

# **Neuro Nutrients After Brain Injury**

**Presented by:**

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**6<sup>th</sup> Annual Pediatric Brain Injury Conference and Resource Fair**

**November 4<sup>th</sup>, 2022**

# Who Am I?



- DNP Johns Hopkins
- C-PNP University of Texas at Austin
- Pediatric Primary Care Mental Health Specialist
- Institute of Functional Medicine Certified Practitioner
- Certified Clinical Nutritionist
- Founder/owner of Neuronutrition Associates 2015
- Specialization: pediatric functional medicine, neuro focused, nutrition
- Mom of two, wife, nature lover, dog lover

# Disclosure

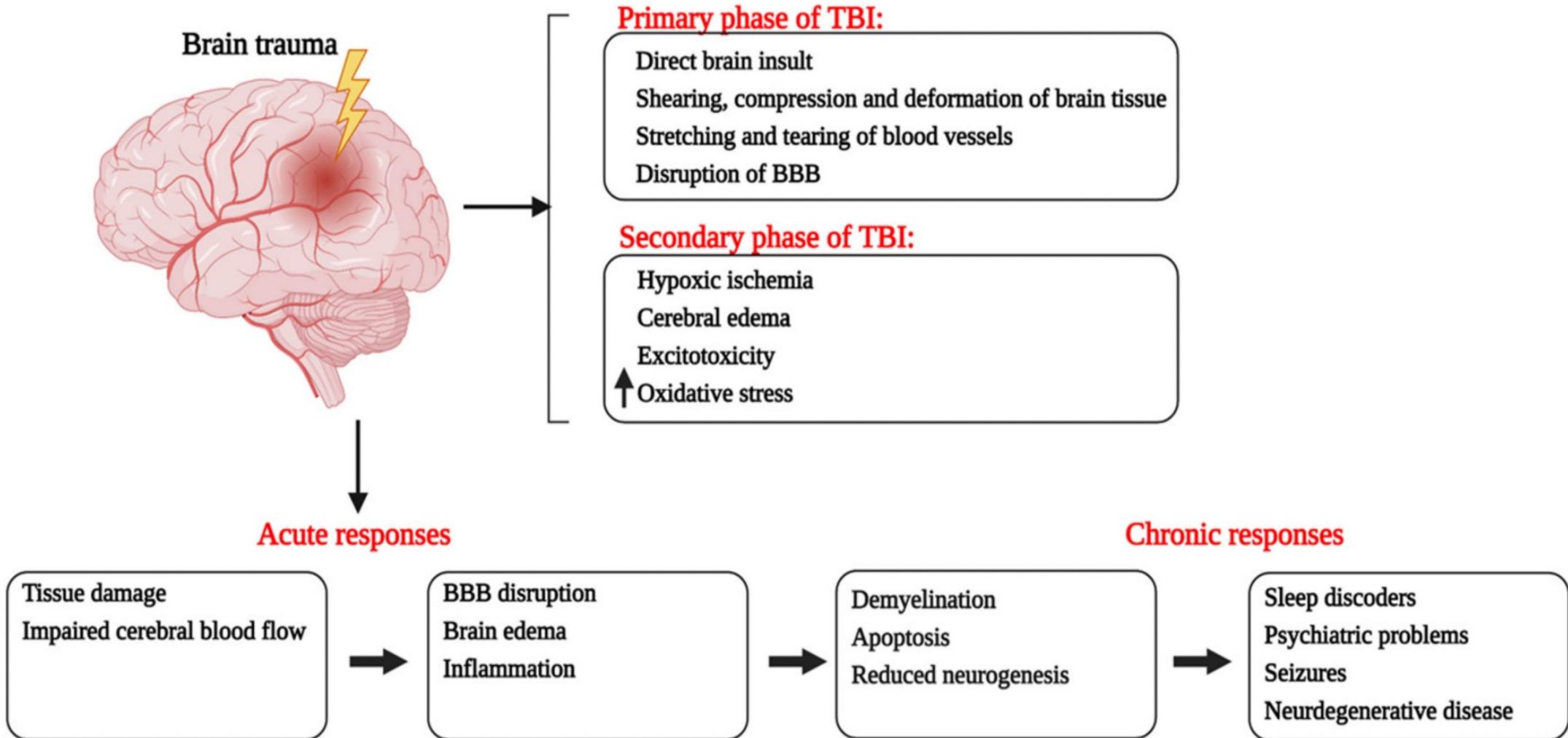
I am the chief scientific formulator and part founder of the supplement company, Neuro Nutrients.



# Learning Objectives

1. Briefly discuss the pathophysiology after brain injury
2. Explore three possible treatment strategies to support restoring brain balance
3. Learn how nutrition and supplementation can play a pivotal role in aiding in recovery and resilience

# Primacy & Secondary Effects of TBI



## Secondary Effects of TBI

- ATP pump dysregulation from depletion of energy stores (due to ischemia/hypoxia)
- Excessive glutamate release and higher intracellular Ca<sup>2+</sup> levels leading to excitotoxicity
- Changes in excitatory-inhibitory balance (glutamate/GABA) result in neuronal dysfunction (free radical injury to cell membranes)
- Excessive glutamate increases reactive oxygen species (ROS)
- Increase ROS leads to increased cell death (apoptosis)

