation

- Decreases oxidative stress via Nrf2-keap1 pathway
- Inhibits nuclear factor-kappaB
- Inhibits Toll-like receptor 4-dependent signaling pathways
- Inhibits activation of a peroxisome proliferator-activated receptor-gamma pathway.

Castro CN, et al. Curcumin ameliorates autoimmune diabetes,. Evidence in accelerated murine models of type 1 diabetes. Clin Exp Immunol. 2014;177(1):149-60.

Curcumin Metaflammation

- Modulates multiple cell signaling molecules
  - TNF-alpha
  - IL 1, IL-6
  - COX-2 and 5-lipoxygenase
  - NF-kappaB
  - CRP
  - PgE2
  - TGF-beta
  - AST/ALT
  - Malondialdehyde MDA
- Lab study reports curcumin ameliorates pancreatic beta cell destruction in autoimmune diabetes

Castro CN, et al. Curcumin ameliorates autoimmune diabetes,. Evidence in accelerated murine models of type 1 diabetes. Clin Exp Immunol. 2014;177(1):149-60.

Curcumin - Completed Human Clinical trials

These performed globally with varied dosages and forms – raw herb, standardized and extracts

- Alzheimer's
- Acute coronary syndrome
- Atherosclerosis
- Diabetes,
- Cancers – colorectal, breast, multiple myeloma, pancreatic, prostate, lung, oral lesions, head/neck squamous cell
- Inflammatory Bowel Diseases (IBDs)
- Osteoarthritis
- Uveitis
- Chronic bacterial prostatitis
- Alcohol intoxication
- Chronic arsenic exposure
- Recurrent respiratory tract infections
- Postoperative inflammation
- Peptic ulcer/H. pylori infection
- Idiopathic orbital inflammatory pseudotumor
- Vitiligo
- Psoriasis
- Dejerine-Sottas Disease
- Renal transplants
- Lupus nephritis
- AIDS
- Beta-thalassemia
- Biliary dyskinesia, gallbladder contractions

Gupta SC, et al. AAPS Journal. 2013;15(1):195-206.

of Types of Curcumin Products on Global Market – Which One to choose?

Prasad S, et al. Cancer Res Treat. 2014;46(1):2-18.

Oral, GI Absorbed Curcumin – Dosage

- Oral encapsulated
  - 500-750mg BID-TID of curcuminoids 98%
  - + added Bioperine (extract of black pepper, piperine) for improved bioavailability – NOT OPTIMAL
- Bioavailability of active curcuminoid compounds still suffers -1st pass effect
- Take with food

Prasad S, et al. Cancer Res Treat. 2014;46(1):2-18.

Recent Curcumin Headlines....

CHEMICAL BIOLOGY

Curcumin Will Waste Your Time

By Derek Lowe | 12 January, 2017

- Curcuminoids (I, II, and III) are poorly bioavailable orally
  - IV curcumin – Asia, Europe, Central and S. America
  - Topical curcumin
  - Intranasal curcumin
  - Improved oral extractions – 95% curcuminoids + bioperine
  - Water-soluble curcumin
  - Sublingual liposomal curcumin
  - Sublingual nanoparticle curcumin
- Led to development of superior bioavailable and clinically useful curcumin product - an oral nanospray
- SMART technology using safe ingredients for the microbiome

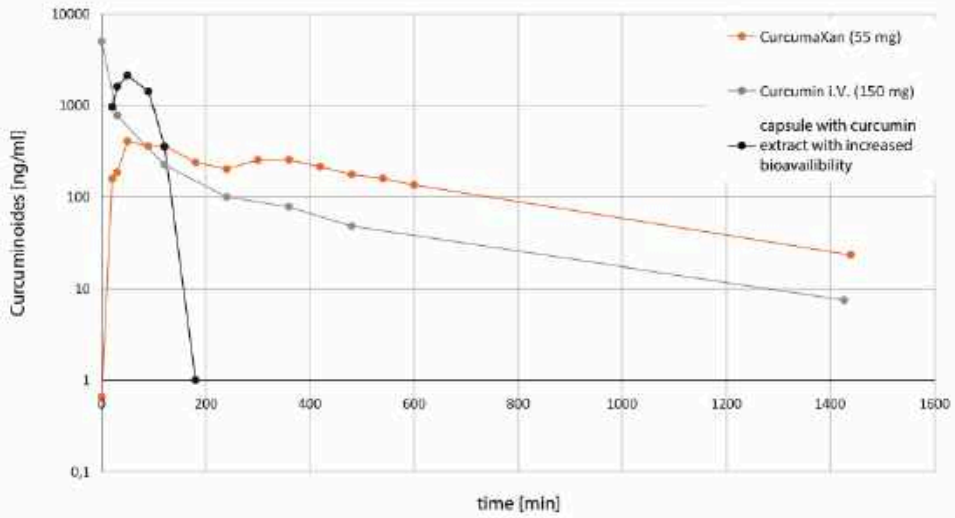
Curcumin- NanoSpray

- 99% curcuminoid oral spray; Curcuminoids I, II and III
- 94% higher absorption than a curcumin capsule with optimized uptake at 1/10 of the dose =
  - 313-fold higher absorption than a curcumin capsule at 3% of the dose
- 410% higher absorption compared to curcumin infusion at a comparable dose =
  - 50% better absorption than 1/3 of the dose of curcumin infusion
- Consistently high level of curcuminoids for daily use at a fract

