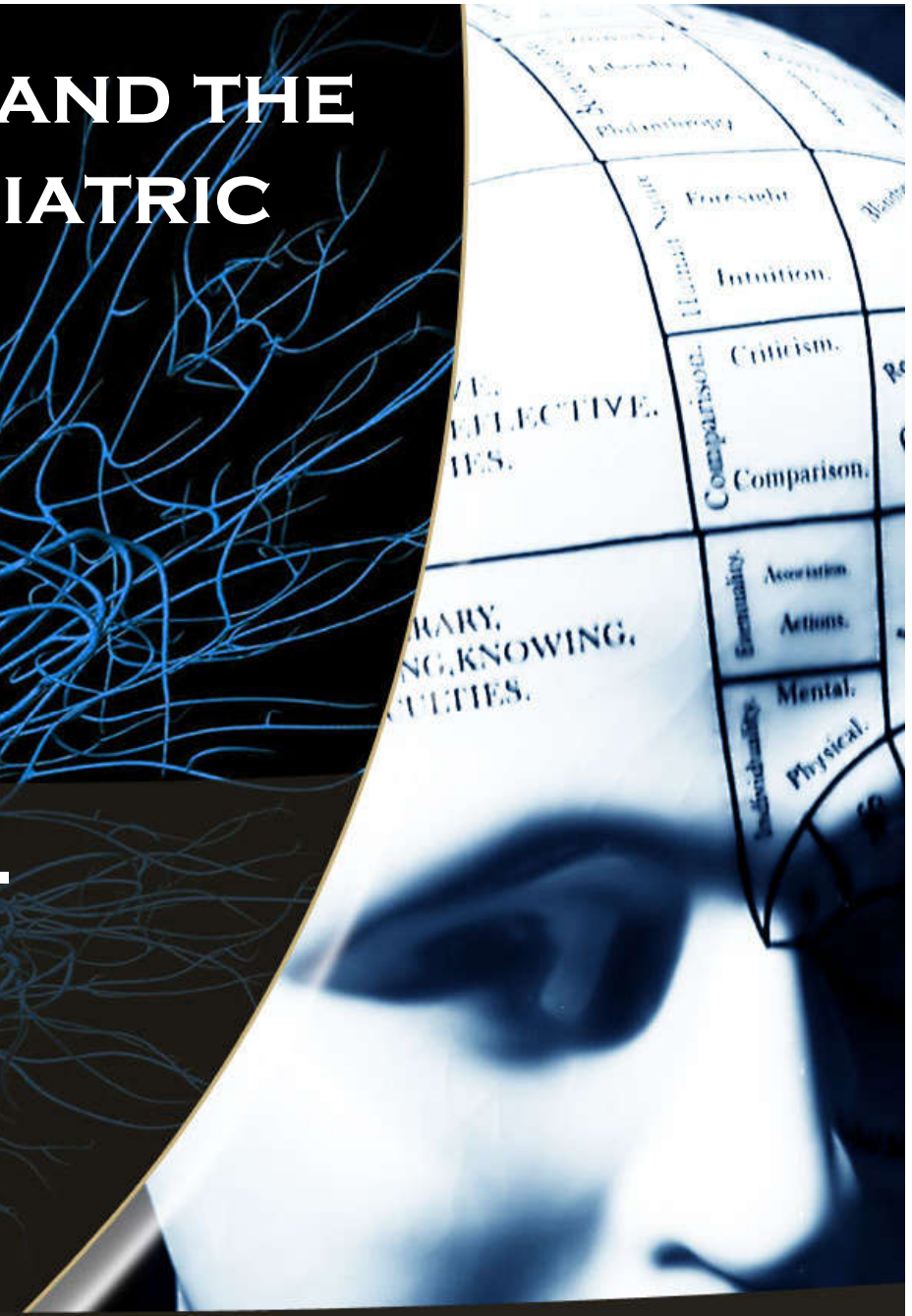
Welcome to the

American Osteopathic Society of Integrative Medicine

Neuroinflammation and the road to neuropsychiatric Illnesses.



Traumatic Brain Injury -

A Clinical Approach to Diagnosis and Treatment.

by Mark L. Gordon, MD

www.TBIHelpNow.org

Neurotrauma

- Damage to the brain includes white and gray matters and their cellular constituents, and an extensive vascular supply network.
- Ischemia causing hypoxia increases Oxidative Stress initiating inflammation and further neuronal and glial death.
- Cavitation of the brain with the loss of brain tissue, is a progressive mechanism led by all aspects of **Oxidative Stress = Neuroinflammation.**

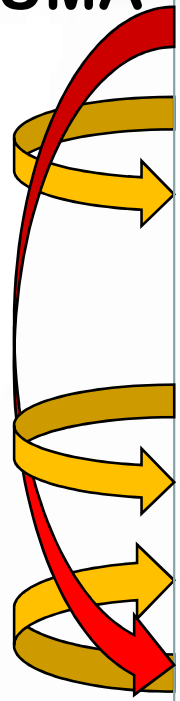
The Impact of Trauma[1]

- **TRAUMA**

Hematoma (SDH-SAH)
Parenchymal Hemorrhage
Ischemia
Hypoxia
Hypoglycemia
Elevation in Cortisol/CRH
Progressive Cerebral Edema
Elevated ICP
Impaired Glymphatic System
Accumulation of toxic metabolites
Oxidative Stress begins.

The Impact of Trauma[2]

- TRAUMA



Loss of Fractalkine (M0 to M1)

Mitochondrial Dysfunction (ATP)

Loss of Membrane Potential (Ion Pump)

Increase in ROS/RNS (Oxidative Load)

Lipid Peroxidation (TL4r)

Activation of NFkB pathway ***

Elevation in Inflammatory Cytokines

Activated Microglia (M1)

Apoptosis

Disruption of Molecular Chemistry

The Impact of Trauma[3]

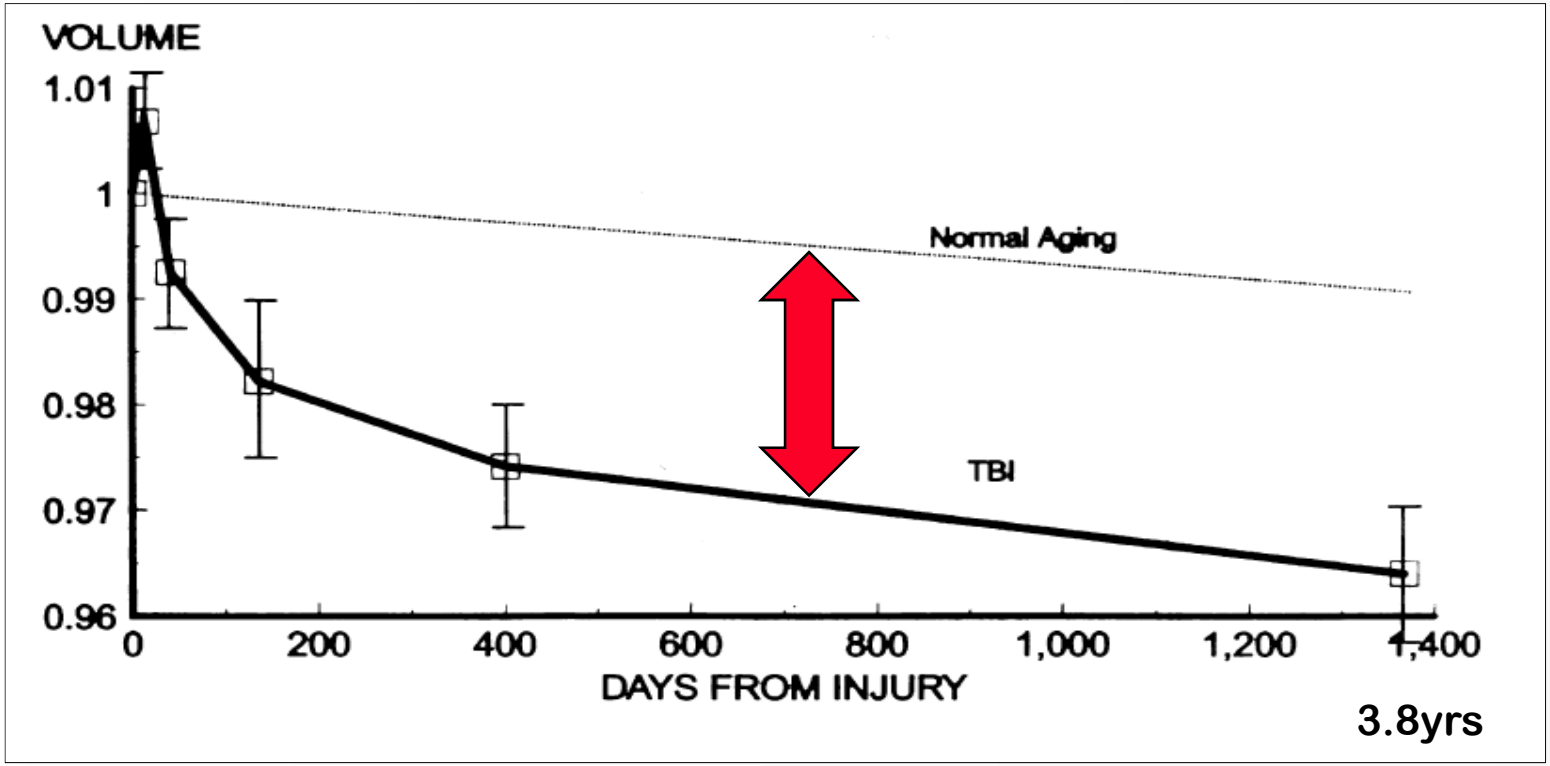
- **TRAUMA**

Neurosteroids Impacted
Neuroactive Steroids Impacted
Loss of Neuro-Permissive Environment
Cognitive Impairment
Neuropsychiatric Pathology
Gliosis
Astrogliosis
Cerebral Atrophy

The lesion(s) in traumatic brain injury: implications for clinical neuropsychology.

Archives of Clinical Neuropsychology 16 (**2001**) 95-131. Erin D. Bigler
Departments of Psychology and Neuroscience, Brigham Young University, 1001 SWKT, Provo, UT 84602, USA

- During the normal aging process there is a progressive loss of brain volume, but after a TBI, there is a greater loss of brain volume due to neuroinflammatory **atrophy**.



Neuroinflammation

"Acute neuroinflammation protects the brain, while chronic neuroinflammation destroys it."

Millennium

Neuroinflammation

1. Neuro**trauma** induces Neuro**inflammation***.
2. Neuroinflammation alters neurochemical pathways leading to insufficiencies of neurosteroids, neurotransmitters, enzymes, cytokines, and regulation of bodily functions
3. Prolonged loss of healthy neurochemistry, gives rise to neuropsychiatric and neurocognitive dysfunction culminating in Neurodegenerative illnesses = AD, PD, MS, ALS.

* **Aging** is a form of neurotrauma.

Inflammation after Trauma: Microglial Activation and Traumatic Brain Injury.