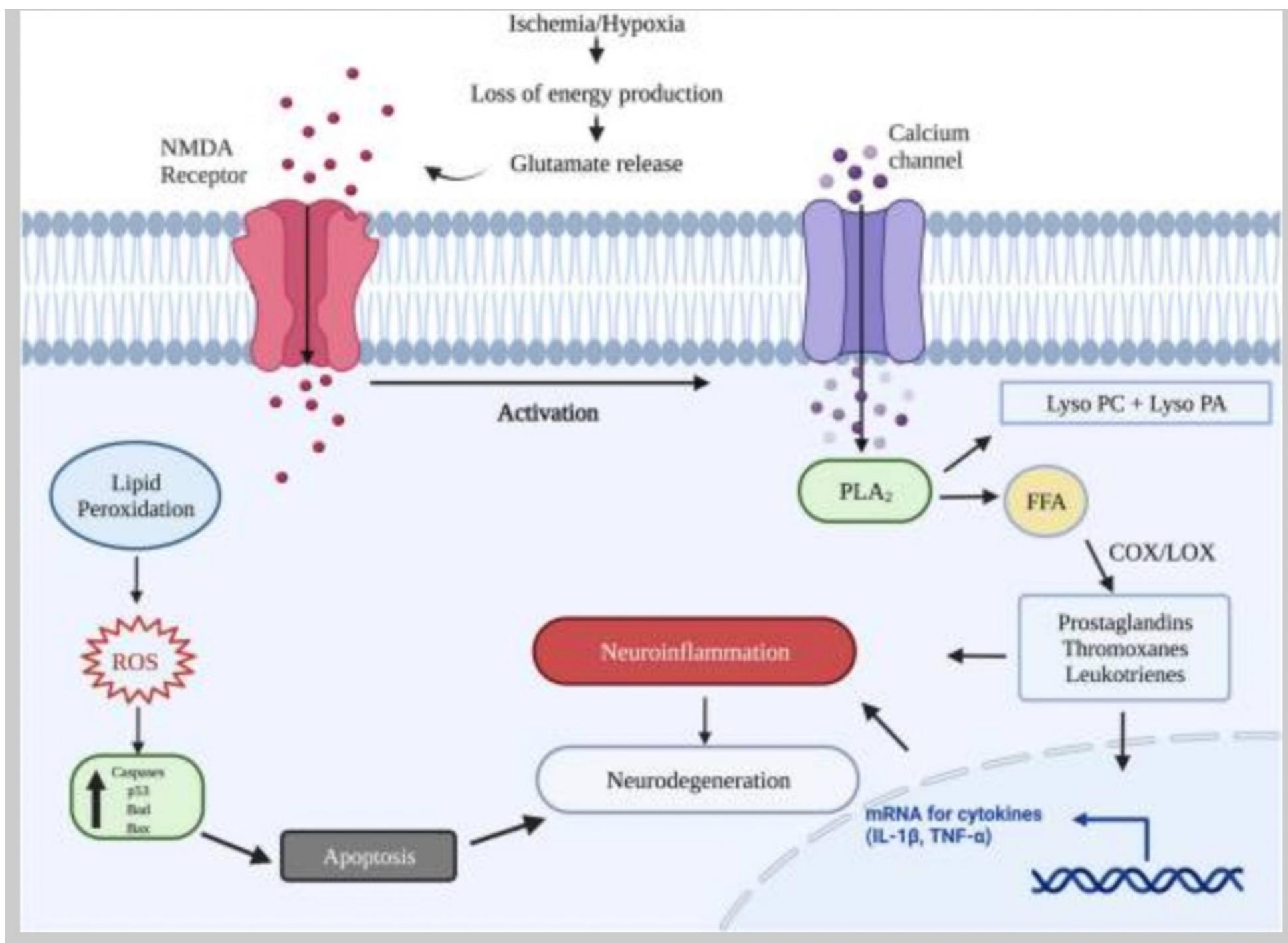
- Cerebral ischemia also causes the activation of phospholipases, including PLA<sub>2</sub>
- Secondary ischemia from vasospasm, focal microvascular occlusion, leading to more vascular injury
- Breakdown of phospholipids, elevates free fatty acids (including arachidonic acid), leading to neuroinflammation

#### References:

Javaid S, Farooq T, Rehman Z, Afzal A, Ashraf W, Rasool MF, Alqahtani F, Alsanea S, Alasmari F, Alanazi MM, Alharbi M, Imran I. Dynamics of Choline-Containing Phospholipids in Traumatic Brain Injury and Associated Comorbidities. *Int J Mol Sci.* 2021 Oct 20;22(21):11313. doi: 10.3390/ijms222111313. PMID: 34768742; PMCID: PMC8583393

Traumatic brain injury: Epidemiology, classification, and pathophysiology

Authors:Craig Williamson, MD, MSVenkatakrishna Rajajee, MBBSSection Editor:Michael J Aminoff, MD, DScDeputy Editor:Janet L Wilterdink, MD, UpToDate, Retrieved 10/2/22

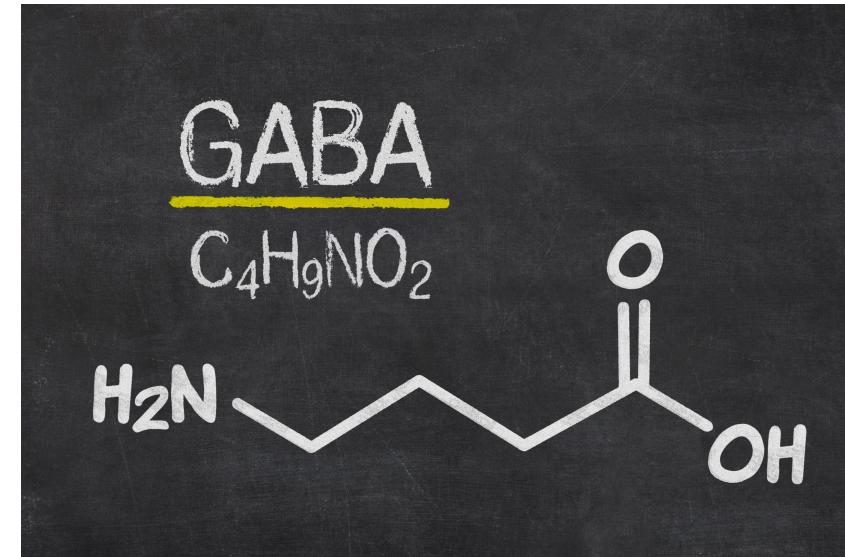
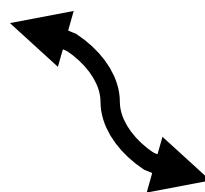
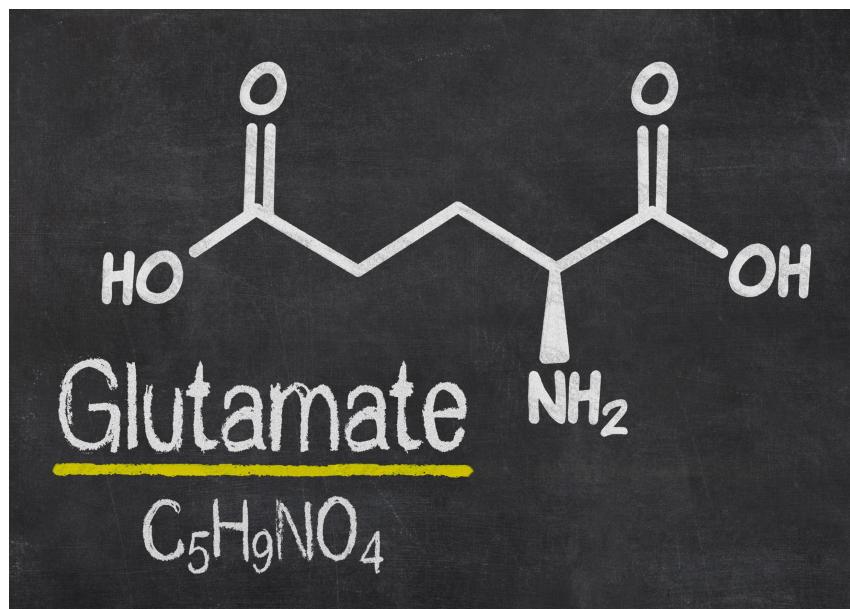


