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Antioxidants and Long Covid

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Abstract

Long Covid has many symptoms that overlap with ME (myalgic encephalomyelitis)/CFS (chronic fatigue syndrome), FM (fibromyalgia), EBV (Epstein-Barr virus), CMV (cytomegalovirus), CIRS (chronic inflammatory response syndrome), MCAS (mast cell activation syndrome), POTS (postural orthostatic tachycardia syndrome), and post viral fatigue syndrome. They all portend a "long haul" with an antioxidant shortfall and elevated Ca:Mg. Oxidative stress is the root cause. Linkage between TGF (transforming growth factor)-β, IFN (interferon)-γ, the RAS (renin angiotensin system), and the KKS (kallikrein kinin system) is discussed. Technical explanations for the renin aldosterone paradox in POTS, the betrayal of TGF-β, and the commonality of markers for the Warburg effect are offered. The etiology of the common Long Covid symptoms of post exertional malaise, fatigue, and brain fog as well as anosmia, hair loss, and GI symptoms is technically discussed. Ca:Mg is critical to the glutamate/GABA balance. The role of GABA and butyrates from the "good" intestinal bacteria in the gut-brain axis and its correlation with chronic fatigue diseases are explored. The crosstalk between the ENS (enteric nervous system) and the ANS (autonomic nervous system) and the role of the vagus in both are emphasized. HRV (heart rate variability), the fifth vital sign, points to an expanded gut-brain-heart/lung axis. A suggested approach to all of these—Long Covid, chronic fatigue diseases, post viral fatigue syndrome, and general health—is presented.

Subject Areas

Pathology

Keywords

Warburg Effect, Oxidative Stress, Magnesuria, Inflammasome, Butyrate

1. Introduction

Nobel laureate and anti Nazi Otto Warburg first presented his Warburg hypo-

thesis in 1924. He believed that cancer should be interpreted as mitochondrial dysfunction. Mitochondria are the energy factories of the cell and their currency is ATP. Optimal mitochondrial function is at the heart of health. This same cancer related mitochondrial dysfunction also arises in a setting of chronic inflammation and oxidative stress. Antioxidants are protective, but under such conditions their consumption is accelerated. Oxygen is a very toxic element, due to the susceptibility of O_2 to form the superoxide radical $\cdot O_2^- \cdot O_2^-$, which along with its partners, hydrogen peroxide H_2O_2 and the hydroxyl radical OH constitute reactive oxygen species (ROS). These can also create reactive nitrogen species (RNS), e.g., peroxynitrite $ONOO^-$.

Pathogens and chronic exposure to biotoxins (CIRS) that elicit chronic inflammation can also produce cellular hypoxia and a Warburg suitable microenvironment for the Warburg effect (mitochondrial dysfunction) [1]. Elevated TGF-β and lactate [2], encountered in Long Covid and the two greatest scourges of mankind, tuberculosis [3] [4] and malaria [5] [6], trigger this phenomenon.

2. Discussion

2.1. Oxidative Stress

The function of antioxidants is to reduce these oxidizing agents (oxidants), which can fatally overwhelm cellular defenses. Oxidative stress develops when oxidants outnumber antioxidants. Cellular hypoxia can develop due to inflammation and ROS production at the gas blood interchange (lungs), during delivery (erythrocytes and endothelial cells), or within the mitochondrion itself. During the latter, intracellular oxidant levels can quickly increase and overcome the onboard antioxidants, which may have been at marginal levels.

This creates the hypoxic microenvironment. ROS are primarily produced in mitochondria where the energy of oxygen is transformed into ATP. These oxidizing agents, if not reduced, are very toxic to cells and threaten their destruction. In order to avoid this, cells shut down their mitochondria, the source of the ROS, to survive. The glycolytic pathway from glucose to pyruvate normally proceeds to the Krebs cycle for oxidative phosphorylation and ATP production within mitochondria. Instead pyruvate proceeds to lactate only. ATP production goes from 38 to 2 ATPs per glucose. Mitochondria are especially dense in muscle cells (skeletal, cardiac, smooth). Fatigue becomes unavoidable. Brain oxygen consumption represents 20% of the total. So, eventually some degree of cognitive compromise is inevitable.

The resulting hypoxia and increased lactic acid trigger release of TGF-β, the primary cytokine of the Warburg effect. This cytokine is elevated in CFS and many other chronic fatigue diseases. TGF-β and IFN-γ counterbalance and suppress each other. IFN-γ possesses C1 (complement component 1 of the CCP) inhibiting properties [7] [8].

With the increase in TGF-β and the suppression of IFN-γ there is increased classic complement pathway (CCP) activity with cross talk to the KKS. There is

no KKS crosstalk with either the alternative complement pathway or the lectin complement pathway [9]. BKN (bradykinin) is the principal hormone of the KKS as angiotensin II is the principal hormone of the RAS. Estrogen down-regulates ACE, which degrades BKN. The subsequent angioedema appears to create the brain fog, post exertional malaise, and fatigue of Long Covid and its cousins.

The interface between insufficient magnesium and elevation of TGF-β in Long Covid begins with cellular hypoxia. Long Covid afflicts a younger age group, predominantly female, the opposite of the Covid-19 group. Perhaps more of the elderly males with Covid-19 died, affecting the gender and age breakdown for Long Covid. Perhaps it is due to decreased magnesium intake, more prevalent in females under 50, especially teens, and males over 50 (see **Figure 1**).

Or perhaps the hypoxia/lactate induced up regulation of TGF-β and consequent suppression of IFN-γ is the explanation? These last two are interrelated. If magnesium is insufficient, then the low grade inflammatory state has given TGF-β the upper hand over IFN-γ.

Magnesium, as will be shown, is critical to the production of antioxidants.

2.2. Antioxidants

The primary problem for these chronic fatigue diseases appears to be a shortage of antioxidants aka mitochondrial optimizers or enhancers. Their inability to quench the increased ROS generated during a respiratory viral infection leads to oxidative stress and pressure on mitochondria.

Most endogenous antioxidants require methylation and SAMe (S-adenosylmethionine) is the universal methyl donor. Magnesium is not only a required cofactor but also an ATP chelate for all SAMe methylations, which occur in the mitochondria [11] [12].

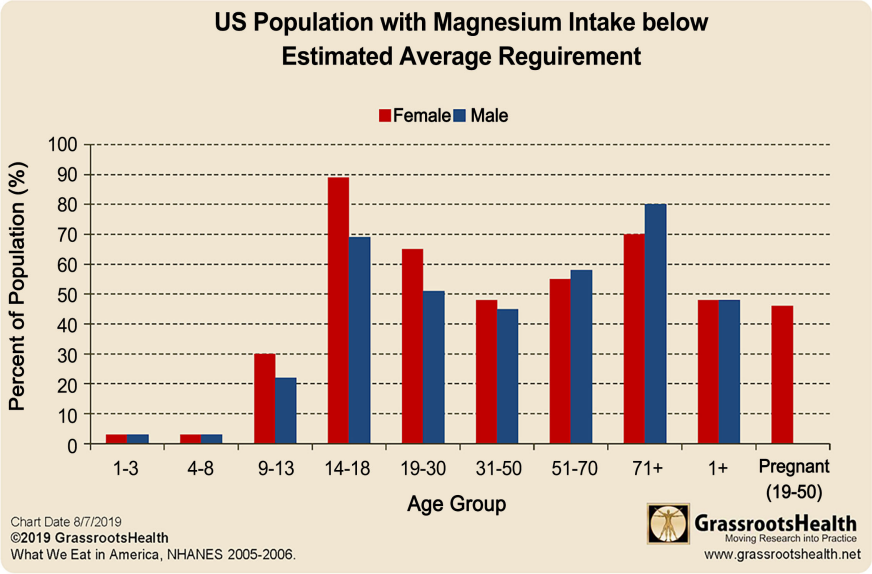

Figure 1. Magnesium deficiency is accentuated in females less than 50 and males over 50 [10].

Glutathione, the master antioxidant, requires SAMe, but does not cross the blood brain barrier. Each molecule of glutathione can be regenerated from several sources, e.g., alpha lipoic acid, cysteine, NAC, …, but several ATPs are required for each pathway to glutathione synthesis. The currency of regeneration is in short supply under oxidative stress conditions.

