Mitochondrial dysfunction drives age-related diseases

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NUTRINED

Professional Disclosures

- Board director ILADEF
  ILADS medical association
- Scientific Consultancy for various Clinics and Laboratories
- Medical Director Nutrined/
  Researched Nutritionals

During our talks we respect the rule that statements need to be based on scientific references & scientific research

In order to make this clinical training as efficient as possible, the organizers have asked me to mention and name products and doses during the lectures I hope this does not disturb you

What drives cognitive decline and neurodegeneration?

- Toxins
- Molds
- Insulin resistance and fluctuating blood sugar levels
- High homocysteine
- Amyloid plaque
- Neurofibrillary tangles
- Mitochondrial dysfunction
- Chronic Herpes Simplex Infection
- Mercury Toxicity
- APP Amplification
- Bad genes

Theories of Alzheimer’s Disease?

They are not the root cause, they are risk factors

Will we finally develop 1 pill for Alzheimer’s?

Impossible , there is no drug that can do all this

Impossible , there is no drug that can do all this

Reduce APP β-cleavage, reduce γ-cleavage, increase α-cleavage,reduce caspase-6 cleavage,reduce caspase-3 cleavage, prevent oligomerization, increase neprilysin, increase IDE, increase microglial clearance of Aβ, increase autophagy, increase BDNF, increase NGF, increase netrin-1, increase ADNP, reduce homocysteine, increase PP2A activity, reduce phospho-tau, increase phagocytosis index, increase insulin sensitivity, improve axoplasmic transport, enhance mitochondrial function and biogenesis, reduce oxidative damage and optimize ROS production, enhance cholinergic neurotransmission, increase synaptoblastic signaling, reduce synaptoclastic signaling, improve LTP, optimize estradiol, progesterone, E2:P ratio, free T3, free T4, TSH, pregnenolone, testosterone, cortisol, DHEA, and insulin, reduce inflammation, increase resolvins, enhance detoxification, improve vascularization, increase cAMP, increase glutathione, provide synaptic components, optimize all metals, increase GABA, increase vitamin D signaling, increase SirT1, reduce NFkB,increase telomerelength, reduce glial scarring, enhance repair, etc.

Treatment of Neurodegenerative diseases fits Functional Medicine

- Consider different contributing factors
- Include lifestyle advise, dietary management and nutritional advise

21st Century Medical care

Alzheimer's Disease and Neurodegenerative Diseases are complex

Neurodegeneration is larger than COVID

It's a pandemic without vaccine...

Prevention or early reversal is better than coming late!

SCI = Subjective Cognitive Impairment
= EARLY DEMENTIA ?

MCI =Mild Cognitive impairment

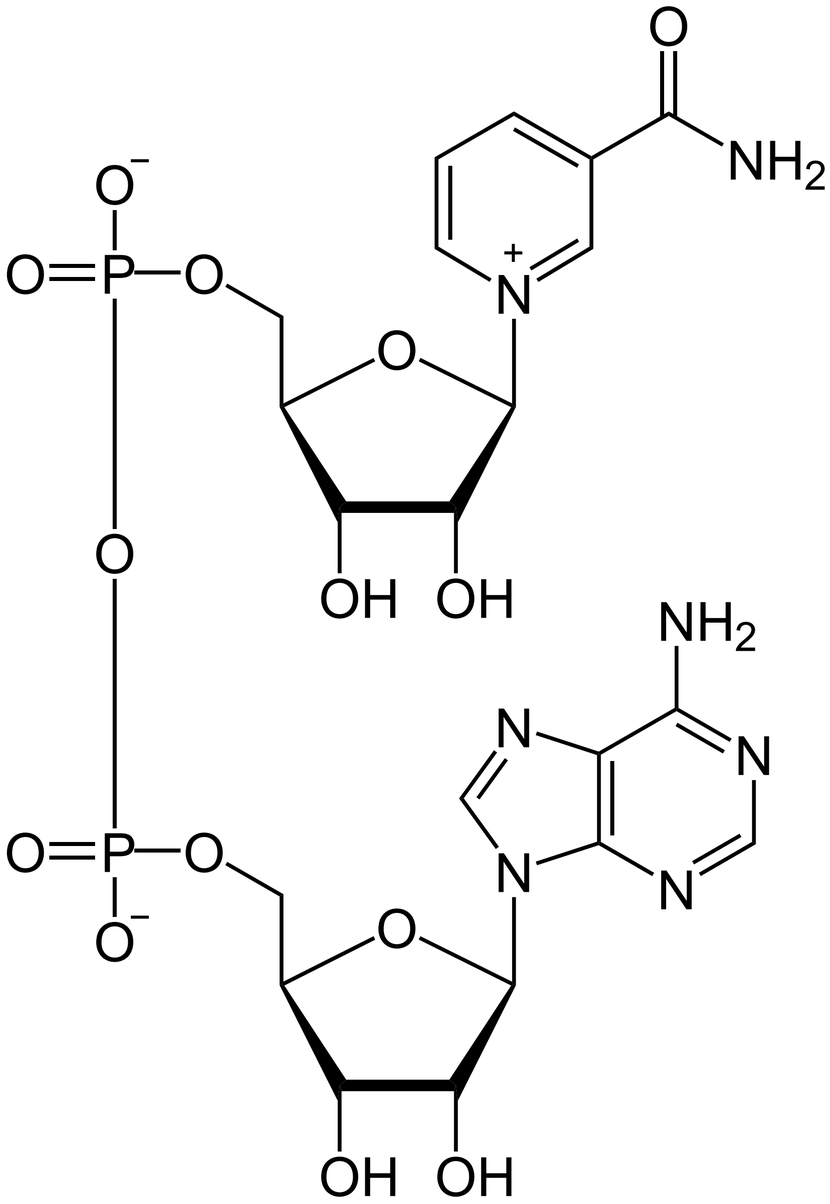
Nowadays we only treat dementia when patients lose their daily activities

Are we treating cancer only in the last metastatic phase?


You said nothing can be done?
Take a deep dive for every patient

Mitochondrial dysfunction is an important component of different diseases associated with aging

Neurodegenerative diseases like AD & Diabetes Type 2

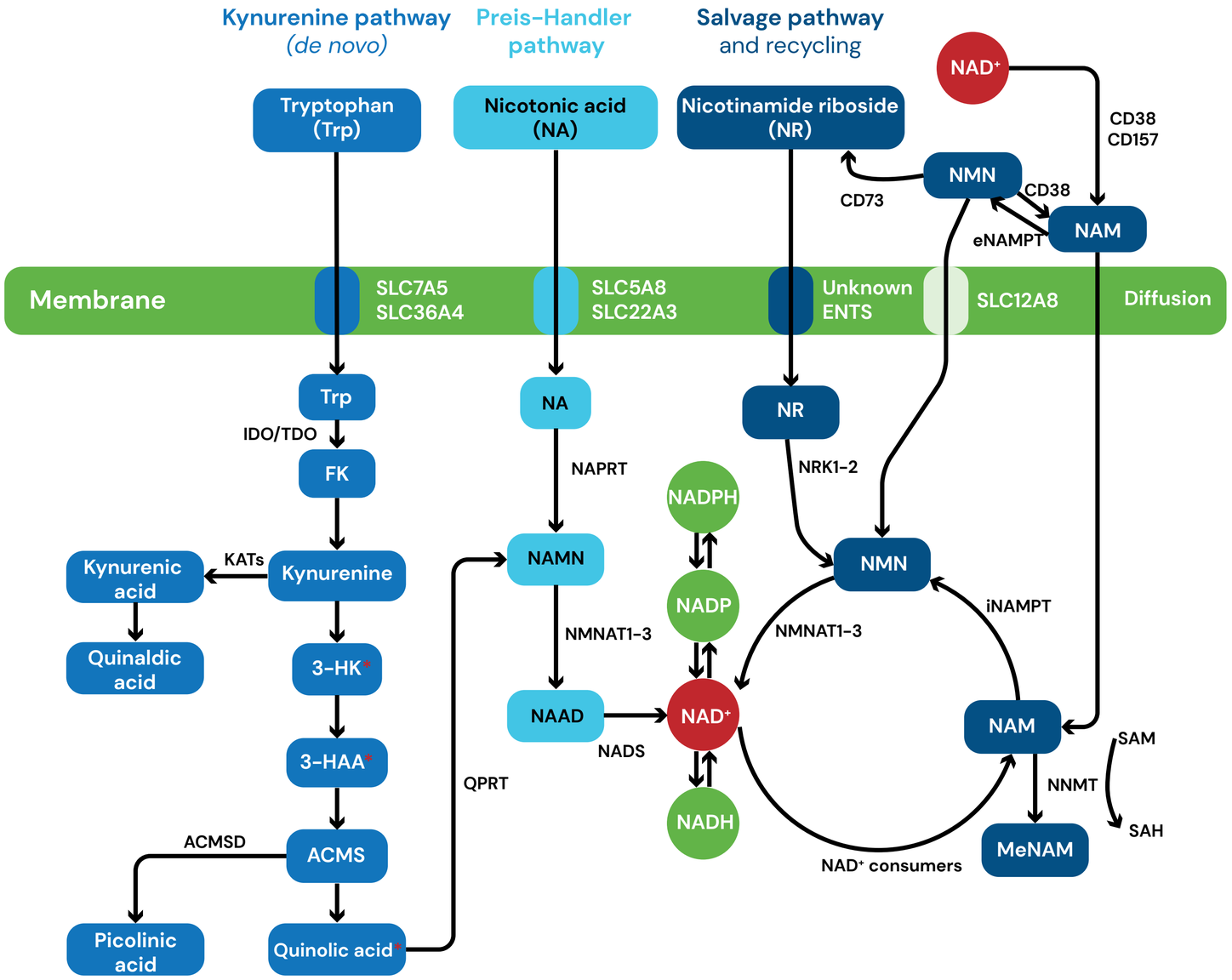


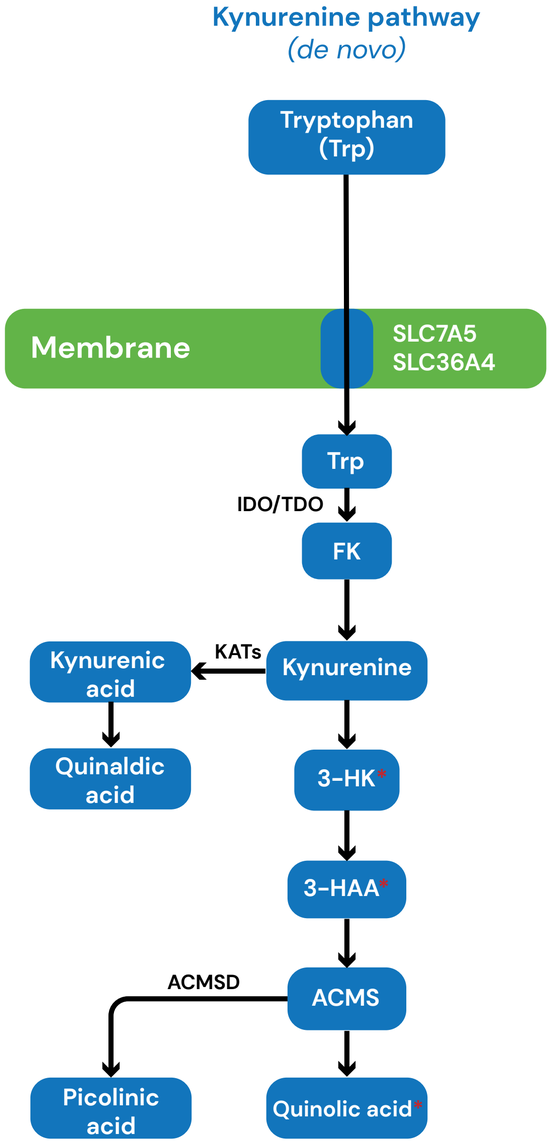
Nicotinamide adenine dinucleotide (NAD)

is a coenzyme central to metabolism. Found in all living cells, NAD is called a dinucleotide because it consists of two nucleotides joined through their phosphate groups.

One nucleotide contains an adenine nucleobase and the other nicotinamide. NAD exists in two forms: an oxidized and reduced form, abbreviated as NAD+ and NADH (H for hydrogen) respectively.

NAD+ is synthesized via 3 major pathways



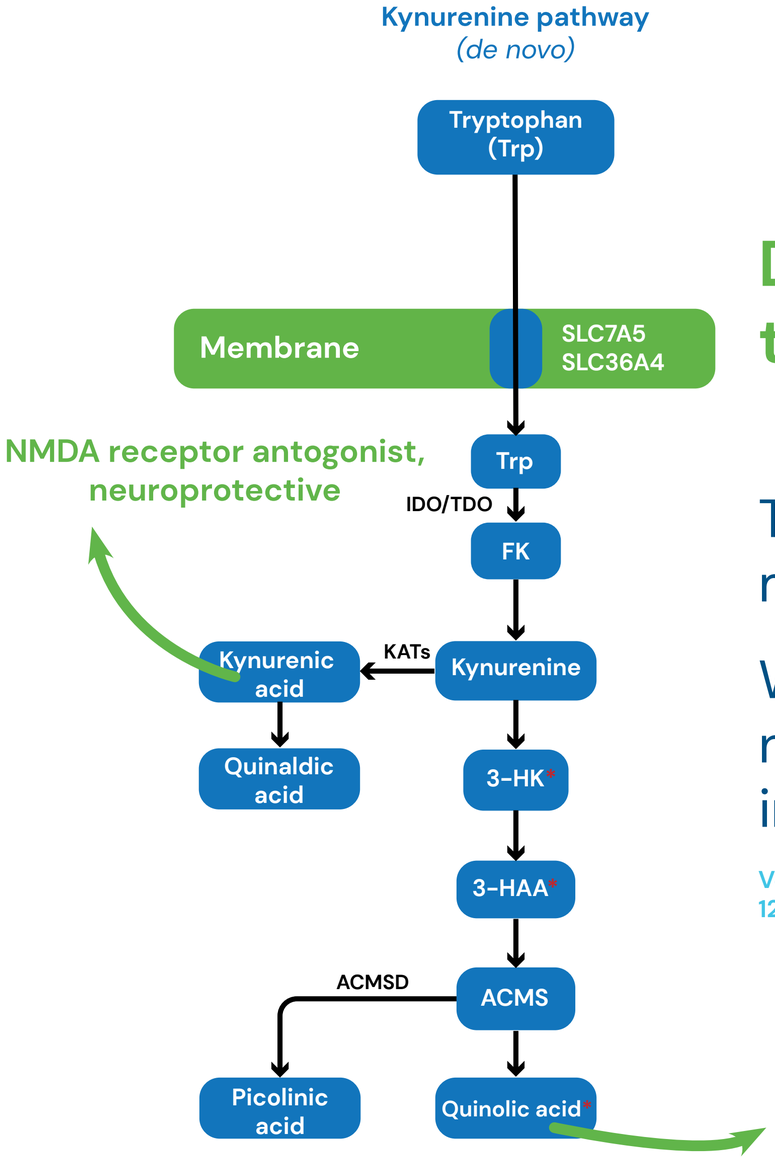


De novo biosynthesis starting from Tryptophan, the kynurenine pathway

This pathway generates different molecules; the level of each molecule is determined by different enzymes

We see impairments of the kynurenine pathway in various neurological conditions like HD, schizophreni, AD & ALS but also in migraine, epileptic seizure, MS, neuropathic pain etc

Vécsei L, Szalárdy L, Fülöp F, and Toldi J (2013). Kynurenines in the CNS: recent advancePARP1s and new questions. Nat. Rev. Drug Discov. 12, 64–82.



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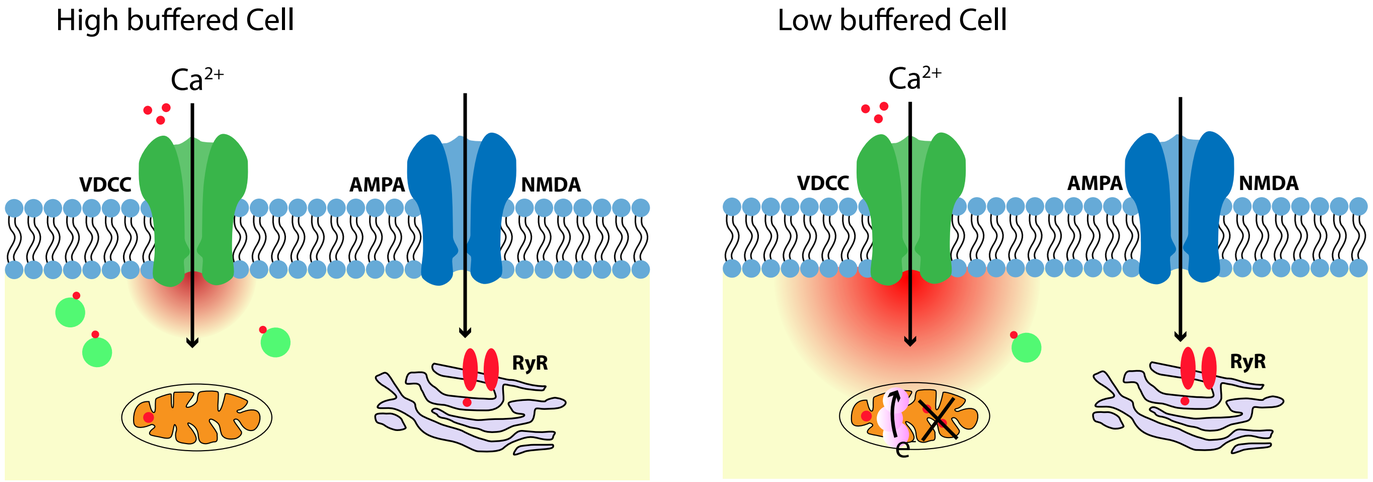
Glutamate is the primary excitatory neurotransmitter produced in CNS, an overactivity of Glutamate and it receptors leads to excitotoxicity

Excitotoxicity = excessive overactivation of NMDA & AMPA receptors triggered by extracellular accumulation of the excitatory neurotransmitter Glutamate

NMDARs & AMPAs mediate Calcium entry into the cells to regulate physiological processes such as synaptic plasticity and memory

Excessive stimulation causes a pathological increase in calcium, which activates enzymes causing damage



Normal Physiological condition (WT)

Excitotoxicity (SOD1 ^{G93A})

What we saw before?

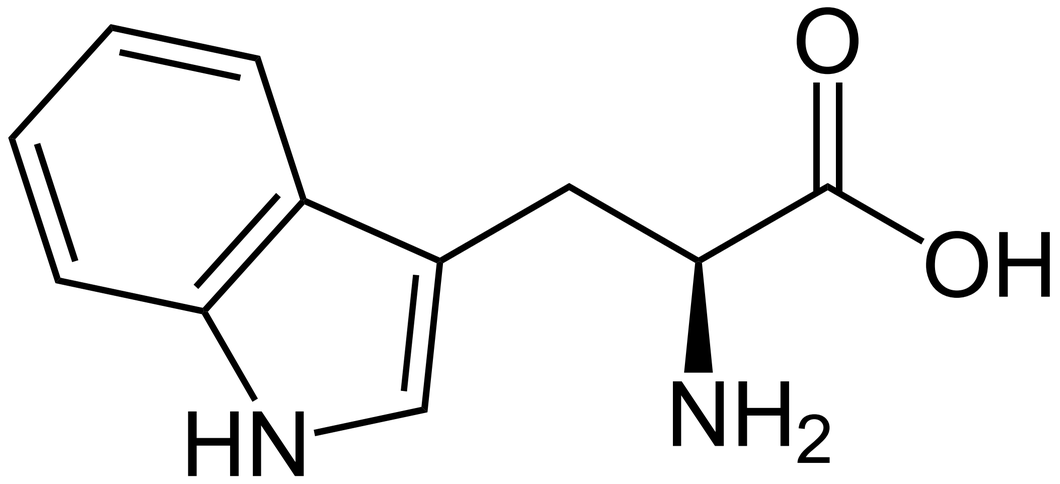
- **Research on PEA in excitotoxicity**
  (PEA with Lipisperse ® coating 4x300mg/day)
- **Magnesium Threonate**
  (Mg C Complex 3x1 caps/day)

Kim, Young-Sung, et al. “Neuroprotective effects of magnesium L-threonate in a hypoxic zebrafish model.” BMC neuroscience 21.1 (2020): 1-11.

Kirkland, Anna E., Gabrielle L. Sarlo, and Kathleen F. Holton. “The role of magnesium in neurological disorders.” Nutrients 10.6 (2018): 730.

Liu, Guosong, et al. “Efficacy and safety of MMFS-01, a synapse density enhancer, for treating cognitive impairment in older adults: a randomized, double-blind, placebo-controlled trial.” Journal of Alzheimer’s Disease 49.4 (2016): 971-990.

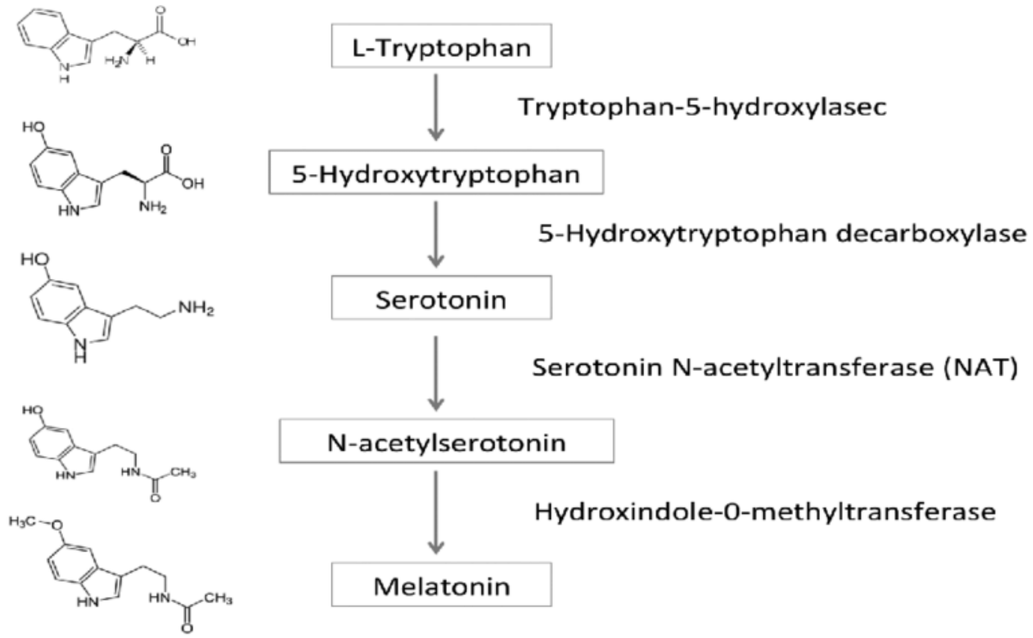
Zarate, Carlos, et al. “New paradigms for treatment□resistant depression.” Annals of the New York Academy of sciences 1292.1 (2013): 21-31.



