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Antioxidants and Long Covid

Patrick Chambers, MD

Department of Pathology, Torrance Memorial Medical Center, Torrance, California
Email: pwc@gte.net

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 hypothesis 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 $\cdot O_2^-$, which along with its partners, hydrogen peroxide H_2O_2 and the hydroxyl radical $\cdot OH$ 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

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(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 figure1).

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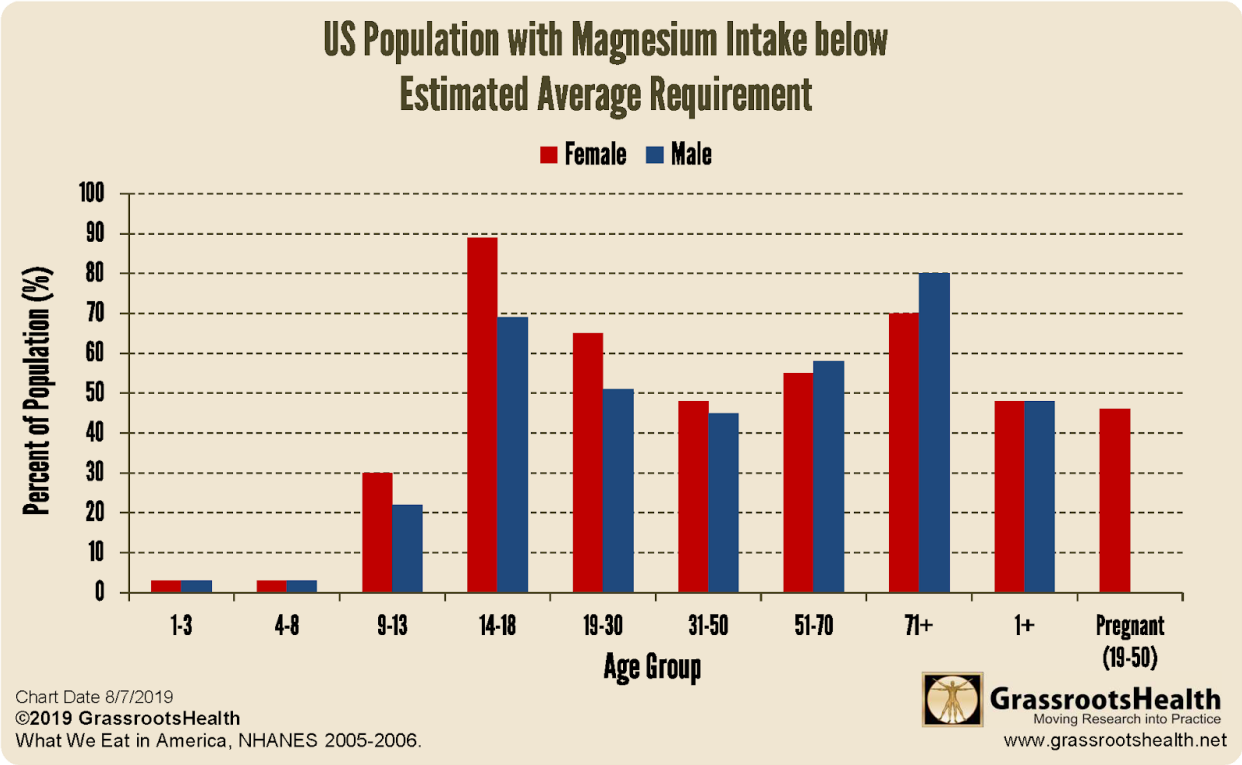

Figure 1. Magnesium deficiency is accentuated in females less than 50 and males over 50(10).

Or perhaps the hypoxia/lactate induced upregulation 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).
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).

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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).