Many antioxidants have been recommended for ME/CFS [13] [14] [15] [16], FM [13] [14] [17], and EBV [18]. Most of these are otherwise endogenously produced, but require methylation to attain active status. Those requiring methylation include melatonin, betaine, choline, cysteine, taurine, CoQ10, carnitine, creatine, creatinine, and lysine. Figures of the biochemical pathways for many of these are available online [19]. Others require just multiple ATPs, e.g., NADH, tryptophan. Unfortunately direct SAMe supplementation has recently been shown to be counterproductive [20].

Vitamins B3,9 (folate), 12 require methylations (Mg^{2+} as cofactor and ATP chelate) to attain active status. Vitamins B1,2,6 require phosphorylations (Mg^{2+} chelated to ATP) to attain this. In short, magnesium is critical to the synthesis of all endogenous antioxidants.

However, some exogenous antioxidants have been suggested—D-ribose [21], zinc, quercetin, curcumin, resveratrol, selenium, zinc, vitamin C, all fat soluble vitamins (A, D, E, K), cannabinoids [22]. D-Ribose—can create one ATP thru pentose phosphate shunt. One study suggested sodium as a nutritional supplement for CFS [23]. Although not an antioxidant, this speaks to the likelihood of some degree of chronic dehydration in many with CFS [24]. Sweat generates much more sodium loss than that of magnesium, but renal resorption of water can cause magnesuria.

This critical role for magnesium is inextricably entwined with serum Ca:Mg. The Western diet has seen this ratio escalate from 2.3 - 2.9 in 1977 to 2.9 - 3.5 in 2007 [25] with a rise in magnesium deficiency.

2.3. POTS Paradox, Hypocortisolism, and Histamine

An elevated Ca:Mg and background oxidative stress may be responsible for the dysautonomic symptoms of POTS and the renin aldosterone paradox (low renin and aldosterone in the face of hypovolemia). Those with Long Covid and those with CFS have lower levels of cortisol [26] [27], and those with POTS [28] in addition have inappropriately low aldosterone and renin in the face of hypovolemia. Aldosterone, corticosterone, and cortisol synthesis occur in mitochondria and all require 11-beta hydroxylase (see **Figure 2**), *i.e.*, ATP and magnesium are essential. Magnesium deficiency not only retards intramitochondrial aldosterone synthase but also increases Ca:Mg and the baroreflex blood pressure threshold ≥ orthostatic hypotension [29].

In addition Mg^{2+} is cofactor for adenyl/guanyl cyclase and chelate for the substrate ATP/GTP in the synthesis of "second messengers" cAMP and cGMP. Endothelial cGMP and NO (nitric oxide) trigger renin secretion [30] [31] [32].

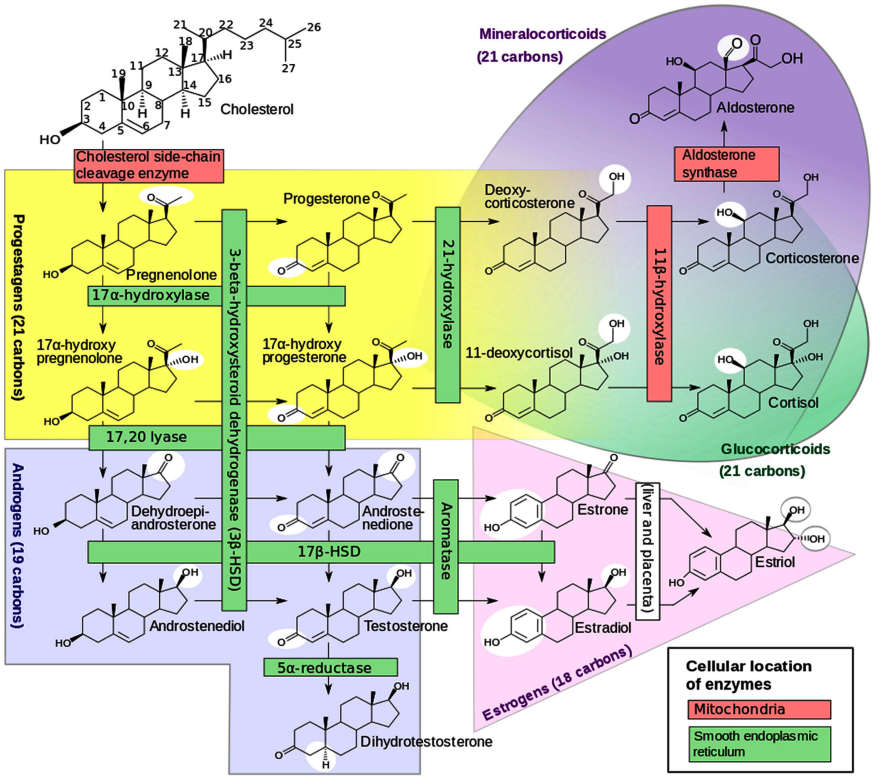

Figure 2. Aldosterone and cortisol require enzymes that are located in the mitochondria and require magnesium as cofactors [33].

The histamine overload in MCAS and some forms of Long Covid may be due to an inability to degrade it. The primary degradation pathway for histamine requires SAMe, Mg^{2+}, and ATP. Some Covid long haulers find relief with anti-histamines [34].

2.4. TGF-β

TGF-β is initially anti-inflammatory. If the oxidative stress persists and IL-6 is added, TGF-β can switch from anti inflammatory to pro-inflammatory [35].

It can also switch from protecting against cancer to promoting it. The mechanism behind these switches is not clear. One possibility is the TGFBR (TGF-β receptor), of which there are three types. Type one and type two require kinases for activation. All kinase reactions (phosphorylations) require magnesium as an ATP chelate. TGFBR3 does not [36]. TGFBR3 also portends a much poorer prognosis than the other two [37] and is associated with Alzheimer's disease [38].

TGF-β is the master cytokine in the etiology of most chronic fatigue diseases, including Long Covid [39], CFS [40] [41] [42], EBV [43], CMV [44], CIRS (biotoxins from chronic mold exposure and chronic Lyme disease) [45].

TGF-β is elevated in Alzheimer's disease [46] and Alzheimer's disease progression is accelerated post Covid-19 [47] [48] and in EBV [49], CIRS [50], FM [51], and CMV [52].

2.5. TGF-β Channels and Inflammasomes

2.5.1. TRPM2 v TRPM5,7

The TGF-β connection between Long Covid and its chronic disease cousins has been demonstrated. An additional Alzheimer's disease connection has also been demonstrated. ROS and TRPMs (transient receptor potential melastatin) are integral to neurodegenerative diseases [53] [54] and the mechanism appears to involve a Ca:Mg imbalance in the Warburg microenvironment (mitochondrial dysfunction). TRPM channels mediate intracellular calcium and magnesium balance. TRPM2 is the calcium channel [55] and TRPM5,7 are the magnesium channels [56].

ROS induce TRPM2 activation in endothelial cells [55]. Increased extracellular Ca:Mg and ROS facilitate TRPM2 activation, which promotes increased intracellular Ca^{2+} and a positive feedback loop with additional input from TRPM2 (see **Figure 3**) [55] [57]. Increased extracellular Mg^{2+} reverses the TRPM2 dominance over TRPM5,7 and reduces Ca^{2+} signaling in endothelial cells [58]. TRPM2 channels also contribute to the pathogenesis of inflammatory bowel disease [59]. A TRPM2 facilitated increase in intracellular Ca^{2+} leads to an assault on mitochondria via the permeability transition pore (see **Figure 4**) [60] [61].

2.5.2. NLRP3 Inflammasome

TGF-β and the NLRP3 (NACHT, LRR and PYD protein 3) inflammasome are connected [62] and both of these are associated with the Warburg effect [63]. The inflammasome is vital to the pathogenesis of ME/CFS [64], FM, Alzheimer's [65], IBD [66] [67], autoimmune disease [68] [69], EBV [70] and Long Covid [71]. The Ca:Mg imbalance is at the root of all these diseases and magnesium therapy reverses the imbalance via CaSRs and TRPM5,7. The CaSR regulates the NLRP3 inflammasome [72] and can be downregulated by increasing Mg^{2+} [73] [74] [75]. Calcium-sensing receptor (CaSR) activates the NLRP3 inflammasome, mediated by increased intracellular Ca^{2+} and decreased cellular cyclic AMP (cAMP).