Tryptophan is an essential amino acid

Digested in the small intestines

Enters the bloodstream



1. Tryptophan is the precursor for the biosynthesis of Serotonin & Melatonin

2. Serotonin = neuroendocrine transmitter

90% of Serotonin in Gastro-Intestinal Tract

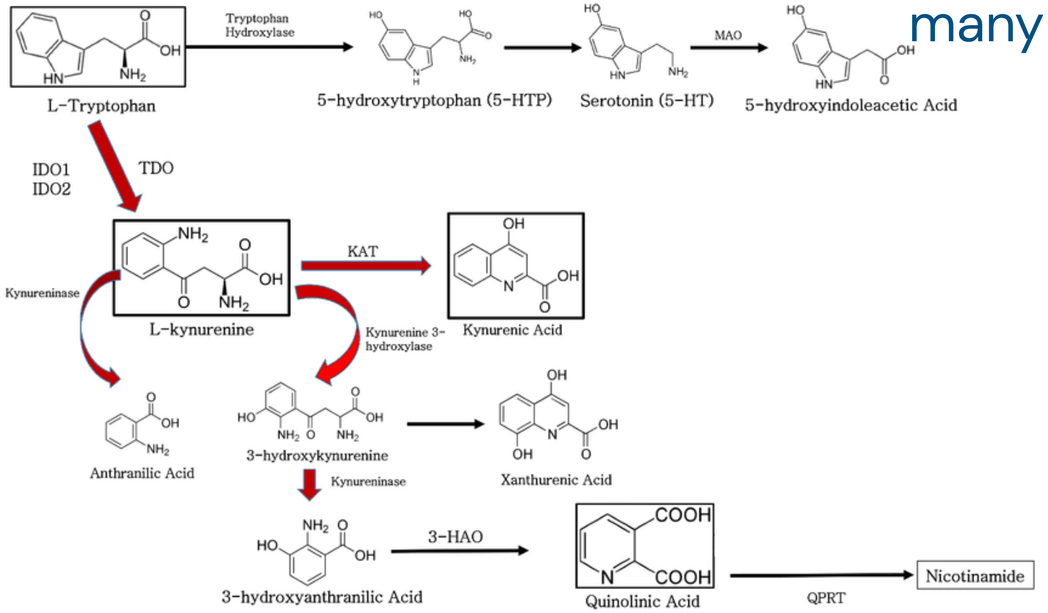
Tryptophan → kynurenine pathway

The Tryptophan metabolism along the kynurenine pathway is initialized by the induction of IDO (indoleamine-2,3-dioxygenase) & TDO (tryptophan 2,3-dioxygenase)

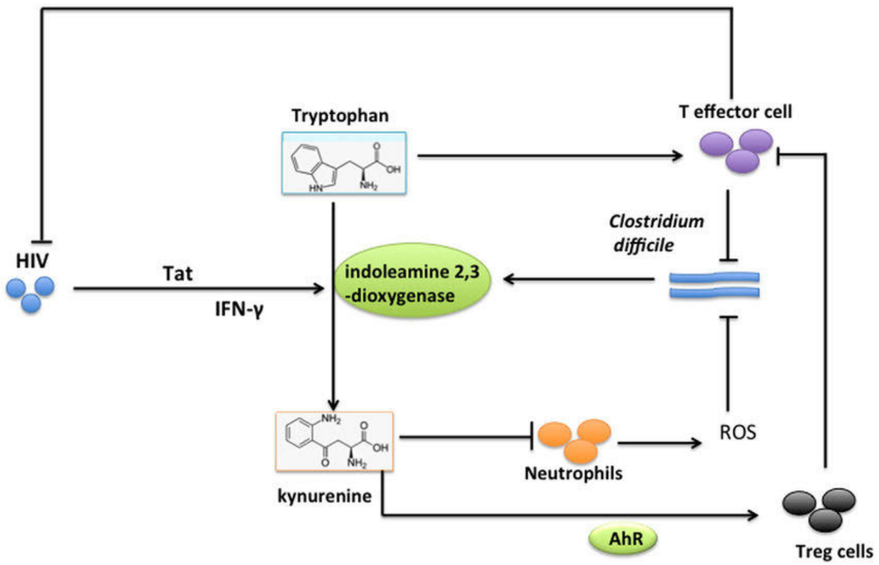
Once kynurenine is produced , it is further metabolized through 2 distinct pathways : Kynurenic Acid & Quinolinic Acid

Furthermore Quinolinic Acid can be converted into NAD

Imbalance between Kynurenic Acid & Quinolinic Acid is seen in many neurologic disorders



Upregulation of IDO promotes Kynurenine and creates a deficiency of Tryptophan, which affects our immune system Tryptophan depletion downregulates CD8, Th17 & NK Cells



- **In chronic viral infections**

  EBV (HHV-4) is the best know cause of mononucleosis
  EBV infects monocytes; macrophages and dendritic cells, which suppresses our phagocytic and antiviral activity
  + EBV is using Tryptophan -IDO1 induced catabolism to evade our i mmune system
  We see the same mechanism in HIV
  The activation goes through Trans-activator Regulatory protein (Tat) & IFN-gamma
  Natural products like EGCG & Trans-Resveratrol have been found to downregulate IDO activation

- **In Clostridium difficile**

  Clostridium diff promotes activation of Indoleamine 2,3-dioxygenase(IDO)
  Kynurenine promotes apoptosis of Neutrophils
  Kynurenine inhibits the production of ROS

- **New experimental research is using IDO-induced catabolism of Tryptophan as an immune suppressive method to ensure long-term survival in transplants**
- **IDO 1 activation is an immune suppressor preventing fetal rejection by maternal T cells**

Viral infections

General antiviral protocol for EBV, CMV, HSV1, HSV2

Promoting NK Cell activity & IL10 Optimizing cellular immune response	**Multimessenger** 90 capsules Dose**:** 3 caps in the morning, right before breakfast
Additionally Specifically targeting reactivating infections incl. EBV, CMV, Herpes, Mycoplasma, Chlamydia, ...	**Messenger N°1** 60 capsules Dose: 2 caps before sleep
Decreasing viral replication	**L-Lysine** 60 tablets Dose: 2 - 3 x 2 tablets times per day, separated from food
Protecting Natural Killer cell against oxidative damage	**Tri-Fortify Watermelon or Orange** 236 ml Dose: 1 teaspoon (5ml) per day, separated from meals
EBV & CMV promote IDO-mediated Tryptophan catabolism The depletion of Tryptophan downregulates CD4, CD8 & NK Cells EGCG & Trans-Resveratrol have been found to inhibit IDO's activation.	**AO Defense** 60 vcaps Dose: 2 x 1 caps per day
Oxidative damage to mitochondria due to increased oxidative load - Lipid Replacement Therapy	**ATP 360** 90 vcaps Dose: 3 caps per day during meal
Lactoferrin prevents the infection of host cell by viruses, but also inhibits the growth if viruses after host cells have been invaded	**Lactoferrin acid resistant 100mg** 84 acid resistant caps Dose: 3 x 2 caps, 20 minutes before meal
Eradication of HSV1 and HSV2 **Houttuynia** antiviral activity against HSV1 and HSV2	**Myc-P** 120 ml Dose: start with 2 x 5 drops per day, 30 minutes before meals + gradually increase the daily dose until 2 x 40 drops per day
Neuropathic pain in viral infections	**PEA – certified grade 300 mg** vcaps Dose: 1 – 4 caps per day

References

Eradication of HSV1 and HSV2 with Myc-P

Chou SC, Su CR, Ku YC, Wu TS. The constituents and their bioactivities of Houttuynia cordata. Chem Pharm Bull (Tokyo). 2009 Nov;57(11):1227-30.

Hayashi K, Kamiya M, Hayashi T. Virucidal effects of the steam distillate from Houttuynia cordata and its components on HSV-1, influenza virus, and HIV. Planta Med. 1995 Jun;61(3):237-41.

PEA: this review is a summary of 23 trails and case reports

Gabrielsson Linda, Mattsson S, Christopher J. Fowler. Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy. British journal of clinical pharmacology 82.4 (2016): 932-942.

Other references

Ellithorpe, Rita, Settineri, Robert, Ellithorpe, Talon & Nicolson, Garth. (2015). Nutrient Supplement Enhances Natural Killer Cell Function in Women with Chronic Fatigue Syndrome and Fibromyalgia: Preliminary Report. Townsend Letter. 60-62.

Fatahzadeh M, Schwartz RA. Human herpes simplex labialis. Clin Exp Dermatol. 2007;32:625-30.

Goc, A., & Rath, M. (2016, June). The anti-borreliae efficacy of phytochemicals and micronutrients: an update. Therapeutic Advances in Infectious Disease, 3(3-4), 75-82.

Huh, E. Houttuynia cordata Improves Cognitive Deficits in Cholinergic Dysfunction Alzheimer's Disease-Like Models. Biomolecules and Therapeutics, 2014. 22(3), 176-183.

Mehraj, Vikram, and Jean-Pierre Routy. "Tryptophan Catabolism in Chronic Viral Infections: Handling Uninvited Guests." International Journal of Tryptophan Research, vol. 8, 2015.

Coxsackie virus

These viruses have a small, positive-sense single stranded RNA genome, and infection occurs primarily through the fecal-oral route.
Coxsackievirus has a remarkably high seroprevalence in human population around the world.

Promoting IL10 and optimizing cellular immune response	**Multimessenger** 90 caps Dose**:** 3 caps in the morning, right before breakfast
Additionally Specifically targeting reactivating infections incl. EBV, CMV, Herpes, Mycoplasma, Chlamydia, ...	**Messenger N°1** 60 caps Dose: 2 caps before sleep
Protecting Natural Killer cell against oxidative damage Optimizing detoxification	**Tri-Fortify Watermelon or Orange** 236 ml Dose: 1 teaspoon (5ml) per day, separated from meals **AO Defense** 60 vcaps Dose: 2 x 1 caps per day
Eradication of pathogens **Isatis root** Antiviral activities against Coxsackie virus due to ingredients like indoxyl-beta-glucoside, beta-sitosterol and isatin	**Myc-P** 120 ml Dose: start with 2 x 5 drops per day, 30 minutes before meals + gradually increase the daily dose until 2 x 40 drops per day

References

Eradication of Coxsackie virus with Myc-P

Chen M, Gan L, et al. Alkaloids from the root of Isatis indigotica. J Nat Prod. 2012 Jun 22;75(6):1167-76.

Chiang LC, Ng LT, Cheng PW. Antiviral activities of extracts and selected pure constituents of Ocimum basilicum. Clin Exp Pharmacol Physiol. 2005; 32: 811-816.

Ellithorpe, Rita, Settineri, Robert, Ellithorpe, Talon & Nicolson, Garth. (2015). Nutrient Supplement Enhances Natural Killer Cell Function in Women with Chronic Fatigue Syndrome and Fibromyalgia: Preliminary Report. Townsend Letter. 60-62.

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Liu YF, Chen MH, et al. Antiviral glycosidic bisindole alkaloids from the roots of Isatis indigotica. J Asian Nat Prod Res. 2015;17(7):689-704

Sinha, R., Sinha, I., Calcagnotto, A., Trushin, N. Oral supplementation with liposomal glutathione elevates body stores of glutathione and markers of immune function. Eur J Clin Nutr. 2018 Jan;72(1):105-111.

Enterovirus 71

Enteroviruses are members of the Picornaviridae family. They possess a positive-sense ssRNA genome and are non-enveloped. These viruses are ordinarily transmitted by fecal-oral route, but transmission by respiratory droplet is also possible.
The genus of Enterovirus includes notable members such as Enterovirus 71 (= foot and-mouth disease virus), poliovirus, rhinovirus.
Some Enteroviruses, particularly Enterovirus-71 (EV71) in Asia, are considered to be harmful emerging CNS pathogens. Another important member of the Enterovirus genus is Coxsackievirus.

Promoting IL10 and optimizing cellular immune response	**Multimessenger** 90 caps Dose**:** 3 caps in the morning, right before breakfast
ADDITIONALLY Specifically targeting reactivating infections incl. EBV, CMV, Herpes, Mycoplasma, Chlamydia, ...	**Messenger N°1** 60 caps Dose: 2 caps before sleep
Protecting Natural Killer cell against oxidative damage Optimizing detoxification	**Tri-Fortify Watermelon or Orange** 236 ml Dose: 1 teaspoon (5 ml) per day, separated from meals
Eradication of pathogens **EGCG** Interferes with enteroviral replication via modulation of the cellular redox environment	**AO Defense** 60 vcaps Dose: 2 x 1 caps per day

References

Ellithorpe, Rita, Settineri, Robert, Ellithorpe, Talon & Nicolson, Garth. (2015). Nutrient Supplement Enhances Natural Killer Cell Function in Women with Chronic Fatigue Syndrome and Fibromyalgia: Preliminary Report. Townsend Letter. 60-62.

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Ho HY, Cheng ML, Weng SF. Antiviral effect of epigallocatechin gallate on enterovirus71. J Agric Food Chem. 2009;57: 6140-7.

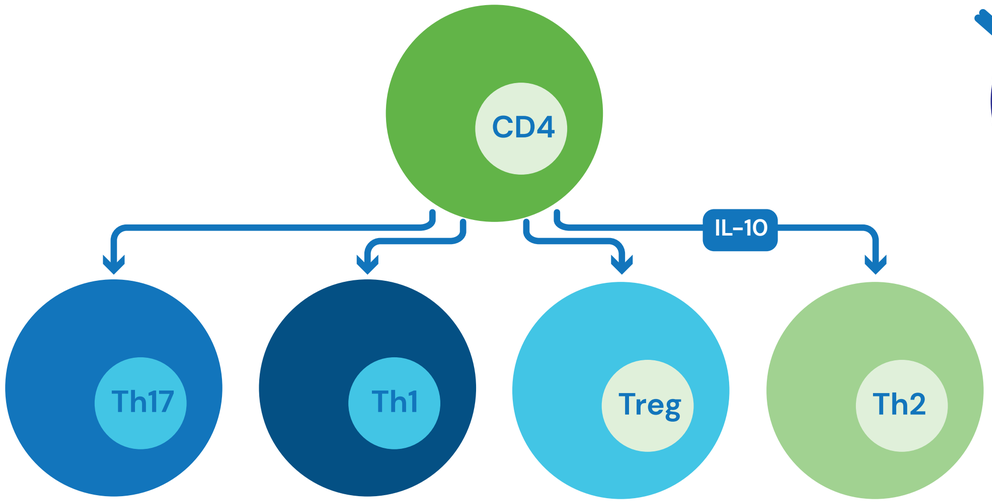
INHIBITION versus Activation of NK Cells

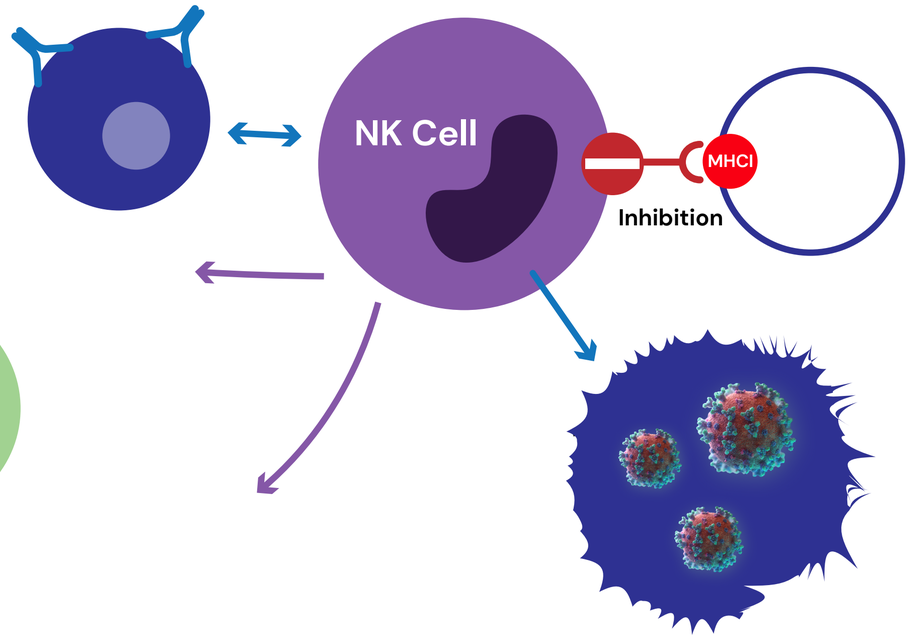
INHIBITION

MHC I (Major Histocompatibility Complex 1) is expressed on the cell surface of all nucleated cells

MHC I acts as a ligand and binds to inhibitory receptors on NK cells

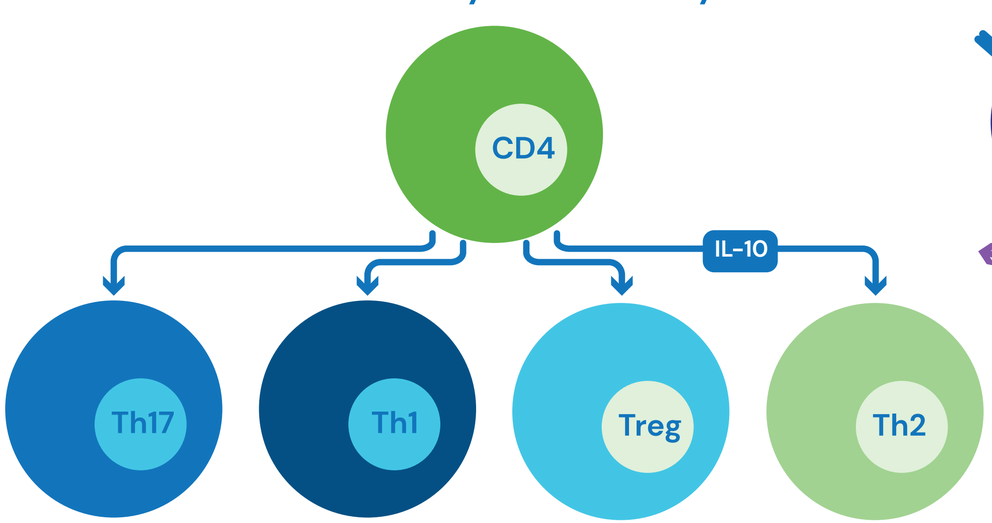
Self tolerance

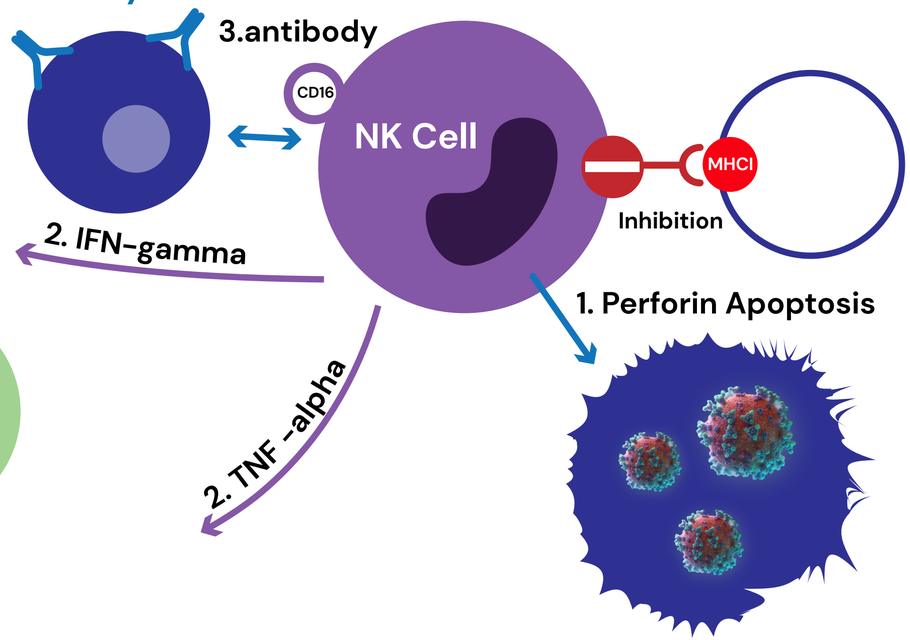


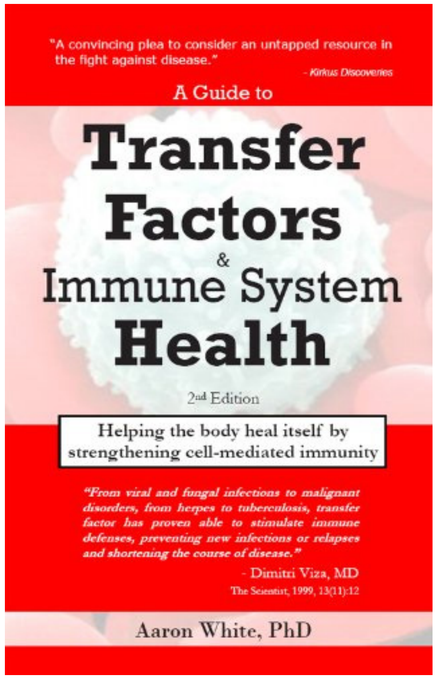


Activation

1. Degradation of the membranes of cells that have been infected by intracellular germs
   = lysis, using enzymes mainly perforin
2. Indirect elimination of target cells through production of inflammatory cytokines such as IFN-gamma & TNF-alpha
3. NK Cells express CD16 on their surface
   CD16 detects antibody-coated target cells which leads to cytotoxicity of the antibody-coated cells







The activation of Natural Killer Cells through Transfer Factors is based on a direct interaction between Transfer Factors & activating receptors on the surface of NK cells

Transfer Factors are like a cross between interleukins and antibodies

Carrying messages from immune cell to immune cell like Interleukins

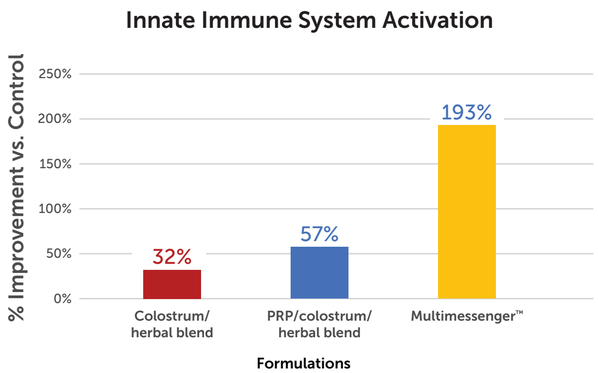
= strengthening NK Cells

= rebuilding balance Th1/Th2/Th17 & downregulate autoimmunity and exsessive inflammation

Multimessenger™ 90 capsules

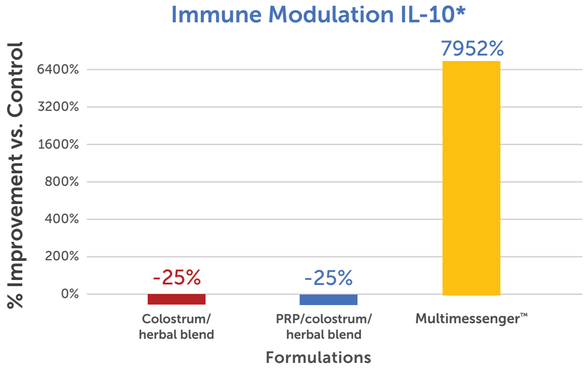
Take 3 caps per day 30 min. before breakfast

Natural Killer Cell Activation*



*% improvement in Mean Fluorescent Intensity for CD 69 Receptor on Natural Killer Cells. (CD69 is highly correlated with NK cell activity)

Immune Modulation IL-10*



* % Improvement In Mean Fluorescent Intensity for IL-10 on Peripheral Blood Mononuclear Cell Cultures (PBMC)

Specific Transfer Factors bind to antigens on infected cells like antibodies

Specific Transfer Factors based on composition in comparison table

Messenger N° 1™ 60 gelcapsules

Take 2 caps per day before sleep

Specific transfer factors target reactivating infections incl. EBV, CMV, Herpes, Mycoplasma, Chlamydia...

Transfer Factor L+™ 60 gelcapsules

Take 2 caps per day before dinner

Specific transfer factors target vector-borne infections incl. Bartonella, Babaesia, Ehrlichia …

Transfer Factors

Khan A., Hansen B., Hill N.O., Loeb E. Transfer factor is the treatment of herpes simplex types 1 and 2. Dermatologica 163, 177-85.

Comparative study of transfer factor and acyclovir in the treatment of herpes zoster. Int J Immunopharmacol. 1998 Oct;20(10):521-35.

Review: Pizza, E. (1998). Transfer Factors reduced both frequency and duration of outbreaks in patients + Only TF increased the number of T-cells.

Rita, R., Ellithorpea, B., Settineria, R., & Ellithorpeb, T. Nutrient supplement enhances natural killer cell function in women with chronic fatigue syndrome and fibromyalgia: preliminary report. 2015 November. Townsendletter.

Sinha, R., Sinha, I ., Calcagnotto, A., Trushin, N. Oral supplementation with liposomal glutathione elevates body stores of glutathione and markers of immune function. Eur J Clin Nutr. 2018 Jan;72(1):105-111.

