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Long Covid Practitioner Programme

WEBINAR FVE

Presented by Antony Haynes, Nutritional Therapist
BA(Hons), Dip ION, mCNHC, mBANT

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1. Monday 23rd September 12 noon
Introduction to Long Covid, review of symptoms, example case history. Review of Nutritional Therapy solutions.

2. Friday 27th September 12 noon
Functional Medicine model of Long Covid from Dr Leo Galland, including blood clotting, viral persistence, and mitochondrial disruption. Nutritional Therapy solutions.

3. Monday 30th September 12 noon
Exploration into Mast Cell Activation Syndrome (MCAS) and its involvement in Long Covid symptomology. Nutritional Therapy solutions.

4. Friday 4th October 12 noon
Viral persistence and viral reactivation as causes of Long Covid & Haematological problems caused by spike protein. Nutritional Therapy solutions.

5. Monday 7th October 12 noon
Neurotransmitter imbalances as an explanation for multiple Long Covid symptoms. Nutritional Therapy solutions.

6. Monday 14th October 12 noon
Spike protein pathogenesis. Nutritional Therapy solutions. Review and summary and presentation of Model of Long Covid including lab tests and potential therapeutic interventions.

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5. Monday 7th October 12 noon

Neurotransmitter imbalances as an explanation for multiple Long Covid symptoms.

Nutritional Therapy solutions.

- Prevalence of Neurological Symptoms in Long Covid
- Review of Neurotransmitter Function
- How inflammation upsets Neurotransmitter Function
- Disturbed amino acid metabolism and neurotransmitter synthesis in patients with LC and ME/CFS

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Prevalence of Neurological Symptoms in Long Covid

Neurological Symptoms are high on the list

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- Headaches
- Brain fog
- Confusion
- Memory loss
- Poor Concentration
- Irritability
- Cognitive impairment
- Anxiety
- Depression
- Sleep disturbances
- Restless leg syndrome
- Tremors
- Seizures (rare)
- Hallucinations (rare)
- Delusions (rare)
- Panic attacks
- PTSD-like symptoms
- Suicidal ideation
- Lack of motivation
- Social withdrawal
- Emotional reactivity
- Dissociative symptoms

Characterising Long-Covid in an International Cohort: 7 months of symptoms and their impact

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- Most common symptoms: fatigue, post exercise malaise, cognitive dysfunction.
- Virus finds its way into any and every organ and tissue, as post-mortem studies have shown.
- No difference in symptoms in different age groups. In fact, younger cohorts were affected more severely in these categories:
    - Attention
    - Thinking
    - Executive Function
    - Problem Solving
    - Slowed Thoughts
    - Confusion
    - Fast Thoughts

Characterising Long-Covid in an International Cohort: 7 months of symptoms and their impact

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Sensorimotor Symptoms

- **80.5%** had tingling, pins and needles, electric zaps, facial paralysis, facial pressure / numbness, & weakness experiences

Sleep

- **78.6%** had difficulty with sleep

Headaches

- **77%**, often acting as the precursor to post exertional malaise.

Emotions and Mood

- **88.3%**, with anxiety being the predominant symptom. (we will explore this in depth in Webinar FIVE – here we are)

Most Common Long Covid Signs & Symptoms

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1. **Respiratory:** shortness of breath, congestion, persistent cough, etc.
2. **Neurological/psychiatric:** brain fog, malaise, tiredness, headaches, migraines, depression, inability to focus or concentrate, altered cognition, insomnia, vertigo, panic attacks, tinnitus, anosmia, phantom smells, etc.
3. **Musculoskeletal:** myalgias, fatigue, weakness, joint pains, inability to exercise, post-exertional malaise, inability to perform normal activities of daily life.
4. **Cardiovascular:** Palpitations, arrhythmias, Raynaud-like syndrome, hypotension, and tachycardia on exertion.
5. **Autonomic:** Postural tachycardia syndrome (POTs), abnormal sweating.
6. **Gastrointestinal disturbance:** anorexia, diarrhoea, bloating, vomiting, nausea, etc.
7. **Dermatologic:** itching, rashes, dermatographia.
8. **Mucus membranes:** running nose, sneezing, burning and itchy eyes.

What covid-19 does to the brain

- Over the past two years, we have learned that covid-19 can have profound consequences for the brain – in the short and long term.
- Rates of neurological problems appear to be higher after covid-19 than after other viral infections.
- The latest insights suggest that the virus seldom infects brain cells directly, but instead causes harm through blood clots or by spurring a destructive immune response.
- Encouragingly, many of the effects caused by harmful immune changes are likely to be reversible.

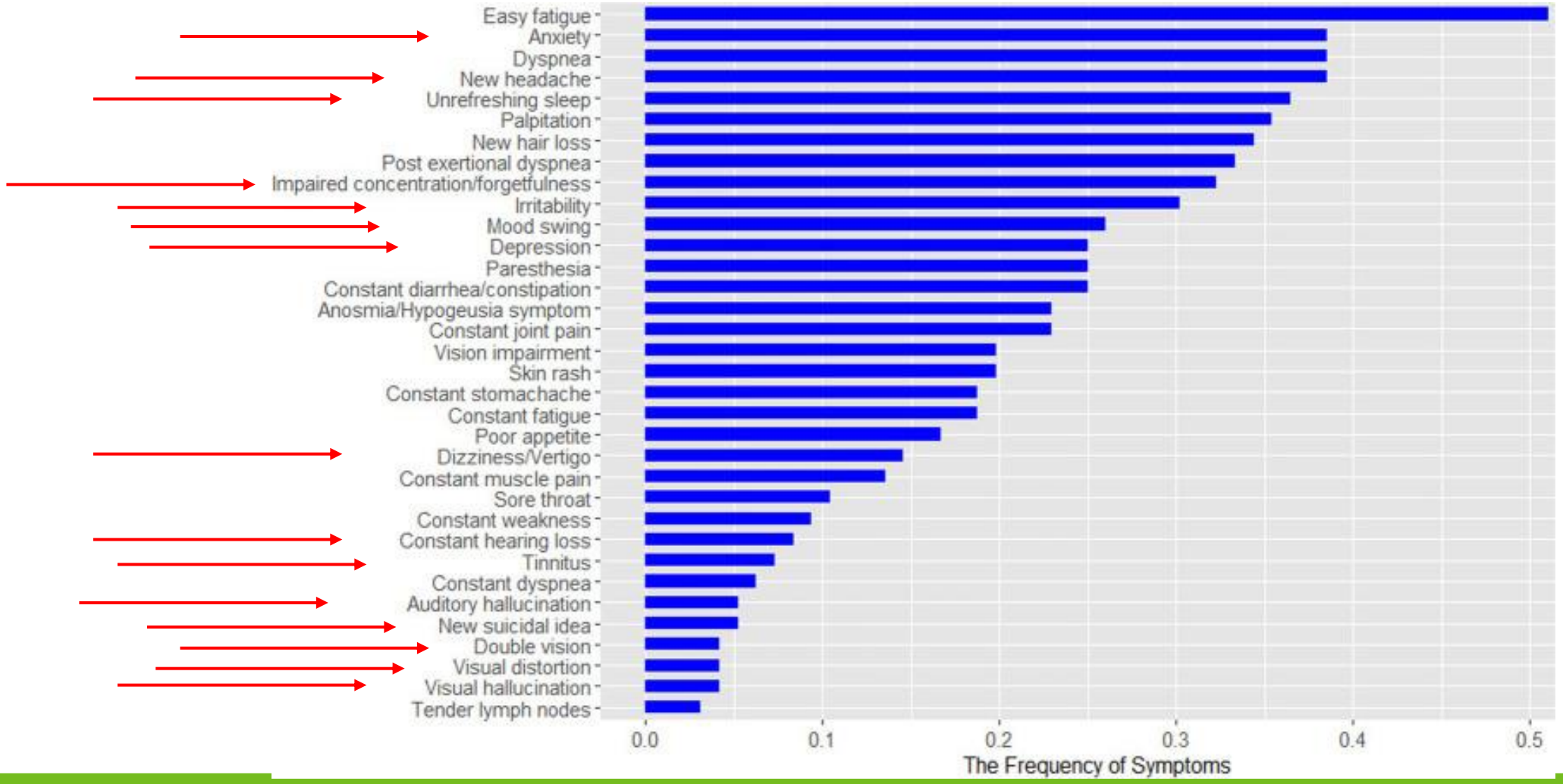
Hamzelou J. What covid-19 does to the brain. New Scientist, Volume 253, Issue 3371, 2022, Page 19, ISSN 0262-4079, View Link

What covid-19 does to the brain

- The effects on the brain may largely be down to two other important factors. One is the impact of covid-19 on blood vessels.
- Multiple studies have found abnormal clotting, which can cause stroke, in people with severe cases of covid-19.
- Autopsies have also revealed damage to blood vessels in the brain after covid-19 – vessel walls have become thinner, and they appear to leak proteins that might trigger an immune response.
- This altered immune response has come to the fore as potentially the most significant culprit.

