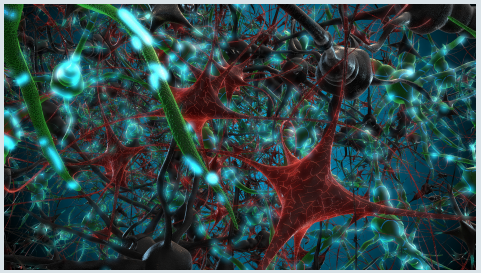
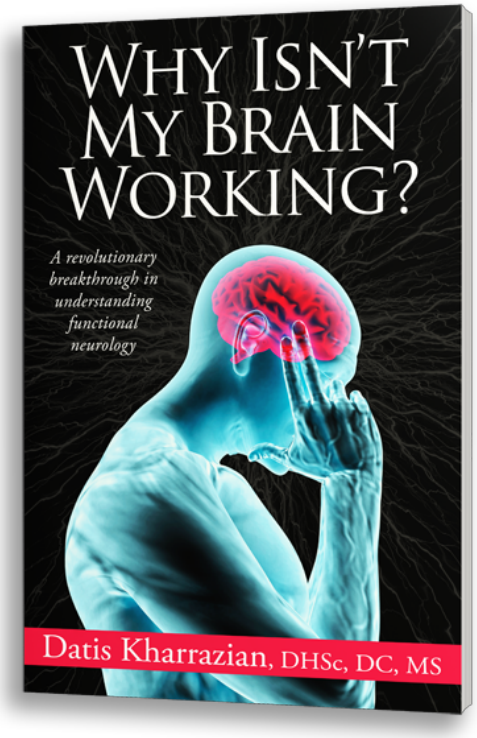
DR. HYMAN+

# 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

**drknews.com**


WHY ISN'T MY BRAIN WORKING?
A revolutionary breakthrough in understanding functional neurology
Datis Kharrazian, DHSc, DC, MS

Vol 457|5 February 2009 nature

Q&A

NEUROSCIENCE

# Glia — more than just brain glue

Nicola J. Allen and Ben A. Barres

**Glia make up most of the cells in the brain, yet until recently they were believed to have only a passive, supporting role. It is now becoming increasingly clear that these cells have other functions: they make crucial contributions to the formation, operation and adaptation of neural circuitry.**

### How do glia differ from neurons?

The defining characteristic of a neuron is its ability to transmit rapid electrical signals in the form of action potentials. All other neural cells that lack this property are categorized into a broad class termed glia. Neurons are arranged in networks (circuits), and communicate with each other via specialized intercellular adhesion sites called synapses. Neuronal signalling involves the propagation of an action potential down a neuron's axonal process to a presynaptic terminal; the depolarization of the terminal and release of neurotransmitters; binding of the released neurotransmitters to receptors on the postsynaptic membrane of another neuron; and the subsequent depolarization of this second neuron, propagating the signal further. Glia do not fire action potentials, but instead surround and ensheath neuronal cell bodies, axons and synapses throughout the nervous system.

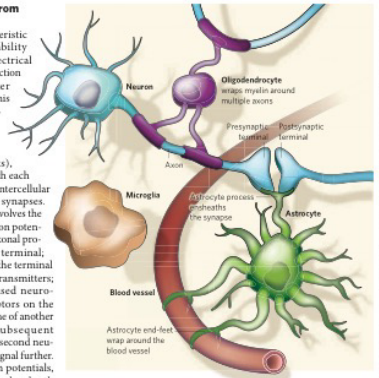



**Figure 1 | Glia–neuron interactions.** Different types of glia interact with neurons and the surrounding blood vessels. Oligodendrocytes wrap myelin around axons to speed up neuronal transmission. Astrocytes extend processes that ensheath blood vessels and synapses. Microglia keep the brain under surveillance for damage or infection.

### Are all glia the same?

No. On the basis of morphology, function and location in the nervous system, there are several classes of glia. In mammals, for example, glia are classified as microglia, astrocytes and the related Schwann cells and oligodendrocytes (Fig. 1).

### Where do they originate from?

Glia and neurons mainly share a common origin — precursor cells derived from the embryonic germ layer known as the neuroectoderm. A notable exception is microglia, which are part of the immune system and enter the brain from the blood circulation early in an organism's development.

### What is known about the evolution of glia?

Glia are evolutionarily conserved, being present in one form or another in most species examined, from the simplest invertebrates to humans. The proportion of glia seems to be correlated with an animal's size: the tiny nematode worm has only a few glia; some 25% of the fruitfly brain consists of glia; the mouse brain has roughly 65% of these cells; the human brain has about 90%; and the elephant brain consists of some 97% glia. As animals have evolved, glia have become not only more diverse and specialized, but also essential: without them neurons die. Furthermore, astrocytes in the human cerebral cortex are much more complex than those of other mammals, and are thought to be involved in information processing.

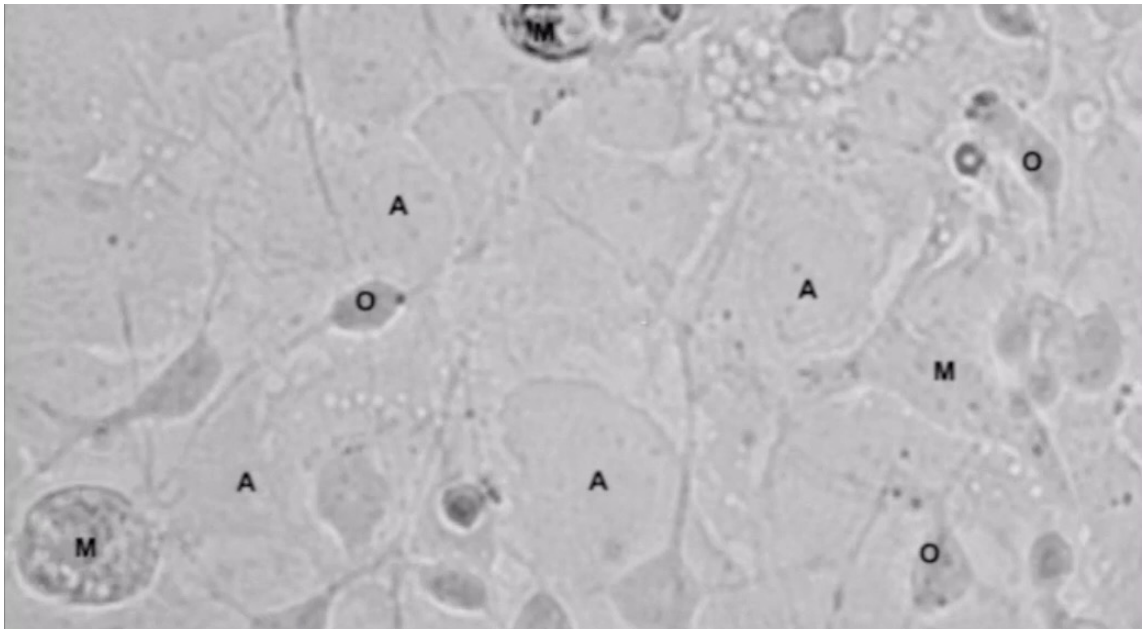
### So what exactly do glia do?

Lots of things. The traditional view has been that glia look after neurons and maintain their proper functioning, having a somewhat passive role themselves. Established functions of glia include supporting neurotransmission, maintaining ionic balance in the extracellular space, and insulating axons to speed up electrical communication. But emerging research suggests that glia, particularly astrocytes, also have an active role in brain function and information processing — both during development and in adulthood.

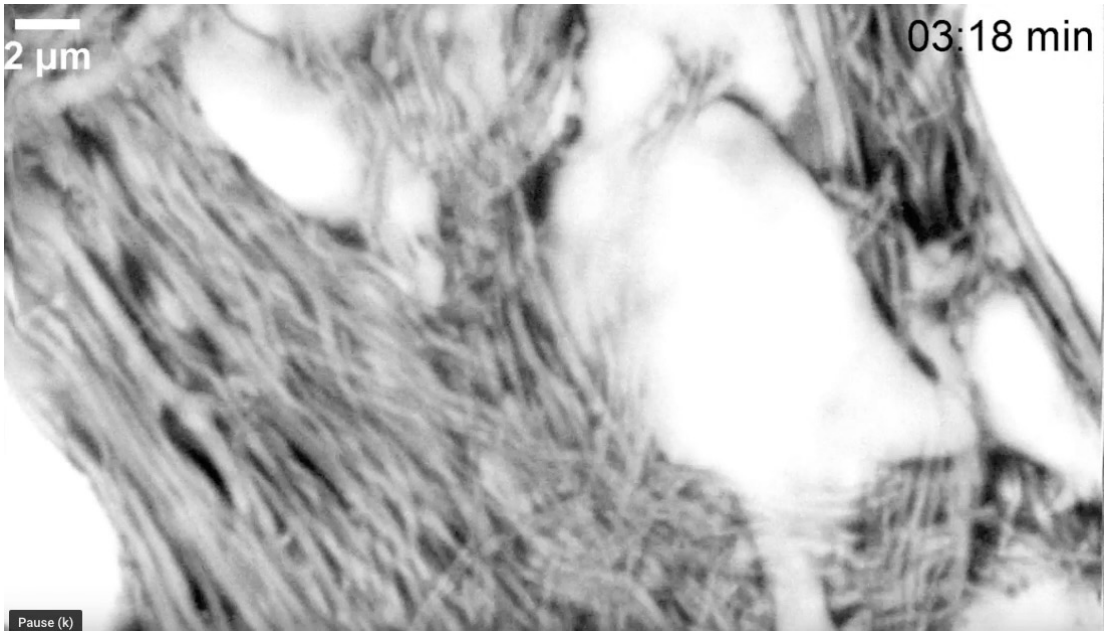
### What is the specific function of microglia?

These resident immune cells of the nervous system survey the brain for damage and infection, engulfing dead cells and debris. Microglia have also been implicated in synaptic remodelling during the development of the nervous system, when they are proposed to remove inappropriate synaptic connections through the process of phagocytosis. Moreover, they are activated in many neurodegenerative diseases, but whether they are helpful or harmful in these conditions is a matter of debate.

# Culture of Microglia, Astrocytes, and Oligodendrocytes



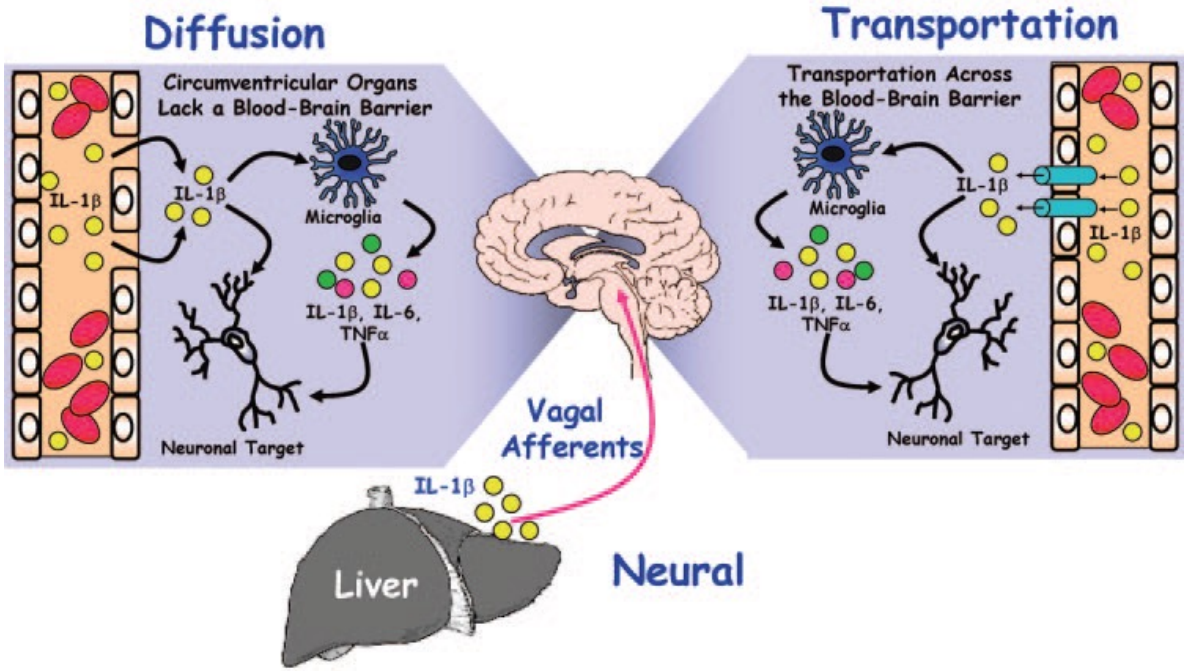
# Microglia Roaming Through the Brain, Super Resolution Shadow Imaging



# Pathways That Activate Neuroinflammation

## Immune-to-Brain Communication

### Activation of the Brain's Innate Immune System




Journal of Leukocyte Biology Volume 84, October 2008

*Dilger and Johnson* **Aging as a factor for microglial priming**

# Microglia “Steady” Versus “Activated” State

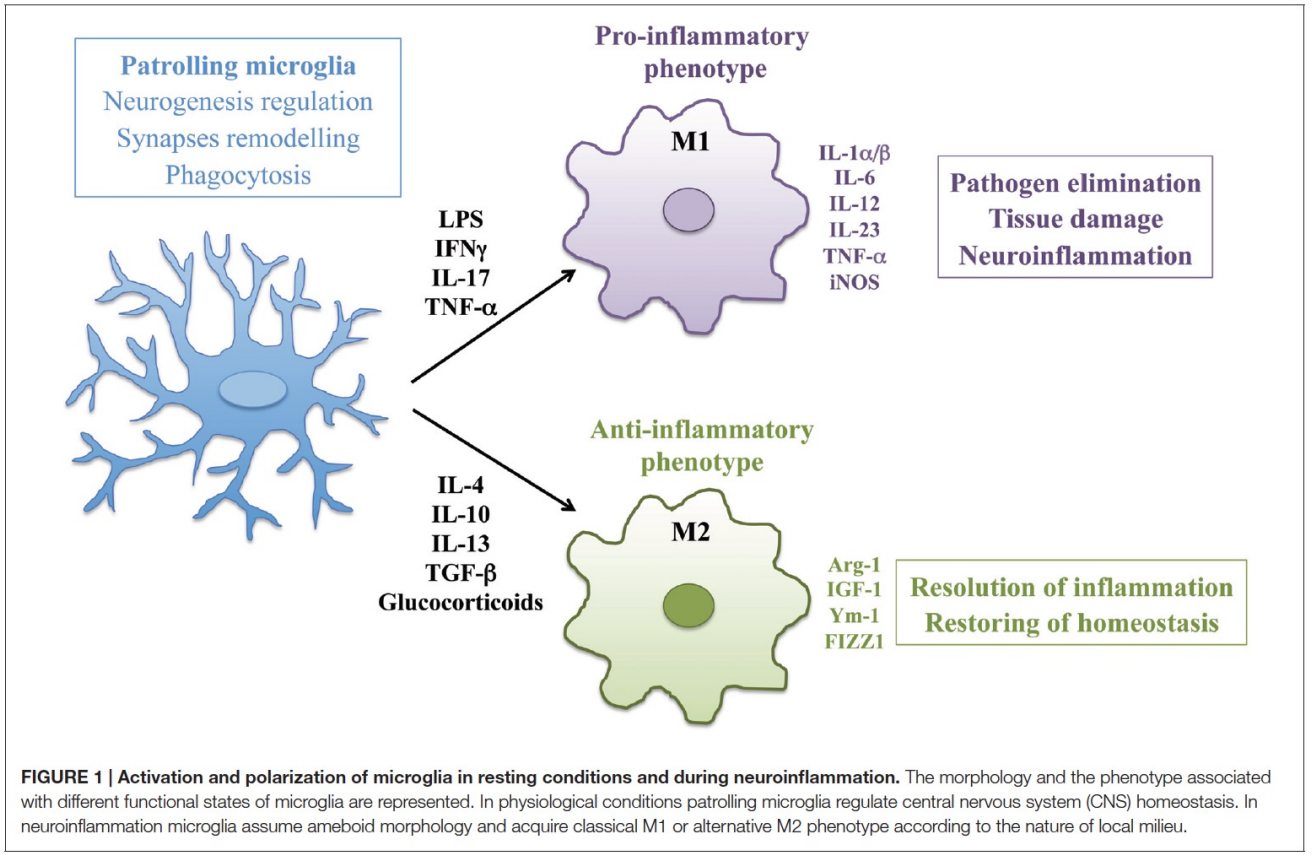


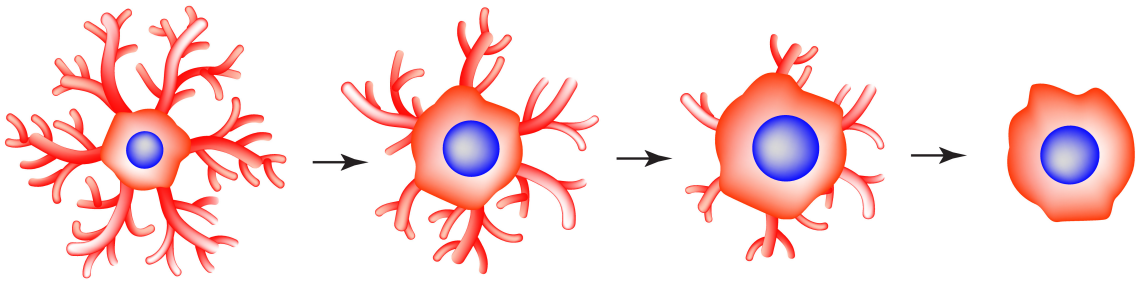

**FIGURE 1 | Activation and polarization of microglia in resting conditions and during neuroinflammation.** The morphology and the phenotype associated with different functional states of microglia are represented. In physiological conditions patrolling microglia regulate central nervous system (CNS)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

frontiers in Aging Neuroscience

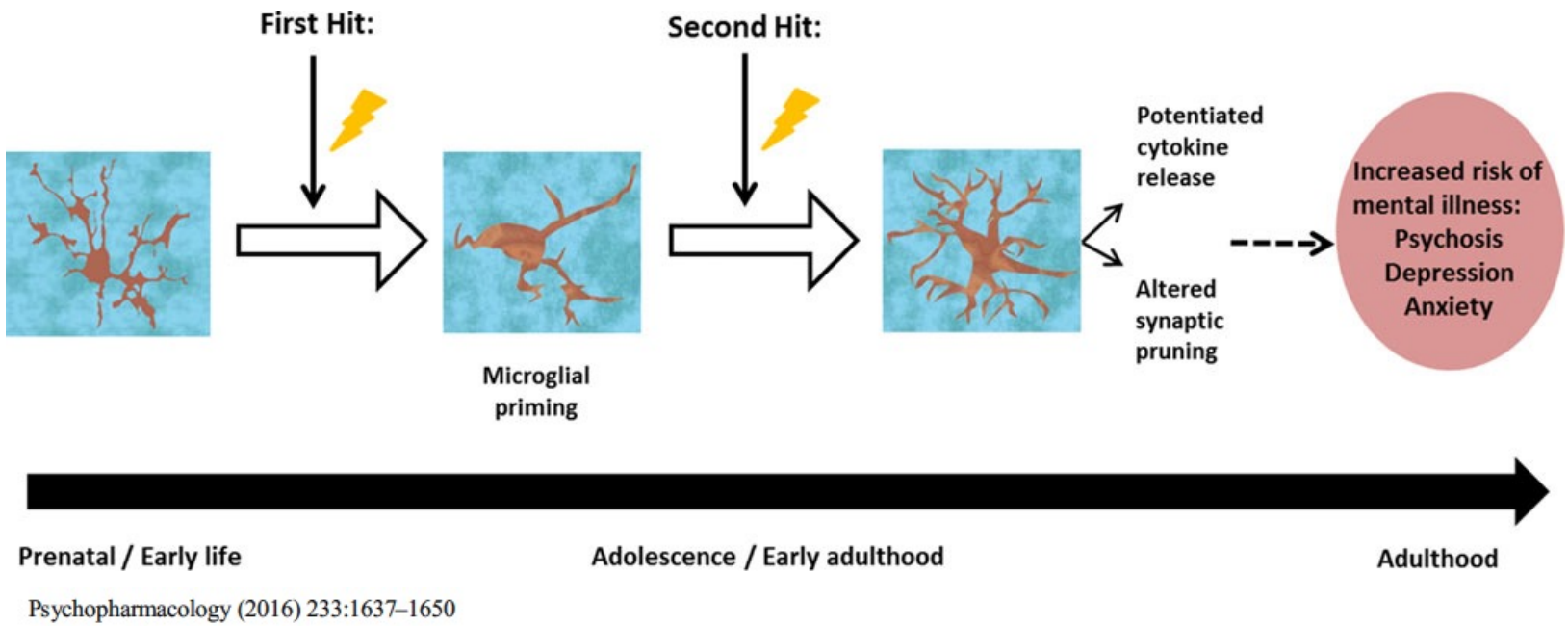
**Role of Atypical Chemokine Receptors in Microglial Activation and Polarization**