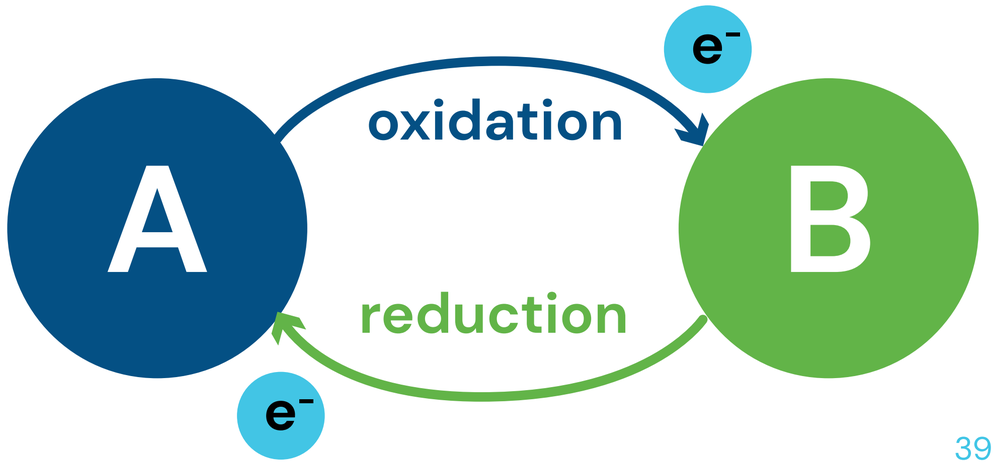
Debby Hamilton. Immune Modulation: Research Summary Transfer Factor vs. Colostrum vs. Proline-Rich Peptides. 2019. – on request

Comparison table

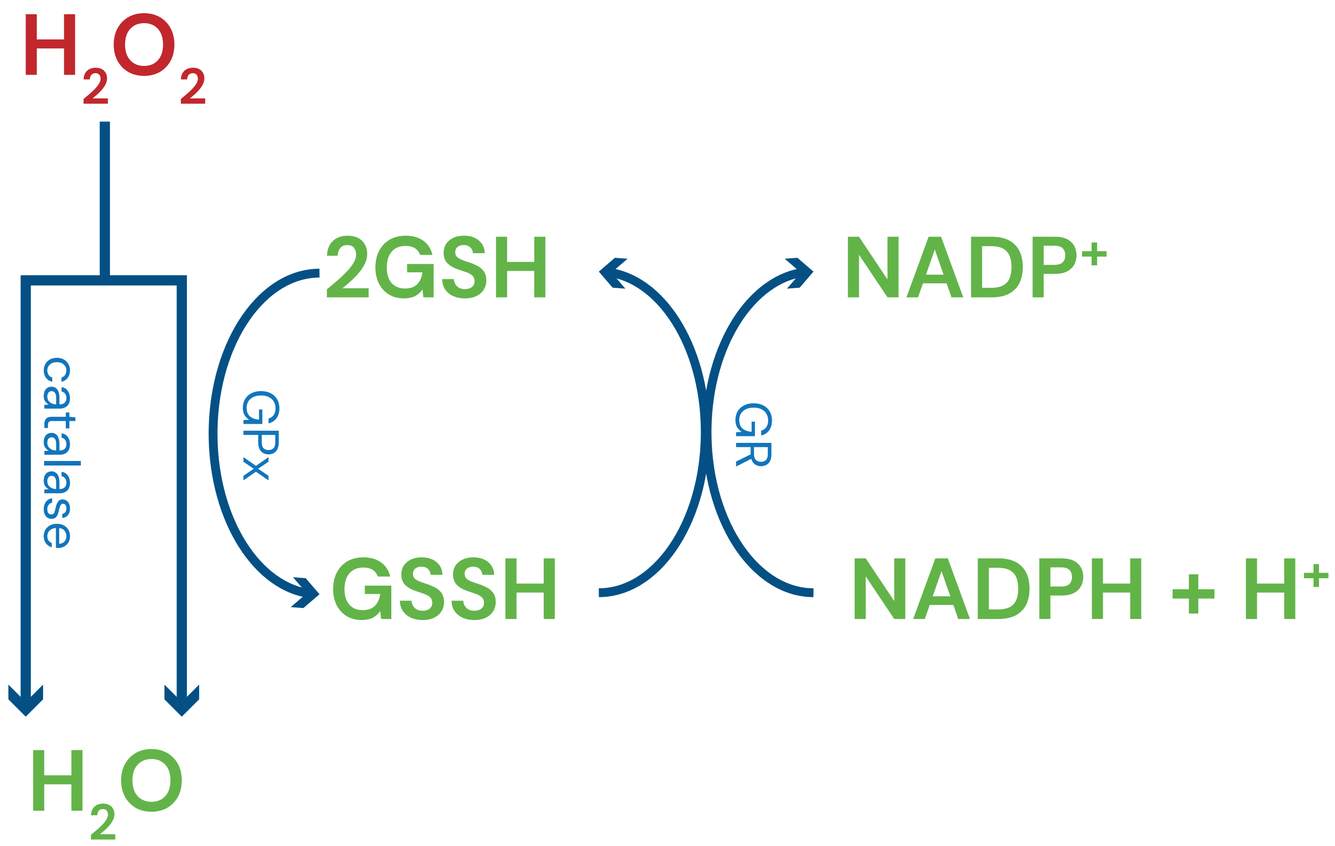
	Multimessenger	Multi messenger (mushroom-free)	Transfer Factor Sensitive™	Transfer Factor L-Plus™	Messenger N°·1	Transfer Factor Enviro™
Natural Killer Cell - General Immune Support	x	x	x			
Bartonella				x		
Borrelia burgdorferi				x	x	
Babesia				x		
Ehrlichia				x		
EBV				x	x	
HHV6 B				x		
HHV6 A&B					x	
CMV	x	x	x	x	x	
Chlamydia pneumoniae				x	x	
Pneumocystic carinii					x	
Human TB					x	
Bovine TB					x	
Herpes 1					x	
Herpes 2					x	
Cryptosporosis					x	
Mycobacterium avian					x	
Hepatitis A, B, C					x	
Staphylcocci					x	
Streptococci						x	
E. coli						x	
Parvo virus B19						x	
Varicella Zoster						x	
Candida (multiple strains)						x	x
MMR						x	
Mycoplasma – 14 strains						x	
Ureaplasma urealyticum						x	
Nanobacterium						x	
Human Papillomaviruses						x	
Penicillium							x
Epicoccum							x
Aspergillus fumigatus							x
Aspergillus niger							x
Aspergillus versicolor							x
Cladosporium							x
Fusarium							x
Geotrichum							x
Pithomyces							x
Ustilago							x

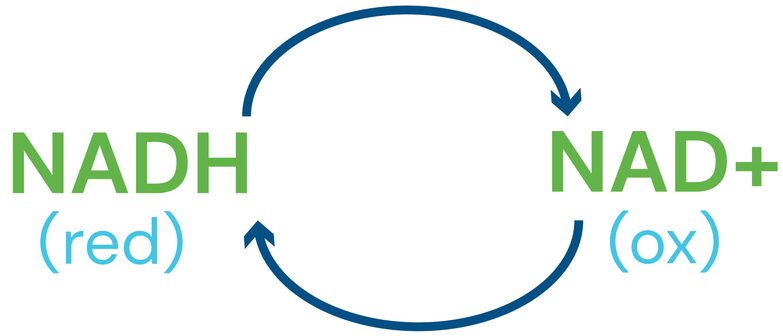
NAD+ is a vital redox co-factor,
a key substrate for different enzymes

An oxidation reaction strips an electron from an atom in a compound, and the addition of this electron to another compound is a reduction reaction. Because oxidation and reduction usually occur together, these pairs of reactions are called oxidation reduction reactions, or redox reactions



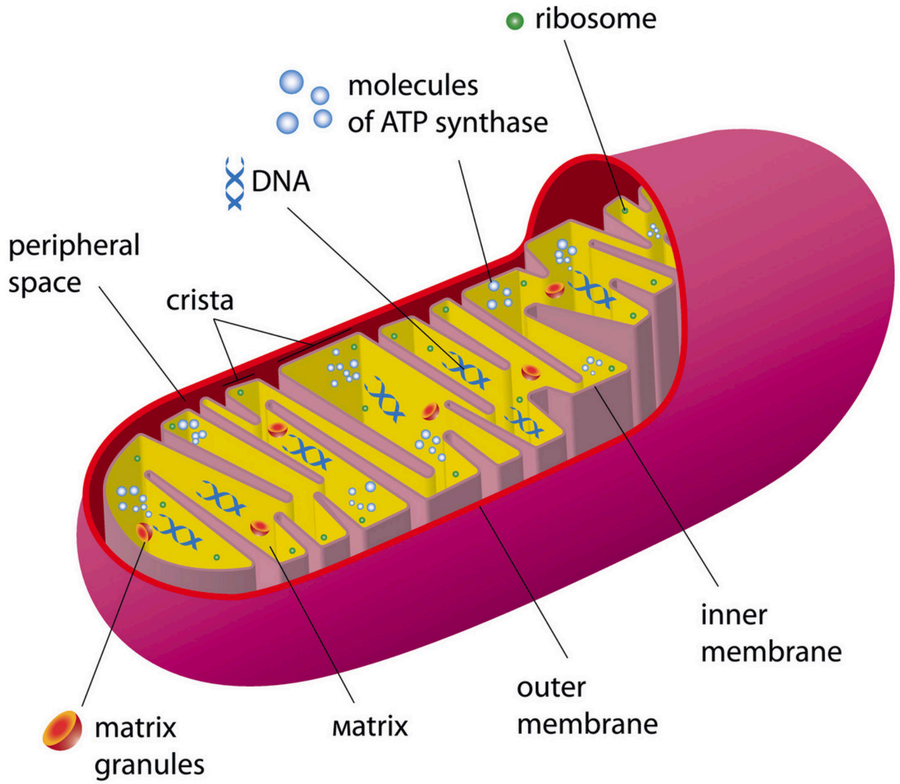
Examples


H_2O_2
catalase
H_2O
2GSH
GSSH
GPx
GR
$NADP^+$
$NADPH + H^+$

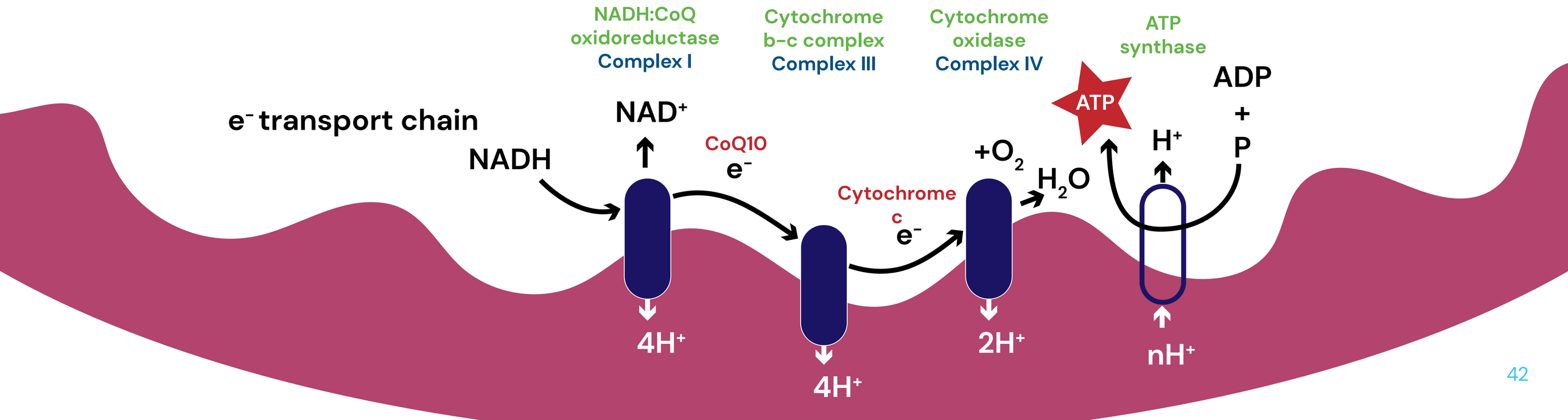

NADH
(red)
NAD+
(ox)

NADH/NAD+ essential in mitochondrial metabolism,
mitochondria are the power generators of the cells

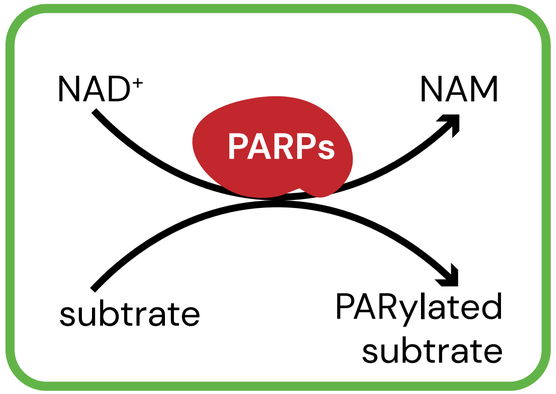
oxygen + nutrients → **ATP**



- NADH is one of the essential electron donors in the oxidative phosphorylation where finally ATP is formed in our mitochondria
- NADH provides electrons to the electron transport chain
- The ratio NAD+/NADH is important for the efficiency to generate ATP



The major NAD+ consuming enzymes

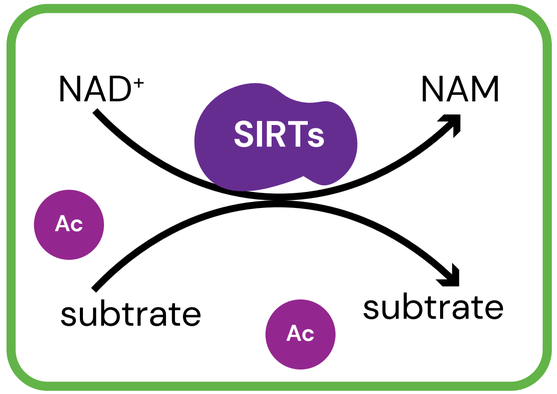


Genomic integrity
Healthy aging

Poly (ADP-Ribose) polymerases = PARPS
Especially PARP1 & PARP2

Substrates are PARylated,
NAD+ is a co-substrate converted
in NAM (Nicotinamide) as a by-product

As DNA damage accumulates over time,
the activation of PARP's increase

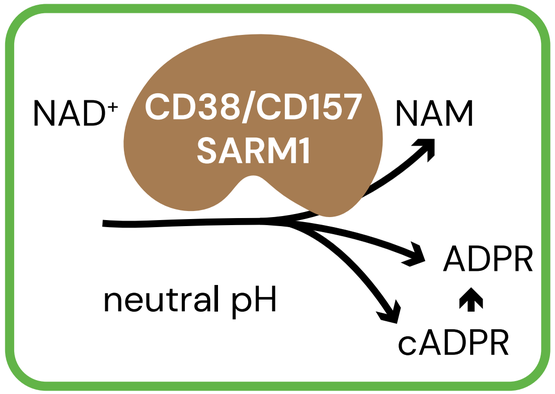


Metabolism, neuroplasticity,
Healthspan/Lifespan

Sirtuins are NAD+ dependent deacetylase enzymes

NAD+ is co-substrate converted
in NAM (Nicotinamide) as a by-product

Sirtuins are regulators of aging and longevity
in diverse organisms



Mitochondria transfer,
immunity, social behavior

CD38 & CD157 (NAD ases or cyclic ADP-ribose synthases) hydrolize NAD+ to NAM (Nicotinamide), generating ADPR & c ADPR

There should be a constant equilibrium between NAD+ synthesis, consumption and recycling

The systemic decrease in NAD+ in aging results from lowered biosynthesis and increased use of NAD+ in many redox reactions

Competition between the different NAD+ consuming enzymes?
The different enzymescompete with each other to consume NAD+

Hyperactivity of 1 enzyme impairs the other enzymes

The Kynurenine pathway,
with regular dietary intake of Tryptophan

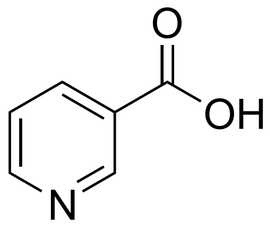
\+ Dietary intake of nicotinamide through
intake of eggs, meat, fish and mushrooms

should be sufficient for the baseline requirements of NAD+

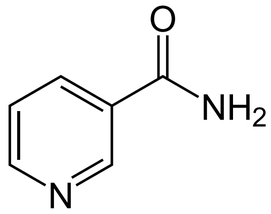
However growing evidence demonstrates that greater rates of NAD+ show numerous benefits and therapeutic effects
which can be achieved by supplementation of the precurors

The Chemical structure of NAD+ and the different NAD+ precursors,

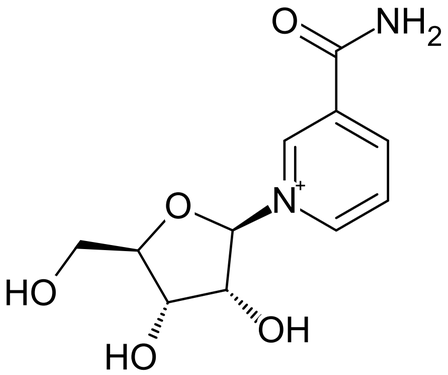
- Nicotinic acid enters the salvage pathway and acts as a NAD+ precursor but undesirable flushing shows up at therapeutic doses (Gpr 109 receptor on epithelial cells)
- Nicotinamide does not reliably activate sirtuins despite raising concentrations of NAD+



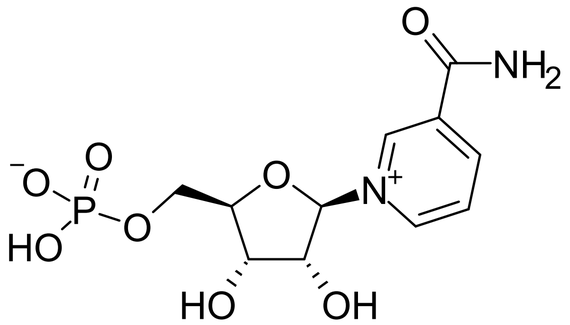
Nicotonic acid (NA)



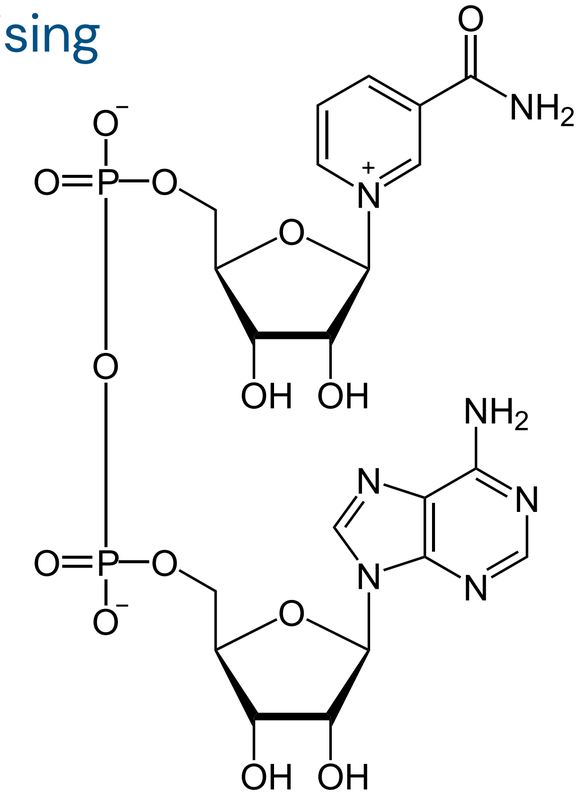
Nicotinamide (NAM)



Nicotinamide riboside (NR)



Nicotinamide mononucleotide (NMN)



Nicotinamide adenine dinucleotide (NAD^+)

MacKay, D., Hathcock, J. & Guarneri, E. Niacin: chemical forms, bioavailability, and health effects. Nutr. Rev. 70, 357–366 (2012).

Bitterman, K. J., Anderson, R. M., Cohen, H. Y., Latorre-Esteves, M. & Sinclair, D. A. Inhibition of silencing and accelerated aging by nicotinamide, a putative negative regulator of yeast Sir2 and human SIRT1. J. Biol. Chem. 277, 45099–45107 (2002)

Trammell, S. A. et al. Nicotinamide riboside is uniquely and orally bioavailable in mice and humans. Nat. Commun. 7, 12948 (2016).

Tunaru, S., Lattig, J., Kero, J., Krause, G. & Offermanns, S. Characterization of determinants of ligand binding to the nicotinic acid receptor GPR109A (HM74A/PUMA-G). Mol. Pharmacol. 68, 1271–1280 (2005).

NAD+ in brain aging

- Lower NAD+ levels are observed during normal aging
- Treatment with NAD+ precursors improved cognition in knockdown mice model
- Possible explanations for reduced cellular NAD+ during aging include increased NAD+ consumption by the different enzymes and reduced NAD+ production

Zhu XH, Lu M, Lee BY, Ugurbil K, and Chen W (2015). In vivo NAD assay reveals the intracellular NAD contents and redox state in healthy human brain and their age dependences. Proc. Natl. Acad. Sci. USA 112, 2876–2881

Johnson S, Wozniak DF, and Imai S (2018). CA1 Nampt knockdown recapitulates hippocampal cognitive phenotypes in old mice which nicotinamide mononucleotide improves. NPJ Aging Mech. Dis 4, 10.

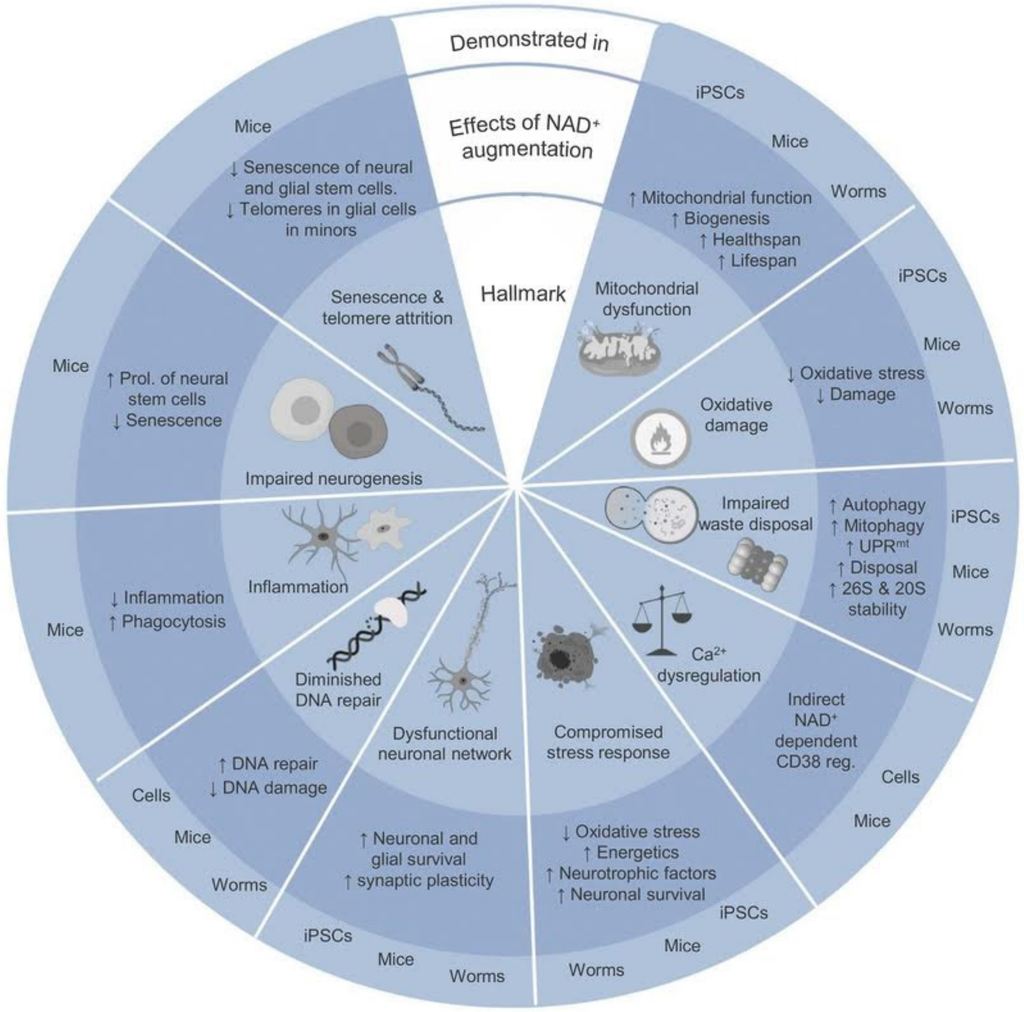
Camacho-Pereira J, Tarragó MG, Chini CCS, Nin V, Escande C, Warner GM, Puranik AS, Schoon RA, Reid JM, Galina A, et al. (2016). CD38 dictates age-related NAD decline and mitochondrial dysfunction through an SIRT3-dependent mechanism. Cell Metab. 23, 1127–1139.

Yoshida M, Satoh A, Lin JB, Mills KF, Sasaki Y, Rensing N, Wong M, Apte RS, and Imai SI (2019). Extracellular vesicle-contained eNAMPT delays aging and extends lifespan in mice. Cell Metab. 30, 329–342

- **NAD+ depletion** is observed not only during normal aging but **also in accelerated aging**
- **NAD+ augmentation restored mitochondrial function** leading to enhanced neuronal survival and improved cognitive function in premature aging process

Fang EF, Kassahun H, Croteau DL, Scheibye-Knudsen M, Marosi K, Lu H, Shamanna RA, Kalyanasundaram S, Bollineni RC, Wilson MA, et al. (2016a).
NAD(+) replenishment improves lifespan and healthspan in ataxia telangiectasia models via mitophagy and DNA repair.
Cell Metab. 24, 566–581. [PMC free article] [PubMed] [Google Scholar]

Fang EF, Scheibye-Knudsen M, Chua KF, Mattson MP, Croteau DL, and Bohr VA (2016b).
Nuclear DNA damage signalling to mitochondria in ageing. Nat. Rev. Mol. Cell Biol. 17, 308–321.



Mattson & Arumugan have identified the 10 hallmarks of brain aging

Mattson MP, and Arumugam TV (2018).
Hallmarks of brain aging: adaptive and pathological modification by metabolic states. Cell Metab. 27, 1176–1199

Emerging findings reveal a linkage between age-related NAD+ depletion and the 10 hallmarks of brain aging

Fang EF, Kassahun H, Croteau DL, Scheibye-Knudsen M, Marosi K, Lu H, Shamanna RA, Kalyanasundaram S, Bollineni RC, Wilson MA, et al. (2016a).
NAD(+) replenishment improves lifespan and healthspan in ataxia telangiectasia models via mitophagy and DNA repair.
Cell Metab. 24, 566–581. [PMC free article] [PubMed] [Google Scholar]

Fang EF, Scheibye-Knudsen M, Chua KF, Mattson MP, Croteau DL, and Bohr VA (2016b).
Nuclear DNA damage signalling to mitochondria in ageing. Nat. Rev. Mol. Cell Biol. 17, 308–321.

Mitochondria → **ATP**

- **Support neuronal activities**
- **neurotransmission**
- **Ca++ homeostatis**
- **neuronal survival and death**

Mattson MP, Gleichmann M, and Cheng A (2008). Mitochondria in neuro-plasticity and neurological disorders. Neuron 60, 748–766.