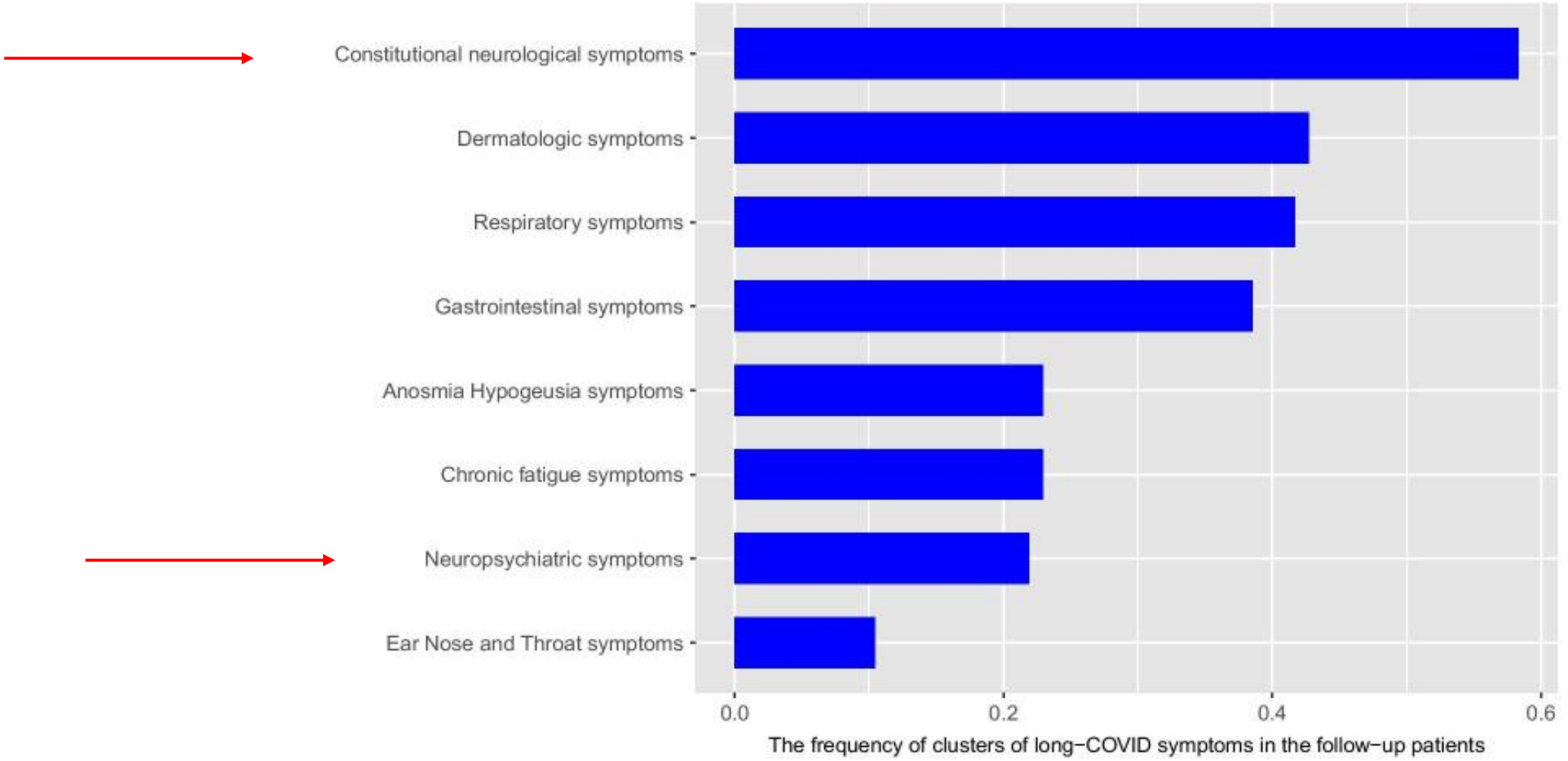
Hamzelou J. What covid-19 does to the brain. New Scientist, Volume 253, Issue 3371, 2022, Page 19, ISSN 0262-4079, View Link

The frequency of long-COVID symptoms in the follow-up of 95 patients with a history of COVID-19



Mirfazeli FS et al. Chronic fatigue syndrome and cognitive deficit are associated with acute-phase neuropsychiatric manifestations of COVID-19: A 9-month follow-up study. Neurol Sci. 2022 Apr;43(4):2231-2239. Full Paper

The frequency of clusters of long-COVID symptoms in the follow-up of 95 patients with a history of COVID-19



Mirfazeli FS et al. Chronic fatigue syndrome and cognitive deficit are associated with acute-phase neuropsychiatric manifestations of COVID-19: A 9-month follow-up study. Neurol Sci. 2022 Apr;43(4):2231-2239. Full Paper

Long Neuro-COVID-19

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- Long-lasting COVID-19 (long COVID) diseases constitute a real life-changing burden for many patients around the globe and, overall, can be considered societal and economic issues.
- They include a variety of symptoms, such as fatigue, loss of smell (anosmia), and neurological–cognitive sequelae, such as memory loss, anxiety, brain fog, acute encephalitis, and stroke, collectively called long neuro-COVID-19 (long neuro-COVID).
- The main mechanistic hypotheses that explain the multiple long neuro-COVID symptoms are: immune dysregulation and prolonged inflammation, persistent viral reservoirs, vascular and endothelial dysfunction, and the disruption of the neurotransmitter signaling along various paths.
- **The nucleoprotein N of SARS-CoV-2 constitutes a "hub" between the virus and the host inflammation, immunity, and neurotransmission**.

Slama Schwok A, Henri J. Long Neuro-COVID-19: Current Mechanistic Views and Therapeutic Perspectives. Biomolecules. 2024; 14(9):1081. Full Paper

Long Neuro-COVID-19

- Slama Schwok & Henri (2024) present their current hypotheses and biochemical model for long neuro-COVID based on the altered neurotransmission of selected neuropeptides, namely cholestocytokinin, enkephalin, and substance P, between the brain and the gut through the vagus nerve and the CNS.
- They cannot rule out the contributions of other viral proteins, such as the spike protein S, as both N and S have been found in the brains of COVID-19 patients and are associated with microvascular and immune cells' activation.
- The administration of antivirals in cases of incomplete viral clearance from "reservoirs" would likely be beneficial to some long neuro-COVID patients.

Slama Schwok A, Henri J. Long Neuro-COVID-19: Current Mechanistic Views and Therapeutic Perspectives. Biomolecules. 2024; 14(9):1081. Full Paper

Long Neuro-COVID-19

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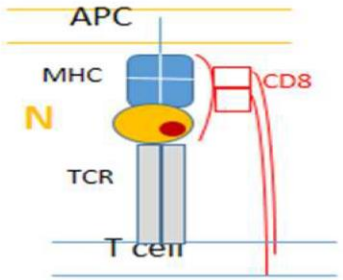
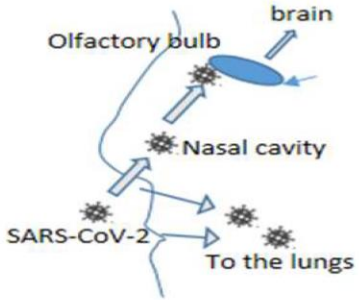
IMMUNITY

N C-terminal induced T memory cells-mediated increase in IL-6 and IFN-γ production in long Neuro-COVID, which correlated with clinical symptoms



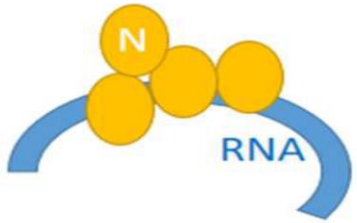
INFLAMMATION

N ? in Olfactory neurons
Inflammation



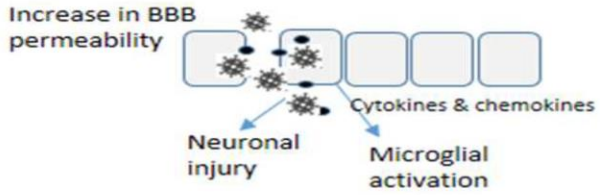
PERSISTENT SARS-CoV-2 VIRUS and

N In « reservoirs » of the body/ viral reactivation & N in plasma



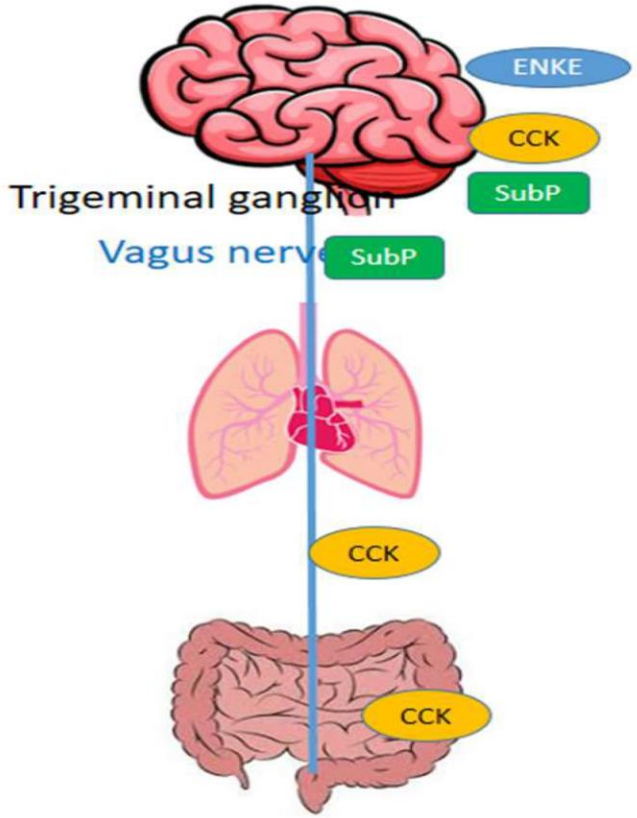
Endothelial/ Vascular dysfunction/ Clotting

N activation of brain endothelial cells



N- mediated dysfunction In Neurotransmission?

Sequestration of Neuropeptides



Slama Schwok A, Henri J. Long Neuro-COVID-19: Current Mechanistic Views and Therapeutic Perspectives. Biomolecules. 2024; 14(9):1081. Full Paper

Long Neuro-COVID-19

Neuropeptides (NP): ENKE SubP CCK

Neuropeptides Receptors : μ-opioid, Neurokinin-1, CCKR1 & CCKR2

NP Receptors Antagonists : naltrexone, aprepitant
(NPrA)

(1) N + NP → complex C1 ↓ viral replication and ↓ neurotransmission

(2) Neuropeptide Receptor + NP → complex C2

(3) Complex C2 + antagonist → neuropeptide-receptor-antagonist + free neuropeptide ↑

(4) N + antiviral ↓ viral replication + ↓ N-induced inflammation

Enkephalin ENKE **Substance P** SubP **Cholecystokinin** CCK

Slama Schwok A, Henri J. Long Neuro-COVID-19: Current Mechanistic Views and Therapeutic Perspectives. Biomolecules. 2024; 14(9):1081. Full Paper

Long Neuro-COVID-19

- Proposed model:
- (1) depicts the reversible binding of the neuropeptides (NPs) to N, affecting both replication and neurotransmission;
- (2) depicts the reversible binding of the neuropeptide to its receptor;
- in (3), a receptor antagonist can release the free neuropeptide and block the receptor;
- (4) depicts the direct action of an N-directed antiviral or an indirect action of an RNP-directed antiviral on N.

- Nigella sativa (Black Cumin) may be protective vs the nucleoprotein N of SARS-CoV-2 (see Nutritional Solutions Summary).

