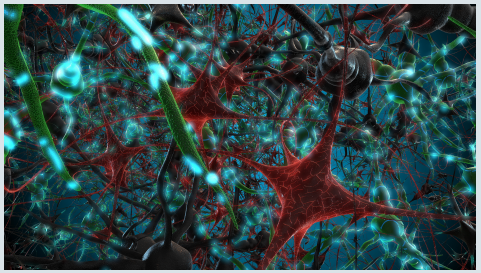
DR. HYMAN+

The Role of Brain Inflammation in Chronic Fatigue and Depression

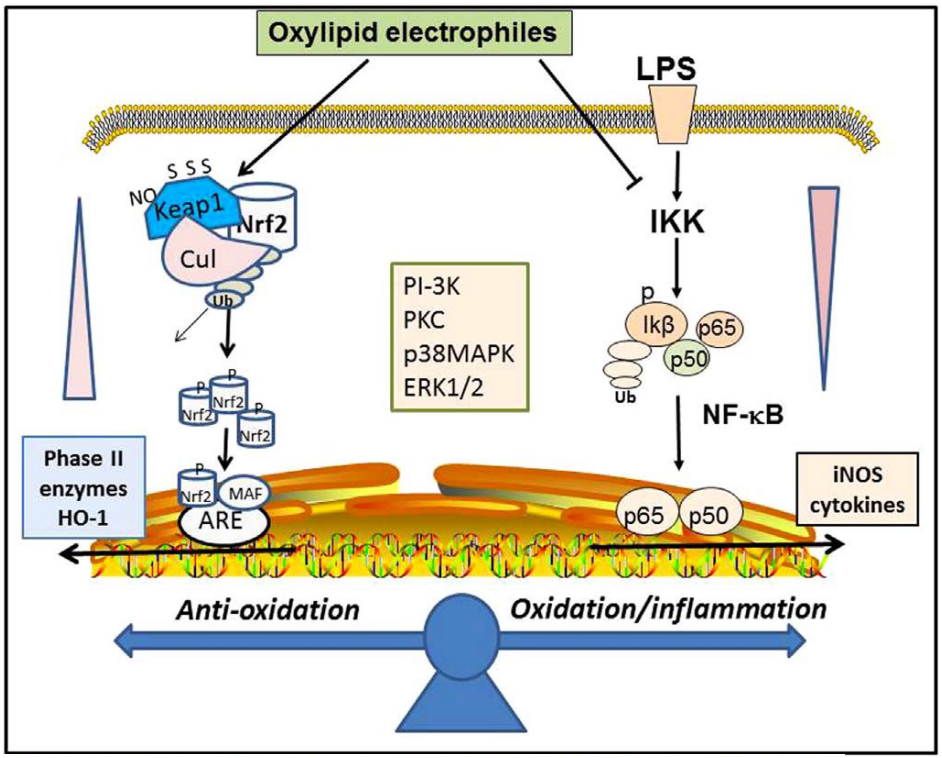


Datis Kharrazian, PhD, DHSc, DC, MS, MMSc, FACN
Harvard Medical School Research Fellow
Department of Neurology Massachusetts General Hospital Research Fellow Associate
Associate Clinical Professor Loma Linda University School of Medicine
Fellow of the American College of Nutrition

DR. HYMAN+

Essential Fatty Acids

Docosahexaenoic acid (DHA): An essential nutrient and a nutraceutical for brain health and diseases



Prostaglandins, Leukotrienes and Essential Fatty Acids 136 (2018) 3–13

Key Concepts

- DHA is the most abundant fatty acid in the brain and regulates several key functions at the phospholipid membrane of neurons.
- With significant inflammation, cell membrane DHA breaks down to modulate neuroinflammation.
- DHA can cross the blood-brain barrier after oral ingestion and may be required during times of neuroinflammation.

Molecular Aspects of Medicine 64 (2018) 109–134

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

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

Brain docosahexaenoic acid uptake and metabolism

R.J.Scott Lacombe, Raphaël Chouinard-Watkins, Richard P. Bazinet*

Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, 150 College St., Toronto, Ontario, M5S 3E2, Canada

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Keywords:
Docosahexaenoic acid
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Metabolism
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Uptake
Transport

ABSTRACT

Docosahexaenoic acid (DHA) is the most abundant n-3 polyunsaturated fatty acid in the brain where it serves to regulate several important processes and, in addition, serves as a precursor to bioactive mediators. Given that the capacity of the brain to synthesize DHA locally is appreciably low, the uptake of DHA from circulating lipid pools is essential to maintaining homeostatic levels. Although, several plasma pools have been proposed to supply the brain with DHA, recent evidence suggests non-esterified-DHA and lysophosphatidylcholine-DHA are the primary sources. The uptake of DHA into the brain appears to be regulated by a number of complementary pathways associated with the activation and metabolism of DHA, and may provide mechanisms for enrichment of DHA within the brain. Following entry into the brain, DHA is esterified into and recycled amongst membrane phospholipids contributing the distribution of DHA in brain phospholipids. During neurotransmission and following brain injury, DHA is released from membrane phospholipids and converted to bioactive mediators which regulate signaling pathways important to synaptogenesis, cell survival, and neuroinflammation, and may be relevant to treating neurological diseases. In the present review, we provide a comprehensive overview of brain DHA metabolism, encompassing many of the pathways and key enzymatic regulators governing brain DHA uptake and metabolism. In addition, we focus on the release of non-esterified DHA and subsequent production of bioactive mediators and the evidence of their proposed activity within the brain. We also provide a brief review of the evidence from post-mortem brain analyses investigating DHA levels in the context of neurological disease and mood disorder, highlighting the current disparities within the field.

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Brain docosahexaenoic acid uptake and metabolism

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During neurotransmission and following brain injury, DHA is released from membrane phospholipids and converted to bioactive mediators, which regulate signaling pathways important to synaptogenesis, cell survival, and neuroinflammation, and may be relevant to treating neurological diseases.

Keywords:
Docosahexaenoic acid
Fatty acid
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Transport

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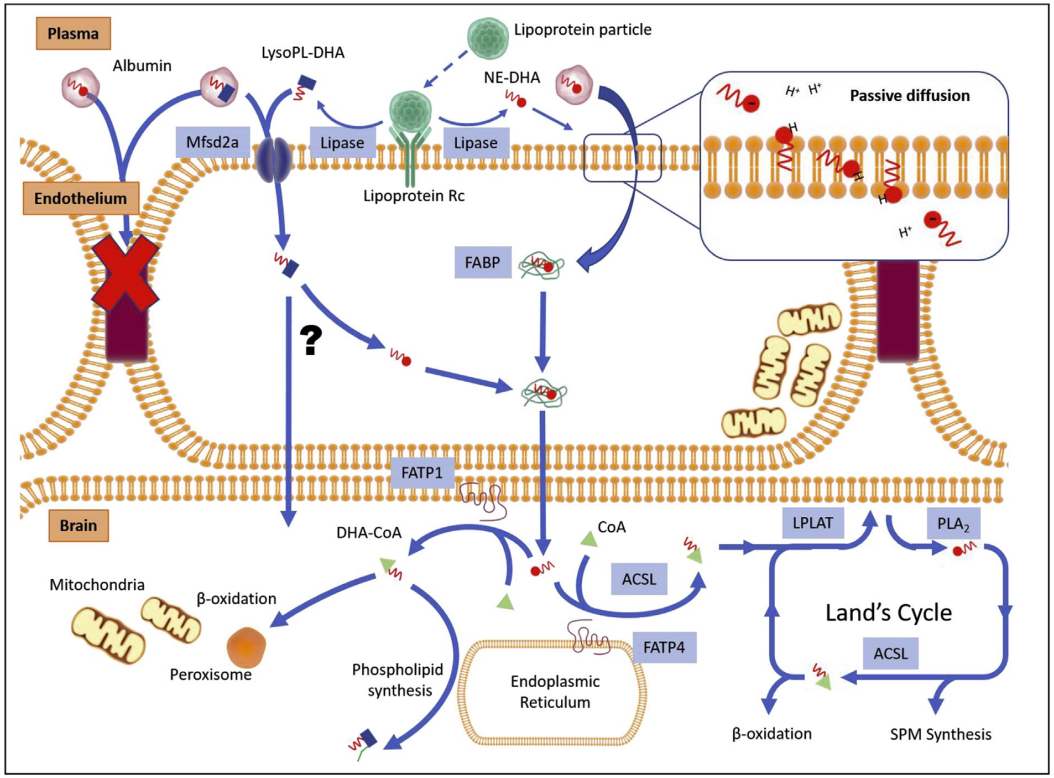
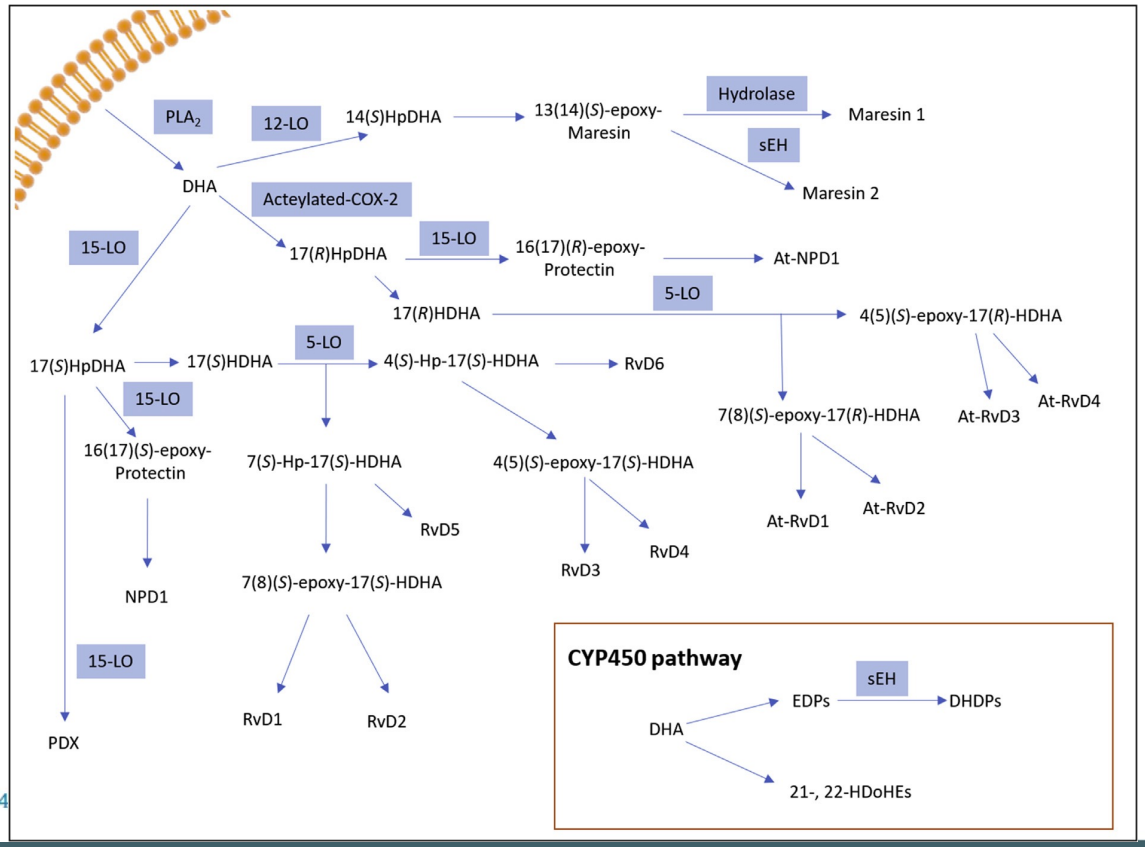
Rapid DHA Passive Diffusion Across BBB