Mitochondrial dysfunction in aging brain

Post-mortem human brain tissues show mitochondrial dysfunction

- Reduced function of the electron chain transport
  → Increased oxidative damage
- Disrupted membrane potential impaired Ca++ concentration
- Age-dependent reduction in the ability to clear damaged mitochondria
  = Accumulation of dysfunctional mitochondria

Together with mitochondrial dysfunction, we see a decline in NAD+ levels in brain aging and neurodegenerative disorders

Fang EF, Scheibye-Knudsen M, Brace LE, Kassahun H, SenGupta T, Nilsen H, Mitchell JR, Croteau DL, and Bohr VA (2014).
Defective mitophagy in XPA via PARP-1 hyperactivation and NAD(+)/SIRT1 reduction. Cell 157, 882–896

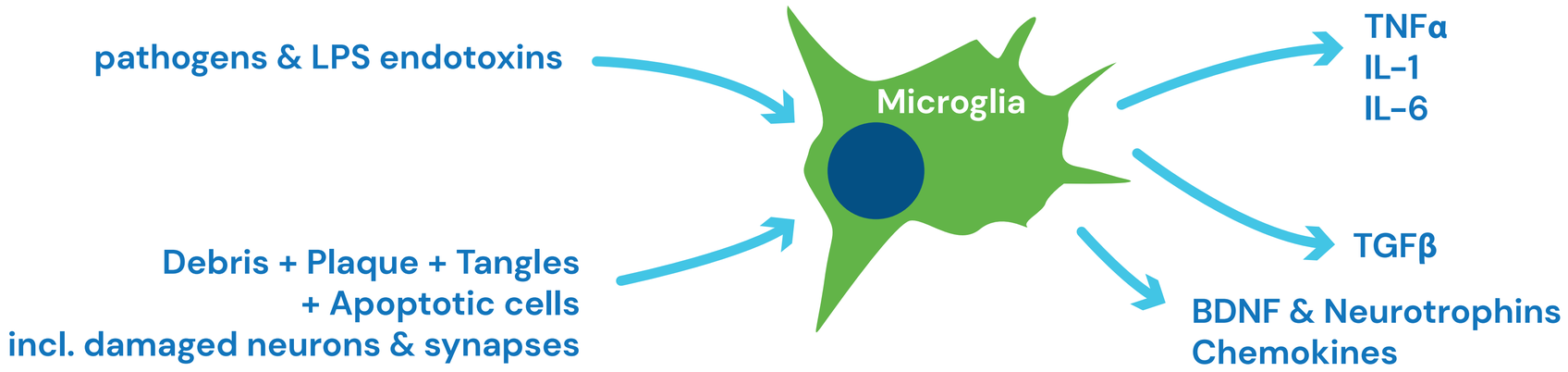
Mouchiroud L, Houtkooper RH, Moullan N, Katsyuba E, Ryu D, Cantó C, Mottis A, Jo YS, Viswanathan M, Schoonjans K, et al. (2013).
The NAD(+)/sirtuin pathway modulates longevity through activation of mitochondrial UPR and FOXO signaling. Cell 154, 430–441.

The impact of NAD+ supplementation on microglial activity & neuroinflammation

Microglial cells are the resident macrophages of the brain that form the innate immune defense system

Microglia are in constant surveillance

After conversion from a resting state to an activated form, they detect and remove pathogens, endotoxins and self-antigens like amyloid plaque, myelin debris, apoptotic cells

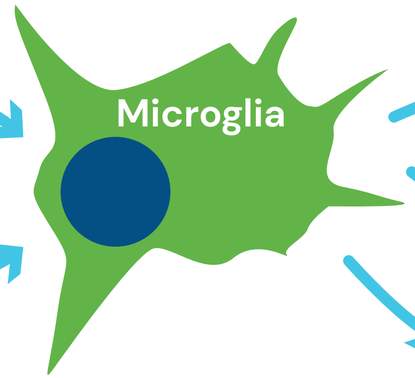


Simultaneously a wide variety of soluble factors are released : inflammatory mediators like TNFα, IL-1, IL-6, Prostaglandins, Neuroptrophic factors like BDNF
Goal = reorganization and recruitment of more immune cells like Astrocytes

pathogens & LPS endotoxins

Incomplete clearance / poor sleep

Debris + Plaque + Tangles
+ Apoptotic cells
incl. damaged neurons & synapses

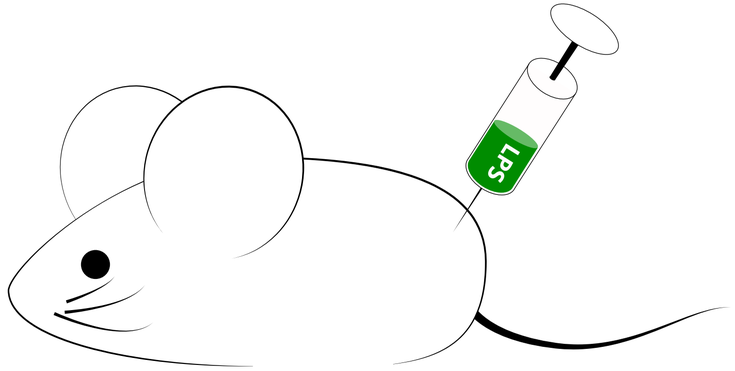


Excessive release of inflammatory mediators
= neuroinflammation

TNFα ▲
IL-1 ▲
IL-6 ▲

TGFβ

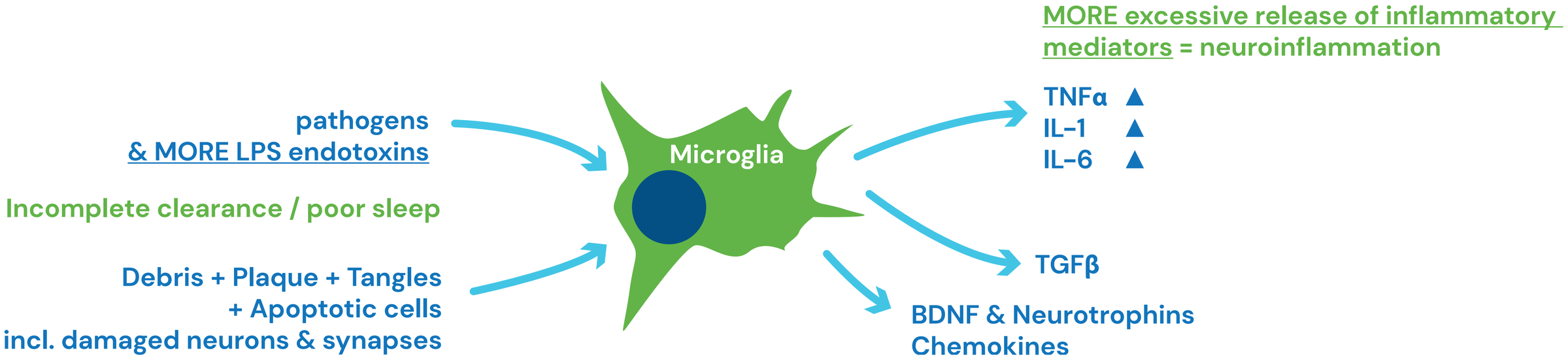
BDNF & Neurotrophins
Chemokines



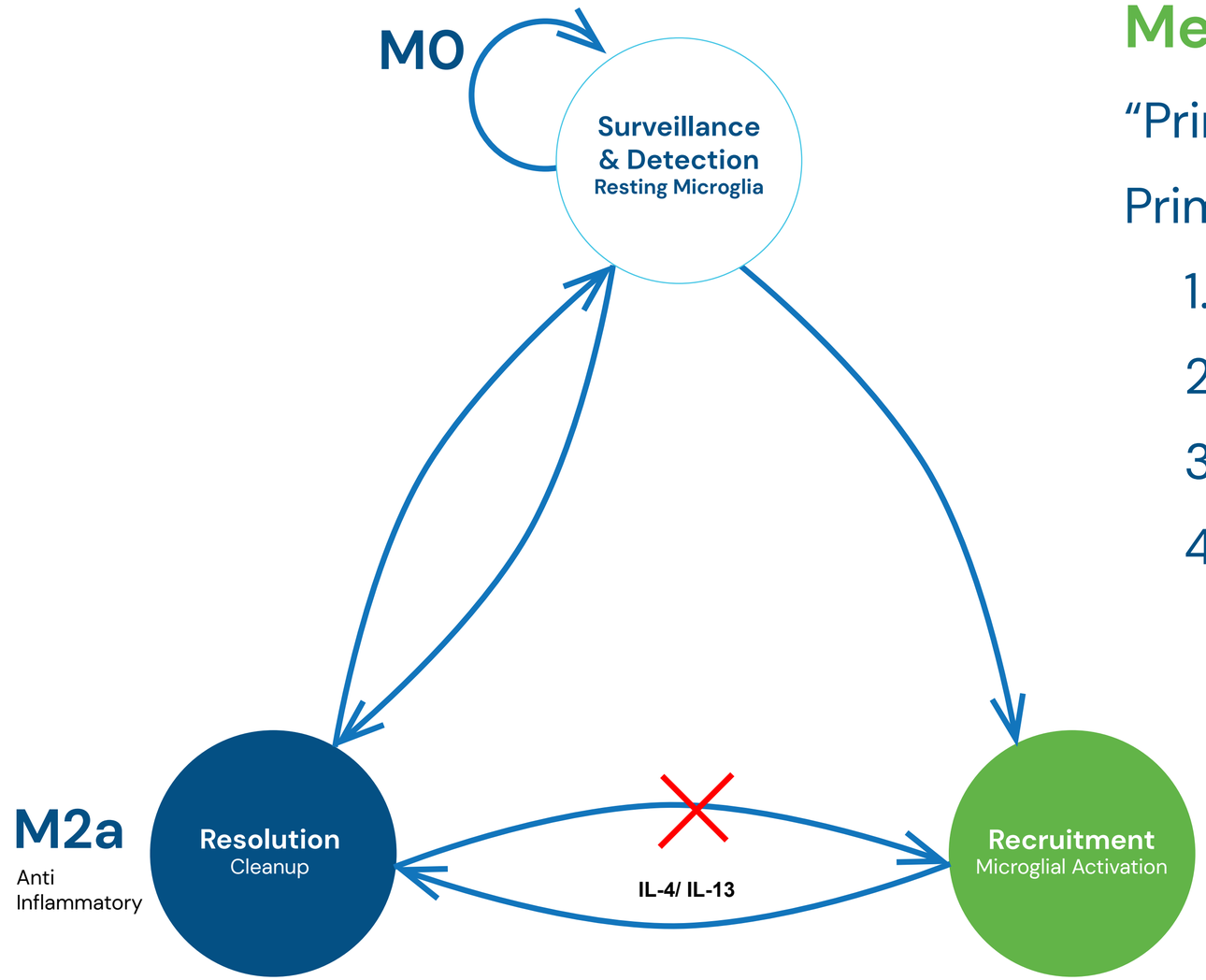
Repeated exposure to systemic immune challenge increased brain IL-1β

LPS challenge on a regular basis

+ higher levels inflammatory mediators cause cognitive issues, behavior issues



Hoogland, Inge, et al. "Microglial activation after systemic stimulation with lipopolysaccharide and Escherichia coli."

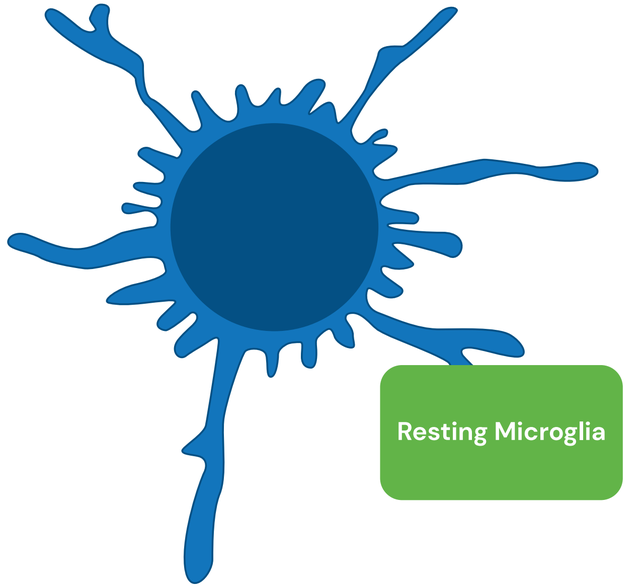


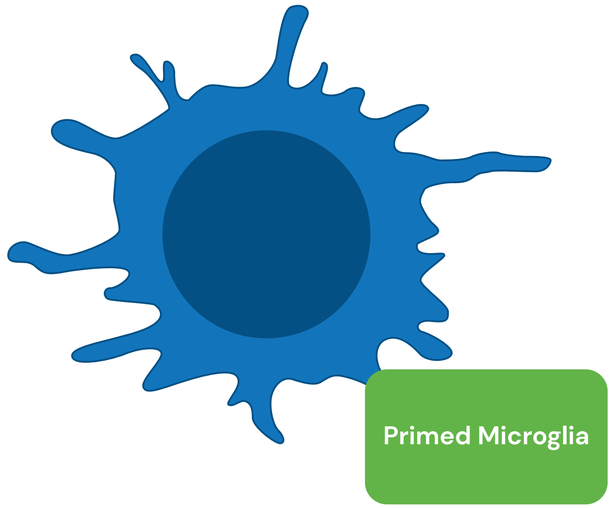
Medical history causing primed microglia

"Priming is a stage with no way back"

Priming results from

1. Traumatic Brain Injury (TBI)
2. Stress
3. Aging
4. Pre-existing inflammation





What are primed microglia?

Primed microglia have changed morphology:

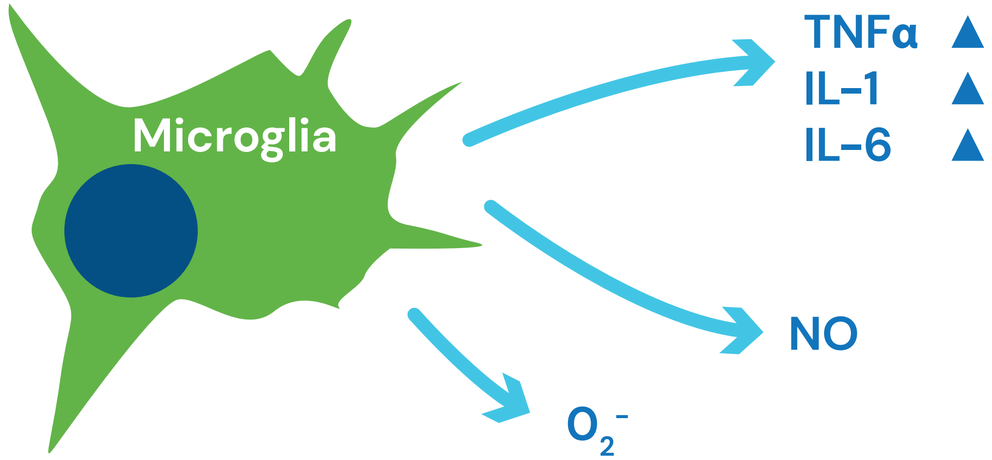
- Less branches or no branches
- Amoeboid structure
- Exaggerated and uncontrolled inflammatory response to any kind of secondary challenge
  = More reactive to secondary insults
- Microglia are in a dominant M1 shift and stay chronically inflamed

Hanisch, Uwe-Karsten, and Helmut Kettenmann. “Microglia: active sensor and versatile effector cells in the normal and pathologic brain.” Nature neuroscience 10.11 (2007): 1387-1394.

Matta, Samantha M., Elisa L. Hill-Yardin, and Peter J. Crack. “The influence of neuroinflammation in Autism Spectrum Disorder.” Brain, behavior, and immunity 79 (2019): 75-90.

Neuro-Inflammation is commonly seen in brain aging and involves activated microglia

- In AD mouse models **supplementation with NAD+** precursor **reduced** the excessive release of **pro-inflammatory** mediators and **the numbers of activated microglia and astrocytes**



Latta CH, Sudduth TL, Weekman EM, Brothers HM, Abner EL, Popa GJ, Mendenhall MD, Gonzalez-Oregon F, Braun K, and Wilcock DM (2015). Determining the role of IL-4 induced neuroinflammation in microglial activity and amyloid-beta using BV2 microglial cells and APP/PS1 transgenic mice. J. Neuroinflamm 12, 41

Hou Y, Lautrup S, Cordonnier S, Wang Y, Croteau DL, Zavala E, Zhang Y, Moritoh K, O'Connell JF, Baptiste BA, et al. (2018). NAD(+) supplementation normalizes key Alzheimer's features and DNA damage responses in a new AD mouse model with introduced DNA repair deficiency. Proc. Natl. Acad. Sci. USA 115, E1876–E1885.

Lautrup S, Lou G, Aman Y, Nilsen H, Tao J, and Fang EF (2019). Micro-glial mitophagy mitigates neuroinflammation in Alzheimer's disease. Neurochem. Int 129, 104469.

We also saw a strong depletion of NAD+ during excitotoxicity

Mice injected with NAD+ were protected from excitotoxicity

Kim S.H., Lu H.F., Alano C.C. Neuronal Sirt3 Protects against Excitotoxic Injury in Mouse Cortical Neuron Culture. PLoS ONE. 2011;6:e14731. doi: 10.1371/journal.pone.0014731

Liu D., Pitta M., Mattson M.P. Preventing NAD+ Depletion Protects Neurons against Excitotoxicity. Ann. N. Y. Acad. Sci. 2008;1147:275–282. doi: 10.1196/annals.1427.028.

Liu D., Gharavi R., Pitta M., Gleichmann M., Mattson M.P. Nicotinamide prevents NAD+ depletion and protects neurons against excitotoxicity and cerebral ischemia: NAD+ consumption by SIRT1 may endanger energetically compromised neurons. Neuromolecular Med. 2009;11:28–42. doi: 10.1007/s12017-009-8058-1

Zhang W., Xie Y., Wang T., Bi J., Li H., Zhan L.Q., Ye S.Q., Ding S. Neuronal protective role of PBEF in a mouse model of cerebral ischemia. J. Cereb. Blood Flow Metab. 2010;30:1962–1971. doi: 10.1038/jcbfm.2010.71

Vaur P., Brugg B., Mericskay M., Li Z., Schmidt M.S., Vivien D., Orset C., Jacotot E., Brenner C., Duplus E. Nicotinamide riboside, a form of vitamin B3, protects against excitotoxicity-induced axonal degeneration. FASEB J. 2017;31:5440–5452. doi: 10.1096/fj.201700221RR

More specifically

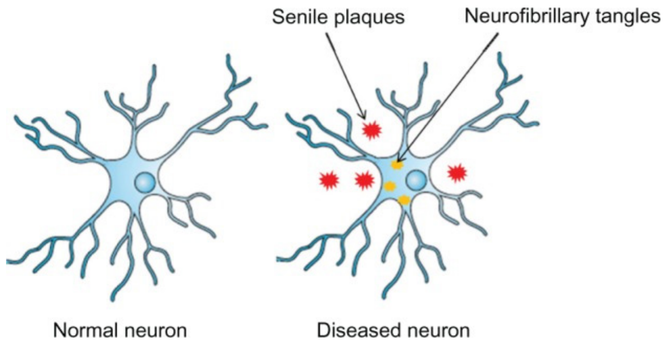
- **Alzheimer's disease (AD)**

Characteristic is the presence of neurofibrillary tangles and senile plaque

1. Tau proteins form tangles
2. Amyloid plaque

Defining neuropathological hallmarks:

- Amyloid Beta-peptide plaques (AB) and neurofibrillary tangles (NFTs)
- People with APoE4 isoform are at increased risk for onset of AD



Neurons affected by AB and p-Tau neurofibrillary tangles will exhibit

- damage
- impaired Ca++ handling
- defective mitophagy
- reduced DNA repair

Canter, Rebecca G., Jay Penney, and Li-Huei Tsai. “The road to restoring neural circuits for the treatment of Alzheimer’s disease.” Nature 539.7628 (2016): 187-196.

Fang, Evandro F. “Mitophagy and NAD+ inhibit Alzheimer disease.” Autophagy 15.6 (2019): 1112-1114.

Mattson, Mark P., and Thiruma V. Arumugam. “Hallmarks of brain aging: adaptive and pathological modification by metabolic states.” Cell metabolism 27.6 (2018): 1176-1199.

Polanco, Juan Carlos, et al. “Amyloid-β and tau complexity—towards improved biomarkers and targeted therapies.” Nature Reviews Neurology 14.1 (2018): 22.

NAD+↓ depletion has been demonstrated in AD↑

Dong, Yue, and Gregory J. Brewer. “Global metabolic shifts in age and Alzheimer’s disease mouse brains pivot at NAD+/NADH redox sites.” Journal of Alzheimer’s disease 71.1 (2019): 119-140.

Hou, Yujun, et al. “NAD+ supplementation normalizes key Alzheimer’s features and DNA damage responses in a new AD mouse model with introduced DNA repair deficiency.” Proceedings of the National Academy of Sciences 115.8 (2018): E1876-E1885.

NAD+↑ augmentation inhibited AD↓-related pathology with cognitive decline

Gong, Bing, et al. “Nicotinamide riboside restores cognition through an upregulation of proliferator-activated receptor-γ coactivator 1α r egulated β-secretase 1 degradation and mitochondrial gene expression in Alzheimer’s mouse models.” Neurobiology of aging 34.6 (2013): 1581-1588..

Fang, Evandro F., et al. “Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer’s disease.” Nature neuroscience 22.3 (2019): 401-412.

This provides strong support for the contribution of NAD+ depletion to AD progression

More specifically

- **Parkinson's disease (PD)**

Defining neuropathological hallmarks:

- Progressive neurological disorder where the loss of dopaminergic neurons in the substantia nigra impairs one's ability to control body movements
- Dopaminergic neurons die because they build up misfolded proteins into Lewy Bodies.

Kam, Tae-In, et al. "Poly (ADP-ribose) drives pathologic α-synuclein neurodegeneration in Parkinson's disease." Science 362.6414 (2018).

Spillantini, Maria Grazia, et al. "α-Synuclein in Lewy bodies." Nature 388.6645 (1997): 839-840.

Recent studies have shown that the neurons initially affected by alpha-synuclein pathology are the enteric neurons that innervate the gut.

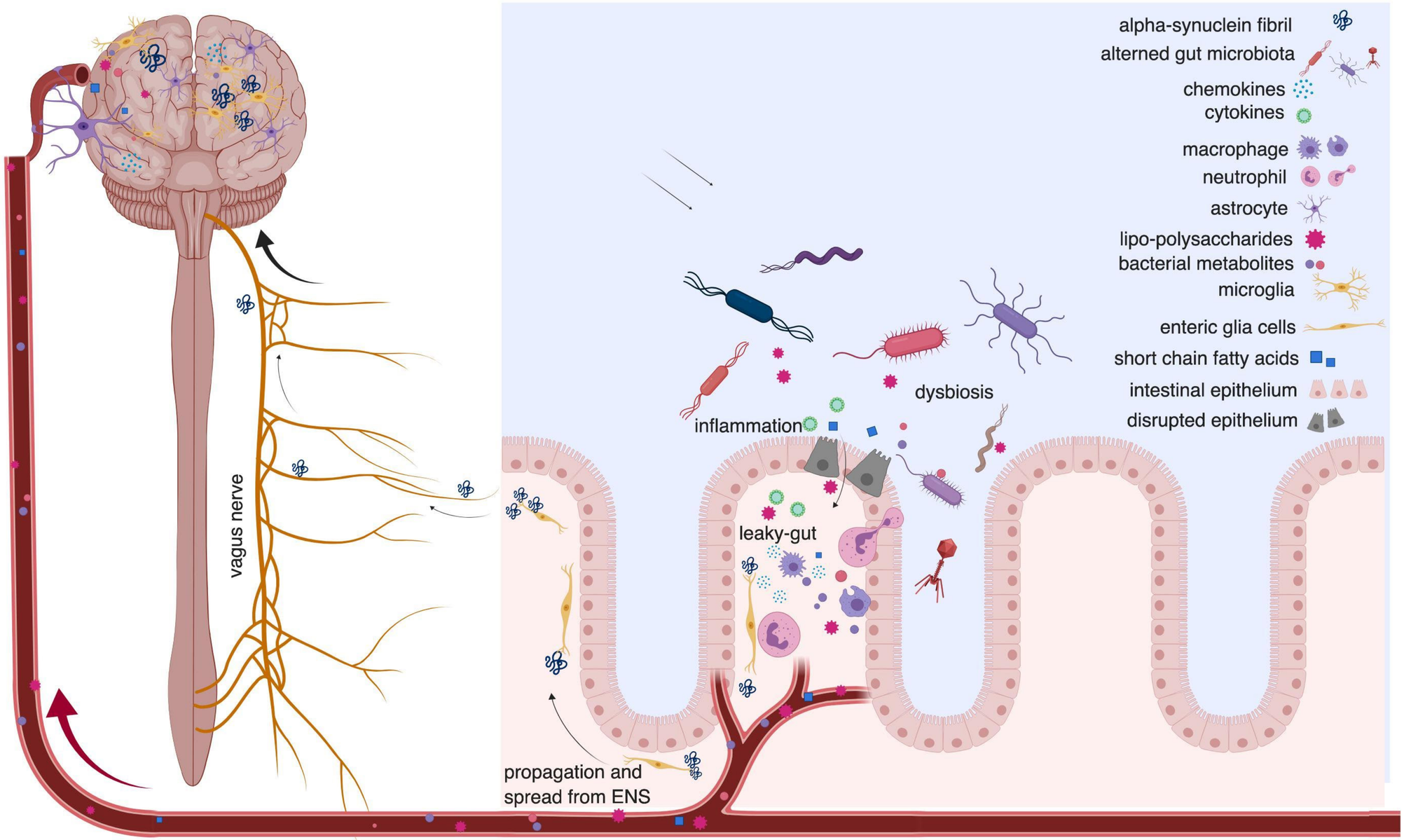
The pathology then spreads via the vagus nerve to the brain

Kim, Sangjune, et al. “Transneuronal propagation of pathologic α-synuclein from the gut to the brain models Parkinson’s disease.” Neuron 103.4 (2019): 627-641.