Of oral doses

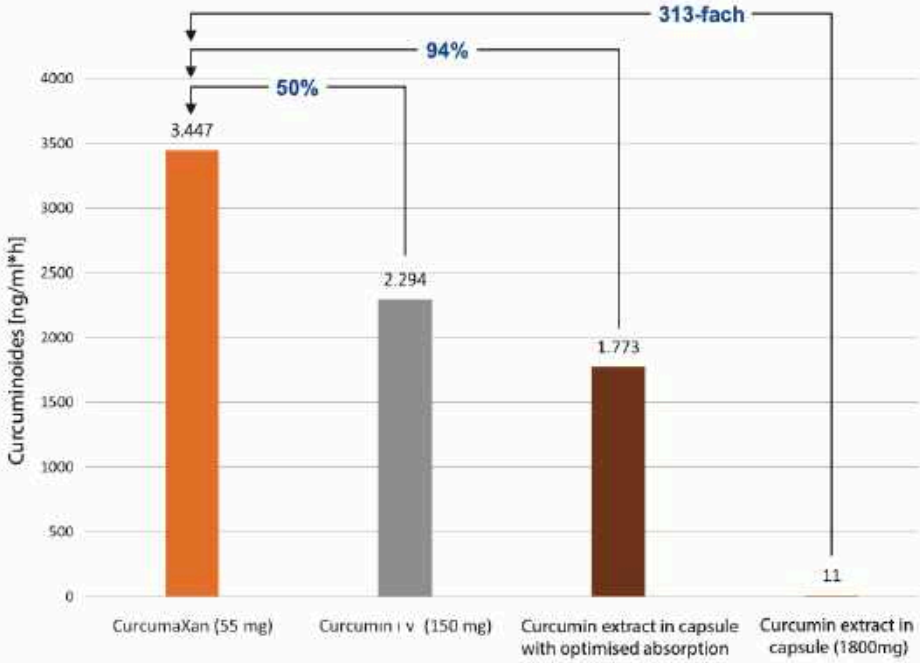
Castro CN, et al. Curcumin ameliorates autoimmune diabetes,. Evidence in accelerated murine models of type 1 diabetes. Clin Exp Immunol. 2014;177(1):149-60.

Comparison of pharmacokinetics data from a curcumin infusion and a curcumin capsule with optimised uptake



Comparison of the pharmacokinetics data of [illegible] at a dose of 55 mg curcumin and a curcumin infusion at a dose of 150 mg.

Comparison of AUC values [ng/ml*h] over 24 h of [illegible] curcumin infusion and curcumin capsules



Apurano Pharmaceuticals, Warngau Germany

Curcumin NanoSpray Indications

- Control metainflammatory responses
- Osteoarthritis
- MetS – insulin/blood glucose,
- Cardiovascular support – atherosclerosis;
- Exercise recovery
- Oncological indications - cancer
- IBDs - inflammatory bowel diseases
- Postoperative inflammation/pain
- Skin issues – psoriasis, eczema, dermatitis

Curcumin Oral Spray – Dosage

- Oral Water soluble nanospray
  - 9 sprays daily (3 sprays TID) = 54mg curcuminoids daily total
  - 54 mg is bioequivalent to approx. 600mg (300mg BID) "regular" 95% curcumin extracts
  - **Nanocurcumin effective at 9% of general oral dose**
  - 20ml bottle contains 840mg curcumin
  - EU proprietary formulation
  - Improved bioavailability over C3 and other curcumin products
  - Stability studies x 2yrs
  - Sublingual delivery
  - Pharmaceutically manufactured - sterile

Prasad S, et al. Cancer Res Treat. 2014;46(1):2-18.

Curcumin Contraindications/Side Effects

- Studies have assessed safety of doses from 500mg - 12,000 mg
  - Transient side effects most common – diarrhea, headache, rash, yellow stool, abdominal pain

- Potential to increase ALP (alkaline phosphatase) & LD (lactate dehydrogenase)

- As per German Commission E monographs:
- Turmeric should not be used in biliary obstruction
- Curcuminoids are reported to have biliary stimulatory activity

Gupta SC, et al. AAPS Journal. 2013;15(1):195-206.

Dietary Changes

- Chronic consumption of Western Diet + sedentary behavior = Metaflammation
- High fat, high fructose-based and excessive calories induces metaflammation
- Memorized' by innate immune cells through long-lasting metabolic and epigenetic cellular reprogramming
- Increased link between Western Diet and CKD (chronic kidney disease) and CHF (congestive/chronic heart failure)

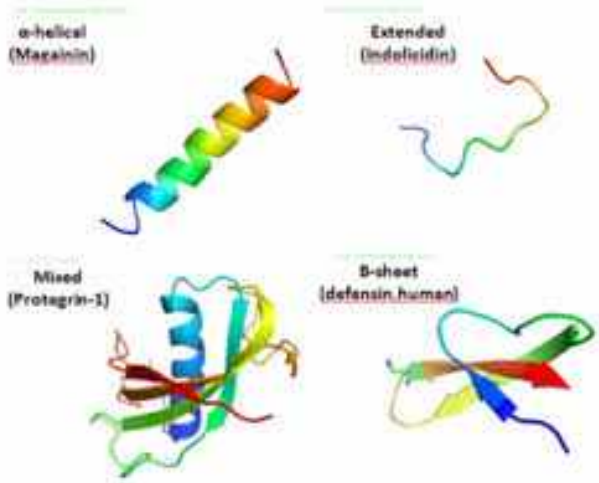
Christ A, et al. The Western lifestyle has lasting effects on metaflammation. 2019;19:267-68.
Kanbay M, et al. A journey from microenvironment to macroenvironment: the role of metaflammation and epigenetic changes in cardiorenal disease. Clin Kidney J. 2019;12(6):861-70.