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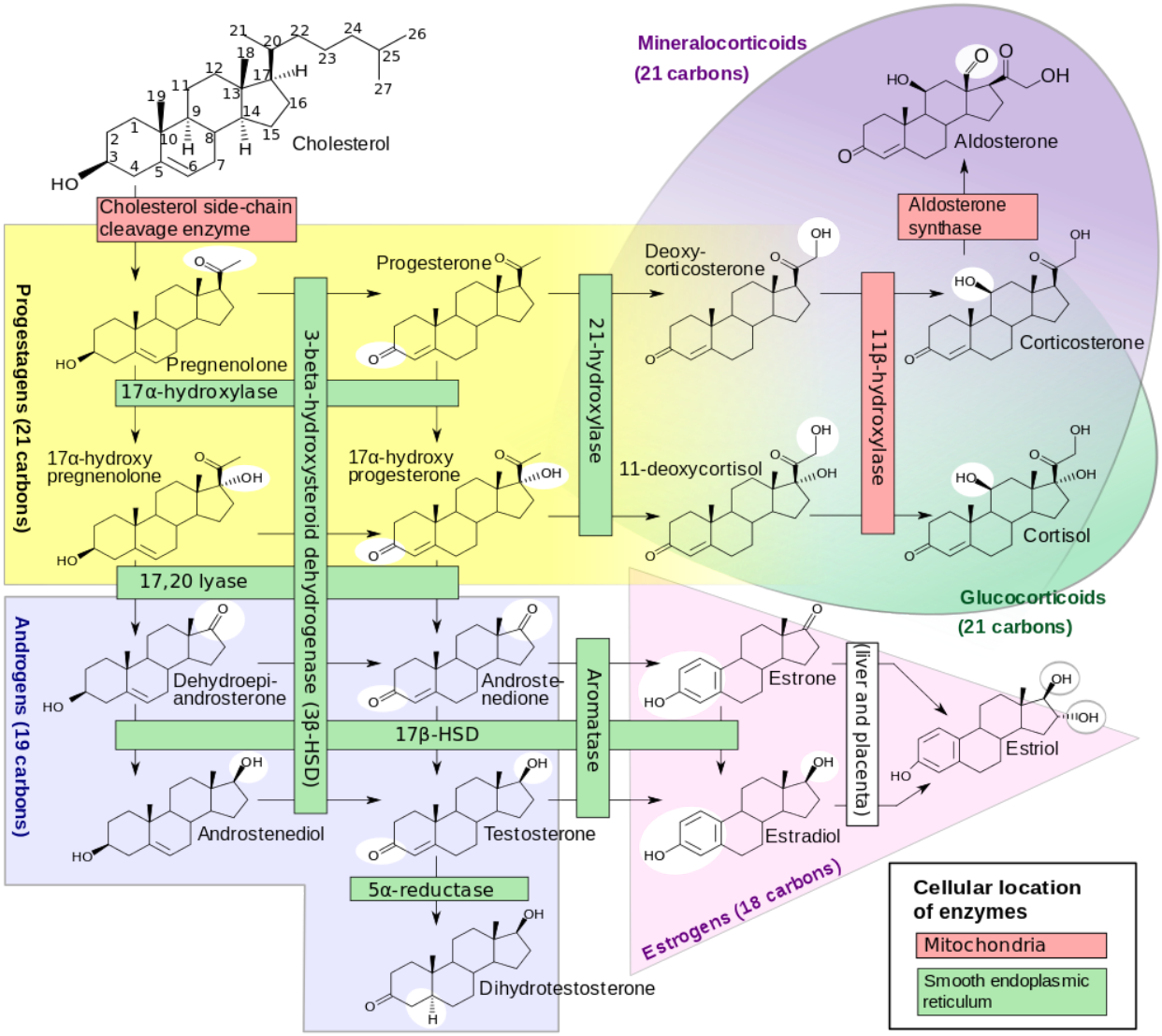

Figure 2. Aldosterone and cortisol require enzymes that are located in the mitochondria and require magnesium as cofactors(33).

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 this requires SAMe, Mg^{2+}, and ATP. Some Covid long haulers find relief with antihistamines(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).

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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

2.5.1.0 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).

