How Immunity Impacts Mental Health and Clinical Application

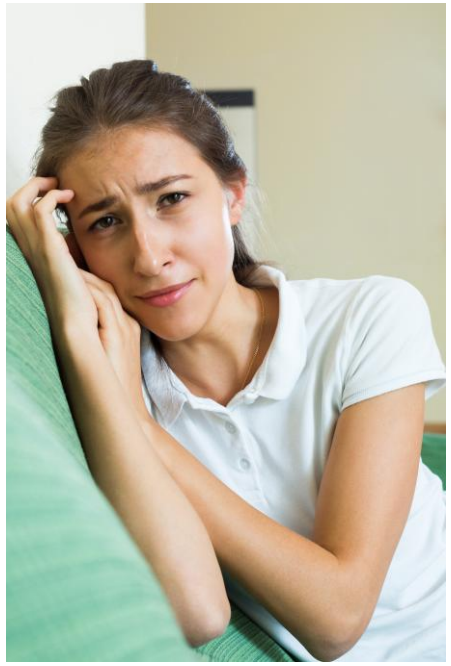
Datis Kharrazian, PhD, DHSc, DC, MS, MMSc, FACN
Director of the Kharrazian Institute
Associate Clinical Professor of Medicine - Loma Linda University School of Medicine

Clinical Scenario

- 45-year-old woman with chronic depression and diagnosed with major depressive disorder since age 40.
- She has not responded to any antidepressants.
- Her annual physical exam and bloodwork are all normal.

What is her future in the healthcare system?

Clinical Scenario



- A 17-year-old girl has episodes of depression and anxiety. She is unable to focus on schoolwork and develop friendships.
- Her primary care physician told her parents that it is just teenage hormones and she will grow out of it.

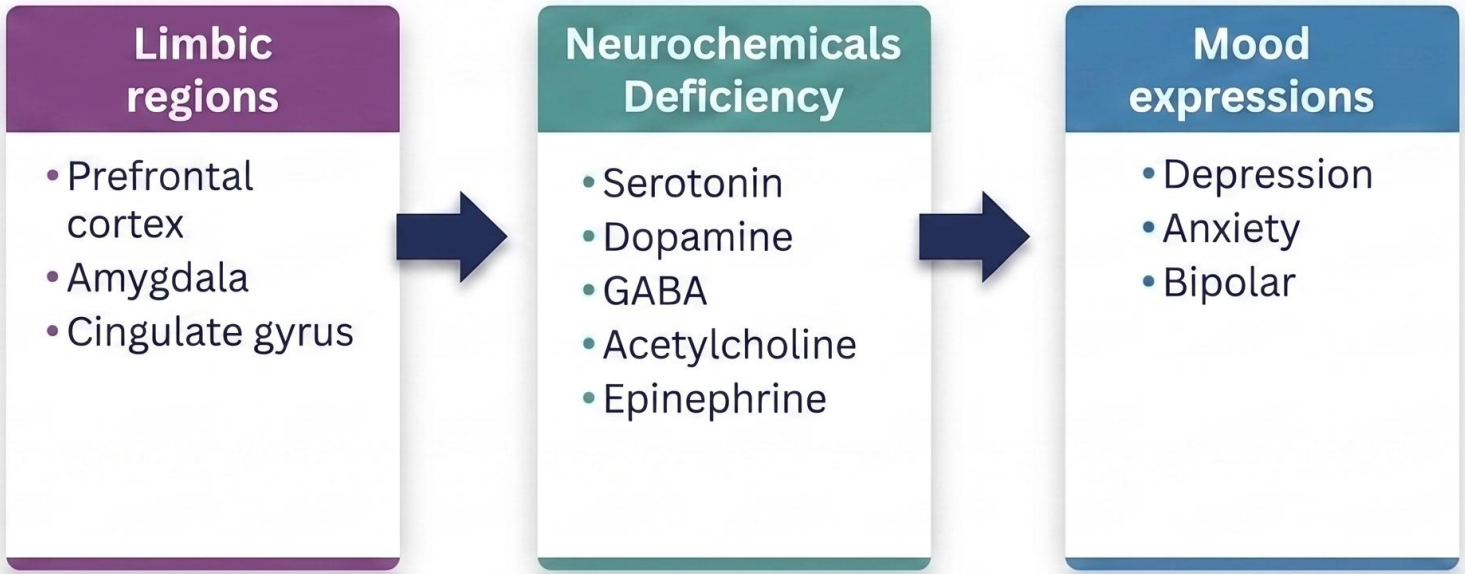
What is her future in the healthcare system?

Clinical Scenario

- 38-year-old woman with episodes of anxiety that are unpredictable and debilitating.
- She responds to anti-anxiety medications to dampen her anxiety, but she falls asleep and is unable to function the rest of the day from the anxiolytics.

What is her future in the healthcare system?

The Monoamine Model of Mood Disorders



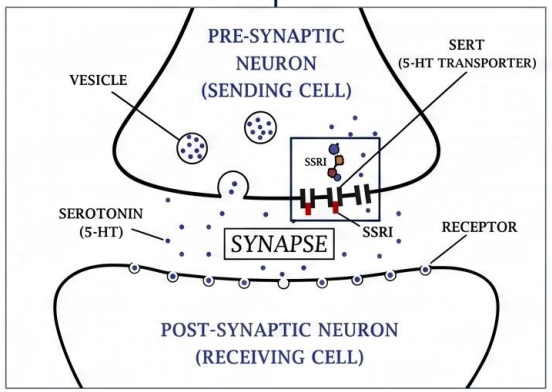
Basic Pharmaceutical Approach to Mood Disorders

Neurochemical imbalance →

- Serotonin
- Dopamine
- GABA
- NMDA

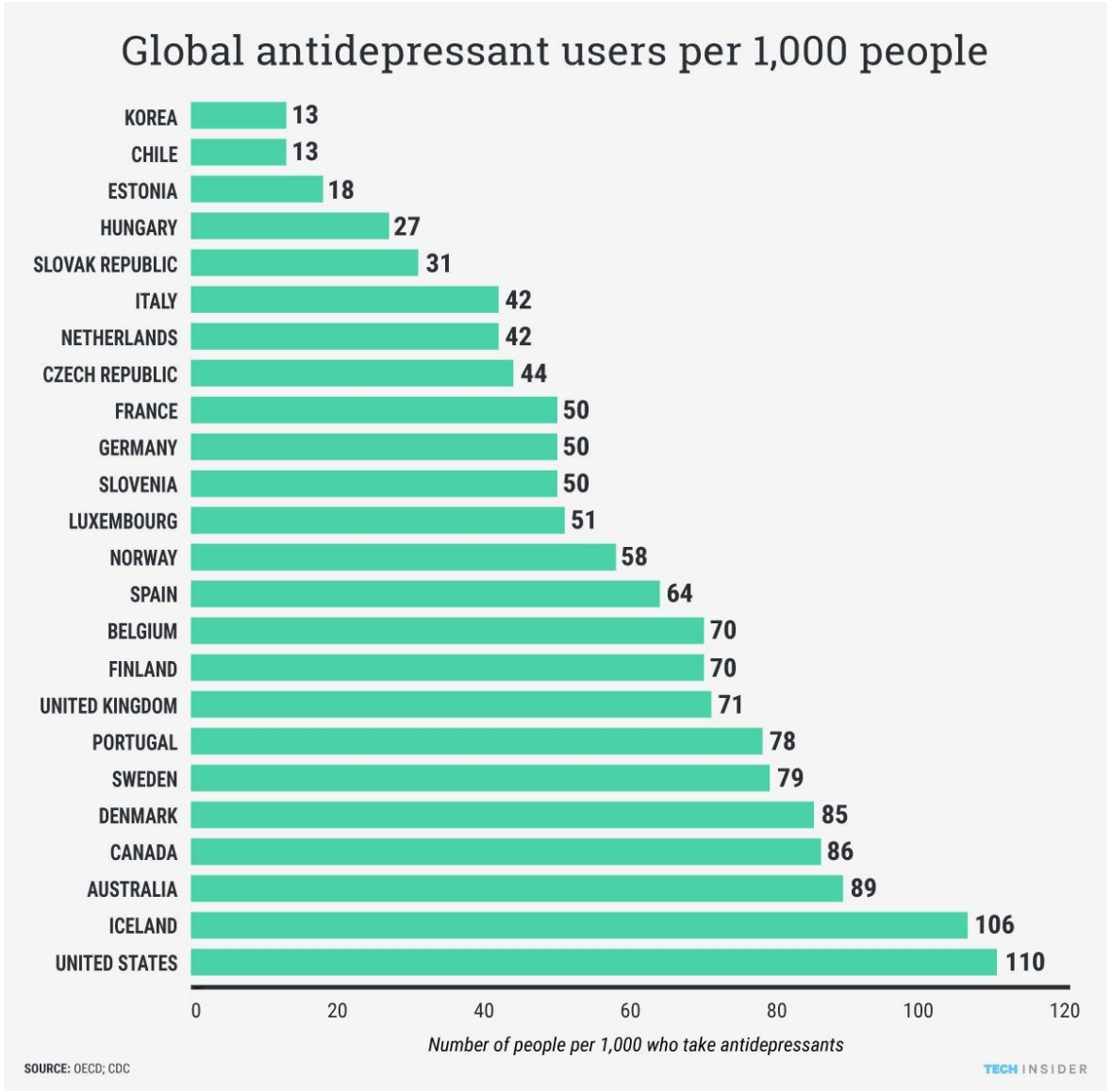
→

- Reuptake inhibitors
- Receptor agonists
- Receptor antagonists



Major classes of antidepressant drugs

1. Serotonin reuptake inhibitors (SSRIs)
2. Monoamine oxidase inhibitors (MAOs)
3. Serotonin-norepinephrine reuptake inhibitors (SNRIs)
4. Serotonin antagonist and uptake inhibitors (SARIs)
5. Tricyclic antidepressants (TCAs)
6. Tetracyclic and unicyclic antidepressants


Global antidepressant users per 1,000 people
KOREA 13
CHILE 13
ESTONIA 18
HUNGARY 27
SLOVAK REPUBLIC 31
ITALY 42
NETHERLANDS 42
CZECH REPUBLIC 44
FRANCE 50
GERMANY 50
SLOVENIA 50
LUXEMBOURG 51
NORWAY 58
SPAIN 64
BELGIUM 70
FINLAND 70
UNITED KINGDOM 71
PORTUGAL 78
SWEDEN 79
DENMARK 85
CANADA 86
AUSTRALIA 89
ICELAND 106
UNITED STATES 110
0 20 40 60 80 100 120
Number of people per 1,000 who take antidepressants
SOURCE: OECD; CDC
TECH INSIDER

Reported Side Effects of Long-Term Antidepressant Use

Sexual problems

Weight gain

Feeling dependent on the medication

Reduced positive feelings

Feeling emotionally numb

Long-Term Effects of Antidepressants

The Main Side Effects Reported:

- Sexual problems (72%), including the inability to reach orgasm (65%).
- Weight gain (65%).
- Feeling emotionally numb (65%).
- Not feeling like themselves (54%).
- Reduced positive feelings (46%).
- Feeling as if they're addicted (43%).
- Caring less about other people (36%.)
- Feeling suicidal (36%).

30% still said they had moderate or severe depression.

Long-term antidepressant use: patient perspectives of benefits and adverse effects

Patient Preference and Adherence 2016:10

Basic Model of Nutrition for Mood Disorders

Depression: Nutrient Deficiencies

Depression = Nutrient deficiency ⟶

- Folate
- Methylfolate
- B-6
- B-12 (methyl B12)
- Tryptophan
- 5-HTP

Anxiety: Nutrient Deficiencies

Anxiety = Nutrient deficiency ⟶

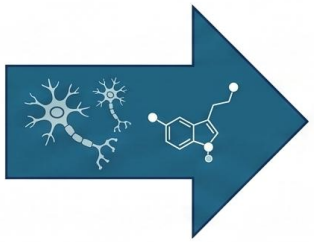
- Magnesium
- Potassium
- Calcium
- Lithium

Basic Herbal Model for Mood Disorders

"Green Medicine"

Depression Support

Depression = Use botanicals that support neurotransmitters



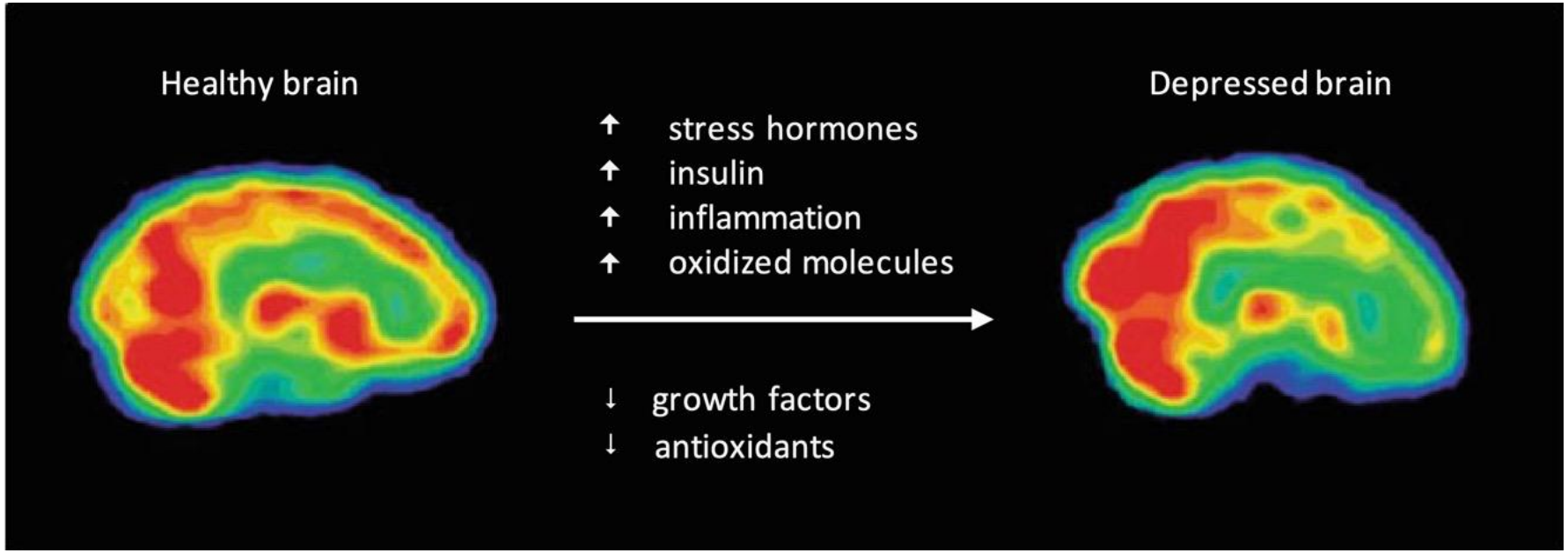
- St. John's wort
- Rhodiola
- Saffron

Anxiety & Sedation Support

Neurotransmitters = Use botanicals that support sedation

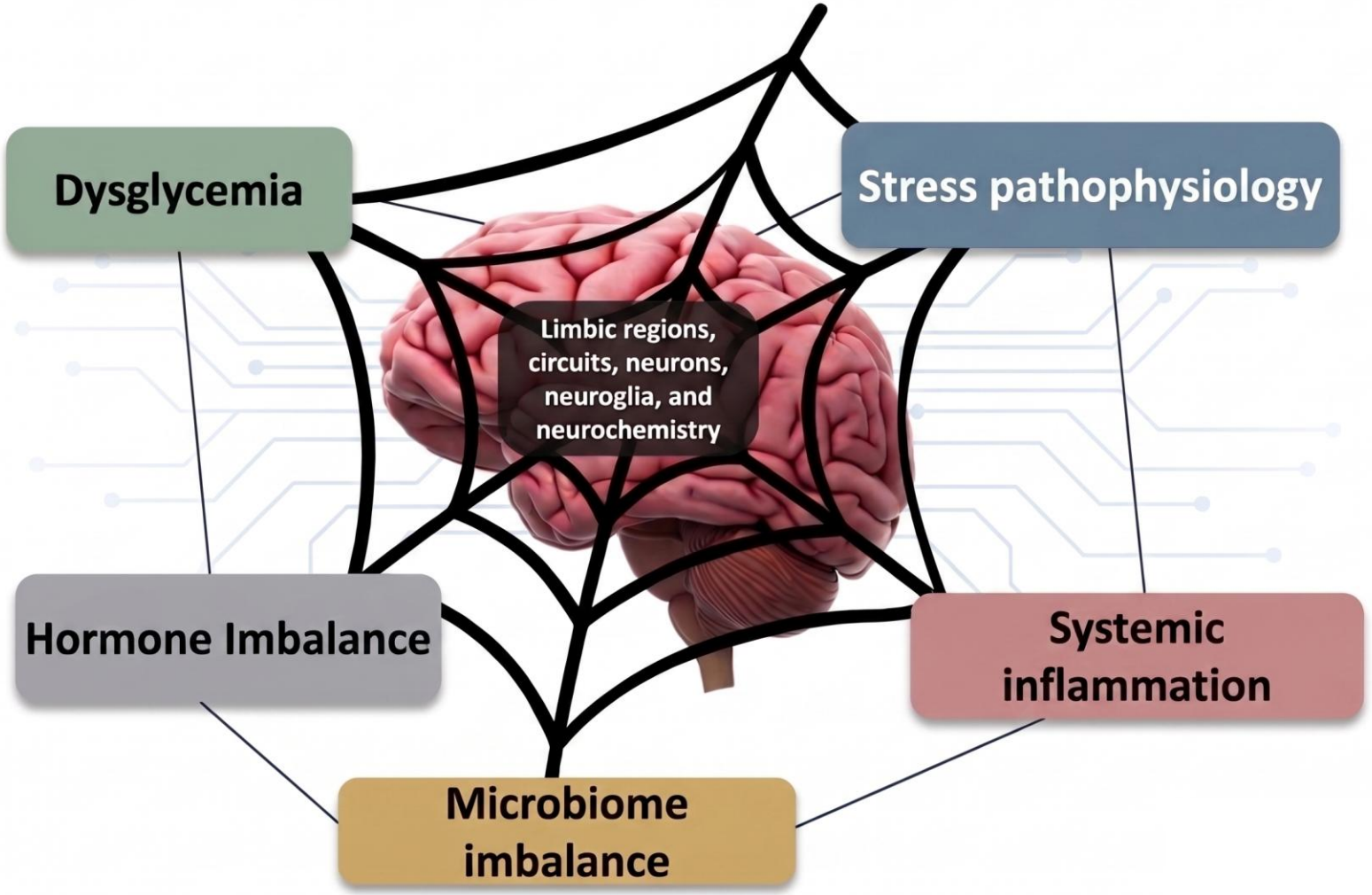
- Passionflower
- Chamomile
- Kava root

The Neurochemistry of Depression

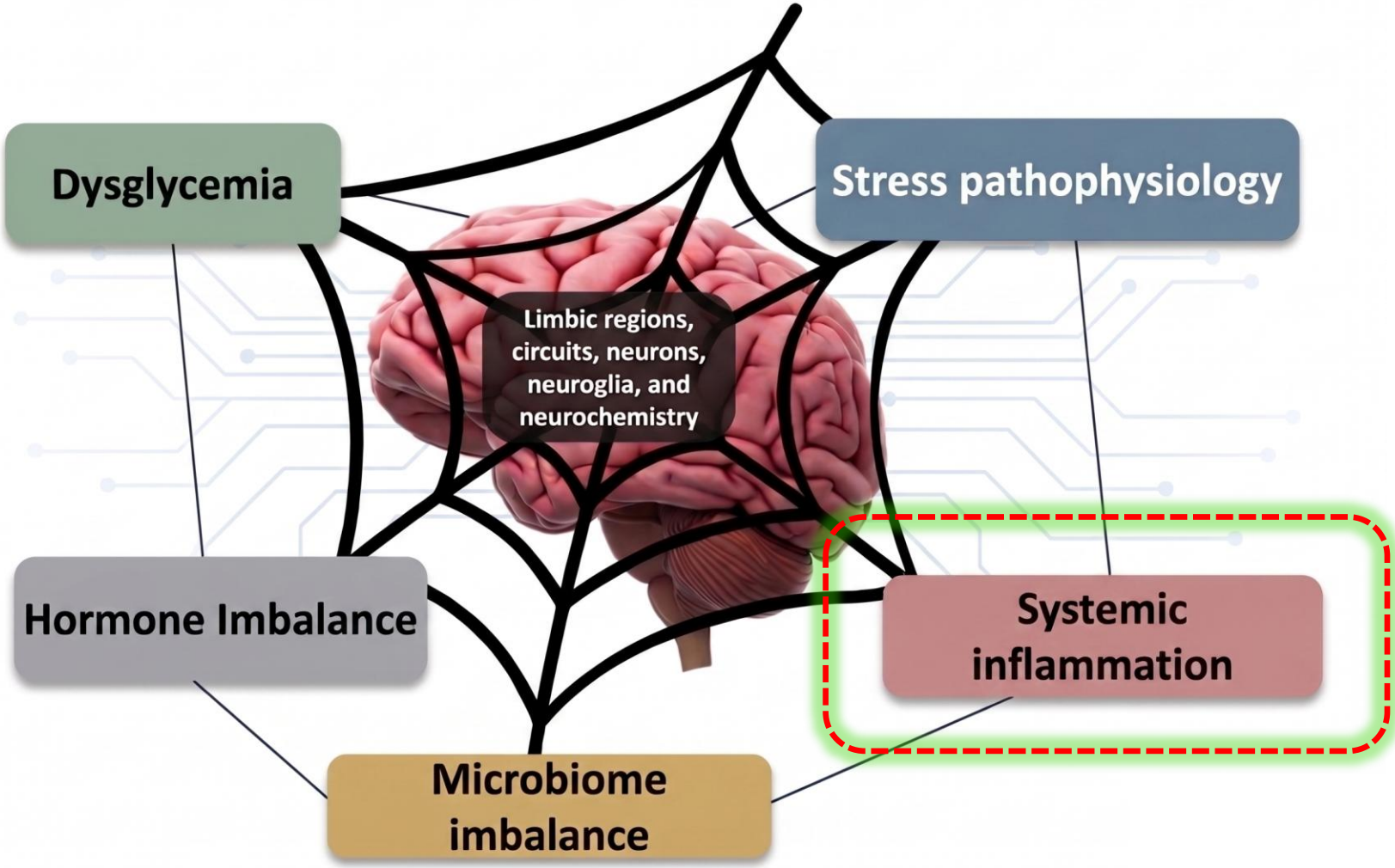


P.C. Guest, *Biomarkers and Mental Illness*,
DOI 10.1007/978-3-319-46088-8_5

The Physiologic Web of Mental Disorders



The Physiologic Web of Mental Disorders



Presentation Overview

Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

Presentation Overview

Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

Presentation Overview

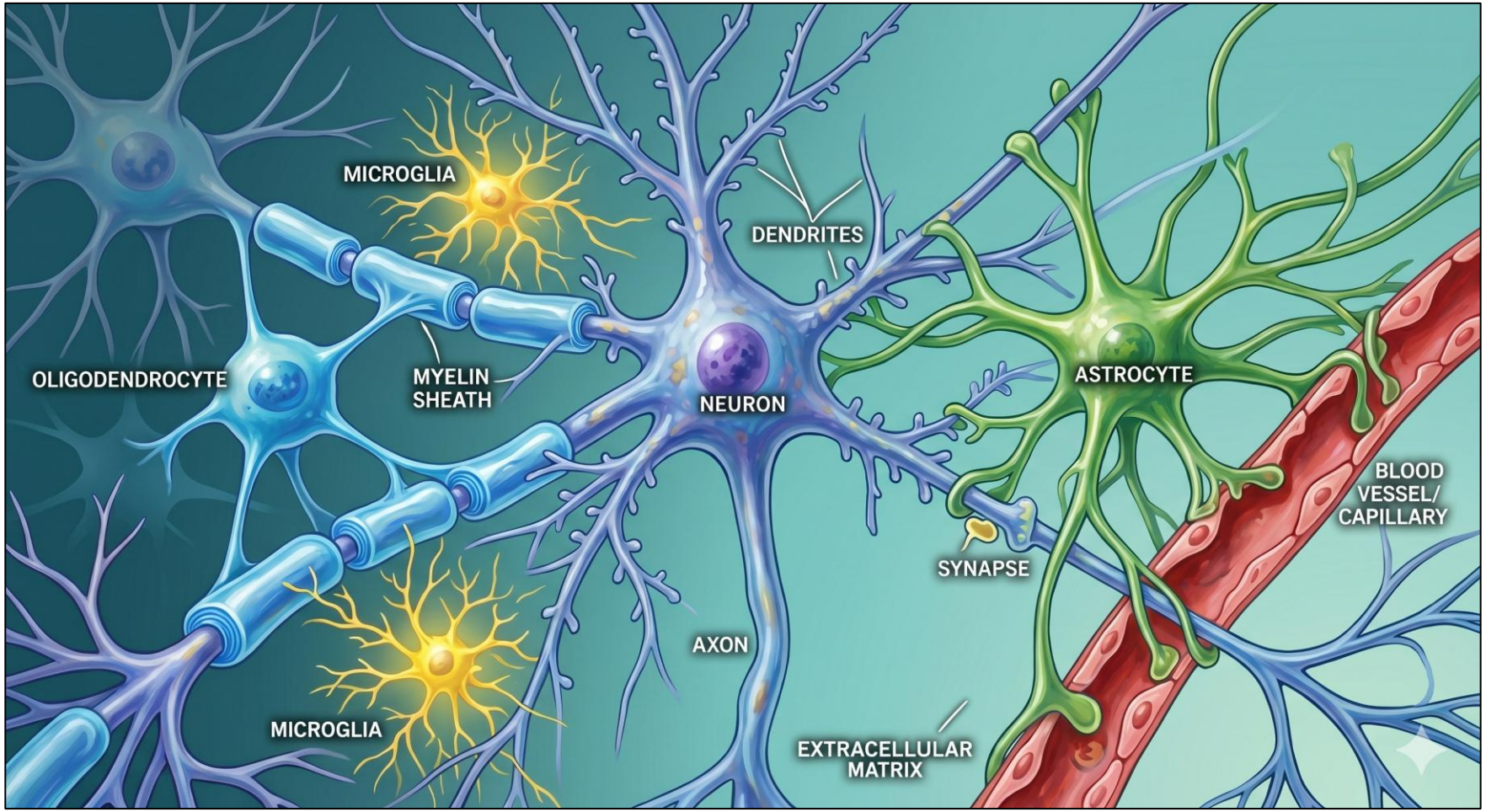
Neuroinflammatory Pathophysiology

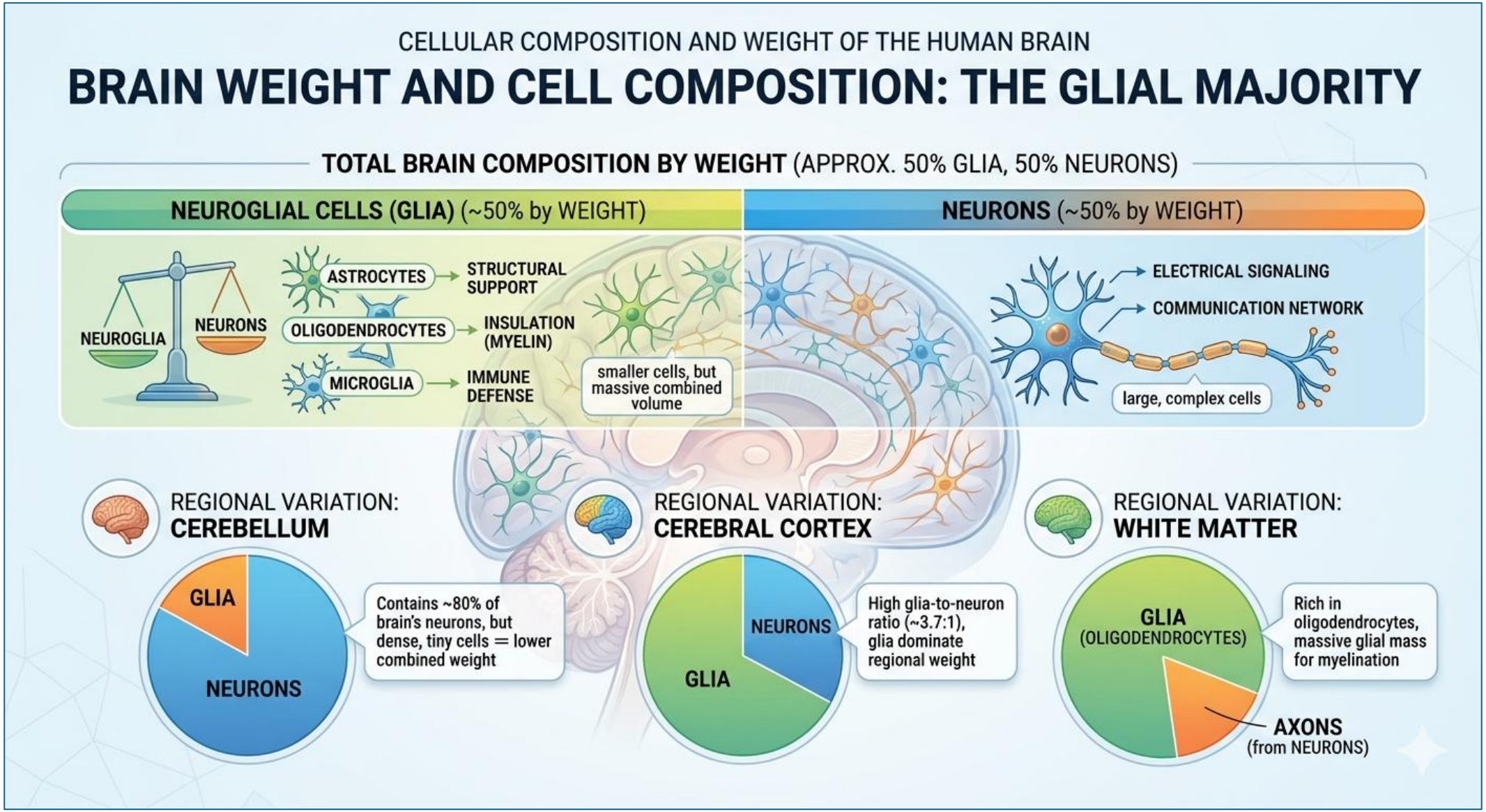
- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

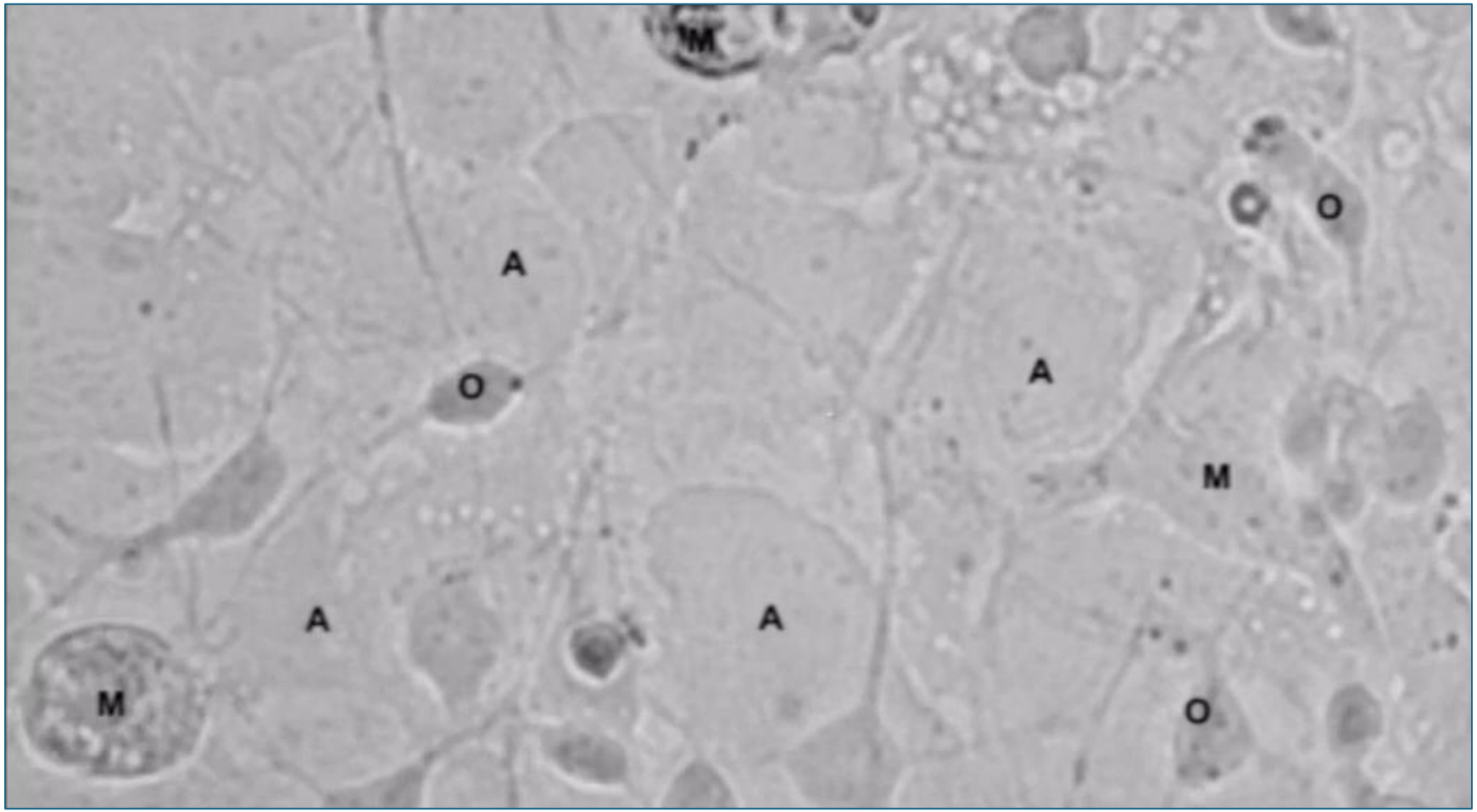
Cells of the Brain



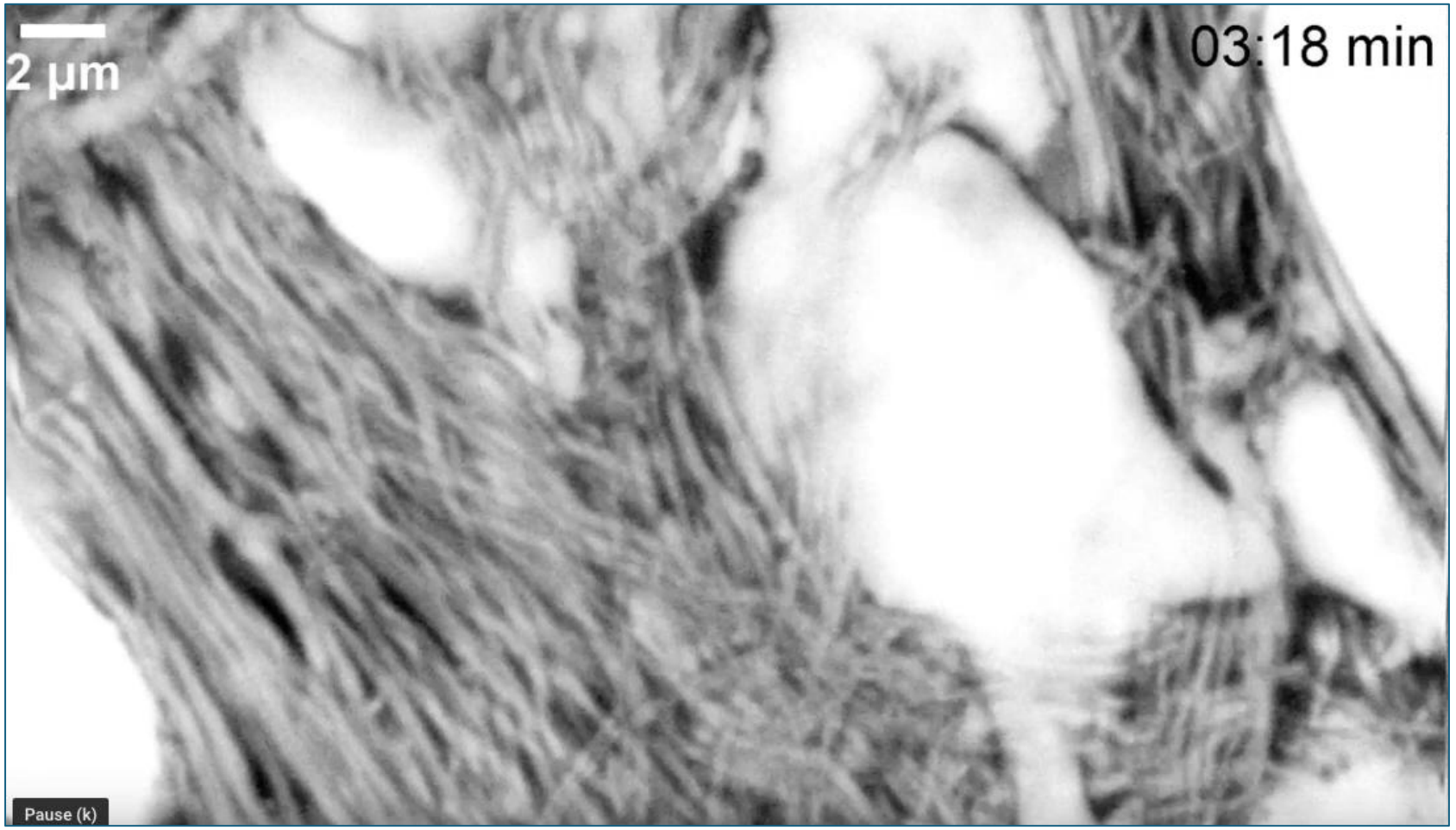


A review of 150 years of cell counting. J Comp Neurol. 2016 Dec 15;524(18):3865-3895.