Ann Neurology 2011;. Anil F. Ramlackhansingh, MRCP, David J.Brooks, MD,DSc, Richard J. Greenwood, FRCP, MD, **David J. Sharp**, MRCP, PhD. Et al Centre for Neuroscience, Dept of Medicine, **Imperial College London**, London, UK; Institute of Neurology, UC London, MRC Clinical Sciences Centre, Imperial College London, UK; Goldsmiths, University of London, London, UK; and Neurodisease Foundation , CERMEP Imagerie du Vivant, Lyon, France

- TBI triggers a chronic inflammatory response particularly in **subcortical regions** (pituitary gland, **limbic system**, and basal ganglia.)
- This highlights the importance of considering the response to TBI as evolving over **time** and suggests intervention may be beneficial for longer intervals.
- Increased microglial activation (IL-6/TNFa) has been found present up to 17 years after TBI.

Inflammation after Trauma: Microglial Activation and Traumatic Brain Injury.

Ann Neurology 2011;. Anil F. Ramlackhansingh, MRCP, David J.Brooks, MD,DSc, Richard J. Greenwood, FRCP, MD, **David J. Sharp**, MRCP, PhD. Et al Centre for Neuroscience, Dept of Medicine, **Imperial College London**, London, UK; Institute of Neurology, UC London, MRC Clinical Sciences Centre, Imperial College London, UK; Goldsmiths, University of London, London, UK; and Neurodisease Foundation , CERMEP Imagerie du Vivant, Lyon, France

Areas Most Affected by Inflammation:

- **Diencephalon**: relaying sensory and motor signals to the cerebral cortex and regulating consciousness, sleep, and alertness.
- **Basal Ganglia**: involved in the integration and selection of voluntary behavior.
- **Limbic Structures**: involved in our behavioral and emotional responses for survival.
- **Pituitary Gland**: releases 8 tropic hormones to regulate our hormonal homeostasis.

Current understanding of Neuroinflammation after traumatic brain injury and cell-based therapeutic opportunities

Michael Chopp, et al. Dept of Neurosurgery Henry Ford Health System. Dept of Neurology, Henry Ford Health System, Detroit, MI, 48202, USA. Dept of Physics, Oakland University, Rochester, MI, USA. 2018

- **Secondary injury** is sustained through a complex cascade of events including **ischemic** and **hypoxic damage**, cerebral edema, raised intracranial pressure, hydrocephalus, and infection;
- all are induced by multifactorial events including **excitotoxicity**, inflammation, **mitochondrial dysfunction**, increased **free radicals**, **lipid peroxidation**, apoptosis, and **diffuse axonal injury**.

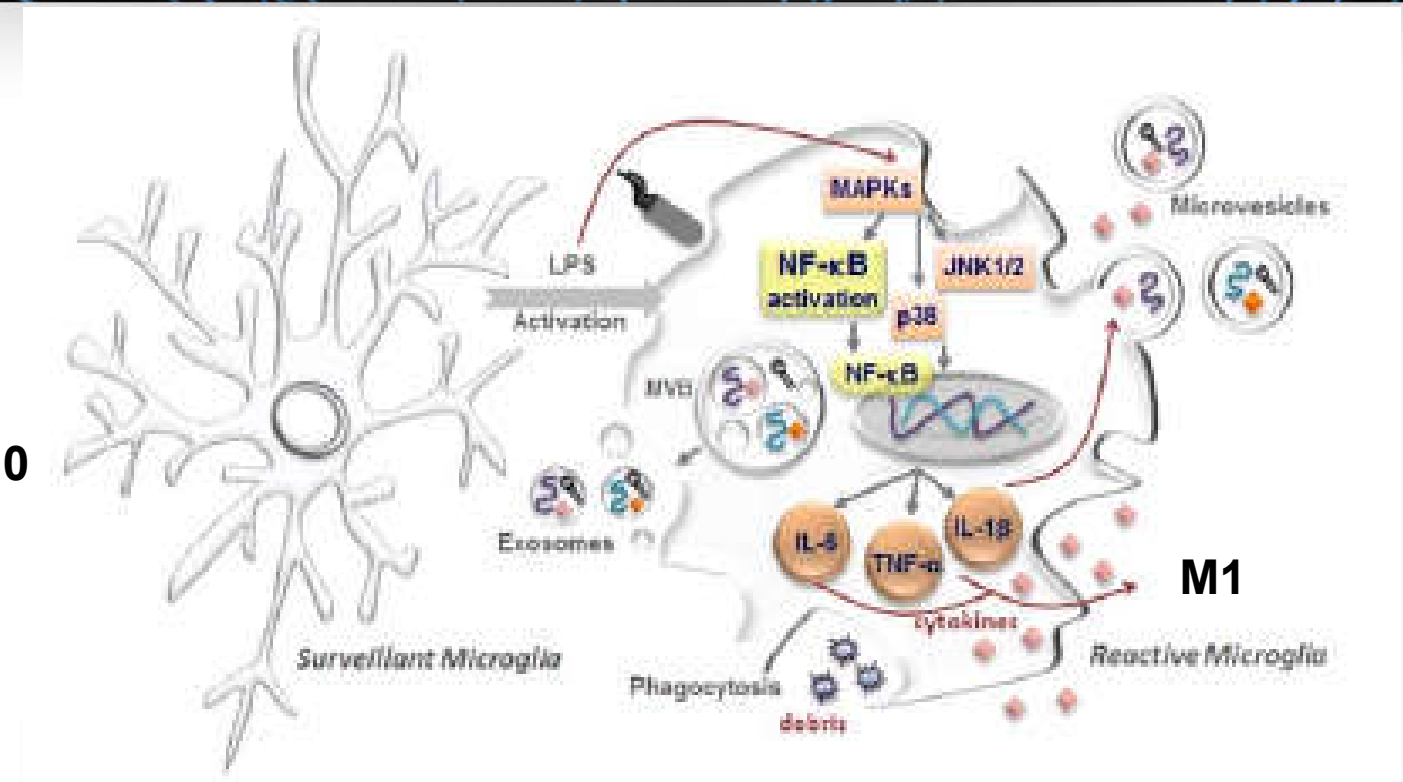
Current understanding of Neuroinflammation after traumatic brain injury and cell-based therapeutic opportunities

Michael Chopp, et al. Dept of Neurosurgery Henry Ford Health System. Dept of Neurology, Henry Ford Health System, Detroit, MI, 48202, USA. Dept of Physics, Oakland University, Rochester, MI, USA. **2018**

- Proinflammatory cytokines are produced mainly by **microglia**, with some by **astrocytes**, **neurons** and **endothelial cells**, which in turn **activate glial cells**, inducing further cytokine production.
- Preclinical studies indicate that chronic post-TBI Neuroinflammation is associated with neurodegeneration which **may be treatable long after the initiating brain injury.**

Neuroinflammation and Depression: Microglia activation, extracellular microvesicles and microRNA dysregulation.

Frontiers in Cellular Neuroscience. December 2015 | Volume 9 | Article 476. Dora Brites1 and Adelaide Fernandes Research Institute for Medicines, Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal, Dept of Biochemistry and Human Biology, Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portuga

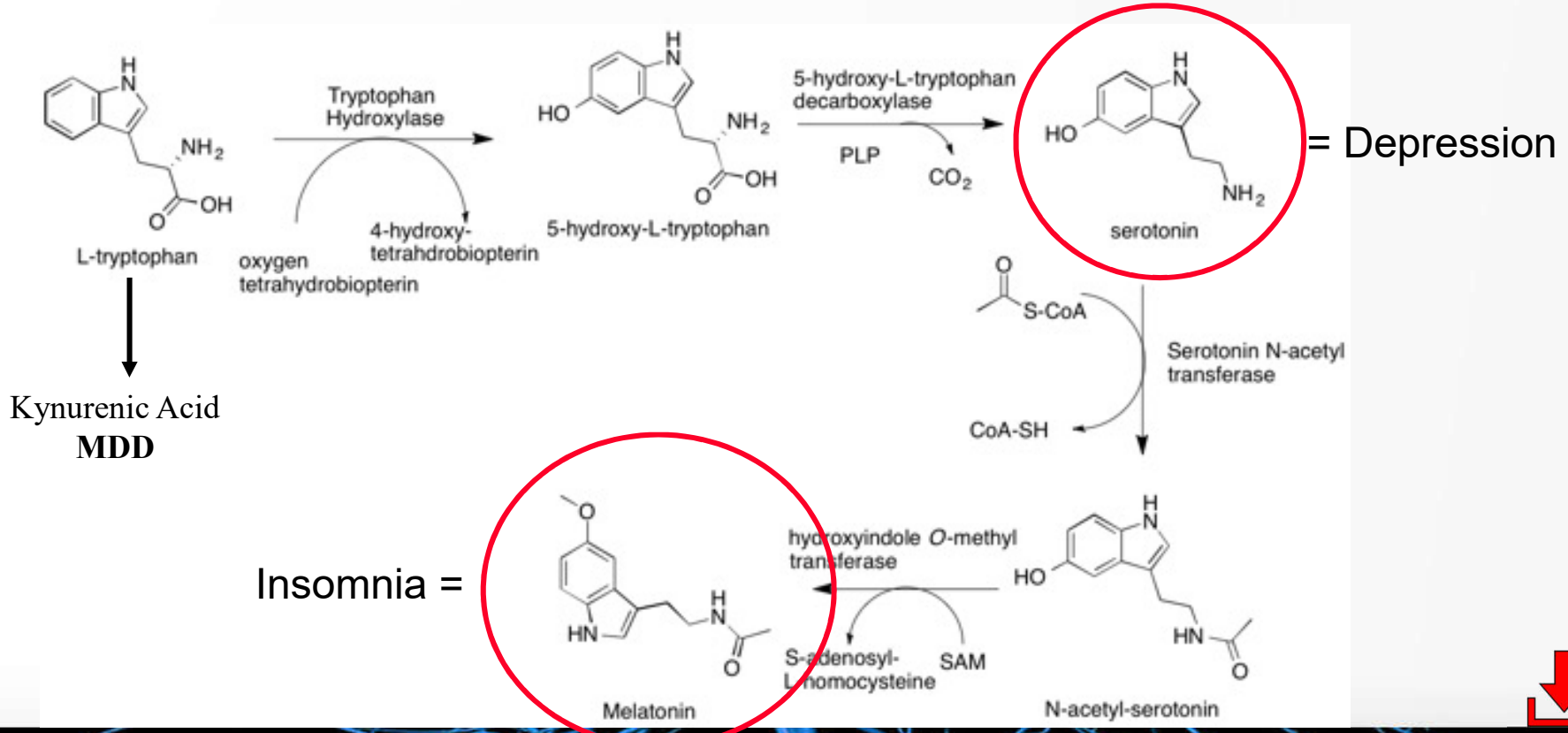


Characteristic pathophysiological hallmark features include **monoamine depletion**, down-regulation of neurotrophin signaling, and glucocorticoid receptor resistance, as well as excess of glutamate, corticotrophin-neurotrophin signaling, and cortisol levels.