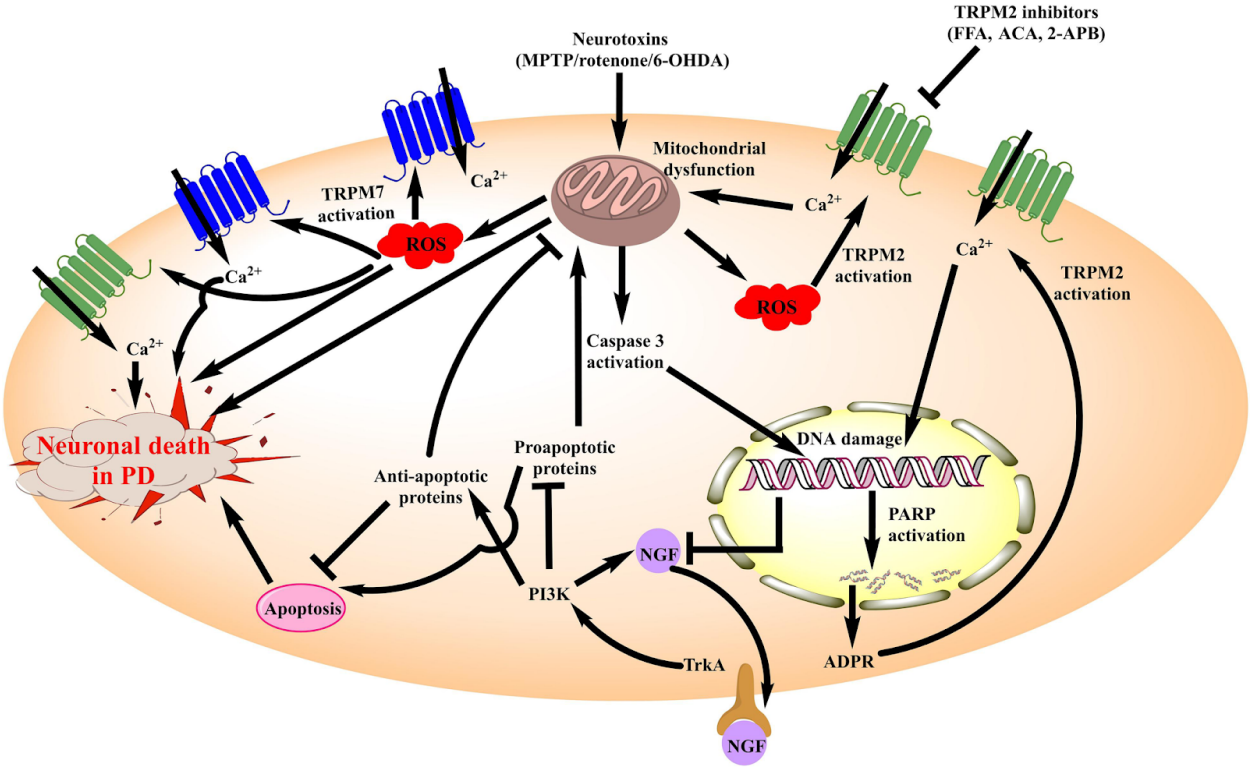

Figure 3. ROS facilitate dominance of TRPM2 and increase intracellular Ca^{2+} and mitochondrial dysfunction(53).

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 figure4)(60,61).

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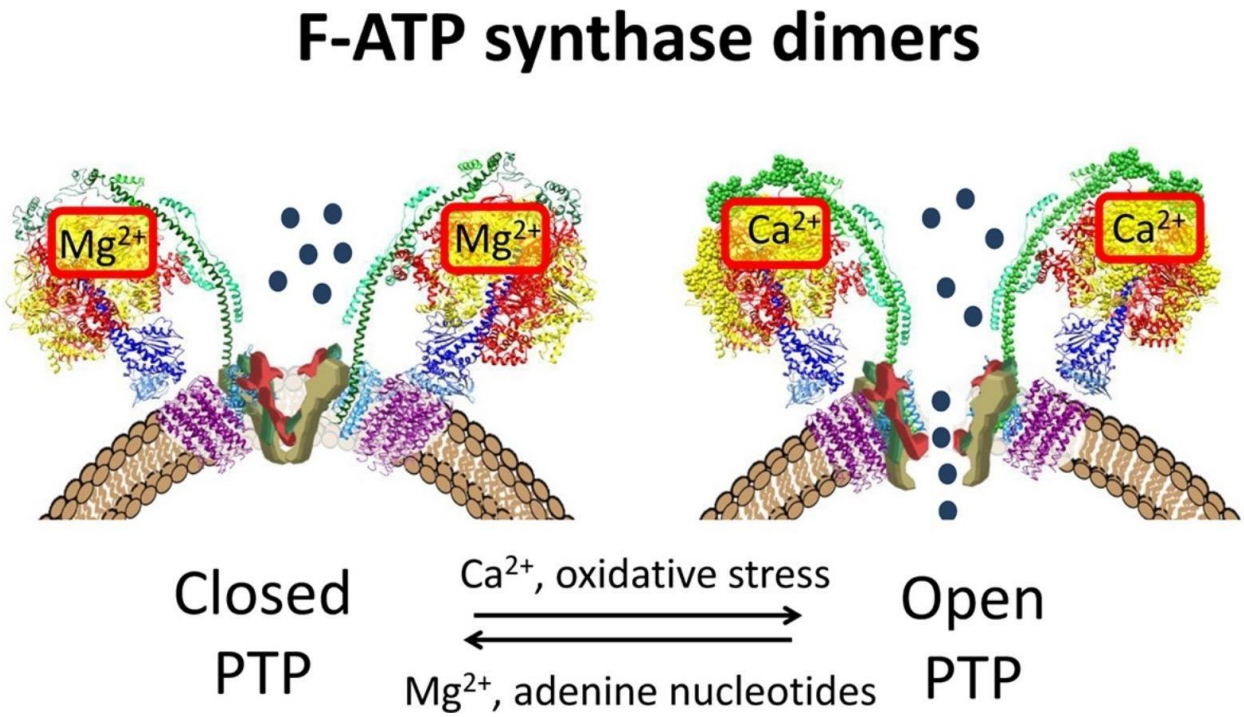