# Transition Into a New Structure

MICROGLIAL ACTIVATION

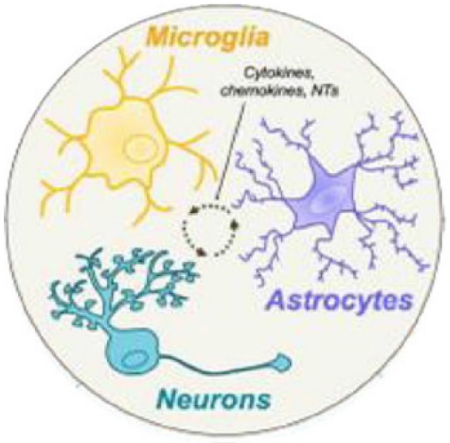


# Basic Concept of Microglia Priming

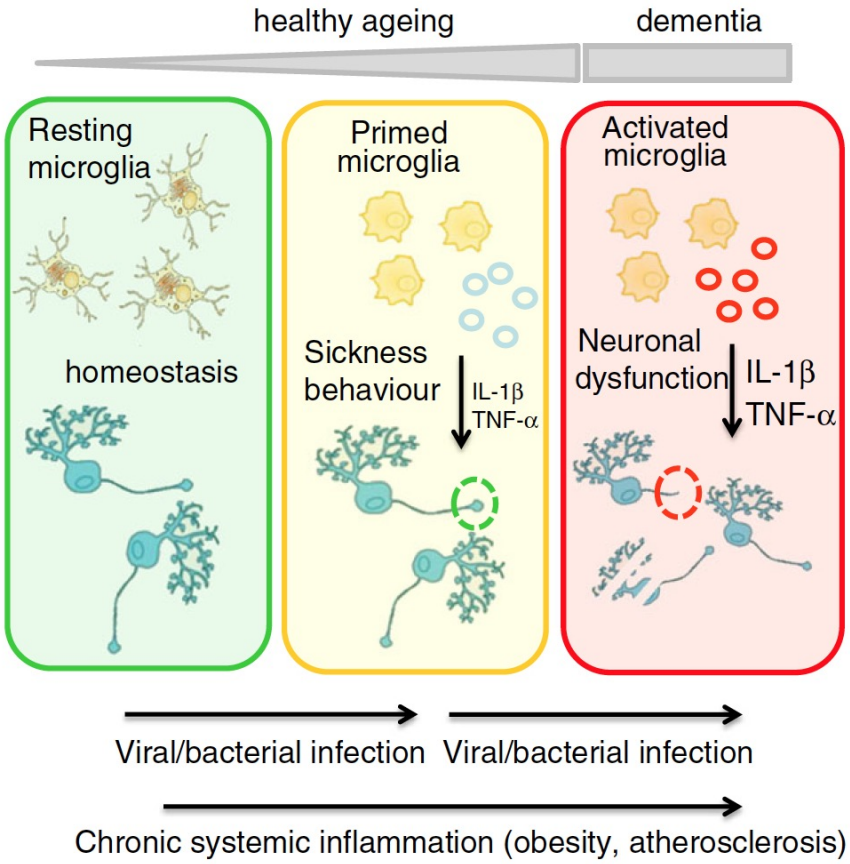



Psychopharmacology (2016) 233:1637–1650

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



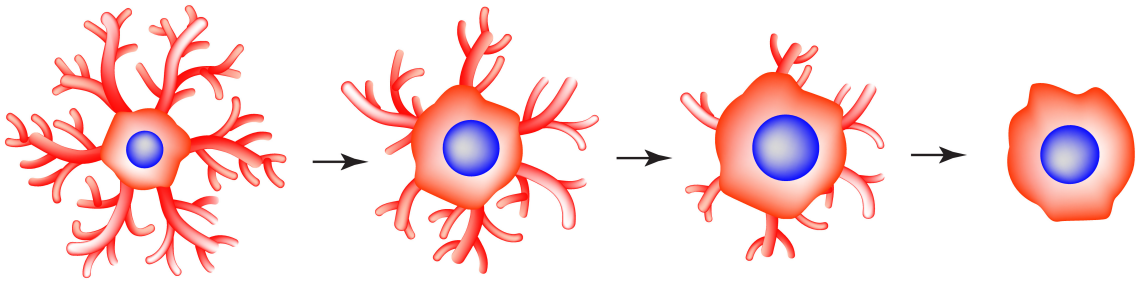

changes in microenvironment
=
changes in microglia adaptive/maladaptive



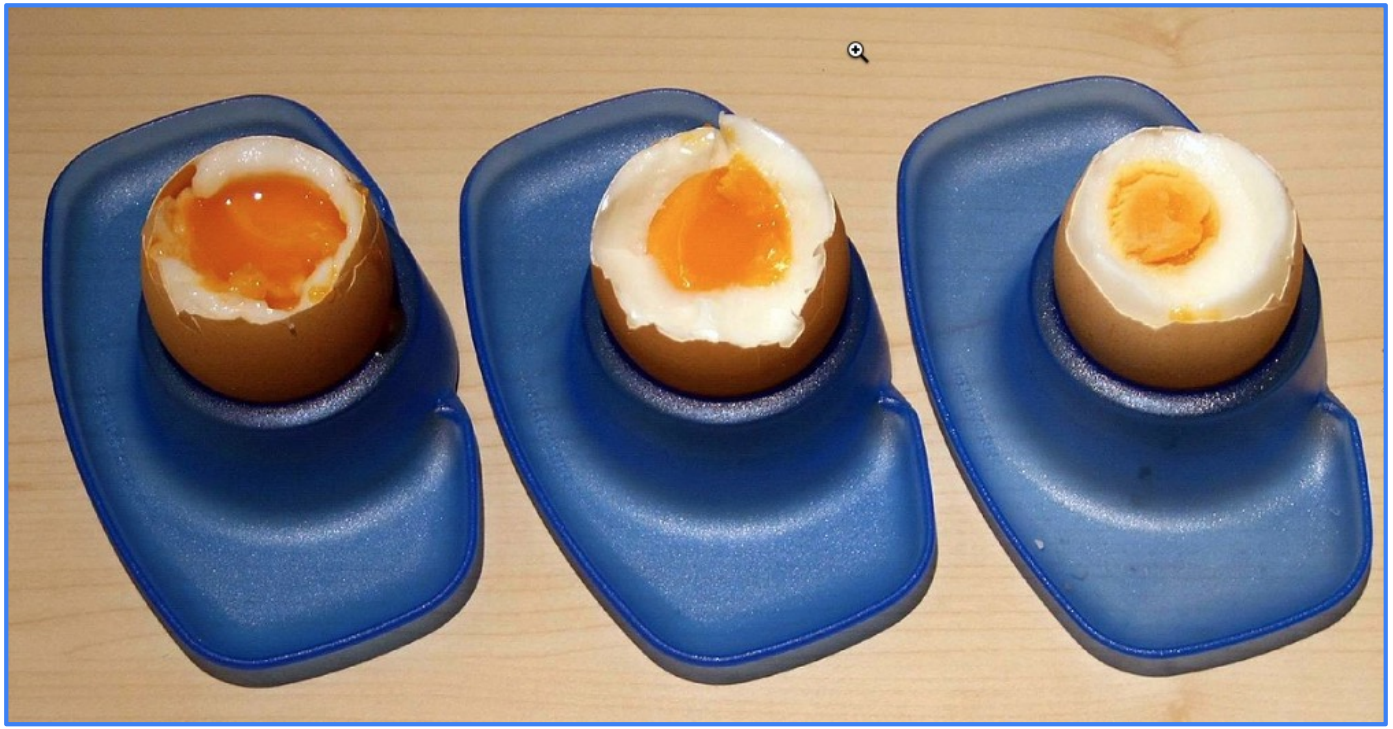

Semin Immunopathol (2013) 35:601–612

# Transition Into a New Structure

MICROGLIAL ACTIVATION



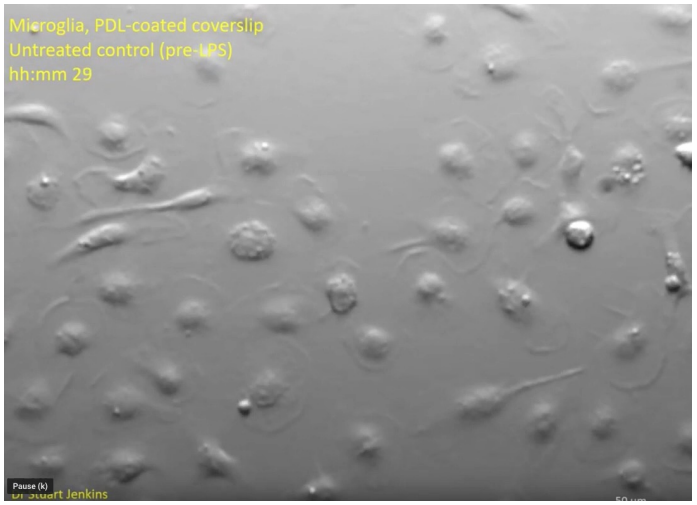
# Transition Into a New Structure



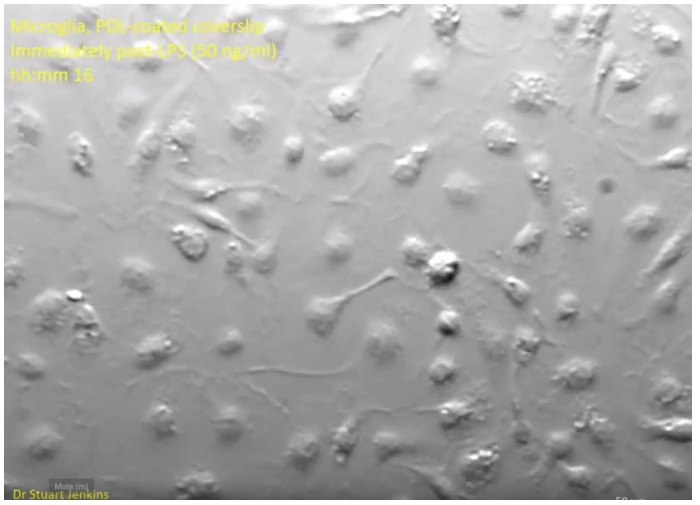
Picture with permission Aristo Vojdani, PhD

# Microglia Pre- and Post-LPS Stimulation

## Microglia Pre LPS

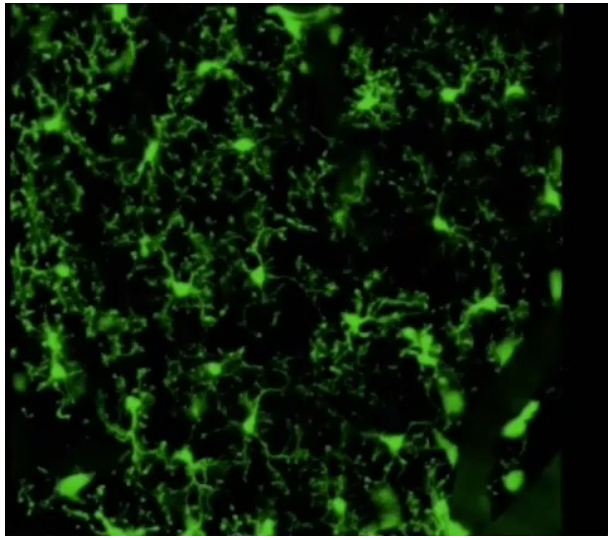



## Microglia Post LPS

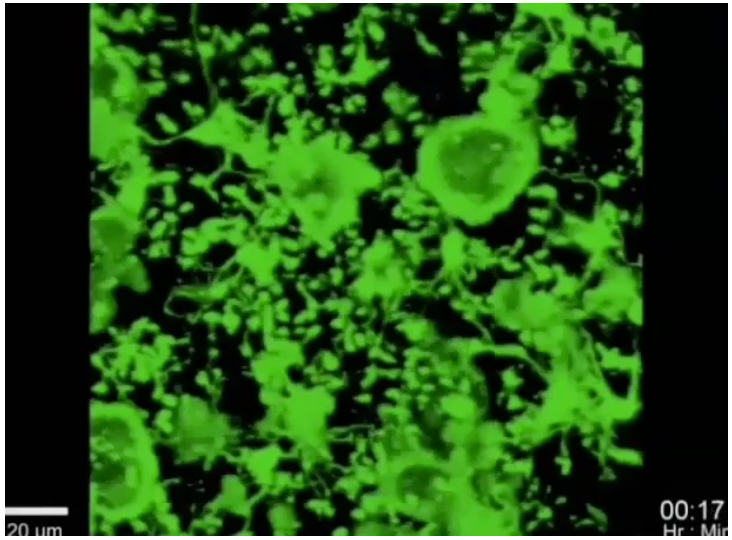


# Inflammation and Neuroprotection In Traumatic Brain Injury

## Resting Neuroglia Before TBI



## Activated Neuroglia After TBI




Kara N. Corps, DVM, DACVP[1]; Theodore L. Roth, MS[1]; Dorian B. McGavern, PhD[1]

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

Trends in Neurosciences

CellPress

Special Issue: Neuroimmunology

Review

# Priming the Inflammatory Pump of the CNS after Traumatic Brain Injury

Kristina G. Witcher,[1] Daniel S. Eiferman,[2] and Jonathan P. Godbout[1,3,4,*]

**Traumatic brain injury (TBI) can lead to secondary neuropsychiatric problems that develop and persist years after injury. Mounting evidence indicates that neuroinflammatory processes progress after the initial head injury and worsen with time. Microglia contribute to this inflammation by maintaining a primed profile long after the acute effects of the injury have dissipated. This may set the stage for glial dysfunction and hyperactivity to challenges including subsequent head injury, stress, or induction of a peripheral immune response. This review discusses the evidence that microglia become primed following TBI and how this corresponds with vulnerability to a 'second hit' and subsequent neuropsychiatric and neurodegenerative complications.**

## Introduction to TBI

TBI is a leading cause of neurological disability in the USA and is associated with increased risk for development of neuropsychiatric illness. TBI occurs when brain physiology and structure are either focally or diffusely disrupted following high-impact contact between the skull and another object. TBIs most commonly occur in persons aged 0–4, 15–19, or above 65 years [1]. The high incidence in pediatric and young-adult populations is significant as these individuals may face a lifetime of compromised physical and mental health after TBI.

TBIs are heterogeneous, with many etiologies and clinical presentations. Diffuse injury results from movement of the brain within the skull. By contrast, focal injury results from penetrating trauma, when either a foreign body or a fractured portion of the skull enters the brain. Blast injuries in military veterans are most commonly classified as concussive; however, shrapnel or skull fractures can cause penetrating injury [2]. Etiology and experimental models for diffuse and focal injuries are outlined in Figure 1.

Experimental paradigms in rodents, pigs, and nonhuman primates can model the complex pathophysiology of human brain injury. Some models produce pathology that is more consistent with a penetrating head injury and result in lesion formation, focal cell death, and infiltration of leukocytes. For example, **controlled cortical impact (CCI)** (see Glossary) [3–5], ballistic penetrating injury [6], and lateral fluid percussion injury [7,8] produce unilateral focal lesions. Other techniques model diffuse head injury, characterized by diffuse axonal injury that occurs in the absence of cell death or a focal lesion. These models include **midline fluid percussion injury (mFPI)** [9] and closed-head impact acceleration models [10,11]. Modifications of these models are used to induce repeated head injuries and mild TBI [12,13]. Animal models are integral in developing our understanding of the pathophysiology of TBI.

### Trends

Microglia are rapidly activated following TBI and produce cytokines and chemokines in addition to exhibiting morphological alterations such as hypertrophy and de-ramification of processes.

Experimental and clinical evidence indicates that microglia do not return to homeostasis after injury but instead develop a primed and potentially hyper-reactive phenotype.

Primed microglia are characterized by exaggerated responses to secondary insults such as repeated TBI, immune challenge, or stress. This results in amplified and prolonged neuroinflammation that negatively influences cognitive and behavioral processes.

TBI patients are at increased risk for the development of depression or neuropathologies (tau, Aβ) after injury.

Microglia-mediated inflammatory processes may represent a useful clinical target in the treatment of neurological and psychiatric complications associated with TBI.

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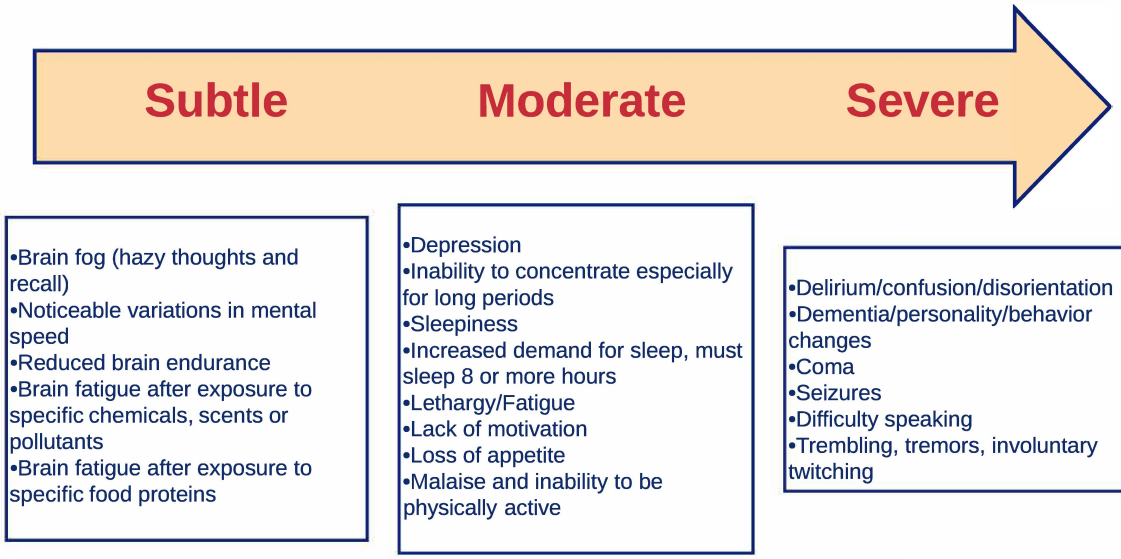
[4]Institute for Behavioral Medicine Research, The Ohio State University, 460 Medical Center Drive, Columbus, OH, USA

*Correspondence: jonathan.godbout@osumc.edu (J.P. Godbout).