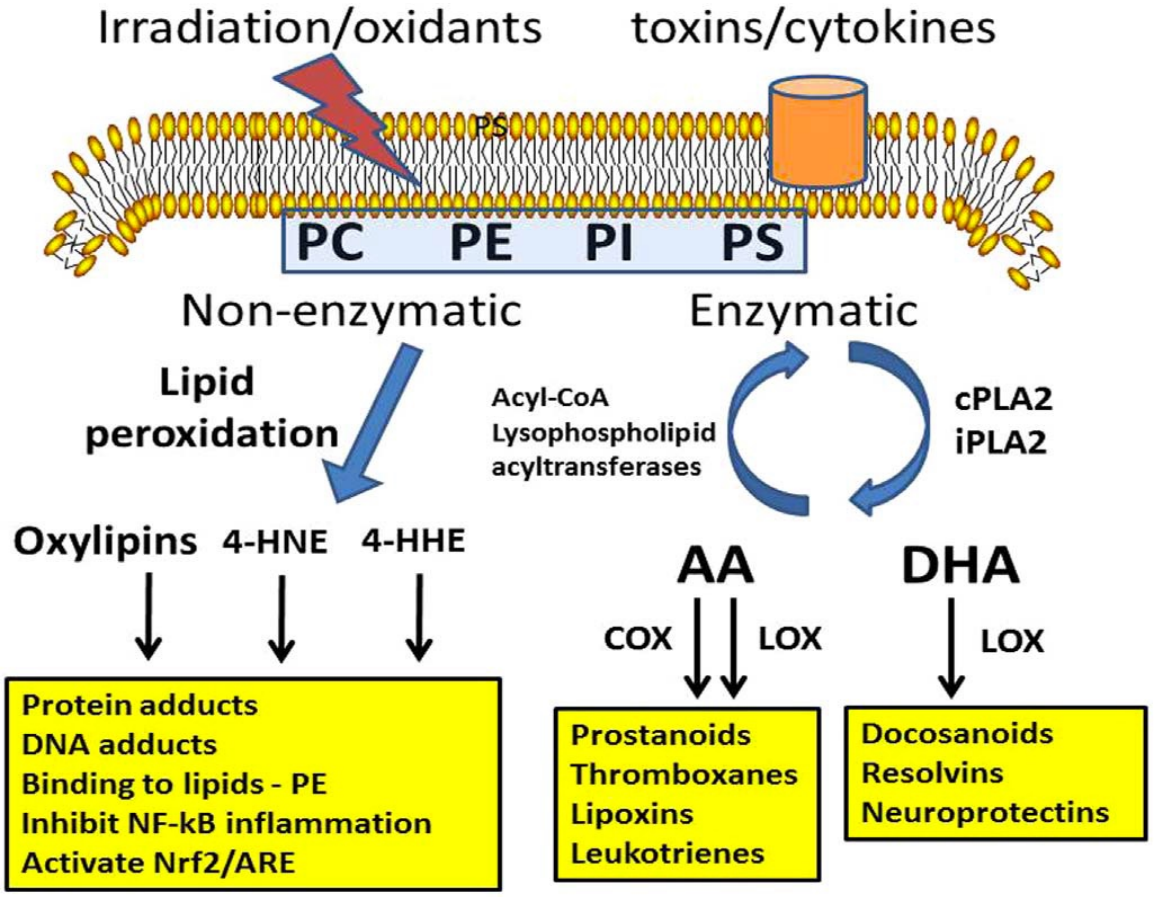


Molecular Aspects of Medicine 64 (2018) 109–134

DHA Breakdown From Neuronal Membrane



Molecular Aspects of Medicine 64 (2018) 109–134

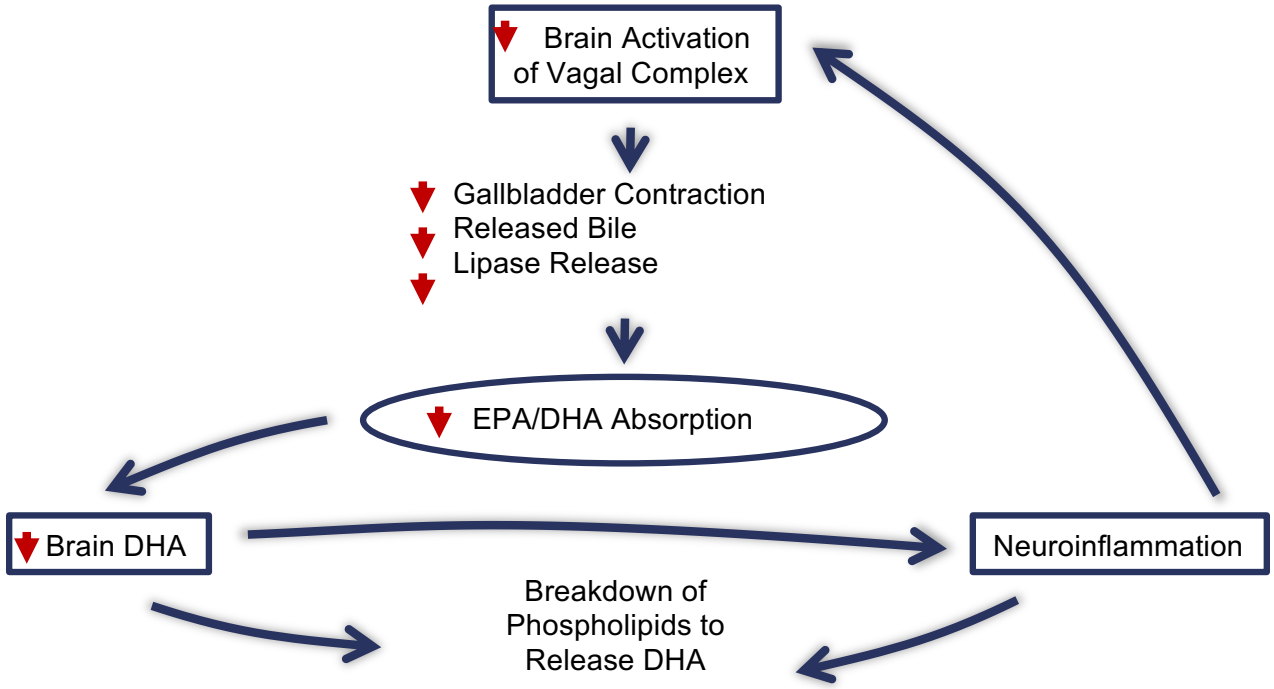


Prostaglandins, Leukotrienes and Essential Fatty Acids 136 (2018) 3–13

Clinical Pearls

- DHA and EPA cannot get to the brain if they cannot be absorbed.
- You need healthy gallbladder function to absorb EFAs.

Brain-Gut Axis and EFA Absorption



Symptoms of Bile Stasis

- Bloating after fatty or fried meals.
- Burping after fatty meals or fish oils.
- Referral visceral pain between the rhomboids after fatty meals.
- Floating stool.

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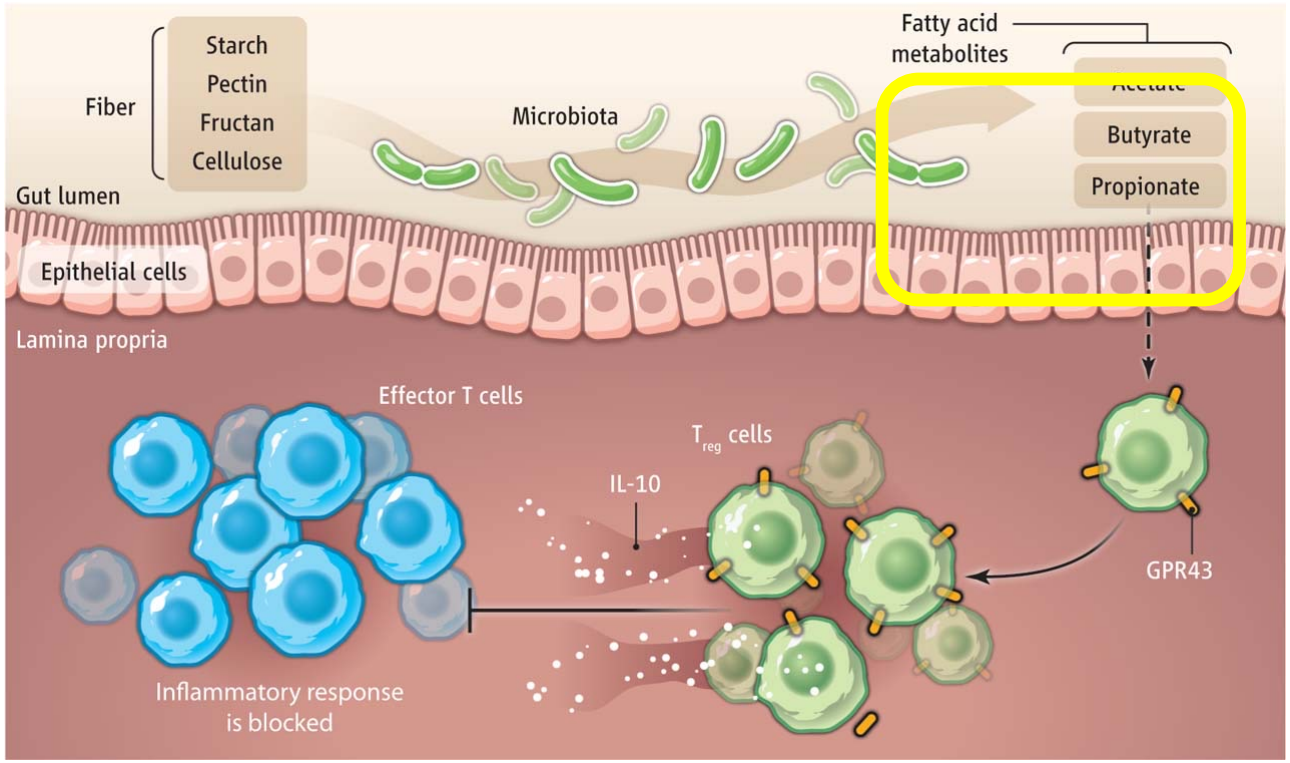
Short-Chain Fatty Acids

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.