Culture of Microglia, Astrocytes, and Oligodendrocytes



Microglia roaming through the brain, Resolution Imaging



Presentation Overview

Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

Presentation Overview

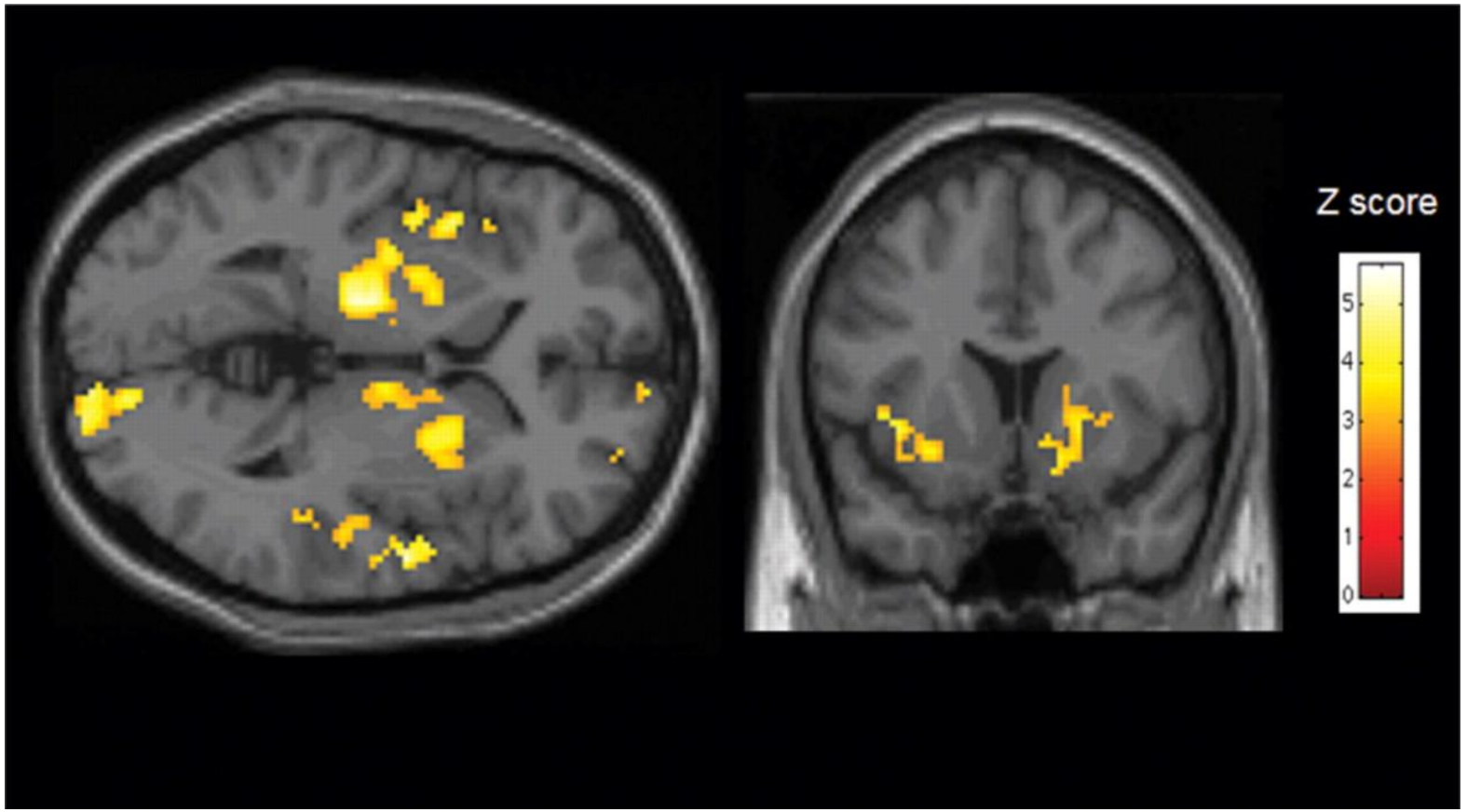
Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

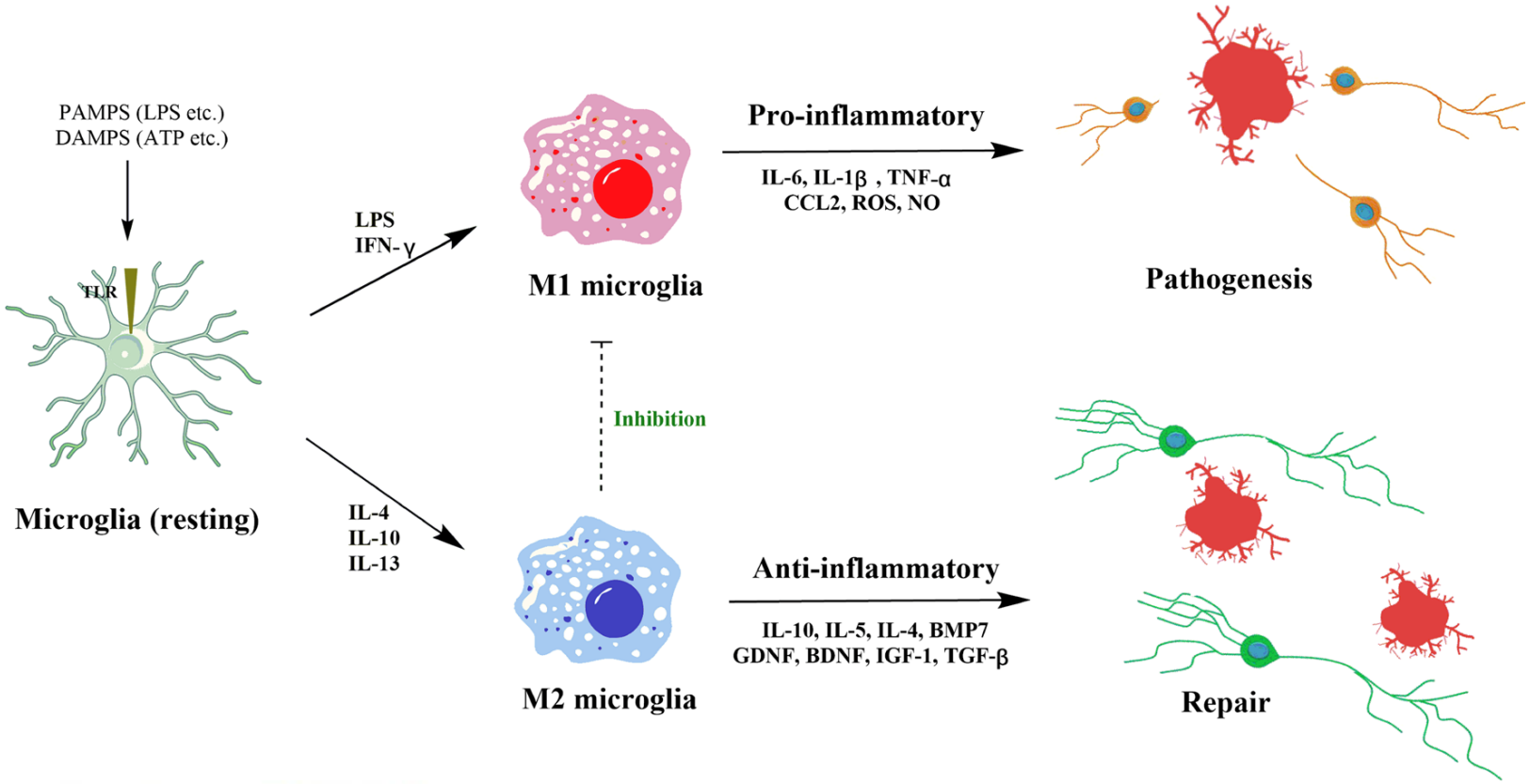
Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

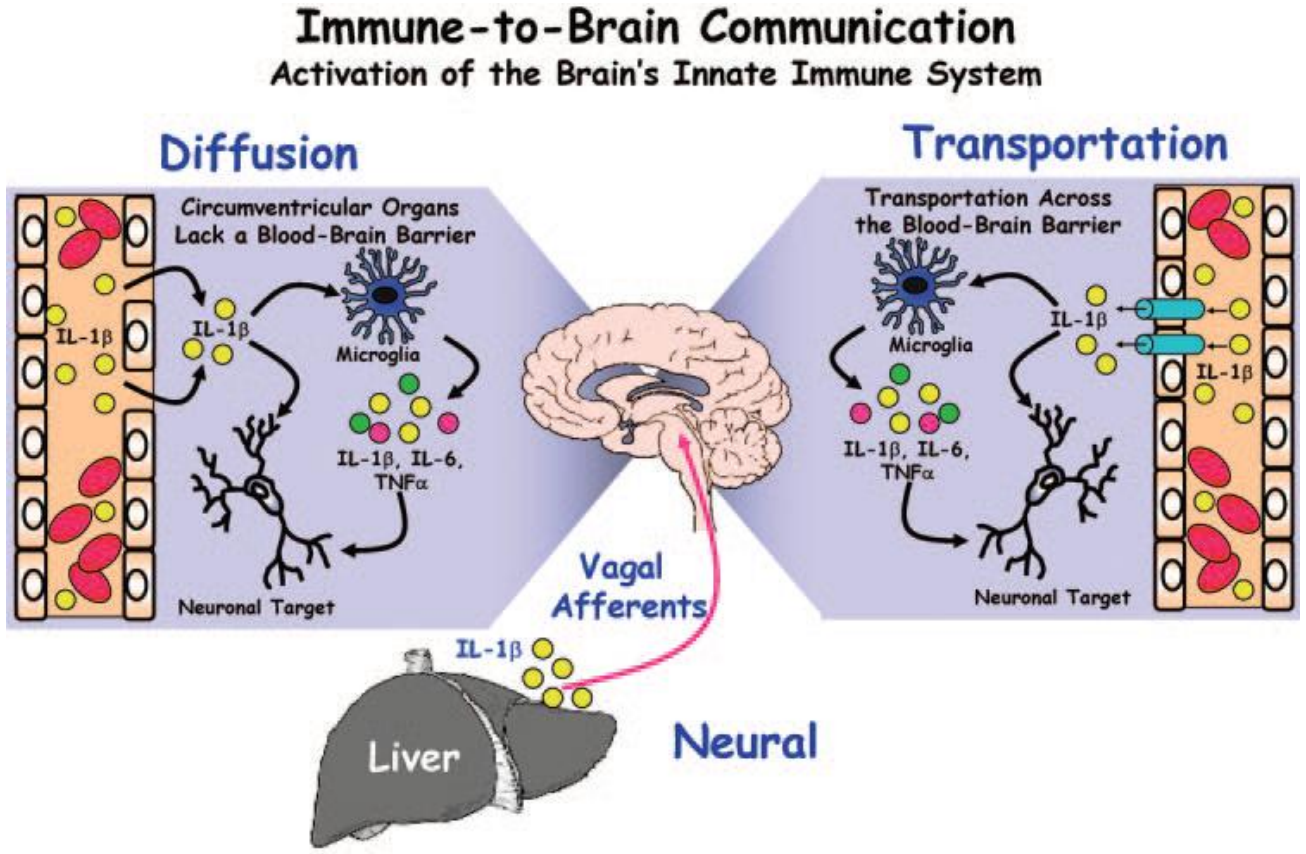
Neuroglia Activation



Microglia Resting, M1 and M2 Functions

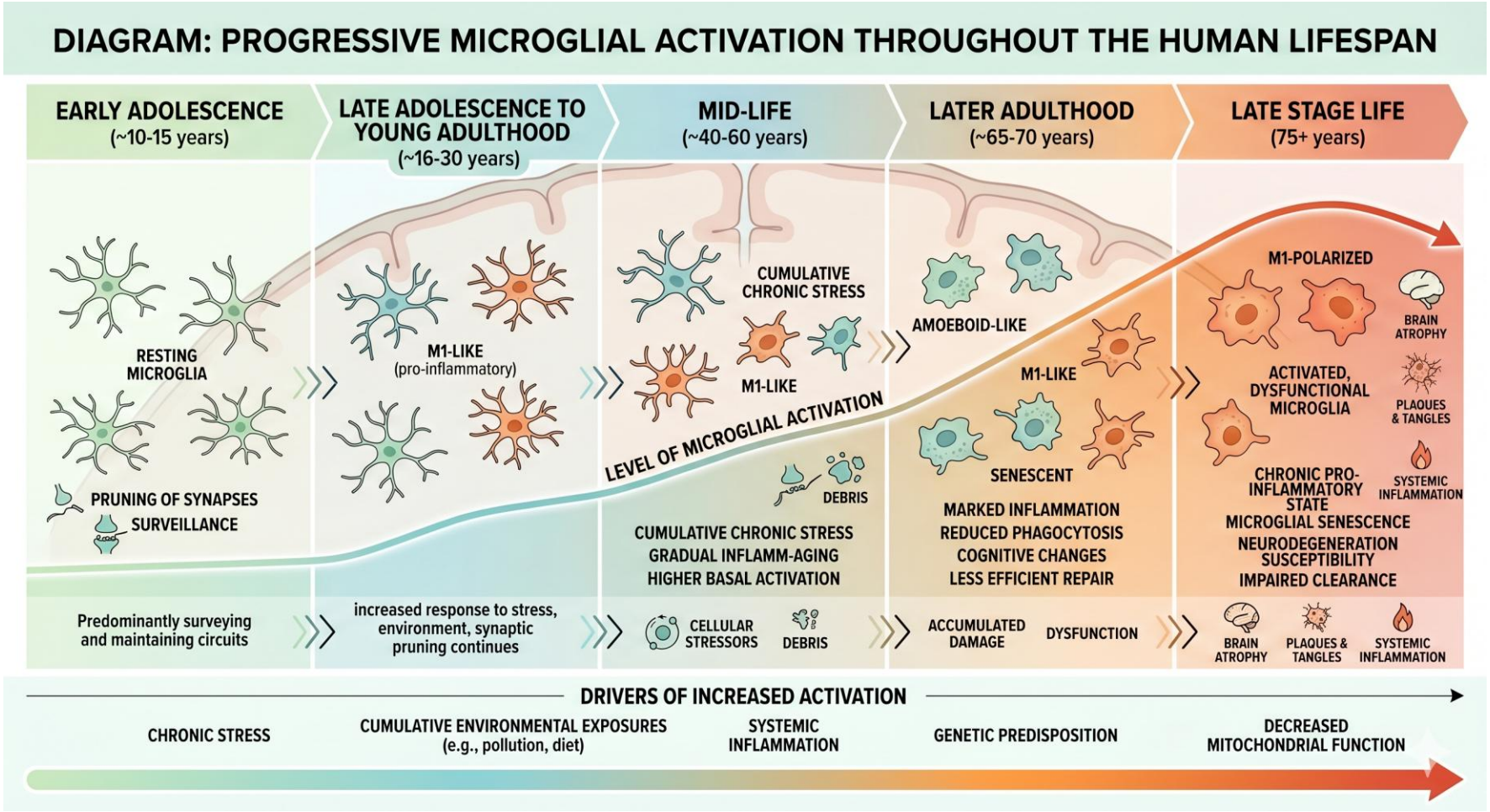


Wang *et al. Journal of Neuroinflammation* (2022) 19:132

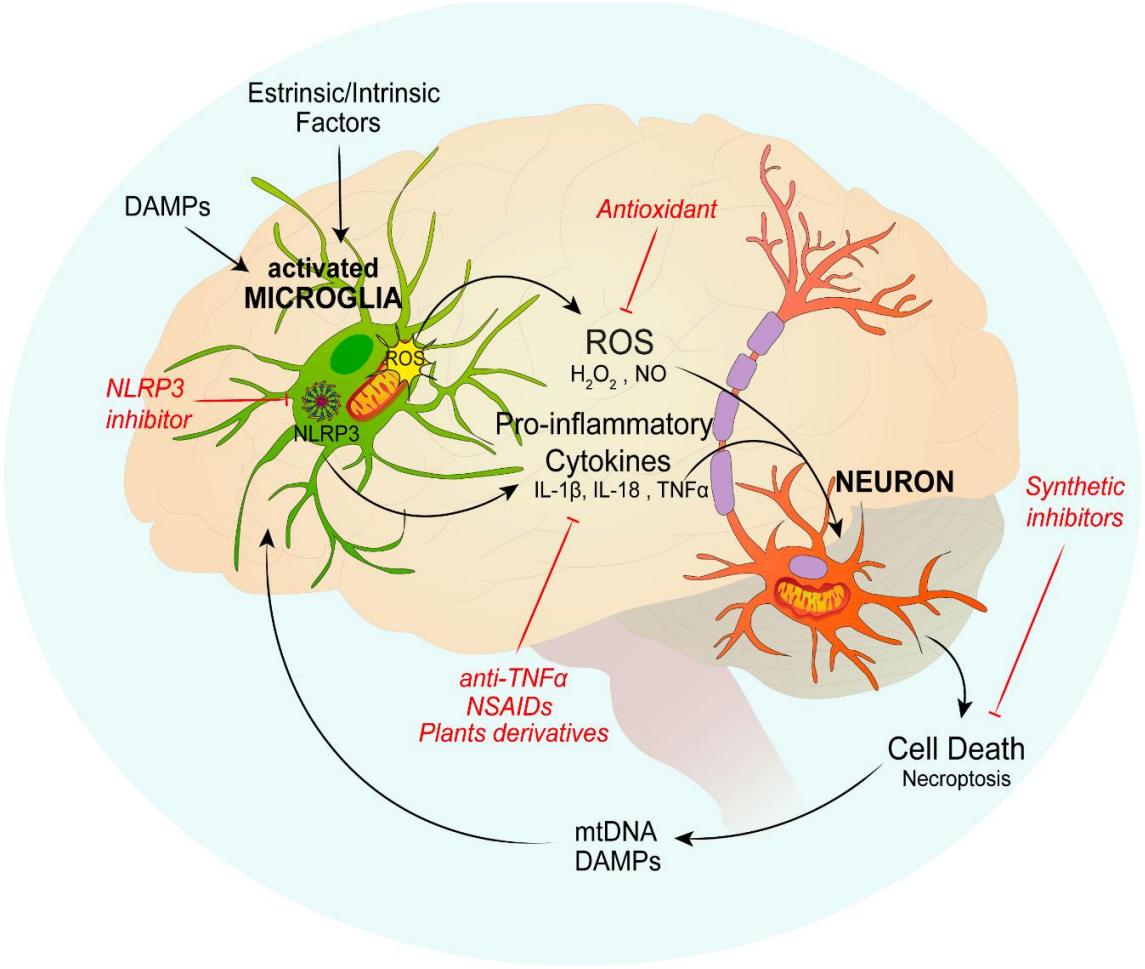


Journal of Leukocyte Biology Volume 84, October 2008

Microglia Activation Throughout the Lifespan



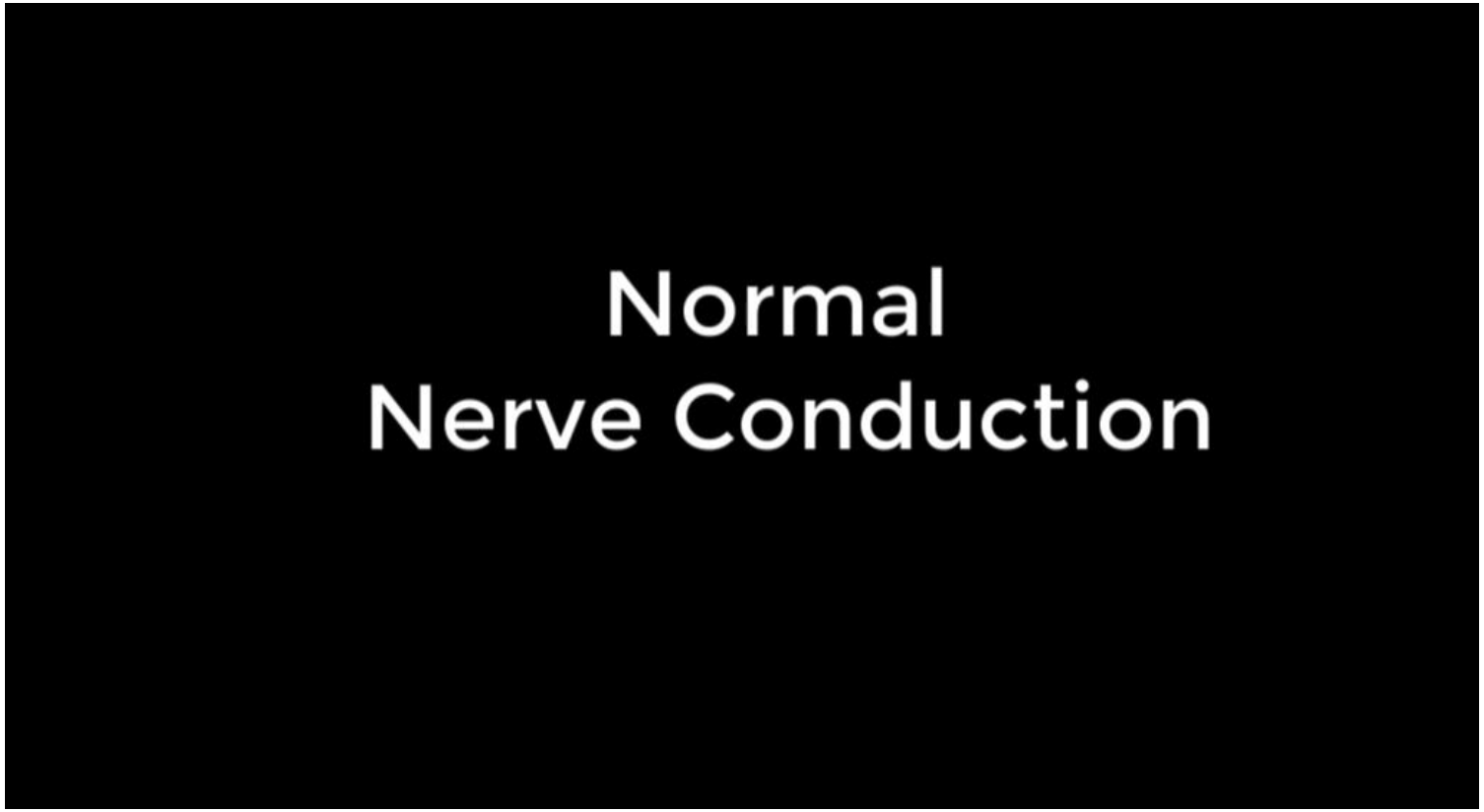
Mitochondrial Dysfunction and Neuroinflammation

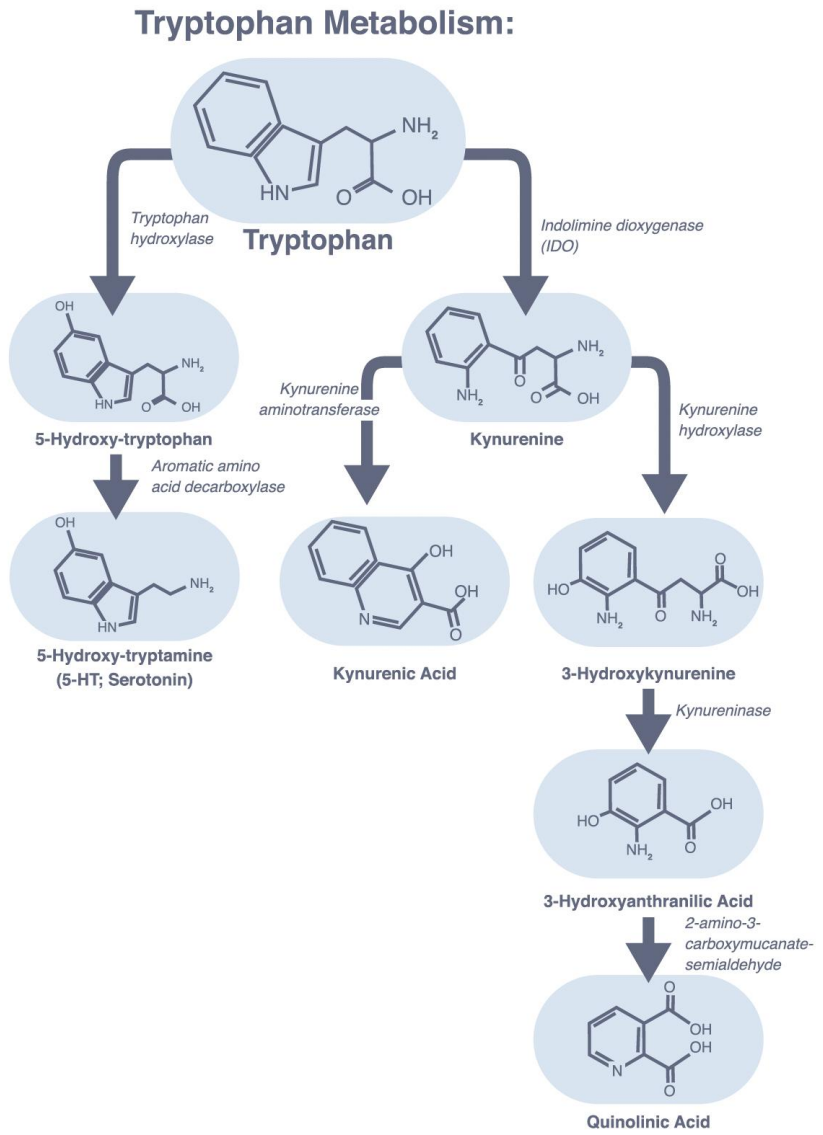


The Role of Mitochondria in Inflammation: From Cancer to Neurodegenerative Disorders

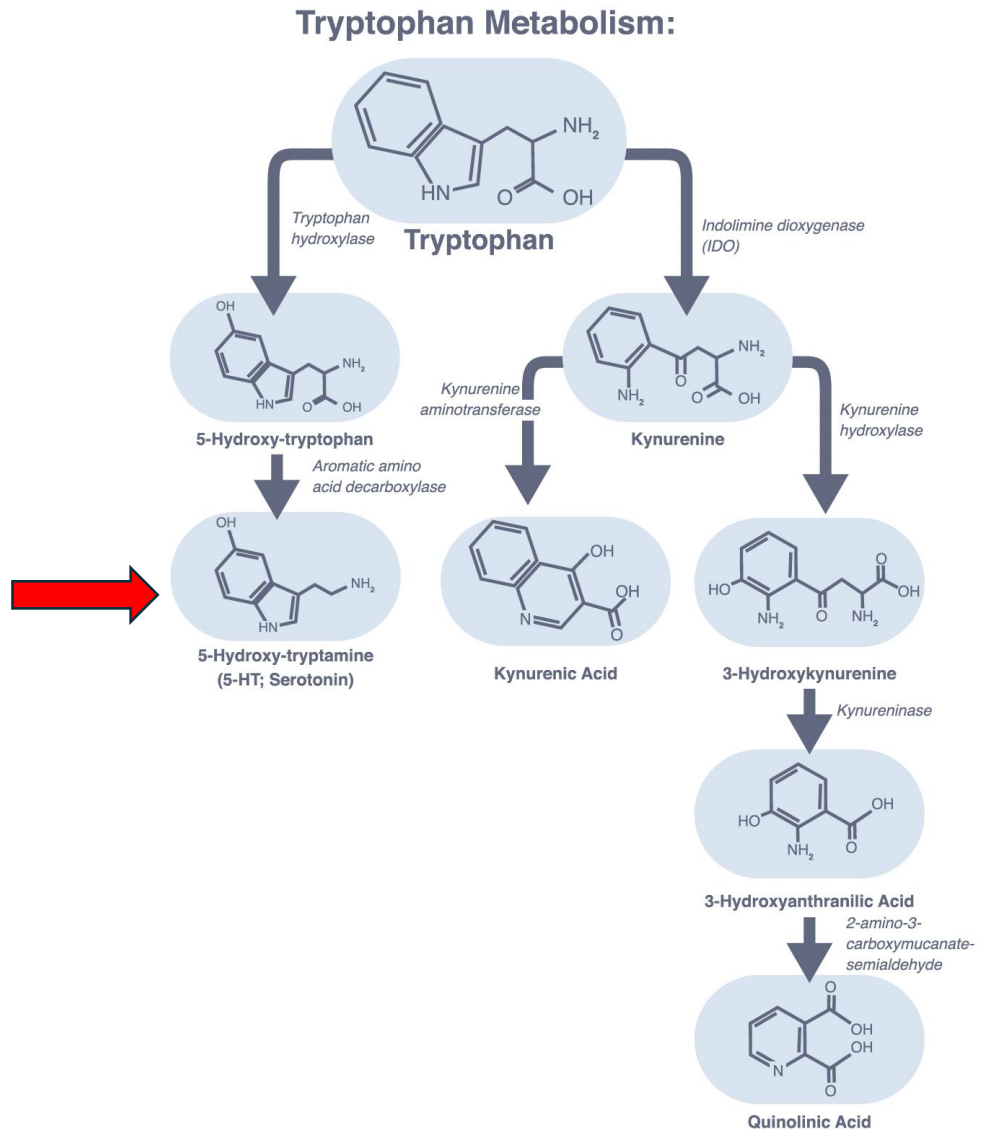
J. Clin. Med. **2020**, *9*, 740; doi:10.3390/jcm9030740

Neuroinflammation Reduces Nerve Conduction Speed



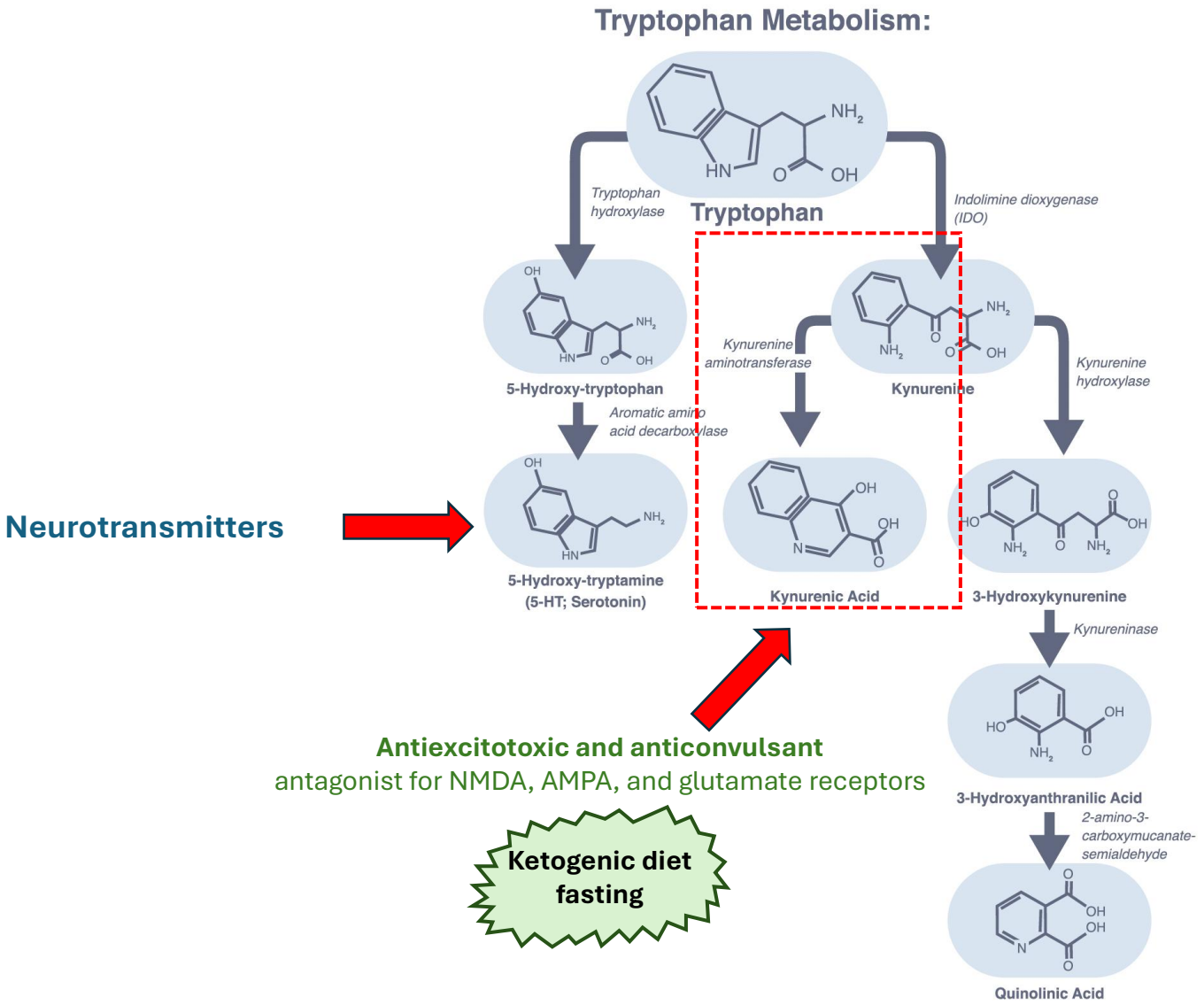

Tryptophan Metabolism:
Tryptophan
Tryptophan hydroxylase
Indolimine dioxygenase (IDO)
5-Hydroxy-tryptophan
Aromatic amino acid decarboxylase
Kynurenine aminotransferase
Kynurenine
Kynurenine hydroxylase
5-Hydroxy-tryptamine (5-HT; Serotonin)
Kynurenic Acid
3-Hydroxykynurenine
Kynureninase
3-Hydroxyanthranilic Acid
2-amino-3-carboxymucanate-semialdehyde
Quinolinic Acid

Neurotransmitters



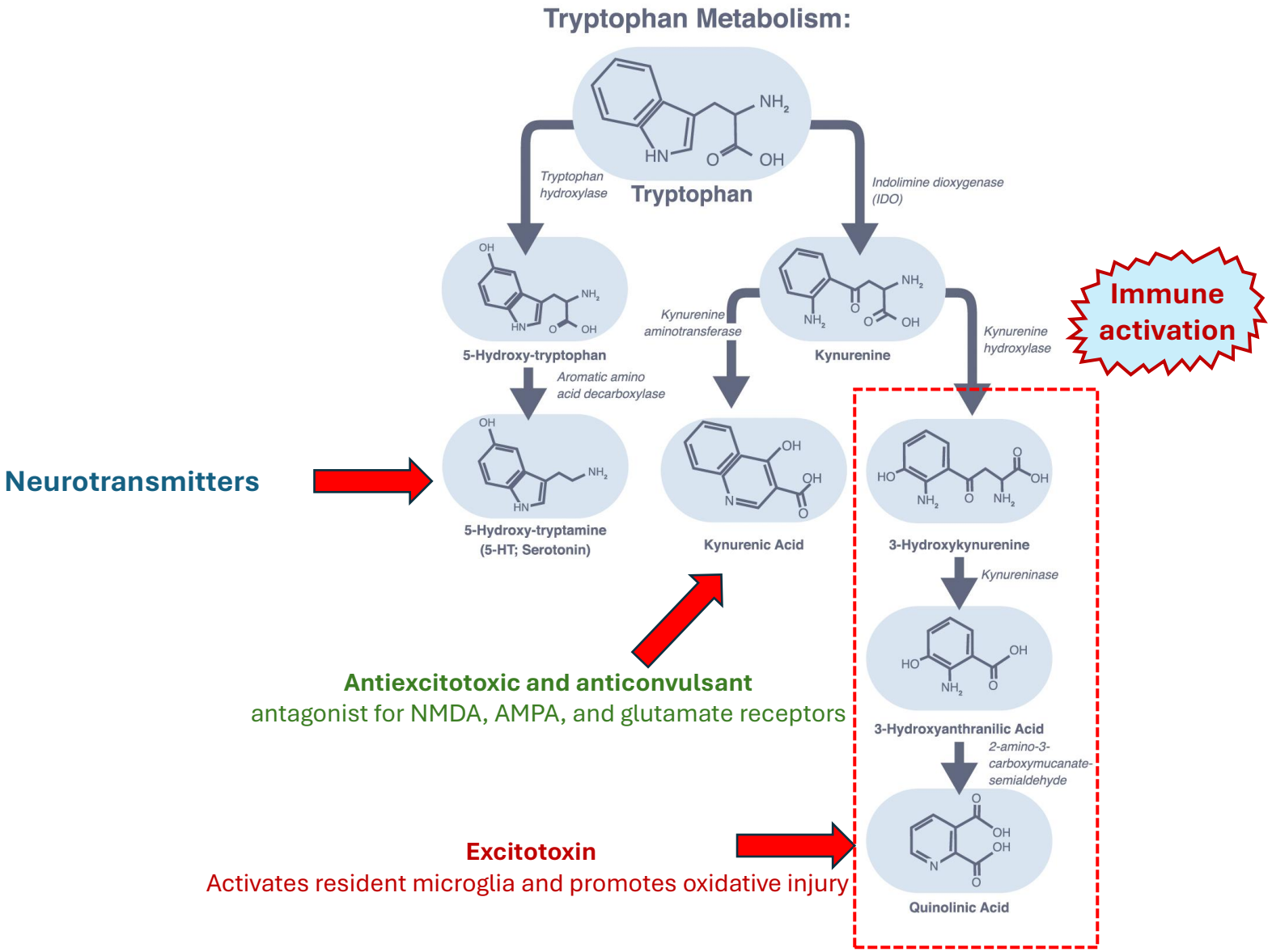
Finding intestinal fortitude: Integrating the microbiome into a holistic view of depression mechanisms, treatment, and resilience

Neurobiology of Disease 135 (2020) 104578



Finding intestinal fortitude: Integrating the microbiome into a holistic view of depression mechanisms, treatment, and resilience