Kishimoto, Yuki, et al. “Chronic mild gut inflammation accelerates brain neuropathology and motor dysfunction in α-synuclein mutant mice.” Neuromolecular medicine 21.3 (2019): 239-249.

Brain

Gut


vagus nerve
alpha-synuclein fibril
alterned gut microbiota
chemokines
cytokines
macrophage
neutrophil
astrocyte
lipo-polysaccharides
bacterial metabolites
microglia
enteric glia cells
short chain fatty acids
intestinal epithelium
disrupted epithelium
dysbiosis
inflammation
leaky-gut
propagation and
spread from ENS

NAD+↓ depletion has been demonstrated in PD↑
Supplementation with NAD+ precursors ameliorated PD phenotype

Schöndorf, David C., et al. “The NAD+ precursor nicotinamide riboside rescues mitochondrial defects and neuronal loss in iPSC and fly models of Parkinson’s disease.” Cell reports 23.10 (2018): 2976-2988.

Schwab, Andrew J., et al. “Decreased sirtuin deacetylase activity in LRRK2 G2019S iPSC-derived dopaminergic neurons.” Stem cell reports 9.6 (2017): 1839-1852.

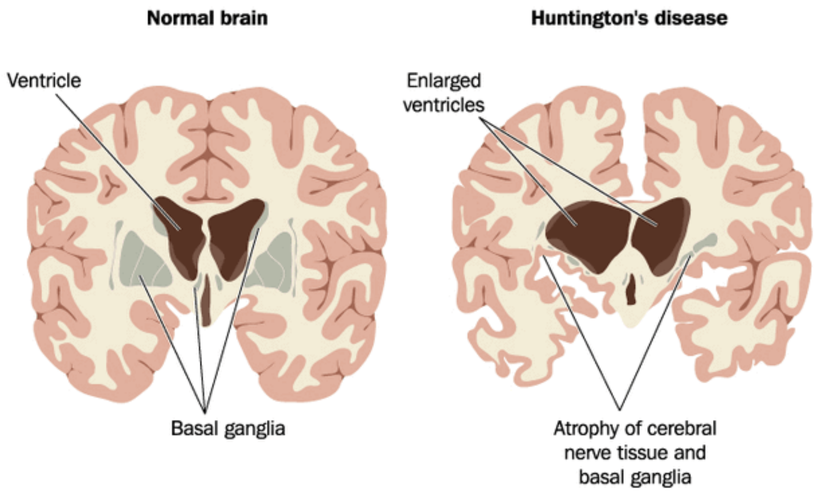
Sison, Samantha L., and Allison D. Ebert. “Decreased NAD+ in dopaminergic neurons.” Aging (Albany NY) 10.4 (2018): 526.

Essuman, Kow, et al. “The SARM1 Toll/interleukin-1 receptor domain possesses intrinsic NAD+ cleavage activity that promotes pathological axonal degeneration.” Neuron 93.6 (2017): 1334-1343.

More specifically

- **Hungtington's disease (HD)**

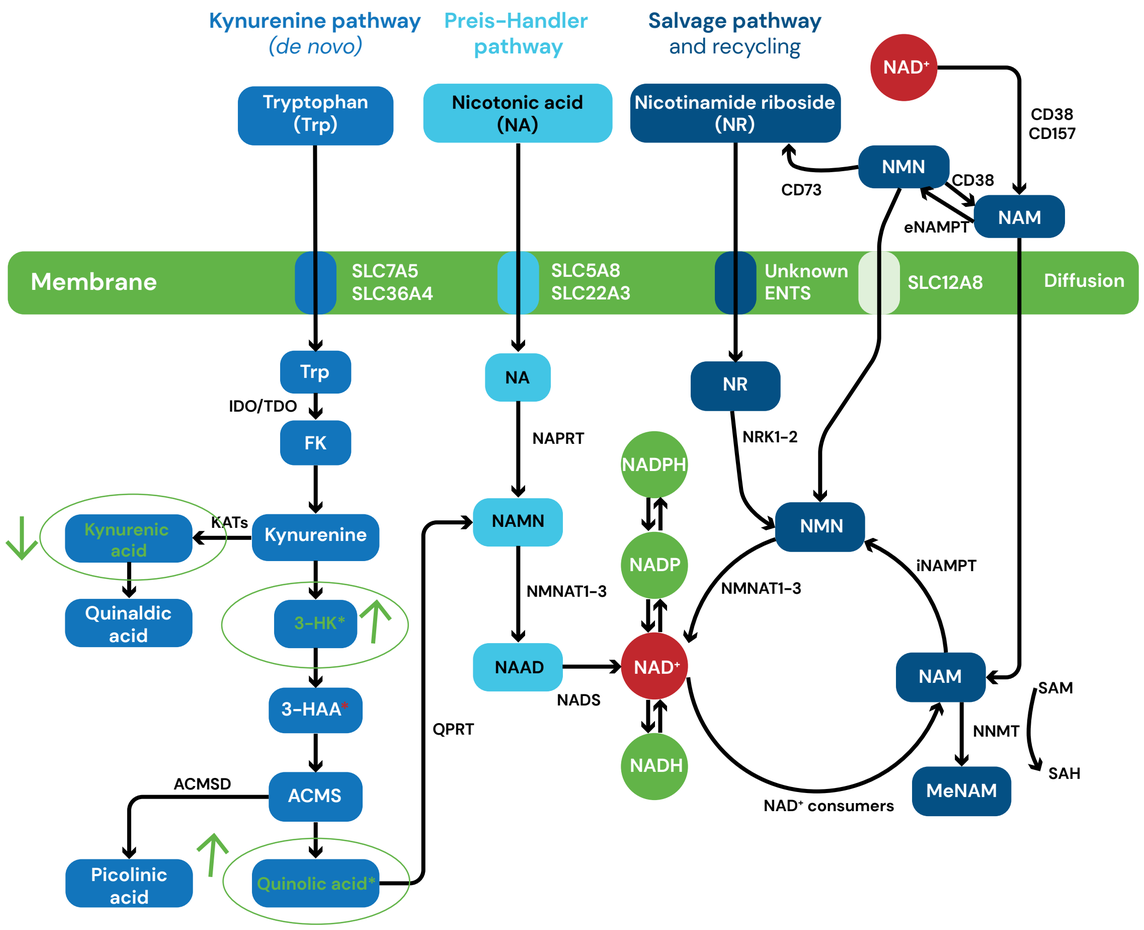
Defining neuropathological hallmarks:



- HD is a neurodegenerative disease with a clinical presentation of involuntary choreiform movements that result from degeneration of medium spiny neurons in the striatum
- Hyperkinetic movements
- Loss of coordination
- Involuntary body movements
- As the disease progresses, neuronal circuits in the cerebral cortex are affected what results in cognitive impairment and psychiatric symptoms

Lloret, Alejandro, and M. Flint Beal. "PGC-1α, sirtuins and PARPs in Huntington's disease and other neurodegenerative conditions: NAD+ to rule them all." Neurochemical research 44.10 (2019): 2423-2434.

NAD+↓ depletion has been demonstrated in HD↑
Supplementation with NAD+ precursors ameliorated HD phenotype



Impairment of the kynurenine pathway in HD has been documented

The impairment contributes to elevated glutamate neurotransmission, impaired mitochondrial function and lowered NAD+ , finally causing neuronal dysfunction and cell death

Therapeutic potential in HD are modulation of the kynurenine pathway (inhibition of KMO) and agonistic augmentation of NAD+ with precursors

Stone, Trevor W., and L. Gail Darlington. "The kynurenine pathway as a therapeutic target in cognitive and neurodegenerative disorders." British journal of pharmacology 169.6 (2013): 1211-1227.

Beal, M. Flint, et al. "Kynurenine pathway measurements in Huntington's disease striatum: evidence for reduced formation of kynurenic acid." Journal of neurochemistry 55.4 (1990): 1327-1339.

Campesan, Susanna, et al. "The kynurenine pathway modulates neurodegeneration in a Drosophila model of Huntington's disease." Current Biology 21.11 (2011): 961-966.

Zwilling, Daniel, et al. "Kynurenine 3-monooxygenase inhibition in blood ameliorates neurodegeneration." Cell 145.6 (2011): 863-874.

More specifically

- **Amyotrophic lateral sclerosis (ALS)**

Defining neuropathological hallmarks:

- ALS is a group of neurological disorders with progressive degeneration of motor neurons in the spinal cord, brain stem and motor cortex causing impairment of voluntary muscle movement, muscle weakness and finally paralysis
- Pathology is complex where mitochondrial dysfunction and increased oxidative stress are common and prominent features

Tang, Bor Luen. “Could sirtuin activities modify ALS onset and progression?.” Cellular and molecular neurobiology 37.7 (2017): 1147-1160.

Carrì, Maria Teresa, Nadia D’Ambrosi, and Mauro Cozzolino. “Pathways to mitochondrial dysfunction in ALS pathogenesis.” Biochemical and biophysical research communications 483.4 (2017): 1187-1193.

NAD+depletion has been demonstrated in ALS
Supplementation with NAD+ precursors

Treatment with SIRT 1 activators like Resveratrol ameliorates the disease progression

Enhancement of NAD+ protects astrocytes and promotes neuron survival

Tang, Bor Luen. “Could sirtuin activities modify ALS onset and progression?.” Cellular and molecular neurobiology 37.7 (2017): 1147-1160.

Harlan, Benjamin A., et al. “Enhancing NAD+ salvage pathway reverts the toxicity of primary astrocytes expressing amyotrophic lateral sclerosis-linked mutant superoxide dismutase 1 (SOD1).” Journal of Biological Chemistry 291.20 (2016): 10836-10846.

NAD+ restoration with NAD+ precursors as a therapeutic strategy

Different independent clinical trials & studies indicate that supplementation with Nicotinamide Riboside is orally bioavailable and safe

Trammell, Samuel AJ, et al. “Nicotinamide riboside is uniquely and orally bioavailable in mice and humans.” Nature communications 7.1 (2016): 1-14.

Martens, Christopher R., et al. “Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD+ in healthy middle-aged and older adults.” Nature communications 9.1 (2018): 1-11.

Dollerup, Ole L., et al. “A randomized placebo-controlled clinical trial of nicotinamide riboside in obese men: safety, insulin-sensitivity, and lipid-mobilizing effects.” The American journal of clinical nutrition 108.2 (2018): 343-353.

Advantages compared to other NAD+ precursors

- Better pharmacokinetic and pharmacological properties
- More stimulation of Sirtuins , ADPR
- Higher NAD+ levels in mitochondrial and nuclear compartments

The overall advantages suggest that Nicotinamide Riboside should fully replace Niacin and the other precursors in the near future

Poddar S.K., Sifat A.E., Haque S., Nahid N.A., Chowdhury S., Mehedi I. Nicotinamide Mononucleotide: Exploration of Diverse Therapeutic Applications of a Potential Molecule. Biomolecules. 2019;9:34. doi: 10.3390/biom9010034.

Trammell S.A., Schmidt M.S., Weidemann B.J., Redpath P., Jaksch F., Dellinger R.W., Li Z., Abel E.D., Migaud M.E., Brenner C. Nicotinamide riboside is uniquely and orally bioavailable in mice and humans. Nat. Commun. 2016;7:12948. doi: 10.1038/ncomms12948

Cantó C., Houtkooper R.H., Pirinen E., Youn D.Y., Oosterveer M.H., Cen Y., Fernandez-Marcos P.J., Yamamoto H., Andreux P.A., Cettour-Rose P., et al. The NAD(+) precursor nicotinamide riboside enhances oxidative metabolism and protects against high-fat diet-induced obesity. Cell Metab. 2012;2012. 15:838–847. doi: 10.1016/j.cmet.2012.04.022

More clinical applications with Nicotinamide Riboside

cardiovascular: Reducing blood pressure and arterial stiffnesss

The increase in CVD risk with aging is mainly driven by increases in blood pressure and decrease in elasticity of the aorta

Sirtuin enzymes mediate maintenance of cardiovascular function
Sirtuin activity is improved:

- In calorie restriction
- When NAD+ bio-availability goes up

Placebo – controlled study of NR supplementation (2x/day 500mg) during 6 weeks

NAD+ level in peripheral blood was i**ncreased with 60%** compared with placebo

ATP levels were also increased

Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD+ in healthy middle-aged and older adults

Christopher R. Martens, Blair A. Denman, Melissa R. Mazzo, Michael L. Armstrong, Nichole Reisdorph, Matthew B. McQueen, Michel Chonchol & Douglas R. Seals

de Picciotto, N. E. et al. Nicotinamide mononucleotide supplementation reverses vascular dysfunction and oxidative stress with aging in mice. Aging Cell 15, 522–530 (2016).

diabetic retinopathy , photoreceptor degeneration

SIRT3 activity is sensitive to reduction of NAD+

Upregulating NAD+ with Nicotinamide Riboside is potential treatment in multiple disorders with retinal degeneration

Lin J.B., Kubota S., Ban N., Yoshida M., Santeford A., Sene A., Nakamura R., Zapata N., Kubota M., Tsubota K., et al. NAMPT-Mediated NAD+ Biosynthesis Is Essential for Vision in Mice. Cell Rep. 2016;17:69–85. doi: 10.1016/j.celrep.2016.08.073.

Lautrup, Sofie, et al. "NAD+ in brain aging and neurodegenerative disorders." Cell metabolism 30.4 (2019): 630-655.

Remedies complementary to Nicotinamide Riboside in treatment of neurodegenerative disorders

1. Coffee whole fruit extract

Coffee fruits are often called coffee berries

Other than the seeds (coffee beans),
the berries have always been considered as waste material

Neuroprotective benefit

- Increased levels of BDNF were measured after intake of 100mg Coffee whole fruit extract
- Antioxidant activity , mainly attributed to hydroxyl-scavenging capacity
- Acute single-dose study
- **BDNF increased by 143% compared to control**

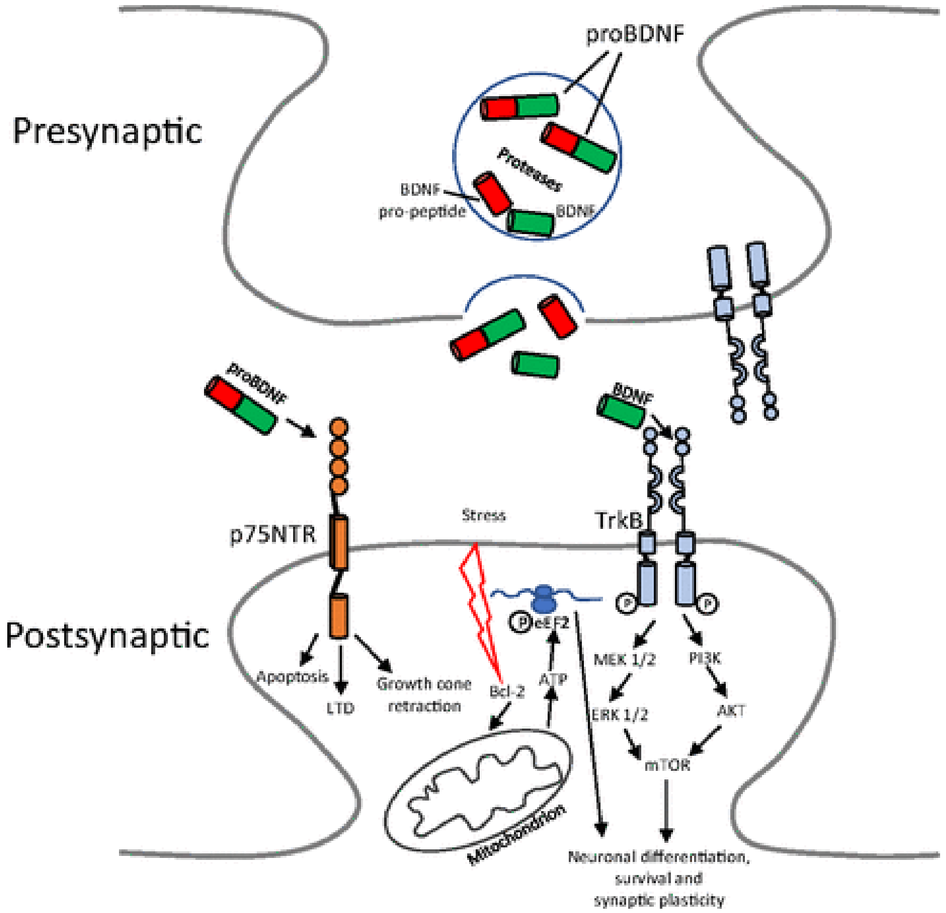
BDNF Brain-derived Neurotrophic Factor
Protein, member of the neurotrophin-family (+ NT-3 , NT-4/5) other members are Neurotrophin3 & Neurotrophin 4/5

BDNF acts on neurons
Supports survival of existing neurons
Supports growth and differentiation of new neurons and synapses

BDNF binds at least 2 receptors:
T rk B (Track B pronounced) a tyrosine kinase receptor , ligand induced activation results in kinase activation

P75 (activation of P75 , leads to activation of NFKB & apoptosis)

Most functions of BDNF are attributed to T rk B interaction



Neurogenesis
Neurogenesis is enhanced
Number of neurons is increased
+ Synpaptogenesis
+ Dendritogenesis, dentritic growth

Effects on synaptic transmission
Learning and memory

Neurogenerative diseases
Neurodegeneration may result from insufficient supply of neurotrophic factors

Alzheimer's Disease
= reduction of BDNF in hippocampus has been reported
Parkinson's Disease
= reduction of BDNF in the Substantia nigra

BDNF is a critical mediator of vulnerability to stress, memory of fear/ trauma and stress-related disorders like post traumatic stess disorder

Neurodegeneration may result from insufficient supply of neurotrophic factors & BDNF

Post – mortem biopsy showed extreme low levels BDNF in neurodegeneration

References

Binder, Devin K., and Helen E. Scharfman. “Brain-derived neurotrophic factor.” Growth factors (Chur, Switzerland) 22.3 (2004): 123.

Kumar, Navneet, et al. “Efficacy of standardized extract of Bacopa monnieri (Bacognize®) on cognitive functions of medical students: a six-week, randomized placebo-controlled trial.” Evidence-Based Complementary and Alternative Medicine 2016 (2016).

Kowiański, Przemysław, et al. “BDNF: a key factor with multipotent impact on brain signaling and synaptic plasticity.” Cellular and molecular neurobiology 38.3 (2018): 579-593.

What is the active ingredient responsible for the raise in BDNF?

- ~~chlorogenic acid , specific polyphenolic acid?~~
- ~~caffeine?~~
  Coffee whole fruit extract contains less than 0.7% caffeine
  Green Coffee with 72.8% caffeine showed only modest increase in BDNF
- **procyanidins** ✓

Specifications of the extract?

- Multi-step property extraction
- No mutagenic or genotoxic potential
- Oral toxicity studies were performed
- hematology , coagulation and clinical chemistry parameters revealed no adverse changes

Reyes-Izquierdo T, Nemzer B, Shu C et al. (2013) Modulatory effect of coffee fruit extract on plasma levels of brainderived neurotrophic factor in healthy subjects. Br J Nutr 110, 420-425

Mullen, W., et al. "The antioxidant and chlorogenic acid profiles of whole coffee fruits are influenced by the extraction procedures." Journal of agricultural and food chemistry 59.8 (2011): 3754-3762.

Kobayashi, T., et al. "Effects of coffee cherry on the immune system in SHN mice." Anticancer research 16.4A (1996): 1827-1830.

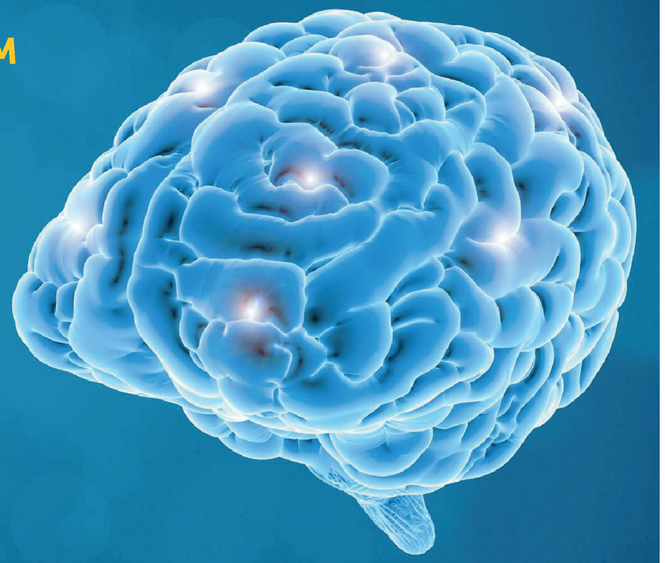
Heimbach, J. T., et al. "Safety studies on products from whole coffee fruit." Food and chemical toxicology 48.8-9 (2010): 2517-2525.

García, Ramiro, et al. "Extraction of condensed tannins from Mexican plant sources." Zeitschrift für Naturforschung C 63.1-2 (2008): 17-20.

BDNF Essentials™

Promote Healthy Brain Function

New research demonstrates the adult brain is capable of reorganizing its neural network by forming new connections —– and this is known as neuroplasticity. Neuroplasticity means the brain continues to generate new neurons & synapses throughout life, helping the brain heal from injuries.



KEY ACTIVITIES TO INCREASING NEUROPLASTICITY INCLUDE:

- ✓ Physical Exercise
- ✓ Learning New Skills
- ✓ Increase BDNF (Brain Derived Neurotrophic Factor)
- ✓ Good Nutrition
- ✓ Sleep
- ✓ Intermittent Fasting

indication	Rebuild neuroplasticity by increasing BDNF. Improve cognitive function. More tolerance to stress.	
dosage	1 – 2 x 2 caps per day with or without food. Children under 6 years: 2 x 1 caps per day.	
packaging	120 vegecaps per container	
composition (amount per 2 vegecaps)	Lions Mane Mushroom (Hericium erinaceus) Skullcap (Scuttelaria lateriflora) Billberry (Vaccinium myrtillus) Bacopa (Bacopa monnieri) Sensoril® Ashwagandha (Withania somnifera) CDP Choline® Sharp-PS® phosphatidylserine	500 mg 200 mg 200 mg 150 mg 125 mg 125 mg 50 mg

Please find our referenced version on the professional section of our website.
All information is exclusively aimed at and released to an audience of health care professionals.

2. Centella asiatica (Gotu kola)

Antioxidant properties

- reduced hydrogen peroxide-induced cell death
- decreased concentrations of free radicals
- inhibits beta-amyloid cell death

Identified compounds that mediate the positive effects were triterpenes (Asiatic acid and asiaticoside) caffeoylquinic acids (CQAs)

Cervenka F, Jahodar L: [Plant metabolites as nootropics and cognitives]. Ceska Slov Farm. 2006, 55: 219-229. Article in Czech

Dhanasekaran M, Holcomb LA, Hitt AR, Tharakan B, Porter JW, Young KA, Manyam BV: Centella asiatica extract selectively decreases amyloid beta levels in hippocampus of Alzheimer's disease animal model. Phytother Res. 2009, 23: 14-19. 10.1002/ptr.2405.

da Rocha MD, Viegas FP, Campos HC, Nicastro PC, Fossaluzza PC, Fraga CA, Barreiro EJ, Viegas C: The role of natural products in the discovery of new drug candidates for the treatment of neurodegenerative disorders II: Alzheimer's disease. CNS Neurol Disord Drug Targets. 2011, 10: 251-270.

Veerendra Kumar MH, Gupta YK: Effect of Centella asiatica on cognition and oxidative stress in an intracerebroventricular streptozotocin model of Alzheimer's disease in rats. Clin Exp Pharmacol Physiol. 2003, 30: 336-342. 10.1046/j.1440-1681.2003.03842.x.