Slama Schwok A, Henri J. Long Neuro-COVID-19: Current Mechanistic Views and Therapeutic Perspectives. Biomolecules. 2024; 14(9):1081. Full Paper

Anxiety & Neurological Symptoms are high on the list of Post Viral Syndrome (PVS)

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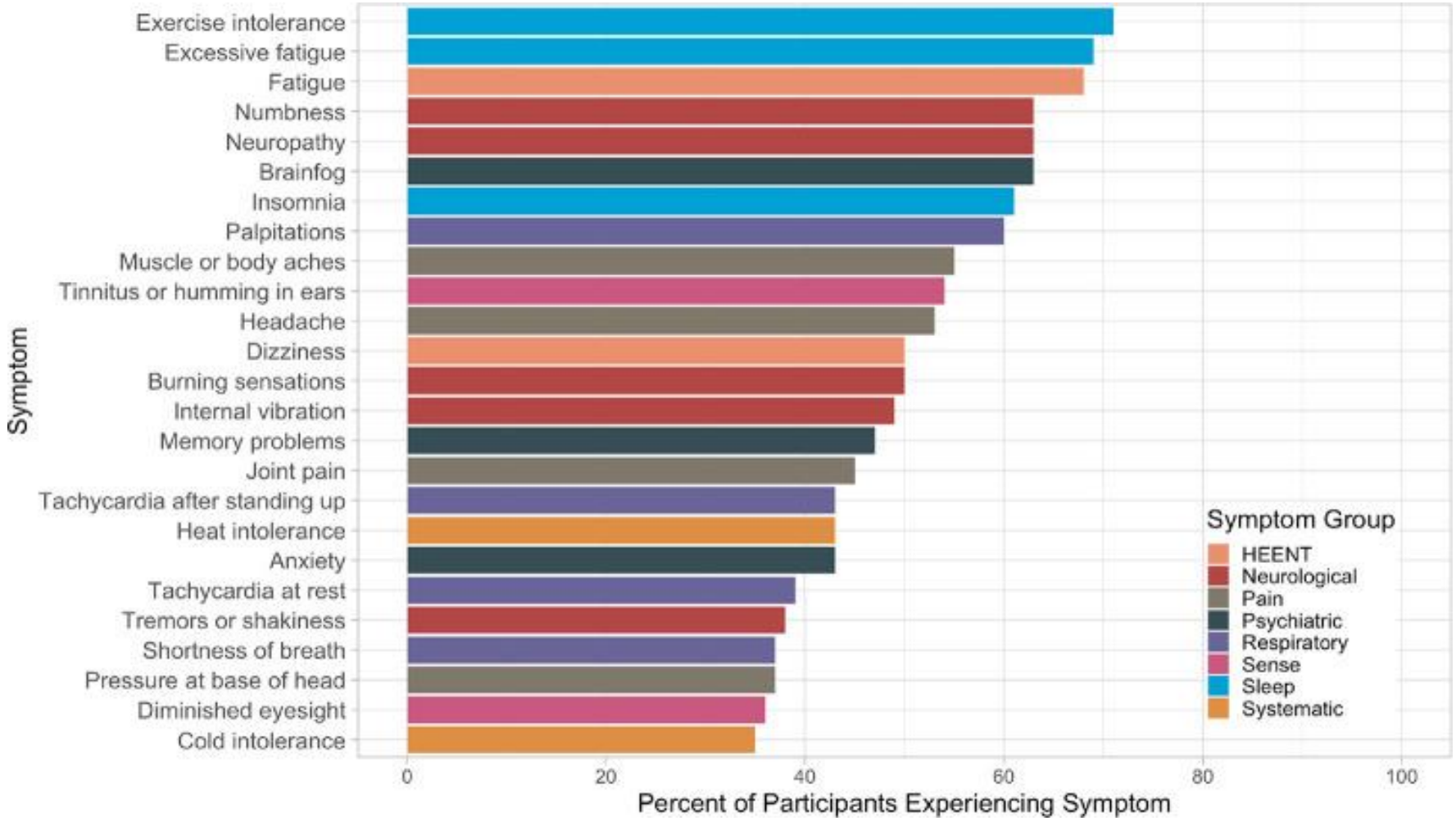
- Krumholz et al 2023 241 individuals aged 18 and older who self-reported PVS after covid-19 vaccination and who joined the online Yale Listen to Immune, Symptom and Treatment Experiences Now (LISTEN) Study from May 2022 to July 2023.
- Krumholz et al summarised their demographics, health status, symptoms, treatments tried, and overall experience.
- The average number of symptoms attributed to PVS was 22.
- The most common new diagnoses in the study sample since the beginning of the pandemic were anxiety (49 (36%) participants), neurological conditions (79 [33%]), gastrointestinal issues (73 [30%]), and postural orthostatic tachycardia syndrome (POTS) (70 [29%]).
- There were 53 (22%) participants who reported migraine and 49 (20%) who reported depression.

Krumholz HM, Wu Y, et al. Post-Vaccination Syndrome: A Descriptive Analysis of Reported Symptoms and Patient Experiences After Covid-19 Immunization. medRxiv [Preprint]. 2023 Nov 10:2023.11.09.23298266. Full Paper - PrePrint

Post-COVID-19 vaccination syndrome, PCVS

- Top 25 most common symptoms with their corresponding symptom groups within 241 participants who reported PVS.
- People reporting PVS after covid-19 vaccination in this study are highly symptomatic, have poor health status, and have tried many treatment strategies without success.
- As PVS is associated with considerable suffering, there is an urgent need to understand its mechanism to provide prevention, diagnosis, and treatment strategies.



Krumholz HM, Wu Y, et al. Post-Vaccination Syndrome: A Descriptive Analysis of Reported Symptoms and Patient Experiences After Covid-19 Immunization. medRxiv [Preprint]. 2023 Nov 10:2023.11.09.23298266. Full Paper - PrePrint

Post-COVID-19 vaccination syndrome, PCVS

- PCVS affecting the nervous system has been studied by Gerhard et al, 2023.
- The most frequently reported symptoms were paraesthesia (56%), fatigue (46%) and cognitive impairment (36%).
- Neurological, routine laboratory, and electrophysiological examinations did not yield distinct pathological findings.
- Neuropsychological testing of a subgroup revealed deficits in attention, executive function and memory.
- “Our data does not allow conclusions whether the symptoms occurred in temporal relationship to the COVID-19 vaccination, or whether the vaccine may be considered as a triggering factor or a cause of these symptoms.
- While there is limited data, several pathomechanisms have been suggested to explain the occurrence of diseases following SARS-CoV-2 vaccination, e.g., molecular mimicry, production of cross-reactive (anti-idiotype) autoantibodies, involvement of vaccine adjuvants, and persistence of spike protein.”

Gerhard A, Raeder V, et al. Neurological symptoms after COVID-19 vaccination: a report on the clinical presentation of the first 50 patients. J Neurol. 2023 Oct;270(10):4673-4677. Full Paper

Post-COVID-19 vaccination syndrome, PCVS

- PCVS affecting the nervous system has also been studied by Arlt et al, 2024.

- Compared with controls, PCVS patients had a significantly greater frequency of autoantibodies against peripheral nervous system structures (9/50 (18%) vs 1/35(3%).

- Conclusion
- Our data suggest that autoantibodies against nervous system tissue could be relevant in PCVS patients.

Arlt FA, Breuer A, et a;. High serum prevalence of autoreactive IgG antibodies against peripheral nerve structures in patients with neurological post-COVID-19 vaccination syndrome. Front Immunol. 2024 Aug 2;15:1404800. Full Paper

Post-COVID-19 vaccination neurological syndromes

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- In this study, the wide variety of neurological syndromes was temporally associated with COVID-19 vaccination: 51 cases out of 4,672 (ca 1%).
- Further studies with larger sample size and longer duration of follow-up are needed to prove or disprove causality association of these syndromes with COVID-19 vaccination.
- Neurological spectrum included:
  - CNS demyelination (n = 39, 76.5 %)
  - Guillain-Barré-syndrome (n = 3, 5.9 %)
  - Stroke (n = 6, 11.8 %)
  - Encephalitis (n = 2, 3.9 %)
  - Myositis (n = 1, 2.0 %).

Samim MM, Dhar D et al. Co-VAN study: COVID-19 vaccine associated neurological diseases- an experience from an apex neurosciences centre and review of the literature. J Clin Neurosci. 2023 Feb;108:37-75. Full Paper

Post-COVID-19 vaccination neurological syndromes - references

- Arlt FA et al. High serum prevalence of autoreactive IgG antibodies against peripheral nerve structures in patients with neurological post-COVID-19 vaccination syndrome. Front Immunol. 2024 Aug 2;15:1404800. Full Paper
- Dennis E et al. Acute and Chronic Demyelinating Neuropathies After COVID-19 Vaccination: A Report of 4 Cases. J Clin Neuromuscul Dis. 2023 Mar 1;24(3):147-156. View Abstract
- Hamed Y et al. CNS Demyelination Syndromes Following COVID-19 Vaccination: A Case Series. J Pharm Bioallied Sci. 2024 Feb;16(Suppl 1):S1002-S1006. Full Paper
- Lim N et al. COVID-19 Vaccination in Young People with Functional Neurological Disorder: A Case-Control Study. Vaccines (Basel). 2022 Nov 28;10(12):2031. Full Paper
- Salunkhe M et al. Spectrum of various CNS inflammatory demyelination diseases following COVID-19 vaccinations. Acta Neurol Belg. 2024 Feb;124(1):193-203. View Abstract
- Samim MM, Dhar D et al. Co-VAN study: COVID-19 vaccine associated neurological diseases- an experience from an apex neurosciences centre and review of the literature. J Clin Neurosci. 2023 Feb;108:37-75. Full Paper

Nutri-Link Long Covid Symptom Tracker

Most Common Symptoms of Long Covid

Mild = 1, Moderate = 2, Severe = 3

SYMPTOM / SIGN	SCORE
Fatigue	
Brain Fog	
Poor Memory	
Anxiety / Poor Mood	
Shortness of breath	
Cough	
Altered sense of smell / taste	
Aches & pains (anywhere in the body)	
Muscle weakness	
Muscle / Joint pains	
Tingling and or numbness in arms, hands, legs, feet	
Palpitations	
Feeling Faint	
Cold hands, fingers, feet, toes	
Poor coordination	
Sleep disturbances	
Hearing loss	
Sensitivity to noise	
Gut symptoms	
Changes in menstrual cycle	
Have you passed blood clots during your periods more than usual?	
Worse PMT	
Swollen glands / lymph nodes	
Increased allergic reactivity	
Headaches	
TOTAL	

