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REVIEW

Recent findings within the microbiota–gut–brain–endocrine metabolic interactome

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Purpose of review: We have established that many metabolic biomes exist within the complex mammalian gut. Substantial metabolism occurs within these biomes and is called co-metabolism of the host and resident microorganisms. This gut–brain–endocrine metabolic interaction emphasizes how bacteria can affect the brain and the hormonal axes in the process of co-metabolism. This review highlights new findings in this regard.

Recent findings: In this review, we explore how the gut microbiota affect the development and regulation of the hypothalamic–pituitary–adrenal axis and neurochemistry from mental health and behavioral health to memory, depression, mood, anxiety, obesity, and the development of the blood–brain barrier.

Summary: This review describes the implications of the findings for clinical practice or research. Interaction of small molecules within these biomes is now described collectively as a "metabolic interactome". Metabolites of the gut–brain–endocrine axis and our overall gut health constantly shape the host phenotype in ways previously unimagined, and this niche represents potential targets for treatment and drug design, since the interaction or biochemical interplay results in net metabolite production and/or end products to exercise either positive or negative effects on human health.

Keywords: neurotransmitters, gut brain axis, metabolomics, microbiota, microbiome, HPA

Introduction

The microbiome is the collective genomes of all the microorganisms in a microbiota, which are the labile and variable collective bacterial, fungal, or parasitic organisms that reside within or upon the host at any given point in time. There is no question that each species of gut bacteria engage in complex biochemistry with the host and host systems, which we refer to here as "co-metabolism", namely, the metabolism that occurs between the microbiome and host metabolic systems, eg, metabolism derived from such organs as the liver, the kidney, and other human metabolic processes and enzymes, which come in contact with the circulation by any means and can serve as substrates or carbon courses for the microbiome. An individual's gut microbiota composition depends on several modes of exposure at birth, one's genetic predisposition, infections, nutritional status, and antibiotic exposure. The microbiota changes across the lifespan and can be radically different from birth to death, and as we age, this milieu is affected by additional factors, such as physical activity, environmental factors, stress, and disease process. Co-metabolism is a complex phenomenon between the microbiota and the host.[1,2] A mutually beneficial relationship exists between the host

and its resident microorganisms. Perhaps one could envision scenarios where considerable metabolism research was driven by microbial metabolism, without ever fully understanding the implications of the so-called second genome within us. In regard to the microbiota–gut–brain axis, co-metabolism is not limited to commensal microbes. The intestinal microbiota consists of a vast bacterial community that resides primarily in the lower gut and largely lives in a symbiotic relationship with the host. This interaction results in "biochemical metabolite crosstalk" between the small molecules that arise from co-metabolism, which is ultimately measured as a net end product accumulation of said metabolites.[3]

The cross-talk can be thought of as signaling between host metabolism and pathogenic or commensal resident gastrointestinal (GI) bacterial metabolism. The microbiota–gut–brain axis is a network of communication signaling of metabolites and other molecules between the gut and the brain, which modulates the GI tract and the central nervous system (CNS). Furthermore, in regard to co-metabolism , the concept of a "leaky gut" may play a role in the movement of metabolites. In that regard, we explored the gut–brain metabolic interaction, which is one segment of the "gut–brain–endocrine axis".[4] The concept of the microbiota–gut–brain axis is simply not the endocrine system and the stress axis, nor is it the hypothalamic–pituitary–adrenal (HPA) axis, or even the immune system, but they all play a part in its modern and current definition (refer Figure 1 for HPA axis and the effect of stressors on metabolite flux, both retrograde and anterograde noted by black broken arrows).

This cross-talk is not well characterized, such that the movement of metabolites can occur anterograde, retrograde, or some version of both. There is suggestion that a bidirectional communication system exists between the intestinal microbiota and the brain, which is important in psychiatric disease, according to Collins et al.[5] However, this microbiota–gut–brain analogy addresses only the neurocognitive component of a very complex metabolic interaction within mammalian systems. Moreover, to underscore the relationship between the digestive system and cognitive-hormonal function or dysfunction, we have now adopted a more informative term to include the neuroendocrine aspect of the gut–brain metabolic interactome, as in the HPA and other axes.