2.6. GABA

Glutamate is synthesized primarily from TCA cycle substrates. GABA (gamma amino butyric acid) is synthesized directly from glutamate and requires cofactors P5P (pyridoxal-5-phosphate) and Mg^{2+} (see **Figure 5**). Beta and gamma isomers of hydroxybutyrate (butyrate from "good" intestinal bacteria) can replace glutamate [76] [77] in the synthesis of GABA. The ketone body butyrate is hydroxylated in the liver to produce the isomers beta and gamma hydroxybutyrate. GABA cannot normally pass the blood brain barrier, but GHBA and BHBA can. Glutamatergic neurons release glutamate and primarily employ NMDA (N-methyl-D-aspartate) receptors.

Mg^{2+} can bind to both NMDA receptors (see **Figure 6**) [79] and GABA receptor sites [80]. In addition P5P is a required cofactor for GAD (glutamic acid decarboxylase) and GABA synthesis (see **Figure 5**). GABA plays the lead role in

the gut-brain axis and probably determines the anosmia/ageusia, headaches, and depression of Long Covid. Post Covid anosmia/ageusia are thrice as likely in Caucasians versus Asians [81]. Asians tend to exhibit lower serum Ca:Mg. Excitatory NMDA receptor activity reflects this (see **Figure 6**). Might this chemosensory dysfunction be excess glutamatergic tone [82] [83] and not some olfactory bulb related etiology? Anosmia/ageusia may be minor seizure symptoms [84] that would otherwise have been inhibited by functioning GABAergic neurons. Gabapentin, anticonvulsant and GABA analog, has been used to treat anosmia and ageusia. Hair loss is also associated with magnesium deficiency [85] and vitamin D deficiency. Decreased rbc deformability due to oxidation, documented in Long Covid (increased RDW or red cell distribution width), ME/CFS, FM, slows

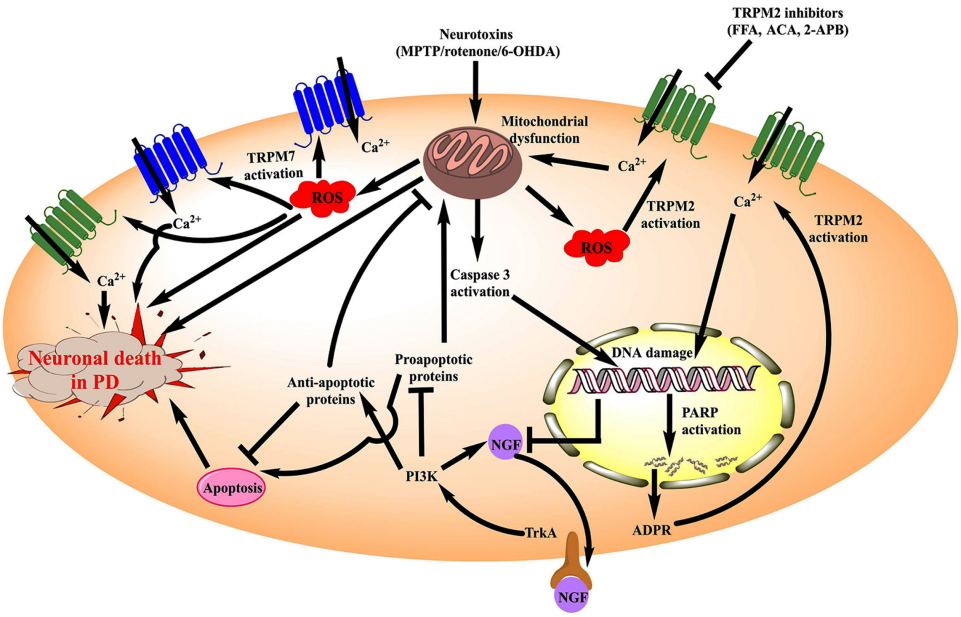

Figure 3. ROS facilitate dominance of TRPM2 and increase intracellular Ca^{2+} and mitochondrial dysfunction [53].

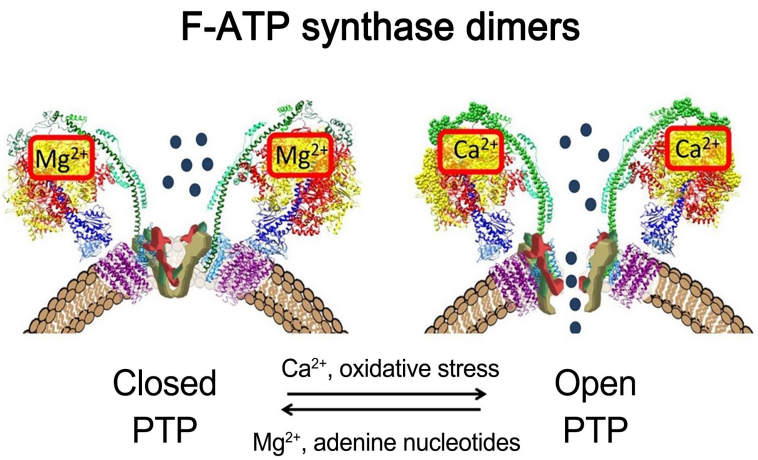

Figure 4. Ca^{2+} competes with PTP-inhibitory Mg^{2+} and is an essential permissive factor for PTP (permeability transition pore) opening [61].

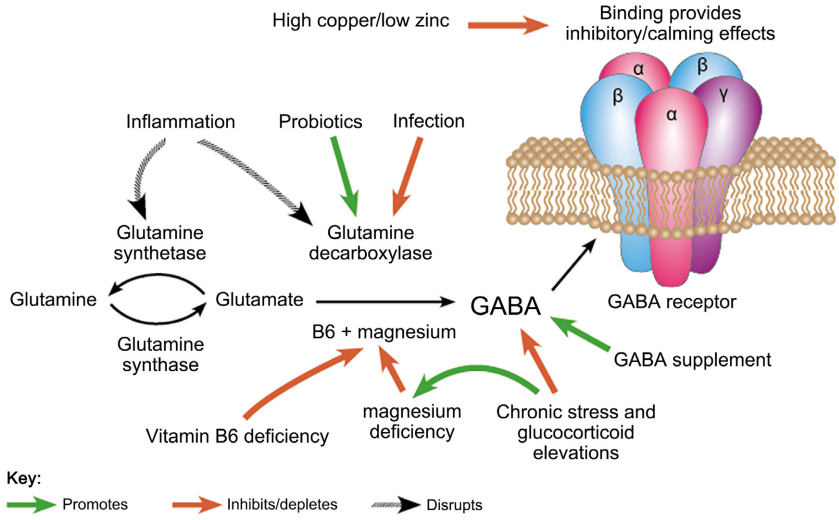

Figure 5. GABA enabling roles for B6, Mg^{2+}, GABA supplements (butyrates), and probiotics are shown [78].

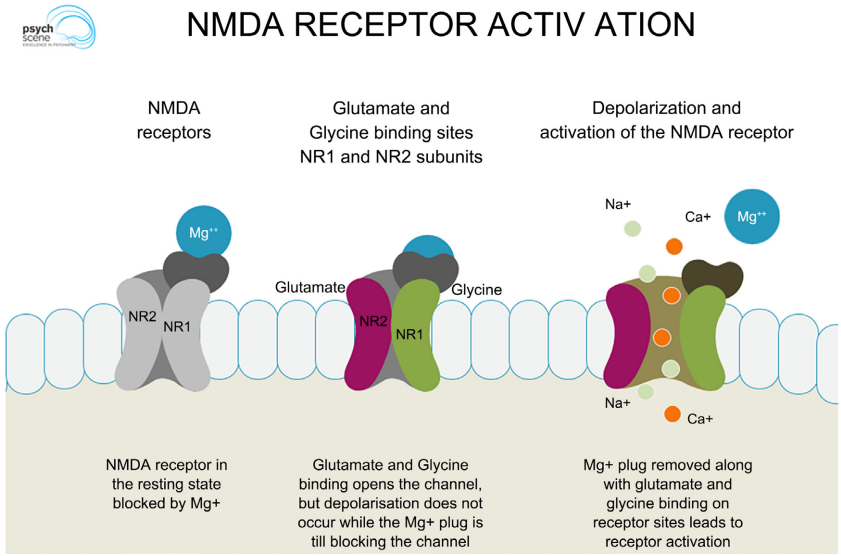

Figure 6. Glutamate favors NMDA receptors. The Mg^{2+} plug closes the Ca^{2+} channel. Its removal opens the channel [79].

microcirculation and enhances thrombogenesis (basigin binds spike S) [86].

