Review

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

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aReview

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

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Abstract: "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, triggers altered tryptophan metabolism and release of proinflammatory cytokines, predominantly TNF-α, IL-6, and IL-1β, that 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 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. The triple play of a prebiotic (d-mannose), probiotic (bifidobacteria and lactobacilli), and postbiotic (butyrate) might improve intestinal barrier integrity, suppress the inflammatory cytokine triad, balance IFN-γ and TGF-β, depress KTR, elevate HRV, and extend lifespan.

Highlights

1. Butyrate (and γ-aminobutyric acid or GABA) producing bacteria are hallmarks of a healthy gut microbiome
2. Butyrate immuno-modulates IFN-γ and TGF-β, which are imbalanced in gut dysbiosis
3. TGF-β regulates tolerogenesis - too little and some self antigens may not be tolerated, too much and some tumor associated antigens may be tolerated
4. Excesses of either IFN-γ or TGF-β upregulate IDO
5. Females are robust producers of IFN-γ, which triggers the enzyme IDO, increasing the risk of neurodegeneration and autoimmune disease (female preponderance)
6. Angiotensin II (comorbidities) stimulates TGF-β, which triggers intracellular signaling by IDO, increasing the risk for TME and cancer (male preponderance)

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Introduction

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

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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 neurotransmitters glutamate and GABA 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, 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 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 that of the four traditional vital signs.