The net interactions produce protein–protein, protein–carbohydrate, carbohydrate–nucleic acid, or multiple lipid interactions, which are often contribution byproducts of another genome's metabolism, where the intestinal

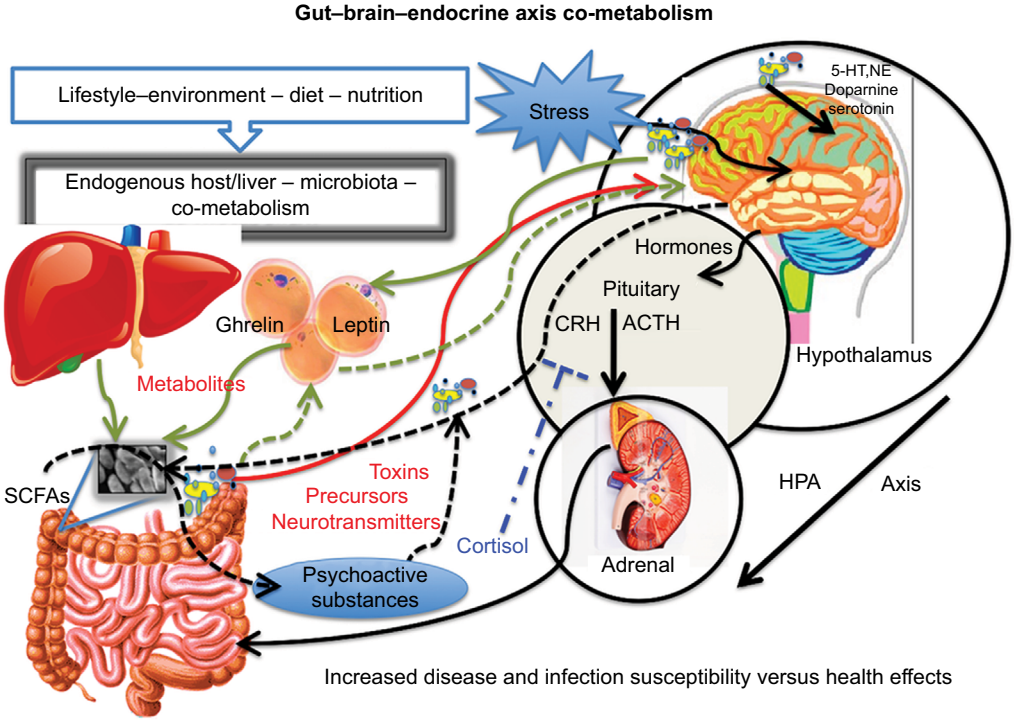

Figure 1 The HPA microbiota–gut–brain–endocrine pathway and intersecting organs demonstrating a known afferent and efferent cross-talk, which is yet to be well characterized and is very complex.
Note: Movement of metabolites, anterograde, retrograde, or both, from the gut and the brain to distal organs constitutes co-metabolism in a metabolic interactome.
Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin releasing hormone; HPA hypothalmus pituitary adrenal; SCFA, short chain fatty acid; NE, norepinephrinegiven; HPA, hypothalamic–pituitary–adrenal; 5-HT, 5-hydroxytryptamine.

microbiota communicates with the brain via these axes to influence aspects such as brain development and behavior and influence a broad spectrum of diseases.

The microbiota–gut–brain–neuroendocrine axis and psychiatric disorders

The co-metabolism between a host and its commensal microbiota is essential for life processes, wherein otherwise indigestible nutrients become cofactors, essential amino acids, and vitamins that are key to health and nutrition. Our diet, lifestyle, and medications, particularly antibiotics, influence and shape the gut microbiome. The interaction is always in flux, and the result is net metabolite or end product production, with positive and negative effects on human health.