Ca^{2+} and Mg^{2+} share the CaSR and when elevated, both tell the parathyroid glands to decrease PTH secretion. However, at low concentrations Mg^{2+} delivers the same message, to decrease PTH secretion [87], inappropriately suppressing synthesis of $1,25(OH)_2D$. Is Mg^{2+} triaged from cytoplasmic PTH synthesis to mitochondrial hydroxylations of D? Increasing magnesium intake without addressing the calcium overage may also elicit the laxative effect.

2.7. HRV and the Gut-Brain-Heart/Lung Axis

HRV is the fifth vital sign and, like serum CRP (C reactive protein), is an early warning indicator of some health issue. Many studies have demonstrated an in-

verse relationship between CRP and HRV [88]. Both can be excellent early indicators of deteriorating health, response to therapy, and prognosis on any behavioral, biologic, or epidemiological path [89]. They offer high sensitivity but low specificity. The list of such detectable problems is quite comprehensive, e.g., cardiovascular disease [88], Covid-19 [90], sudden cardiac death [91], seizures [92], Crohn's disease [93], ulcerative colitis [94], ME/CFS [95], depression [96].

HRV, a measure of vagal tone, is also inversely linked to Ca:Mg [97]. The vagus nerve or the wandering nerve is the longest in the body. It links the ENS with the ANS and, when dysfunctional, is responsible for such diverse health issues as lone atrial fibrillation, orthostatic hypotension, Prinzmetal angina, and dysphagia. Many of these have been reported in Long Covid and a strong connection between vagus nerve dysfunction implicated [98].

Most, if not all, of these vagal correlations are due to a Ca:Mg imbalance or a glutamate/GABA imbalance, e.g., lone atrial fibrillation [99] [100] [101]. Both imbalances are tightly linked and diet dependent. Intestinal "friendly" bacteria (Bifidobacterium pseudocatenulatum and Faecalibacterium prausnitzii) that produce butyrates are deficient in those with Long Covid [102], FM [103], and MS (multiple sclerosis) [104]. Glutamate producing intestinal bacteria are more numerous in ME/CFS (lactic acid bacteria and MSG (monosodium glutamate)) [105].

2.8. Diet

Increased daily intake of omega-3 polyunsaturated fatty acids (DHA and EPA) significantly increased the density of bacteria that are known to produce butyrate [106] [107]. Aged cheese (up to 25 Ca:Mg) can aggravate Long Covid. Exogenous antioxidants that don't require additional energy to activate might be helpful in an energy challenged host. Careful attention to hydration is highly advisable, especially in the active and in the elderly, as the thirst reflex diminishes with age. The 30:1 gradient is between intracellular K+ and that extracellular requires ATP and magnesium. If Mg^{2+} is low, then K^{+} is probably also low (lots of ectopic beats) [100].

The ketogenic diet, popular for weight loss, encourages dairy, but this increases Ca:Mg. The Mediterranean and Paleolithic diets, which encourage nuts and seeds (Mg^{2+} rich) and discourage dairy, might be better. But biologic individuality dictates an experimental approach.

2.9. Summary

In summary, Covid-19 severity is directly related to RAS activity. TGF-β, activated by angiotensin II type 1 receptors, is elevated in the elderly and those with comorbidities. Many of these never fully recover from the initial illness. Long Covid, characterized by symptoms such as brain fog, post exertional malaise, fatigue, anosmia, ageusia, headaches, hair loss, and many others [108], selects those with less RAS and more KKS. Magnesium, critical to the synthesis of endogenous antioxidants, is suboptimal. The virus that was at first asymptomatic or manifested few symptoms is not cleared (see **Figure 7**).

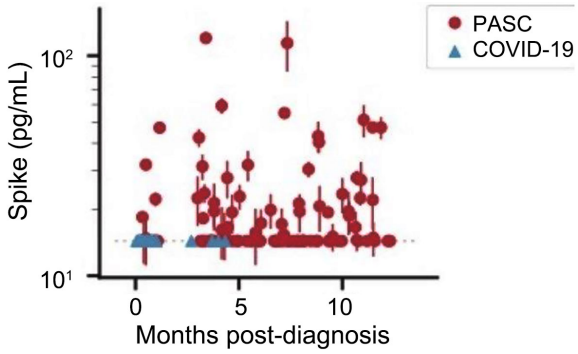

Figure 7. Spike protein S persistence in PASC (posts-acute sequelae of Covid-19) v primary SARS Cov 2 [109].

Inflammation smolders. A Warburg microenvironment (mitochondrial dysfunction) develops. TGF-β is elevated in both groups. The primary risk factor for any illness including cancer is immune function, and antioxidant sufficiency is critical in this. The ability to properly methylate protein is paramount to preventing chronic inflammation. The ability to properly methylate DNA is paramount to preventing cancer. Following a diet that maintains the Ca:Mg between 1.7 and 2.6, one that preserves the excitatory glutamate/inhibitory GABA balance, one that slows the sympathetic takeover of the ANS is highly advisable. Cultivate some intestinal "friendlies" that produce butyrates. The efficacy of vitamin D is maximized with such a diet. The hydroxylations required to produce the active form of vitamin D 1,25$(OH)_2$ cholecalciferol, from either sunlight or D3 occur in mitochondria and the full efficacy of vitamin D is not realized outside this Ca:Mg range.

3. Conclusions

Long Covid and ME/CFS, FM, EBV, CMV, POTS, MCAS, CIRS, and post viral fatigue syndrome are linked by antioxidant deficiency, elevated TGF-β, and the Warburg effect. "Friendly" butyrate producing intestinal bacteria are in short supply. Butyrates rectify the glutamate-GABA imbalance. These two neurotransmitters determine autonomic tone via the vagus nerve, which reflects general health through the fifth vital sign, HRV. Perhaps the gut-brain axis should be expanded to include two other vital organs under vagal control—the gut-brain-heart/lung axis.

The slowly increasing Ca:Mg in the Western diet incriminates magnesium deficiency as a central player in the pathogenesis of most chronic fatigue diseases. With age there is a steady progression from parasympathetic to sympathetic tone, from GABAergic to glutamatergic predominance, and from a balanced Ca:Mg to a calcium predominant one, at least on a Western diet.

Improving Ca:Mg starts with knowing what it is. A comprehensive chem panel including serum calcium and magnesium in an otherwise healthy individual without renal disease or medication should provide this information. The ionized states of calcium and magnesium are the active forms. iCa:iMg = 50% se-

rum Ca/70% serum Mg [110]. Addressing excess dietary calcium (Ca:Mg > 2.6) first and then slowly increasing magnesium intake might minimize any laxative effect. But for some, changing religion is easier than adjusting diet.

Conflicts of Interest

The author declares no conflicts of interest.