Figure 4. Ca^{2+} competes with PTP-inhibitory Mg^{2+} and is an essential permissive factor for PTP (permeability transition pore) opening(61).

2.5.2.0 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 calcium-sensing receptors (CaSRs) and TRPM5,7. The CaSR regulates the NLRP3 inflammasome(72) and can be downregulated by increasing Mg^{2+}(73,74,75). CASR activates the NLRP3 inflammasome, mediated by increased intracellular Ca^{2+} and decreased cellular cyclic AMP (cAMP).

2.6 GABA

Glutamate is synthesized 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 pass the blood brain barrier, but GHBA and BHBA can. Glutamatergic neurons release glutamate and primarily employ NMDA(N-methyl-D-aspartate) receptors.

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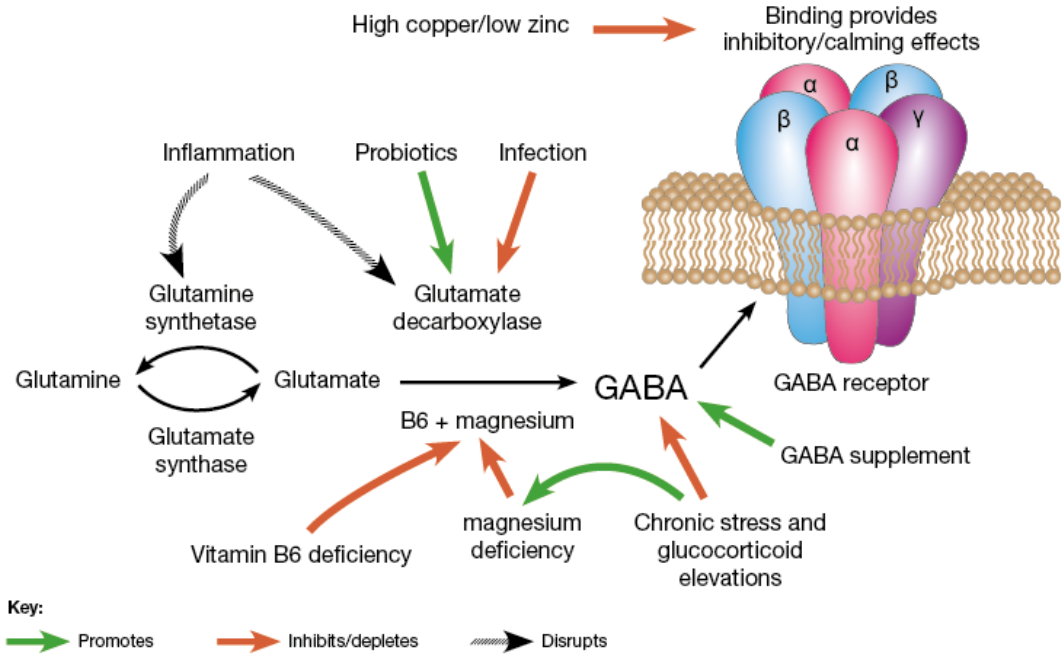

Figure 5. GABA enabling roles for B6, Mg^{2+}, GABA supplements (butyrates), and probiotics are shown(79).