Recently, it was established that intestinal bacterial microbiome plays important roles, including controlling integral segments of our neurobiology, such as mental health and even behavioral health, memory, depression, mood, anxiety, and even affecting food preferences.[6] The degree to which intestinal microbiota affects this neurobiology is not well defined,[7] but there is abundant evidence that dopamine and serotonin generated by gut microbiota do play a significant regulatory role.[8,9] 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.[8]

The microbiota is implicated in manic episodes in hospitalized patients who have higher rates of bacterial infections and antimicrobial prescription usage, with respiratory tract and urinary tract infections topping the list. A recent study shows higher rates of antibiotic use in a group of bipolar patients with mania.[10] It is suspected that the underlying bacterial infection, the usage of antimicrobial agents and the subsequent immune activation lead to mania onset. Moreover, psychiatric patients receiving antimicrobials are even more likely to have more severe psychiatric symptoms, at the time of assessment, than those not receiving antimicrobials. This raises the question as to whether antimicrobial usage is a contributing factor to the development of acute mania and even more serious psychiatric disorders. Under physiological and pathological stressors and disease conditions, intestinal dysbiosis can occur and adversely influence gut physiology leading to inappropriate metabolite cross-talk. Environment, diet, and antibiotic use are among the main factors that could affect stability of the gut microbiota. We know that the administration of antibiotics can damage the individual microbiome and now suggest that this may increase the risk of altered mood states. Abnormal behavior and cognition together with dysbiosis, the so-called pathobiont overgrowth syndrome, can be the cause and consequence of the leaky gut and promote loss of the intestinal barrier.[11] Conversely, probiotics may prevent leaky gut consequences and restore colonization resistance to the species contributing to "leakiness".[12] It is not surprising that intestinal organisms and pathogens influence health and disease through a diverse biochemical and signal-transducing metabolic exchange as well as through proinflammatory cytokines mediated by T cells and via the innate immune system that is associated with brain and nervous system functions and neuropathology, which can induce inflammation. These factors involve the HPA (endocrine axis), immune (chemokines and cytokines), autonomic nervous, and enteric nervous systems.

Psychotropic and immune-active substances derived from the intestinal lumen can pass the gut mucosa and cross the blood–brain barrier (BBB) to affect the CNS. The converse is true, whereby gut microbiota is influenced by emotional stress and physiological stress (refer Figure 1 for the effect of stress on small molecule production). Moreover, acute and chronic stress can increase GI and brain barrier permeability through the activation of mast cells, which are key modulatory cells in innate immunity, inflammation, and subsequent neuronal damage,[13] impair immune homeostasis, and contribute to chronic inflammation implicated in mood disorders. In that regard, depression is associated with increased inflammatory biomarkers, such as interleukin-6, tumor necrosis factor-α (TNF-α), and C-reactive protein,[14] and as stated, schizophrenia has been linked to intestinal inflammation.[15]

This is not surprising since key to co-metabolism of the gut–brain is a well-known finding that the microbiota produces >40 known neurotransmitters, including an approximate estimate of 50% of the dopamine and 90% of the serotonin in the body used in neurotransmission.[16] A wide mix of extrinsic and intrinsic neuropsychotropic-modulating microbes and pathogens affect these and other gut processes. Gut microbes do promote colonic serotonin production via effecting the short-chain fatty acids on enterochromaffin cells.[16] 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 neuropsychotropic-modulating microbes and pathogens.