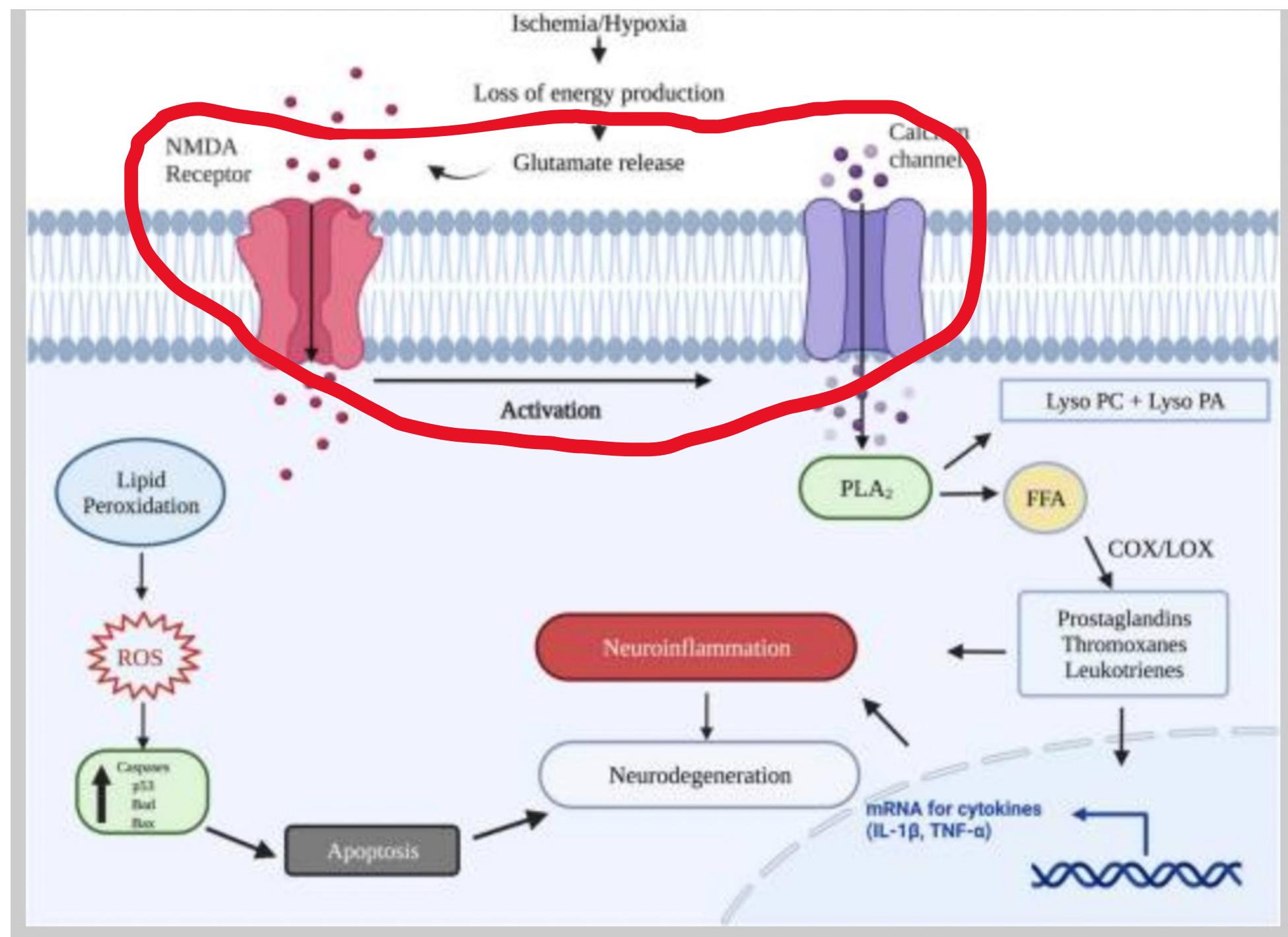
# Goals for Treatment

- Decrease excitotoxicity (glutamate/GABA balance)
- Support restoration of phospholipids
- Decrease neuroinflammation

# Goal #1

## Support Restoration of the Glutamate/GABA Balance





# Magnesium



- Plays an essential role in more than 300 cellular reactions
- Extracellular magnesium is critical to both maintaining nerve and muscle electrical potentials and transmitting impulses across neuromuscular junctions
- Magnesium has been shown to have neuroprotective effects, preventing post-hypoxic brain injury by blocking the excess release of glutamate in the calcium channel

Reference:

Slutsky I, Abumaria N, Wu LJ, Huang C, Zhang L, Li B, Zhao X, Govindarajan A, Zhao MG, Zhuo M, Tonegawa S, Liu G. Enhancement of learning and memory by elevating brain magnesium. *Neuron*. 2010 Jan 28;65(2):165-77. doi: 10.1016/j.neuron.2009.12.026. PMID: 20152124.