# Neuroinflammation Symptom Scale



# Clinical Severities of Neuroinflammation

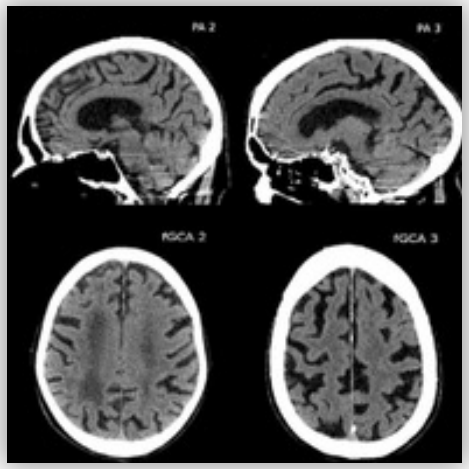
Transient Neuroinflammation

Chronic Neuroinflammation

Microglia-Primed Neuroinflammation

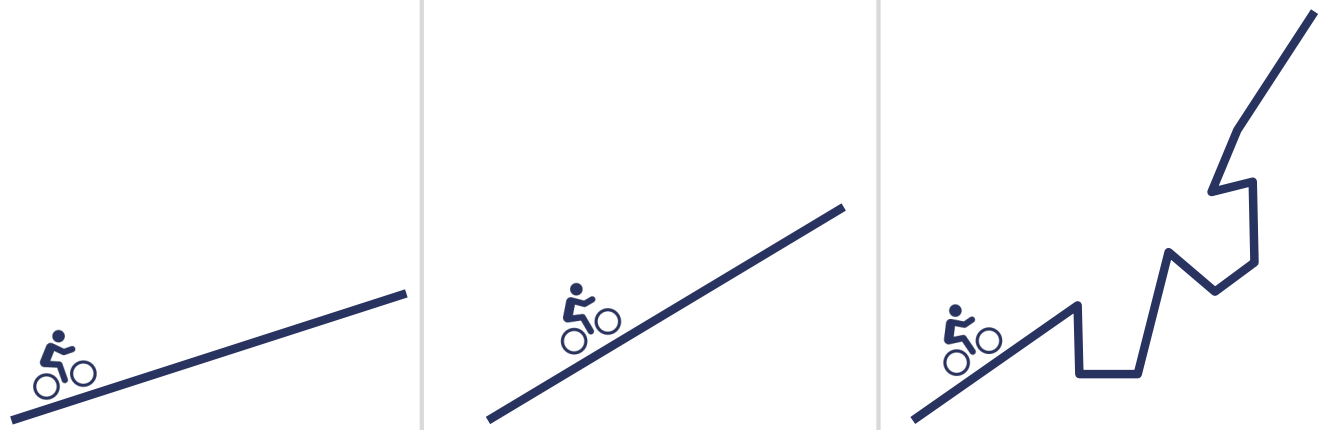
Neurological Autoimmunity

Neurodegeneration



# Clinical Management of Neuroinflammation

| Transient Neuroinflammation | Chronic Neuroinflammation | Primed Glia |
| --- | --- | --- |



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TBI patients are at increased risk for the development of depression or neuropathologies (tau, Aβ) after injury.

Microglia-mediated inflammatory processes may represent a useful clinical target in the treatment of neurological and psychiatric complications associated with TBI.

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**Trends Box**

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**Priming the Inflammatory Pump of the CNS after Traumatic Brain Injury** *Trends Neurosci*. 2015 October ; 38(10): 609–620.

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# Clinical Pearls

- TBIs can lead to symptoms 5–10 years after the initial injury.
- Any time you see a case history with symptoms of neuroinflammation you must evaluate the medical history timeline for a TBI.
- TBI is most concerning if the patient lost consciousness after the injury.

# Clinical Pearls

- The force of the impact is not the only variable that determines the severity of the TBI and the potential for microglia priming.

- All the physiological variables that can impact the shift of microglia to greater M1 activity before the impact can have a profound impact on the severity of TBI.

# Clinical Strategy for Neuroinflammation

# Dietary Interventions for Neuroinflammation

## Anti-Inflammatory

- ↑ Essential fatty acids
- ↓ Fried food
- ↓ Hydrogenated fats

↓

Gluten-free
Dairy-free

↓

Paleo diet (grain-free)

↓

Autoimmune Paleo Diet
(grain- and lectin-free)

## Stabilize Blood Glucose

- No missed meals
- Avoid sugar
- Limit carbohydrates
- Small portion size

## Modified Ketogenic Diet

- Less than 20–50 grams of carbs per day
- 70–80% of calories are from fat

## Intermittent Fasting

- Eat first meal of the day 12–18 hours after dinner the night before

Published in final edited form as:
*Neurochem Res*. 2017 July ; 42(7): 2011–2018. doi:10.1007/s11064-017-2253-5.

# Ketone Bodies as Anti-Seizure Agents

There is growing evidence that ketone bodies (KB)—derived from fatty acid oxidation and produced during fasting or consumption of high-fat diets—can exert broad neuroprotective effects.

Moreover, ketone bodies appear to exert both epigenetic and anti-inflammatory effects.

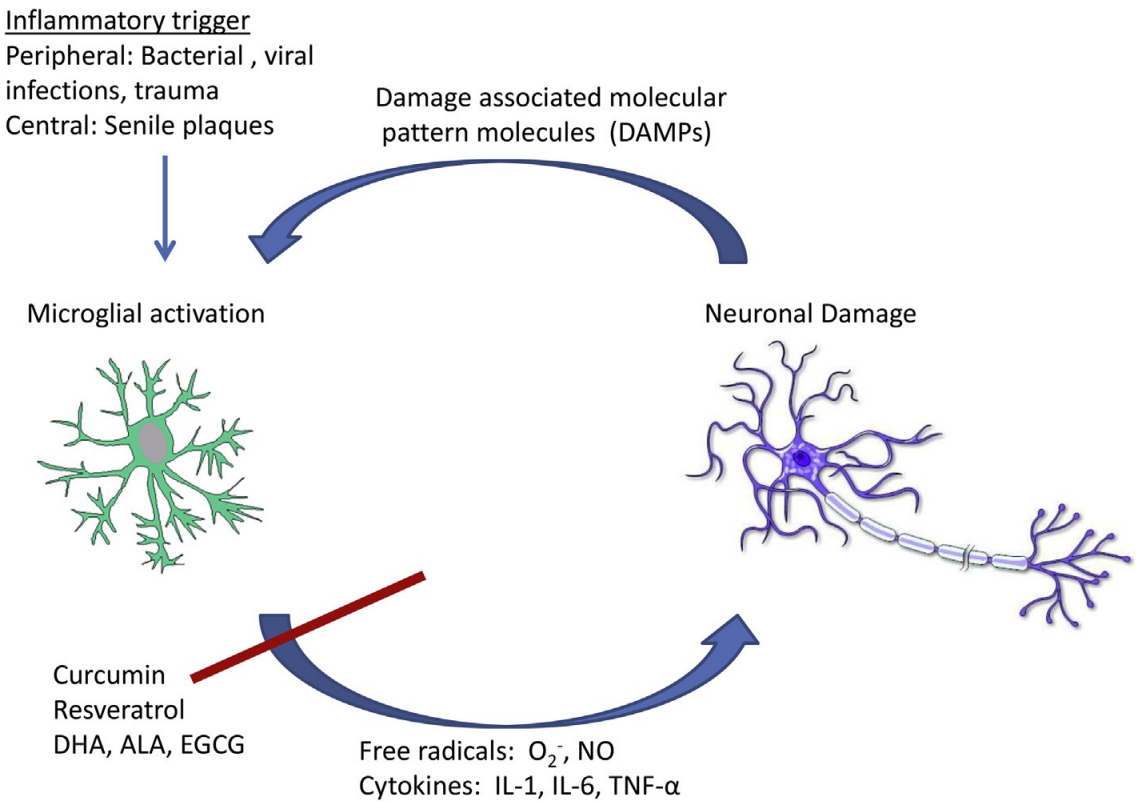
Notwithstanding this limitation, there is growing evidence that ketone bodies are more than just cellular fuels, and can exert profound biochemical, cellular, and epigenetic changes favoring an overall attenuation in brain network excitability.

been shown to block acutely induced and spontaneous recurrent seizures in various animal models. Although the mechanisms underlying the anti-seizure effects of KB have not been fully elucidated, recent experimental studies have invoked ketone-mediated effects on both inhibitory (e.g., GABAergic, purinergic and ATP-sensitive potassium channels) and excitatory (e.g., vesicular glutamate transporters) neurotransmission, as well as mitochondrial targets (e.g., respiratory chain and mitochondrial permeability transition). Moreover, BHB appears to exert both epigenetic (i.e., inhibition of histone deacetylases or HDACs) and anti-inflammatory (i.e., peripheral modulation of hydroxycarboxylic acid receptor and inhibition of the NOD-like receptor protein 3 or NRLP3 inflammasome) activity. While the latter two effects of BHB have yet to be directly linked to ictogenesis and/or epileptogenesis, parallel lines of evidence indicate that HDAC inhibition and a reduction in neuroinflammation alone or collectively can block seizure activity. Nevertheless, the notion that KB are themselves anti-seizure agents requires clinical validation, as prior studies have not revealed a clear correlation between blood ketone levels and seizure control. Notwithstanding this limitation, there is growing evidence that KB are more than just cellular fuels, and can exert profound biochemical, cellular and epigenetic changes favoring an overall attenuation in brain network excitability.

DR. HYMAN+

# Nutraceutical Approaches to Neuroinflammation

# The Big Picture

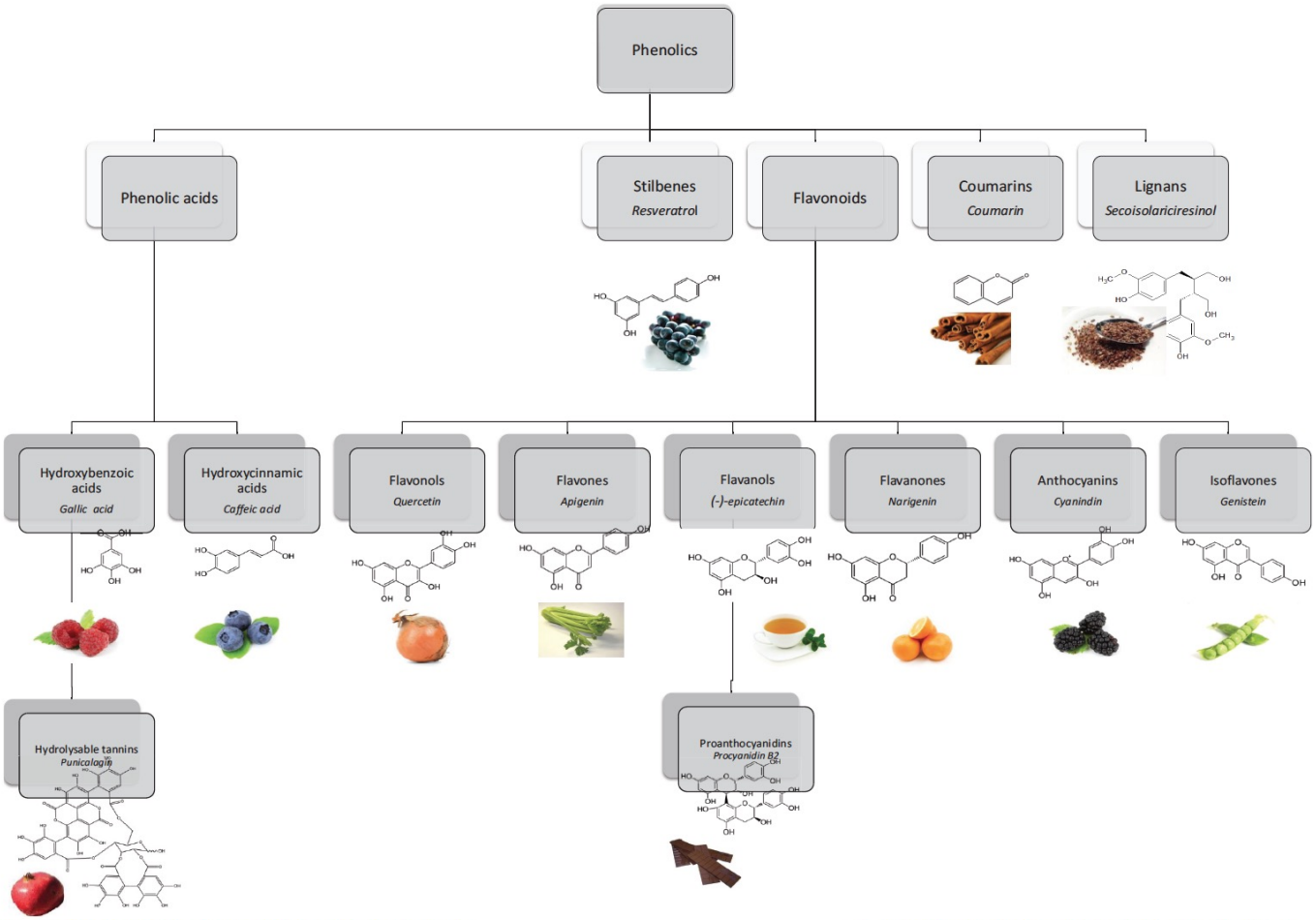


DR. HYMAN+

# Polyphenols

A category of chemicals that naturally occur in plants.

There are more than 500 polyphenols.



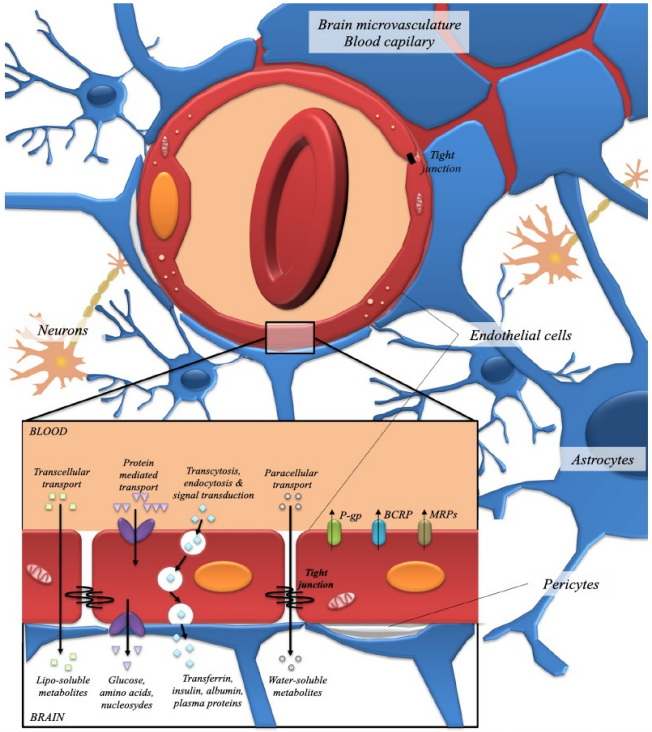

*Polyphenols Beyond Barriers: A Glimpse into the Brain* *Current Neuropharmacology,* **2017**, *Vol. 15, No. 4*

# Key Concepts

- 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.

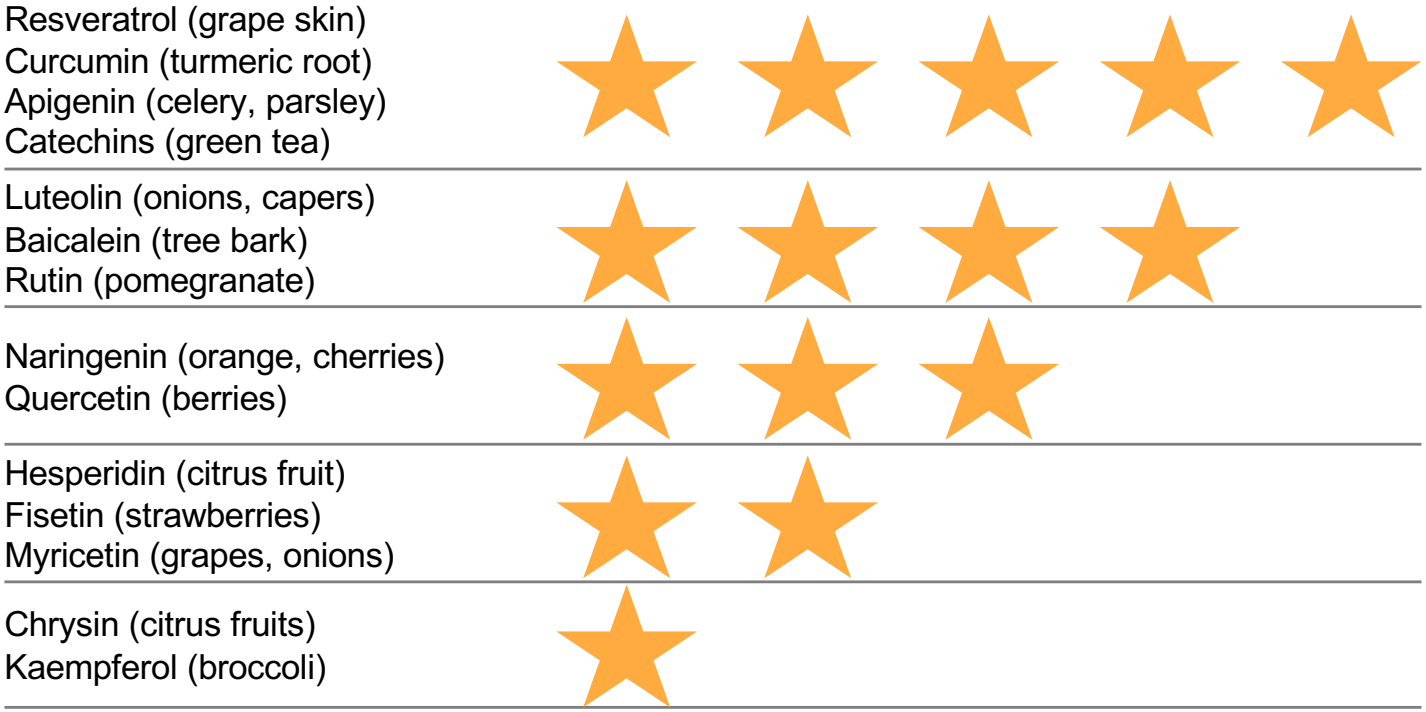
# Natural Compounds That Can Cross the BBB Are Ideal for Neuroinflammation



