Review Article

Staunch the Age Related Decline into Dementia, Cancer, Autoimmunity (Long Covid), Obesity, and Other Diseases with a Prebiotic, Probiotic, Postbiotic Triple Play

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“All diseases originate in the gut.” Hippocrates (400 BC)

A healthy gut microbiome via the gut-brain-axis (GBA) elevates heart rate variability (HRV), a general measure of health and well-being. A dysbiotic gut microbiome, low in biodiversity and butyrate producers, alters tryptophan metabolism with release of proinflammatory cytokines, predominantly TNF-α, IL-6, and IL-1β. These also characterize chronic inflammation, oxidative stress, and a multitude of diseases, all exhibiting low HRV. Gut dysbiosis upregulates IFN-γ and with it IDO (indoleamine 2,3 dioxygenase). Tryptophan pivots from serotonin synthesis to that of IDO induced kynurenine, increasing the kynurenine to tryptophan ratio (KTR). An elevated KTR is positively linked to neurodegenerative and autoimmune diseases and negatively linked to HRV. Elevated IDO activity is not only enzymatic but also an intracellular signal transducer potentiated by TGF-β. This cytokine is the primary determinant of the TME. Also proposed is the gut-lung dysbiosis concept and consequent degradation of ACE2 (richest in lungs and gut). Leaky gut induced autoantibodies related to G-protein coupled receptors (GPCRs) in combination with increased Ang II further potentiate oxidative stress. Aldosterone and paroxysmal orthostatic tachycardia syndrome (POTS) paradoxes are highlighted in the context of GPCR and gut dysbiosis, and the role of Candida is explored. The efficacy of fecal microbiome transplantation (FMT) in treating dementia, cancer, and autoimmunity supports the plausibility of success with “FMT-lite”. This triple play of a prebiotic (d-mannose), probiotic (bifidobacteria and lactobacilli), and postbiotic (butyrate) might improve intestinal barrier integrity, oppose entry of GPCR antigens, suppress the inflammatory cytokine triad, balance IFN-γ and TGF-β, suppress oxidative stress, depress KTR, elevate HRV, and extend lifespan and its quality.

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Highlights

1. Gut dysbiosis causes an imbalance between reciprocal cytokines IFN-γ and TGF-β, both of which upregulate IDO
2. IFN-γ triggers the enzyme IDO, increasing risks for dementia and autoimmunity (female preponderance)
3. TGF-β triggers intracellular signaling by IDO, increasing the risk for TME and cancer (male preponderance)
4. TGF-β regulates tolerogenesis; too little, self antigens targeted, too much, tumor antigens not targeted
5. Gut dysbiosis depresses ACE2, increases permeability
6. Invading GPCR laden fungi, especially Candida, induce antibodies that cross react with host GPCRs
7. Autoimmune GPCR antibodies are the sequel to gut dysbiosis and drive autoimmunity, cancer, dementia
8. Estrogen facilitates immune evasion by Candida
9. Females produce abundant IFN-γ and Candida elicits a robust IFN response
10. The triple play (mini FMT) immuno-modulates IFN-γ and TGF-β and opposes GPCR mediated autoimmunity

1. Introduction

Pursuit of a healthier and happier lifestyle is a universal goal.

Better diet and more exercise are at the top of New Year's resolutions. But eating favorite foods is one of the great joys in life and exercise, not so much. Balance is the key to achieving these goals, whether it be between the opposing enzymes ACE and ACE2 or the pleiotropic cytokines IFN-γ and TGF-β. However, several supplements readily available may assist in this pursuit of balance.

Although this article cites an abundance of recent research supporting its content, it is speculative and the inferences are in part theoretical. It attempts to connect pleiotropic cytokines, gut dysbiosis, GPCR autoantibodies, and disease with oxidative stress under the HRV umbrella (see figure 1). Prebiotic d-mannose (a dietary fiber substitute), a probiotic rich in bifidobacteria and lactobacilli, and postbiotic

butyrate (best short chain fatty acid or SCFA) are proposed as partial solutions. HRV is proposed as a monitor of efficacy. It is the fifth vital sign and is more comprehensive and predictive in its assessment than those of the four traditional vital signs.