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Ruhr-University Bochum,
Bochum, Germany

Keywords: Animal model, immunology, disease-modifying therapies

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

Immunity
Article

CellPress

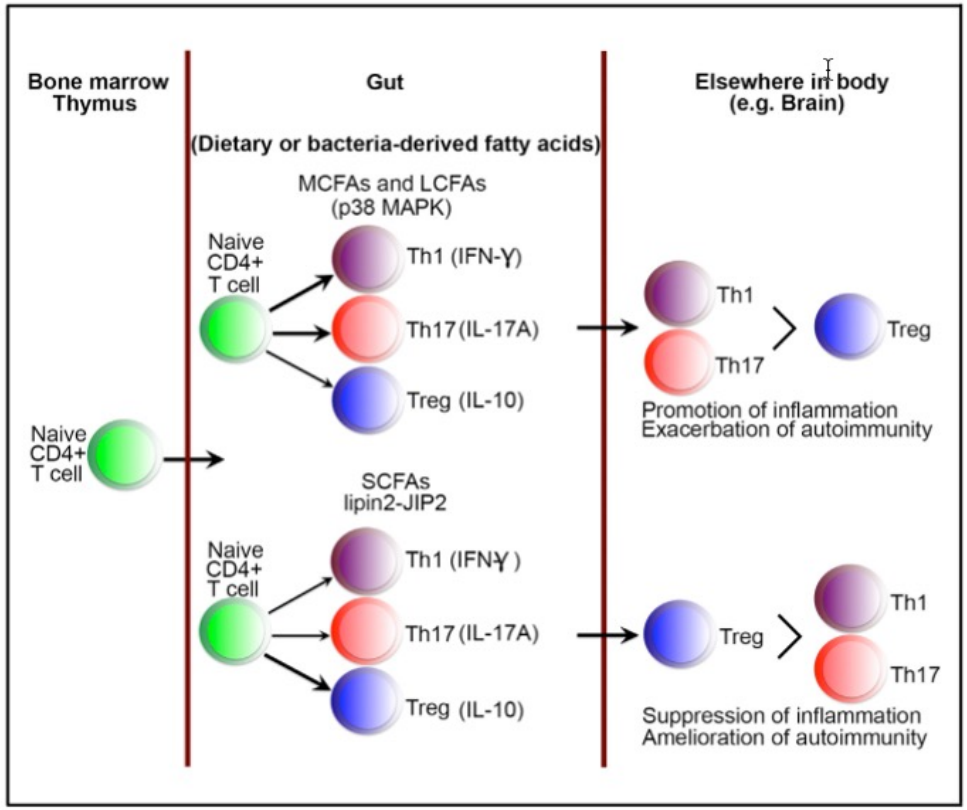
Dietary Fatty Acids Directly Impact Central Nervous System Autoimmunity via the Small Intestine

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
[2]Department of Neurology, Friedrich-Alexander-University Erlangen-Nuremberg, 91054 Erlangen, 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



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

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Nutrients (Vitamins and Minerals)

Vitamins and Nutrients as Primary Treatments in Experimental Brain Injury: Clinical Implications for Nutraceutical Therapies

		Excitotoxicity	Oxidative Stress	Energy Supplementation (mitochondria function, ATP, etc)	Cell Death	Edema	Plasticity & Neuromodulation	Inflammation
Vitamins	B_2		X					
	B_3		X	X				
	B_6	X		X				
	B_9				x			
	C		X					
	D		X					X
	E		X					
Herbs	Ginseng		X					X
	Ginkgo	X				X		
Flavonoids	Luteolin		X					X
	Quercetin		X					X
	Baicalein		X					
	Puerarin		X					
	Formononetin		X					
	7,8-DHF						X	
	Wogonin							X
	Flavopiridol							X
Other Nutrients	Magnesium	X	X					
	Zinc		X					
	Carnitine			X				
	Omega-3 Acids	X	X				X	X

Brain Res. 2016 June 1; 1640(Pt A): 114–129. doi:10.1016/j.brainres.2015.12.030.

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
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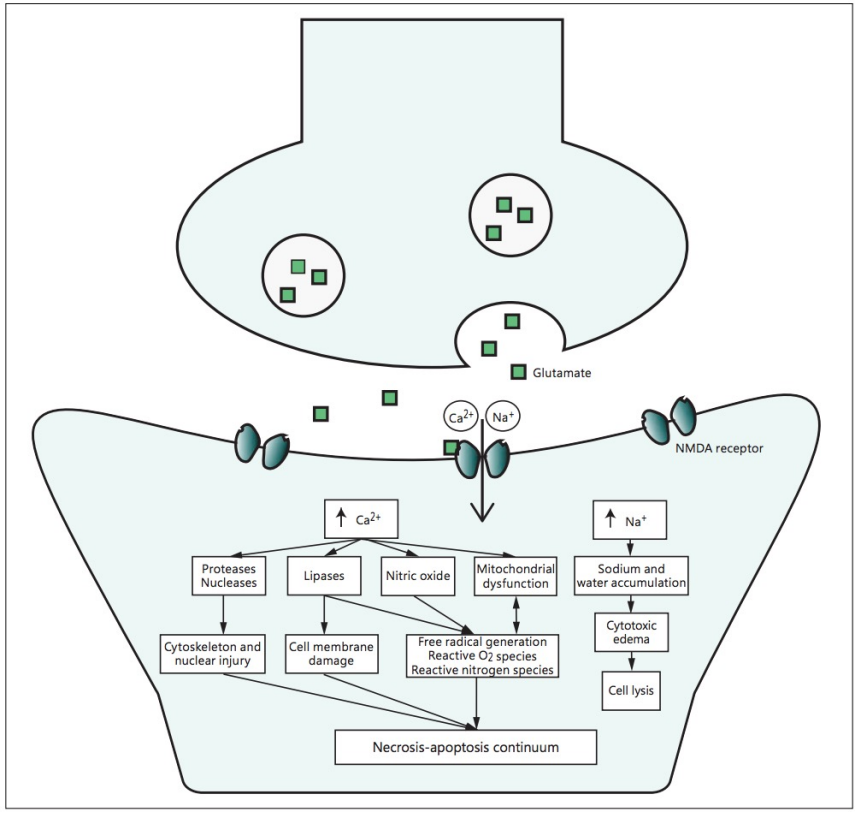
Published online: February 7, 2018

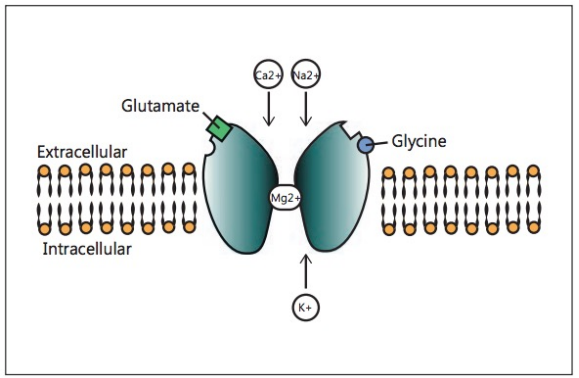
Magnesium as a Neuroprotective Agent: A Review of Its Use in the Fetus, Term Infant with Neonatal Encephalopathy, and the Adult Stroke Patient

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

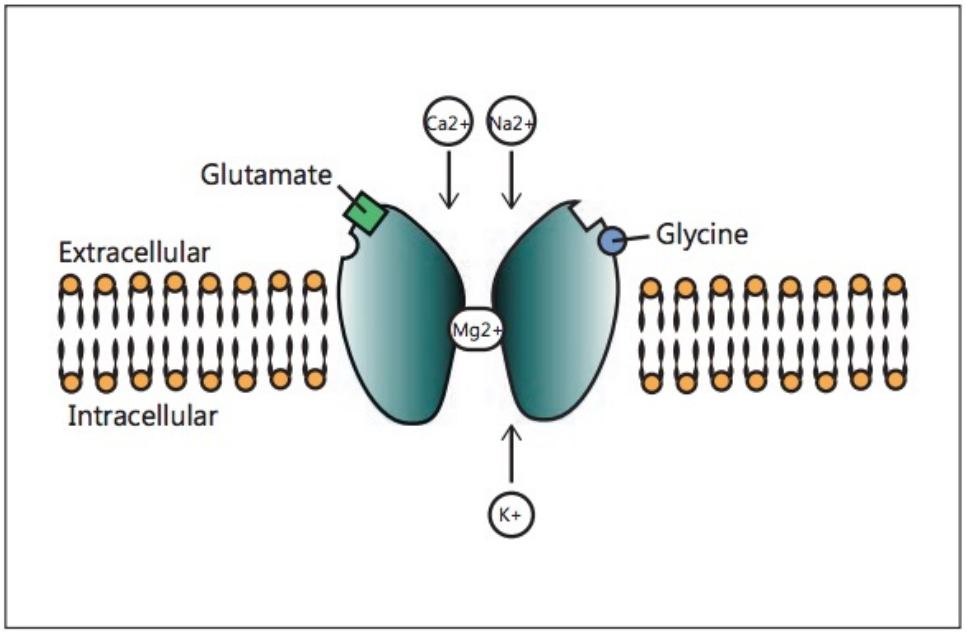
Mechanisms of excitotoxic-mediated injury