- Dietary sources of magnesium include legumes, whole grains, vegetables (especially broccoli, squash, and green leafy vegetables), pumpkin\*, chia seeds, and nuts (especially almonds and cashews)
- Multiple different salt forms: **magnesium threonate** enhances memory and learning (crosses BBB more easily); citrate for bowels; glycinate for body
- Picky eaters at risk for deficiency; Epsom salt (mg sulfate) baths are alternatives to oral administration

**\*pumpkin seeds are the food with the highest magnesium content; serving Size 1 oz, 168 mg**

#### References:

- Clerc P, Young CA, Bordt EA, Grigore AM, Fiskum G, Polster BM. Magnesium sulfate protects against the bioenergetic consequences of chronic glutamate receptor stimulation. *PLoS One.* 2013 Nov 13;8(11):e79982. doi: 10.1371/journal.pone.0079982. PMID: 24236167; PMCID: PMC3827425.
- Hemamy, M., Pahlavani, N., Amanollahi, A. *et al.* The effect of vitamin D and magnesium supplementation on the mental health status of attention-deficit hyperactive children: a randomized controlled trial. *BMC Pediatr* **21**, 178 (2021). <https://doi.org/10.1186/s12887-021-02631-1>



# More Clinical Benefits of Magnesium

- Activates nerve channels in the brain that are fundamental to the process of learning, memory, and function
- Lowers excitatory neurotransmitter glutamate in the brain; high glutamate can contribute to agitation, irritability, treatment resistant depression, headaches, insomnia, anxiety, and inattention
- A study evaluating over 100 children with ADHD, found that 95% of them were magnesium deficient
- Improves executive function and cognitive processing; can reduce hyperactivity, aggression, and inattention

# N-Acetyl-L-Cysteine (NAC)

- Amino acid antioxidant
- Decreases neuronal glutamate release
- Decreases irritability
- Can reduce motor or vocal tics
- Can reduce OCD
- Helps increase glutathione
- Protects upper airways
- Antiviral, supports influenza infections

References:

McQueen, G., Lally, J., Collier, T. *et al.* Effects of N-acetylcysteine on brain glutamate levels and resting perfusion in schizophrenia. *Psychopharmacology* **235**, 3045–3054 (2018). <https://doi.org/10.1007/s00213-018-4997-2>

Dean, O., Giorlando, F., & Berk, M. (2011). N-acetylcysteine in psychiatry: current therapeutic evidence and potential mechanisms of action. *Journal of psychiatry & neuroscience : JPN*, 36(2), 78–86. <https://doi.org/10.1503/jpn.100057>

# Supplement Facts

Serving Size 1 Capsule

Servings Per Container 60

	Amount Per Serving	%DV
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N-Acetyl-L-Cysteine (NAC)	800 mg	†
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† Daily Value (DV) not established

Other ingredients: Vegetable Capsule (cellulose, purified water).

Wheat Free, Dairy/ Milk Free, Free of Artificial Colors/Flavors, Egg Free, Shellfish Free, Tree Nut Free, Peanut Free

NAC is an RX in inhaled and injection forms, however oral is over the counter

**Dose Matters!**  
**Glutamate modulation dose is typically 2400mg/day**



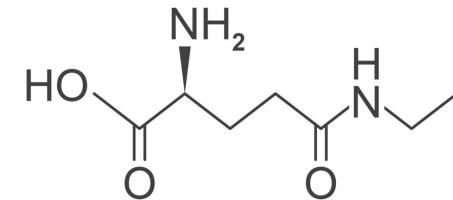
# Clinical Benefits of L-theanine

- Non protein amino acid found in green tea that is the component responsible for the promotion of relaxation
- Binds to and down regulates glutamate receptors (that cause excitability in the brain) and can increase GABA receptor sensitivity, which can help increase calmness in the brain
- In a clinical trial, after four weeks of L-theanine, stress related symptoms decreased, and cognitive function and verbal fluency scores increased
- Another study demonstrated after administration of 200mg of L-theanine, a significant increase in alpha (calming) brain waves were noted after 40 minutes

# Read the label closely... are you getting the right form?

*SUNTHEANINE® is a patented form of L-theanine that is patented for its enzymatic process that results in an enantiomerically pure L-theanine. This is not an extract of green tea but rather is produced via a patented process that mimics the natural process in green tea leaves, resulting in a 100% pure L-isomer-theanine.*

*L-theanine*



Reference: Nathan PJ, Lu K, Gray M, Oliver C. The neuropharmacology of L- theanine(N-ethyl-L-glutamine): a possible neuroprotective and cognitive enhancing agent. J Herb Pharmacother. 2006;6(2):21-30. PMID: 17182482.



**GMP REGISTERED**  
Dietary Supplements





# Clinical Benefits of B6

- Helps regulation of the nervous system by facilitating the development of neurotransmitters, such as GABA, serotonin, and dopamine
- Genetic mutations can impair the way B6 is metabolized in the body, such as rapid clearance or inactivation, leading to less bioavailability (more common in patients with ADHD and seizure disorders)
- Deficiencies in B6 have been correlated with seizure disorders, high homocysteine (impaired methylation), autism, depression, MSG reactivity, carpal tunnel syndrome, cardiovascular disease, kidney stones, and asthma
- Supplementing with B6 and magnesium has reduced hyperactivity and aggression in children with ADHD

# B6 Related to Seizures and Seizure Meds

- Some seizure disorders are due to a genetic deficiency (ALDH7A1) that rapidly inactivates B6, leading to deficiencies Replacing B6 in high doses can control seizures for some
- Seizure meds, such as Keppra, may deplete B6 in some patients
- Replacing B6 (P5P) has helped with decreasing irritability and helped make medication side effects more tolerable