The afferent pathways of the microbiota–gut–brain–endocrine axis reflect alteration in the circulating levels of

pro/anti-inflammatory cytokines that affect brain function and the co-modulation of various host metabolic reactions to produce essential small-molecule metabolites, such as vitamins, bile acids, choline, short-chain fatty acids, and neurotransmitters and neuroactive substances in the intestinal lumen, to stimulate afferent axons. The efferent pathway from HPA axis activation helps to regulate immune cells locally in the gut affecting gut permeability, motility, secretion, barrier function, and gut microbiota composition locally and distally to affect anti-inflammatory cholinergic reflex, sympathetic activation, and release of neurotransmitters that could affect gut microbiota composition, intestinal permeability, and local immunity.[17]

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 are implicated in the development of various neurodegenerative diseases.[19] For example, in Alzheimer disease (AD), yeast and fungal proteins such as (1,3)-β-glucan, fungal polysaccharides, or bacterial lipopolysaccharides (LPS) can lead to disseminated and diffuse mycoses in the peripheral blood of AD patients.[18]

Co-metabolism within the gut–brain–endocrine interactome is suspected to play a role in other neurodegenerative disorders with microbial-driven connection,[19] such as Parkinson disease (PD) and amyotrophic lateral sclerosis (ALS),[20] where known microbes have been implicated in contributing to the susceptibility and pathogenesis of these[21] and the AD processes, 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.[22]

Furthermore, there are compounds chemically related to the catecholamines and 5-hydroxytryptamine (5-HT). CSF levels of 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA) are derived from and may provide an index of metabolism of the parent amines (5-HT and dopamine)[23] in the CNS. Bacteria can produce these, where they are traced to the CNS.[24]

It is known that psychiatric disorders frequently occur in patients with GI diseases, illustrating that the microbiota–gut–brain axis is clinically relevant in neural and endocrine pathways and neuropsychiatry. This is either through inflammatory mechanisms or through functional mechanisms, such as irritable bowel syndrome (IBS), which is also suspected as being a disorder of the brain–gut axis, where GI symptoms are associated with frequent comorbidities of depression and anxiety. Here, the intestinal microbiota is implicated to play a role in anxiety, depression, autism, schizophrenia, and AD. In addition, translational research approaches, including colonization of germ-free mice with microbiota from patients with primary psychiatric disorders, have lead to microbiota–gut–brain linkages.[25]

Autism, autistic spectrum disorder (ASD), and relationship to the microbiota

Although there has been much research into autism or 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.[26,27] The presenting symptoms are quite diverse and are characterized by impaired brain development and behavioral, cognitive, and/or physical abnormalities, which often create difficulty when assigning a specific diagnostic category for patients. Several GI abnormalities are associated with autism and ASD, which are linked to microbiota composition and functional alteration.[28] Much of this is correlated with high rates of antibiotic use and other variations in these patients.[29] In ASD model mice, studies of germ-free conditions show reproducible social deficits and increases in repetitive behaviors similar to that observed in ASD,[30] where autism-like behavior traits and GI phenotypes are associated with altered microbiota.[31,32] Here, studies support a role for the gut microbiota in the pathogenesis of ASD and autism. One candidate marker is (3-hydroxyphenyl)hydracrylate (HPHPA), an organic acid, which is detected in human and rodent urine and has been implicated in dysbiosis, autism, and schizophrenia.[33–35] To flush out the autism and schizophrenia assertions, one should see if the literature supports these claims. In one example, a probiotic *Bacteroides fragilis* that was given in early adolescence has been shown to ameliorate some behavioral deficits in a rodent autism model.[36–38] Whether neurodevelopmental disorders, such as schizophrenia and attention-deficit hyperactivity disorder (ADHD), are associated with microbiota changes is unclear and remains under investigation.[39]

Microbiota and metabolic endocrine pathways

In terms of one's brain chemistry, leptin, ghrelin activity, and so forth are associated with the microbiota, and neurotransmitters involved in craving particular types of food,[40] more than satiety factors, are the influence found

with particular gut microbiota that can influence or help determine the types of foods you crave (Figure 1, leptin and fat metabolism).[23,41] Furthermore, the gut microbiota can reduce leptin sensitivity and the expression of obesity suppressing neuropeptides.[42]

The obese leptin-deficient ob/ob mice are associated with a reduction in the abundance of *Bacteroidetes* with a proportional increase in *Firmicutes*.[43] 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. Furthermore, recent evidence suggests that gut microbiota play a major role in the digestion and energy conversion of nutrients,[44] 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.[45] Investigating the mechanistic basis of the therapeutic surveillance of the gut microbial activity and probiotic action related to dietary supplementation of probiotics may be one means to affect the secretion of HPHPA and other metabolites.[46] Fecal transplant material (FTM) is the transfer of gut microbes from one person to another, which is not without some risk, but holds promise for a rapid exchange of an entire genome within an individual. 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 had a rapid weight gain of ~50 pounds.[47] FTM can also be used for changing the microbiota for IBS and other diseases, perhaps even for psychiatric disorders.