References

[1] Palsson-McDermott, E.M. and O'Neill, L.A.J. (2013) The Warburg Effect Then and Now: From Cancer to Inflammatory Diseases. *BioEssays*, **35**, 965-973. https://doi.org/10.1002/bies.201300084

[2] Pascale, R.M., Calvisi, D.F., Simile, M.M., Feo, C.F. and Feo, F. (2020) The Warburg Effect 97 Years after Its Discovery. *Cancers*, **12**, Article No. 2819. https://doi.org/10.3390/cancers12102819

[3] Kieran, D. and Basaraba, R.J. (2012) Lactate Metabolism and Signaling in Tuberculosis and Cancer: A Comparative Review. *Frontiers in Cellular and Infection Microbiology*, **11**, Article ID: 624607. https://doi.org/10.3389/fcimb.2021.624607

[4] Cumming, B.M., Pacl, H.T. and Steyn, A.J.C. (2020) Relevance of the Warburg Effect in Tuberculosis for Host-Directed Therapy. *Frontiers in Cellular and Infection Microbiology*, **10**, Article ID: 576596. https://doi.org/10.3389/fcimb.2020.576596

[5] de Jong, G.M., McCall, M.B.B., Dik, W.A., Urbanus, R.T., Wammes, L.J., *et al.* (2020) Transforming Growth Factor-Beta Profiles Correlate with Clinical Symptoms and Parameters of Haemostasis and Inflammation in a Controlled Human Malaria Infection, *Cytokine*, **125**, Article ID: 154838. https://doi.org/10.1016/j.cyto.2019.154838

[6] Possemiers, H., Vandermosten, L. and Van den Steen, P.E. (2021) Etiology of Lactic Acidosis in Malaria. *PLOS Pathogens*, **17**, e1009122. https://doi.org/10.1371/journal.ppat.1009122

[7] Lotz, M. and Zuraw, B.L. (1987) Interferon-γ Is a Major Regulator of C1-Inhibitor Synthesis by Human Blood Monocytes. *The Journal of Immunology*, **139**, 3382-3387. https://pubmed.ncbi.nlm.nih.gov/3119706/

[8] Zuraw, B.L. and Lotz, M. (1990) Regulation of the Hepatic Synthesis of C1 Inhibitor by the Hepatocyte Stimulating Factors Interleukin 6 and Interferon γ. *The Journal of Biological Chemistry*, **265**, 12664-12670. https://doi.org/10.1016/S0021-9258(19)38395-4

[9] Chambers, P.W. (2022) Long Covid, Short Magnesium. *Open Access Library Journal*, **9**, e8736. https://www.scirp.org/journal/paperinformation.aspx?paperid=117413

[10] Grassrootshealth Nutrient Research Institute (2020) Could a Lack of Magnesium be Worsening Your Ability to Handle Stress? https://www.grassrootshealth.net/blog/lack-magnesium-worsening-ability-handle-stress/

[11] Małecki, J.M., Davydova, E. and Falnes, P.O. (2022) Protein Methylation in Mitochondria. *Journal of Biological Chemistry*, **298**, Article ID: 101791. https://doi.org/10.1016/j.jbc.2022.101791

[12] Rhein, V.F., Carroll, J., He, J., Ding, S., Fearnley, I.M. and Walker, J.E. (2014) Human METTL20 Methylates Lysine Residues Adjacent to the Recognition Loop of the

Electron Transfer Flavoprotein in Mitochondria. *The Journal of Biological Chemistry*, **289**, 24640-24651. https://doi.org/10.1074/jbc.M114.580464

[13] Know, L. (2018) Mitochondria and the Future of Medicine: The Key to Understanding Disease, Chronic Illness, Aging, and Life Itself. Chelsea Green Publishing, Hartford.

[14] Porter, N.S., Jason, L.A., Boulton, A., Bothne, N. and Coleman, B. (2010) Alternative Medical Interventions Used in the Treatment and Management of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Fibromyalgia. *The Journal of Alternative and Complementary Medicine*, **16**, 235-249. https://doi.org/10.1089/acm.2008.0376

[15] Kim, S.H., Kim, H.J., Kim, S., Kang, J.S., Koo, Y.T., *et al.* (2022) A Comparative Study of Antifatigue Effects of Taurine and Vitamin C on Chronic Fatigue Syndrome *Pharmacology & Pharmacy*, **13**, 300-312. https://doi.org/10.4236/pp.2022.138023

[16] Bounous, G. and Molson, J. (1999) Competition for Glutathione Precursors between the Immune System and the Skeletal Muscle: Pathogenesis of Chronic Fatigue Syndrome. *Medical Hypotheses*, **53**, 347-349. https://doi.org/10.1054/mehy.1998.0780

[17] Alves, C.R.R., Santiago, B.M., Lima, F.R., Otaduy, M.C.G., Calich, A.L., *et al.* (2013) Creatine Supplementation in Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis Care & Research*, **65**, 1449-1459. https://doi.org/10.1002/acr.22020

[18] Dworzański, J., Strycharz-Dudziak, M., Kliszczewska, E., Kiełczykowska, M., Dworzańska, A., Drop, B., *et al.* (2020) Glutathione Peroxidase (GPx) and Superoxide Dismutase (SOD) Activity in Patients with Diabetes Mellitus Type 2 Infected with Epstein-Barr Virus. *PLOS ONE*, **15**, e0230374. https://doi.org/10.1371/journal.pone.0230374

[19] Miller, A.L., Kelly, G.S. and Tran, J. (1997) Homocysteine Metabolism: Nutritional Modulation and Impact on Health and Disease. https://musculoskeletalkey.com/homocysteine-metabolism-nutritional-modulation-and-impact-on-health-and-disease/

[20] Fukumoto, K., Ito, K., Saer, B., *et al.* (2022) Excess S-Adenosylmethionine Inhibits Methylation via Catabolism to Adenine. *Communications Biology*, **5**, Article No. 313. https://doi.org/10.1038/s42003-022-03280-5

[21] Mahoney, D.E., Hiebert, J.B., Thimmesch, A., Pierce, J.T., Vacek, J.L., *et al.* (2018) Understanding D-Ribose and Mitochondrial Function. *Advances in Bioscience and Clinical Medicine*, **6**, 1-5. https://doi.org/10.7575/aiac.abcmed.v.6n.1p.1

[22] Dawidowicz, A.J., Olszowy-Tomczyk, M. and Typek, R. (2021) Synergistic and Antagonistic Antioxidant Effects in the Binary Cannabinoids Mixtures. *Fitoterapia*, **153**, Article ID: 104992. https://doi.org/10.1016/j.fitote.2021.104992

[23] Bjørklund, G., Dadar, M., Pen, J.J., Chirumbolo, S. and Aaseth, J. (2019) Chronic Fatigue Syndrome (CFS): Suggestions for a Nutritional Treatment in the Therapeutic Approach. *Biomedicine & Pharmacotherapy*, **109**, 1000-1007. https://doi.org/10.1016/j.biopha.2018.10.076

[24] Stark, C.M., Nylund, C.M., Gorman, G.H. and Lechner, B.L. (2016) Primary Renal Magnesium Wasting: An Unusual Clinical Picture of Exercise-Induced Symptoms. *Physiological Reports*, **4**, e12773. https://doi.org/10.14814/phy2.12773

[25] Rosanoff, A. (2010) Rising Ca:Mg Intake Ratio from Food in USA Adults: A Concern? *Magnesium Research*, **23**, S181-S193. http://mgwater.com/Ca-Mg.pdf

[26] Klein, J., Wood, J., Jaycox, J., Lu, P. and Dhodapkar, R.M. (2022) Distinguishing Features of Long COVID Identified through Immune Profiling. MedRxiv 2022. 08.09.22278592. https://doi.org/10.1101/2022.08.09.22278592

[27] Phoenix Rising: A Community for People with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (2012) The Hypocortisolism in Chronic Fatigue Syndrome (ME/CFS)—Artifact or Central Factor? https://phoenixrising.me/myalgic-encephalomyelitis-chronic-fatigue-syndrome-mecfs-research/pharmacogenomics/the-hypocortisolism-in-chronic-fatigue-syndrome-mecfs-artifact-or-central-factor/

[28] Hoad, A., Spickett, G., Elliott, J. and Newton, J. (2008) Postural Orthostatic Tachycardia Syndrome Is an Under-Recognized Condition in Chronic Fatigue Syndrome. QJM: *An International Journal of Medicine*, **101**, 961-965. https://doi.org/10.1093/qjmed/hcn123

[29] Kinsey, D.L. (1979) Calcium and Magnesium Sensitivity of the Carotid Baroreceptor Reflex in Cats. *Circulation Research*, **45**, 815-821. https://doi.org/10.1161/01.RES.45.6.815

[30] Sayago, C.M. and Beierwaltes, W.H. (2001) Nitric Oxide Synthase and cGMP-Mediated Stimulation of Renin Secretion. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, **281**, R1146-R1151. https://doi.org/10.1152/ajpregu.2001.281.4.R1146

[31] Howard, A.B., Alexander, R.W. and Taylor, W.R. (1995) Effects of Magnesium on Nitric Oxide Synthase Activity in Endothelial Cells. *American Journal of Physiology-Cell Physiology*, **269**, C612-C618. https://doi.org/10.1152/ajpcell.1995.269.3.C612

