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Review Article

# Dietary Co-Metabolism within the Microbiota-Gut-Brain-Endocrine Metabolic Interactome

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## Abstract

We have established that many metabolic biomes exist within the complex mammalian gut. Substantial metabolism happens between the host and resident microorganisms within these biomes and is called co-metabolism. The net result of small molecule interactions within these biomes has now described collectively as a "metabolic interactome". In this review, we discuss diet-microbiota-gut-brain-endocrine axis delving deeper into understanding of mammalian biochemistry to include metabolism arising from diverse metabolomes within biologic compartments of the host and their metabolic interactions to emphasize how bacteria can affect the brain and the hormonal axes in a process of co-metabolism. Recent findings stemming from exploration of the microbiota-gut-brain axis suggests hormonal and neuroendocrine activity of this metabolic interaction can affect vastly diverse and distal host systems. We also explore how disruption of the gut microbiota affect processes such as dysbiosis, the regulation of the hypothalamic-pituitary-adrenal axis and even our neurochemistry from mental and behavioral health to memory, depression, mood, anxiety, obesity and the development of the blood brain barrier. Metabolites of the gut-brain-endocrine axis and our overall gut health constantly shape the host phenotype in ways previously unimagined to exercise either positive or negative effects on human health.

**Keywords**: Antibiotics; Microbiota; Neurotransmitters; Gut Brain Axis; Metabolomics; Endocrinology; Microbiome; Behavior; Gastrointestinal; Hormones; HPA; CRISPR-Cas

## Introduction

A mutually beneficial relationship exists between the host and its resident microbiota. Bacterial products or metabolites from gut commensals are often useful for the host in many aspects including co-metabolism and chemical signaling. This review focuses on a several of pathways of this symbiotic co-metabolic relationship. When one considers the microbiota we think of a labile and varied collection of species of bacteria, *fungi* or parasitic organisms that reside within or upon a host at any given point in time. Often the literature focuses on the vast bacterial community that resides primarily in the lower gut and largely lives in a symbiotic relationship with the host. However, one can include exogenous and endogenous microorganisms that also contribute to the net effect on the host through these same systems. The intestinal microbiome is increasingly important as it can exert some control over our biochemistry; including hormones, hypothalamic-pituitary-adrenal axis (HPA) and neurobiology to contribute to the evolutionary fitness of the host and adaptation of the organism as well as to disease.

There is no question each species of gut bacteria can engage in complex biochemistry with the host and host systems, which we refer to here as "co-metabolism". We know commensal, symbiotic and pathogenic microorganisms in any microbiota do contribute to co-metabolism [1]. Co-metabolism is metabolism that occurs between the microbiome and host metabolic systems, e.g., metabolism derived from such organs as liver, kidney and other human metabolic process and enzymes, which come in contact with the circulation by any means and can serve as substrates or

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carbon courses for the microbiome. This interaction results in "biochemical metabolite crosstalk between the small molecules that arise from co-metabolism, which ultimately manifests as a net end-product accumulation of small molecule metabolites [2]. The microbiota and their collective genetic material are known as the "second genome" within us [1]. This second genome expresses phenotypic effects that are distinguishable from the host, but may be measured commonly as metabolism indistinguishable from that of the host as the production of microbial metabolites along with those of the host. Many of these effects occur indirectly and through yet unknown mechanisms. Perhaps one could envision scenarios where metabolism research was driven by intestinal microbiota without our ever fully understanding the implications of the second genome and its contribution to our physiology and biochemical research.

The microbiota-gut-brain (MGB) axis is a network of communication signaling of metabolites and other molecules between the gut and the brain, which among other things, modulates the GI tract and the central nervous system (CNS) contributing to a relationship between digestive health and cognitive function. The MGB axis effectively demonstrates metabolite cross-talk, which is the biochemical co-metabolism that occurs between the host and the microbiota that can be thought of as signaling pathways between host metabolism and pathogenic or commensal resident gastrointestinal (GI) bacterial metabolism. Previously, we explored the gut-brain metabolic interaction, which is one segment of the "gut-brain-endocrine axis" [3]. However, this microbiota-gut-brain analogy only addresses the neuro-cognitive component of a very complex metabolic interaction within mammalian systems [3]. The concept of the MGB axis can be considered part larger system that includes the endocrine stress, HPA, and immune system. Moreover, to underscore the relationship between the digestive system and cognitive-hormonal function or dysfunction we have now adopted a more informative term, namely the microbiota-gut-brain-endocrine interactome, building on the molecular biology concept of an interactome, which is the whole set of molecular interactions in a particular cell or biochemical system. The term interactome is used here to describe the co-metabolism as net product of complex interactions among and between these systems.

In terms of metabolite axis, what we do not know is whether this flow occurs largely anterograde or retrograde or some version of both. There is suggestion that a bi-directional communication system exists between the intestinal microbiota and the brain which is important in psychiatric disease, according to Collins and colleagues [4]. Further, what is also not well characterized, in regard to co-metabolism, is the concept of "Leaky Gut" that may play a role in the movement of metabolites. It is often described as an increase in the permeability of the intestinal mucosa, which could allow bacteria, toxic metabolites and bacterial toxins to leak into the bloodstream. Finally, we need better understand the role of the liver and portal system in further processing or moving these bacteria-derived metabolites to distal sites. Also, the concept of dysbiosis, defined as a microbial imbalance involving the body, often localized to the gut, can be another factor when considering microbiota-gut-brain homeostasis.

When considering dietary aspects of these net interactions the reader must understand the new concepts represent novel pathways and divergent views from dogma and classic understanding, which builds on our previous work of the metabolic interaction between any host and any given organism at the small molecule level [5]. Therefore, we must start with a carbon source for these small molecule metabolites, either dietary or from metabolism. The co-metabolism produces protein-protein, protein-carbohydrate, carbohydrate-nucleic acid or multiple lipid interactions that often contribute by-products to the host of another genome's metabolism. Ultimately, the intestinal microbiota can communicate with the brain via these axes' to influence aspects such as brain development and behavior and influence a broad spectrum of diseases. The interactions can be either enzymatic or non-enzymatic integrating metabolism between the endogenous host and the exogenous organisms residing within or upon the host that produce direct products or by-products of co-metabolism. We can call these transgenomic metabolic effects; gene products, whether phenotypic or derived from humanized animal models (also called humanized extended genome mice), which are mice that have human-derived genes in extended genomic system or in experimental conditions like germ free mice colonized with human flora [6].

## The Microbiota-Gut-Brain-Endocrine Axis

The co-metabolism is a complex phenomenon between a host and its commensal microbiota are essential for life processes and represents symbiosis at a biochemical level, wherein otherwise indigestible nutrients become cofactors, essential amino acids, and vitamins all of which are vital to health and nutrition [8,9]. This interchange appears to be more critical than previously appreciated [7] and a bidirectional neuro-humoral and neuroendocrine communication system is suggested. Indeed, the microbiota-gut an integral component of the gut-brain metabolic axis, which captures the relationship between the digestive system and neural function including cognitive functions. Our diet, lifestyle and medications, particularly antibiotics, influence and shape the gut microbiome throughout our life. The converse is also true. The interaction is always in flux and the result is net metabolite or end-product production, with positive and negative effects on human health.