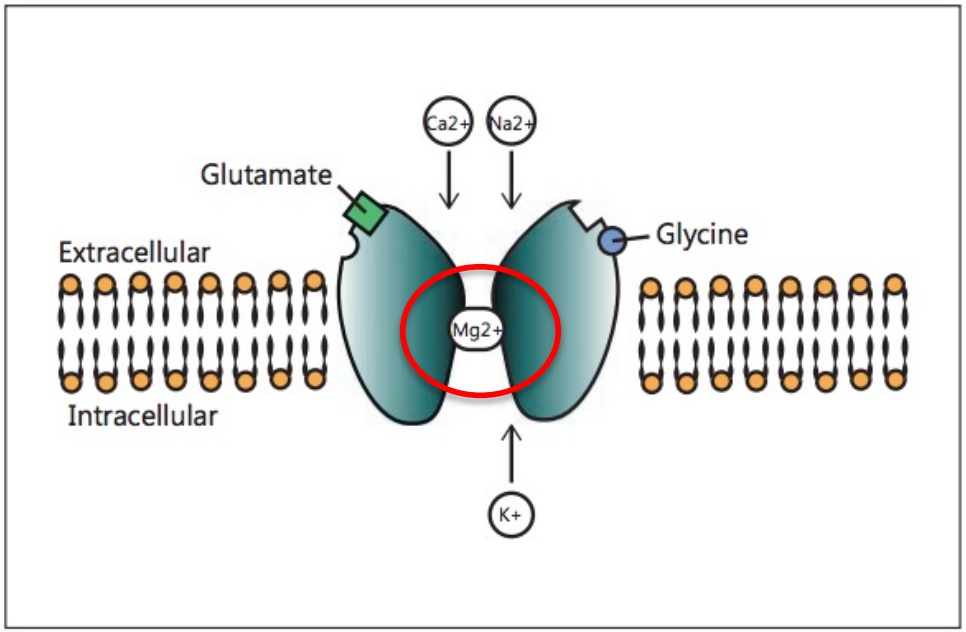
Dev Ne··rosci 2018;40:1–12

Mechanisms of excitotoxic-mediated injury



Dev Neurosci 2018;40:1–12

Mechanisms of excitotoxic-mediated injury



Dev Neurosci 2018;40:1–12

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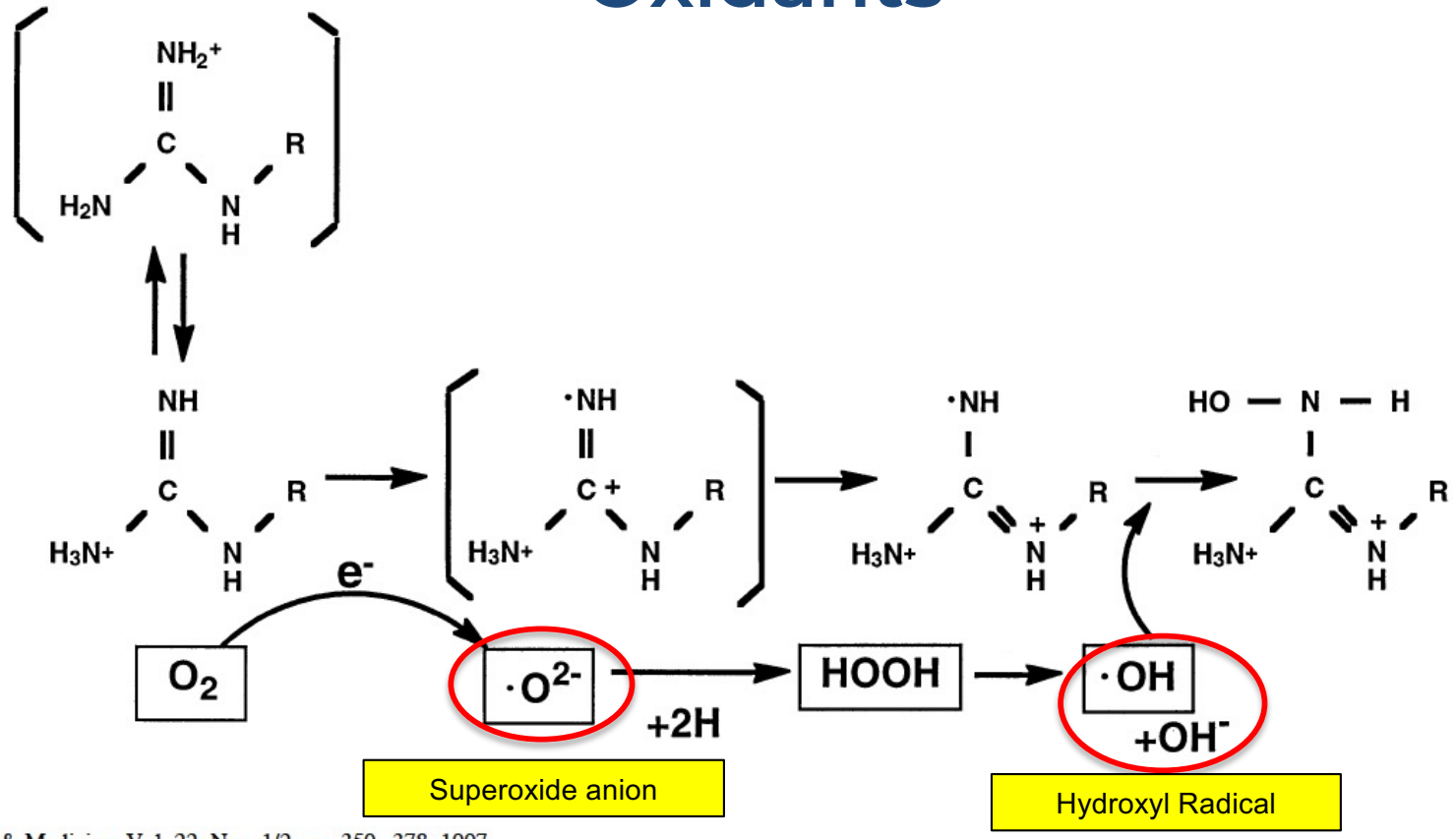
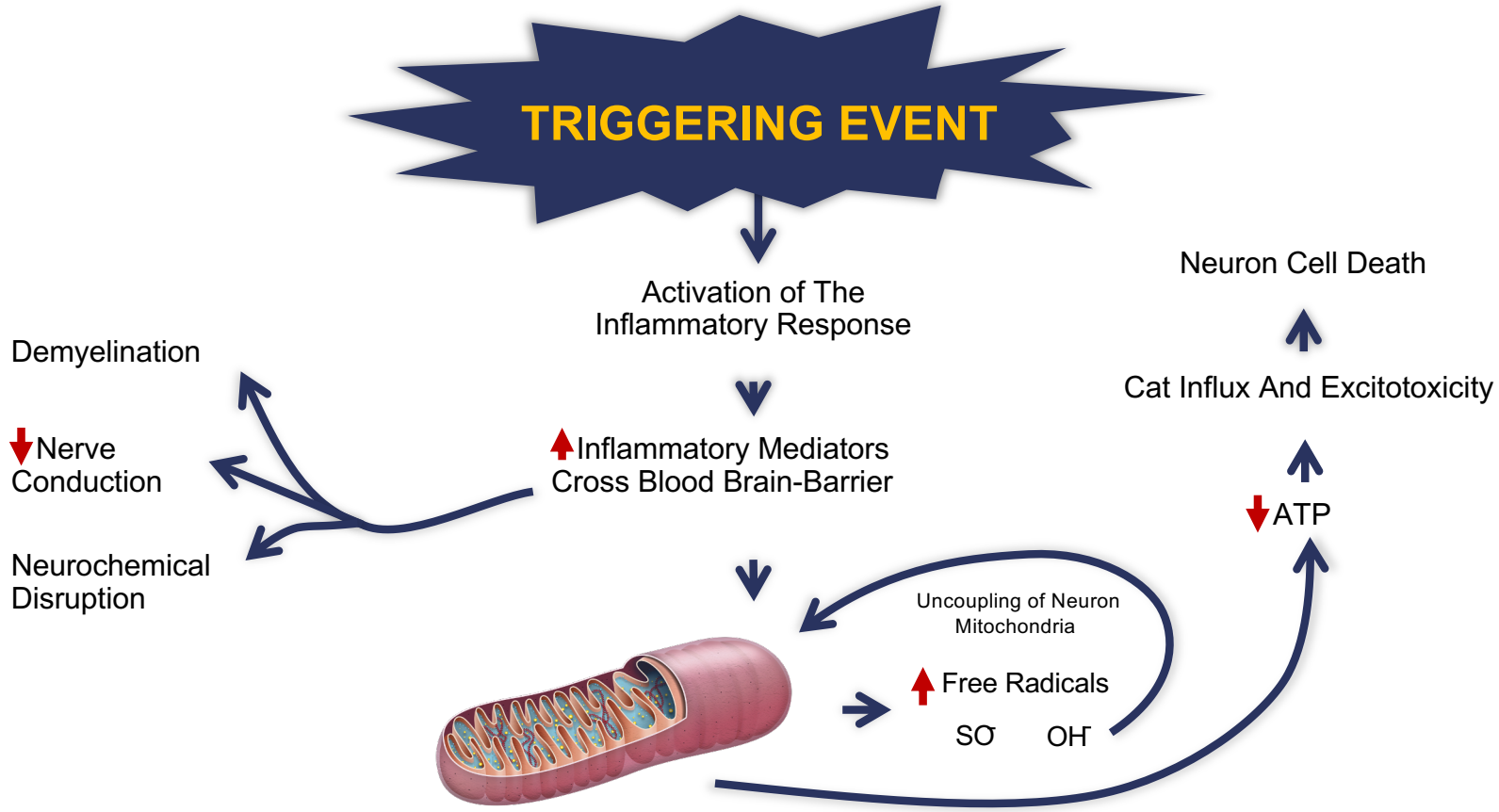
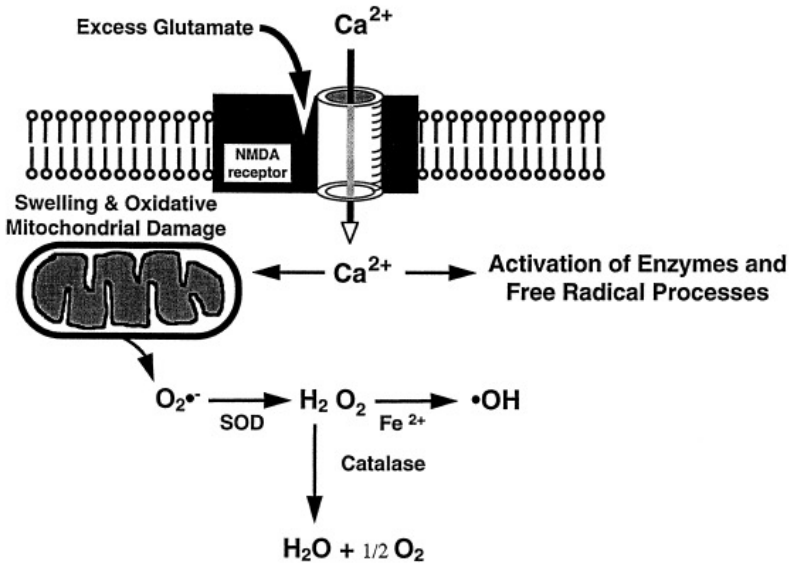
Antioxidants

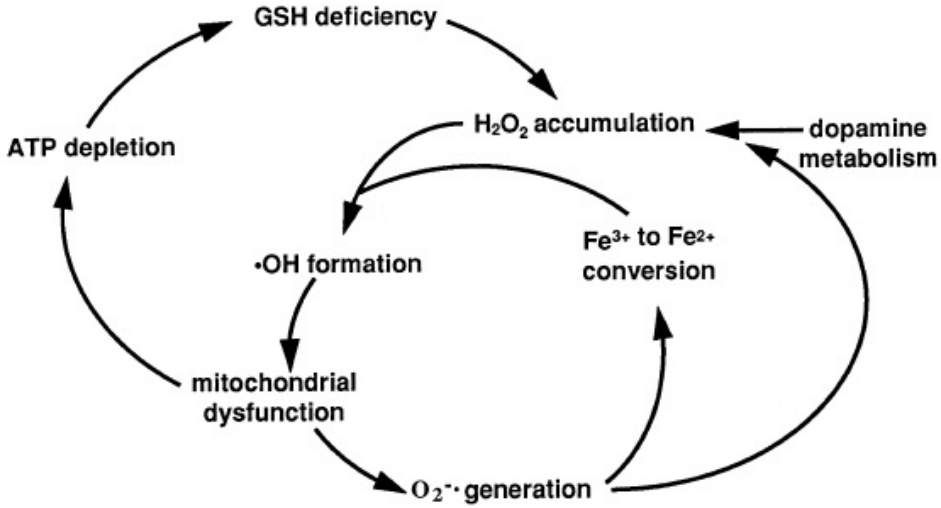
Oxidants



Free Radical Biology & Medicine, Vol. 22, Nos. 1/2, pp. 359–378, 1997


TRIGGERING EVENT
Activation of The Inflammatory Response
Demyelination
Nerve Conduction
Neurochemical Disruption
Inflammatory Mediators Cross Blood Brain-Barrier
Uncoupling of Neuron Mitochondria
Free Radicals
SO
OH
ATP
Cat Influx And Excitotoxicity
Neuron Cell Death