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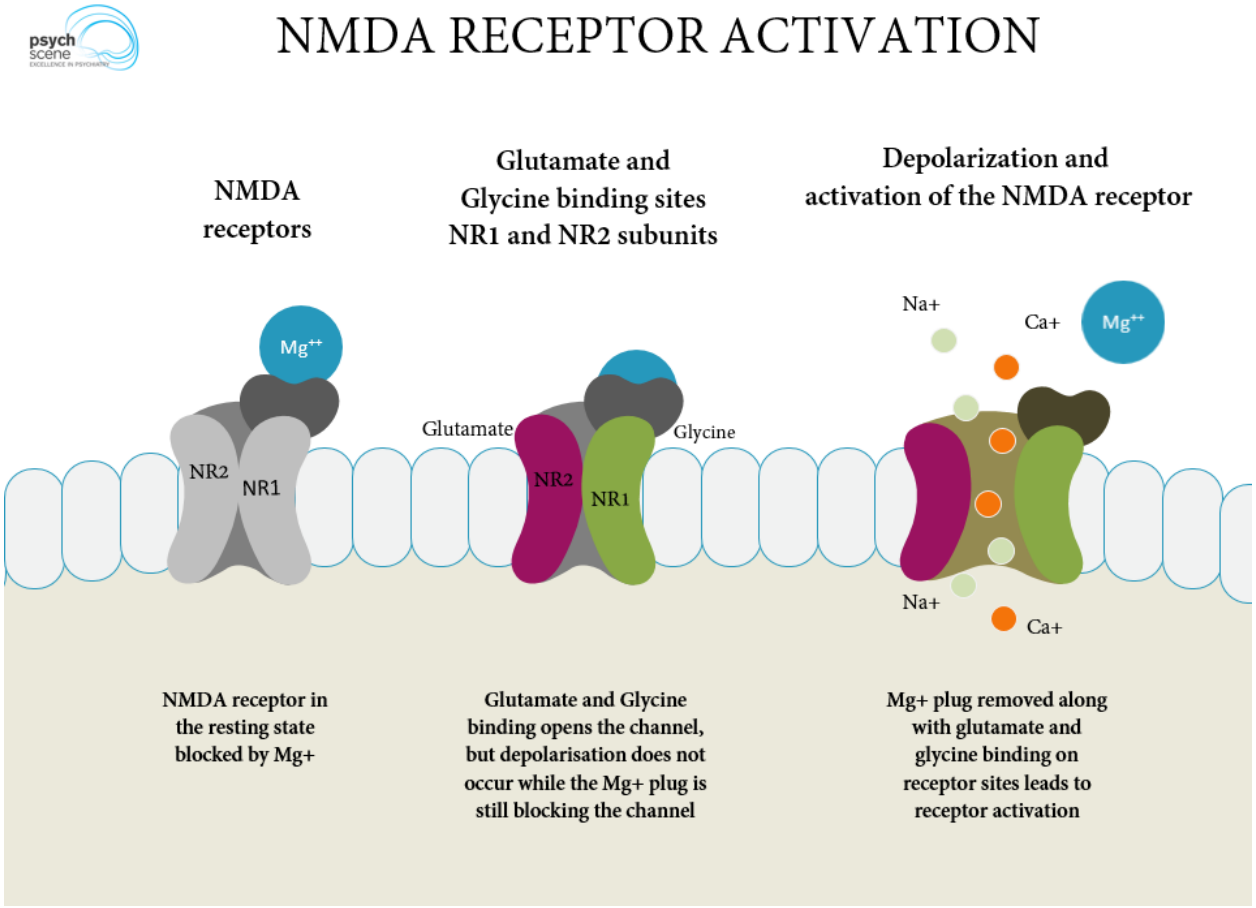

Figure 6. Glutamate favors NMDA receptors. The Mg^{2+} plug closes the Ca^{2+} channel. Its removal opens the channel(78).

Mg^{2+} can bind to both NMDA receptors (see figure 6)(78) and GABA receptors(80). In addition P5P is a required cofactor for GAD (glutamic acid decarboxylase) and GABA synthesis (see figure 5). GABA plays a 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 due to 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/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 microcirculation and enhances thrombogenesis (basigin on spike S).

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(86), inappropriately suppressing synthesis of $1,25(OH)_2D$. Is Mg^{2+} triaged from PTH synthesis to D synthesis? Increasing magnesium intake without addressing the calcium overage may also elicit the laxative effect.

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

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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 inverse relationship between CRP and HRV(87). Both can be excellent early indicators of deteriorating health, response to therapy, and prognosis on any behavioral, biologic, or epidemiological path(88). They offer high sensitivity but low specificity. The list of such detectable problems is quite comprehensive, e.g., cardiovascular disease(87), Covid-19(89), sudden cardiac death(90), seizures(91), Crohn's disease(92), ulcerative colitis(93), ME/CFS(94), depression(95).