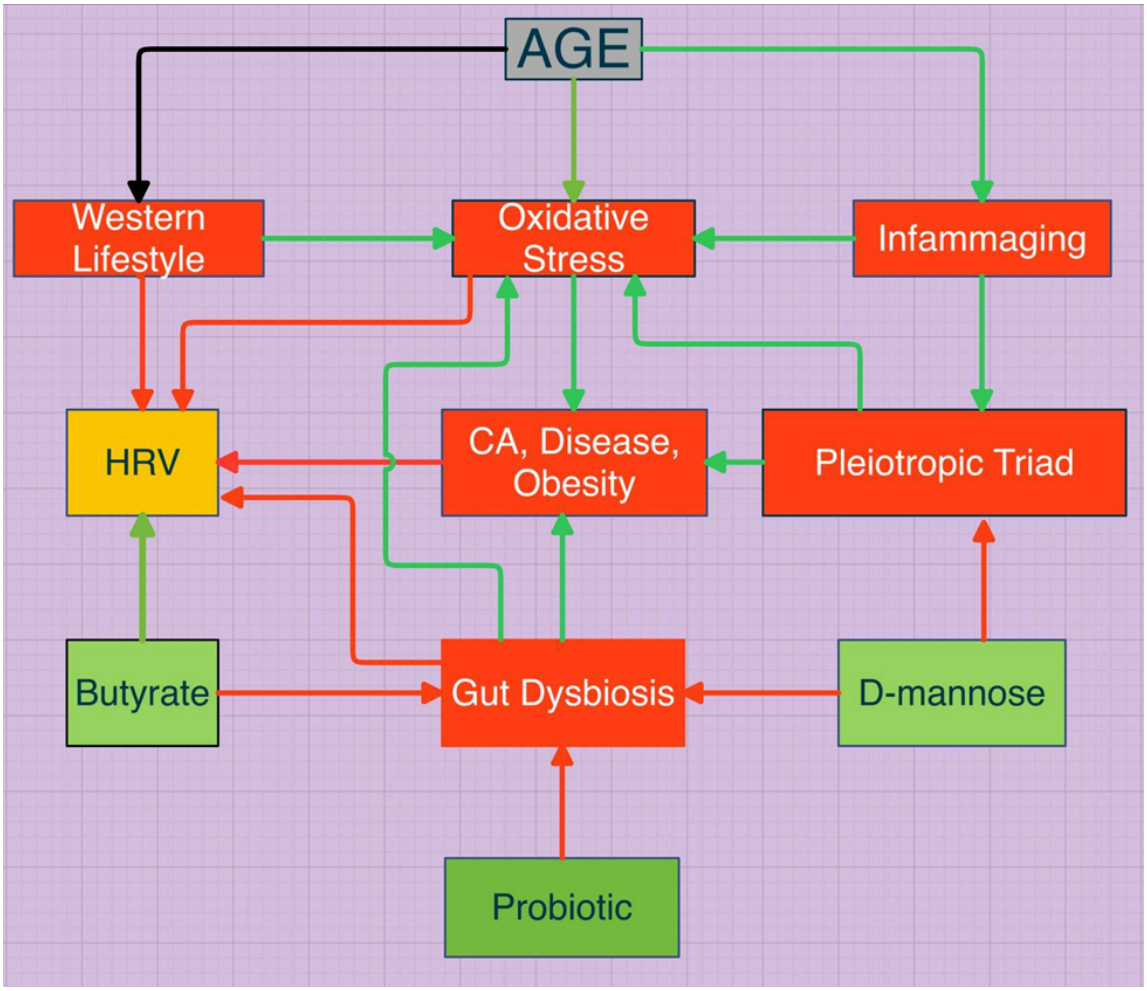

Figure 1. Pathways to a healthy HRV and enhanced lifespan are demonstrated. The Western Lifestyle includes an increased calcium to magnesium ratio, vitamin D deficiency, decreased antioxidants, toxins, e.g., smoking. TNF-α, IL-6, IL-1β comprise the triad. The trigger for the pleiotropic switch is not yet clear. Biologic individuality is also a prime determinant of differential pathway traffic.

2. Oxidative Stress and Gut Dysbiosis

Aging reflects the accumulated damage over a lifetime wrought by oxidative stress. This stress arises when energy needs increase and reactive oxygen species (ROS) generated within mitochondria remain unquenched due to insufficient onboard antioxidants. Psychological stress induces oxidative stress by

increasing circulating cortisol and norepinephrine, which generate mitochondrial ROS[1]. Mental stress is also linked with gut dysbiosis[2], which upregulates oxidative stress[3]. Excess ROS compromise mitochondrial efficiency and gut microbial diversity. Gut microbes themselves impact ROS generation.

Gut dysbiosis occurs when the gut microbiome is unbalanced, i.e., gut microbiota are not diverse and SCFA producing bacteria are in short supply. SCFAs are the end products of fermentation of dietary fibers by anaerobic intestinal bacteria and exert multiple beneficial effects on energy metabolism[4].

They are the primary energy substrate for colonic epithelial cells. Propionate and butyrate comprise 25% and 15% respectively of these SCFAs[5]. Acetate, which comprises ~60%, promotes obesity by stimulating insulin secretion and hyperphagia[6][7]. Propionate and butyrate stimulate secretion of glucagon-like peptide 1 (GLP-1), which suppresses appetite and insulin secretion[8][9]. On the other hand, oxidative stress enhances acetate dependent lipogenesis, i.e., promotes obesity[10]. Persistent low grade oxidative stress is tightly linked to excitatory glutamate neurotransmission[11]. Glutamate producing gut bacteria outperform their butyrate/γ-amino butyric acid producing counterparts and create an imbalance in excitatory and inhibitory neurotransmission in the autonomic nervous system[12]. The aging process and low grade chronic inflammation (increased ROS) are linked with upregulation of kynurenine and a shift in tryptophan metabolism from serotonin synthesis (decreased serotonergic inhibitory neurotransmission) to the kynurenine pathway[13], increasing KTR.