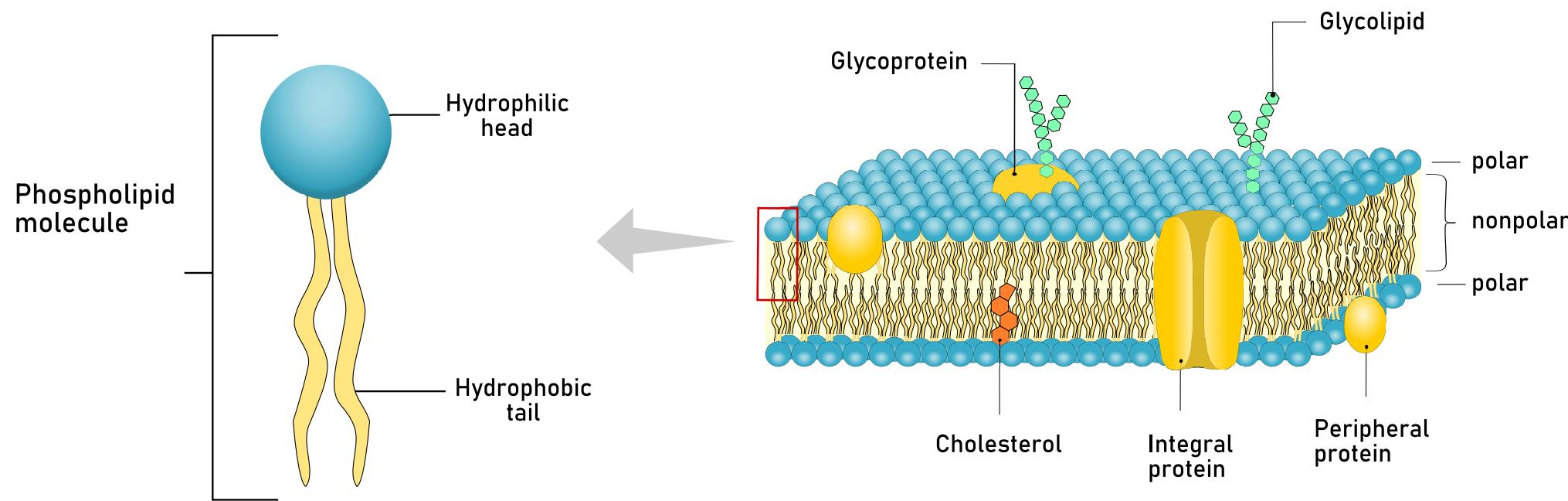
## References:

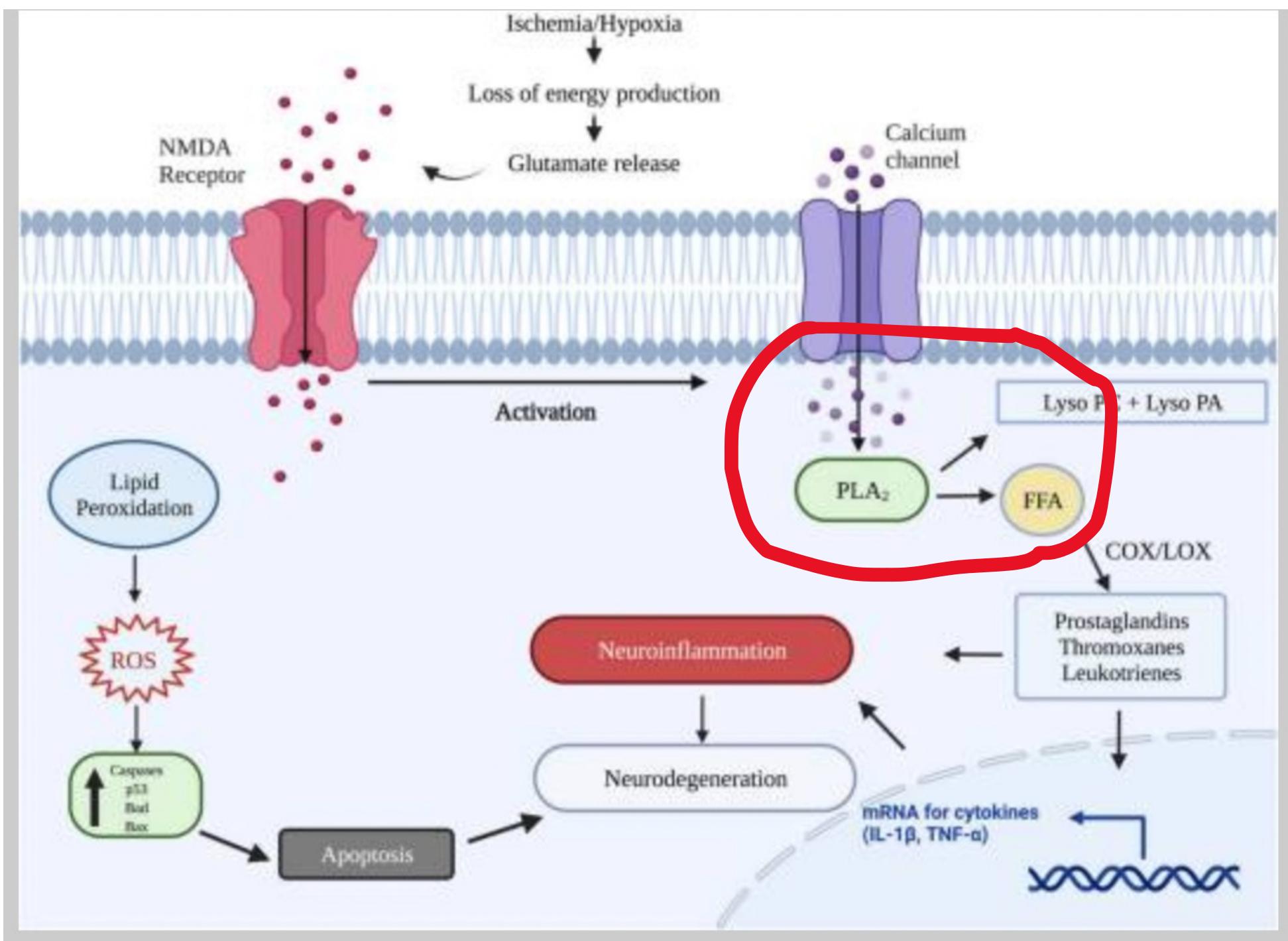
- Wilson MP, Plecko B, Mills PB, Clayton PT. Disorders affecting vitamin B<sub>6</sub> metabolism. *J Inherit Metab Dis.* 2019;42(4):629-646. doi:10.1002/jimd.12060
- Dreischmeier E, Zuloaga A, Kotloski RJ, Karasov AO, Gidal BE. Levetiracetam-associated irritability and potential role of vitamin B6 use in veterans with epilepsy. *Epilepsy Behav Rep.* 2021 May 3;16:100452. doi: 10.1016/j.ebr.2021.100452. PMID: 34142077; PMCID: PMC8188361.
- Gospe SM Jr. Pyridoxine-Dependent Epilepsy – ALDH7A1. 2001 Dec 7 [Updated 2022 Sep 22]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022.
- Novell, R., Esteba-Castillo, S., & Rodriguez, E. (2020). Efficacy and safety of a GABAergic drug (Gamalate® B6): effects on behavior and cognition in young adults with borderline-to-mild intellectual developmental disabilities and ADHD. *Drugs in context*, 9, 212601.  
[https://doi.org/10.7573/ dic.212601](https://doi.org/10.7573/dic.212601)