Dietary Changes

- Improvements in CRP-hs noted with:
  - Weight reduction
  - Improved glycaemic control
  - Low degree of liver steatosis
- Randomized, controlled study : Metainflammation and Mediterranean Diet n=30
- Adherence to the Mediterranean diet decreased :
  - CRP levels
  - TNFα
  - IL-6
  - Parallel to the improvement of glycemic control in T2D patients

Kurylowicz A, et al. Antiinflammatory strategies targeting metainflammation in type 2 diabetes. Molecules. 2020;25:2224.

Peptides and Metaflammation



- Short chains of amino acids linked

By amide bonds

- < 50 amino acids
- Less likely to evoke immune response when administration
- Peptide from Greek word meaning “to digest”
- Played a role in therapeutics since the 1920s – insulin

Peptides

- High specificity and affinity for target
- Highly efficacious, good tissue penetration
- Low allergenicity
- Natural compounds
- Safe, well tolerated
- Fast clearance
- Low Toxicity
- Over 7,000 naturally occurring peptides identified
- Crucial roles in human physiology – improves metabolic signaling

Fosgerau K, Hoffmann T. Peptide therapeutics: current status and future directions. Drug Disc Today. 2015;20(1): 122-28.

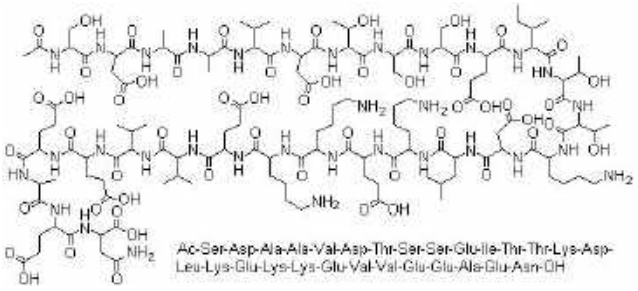
Peptides

- Only use peptides manufactured in licensed Compounding Pharmacies

- Problems associated with internet Chinese peptides
  - Potential for adulteration
  - < 95% purity
  - Sterility issues

Fosgerau K, Hoffmann T. Peptide therapeutics: current status and future directions. Drug Disc Today. 2015;20(1): 122-28.

Peptide Immune Support - TA1



Thymosin Alpha-1 (TA1)

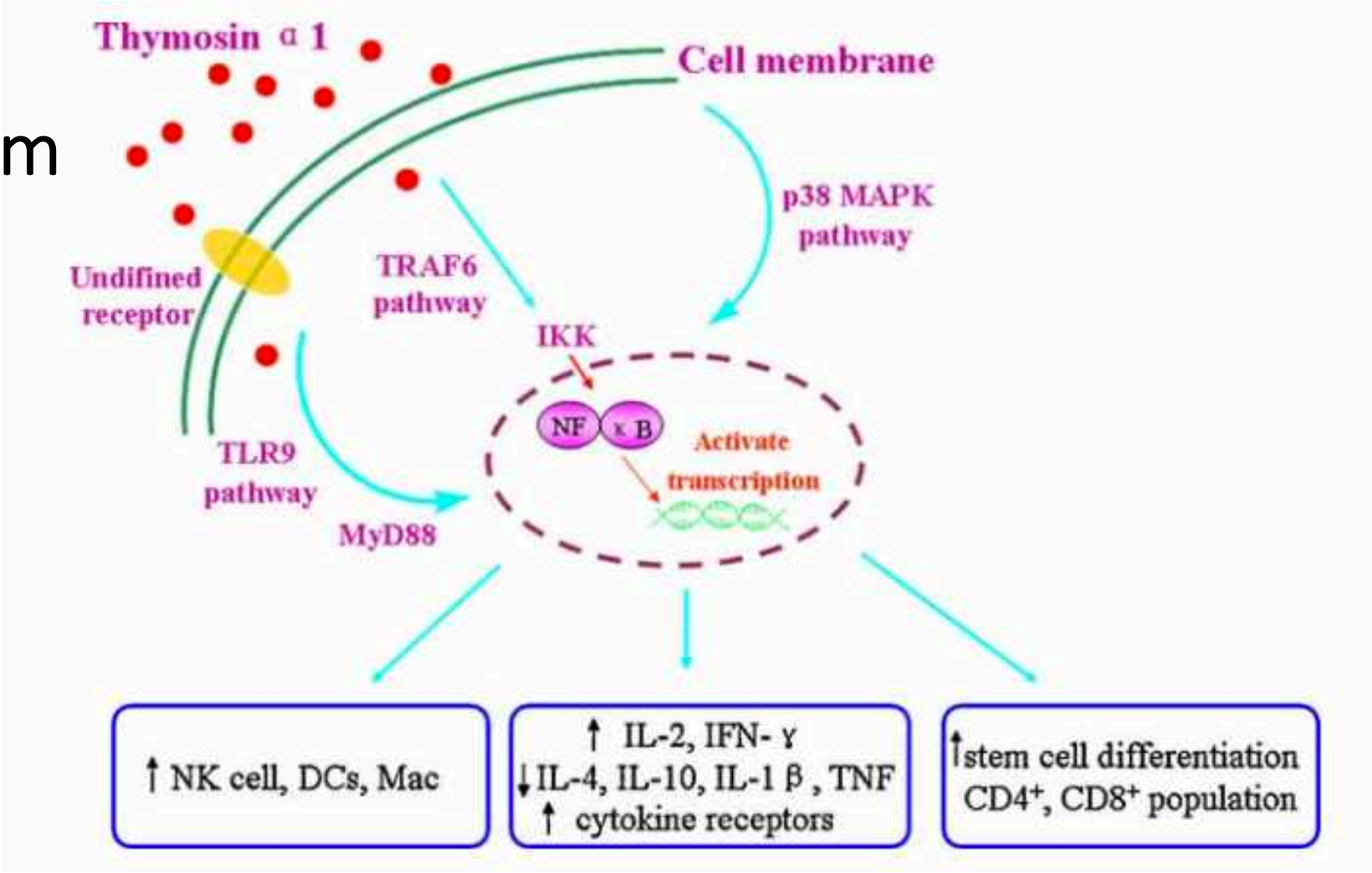
- Synthetic thymic peptide
- Zadaxin® (thymalfasin) is patented pharmaceutical version for Hepatitis B&C