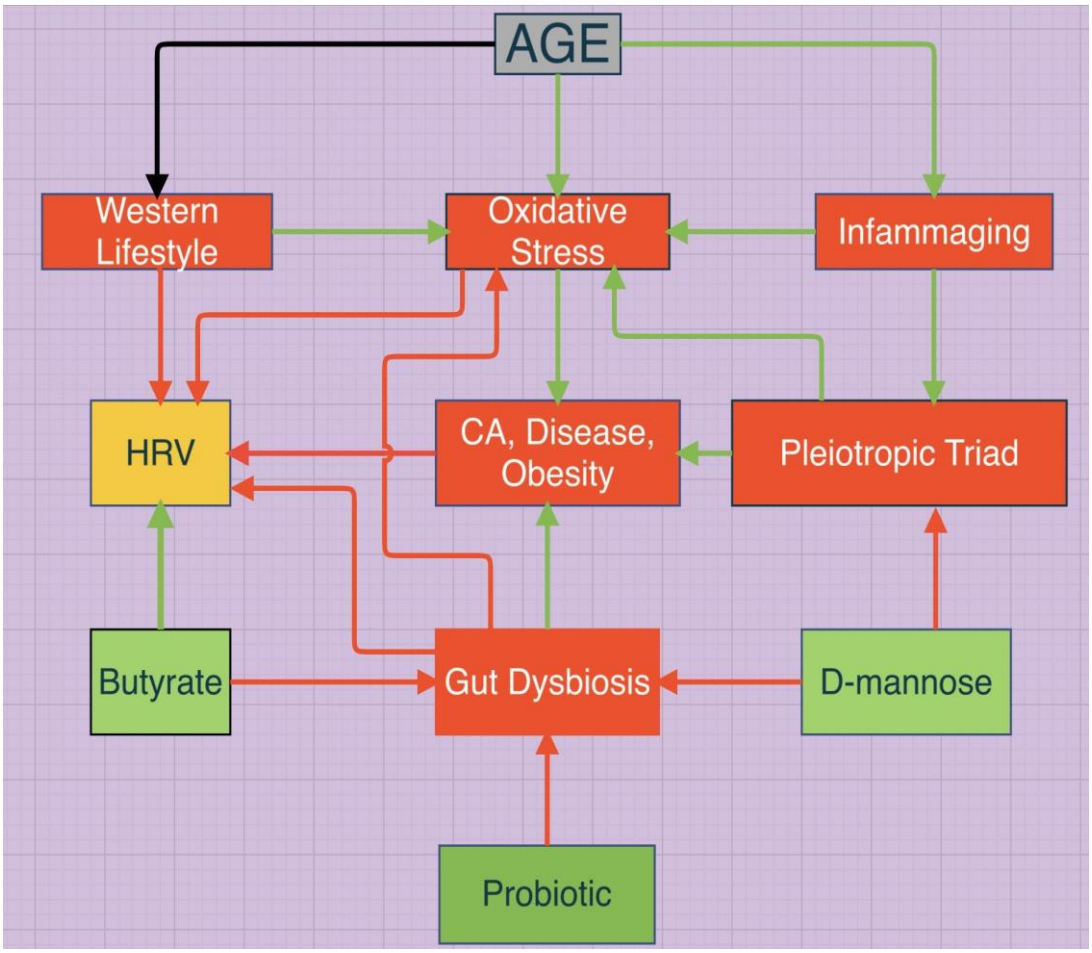

Figure 1. Pathways to a healthy HRV and enhanced lifespan are demonstrated. The western lifestyle includes an increased calcium to magnesium ratio, vitamin D deficiency, decreased antioxidants, toxins, e.g., smoking. TNF-α, IL-6, IL-1β comprise the triad. The trigger for the pleiotropic switch is not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

1. **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.

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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 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 GABA producing counterparts and create an imbalance in excitatory and inhibitory neurotransmission in the ANS [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.

2. 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, 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 glucagon-like peptide 1 (GLP-1). Benefits of GLP-1 include appetite suppression, stimulation of insulin [15], and decrease in fasting blood sugar [16], curbing 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 (see Figure 2) and may drive the pivot [19] (see Figure 2). Tryptophan depletion lowers HRV (and increases KTR) [20]. Increased tryptophan intake (eggs) increases HRV, which appears to be driven by the subsequent increase in serotonin [21].

KTR, an indicator of rate-limiting IDO/TDO 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 RA [29], and SLE [30]. Infectious diseases are also linked to an elevated KTR [31] with a ratio that 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.

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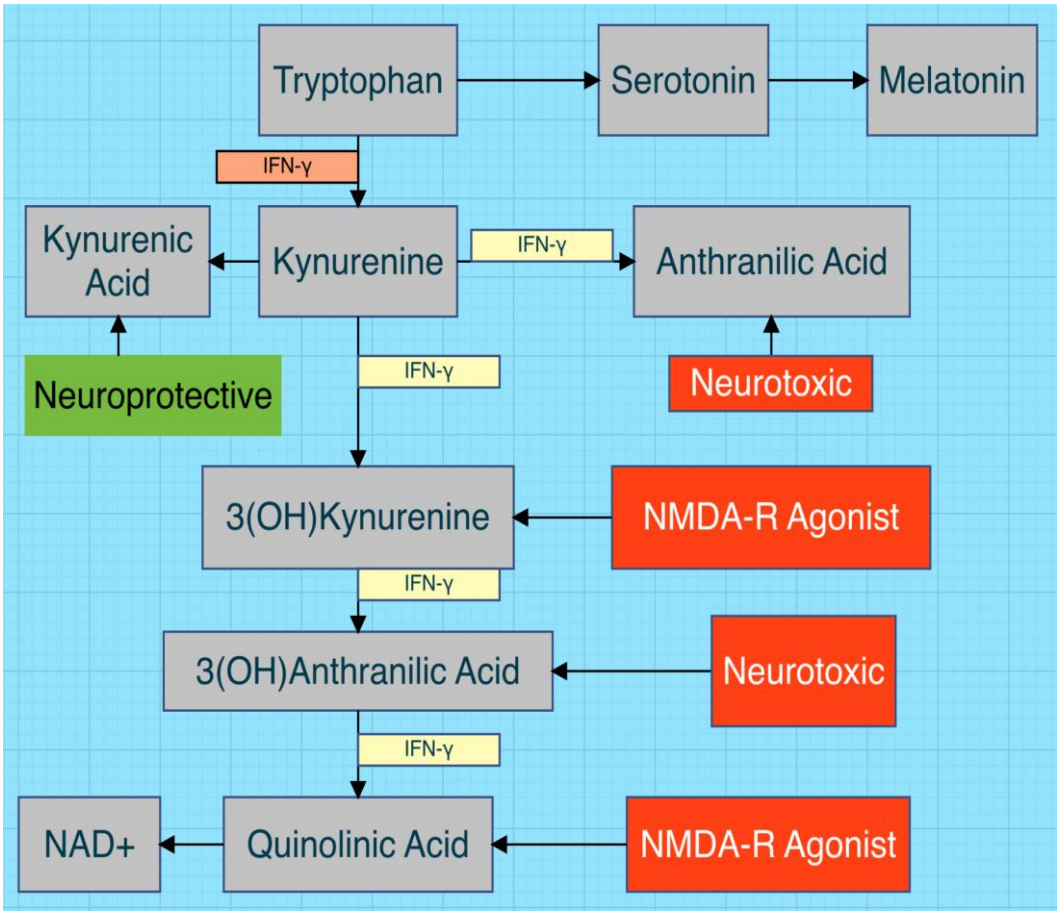