Peroxynitrite Inactivates Tryptophan Hydroxylase via Sulfhydryl Oxidation.

The Journal of Biological Chemistry. Vol. 274, No. 42, Issue of October 15, pp. 29726–29732, **1999**

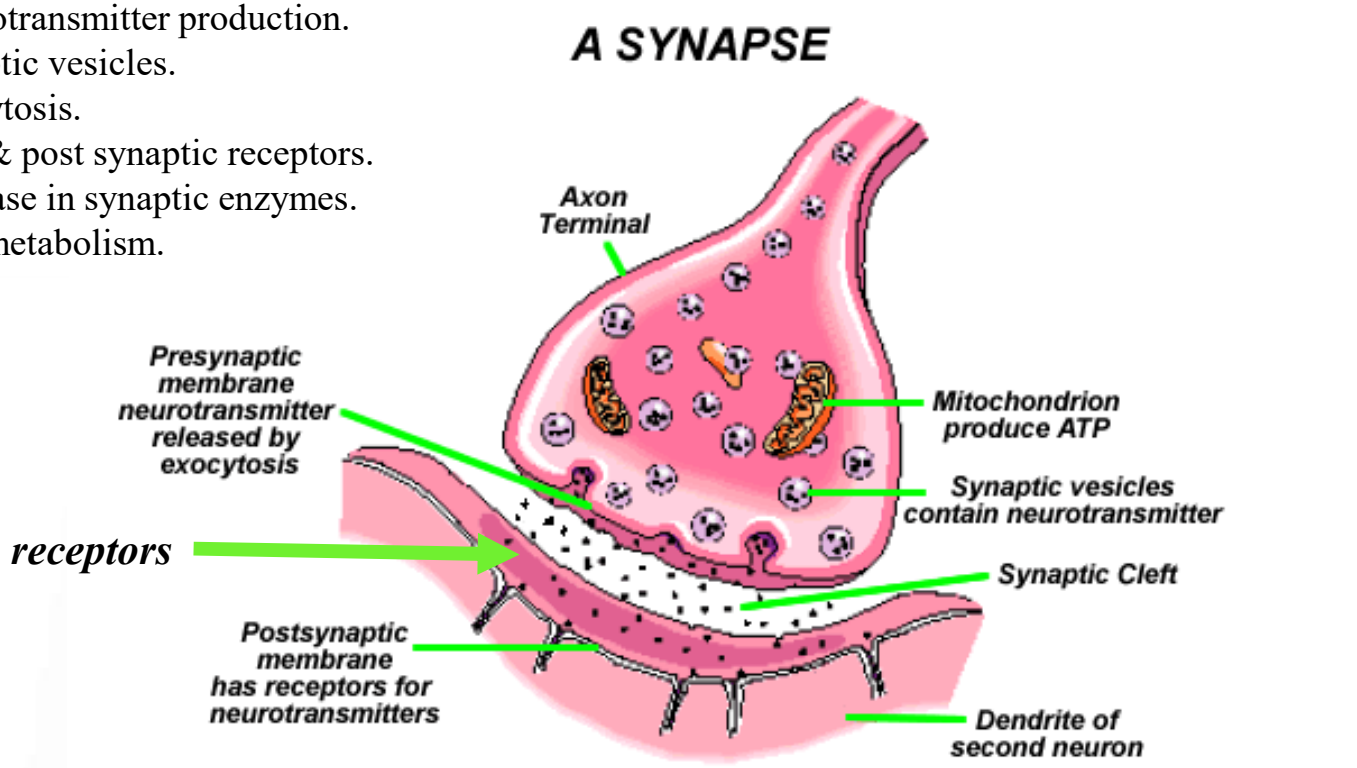
- Tryptophan hydroxylase, the rate-limiting enzyme in **serotonin biosynthesis**, is inactivated by **peroxynitrite** in a concentration-dependent manner.



Key Concept

Altered Synapses

Loss of Neurotransmitter production.
Loss of synaptic vesicles.
Loss of exocytosis.
Loss of pre- & post synaptic receptors.
Loss or increase in synaptic enzymes.
Accelerated metabolism.

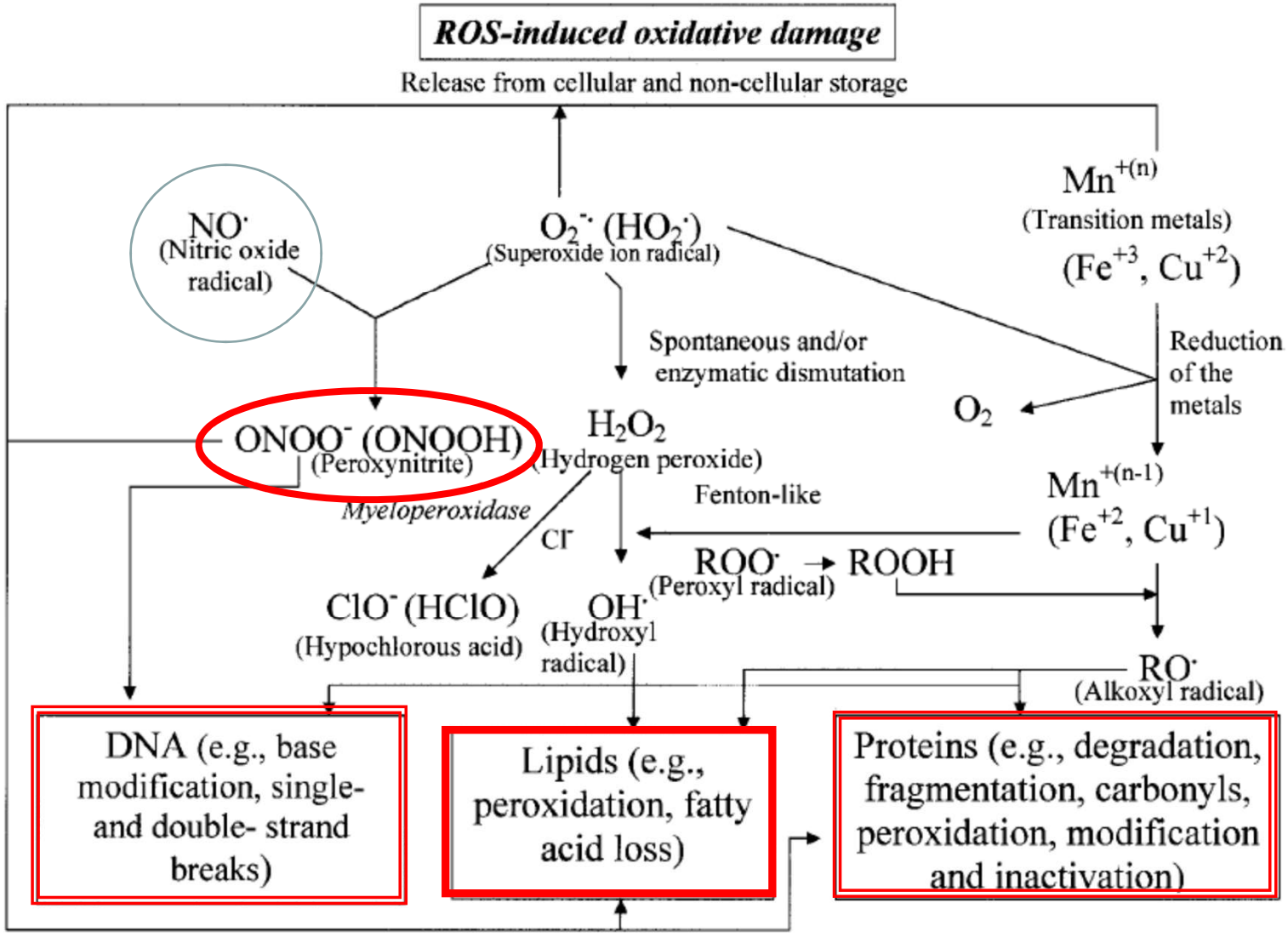


Cytokines, ROS, Peroxynitrite, and other oxidative products alter the functionality of the pre- and post synaptic processes required for signal propagation.

A Five-Year Prospective Investigation of Anterior Pituitary Function after Traumatic Brain Injury: Is Hypopituitarism Long-Term after Head Trauma Associated with Autoimmunity? JOURNAL OF NEUROTRAUMA 30:1426–1433. **2013**.

- The first prospective study from a single center evaluating anterior pituitary function at **one, three, and five years after TBI.**
- Findings show a significant association between strong **Anti-Hypothalamic** and **Anti-Pituitary** antibodies and the development of **Hypopituitarism**.

Reactive Oxygen Species



Reactive Oxygen Species in the Regulation of Synaptic Plasticity and Memory.

ANTIOXIDANTS & REDOX SIGNALING Volume 14, Number 10, . 2011 . Cynthia A. Massaad1 and Eric Klann. Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, Texas.
2Center for Neural Science, New York University, New York, New York.

- ROS are **neurotoxic molecules** and exert their effects via oxidation of essential macromolecules such as enzymes and cytoskeletal proteins.
- However, **at physiological concentrations**, ROS are involved in functional changes necessary for synaptic plasticity and hence, for normal cognitive functions.

Oxidative Stress in Closed-Head Injury: Brain Antioxidant Capacity as an Indicator of Functional Outcome.

J Cereb Blood Flow Metab. Vol. 17. No. 10, 1997. Esther Shohami, Elie Beit-Yannai, Michal Horowitz, and Ron Kohen Dept of Pharmacology, Pharmaceutics, and Physiology, The Hebrew University, Schools of Pharmacy and Medicine, Jerusalem, Israel

- Blunt head trauma leads to a common pathway of neuronal death involving loss of **cellular calcium homeostasis**, **production of free radicals**, and **tissue acidosis.**
- "**ROS** plays a key role in the pathophysiology of brain injury, and **their neutralization by Endogenous or Exogenous anti-oxidants has a significant protective effect.**"

Endogenous: Glutathione/SOD
Exogenous : Vit C, Vit E, PQQ, OM3, Quercetin, Curcumin, Zn.

Oxidative Stress and Proinflammatory Cytokines Contribute to Demyelination and Axonal Damage in a Cerebellar Culture Model of Neuroinflammation

PLOS ONE. 2013. Vol. 8. No. 2. Alessandra di Penta1 et. Al., Center of Neuroimmunology, Institute of Biomedical Research August Pi Sunyer – Hospital Clinic of Barcelona.