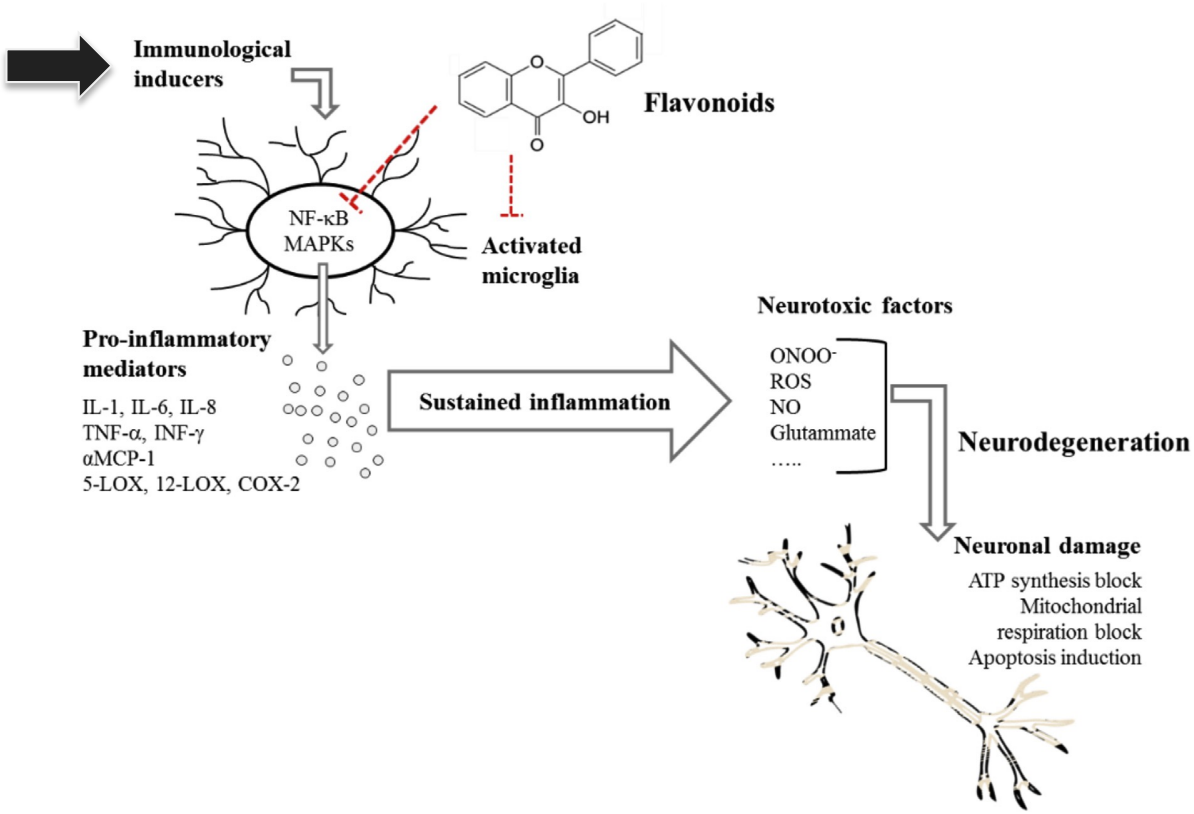

*Polyphenols Beyond Barriers: A Glimpse into the Brain* *Current Neuropharmacology*, 2017, *Vol. 15, No. 4*

| Polyphenol | Evidence of BBB Penetration | Evidence of Neuroprotection | Efflux Transporter Interaction | Experimental Setup | Refs. |
|---|---|---|---|---|---|
| Apigenin | Yes [307] | Yes [307] | P-gp inhibitor | Rat BMEC | [307] |
| | | | P-gp inhibitor | CCRF-CEM, CEM/ADR5000 leukemia cells | [308] |
| | | | BCRP inhibitor | MDA-MB-231-BCRP cells | [308] |
| Catechin / epicatechin | Yes [278] | Yes [309, 310] | P-gp activator | NIH-3T3-G185 cells | [189] |
| | | | MRP2 substrate | Caco-2 cells | [311] |
| | | | MRP1/MRP2 substrate | MDCKII/MRP1 cells & MDCKII/MRP2 cells | [312] |
| Chrysin | N. D. | Yes [313, 314] | P-gp inhibitor | Mouse BMEC | [315] |
| | | | MRP2 substrate | Caco-2 cells | [316] |
| | | | BCRP inhibitor | MCF-7 MX100 cells | [317] |
| Curcumin | Yes [227] | Yes [318] | P-gp inhibitor | MCF-7 cells | [319] |
| | | | BCRP inhibitor | Rat brain capillaries | [320] |
| Fisetin | Yes [321] | Yes [321] | MRPs inhibitor | Caco-2 cells | [322] |
| Genistein | Yes [323] | Yes [324, 325] | P-gp inhibitor | MCF7/BC19-3, rats | [326, 327] |
| | | | MRP2 inhibitor | TR-rats | [328] |
| | | | BCRP inhibitor | K562/BCRP cells | [329] |
| Hesperitin | Yes [260] | Yes [330] | P-gp inhibitor | Mouse BMEC | [315] |
| | | | BCRP inhibitor | ABCG2 over-expressing cells | [331] |
| Kaempferol | Yes [307] | Yes [332] | P-gp inhibitor | Mouse BMEC | [315] |
| | | | MRPs inhibitor | Human glioblastoma cell line T98G | [333] |
| | | | BCRP inhibitor | MDCK/Bcrp1 cells | [334] |
| Myricetin | Yes [335] | Yes [335] | P-gp inhibitor | MCF-7/ADR cells | [336] |
| | | | BCRP inhibitor | HEK293/ABCG2 cells | [280] |
| Naringenin | Yes [287, 337] | Yes [338] | P-gp inhibitor | Mouse BMEC | [315] |
| | | | MRPs inhibitor | HEK293/ABCG2 cells | [280] |
| Quercetin | Yes [261] | Yes [339] | P-gp inhibitor | Mouse BMEC | [315] |
| | | | MRPs inhibitor | HEK293/MRP1, HEK/MRP4, HEK/MRP5 cells | [340] |
| | | | BCRP inhibitor | ABCG2 over-expressing cells | [331] |
| Resveratrol | Yes [341] | Yes [342] | P-gp inhibitor | MCF-7/ADR cells | [343] |
| | | | BCRP inhibitor | ABCG2 over-expressing cells | [331] |
| Rutin | Yes [307] | Yes [344] | P-gp inhibitor | Rat BMEC | [307] |

# Ratings of Polyphenols in Clinical Practice for Neuroinflammation



# The Basic Concept



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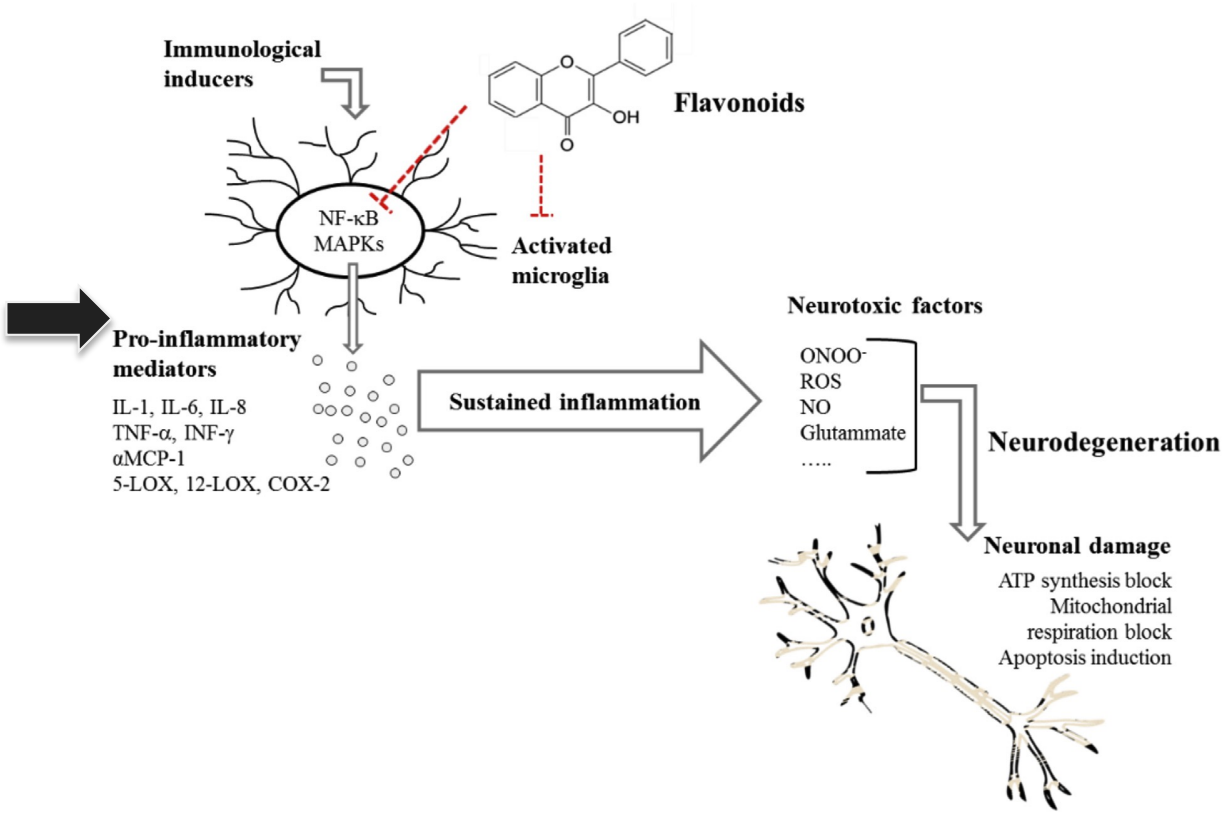

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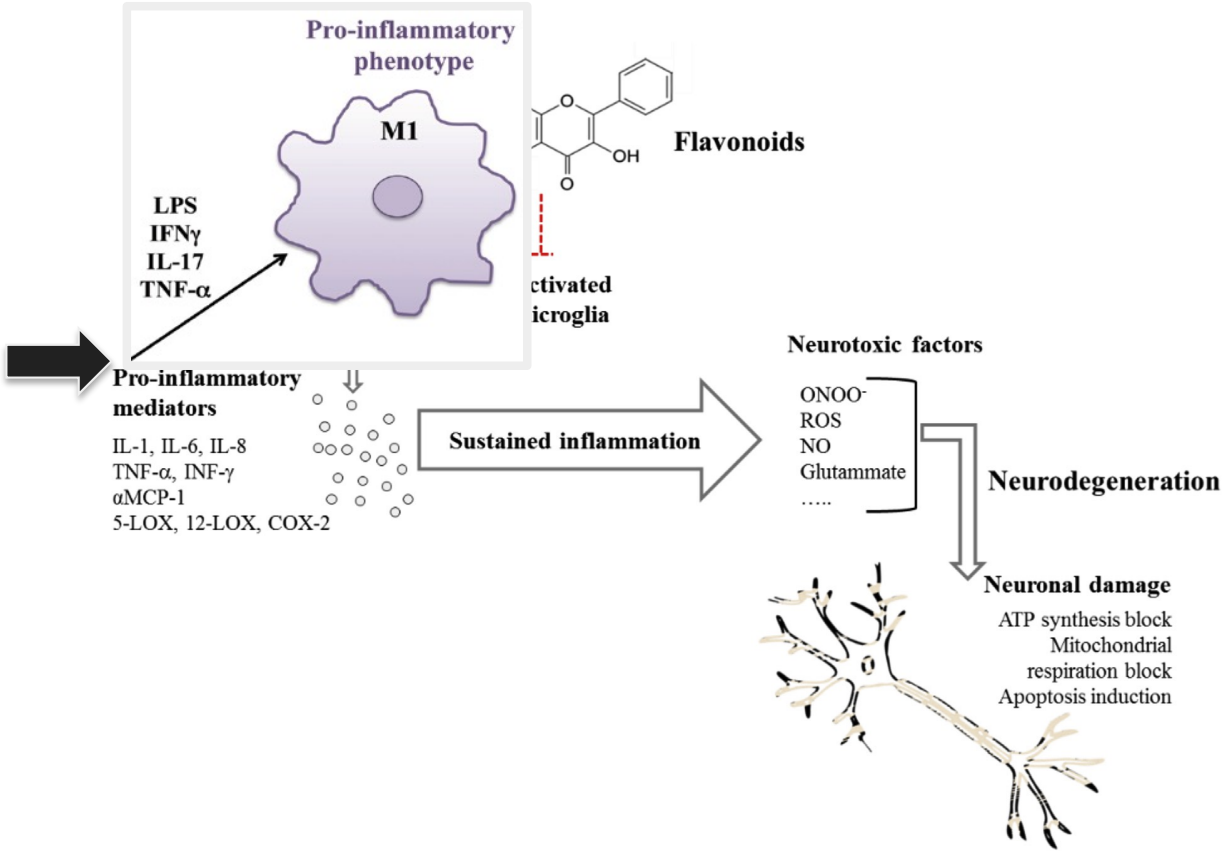

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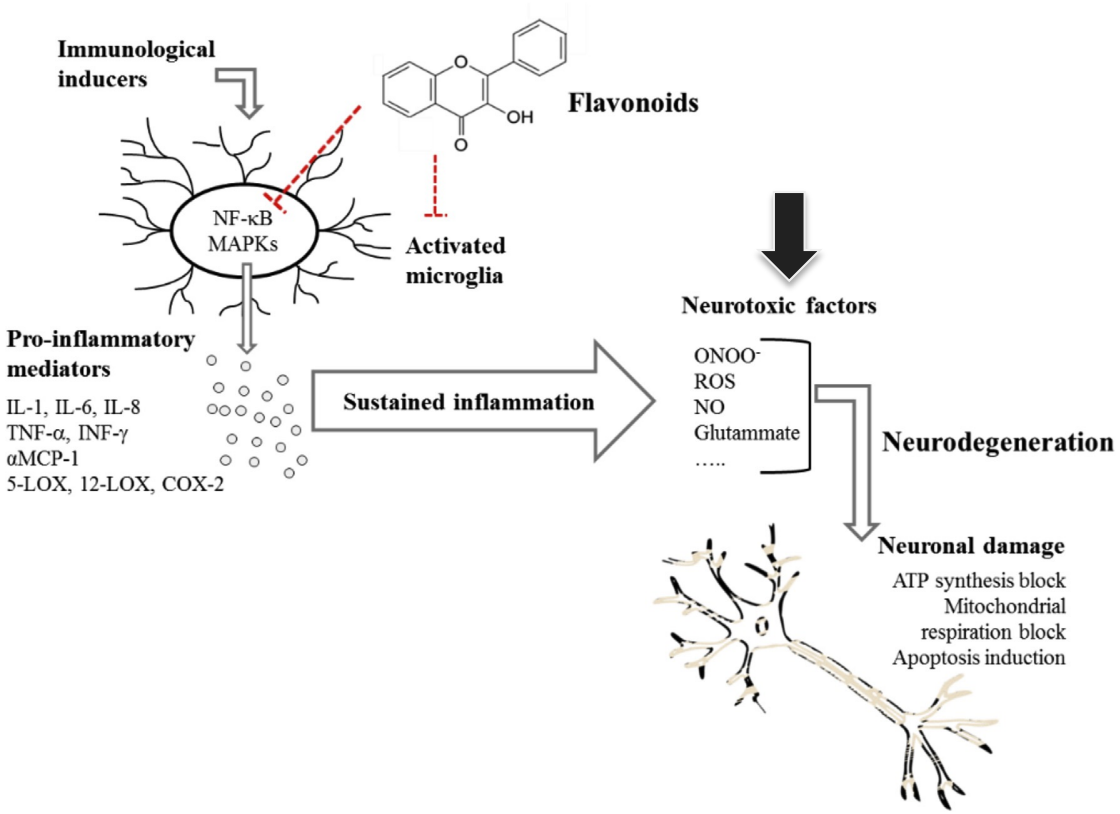
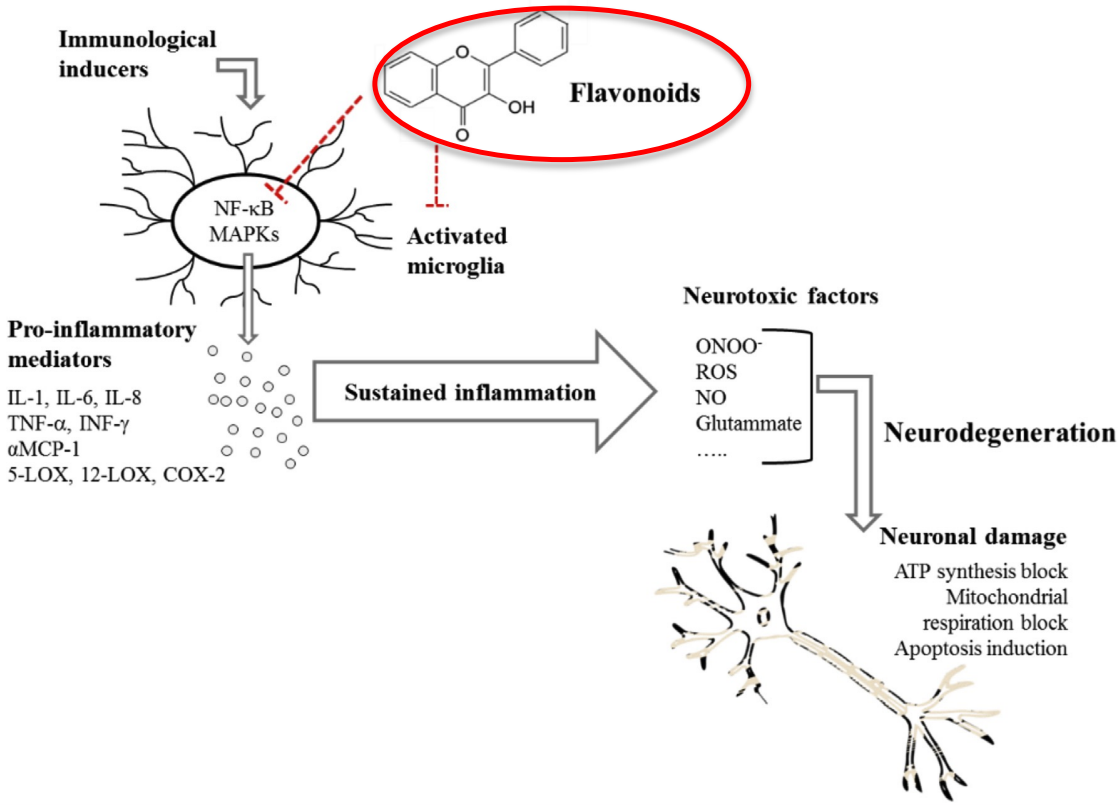
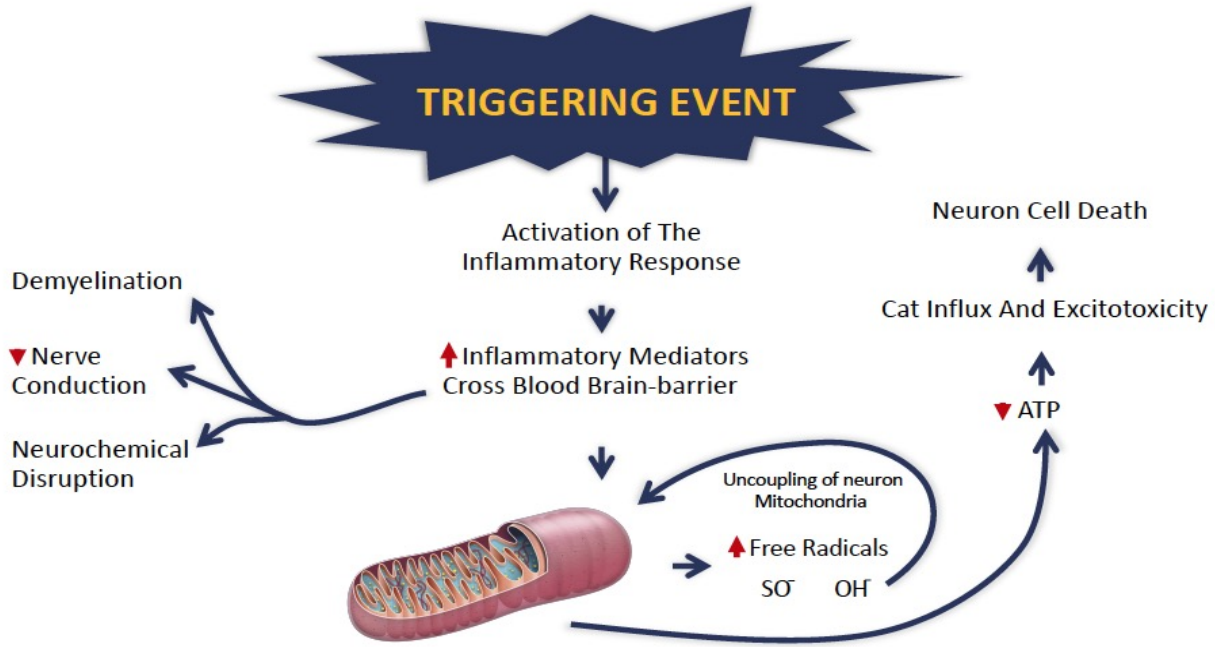
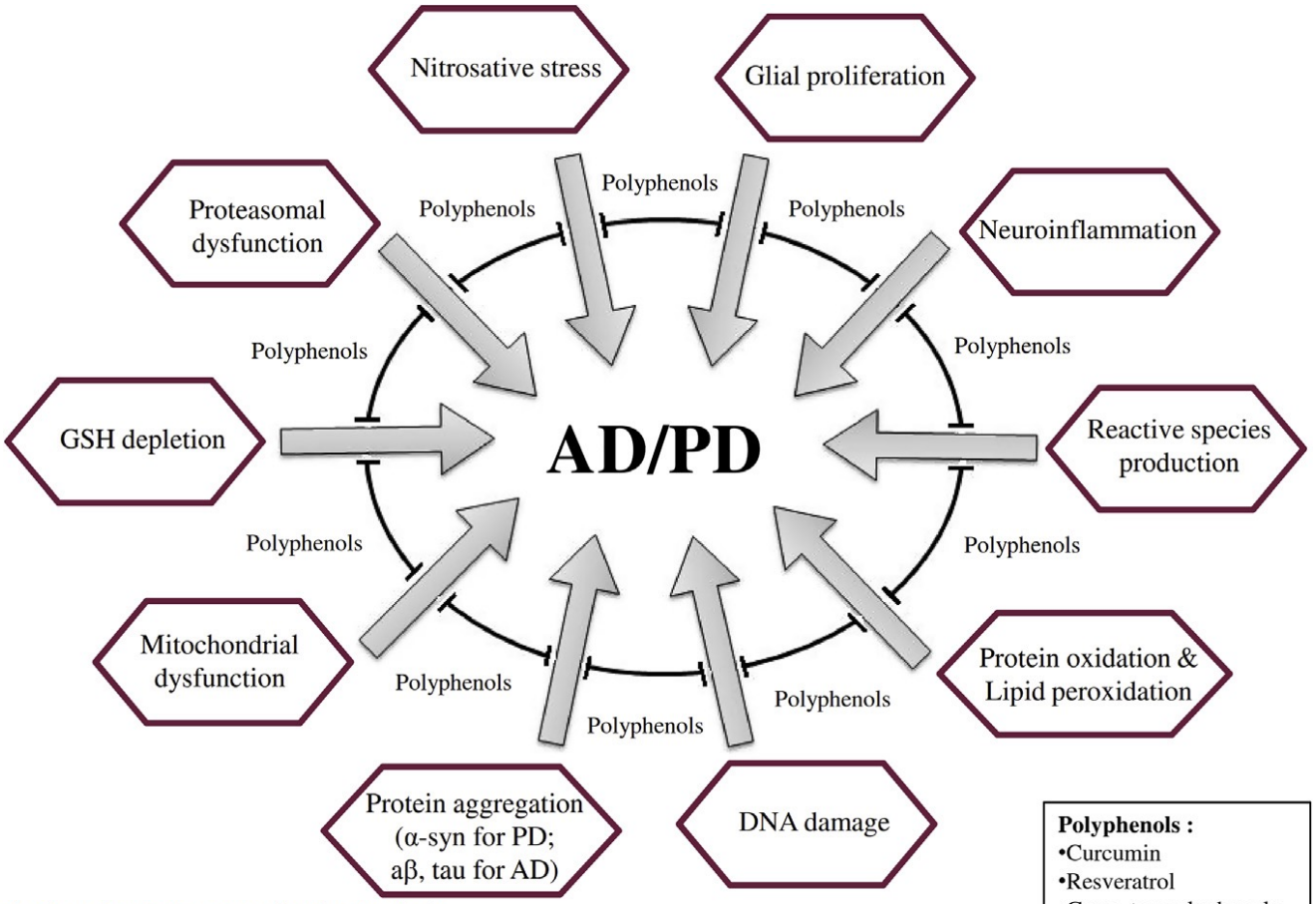