The interaction of chemical signaling molecules and electrical messages between the brain and gut can modify our phenotype [10]. Newer and integrative analysis of diverse metabolomic data, beyond correlative analysis, has led to the discovery of previously unknown relationships between our gut microbiota and human health and disease states with a complex interchange beyond the scope of current understanding. It has fostered a new branch of the so-called 'omics' areas of research. To demonstrate the complexity, a recent study involved the metabolic reconstruction of *Bacteroides thetaiotaomicron* of the human microbiota, which alone consisted of 1,488 reactions, 1,152 metabolites, and 991 known genes. The net result of this interactome model expands to consist of 7,239 reactions, 5,164 metabolites, and 2,769 genes [11]. Thus, factors disturbing the microbial homeostasis potentially disturb

the integrity of the host metabolism and could contribute to pathophysiology. Conversely, we can utilize this approach to find new ways to affect health and wellness.

Key to co-metabolism of the gut-brain is a well-known finding that the microbiota produces over 40 known neurotransmitters, including an approximate estimate 50% of the dopamine and 90% of the serotonin in the body used in neurotransmission [12]. A wide mix of extrinsic and intrinsic neuro-psychotrophic-modulating microbes and pathogens affects these and other gut processes. Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells [12]. The impact of the gut microbiota on the CNS serotonergic system is not limited solely to microbiota-deficient animals, since administration of *Bifidobacteriuminfantis* to rats resulted in reduced 5-HIAA concentrations when one considers the cortex [13]. Considering the net metabolic cross-talk is staggering, so it is not surprising that the human CNS is under constant assault or, conversely, does benefit from a wide mix of extrinsic and intrinsic neuro-psychotropic-modulating microbes and pathogens. In addition to bacteria, other pathogens included are viruses, fungi, environmental and microbial-derived small non-coding RNAs, and so forth, so understanding the net metabolic cross talk is a formidable task [14].

## Microbiota-Gut-Brain-Neuroendocrine Axis and Psychiatric Disorders

In regard to the microbiota-gut-brain axis, co-metabolism is not limited to commensal microbes. It includes contributions from pathogenic microbes, fungi and other parasitic life forms that have coevolved with humans and can produce altered microbiome-derived signaling or produce toxins and other disease-inducing agents, which have been implicated in the development of numerous neurodegenerative diseases [15]. For example, Alzheimer disease (AD) where yeast and fungal proteins like (1,3)-β-glucan, fungal polysaccharides or bacterial lipopolysaccharides (LPS), can lead to disseminated and diffuse mycoses in the peripheral blood of AD patients [15]. Viral agents like viroids, viroid-specific ssRNA, miRNAs, adenovirus, herpes simplex virus-1 (HSV-1), HIV-1, CMV, EBV and Hepatitis has been associated with AD and AD pathology, as well as contribute to toxic metabolites associated with other diseases [16].

Pathogenic microbes, particularly gram negative obligate intracellular bacteria, pneumonia-causing *Chlamydophilapneumoniae* and *Toxoplasma gondii* have also been associated with AD [17] new connections are sure to be found, such as in cancer [18] and other diseases as useful diagnostic tools such as "The Ames Test " had demonstrated decades ago [19]. Moreover, many diseases have an inflammatory or oxidative stress component to their pathobiology. Pathogenic or even innocuous microorganisms through these inflammatory pathways could mediate many of the deleterious effects observed [20,21].

Recently, it was established that intestinal bacterial microbiomes play important roles including controlling integral segments of our neurobiology. Mental and even behavioral health including; memory, depression, mood, anxiety or even food preferences are affected [22]. While the degree to which intestinal microbiota affects dietary preference is not well defined [23] there is abundant evidence that that the dopamine and serotonin generated by gut microbiota do play a regulatory role [24,25]. In mice, certain strains of bacteria increase behaviors considered to be an index of anxiety. In humans, drinking a probiotic containing *Lactobacillus casei* improved mood in those with anxiety or vegetative signs of depression [24,26]. Abnormal behavior and cognition together with dysbiosis, the so-called pathobiont overgrowth syndrome, can be cause and consequence of the leaky gut and promote loss of the intestinal barrier [27,28].Conversely, probiotics may prevent leaky gut consequences and restore colonization resistance to the species contributing to "leakiness [29].

Co-metabolism within the gut-brain-endocrine interactome is suspected to play a rolein other neurodegenerative disorders with microbial-driven connection [30] such as, Parkinson disease (PD) and Amyotrophic Lateral Sclerosis (ALS) [31] where known microbes have been implicated in contributing to the susceptibility and pathogenesis of these [32] and the AD processes. Because AD is clearly a multifactorial disease, and there are multiple biological pathways by which brain cells can dysfunction, perhaps it is not too surprising that multiple and complex microbial insults could contribute to AD, including the spreading of pathological signals throughout the CNS and in a variety of Gut Brain Endocrine axis pathways. Conversely, probiotic treatment has been shown to improve diabetic complications in synaptic activity and cognitive function [33].

There is increasing interest in the functional significance of the trace amines and their possible role in the etiology of neuropsychiatric disorders [34]. These are compounds chemically related to the catecholamines and 5- hydroxytryptamine (5HT). CSF levels of 5-hydroxyindoleacetic acid (5HIAA) and homovanillic acid (HVA) are derived from and may provide an index of metabolism of the parent amines (5HT, dopamine) [35] in the CNS. Bacteria can produce these metabolites, which are traced to the CNS [36]. However, the presence of the metabolites of various catecholamine, phenolic [37] and indolic trace amines has been studied in the CSF [38], but until recently, relatively little was known about the contribution of thesecatecholamines from the gut microbiota [39]. Collins and colleagues found changes in both brain chemistry and behavior regarding the microbiota [30].

We engage in approaches to assess and characterize the gut intestinal microbiota with culture and sequencing-based techniques and this has been carried out by Collins et al. to include patients with primary psychiatric disorders such as anxiety and depression. In addition, translational research approaches have included the colonization of germ-free mice with microbiota from patients with primary psychiatric disorders to examine brain-gut linkage and identify classes of bacteria that influence brain function that may be beneficial in treating disorders such as anxiety or depression, that occur in patients with chronic gastrointestinal illnesses, such

as irritable bowel syndrome [40,41].

It is known that psychiatric disorders frequently occur in patients with gastrointestinal diseases, illustrating that the microbiota-gut brain axis is clinically relevant in neural and endocrine pathways and neuropsychiatry. This is either through inflammatory or functional mechanisms, for example irritable bowel syndrome, which is also suspected as being a disorder of the gut-brain axis, where GI symptoms are associated with frequent comorbidities of depression and anxiety. Here, it is the intestinal microbiota that is implicated to play a role in anxiety, depression, autism, schizophrenia and Alzheimer disease to name a few.