This may impact the host through the microbiota–gut–brain–endocrine axis. Moreover, the adoptive transfer of behavioral phenotype via the intestinal microbiota has been described,[48] and exposure to diverse microbiota can lead to better long-term immunological health. Early-life antibiotic exposure and obesity were explored in central adiposity in children and have been associated with disruption of the gut microbiota.[49] These investigators found that children given antibiotics during their first year of life were more likely to be overweight in later childhood 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.

New evidence indicates that gut bacteria also alter the way we store fat, how we balance the levels of glucose in the blood, and how we respond to hormones that induce hunger or satiety (refer Figure 1 for the microbial effect on fat cells and the leptin pathway).[50] The wrong mix of microbes, it seems, can help set the stage for obesity and diabetes from the moment of birth.[44,51,52] Animal studies recapitulate these findings, where mice house together consumed the same chow ad libitum in equal amounts, yet the animals that received bacteria from an obese mouse grew heavier and had more body fat than mice with microbes from thin rodents.[52] As expected, these fat mice also had a less diverse community of microbes in the gut.[53] Nevertheless, it would bear repeating that programming[54] or as we suggest reprogramming the host metabolism through the gut is a novel approach to modulating health and disease.

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 (CRF), serotonin, dopamine, and glucocorticoid receptor.[55] 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 receptors.[56] The gut–brain axis consists of neurons embedded in the alimentary canal containing millions of neurons.[57] Thus, neuronal signaling 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 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.[58] Conversely, these metabolites can affect the vagus nerve and affect the brain through the vagal route.[59] The metabolite could itself activate the release of a second or third level chemicals or hormones that crosses the BBB, while the metabolite itself could be sequestered outside of the BBB pass through the gut lumen to the systemic circulation and enter the CSF,[60] thus affecting the brain or neurocognitive processes or acting through the HPA axis.

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 axis 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.[61] Therefore, the gut microbiota collectively is said to resemble a unique collective endocrine organ.[57]

The immune system signaling is important for key developmental processes where the microbiota is concerned.[62] The gut–brain axis also has a "gut–immunity axis", creating and maintaining the BBB.[63]

Thus, neurons and hormones are combined allowing the brain to affect the activities of intestinal functional effector cells;[64] as these intestinal cells are influenced by the intestinal microbiota, the brain–gut interaction is completed.[65] In the brain, cerebral endothelium forms the BBB and the epithelium of the choroid plexuses forms the blood–CSF barrier (BCSFB). The BBB is one such barrier that shields this most vital organ from blood-borne infections, toxins, or poisons.[63] 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.[63]

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;[66] even in some cases, bacterial presence in the amniotic fluid is associated with a diseased state.[67] 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,[68] thereby promoting the proliferation of specific intestinal microbes.[69]

Molecules that affect the gut–brain–endocrine axis

Microbiota–gut–brain–endocrine axis communication occurs through small molecules, such as serotonin, leptin, ghrelin and cortisol among others. 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 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 occur 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. Under physiological 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 cognition, behavior, stress response, neurochemistry, and visceral pain perception.[5]

Recently, a team of scientists from The Ohio State University assessed the gut microbiota in children aged 18–27 months for a correlation between diversified intestinal bacteria and specific behavioral attributes[70] and the 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.