# Goal #2

## Support Restoration of Brain Phospholipids

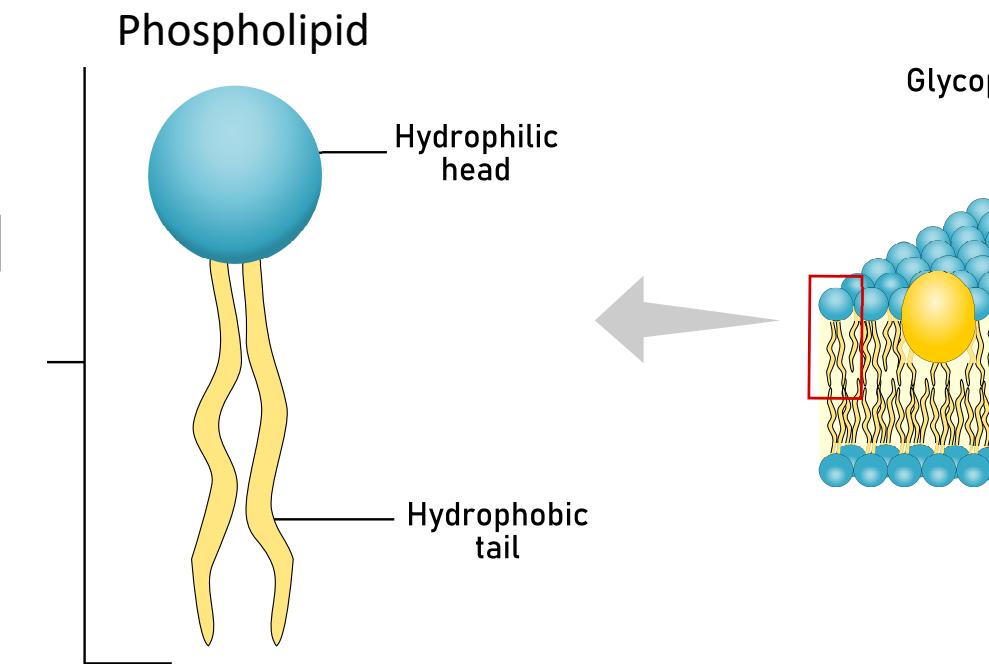
### CELL MEMBRANE





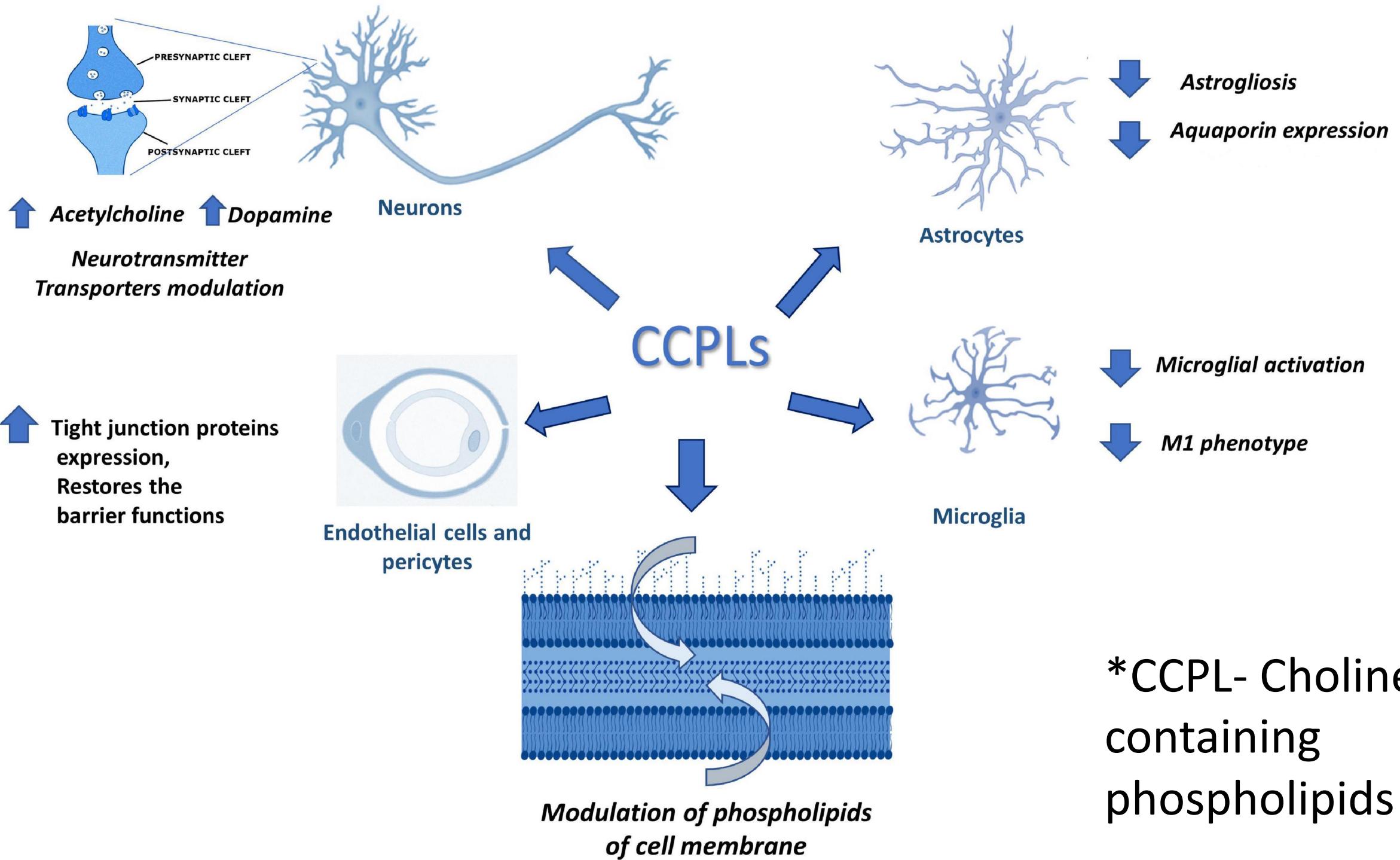
# Phospholipids in the Brain

- Phospholipids are molecules which form membrane lipid bilayers
- They are ubiquitous to every cell in the brain
- Omega-3 intake into brain is highly dependent on being part of a phospholipid
- Phospholipids are supplemented to facilitate the uptake of omega-3 fatty acids into brain
- PLA2 breaks down phospholipids and is apart of the pathognomonic sequela in brain injury



# Phospholipids, Continued

- The most abundant phospholipid in the brain is phosphatidylcholine (PC)
- PC enhances neuronal differentiation under inflammatory stress
- PC increases the population of healthy normal neurons
- PC ameliorates the damage of neurons and modulates neuronal plasticity
- PC is needed to make acetylcholine (a neurotransmitter involved in synaptic transmission and neuronal excitability)