## Autism and Relationship to the Microbiota

Although there has been much research into autism or autistic spectrum disorder (ASD), there is room for considerable conjecture regarding the etiology of these developmental brain disorders. The microbiota–gut–brain axis is but one proposed mechanism[42,43]. Beyond maternal infection and the stress of pregnancy, it has been shown these factors may increase the risk for neuro-developmental disorders such as schizophrenia, autism or other cognitive and behavioral symptoms in later life, depending on the timing of the prenatal insult. Autism and ASD are serious problems and present particular challenges for any discipline of medicine. The presenting symptoms are quite diverse and are characterized by impaired brain development and behavioral, cognitive, and/or physical abnormalities, which often creates difficulty when assigning a specific diagnostic category for patients. The etiology of these broad spectrums of disorders is unclear, but genetic and environmental factors are thought to play a role in its pathogenesis that is manifested by behavioral abnormalities in sociability, communication, and/or compulsive activity [44].

Several GI abnormalities are associated with Autism and ASD, which are linked to microbiota composition and functional alteration [45]. Much of this is correlated with high rates of antibiotic use and other variations in these patients[46,47]. In ASD model mice, studies under germ-free conditions show reproducible social deficits and increases in repetitive behaviors similar to that observed in ASD [14], where autism-like behavior traits and GI phenotypes are associated with altered microbiota [6,10]. These studies support a role for the gut microbiota in the pathogenesis of ASD and autism.

In that regard, we have explored a potential neuro-modulatory phenylalanine and tyrosine metabolite, 3-(3-hydroxyphenyl) 3-hydroxypropionic acid (HPHPA), an organic acid, which is detected in human and rodent urine and has been implicated in dysbiosis, autism and schizophrenia [48,49,50,51]. The current literature does support the autism and schizophrenia assertions. For example, a probiotic *Bacteroides fragilis* was given in early adolescence has been shown to ameliorate some behavioral deficits in a rodent autism model [52,53,54]. Shaw (2010) has made the assertion that several *Clostridia* bacterial species are at the heart of the schizophrenia and autism connection [50]. However, no reports have been published where this marker (HPHPA) was observed in CSF and data is limited on the origin or significance of the compound in urine. We expect that the HPHPA is water soluble but also relatively lipophilic and would diffuse across the blood-CSF barrier rather easily, if not transported by facilitative or active means [55,56].

Studies have shown that various compounds can pass through the blood brain barrier by different mechanisms. Indole propionic acid (IPA), indole 3-acetic acid (IAA) [59], m-Tyrosine, HPHPA and others that are derived from intestinal bacteria likely reach to the CSF by diffusion. Once in the brain, either from endogenous or exogenous sources, many compounds are modified, conjugated, stored or excreted. If not exported, one could argue that a mechanism for neuropathology could arise when toxins and bacterial metabolites are not functionally resolved [60].Whether neuro-developmental disorders such as schizophrenia and ADHD are associated with microbiota changes is unclear and remains under investigation [57,58].

## Microbiota and Metabolic Endocrine Pathways

The intestinal microbiota can be largely classified phylogenously into the Gram-positive *Firmicutes* and *Actinobacteria*, the Gram-negative, *Proteobacteria* and the *Bacteroidetes*, where *Firmicutes* and *Bacteroidete*, typically dominate in healthy mammals [11,61]. In terms of one's brain chemistry, leptin, ghrelin activity etc., are associated with the microbiota and neurotransmitters involved in craving particular types of food [62], more than satiety factors, are the influence found with particular gut microbiota that can influence or help determine the types of foods you crave [35,63]. The obese leptin-deficient ob/ob mice are associated with a reduction in the abundance of *Bacteroidetes* with a proportional increase in *Firmicutes* [64]. Conversely, reduced cravings have been suggested after antibiotics and restoration with a new flora. In relation to obesity and neuromodulation, the research on how to change the microbiota without risk is neither comprehensive nor well established. However, it was recently found that *Lactobacillus* was significantly increased in the stools of obese patients [65]. Further, recent evidence suggests that gut microbiota play a major role in the digestion and energy conversion of nutrients [66], which also can affect our neurochemistry including brain metabolism.

Probiotic exposure can exert microbiome modification and produce bioactive metabolites or 'pharmabiotics', including bioactive lipids, and result in altered hepatic lipid metabolism coupled with lowered plasma lipoprotein levels and apparent stimulated glycolysis [67]. Probiotic treatments also altered a diverse range of pathway outcomes, including amino-acid metabolism, methylamines and short chain fatty acids (SCFAs), suggesting differences in fermentation patterns [12]. SCFAs and ketones may pass through the intestinal mucosa entering the systemic circulation where they may affect immune regulation and CNS function interacting with nerve cells by stimulating the sympathetic nervous system [68].

Investigating the mechanistic basis of probiotic action and the therapeutic surveillance of the gut microbial activity related to dietary supplementation of probiotics may be one means to affect secretion of HPHPA and other metabolites [69]. In that regard, SCFAs are implicated in ASD and treatment [70]. Important in

this process are the prebiotics that include the short-chain fatty acids and bacterial products largely of carbohydrate fermentation [71]. They are analogous to hormones of the microbiota and signal or mediate many functions of the endocrine mechanisms and may modulate endocrine serotonin (5-HT) secretion, peptide YY (PYY) release and other important neuropeptides at multiple levels [72] and affect insulin signaling and adiposity [73,74]. Other metabolites and precursors from yogurt cultures have been shown to alter the catabolism of the flavanones to phenolic acids by the colonic microbiota [75].

The transfer of gut microbes from one person to another is not without some risk. However, the alternative, such as constant diarrhea from *Clostridium difficile* responsible for an estimated almost half a million infections (where cases are classified as community-associated or health care–associated) and was associated with approximately 29,000 deaths in 2011 [76], leaves little choice in the matter. That said, a recent case was discussed of a woman of relatively normal weight and a *Clostridium difficile* infection (CDI) who was relieved of her distress after a fecal transplant with widely different gut bacteria, but also had a rapid weight gain of about 50 pounds [77]. It must be said that those authors do not identify the mechanism for transmission of the obese phenotype, nor did they directly demonstrate a causal relationship or sequence and fully identify the species involved over the course of the treatment. Yet it is inferred that the microbiota plays an important role in the weight gain [78,79].

New evidence indicates that gut bacteria alter the way we store fat, how we balance levels of glucose in the blood, and how we respond to hormones that induce hunger or satiety [80]. The wrong mix of microbes, it seems, can help set the stage for obesity and diabetes from the moment of birth [66,81,82]. With mice housed together and consuming the same chow ad libitum in, the animals that received bacteria from an obese mouse grew heavier and had more body fat than mice with microbes from thin rodents [82]. As expected, these fat mice also had a less diverse community of microbes in the gut [83]. Nevertheless, it would bear repeating that programming [84] or as we suggest reprogramming the host metabolism through the gut is a novel approach to modulating health and disease. Therefore, a steady supply of good probiotics and avoiding antibiotics as much as possible is a sage suggestion until the time comes when we can use both to reprogram the second or third genome within us as an approach to personalized medicine.