# The Basic Concept




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




Bioavailability of dietary polyphenols: Factors contributing to their clinical application in CNS diseases Neurochemistry International 89 (2015) 198–208

# Key Concepts

- Polyphenols do not have the same impact on everyone.
- Polyphenols only become active when they are converted to metabolites by enzymes in the microbiome.
- Different microbiomes have different responses to polyphenols.

ACS Chemical Neuroscience

Letter

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# Pomegranate's Neuroprotective Effects against Alzheimer's Disease Are Mediated by Urolithins, Its Ellagitannin-Gut Microbial Derived Metabolites

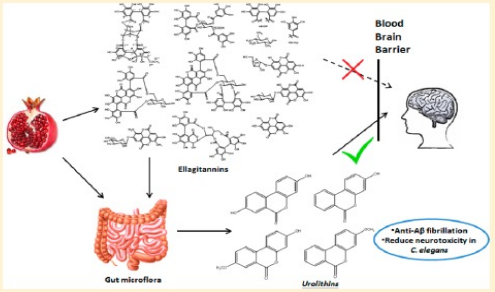
Tao Yuan,[†] Hang Ma,[†] Weixi Liu,[†] Daniel B. Niesen,[†] Nishan Shah,[†] Rebecca Crews,[‡] Kenneth N. Rose,[†] Dhiraj A. Vattem,[‡] and Navindra P. Seeram*[,†]

[†]Bioactive Botanical Research Laboratory, Department of Biomedical and Pharmaceutical Sciences, College of Pharmacy, University of Rhode Island, Kingston, Rhode Island 02881, United States

[‡]Nutrition Biomedicine and Biotechnology, Texas State University, San Marcos, Texas 78666, United States

Supporting Information

**ABSTRACT:** Pomegranate shows neuroprotective effects against Alzheimer's disease (AD) in several reported animal studies. However, whether its constituent ellagitannins and/or their physiologically relevant gut microbiota-derived metabolites, namely, urolithins (6*H*-dibenzo[*b*,*d*]pyran-6-one derivatives), are the responsible bioactive constituents is unknown. Therefore, from a pomegranate extract (PE), previously reported by our group to have anti-AD effects in vivo, 21 constituents, which were primarily ellagitannins, were isolated and identified (by HPLC, NMR, and HRESIMS). In silico computational studies, used to predict blood-brain barrier permeability, revealed that none of the PE constituents, but the urolithins, fulfilled criteria required for penetration. Urolithins prevented $\beta$-amyloid fibrillation in vitro and methyl-urolithin B (3-methoxy-6*H*-dibenzo[*b*,*d*]pyran-6-one), but not PE or its predominant ellagitannins, had a protective effect in *Caenorhabditis elegans* post induction of amyloid $\beta_{1-42}$ induced neurotoxicity and paralysis. Therefore, urolithins are the possible brain absorbable compounds which contribute to pomegranate's anti-AD effects warranting further in vivo studies on these compounds.




**KEYWORDS:** *Pomegranate, Alzheimer's disease, microbial metabolites, ellagitannins, urolithins, blood-brain barrier*

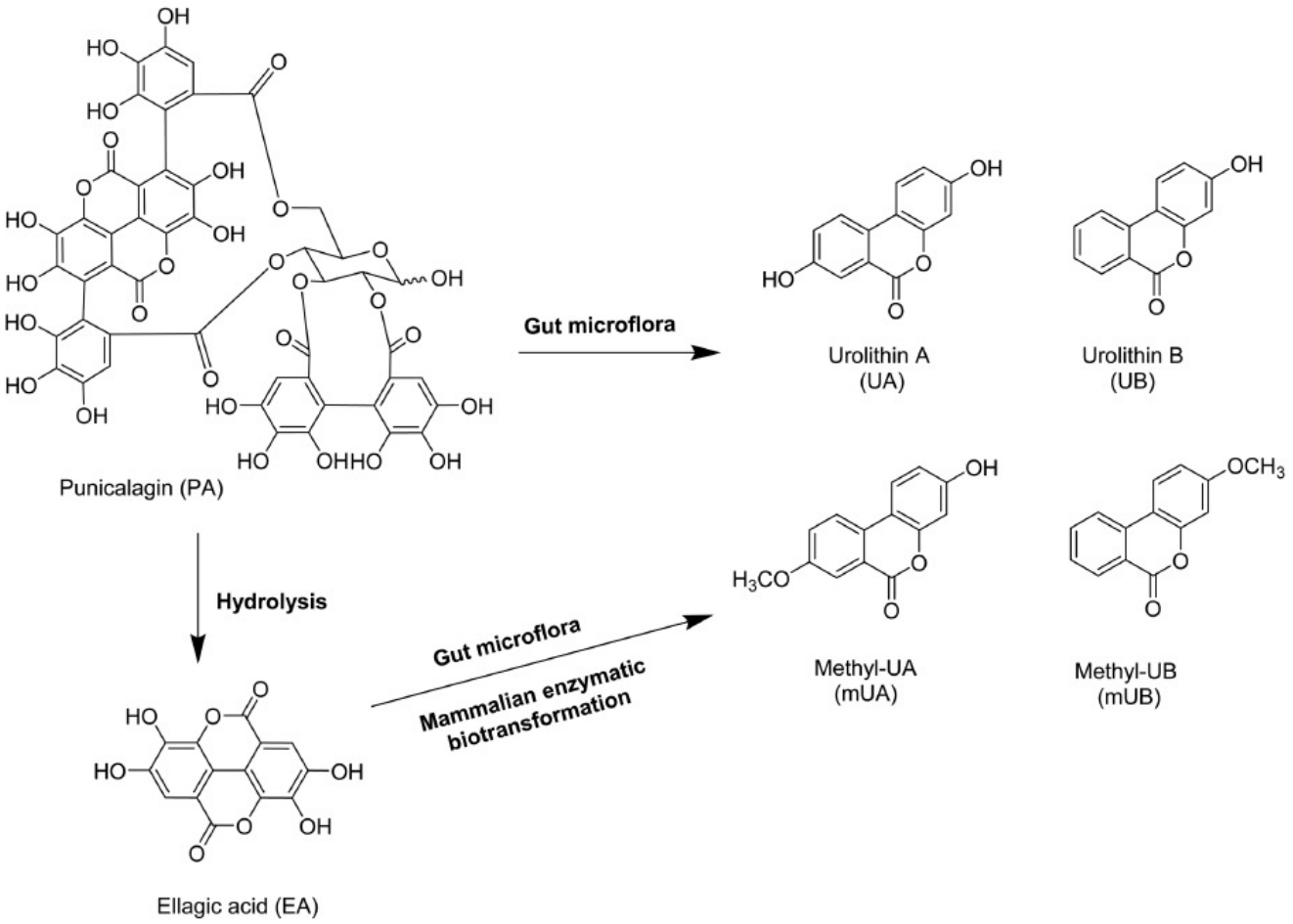

Punicalagin (PA)
Gut microflora
Urolithin A
(UA)
Urolithin B
(UB)
Hydrolysis
Gut microflora
Mammalian enzymatic
biotransformation
Methyl-UA
(mUA)
Methyl-UB
(mUB)
Ellagic acid (EA)

**Table 1**
Summary of the bioavailability of polyphenols and their metabolites in the brain following oral administration.

| Polyphenols | Source | Metabolites | Oral dose | Brain (pmol/g) | Reference |
|---|---|---|---|---|---|
| Quercetin | Fruits, vegetables, leaves, grains | quercetin-3-*O*-glucuronide | 0.09 mg/g | 2.41 ± 0.47 | (Wang et al., 2014) |
| | | OMe-quercetin-*O*-glucuronide | 0.09 mg/g | 0.69 ± 0.05 | (Wang et al., 2014) |
| Catechin | Green tea, peaches, vinegar, red wine | catechin-5-*O*-glucuronide | 5.6 mg/g | 485.79 ± 85.07 | (Wang et al., 2014) |
| | | 3-*O*-Me-Catechin-5-*O*-Glucuronide | 5.6 mg/g | 664.29 ± 133.65 | (Wang et al., 2014) |
| Epicatechin | | epicatechin-5-*O*-glucuronide | 6.49 mg/g | 637.22 ± 93.85 | (Wang et al., 2014) |
| | | 3-*O*-Me-epicatechin-5-*O*-glucuronide | 6.49 mg/g | 853.83 ± 142.77 | (Wang et al., 2014) |
| Malvidin glucoside | Grapes, berries, red wine | malvidin glucoside | 0.014 mg/g | 0.17 ± 0.02 | (Wang et al., 2014) |
| | | malvidin-3-glucoside | 585.09 μg/g | 12.3 ± 3.85 | (Ho et al., 2013) |
| | | malvidin-3-glucopyruvate | 334.86 μg/g | 6.4 ± 5.2 | (Ho et al., 2013) |
| Resveratrol | Red wine, grapes | resveratrol-3-*O*-glucuronide | 114 mg/g | 746.57 ± 121.73 | (Wang et al., 2014) |
| Petunidin glucoside | Red berries | – | 0.015 mg/g | 0.10 ± 0.00 | (Wang et al., 2014) |
| Delphinidin glucoside | Canberries, pomegranate, concord grapes | – | 0.03 mg/g | 0.07 ± 0.00 | (Wang et al., 2014) |
| Peonidin glucoside | Peony, roses, blue flowers | – | 0.01 mg/g | 0.12 ± 0.01 | (Wang et al., 2014) |
| Cyanidin glucoside | Grapes, bilberry, blackberry, blueberry, cherry, canberry, elderberry, hawthorn, loganberry, acaiberry, raspberry, apple, plum, red cabbage, red onion | – | 0.023 mg/g | 0.07 ± 0.00 | (Wang et al., 2014) |

Bioavailability of dietary polyphenols: Factors contributing to their clinical application in CNS diseases Neurochemistry International 89 (2015) 198–208

# Metabolites are synthesized by the microbiome

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Bioavailability of dietary polyphenols: Factors contributing to their clinical application in CNS diseases Neurochemistry International 89 (2015) 198–208

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# The gut microbiota composition affects dietary polyphenols-mediated cognitive resilience in mice by modulating the bioavailability of phenolic acids

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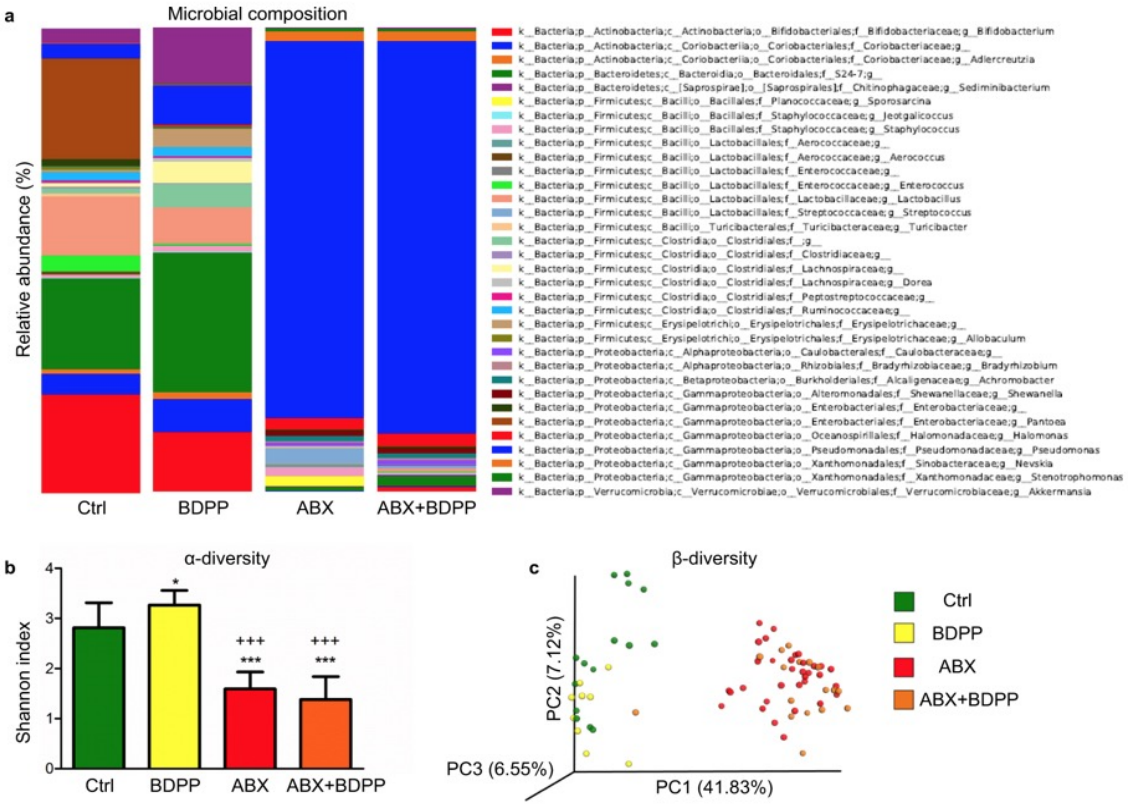
Tal Frolinger[1], Steven Sims[1], Chad Smith[1], Jun Wang[1], Haoxiang Cheng[3,4], Jeremiah Faith[3], Lap Ho[1], Ke Hao[3,4] & Giulio M. Pasinetti[1,2]

Dietary polyphenols promote memory in models of sleep deprivation (SD), stress, and neurodegeneration. The biological properties of dietary polyphenols greatly depend upon the bioavailability of their phenolic metabolites derivatives, which are modulated by gut microbiota. We recently demonstrated that supplementation with grape-derived bioactive dietary polyphenol preparation (BDPP) improves SD-induced cognitive impairment. This study examined the role of the gut microbiota in the ability of BDPP to prevent memory impairment in response to SD. C57BL6/J mice, treated with antibiotics mix (ABX) or BDPP or both, were sleep-deprived at the end of a fear conditioning training session and fear memory was assessed the next day. Gut microbiota composition was analyzed in fecal samples and BDPP-driven phenolic acid metabolites extraction was measured in plasma. We report that the beneficial effect of BDPP on memory in SD is attenuated by ABX-induced dysbiosis. We identified specific communities of fecal microbiota that are associated with the bioavailability of BDPP-derived phenolic acids, which in turn, are associated with memory promotion. These results suggest the gut microbiota composition significantly affects the bioavailability of phenolic acids that drive the dietary polyphenols' cognitive resilience property. Our findings provide a preclinical model with which to test the causal association of gut microbiota-polyphenols, with the ultimate goal of potential developing dietary polyphenols for the prevention/treatment of cognitive impairment.

# Figure 3

From: The gut microbiota composition affects dietary polyphenols-mediated cognitive resilience in mice by modulating the bioavailability of phenolic acids




*Scientific Reports* **9**, Article number: 3546 (2019)

# Key Concepts

- Polyphenols only become active when they are converted to metabolites by enzymes in the microbiome.

- They are not able to cross the blood-brain barrier until they are metabolized by the microbiome metabolites.