Figure 2. Altered tryptophan metabolism is demonstrated. NMDA-R is an excitatory glutamate receptor. Note the upregulating presence of the proinflammatory cytokine IFN-γ [24,36,37].

3. 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 transplant in both cancer and autoimmune disease.

Elevated IFN-γ characterizes parasitic infestations. In such patients this cytokine was positively associated with a good prognosis in Covid-19 [41]. Low baseline IFN-γ response could predict hospitalization [42] and post discharge fibrosis in COVID-19 patients [41]. On the other hand its reciprocal, TGF-β, was positively associated with Covid-19 severity [43] and fibrosis [44]. 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 [45]

However, IDO is not only an enzyme induced by IFN-γ (increased KTR) but also an intracellular signal transducer induced by TGF-β (TME) [46–48]

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 [49]. 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) [50]. TGF-β is generally considered anti

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inflammatory and a tumor suppressor, but in the TME it becomes a tumor promoter, triggering cancer associated fibroblasts (CAF), vascular endothelial growth factor (VEGF), and epithelial/endothelial mesenchymal transformation (EMT), possibly mediated by methylation of its epigenome. The switch seems to occur in the TME. The relative concentrations of IFN-γ and TGF-β [51] or local hypoxia [52] may instigate this. Interestingly tumors treated with low-dose IFN-γ acquired metastatic properties while tumors infused with high dose IFN-γ regressed [51].

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 [53]. Angiotensin II stimulates the TGF-β signaling pathway [54]. 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 [55]. 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) [56]. If TGF-β/IFN-γ is high, tumor associated antigens may be tolerated (cancer) [57]. An increased TGF-β/IFN-γ is also a risk factor for tissue fibrosis [58–60]