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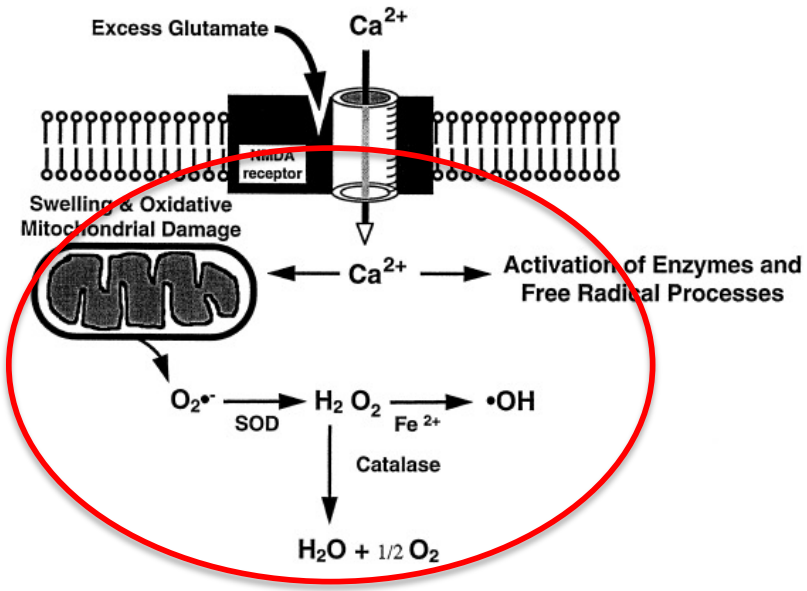
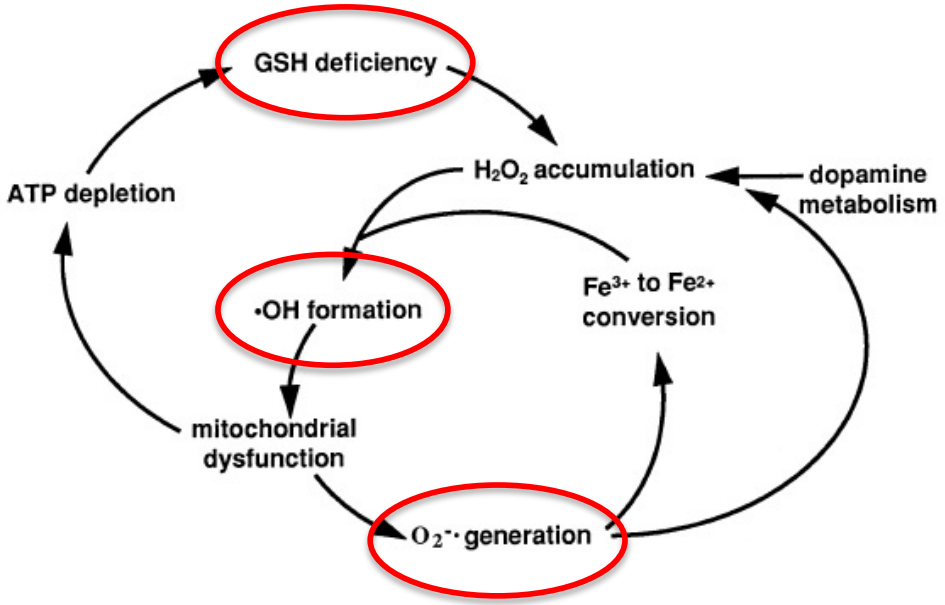
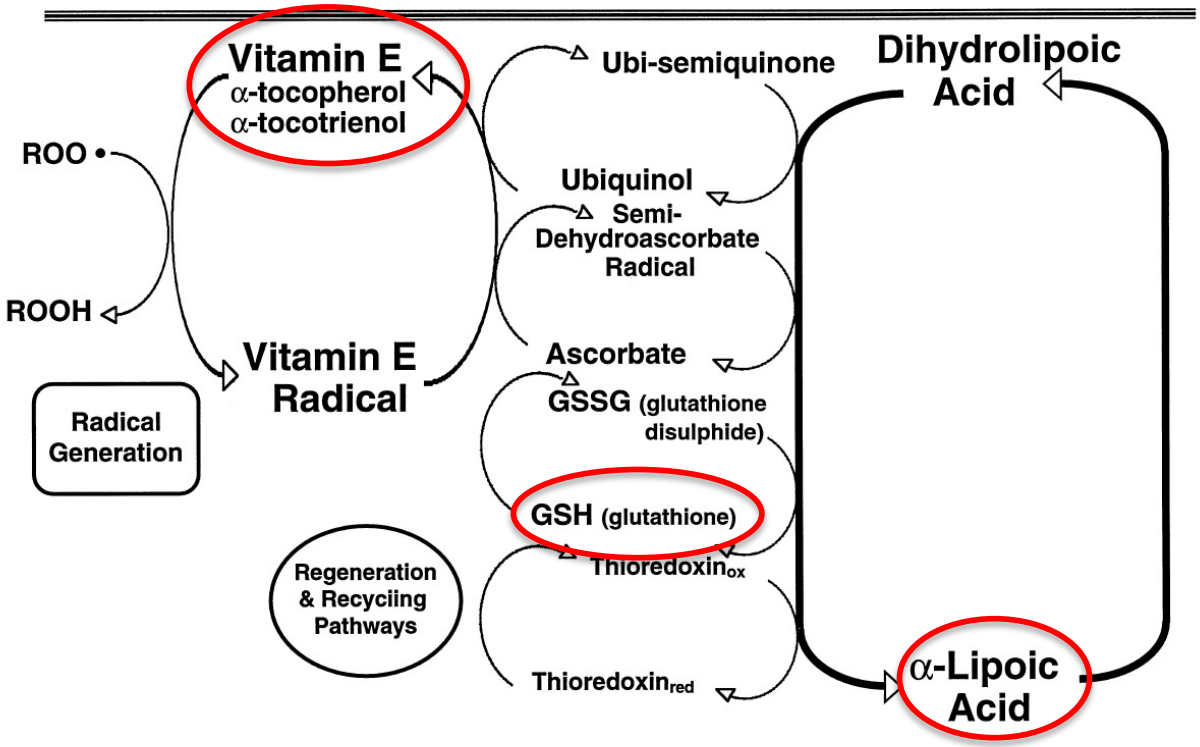




Free Radical Biology & Medicine, Vol. 22, Nos. 1/2, pp. 359–378, 1997

Dihydrolipoate Acid Reduces (Recycles) the Major Cell Antioxidants- Vitamin C, E, Glutathione Thioredoxin and Ubiquinol



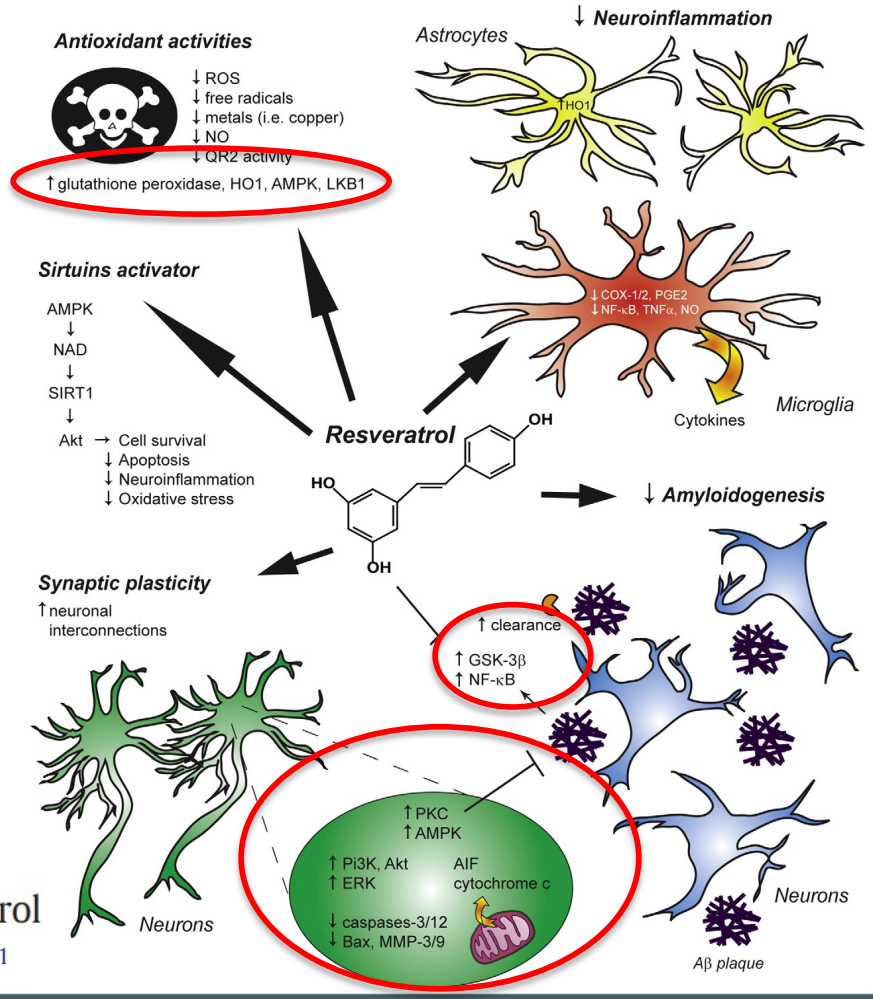
Free Radical Biology & Medicine, Vol. 22, Nos. 1/2, pp. 359–378, 1997

Table 1 Antioxidant and Anti-inflammatory Effects of Nutraceuticals in Human Interventions

Study	Nutraceutical	Treatment Duration	Subjects	Oxidative Stress Markers	Inflammatory Cytokines
Nieman, Cialdella-Kam, Knab, and Shanely (2012)	*Curcuma longa* extract	4 weeks	Overweight/obese women	↔ Isoprostanes	↔ TNF-α, IL-6
Srivastava, Saksena, Khattri, Kumar, and Dagur (2016)		120 days	Osteoarthritis	↓ MDA	↓ IL-1β
Zern et al. (2005)	Grape powder	4 weeks	Postmenopausal women	↓ Isoprostanes	↓ TNF-α
Barona et al. (2012)		4 weeks	Dyslipidemic	↔ Isoprostanes	↔ TNF-α, IL-6
Bogdanski et al. (2012)	Green tea extract	3 months	Obese	↑ TAC	↓ TNF-α
Hsu et al. (2007)		7 months	Hemodialysis	↓ Peroxides	↓ TNF-α
Markovits, Ben Amotz, and Levy (2009)	Lycopene	4 weeks	Obese	↔ Dienes	↔ TNF-α, IL-6
Wood et al. (2012)		14 weeks	Asthmatic	↔ Isoprostanes	↔ TNF-α, IL-6
Hosseini, Saedisomeolia, Wood, Yaseri, and Tavasoli (2016)	Pomegranate extract	30 days	Overweight/obese	↓ MDA	↓ IL-6
Wu et al. (2015)		6 weeks	Hemodialysis	↔ TAC and oxLDL	↔ IL-6