3. Altered Tryptophan Metabolism (ATM) and KTR

Tryptophan, an essential amino acid, from diet or synthesized by intestinal bacteria can follow one of three major metabolic pathways: 1) intestinal bacterial indole synthesis, 2) the kynurenine pathway in immune and epithelial cells (95% of tryptophan), or 3) the serotonin pathway (90% of total body serotonin) in enteroendocrine aka enterochromaffin cells and initiation of vagal afferent signals[14]. During ATM tryptophan pivots away from the serotonin pathway and synthesis of serotonin and melatonin to the kynurenine pathway (see figure 2). Inhibitory parasympathetic signals are suppressed due to the increase in excitatory glutamate activity. This pivot down-regulates bacterial indole synthesis with loss of indole induced GLP-1. Benefits of GLP-1 include appetite suppression, stimulation of insulin[15], decrease in fasting blood sugar[16], suppression of obesity and T2DM[17]. Many of the same bacteria that produce SCFAs, e.g., bifidobacteria and lactobacilli, also synthesize indoles from tryptophan[18]. Although the end product NAD+ (see figure 2) assists dysfunctional mitochondria in ATP

production, what drives the ATM pivot is not exactly clear. However, IFN-γ, upregulated in females, is a cofactor for many enzymes in the kynurenine pathway and may drive this pivot[19] (see figure 2). Tryptophan depletion lowers HRV (and increases KTR)[20]. Increased tryptophan intake (eggs) increases HRV, which appears to be due to the subsequent increase in serotonin[21]. KTR, an indicator of rate-limiting IDO activity, is positively correlated with cardiovascular disease mortality[22][23], depression, bipolar disorder, schizoprenia,[24] Alzheimer's disease, fronto-temporal dementia,[25] Parkinson's disease[26], and neurological disease in general[27]. Increased KTR has also been reported in cancer[28], autoimmune disease, including rheumatoid arthritis (RA)[29], and systemic lupus erythematosis (SLE)[30]. Infectious diseases are also linked to an elevated KTR[31] with a ratio that directly reflects severity[32][33]. This includes SARS CoV2[34]. SARS CoV2 induced loss of ACE2 receptor bearing intestinal epithelial cells decreases absorption of the essential amino acid tryptophan[35] with additional negative influence on KTR and prognosis. But there is another non enzymatic pathway from tryptophan that involves TGF-β.