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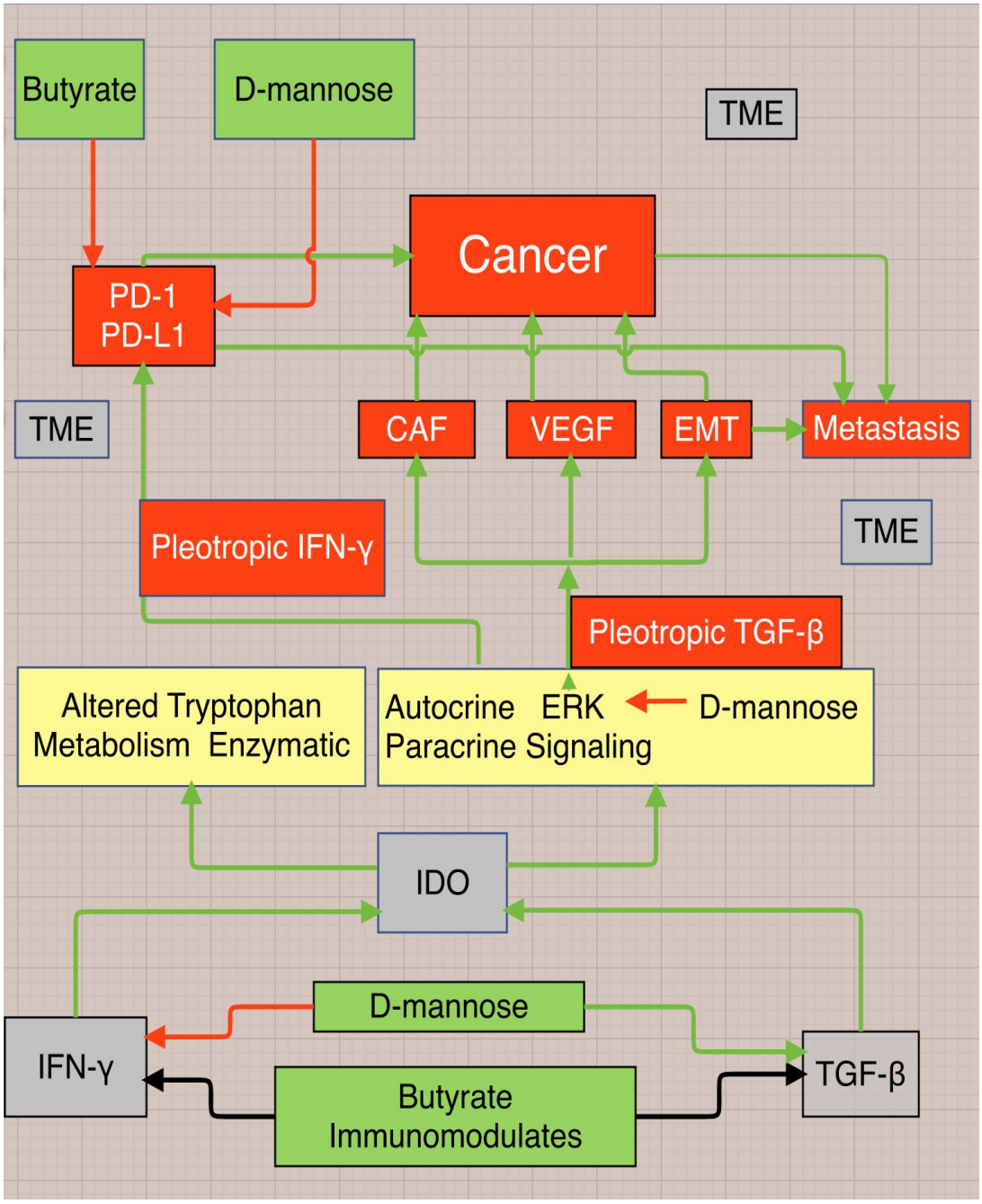

Figure 3. Proposed flow chart leading to cancer, demonstrating behavior of the cytokines TGF-β and IFN-γ in the tumor microenvironment (TME) that pleiotropically pivot from anti-inflammatory/tumor suppressor to tumor promoter (TGF-β) and from pro-inflammatory/tumor suppressor to tumor promoter (IFN-γ). 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.

4. HRV and Inflammatory Cytokines, Cancer, Disease, Obesity

The cytokine triad of TNF-α [61–63], IL-6 [61,64], and IL-1β [61] are negatively linked to HRV and positively linked to CRP [64]. Cancer diagnosis and prognosis are linked to TNF-α [65], IL-1β [66,67], and IL-6. Low HRV can alert one to asymptomatic infection and inflammation [68,69], anxiety [70], depression [71,72], cognition and neurodegenerative disorders [73,74], psychosis spectrum disorders [75], cancer [76,77], cardiovascular disease [78,79], stroke [80,81], T2DM [82,83], severe

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Covid-19 [84], Long Covid [85–87], SLE [63,89], and RA [90]. Central aka visceral adiposity (WHR, WC) is negatively related to HRV and a much more sensitive indicator than BMI [91–93]. Peripheral obesity is not only not associated with a low HRV but is protective with elevated HRV [94].

5. Butyrate, D-mannose, and Probiotics

A. Butyrate

Butyrate enhances mitochondrial function during oxidative stress [95] and rescues tryptophan [96]. Serotonin cannot cross the BBB, but tryptophan can, and by rescuing tryptophan, butyrate can increase brain serotonin (inhibitory neurotransmitter). Butyrate also suppresses IDO activity [97] and immuno-modulates IFN-γ and TGF-β [98]. Many of the same intestinal bacteria that produce butyrate possess glutamate dehydrogenase and can produce GABA [99] and the most recent research suggests that GABA can not only activate GABA receptors locally but may also enter circulation and cross the blood brain barrier (BBB) [100,101] to activate predominantly inhibitory signals. Some GABAergic nuclei in circumventricular organs are parasympathetic centers and don't have a BBB.