- Axonal damage is a critical process in the pathogenesis of several chronic brain diseases, including neurodegenerative diseases:

I. Alzheimer's disease

II. Parkinson's diseases

III. Amyotrophic lateral sclerosis (ALS)*

IV. Multiple Sclerosis

V. Stroke and CTE

VI. Exasperation of Brain Trauma. (▲ Stress)

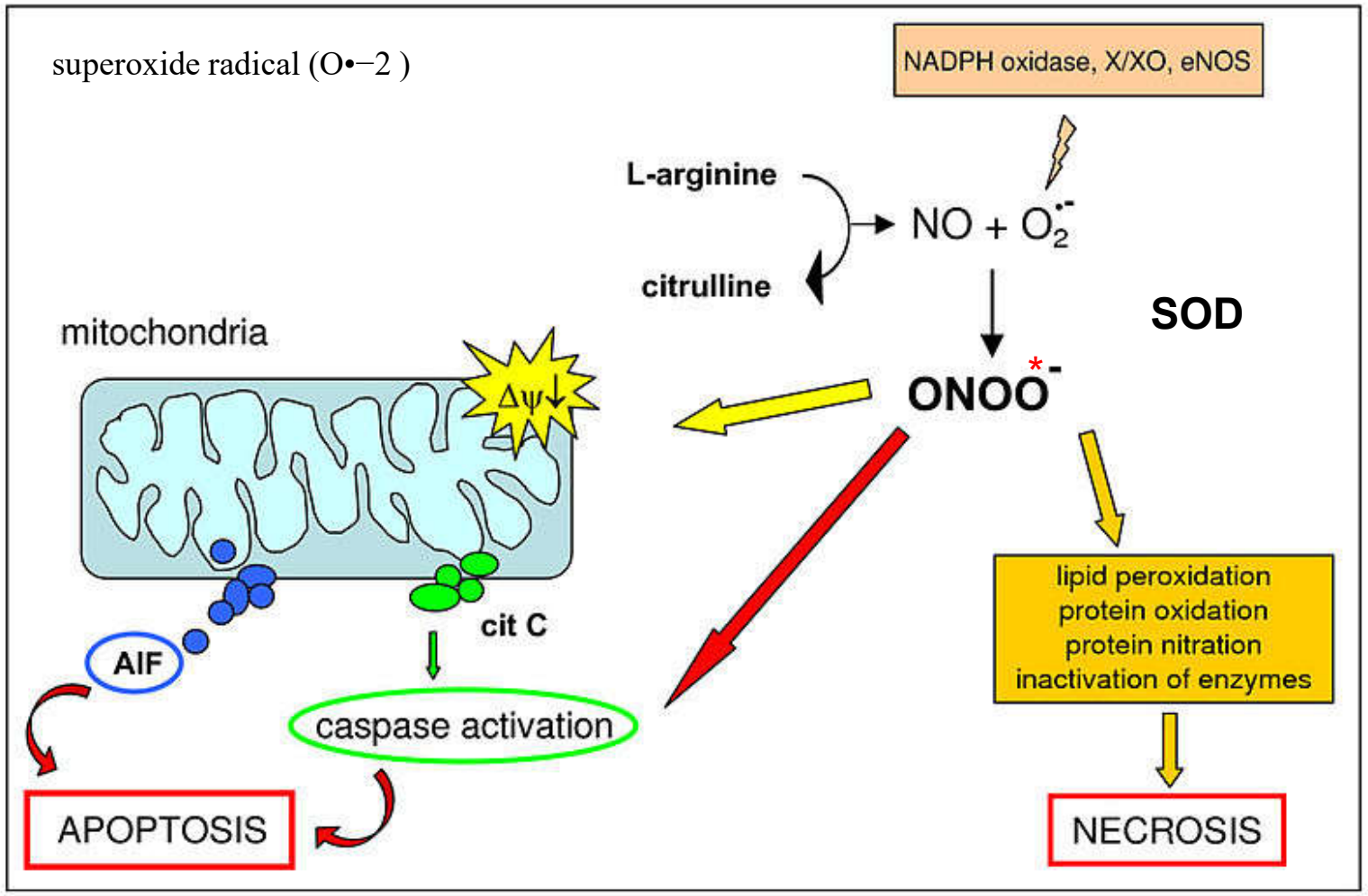
Strategies for Reducing or Preventing the Generation of Oxidative Stress

Oxidative Medicine and Cellular Longevity. **2011**, ID 194586, Poljsak Laboratory for Oxidative Stress Research, Faculty of Health Sciences, University of Ljubljana, Zdravstvena Pot 5, 1000 Ljubljana, Slovenia

- The reduction of Oxidative Stress could be achieved by implementation of strategies at three levels:

1. **Lowering exposure to environmental pollutants that have** oxidizing properties. **(Burn Pits)**
2. **Increasing the levels of endogenous and exogenous antioxidants** with the use of supplementation.
3. **Stabilizing and enhancing Mitochondrial energy production and efficiency (**with PQQ, CoQ10, NO, and Quercetin).

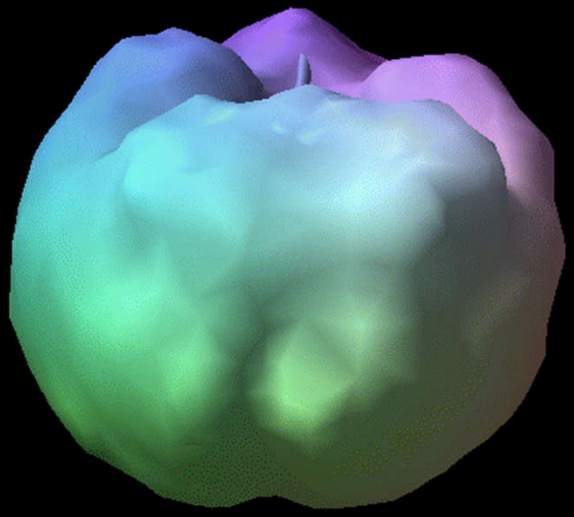
Peroxynitrite (PN)



* Blocked by Glutathione, NAC, Quercetin, Melatonin, and Mn/Fe.

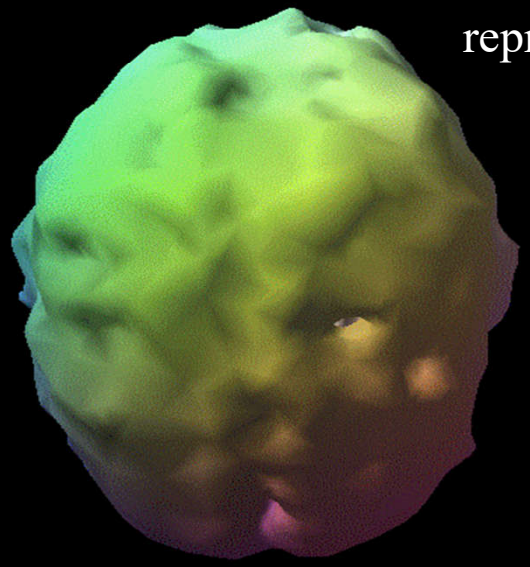
TBI SPECT Scan

^{99m}Tc is taken up by brain tissue proportionate to brain blood flow, allowing blood flow to be assessed with the nuclear gamma camera.



Normal

Punched out areas represent ischemia.



Abnormal

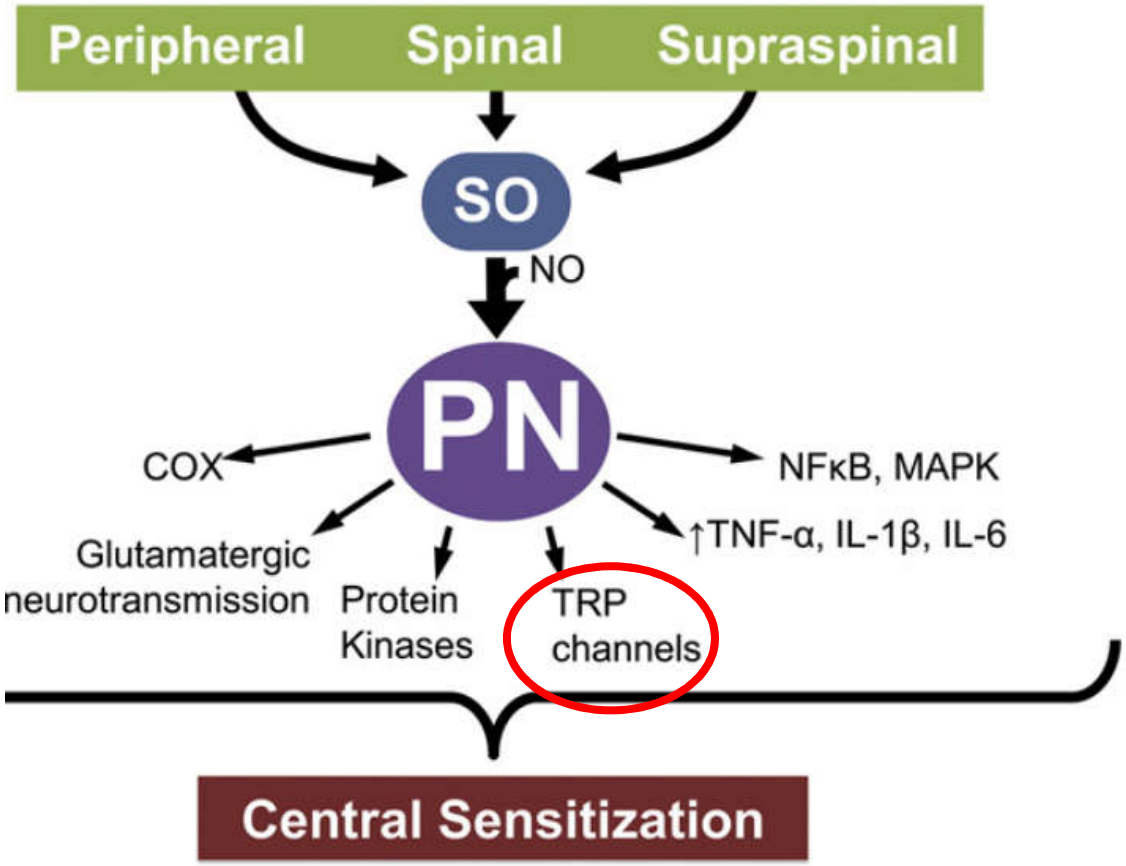
Nitric Oxide and Peroxynitrite in Health and Disease

Physiol Rev 87: 315–424, 2007 P´ L Pacher, et al. Section on Oxidative Stress Tissue Injury, Laboratory of Physiologic Studies, National Institutes of Health, National Institute of Alcohol Abuse and Alcoholism, Bethesda, Maryland; Linus Pauling Institute, Dept of Biochemistry and Biophysics, Oregon State University, Corvallis, Oregon; and Dept of Intensive Care Medicine, University Hospital, Lausanne,

- Peroxynitrite contributes to the loss of intracellular glutathione from **Substantia Nigra** by **inactivating Glutathione Reductase**, the enzyme required to regenerates glutathione.
- Additionally, ***Peroxynitrite*** induces apoptosis in dopaminergic neurons furthering the development of **Parkinson's Disease**.

Anti-superoxide and anti-peroxynitrite strategies in pain suppression.

Biophysica Acta 1822 (2012) 815–821 Kali Janes, William L. Neumann, Daniela Salvemini.