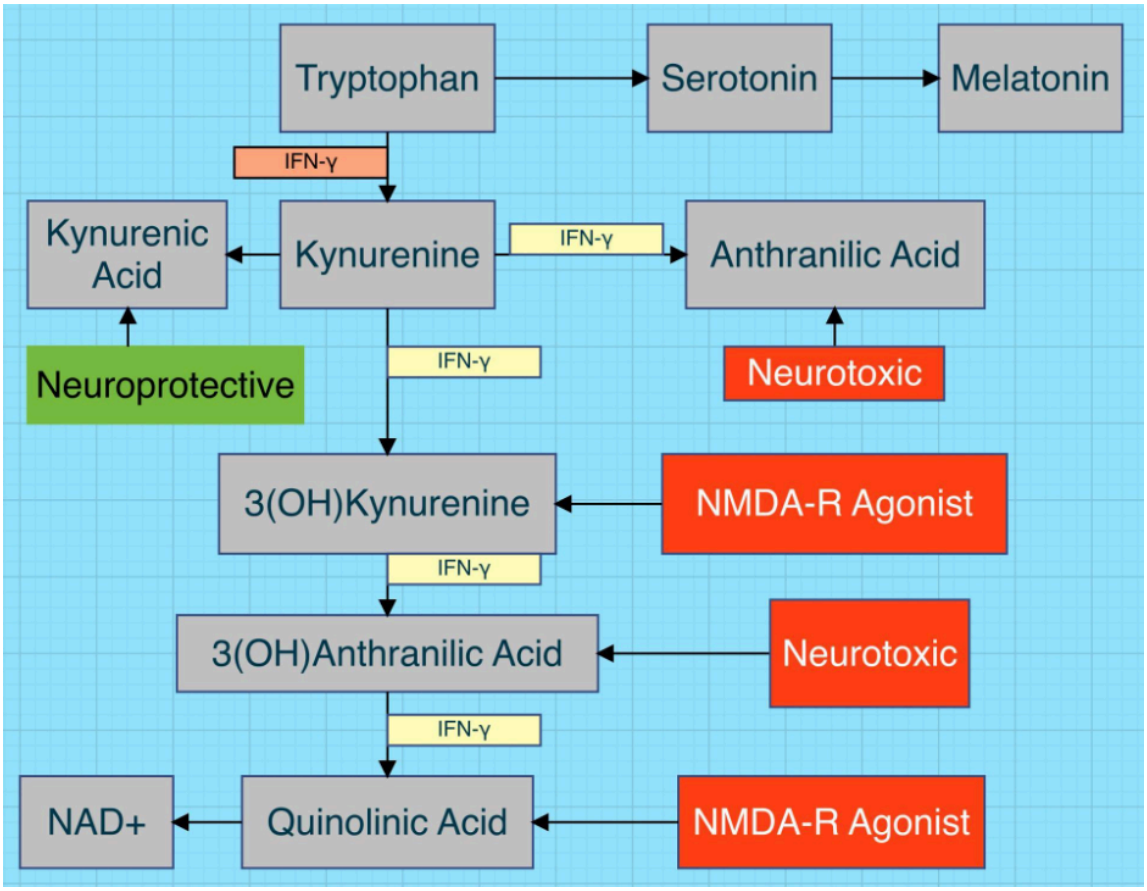

Figure 2. Altered tryptophan metabolism is demonstrated. NMDA-R=N-methyl-D-aspartate receptor is an excitatory glutamate receptor. Note the upregulating presence of the proinflammatory cytokine IFN-γ[36][24][37].

4. IFN-γ and TGF-β

IFN-γ and TGF-β are polarizing cytokines (reciprocal relationship)[38] and counterbalance each other[39]. IFN-γ is pro-inflammatory and TGF-β is anti-inflammatory. When an imbalance arises, autoimmune disease/IFN-γ and cancer/TGF-β, two immunological opposites[40], can develop. These counterbalancing cytokines are in turn immuno-modulated by the gut microbiome. This is demonstrated by the utility of fecal microbiota transplantation (FMT) in cancer[41], autoimmune disease[42], and dementia[43].

Reports on the efficacy of FMT for obesity are mixed. However, most of these studies include no concomitant prebiotic. Whether the microbiome is upgraded via probiotics or FMT, failure to

simultaneously upgrade the diet or otherwise provide sustenance to the new microbiota compromises efficacy.

Elevated IFN-γ characterizes parasitic infestations. In such patients this cytokine was positively associated with a good prognosis in Covid-19[44]. Low baseline IFN-γ response could predict hospitalization[45] and post discharge fibrosis in COVID-19 patients[44]. On the other hand its reciprocal, TGF-β, was positively associated with Covid-19 severity[46] and fibrosis[47]. Even outside the TME TGF-β promotes fibrosis, counterbalanced by IFN-γ. These cytokines are directly linked to the KTR and IDO. IDO, the enzyme, works to restrain excessive or inappropriate immune activation in the TME[48]

However, IDO is not only an enzyme induced by IFN-γ (increased KTR) but also an intracellular signal transducer induced by TGF-β (TME)[49][50][51]

Pleiotropism is the expression of different traits by the same gene. IFN-γ can pivot from pro-inflammatory and anti-proliferative to tumor promoter and TGF-β can pivot from tumor suppressor to tumor promoter. What triggers the pleiotropic switch from tumor suppressor to tumor promoter for either IFN-γ or TGF-β is not clear, but may be related to the TME milieu, where TGF-β appears to dominate[52]. In an imbalanced (elevated TGF-β/IFN-γ) TGF-β may trigger fibrosis and the TME via paracrine transmission.

IFN-γ is generally considered pro-inflammatory but anti-proliferative. But in the TME it can induce PD-1 expression linked to metastasis (see figure 3)[53]. TGF-β is generally considered anti inflammatory and a tumor suppressor, but in the TME it becomes a tumor promoter, triggering cancer associated fibroblasts (CAF), epithelial/endothelial mesenchymal transformation (EMT), and vascular endothelial growth factor (VEGF), possibly mediated by methylation of its epigenome. The switch seems to occur in the TME. The relative concentrations of IFN-γ and TGF-β[54] or local hypoxia[55] may instigate this. Interestingly tumors treated with low-dose IFN-γ acquired metastatic properties while tumors infused with high dose IFN-γ regressed[54].

Perhaps TGF-β concentration in the TME can trigger a pleiotropic switch in low dose IFN-γ but at a higher dose IFN-γ can modulate its reciprocal in the TME. Cancer cells can also produce TGF-β. Pleiotropic IFN-γ is linked with metastatic behavior via upregulation of PD-1[56]. Angiotensin II stimulates the TGF-β signaling pathway[57]. This may in part explain the predilection for and severity of Covid-19 in males with comorbidities and for recurrent cancer in those previously in remission (see figure 3). On the other hand, females are robust producers of type I interferon[58]. Type 1 IFNs (IFN-α and IFN-β)

are first responders to any invading pathogen and trigger release of interferon-stimulated genes for synthesis of IFN-γ.

Its reciprocal, TGF-β, is vital to the maintenance of tolerogenesis and avoidance of autoimmunity. If TGF-β/IFN-γ is low, self recognition and tolerance may be compromised (autoimmunity)[59]. If TGF-β/IFN-γ is high, tumor associated antigens may be tolerated (cancer)[60]. An increased TGF-β/IFN-γ is also a risk factor for tissue fibrosis[61][62][63].