Natural Anti-Virals & Anti-Inflammatory Supplements

- Humic Acid Cell Membrane Active (AR) - Humic Acid x 60 Capsules | Nutri-Link (nutrilink.co.uk) – 1 with breakfast & dinner

or

- Humic Monolaurin Complex (AR) - Humic Monolaurin x 120 Capsules | Nutri-Link (nutrilink.co.uk) – 2 with breakfast & dinner
- Aqueous Selenium (BR) – Aqueous Selenium x 15ml | Nutri-Link.co.uk (nutrilink.co.uk) = 1 drop with two or three meals
- NAC (BR) & (AR) – 1 on empty stomach twice daily (supports Th1 immune response)
- Ashwagandha Complex (AR) (incl licorice) – 2 with breakfast & 1-2 with lunch - Ashwaganda Complex x 60 Capsules | Nutri-Link.co.uk (nutrilink.co.uk)

Nutritional Solutions vs Spike Protein

- Nattokinase 50mg (AR) – 2 caps twice daily on empty stomach (8+ hours apart)
- Nattokinase NSK-SD 50mg x 90 Capsules | Nutri-Link.co.uk (nutrilink.co.uk)
- Bromelain Plus (BR) – 5 tabs on empty stomach once a day
- Bromelain Plus x 100 Tablets | Nutri-Link.co.uk (nutrilink.co.uk)
- CurcuWIN 500 (AR) – 1 with breakfast & 1 with dinner
- CurcuWIN 500 x 60 Capsules | Nutri-Link.co.uk (nutrilink.co.uk)
- Augmented NAC – 1 before breakfast & dinner by 20-15 mins
- NAC Augmented (N-Acetylcysteine) 90's: The Natural Dispensary

Anti-Inflammatory

- KappArest (BR) – 2-3 caps with two or three meals
- KappArest x 180 Capsules | Nutri-Link.co.uk (nutrilink.co.uk)

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All About Neurotransmitters

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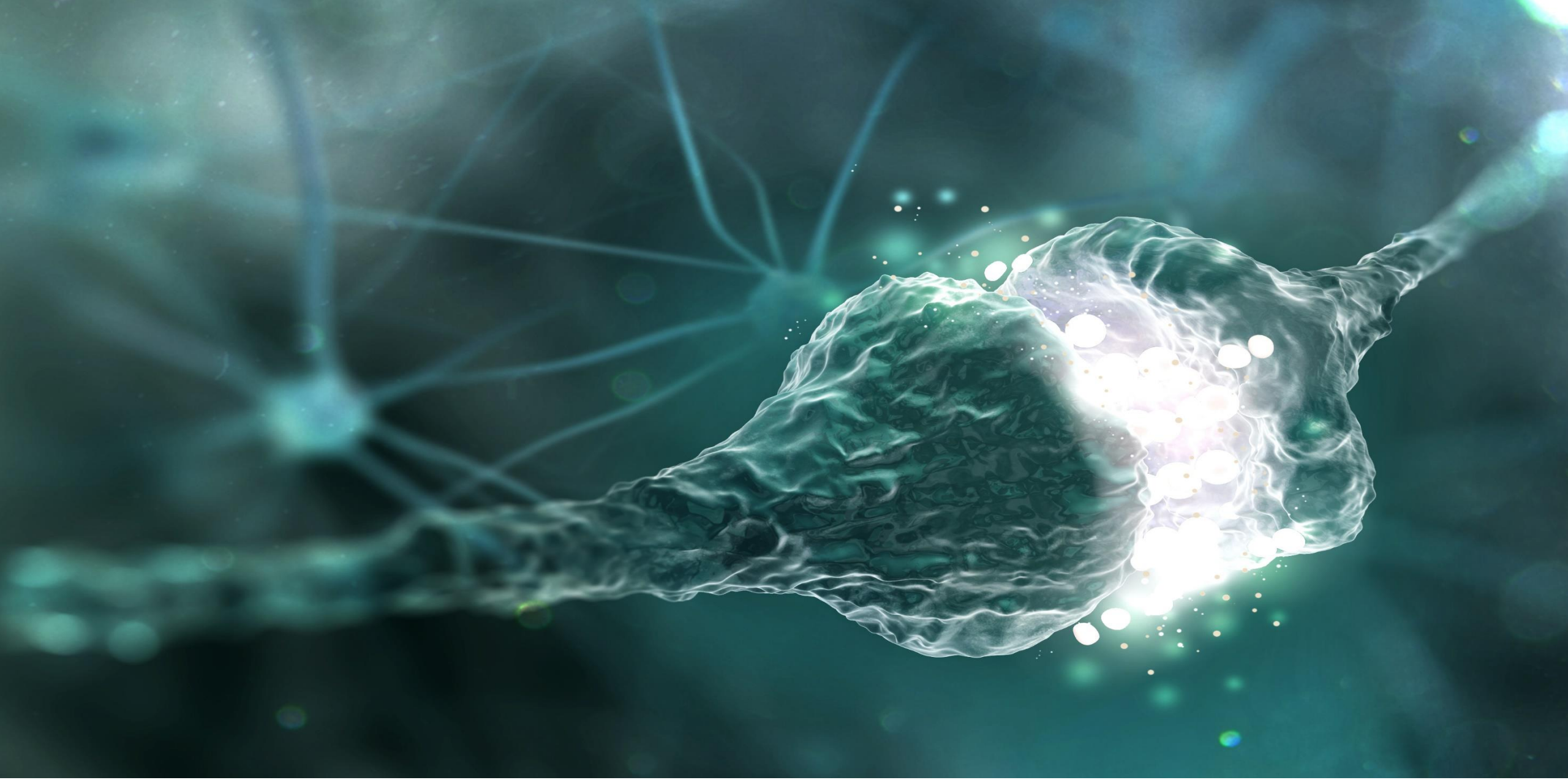
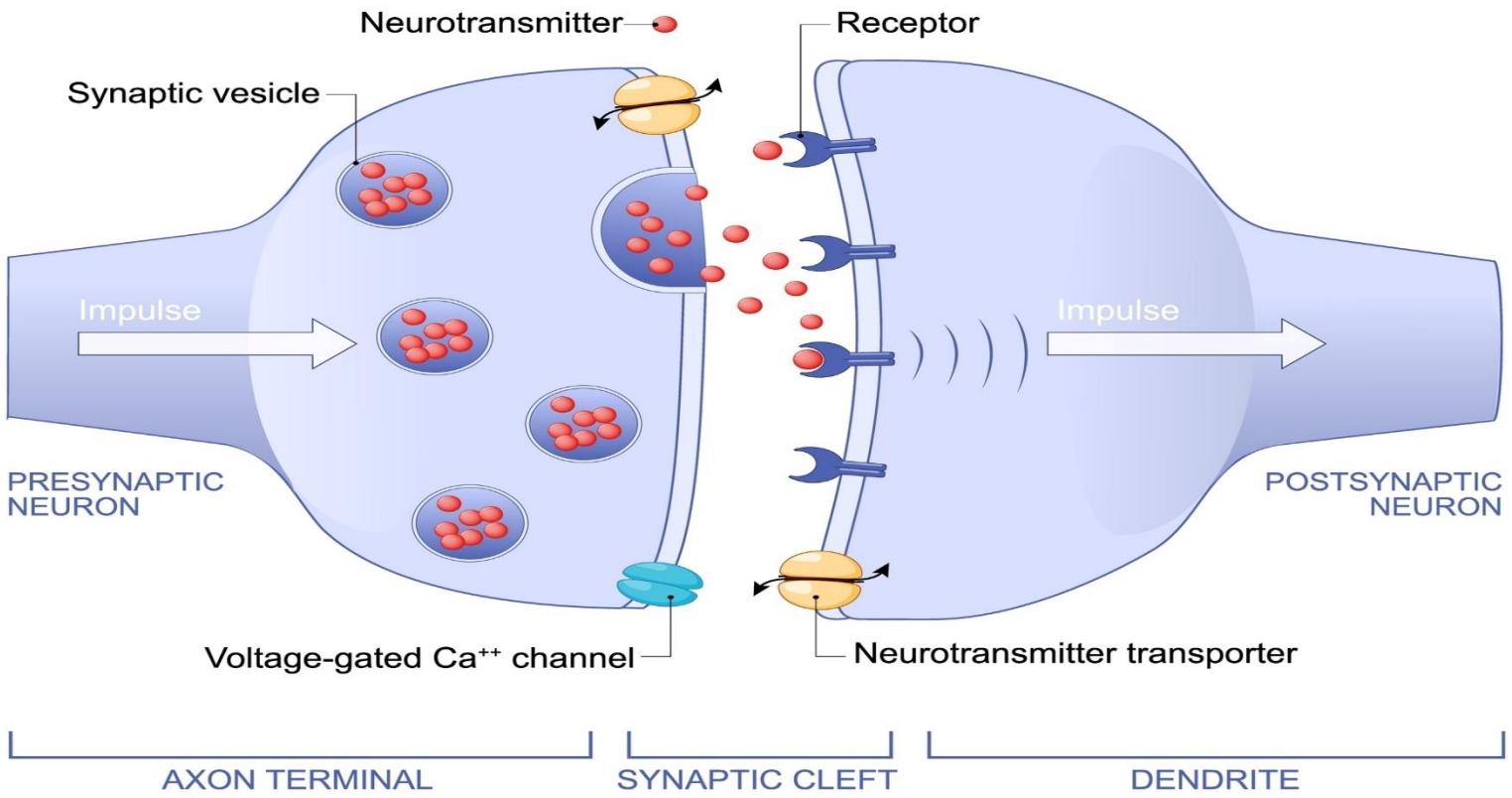
What is a Neurotransmitter?

- A neurotransmitter is a molecule (chemical) that carries a signal between nerve cells.
- A *neuromodulator* is a molecule that alters a nerve cells' response to a neurotransmitter signal.
- Neurotransmitters and neuromodulators have effect when they bind to specialised receptors on other cells, or inside a cell.
- Neurotransmitters are necessary because all nerve cells are separated by minute spaces called *synapses*.