The human gut microbiota is estimated to outnumber the trillions of cells in the human body, and we can easily understand this proportion when we recall the size of a eukaryotic cell as compared to a bacterial cell. Therefore, it is not surprising that intestinal organisms and pathogens influence health and disease through a diverse biochemical and signal-transducing metabolic exchange. Due to mass action, and drug interaction, this exchange can happen very quickly as well as exert its effects over a protracted period of time. Our phenotype is arguably even more complex than ever imagined. Environment, diet and antibiotic use are among the main factors that could affect stability of the gut microbiota both quantitatively and qualitatively. For example, food rich in polyphenols are abundantly present in the human diet and are often modified by the gut microbiota to produce antimicrobial effects inducing selective changes in the microbiota composition, with potential beneficial effects for the human health [85]. Moreover, the effect that diet, antibiotic therapy [86], symbiotic or prebiotic and probiotic intervention or dysbiosis has on our neurochemistry is often overlooked in favor of conventional therapies [87] with ever-increasing cost and often tremendous uncertainty. Regardless of our personal considerations, we must acknowledge that the microbes living in our bodies serve many diverse functions ranging from digestion and cofactor production to disease prevention and even pathology (Table 1).

Histamine and signaling molecules, like the SCFAs, are part of the co-metabolism and signaling via molecular cross-talk that occurs between the Gut-Brain and Endocrine axes.

In that regard, some of the known metabolic functions of the intestinal microbiota is to metabolize nutrients such as sugars, plant polyphenols, bile salts as well as to produce vitamin K or various enzymatic conversions like cholesterol tocoprostanol and bilirubin to urobilinogen [135,136,137]. Moreover, when one considers the microbiota and its ability to produce numerous small molecules and psychoactive chemicals, some of which have a direct hormonal nature, or are hormones themselves, we can turn our attention to the gut-derived hormones and metabolites to complement our understanding of the HPA or brain endocrine interactome more comprehensively than in the past. Not until recently did we fully understand the implication of the microbiota to regulate multiple hormonal and hormone-like compounds that are released into the bloodstream where they influence the function of distal organs and systems in paracrine, autocrine and endocrine fashion [138]. Therefore, the gut microbiota collectively is said to resemble a unique collective endocrine organ [139]. Nevertheless, the hormonal aspects of the gut have been long known since Edkins discovered gastrin in 1905 [140], followed by Gregory and Tracy's isolation and synthesis of the so called antral hormone [141] and establishment that the concept of gastric secretory mechanism were hormonal rather than nervous in nature [90,142].

Previously we discussed the gut-brain axis and in regard that mechanistically gut bacteria are shown to affect brain neurotransmitters, such as monoamine levels, corticosterone, corticotropin releasing factor, serotonin, dopamine, glucocorticoid receptor [95]. This then affects behavior, mood and even eating decisions, in part by acting through the vagus nerve, which couples the digestive tract to the brain and can lead to altered taste perceptions [143]. It is known that the microbiota can express signals via the vagal nerve to the brain and vice versa [19,31,32]. The gut-brain axis consists of neurons embedded in the alimentary canal containing millions of neurons [139]. Thus, the neuronal signals from the microbiota to the vagus nerve may affect our mood, even cognitions or behavior. Others support the notion that the gut-brain endocrine metabolic interactome can control

**Table 1.** Candidate neurotransmitters, hormones, peptides and small molecules of the microbiota-gut-brain.

| Neurotransmitters and metabolite precursors | Psychotropic Small Molecules and precursors | GI-active Hormones | Stress Hormones With Bacterial interactions | Short Chain Fatty Acids |
|---|---|---|---|---|
| **Serotonin/ 5-hydroxytryptamine (5HT)** [88, 89, 90] | **Lipopoly-saccharides (LPS)** [91] | **Ghrelin** [90, 92, 93, 94] | **Cortisol** [72, 95, 96, 133, 134] | **Formate** [69] |
| **Dopamine, m-Tyrosine** [97, 98] **Carnoside of carnosine and carnitine.** [98] | **3,4-dihydroxyphenyl -L-alanine** [72] **Phenylalanine** [72] **3-(3-Hydroxyphenyl)-3-hydroxypropanoic acid(HPHPA)** [72, 12, 13] **Indole 3-acetic acid** [99, 100] | **Leptin** [90, 101] | **Adrenalin** [90, 72, 102] | **Acetate** [69, 103] |
| **5-hydroxy-indoleacetic acid (5HIAA)** [104, 105] **Tryptophan gamma-aminobutyric acid** [97] | **4-ethylphenyl sulphate (4EPS)** **3,4-dihydroxyphenyl-L-alanine,** **phenylalanine,** **4-ethylphenyl sulphate (4EPS),** **Galacto-oligosaccharide (GOS), Homovanillic acid (HVA)** **Histamine** [34, 100, 106, 107, 108] | **Glucagon-like peptide-1 and 2** [90, 109, 110, 111] **Peptide YY(PYY)** [112, 113, 114, 115, 116] **proglucagon (Gcg)** [117] **brain-derived neurotrophic factor (Bdnf)** [118] | **Noradrenalin** [72, 95, 119] | **Propionate** [69, 120] |
| **GABA** [121, 122, 123] | **Acetyl-Choline** [124] | **Histamine** [125, 126] | **Glucocorticoid Metabolites (GCMs)** [72, 96, 127, 128] | **Butyrate** [69, 120] **Isobutyrate** [120, 123] |
| **KynurenineKyneurenic acid** [129] **Inulin** [88, 130, 131] | | **Gut Endocrine Hormones Not Otherwise Specified** [94, 132] | | **Valerate** [69] **Isovalerate** [69, 120] |

behavior perhaps even independently of the brain through the gut since the "primary visceral" or the vagus nerve, which carries information from the gut to the brain in retrograde fashion, uses these metabolites, neurotransmitters and so forth [144,145] [146]. Conversely, these metabolites can affect the vagus nerve and affect the brain through the vagal route [147]. The metabolite could itself activate the release of a second or third level chemicals or hormones that crosses the blood brain barrier (BBB) while the metabolite itself could be sequestered outside of the BBB [6,148], pass through the gut lumen to the systemic circulation and enter the CSF [149], thus affecting the brain or neurocognitive processes or acting through the HPA in anterograde or retrograde fashion.

## Role of the Microbiota in Immunity and Early Brain Development

The cerebral endothelium forms the blood-brain barrier (BBB) and the epithelium of the choroid plexuses forms the blood-CSF barrier (BCSFB). It was shown that exposure of the vulnerable developing brain to chemical insults can have dramatic consequences for brain maturation and lead to life-long neurological diseases [150]. The blood-brain interfaces efficiently protect the immature brain from non-specific diffusion and promote efflux through multi-specific transporters of the ATP-binding cassette transporter families, organic anion and cation transporters of the solute carrier families and the peptide transporter [150]. It also does this in transporting,

clearing and preventing entry of blood-borne molecules such as drugs, environmental toxicants, and endogenous metabolites from the brain. In terms of the gut-brain axis and the ongoing shaping of the microbial landscape, the developing fetus or adult is thus driven by a series of complex and dynamic interactions throughout life or during disease states, which includes diet, life-style and antibiotic use among others [87].