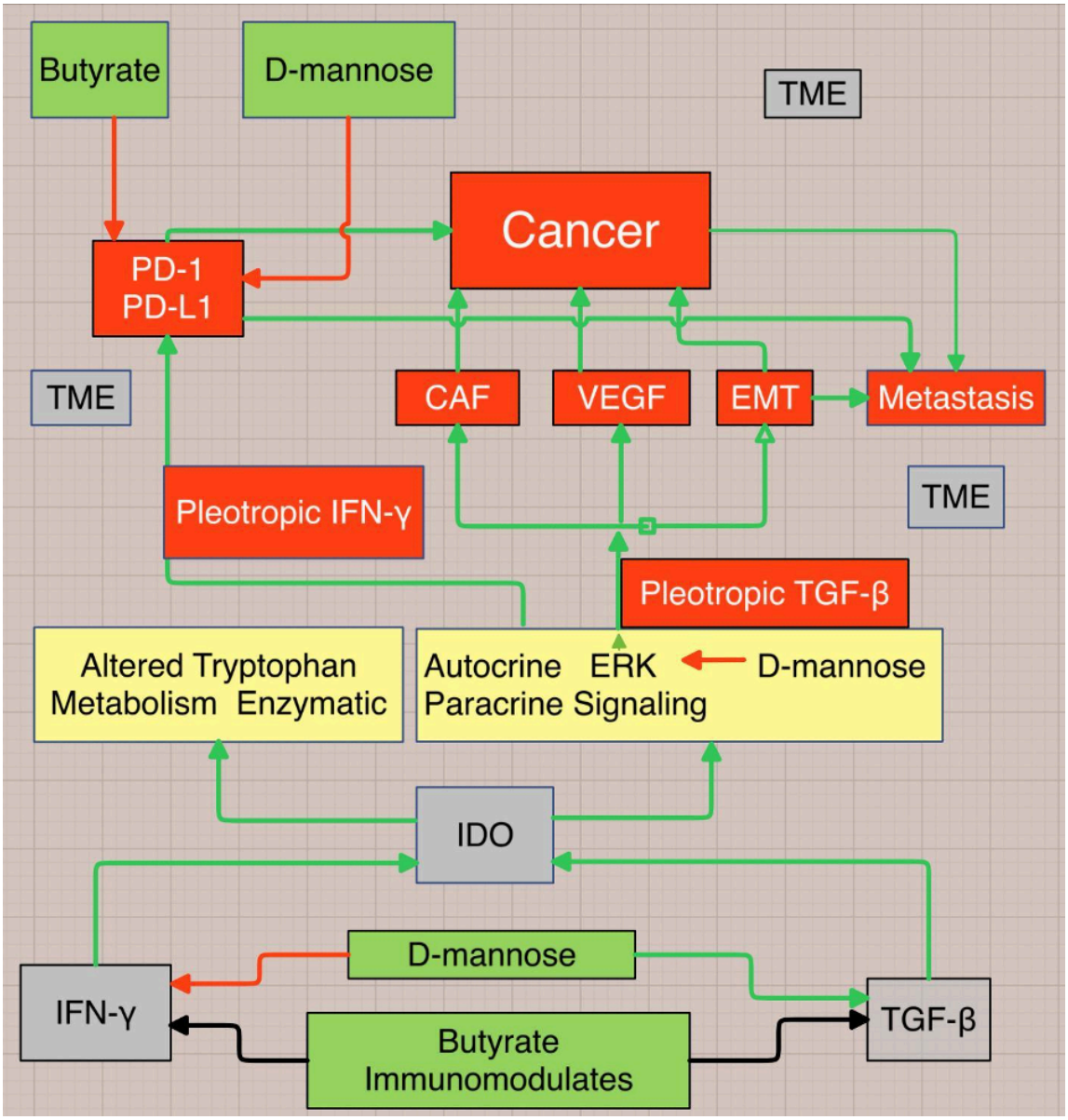

Figure 3. Proposed flow chart leading to cancer, demonstrating behavior of the cytokines TGF-β and IFN-γ in the tumor microenvironment (TME) that pleiotropically pivot from anti-inflammatory/tumor suppressor to tumor promoter (TGF-β) and from pro-inflammatory/tumor suppressor to tumor promoter (IFN-γ). TME=tumor microenvironment, CAF=cancer associated fibroblast, VEGF=vascular endothelial growth factor, EMT=epithelial or endothelial mesenchymal transformation, PD=programmed cell death protein-1, ERK=extracellular signal regulated kinase, IDO=indoleamine 2,3-dioxygenase. Figure 3 complements figure 2.