and HIV

- Immune supportive – modulates innate immunity (pleiotropic)
- Improves Th1/Th2 balance
- Helps modulate human GUT mucosal immune system

Ershler WB, et al. Thymosin alpha 1 as an adjunct to influenza vaccination in the elderly. Ann NY Acad Sci. 2007;1112:375-84.
Zadaxin prescribing information SciClone Pharmaceuticals. www.scicloneinternational.com
Elltsur Y, et al Thymosin alpha 1 and thymosin beta 4 modulate human colonic lamina propria lymphocyte function. Immunopharmacology. 1990;20(2):89-96.

TA1 Mechanism



Peptide Immune Support - TA1

- Used in over 3,000 patients in over 70 clinical studies for immune support either alone or in conjunction w/ pharmaceuticals
- Used in conjunction with vaccines to support immunity
- Dosage TA1
  - 3,000 mcg/ml 5ml vial
  - 0.15 ml SQ daily
  - Transient increases in ALT may occur

Ershler WB, et al. Thymosin alpha 1 as an adjunct to influenza vaccination in the elderly. Ann NY Acad Sci. 2007;1112:375-84.
Zadaxin prescribing information SciClone Pharmaceuticals. www.scicloneinternational.com

BPC-157

- BPC-157 – Body Protection Compound
- Gastric Pentadecapeptide – 15 Amino Acids
- Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val
- Derived from human gastric juice
- GUT IMMUNE BRAIN axis
- Cytoprotective
- Anti-inflammatory
- Supports GUT mucosal lining
- Protects and heals inflamed GUT mucosa

Sikiric P, et al. Brain-gut axis and pentadecapeptide BPC 157: Theoretical and practical implications. Curr Neuropharmacol. 2016;14:857-65.
Seiwerth S, et al. BPC157 and blood vessels. Curr Pharm Des. 2014;20(7):1121-5.

BPC-157

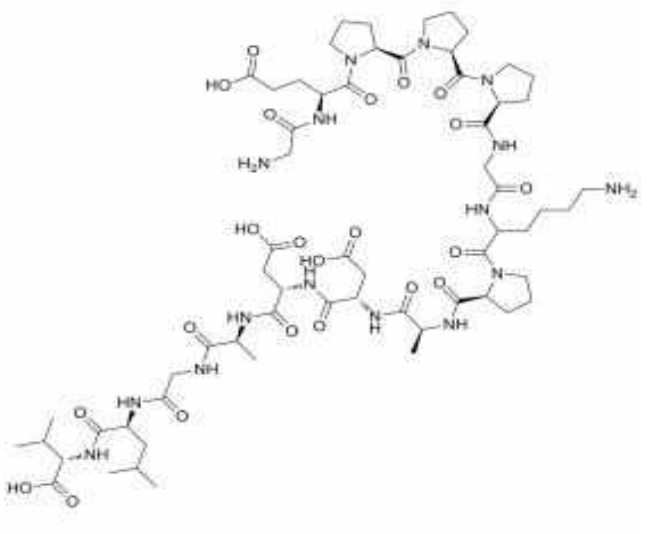
- Effective in decreasing metainflammatory signaling
- Downregulates TNF-alpha
- Improves cell survival under oxidative stress conditions
- Decreases neuroinflammation

Sikiric P, et al. Brain-gut axis and pentadecapeptide BPC 157: Theoretical and practical implications. Curr Neuropharmacol. 2016;14:857-65.

Seiwerth S, et al. BPC157 and blood vessels. Curr Pharm Des. 2014;20(7):1121-5.

BPC-157 Patient Benefits

- Accelerated wound healing
- Decreases inflammation
- Increased fibroblast
- Nitric oxide improvement
- Improves digestive function
- Enhanced vascular expression of VEGFR2



Sikiric P, et al. Brain-gut axis and pentadecapeptide BPC 157: Theoretical and practical implications. Curr Neuropharmacol. 2016;14:857-65.