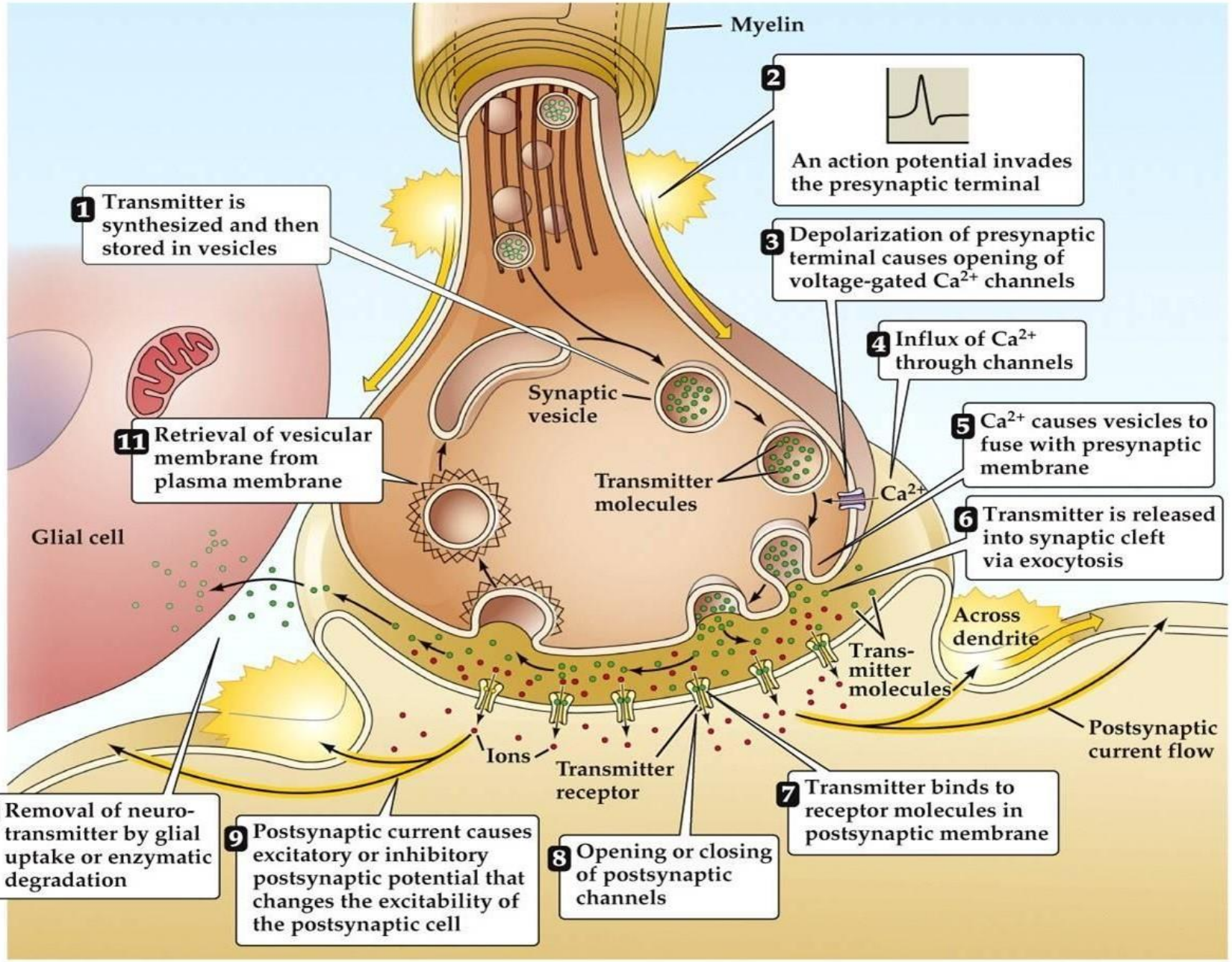
Neurotransmission

(the presynaptic neuron releases a neurotransmitter, which activates receptors on the postsynaptic neuron)



How does neurotransmission occur?

- The release of neurotransmitters is dependent on changes in intracellular voltage - which is mediated by ligand and gated ion channels in the presynaptic cell. Depolarisation of the cell results in action potential propagation through the entire axon. At the presynaptic terminal, calcium influx stimulates the extracellular release of the neurotransmitter vesicles.
- After traversing the synapse, neurotransmitters bind to postsynaptic receptors on the dendrites and exert either an excitatory or inhibitory response.
- Following the action potential, the presynaptic cell repolarises using the action of ion channels and ATP-dependent transporters. Neurotransmission is terminated by neurotransmitter enzymatic degradation in the synaptic cleft, transported-mediated recycling to its original axon terminal, or by transporter-mediated astrocytic uptake.


Myelin
2 An action potential invades the presynaptic terminal
1 Transmitter is synthesized and then stored in vesicles
3 Depolarization of presynaptic terminal causes opening of voltage-gated Ca^{2+} channels
4 Influx of Ca^{2+} through channels
Synaptic vesicle
11 Retrieval of vesicular membrane from plasma membrane
5 Ca^{2+} causes vesicles to fuse with presynaptic membrane
Transmitter molecules
Ca^{2+}
Glial cell
6 Transmitter is released into synaptic cleft via exocytosis
Across dendrite
Trans-mitter molecules
Postsynaptic current flow
Ions
Transmitter receptor
7 Transmitter binds to receptor molecules in postsynaptic membrane
10 Removal of neuro-transmitter by glial uptake or enzymatic degradation
9 Postsynaptic current causes excitatory or inhibitory postsynaptic potential that changes the excitability of the postsynaptic cell
8 Opening or closing of postsynaptic channels

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Neurotransmitters Influence Many Aspects of Health

Neurotransmitters Influence Many Aspects of Health

- Neurotransmitters are chemical moieties that can carry and amplify signals, ensuring information transmission throughout the nervous system.
- As they comprise a wide range of molecules (e.g., amino acids, amines, purines, soluble gases, neuropeptides) and are involved in numerous functions (e.g., emotions, thoughts, memories, movements, learning, sleep patterns, behaviour, alertness, arousal, vasoconstriction, respiration), neurotransmitters are essential factors in maintaining brain health.
- **Consequently, disturbed neurotransmitters' homeostasis and/or impaired neurotransmission results in severe diseases that significantly impact patients' lives and the global health system.**

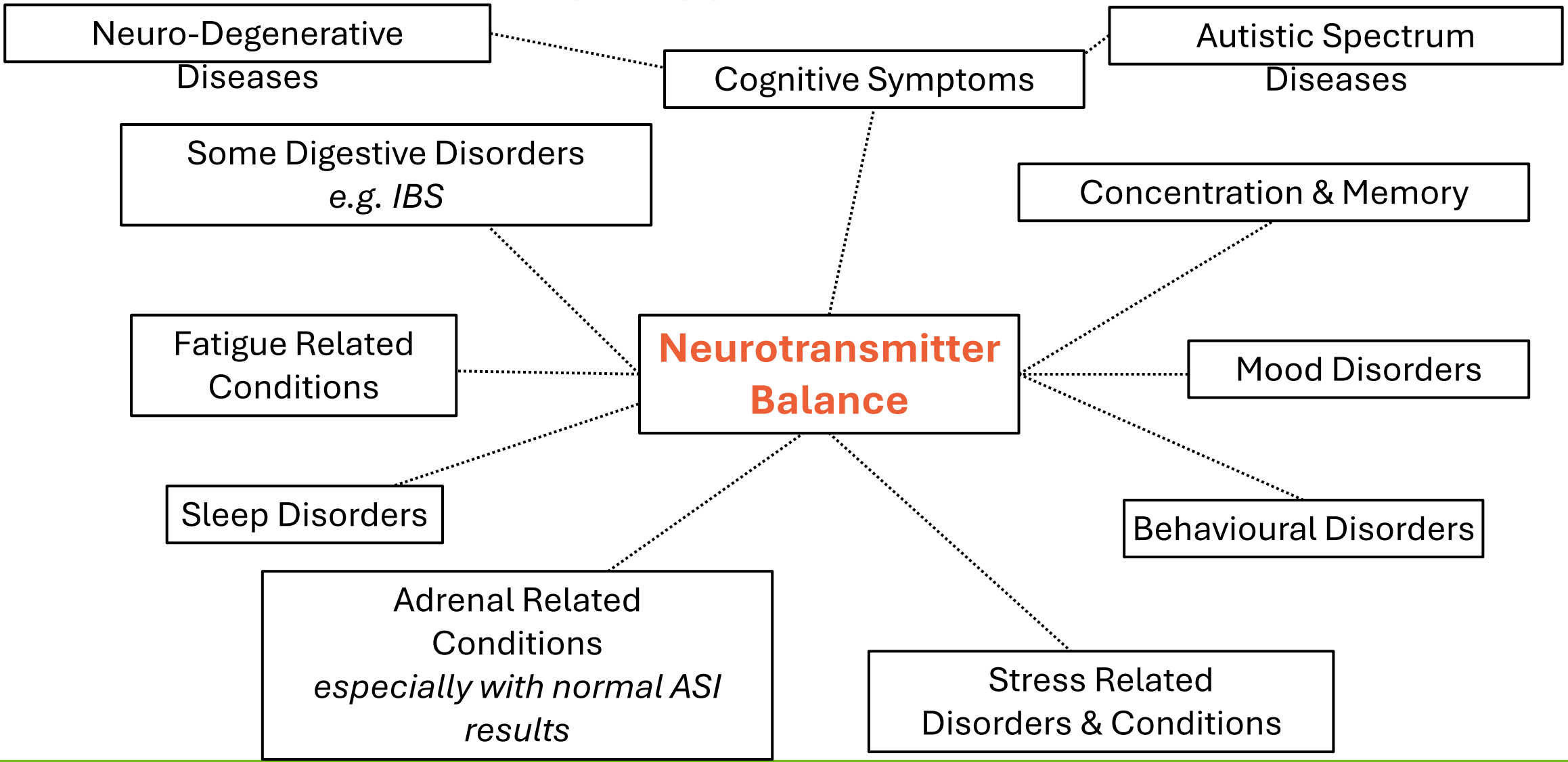
- Teleanu RI, Niculescu AG, Roza E, Vladâcenco O, Grumezescu AM, Teleanu DM. Neurotransmitters-Key Factors in Neurological and Neurodegenerative Disorders of the Central Nervous System. Int J Mol Sci. 2022 May 25;23(11):5954. Full Paper

Neurotransmitters Influence Many Aspects of Health

- Altered levels of neurotransmitters, such as glutamate, GABA, dopamine, serotonin, norepinephrine, histamine, and acetylcholine, were noticed to be involved in the pathophysiology of a long list of diseases, including autism spectrum disorders, schizophrenia, epilepsy, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, Alzheimer's disease, drug addiction, depression, and sleep disorders.
- Hence, monitoring and detecting NTs at early disease stages is mandatory to avoid complications of these associated disorders.