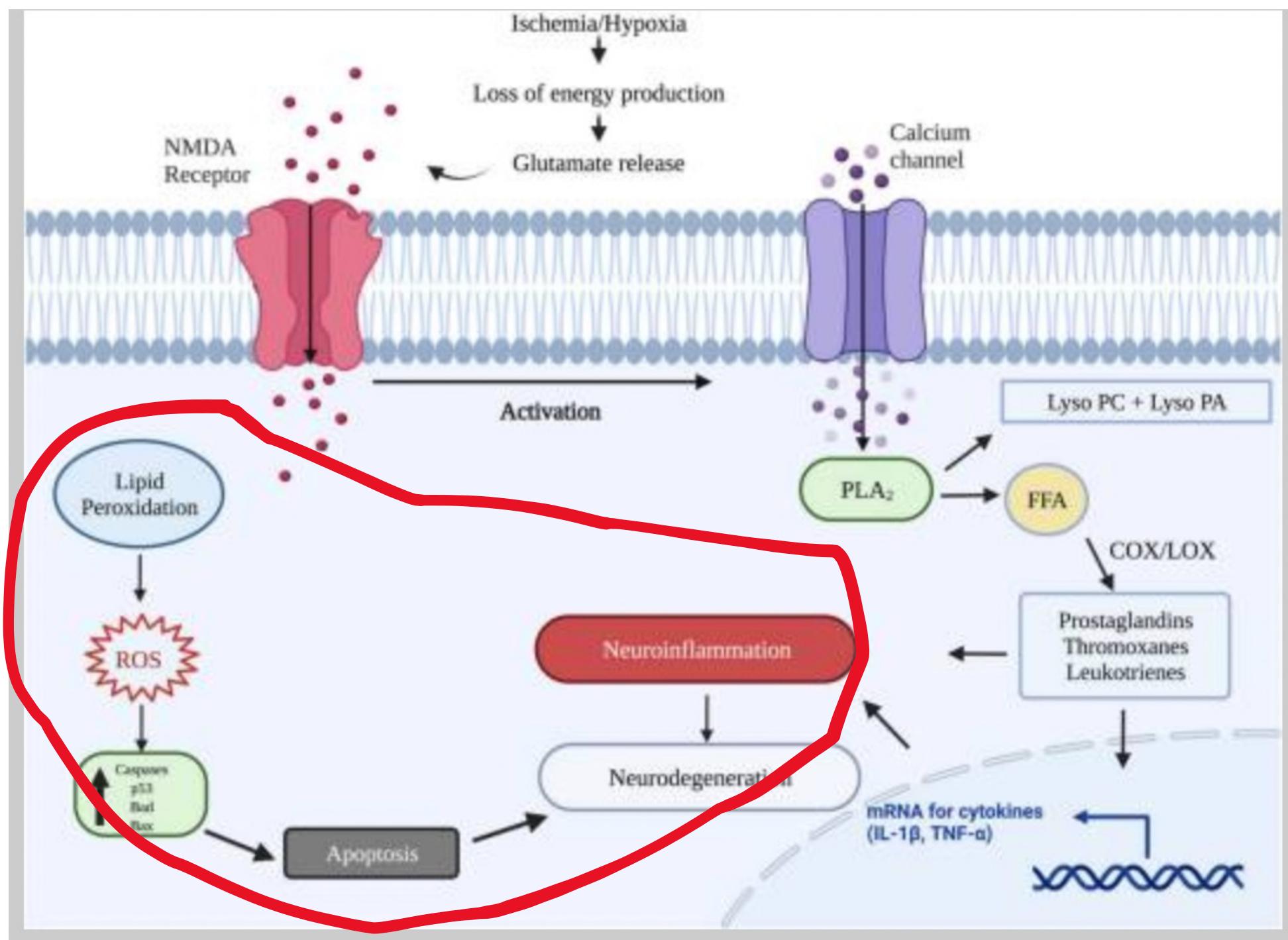
# References

- Choi J, Yin T, Shinozaki K, Lampe JW, Stevens JF, Becker LB, Kim J. Comprehensive analysis of phospholipids in the brain, heart, kidney, and liver: brain phospholipids are least enriched with polyunsaturated fatty acids. *Mol Cell Biochem.* 2018 May;442(1-2):187-201. doi: 10.1007/s11010-017-3203-x. Epub 2017 Oct 9. PMID: 28993959; PMCID: PMC5882520.
- Roy Proshanta, Tomassoni Daniele, Nittari Giulio, Traini Enea, Amenta Francesco; Effects of choline containing phospholipids on the neurovascular unit: A review. *Frontiers in Cellular Neuroscience*, 16, 2022.
- Klein J. Membrane breakdown in acute and chronic neurodegeneration: Focus on choline-containing phospholipids. *J Neural Transm.* 2000;107:1027–63.
- Magaquian, D., Delgado Ocaña, S., Perez, C. *et al.* Phosphatidylcholine restores neuronal plasticity of neural stem cells under inflammatory stress. *Sci Rep* **11**, 22891 (2021). <https://doi.org/10.1038/s41598-021-02361-5>

# Goal #3

## Decrease neuroinflammation





# DHA Role In Neuroinflammation

- Docosahexaenoic acid (DHA; 22:6n-3) is the predominant n-3 polyunsaturated fatty acid (PUFA) within the brain, representing upwards of 40% of total brain PUFA
- PLA2 enzymes catalyze the release of DHA from bound phospholipids
- In brain injury, PLA2 is activated, breaking down phospholipid layers, releasing DHEA and arachidonic acid
- Arachidonic acid is pro inflammatory for the brain and body

Reference:

R.J.Scott Lacombe, Raphaël Chouinard-Watkins, Richard P. Bazinet, Brain docosahexaenoic acid uptake and metabolism, Molecular Aspects of Medicine, Volume 64, 2018,  
Pages 109-134,ISSN 0098-2997, <https://doi.org/10.1016/j.mam.2017.12.004>.

# Omegas and Brain Pathology



- Omega 3 fatty acids (EPA and DHA) has a long and robust history of evidence for reducing brain pathologies such as ADHD, anxiety, depression, autism, and more
- Giving mega doses of EPA/DHA combo supplement (2:1 ratio) right after brain injury has demonstrated improved outcomes
- In brain injury recovery, replacing omegas with phospholipids can provide a synergistic and positive effect on the brain

## References:

Thau-Zuchman O, Ingram R, Harvey GG, et al. A single injection of docosahexaenoic acid induces a pro-resolving lipid mediator profile in the injured tissue and a long-lasting reduction in neurological deficit after traumatic brain injury in mice. *J Neurotrauma*. 2020;37(1):66–79.  
Omega-3 fatty acid supplementation in severe brain trauma: case for a large multicenter trial  