Xu Y, Cao Z, Khan I, Luo Y: Gotu Kola (Centella asiatica) extract enhances phosphorylation of cyclic AMP response element binding protein in neuroblastoma cells expressing amyloid beta peptide. J Alzheimers Dis. 2008, 13: 341-349

3. PQQ (Pyrroloquinoline Quinone Disodium Salt)

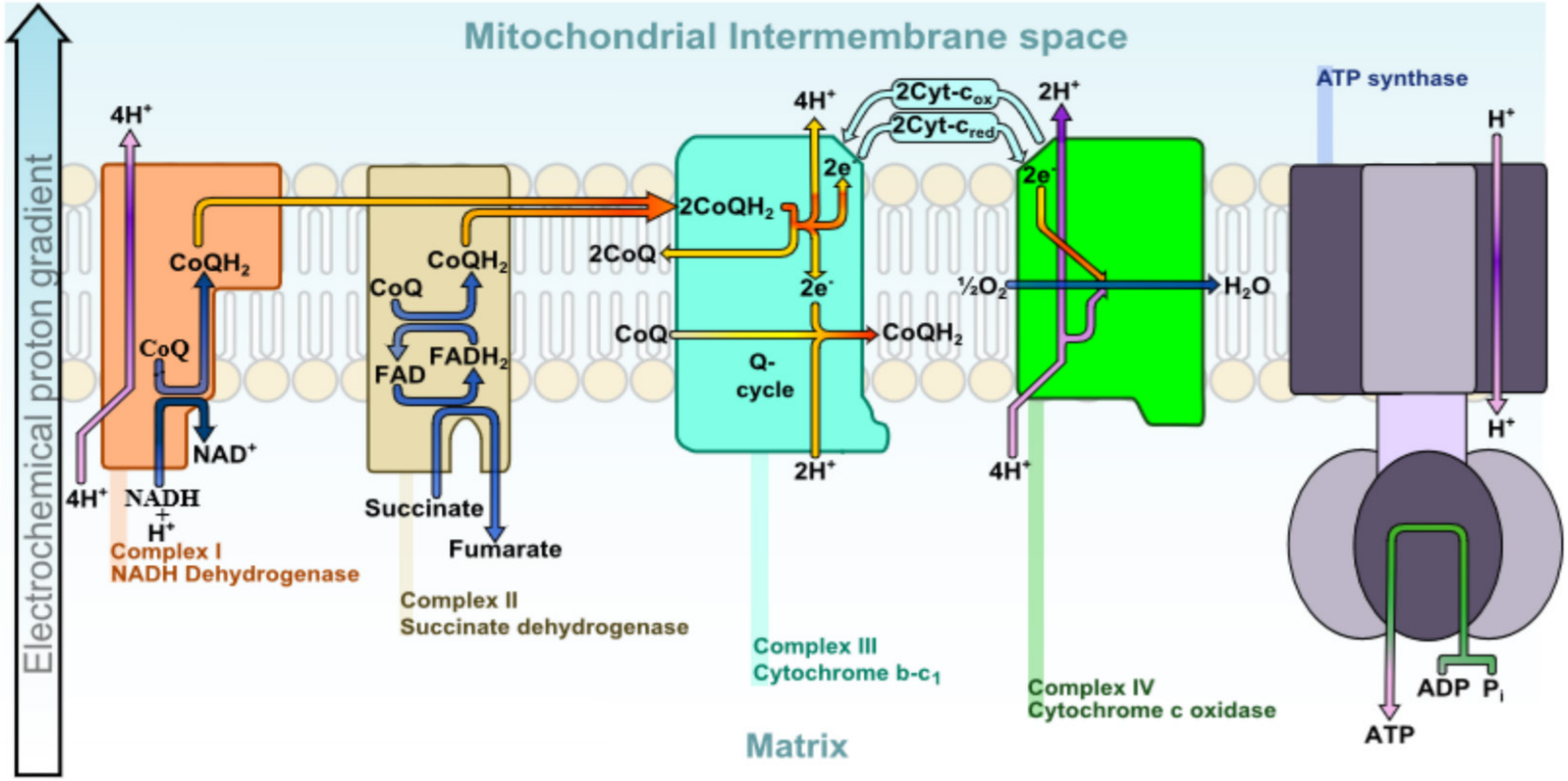
PQQ is widely distributed in daily life

- Fermented food
- Potato's, soybeans, celery, cabbage, apples, tomato, green tea
- **breast milk**
- supplemented PQQ (10-20mg/day)

Function claims of PQQ

- PQQ is a redox-agent; antioxidant effect in a redox reaction
- Very stable
- Protects with powerful antioxidant support
- Participates to the electron transport chain

Pyrroloquinoline quinone (PQQ) is the third redox cofactor after nicotinamide and flavin



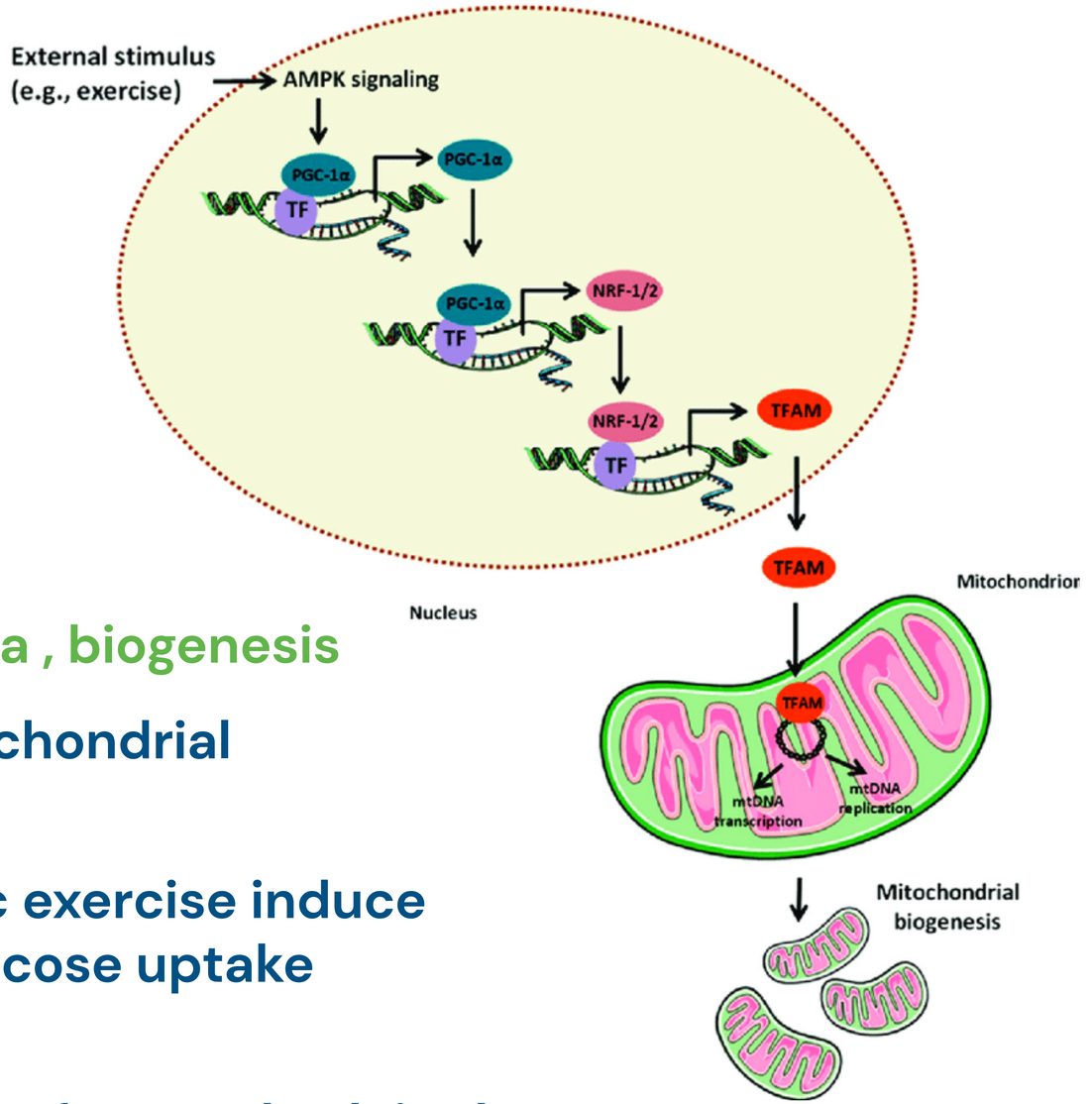
Additionally:

PQQ is the co-factor of Glucose Dehydrogenase in Glucose teststrips

The oxidation of Glucose by **Glucose Dehydrogenase: - e^-**

Simultaneously you ‘ll need a **cofactor: + e^-**

Guo, Zhong, et al. “Engineered PQQ-glucose dehydrogenase as a universal biosensor platform.” Journal of the American Chemical Society 138.32 (2016): 10108-10111.

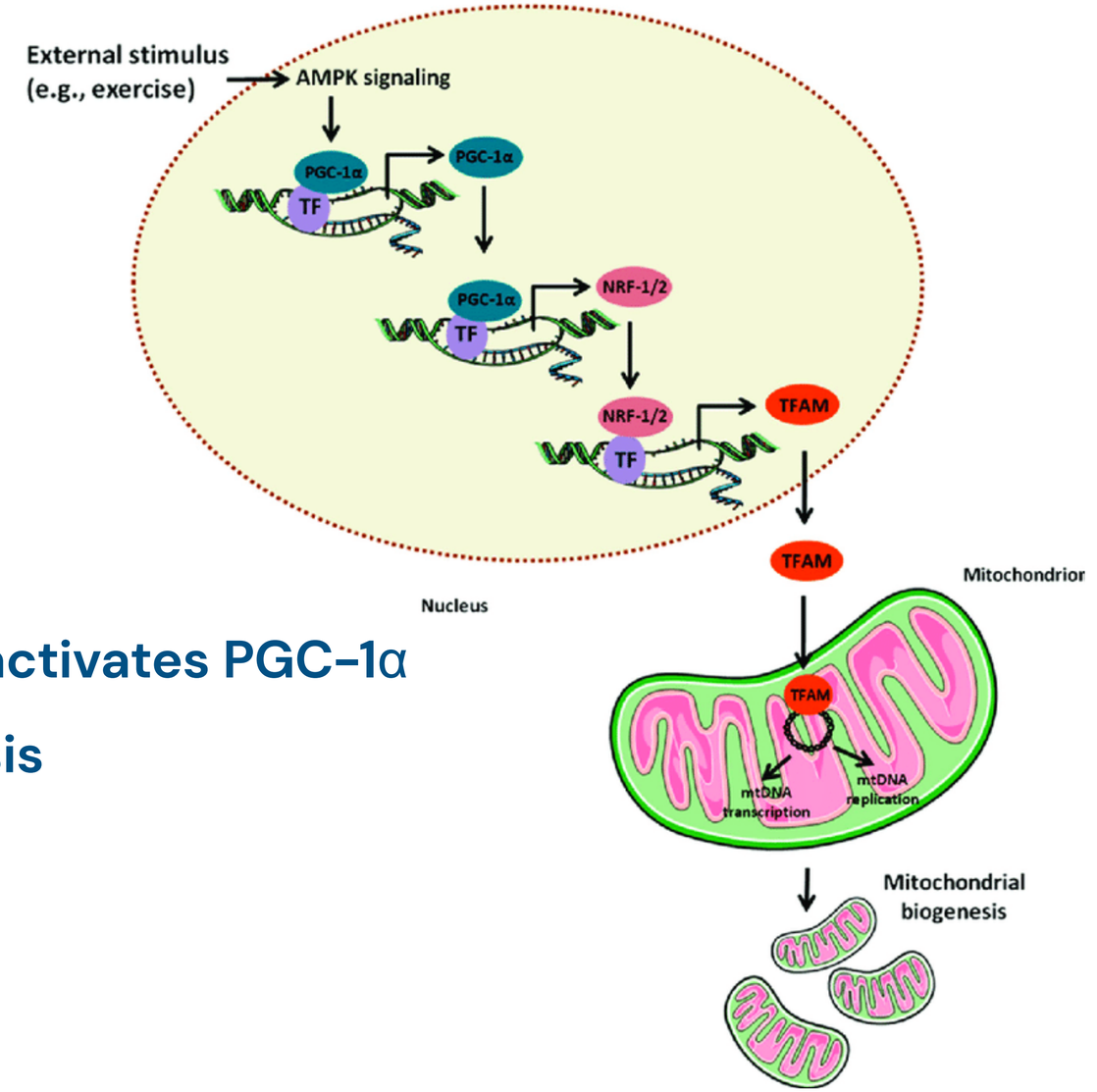


PQQ promotes the generation of new mitochondria , biogenesis

Mitochondrial biogenesis is how we increase mitochondrial mass/content.

External triggers like endurance exercise / aerobic exercise induce mitochondrial biogenesis, which leads to more glucose uptake by muscles and more ATP

Mitochondria are produced from the transcription of genes, both in the nuclear genome and the mitochondrial genome



AMP-activated kinase (AMPK) phosphorylates and activates PGC-1α

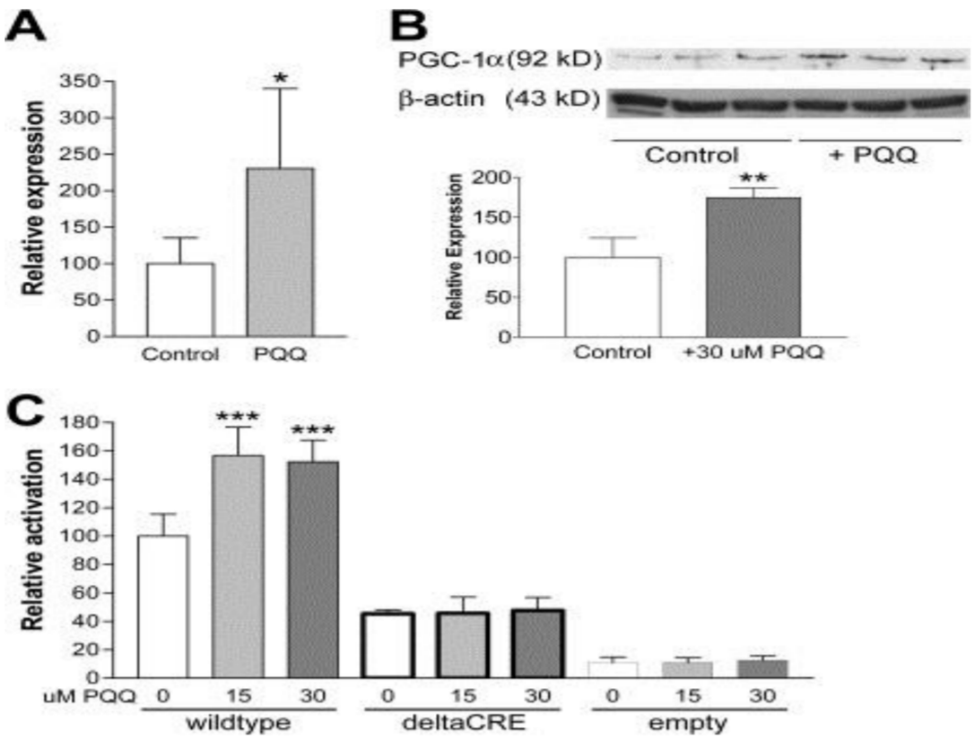
PGC -1α, master regulator of mitochondrial biogenesis

NRF2/NRF1, nuclear respiratory factor 2 & 1

The different processes allow the mitochondrial network to constantly remodel itself

Another hypothesis of aging?

- The loss of telomeres and TERT suppresses PGC-1α
- AMPK activity has been shown to decrease with age



Chowanadisai, Winyoo, et al. “Pyrroloquinoline quinone (PQQ) stimulates mitochondrial biogenesis.” (2007): A1104–A1104.

Mitochondrial biogenesis occurs through the combined effects of genes activated by PQQ via the following three mechanisms:

1. PQQ increases expression of PGC-1α
2. PQQ activates a signaling protein known as cAMPresponse element-binding protein or CREB
3. PQQ regulates a recently discovered gene called DJ-1. As with PGC-1α and CREB, DJ-1 is intrinsically involved in cell function and survival.

Valero T (2014). “Editorial (Thematic Issue: Mitochondrial Biogenesis: Pharmacological Approaches)”. Current Pharmaceutical Design. 20 (35): 5507–5509. doi:10.2174/1381612820351409111 42118. hdl:10454/13341. PMID 24606795.

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Sahin E, DePinho RA (May 2012). “Axis of ageing: telomeres, p53 and mitochondria”. Nature Reviews. Molecular Cell Biology. 13 (6): 397–404. doi:10.1038/nrm3352. PMC 3718675. PMID 22588366.

Physiological importance of PQQ?

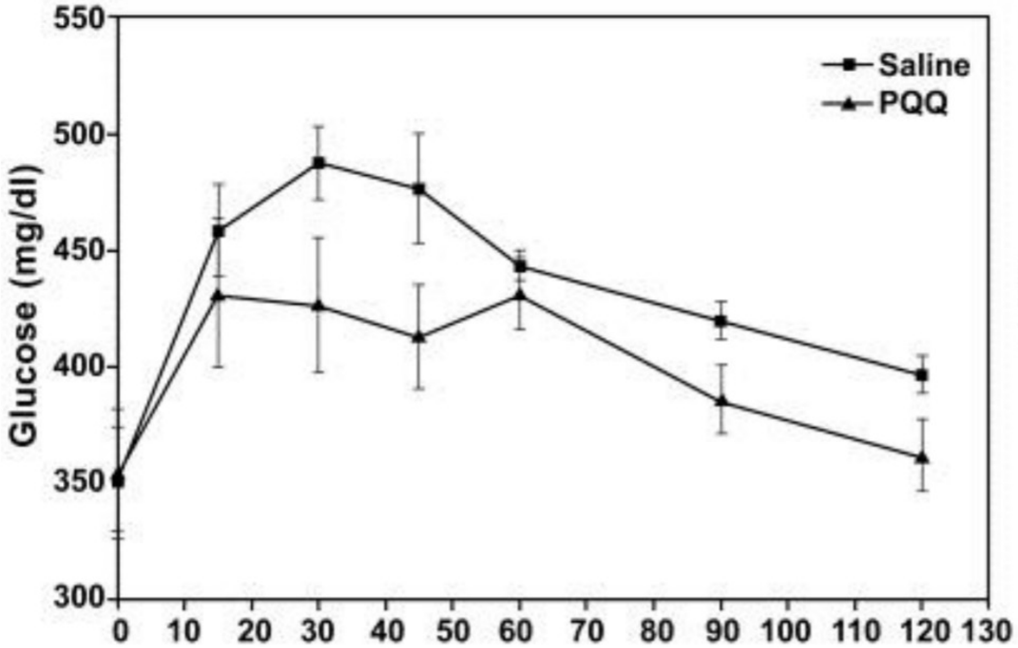
- Cognitive support (improves short term memory) & Protects the brain

Physiological importance of PQQ?

- Cognitive support (improves short term memory) & Protects the brain

  Evidence of PQQ protecting the brain:

  - PQQ promotes new mitochondrial formation
  - PQQ promotes Nerve Cell Growth
  - PQQ protects against oxidative damage
  - PQQ protects against neuroinflammation
  - PQQ protects against Excitotoxicity
  - PQQ prevents Glucose-induced Brain damagePQQ inhibits malformed Brain-proteins
  - PQQ improves cerebral blood flow

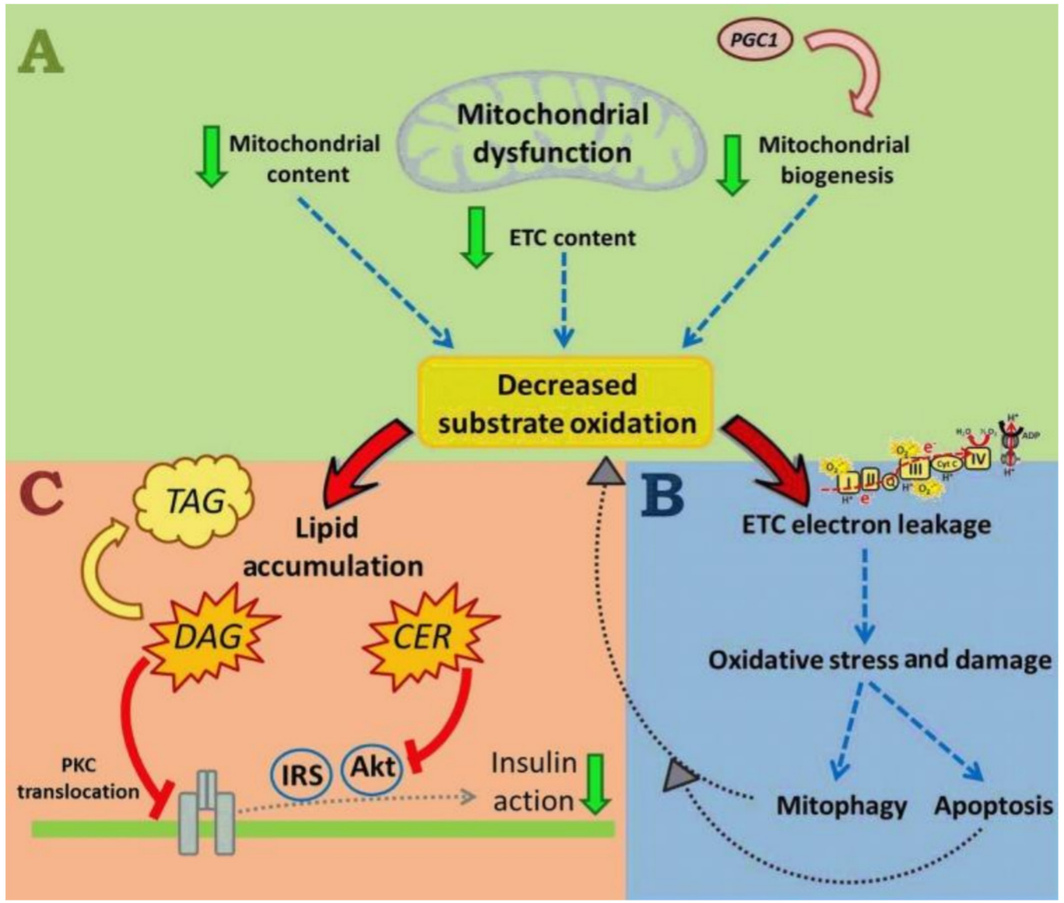


Oral glucose tolerance in response to a glucose load in diabetic UCD-T2DM Rats following the administration of PQQ (i.p.) at 4.5 mg PQQ/Kg BW for 3 days or saline.

PLoS One. 2011; 6(7): e21779.

Physiological importance of PQQ?