- Teleanu RI, Niculescu AG, Roza E, Vladâcenco O, Grumezescu AM, Teleanu DM. Neurotransmitters-Key Factors in Neurological and Neurodegenerative Disorders of the Central Nervous System. Int J Mol Sci. 2022 May 25;23(11):5954. Full Paper

Neurotransmitters Influence Many Aspects of Health



Review of The Major Neurotransmitters

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- Serotonin
- GABA
- Glutamate
- Dopamine
- Noradrenaline
- Adrenaline
- Acetylcholine
- Histamine
- ATP
- Nitric Oxide
- Endorphins

Review of The Major Neurotransmitters

- **Serotonin** - is a key messenger that mediates a range of central and peripheral functions in the human body. In the central nervous system (CNS), it is required for several brain functions and is associated with anxiety and behaviour. It is an inhibitory neurotransmitter.
- **GABA** - GABA is an inhibitory neurotransmitter that participates in various metabolic and physiological activities.
- **Glutamate** - the most abundant excitatory neurotransmitter in the brain, is responsible for sending signals between nerve cells.
- **Dopamine** - the most abundant catecholamine neurotransmitter in the brain, Dopamine and its receptors are widely distributed in the intestinal tract and affect gastric secretion, motility, and mucosal blood flow.

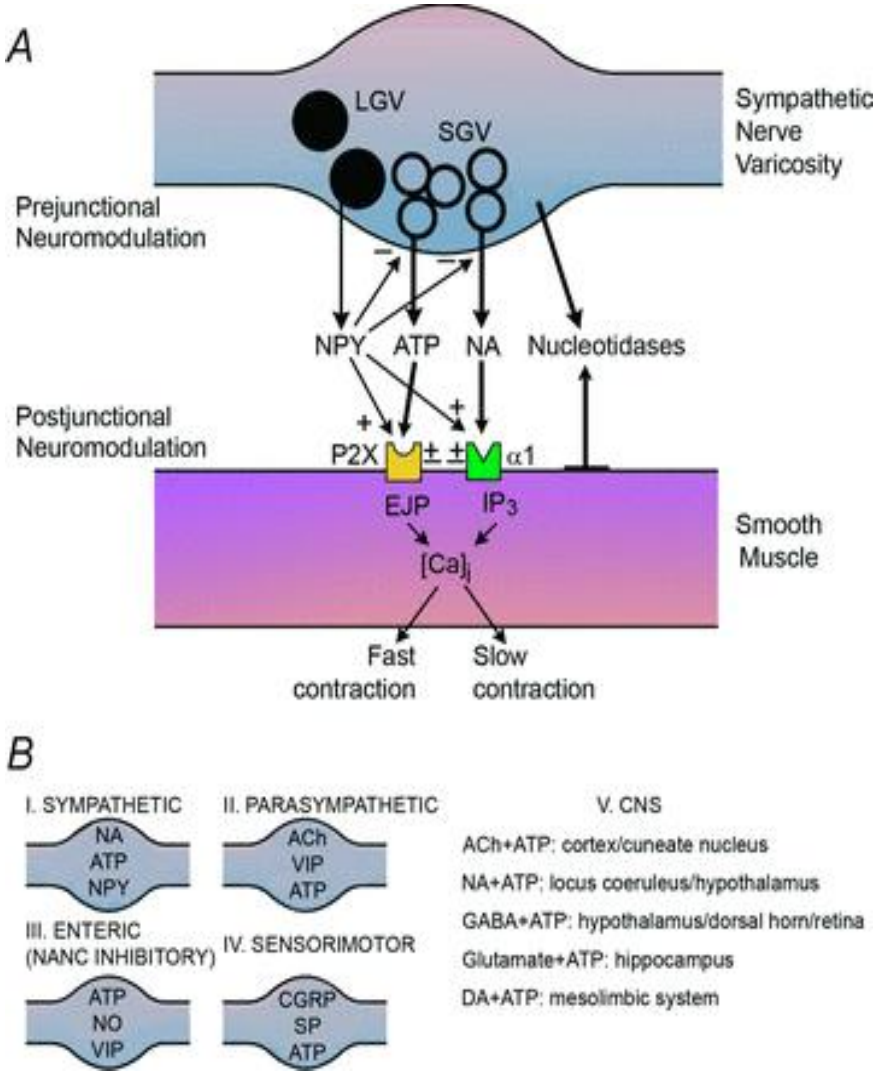
Review of The Major Neurotransmitters

- **Noradrenaline** - is both a neurotransmitter and a hormone. As a neurotransmitter, derived from dopamine, it is a chemical messenger that helps transmit nerve signals across nerve endings to another nerve, muscle or gland cell.
- **Adrenaline** – A central nervous system neurotransmitter, it is a chemical messenger that helps transmit nerve signals across nerve endings to another nerve, muscle or gland cell.
- **Acetylcholine** - Acetylcholine is a common cholinergic neurotransmitter that functions as a local mediator in the central and peripheral nervous systems by transducing excitatory signals between neurons.
- **Histamine** - acts as both a hormone and a neurotransmitter. It is synthesised by neurons to regulate the functionality of the nervous system. When it acts as a neurotransmitter, histamine is responsible for regulating tiredness and alertness, as well as the secretion of hormones by the hypothalamic system.

ATP as Neurotransmitter

- **ATP as neurotransmitter** – ATP is an important mediator in neuronal and glial cell signaling by increasing the speed of post-synaptic signal transmission.
- In the central nervous system, ATP, released from synaptic terminals, induces fast excitatory post-synaptic currents.
- **Adenosine**, a degradation product of ATP, inhibits acetylcholine release and increases cAMP. It is neuroprotective under conditions of hypoxia, ischaemia, and neuroinflammation.
- In the peripheral nervous system, ATP is involved in chemical transmission in sensory and autonomic ganglia.
- ATP may also act pre-synaptically rather than solely post-synaptically in the nervous system.

ATP as Neurotransmitter



- Schematic diagrams of cotransmission in both peripheral and central nervous systems
- A, schematic diagram of sympathetic cotransmission. Adenosine triphosphate and NA released from small granular vesicles (SGV) act on P2X and α1-adrenoceptors on smooth muscle, respectively. Adenosine triphosphate acting on inotropic P2X receptors evokes excitatory junction potentials (EJPs), increase in intracellular calcium ([Ca2+]i) and fast contraction, while occupation of metabotropic α1-adrenoceptors leads to production of inositol trisphosphate (IP3), increase in [Ca2+]i and slow contraction. Neuropeptide Y (NPY) stored in large granular vesicles (LGV) acts after release both as a prejunctional inhibitory modulator of release of ATP and NA and as a postjunctional modulatory potentiator of the actions of ATP and NA. Soluble nucleotidases are released from nerve varicosities and are also present as ectonucleotidases.
- B, schematic diagram of the principal cotransmitters with ATP in the nervous system. Nerve terminal varicosities of sympathetic, parasympathetic, enteric (NANC inhibitory), sensory-motor neurons and central nervous system (CNS) are illustrated.
- Abbreviations: CGRP, calcitonin gene-related peptide; DA, dopamine; GABA, γ-aminobutyric acid; NO, nitric oxide; SP, substance P; and VIP, vasoactive intestinal polypeptide.

Burnstock G. Purinergic cotransmission. Exp Physiol. 2009 Jan;94(1):20-4. View Abstract

Nitric Oxide as Neurotransmitter

- **Nitric Oxide -** oxidative radical that is a potent vasodilator and has the ability to induce the release of acetylcholine, catecholamine, and other neurotransmitters.
- Nitrergic regulation is extremely important in GI motility, as NO is a major inhibitory neurotransmitter in nearly every region and a mediator of inflammatory effects.
- Maintaining adequate levels of NO is crucial for cognitive functions such as memory, focus, and the ability to process information. When NO levels are low, individuals may experience cognitive decline, characterised by difficulties in concentrating, memory lapses, and a general decline in mental acuity.

- Neurotransmitters, Receptors, and Transporters (cellsignal.com)
- Sanders KM, Ward SM. Nitric oxide and its role as a non-adrenergic, non-cholinergic inhibitory neurotransmitter in the gastrointestinal tract. Br J Pharmacol. 2019 Jan;176(2):212-227. Full Paper

Endorphins as Neurotransmitters

- **Endorphins** – are a type of neurotransmitter. They attach to the brain's reward centres (opioid receptors) and carry signals across the nervous system.
- Endorphin comes from the words "endogenous," which means within the body, and "morphine," an opiate pain reliever. Put together, that means endorphins are natural pain relievers. They are "feel-good" chemicals because they can make you feel better and put you in a positive state of mind.
- There are more than 20 types of endorphins in your body. Beta-endorphins are the endorphins involved in stress relief and pain management. Beta-endorphins have a stronger effect than morphine on your body.
- Endorphins boost the release of dopamine in your body, which affects mood. People with a lack of endorphins may show signs of depression. This may be due to a lack of dopamine.

- https://my.clevelandclinic.org/health/body/23040-endorphins

Nutri Link
Linking Science and Nutrition

Disturbed amino acid metabolism and neurotransmitter synthesis in patients with LC and ME/CFS

Disturbed amino acid metabolism and neurotransmitter synthesis in patients with LC and ME/CFS

Nutri Link
Linking Science and Nutrition

- Around 10% of people who had COVID-9 infection suffer from persistent symptoms such as fatigue, dyspnoea, chest pain, arthralgia/myalgia, sleep disturbances, cognitive dysfunction and impairment of mental health. Different underlying pathomechanisms appear to be involved, in particular inflammation, alterations in amino acid metabolism, autonomic dysfunction and gut dysbiosis.
- As routine tests are often inconspicuous in patients with Long COVID (LC), similarly to patients suffering from myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), accessible biomarkers indicating dysregulation of specific pathways are urgently needed to identify underlying pathomechanisms and enable personalised medicine treatment. Within this pilot study we aimed to proof traceability of altered metabolism by urine analysis.