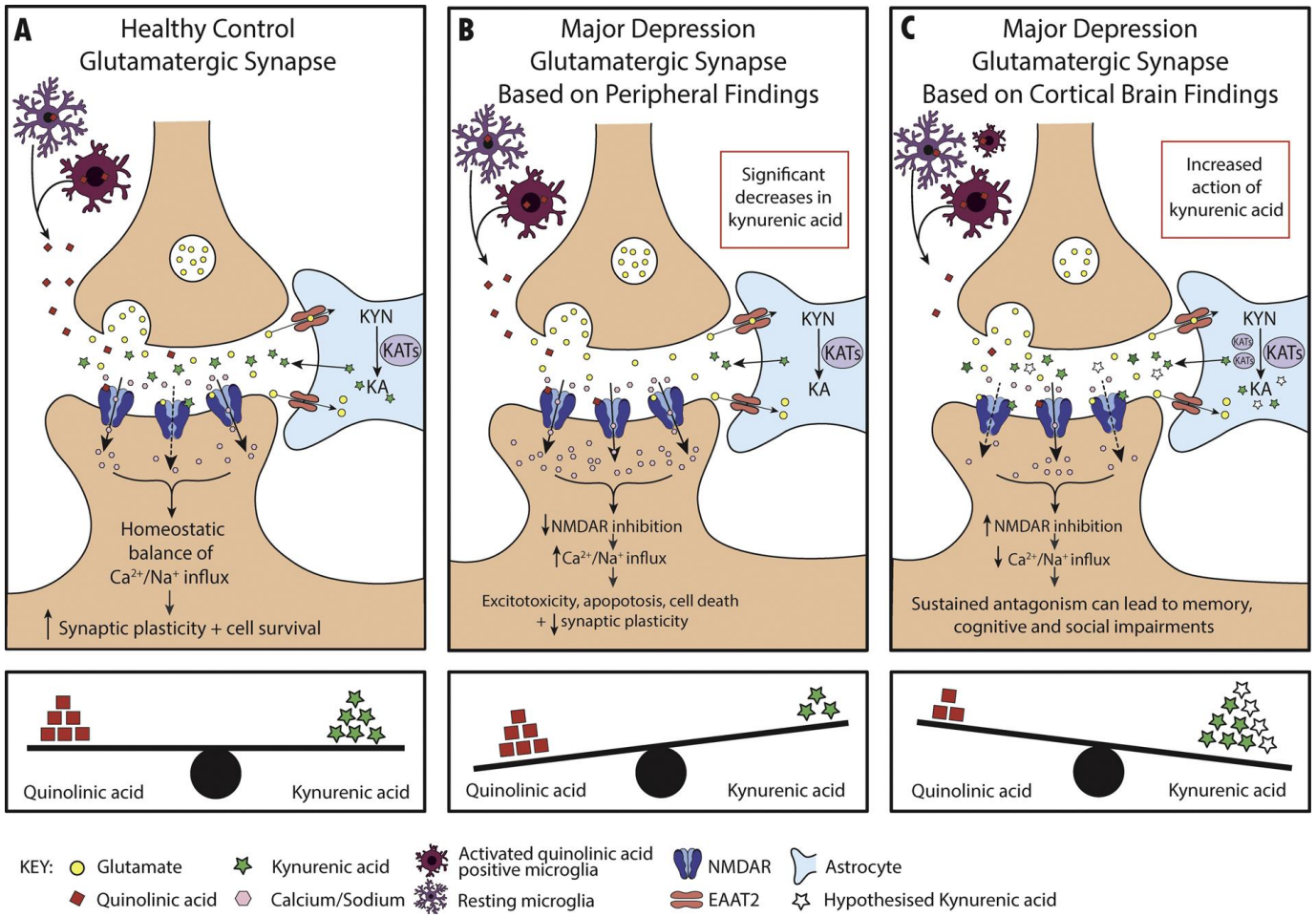
Neurobiology of Disease 135 (2020) 104578



Finding intestinal fortitude: Integrating the microbiome into a holistic view of depression mechanisms, treatment, and resilience

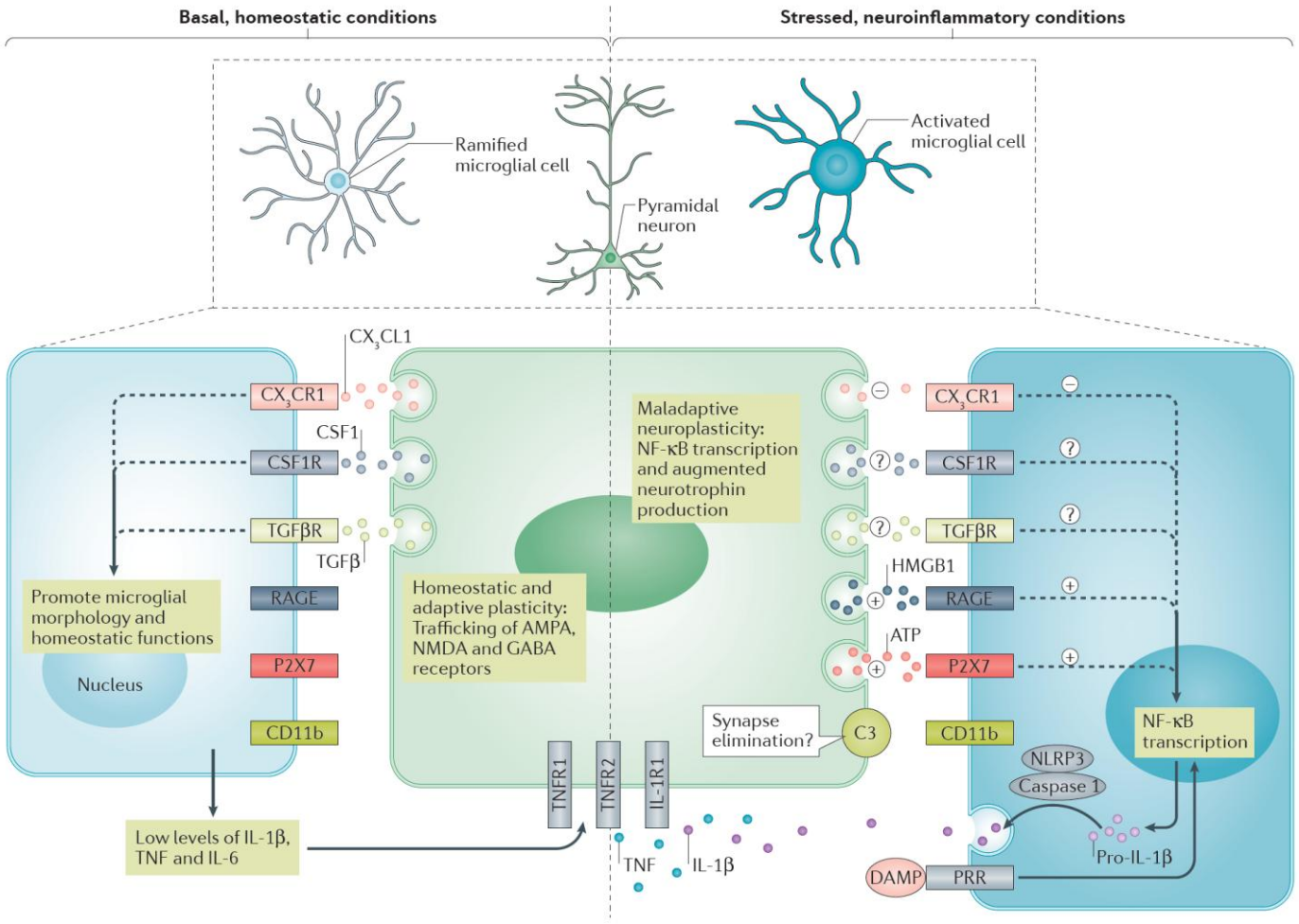
Neurobiology of Disease 135 (2020) 104578

The Kynurenine Pathway in Major Depression



The kynurenine pathway in major depression: What we know and where to next Neuroscience and Biobehavioral Reviews 127 (2021) 917–927

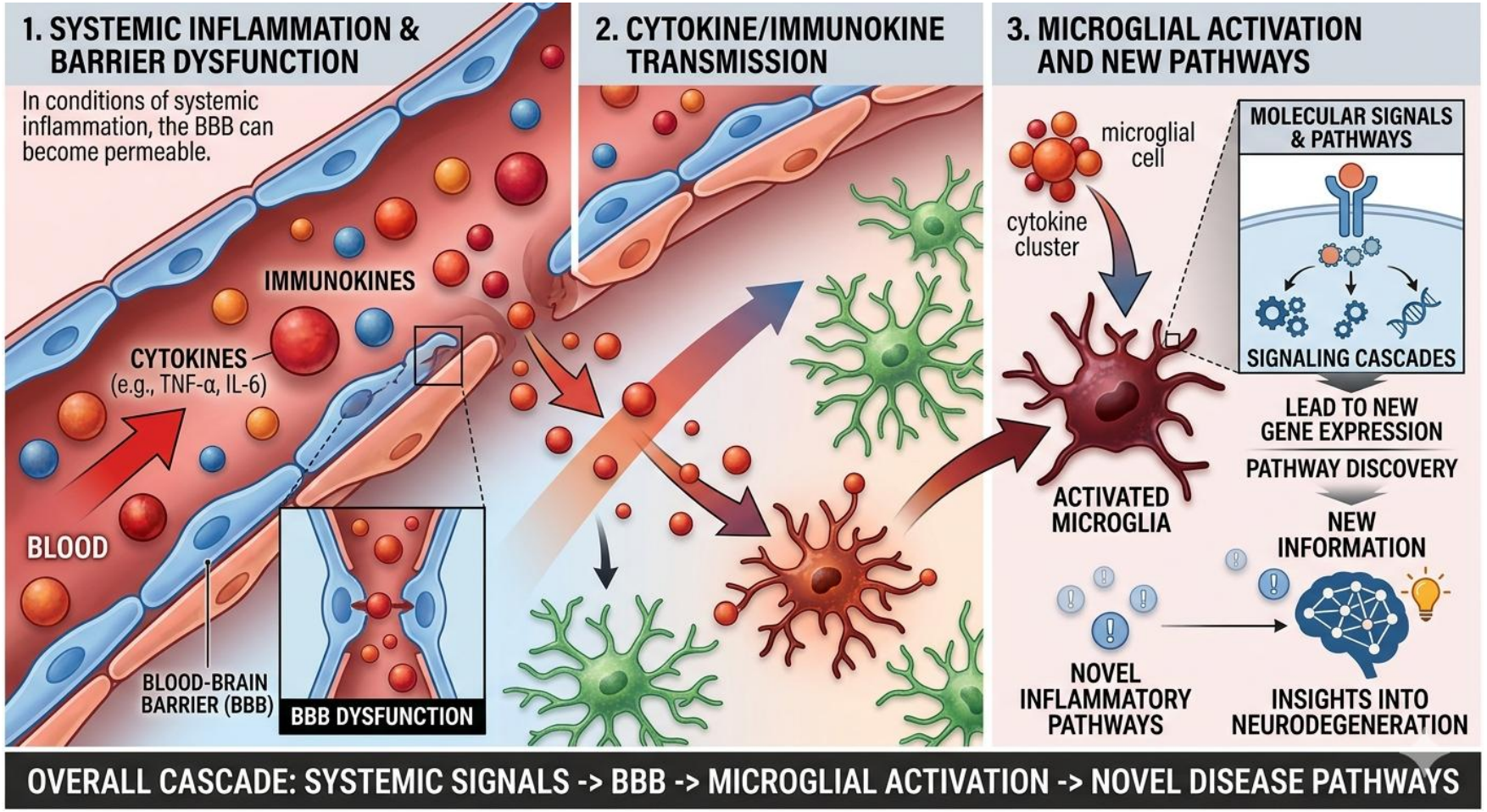
Synaptic Dysfunction in Neuroinflammation



Integrating neuroimmune systems in the neurobiology of depression

NATURE REVIEWS | NEUROSCIENCE

Blood-Brain Barrier Permeability with Neuroinflammation

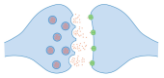


The Impact of Neuroinflammation on the Brain

Neuroinflammation

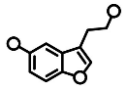
Mitochondria uncoupling

- ↓ ATP for neurons and neuroglia functions
- ↓ Neuron and neuroglia endurance



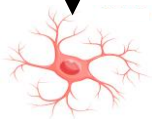
↓ Nerve conduction

- Reduced nerve transmission speed



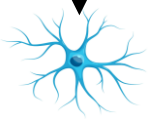
Activation of kynurenine pathway

- ↓ Serotonin activity
- ↓ Anticytotoxic kynurenic acid
- ↑ Neurotoxic quinolinic acid



Activation of microglia

- ↑ Brain inflammation
- ↑ Neuron injury
- Reactivate primed glia



Astrocyte dysfunction

- Synapse dysfunction
- ↓ Nerve growth factors

Blood-brain barrier permeability

- Increase susceptibility to inflammation

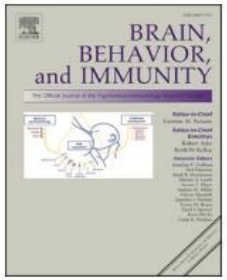
↑ Synaptic dysfunction, ↑ Neuron degeneration, ↓ Plasticity

Brain, Behavior, and Immunity 91 (2021) 505–518

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi



Neuroinflammation induces anxiety- and depressive-like behavior by modulating neuronal plasticity in the basolateral amygdala

Zhi-Heng Zheng [a,1], Jiang-Long Tu [b,1], Xiao-Han Li [c], Qing Hua [c], Wei-Zhu Liu [a], Yu Liu [d], Bing-Xing Pan [a], Ping Hu [e], Wen-Hua Zhang [a,*]

[a] Laboratory of Fear and Anxiety Disorders, Institutes of Life Science, Nanchang University, Nanchang 330031, PR China
[b] Department of Neurology, The Second Affiliated Hospital of Nanchang University, Nanchang 330006, PR China
[c] Department of Clinic Medicine, School of Queen Mary, Nanchang University, Nanchang, PR China
[d] Rehabilitation Department, Second Affiliated Hospital of Nanchang University, PR China
[e] Institute of Translational Medicine, Nanchang University, Nanchang 330001, PR China

Translational Psychiatry www.nature.com/tp

REVIEW ARTICLE OPEN

Check for updates

Neuroinflammation mechanisms of neuromodulation therapies for anxiety and depression

Bingqi Guo[1,2], Mengyao Zhang[1,2], Wensi Hao[1,2], Yuping Wang[1,2,3], Tingting Zhang[1,2]✉ and Chunyan Liu[1,2]✉

Mood disorders are associated with elevated inflammation, and the reduction of symptoms after multiple treatments is often accompanied by pro-inflammation restoration. A variety of neuromodulation techniques that regulate regional brain activities have been used to treat refractory mood disorders. However, their efficacy varies from person to person and lack reliable indicator. This review summarizes clinical and animal studies on inflammation in neural circuits related to anxiety and depression and the evidence that neuromodulation therapies regulate neuroinflammation in the treatment of neurological diseases. Neuromodulation therapies, including transcranial magnetic stimulation (TMS), transcranial electrical stimulation (TES), electroconvulsive therapy (ECT), photobiomodulation (PBM), transcranial ultrasound stimulation (TUS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS), all have been reported to attenuate neuroinflammation and reduce the release of pro-inflammatory factors, which may be one of the reasons for mood improvement. This review provides a better understanding of the effective mechanism of neuromodulation therapies and indicates that inflammatory biomarkers may serve as a reference for the assessment of pathological conditions and treatment options in anxiety and depression.

Translational Psychiatry (2023)13:5 ; https://doi.org/10.1038/s41398-022-02297-y

Pharmacology & Therapeutics 269 (2025) 108825

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

The (neuro)inflammatory system in anxiety disorders and PTSD: Potential treatment targets

Anupam Sah, Nicolas Singewald *

Institute of Pharmacy, Department of Pharmacology and Toxicology, Center for Molecular Biosciences Innsbruck, Leopold Franzens University Innsbruck, Innsbruck, Austria

ARTICLE INFO

Available online 19 February 2025

Editor: M. Curtis

Keywords:
Anxiolytic
Inflammation
Microglia
Cytokines
Anti-inflammatory
Minocycline
Microbiome

ABSTRACT

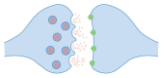
Targeting the immune system has recently garnered attention in the treatment of stress- associated psychiatric disorders resistant to existing pharmacotherapeutics. While such approaches have been studied in considerable detail in depression, the role of (neuro)inflammation in anxiety-related disorders, or in anxiety as an important transdiagnostic symptom, is much less clear. In this review we first critically review clinical and in part preclinical evidence of central and peripheral immune dysregulation in anxiety disorders and post-traumatic stress disorder (PTSD) and briefly discuss proposed mechanisms of how inflammation can affect anxiety-related symptoms. We then give an overview of existing and potential future targets in inflammation-associated signal transduction pathways and discuss effects of different immune-modulatory drugs in anxiety-related disorders. Finally, we discuss key gaps in current clinical trials such as the lack of prospective studies involving anxiety patient stratification strategies based on inflammatory biomarkers. Overall, although evidence is rather limited so far, there is data to indicate that increased (neuro)inflammation is present in subgroups of anxiety disorder patients. Although exact identification of such immune subtypes of anxiety disorders and PTSD is still challenging, these patients will likely particularly benefit from therapeutic targeting of aspects of the inflammatory system. Different anti-inflammatory treatment approaches (microglia-directed treatments, pro-inflammatory cytokine inhibitors, COX-inhibitors, phytochemicals and a number of novel anti-inflammatory agents) have indeed shown some efficacy even in non-stratified anxiety patient groups and appear promising as novel alternative or complimentary therapeutic options in specific ("inflammatory") subtypes of anxiety disorder and PTSD patients.

The Impact of Neuroinflammation on the Brain

Neuroinflammation

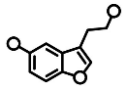
Mitochondria uncoupling

- ↓ ATP for neurons and neuroglia functions
- ↓ Neuron and neuroglia endurance



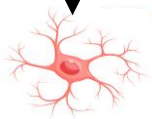
↓ Nerve conduction

- Reduced nerve transmission speed



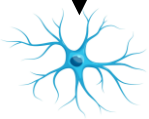
Activation of kynurenine pathway

- ↓ Serotonin activity
- ↓ Anticytotoxic kynurenic acid
- ↑ Neurotoxic quinolinic acid



Activation of microglia

- ↑ Brain inflammation
- ↑ Neuron injury
- Reactivate primed glia



Astrocyte dysfunction

- Synapse dysfunction
- ↓ Nerve growth factors

Blood-brain barrier permeability

- Increase susceptibility to inflammation

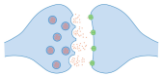
↑ Synaptic dysfunction, ↑ Neuron degeneration, ↓ Plasticity

WHAT IS THE IMPACT?

Antidepressant

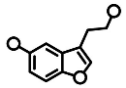
Mitochondria uncoupling

- ↓ ATP for neurons and neuroglia functions
- ↓ Neuron and neuroglia endurance



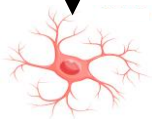
↓ Nerve conduction

- Reduced nerve transmission speed



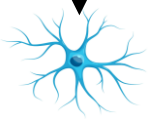
Activation of kynurenine pathway

- ↓ Serotonin activity
- ↓ Anticytotoxic kynurenic acid
- ↑ Neurotoxic quinolinic acid



Activation of microglia

- ↑ Brain inflammation
- ↑ Neuron injury
- Reactivate primed glia



Astrocyte dysfunction

- Synapse dysfunction
- ↓ Nerve growth factors

Blood-brain barrier permeability

- Increase susceptibility to inflammation

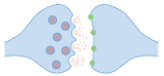
↑ Synaptic dysfunction, ↑ Neuron degeneration, ↓ Plasticity

WHAT IS THE IMPACT?

FISH OILS

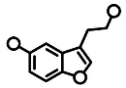
Mitochondria uncoupling

- ↓ ATP for neurons and neuroglia functions
- ↓ Neuron and neuroglia endurance



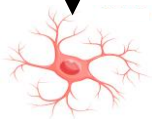
↓ Nerve conduction

- Reduced nerve transmission speed



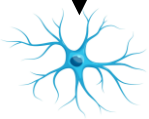
Activation of kynurenine pathway

- ↓ Serotonin activity
- ↓ Anticytotoxic kynurenic acid
- ↑ Neurotoxic quinolinic acid



Activation of microglia

- ↑ Brain inflammation
- ↑ Neuron injury
- Reactivate primed glia



Astrocyte dysfunction

- Synapse dysfunction
- ↓ Nerve growth factors

Blood-brain barrier permeability

- Increase susceptibility to inflammation

↑ Synaptic dysfunction, ↑ Neuron degeneration, ↓ Plasticity

WHAT IS THE IMPACT?

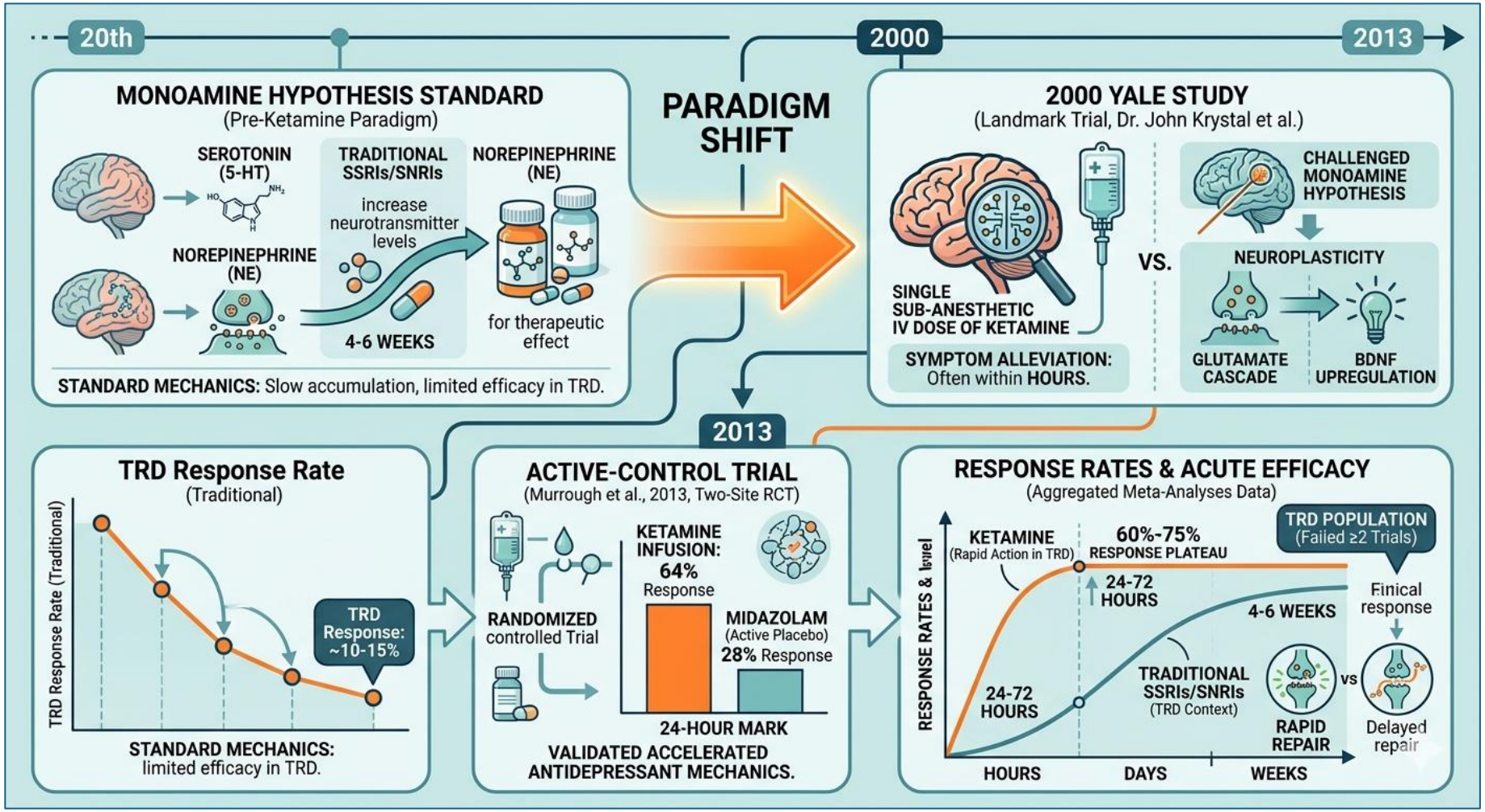
ST JOHN'S WART

Mitochondria uncoupling	↓ Nerve conduction	Activation of kynurenine pathway	Activation of microglia	Astrocyte dysfunction	Blood-brain barrier permeability
• ↓ ATP for neurons and neuroglia functions • ↓ Neuron and neuroglia endurance	• Reduced nerve transmission speed	• ↓ Serotonin activity • ↓ Anticytotoxic kynurenic acid • ↑ Neurotoxic quinolinic acid	• ↑ Brain inflammation • ↑ Neuron injury • Reactivate primed glia	• Synapse dysfunction • ↓ Nerve growth factors	• Increase susceptibility to inflammation

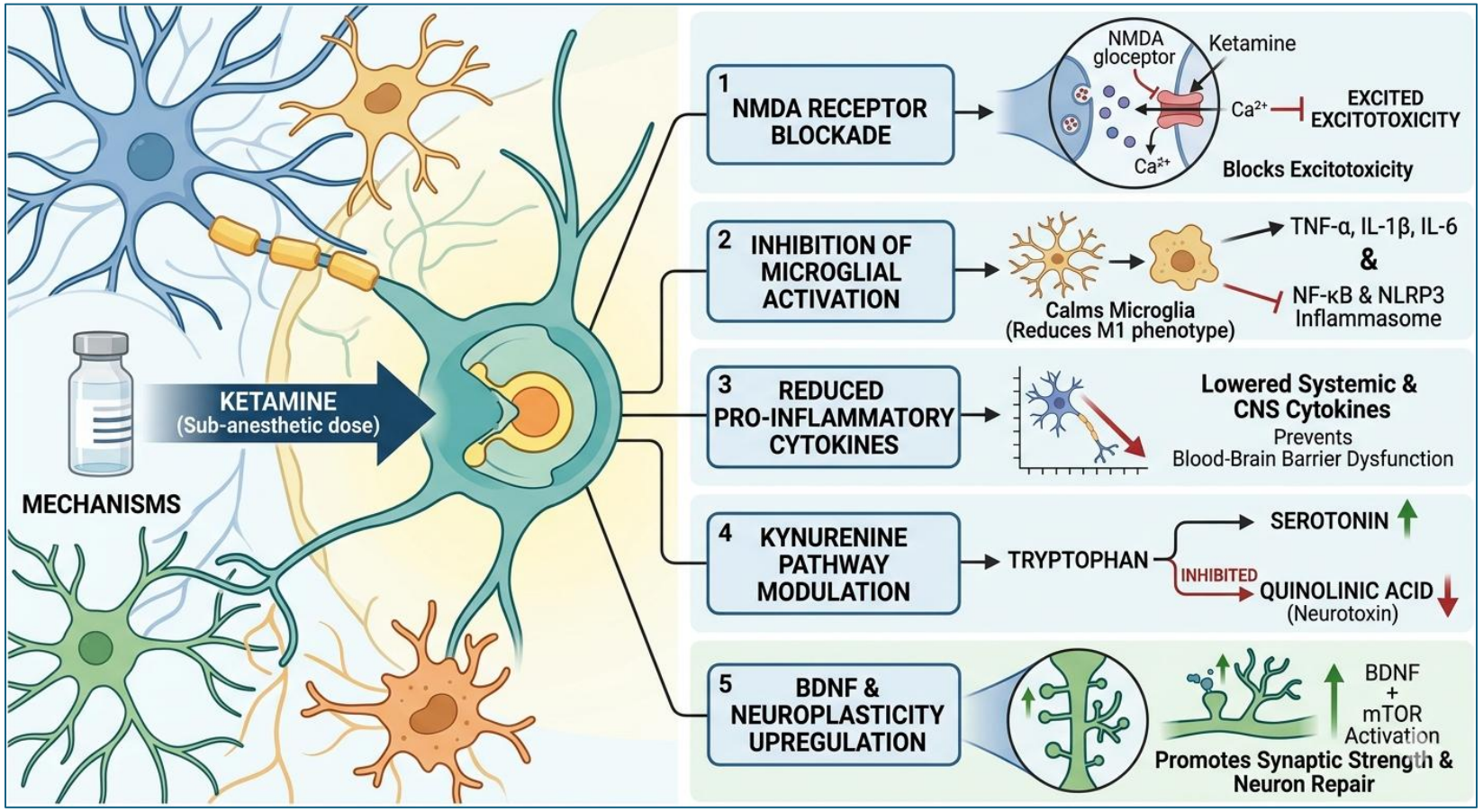
↑ Synaptic dysfunction, ↑ Neuron degeneration, ↓ Plasticity

The Drug That Changes the Paradigm Shift

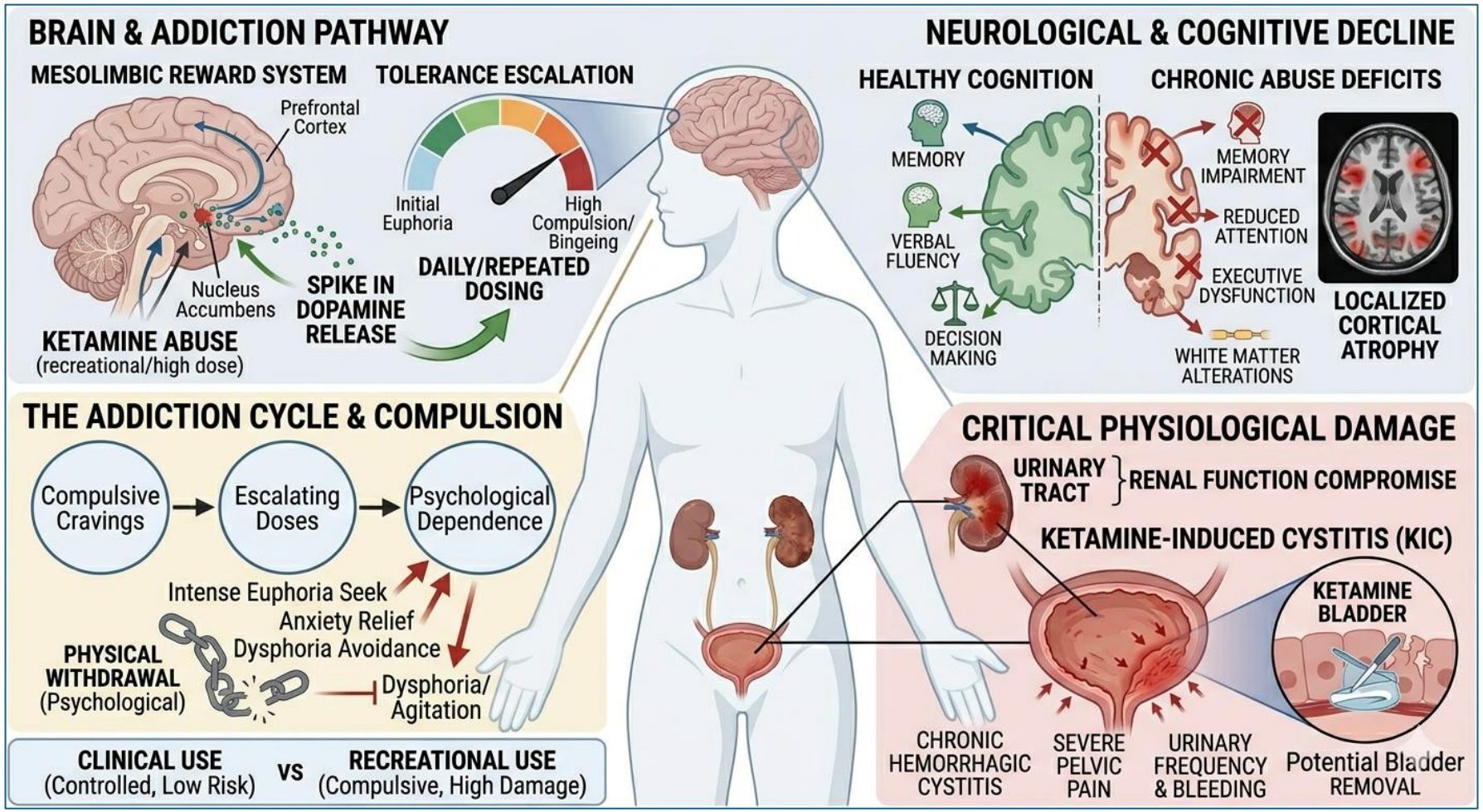
Ketamine Paradigm Shift for Depression Pharmacology



Physiological Impacts of Ketamine on Neuroinflammation



Ketamine Use Disorder (KUD)



Presentation Overview

Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

Presentation Overview

Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

CLINICAL SEVERITIES OF NEUROINFLAMMATION

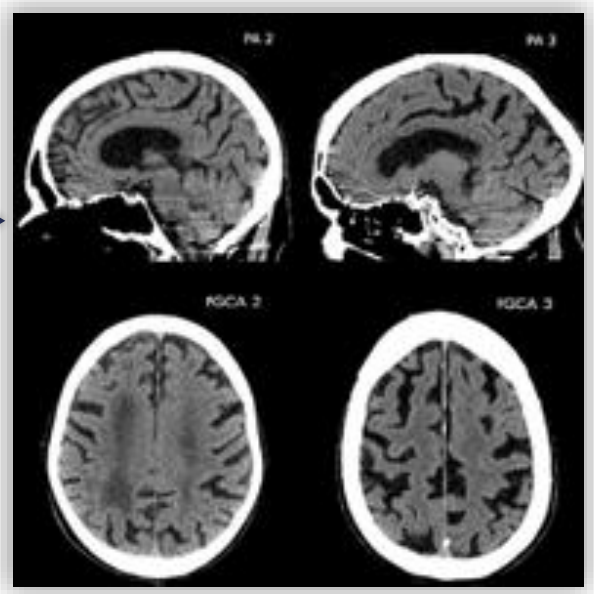
Transient Neuroinflammation

Chronic Neuroinflammation

Microglia-Primed Neuroinflammation

Neurological Autoimmunity

Neurodegeneration



"Our childhood determines the questions we spend the rest of our lives trying to answer." — *Inspired by Sigmund Freud*

Aristo Vojdani, PhD

Professor of Medicine at Loma Linda University School of Medicine

Immunosciences Lab., Inc.
Rahim Karjoo, M.D. Medical Director

Patient Name:

Patient I.D.: DOB 3/29/81

Blood Drawn	Processed	Reported	ISL No.
03/10/06	03/11/06	03/27/06	197260

TEST	RESULTS NORMAL	RESULTS ABNORMAL	REFERENCE RANGE	UNITS
*** MAG ANTIBODY ***				
MAG IgG	39		0 - 100	ELISA
MAG IgM		103	0 - 68	ELISA
MAG IgA	11		0 - 27	ELISA

Human peripheral nerve myelin contains several glycoproteins in which one of them is myelin associated glycoprotein (MAG) Antibody against MAG has been detected in neurological disorders including peripheral neuropathy. Multiple sclerosis(MS) is a chronic demyelinating disease of the CNS characterized by focal areas of demyelination(lesions or plaques).Although the exact etiology of MS is unknown,it is generally accepted that autoimmunity is involved and that the autoantigen(s) probably reside in CNS myelin, the target of the immune response. Myelin consist of numerous candidate autoantigenic proteins among which are major myelin constituents like myelin basic protein(MBP) and proteolipid protein(PLP), and minor myelin constituents like myelin oligodendrocyteglycoprotein (MOG), myelin associated glycoprotein(MAG) and alpha-beta crystallin, a small heat shock protein which appear to be dominant antigens for CD4+ T cells.Autoaggressive T-cell that recognize different myelin antigen in the context of ClassII MHC molecules can initiate antibody production and CNS inflammation.Antibodies reacting to glycoconjugates have been implicated in the development of neuropathies and a relationship between specific target antigens and clinical symptomatology has been suggested. In particular high titers of antibodies to GM1 ganglioside are frequently found in patients with multifocal motor neuropathy while anti-MAG antibodies are present in patients with chronic demyelinating sensorimotor neuropathy. Antibodies to chondroitin sulfate and sulfatide have been implicated in the pathogenesis of predominantly sensory neuropachies associated or not with immunoglobulin M(IgM) paraproteinemias. More recently, antibodies to MOG and alpha-beta crystallin were detected in the majority of patients with multiple sclerosis. Antibodies against this brain antigens as well as neurotypic and glycotypic proteins were developed as a marker of subclinical neurotoxicity induced by metals and other neurotoxicants.

REFERENCES:

1-Nemni et al.Antibodies to sulfatide and chondroitin sul-

CONTINUED ON NEXT PAGE

Immunosciences Lab., Inc.
Rahim Karjoo, M.D. Medical Director

Patient Name:

Patient I.D.: DOB 3/29/81

Blood Drawn	Processed	Reported	ISL No.
03/10/06	03/11/06	03/27/06	197260

TEST	RESULTS NORMAL	RESULTS ABNORMAL	REFERENCE RANGE	UNITS
*** SEROTONIN ANTIBODY TEST ***				
SEROTONIN IgG ANTIBODY	19		0 - 20	ELISA
SEROTONIN IgM ANTIBODY		26	0 - 20	ELISA

Serotonin is a neurotransmitter produced by the amine precursor uptake and decarboxylation system. Most serotonin in blood is usually concentrated in platelets. Antibodies against serotonin have been demonstrated in patients with primary fibromyalgia syndrome and in neuroimmune disorders.

1. Klein R., Bansch M., Berg P.A., Clinical Relevance of Antibodies Against Serotonin and Gangliosides in Patients with Primary Fibromyalgia Syndrome. Psychoneuroimmunology 17:593, 1992.

This test was developed and its performance characteristics were determined by Immunosciences Laboratory Inc. It does not require FDA clearance, pursuant to Act 21 CFR 9 30 (e). Analyte-specific reagents used in this assay are exempt from pre-market notification requirements of Section 510 (K) of the act.

CONTINUED ON NEXT PAGE

Immunosciences Lab., Inc.
Rahim Karjoo, M.D. Medical Director

Patient Name:

Patient I.D.: DOB 3/29/81

Blood Drawn	Processed	Reported	ISL No.
03/10/06	03/11/06	03/27/06	197260

TEST	RESULTS NORMAL	RESULTS ABNORMAL	REFERENCE RANGE	UNITS
*** TH1/TH2 CYTOKINES ***				
INTERLEUKIN-2 LEVEL	<31.2		<31.2	pg/ml
INTERFERON GAMMA		26.40	<15.6	pg/mL
INTERLEUKIN-4 LEVEL	<31.20		<31.2	pg/mL
INTERLEUKIN-10 LEVEL	<5.00		<5- 8.02	Pg/ml

T HELPER-1/T HELPER-2 IMBALANCE

CD4 positive cells or T-Helper cells are classified into two types; T Helper-1 and T Helper-2. This classification is done based on the type of cytokines they secrete.
T Helper-1 polarized cells secrete Interleukin-2, Interferon gamma, and tumor necrosis factor alpha (TNF-alpha) which are efficient at eliminating intracellular pathogens.T-Helper-2 cells secrete IL-4, IL-5, IL 10 and IL-13, which affect humoral immunity to helminthic parasites and responses to persistent antigens such as allergens. TH1/TH2 imbalance plays an important role in susceptibility to allergy or immunity. Polarization of TH1 may result in multiple sclerosis,diabetes, arthritis,uveitis,mercury-induced autoimmunity,atopic dermatitis or inflammatory bowel disease. While polarization of TH2 may result in lupus,lead-induced autoimmunity,allergy, asthma,chemical sensitivity and parasitic infection.

References:

1-Kono et al., The Prototype TH2 Autoimmunity Induced By Mercury Is Dependent on Interferon Gamma and Not TH1/TH2 Imbalance.J.of Immunology 161:234,1998
2-Kengarajin et al., Transcriptional Regulation of TH1/TH2 Polarization.Immunology Today 21:479,2000

**********PLEASE NOTE NEW REFERENCE RANGES**********

****

***NOTE:

TEST WAS PERFORMED ON KITS AND ON AUTOMATED IMMULITE-DPC INSTRUMENT. THE MEASUREMENT HAS BEEN CONFIGURED "FOR RESEARCH USE ONLY" AND IS NOT TO BE USED FOR DIAGNOSTIC PROCEDURES.