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5. GPCR

A. GPCR and SARS Cov2

Recent research, including a 2023 international symposium, has focused on autoantibodies targeting G-protein coupled receptors[64]. Their roles in Covid-19[65] and LC have been reported[66]. More than 800 different GPCRs have been identified, as of 2020[67]. In one study a majority of those with POTS possessed adrenergic and muscarinic cholinergic receptor autoantibodies. These are all G-protein coupled receptors, as is AT1R. Antibodies to these receptors are also associated with chronic fatigue syndrome (CFS), fibromyalgia (FM), Covid, LC[68],[69] and with other autoimmune diseases (including SLE, RA, Crohn's disease[70]). Many of these did poorly during the pandemic[71]. POTS or POTS-like symptoms develop in 10-50% of long haulers, yet there are significant hormonal differences, e.g., low cortisol in LC[72] but high cortisol in POTS[73],[74]. In POTS the adrenals respond to ACTH[75], but in LC they do not and symptoms can mimic adrenal insufficiency. ACTH receptors are GPCRs and autoantibodies might inactivate receptors, as GPCR antibodies can activate or inactivate[76]. POTS is easily diagnosed and pathogenesis points to the baroreflex and the neurohypophysis (see figure 4). The wealth of GPCRs in the involved nuclei[77] and the link between GPCRs and autoimmunity underscore the probable GPCR induced autoimmune pathogenesis for LC. Although LC and POTS are distinctly different and considered autoimmune, perhaps the wide variety of GPCR autoantibodies in combination with biologic individuality explains how one can be a subset of the other. It also appears, not surprisingly, that Covid-19 is also of autoimmune etiology in those with suboptimal gut microbiomes. The gut microbiome in LC[78] reflects that of Covid-19[79]. MCAS and EDS are linked to POTS[68]. Mast cells are activated by GPCR[80] and GPCRs are involved in the synthesis of collagen[81], as well as the perception of pain[82]. The microthrombosis in Covid-19 may be due to autoantibodies to GPCR bearing platelets[83][84] or phospholipids[85], perhaps reflecting some degree of gut dysbiosis. Autoantibodies were present in 50% of those with Covid-19 versus only 15% in healthy controls[86]. These 15% should probably re-evaluate their diets and gut microbiomes.

B. GPCR and Gut Dysbiosis

Gut-lung axis is based on the concept of continuity between their microbiota forming a microbial community[87][88]. ACE2 receptors are highest in lung and GI tract[89], primary targets for SARS. But

ACE2 is more than just an enzyme. It is negatively associated with gut dysbiosis[90]. If in addition to autoantibodies, ACE2 is depressed due to SARS, Ang II is additionally increased (see figure 4). This increases the risk of LC and POTS. Indeed the orthostatic intolerance in endurance athletes may be more a reflection of gut dysbiosis than dehydration and bradycardia.

G-protein-coupled receptors (GPCRs) are the largest class of cell surface receptors in fungi[91] and Candida is tightly linked to gut dysbiosis and LC[92]. GPCRs induce transition of commensal yeast forms to pathogenic hyphal forms[93] and are required for Candida biofilm formation[94]. Hyphal cell walls are rich in GPCRs[95] and may constitute the primary initial target of anti-GPCR autoantibodies. Surprisingly estrogen promotes innate immune evasion of Candida albicans through inactivation of the alternative complement system[96]. Candida may foster gut dysbiosis, when it moves from intestinal commensal to pathogen, e.g., after antibiotic therapy. SARS CoV2 may also be a ligand for GPCRs[97][98], especially those in the brain[99], e.g., NMDA-Rs that control taste, smell, and baroreflex and symptoms like brain fog and fatigue[100]. SARS CoV2 may trigger autoantibodies to GPCRs even in the absence of severe disease[101]. But females exhibit more robust T cell activation than males[102] and produce higher levels of interferon[103], predisposing autoimmunity (see figure 2). Fungal infections, especially Candida, elicit a robust IFN-γ response[104][105] and drive the serotonin to kynurenine pathway pivot (see figure 2).

Ang II also activates JAK/STAT pathways via the AT1 receptor (AT1R)[106]. JAK/STAT pathways are strongly linked to cancer, autoimmunity, and dementia. Cytokine receptors targeted by JAK/STAT signaling are GPCRs[107] and can be activated by autoantibodies[76]. For example, in alopecia areata, an autoimmune disease increased in LC, JAK transducers are upregulated[108]. The role of GPCRs in driving cancer has been acknowledged but remains unexplained. Perhaps the gut microbiome might provide answers[109]. JAK inhibitors are very popular in the treatment of autoimmune disease, cancer and dementia, all linked to the inflammatory triad of TGF-β, IL-6, IL-1β. Subclinical autoantibodies to GPCR can be present in otherwise healthy individuals[2].