- Taenzer M, Löffler-Ragg J, Schroll A, Monfort-Lanzas P, Engl S, Weiss G, Brigo N, Kurz K. Urine Metabolite Analysis to Identify Pathomechanisms of Long COVID: A Pilot Study. Int J Tryptophan Res. 2023 Dec 22;16:11786469231220781. Full Paper

- Medical University of Innsbruck, Innsbruck, Austria.

Disturbed amino acid metabolism and neurotransmitter synthesis in patients with LC and ME/CFS

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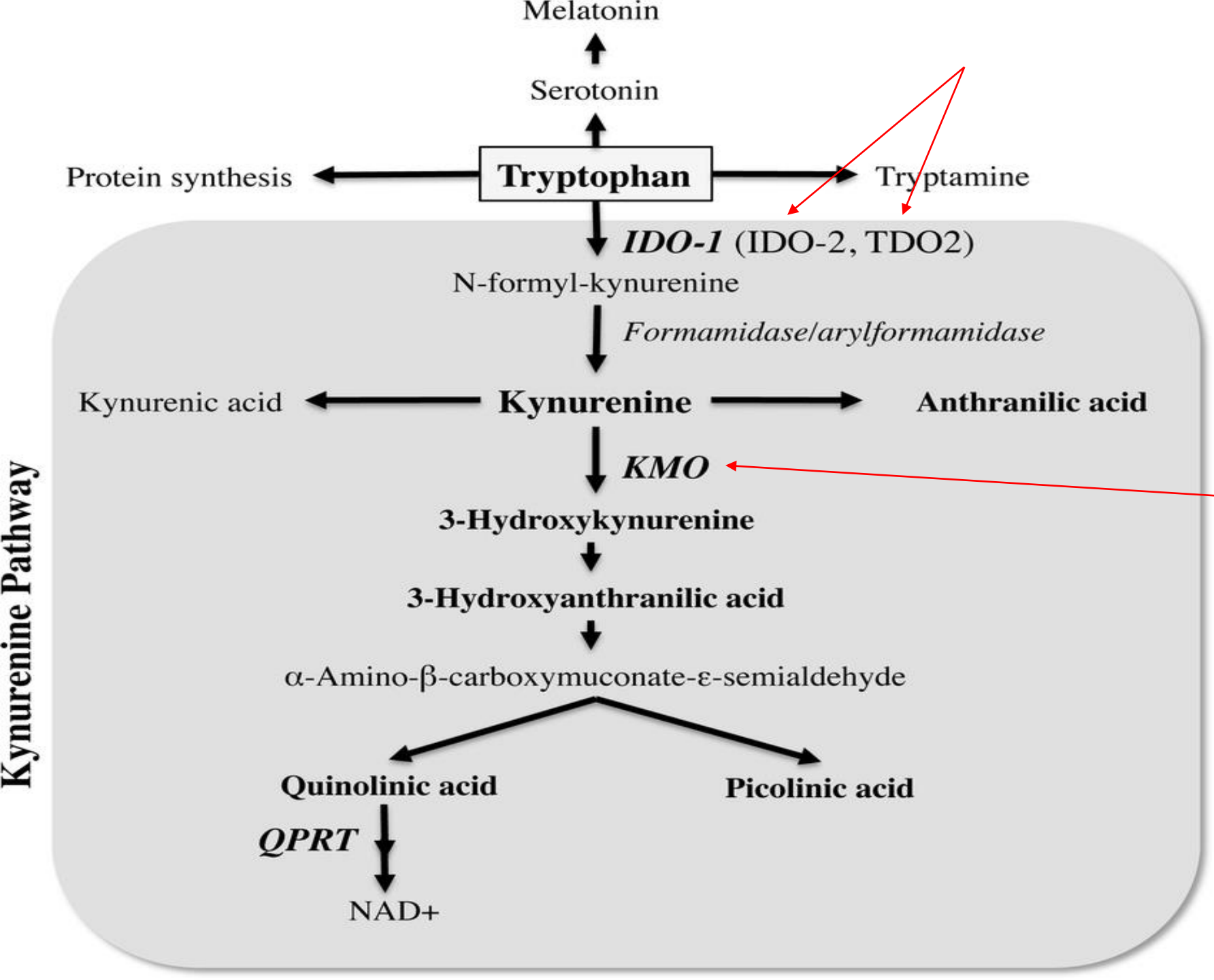
- Urine metabolome analyses were performed to investigate the metabolic signature of patients with LC (n = 25; 20 women, 5 men) in comparison to healthy controls (Ctrl, n = 8; 7 women, 1 man) and individuals with ME/CFS (n = 8; 2 women, 6 men).
- Concentrations of neurotransmitter precursors tryptophan, phenylalanine and their downstream metabolites, as well as their association with symptoms (fatigue, anxiety and depression) in the patients were examined.

- Taenzer et al. Urine Metabolite Analysis to Identify Pathomechanisms of Long COVID: A Pilot Study. Int J Tryptophan Res. 2023 Dec 22;16:11786469231220781. Full Paper

Disturbed amino acid metabolism and neurotransmitter synthesis in patients with LC and ME/CFS

- Results and Conclusion (i)
- Phenylalanine levels were significantly lower in both the Long Covid and ME/CFS patient groups when compared to the Ctrl group.
- In many Long Covid patients, the concentrations of downstream metabolites of tryptophan and tyrosine, such as serotonin, dopamine and catecholamines, deviated from the reference ranges.
- Several symptoms (sleep disturbance, pain or autonomic dysfunction) were associated with certain metabolites. Patients experiencing fatigue had lower levels of kynurenine, phenylalanine and a reduced kynurenine to tryptophan ratio (Kyn/Trp).

- Taenzer et al. Urine Metabolite Analysis to Identify Pathomechanisms of Long COVID: A Pilot Study. Int J Tryptophan Res. 2023 Dec 22;16:11786469231220781. Full Paper



Tryptophan Metabolism

Disturbed amino acid metabolism and neurotransmitter synthesis in patients with LC and ME/CFS

Nutri Link
Linking Science and Nutrition

- Results and Conclusion (ii)
- Lower concentrations of gamma-aminobutyric acid (GABA) and higher activity of kynurenine 3-monooxygenase (KMO) were observed in patients with anxiety.
- Conclusively, our results suggest that amino acid metabolism and neurotransmitter synthesis is disturbed in patients with LC and ME/CFS.
- The identified metabolites and their associated dysregulations could serve as potential biomarkers for elucidating underlying pathomechanisms thus enabling personalised treatment strategies for these patient populations.

- Taenzer et al. Urine Metabolite Analysis to Identify Pathomechanisms of Long COVID: A Pilot Study. Int J Tryptophan Res. 2023 Dec 22;16:11786469231220781. Full Paper

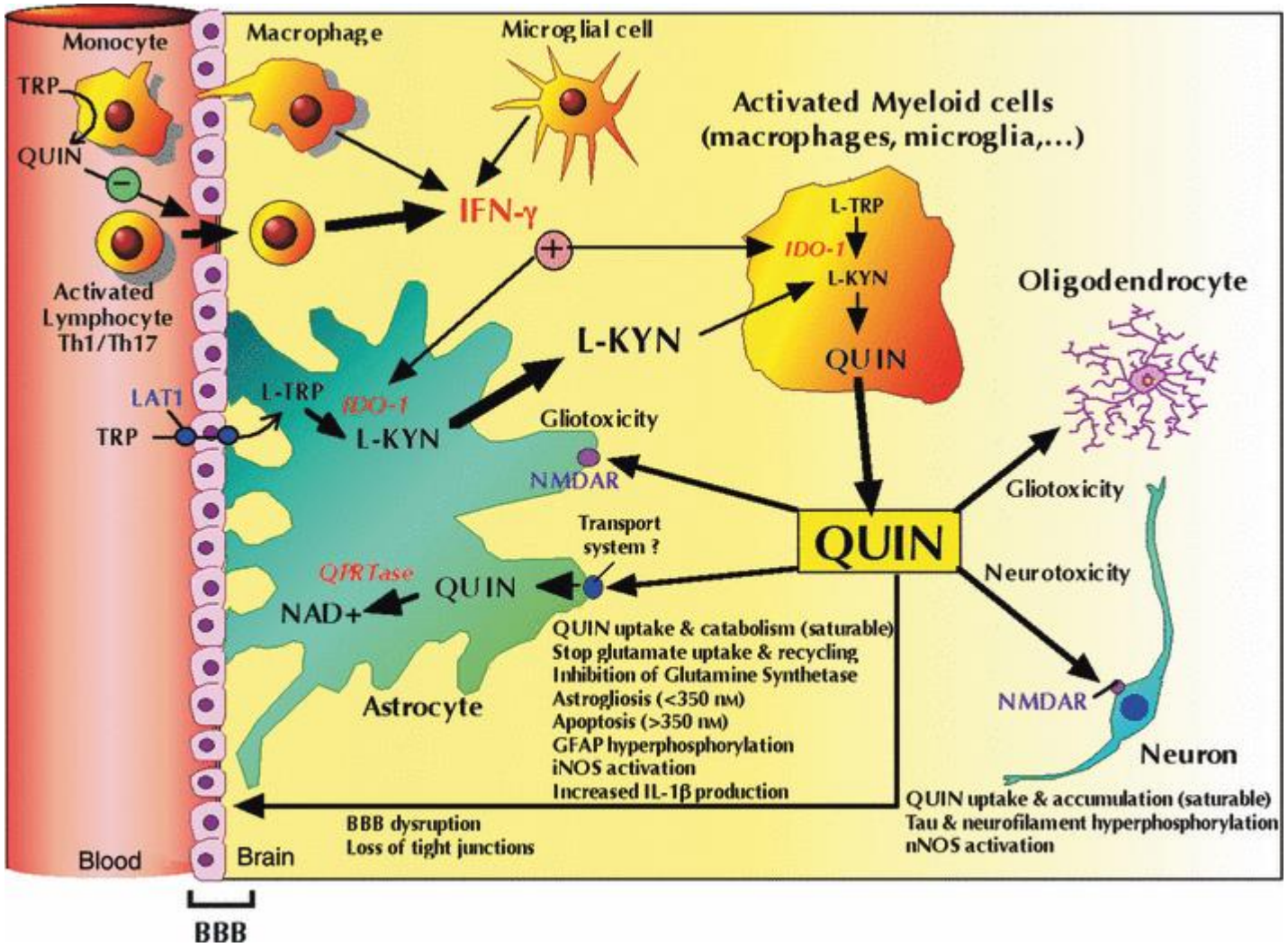
Quinolinic Acid – “the inescapable neurotoxin”

- Quinolinic acid acts as a neurotoxin, gliotoxin, proinflammatory mediator, pro-oxidant molecule and can alter the integrity and cohesion of the blood-brain barrier.
- Interferon-γ (IFN-γ) and to a lesser extent IFN-β, IFN-α, tumour necrosis factor α (TNF-α), platelet activating factor, cytotoxic T-lymphocyte antigen 4, HIV-1 proteins Nef and Tat and amyloid beta peptide 1–42 can lead to upregulation of the cellular expression of IDO-1 with consequent increased production of quinolinic acid.