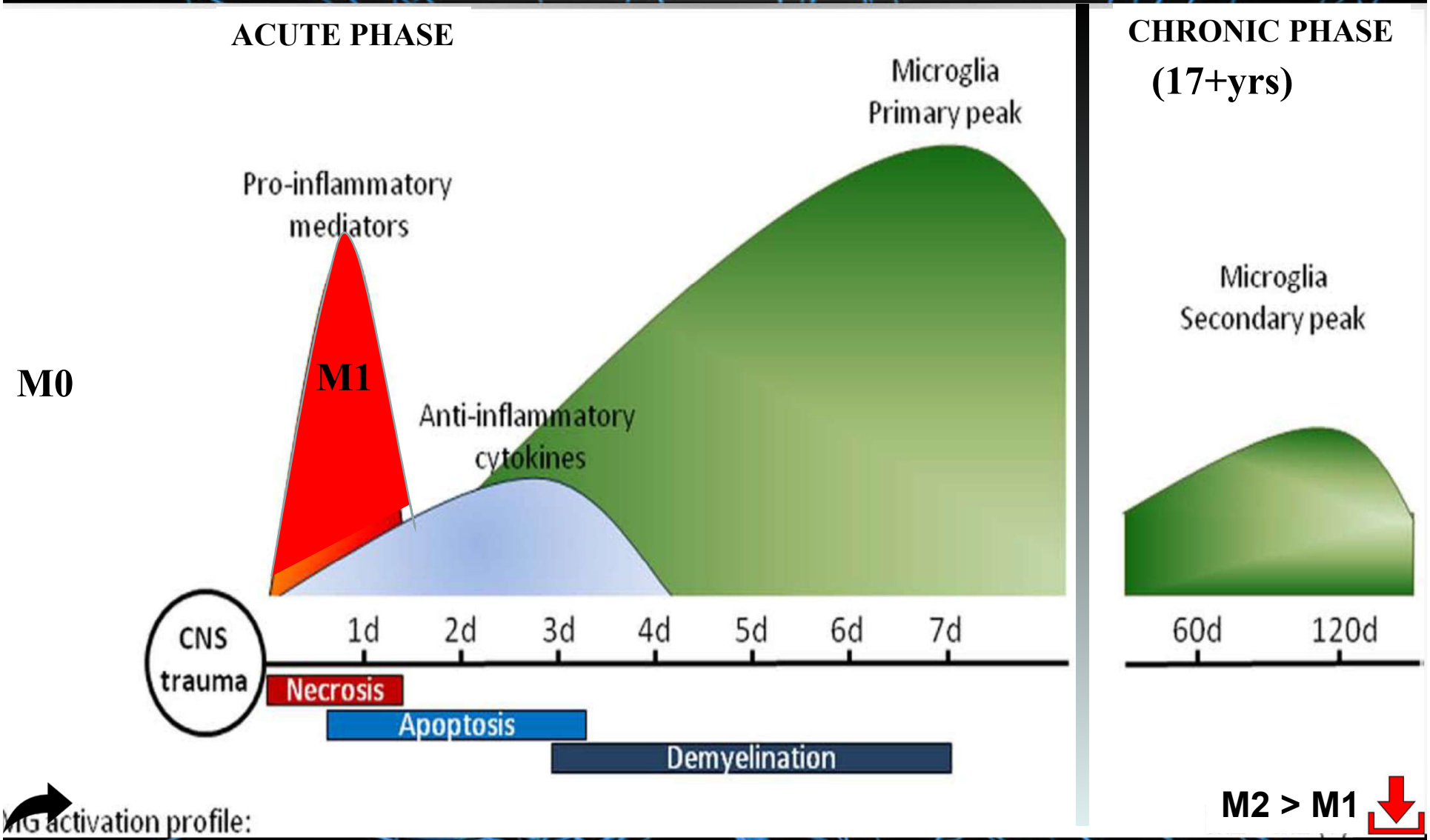
Hyperalgesia

- Peroxynitrite (**PN**) alters the **TRP** channels increasing pain perception.
- **SO** = Super Oxide radical.
- **NO** = Nitric Oxide

Role of Microglia in Neurotrauma.

Neurotherapeutics. Vol. 7, 366–377, October **2010**,

David J. **Loane*** and Kimberly R. **Byrnes** Dept of Anesthesiology & Center for Shock, Trauma and Anesthesiology Research (STAR), National Study Center for Trauma and EMS, and Dept of Anatomy, Physiology and Genetics, Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814



activation profile:

Fractalkine receptor deficiency impairs microglial and neuronal responsiveness to chronic stress.

Brain Behav. Immun. (2015). Giampaolo Milior, et al. Dept of Physiology and Pharmacology, Istituto Pasteur-Fondazione Cenci Bolognetti, Sapienza University of Rome, Axe Neurosciences, Québec, Canada. Section of Behavioural Neurosciences, Dept of Cell Biology and Neurosciences, Rome, Italy.

- **Fractalkine** is a chemokine produced by **neurons** to keep Microglia in the M0 surveillance state.
- Exposure Mental and Physical stress represents the **most powerful triggers of depressive episodes** and challenges Fractalkine production due to Cortisol.
- This vulnerability differs between individuals; serious life-threatening stress may not affect some individuals, but milder stress can trigger depression in others.

Control of microglial neurotoxicity by the Fractalkine Receptor.

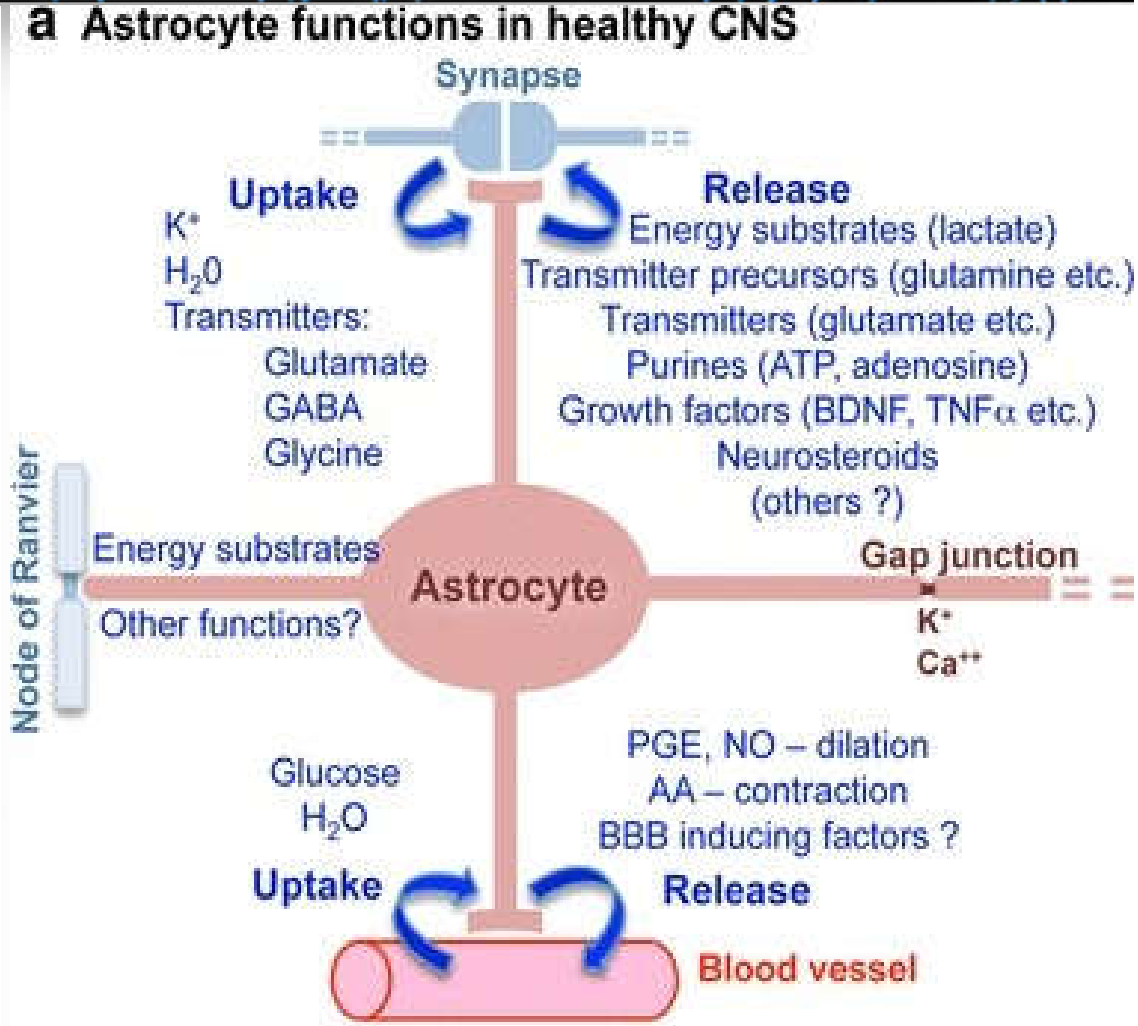
NATURE NEUROSCIENCE. VOL. 9, No. 7. 2006. Astrid E Cardona, et al.,

- Microglia, express the Fractalkine **receptor - CX3CR1**.
- The **Fractalkine ligand**, **CX3CL1**, suppresses neuronal cell death in LPS- and ɣ-Interferon stimulated microglial and neuronal co-cultures.
- "It has been proposed that neuron signaling to microglia might be mediated through this ligand-receptor pair to regulate neuroinflammation."

❖ Fractalkine can both increase and decrease Microglial activation.

Traumatic Astrocytic Functions

- Oxidative Stress and inflammation cause dysfunctioning of Astrocytes which break down leading to the loss of cellular metabolism, damage to the BBB, and a toxic environment that causes neuronal apoptosis and death.



A Dural lymphatic vascular system that drains brain interstitial fluid and macromolecules.

J. Exp. Med. 2015 Vol. 212 No. 7 991–999. Aleksanteri Aspelund, et. Al., Wihuri Research Institute and Translational Cancer Biology Program, Biomedicum Helsinki, University of Helsinki,00014 Helsinki, Finland

- **Glymphatic System** = Glial Lymphatic System of the Brain. Discovered in 2015 and in Humans 2017.
- The glymphatic system facilitates brain-wide distribution of glucose, lipids, amino acids, growth factors, and neuro- modulators.
- TBI impairs the **Glymphatic System** allowing waste products to accumulate which leads to elevated OS, neuroinflammation, cavitation, and enhanced risk for developing Neurodegenerative Diseases.

A Tilted Axis: Maladaptive Inflammation and HPA Axis Dysfunction Contribute to Consequences of TBI. Frontiers in Neurology **2019**. Zoe M. Tapp, Jonathan P. Godbout and Olga N. Kokiko-Cochran, Dept of Neuroscience, Institute for Behavioral Medicine Research, College of Medicine, The Ohio State University, Columbus, OH, USA

- "Neuroinflammation, due in part to microglia, can worsen or even cause neuropsychiatric disorders after Traumatic Brain Injury."
- "HPA axis dysfunction after brain injury contributes to the dynamic nature of the neuroinflammatory response to brain injury."
- "Screening for **Neuroendocrine abnormalities** is not part of the Standard Of Care in the treatment of TBI and thus these deficiencies will often go undiagnosed."