****

CONTINUED ON NEXT PAGE

8693 Wilshire Boulevard / Suite 200 / Beverly Hills, CA 90211 • Tel: (310) 657-1077 • Fax: (310) 657-1053

Immunosciences Lab., Inc.
Rahim Karjoo, M.D. Medical Director

AUTOIMMUNE CASE 2 PAGE —

Patient Name:

Patient I.D.:
DOB 3/29/81

Blood Drawn	Processed	Reported	ISL No.
03/10/06	03/11/06	03/27/06	197260

TEST	RESULTS NORMAL	RESULTS ABNORMAL	REFERENCE RANGE	UNITS
**** INTERLEUKIN-2 PRODUCTION ****				
INTERLEUKIN-2 PRODUCTION	99.0		<31.2	pg/ML

******RESULTS CALCULATED PER MILLION LYMPHOCYTE.******
******PLEASE NOTE NEW REFERNCE RANGES****

Lymphokines are soluble proteins or glycoproteins that are produced by mononuclear leukocytes in response to mitogen or antigen stimulation and that function to regulate both humoral and cell-mediated immune responses.
Interleukin-2 (IL-2), previously named T-cell growth factor, was first described by Morgan and Ruscetti in 1967 as a factor in the supernatants of phytohemagglutinin (PHA)-stimulated human mononuclear cells.
IL-2 has been shown to enhance natural killer cell activity and to be required for the generation of cytotoxic T-cells and the induction of antigen-specific antibody responses.
Perhaps a more pivotal role for IL-2 is its ability to induce the production of tumor necrosis factors and gamma interferon, a lymphokine with anticancer, antiviral, and immunoregulatory activities different from those of IL-2.
The importance of IL-2 stems from the fact that it can regulate immune functions both directly and indirectly via the induction of other lymphokines, and,THEREFORE,THE MEASUREMENT OF IL-2 PRODUCTION CAN BE A SENSITIVE MONITOR OF GENERAL IMMUNE STATUS.
Several studies have associated abnormalities in IL-2 production, IL-2 levels, or IL-2R expression with pathogenesis. Example are:
1) AIDS
2) Autoimmune diseases including multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus and type I diabetes.
3) Transplant rejection.
4) Chronic fatigue immune dysfunction syndrome
5) Chemically induced immune dysfunction.
6) Cancer.

****

***NOTE:
THE KITS USED FOR MEASUREMENT OF CYTOKINES HAS BEEN CONFIGURED "FOR RESEARCH USE ONLY" AND IS NOT TO BE USED FOR DIAGNOSTIC PROCEDURES.

CONTINUED ON NEXT PAGE

Immunosciences Lab., Inc.
Rahim Karjoo, M.D. Medical Director

Patient Name:

Patient I.D.: DOB 3/29/81

Blood Drawn	Processed	Reported	ISL No.
03/10/06	03/11/06	03/27/06	197260

TEST	RESULTS NORMAL	RESULTS ABNORMAL	REFERENCE RANGE	UNITS
*** LYMPHOCYTE SUB-POPULATION ***				
TOTAL WBC	6300		4000-10000	mm3
TOTAL LYMPHOCYTE	2142		960-4320	mm3
% LYMPHOCYTE	34.0		20 - 40%	PERCENT
TOTAL T-CELL	1549		586-3672	mm3
% T CELL (T11, CD2)	72.0		61 - 85%	PERCENT
TOTAL T HELPER CELL (T4)	964		336-2376	mm3
% T HELPER CELL (T4)	45.0		35-55%	PERCENT
TOTAL SUPPRESSOR CELL	578		192-1598	mm3
% SUPPRESSOR CELL (T8)	27.0		20-37%	PERCENT
T-HELPER/T-SUPPRESSOR	1.7		1-2.5	RATIO
TOTAL B CELL	214		48-640	mm3
% B-CELL (B1,CD20)	10.0		5 - 15%	PERCENT
TOTAL NATURAL KILLER	386		52-864	mm3
%NATURAL KILLER CELLS	18.0		5.5-20%	PERCENT
TOTAL IMMUNOCOMPETENT	43		14-216	mm3
% IMMUNOCOMPETENT -NKHT3+	2.0		1.5-5%	PERCENT
TOTAL NKHT3 NEGATIVE	343		38-648	mm3
% NKHT3 NEGATIVE		16.0	4-15%	PERCENT
TOTAL CD3+ CD26+	728		10-1944	mm3
% CD3+ CD26+ (TA1)	34.0		1-45%	PERCENT
TOTAL T3 (CD3) POSITIVE C	1500		509-3413	mm3
% T3 POSITIVE CELLS	70.0		53-79%	PERCENT

CONTINUED ON NEXT PAGE

Immunosciences Lab., Inc.
Rahim Karjoo, M.D. Medical Director

Patient Name:

Patient I.D.: DOB 3/29/81

Blood Drawn	Processed	Reported	ISL No.
03/10/06	03/11/06	03/27/06	197260

TEST	RESULTS NORMAL	RESULTS ABNORMAL	REFERENCE RANGE	UNITS
*** NK CELL ACTIVITY PANEL ***				
NK CELL ACTIVITY		7.70	20-50	LUs
NK CELL ACTIVITY/CELL		2.00	5.1-10	LUs
%NATURAL KILLER CELLS	18.0		5.5-20%	PERCENT
% IMMUNOCOMPETENT -NKHT3+	2.0		1.5-5%	PERCENT
% NKHT3 NEGATIVE		16.0	4-15%	PERCENT
% T3 POSITIVE CELLS	70.0		53-79%	PERCENT

One of the major mechanisms by which the immune response deals with foreign or abnormal cells is to damage or destroy them. Such immunologic cytotoxicity may lead to complete loss of viability of the target cells (cytolysis) or an inhibition of the ability of the cells to continue growing (cytostasis). Immunologic cytotoxicity can be manifested against a wide variety of target cells. These include malignant cells, normal cells from individuals unrelated to the responding host, and normal cells of the host that are infected with viruses or other microorganisms. In addition, the immune system can cause direct cytotoxic effects on some microorganisms, including bacteria, parasites, and fungi. Immunologic cytotoxicity is a principal mechanism by which the immune response copes with and often eliminates foreign materials or abnormal cells. Natural killer cell activity is influenced by a variety of conditions including stress, chemical exposure, infections, chronic fatigue syndrome, immune deficiencies and cancer. In an increasing number of studies of clinical treatments of patients with various diseases, serial monitoring of cytotoxic reactivity is performed. The objective is to determine whether the treatment can produce a significant alteration from the pretreatment levels of NK activity, Antibody Dependent Cytotoxic activity, or both. Interleukin 2, interferon and natural killer cytotoxic factor has been shown to enhance NK cell activity. Therefore enhancement of Interleukin 2 Production may be useful in reactivation of NK cells in patients with the above mentioned conditions.

****

REFERENCE RANGE:

CONTINUED ON NEXT PAGE

1-1-2018

Association between Immunological Reactivity with Tetrabromobisphenol-A and Autoimmune Target Sites of the Nervous System

Datis Kharrazian
Nova Southeastern University

Martha Herbet, M.D., Ph.D.,
Professor of Neurology at Harvard Medical School

Presentation Overview

Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

Presentation Overview

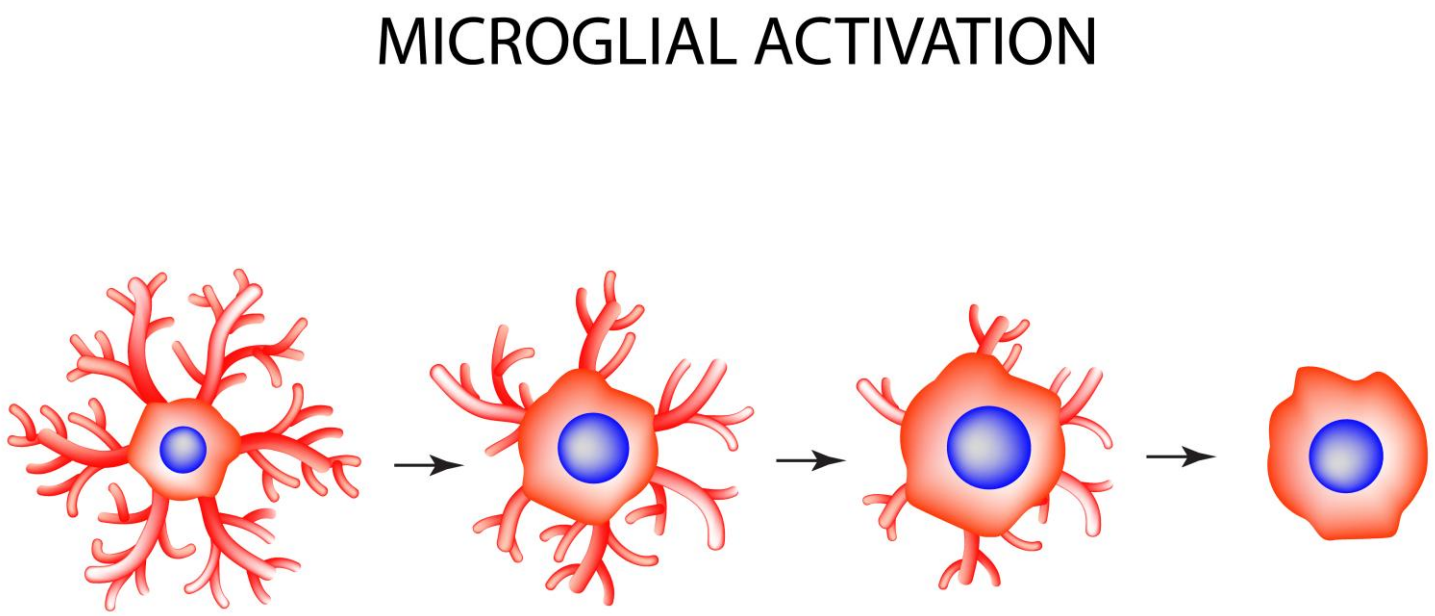
Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

Microglia “Steady” Versus “Activated” State



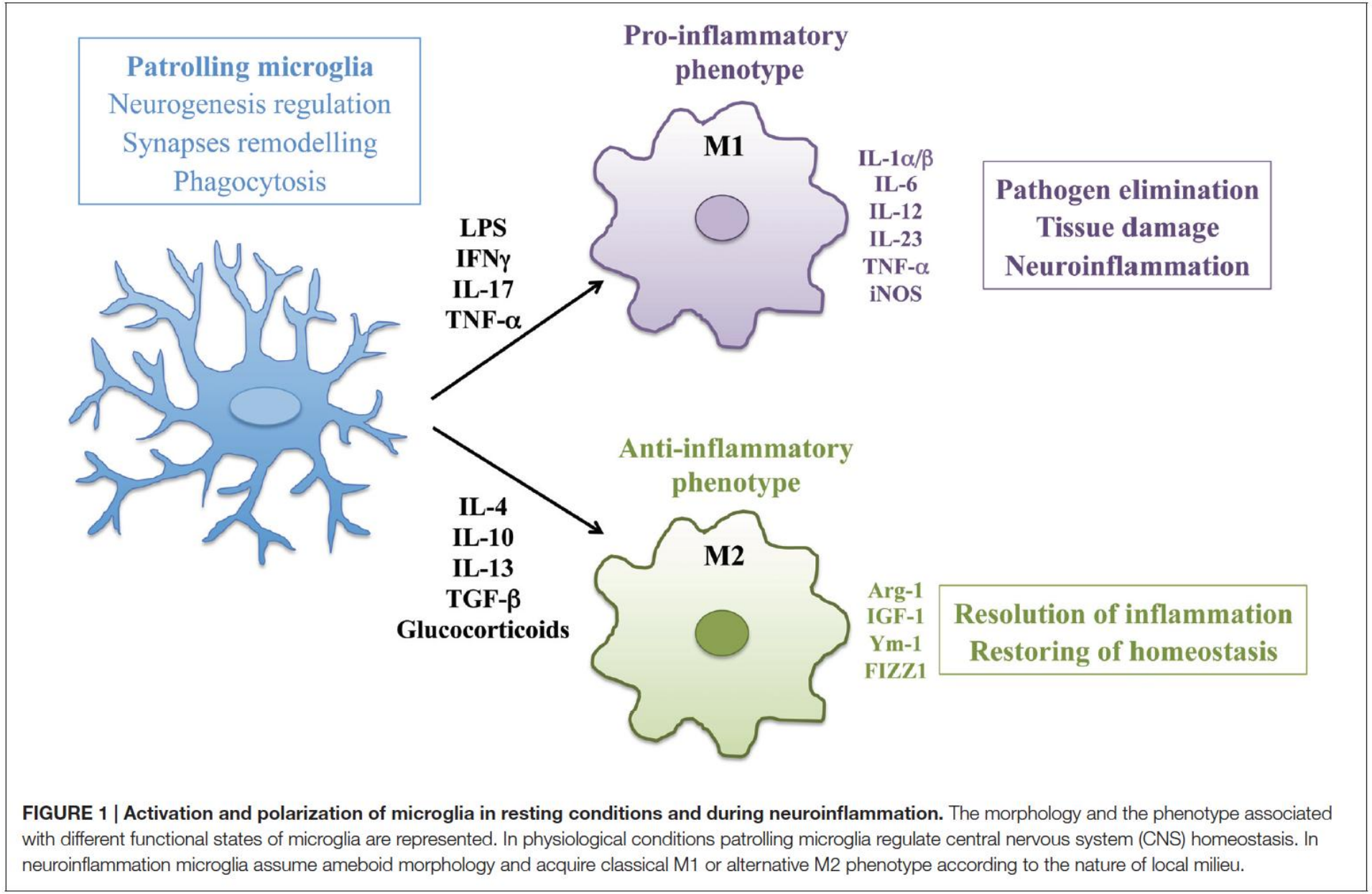
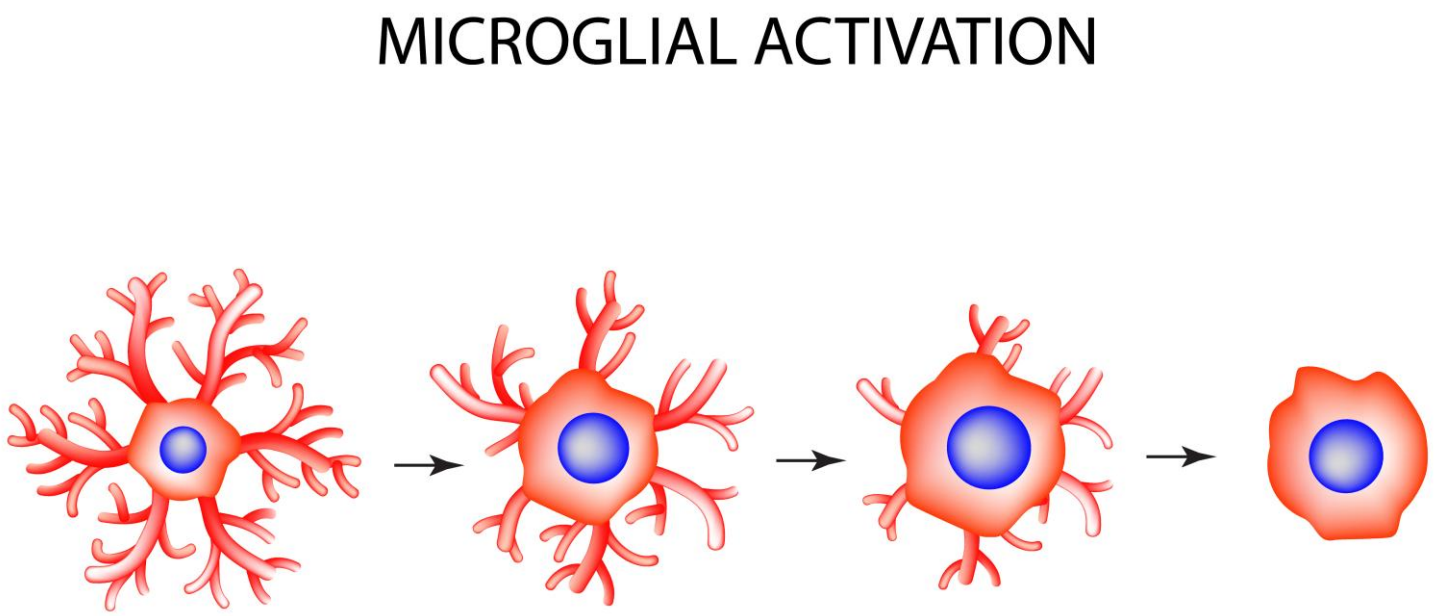


FIGURE 1 | Activation and polarization of microglia in resting conditions and during neuroinflammation. The morphology and the phenotype associated with different functional states of microglia are represented. In physiological conditions patrolling microglia regulate central nervous system (CNS) homeostasis. In neuroinflammation microglia assume ameboid morphology and acquire classical M1 or alternative M2 phenotype according to the nature of local milieu.

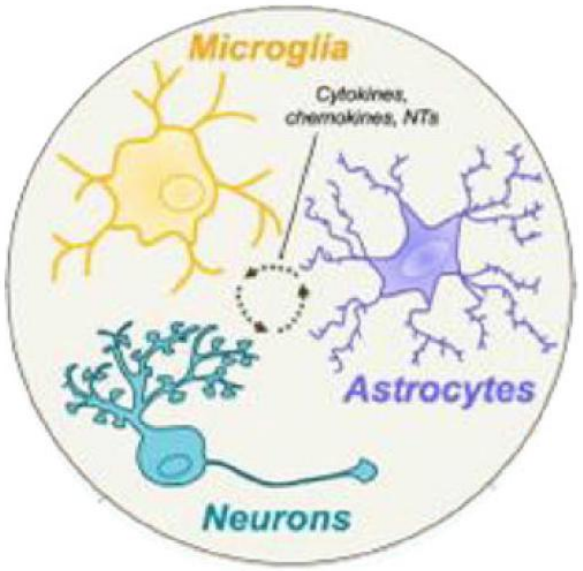
Microglia “Steady” Versus “Activated” State



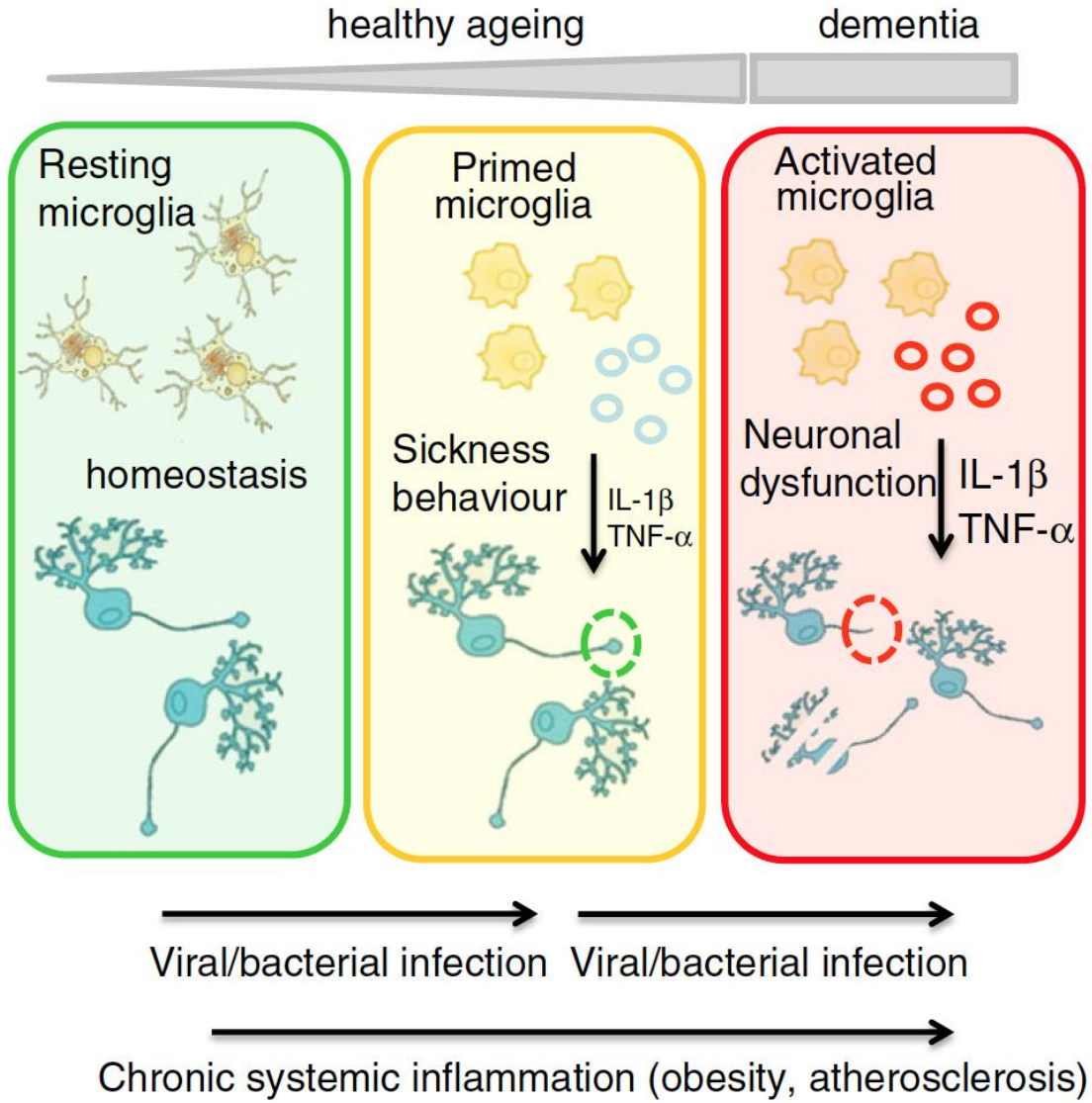
Transition Into a New Structure

Picture with permission Aristo Vojdani, PhD

Neuron-Glial interactions keep microglia in a down-regulated state

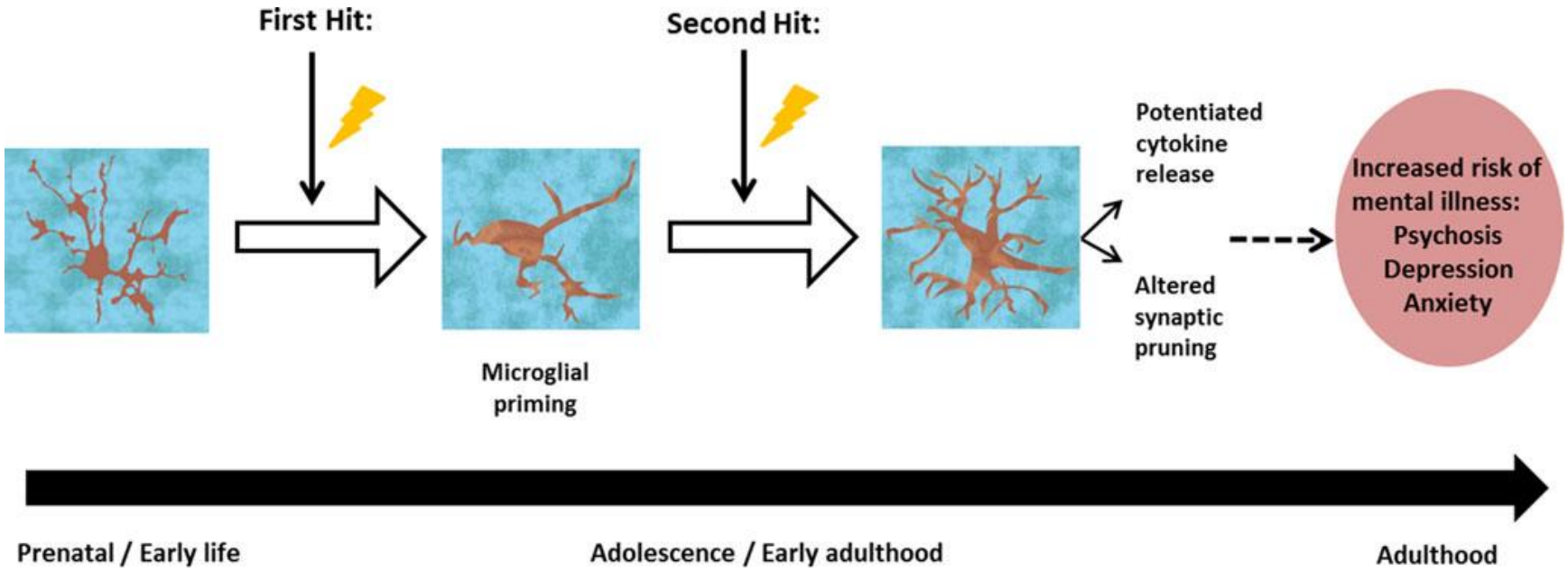


changes in microenvironment
=
changes in microglia adaptive/maladaptive



Semin Immunopathol (2013) 35:601–612

Basic Concept of Microglia Priming



Psychopharmacology (2016) 233:1637–1650

diagnostics

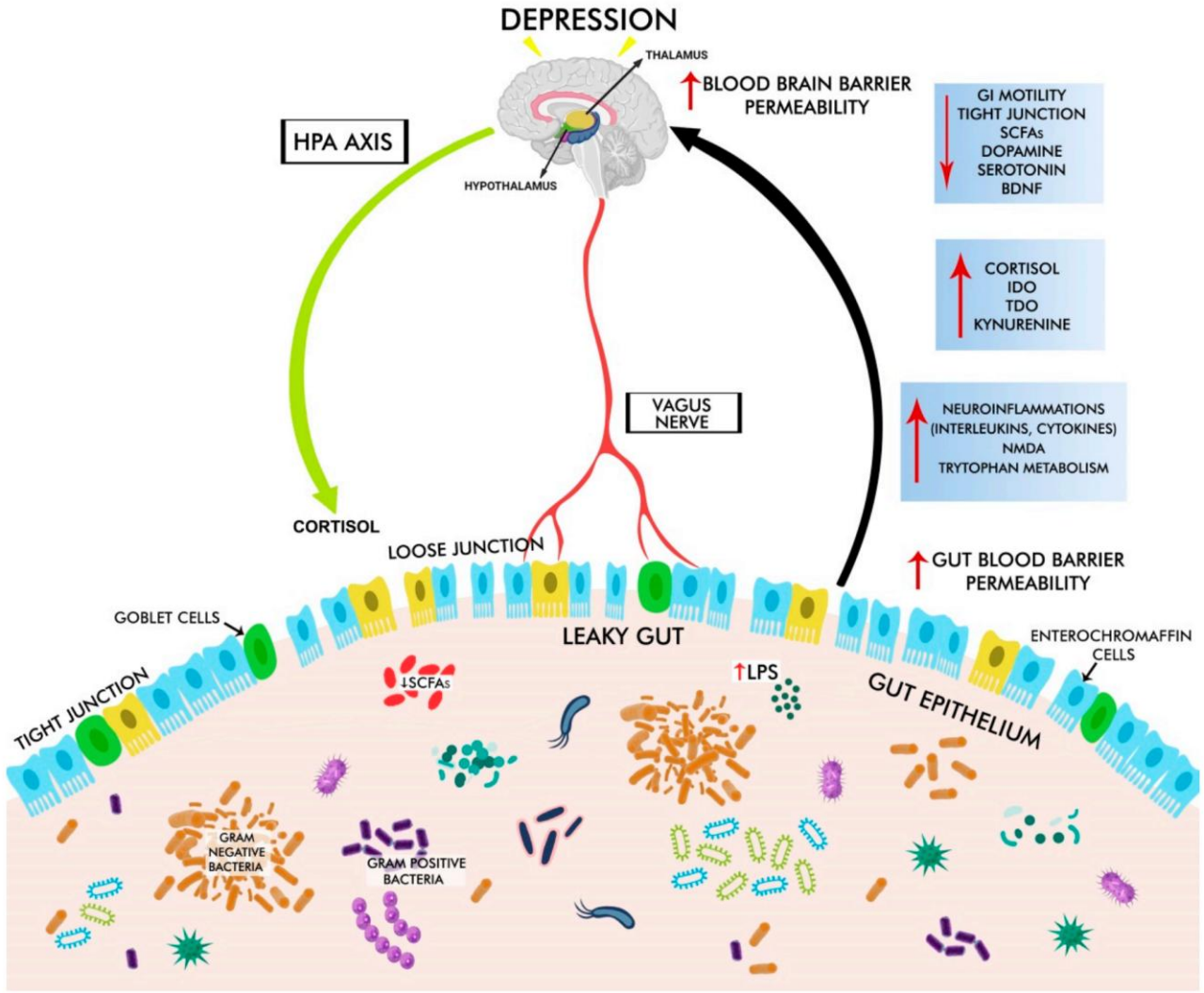
MDPI

Systematic Review

Leaky Gut Biomarkers as Predictors of Depression and Suicidal Risk: A Systematic Review and Meta-Analysis

Donato Morena [1,*], Matteo Lippi [1], Matteo Scopetti [2], Emanuela Turillazzi [3] and Vittorio Fineschi [1]

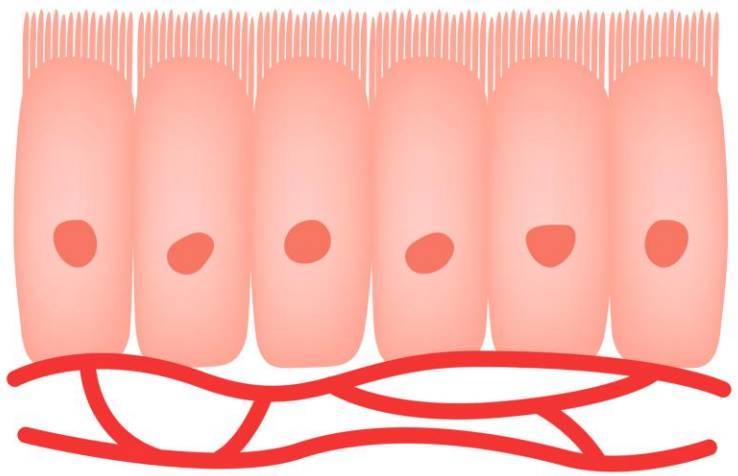
1 Department of Anatomical, Histological, Forensic and Orthopedic Sciences, Sapienza University of Rome, 00161 Rome, Italy; matteo.lippi@uniroma1.it (M.L.); vittorio.fineschi@uniroma1.it (V.F.)
2 Department of Medical Surgical Sciences and Translational Medicine, Sapienza University of Rome, 00189 Rome, Italy; matteo.scopetti@uniroma1.it
3 Department of Surgical Pathology, Medical, Molecular and Critical Area, University of Pisa, 56126 Pisa, Italy; emanuela.turillazzi@unipi.it
* Correspondence: donato.morena@uniroma1.it



Cells **2022**, *11*, 1362.

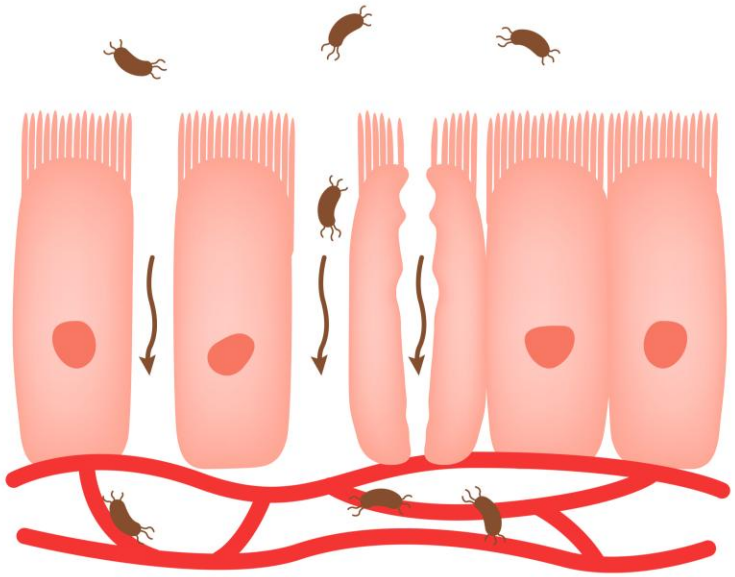
Endotoxemia

Healthy intestinal barrier



Normal Tight Junction

Leaky gut with dysbiosis

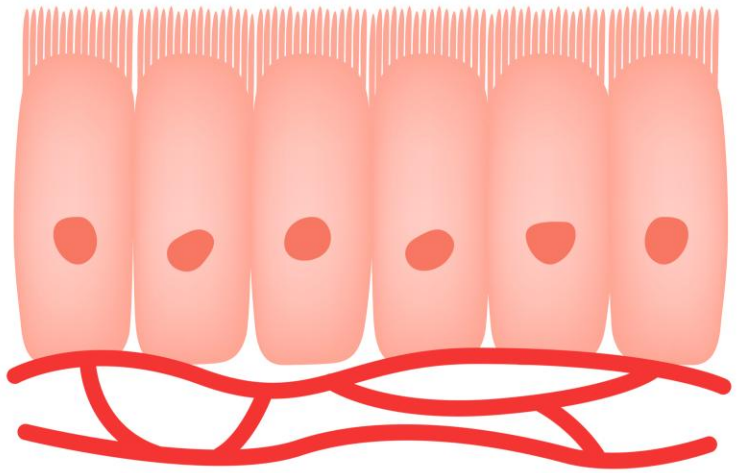


Unhealthy gut bacteria into circulation

“Endotoxemia”

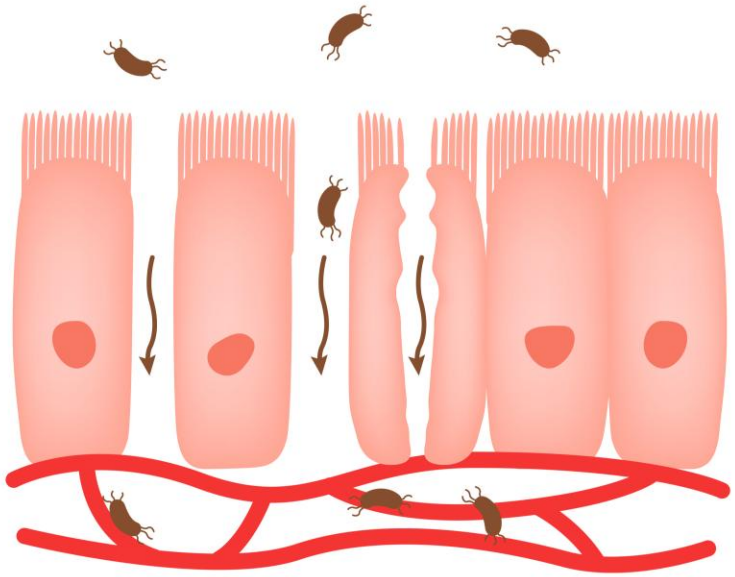
Endotoxemia

Healthy intestinal barrier



Normal Tight Junction

Leaky gut with dysbiosis

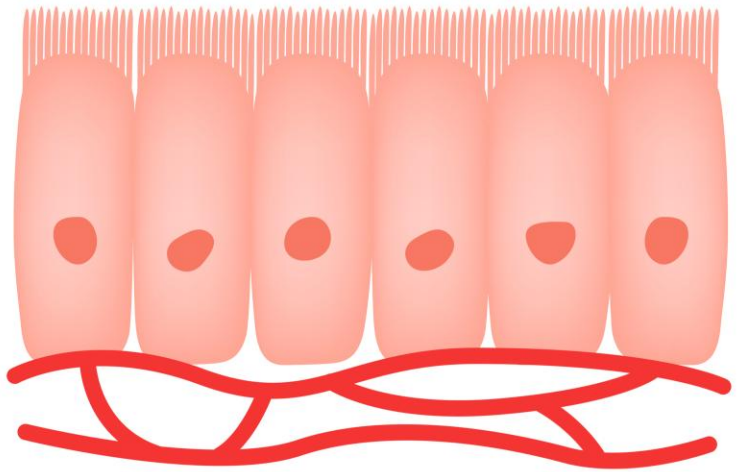


Unhealthy gut bacteria into circulation

“Endotoxemia”

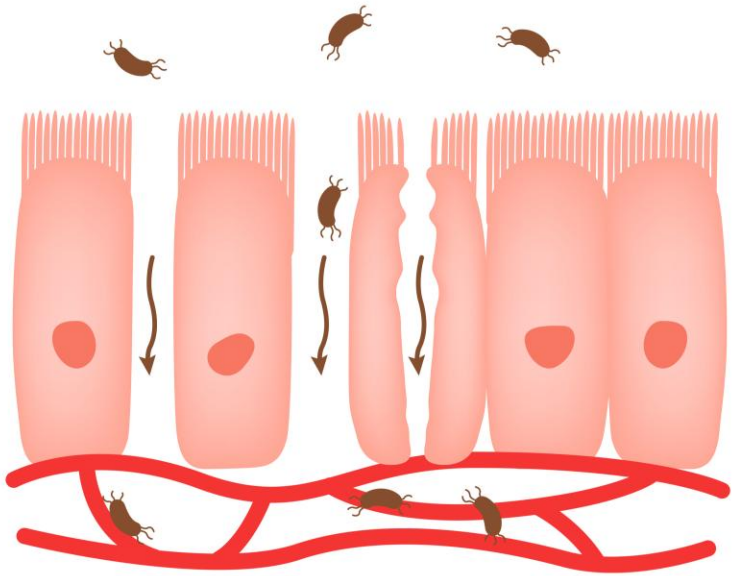
Endotoxemia

Healthy intestinal barrier



Normal Tight Junction

Leaky gut with dysbiosis

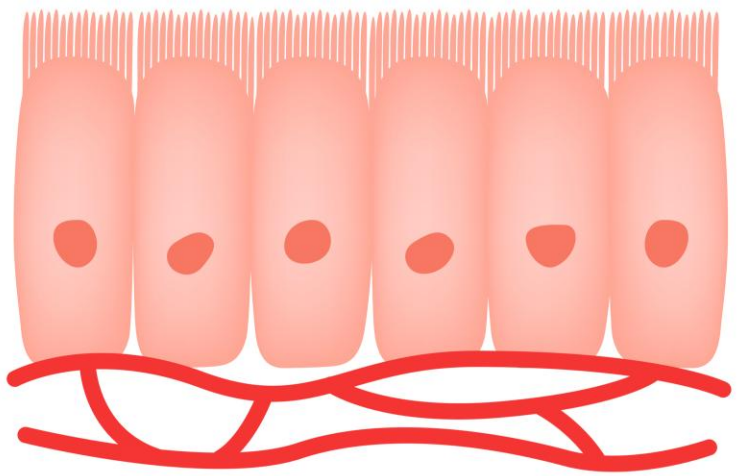


Unhealthy gut bacteria into circulation

“Endotoxemia”