It is important to note that the ratio of particular flora changes significantly and characteristically throughout our lifespan concurrently affecting the microbiota signals. The immune system signaling is important for key developmental processes where the microbiota is concerned [151]. The gut-brain axis also has a 'gut-immunity axis', beyond innate immunity or complement and phagocytic expression, such as the creation and maintenance of the blood brain barrier [152]. For example, it is known that secretion of Corticotropin-Releasing Factor (CRF) from the hypothalamus(induced by the elevation of proinflammatory cytokines) stimulate the secretion of Adrenocorticotropic Hormone (ACTH) from the pituitary gland with the consequent release of the major stress hormone Cortisol from the adrenal gland. Further, it has been demonstrated that this will affect many human organs, including the brain [153]. The immune system aspects do exert bidirectional communication with the CNS [16], where indirect effects of the gut microbiota or direct effects of antibiotics or probiotics on the innate immune system can result in alterations in the circulating levels of proinflammatory and anti-inflammatory cytokines to modify brain function.

Thus, neurons and hormones combined allow the brain to affect the activities of intestinal functional effector cells [154]; as these intestinal cells are influenced by the intestinal microbiota, the brain-gut interaction is completed [155]. However, in order for these metabolites or pathogens to breach the body's defenses, they must pass several hurdles, leave the gut lumen and evade the immune system, liver and other barriers, largely unchanged. They may have to act as small molecule messengers, where they deceive and suppress the body's defenses, such as energy or other inhibitory or immuno-suppressive mechanisms. Therefore, the immune system is an important target when considering the microbial metabolite effect on any organ or pathway, as it is a second line of defense.

The impact of a lifetime of exposure to deleterious pathogens and other factors are considered to influence aging, disease and health. These may simply be proxies for the state of the immune system or metabolic dysfunction due to aging of the immune system, break down of barriers and other dysfunction, since T-cell mediated immunity [156] and innate-immune and physiological barriers are often compromised with age, which enables easier access of any number nefarious species or metabolites into the CNS.

It is well known that the brain is immune privileged and set apart from the rest of the body and systemic circulation by several, largely impermeable barriers. The blood brain barrier (BBB) is one such barrier that shields this most vital organ from blood-borne infections, toxins or poisons [152]. In fact, it has been recently shown that the BBB is formed in part by gut microbes themselves, which can modulate brain function and development [152]. In that regard, we have explored trace amines (which are compounds present in brain and CSF in small amounts) that can affect catecholaminergic transmission and are among the psychoactive substances found in the brain that are produced by the microbiota through immune-neural connections, which we know influence behavior, mood and cognition [139].

Recently, it was established that the development of the BBB and the microbial engraftment begins before the infant is born, or at least early in development, and continues after birth. Contrary to what was previously thought, amniotic fluid is not sterile [20]; even in some cases, bacterial presence in the amniotic fluid is associated with a diseased state [157]. Moreover, the mode of delivery may determine early colonization patterns. In that regard, human breast milk, in addition to meeting the nutritional needs of infants confers protection against pathogens by having its own microbial niche, which transmits antibodies to the infant along with other complex compounds [158], thereby promoting proliferation of specific intestinal microbes [159]. It is believed that a baby consumes about 800 ml of human breast milk per day,thus ingesting about $1 \times 10^5$ to $1 \times 10^7$ commensal bacteria during this period [160]. However, the exact origin of these microbes remains unclear, such as the case with unpasteurized or other sources of microbiota.

As we can see, the gut of the baby has developmental milestones from birth, where colonization with microorganisms plays a decisive role [161] and primes several important physiologic interactions from mice to men[162]. In the first three years of life, children's behavior of placing objects in their mouths and feeding directly from the mother promotes a significant exposure to microbes, which leads to more children suffering from infectious diseases than adults[163].

Of course, genetic influence contributes to the ecologic niche of the bacteria and the mother's own stress can influence the pregnancy and impact birth delivery or other systems [164]**.** This all may impact the microbiota-gut-brain-endocrine axis. Moreover, the adoptive transfer of behavioral phenotype via the intestinal microbiota has been described [165] and exposure to diverse microbiota can lead to better long-term immunologic health. Thus, it is expected that the microbiota in children under 3 years old fluctuates considerably and is dependent on environmental factors more so than in adults [166]. The exposure to microbes is very important for the overall future health and immunity of the children into adulthood [167]. In fact, some children in certain under developed countries are immunologic giants in comparison to adults in developed countries, where exposure to cholera or other pathogens would clearly adversely affect the lives of the adults.

Recently, a team of scientists from The Ohio State University assessed the gut microbiota in 77 boys and girls aged 18-27 months for a correlation between diversified intestinal bacteria and specific behavioral attributes [168]. The authors grouped the subjects by sex, to avoid gender bias. What they found was interesting. Girls who had a lower diversification of intestinal microbiota, had higher behavior correlations of self-restraint, cuddliness, and focused attention. The population densities of specific families of bacteria in boys were found to have a correlation with extroverted behavioral

traits. Assessment of subjects' gut biome utilized a deep sequencing DNA-based identification method that allowed for the phyla identification of bacteria and offered conclusive evidence relating specific bacterial phyla present in the subjects' gut biome to specific behavioral traits being exhibited. What we do not know is whether the bacteria were causing the behaviors or if the converse behaviors were evident when the microbiota was mismatched. Moreover, the association between early-life antibiotic exposure and obesity was explored to understand development of central adiposity in children. Obesity has been associated with disruption of the gut microbiota, which is established during infancy and vulnerable to disruption by antibiotics [169]. These investigators found that children given antibiotics during their first year of life were more likely to be overweight in later childhood when compared to age-matched controls and after adjusting for birth weight, breastfeeding, maternal weight and other potential confounders. They concluded that antibiotic exposure during the first year of life indeed increased the risk of being overweight and central adiposity in preadolescence.

In contrast, one group found that host-derived hormones can increase the bacterial proliferative capacity and pathogenicity in the gut lumen [94]. They found cross talk between microorganisms affecting the hypothalamic-pituitary-adrenal [HPA] response, behaviors and the role of gut luminal catecholamines and γ-aminobutyric acid. They were strongly correlated with anxiety, depression, and functional gastrointestinal disorders [40], contradicting early suspicions. The high prevalence provides epidemiological evidence favoring brain-gut and gut-brain syndromes, where miscommunication between the brain and gut underlies the changes in motility, absorpto-secretory function and pain sensitivity particularly associated with IBS [40].

Stress is a prototypic model for understanding the gut brain interaction. It is established that psychological distress can predict later onset of a functional gastrointestinal disorder and vice versa [123]. Brain-gut pathways include the autonomic nervous system and hypothalamic-pituitary-adrenal axis including corticotrophin releasing factor directly acting on the gut through psychoactive chemicals of bacterial origin [123]. These researchers found that gut-brain pathways involving cytokines, such as tumor necrosis factor alpha (TNF alpha) gamma-aminobutyric acid, fatty acids and 5-hydroxytryptamine precursors are response to bacterial processes and inflammation in IBS [40]. One such chemical identified was secreted by entero-endocrine cells namely 5-hydroxytryptamine, which then may enter the blood stream [170]. The ability to control rodent temperament and HPA responsiveness with early modification of gastrointestinal flora, and the effects of early stress on the barrier function of the gastrointestinal tract and flora, suggests an ability of both systems to prime each other in early life for later problems. This hypothesis seems to be supported by a possible protective effect of a probiotic strain of bacteria in a model of early rat psychological trauma [123].