[32] Neubauer, B., Machura, K., Kett, R., Luisa, M. and Lopez, S.S. (2013) Endothelium-Derived Nitric Oxide Supports Renin Cell Recruitment through the Nitric Oxide-Sensitive Guanylate Cyclase Pathway. *Hypertension*, **61**, 400-407. https://doi.org/10.1161/HYPERTENSIONAHA.111.00221

[33] Atanassova, N. and Koeva, Y. (2012) Hydrohysteroid Dehydrogenases—Biological Role and Clinical Importance—Review. In: Canuto, R.A., Ed., *Dehydrogenases*, IntechOpen, London. https://doi.org/10.5772/54149

[34] Pinto, M.D., Lambert, N., Downs, C.A., Abrahim, H., Hughes, T.D. and Rahmani, A.M. (2022) Antihistamines for Post Acute Sequelae of SARS-CoV-2 Infection. *The Journal for Nurse Practitioners*, **18**, 335-338. https://doi.org/10.1016/j.nurpra.2021.12.016

[35] Gewin, L. (2019) The Many Talents of Transforming Growth Factor-β in the Kidney. *Current Opinion in Nephrology and Hypertension*, **28**, 203-210. https://doi.org/10.1097/MNH.0000000000000490

[36] Vander Ark, A., Cao, J. and Li, X. (2018) TGF-β Receptors: In and beyond TGF-β Signaling. *Cellular Signalling*, **52**, 112-120. https://doi.org/10.1016/j.cellsig.2018.09.002

[37] Zhang, X., Chen, Y., Li, Z., Han, X. and Liang, Y. (2020) TGFBR3 Is an Independent Unfavourable Prognostic Marker in Oesophageal Squamous Cell Cancer and Is Positively Correlated with Ki-67. *International Journal of Experimental Pathology*, **101**, 223-229. https://doi.org/10.1111/iep.12380

[38] Song, H., Yang, J. and Yu, W. (2022) Promoter Hypomethylation of TGFBR3 as a Risk Factor of Alzheimer's Disease: An Integrated Epigenomic-Transcriptomic Analysis. *Frontiers in Cell and Developmental Biology*, **9**, Article ID: 825729. https://doi.org/10.3389/fcell.2021.825729

[39] Oronsky, B., Larson, C., Hammond, T.C., *et al.* (2021) A Review of Persistent Post-COVID Syndrome (PPCS). *Clinical Reviews in Allergy & Immunology.* https://doi.org/10.1007/s12016-021-08848-3

[40] Montoya, J.G., Holmes, T.H. and Anderson, J.N. (2017) Cytokine Signature Associated with Disease Severity in Chronic Fatigue Syndrome Patients. *Proceedings of the National Academy of Sciences of the United States of America*, **114**, E7150-E7158. https://doi.org/10.1073/pnas.1710519114

[41] Lidbury, B.A., Kita, B., Lewis, D.P., *et al.* (2017) Activin B Is a Novel Biomarker for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) Diagnosis: A Cross Sectional Study. *Journal of Translational Medicine*, **15**, Article No. 60. https://doi.org/10.1186/s12967-017-1161-4

[42] Zhang, H.Y., Liu, Z.D., Hu, C.J., Wang, D.X., *et al.* (2011) Up-Regulation of TGF-β1 mRNA Expression in Peripheral Blood Mononuclear Cells of Patients with Chronic Fatigue Syndrome. *Journal of the Formosan Medical Association*, **110**, 701-704. https://doi.org/10.1016/j.jfma.2011.09.006

[43] Iempridee, T., Das, S., Xu, I. and Mert, J.E. (2011) Transforming Growth Factor β-Induced Reactivation of Epstein-Barr Virus Involves Multiple Smad-Binding Elements Cooperatively Activating Expression of the Latent-Lytic Switch *BZLF1* Gene. *Journal of Virology*, **85**, 7836-7848. https://doi.org/10.1128/JVI.01197-10

[44] Kossmann, T.M., Morganti-Kossmann, M.C., Orenstein, J.M., Britt, W.J., Wahl, S.M., *et al.* (2003) Cytomegalovirus Production by Infected Astrocytes Correlates with Transforming Growth Factor-β Release. *The Journal of Infectious Diseases*, **187**, 534-541. https://doi.org/10.1086/373995

[45] Hoffman, B. (2021) Chronic Inflammatory Response Syndrome (CIRS) Evaluation and Treatment. Hoffman Centre for Integrative and Functional Medicine, Calgary. https://hoffmancentre.com/chronic-inflammatory-response-syndrome-cirs-evaluation-and-treatment/

[46] Zhang, X., Huang, W.J. and Chen, W.W. (2016) TGF-β1 Factor in the Cerebrovascular Diseases of Alzheimer's Disease. *European Review for Medical and Pharmacological Sciences*, **20**, 5178-5185. https://pubmed.ncbi.nlm.nih.gov/28051272/

[47] Wang, L., *et al.* (2022) Association of COVID-19 with New-Onset Alzheimer's Disease. *Journal of Alzheimer's Disease*, **89**, 411-414. https://doi.org/10.3233/JAD-220717

[48] Xia, X., Wang, Y. and Zheng, J. (2021) COVID-19 and Alzheimer's Disease: How One Crisis Worsens the Other. *Translational Neurodegeneration*, **10**, Article No. 15. https://doi.org/10.1186/s40035-021-00237-2

[49] Carbone, I., Lazzarotto, T., Ianni, M., Porcellini, E., Forti, P., *et al.* (2014) Herpes Virus in Alzheimer's Disease: Relation to Progression of the Disease. *Neurobiology of Aging*, **35**, 122-129. https://doi.org/10.1016/j.neurobiolaging.2013.06.024

[50] Bredesen, D.E. (2016) Inhalational Alzheimer's Disease: An Unrecognized-and Treatable-Epidemic. *Aging*, **108**, 304-313. https://doi.org/10.18632/aging.100896

[51] Tzeng, N.S., Chung, C.H., Liu, F.C., Chou, Y.C., Lin, F.H., *et al.* (2018) Fibromyalgia and Risk of Dementia—A Nationwide, Population-Based, Cohort Study. *American Journal of the Medical Sciences*, **355**, 153-161. https://doi.org/10.1016/j.amjms.2017.09.002

[52] Barnes, L.L., Capuano, A.W., Aiello, A.E., Turner, A.D., Yolken, R.H., *et al.* (2015) Cytomegalovirus Infection and Risk of Alzheimer Disease in Older Black and White Individuals. *The Journal of Infectious Diseases*, **211**, 230-237. https://doi.org/10.1093/infdis/jiu437

[53] Vaidya, B. and Sharma, S.S. (2020) Transient Receptor Potential Channels as an Emerging Target for the Treatment of Parkinson's Disease: An Insight into Role of Pharmacological Interventions. *Frontiers in Cell and Developmental Biology*, **8**, Article ID: 584513. https://doi.org/10.3389/fcell.2020.584513

[54] Belrose, J. and Jackson, M. (2018) TRPM2: A Candidate Therapeutic Target for Treating Neurological Diseases. *Acta Pharmacologica Sinica*, **39**, 722-732. https://doi.org/10.1038/aps.2018.31

[55] Ding, R., Yin, Y.-L. and Jiang, L.-H. (2021) Reactive Oxygen Species-Induced TRPM2-Mediated Ca^{2+} Signalling in Endothelial Cells. *Antioxidants*, **10**, Article No. 718. https://doi.org/10.3390/antiox10050718

[56] Zhu, D., You, J., Zhao, N. and Xu, H. (2019) Magnesium Regulates Endothelial Barrier Functions through TRPM7, MagT1, and S1P1. *Advanced Science*, **6**, Article ID: 1901166. https://doi.org/10.1002/advs.201901166

[57] Starkus, J., Beck, A., Fleig, A. and Penner, R. (2007) Regulation of TRPM2 by Extra- and Intracellular Calcium. *Journal of General Physiology*, **130**, 427-440. https://doi.org/10.1085/jgp.200709836

[58] Zhou, J., Gao, G., Zhang, S., Wang, H., Ke, L., *et al.* (2020) Influences of Calcium and Magnesium Ions on Cellular Antioxidant Activity (CAA) Determination. *Food Chemistry*, **320**, Article ID: 126625. https://doi.org/10.1016/j.foodchem.2020.126625