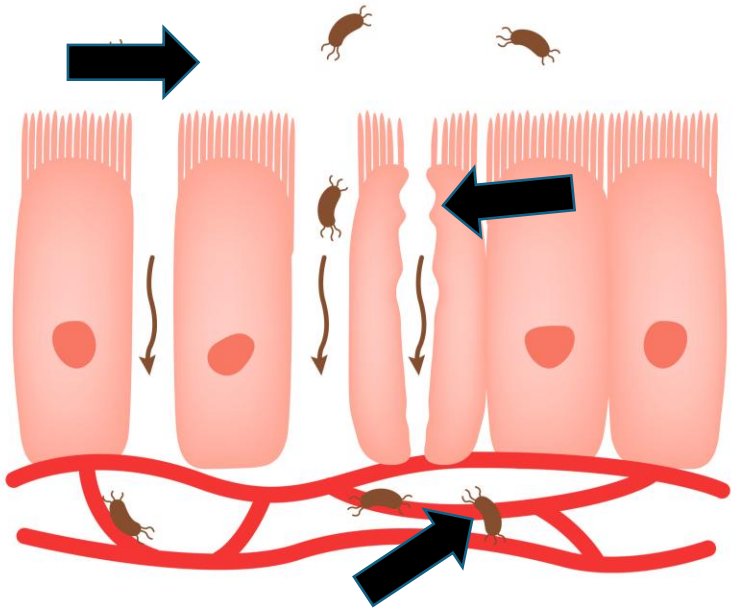
Endotoxemia

Healthy intestinal barrier



Normal Tight Junction

Leaky gut with dysbiosis

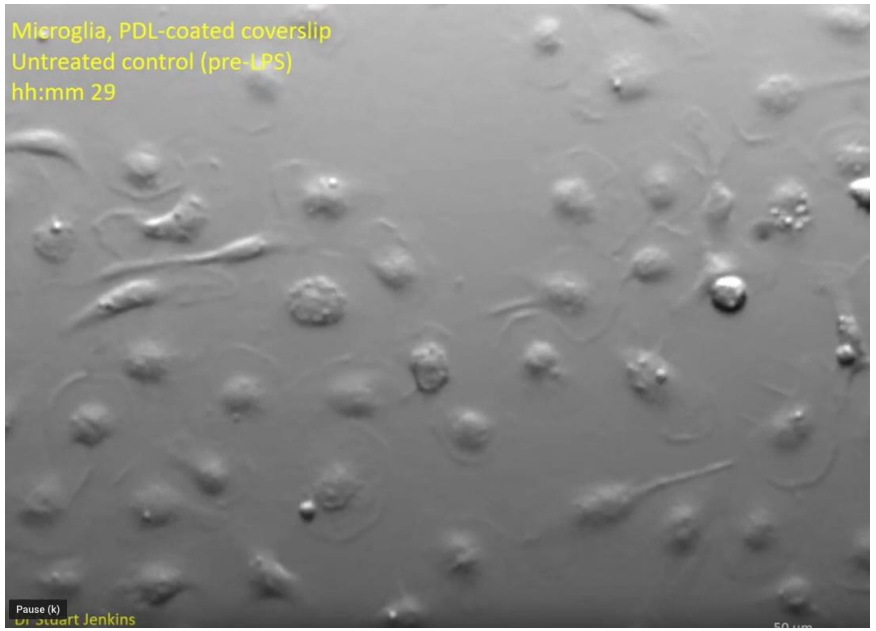


Unhealthy gut bacteria into circulation

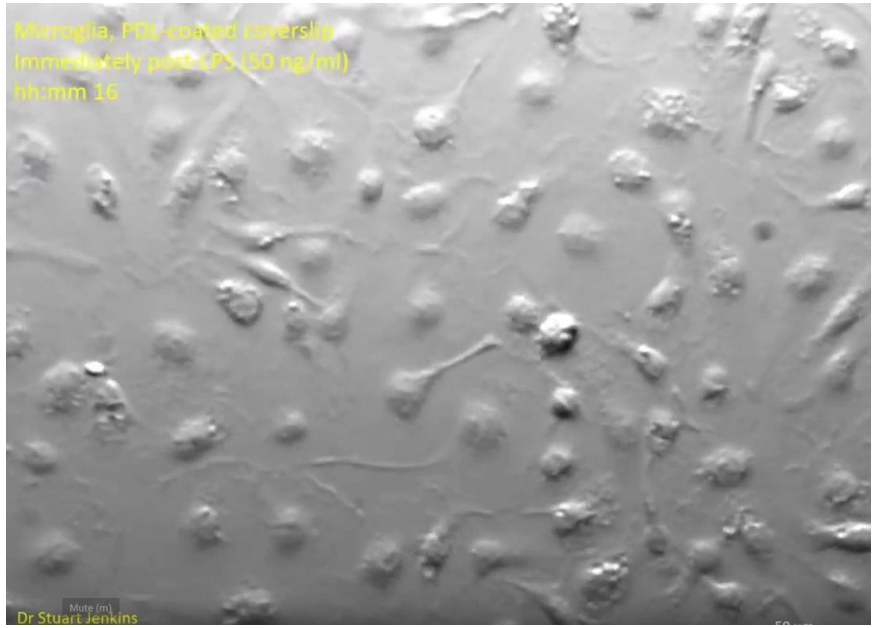
“Endotoxemia”

Microglia Pre and Post LPS Stimulation

Microglia Pre LPS

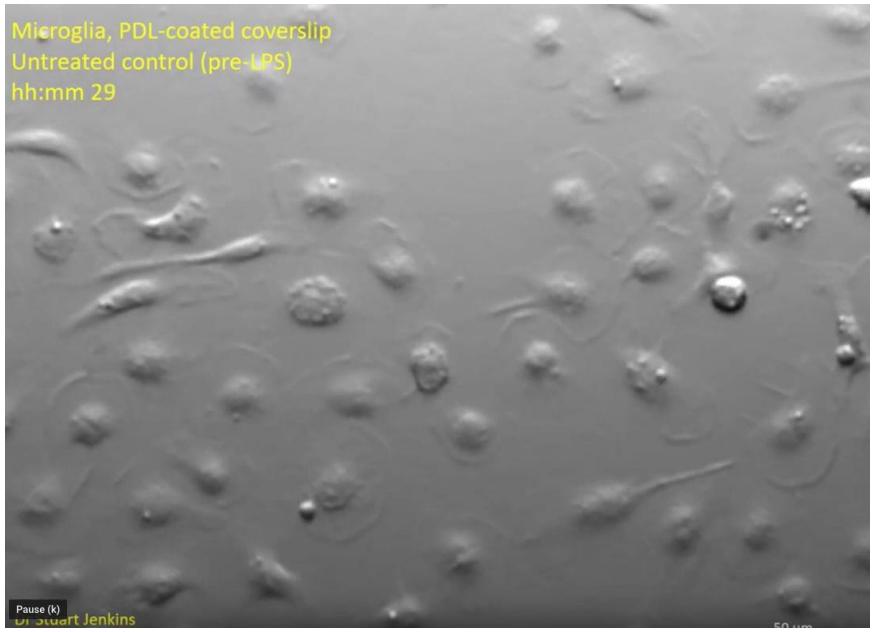


Microglia Post LPS

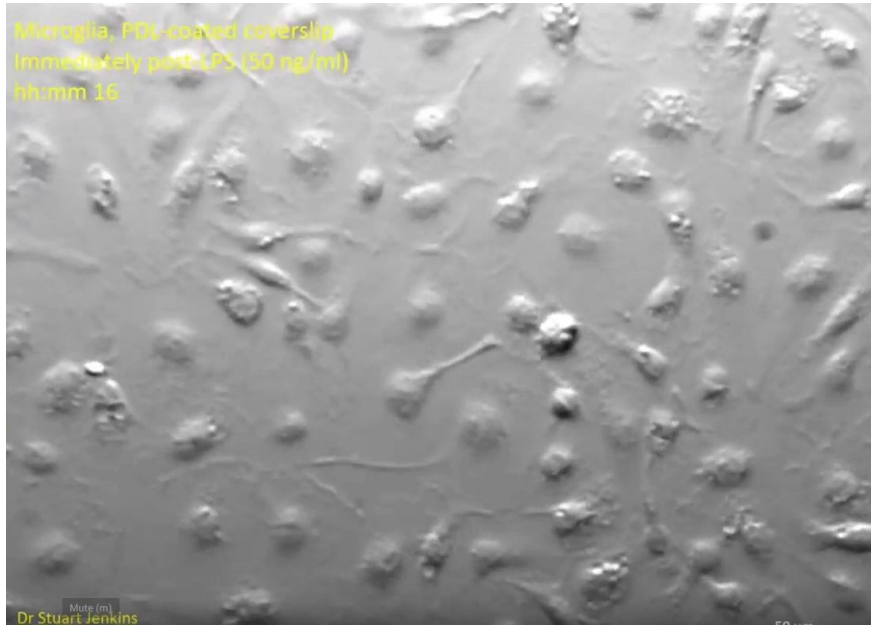


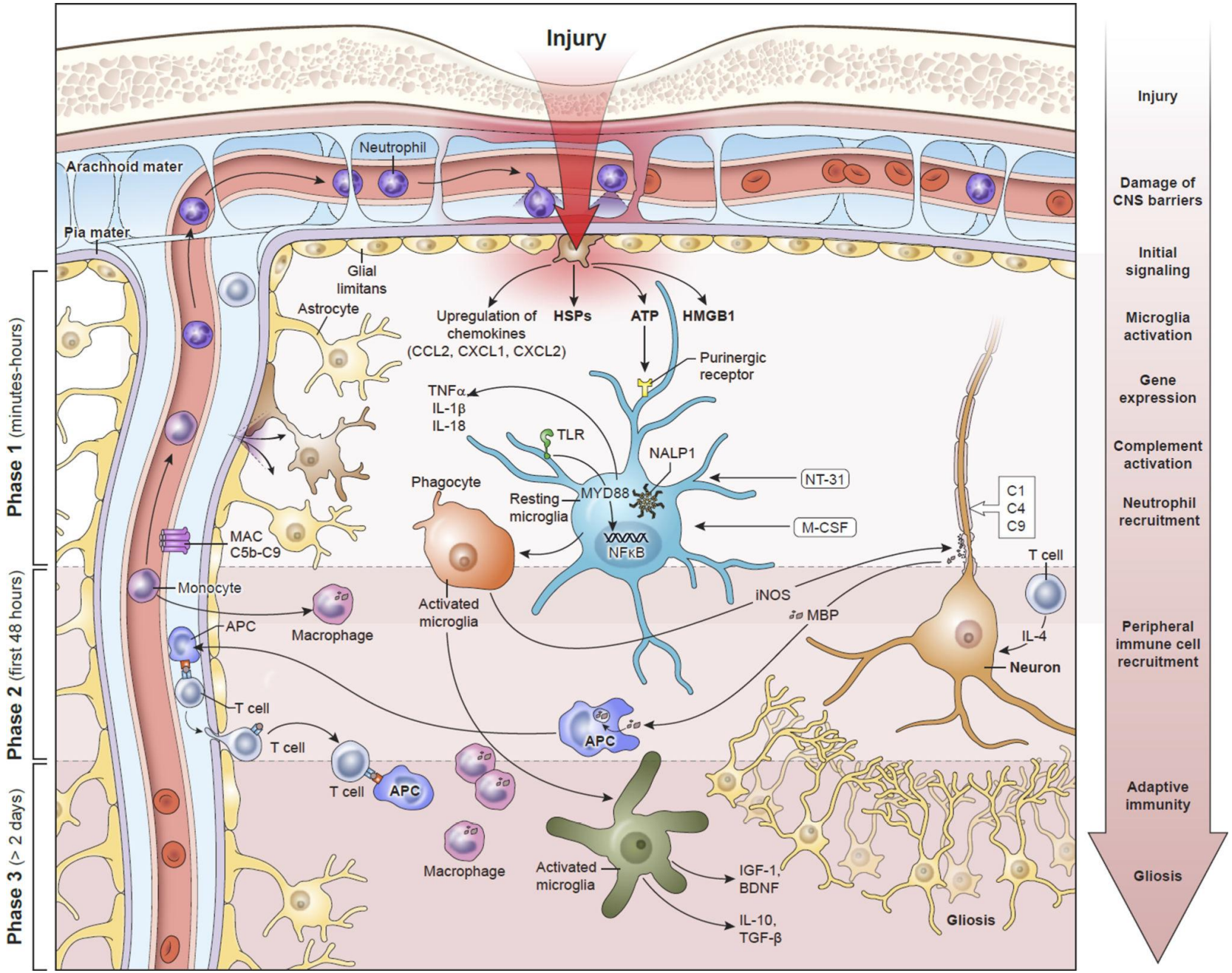
Microglia Pre and Post LPS Stimulation

Microglia Pre LPS



Microglia Post LPS

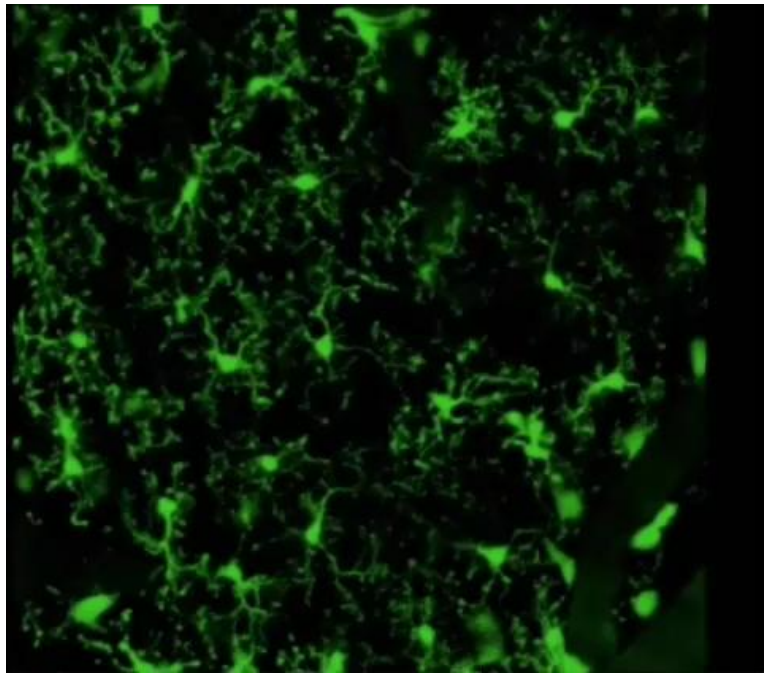




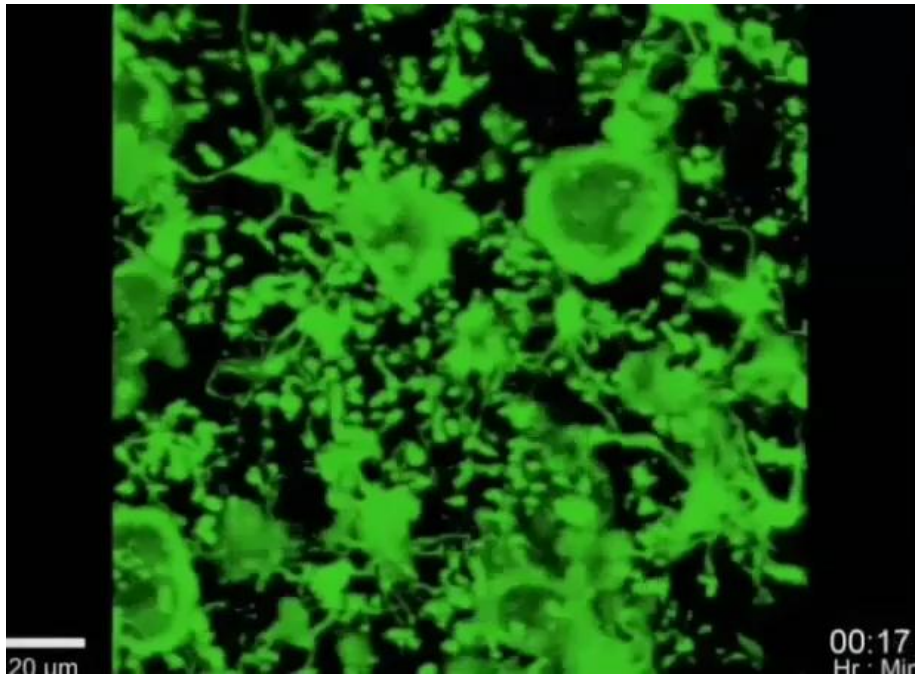
Neuron. 2017 September 13; 95(6): 1246–1265.

Inflammation and Neuroprotection in Traumatic Brain Injury

Resting Neuroglia Before TBI



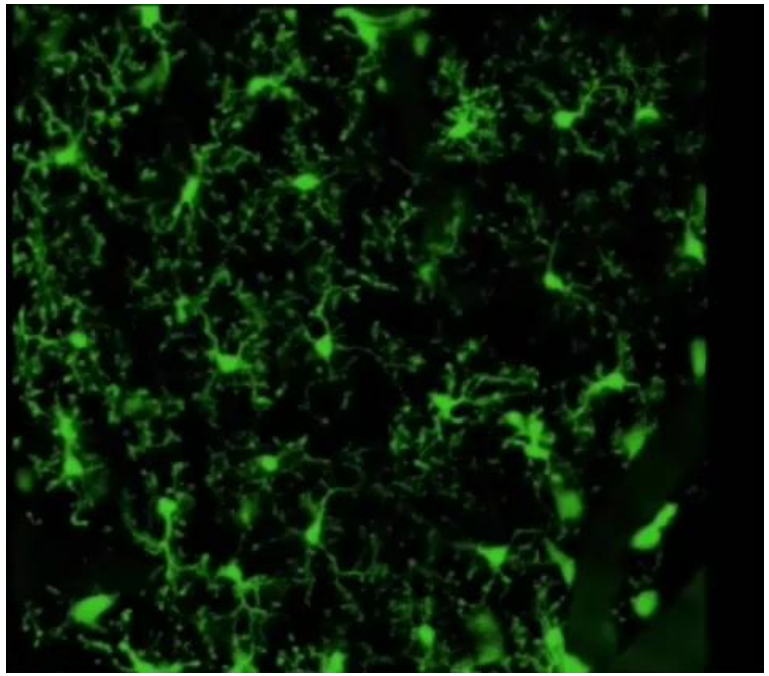
Activated Neuroglia After TBI



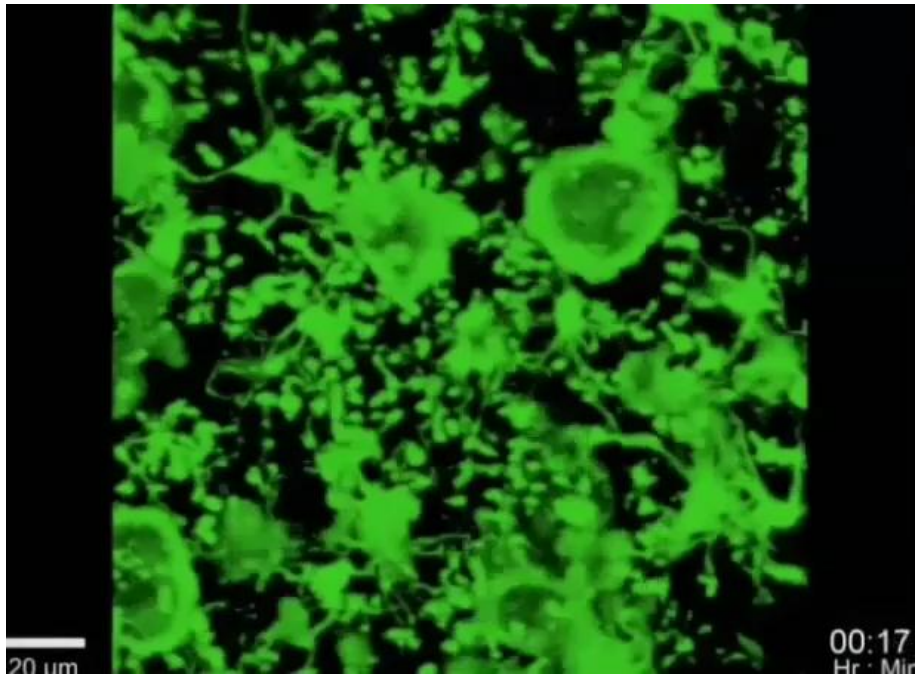
JAMA Neurol. 2015;72(3):355-362. doi:10.1001/jamaneurol.2014.3558

Inflammation and Neuroprotection in Traumatic Brain Injury

Resting Neuroglia Before TBI



Activated Neuroglia After TBI



JAMA Neurol. 2015;72(3):355-362. doi:10.1001/jamaneurol.2014.3558

Presentation Overview

Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

Presentation Overview

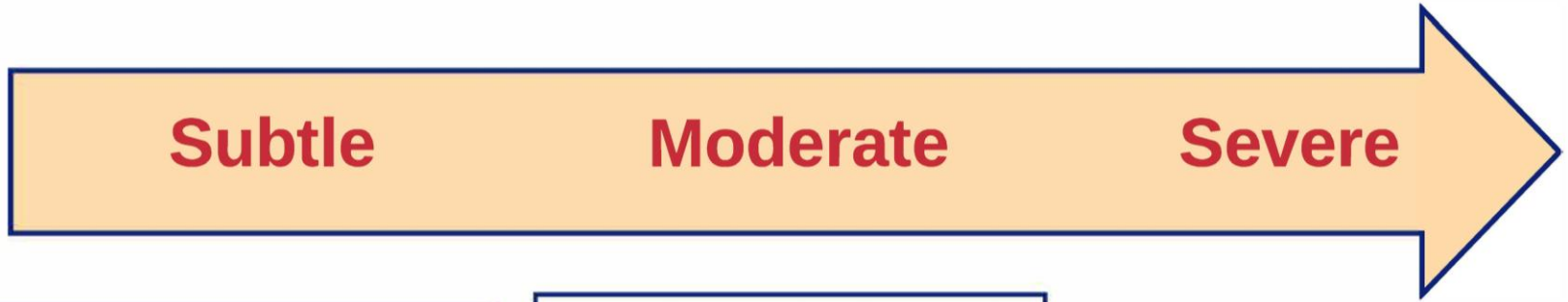
Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

Neuroinflammation Symptom Scale



- Brain fog (hazy thoughts and recall)
- Noticeable variations in mental speed
- Reduced brain endurance
- Brain fatigue after exposure to specific chemicals, scents or pollutants
- Brain fatigue after exposure to specific food proteins

- Depression
- Inability to concentrate especially for long periods
- Sleepiness
- Increased demand for sleep, must sleep 8 or more hours
- Lethargy/Fatigue
- Lack of motivation
- Loss of appetite
- Malaise and inability to be physically active

- Delirium/confusion/disorientation
- Dementia/personality/behavior changes
- Coma
- Seizures
- Difficulty speaking
- Trembling, tremors, involuntary twitching

Clinical Pearl

An ***unproportionable deficit*** in neurological function from various triggers that impact the immune system (dietary proteins, lack of sleep, environmental exposure) suggests **microglia priming.**

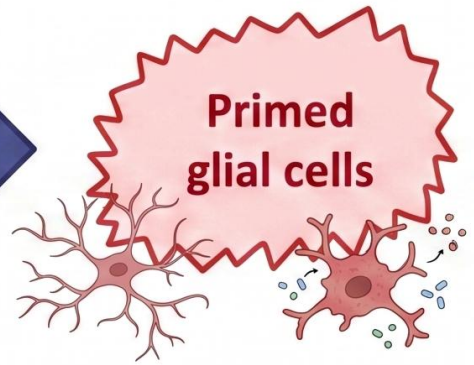
Clinical Presentation of Primed Glial Cells

Immunological Trigger

- **Dietary protein reactivity**
- **Infection**
- **Oxidative stress**
- **Cigarette smoke**
- **Toxic chemicals**
- **Air pollution**

Loss of Neurological Integrity

- → Dizziness
- → Anxiety
- → Numbness of face or limbs
- → Tinnitus
- → Difficulty with motor tasks
- → Cognitive decline
- → Depression



★ ***Cannot handle neuroinflammatory stimuli***

Presentation Overview

Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

Presentation Overview

Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

Clinical Strategy for Neuroinflammation

Presentation Overview

Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

DIETARY INTERVENTIONS FOR NEUROINFLAMMATION

Anti-Inflammatory

↑ Essential Fatty Acids

↓ Fried & Hydrogenated Fats

Phase 1
Gluten-Free & Dairy-Free Diet

Phase 2
Paleo Diet (Grain-Free)

Phase 3
Autoimmune Paleo (Grain & Lectin-Free)

Stabilize Blood Glucose

- **No Missed Meals:** Maintain steady glycemic levels to prevent cellular stress.
- **Avoid Sugar:** Eliminate high-glycemic spikes and inflammation triggers.
- **Limit Carbohydrates:** Keep simple carb intake to a minimal baseline.
- **Small Portion Size:** Reduce metabolic burden per meal.

Modified Ketogenic Diet

- **Low Carb Intake:** Keep carbohydrates strictly under 20–50 grams per day.
- **High Healthy Fats:** Target 70–80% of total daily calories sourced directly from clean fats.
- **Ketone Energy:** Promotes direct mitochondrial fuel sources to reduce neural inflammation.

Intermittent Fasting

- **Delayed First Meal:** Break fast 12–18 hours after the previous night's dinner.
- **Systemic Auto-phagy:** Encourages metabolic cellular cleanup and recovery.
- **Advanced Progression:** Gradually work up to supportive 1-5 day fasts.

DIETARY INTERVENTIONS FOR NEUROINFLAMMATION

Anti-Inflammatory

↑ Essential Fatty Acids

↓ Fried & Hydrogenated Fats

Phase 1
Gluten-Free & Dairy-Free Diet

Phase 2
Paleo Diet (Grain-Free)

Phase 3
Autoimmune Paleo (Grain & Lectin-Free)

Stabilize Blood Glucose

- **No Missed Meals:** Maintain steady glycemic levels to prevent cellular stress.
- **Avoid Sugar:** Eliminate high-glycemic spikes and inflammation triggers.
- **Limit Carbohydrates:** Keep simple carb intake to a minimal baseline.
- **Small Portion Size:** Reduce metabolic burden per meal.

Modified Ketogenic Diet

- **Low Carb Intake:** Keep carbohydrates strictly under 20–50 grams per day.
- **High Healthy Fats:** Target 70–80% of total daily calories sourced directly from clean fats.
- **Ketone Energy:** Promotes direct mitochondrial fuel sources to reduce neural inflammation.

Intermittent Fasting

- **Delayed First Meal:** Break fast 12–18 hours after the previous night's dinner.
- **Systemic Auto-phagy:** Encourages metabolic cellular cleanup and recovery.
- **Advanced Progression:** Gradually work up to supportive 1-5 day fasts.

DIETARY INTERVENTIONS FOR NEUROINFLAMMATION

Anti-Inflammatory

↑ Essential Fatty Acids

↓ Fried & Hydrogenated Fats

Phase 1
Gluten-Free & Dairy-Free Diet

Phase 2
Paleo Diet (Grain-Free)

Phase 3
Autoimmune Paleo (Grain & Lectin-Free)

Stabilize Blood Glucose

- **No Missed Meals:** Maintain steady glycemic levels to prevent cellular stress.
- **Avoid Sugar:** Eliminate high-glycemic spikes and inflammation triggers.
- **Limit Carbohydrates:** Keep simple carb intake to a minimal baseline.
- **Small Portion Size:** Reduce metabolic burden per meal.

Modified Ketogenic Diet

- **Low Carb Intake:** Keep carbohydrates strictly under 20–50 grams per day.
- **High Healthy Fats:** Target 70–80% of total daily calories sourced directly from clean fats.
- **Ketone Energy:** Promotes direct mitochondrial fuel sources to reduce neural inflammation.

Intermittent Fasting

- **Delayed First Meal:** Break fast 12–18 hours after the previous night's dinner.
- **Systemic Auto-phagy:** Encourages metabolic cellular cleanup and recovery.
- **Advanced Progression:** Gradually work up to supportive 1-5 day fasts.

DIETARY INTERVENTIONS FOR NEUROINFLAMMATION

Anti-Inflammatory

↑ Essential Fatty Acids

↓ Fried & Hydrogenated Fats

Phase 1
Gluten-Free & Dairy-Free Diet

Phase 2
Paleo Diet (Grain-Free)

Phase 3
Autoimmune Paleo (Grain & Lectin-Free)

Stabilize Blood Glucose

- **No Missed Meals:** Maintain steady glycemic levels to prevent cellular stress.
- **Avoid Sugar:** Eliminate high-glycemic spikes and inflammation triggers.
- **Limit Carbohydrates:** Keep simple carb intake to a minimal baseline.
- **Small Portion Size:** Reduce metabolic burden per meal.

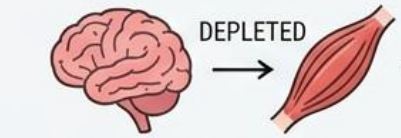
Modified Ketogenic Diet

- **Low Carb Intake:** Keep carbohydrates strictly under 20–50 grams per day.
- **High Healthy Fats:** Target 70–80% of total daily calories sourced directly from clean fats.
- **Ketone Energy:** Promotes direct mitochondrial fuel sources to reduce neural inflammation.

Intermittent Fasting

- **Delayed First Meal:** Break fast 12–18 hours after the previous night's dinner.
- **Systemic Auto-phagy:** Encourages metabolic cellular cleanup and recovery.
- **Advanced Progression:** Gradually work up to supportive 1-5 day fasts.

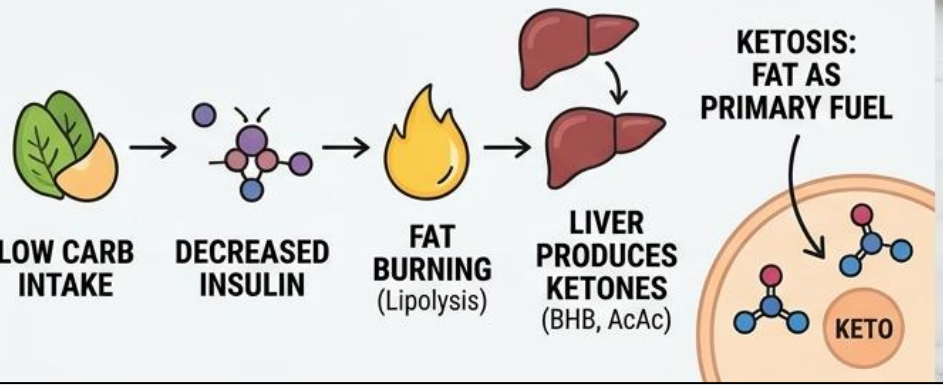
PRINCIPLES OF A KETOGENIC DIET



CARBOHYDRATE FUEL → INDUCTION OF KETOSIS

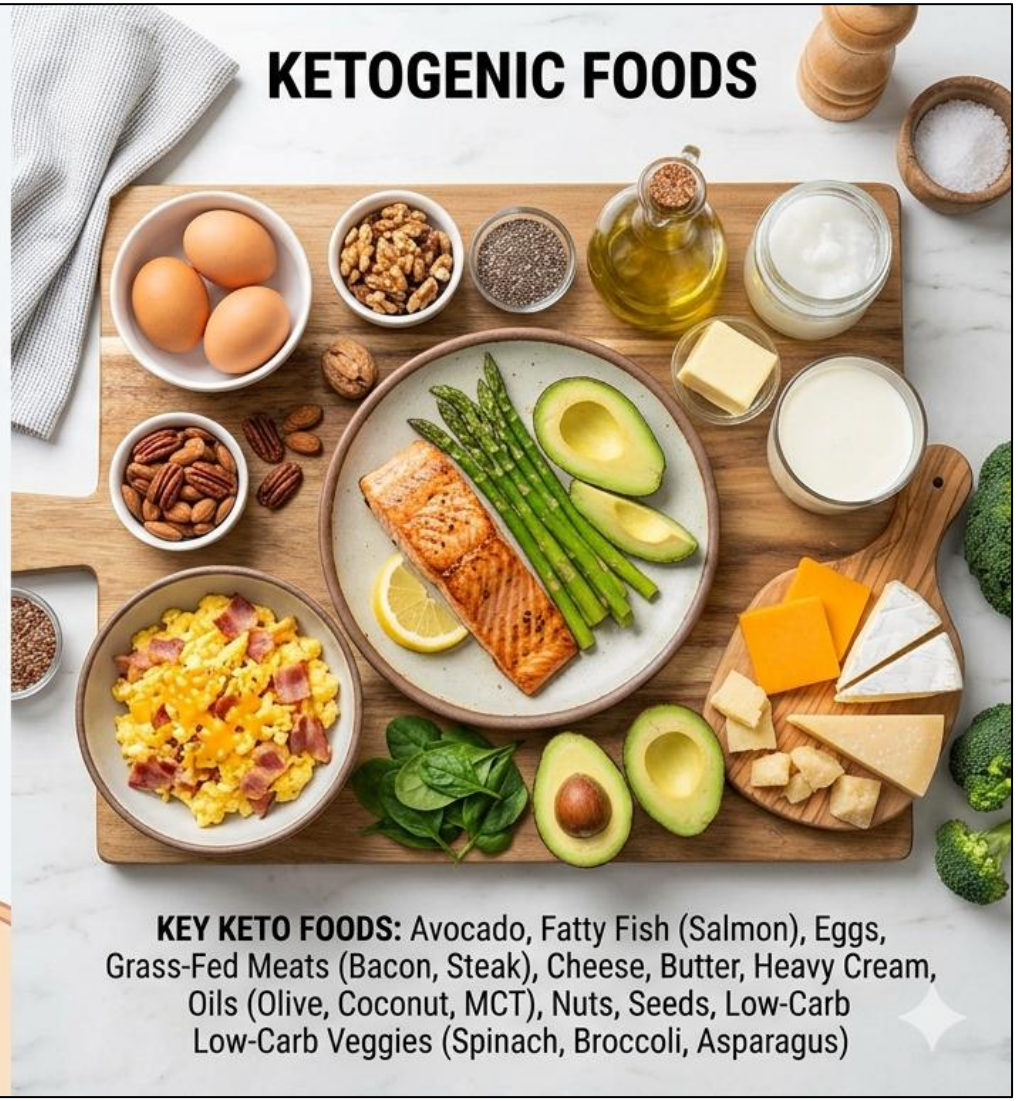
1. **HIGH FAT** (70-80%)
2. **MODERATE PROTEIN** (15-20%)
3. **VERY LOW CARB** (<5%)

KETOGENIC DIET PRINCIPLES



LOW CARB INTAKE → **DECREASED INSULIN** → **FAT BURNING** (Lipolysis) → **LIVER PRODUCES KETONES** (BHB, AcAc)

KETOGENIC FOODS



KEY KETO FOODS: Avocado, Fatty Fish (Salmon), Eggs, Grass-Fed Meats (Bacon, Steak), Cheese, Butter, Heavy Cream, Oils (Olive, Coconut, MCT), Nuts, Seeds, Low-Carb Low-Carb Veggies (Spinach, Broccoli, Asparagus)

frontiers | Frontiers in Immunology

TYPE Review
PUBLISHED 12 August 2024
DOI 10.3389/fimmu.2024.1425816

OPEN ACCESS

EDITED BY
Michele Costanzo,
University of Naples Federico II, Italy

REVIEWED BY
Han-Qing Pang,
Yangzhou University, China

Exploring the ketogenic diet's potential in reducing neuroinflammation and modulating immune responses

[illegible]

[illegible] Naples, Italy, [illegible] Dietetics and Sports Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy, [5]Department of Exercise Sciences and Well-Being, University of Naples "Parthenope", Naples, Italy, [6]Department of Wellbeing, Nutrition and Sport, Pegaso Telematic University, Naples, Italy, [7]Department of Humanistic Studies, University of Foggia, Foggia, Italy

ACCEPTED 30 July 2024
PUBLISHED 12 August 2024

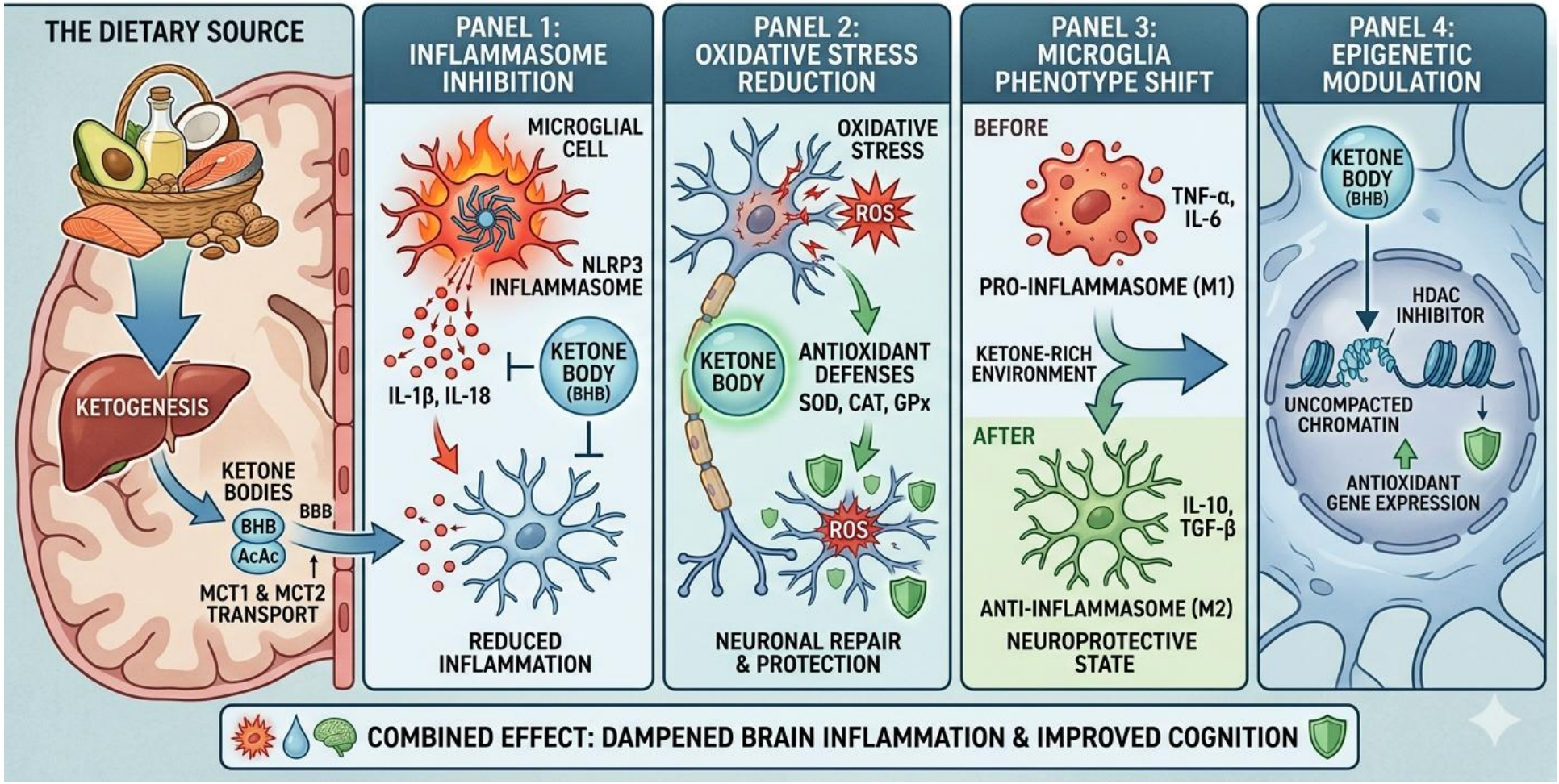
CITATION
Monda A, La Torre ME, Messina A, Di Maio G, Monda V, Moscatelli F, De Stefano M, La Marra M, Padova MD, Dipace A, Limone P, Casillo M, Monda M, Messina G and Polito R (2024) Exploring the ketogenic diet's potential in reducing neuroinflammation and modulating immune responses.
Front. Immunol. 15:1425816.
doi: 10.3389/fimmu.2024.1425816

The ketogenic diet (KD) is marked by a substantial decrease in carbohydrate intake and an elevated consumption of fats and proteins, leading to a metabolic state referred to as "ketosis," where fats become the primary source of energy. Recent research has underscored the potential advantages of the KD in mitigating the risk of various illnesses, including type 2 diabetes, hyperlipidemia, heart disease, and cancer. The macronutrient distribution in the KD typically entails high lipid intake, moderate protein consumption, and low carbohydrate intake. Restricting carbohydrates to below 50 g/day induces a catabolic state, prompting metabolic alterations such as gluconeogenesis and ketogenesis. Ketogenesis diminishes fat and glucose accumulation as energy reserves, stimulating the production of fatty acids. Neurodegenerative diseases, encompassing Alzheimer's disease, Parkinson's disease are hallmarked by persistent neuroinflammation. Evolving evidence indicates that immune activation and neuroinflammation play a significant role in the pathogenesis of these diseases. The protective effects of the KD are linked to the generation of ketone bodies (KB), which play a pivotal role in this dietary protocol. Considering these findings, this narrative review seeks to delve into the potential effects of the KD in neuroinflammation by modulating the immune response. Grasping the immunomodulatory effects of the KD on the central nervous system could offer valuable insights into innovative therapeutic approaches for these incapacitating conditions.