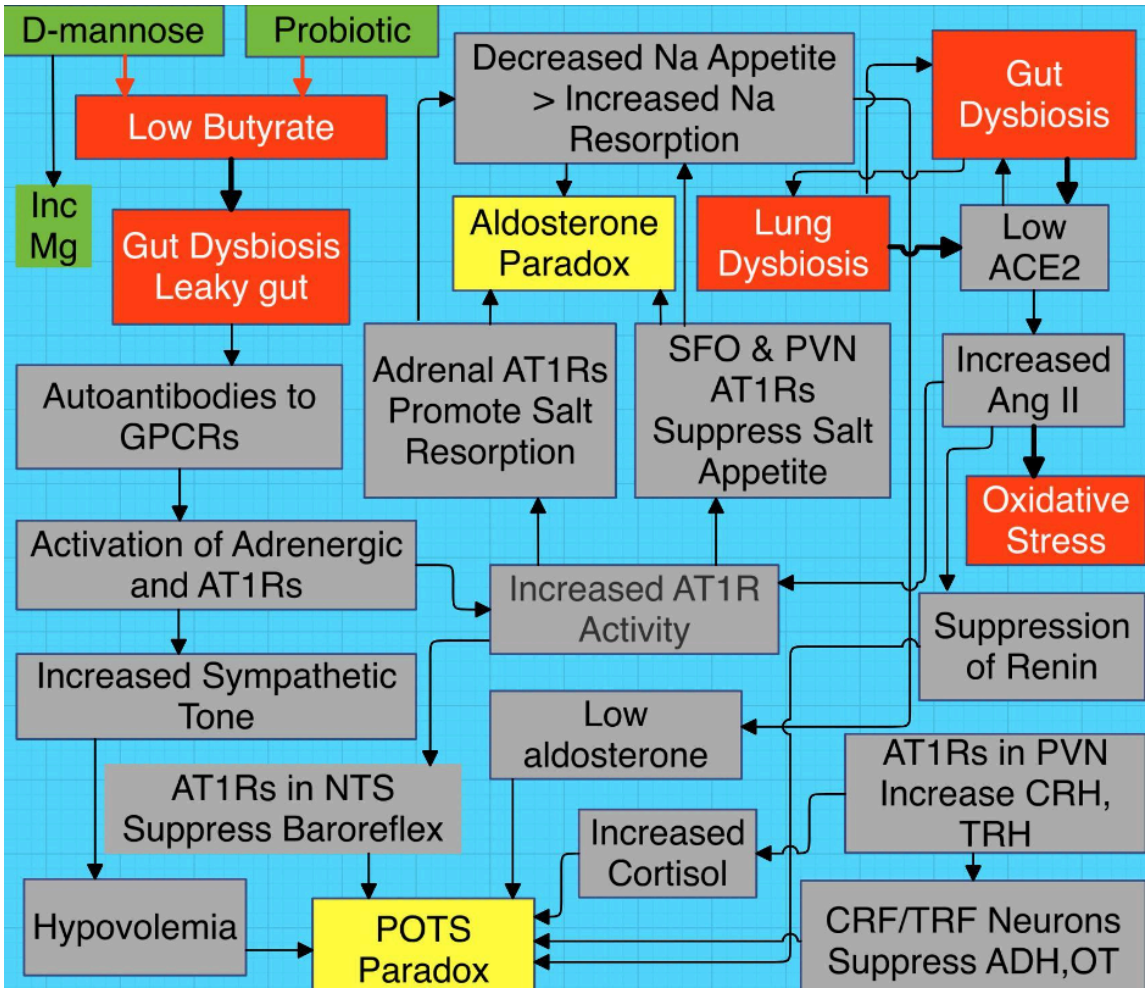

Figure 4. Proposed schema connecting gut dysbiosis (leaky gut) with elevated Ang II, elevated AT1R activity, and oxidative stress. Input from the aldosterone and POTS paradoxes are emphasized. PVN ADH/OT secreting neurons are type 1 magnocellular neurons and CRH/TRH are type 2. Activation of type 2's inhibit release of type 1's[110][111]. GPCR=G-protein coupled receptors, NTS=nucleus tractus solitarius, PVN= paraventricular nucleus, CRF= corticotropin releasing factor, TRF=thyroid releasing factor, AVP=arginine vasopressin, OT=oxytocin, Mg=magnesium

6. HRV and the Triple Play

A. HRV

The cytokine triad of TNF-α[77][112][113], IL-6[111][114], and IL-1β[111] are negatively linked to HRV and positively linked to CRP[64]. Cancer diagnosis and prognosis are linked to TNF-α[115], IL-1β[116][117], and IL-

6. Low HRV can alert one to asymptomatic infection and inflammation[118][119], anxiety[120], depression[121][122], cognition and neurodegenerative disorders[123][124], psychosis spectrum disorders[125], cancer[126][127], cardiovascular disease[128][129], stroke[130][131], T2DM[132][133], severe Covid-19[134], Long Covid[135][136][137], MS[138], SLE[139], and RA[140]. Central aka visceral adiposity (waist hip ratio, waist circumference) is negatively related to HRV and a much more sensitive indicator than BMI[141][142][143]. Peripheral obesity is not only not associated with a low HRV but is protective with elevated HRV[144].