Neuro Steroids

Pregnenolone

Progesterone

Allopregnanolone

Cortisol

DHEA

DHEA-s

Testosterone

DHT

Estradiol

Estrone

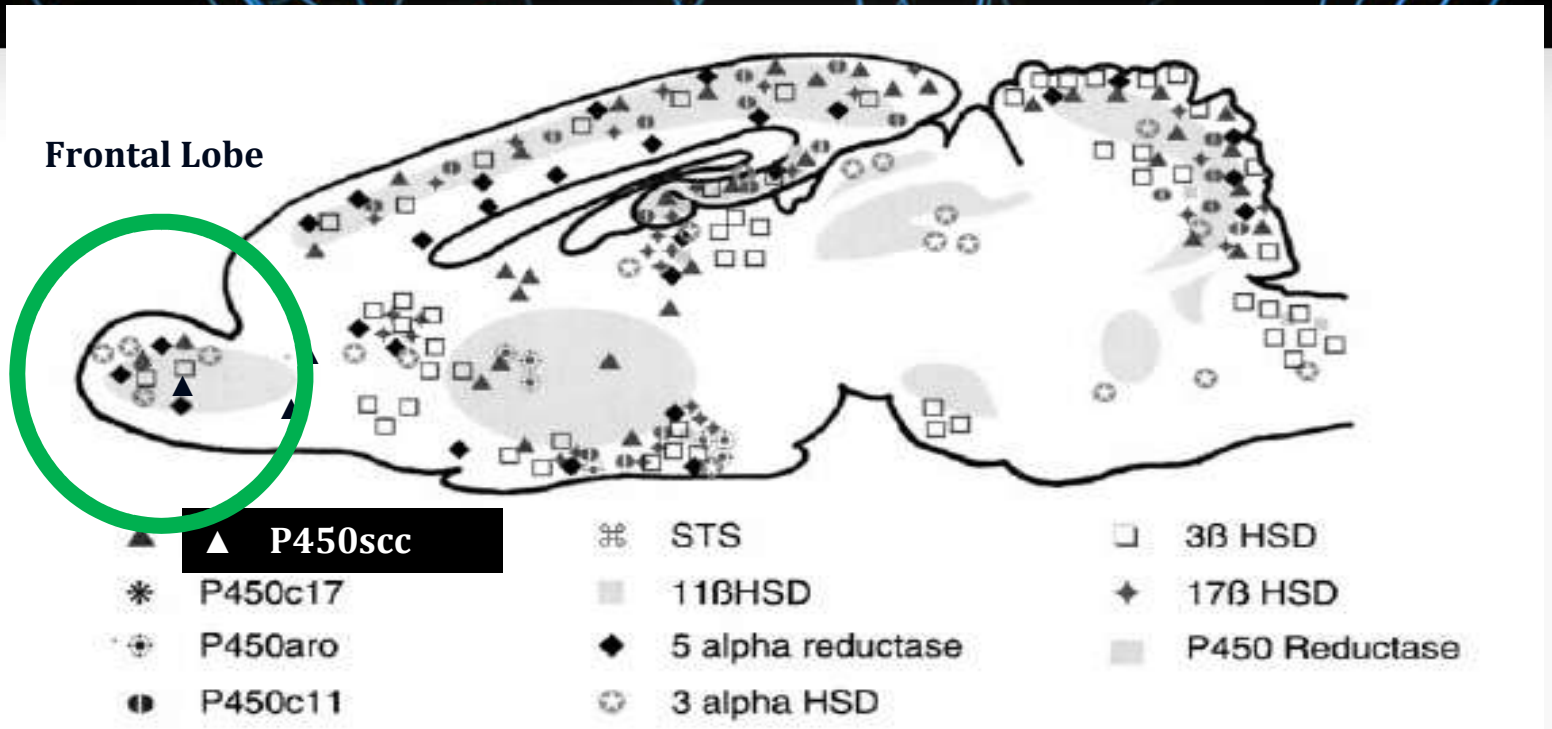
- **Neurosteroids are endogenous steroids synthesized in the brain and influence neuronal and neuropsychiatric activities.**
- They are produced de nova in the brain from cholesterol.
- The enzymes responsible for production of NeuroSteroids have been identified within both neurons and glia; microglia, astrocytes, and oligodendrocytes.

Neurosteroids: Biosynthesis and Function of These Novel Neuromodulators.

Frontiers in Neuroendocrinology 21, 1–56. 2000. Nathalie Compagnone, Synthia Mellon, Dept of Obstetrics, Gynecology, and Reproductive Sciences, Center for Reproductive Sciences, and The Metabolic Research Unit, UCSF, CA

- Neurosteroid actions are mediated through ion-gated neurotransmitter receptors. (**Ionotropic**)
- The functional effects of NeuroSteroids include modulation of $GABA_A$ and NMDA receptors, modulation of sigma-1 receptors, regulation of myelinization, neuroprotection, and growth of axons and dendrites.

NS Regional Production



Schematic representation of an adult brain showing regional expression of enzymes involved in neurosteroidogenesis. P450scc uses the ER-stores of cholesterol to produce pregnenolone in the inner membrane of the mitochondria. Frontal lobe where major loss of Neurosteroids occurs in frontal lobe dementia/Alzheimer's Disease.

CYP11A1 = P450scc

Neuroactive steroids, their metabolites, and Neuroinflammation. Journal of Molecular Endocrinology (**2012**) 49, R125–R134

- **Neuroactive steroids** act as important physiological regulators of CNS functions.
- **Neuroactive steroids** favor several protective and reparative processes like inhibition of neuronal death, promotion of neurogenesis, and myelination, as well as direct reduction of Neuroinflammation.

Pregnenolone-s, Progesterone, Allopregnanolone-s, Pregnanediol, DHT, DHEA-s, Estradiol, Estrone, and Testosterone.

Role of Glia in the Regulation of Gonadotropin-Releasing Hormone Neuronal Activity and Secretion. Neuroendocrinology **2013**;98:1–15. Ariane Sharif Marc Baroncini Vincent Prevot. INSERM, Jean-Pierre Aubert Research Center, Development and Plasticity of the Postnatal Brain, Unit 837, and UDSL, School of Medicine, Lille , France

- Glial cell-derived Prostaglandin-E2 (PGE-2) is a potent stimulator of the GnRH system primarily derived from Astrocytes.
- **PGE-2** up-regulates Hypothalamic release of GnRH causing release of Pituitary **LH** and **FSH**.
- Neuroinflammation shuts down the glia's production of PGE-2 hindering release of GnRH.

PGE-2 + Hypothalamus = GnRH release

estradiol

testosterone

pregnenolone

cortisol

aldosterone

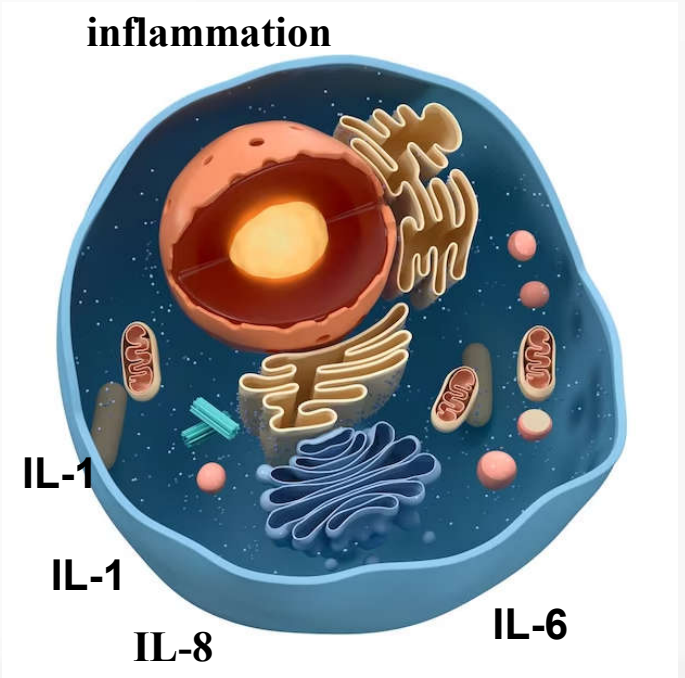
Regulation of NF-κB by TNF Family Cytokines.

Semin Immunol. 2014 June ; 26(3): 253–266. Matthew S Haydenet al., Dept of Microbiology and Immunology, Columbia University, College of Physicians & Surgeons, New York, Dept of Dermatology, Columbia University, College of Physicians & Surgeons, New York, NY

- **Cytokines** belong to the **TNF** family and induce transcription of genes regulating inflammation, cell survival, and proliferation, primarily through activation of the **NFκB pathway***.

TNF-a

NF-kB +IkB



* Blocked by Quercetin, NAC, and Vit-E.

Function of Nuclear Factor kappa B (NF-kB) in human diseases.