3950 J. Agric. Food Chem. 2010, 58, 3950–3956
DOI:10.1021/jf903529m

JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY
ARTICLE

# Xenobiotic Metabolism and Berry Flavonoid Transport across the Blood−Brain Barrier†

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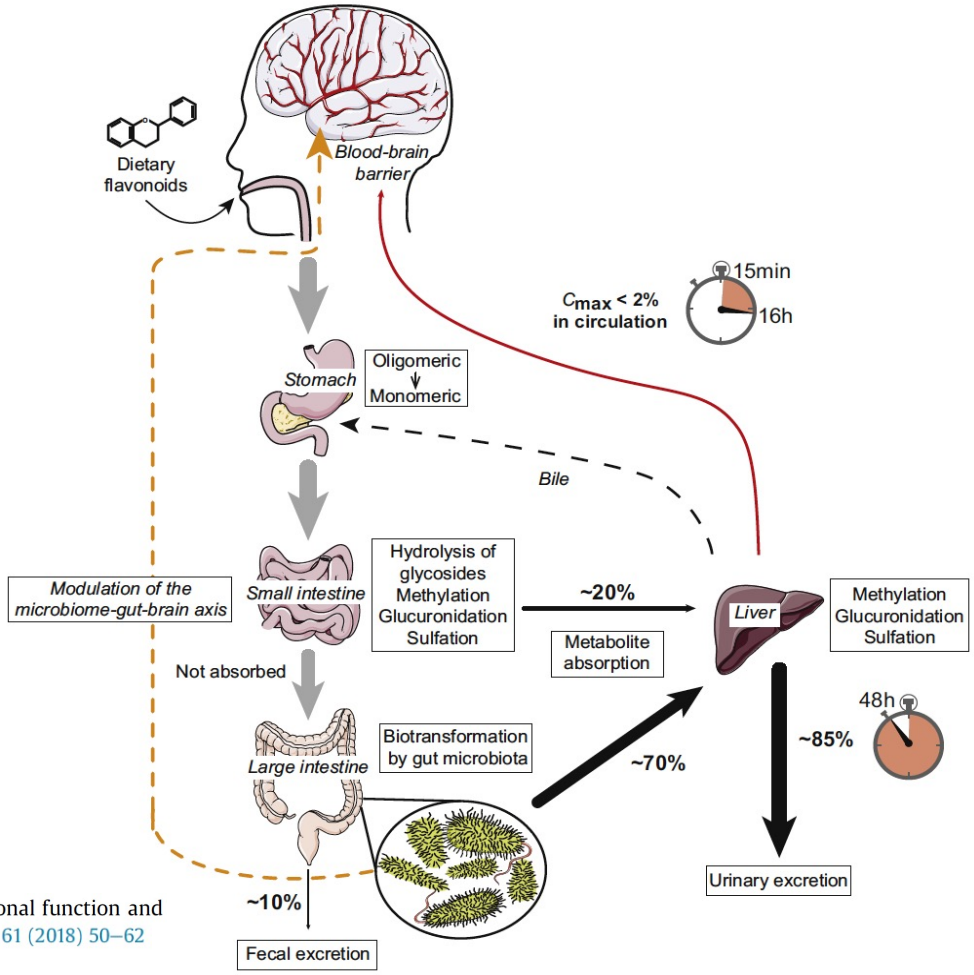
§Jean Mayer USDA Human Nutrition Center on Aging at Tufts University, Boston, Massachusetts 02111, and #Atlantic Food and Horticulture Research Centre, Agriculture and Agri-Food Canada, Kentville, Nova Scotia B4N 1J5, Canada

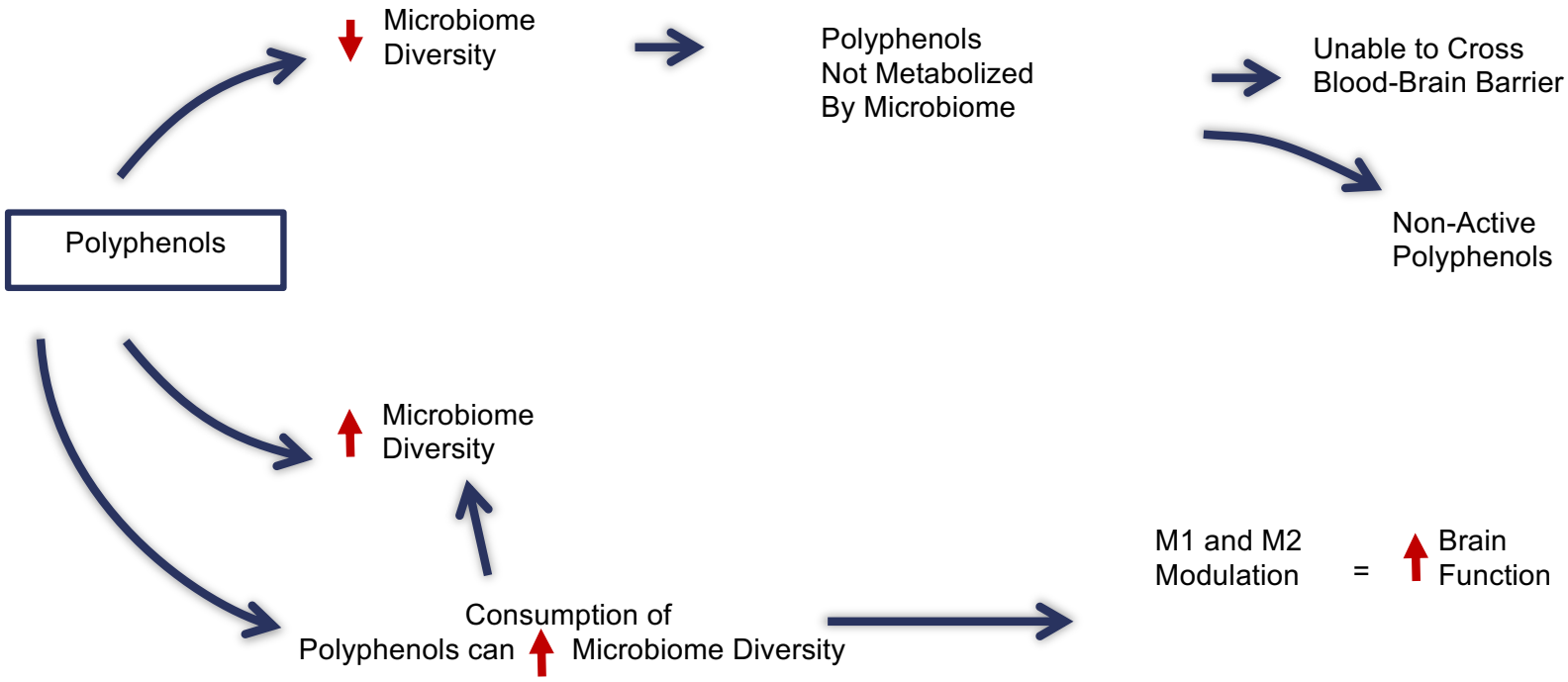
A compelling body of literature suggests berry phytochemicals play beneficial roles in reversing age-related cognitive impairment and protect against neurodegenerative disorders. Anthocyanins are bioactive phytochemicals in berries suspected to be responsible for some of these neuroprotective effects. The plausible mechanisms of anthocyanin bioactivity in brain tissue are dependent on their bioavailability to the brain. Pigs were fed 2% whole freeze-dried, powdered blueberry in the diet for 8 weeks. Anthocyanin and anthocyanin glucuronides were measured in the cortex, cerebellum, and midbrain and diencephalon by LC-MS/MS. Anthocyanins and their glucuronides were found in the range of femtomoles per gram of fresh weight of tissue at 18 h postprandial, after anthocyanins had been removed from the blood by xenobiotic metabolism. Xenobiotic metabolism, anthocyanin interaction, and transporter barriers to brain bioavailability are briefly discussed. The plausible mechanism of neuroprotective action of anthocyanins may be via modulation of signal transduction processes and/or gene expression in brain tissue rather than by direct antioxidant radical quenching.

KEYWORDS: Berries; blueberries; anthocyanins; brain; bioavailability; xenobiotic; hormesis; metabolism




Mechanisms of dietary flavonoid action in neuronal function and neuroinflammation Molecular Aspects of Medicine 61 (2018) 50–62

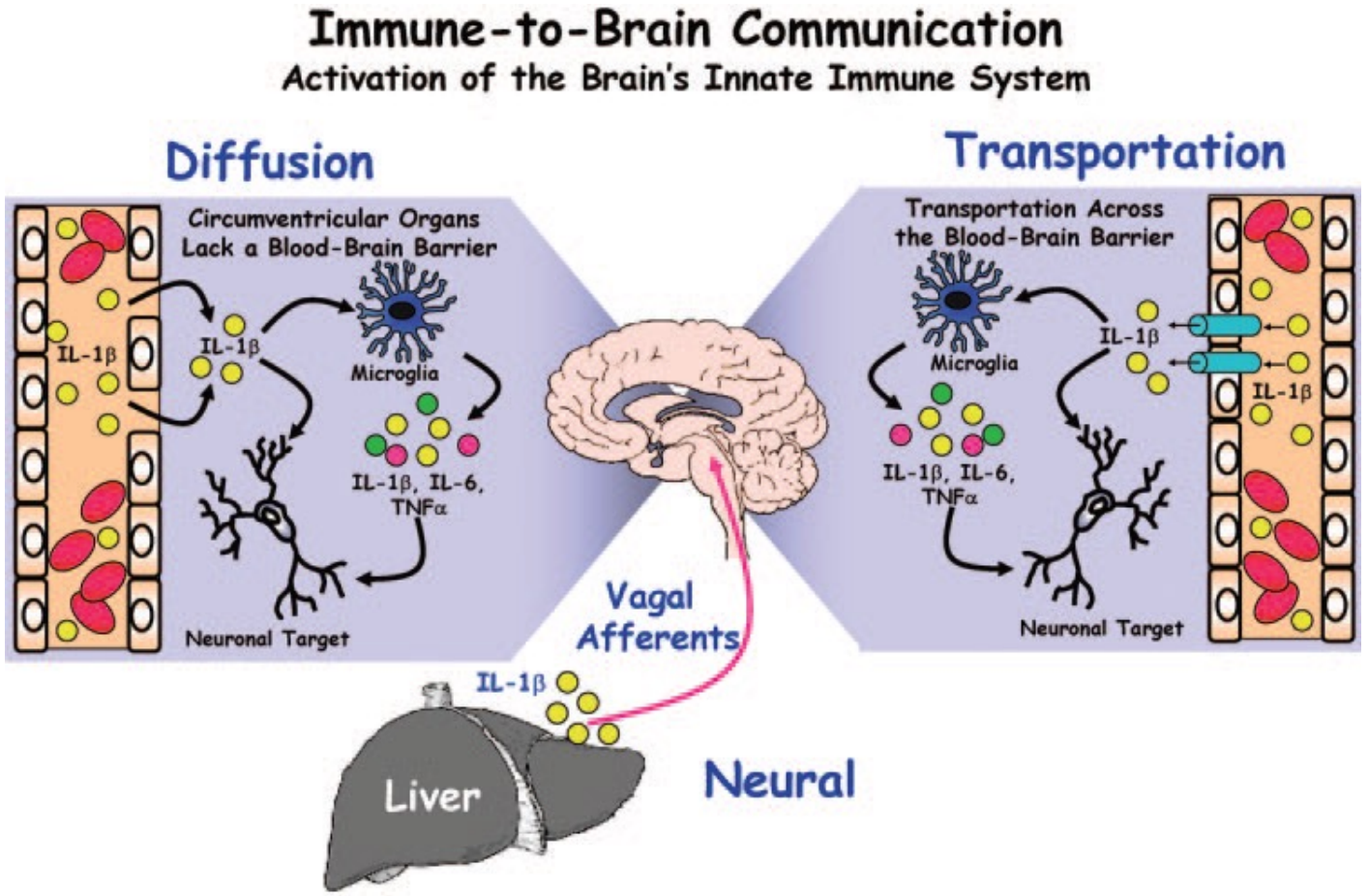
# Polyphenols and Gut Microbiome

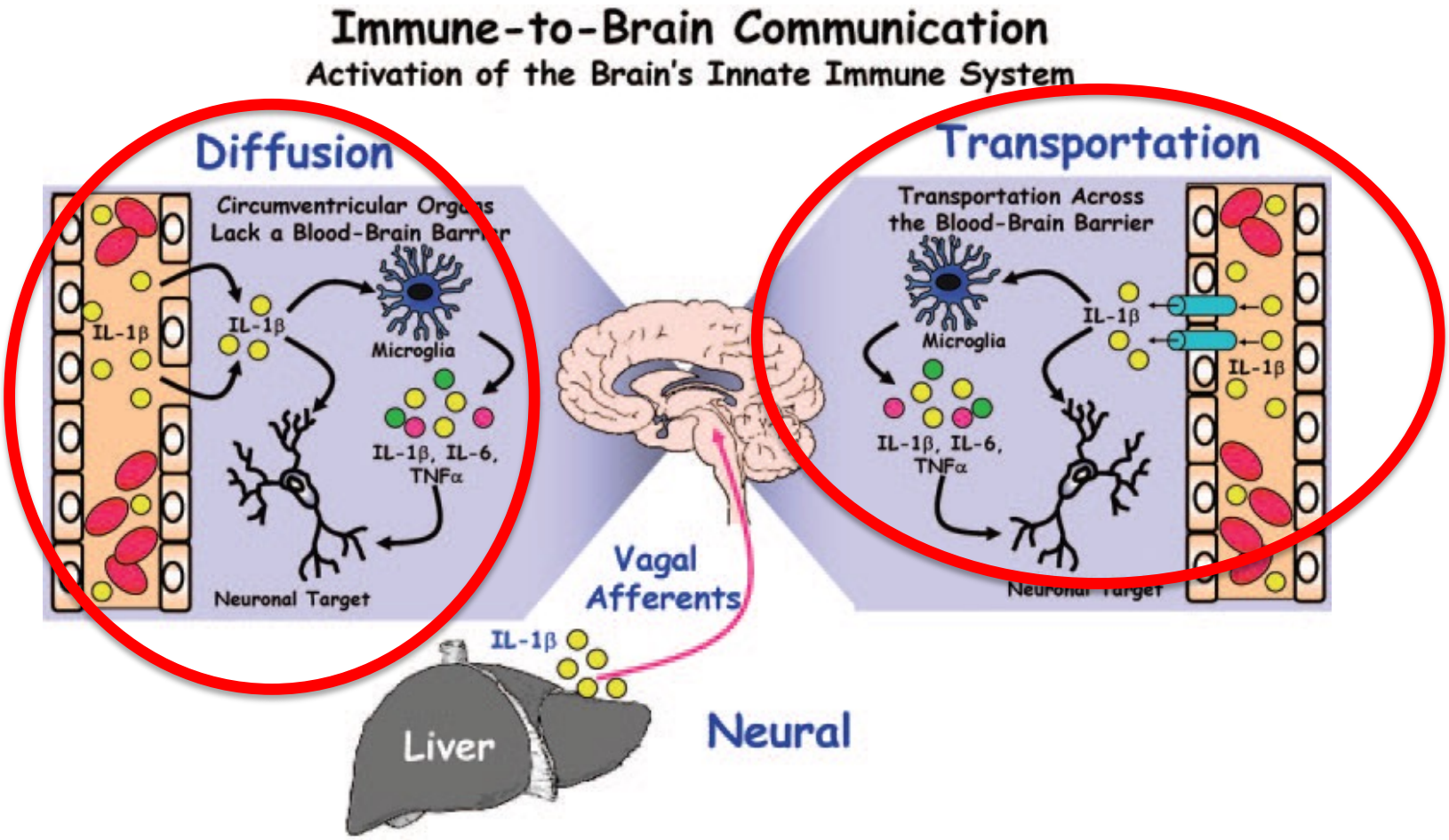


# Clinical Pearls

- Please note that polyphenols may not cross an inflamed/permeable blood-brain barrier.

- These flavonoids cross the brain through healthy active and passive diffusion pathways.


Immune-to-Brain Communication
Activation of the Brain's Innate Immune System
Diffusion
Transportation
Circumventricular Organs
Lack a Blood-Brain Barrier
IL-1β
IL-1β
Microglia
IL-1β, IL-6,
TNFα
Neuronal Target
Transportation Across
the Blood-Brain Barrier
Microglia
IL-1β
IL-1β
IL-1β, IL-6,
TNFα
Neuronal Target
Vagal
Afferents
IL-1β
Liver
Neural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Afferents
IL-1β
Liver
Neural

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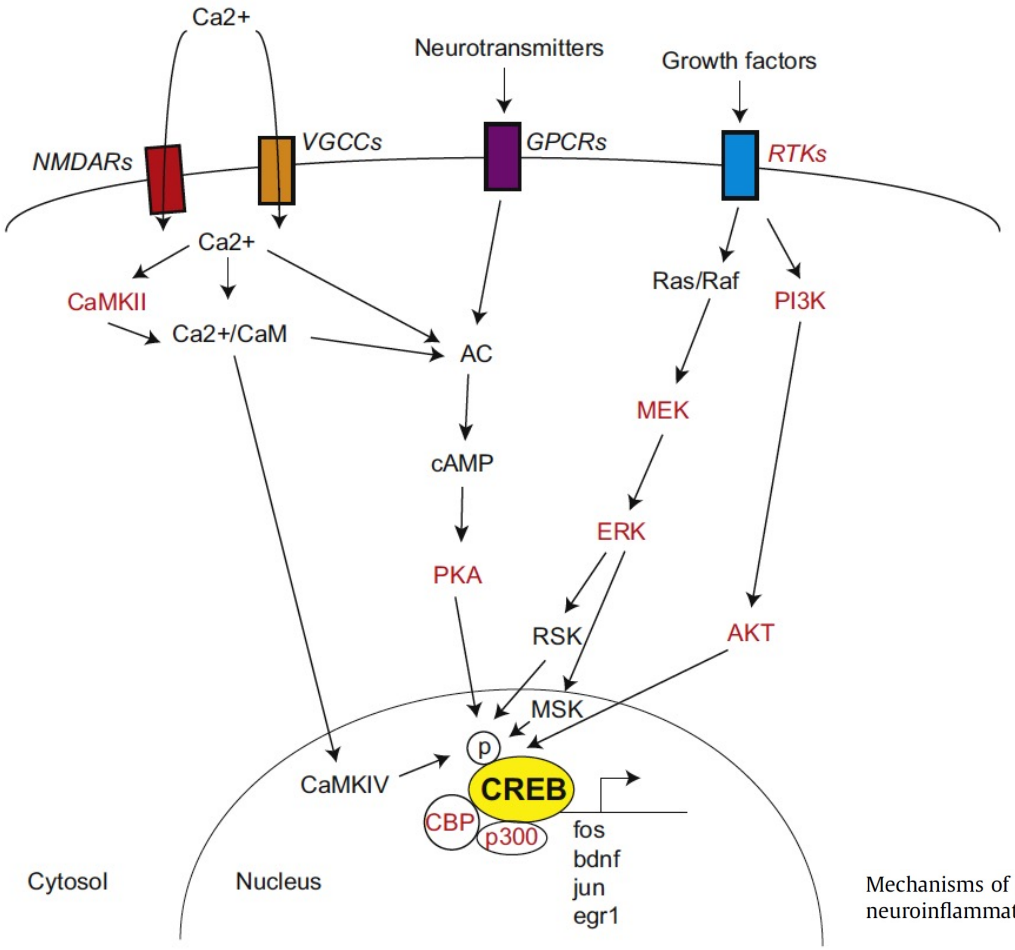
# Key Pathways of Polyphenols




Mechanisms of dietary flavonoid action in neuronal function and neuroinflammation Molecular Aspects of Medicine 61 (2018) 50–62