KEYWORDS
ketogenic diet, neuroinflammation, ketone bodies, central nervous system, immunomodulation

"The **ketogenic diet** has been shown to exert specific effects on neuroinflammation within the central nervous system (CNS). ***Ketone bodies can penetrate the blood-brain barrier and modulate microglial activation, thereby reducing neuroinflammation***..."

DIETARY KETONES DAMPEN BRAIN INFLAMMATION: MULTIPLE PATHWAYS OF ACTION



Key Clinical Concept

If a person's cognitive and mental function dramatically improve while in **ketosis**, it strongly suggests neuroinflammation as an underlying mechanism.

Presentation Overview

Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

Presentation Overview

Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

DIETARY INTERVENTIONS FOR NEUROINFLAMMATION

Anti-Inflammatory

↑ Essential Fatty Acids

↓ Fried & Hydrogenated Fats

Phase 1
Gluten-Free & Dairy-Free Diet

Phase 2
Paleo Diet (Grain-Free)

Phase 3
Autoimmune Paleo (Grain & Lectin-Free)

Stabilize Blood Glucose

- **No Missed Meals:** Maintain steady glycemic levels to prevent cellular stress.
- **Avoid Sugar:** Eliminate high-glycemic spikes and inflammation triggers.
- **Limit Carbohydrates:** Keep simple carb intake to a minimal baseline.
- **Small Portion Size:** Reduce metabolic burden per meal.

Modified Ketogenic Diet

- **Low Carb Intake:** Keep carbohydrates strictly under 20–50 grams per day.
- **High Healthy Fats:** Target 70–80% of total daily calories sourced directly from clean fats.
- **Ketone Energy:** Promotes direct mitochondrial fuel sources to reduce neural inflammation.

Intermittent Fasting

- **Delayed First Meal:** Break fast 12–18 hours after the previous night's dinner.
- **Systemic Auto-phagy:** Encourages metabolic cellular cleanup and recovery.
- **Advanced Progression:** Gradually work up to supportive 1-5 day fasts.

Presentation Overview

Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

Presentation Overview

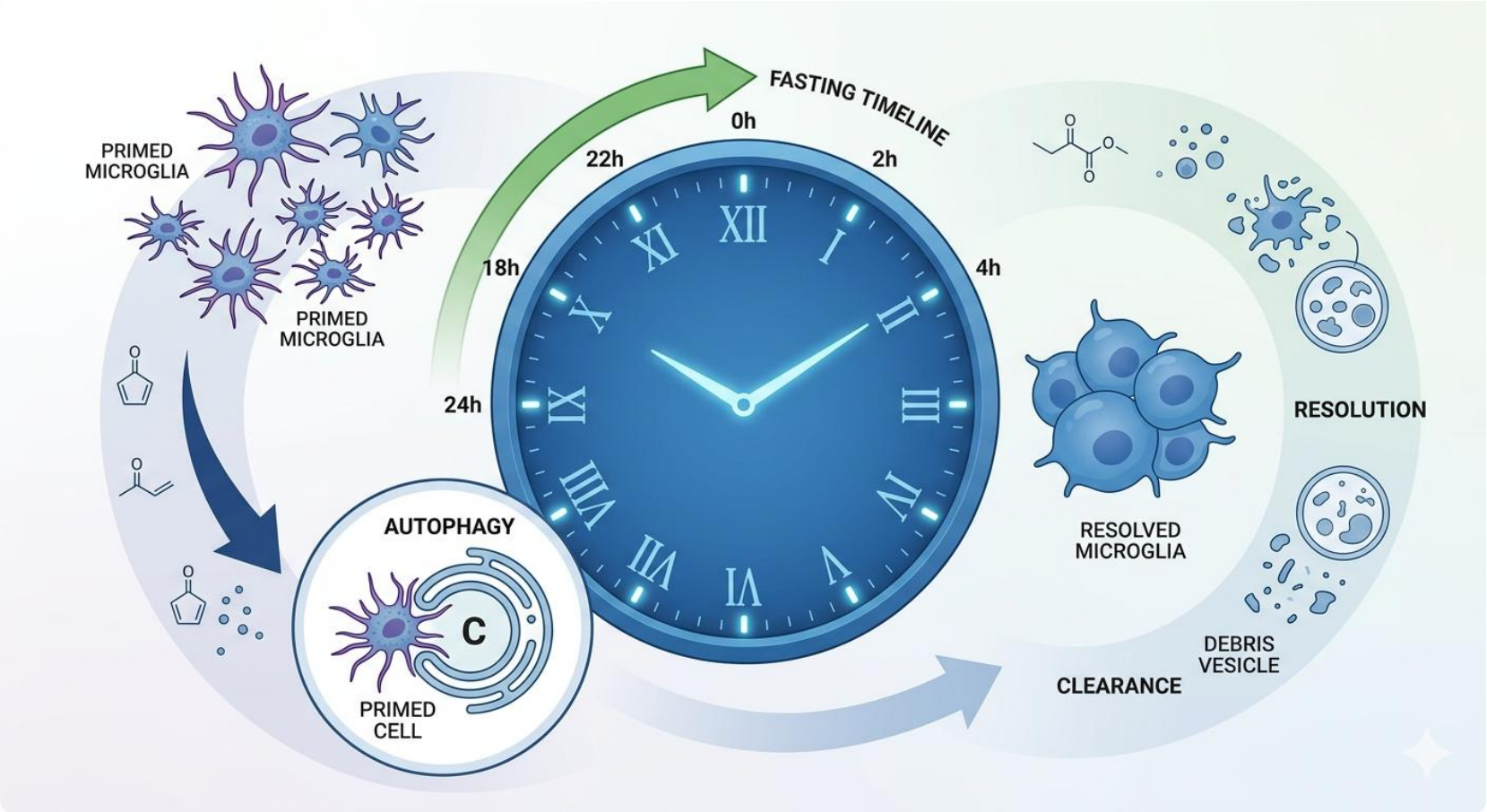
Neuroinflammatory Pathophysiology

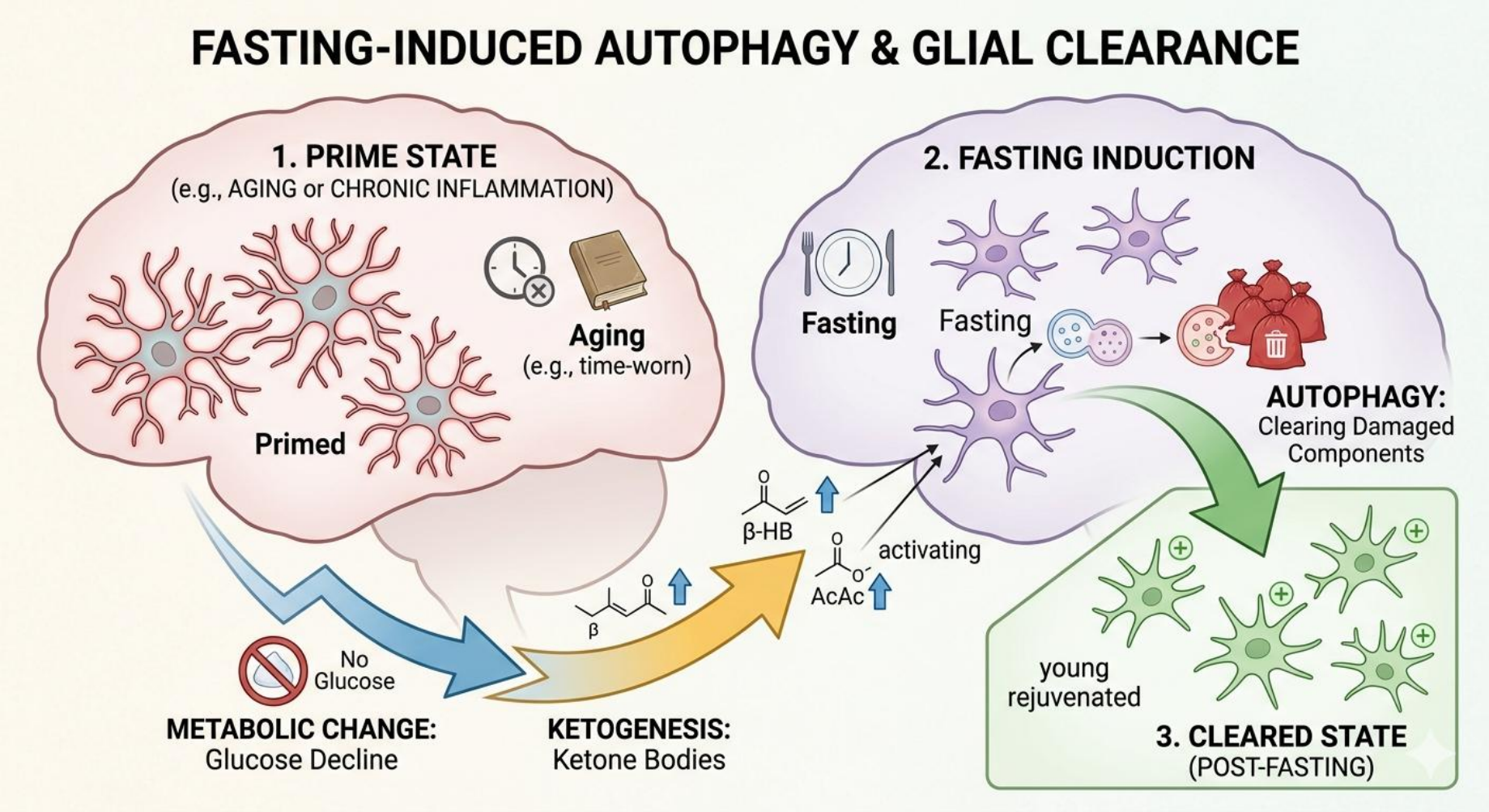
- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

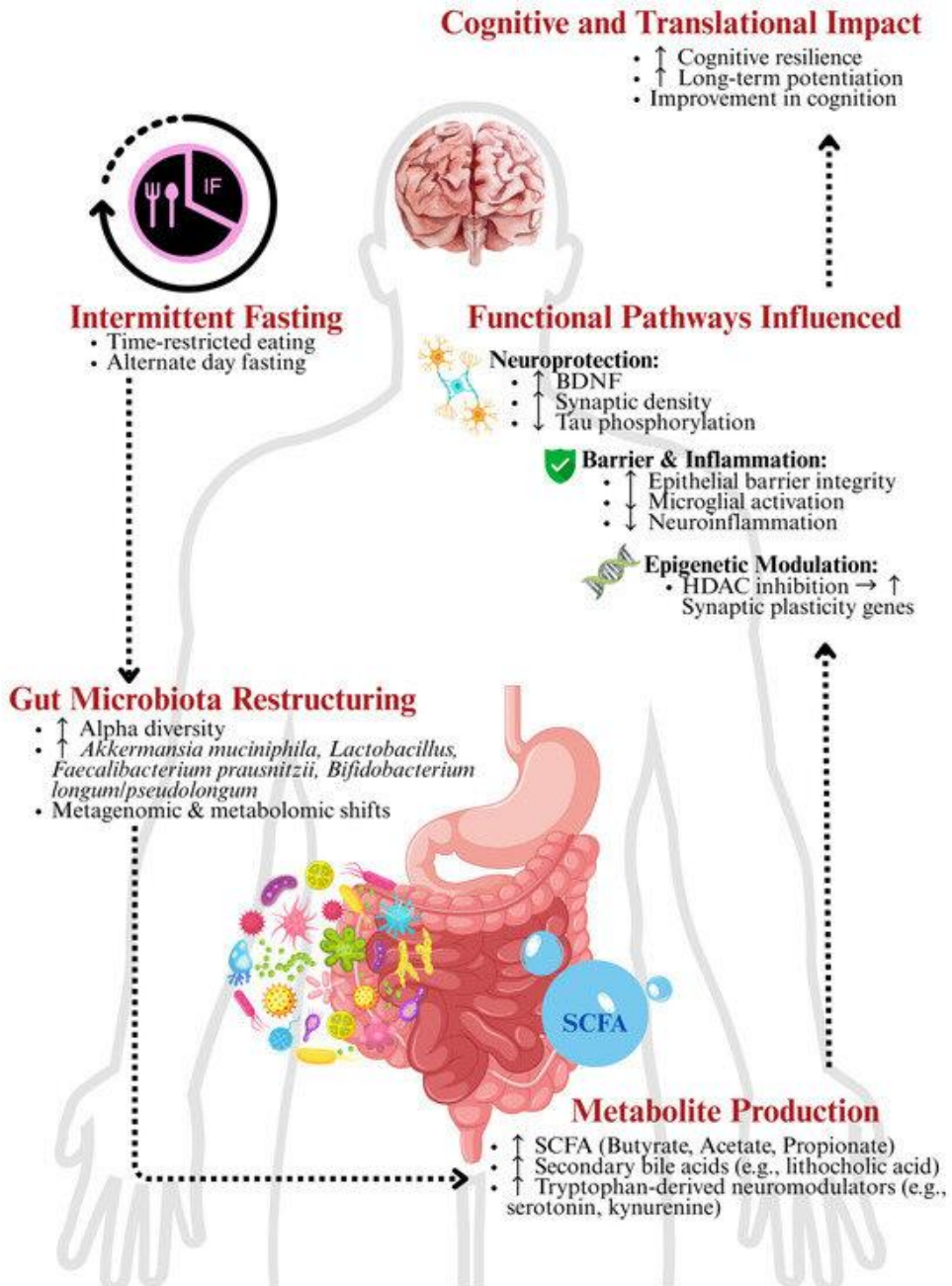
Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

Fasting to Promote Autophagy of Primed Glial Cells

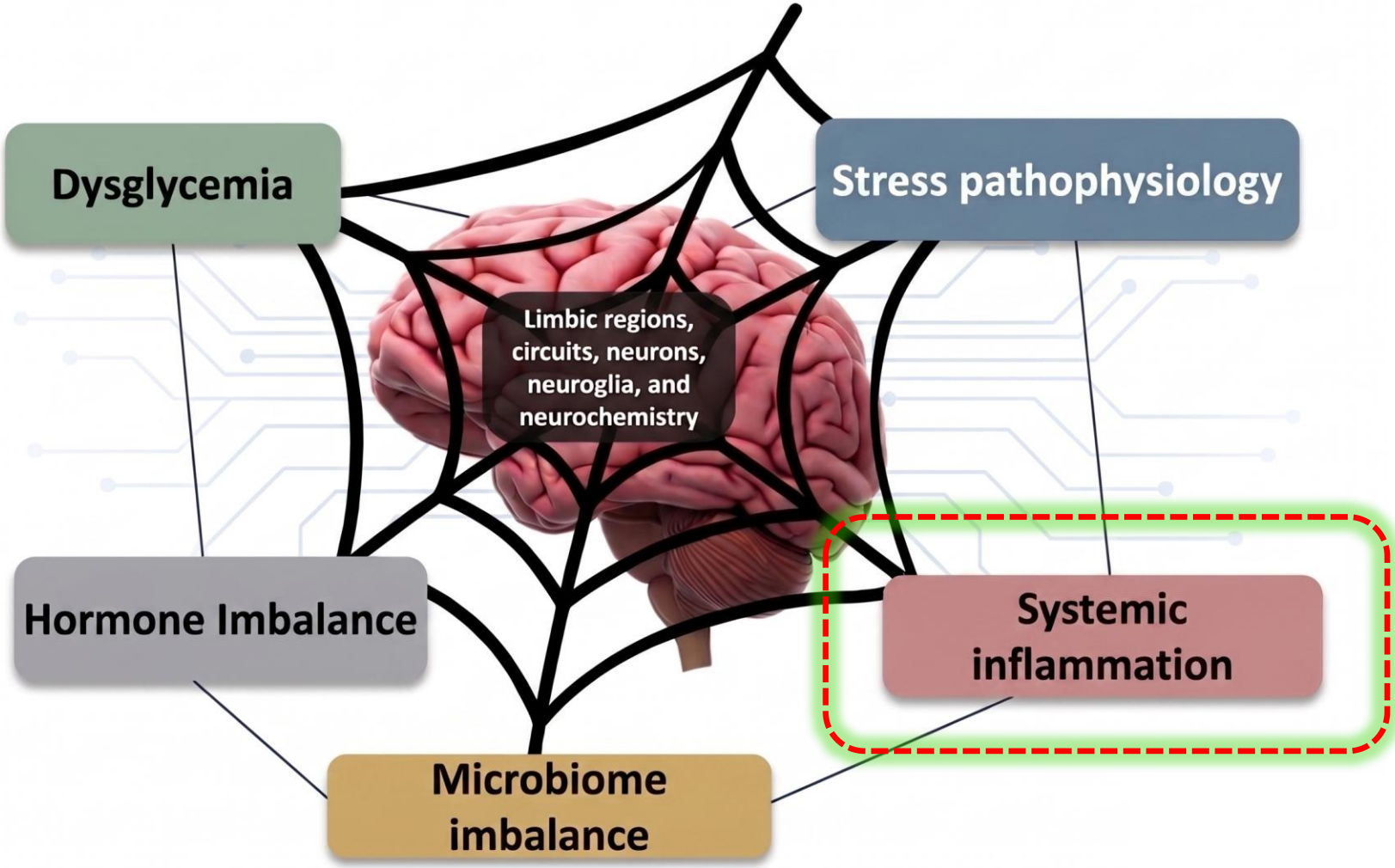



FASTING-INDUCED AUTOPHAGY & GLIAL CLEARANCE
1. PRIME STATE
(e.g., AGING or CHRONIC INFLAMMATION)
Primed
Aging
(e.g., time-worn)
2. FASTING INDUCTION
Fasting
Fasting
AUTOPHAGY:
Clearing Damaged
Components
β-HB
activating
AcAc
β
No
Glucose
METABOLIC CHANGE:
Glucose Decline
KETOGENESIS:
Ketone Bodies
young
rejuvenated
3. CLEARED STATE
(POST-FASTING)



Nutrients 2025, *17*, 2266.

The Physiologic Web of Mental Disorders



Presentation Overview

Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

Presentation Overview

Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

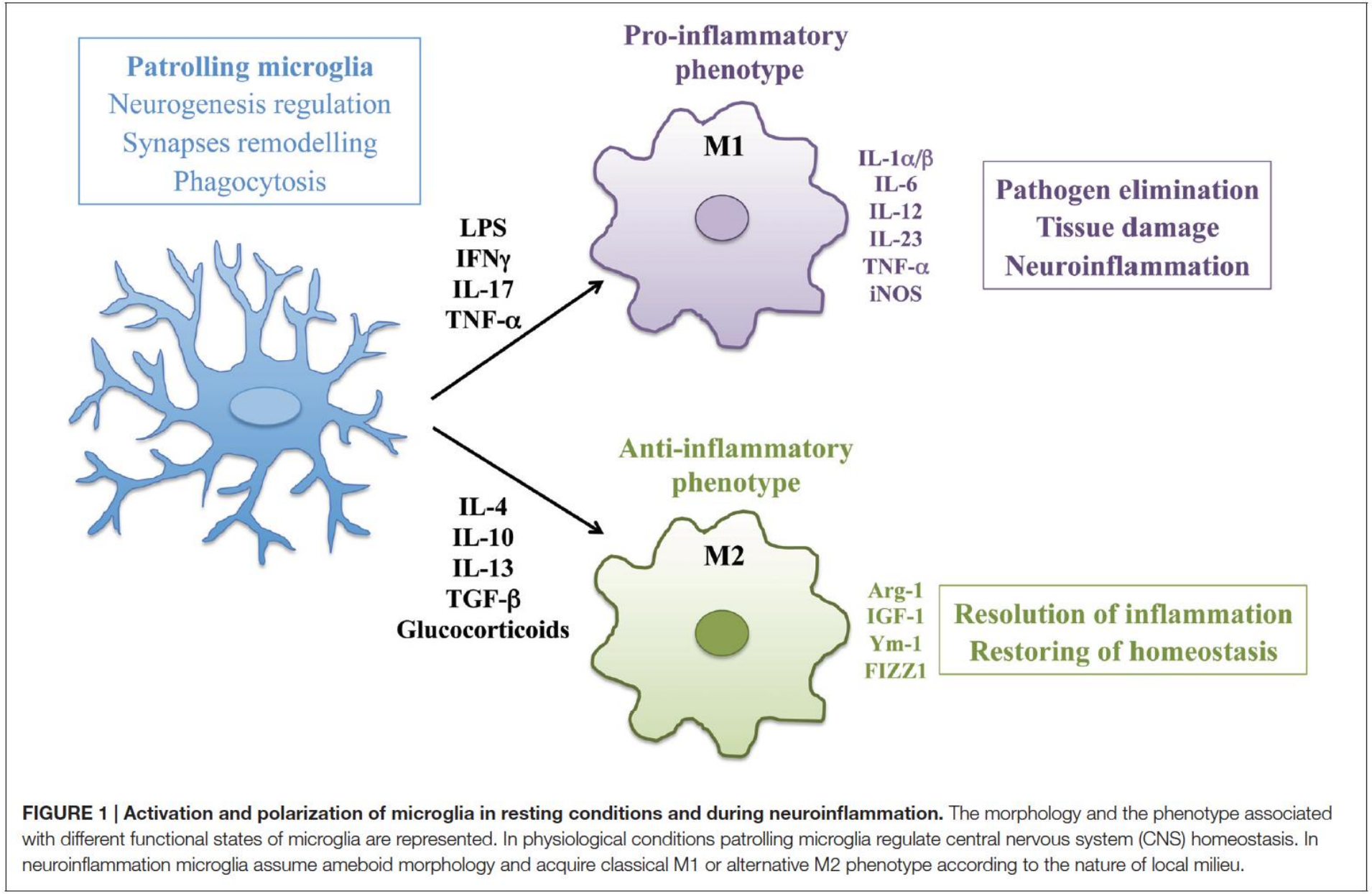
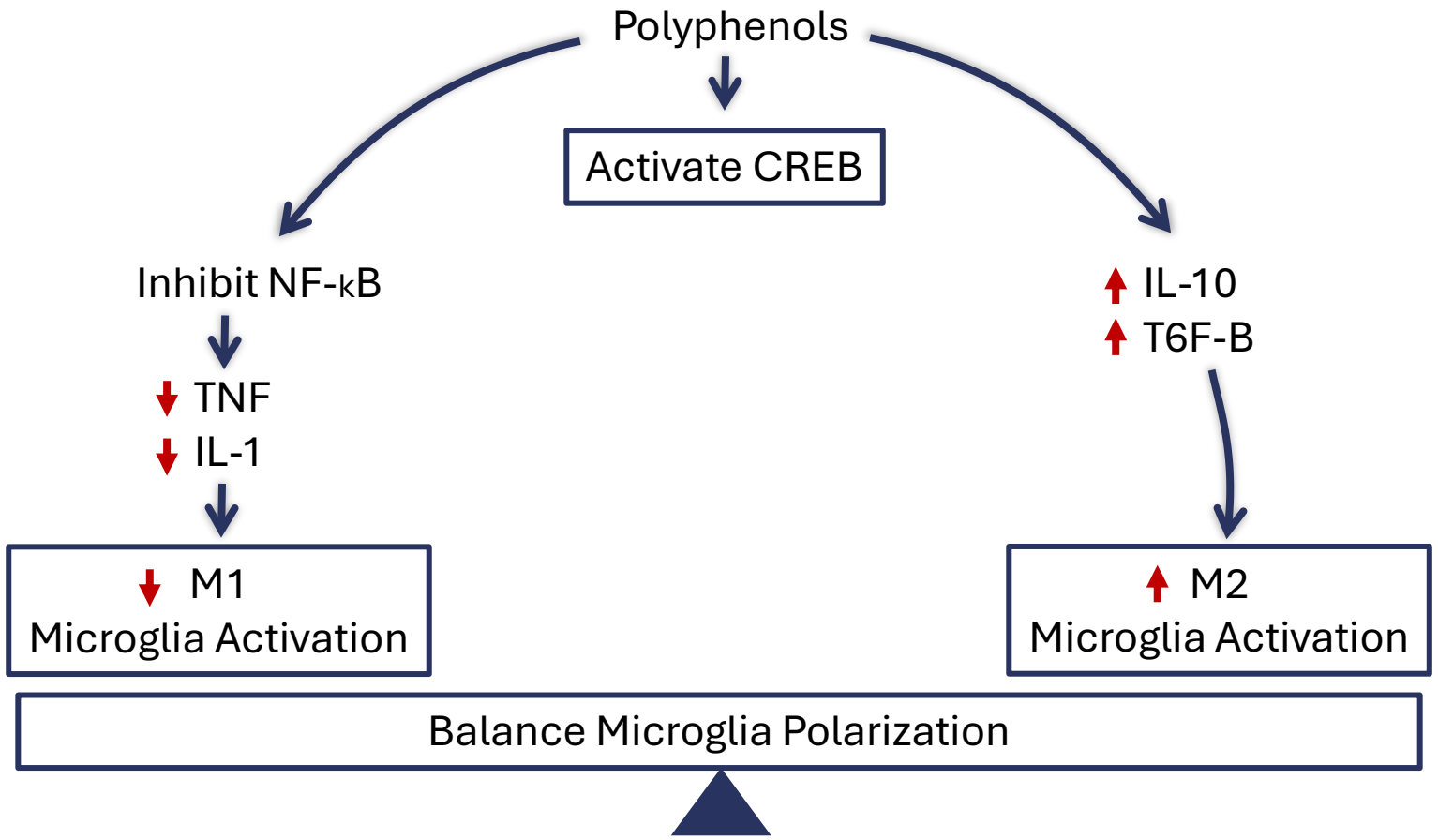


FIGURE 1 | Activation and polarization of microglia in resting conditions and during neuroinflammation. The morphology and the phenotype associated with different functional states of microglia are represented. In physiological conditions patrolling microglia regulate central nervous system (CNS) homeostasis. In neuroinflammation microglia assume ameboid morphology and acquire classical M1 or alternative M2 phenotype according to the nature of local milieu.

Polyphenol Modulation of Microglia

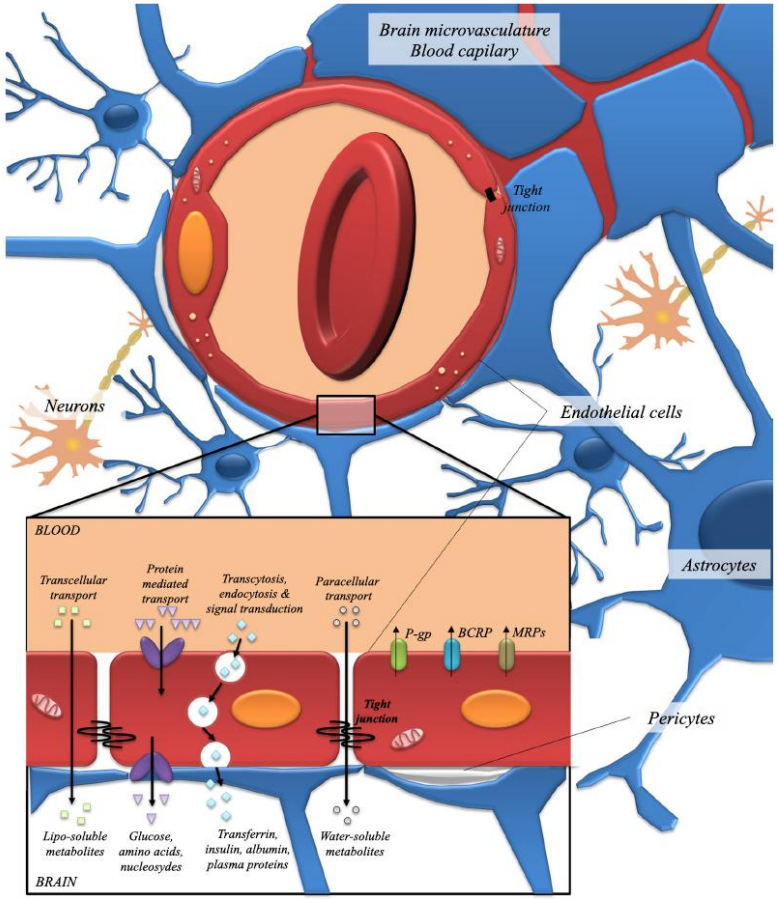


Key Clinical Concept

Natural compounds that can **cross the blood-brain barrier** are the most effective agents for neuroinflammation.

Antioxidants or natural compounds that cannot cross the BBB have limited impact on neuroinflammation.

Natural Compounds that Can Cross the BBB are Ideal for Neuroinflammation



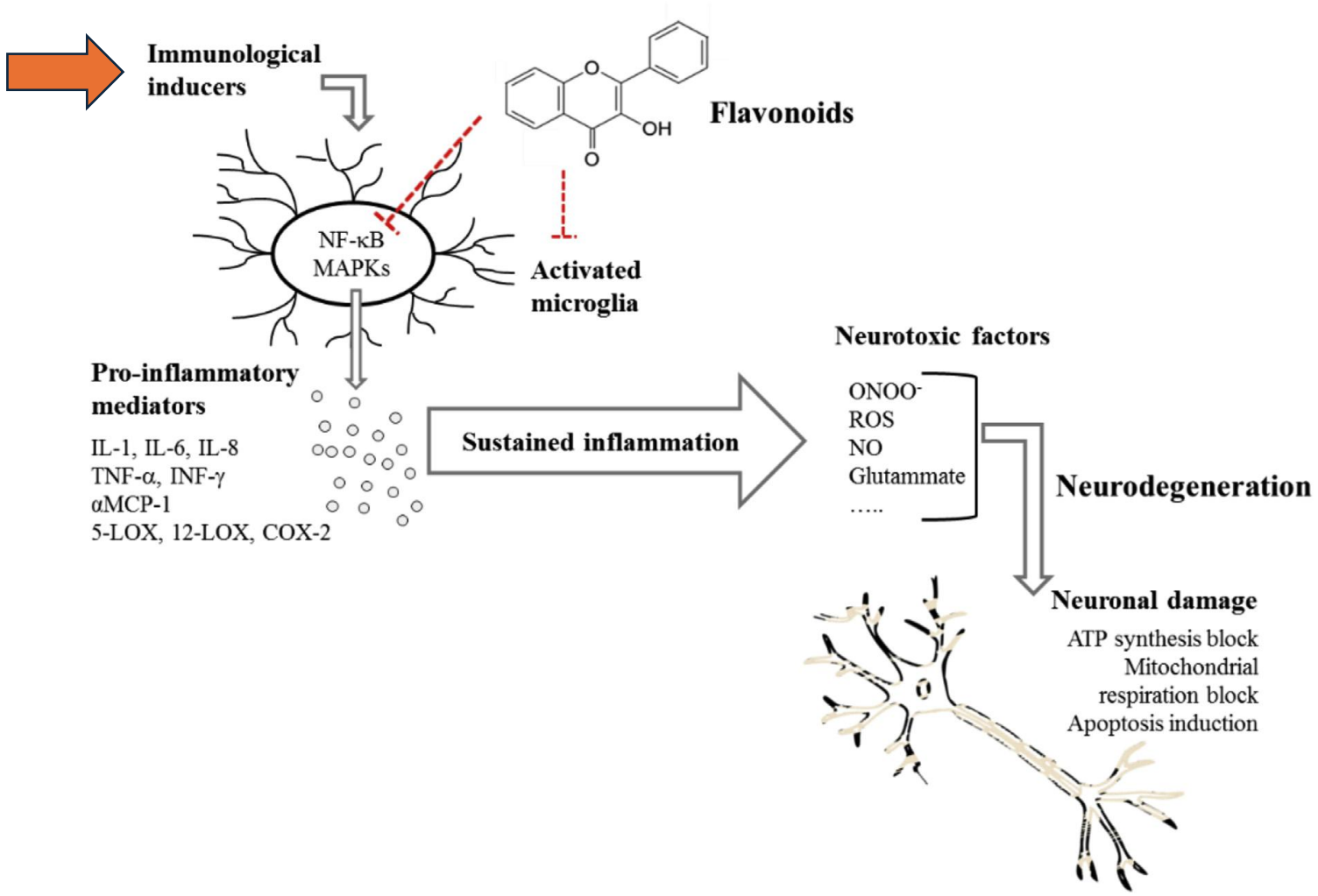
Polyphenols Beyond Barriers: A Glimpse into the Brain

Current Neuropharmacology, 2017, *Vol. 15, No. 4*

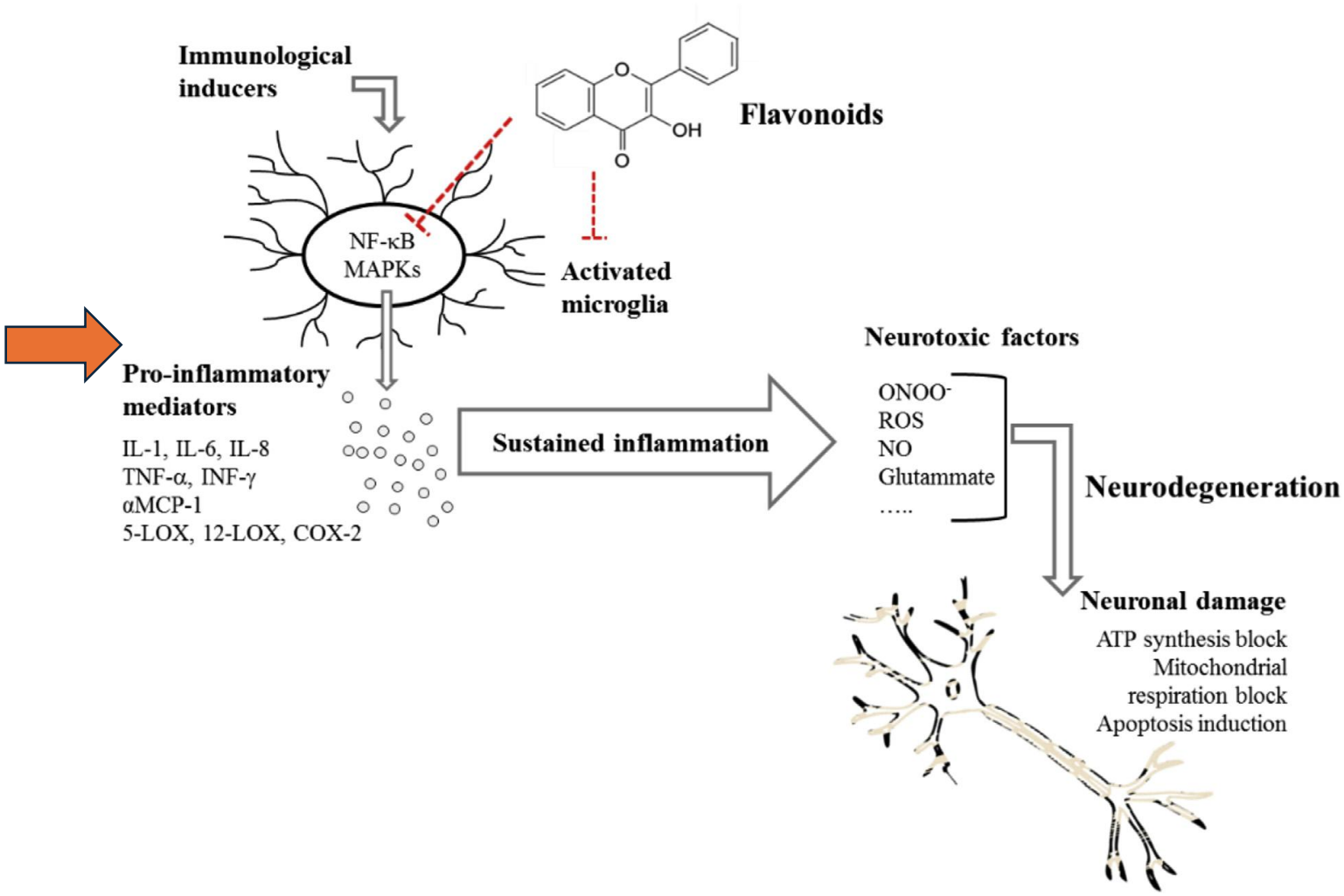
RATINGS OF POLYPHENOLS IN CLINICAL PRACTICE FOR NEUROINFLAMMATION

Resveratrol (Grape Skin) Curcumin (Turmeric Root) Apigenin (Celery, Parsley) Catechins (Green Tea)	★★★★★
Luteolin (Onions, Capers) Baicalein (Tree Bark) Rutin (Pomegranate)	★★★★
Naringenin (Orange, Cherries) Quercetin (Berries)	★★★
Hesperidin (Citrus Fruit) Fisetin (Strawberries) Myricetin (Grapes, Onions)	★★
Chrysin (Citrus Fruits) Kaempferol (Broccoli)	★