## Consequences to Perturbation in the Gut Microbiota

We can argue that any factor that modulates the microbiota, such as antibiotic use, distress, disease or anything that prevents the offspring from receiving microbial aliquots from the mother, even during birth, can lead to permeability of the blood-brain barrier after birth and likely affect the transmission of virulence factors, pathogens or deleterious metabolites for an undetermined length of time. Besides the known metabolic disorders, such as obesity, and gastrointestinal disorders such as inflammatory bowel disease and irritable bowel syndrome, altered microbiota has been linked to neuropsychological disorders; for example, as in depression and ASD [171]. Although it has been postulated, it is not well established that these factors indeed contribute to disease pathogenesis, in cases with autism, ASD or schizophrenia, and remains to be determined.

While the degree to which intestinal microbiota affects dietary preference is not well defined the converse is evident in that diet can rapidly change the microbiome [172]. Nevertheless, viewing the gut microbiota as a virtual endocrine organ is a concept generated from a number of important observations. This concept arises from its metabolic capacity to produce and regulate compounds, reaching distal organs and systems through the circulation, and act to influence their function [90,139]. There is abundant evidence that dopamine and serotonin produced by gut microbiota do play a role in our GI and neurochemistry [24,173]. In mice, certain strains of bacteria increase anxiety-related behaviors; in humans, consumption of a probiotic containing *Bifidobacteriumlongum* and *Lactobacillus casei* improved the mood of those with signs of anxiety or depression [26,174]. Conversely, *Campylobacter jejuni* infection may increase anxiety-like behavior [175]. Just to note, the gut-brain-endocrine axis also has a "gut-immunity axis" beyond innate immunity or complement and phagocytic expression, such as the creation and maintenance of the blood brain barrier [152], where chronic inflammation of the GI system can lead to anxiety [176].

Therapeutic targeting of the microbiota may treat stress-related disorders and metabolic diseases. It is important to note that chronic stress and aging are associated with dysregulation of the immune system, altered brain plasticity, and an increased risk of developing brain pathology. Further, aging can have a detrimental effect on the composition of the gut microbiota, which in turn might influence health outcomes at later, more vulnerable stages of life [174] [178]. Because the gut microbiota has a large impact on human metabolism and immunology, it is possible determinant of healthy ageing and cognitive health. The gut microbiome evolves throughout the lifespan, but microbiota diversity and stability decline with aging; the families *Ruminococcaceae*, *Lachnospiraceae*, and *Bacteroidaceae* dominate with a relative abundance but decrease with age. In addition to dietary and medicinal regimens used by the elderly, impaired digestive and motility functions, malabsorption of nutrients, and a weakened immune system

can disturb the homeostasis and stability of the gut microbiota composition [179,180]. Decreased stability and diversity of the gut microbiota in the elderly is accompanied by reduced brain volume and cognitive function, which may or may not be a causative factor in age–related decline.

The dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis is suggested to be brought about through metabolic changes that include changes in the microbiota–gut–brain axis, along with behavioral changes during aging and emotional states such as anxiety, depressive-like behavior, cognition and sociability in rodent models and humans. Dysregulation of neurotransmission and neurotrophic factor signaling coupled with an increased inflammatory state, and epigenetic changes, oxidativestress that are age associated [181].

## Treatment Approaches and Consequences of Modulating Microbiota

We have established the collateral effects on the gut microbiome whenever antibiotics are used [182] due to targeting conserved bacterial pathways or growth functions, biochemistry, and metabolism [183]. It has been shown, for example, that four weeks of ciprofloxacin treatment in humans can result in delayed recolonization or the failure of recovery of several taxa common in humans [184], which can lead to the possible complete loss of some commensal gut flora. However, there are challenges to engineered therapeutic bacteria that will successfully engraft in the human gut as well as be acid stable. Hence, use of antibiotics is a double-edge-sword. We suggest an approach to address such a dichotomy is through using the bacterial adaptive immune system to eliminate itself, which could be an effective alternative. Many microbes employ an RNA-based adaptive immune system known as clustered regularly interspaced palindromic repeats (CRISPRs) and CRIPSR-associated (Cas) proteins also known as CRISPR-Cas9, which consists of short repetitions of base sequences followed by segments of phage or plasmid DNA. The CRISPR-Cas9 locus consists of Cas genes as well as an array of alternating spacers and direct repeats (~20-50bp). The spacers are variable base sequences with constant length that are derived from previously encountered phage or plasmid DNA. Upon detecting virus or exogenous DNA, the spacer will serve as a molecular vaccination card, and the repeat-spacer pair will be transcribed and processed into mature CRISPR-derived RNAs (crRNAs), when bacteria detect previously encountered foreign viral DNA. The crRNA serve as a guide RNA (gRNA) for CRISPR-associated (Cas) proteins, and guide the Cas proteins to identify and eliminate the foreign nucleic acids through DNA cleavage [185,186,187]. An alternative, to these approaches is to engineer a genetic "kill switch" triggered by a compound that is harmless to human tissues as well as the non-expressing members of microbiota.

In that regard, recent studies have demonstrated that this system can also be exploited by delivering segments of bacteria's own genomic sequences as a gRNA, through phage or conjugation system, thus resulting in its own demise and providing an alternative antimicrobial solution in future [188,189]. Similar approach could also be used to eradicate malicious bacteria like *E. coli* in gut microbiome. In contrast to the antibiotic treatment, the elegance of CRISPR/Cas technology requires delivering of bacterial strain-specific gRNA, leveraging the target bacteria's own CRISPR/Cas system for precise targeted treatment. We are working on novel probiotics, as are researchers in Europe who currently use *E. coli* prescribed as a digestive probiotic [190]. According to this group, a probiotic must pass certain criteria before a bacterial strain can be considered. Criteria include: 1) it must be fully identified, 2) is safe for ingestion and is non-toxigenic, 3) adhere to the luminal mucosa, 4) have the ability to colonize the gut and 5) have known documented health benefits [190]. Further considerations include formulation, stability, shelf life, colony number, viability, reliability, and digestibility (acid and enzyme stable). Since probiotics are not currently regulated, it is hoped the quality content and production be accurately assessed.

It has been shown that manipulating the microbial composition of the gastrointestinal tract modulates plasma concentrations of tryptophan, an essential amino acid and precursor to serotonin, which is a key neurotransmitter within both the enteric and central nervous systems [191,192].