Seiwerth S, et al. BPC157 and blood vessels. Curr Pharm Des. 2014;20(7):1121-5.

BPC-157

- Potent angiomodulatory factor
- Improves tissue regeneration
  - Granulation
  - Fibroblast recruitment
  - Collagen formation
- Upregulates growth hormone

Sikiric P, et al. Brain-gut axis and pentadecapeptide BPC 157: Theoretical and practical implications. Curr Neuropharmacol. 2016;14:857-65.
Seiwerth S, et al. BPC157 and blood vessels. Curr Pharm Des. 2014;20(7):1121-5.

BPC-157

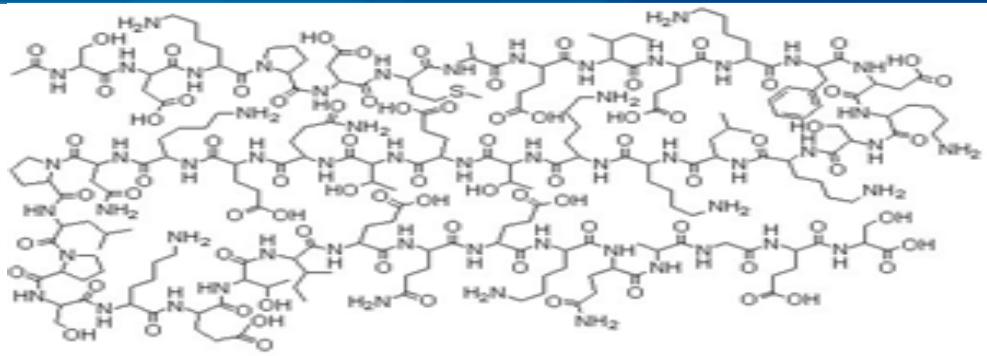
- INJECTION - Prescribing is often based on body weight using 2mcg/kg to as much as 10mcg/kg twice daily
- Commonly used doses range from 200mcg - 400mcg twice daily (400mcg to 800mcg daily)
- If used twice daily, intramuscular injection as close to the injury as possible or via subcutaneously for systemic purposes
- Use for 2-4 weeks before discontinuing; cease therapy for 2weeks, then restart therapy if needed

- BPC-157 is angio**modulatory** – however, use with caution in conditions where angiogenesis may be a problem (tumors)

Sikiric P, et al. Brain-gut axis and pentadecapeptide BPC 157: Theoretical and practical implications. Curr Neuropharmacol. 2016;14:857-65.

Seiwerth S, et al. BPC157 and blood vessels. Curr Pharm Des. 2014;20(7):1121-5.

Thymosin Beta-4 (TB4)



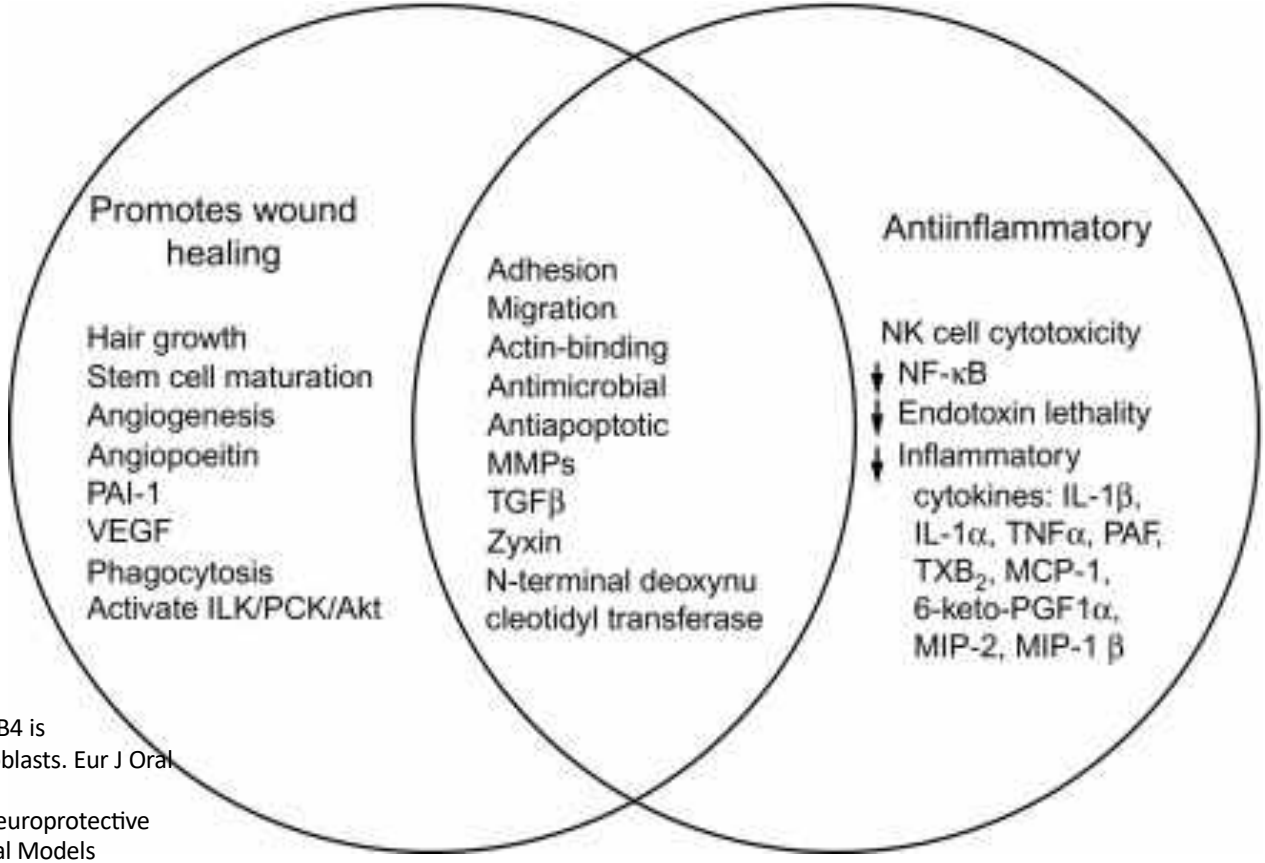
- Thymosin β-4 (TB4 or TB-500)
  - Originally isolated from calf thymus
  - More ubiquitous – occurs in most all cells
  - 43 amino acids
  - Ac-Ser-Asp-Lys-Pro-Asp-Met-Ala-Glu-Ile-Glu-Lys-Phe-Asp-Lys-Ser-Lys-Leu-Lys-Lys-Thr-Glu-Thr-Gln-Glu-Lys-Asn-Pro-Leu-Pro-Ser-Lys-Glu-Thr-Ile-Glu-Gln-Glu-Lys-Gln-Ala-Gly-Glu-Ser
  - Higher levels in platelets and white cells