[59] Du, Y., Chen, J., Shen, L. and Wang, B. (2022) TRP Channels in Inflammatory Bowel Disease: Potential Therapeutic Targets. *Biochemical Pharmacology*, **203**, Article ID: 115195. https://doi.org/10.1016/j.bcp.2022.115195

[60] Smith, R.A.J., Hartley, R.C., Cochemé, H.M. and Murphy, M.P. (2012) Mitochondrial Pharmacology. *Trends in Pharmacological Sciences*, **33**, 341-352. https://doi.org/10.1016/j.tips.2012.03.010

[61] Giorgio, V., Guo, L., Bassot, C., Petronilli, V. and Bernardi, P. (2018) Calcium and Regulation of the Mitochondrial Permeability Transition. *Cell Calcium*, **70**, 56-63. https://doi.org/10.1016/j.ceca.2017.05.004

[62] Kang, H., Seo, E., Oh, Y.S., *et al.* (2022) TGF-β Activates NLRP3 Inflammasome by an Autocrine Production of TGF-β in LX-2 Human Hepatic Stellate Cells. *Molecular and Cellular Biochemistry*, **477**, 1329-1338. https://doi.org/10.1007/s11010-022-04369-5

[63] Wang, R., Wang, S.Y., Wang, Y., Xin, R., Xia, B., *et al.* (2020) The Warburg Effect Promoted the Activation of the NLRP3 Inflammasome Induced by Ni-Refining Fumes in BEAS-2B Cells. *Toxicology and Industrial Health*, **36**, 580-590. https://doi.org/10.1177/0748233720937197

[64] Zhang, Z.T., Du, X.M., Ma, X.J., *et al.* (2016) Activation of the NLRP3 Inflammasome in Lipopolysaccharide-Induced Mouse Fatigue and Its Relevance to Chronic Fatigue Syndrome. *Journal of Neuroinflammation*, **13**, Article No. 71. https://jneuroinflammation.biomedcentral.com/articles/10.1186/s12974-016-0539-1

[65] Song, L., Pei, L., Yao, S., Wu, Y. and Shang, Y. (2017) NLRP3 Inflammasome in Neurological Diseases, from Functions to Therapies. *Frontiers in Cellular Neuroscience*, **11**, Article No. 63. https://doi.org/10.3389/fncel.2017.00063

[66] Zhen, Y. and Zhang, H. (2019) NLRP3 Inflammasome and Inflammatory Bowel Disease. *Frontiers in Immunology*, **10**, Article No. 276. https://doi.org/10.3389/fimmu.2019.00276

[67] Xiao, W. (2010) NLRP3 Inflammasome-Mediated Inflammatory Process in Patients with Irritable Bowel Syndrome Dissertation Topic. Shandong University, Jinan. https://www.dissertationtopic.net/doc/663467

[68] Olcum, M., Tastan, B., Kiser, C., Genc, S. and Genc, K. (2020) Chapter Seven—Microglial NLRP3 Inflammasome Activation in Multiple Sclerosis. In: Donev, R., Ed., *Advances in Protein Chemistry and Structural Biology*, Vol. 119, Academic Press, Cambridge, 247-308. https://doi.org/10.1016/bs.apcsb.2019.08.007

[69] Shen, H.H., Yang, Y.X., Meng, X., Luo, X.Y., Li, X.M., *et al.* (2018) NLRP3: A Promising Therapeutic Target for Autoimmune Diseases. *Autoimmunity Reviews*, **17**, 694-702. https://doi.org/10.1016/j.autrev.2018.01.020

[70] Reinhart, N.M., Akinyemi, I.A., Frey, T.R., Xu, H., Agudelo, C., *et al.* (2022) The Danger Molecule HMGB1 Cooperates with the NLRP3 Inflammasome to Sustain Expression of the EBV Lytic Switch Protein in Burkitt Lymphoma Cells. *Virology*, **566**, 136-142. https://doi.org/10.1016/j.virol.2021.12.002

[71] Bazrafkan, M., Hosseini, E., Nazari, M., Amorim, C.A. and Sadeghi, M.R. (2021) NLRP3 Inflammasome: A Joint, Potential Therapeutic Target in Management of COVID-19 and Fertility Problems. *Journal of Reproductive Immunology*, **148**, Article ID: 103427. https://doi.org/10.1016/j.jri.2021.103427

[72] Lee, G.S., Subramanian, N., Kim, A., *et al.* (2012) The Calcium-Sensing Receptor Regulates the NLRP3 Inflammasome through Ca^{2+} and cAMP. *Nature*, **492**, 123-127. https://doi.org/10.1038/nature11588

[73] Chang, Y.Y., Kao, M.C., Lin, J.A., Wong, C.S. and Tzeng, I.S. (2018) Effects of $MgSO_4$ on Inhibiting Nod-Like Receptor Protein 3 Inflammasome Involve Decreasing Intracellular Calcium. *Journal of Surgical Research*, **221**, 257-265. https://doi.org/10.1016/j.jss.2017.09.005

[74] Zhao, X.J., Yang, Y.Z., Zheng, Y.J., Wang, S.C., Gu, H.M., *et al.* (2017) Magnesium Isoglycyrrhizinate Blocks Fructose-Induced Hepatic NF-κB/NLRP3 Inflammasome Activation and Lipid Metabolism Disorder. *European Journal of Pharmacology*, **809**, 141-150. https://doi.org/10.1016/j.ejphar.2017.05.032

[75] Jiang, X., Zhong, L., Sun, D. and Rong, L. (2016) Magnesium Lithospermate B Acts against Dextran Sodium Sulfate-Induced Ulcerative Colitis by Inhibiting Activation of the NRLP3/ASC/Caspase-1 Pathway. *Environmental Toxicology and Pharmacology*, **41**, 72-77. https://doi.org/10.1016/j.etap.2015.10.009

[76] Lund, T.M., Obel, L.F., Risa, Ø. and Sonnewald, U. (2011) *β*-Hydroxybutyrate Is the Preferred Substrate for GABA and Glutamate Synthesis While Glucose Is Indispensable during Depolarization in Cultured GABAergic Neurons. *Neurochemistry International*, **59**, 309-318. https://doi.org/10.1016/j.neuint.2011.06.002

[77] Gobaille, S., Hechler, V., Andriamampandry, C., Kemmel, V. and Maitre, M. (1999) γ-Hydroxybutyrate Modulates Synthesis and Extracellular Concentration of γ-Aminobutyric acid In Discrete Rat Brain Regions in Vivo. *Journal of Pharmacology and Experimental Therapeutics*, **290**, 303-309 https://pubmed.ncbi.nlm.nih.gov/10381791/

[78] Boyd, A. (2015) Gamma-Aminobutyric Acid (GABA) Monograph. https://www.fxmedicine.com.au/blog-post/gamma-aminobutyric-acid-gaba-monograph

[79] Zanos, P. (2016) Ketamine and Esketamine in Depression—A Synopsis on Efficacy and Mechanism of Action. Psych Scene Hub. https://psychscenehub.com/psychinsights/ketamine-and-depression/

[80] Möykkynen, T., Uusi-Oukari, M., Heikkilä, J., Lovinger, D.M., Lüddens, H., *et al.* (2001) Magnesium Potentiation of the Function of Native and Recombinant $GABA_A$ Receptors. *Neuroreport*, **12**, 2175-2179. https://doi.org/10.1097/00001756-200107200-00026

[81] Von Bartheld, C.S., Hagen, M.M. and Butowt, R. (2020) Prevalence of Chemosensory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-Analysis Reveals Significant Ethnic Differences. *ACS Chemical Neuroscience*, **11**, 2944-2961. https://doi.org/10.1021/acschemneuro.0c00460

[82] Levy, L.M. and Henkin, R.I. (2004) Brain Gamma-Aminobutyric Acid Levels Are Decreased in Patients with Phantageusia and Phantosmia Demonstrated by Magnetic Resonance Spectroscopy. *Journal of Computer Assisted Tomography*, **28**, 721-727. https://doi.org/10.1097/00004728-200411000-00001

[83] Henkin, R.I. (2006) Treatment of Distortions of Taste and Smell. Taste and Smell Clinic. http://www.tasteandsmell.com/sep06.htm