Indirectly and by unknown mechanisms, it has been shown the gut microbiota exerts control over the hypothalamic-pituitary-adrenal axis. In rats, the absence of the gut microbiota exacerbates the neuroendocrine and behavioral responses to acute stress and the results coexist with alterations of the dopaminergic turnover rate in the brain, increasing stress and anxiety [97]. This work clearlydemonstrates in germ-free (GF) animal models and in response to the open-field stress, serum corticosterone concentrations were 2.8-fold higher in GF than in specific pathogen free (SPF) rats [193]. Moreover, an exaggerated response to cortisol and psychological stress was normalized after monocolonization by specific bacterial species including *Bifidobacteriuminfantis* [90]. A group at the Vanderbilt University engineered bacteria to make a satiety factor called NAPE, from the *E. coli* Nissle strain, to produce a lipid compound that was administered to mice. The NAPE-producing bacteria acted as a satiety supplement in the study, where the mice drinking the NAPE probiotic in water gained 15 percent less weight over 12 weeks [194]. This is one example of a therapeutic compound in the gut that may counteract the effects of a high-fat diet. The research priorities of obesity, diabetes, cardiovascular disease and caloric restriction mimetics hold promise to improve the health of the nation, where this kind of research is one potential piece of the larger overall puzzle.

## Models of the Gut Brain Endocrine Interactome

The HPA and deeper modulation of the host can be suggested though the gut-brain-endocrine interactome [132]. Moreover, the host-gut metabolism is greatly affected when these processes of metabolite cross-talk are perturbed by antibiotic use. We examine gut metabolites in real time, following the inoculation and administration of antibiotics or in conventional states.

One of the rate limiting steps in this metabonomic, or rather; metabolomic research is to identify tissue or bacterial-specific metabolites from thousands of compounds among the 1000 to 200,000 different chemicals suggested to be present in any one metabonome. Essentially, it is comparable to trying to find a needle in a haystack. Metabolic profiling, which is rapidly gaining importance in pharmaceutical, nutritional intervention, gut health and disease studies holds promise for important discovery in the context of personalized medicine and the management of patient health [195]. In that regard, the gut microbiota plays a crucial role in modulating the bioavailability of low and high molecular weight compounds, including proteins, amino acids, lipids, sugars and others, which generate numerous compounds including phenol, indole [106], glycine, thiols, branched or short chain fatty acids just to name a few. Validation of the hypothesis linking abnormal brain metabolism to mental disorders will ultimately depend on measurement of bacterial metabolites in the human brain. Such an approach has demonstrated the beneficial role that commensal bacteria can play [34].

We have identified several potential biomarkers using animal models, coupled with antibiotic administration and then quantified the metabolites by LC-MS/MS, which show well-established and reproducible performance characteristics involving colonization resistance [183] as well as other useful parameters in our models. The basis for this work stems from a non-targeted survey and metabolomic screening approach involving fecal samples [107] as well as from the literature for the identification and relative quantification of the small-molecules involved in colonization resistance. We use the same approach to explore the gut-brain-endocrine axis and co-metabolomic interactome.

There are many caveats to developing these newer techniques, especially if one has limited experience with small molecule metabolomics. Pretreatment, clean up steps and sample prep is an even more important factor in terms of metabolite recovery, abundance and stability than arguably is even chromatography, which we know is tantamount to the process. Here, many metabolites can be measured in free from, but some metabolites undergo phase II or other conjugation that makes accurate quantitation impossible without knowing the actual modification and posttranslational changes that occur in various body compartments or tissues. The mammalian organs, like liver and kidney and enzymes such as those involved in conjugation or other systems are but a few mechanisms for detoxification of microbial metabolites and their byproducts. Further, there are dietary regulators for the composition and disposition of not only bacterial metabolites, but strains of bacteria and we call that colonization resistance. Any microbiome modification can alter metabolism of compounds such as amino acids, methylamines and SCFAs [6].

Through this elaborate approach, we have established a scientific framework and body of evidence, which elucidates the toxicological and physiologic parameters of microbiome test results in mice that we expect to be of clinical significance in human subjects during colonization resistance or other states. We and other groups have been trying to figure out a possible connection between the gut, brain and even endocrine systems by looking at gut microbes in mice [108,196]. To accomplish this objective, we utilize mice housed in conventional setting or in germ-free (GF) housing or when given various classes of antibiotics, which offers an interesting backdrop to environmental influences allowing us to sort out the contribution of the gut microbiota to the entire metabolism of an animal. We can then uncouple the contribution from the microbiota as well as explore how antibiotics affect intestinal colonization. It is important to note that there is a marked difference between animal and human flora in terms of variety and of species and homogeneity between subjects. Using a denaturing gel electrophoresis assay (DGGE), we found that mice housed together have stable and relatively uniform microbial profiles, which are markedly different from humans, which are complex and extremely variable between patients(unpublished results).

Transgenomic metabolic effects can be achieved without antibiotics through induced changes in intestinal flora. For instance, *Lactobacillus paracasei* or *Lactobacillusrhamnosus* probiotics have been measured and mapped in humanized extended genome mice (defined as germ-free mice colonized with human flora) [191]. A systems biology view of the host response to probiotic intervention may be one way to affect the secretion of psychoactive metabolites like serotonin or HPHPA or organic acids, if they are indeed relevant to microbial-derived effects or neuromodulation [69]. Therefore, it is now possible to exchange most of the toxigenic bacteria for healthier microbes in around 24 hours and potentially create an effective cure or reversal of acute neurologic phenomena. These effects could be as simple as mood and cravings but it could also be as profound as depressive conditions. Largely innocuous and certainly beneficial, it appears that fecal material transplantation may be averted by starving the gut bacteria of incompatible food and nutritional status [197] or by changing the metabolic precursor substrates that may help change any particular flora.

## Molecules that Affect the Gut Brain Endocrine Axis

Microbiota–gut–brain-endocrine axis communication occurs through small molecules. Under physiologic and pathological stressors and disease conditions, intestinal dysbiosis can occur and adversely influence gut physiology leading to inappropriate metabolite cross-talk. This has associated consequences for CNS functions and disease states, which can induce inflammation through proinflammatory cytokines mediated by T-cells and via the innate immune system. These mechanisms potentially lead to impaired CNS function such as altered neurochemistry, cognition, behavior, stress response, and visceral pain [4].

Numerous small molecules from the microbiota have been described to affect the host via endocrine or neuroendocrine means (Table 1), namely the neurotransmitters, and metabolite precursors, Serotonin, Dopamine, 5-hydroxyindoleacetic acid (5HIAA) gamma-aminobutyric acid (GABA), Tryptophan gamma-aminobutyric acid and 5-hydroxytryptamine (5HT), 3,4-dihydroxyphenyl-L-alanine, pheylalanine, 4-ethylphenyl sulphate (4EPS), Beta-N-Methylamino-L- Alanine, Galacto-oligosaccharide (GOS), homovanillic acid (HVA) histamine [198,199,200,201] acetylcho-

line and the short chain fatty acids (SCFAs), which range in size from MW of 46-102 Da, respective salts and the hormones, leptin, ghrelin, gastrin, which controls gastric H+ secretion via specific receptors stimulated by vagal nerves through cyclic AMP histamine [202]or Ca2+ ions in the case of gastrin and through protein kinase pathways [90]. Table 1 lists select neurotransmitters, GI and stress hormones, putative psychoactive small molecules and SCFA is derived from the microbiota. While not meant to be a complete list, this table serves to illustrate the importance of the gut-brain-endocrine axis interactome, where these molecules are produced shared and affects in anterograde and retrograde fashion a host of chemical, hormonal and biochemical processes.