TB4

- Helps decrease scar tissue formation
  - Reduces level of myofibroblasts
- Supports immunity
  - Antimicrobial
  - Improves T cells
  - Use with Thymosin alpha 1
  - Helps modulate human GUT mucosal immune system
- Neuroprotective

Elltsur Y, et al Thymosin alpha 1 and thymosin beta 4 modulate human colonic lamina propria lymphocyte function. Immunopharmacology. 1990;20(2):89-96.
Reti R, Kwon E, Qui P, et al. Thymosin B4 is cytoprotective in human gingival fibroblasts. Eur J Oral Sci. 2008;116(5):424-30.
Popoli PR, Pepponi A, Martire et al. Neuroprotective Effects of Thymosin B4 in Experimental Models of Excitotoxicity. Ann. N.Y. Acad. Sci.2007;1112: 219–224.

TB4 Summary



Reti R, Kwon E, Qui P, et al. Thymosin B4 is cytoprotective in human gingival fibroblasts. Eur J Oral Sci. 2008;116(5):424-30.

Popoli PR, Pepponi A, Martire et al. Neuroprotective Effects of Thymosin B4 in Experimental Models of Excitotoxicity. Ann. N.Y. Acad. Sci.2007;1112: 219–224.

TB4 Applications

- Immune support in conjunction w/ TA1
- Soft Tissue Repair – tendon, ligament, muscle
  - Sports/athletic injuries
- Pressure or venous stasis ulcers
- Conditions requiring immune response modulation
- Brain issues if autoimmunity suspected
- Ischemic stroke

- Kleinman HK, Sosne G. Thymosin B4 promotes dermal healing. Vitam Horm. 2016;102:251-75.
- Yarmola EG, Kilmenko ES, Fujita G, et al. Thymosin beta4: actin regulation and more. Ann NY Acad Sci. 2007;1112:76-85.

TB4 Applications

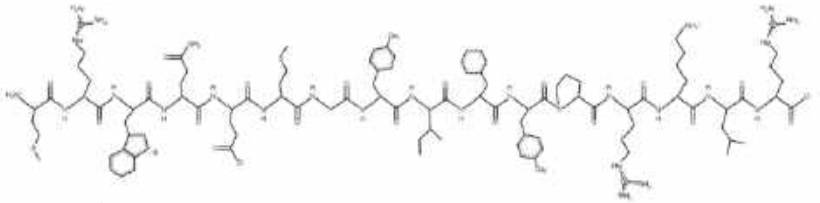
- Decreases endotoxemia – use in sepsis
- Reported in lab studies to reduce polymerization fo G-actin into F-actin
- Improves mortality rate in sepsis

Badamchian M, et al. Thymosin beta 4 reduces lethality and down-regulates inflammatory mediators in endotoxin-induced septic shock. Int Immunopharmacol. 2003;3(8):1225-33.

TB4 Dosage

- General dosage
  - 300 mcg – 1 gram daily, SubQ
  - Depending upon clinical presentation
  - Do not dose for more than 3 months
  - Cycle if needed long-term – 3 months on, 1 month off
- TB4 use with Thymosin alpha 1 and BPC-157 concurrently
- Individual dosage requirements may vary based on clinical presentation

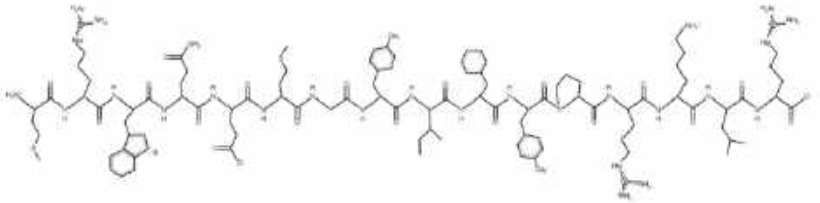
MOTS-c



- Mitochondrial-derived protein (MDP)
- Preserves mitochondrial function and cell viability under stress
- Key role in cellular stress response
- TARGETS =
  - Metaflammation
  - Metabolic signaling issues
  - Anti-aging

Cohen P. Mitochondrial-derived peptides: novel hormones that regulate metabolism during aging. Innovation Aging. 2018;2(1):333-34.