HRV, a measure of vagal tone, is also inversely linked to Ca:Mg(96). 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, diarrhea, and dysphagia. Many of these have been reported in Long Covid and a strong connection between vagus nerve dysfunction implicated(97).

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 (98,99,100). Both imbalances are tightly linked and diet dependent. Intestinal "friendly" bacteria (Bifidobacterium pseudocatenulatum and Faecalibacterium prausnitzii) that produce butyrates were deficient in those with Long Covid(101), FM(102), and MS(multiple sclerosis)(103). Glutamate producing intestinal bacteria were more numerous in ME/CFS(lactic acid bacteria and MSG(monosodium glutamate))(104).

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(105,106). 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 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)(99).

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(107), 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).

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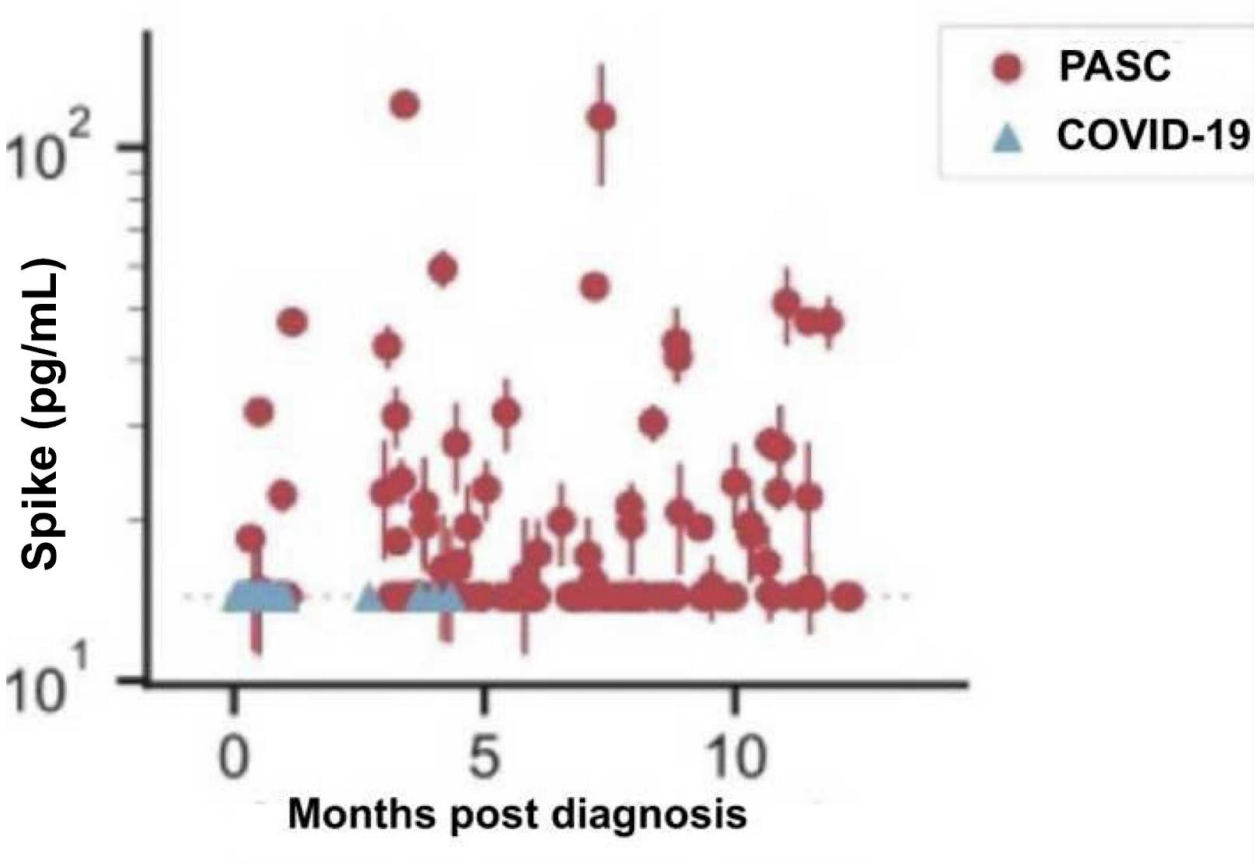

Figure 7. Spike protein S persistence in PASC (posts-acute sequelae of COVID-19) v primary SARS Cov 2(108).

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.

3.0 Conclusion

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% serum Ca/70% serum Mg(109). 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.

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