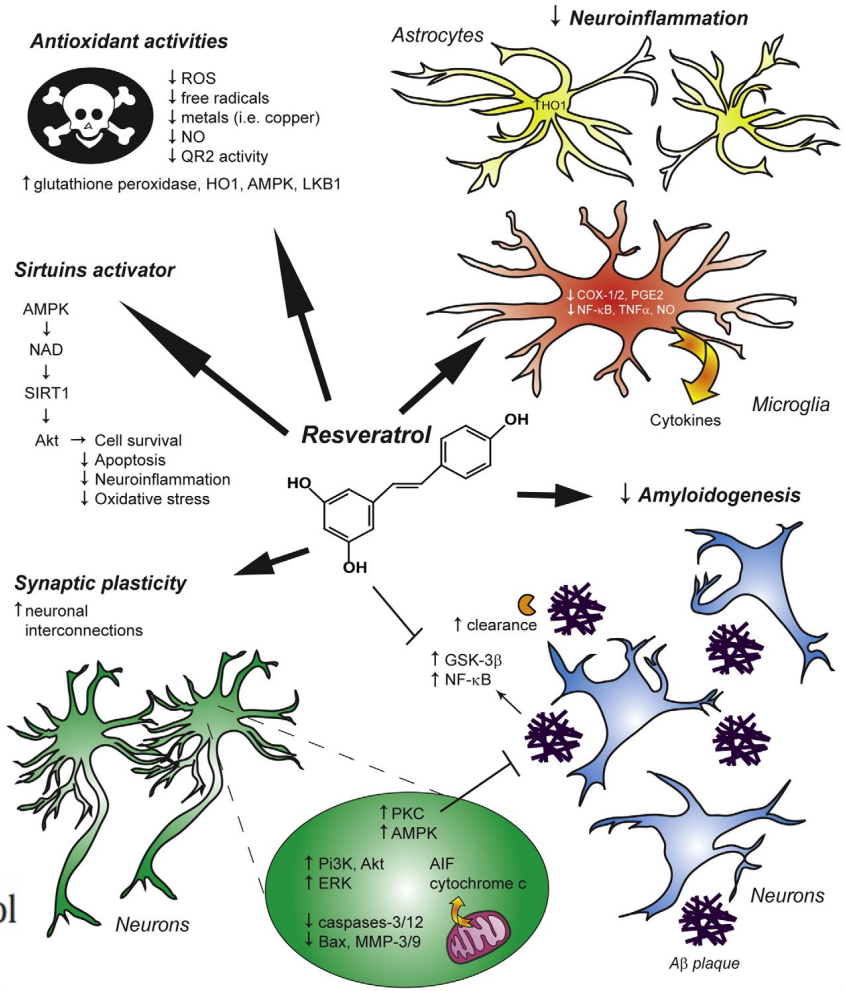
↔: unchanged; ↓: decrease; ↑: increase; *IL*: interleukin; *MDA*: malondialdehyde; *oxLDL*: oxidized low-density lipoprotein; *TAC*: total antioxidant capacity; *TNF*: tumor necrosis factor.

Advances in Protein Chemistry and Structural Biology, Volume 108



Neuroprotective action of resveratrol

Biochimica et Biophysica Acta 1852 (2015) 1195–1201



Neuroprotective action of resveratrol

Biochimica et Biophysica Acta 1852 (2015) 1195–1201

TOXICOLOGICAL SCIENCES **51,** 161–177 (1999)

FORUM

Symposium Overview: The Role of Glutathione in Neuroprotection and Neurotoxicity

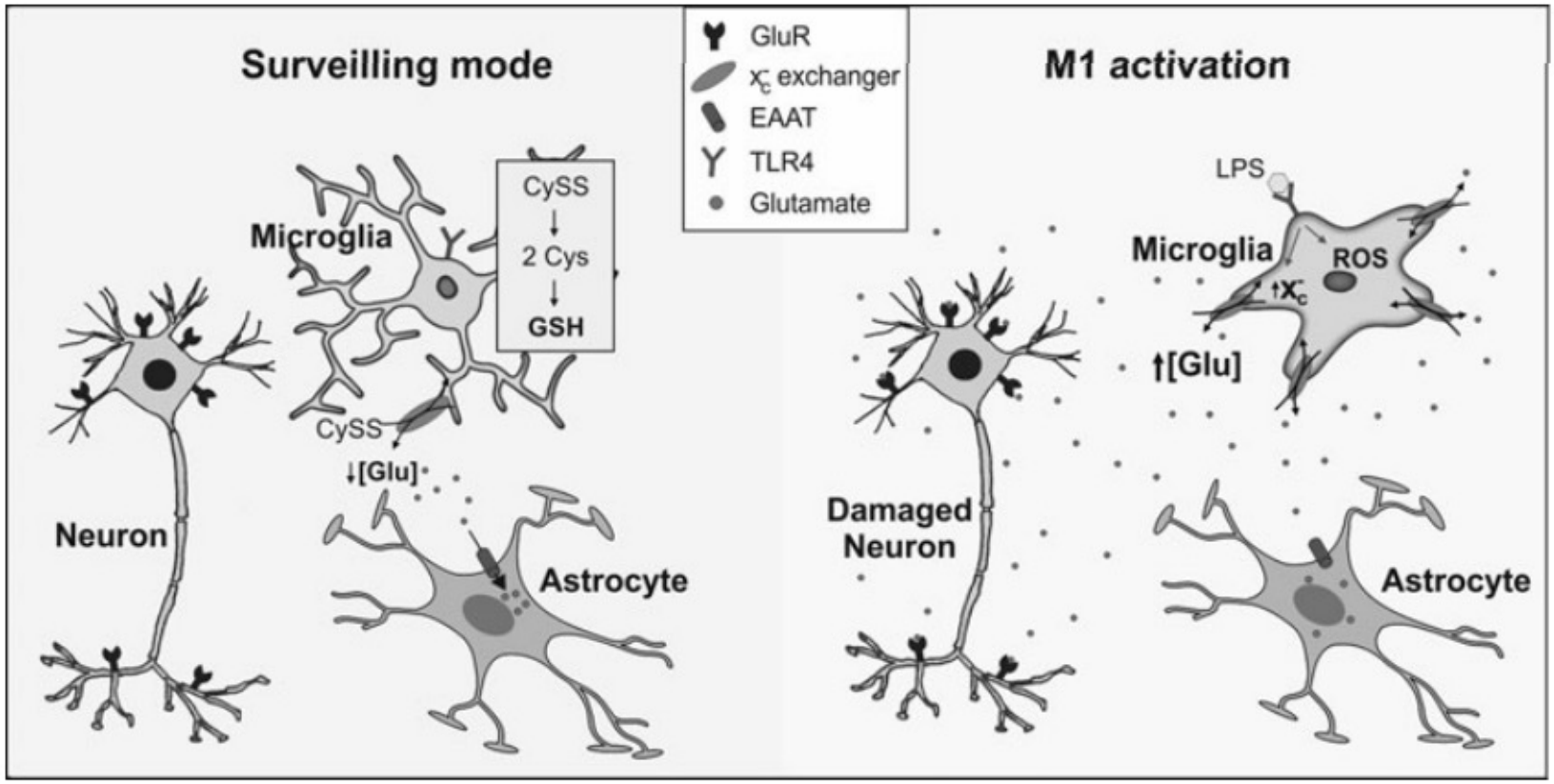
Terrence J. Monks,*[,1] Jean-François Ghersi-Egea,† Martin Philbert,‡ Arthur J. L. Cooper,§ and Edward A. Lock¶

**Division of Pharmacology and Toxicology, College of Pharmacy, University of Texas at Austin, Austin, Texas 78712–1074; †INSERM U325, Institut Pasteur de Lille, Lille, France; ‡Neurotoxicology and Experimental Neuropathology Laboratories, Toxicology Program, The University of Michigan, 1420 Washington Heights, Ann Arbor, Michigan 48109–2029; §Departments of Biochemistry and Neurology and Neuroscience, Cornell University Medical College, New York, New York, and Burke Medical Research Institute, Cornell University Medical College, White Plains, New York; and ¶Zeneca, Central Toxicology Laboratory, Alderley Park, Cheshire, England.*

Received May 28, 1998; accepted May 17, 1999

Although the cytoprotective effects of glutathione (GSH) are well established, additional roles for GSH in brain function are being identified that provide a pharmacological basis for the relationship between alterations in GSH homeostasis and the development of certain neurodegenerative processes. Thus, GSH and glutathione disulfide (GSSG) appear to play important functional roles in the central nervous system (CNS). A symposium, focussing on the emerging science of the roles of GSH in the brain, was held at the 37th annual meeting of the Society of Toxicology, with the emphasis on the role of glutathione in neuroprotection and neurotoxicity. Jean Francois Ghersi-Egea opened the symposium conjugation with GSH, and Arthur Cooper described how the pyridoxal 5′-phosphate-dependent, cysteine conjugate β-lyases might predispose the brain to chemical injury in a GSH-dependent manner. The theme of GSH as a potential mediator of chemical-induced neurotoxicity was extended by Terrence Monks, who presented evidence for a role for GSH conjugation in (±)-3,4-methylenedioxyamphetamine-mediated serotonergic neurotoxicity.