- Cardiovascular support
- Liver metabolism support in acute and chronic liver injury caused by various factors
- Insulin sensitivity



The Link between insulin sensitivity & mitochondrial metabolism

PQQ contributes with its effect on mitochondrial activity & mitochondrial biogenesis

Ac-Carnitine might contribute as well, it shuttles fatty acids into the mitochondrial matrix where the beta-oxidation takes place

+ R-ALA + Q10

Global approach in insulin resistance

Cognifuel, Krebsplus, Glycosense

El-Gharbawy, Areeg, and Jerry Vockley. "Inborn errors of metabolism with myopathy: defects of fatty acid oxidation and the carnitine shuttle system." Pediatric Clinics 65.2 (2018): 317-335

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PQQ is a growth factor : PQQ deprivation in mice diet

- Poor growth
- Impaired reproductive capability
- Fewer mitochondria in tissue

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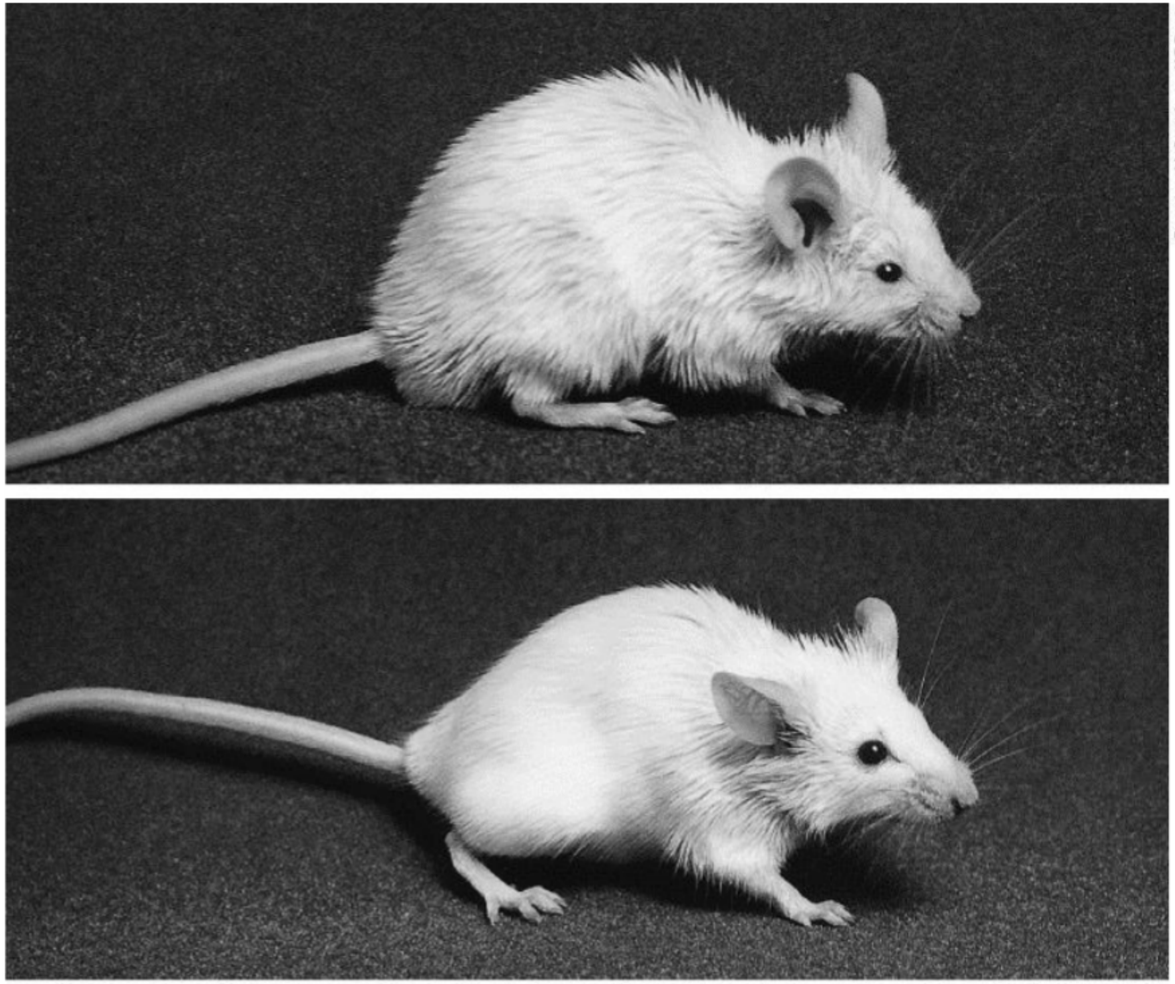


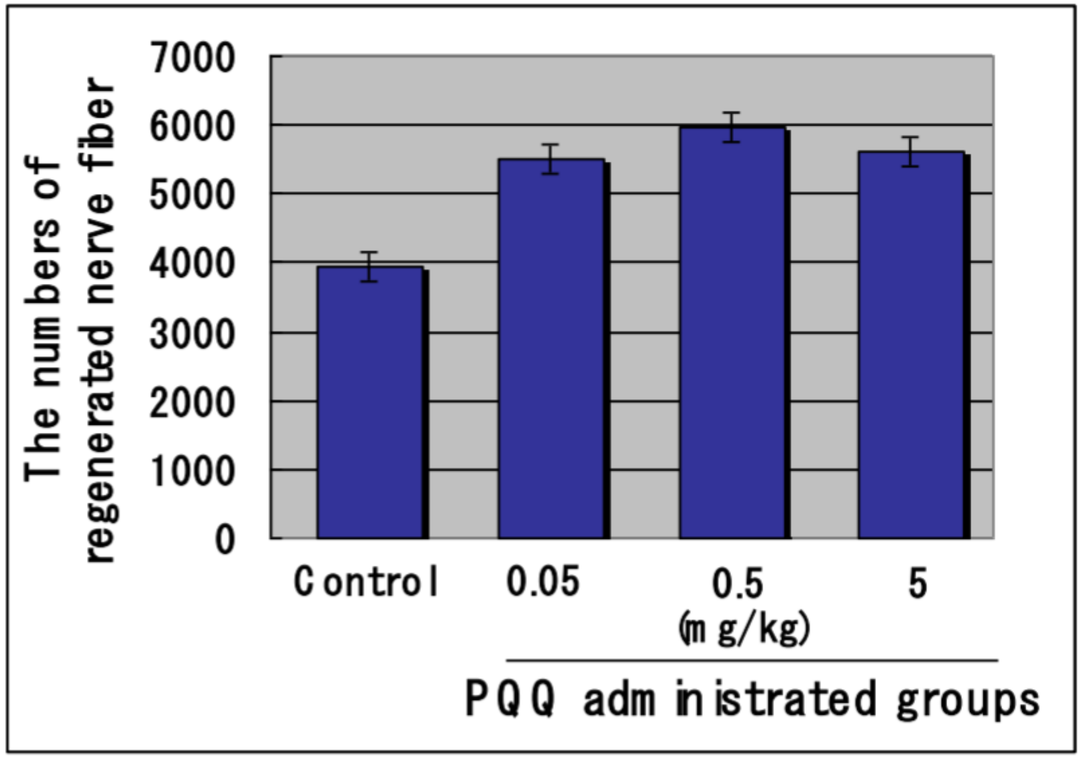
Francine M. Steinberg, UC Davis

Biofactors in food play a role in enhancing mitochondrial function, thereby decreasing the risk of some chronic diseases. *Top,* a mouse that has been deprived of pyrroloquinoline quinone (PQQ), a ubiquitous bacterial compound found in fermented products, tea, cocoa and legumes. *Above,* a mouse fed a diet containing PQQ.

PQQ in Peripheral Neuropathy

PQQ ‘s effect on NGF, which promotes growth, maintenance and survival of neurons

+ the association of Nicotinamide Riboside & PQQ makes sense in Neuropathy
+ R-ALA
+ PEA



Oral administration for 2 wks in rat

Koyama T. et al. (2006)

Vallianou, Natalia, Angelos Evangelopoulos, and Pavlos Koutalas. “Alpha-lipoic acid and diabetic neuropathy.” The review of diabetic studies: RDS 6.4 (2009): 230.

Hesselink, Jan M. Keppel, and Thecla AM Hekker. “Therapeutic utility of palmitoylethanolamide in the treatment of neuropathic pain associated with various pathological conditions: a case series.” Journal of Pain Research 5 (2012): 437.

Neuropathy

PQQ promotes Nerve Cell Growth	**CogniFuel** 90 vcaps Dose: 3 x 1 caps per day just before or during meals
Pure alpha-lipoic acid: anti-oxidative support	**R-ALA 300mg** 90 caps Dose: 2 x 1 caps per day
Neuropathic pain	**PEA 300mg – certified grade 300 mg** 120 vcaps Dose: 4 x 1 caps per day during meals

References

Keppel, Jan M. Hesselin., and Thecla A. M. Hekker. “Therapeutic Utility of Palmitoylethanolamide in the Treatment of Neuropathic Pain Associated with Various Pathological Conditions: A Case Series.” Journal of Pain Research, vol. 5, 2012, pp. 437–42.

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Brown, Guy C., et al. “Regulation of mitochondrial biogenesis.” Essays in biochemistry 47 (2010): 69-84.

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Ad Exp Med Biol. 2016;923:215-22. Effects of Antioxidant Supplements (BioPQQ™) on Cerebral Blood Flow and Oxygen Metabolism in the Prefrontal Cortex.

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Anal Biochem. 1999 May 1;269(2):317-25. Characterization of pyrroloquinoline quinone amino acid derivatives by electrospray ionization mass

spectrometry and detection in human milk.

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Biochim Biophys Acta. 1992 Dec 8;1156(1):62-6. Trace levels of pyrroloquinoline quinone in human and rat samples detected by gas chromatography/mass spectrometry.

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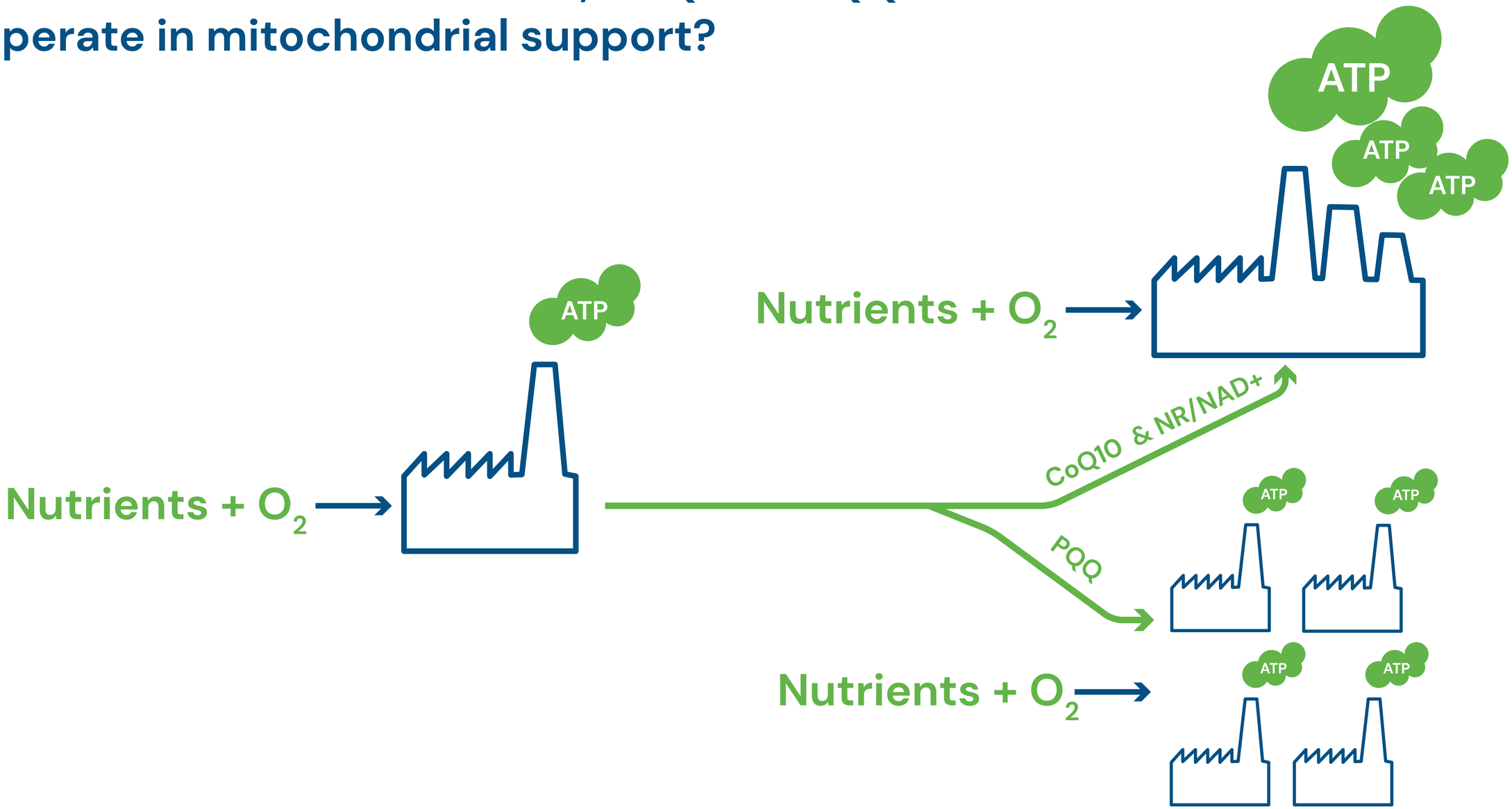
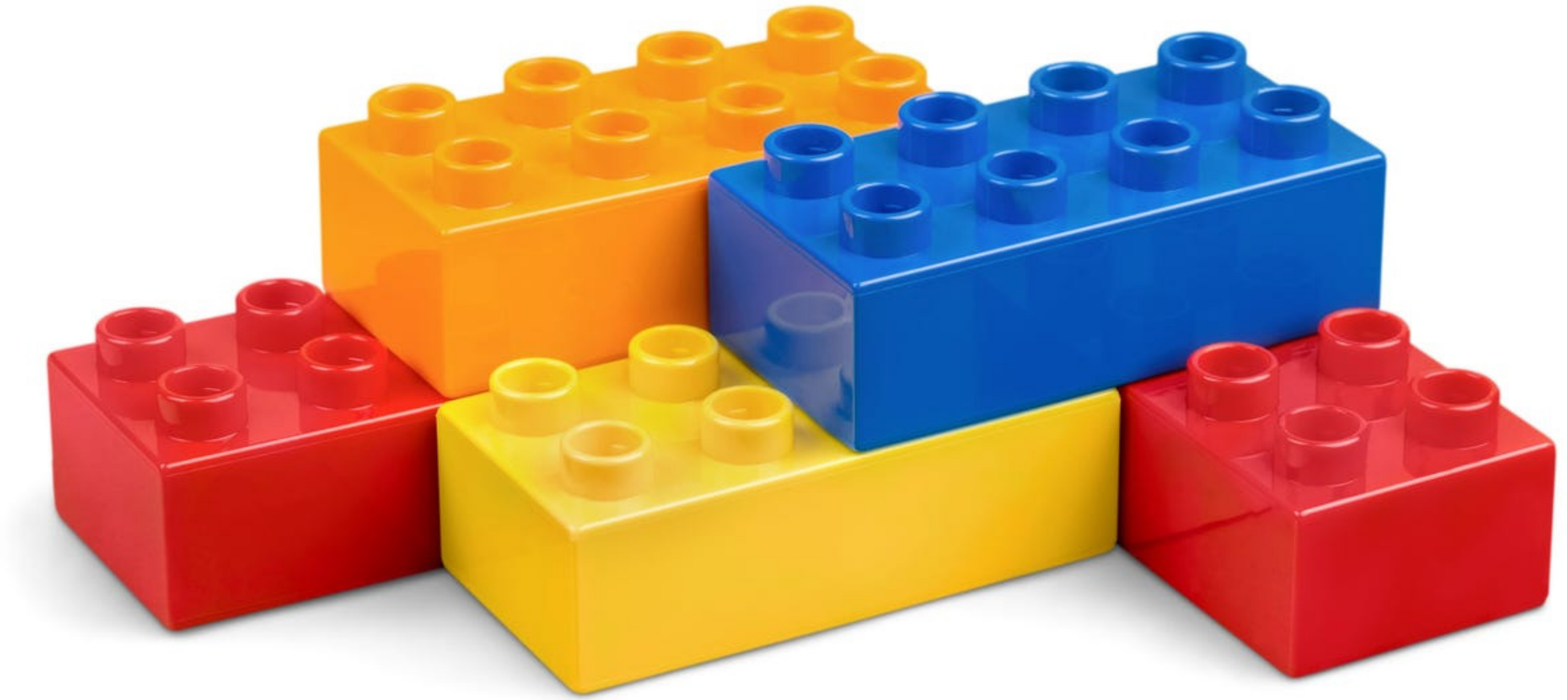
Biochem J. 1986 Nov 1; 239(3): 789–791. Covalently bound pyrroloquinoline quinone is the organic prosthetic group in human placental lysyl oxidase

How do Nicotinamide Riboside, CoQ10 & PQQ cooperate in mitochondrial support?



- Cognifuel the answer to brain aging
- Cognifuel counters brain aging
- Facilitates healthy brain aging
- Treatment for a range of neurologic disorders
- Slows down the brain aging process

Build your own personalized & global treatment plan in neurodegenerative conditions

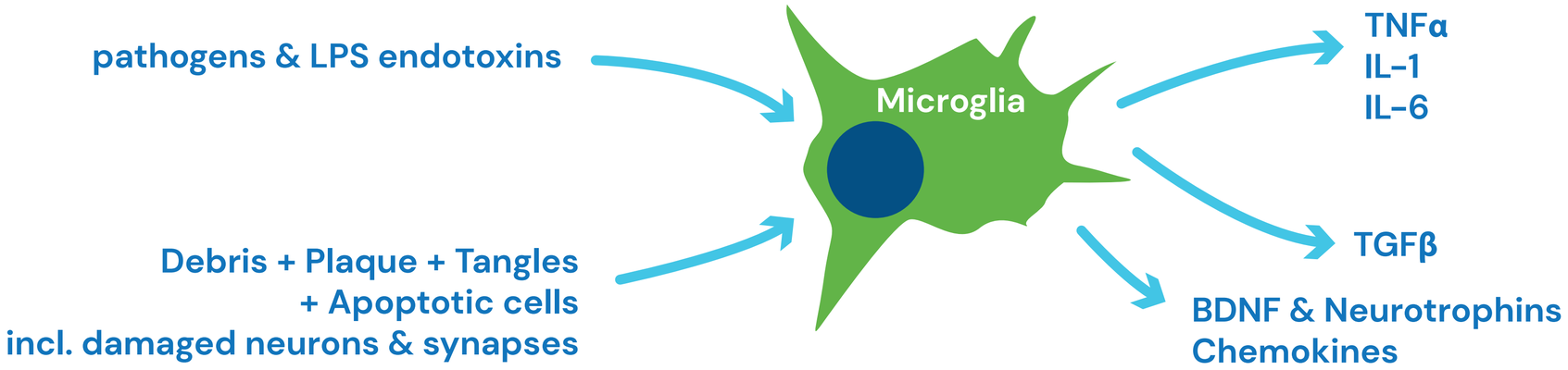


Lifestyle advice

- **Sleep** individualized approach
  Microglial clearance is programmed at night
  Benzodiazepines shorten deep sleep

Fonken, Laura K., Zachary M. Weil, and Randy J. Nelson. “Mice exposed to dim light at night exaggerate inflammatory responses to lipopolysaccharide.” Brain, Behavior, and Immunity 34 (2013): 159-163.

Zhu, Biao, et al. “Sleep disturbance induces neuroinflammation and impairment of learning and memory.” Neurobiology of disease 48.3 (2012): 348-355.



- **Stress & alcohol consumption are your worst enemies**
  Studies looking at the effects of alcohol on sleep have found that alcohol reduces the time required to fall asleep (sleep onset latency), increases the amount of deep sleep, and reduces the amount of REM sleep

Walter, Thomas Jordan, Ryan P. Vetreno, and Fulton T. Crews. "Alcohol and stress activation of microglia and neurons: brain regional effects." Alcoholism: Clinical and Experimental Research 41.12 (2017): 2066-2081.

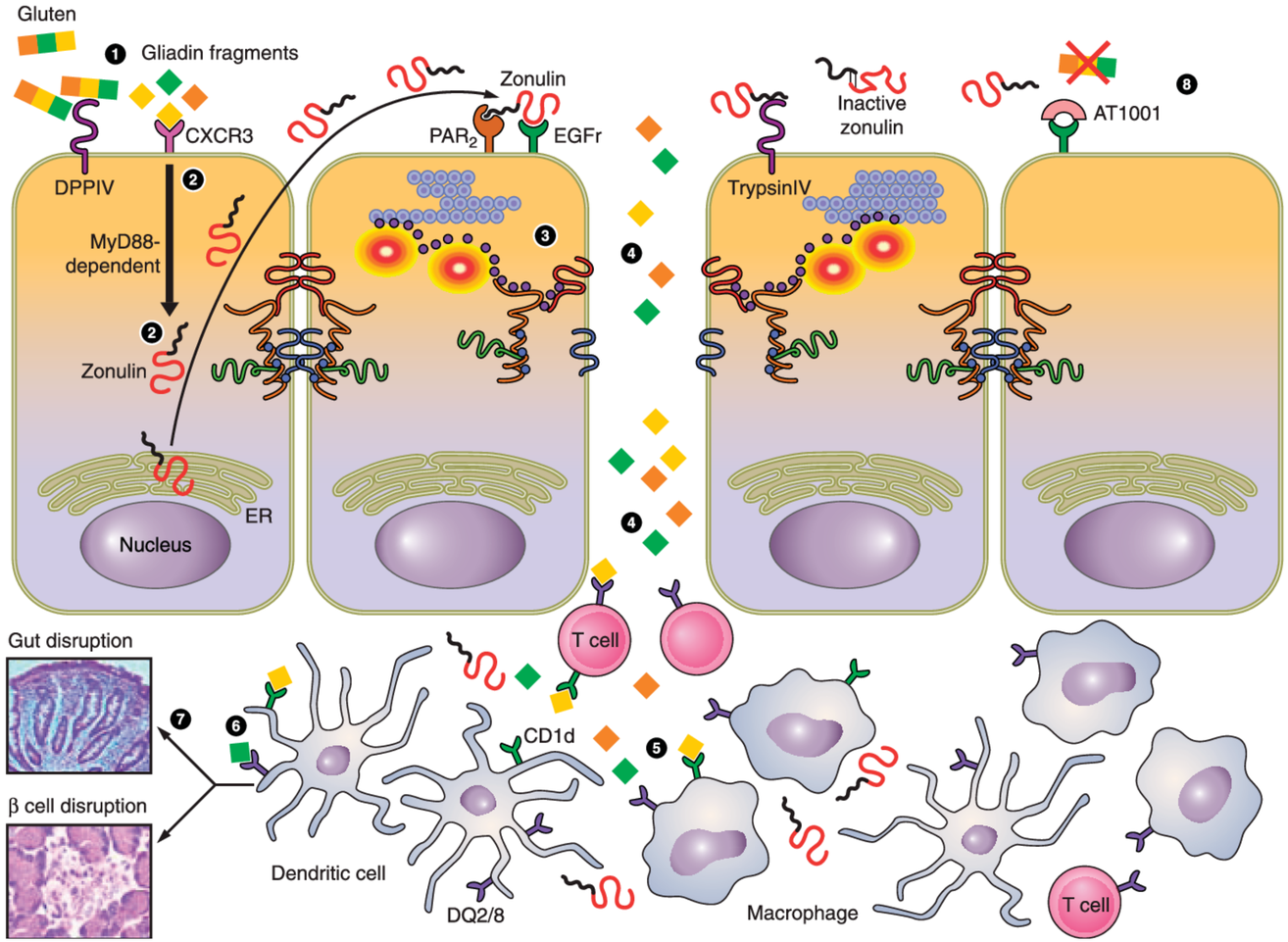
Henriques, Joana F., et al. "Microglia and alcohol meet at the crossroads: Microglia as critical modulators of alcohol neurotoxicity." Toxicology letters 283 (2018): 21-31.

McClain, Justin A., et al. "Adolescent binge alcohol exposure induces long-lasting partial activation of microglia." Brain, behavior, and immunity 25 (2011): S120-S128.

Dietary management

- Eliminate gluten
- Eliminate dairy

Gliadin induced Zonulin release



Dietary management

- **stabilize blood sugar balance**

Anti-diabetic therapy improve thyroid function

Metformine

Kalra S, Dhamija P, Unnikrishnan AG. Metformin and the thyroid: An unexplored therapeutic option. Thyroid Res Pract. 2012;9:75–7.

Berberine + Cinnulin

Berberine : different studies show effect on glucose and lipid metabolism

Significant decrease in

- Hemoglobin A1c
- Fasting blood glucose
- Postprandial blood glucose

Some studies are comparative studies between Berberine & Metformine

- The hypoglycemic effect of berberine was similar to that of metformin
- Their effects on lipid metabolism were different:
  Berberine decreased serum triglyceride and total cholesterol

Berberine is a potent oral hypoglycemic agent
with beneficial effects on lipid metabolism

Cinnulin : different studies show the effect on glucose metabolism

- Significant improvement in fasting blood sugar
- Increased insulin receptor sensitivity – reduced insulin resistance
- Glucose uptake and glycogen synthesis increased

+ positive outcome on systolic blood pressure, reduction of body fat

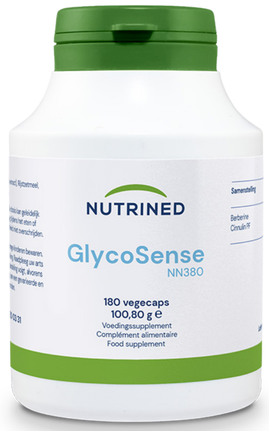
Yina, Jun, H. Xing, and J. Yeb. "Efficacy of berberine in patients with type 2 diabetes." Metabolism 57.5 (2008): 712-717.

Qin, B., M. M. Polansky, and R. A. Anderson. "Cinnamon extract regulates plasma levels of adipose-derived factors and expression of multiple genes related to carbohydrate metabolism and lipogenesis in adipose tissue of fructose-fed rats." Hormone and Metabolic Research 42.03 (2010): 187-193.

Wang, Jeff G., et al. "The effect of cinnamon extract on insulin resistance parameters in polycystic ovary syndrome: a pilot study." Fertility and sterility 88.1 (2007): 240-243.

Qin, B. O. L. I. N., et al. "Cinnamon extract attenuates TNF-□-induced intestinal lipoprotein ApoB48 overproduction by regulating inflammatory, insulin, and lipoprotein pathways in enterocytes." Hormone and Metabolic Research 41.07 (2009): 516-522.