**Table 1**
Studies showing an interaction of single flavonoids with the CREB pathway.

| Model | Compound | Dose | Route | Duration | Memory measure |
|---|---|---|---|---|---|
| Aβ injected rats | 5-Hydroxy-6,7,4′-trimethoxyflavone, apigenin | 1 mg/kg | p.o. | 7d | passive avoidance |
| Aβ injected rats | Rutin | 100 mg/kg | i.p. | 3wk | passive avoidance |
| Aβ injected mice | Quercetin | 20 mg/kg | p.o. | 8d | MWM, passive avoidance |
| Aβ injected mice | Apigenin | 10-20 mg/kg | p.o. | 8d | MWM |
| Aβ injected mice | Fustin | 50-100 mg/kg | p.o. | 11d | contextual and tone fear, passive avoidance |
| APP/PS1 transgenic mice | Apigenin | 40 mg/kg | p.o. | 3mo | MWM |
| APP/PS1 transgenic mice | Pinocembrin | 40 mg/kg | p.o. | 12wk | MWM, passive avoidance |
| Tg2576 AD transgenic mice | 3′-*O*-methyl-epicatechin-5-*O*-β-glucuronide | 300 nM | *in vitro* | acute | LTP |
| MK801 model of schizophrenia in rats | 7,8-dihydroxyflavone | 5 mg/kg | i.p. | 14d | MWM, LTP |
| High fat diet in young mice | Quercetin | 0.01% in diet | p.o. | 12wk | MWM |
| High-cholesterol-induced cognitive deficits in young mice | Troxerutin | 150 mg/kg | p.o. | 20wk | MWM, passive avoidance |
| Young mice | Spinosin | 5 mg/kg | p.o. | 14d | passive avoidance |
| Young rats and mice | Fisetin | 1 μM; 10-25 mg/kg | *in vitro*; p.o. | acute | LTP; novel object |
| Young rats | Baicalein | 1-10 μM; 20 mg/kg | *in vitro*; i.p. | acute | LTP, contextual fear conditioning |
| Young mice | Baicalein | 20 mg/kg | p.o. | acute | MWM, passive avoidance |
| Young mice; rat primary hippocampal neurons | 4′-demethylnobiletin | 30 μM; 10-50 mg/kg | *in vitro*; i.p. | acute; 7d | contextual fear conditioning |
| mouse primary cortical neurons | (−)Epicatechin | 100-300 nM | *in vitro* | acute | None |

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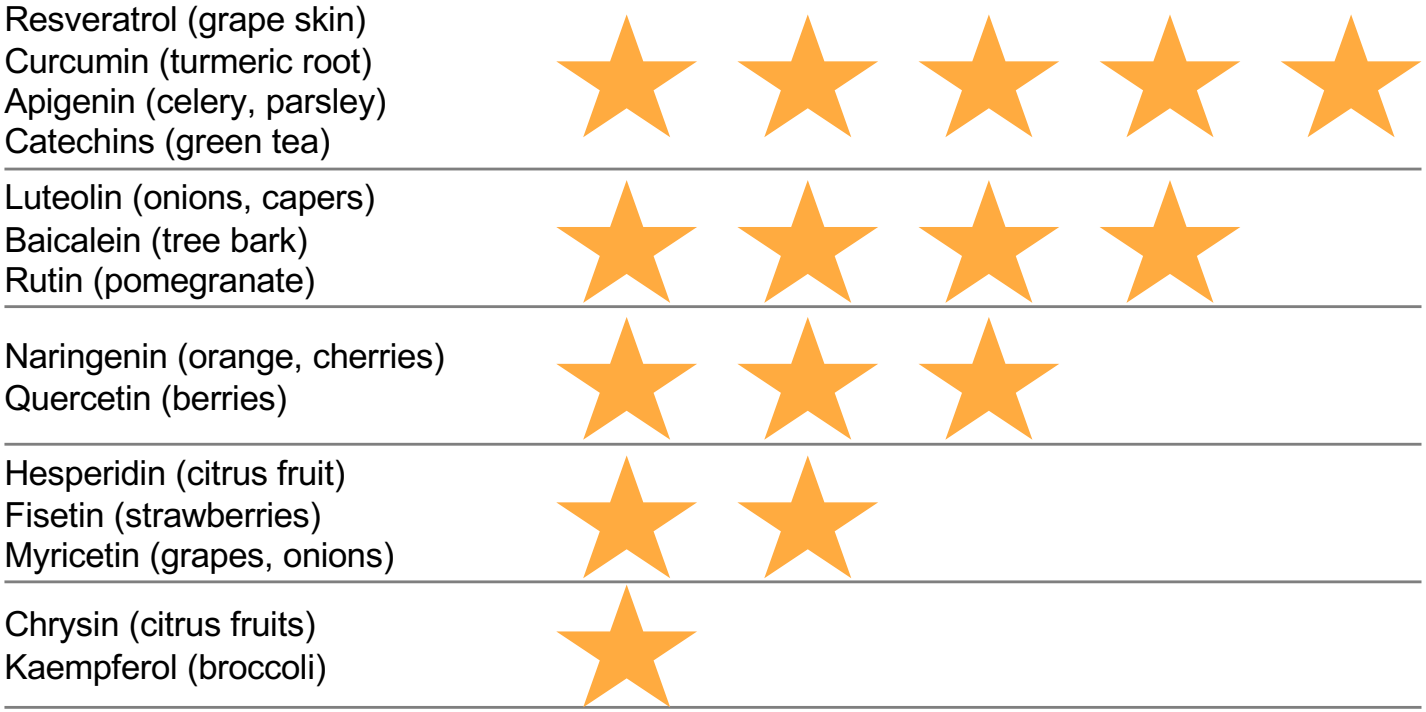
| Aβ injected rats | 5-Hydroxy-6,7,4′-trimethoxyflavone, apigenin | 1 mg/kg | p.o. | 7d | passive avoidance |
| Aβ injected rats | Rutin | 100 mg/kg | i.p. | 3wk | passive avoidance |
| Aβ injected mice | Quercetin | 20 mg/kg | p.o. | 8d | MWM, passive avoidance |
| Aβ injected mice | Apigenin | 10-20 mg/kg | p.o. | 8d | MWM |
| Aβ injected mice | Fustin | 50-100 mg/kg | p.o. | 11d | contextual and tone fear, passive avoidance |
| APP/PS1 transgenic mice | Apigenin | 40 mg/kg | p.o. | 3mo | MWM |
| APP/PS1 transgenic mice | Pinocembrin | 40 mg/kg | p.o. | 12wk | MWM, passive avoidance |
| Tg2576 AD transgenic mice | 3′-*O*-methyl-epicatechin-5-*O*-β-glucuronide | 300 nM | *in vitro* | acute | LTP |
| MK801 model of schizophrenia in rats | 7,8-dihydroxyflavone | 5 mg/kg | i.p. | 14d | MWM, LTP |
| High fat diet in young mice | Quercetin | 0.01% in diet | p.o. | 12wk | MWM |
| High-cholesterol-induced cognitive deficits in young mice | Troxerutin | 150 mg/kg | p.o. | 20wk | MWM, passive avoidance |
| Young mice | Spinosin | 5 mg/kg | p.o. | 14d | passive avoidance |
| Young rats and mice | Fisetin | 1 μM; 10-25 mg/kg | *in vitro*; p.o. | acute | LTP; novel object |
| Young rats | Baicalein | 1-10 μM; 20 mg/kg | *in vitro*; i.p. | acute | LTP, contextual fear conditioning |
| Young mice | Baicalein | 20 mg/kg | p.o. | acute | MWM, passive avoidance |
| Young mice; rat primary hippocampal neurons | 4′-demethylnobiletin | 30 μM; 10-50 mg/kg | *in vitro*; i.p. | acute; 7d | contextual fear conditioning |
| mouse primary cortical neurons | (−)Epicatechin | 100-300 nM | *in vitro* | acute | None |

Mechanisms of dietary flavonoid action in neuronal function and neuroinflammation Molecular Aspects of Medicine 61 (2018) 50–62

# Ratings of Polyphenols in Clinical Practice for Neuroinflammation



Brief Reviews

THE JOURNAL OF IMMUNOLOGY

# The Role of the Transcription Factor CREB in Immune Function

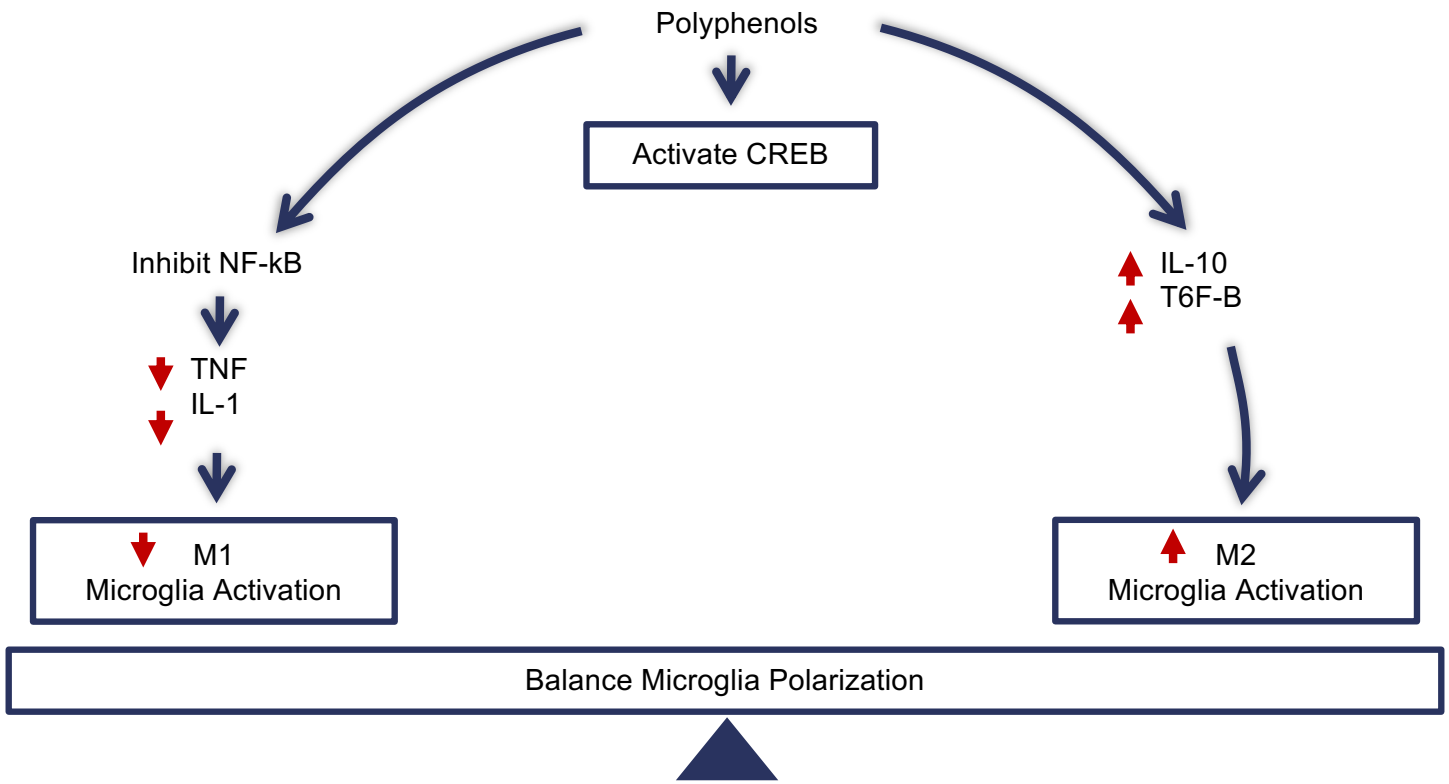
Andy Y. Wen,* Kathleen M. Sakamoto,† and Lloyd S. Miller‡

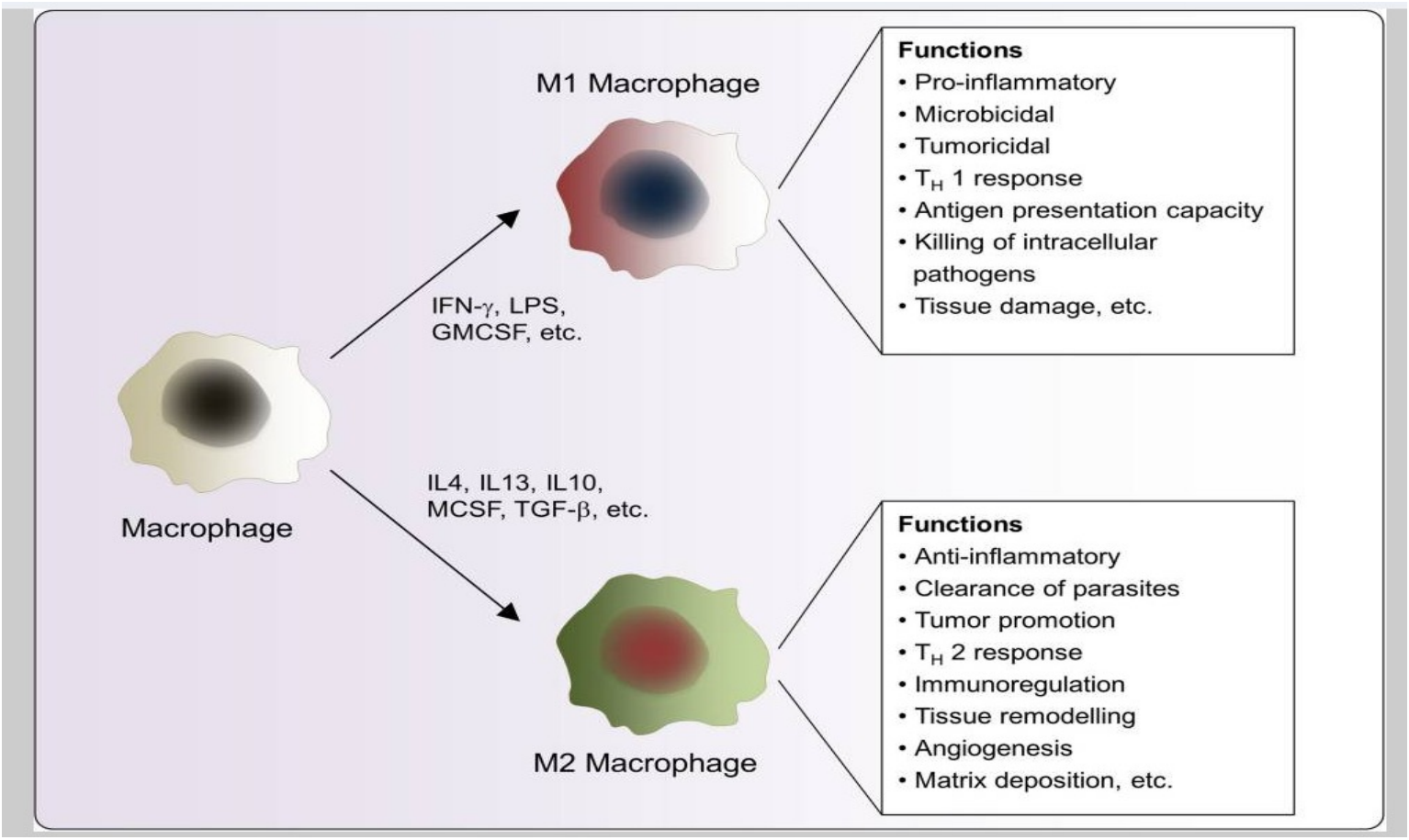
**CREB is a transcription factor that regulates diverse cellular responses, including proliferation, survival, and differentiation. CREB is induced by a variety of growth factors and inflammatory signals and subsequently mediates the transcription of genes containing a cAMP-responsive element. Several immune-related genes possess this cAMP-responsive element, including IL-2, IL-6, IL-10, and TNF-α. In addition, phosphorylated CREB has been proposed to directly inhibit NF-κB activation by blocking the binding of CREB binding protein to the NF-κB complex, thereby limiting proinflammatory responses. CREB also induces an antiapoptotic survival signal in monocytes and macrophages. In T and B cells, CREB activation promotes proliferation and survival and differentially regulates Th1, Th2, and Th17 responses. Finally, CREB activation is required for the generation and maintenance of regulatory T cells. This review summarizes current advances involving CREB in immune function—a role that is continually being defined.** *The Journal of Immunology*, 2010, 185: 6413–6419.

at its transcription activating site, serine 133, including 1) a cAMP-dependent protein kinase A (PKA); 2) protein kinase C (PKC; including PKCε); 3) calmodulin kinases (CaMKs; e.g., CaMK-IV) that respond to calcium fluxes from the extracellular environment or from intracellular calcium stores; and 4) pp90 ribosomal S6 kinase (pp90 RSK; also known as RSK2) (1–6). Once serine 133 of CREB is phosphorylated, CREB interacts with its coactivator protein, CREB-binding protein (CBP), or p300 to initiate transcription of CREB-responsive genes (1–3). CBP is a cofactor for many other transcription factors and helps to stimulate transcription by modulating chromatin through histone acetylation and recruiting factors required for RNA polymerization (1–3). CREB has been shown to be involved in a variety of cellular processes, including cell proliferation, survival, differentiation, adaptive responses, glucose homeostasis, spermatogenesis, circadian rhythms, and synaptic plasticity associated with memory (1–3). However, emerging evidence over the past decade has demonstrated that CREB plays an important role in immune responses.

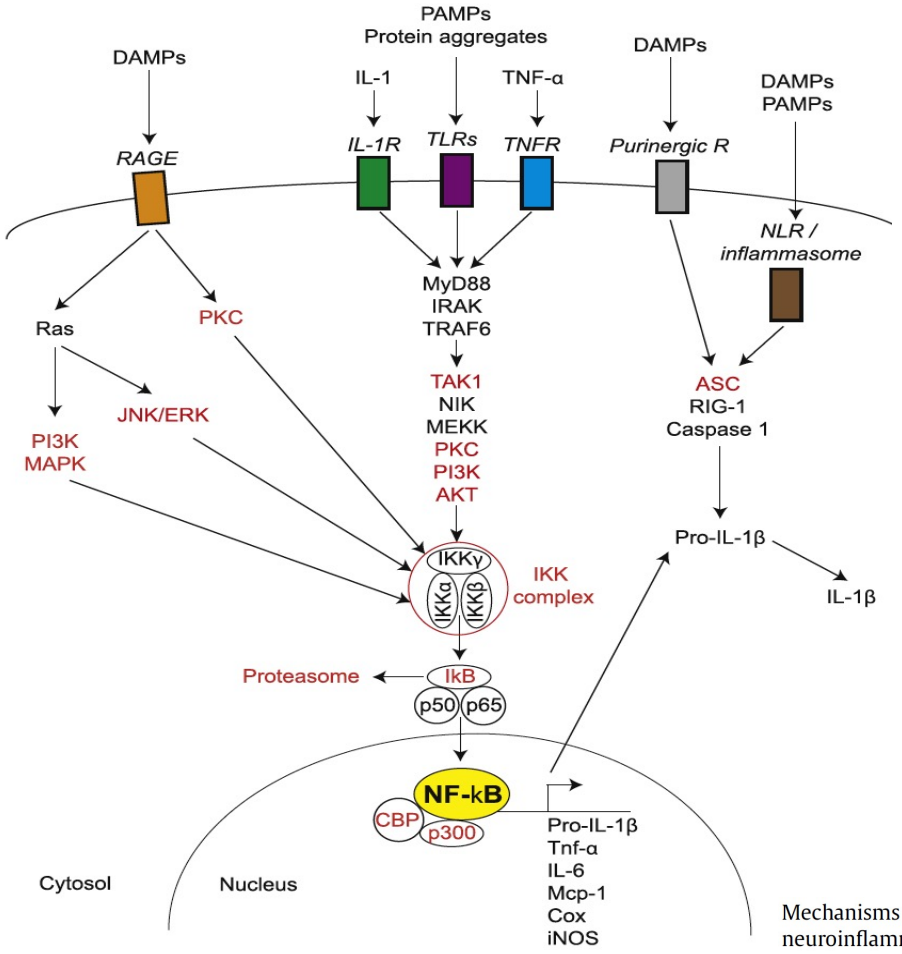
*The CREB family of transcription factors and their structural components*

# CREB and Microglia Polarization






Oncotarget. 2018 Apr 3; 9(25): 17937–17950.