Key Words: **glutathione; cytoprotective effects; neurotprotection; serotonergic neurotoxicity.**



ANTIOXIDANTS & REDOX SIGNALING
Volume 21, Number 12, 2014

ANTIOXIDANTS & REDOX SIGNALING
Volume 21, Number 12, 2014

DOI: 10.1089/ars.2013.5745

COMPREHENSIVE INVITED REVIEW

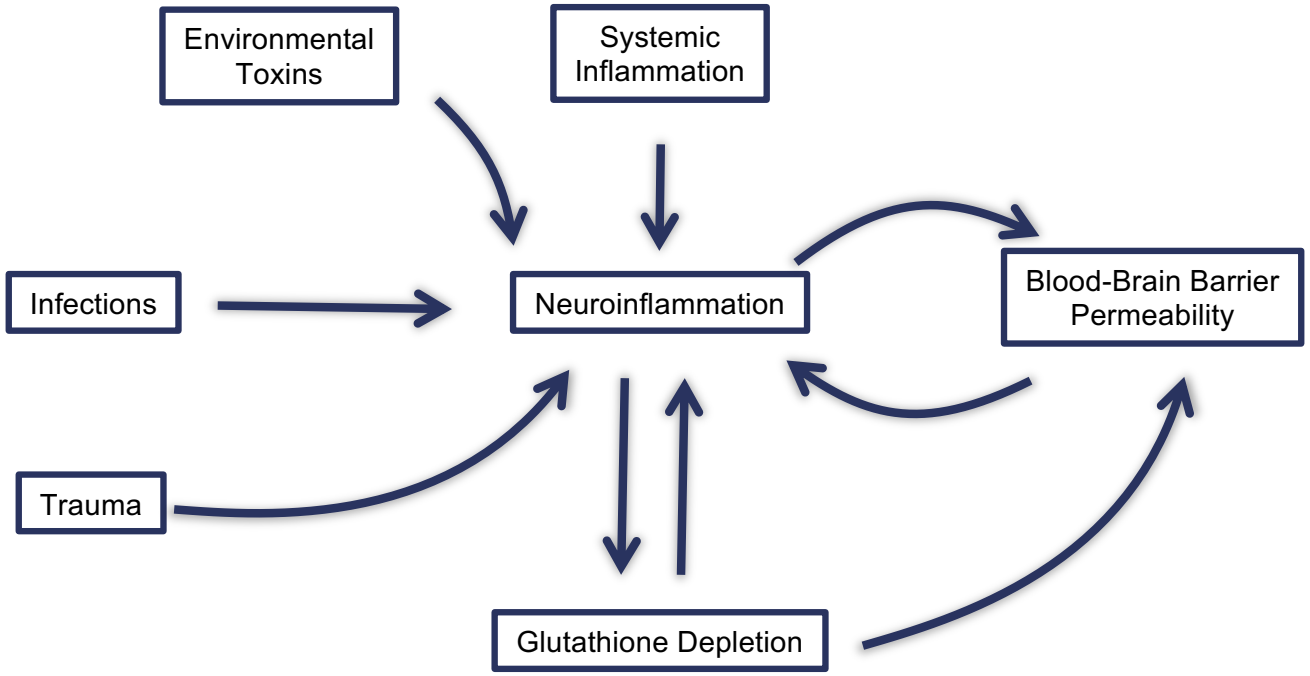
Redox Control of Microglial Function: Molecular Mechanisms and Functional Significance

Ana I. Rojo,[1] Gethin McBean,[2] Marina Cindric,[3] Javier Egea,[4] Manuela G. López,[4] Patricia Rada,[1] Neven Zarkovic,[5] and Antonio Cuadrado[6]

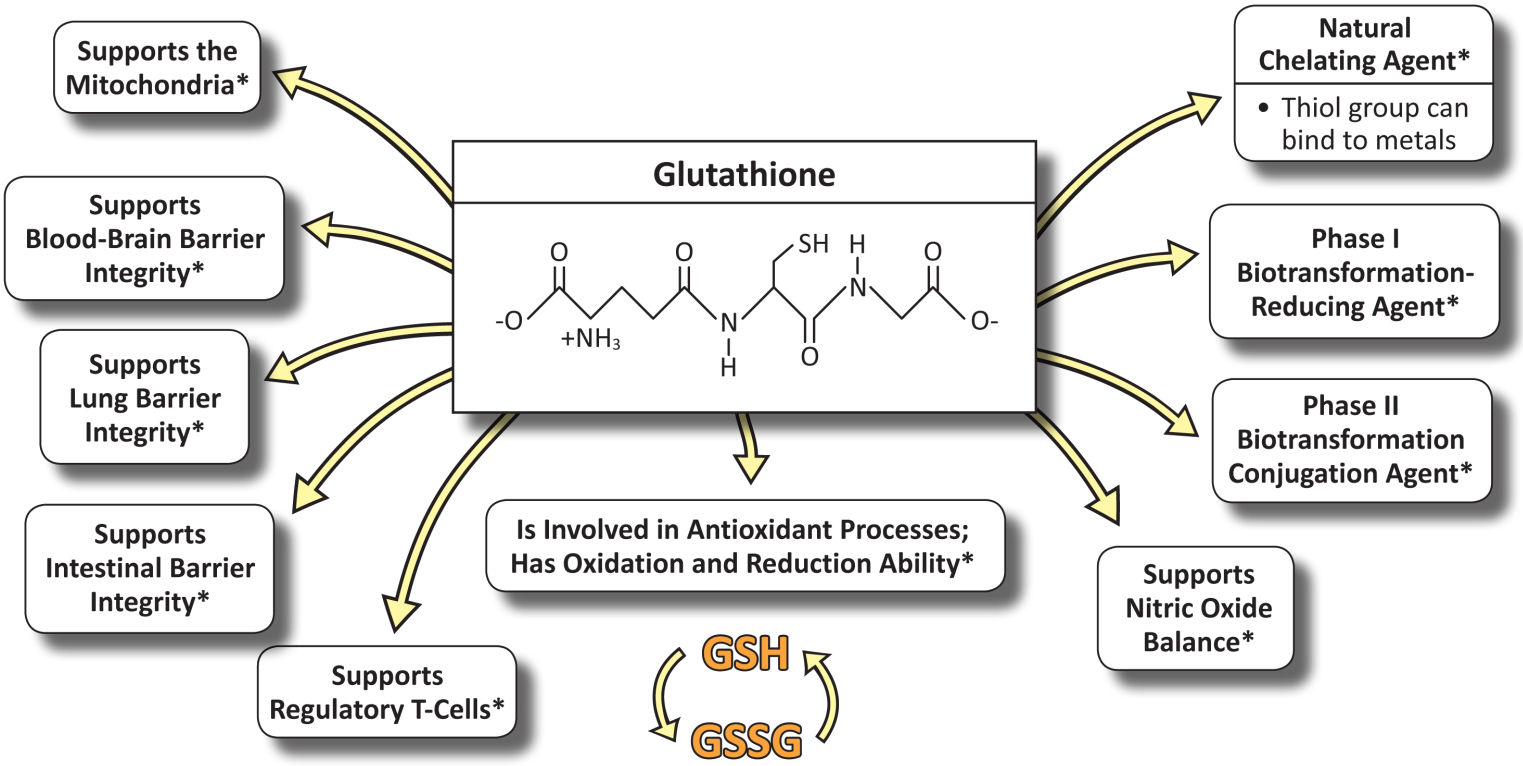
Abstract

Neurodegenerative diseases are characterized by chronic microglial over-activation and oxidative stress. It is now beginning to be recognized that reactive oxygen species (ROS) produced by either microglia or the surrounding environment not only impact neurons but also modulate microglial activity. In this review, we first analyze the hallmarks of pro-inflammatory and anti-inflammatory phenotypes of microglia and their regulation by ROS. Then, we consider the production of reactive oxygen and nitrogen species by NADPH oxidases and nitric oxide synthases and the new findings that also indicate an essential role of glutathione (γ-glutamyl-L-cysteinylglycine) in redox homeostasis of microglia. The effect of oxidant modification of macromolecules on signaling is analyzed at the level of oxidized lipid by-products and sulfhydryl modification of microglial proteins. Redox signaling has a profound impact on two transcription factors that modulate microglial fate, nuclear factor kappa-light-chain-enhancer of activated B cells, and nuclear factor (erythroid-derived 2)-like 2, master regulators of the pro-inflammatory and antioxidant responses of microglia, respectively. The relevance of these proteins in the modulation of microglial activity and the interplay between them will be evaluated. Finally, the relevance of ROS in altering blood brain barrier permeability is discussed. Recent examples of the importance of these findings in the onset or progression of neurodegenerative diseases are also discussed. This review should provide a profound insight into the role of redox homeostasis in microglial activity and help in the identification of new promising targets to control neuroinflammation through redox control of the brain. *Antioxid. Redox Signal.* 21, 1766–1801.