*J Neurosurg* Volume 133 • August 2020

# Therapeutic Effect of Omegas

- Provides antioxidation support
- Counteracts oxidative damage
- Limits excitation
- Protects membranes
- Aids in neurogenesis
- EPA/DHA readily cross the BBB



## References:

- Lewis M, Ghassemi P, Hibbeln J. Therapeutic use of omega-3 fatty acids in severe head trauma. *Am J Emerg Med.* 2013;31:273.e5–8.
- Wu A, Ying Z, Gomez-Pinilla F. The salutary effects of DHA dietary supplementation on cognition, neuroplasticity, and membrane homeostasis after brain trauma. *J Neurotrauma.* 2011;28:2113–22.
- Pu H, Jiang X, Wei Z, Hong D, Hassan S, Zhang W, Liu J, Meng H, Shi Y, Chen L, Chen J. Repetitive and Prolonged Omega-3 Fatty Acid Treatment After Traumatic Brain Injury Enhances Long-Term Tissue Restoration and Cognitive Recovery. *Cell Transplant.* 2017 Apr 13;26(4):555-569. doi: 10.3727/096368916X693842. Epub 2016 Nov 24. PMID: 27938482; PMCID: PMC5531869.

# Supplements for Neuroinflammation Continued

PEA (palmitoylethanolamide)- 300-600mg twice daily

Curcumin (turmeric)- 500-750mg twice daily

Quercetin- 250-500mg twice daily (can support balancing mTOR)

Resveratrol- 250-500mg twice daily (can support turning off microglial activation)

Lions Mane (hericium erinaceus)- 1.5 grams, once to twice daily (can lower TNFa)

Dosing above is for children 12+ and adults. For younger children, decrease dose by  $\frac{1}{2}$  to 1/3.

References:

Zhang S, Gao L, Liu X, Lu T, Xie C, Jia J. Resveratrol Attenuates Microglial Activation via SIRT1-SOCS1 Pathway. Evid Based Complement Alternat Med. 2017;2017:8791832. doi: 10.1155/2017/8791832. Epub 2017 Jul 11. PMID: 28781601; PMCID: PMC5525071.

Wang, et. al; Quercetin Can Improve Spinal Cord Injury by Regulating the mTOR Signaling Pathway. Front. Neurology; 20 May 2022.  
<https://doi.org/10.3389/fneur.2022.905640>

# Common Nutrient Deficiencies in Children

- Iron- low energy, pale appearance, diet heavy in dairy, restless sleep
- Zinc- brittle nails, picky eater, poor immune resilience
- Magnesium- constipation, muscle aches and pains, anxiety, poor sleep
- Fatty Acids/Omega- low cholesterol, dry skin, poor satiety, dry eyes



- Restoring balance in the brain is multifactorial
- Using targeted nutritional supplementation can be beneficial
- Targeting the glutamate/GABA balance should be noticeable within a few weeks
- Using PC and DHA for the brain will likely take up to 3 months for noticeable improvement



# Time for Questions?