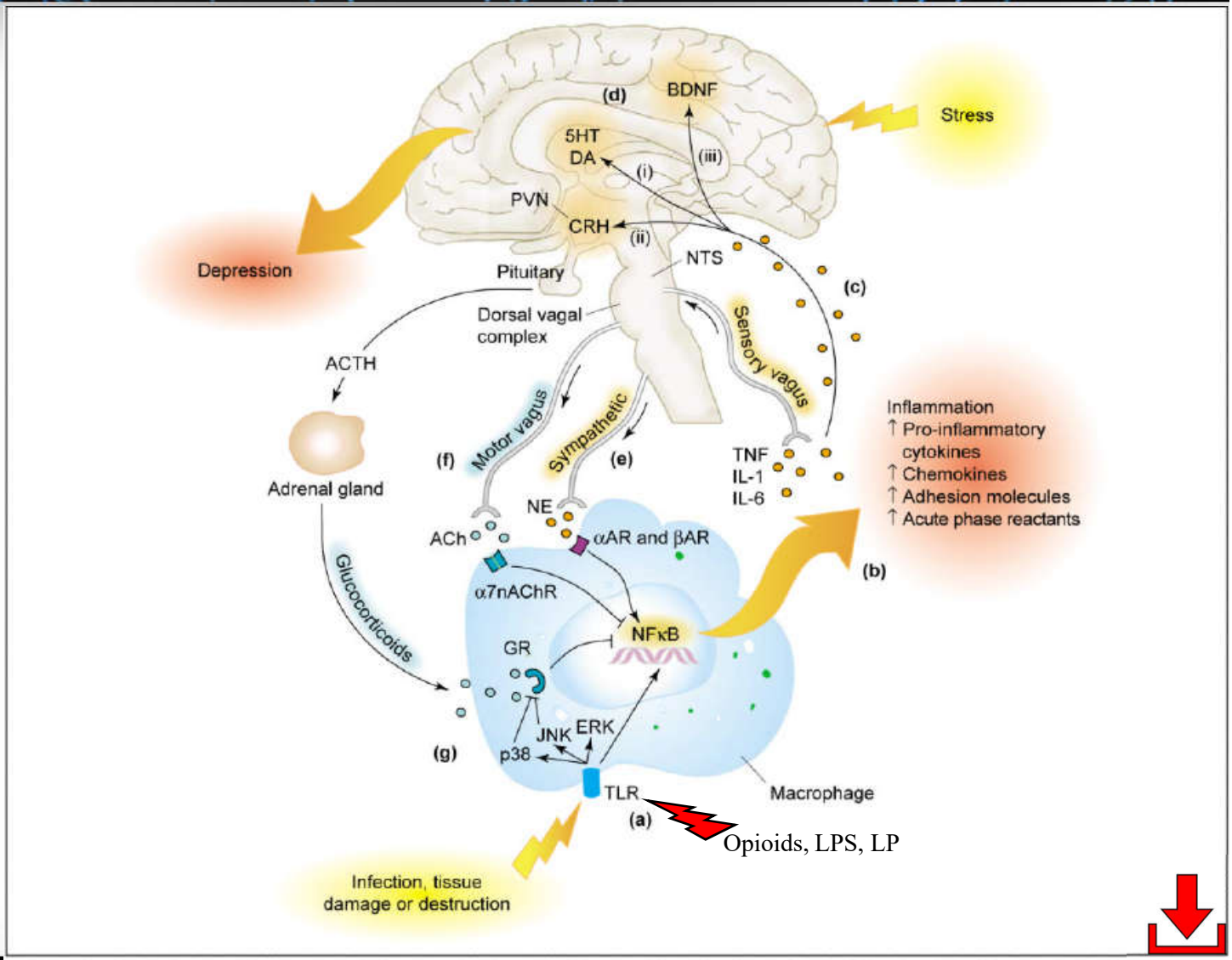
Mamatha Serasanambati et. Al., South Indian Journal Of Biological Sciences **2016**; 2(4); 368-3871Technion – Israel Institute of Technology, Dept of Chemical Engineering and Russell Berrie Nanotechnology Institute, Israel. The Wistar Institute Cancer Center, Philadelphia, USA

- When TNF activates NFkB, it translocates into the nucleus where is regulates 400 immune, growth, and pro-inflammatory genes.
- NFkB regulates **enzymes** (COX-2 and iNOS) **cytokines** (TNF, IL-1, IL-6, IL-8 and chemokines), **adhesion molecules** (**B2-integrin**), **cell cycle regulatory molecules** (P21/P23), and **angiogenic factors.**

Cytokines Sing the Blues: inflammation and the pathogenesis of Depression

Trends Immunol. 2006 January ; 27(1): 24–31 Charles L. Raison, Lucile Capuron, and Andrew H. Miller Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA , USA

HBOT
QEED
NEUROFEEDBACK
BIOFEEDBACK
Medication
Magnetic Therapy
Psychedelics



The Blood Brain Barrier and the Role of Cytokines in Neuropsychiatry. Anita H. Clayton, MD, Et. Al. Psychiatry **2009**;6(11):18–22.

- Cytokine-induced "***Sickness Behavior***", comprising increased sleep, decreased appetite, decreased sexual drive, mood issues, and overwhelming fatigue frequently combined with fever.
  - Long Covid
  - Autoimmune conditions
  - Any form of musculoskeletal trauma.

Microbiome, probiotics and neurodegenerative diseases: deciphering the gut brain axis.

Cell. Mol. Life Sci. (**2017**) 74:3769–3787Biomedical Technology and Cell Therapy Research Laboratory, Dept of Biomedical Engineering, Faculty of Medicine, McGill University, Montreal, QC Canada

- The **Gut–Brain** axis is a **dynamic bidirectional Neuroendocrine system** consisting of direct neurological connections, endocrine signals and immunological factors.
  - Gut cytokines enter the brain.
  - Activate Glia.
  - Rapid escalation of inflammatory cascades.
  - Depletion of endogenous anti-inflammatory systems.

Inflammatory cytokine and chemokine profiles are associated with patient outcome and the hyperadrenergic state following acute brain injury.

Journal of Neuroinflammation (2016) 13:40 Defense Research & Development Canada, Toronto Research Centre, Institute of Medical Science, University of Toronto, Toronto, ON, Canada

- Traumatic brain injury elicits intense sympathetic nervous system activation with profuse catecholamine secretion as part of the generalized host stress response to **Cytokines and Chemokines**.
- This results in a **massive release of catecholamines** (epinephrine, norepinephrine), which can manifest as increased heart rate, increased respiration, increased blood pressure (HTN), diaphoresis, and hyperthermia.

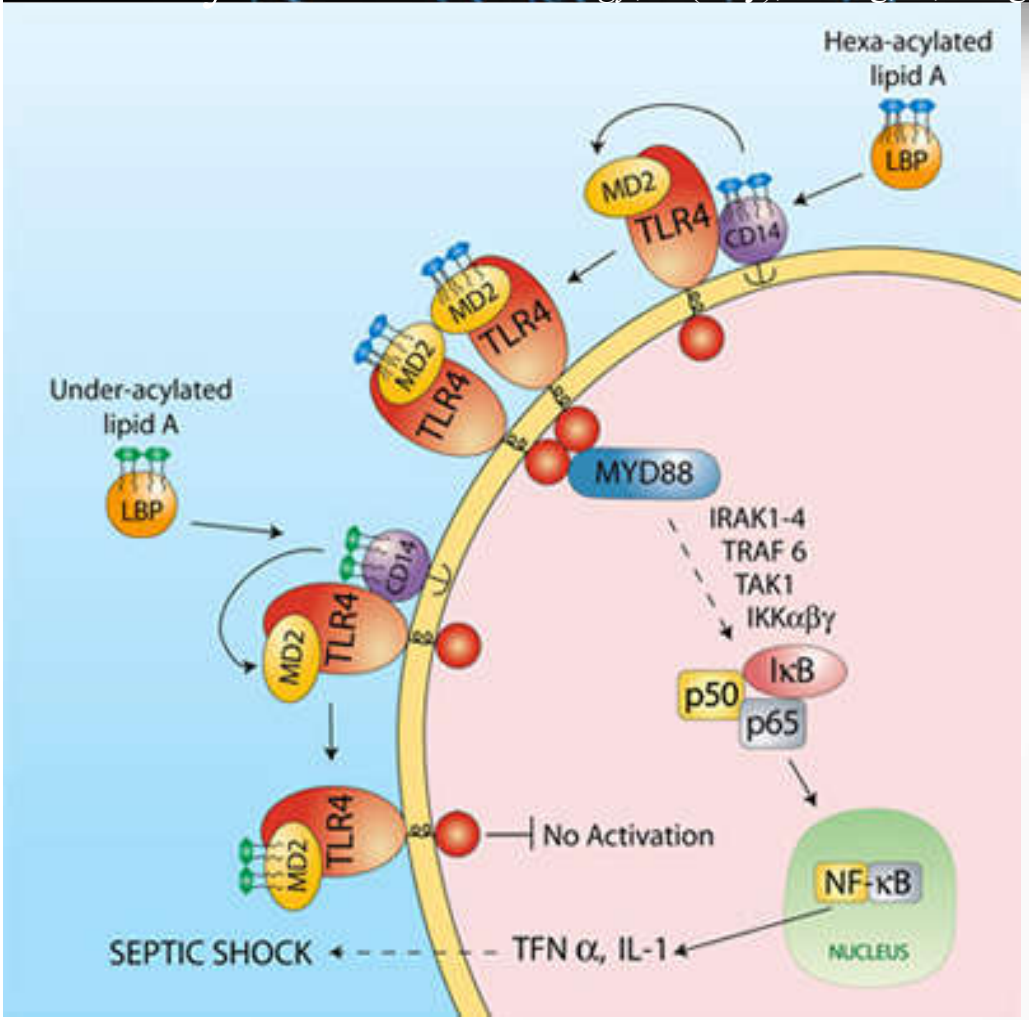
Modulating Neuroinflammation to Treat Neuropsychiatric Disorders.

Franziska A. Radtke, et Al. BioMed Research International Volume 2017,Review Neuroscience and Mental Health Research Institute and School of Biosciences, Cardiff University, Hadyn Ellis Building, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Hadyn Ellis Building, Cardiff UK.

Psychiatric Disorders	Elevated Cytokines
Schizophrenia	**IL-1B**, **IL-6**, **TNF-a**, IL12-p70, sIL-2R, IFN-G
Depression (25-50%TBI)	**IL-1**, **IL-6**, **TNF-a**,sIL-1R, sIL-2R, sIL-6, CRP
Bipolar Disorder	IL-4, **IL-6**, **TNF-a**,IL-10, sIL-2R, sIL-6r,sTNFr1, IL-1r antagonist, INF-g, hs-CRP
Anxiety Disorder	**IL-6**, **TNF-a**,IL-8, IL-10, IL-18,MCP-1, MMP2,
OCD	IL-2, IL-4, **IL-6**, **TNF-a**, IL-10, sTNFr1, sTNFr2
PTSD **(Symptomatic TBI)**	IL-1a,IL-1b, IL-2, IL-4, **IL-6**, IL7, IL-8, IL-10 and, IL12p40, IL12p70, IL-13, IL-15, **TNF-a**, MIP-1a, GM-CSF, IP-10

- Specific cytokines appear to be associated with psychiatric disorders. Coincidental or causative?

Toll-Like Receptor 4 (**TLR4**)/Opioid Receptor Pathway **Crosstalk** and Impact on Opioid Analgesia, Immune Function, and Gastrointestinal Motility. *Frontiers in Immunology*, *11*(July), Zhang, P., Yang, M., Chen, C., Liu, L., Wei, X., & Zeng, S. (**2020**).



The Mu receptors with an Opioid ligand produce analgesia.

Opioids crosstalk with **TLR4** triggering NFkB to translocate into the nucleus and induce transcription of proinflammatory cytokines.

More Pain!!

What Is Nuclear Factor Kappa B (NF-κB) Doing in and to the Mitochondrion?