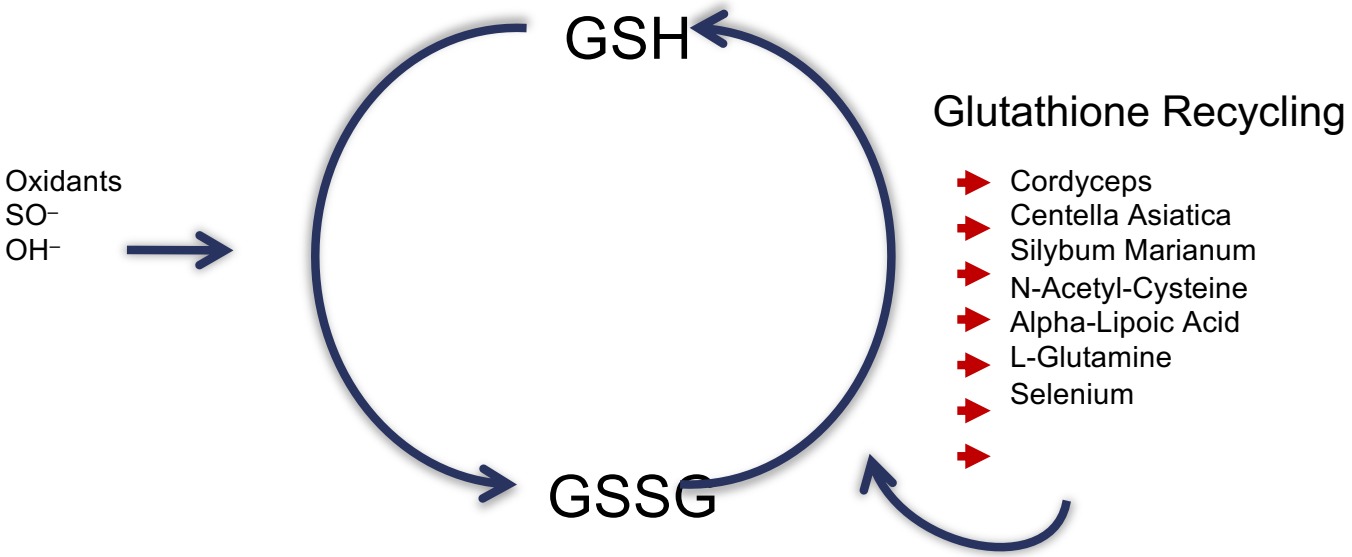
Glutathione and Neuroinflammation



The Role of Glutathione In Immune-Chemical Tolerance



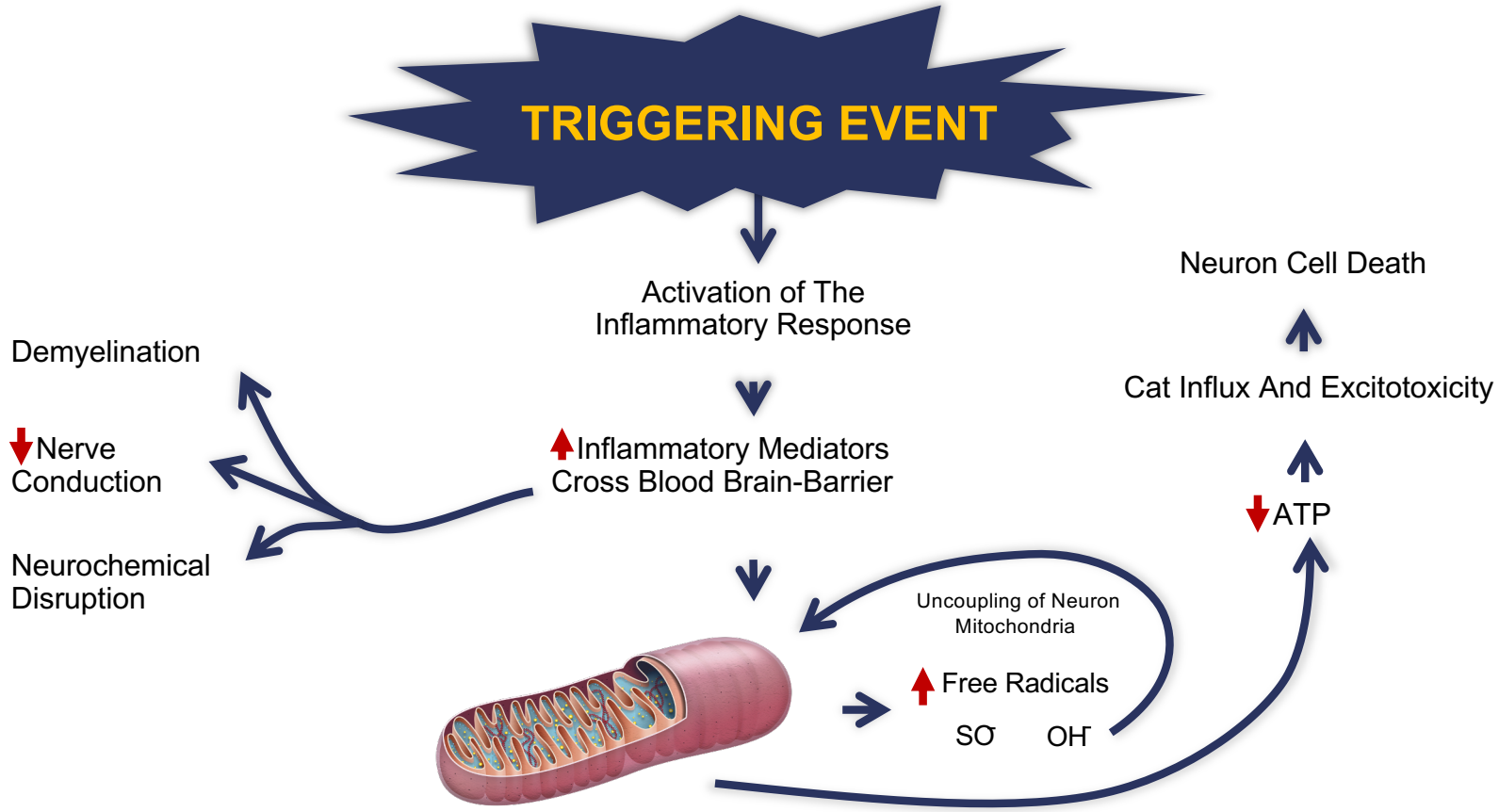
Glutathione Recycling



Ratings of Glutathione Sources

DR. HYMAN+

Summary of Nutraceutical Approaches for Neuroinflammation


TRIGGERING EVENT
Activation of The Inflammatory Response
Demyelination
Nerve Conduction
Neurochemical Disruption
Inflammatory Mediators Cross Blood Brain-Barrier
Uncoupling of Neuron Mitochondria
Free Radicals
SO
OH
ATP
Cat Influx And Excitotoxicity
Neuron Cell Death

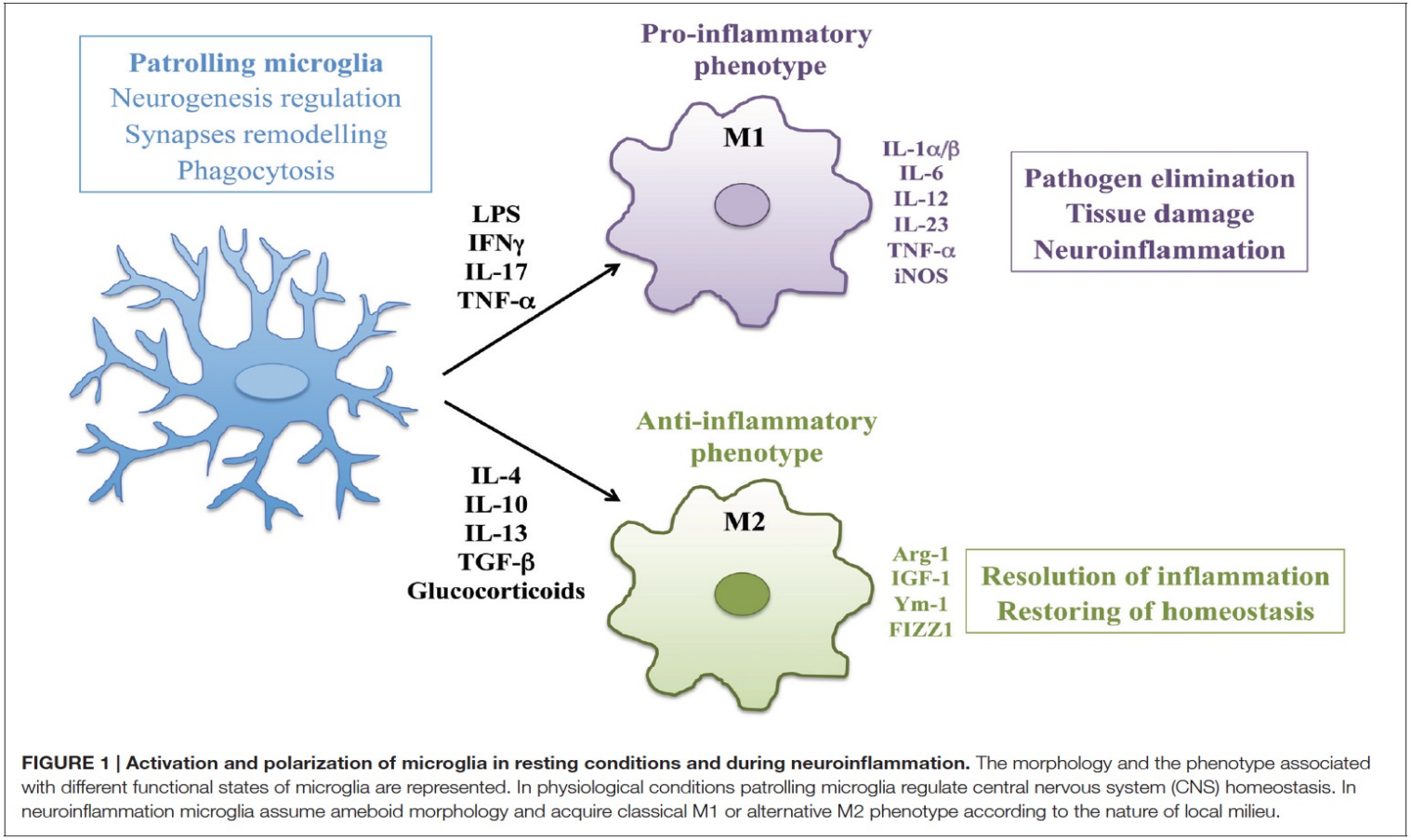
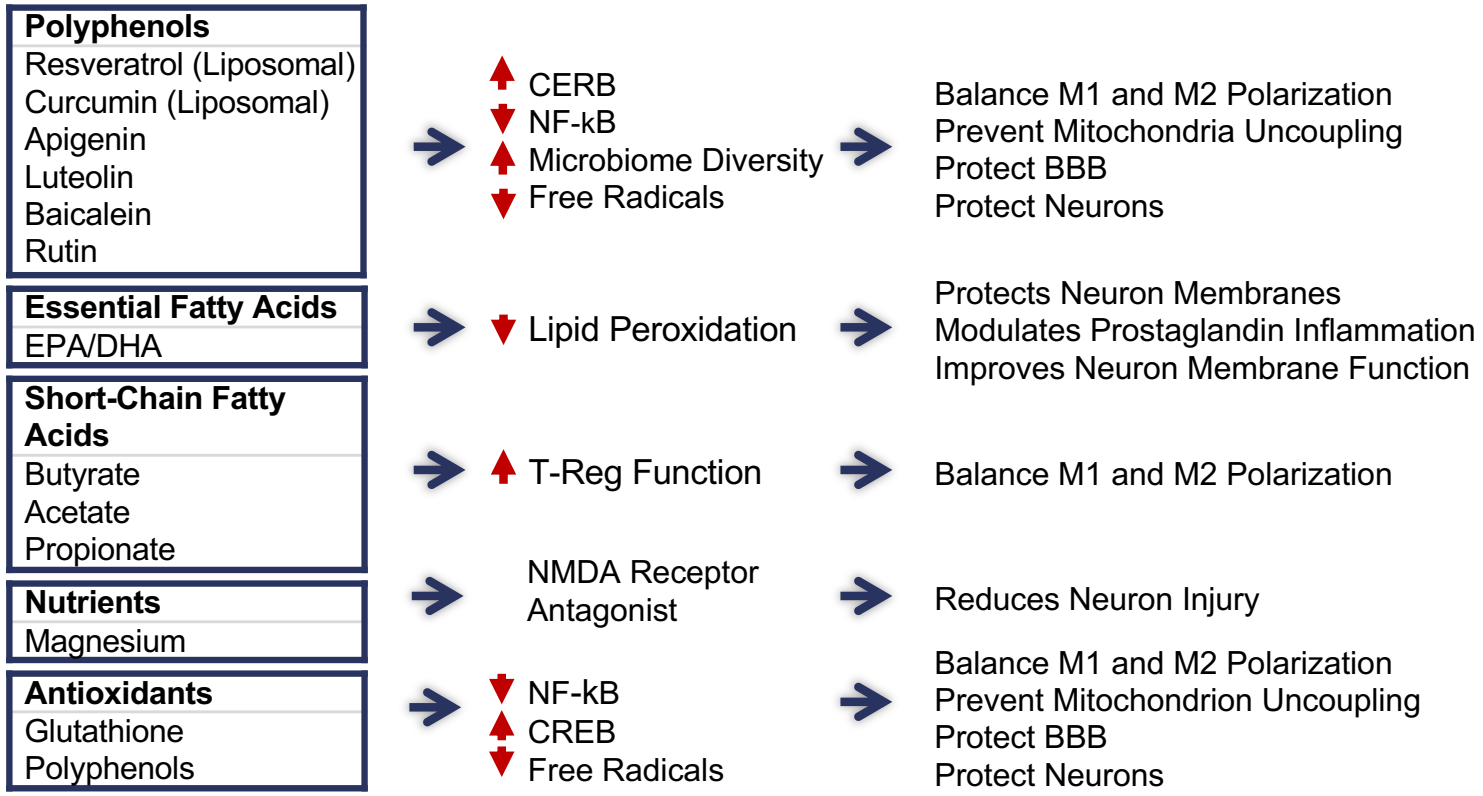


FIGURE 1 | Activation and polarization of microglia in resting conditions and during neuroinflammation. The morphology and the phenotype associated with different functional states of microglia are represented. In physiological conditions patrolling microglia regulate central nervous system (CNS) homeostasis.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

Nutraceutical Management of Neuroinflammation



Thank you for your attention.