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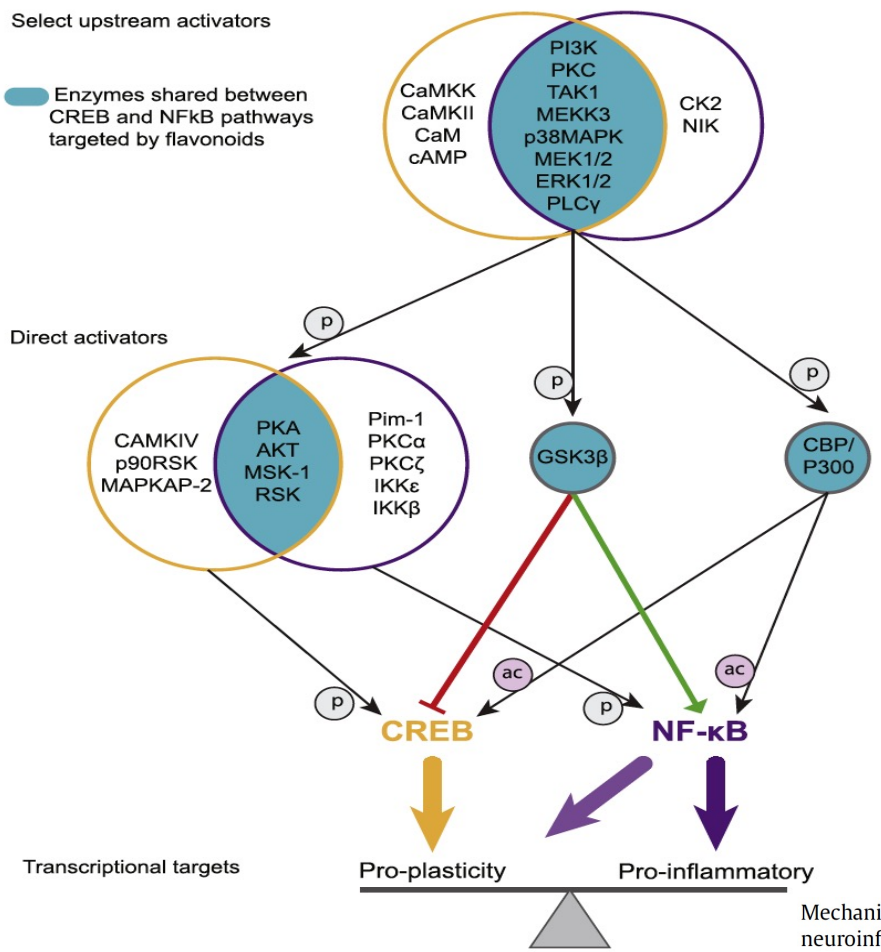


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# Note

- Modulation of M1 and M2 pathways is not only important for inflammatory reactions but also for autophagy pathways to prevent neurodegenerative diseases such as AD and PD.

frontiers in Aging Neuroscience

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# Nutritional and Pharmacological Strategies to Regulate Microglial Polarization in Cognitive Aging and Alzheimer's Disease

*Emiliano Peña-Altamira *, Sabrina Petralla, Francesca Massenzio, Marco Virgili, Maria L. Bolognesi and Barbara Monti*

*Department of Pharmacy and Biotechnology, University of Bologna, Bologna, Italy*

The study of microglia, the immune cells of the brain, has experienced a renaissance after the discovery of microglia polarization. In fact, the concept that activated microglia can shift into the M1 pro-inflammatory or M2 neuroprotective phenotypes, depending on brain microenvironment, has completely changed the understanding of microglia in brain aging and neurodegenerative diseases. Microglia polarization is particularly important in aging since an increased inflammatory status of body compartments, including the brain, has been reported in elderly people. In addition, inflammatory markers, mainly derived from activated microglia, are widely present in neurodegenerative diseases. Microglial inflammatory dysfunction, also linked to microglial senescence, has been extensively demonstrated and associated with cognitive impairment in neuropathological conditions related to aging. In fact, microglia polarization is known to influence cognitive function and has therefore become a main player in neurodegenerative diseases leading to dementia. As the life span of human beings increases, so does the prevalence of cognitive dysfunction. Thus, therapeutic strategies aimed to modify microglia polarization are currently being developed. Pharmacological approaches able to shift microglia from M1 pro-inflammatory to M2 neuroprotective phenotype are actually being studied, by acting on many different molecular targets, such as glycogen synthase kinase-3 (GSK3) β, AMP-activated protein kinase (AMPK), histone deacetylases (HDACs), etc. Furthermore, nutritional approaches can also modify microglia polarization and, consequently, impact cognitive function. Several bioactive compounds normally present in foods, such as polyphenols, can have anti-inflammatory effects on microglia. Both pharmacological and nutritional approaches seem to be promising, but still need further development. Here we review recent data on these approaches and propose that their combination could have a synergistic effect to counteract cognitive aging impairment and Alzheimer's disease (AD) through immunomodulation of microglia polarization, i.e., by driving the shift of activated microglia from the pro-inflammatory M1 to the neuroprotective M2 phenotype.

**Keywords: immunomodulation, microglia, cognitive impairment, aging, Alzheimer's disease, drug therapy, bioactive compounds, nutrition**

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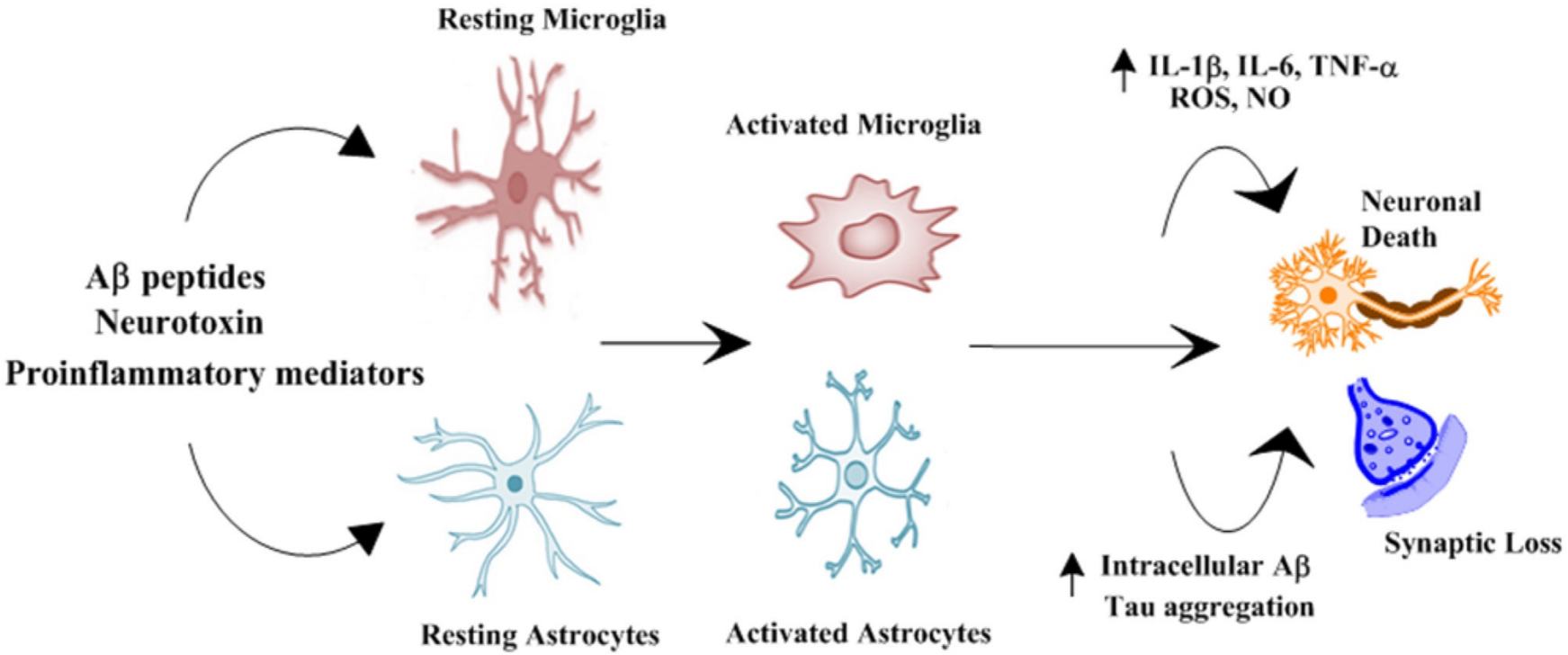


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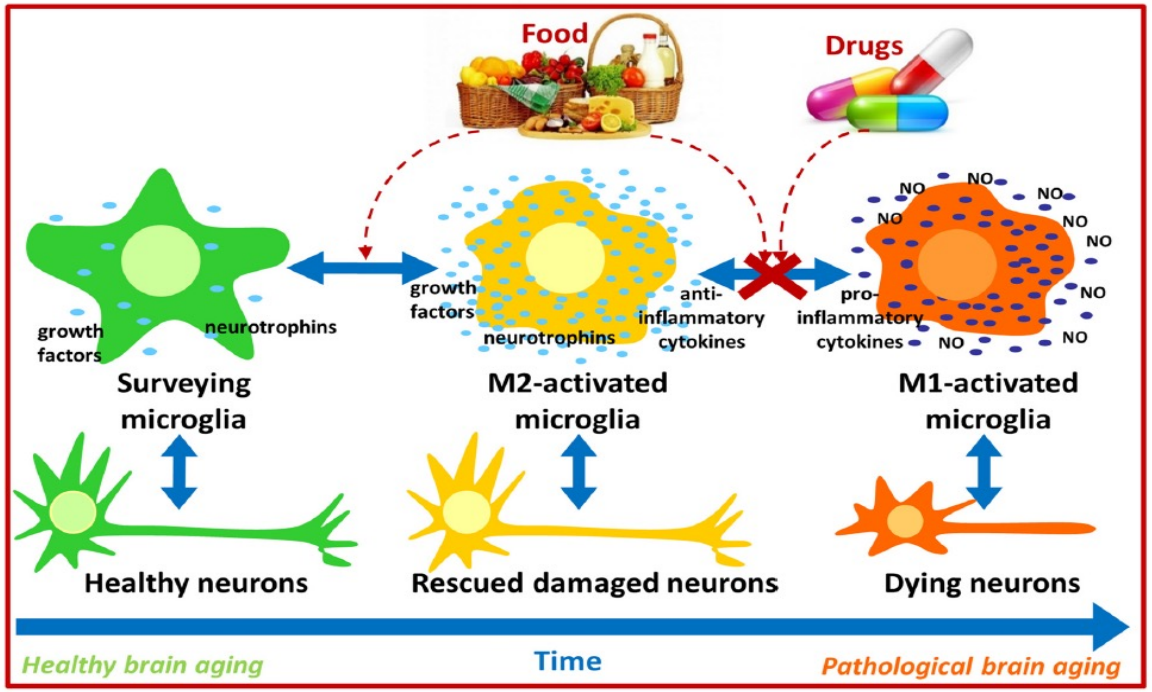

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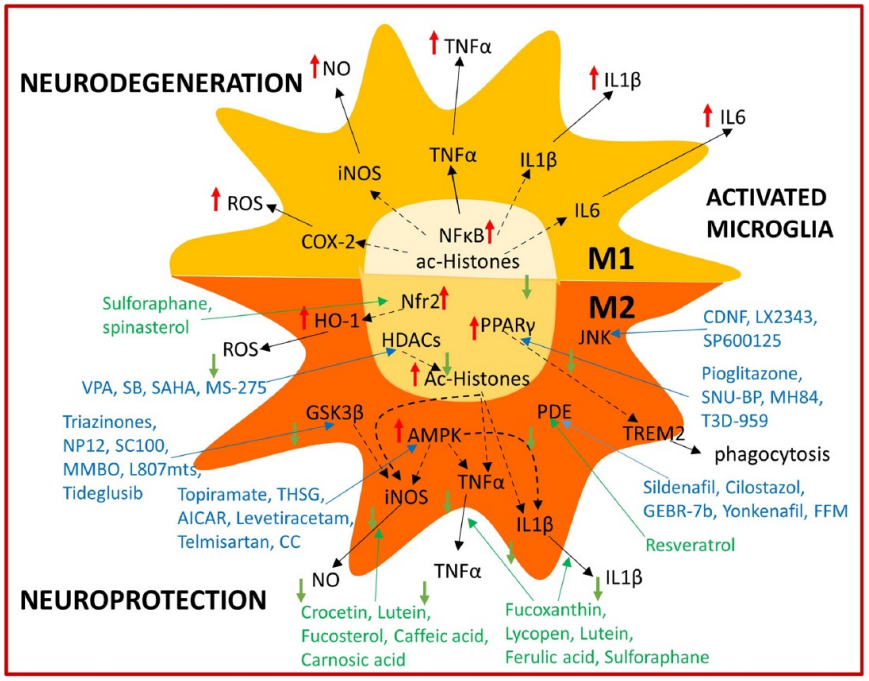

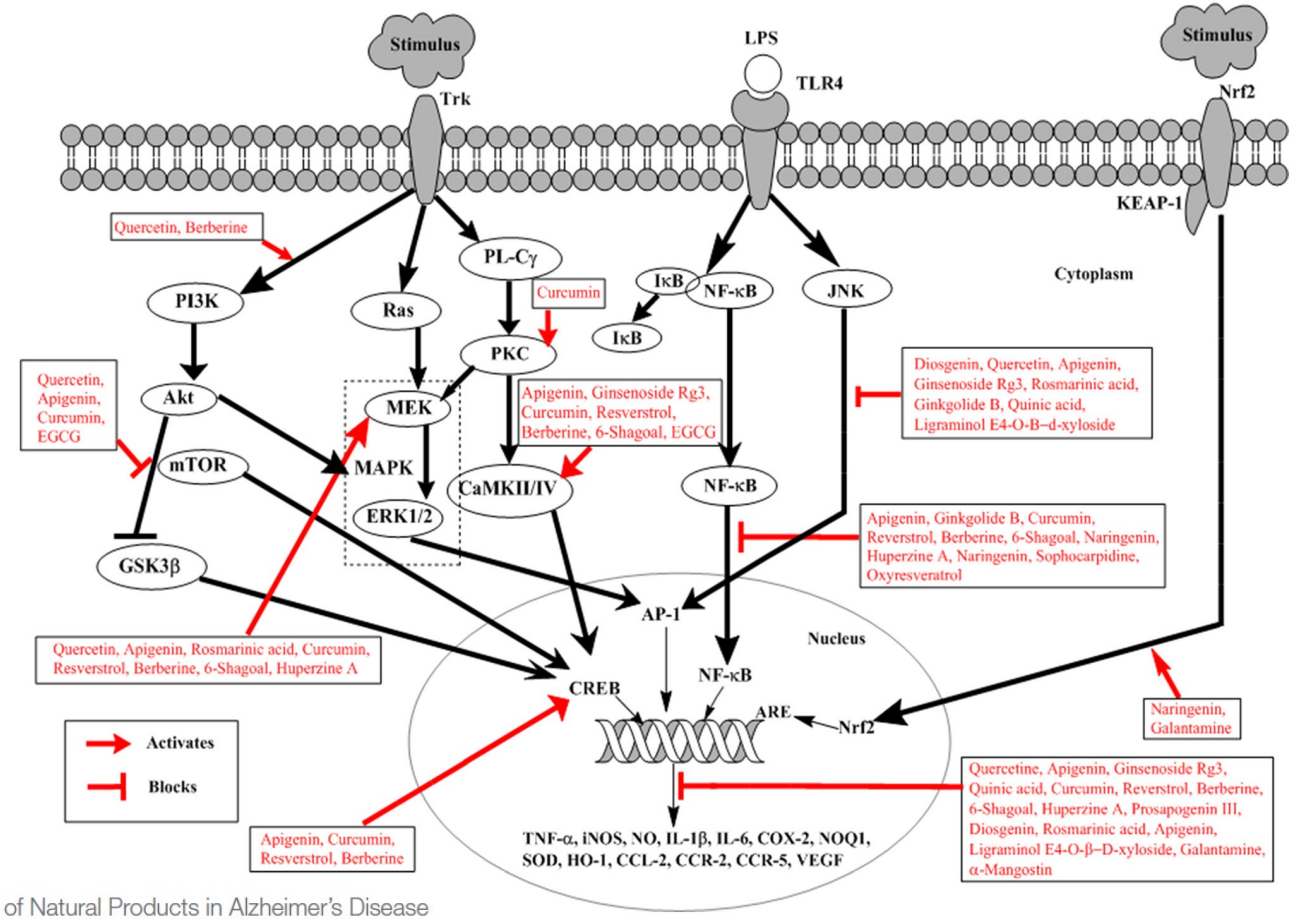


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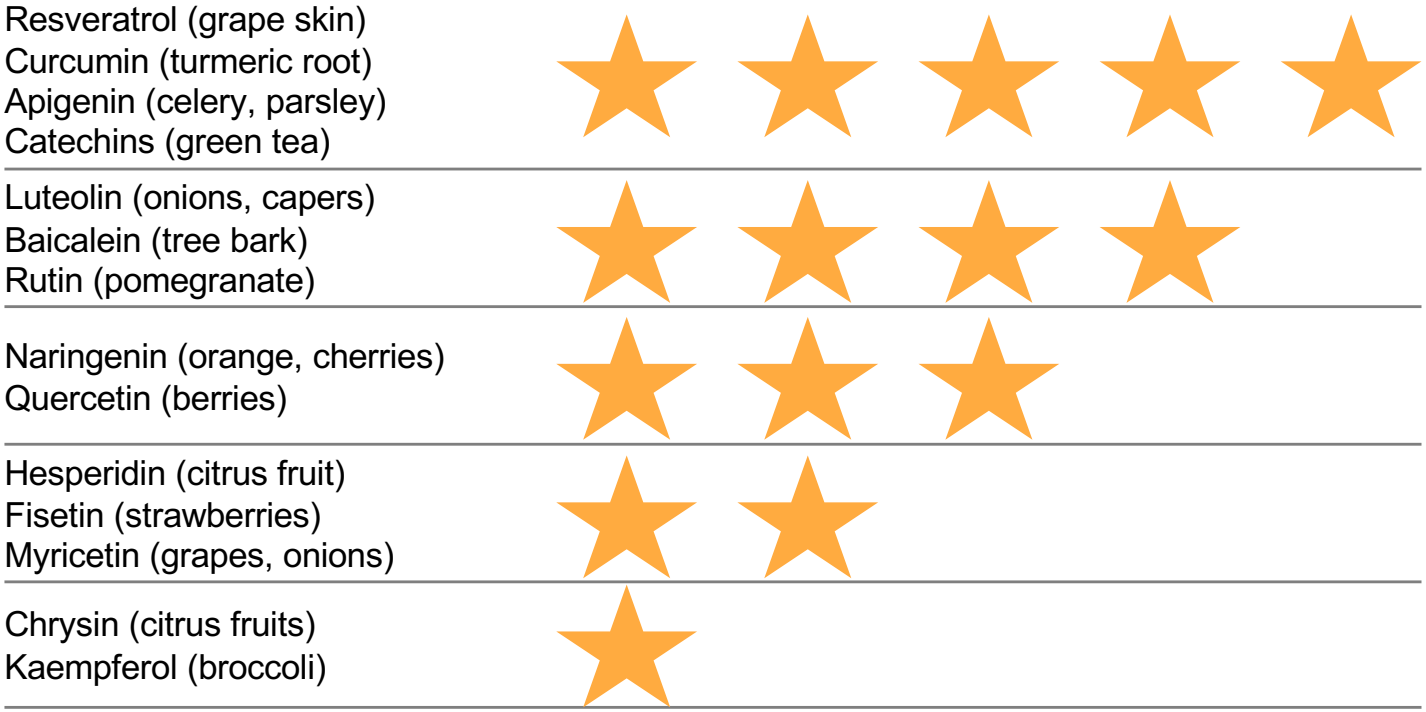

# Clinical Concepts

- How much flavonoids do you use?
- Should you treat the gut before you can use flavonoids?
- Should the blood-brain barrier be healthy for flavonoids to cross?

# Clinical Pearls

- You should include polyphenols throughout your treatment plan.

- They will have different impacts as systems in the body heal and they can help support the blood-brain barrier and microbiome diversity, which are critical in helping the blood-brain barrier work.