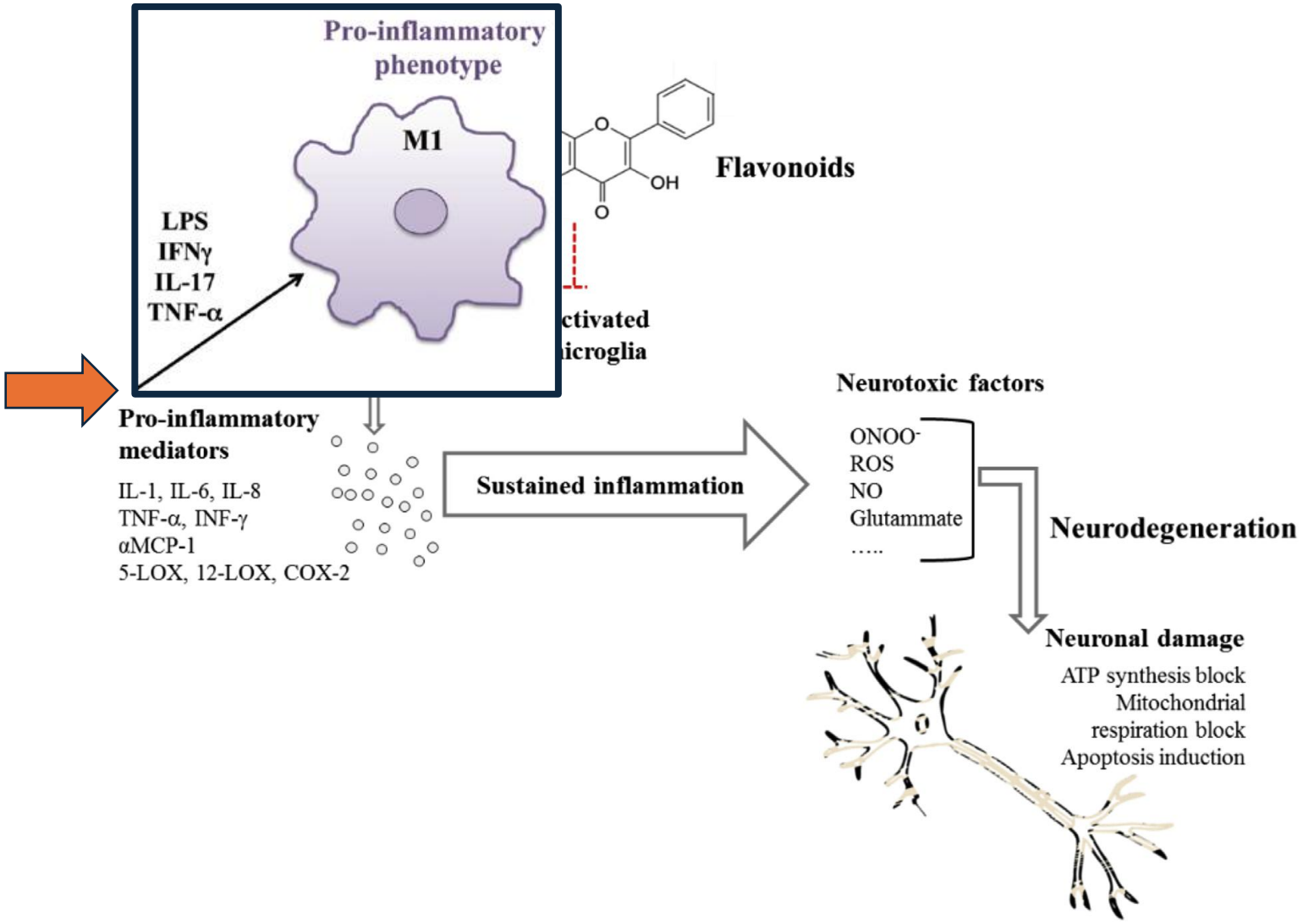
The Basic Concept



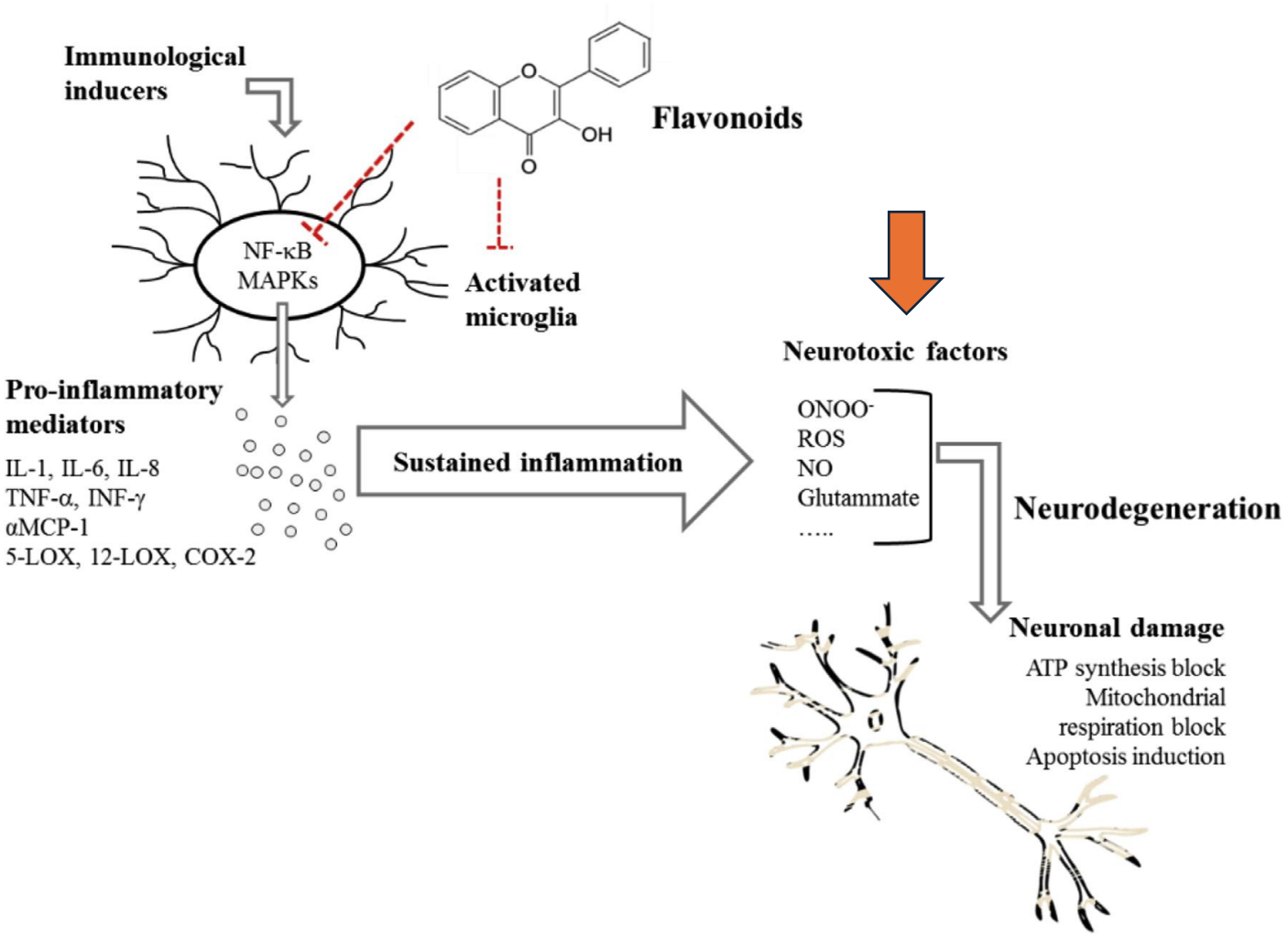
The Basic Concept



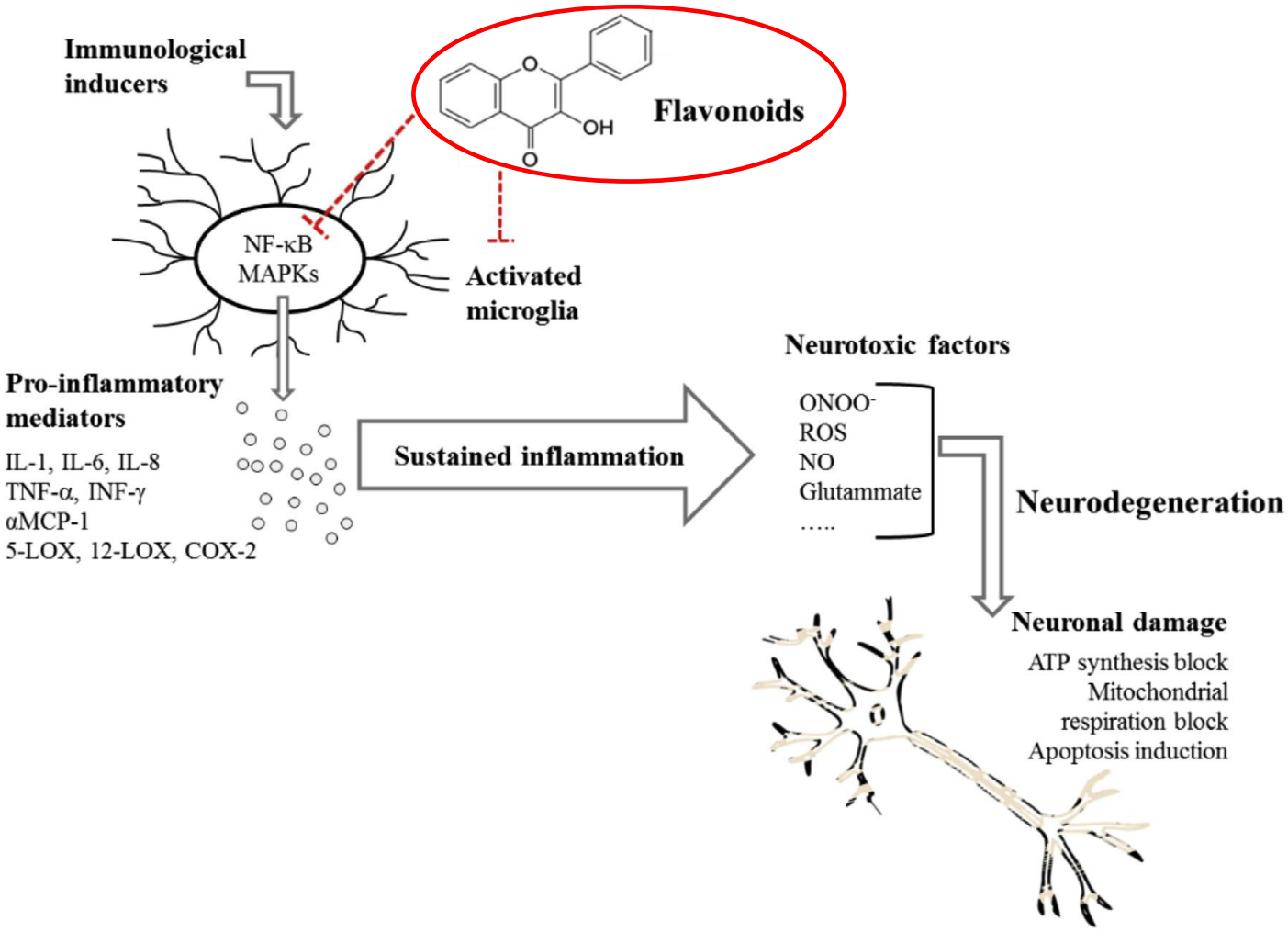
The Basic Concept



The Basic Concept

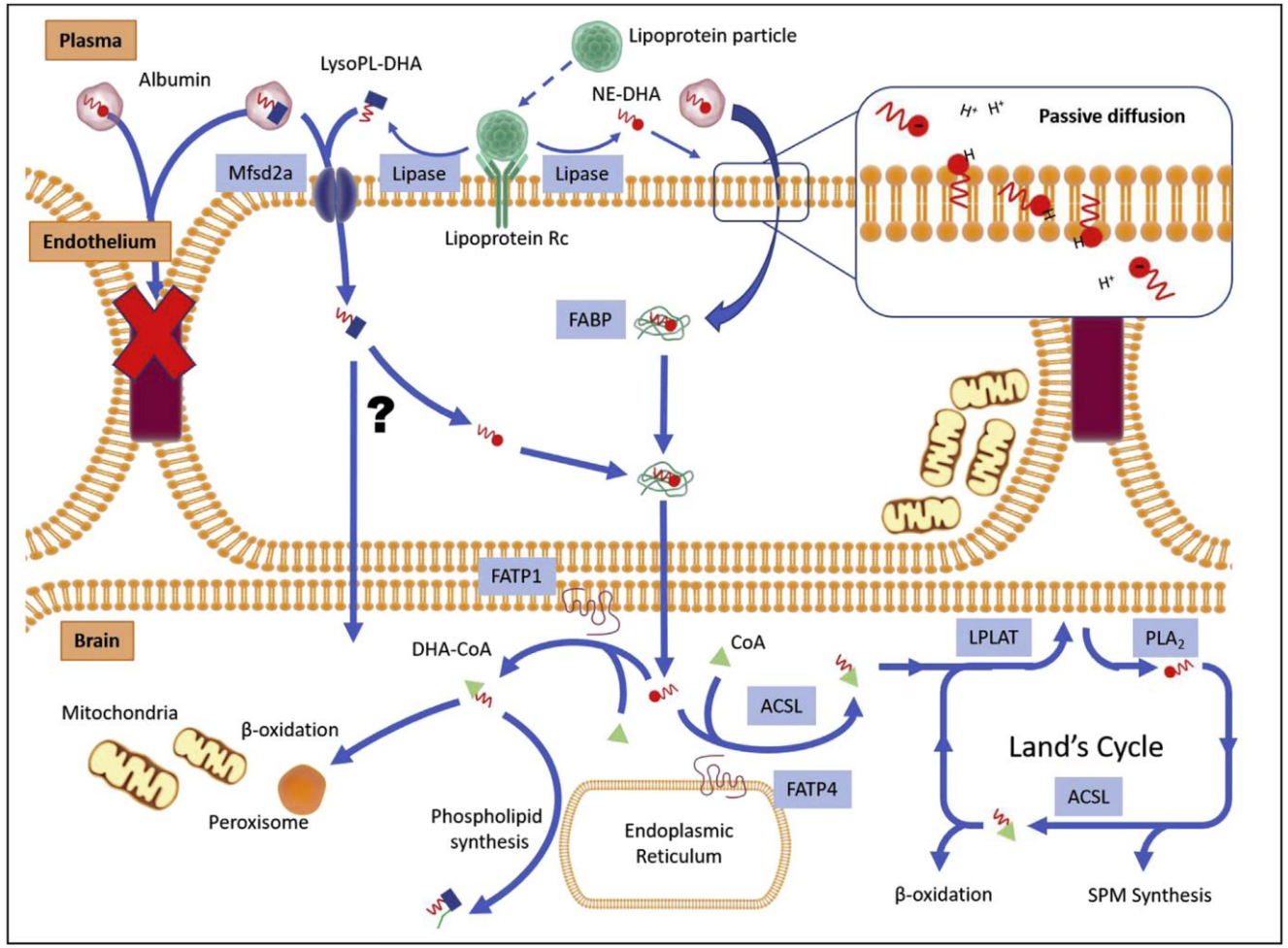


The Basic Concept



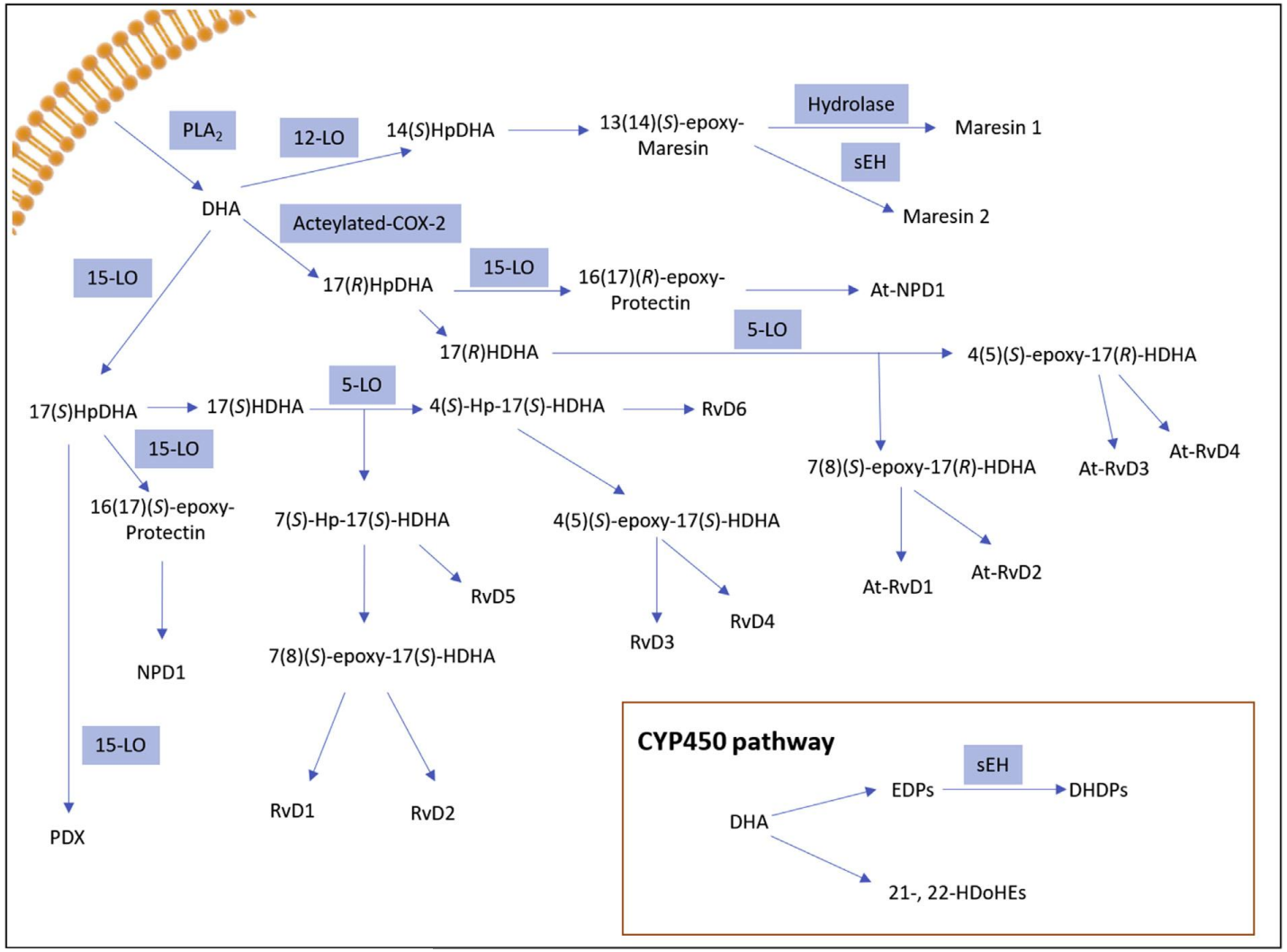
Essential Fatty Acids

Rapid DHA Passive Diffusion Across BBB



Molecular Aspects of Medicine 64 (2018) 109–134

DHA Breakdown from Neuronal Membrane

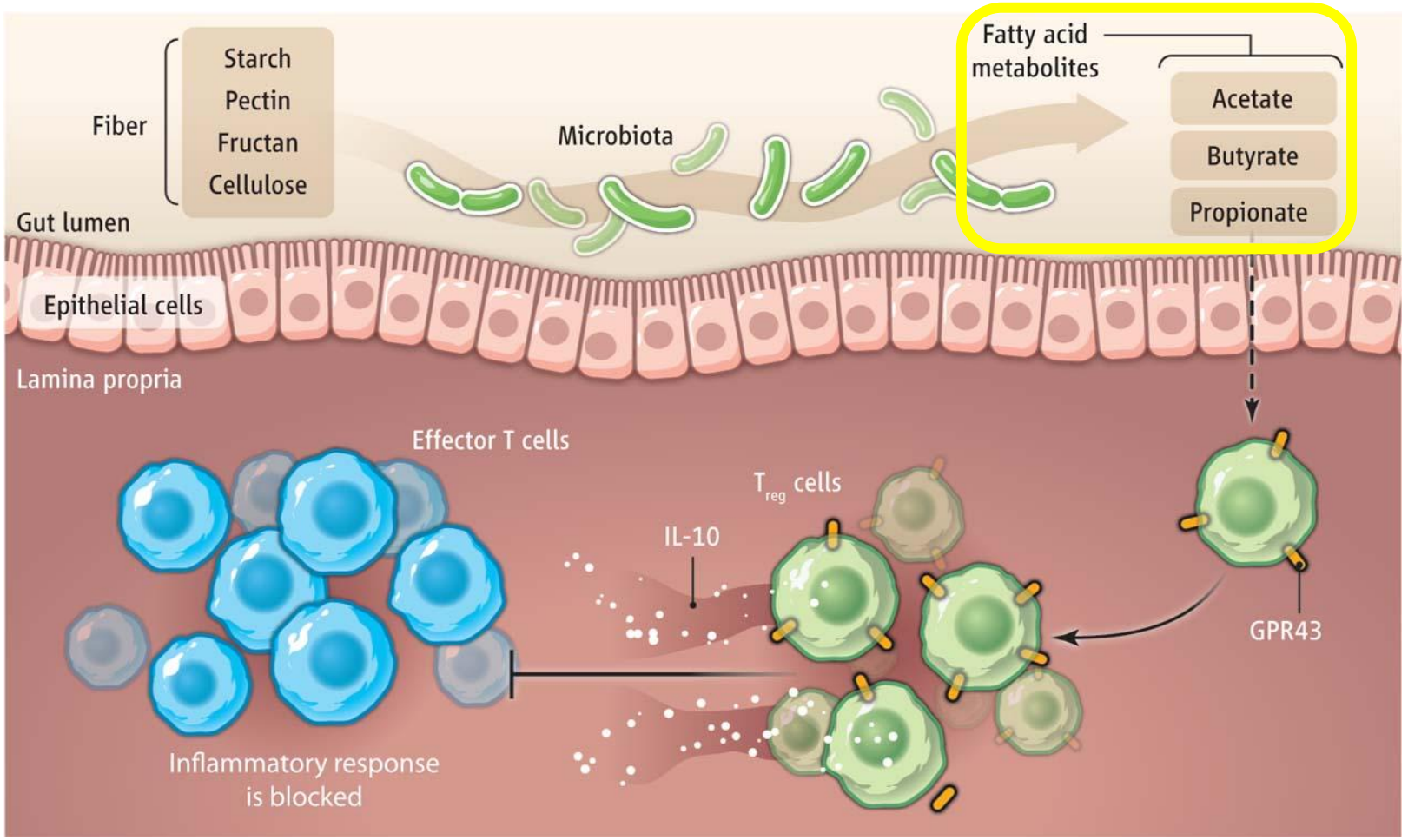


Molecular Aspects of Medicine 64 (2018) 109–134

Short-Chain Fatty Acids

Science. 2013 Aug 2;341:463-464.

Feed your T-regs more fiber



Dietary fatty acids and susceptibility to multiple sclerosis

Stefanie Haase, Aiden Haghikia, Ralf Gold and Ralf A Linker

Multiple Sclerosis Journal

2018, Vol. 24(1) 12–16

DOI: 10.1177/1352458517737372

Abstract

Background: The gut microbiome as well as dietary habits have recently been established as environmental contributors to the pathogenesis of multiple sclerosis (MS), a T-cell-mediated autoimmune disease of the central nervous system (CNS).

Objective: To summarize recent findings on the Janus-faced effects of dietary short-chain fatty acids (SCFAs) and long-chain fatty acids (LCFAs) on T-cell immunity with a special focus on the gut and the microbiome as an interface linking diet and T-cell responses during MS.

Methods: Review article.

Results: The autoimmune basis of MS most likely stems from an imbalance between pro-inflammatory T helper cell (Th)1 and Th17 cells and anti-inflammatory or regulatory mechanisms including regulatory T cells (Treg). Hence, the rationale of currently available therapeutic interventions is to either suppress pathogenic Th1/Th17 and/or to foster Treg responses. Dietary fatty acids are often discussed for their detrimental role in MS. However, recent studies investigating saturated fatty acids in animal models of MS revealed harmful as well as beneficial effects depending on their aliphatic chain length.

Conclusion: Dietary SCFAs constitute interesting candidates as safe and potent add-on therapy in the immunomodulatory treatment armamentarium for relapsing-remitting MS.

Correspondence to:
RA Linker
Department of Neurology, Friedrich-Alexander University Erlangen-Nurnberg, Schloßplatz 4, 91054, Erlangen, Germany.
ralf.linker@uk-elangen.de

Stefanie Haase
Ralf A Linker
Department of Neurology, University Hospital Erlangen, Erlangen, Germany

Aiden Haghikia
Ralf Gold
Department of Neurology, Ruhr-University Bochum, Bochum, Germany

Keywords: Animal model, immunology, disease-modifying therapies

Date received: 2 June 2017; accepted: 14 June 2017

Immunity
Article

CellPress

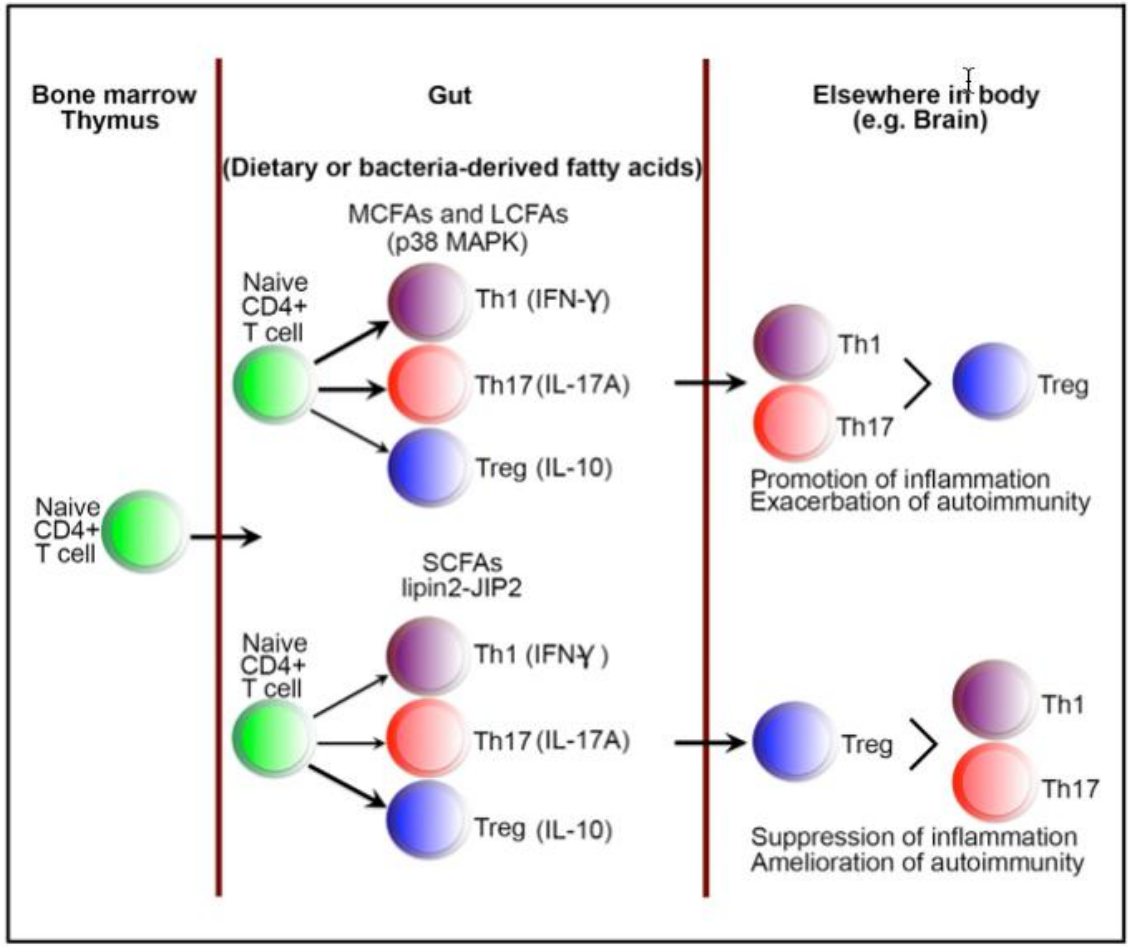
Dietary Fatty Acids Directly Impact Central Nervous System Autoimmunity via the Small Intestine

Aiden Haghikia,[1,10,*] Stefanie Jörg,[2,10] Alexander Duscha,[1] Johannes Berg,[1] Arndt Manzel,[2] Anne Waschbisch,[2] Anna Hammer,[2] De-Hyung Lee,[2] Caroline May,[3] Nicola Wilck,[4] Andras Balogh,[4] Annika I. Ostermann,[5] Nils Helge Schebb,[5,6] Denis A. Akkad,[7] Diana A. Grohme,[8] Markus Kleinewietfeld,[8] Stefan Kempa,[9] Jan Thöne,[1] Seray Demir,[1] Dominik N. Müller,[4] Ralf Gold,[1,11] and Ralf A. Linker[2,11,*]
[1]Department of Neurology, Ruhr-University Bochum, 44801 Bochum, Germany

"...Dietary short-chain FAs (SCFAs) expanded gut T regulatory (Treg) cells by suppression of the JNK1 and p38 pathway."

"Treatment with SCFAs ameliorated EAE and reduced axonal damage via long-lasting imprinting on lamina-propria-derived Treg cells."

Short, but Smart:
SCFAs Train T Cells in the Gut to Fight Autoimmunity in the Brain.



Immunity. 2015 Oct 20;43(4):629-31.

Nutrients

(Vitamins and Minerals)

RATINGS OF VITAMINS AND MINERALS FOR NEUROINFLAMMATION

Vitamin D	
Magnesium	
Vitamin A Vitamin E	
B1 B2 B3 B5 B6 Zinc Calcium	

Review

Developmental Neuroscience

Dev Neurosci 2018;40:1–12
DOI: 10.1159/000484891

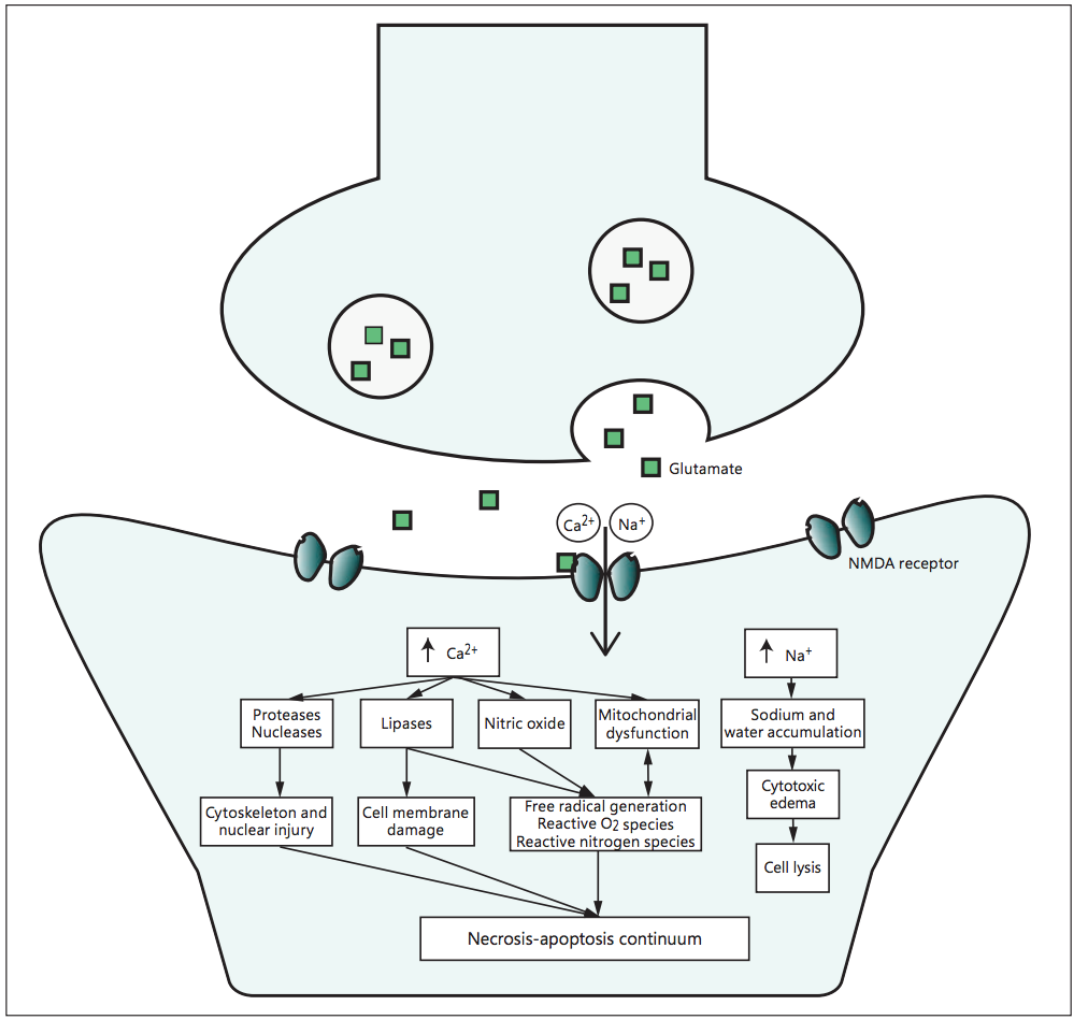
Received: May 4, 2017
Accepted after revision: November 1, 2017
Published online: February 7, 2018

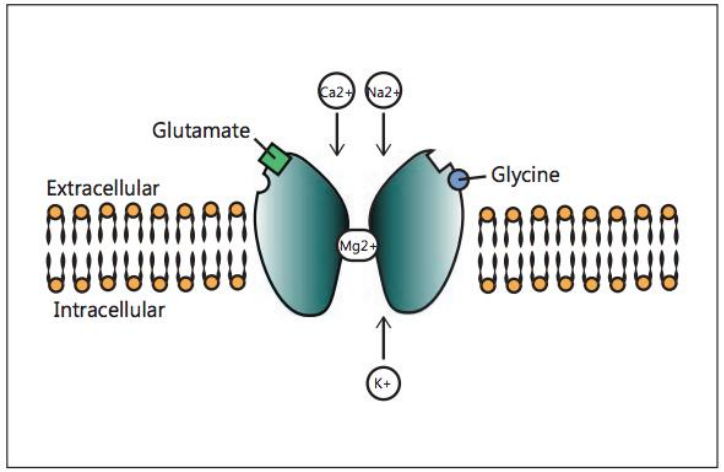
Magnesium as a Neuroprotective Agent: A Review of Its Use in the Fetus, Term Infant with Neonatal Encephalopathy, and the Adult Stroke Patient

Ingran Lingam[a] Nicola J. Robertson[a, b]

[a]Institute for Women's Health, London, UK; [b]Sidra Medicine, NICU level 3, Qatar Foundation, Doha, Qatar

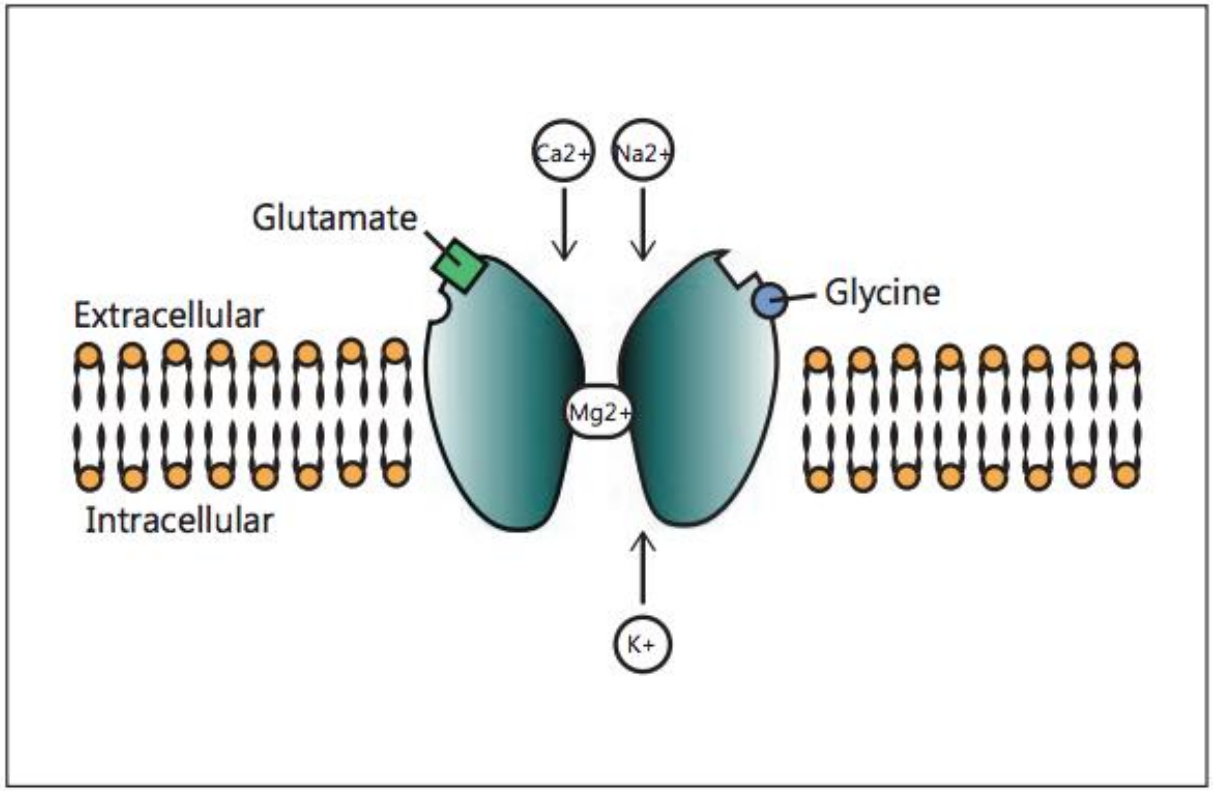
Mechanisms of excitotoxic-mediated injury