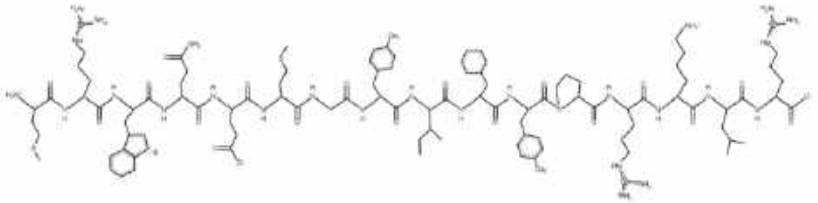
MOTS-c



- Increases intracellular NAD^+ levels
- Effects mediated by SIRT1
- MOTS-c levels decline with age
- Improves insulin sensitivity

Cohen P. Mitochondrial-derived peptides: novel hormones that regulate metabolism during aging. Innovation Aging. 2018;2(1):333-34.

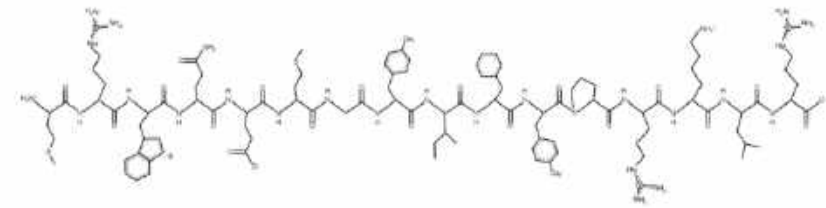
MOTS-c



- Increases glucose utilization and fatty acid oxidation
- Decreases oxidative phosphorylation
- Increases endogenous AICAR levels
- AMPK activation
- Increases glucose update into muscle cells
- Upregulates thermogenic gene expression
- Upregulates brown adipose tissues (BAT)
- Reported to increase adipose thermogenic activation to promote cold adaptation

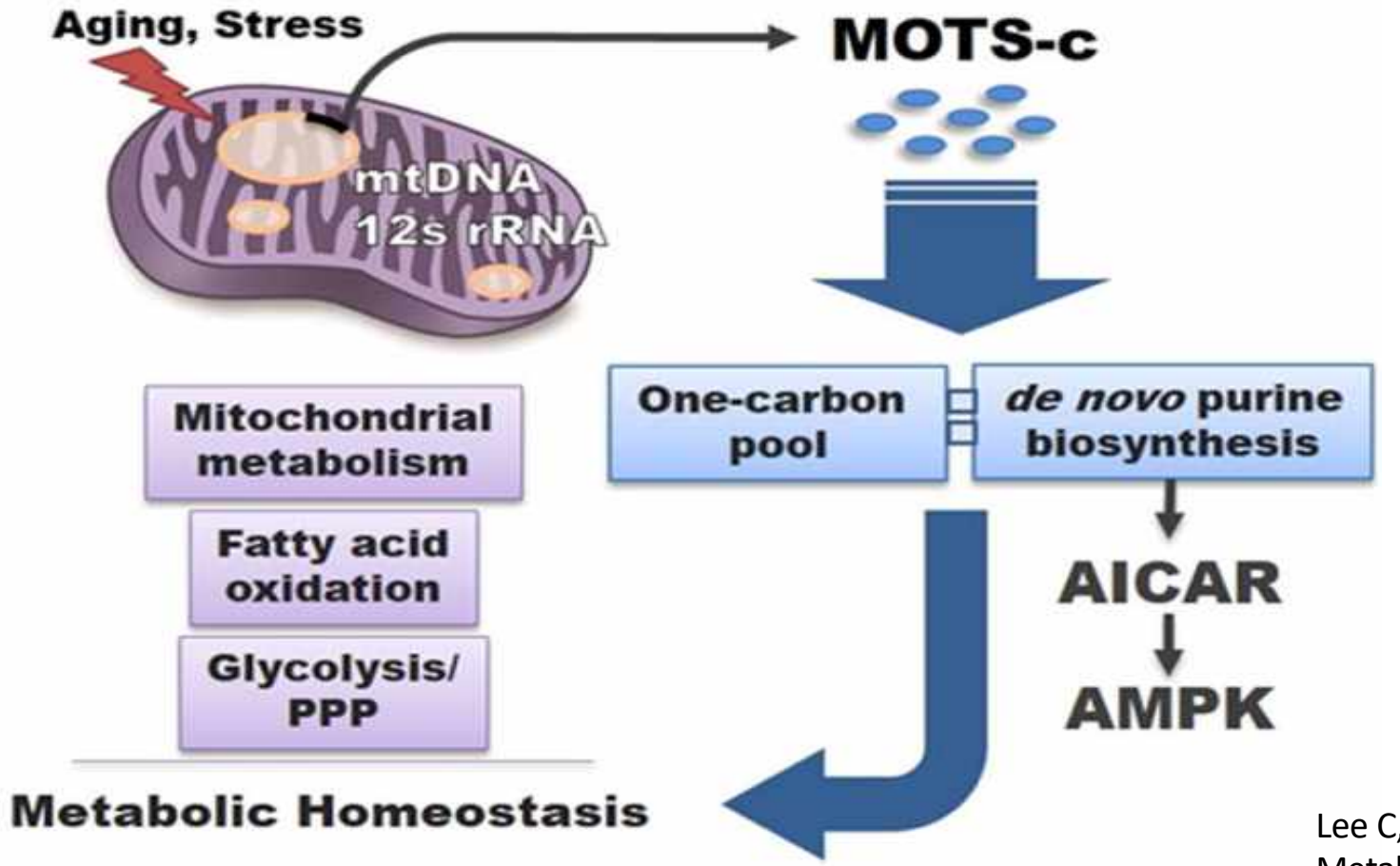
Lee C, et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. Cell Metab. 2015; 21:443–54.