The quantity of butyrate producing bacteria has generally been considered the gold standard for evaluating the health of the gut microbiome and the gut-brain axis [102], but neurotransmission by GABA, produced by these same bifidobacteria and lactobacilli, seems unacknowledged [103,104]. Butyrate producing gut microbiota [105], gut biodiversity, and production of SCFAs [106] are associated with elevated HRV. Unfortunately Bacteroidetes species (and butyrate) decline with age [107]. Butyrate alleviates obesity and related comorbidities [108–110]. But not all SCFAs have beneficial effects on human health. Acetate not only promotes obesity [7,111] but can also be used by tumor cells as an energy substrate during oxidative stress [112]. Postbiotic butyrate bypasses the negative effects [6] of Bacteroides produced acetate [113].

B. D-mannose

Prebiotic D-mannose improves the gut microbiome by increasing its biodiversity and butyrate producers, preventing gut dysbiosis [114,115]. D-mannose prevents diet induced obesity [116], positively associated with CRP and negatively associated with HRV [117]. Central adiposity is adverse and linked to elevated CRP, while peripheral adiposity is favorable and not so linked [118,119]. D-mannose not only downregulates gut dysbiosis by enhancing intestinal barrier integrity [114,115] but also suppresses the adipokine and cytokine triad (TNF-α, IL-6, IL-1β) [120–122], linked to cancer [123,124], cardiovascular disease [125], stroke [126], obesity [127], diabetes [128], neurodegenerative disease [129], and autoimmune disease [130,131].

D-mannose suppresses these autoimmune diseases like T1DM, asthma, and SLE [132] by suppressing IFN-γ [39,115]. D-mannose can suppress ERK (extracellular signal regulated kinase) signaling pathways (see Figure 3) [133] integral to TGF-β induced organ fibrosis [134], transformation of fibroblasts into CAFs [135], epithelial/endothelial mesenchymal transformation (EMT) [136], and VEGF synthesis [137]. D-mannose inhibits programmed cell death protein-1 (PD-1) (see Figure 3) [138], upregulated in Covid-19 [139]. This pathway to tumorigenesis is separate but complementary to that induced by TGF-β [140] (see Figure 3). Probiotics also increase HRV and have proven efficacious in LC [142,142]. They engage the prebiotic d-mannose and enhance the butyrate surge.

6. Other Considerations

There are other determinants of a low HRV, e.g., micronutrient deficiencies, especially vitamin D, which not only increases HRV [143] but also enhances gut biodiversity and growth of SCFA producers [144,145]. Imbalances, especially Ca:Mg [146], of many other micronutrient deficiencies, including B-12, C, E, magnesium, iron, zinc are associated with low HRV but the evidence is not definitive [147–149]. Vitamin B6 goes unnoticed, yet its active form (pyridoxal phosphate) is a required cofactor for conversion of glutamate to GABA and of tryptophan to serotonin and serotonin to melatonin. HRV reflects the state of our personal health and can be utilized to follow the efficacy of any changes in our lifestyle. KTR is negatively linked to HRV, but not yet commercially available [36,79]. CRP is also negatively correlated with HRV [146] and positively correlated with oxidative

stress [149], smoking, heavy metal exposure [150], aromatic hydrocarbon exposure [151]. HRV is negatively linked to the western diet and sedentary lifestyle [152].

Conclusion

The described strong correlations between

1. HRV and gut dysbiosis
2. HRV and inflammatory cytokines
3. HRV/KTR/CRP and disease
4. Gut dysbiosis and disease

make diet (and exercise) the primary controllable causative links to good health. This triple play of prebiotic d-mannose, a probiotic of diverse butyrate producing bacteria, and postbiotic butyrate can provide a strong assist. But it all boils down to limiting oxidative stress (see Figure 1) and embracing antioxidants to maintain mitochondrial health. 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. The triple combination of d-mannose, probiotics rich in bifidobacteria and lactobacilli, and butyrate should increase HRV and curb the risks for the discussed diseases and myriad other maladies. Adding exercise to this regimen further energizes HRV [153]. Monitoring a rising HRV and possibly a falling waistline [93,118] 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 [143] and significant benefits to a more healthful lifestyle and lifespan [154] await.

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

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