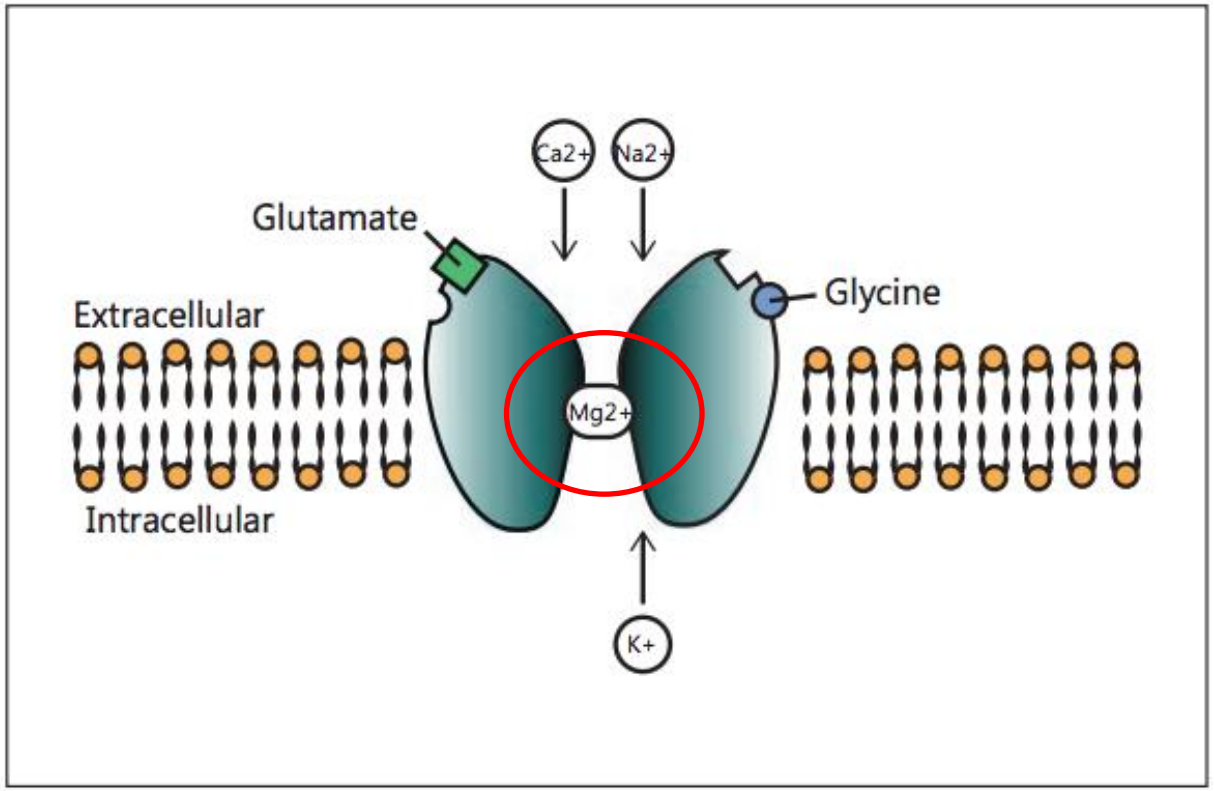
Dev Ne··rosci 2018;40:1–12

Mechanisms of excitotoxic-mediated injury



Dev Neurosci 2018;40:1–12

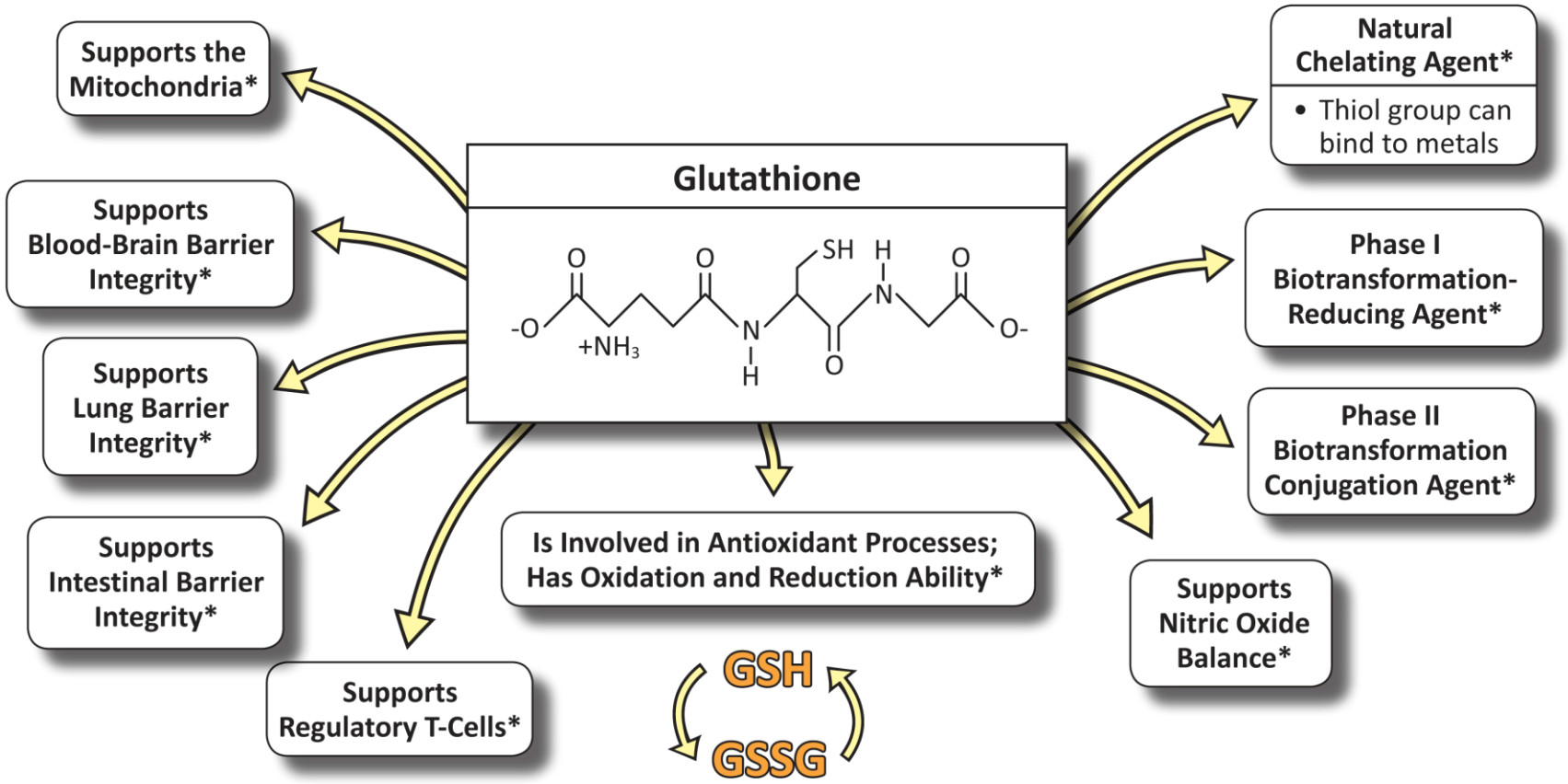
Mechanisms of excitotoxic-mediated injury



Dev Ne rosci 2018;40:1–12

Antioxidants

THE ROLE OF GLUTATHIONE IN IMMUNE-CHEMICAL TOLERANCE

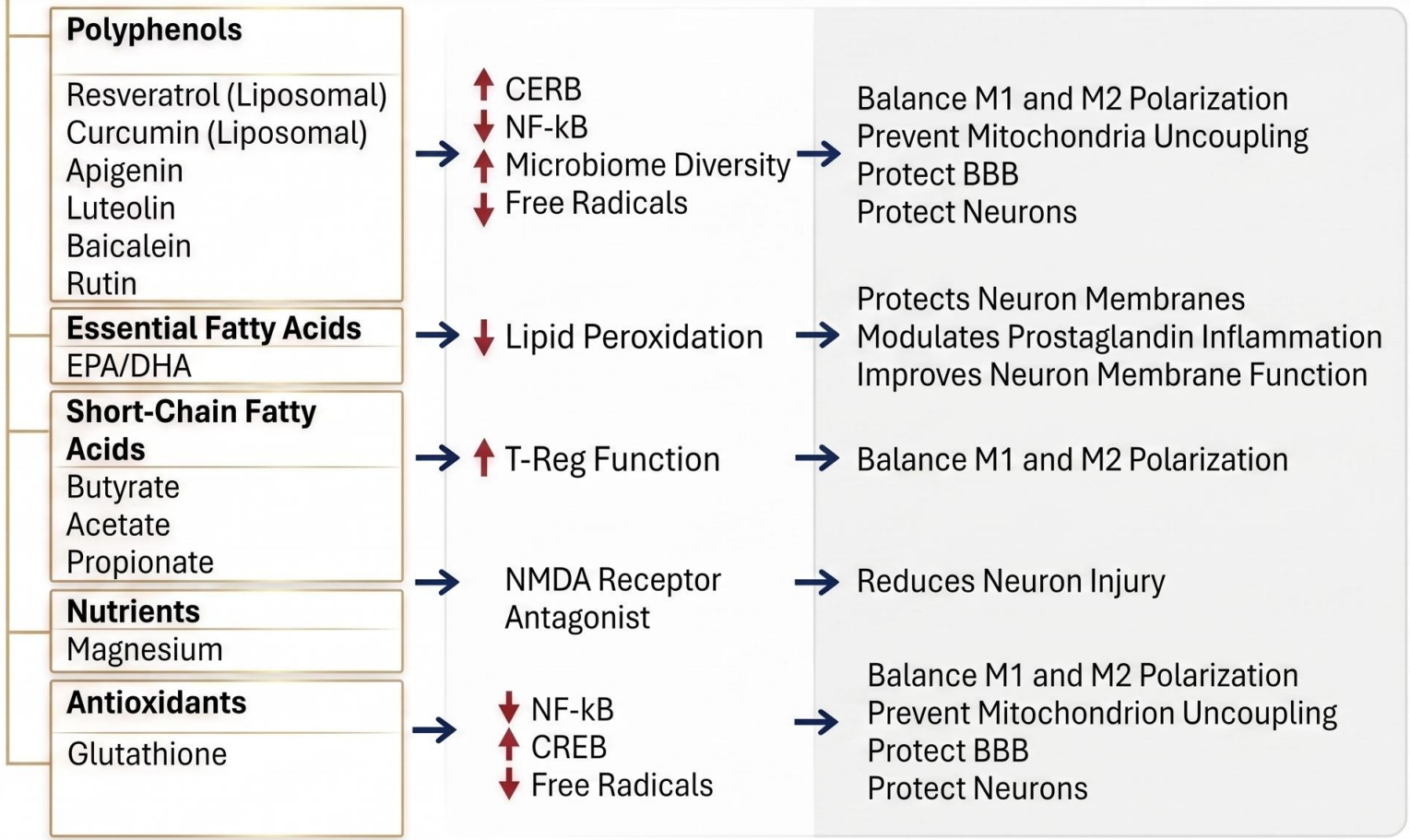


RATINGS OF GLUTATHIONE SOURCES

Liposomal S-Acetyl L-Glutathione	
S-Acetyl Glutathione	
N-Acetyl Cysteine	

Summary of Nutraceutical Approaches for Neuroinflammation

NUTRACEUTICAL MANAGEMENT OF NEUROINFLAMMATION



Presentation Overview

Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

Presentation Overview

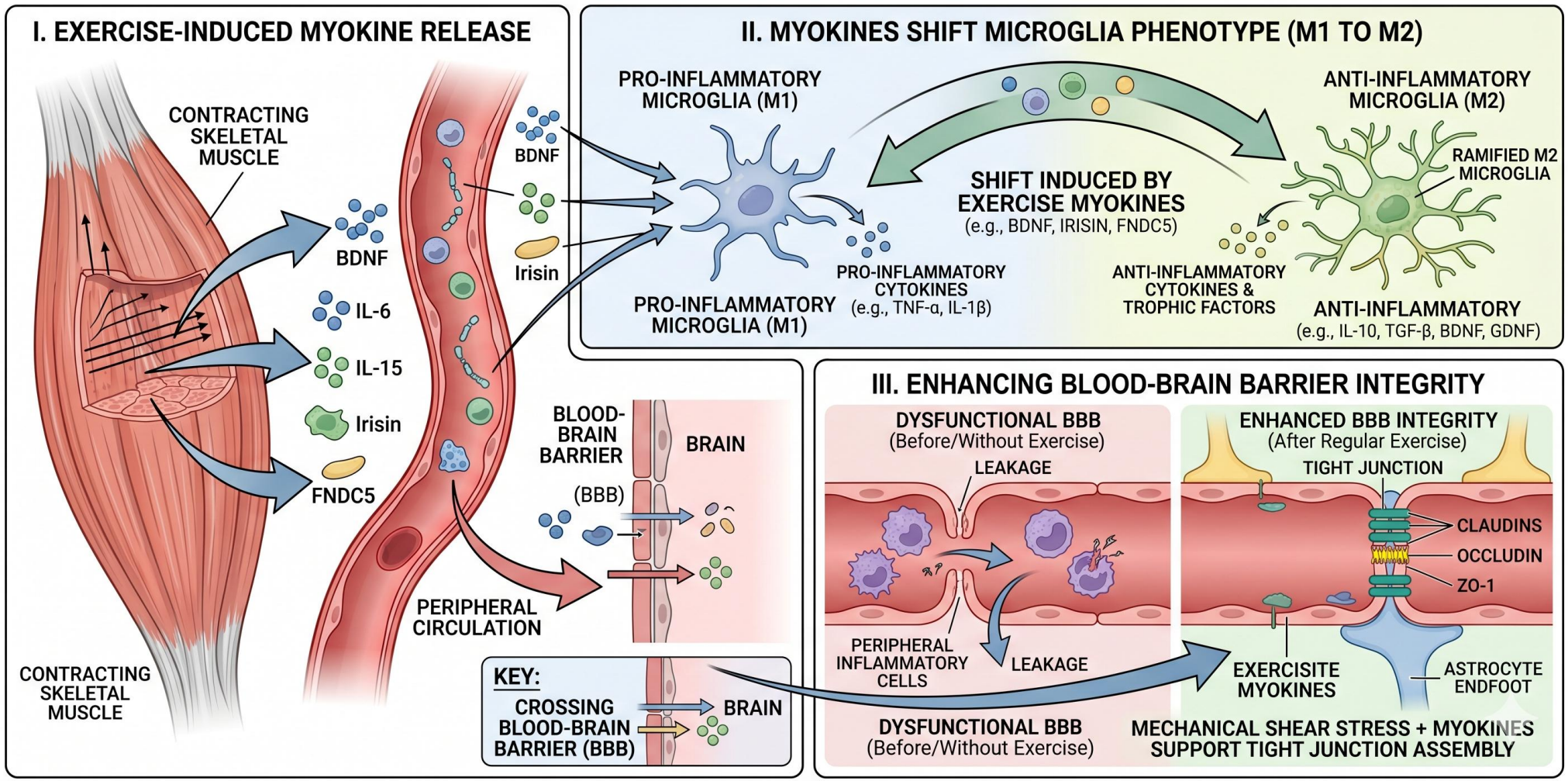
Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

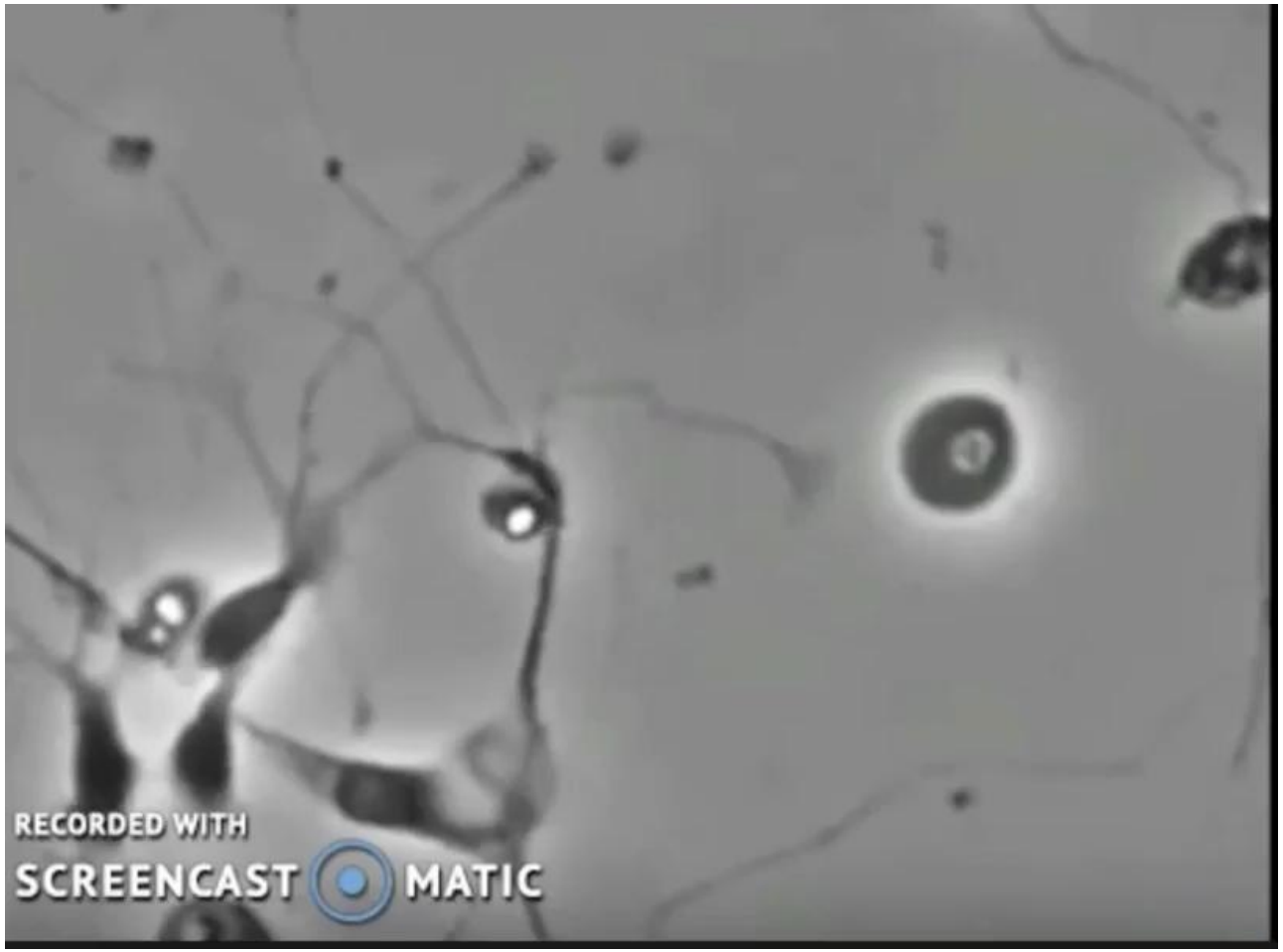
Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

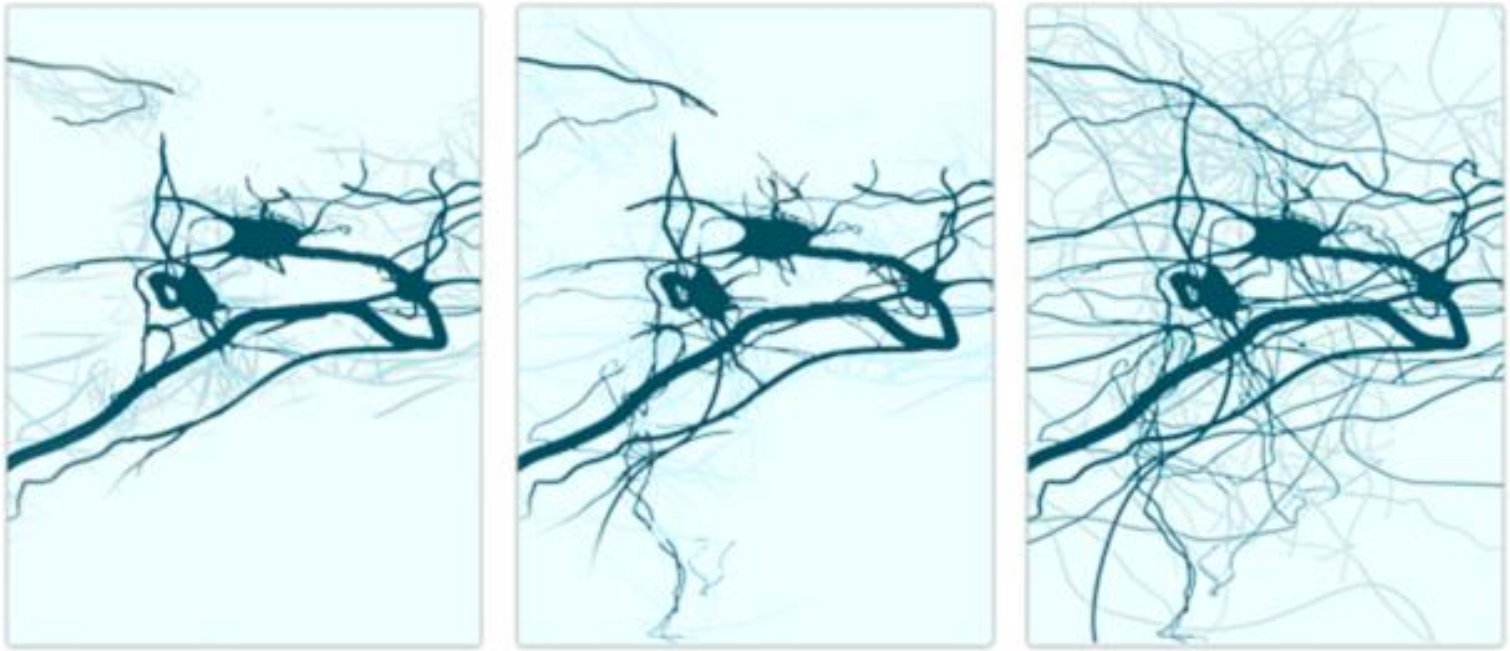
EXERCISE, MYOKINES, AND NEUROPROTECTION



Brain-Derived Neurotropic Factor (BDNF) and Plasticity



Neuroplasticity



Neural networks **before** training

Neural networks **2 weeks** after stimulation

Neural networks **2 months** after stimulation

Clinical Pearls

- Sometimes the stimulation from exercise causes adverse reactions from degenerated areas of the brain that cannot handle activation.

- If there is an adverse reaction, you may need to determine if this is occurring by trying different type of exercises.

Potential Adverse Reactions With Impaired Brain Regions

BRAIN REGIONS	SENSITIVITY TO TYPE OF EXERCISE
Cerebellum →	• Balance exercises (yoga) • Core platform exercises (BOSU) • Lots of ups and downs (burpees)
Vestibular →	• Excessive motion in environment (crowded gym) • Unstable ground (treadmill)
Frontal cortex →	• Exercise that requires focus and concentration
Auditory context/Tectum →	• Environments that are very loud

Presentation Overview

Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

Presentation Overview

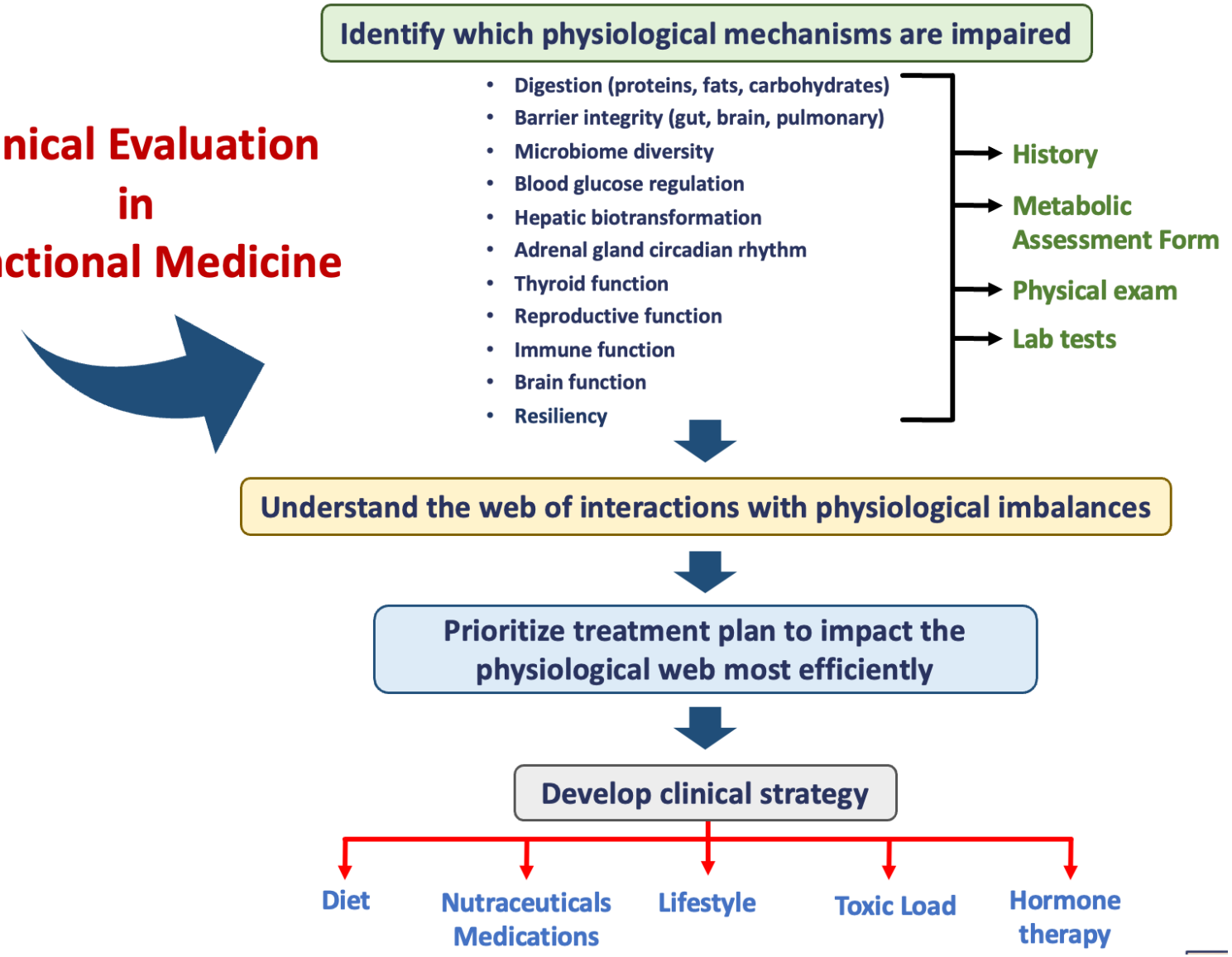
Neuroinflammatory Pathophysiology

- The immune system and the brain
- Neuroinflammation in mental disorders
- Neuroinflammation: a personal story
- The mechanisms of primed glial cells
- How to identify primed glial cells clinically

Clinical Approaches

- Dietary Approaches to Neuroinflammation
- Fasting Protocols
- Nutraceuticals Dampening Glia & Crossing BBB
- Physical and Neurological Exercise
- Other Factors Dampening Inflammation

Clinical Evaluation in Functional Medicine



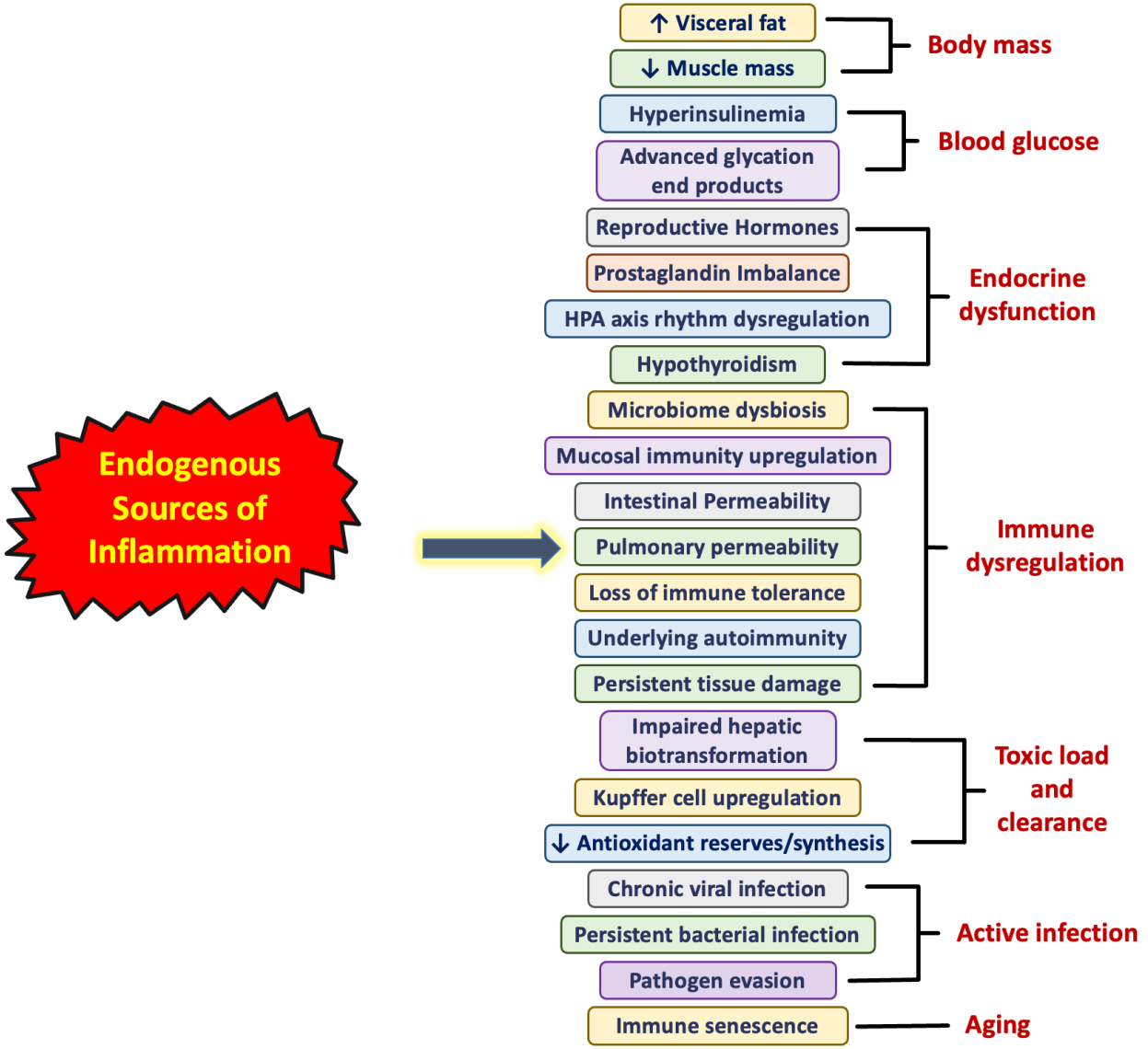
Mechanisms for Brain Inflammation

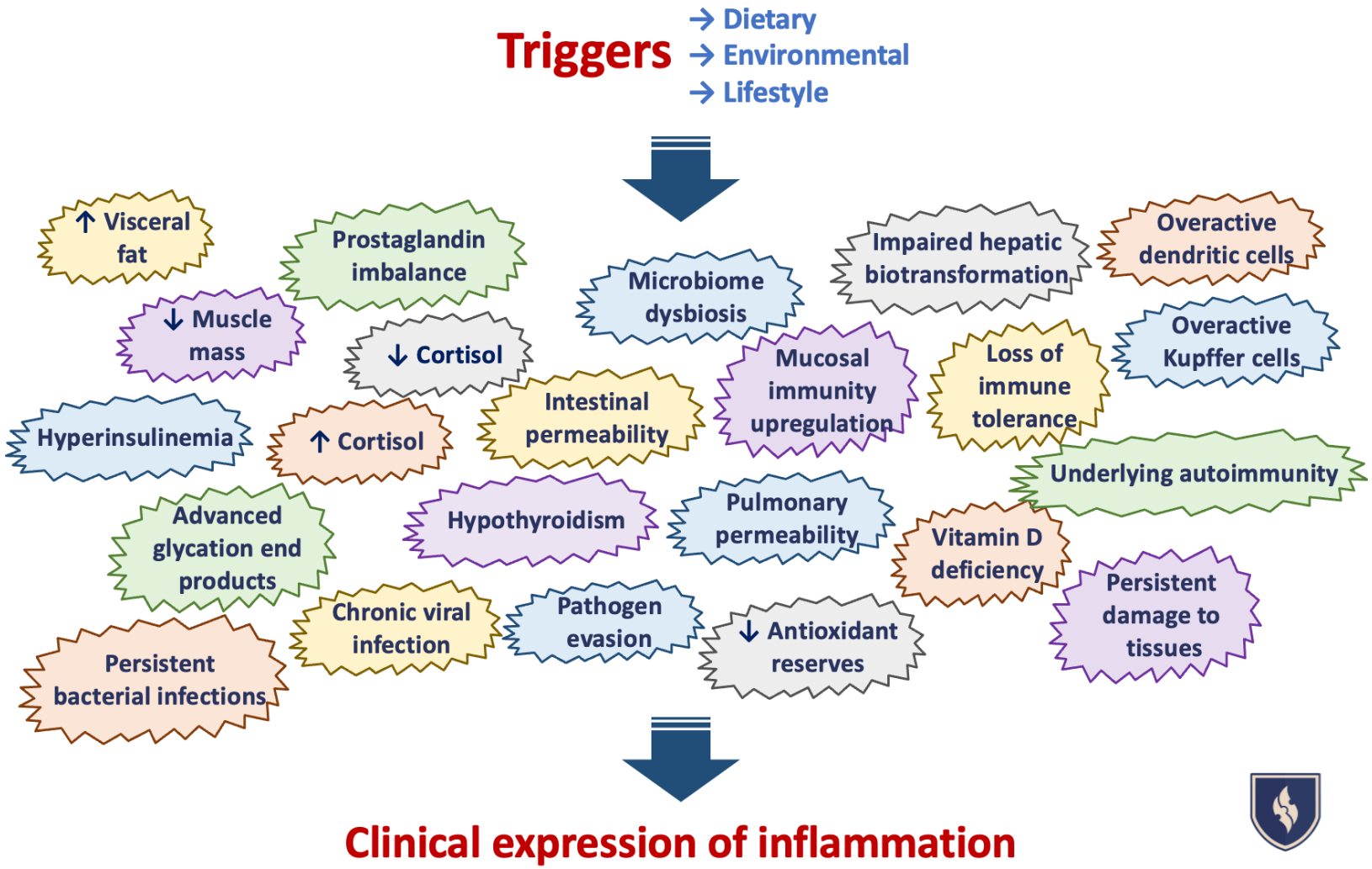
- Head trauma
- Poor circulation
- Anemia
- Autoimmunity
- Systemic inflammation
- Gut permeability
- Gluten sensitivity
- Blood-brain barrier permeability
- Glycosylated end products/diabetes
- Alcohol
- Drug abuse
- Environmental pollutants
- Insulin surges

Activate glial neuroinflammation

Symptoms of Neuroinflammation

- *Brain fog*
- *Unclear thoughts*
- *Poor brain endurance*
- *Slow and varied mental speeds*
- *Loss of brain function after trauma*
- *Brain fatigue and poor mental focus after meals*
- *Brain fatigue promoted by systemic inflammation*
- *Brain fatigue promoted by chemicals, scents and pollutants*


Endogenous Sources of Inflammation
↑ Visceral fat
↓ Muscle mass
Body mass
Hyperinsulinemia
Advanced glycation end products
Blood glucose
Reproductive Hormones
Prostaglandin Imbalance
HPA axis rhythm dysregulation
Hypothyroidism
Endocrine dysfunction
Microbiome dysbiosis
Mucosal immunity upregulation
Intestinal Permeability
Pulmonary permeability
Loss of immune tolerance
Underlying autoimmunity
Persistent tissue damage
Immune dysregulation
Impaired hepatic biotransformation
Kupffer cell upregulation
↓ Antioxidant reserves/synthesis
Toxic load and clearance
Chronic viral infection
Persistent bacterial infection
Pathogen evasion
Active infection
Immune senescence
Aging


Triggers
→ Dietary
→ Environmental
→ Lifestyle
↑ Visceral fat
Prostaglandin imbalance
Microbiome dysbiosis
Impaired hepatic biotransformation
Overactive dendritic cells
↓ Muscle mass
↓ Cortisol
Overactive Kupffer cells
Mucosal immunity upregulation
Loss of immune tolerance
Hyperinsulinemia
↑ Cortisol
Intestinal permeability
Underlying autoimmunity
Advanced glycation end products
Hypothyroidism
Pulmonary permeability
Vitamin D deficiency
Persistent damage to tissues
Chronic viral infection
Pathogen evasion
↓ Antioxidant reserves
Persistent bacterial infections
Clinical expression of inflammation

Thank you
for your attention

Kharrazian Institute

The largest online functional medicine platform

The most comprehensive, science-based functional medicine training programme available.

200 hours of CPD credits

The core curriculum covers immunology, neuroendocrinology, gastrointestinal physiology, chronic inflammation, blood chemistry, and more, earning you foundational and advanced certifications that count towards your annual CPD requirements.

Monthly classes taught by leading functional medicine practitioners

Each month, an expert clinician delivers a clinically applicable class, complemented by 100 hours of case analyses, physical exam lessons, lab discussions, and interviews with successful clinicians.

★★★★★

"Amazing, brilliant knowledge, well organised, very comprehensive, and excellent foundational knowledge that builds with every module."

Dally Ratra, MBChB, UK

★★★★★

"This training is incredibly profound and well-founded. I'm deeply grateful for the opportunity to be part of it. It has completely changed how I work."

Sonja Mihaljevic, The Netherlands

Explore with a 7-day free trial

(No credit card required)

Functional Medicine and Nutrition Training and Certification

kharrazianinstitute.com