MOTS-c Uses



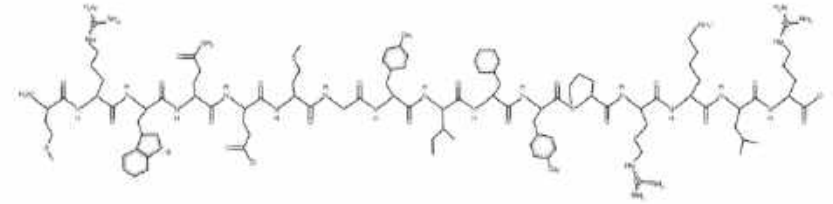
- Metaflammatory conditions
- Obesity and weight gain
- Type 2 diabetes / Insulin Resistance
- Anti-aging
- Cytoprotective
- Mitochondrial dysfunction

Lee C, et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. Cell Metab. 2015; 21:443–54.



Lee C, et al. Cell Metab. 2015;21(3):443–454.

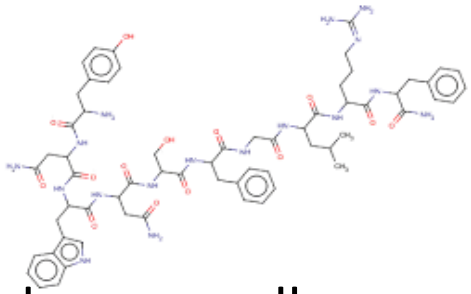
MOTS-c Dosage



- 10mg SQ three times a week for 4 weeks, then 10mg SQ weekly
- Reported safe in recommended dosages
- As with all injections, redness and pain at the site of injection may be present.
- MOTS-c targets folate cycle and de novo purine biosynthesis pathways
- Possible a depletion of intracellular 5-methyl tetrahydrofolate (5-MTHF) may occur when using MOTS-c protocols.
- Recommended check homocysteine and folate levels in patients taking MOTS-c
- Folinic acid or 5-MTHF, up to 1,200 mcg daily, between injections in the protocol, especially in those prone to folate deficiencies

Lee C, et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. Cell Metab. 2015; 21:443–54.

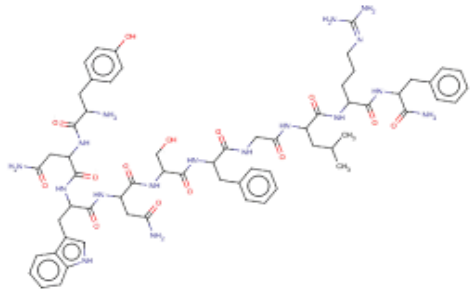
Kisspeptin



- Used to support the sex hormone axis
- First discovered in 1996 as a metastasis inhibitor in melanoma cell lines
- Neuroactive peptide
- Stimulates secretion of gonadotrophin releasing hormone (GnRH) via the kisspeptin receptor
- Loss of kisspeptin signaling causes hypogonadotrophic hypogonadism
- Kisspeptin signaling regulated by nutritional status and stress levels-cortisol related

Gottsch ML, Clifton DK, Steiner RA. From KISS1 to kisspeptins: an historical perspective and suggested nomenclature. Peptides. 2009;30:4–9.

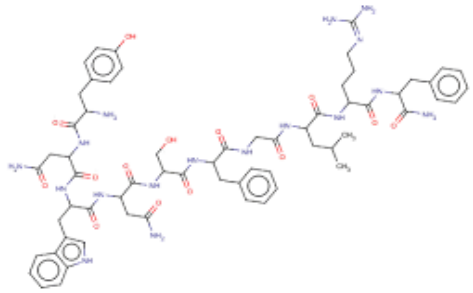
Kisspeptin Uses



- Primary hypogonadism
- Sex hormone axis reset
- Endogenous testosterone support
- Fertility support
  - Improving ovulation and egg implantation
  - Preventing Ectopic Pregnancy
- Physiologic Hormone Replacement Therapy (HRT)
- Physiologic Gonadotropin Hormone Release
- Diabetes/insulin resistance support
- Potential Adjunct of Metastatic Prevention in Cancer

Gottsch ML, Clifton DK, Steiner RA. From KISS1 to kisspeptins: an historical perspective and suggested nomenclature. Peptides. 2009;30:4–9.

Kisspeptin Dosage



- Supplied 1mg/ml. 3ml vial
- 0.1ml (100mcg) SQ daily
- Use at bedtime not required
- Reported safe in recommended dosages

Gottsch ML, Clifton DK, Steiner RA. From KISS1 to kisspeptins: an historical perspective and suggested nomenclature. Peptides. 2009;30:4–9.