Glycosense



indication	Fluctuating blood sugar levels Dysglycemia Poor insulin sensitivity Elevated fasting blood glucose High glycated hemoglobin HbA1c Lipid metabolism (triglycerides & cholesterol)	
dosage	3 x 1 caps per day during meals. The daily dose can be increased gradually up to 3 x 2 caps per day during meals, depending on tolerance & results	
packaging	180 vegecaps per container	
composition (amount per 3 vegecaps)	Berberine Cinnulin PF	750 mg 255 mg

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Additional dietary recommendations

- low-to-moderate carbohydrate diet to prevent blood sugar fluctuations
- frequent small meals
- avoid nutrition with high glycemic index
- avoid caffeine and nicotine

Nutritional Support
Rebuilding GI-metabolism in LPS-induced Neuroinflammation

GUT PROTOCOL

Guttae Pepsine

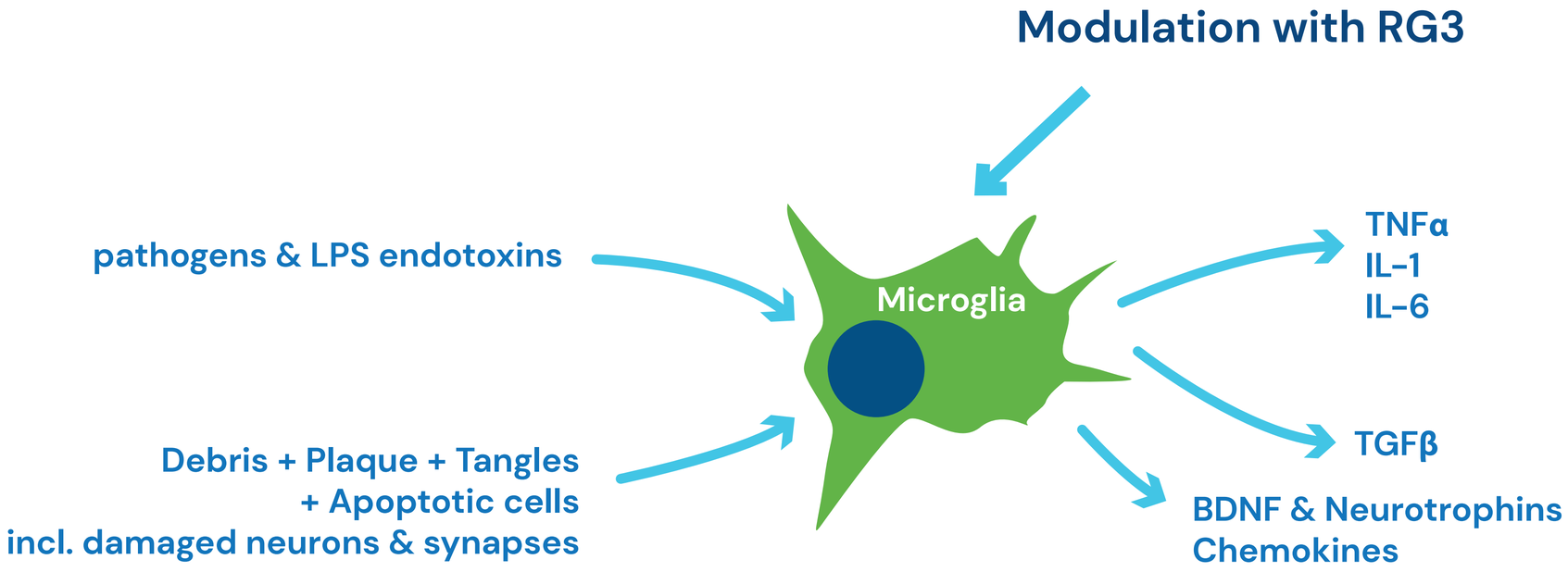
Gluten DPP4

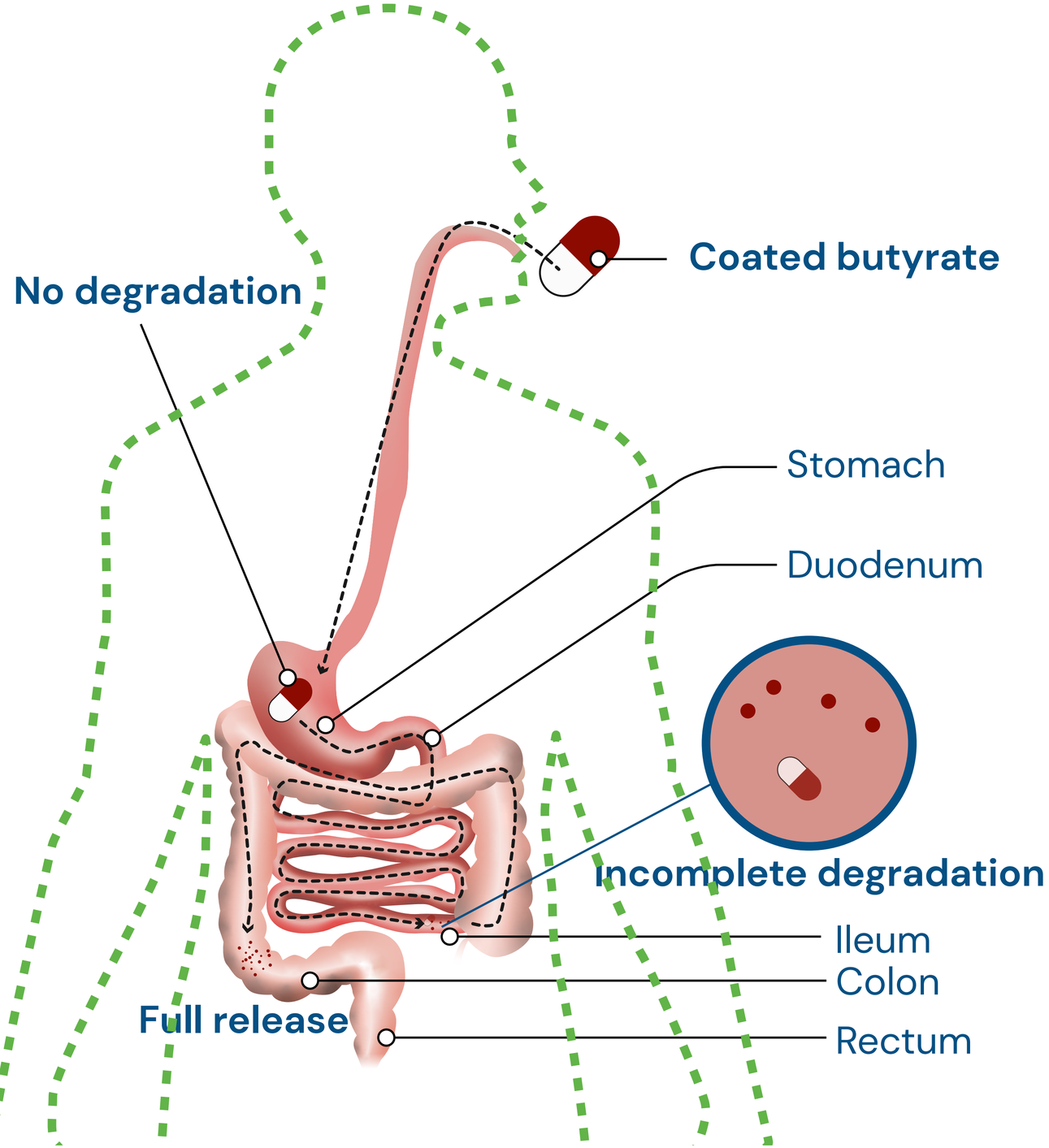
Permplus Coated

Butyflam

Modulation of microglial release of inflammatory mediators

Rg3 Nasal Spray
30 ml
Dose: 2 x 2 sprays in each nostril

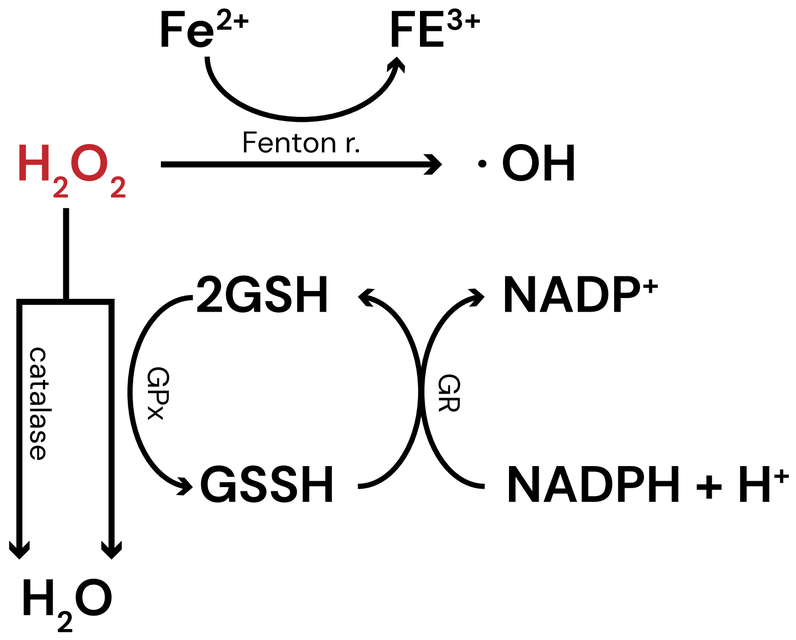


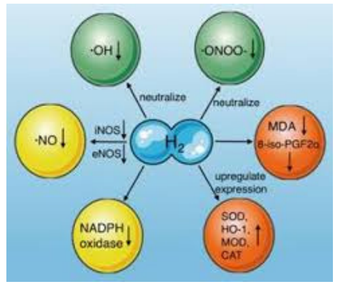


Reducing inflammation with anti-inflammatory molecules crossing the blood brain barrier

Cytoquel
90 caps
Dose: 3 x 1 capsule per day, during meals

Butyflam coated
180 coated caps
Dose: 3 x 2 caps / day, 20 minutes before meals





Antioxidants reducing neuronal inflammation and neuronal damage

Tri-Fortify Watermelon or Orange
236 ml
Dose: 1 teaspoon (5 ml) per day, separated from meals

H2 Absorb
60 tabs
Dose: 2 x 1 tab per day, in a glass of water

Tri-Fortify Watermelon® or Orange®

indication	Detoxification with glutathione in high bioavailable formulation, powerful antioxidant, Natural Killer Cell support	
dosage	1 teaspoon (1 pack) per day, away from food	
packaging	236 ml per tube or 20 packs per box	
composition (amount per 1 teaspoon)	Glutathione Liposomal Vitamin C	450 mg 50 mg

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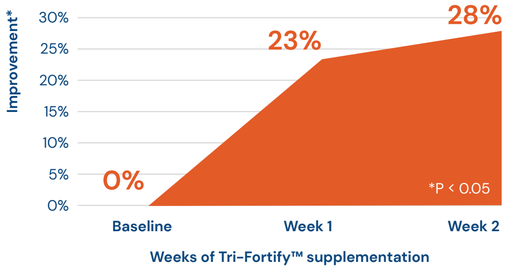
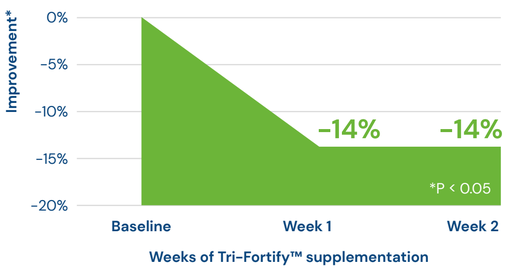
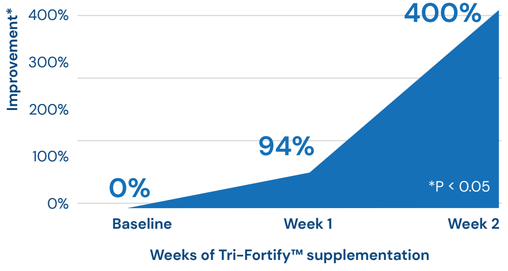
Glutathione levels
Increase in red blood cell levels (Erythrocytes)



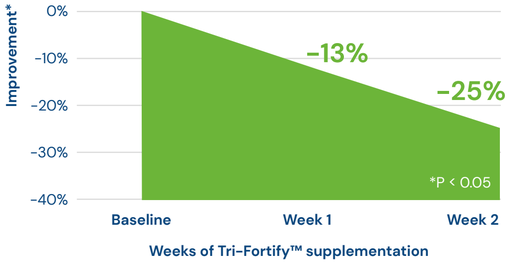
Oxidative stress markers
Oxidized / Reduced GSH



Immune function
Natural Killer Cell activity

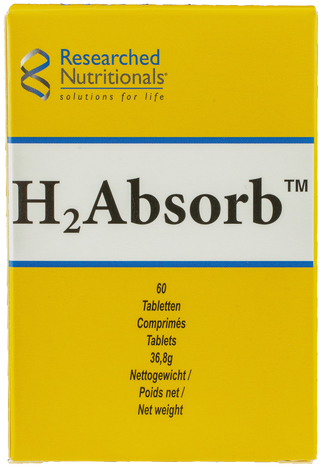


Lipid Peroxidation
(Reduced Cellular Membrane Oxidation)



Published research : Sinha, R., Sinha, I., Calcagnotto, A., Trushin, N. Oral supplementation with liposomal glutathione elevates body stores of glutathione and markers of immune function. Eur J Clin Nutr. 2018 Jan;72(1):105-111.

H_2 Absorb™



indication	Molecular hydrogen. Powerful antioxidant crossing biomembranes like mitochondria and blood brain barrier to neutralize the most reactive ROS and RNS.	
dosage	2 x 1 soluble tablet per day in non-carbonated water. Wait for the tablet to dissolve and drink immediately.	
packaging	60 soluble tablets per container	
composition (amount per 2 soluble tablets)	RN Ionic Hydrogen matrix (Dextrose, Malic acid, tartaric acid) Magnesium (as magnesium oxyde, glycinate, malate)	1040 mg 160 mg

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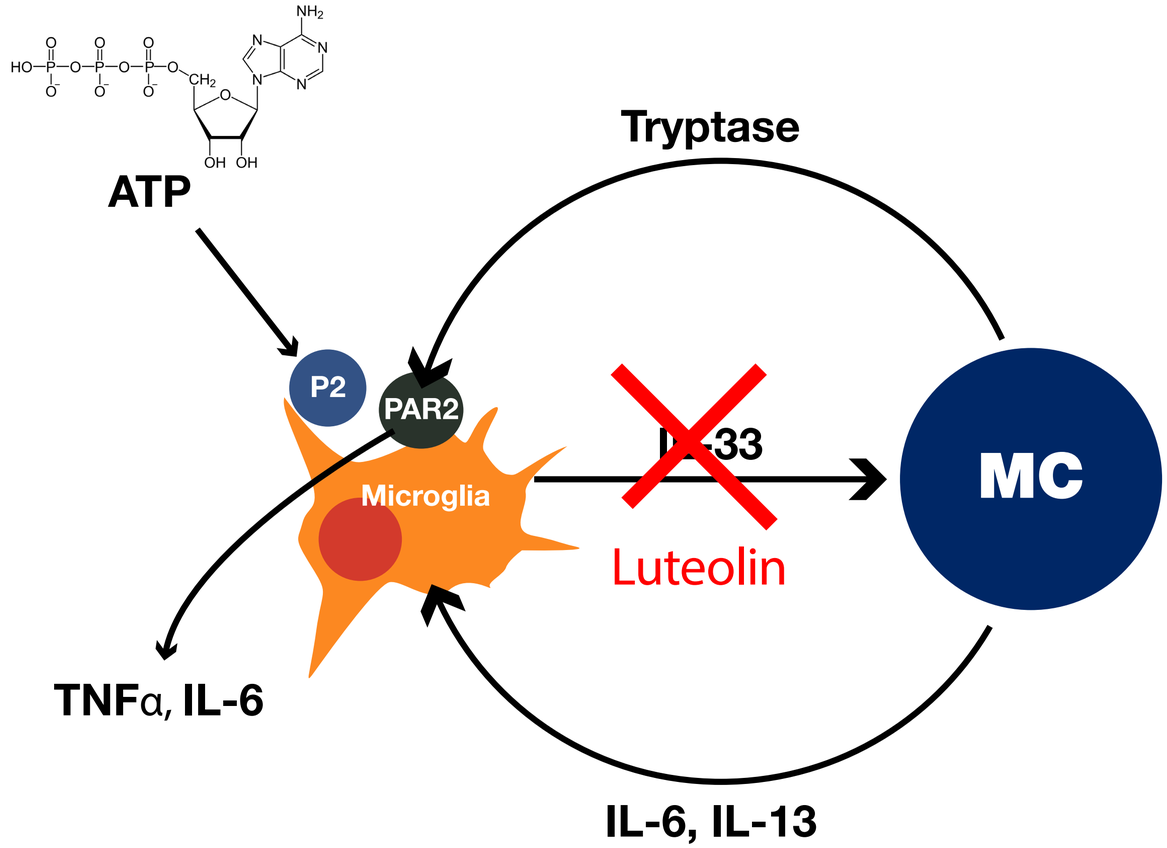
Modulation of mast cells and downregulation of inflammation

HistaQuel
120 vcaps
Dose: 2 x 2 capsules per day, with or without food



HistaQuel™

indication	Mast cell stabilization and downregulation of inflammation	
dosage	2 caps in the morning and 2 caps in the evening	
packaging	120 vegecaps per container	
composition (amount per 4 vegecaps)	Quercetin phytosome® (Quercefit™)	500 mg
	Black cumin seed	250 mg
	Nettle leaf powder	150 mg
	Perilla frutescens leaf extract	100 mg
	Luteolin	100 mg
	Fisetin	50 mg

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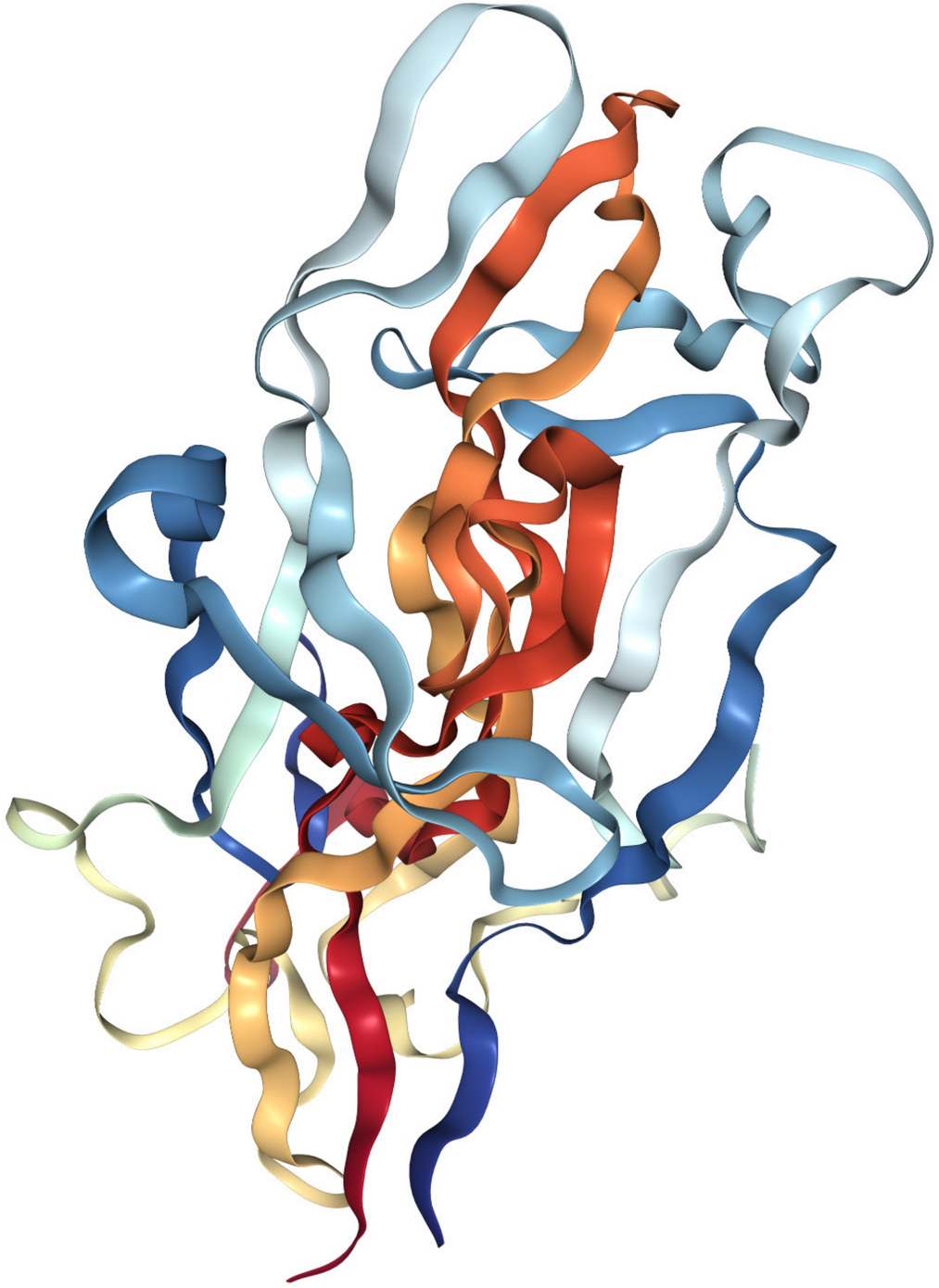
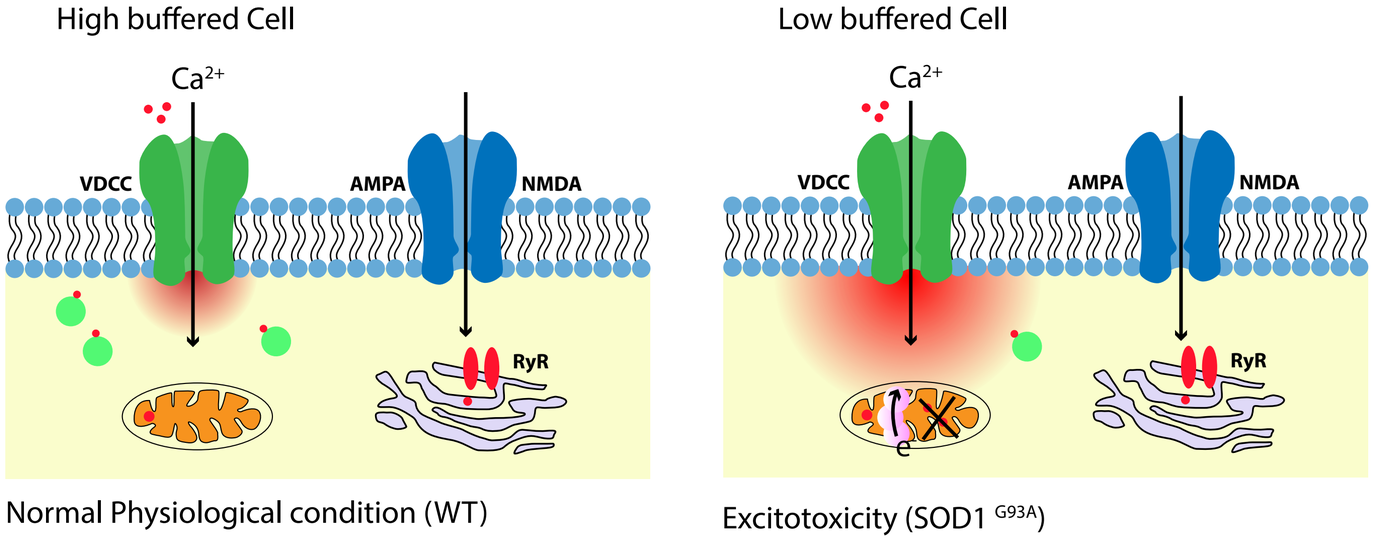


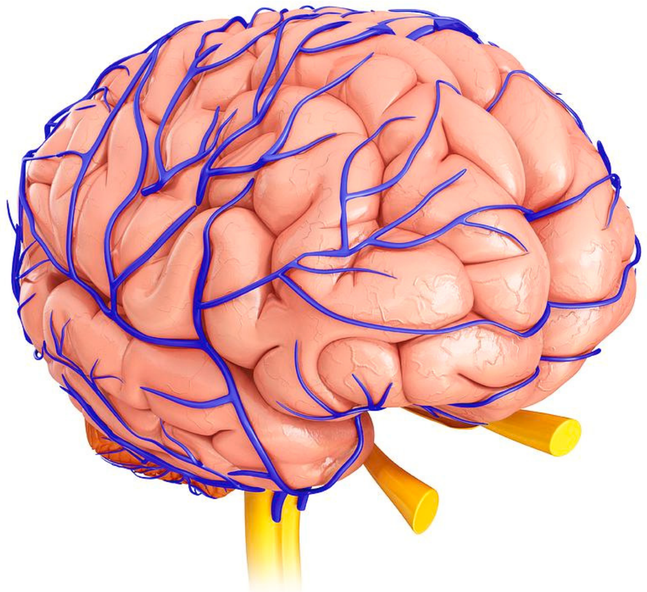
Upregulation of BDNF gene expression

BDNF Essentials
120 vcaps
Dose: 2 x 2 capsules per day



Magnesium L-threonate:
reducing excessive calcium influx & excitotoxicity in neurons

Magnesium C-Complex
90 vcaps
Dose: 3 x 1 capsules per day



Lumbrokinase in cerebral ischemia to optimize blood perfusion

Boluoke
60 or 120 vcaps
Dose: 1 – 4 capsules, separated from meals

Boluoke® Lumbrokinase

indication	Enzymatic breakdown of biofilms, plasminogen activator to reduce thrombosis or hypercoagulation. Cerebral ischemia.
dosage	1 - 2 caps per day away from food. Acute: 3 x 1 - 2 caps per day away from food.
packaging	60 or 120 vegecaps per container
composition (amount per 1 vegecaps)	Proprietary earthworm protein extract 20 mg (Lumbricus rubellus)(= 13 mg Lumbrokinase)

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Mitochondrial dysfunction as a major contributing factor in neurodegenerative diseases

CogniFuel
90 caps
Dose: 1 x 3 capsule per day