These SCFAs provide an important source of nutrients and regulate control over the host digestive system and host metabolism through inulin to influence production of relevant hormones such as glucagon-like peptide-1, peptide YY, ghrelin, and leptin [90]. For example, downstream metabolism of carbohydrates results in the production of short-chain fatty acids (SCFAs), from several enteric species including, but not limited to, *Bacteroides*, *Bifidobacterium*, *Propionibacterium*, *Eubacterium*, *Lactobacillus*, *Clostridium* and others [69,83,203].

The stress hormones, glucocorticoids, cortisol and corticosterone are known to affect the pyschoneuroendocrine hypothalamus pituitary adrenalaxis and contribute to diverse diseases [204]. The catecholamines, noradrenaline and adrenaline, which are released during stress responses, appear to act as environmental cues altering growth of individual organisms in man. While not specifically a gut endocrine interaction, anaerobic microorganism response to catecholamine responses within microbial complexes, illustrate the complexity of microbes to respond to hormonal environmental cues.

From plant biology, a putative connection can be made for stress hormones and abiotic stress. Salicylic acid (SA), jasmonates (JA) and ethylene (ET) are well known to play crucial roles in plant disease and pest resistance [205]. Plant hormones hold important clues as to the role the microbiota play in regulating developmental processes and signaling networks involved in plant responses to a wide range of biotic and abiotic stresses [205]. However, the roles of other hormones in plant defense are not well characterized and thus this model for understanding plant hormone signaling and plant disease resistance may shed clues into our own gut-endocrine process. The converse seems true. Stress and the effects of catecholamines on the growth of periodontal microorganisms that recognize hormones within the host and utilize them to adapt to their surroundings are being explored [118].

Apart from a select few probiotics and prebiotics from yogurt, food sources of prebiotics, which are largely indigestible, ferment carbohydrates that stimulate and promote activity of beneficial gut bacteria. Potential prebiotic candidates include artichokes for insulin and other fermentation precursors, like kombucha, foundin cruciferous vegetables (kale, cabbage, and cauliflower), or polenta for sulfur-containing metabolites, known as glucosinolates, as well as blueberries, bananas, for carbon sources and to reduce inflammation, and beans or legumes which can promote short-chain fatty acid production.

Prebiotics, typically indigestible fiber and the so-called resistant starch, which is metabolized by the microbiota, can be extended to include other carbon sources produced by cohabitants within an ecological niche. Probiotics, the microbiota or live microorganisms, can utilize prebiotics such as those in yogurt that contain beneficial active cultures [63,198]. Taken together, as we propose, would result in novel symbiosis, which is the finely tuned harmony between the two and may be useful as one possible adjunct to transplantation of fecal material. It is not only obesity, but also heart disease [64,82], which may be affected by our microbiota. For example, vancomycin treatment of infective endocarditis was recently linked with acquired obesity and is argued to be the result of the selected microbial flora [180,206]. Further, we show that in CDI patients, it is not just the bacteria that produce harmful metabolites, but it may be co-metabolism from diet with opportunistic bacteria that contribute to heart disease. For instance, our collaborators form the Cleveland Clinic have proposed that, phosphatidyl choline, L-carnitine from meat as well as Trimethylamine (TMA) and trimethylamine N-Oxide (TMANO) also contribute to heart disease [207] and are ultimately metabolites of the gut microbiota. We have gone on to show that one of the major bacterial species involved may be *Clostridium difficile*, in which these markers appear increased in these patients [183].

## Concluding Remarks

A deep mechanistic understanding of the factors that underlie the plasticity of the microbiome and co-metabolism is the key to find the means of manipulating it to improve health. However, the cross-talk that exists in the microbiota-gut brain endocrine axis is not well established including whether it occurs both temporally and spatially in retrograde and anterograde fashion or predominantly unidirectional as an axis. We need to further study these concepts and fully understand the exchanges, as much co-metabolism could be transient or even diet-dependent [208].

Today, this seems increasingly promising [209]. Having the knowledge on how variation in the distal gut microbiome influences host function and will help us to better modulate the gut microbiome in a personalized medicine fashion in order to promote health [210] or treat metabolic diseases. Yet the future of personalized healthcare may largely depend on understanding this second genome we all carry within or uponus [211]. In turn, this has prompted research into modulation of the intestinal microbiota to promote health, positive mood, treat obesity, improve insulin sensitivity, and promote colonization resistance to pathogenic and nefarious bacteria or other species of pathogens or as of yet unforeseen applications. Of course, we have in our hands nutrition, which is key to this interplay [195,212] since the microbiota need a carbon source to survive.

The importance of our digestive system, biochemistry and co-metabolism with microbiota should not be underestimated. The

Internet is filled with tips for promoting "Healthy Microbiota" and those that have scientific merit are only mentioned in this conclusion to help narrow the field. While prebiotics are important because they signal, feed and otherwise support and complement probiotic action, identifying them and increasing their effectiveness is difficult and currently relegated to foods, as we are in the infancy in our understanding of co-metabolism. To synergize the two into a symbiotic approach that will require new research support and an understanding from those who dole out funding. The literature is loaded with support for eating probiotics and prebiotics, which are the compounds, fiber, small molecules and polyphenols derived from such foods as fruits including, berries, grapes apples, bananas, kiwifruit; vegetables, like artichokes, leeks onions, garlic greens, beans, whole grains, like brown rice, corn, buckwheat, flaxseed, barley, nuts, almonds, raisins, honey, green tea and yogurt or Kefir. However, yogurt can contain other bacterial species than the typically stated ingredients, like *Bifidobacillus* and *Lactobacillusspp.*, including others not listed as main ingredients.

The difficulty in assessing each food for their metabolite precursors is the fact that co-metabolism does exist. Further, much of what we know is more or less anecdotal or a general approach to GI health, provided one is free of any illness. What is clear is that we are in the infancy of identifying novel appropriate probiotics that can be added to pills or in combination with supplements to improve human health and modify the microbiome, as relatively few have provided enough data to make specific health claims unequivocal. Nevertheless, following general trends may be prudent, such as eating raw, whole foods and a plant-based diet; decreasing the use of artificial sweeteners, which may negatively affect the microbiome or lead to increased body fat and insulin resistance. This is one reason so many are interested in this second genome.

Other trends that have support in the literature include eating less meat overall to promote a shift from deleterious species within the microbiome to ones that may be more protective; breastfeeding infants to improve the immune gut axis that was discussed. Many experts believe uncovering nature's secrets about microbes will bring about a revolution in health care, and we agree. But we still need approaches for identification of probiotic bacteria that influence brain function and that may be beneficial in treating disorders, such as those mentioned throughout this paper. We are exploring clinical evaluation of this putative therapy, which is underway in collaboration with clinical colleagues in infectious disease and psychiatry. We maintain that microbiota-based therapies be used in humans for treating many disorders and chemical imbalances including mental disorders.

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