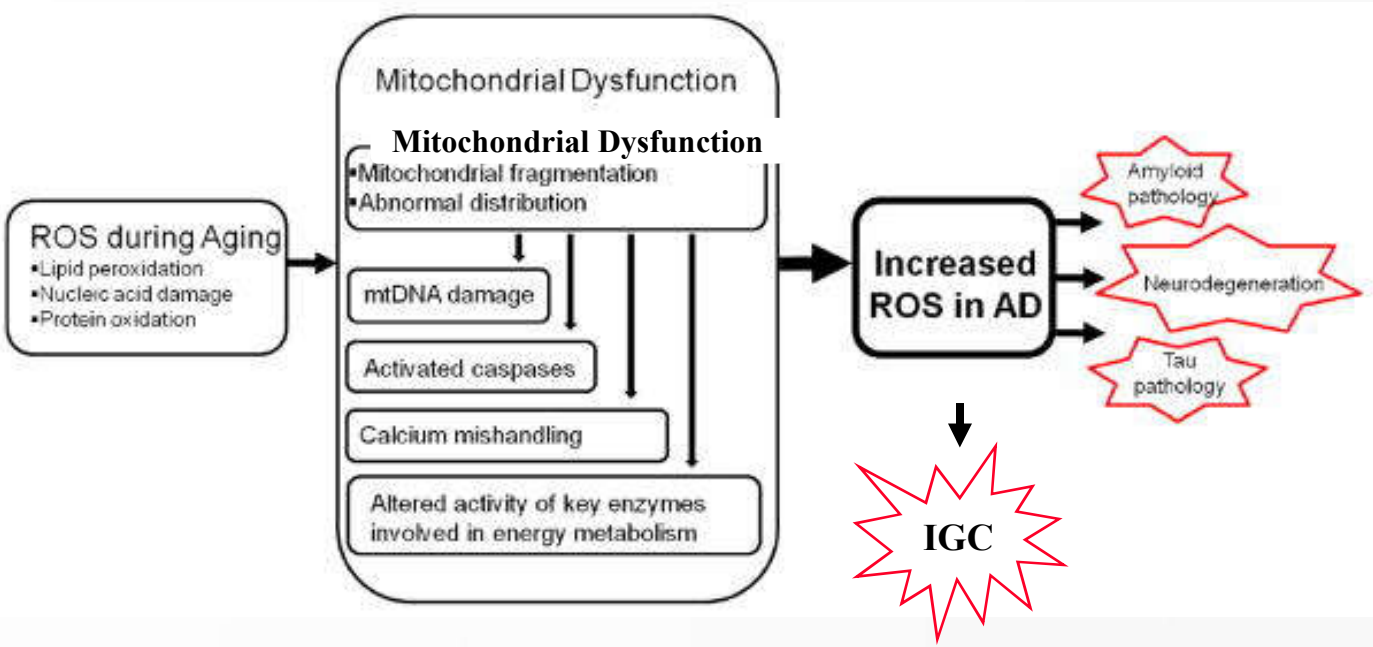
Benedict C. Albensi1, et., al, Division of Neurodegenerative Disorders, St. Boniface Hospital Research, Canada. Dept of Pharmacology and Therapeutics, Max Rady College of Medicine, University of Manitoba, Canada. **2019**

- NF-κB can influence mitochondrial functioning from both inside and outside of the mitochondrion.
- NF-κB activation in the mitochondrion leads to **Cytochrome C** release, triggering caspase cascades and programed cell death (apoptosis).
- TNFα, an activator of NF-κB, is part of an extrinsic pathway of apoptosis.

LPS, TNFa = NFkB Activation.

Oxidative Stress and Mitochondrial Dysfunction in Traumatic Brain Injury and Aging. PhD Dissertation Changxing Shao University of Kentucky. 2007

- Mitochondrial dysfunction increases ROS production overwhelming the body's cellular antioxidant defenses causing systems to fail.



Damaging Mitochondrial function, affects ATP production.

Redox Regulation of Mitochondrial Biogenesis. Free Radic Biol Med. **2012**

December 1; 53(11): 2043–2053. Claude A. Piantadosi, MD and Hagir B. Suliman, PhD, DVM. Depts of Medicine, Anesthesiology, and Pathology Duke University Medical Center and the Durham VA Medical Center Durham, NC USA

- The cell's energy supply is protected from conditions that damage mitochondria by **an inducible transcriptional program of mitochondrial biogenesis.**
- The body fights back through redox signals involving nitric oxide synthase (NOS), heme oxygenase-1 and Carbon monoxide (CO) systems.

Prevalence of Anterior pituitary insufficiency 3 and 12 months after traumatic brain injury.

Europe J Endocrinology. **2006**; 154(2):259-65. **Schneider** HJ; et al. GK. Max Planck Institute of Psychiatry, Clinical Neuroendocrinology Group Kraepelinstr. 10, 80804 Munich, Germany.

	Acute 3 mo	**◄►**	**Chronic 12 mo**
Hormone Deficient	**56%**	**improvement**	**36%**
Gonadotropic	32%	FSH/LH	21%
Corticotropic	19%	CRH	9%
Somatotropic	9%	GH	**10%**
Thyrotrophic	8%	TSH	3%

Loss of Important Pleiotropic Hormones after a TBI

Treatment based upon restoration of hormones and dropping inflammation.

Hormones that Influence Neuroinflammation

Growth Hormone	▼CRP, ▼TNF-a, ▲IL-10
IGF-1	▲Microglial M2, ▼M1 phenotype
Testosterone	▲IL-10, ▼IL-1β, ▼IL-6, ▼TNF-α
DHT	▼NF-κB activation
DHEA & DHEAs	▼IL-6, ▲ DEL-1, ▼ Beta-2-Integrin
Estradiol	▼Intracellular NF-kB transport, ▼MAPK
Vitamin D	▼CRP, ▼TNF-a, ▼Free Radicals
Progesterone	▼NF-κB activation, ▼Free Radicals
Pregnenolone	▼TLR4/2, ▼ Free Radicals
Allopregnanolone	▼TLR4/2, ▼ Free Radicals

Testosterone acts directly on CD4+ T lymphocytes to increase IL-10 production.

Journal of Immunology. **2001** Aug 15;167(4):2060-7. Liva SM, Voskuhl RR.
Department of Neurobiology, University of California School of Medicine, Los Angeles, CA 90095, USA.

- **Free Testosterone˜** acts directly on CD4+ T-lymphocytes to increase **IL-10** production and decrease production of pro-inflammatory cytokines.
- **IL-10** is capable of inhibiting synthesis of pro-inflammatory cytokines: **IFN-γ, IL-1, IL-2, IL-3, IL-6, TNFα and GM-CSF*** made by cells such as macrophages and the Type 1 T helper cells.

*Granulocyte-macrophage colony-stimulating factor

˜Notice Free Testosterone and NOT Total Testosterone.

Summation-1

1. Trauma, stresses a multitude of biological systems that respond with an increase in Oxidative Load from **Free Radicals**.
2. Free radicals activate the glia that mount an initial defensive phenotype(M1) to remove debris and protect the brain from pathogens.
3. Cytokines, chemokines, leukotrienes, and prostaglandins create a neuroinflammatory environment.

Summation-2

4. In an **acute scenario**, the glia transform from a pro-inflammatory (M1) to an anti-inflammatory phenotype (M2) finalizing the “clean up”.
5. In the **chronic state**, supported by cortisol, the glia continue to produce pro-inflammatory cytokines.
6. This chronic and indolent state leads to the breakdown in the biochemistry of the brain causing cognitive and emotional decay.

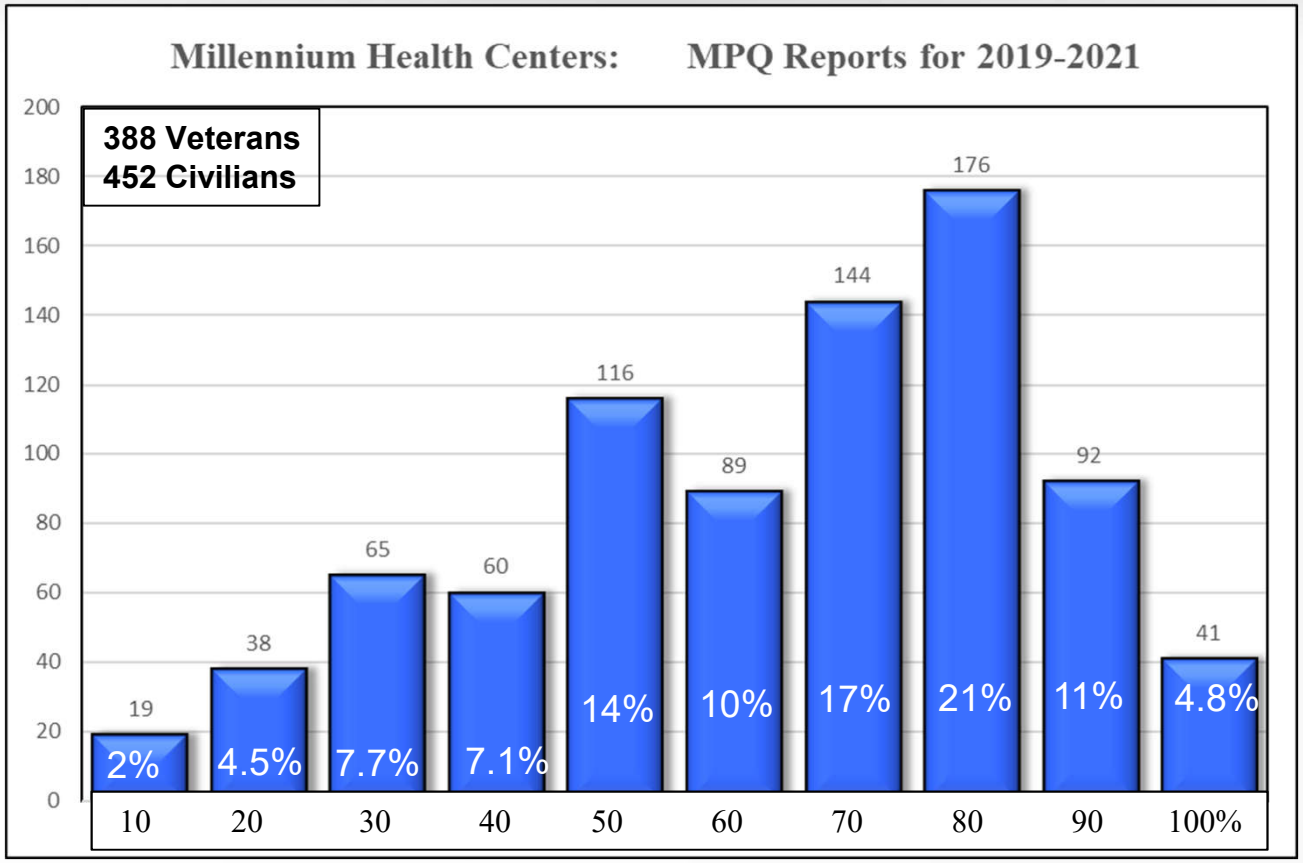
Summation-3

Present Treatment

7. Re-establish a Neuro-permissive environment by replenishing the endogenous free radical defense systems with exogenous supplements and boost mitochondrial production of ATP.
8. Restart production or replenish the deficient and insufficient neurosteroids and neuroactive steroids.

One last slide coming……

840 Clinical Cases: 2019-2021



78.3% of participants were 50 – 100% better within 12 months.

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Little did he anticipate that neuroendocrinology would offer answers to many of his questions and become an answer to those suffering with symptoms from traumatic brain injury.

Andrew Marr, a decorated Green Beret and co-founder of Warrior Angels Foundation, never anticipated that his multiple combat deployments would leave him so incapacitated that he was forced into medical retirement at the age of 33.

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