Not only obesity, but heart disease[43,52] may also 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.[71] Furthermore, 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 (unpublished findings). For instance, our collaborators from the Cleveland Clinic have proposed that phosphatidyl choline and L-carnitine from meat as well as trimethylamine (TMA) and TMA *N*-oxide (TMANO) also contribute to heart disease[72] and are ultimately metabolites of the gut microbiota.

In contrast, one group found that host-derived hormones can increase the bacterial proliferative capacity and pathogenicity in the gut lumen.[73] They found cross-talk between microorganisms affecting the HPA axis response, behaviors, and the role of gut luminal catecholamines and γ-aminobutyric acid. They were strongly correlated with anxiety, depression, and functional GI disorders,[74] 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, absorptosecretory function, and pain sensitivity particularly associated with IBSs and inflammatory bowel disease such as Crohn disease.[74]

Consequences to perturbation in the gut microbiota

Most, if not all, of the neuroactive compounds and metabolites are actively transported by various means and taken up to cross the BBB. Data suggest that many other compounds can pass the BBB by other mechanisms. The cerebral endothelium forms the BBB, and the epithelium of the choroid plexuses forms the 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.[75] The blood–brain interfaces efficiently protect the immature brain from nonspecific diffusion and promote efflux transporters, multiple specific transporters of the ATP-binding cassette transporter families, organic anion and action transporters of the solute carrier families, and the peptide transporter.[75] 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 include diet, lifestyle, and antibiotic use among others.[76]

The immune system signaling is important for key developmental processes where the microbiota is concerned.[62] 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 BBB.[63] For example, it is known that secretion of CRF from the hypothalamus, induced by the elevation of proinflammatory cytokines, stimulates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland with the consequent release of the major stress hormone cortisol from the adrenal gland.

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. The BBB is one such barrier that shields this most vital organ from blood–borne infections, toxins, or poisons.[63] 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.[63] In that regard, the development of the BBB and the microbial engraftment begin before the infant is born, or at least early in development, and continue after birth. Furthermore, 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,[68] thereby promoting the proliferation of specific intestinal microbes.[69]

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Brain–gut pathways include the autonomic nervous system and HPA axis including CRF directly acting on the gut through psychoactive chemicals of bacterial origin.[77] These researchers found that gut–brain pathways involving cytokines, such as TNF-α, are response to bacterial processes and inflammation in IBS

Treatment approaches and consequences of modulating microbiota

We have established the collateral effects on the gut microbiome whenever antibiotics are used[78] due to targeting conserved bacterial pathways or growth functions, biochemistry, and metabolism. (Obrenovich M, Tima M, Zhang R, Polinkovsky A, Emancipator S, Donskey C. A targeted metabolomics approach identifies intestinal microbiota-derived urinary biomarkers of colonization resistance in antibiotic-treated mice. PLoS One, unpublished data, January, 2017) 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. Indirectly and by unknown mechanisms, it has been shown that the gut microbiota exerts control over the HPA 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.[79] Moreover, an exaggerated response to cortisol and psychological stress was normalized after monocolonization by specific bacterial species including *Bifidobacterium infantis*.[80]

A group at the Vanderbilt University engineered bacteria to make a satiety factor called NAPE, from the *Escherichia 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% less weight over 12 weeks.[81] 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.

It is possible now to exchange most of the toxigenic bacteria for healthier microbes in ~24 hours and potentially create an effective cure or reversal of acute neurological phenomena. These could be as simple as mood and cravings but also 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[82] or by changing the metabolic precursor substrates that may help change ones flora. Furthermore, the special and temporal aspects of the gut flora are another level of this interaction as much co-metabolism could be transient.[83]

Conclusion

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 the identification of probiotic bacteria that influence brain function and that may be beneficial in treating disorders, such as those mentioned throughout this article. 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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Disclosure

Dr Levison is named as co-inventor on pending patents held by the Cleveland Clinic relating to cardiovascular and inflammation diagnostics. Dr Levison reports having the right to receive royalty payments for inventions or discoveries related to cardiovascular diagnostics or therapeutics from the Cleveland HeartLab. The other authors report no conflicts of interest in this work.

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