[84] Barker-Haliski, M. and White, H.S. (2015) Glutamatergic Mechanisms Associated with Seizures and Epilepsy. *Cold Spring Harbor Perspectives in Medicine*, **5**, a022863. https://doi.org/10.1101/cshperspect.a022863

[85] Tataru, A. and Nicoara, E. (2004) Idiopathic Diffuse Alopecias in Young Women Correlated with Hypomagnesemia. *Journal of the European Academy of Dermatology and Venereology*, **18**, 393-394. https://doi.org/10.1111/j.1468-3083.2004.00660.x

[86] Chambers, P.W. (2021) Basigin Binds Spike S on SARS-CoV2. *Open Access Library Journal*, **8**, 1-7. https://www.scirp.org/journal/paperinformation.aspx?paperid=113177

[87] Brown, E.M. and Chen, C.J. (1989) Calcium, Magnesium and the Control of PTH Secretion. *Bone and Mineral*, **5**, 249-257. https://doi.org/10.1016/0169-6009(89)90003-2

[88] Haensel, A., Mills, P.J., Nelesen, R.A., Ziegler, M.J. and Dimsdale, J.E. (2008) The Relationship between Heart Rate Variability and Inflammatory Markers in Cardiovascular Diseases. *Psychoneuroendocrinology*, **33**, 1305-1312. https://doi.org/10.1016/j.psyneuen.2008.08.007

[89] Gidron, Y., Deschepper, R., De Couck, M., Thayer, J.F. and Velkeniers, B. (2018) The Vagus Nerve Can Predict and Possibly Modulate Non-Communicable Chronic Diseases: Introducing a Neuroimmunological Paradigm to Public Health. *Journal of Clinical Medicine*, **7**, Article No. 371. https://doi.org/10.3390/jcm7100371

[90] Mol, M.B.A., Strous, M.T.A., van Osch, F.H.M., Vogelaar, F.J., Barten, D.G., Farchi, M., *et al.* (2021) Heart-Rate-Variability (HRV), Predicts Outcomes in COVID-19. *PLOS ONE*, **16**, e0258841. https://doi.org/10.1371/journal.pone.0258841

[91] Sessa, F., Anna, V., Messina, G., Cibelli, G., Monda, V., *et al.* (2018) Heart Rate Variability as Predictive Factor for Sudden Cardiac Death. *Aging*, **10**, 166-177. https://doi.org/10.18632/aging.101386

[92] Behbahani, S., Dabanloo, N.J., Nasrabadi, A.M. and Dourado, A. (2016) Prediction of Epileptic Seizures Based on Heart Rate Variability. *Technology and Health Care*, **24**, 795-810. https://doi.org/10.3233/THC-161225

[93] Engel, T., Ben-Horin, S. and Beer-Gabel, M. (2015) Autonomic Dysfunction Correlates with Clinical and Inflammatory Activity in Patients with Crohn's Disease. *Inflammatory Bowel Diseases*, **21**, 2320-2326. https://doi.org/10.1097/MIB.0000000000000508

[94] Hirten, R.P., Danieletto, M., Scheel, R., Shervey, M., Ji, J., *et al.* (2021) Longitudinal Autonomic Nervous System Measures Correlate with Stress and Ulcerative Colitis Disease Activity and Predict Flare. *Inflammatory Bowel Diseases*, **27**, 1576-1584. https://doi.org/10.1093/ibd/izaa323

[95] Escorihuela, R.M., Capdevila, L., Castro, J.R., *et al.* (2020) Reduced Heart Rate Va-

riability Predicts Fatigue Severity in Individuals with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. *Journal of Translational Medicine*, **18**, Article No. 4. https://doi.org/10.1186/s12967-019-02184-z

[96] Choi, K.W. and Jeon, H.J. (2020) Heart Rate Variability for the Prediction of Treatment Response in Major Depressive Disorder. *Frontiers in Psychiatry*, **11**, Article No. 607. https://doi.org/10.3389/fpsyt.2020.00607

[97] Kim, Y.H., Jung, K.I. and Song, C.H. (2012) Effects of Serum Calcium and Magnesium on Heart Rate Variability in Adult Women. *Biological Trace Element Research*, **150**, 116-122. https://doi.org/10.1007/s12011-012-9518-2

[98] Lladós, G. and Mateu, L. (2022) Pilot Study Suggests Long COVID Could Be Linked to the Effects of SARS-CoV-2 on the Vagus Nerve. E*uropean Society of Clinical Microbiology and Infectious Diseases*. https://www.eurekalert.org/news-releases/943102

[99] Burkhardt, C. (2009) 'Lone' Atrial Fibrillation Precipitated by Monosodium Glutamate and Aspartame. *International Journal of Cardiology*, **137**, 307-308. https://doi.org/10.1016/j.ijcard.2009.01.028

[100] Chambers, P. (2003) Magnesium and Potassium in Lone Atrial Fibrillation. The Magnesium Online Library. http://www.mgwater.com/laf.shtml

[101] Chambers, P.W. (2007) Lone Atrial Fibrillation: Pathologic or Not? *Medical Hypotheses*, **68**, 281-287. https://doi.org/10.1016/j.mehy.2006.07.030

[102] Yeoh, Y.K., Zuo, T., Lui, G.C., *et al.* (2021) Gut Microbiota Composition Reflects Disease Severity and Dysfunctional Immune Responses in Patients with COVID-19. *Gut*, **70**, 698-706. https://doi.org/10.1136/gutjnl-2020-323020

[103] Clos-Garcia, M., Andrés-Marin, N., Fernández-Eulate, G., Abecia, L., Lavín, J.L., *et al.* (2019) Gut Microbiome and Serum Metabolome Analyses Identify Molecular Biomarkers and Altered Glutamate Metabolism in Fibromyalgia. *EBioMedicine*, **46**, 499-511. https://doi.org/10.1016/j.ebiom.2019.07.031

[104] Zhou, X., Baumann, R., Gao, X., Mendoza, M., Singh, S., *et al.* (2022) Gut Microbiome of Multiple Sclerosis Patients and Paired Household Healthy Controls Reveal Associations with Disease Risk and Course. *Cell*, **185**, 3467-3486. https://doi.org/10.1016/j.cell.2022.08.021

[105] Lupo, G.F.D., Rocchetti, G., Lucini, L., *et al.* (2021) Potential Role of Microbiome in Chronic Fatigue Syndrome/Myalgic Encephalomyelits (CFS/ME). *Scientific Reports*, **11**, Article No. 7043. https://doi.org/10.1038/s41598-021-86425-6

[106] Fu, Y., Wang, Y., Gao, H., Li, D.H. and Jiang, R.R. (2021) Associations among Dietary Omega-3 Polyunsaturated Fatty Acids, the Gut Microbiota, and Intestinal Immunity. *Mediators of Inflammation*, **2021**, Article ID: 8879227. https://doi.org/10.1155/2021/8879227

[107] Castro-Marrero, J., Zaragozá, M.C., Domingo, J.C., Martinez-Martinez, A. and Alegre, J. (2018) Low Omega-3 Index and Polyunsaturated Fatty Acid Status in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. *Prostaglandins Leukotrienes and Essential Fatty Acids*, **139**, 20-24. https://www.plefa.com/article/S0952-3278(18)30053-X/fulltext

[108] Pellino, S., Luciano, M., Luciano, R., Mancini, E., Conte, M., Volpe, G. and Zerella, T. (2021) Long-COVID-19 Symptoms after Infection in COVID Long-Haulers. *Open Journal of Epidemiology*, **11**, 473-482. https://doi.org/10.4236/ojepi.2021.114038

[109] Swank, Z., Senussi, Y., Manickas-Hill, Z., Yu, X.G., Li, J.Z., *et al.* (2022) Persistent

Circulating SARS-CoV-2 Spike Is Associated with Post-Acute COVID-19 Sequelae. *Clinical Infectious Diseases*, **2022**, ciac722. https://doi.org/10.1093/cid/ciac722

[110] Chambers, P. (2022) Ca:Mg + D, the Shield that Interdicts the Crown Viruses and Vaccines. *Open Access Library Journal*, **9**, e9249. https://www.scirp.org/journal/paperinformation.aspx?paperid=119926