B. Triple Play

Butyrate enhances mitochondrial function during oxidative stress[145] and rescues tryptophan[146]. Serotonin cannot cross the BBB, but tryptophan can, and by rescuing tryptophan, butyrate can increase brain serotonin (inhibitory neurotransmitter). Butyrate also suppresses IDO activity[147] and immuno-modulates IFN-γ and TGF-β[148]. Butyrate producing gut microbiota[149], gut biodiversity, and production of SCFAs[150] are associated with elevated HRV. Unfortunately butyrate producing Bacteroidetes species decline with age[151]. Butyrate alleviates obesity and related comorbidities[152][153][154]. But not all SCFAs have beneficial effects on human health. Acetate not only promotes obesity[7][155] but can also be used by tumor cells as an energy substrate during oxidative stress[156]. Postbiotic butyrate bypasses the negative effects[6] of Bacteroides produced acetate[157].

Prebiotic D-mannose assists dietary fiber in propagating butyrate producers[158]. It enhances intestinal barrier integrity[159] and opposes the proinflammatory effects of glucose and fructose[160]. D-mannose opposes diet induced obesity[161], positively associated with CRP and negatively associated with HRV[162]. Central adiposity is adverse and linked to elevated CRP, while peripheral adiposity is favorable and not so linked[163][164]. D-mannose not only downregulates gut dysbiosis by enhancing intestinal barrier integrity[158][159] but also suppresses the adipokine and cytokine triad (TNF-α, IL-6, IL-1β)[165][166][167], linked to cancer[168][169], cardiovascular disease[170], stroke[171], obesity[172], diabetes[173], neurodegenerative disease[174], and autoimmune disease[175][176]. D-mannose suppresses autoimmune diseases, e.g., T1DM, asthma, and SLE[177] by suppressing IFN-γ[39][122]. D-mannose can suppress ERK (extracellular signal regulated kinase) signaling pathways (see figure 3)[178] integral to TGF-β induced organ fibrosis[179], transformation of fibroblasts into CAFs[180], epithelial/endothelial mesenchymal transformation (EMT)[181], and VEGF synthesis[182]. D-mannose inhibits programmed cell death protein-

1 (PD-1) (see figure 3)[183], upregulated in Covid-19[184]. This pathway to tumorigenesis is separate but complementary to that induced by TGF-β[185] (see figure 3). Probiotics also increase HRV and have proven efficacious in LC[186][79]. Probiotics and antioxidants are nutraceuticals that have proven most effective in Covid-19 and LC[187]. *Prebiotic is more important than postbiotic*, as SCFA producing bacteria cannot flourish without dietary fiber or its equivalent (d-mannose).

7. Conclusion

Gut (and lung) dysbiosis is at the root of the vast majority of our health problems, including cancer, dementia and autoimmunity, obesity, and post viral fatigue syndrome (LC, CFS, FM, Epstein Barr Virus), infectious diseases. A leaky gut is connected to autoantibodies that activate AT1Rs and adrenergic receptors. The former are at the heart of

baroreflex dysfunction via paracrine pathways involving the aldosterone and POTS paradoxes.

The growing epidemic of LC has spawned tremendous suffering and economic loss. The bidirectional correlations between gut dysbiosis and inflammatory cytokines, disease, and HRV/KTR/CRP make supplementation the most feasible path to better health. This triple play of prebiotic d-mannose, a probiotic of diverse butyrate producing bacteria, and postbiotic butyrate can provide a strong assist. Limit inflammaging and oxidative stress (see figures 1,4) and embrace antioxidants to maintain mitochondrial health. If disease is sufficiently severe, the triple play can be super sized with FMT that has proven very effective in cancer, autoimmune disease, and dementia. The deteriorating nutritional value of our food and the regrettable redirection of our choices driven by the flavor enhancing glutamate additive have accelerated our declining health. This combination of d-mannose, probiotics rich in bifidobacteria and lactobacilli, and butyrate (FMT lite) should increase HRV and curb the risks for the discussed diseases and myriad other maladies. Adding exercise to this regimen further energizes HRV[188]. Monitoring a rising HRV and possibly a falling waistline[142][143] can provide positive feedback and boost incentive during the effort. This approach affords the individual an inexpensive and convenient path to a more healthful existence without necessarily forcing dietary and other lifestyle changes. The physiology and biochemistry are relatively straightforward, but biologic individuality and many other factors make transference to the clinical arena less straightforward. Unfortunately suitable clinical trials are unlikely, given the global emphasis and general preference for pharmaceutical solutions over a supplemental approach for any ailment. However, the approach described in this article doesn't need a randomized

controlled trial for validation, as HRV provides instantaneous feedback on efficacy for the most important individual versus a random group of individuals. Although obtaining an accurate HRV via bluetooth enabled chest strap, armband, finger sensor, or wristwatch can be tedious, HRV is especially useful in following the benefits of dietary changes,[189] and significant benefits to a more healthful lifestyle and lifespan[190] await.

"Death sits in the bowel." Hippocrates (400 BC)

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