- Guillemin GJ. Quinolinic acid, the inescapable neurotoxin. FEBS J. 2012 Apr;279(8):1356-65. Full Paper

Quinolinic Acid – “the inescapable neurotoxin”

- During neuroinflammation QUIN production is one of the early and key events involved in the deleterious pathophysiological cascade within the CNS.
- QUIN disrupts normal glutamatergic neurotransmission within the brain by disrupting the function of, or killing, NMDAR-expressing target neurons.
- QUIN also activates and/or kills astrocytes and this amplifies the inflammatory response in the brain.



Summary of the neurotoxic mechanisms involving QUIN

Guillemin GJ. Quinolinic acid, the inescapable neurotoxin. FEBS J. 2012 Apr;279(8):1356-65. Full Paper

Nutritional Solutions vs Disturbed Amino Acids in Long Covid

Nutri Link
Linking Science and Nutrition

- Phenylalanine 500mg (Lamberts) – 1-2 mid morning, optionally late afternoon (empty stomach)
- L-Phenylalanine 500mg 60's: The Natural Dispensary

- Neuro-5-HTP Plus (BR) – 1 caps mid morning, 1 caps late afternoon (empty stomach)
- Neuro-5-HTP Plus x 90 Capsules | Nutri-Link.co.uk (nutrilink.co.uk)

- Seratonin (AR) – 1-2 caps with dinner or 30 mins before bed
- Seratonin x 90 Capsules | Nutri-Link.co.uk (nutrilink.co.uk)

Nutri Link
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Nigella sativa (Black Cumin) may be protective vs the nucleoprotein N of SARS-CoV-2

Black Cumin vs nucleoprotein N of SARS-CoV-2

- Nigella sativa (Black Cumin), belonging to family Ranunculaceae, is commonly known as black seed or black cumin. In historical and religious texts, N. sativa is known as a miracle curative herb for all ailments, except death (Yimer et al., 2019).
- The seeds and oil of N. sativa contain terpenoids, flavonoids, phenolics, alkaloids, saturated and unsaturated fatty acids (Forouzanfar et al., 2014; Menounos et al., 1986; Yarnell & Abascal, 2011).

- Forouzanfar F, Bazzaz BS, Hosseinzadeh H. Black cumin (Nigella sativa) and its constituent (thymoquinone): a review on antimicrobial effects. Iran J Basic Med Sci. 2014 Dec;17(12):929-38. Full Paper
- Menounos, P., Staphylakis, K., & Gegiou, D. (1986, Jan). The sterols of Nigella sativa seed oil. Phytochemistry, 25(3), 761–763. View Abstract
- Siddiqui S et al. Virtual screening of phytoconstituents from miracle herb nigella sativa targeting nucleocapsid protein and papain-like protease of SARS-CoV-2 for COVID-19 treatment. J Biomol Struct Dyn. 2022 Jun;40(9):3928-3948. Full Paper
- Yarnell, E., & Abascal, K. (2011, Apr). Nigella sativa: Holy herb of the middle East. Alternative and Complementary Therapies, 17(2), 99–105. View Abstract
- Yimer EM, Tuem KB, Karim A, Ur-Rehman N, Anwar F. Nigella sativa L. (Black Cumin): A Promising Natural Remedy for Wide Range of Illnesses. Evid Based Complement Alternat Med. 2019 May 12;2019:1528635. Full Paper

Black Cumin vs nucleoprotein N of SARS-CoV-2

- Siddiqui et al's study (2022) was designed to check the antiviral efficacy of N. sativa main phytoconstituents against five potential targets of SARS-CoV-2.
- Out of 25 phytocomponents, 10 showed best binding affinity against two viral proteins: N-terminal RNA binding domain (NRBD; PDB ID: 6M3M) of nucleocapsid protein and papain-like protease (PL-PRO; PDB ID: 6W9C) of SARS-CoV-2.
- Siddiqui et al's study (2022) are further supported by the previously reported antiviral efficacies of a class of terpenoids and flavonoids (Ghildiyal et al., 2020; Naithani et al., 2010; Yang et al., 2020).

- Ghildiyal, R., Prakash, V., Chaudhary, V. K., Gupta, V., & Gabrani, R. (2020). Phytochemicals as Antiviral Agents: Recent Updates. InPlant-derived Bioactives. (pp. 279–295). Springer. Web-Link
- Naithani, R., Mehta, R. G., Shukla, D., Chandersekera, S. N., & Moriarty, R. M. (2010). Antiviral activity of phytochemicals: A current perspective. In Dietary Components and Immune Function. (pp. 421–468). Humana Press. Web-Link
- Siddiqui S et al. Virtual screening of phytoconstituents from miracle herb nigella sativa targeting nucleocapsid protein and papain-like protease of SARS-CoV-2 for COVID-19 treatment. J Biomol Struct Dyn. 2022 Jun;40(9):3928-3948. Full Paper
- Yang, W., Chen, X., Li, Y., Guo, S., Wang, Z., & Yu, X. (2020, Mar). Advances in Pharmacological Activities of Terpenoids. Natural Product Communications, 15(3), 1934578X2090355. View Abstract

Ten bioactive components from Black Cumin that bind two viral proteins of SARS-CoV-2

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Phytocomponent	Chemical Class of Ligand	Source
24-methylene- cycloartenol	Pentacyclic triterpenoid	Seed oil
Alpha-spinasterol	Steroid	Seed / seed oil
Beta-amyrin	Pentacyclic triterpenoid	Seed oil
Beta-sitosterol	Phytosterol	Seed oil
Campesterol	Phytosterols	Seed / seed oil
Citrostadienol	Sterol	Seed oil
Cycloartenol	Pentacyclic triterpenoid	Seed oil
Cycloeucalenol	Pentacyclic triterpenoid	Seed oil
Taraxerol	Pentacyclic triterpenoid	Seed oil
Tirucallol	Tetracyclic triterpene	Seed oil

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Nutritional Solutions Summary

Nutritional Solutions - Summary

- Nutritional Solutions vs Disturbed Amino Acids in Long Covid
- Protection vs the nucleoprotein N of SARS-CoV-2
- Supplements vs Viral Persistence
- Anti-Spike protein Supplements
- Natural Anti-Viral & Anti-Inflammatory Supplements

Nutritional Solutions vs Disturbed Amino Acids in Long Covid

- **Phenylalanine 500mg** (Lamberts) – 1-2 mid morning, optionally late afternoon (empty stomach)
- L-Phenylalanine 500mg 60's: The Natural Dispensary

- **Neuro-5-HTP Plus** (BR) – 1 caps mid morning, 1 caps late afternoon (empty stomach)
- Neuro-5-HTP Plus x 90 Capsules | Nutri-Link.co.uk (nutrilink.co.uk)

- **Seratonin** (AR) – 1-2 caps with dinner or 30 mins before bed
- Seratonin x 90 Capsules | Nutri-Link.co.uk (nutrilink.co.uk)

Anti-Inflammatory

- **KappArest** (BR) – 2-3 caps with two or three meals
- KappArest x 180 Capsules | Nutri-Link.co.uk (nutrilink.co.uk)

Supplements vs Viral Persistence (helping to resolve amino acid disturbance)

Nutri Link
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- Perm A Vite (AR) - 1 tablespoon in liquid 10 mins before two to three meals
- Laktoferrin with Colostrum (AR) - 3-4 caps at night
- Bromelain Plus (BR) - 5 tabs on empty stomach once or twice daily (biofilm buster)
- NAC (BR) & (AR) – 1 on empty stomach twice daily (anti-viral, biofilm buster)
- Humic Monolaurin Complex (AR) – 2 with breakfast & dinner

Spike Protein Breakdown & Protection from N protein

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- Nattokinase 50mg (1,000 FU) (AR) – 2 caps twice daily on empty stomach (8+ hours apart)(or higher dose)
- Bromelain Plus (BR) – 5 tabs on empty stomach once a day
- CurcuWIN 500 (AR) – 1 with breakfast & 1 with dinner
- Augmented NAC – 1 before breakfast & dinner by 20-15 mins
- Black Cumin (New Roots) – 2 caps with breakfast & 2 caps with dinner

Natural Anti-Viral, Anti-Inflammatory Supplements

- Humic Acid Cell Membrane Active (AR) - Humic Acid x 60 Capsules | Nutri-Link (nutrilink.co.uk) – 1 with breakfast & dinner

or

- Humic Monolaurin Complex (AR) - Humic Monolaurin x 120 Capsules | Nutri-Link (nutrilink.co.uk) – 2 with breakfast & dinner
- Aqueous Selenium (BR) – Aqueous Selenium x 15ml | Nutri-Link.co.uk (nutrilink.co.uk) = 1 drop with two or three meals
- NAC (BR) & (AR) – 1 on empty stomach twice daily (supports Th1 immune response)
- Ashwagandha Complex (AR) (incl licorice) – 2 with breakfast & 1-2 with lunch - Ashwaganda Complex x 60 Capsules | Nutri-Link.co.uk (nutrilink.co.uk)

Anti-Inflammatory

- KappArest (BR) – 2-3 caps with two or three meals
- KappArest x 180 Capsules | Nutri-Link.co.uk (nutrilink.co.uk)

Vital Addition

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Magnesium Powder (AR)

- 3 forms of magnesium:
- glyinate, malate, taurate

Vital for:

- Energy
- Immune energy
- Countering inflammation

THE END

TIME FOR QUESTIONS & COMMENTS

6. Monday 14th October 12 noon
Spike protein pathogenesis. Nutritional Therapy solutions. Review and summary and presentation of Model of Long Covid including lab tests and potential therapeutic interventions.