

REVIEW ARTICLE

MICROBIOTA–GUT–BRAIN SIGNALING: A MINIREVIEW

Klara Kubelkova✉ and Ales Macela

Department of Molecular Pathology and Biology, Faculty of Military Health Sciences, University of Defence, Hradec Kralove, Czech Republic

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Summary

The gut microbiota of vertebrates, including humans, constitutes an integral genomic part that, together with the genome of the host, may be included under the umbrella concept of hologenome, which itself can be seen as one of the possible tools for evolution. Present-day lifestyles, technologically processed nutrients, and various diseases impact significantly upon composition of the intestinal microbiota. Knowledge recently brought to light has shown the gut microbiota to be a component of the microbiota–gut–brain axis having feedback effects on physiological and psychological processes of the host organism and its health. This minireview summarizes current knowledge and opinions on the importance of the microbiota–gut–brain axis and discusses possibilities for beneficially modulating one of the organism's most vital axes.

Key words: Microbiota; microbiome; gut-brain axis.

INTRODUCTION

The basic properties of living matter are to generate diversity and to occupy any space, including even space within living matter. These properties have led to the origin of the eukaryotic cell, the symbiotic nature of whose origin is generally accepted today. Since the time of that origin, there have occurred continual coexistence and coevolution of prokaryotic and eukaryotic (micro)organisms. Over time, however, their symbiotic relationships have acquired different forms (see Box 1). Differentiation of these forms has been a direct consequence of (micro)organisms' development and their adaptation to different environments. One environment that has provided suitable living conditions has been the gut of multicellular organisms. The process of gut colonization is phylogenetically very old and began just with the gut development in *Protostomia* organisms, such as *Chaetognatha*, *Annelida*, *Mollusca* or *Arthropoda*, and continued through the development of *Deuterostomia*, such as *Echinodermata*, *Chordata*, mammals, and humans.

Box 1: Relationships between two organisms

Symbiotism	close relationship in which at least one (micro)organism benefits
Mutualism	symbiotic relationship in which both (micro)organisms benefit
Commensalism	symbiotic relationship in which one benefits while the other is not affected
Parasitism	symbiotic relationship in which one benefits while the other species is harmed
Syntrophy	symbiotic phenomenon defined as "obligately mutualistic metabolism"

✉ University of Defence, Faculty of Military Health Sciences, Department of Molecular Pathology and Biology, Trebesska 1575, 500 01 Hradec Kralove, Czech Republic
klara.kubelkova@unob.cz, ales.macela@unob.cz

+420 973 255 193
+420 973 253 100

The human gut is home to an important and dynamic microbial ecosystem that contributes critically to human health status. The number of bacteria within the gut microbiota has been estimated at somewhere between 10^{13} and 10^{14} in a so-called “reference man” of 70 kg body mass (1). The origin of gut microbiota, and thereby formation of the metaorganism, is generally believed to occur at the time of birth. A vaginally delivered baby acquires a spectrum of bacteria resembling its mother’s vaginal microbiota dominated by the genera *Lactobacillus*, *Prevotella*, and *Sneathia*. Within the microbiota of babies delivered by Cesarean section, the dominant genera are *Staphylococcus*, *Corynebacterium*, and *Propionibacterium*, the latter spectrum being similar to that present on the skin (2). Some studies, however, have demonstrated an association of the gut microbiota’s origin with microbes that were detected in womb tissues, such as the placenta (3,4). Moreover, microbial analysis of the meconium has demonstrated that the gut of a healthy human fetus is not sterile and that therefore gut colonization may have begun prior to birth (5,6). With formation of the metaorganism after birth the development becomes more dynamic, and composition of the gut microbiota is rapidly transforming along with such life events as changes in diet, under the influence of stress or illness, and especially during antibiotic treatment (7). Such interventions cause chaotic shifts in the microbiota. Gut microbiota not only play a principal role in maturation of the mammalian immune system, they also effect the digestion and absorption of macromolecules, and they produce biologically active molecules, including neurotransmitters. Moreover, they protect the gut epithelium by preventing pathogens from binding to mucosal cell binding sites.

Numerous association studies have demonstrated close interrelationship between human health status and the corresponding profile of gut microbiota composition. On the one hand, there are modulations of the host’s biological processes (see Box 2) and, on the other, there are significant changes in the host’s gut microbiome associated with specific health problems (see Box 3).

Box 2: Biological processes regulated by microbiota (references)

Gut physiology	(8,9)
Nutrient production and absorption	(10)
Host development and physiology	(11)
Energy balancing	(12)
Metabolic functions	(13,14)
Immune system functions	(15–17)
Inflammatory processes	(18)
Neurons–brain–behavior system	(19–22)

The majority of those studies cited here have demonstrated improvement in the clinical status of patients after targeted intervention influencing the gut microbiota. Similar studies relatively recently have led to definition of the so-called microbiome–gut–brain axis.

Box 3. Health problems associated with gut microbiota alterations (references)

Neurological disorders		Obsessive–compulsive disorders (OCD)	(35,36)
Alzheimer’s disease	(23,24)	Anxiety disorders	(37,38)
Parkinson’s disease	(25,26)	Stress	(39–41)
Multiple sclerosis	(27,28)	Cognitive impairments	(42–44)
Psychiatric disorders		Obesity	(45,46)
Schizophrenia	(29,30)	Gut inflammatory diseases	(47–49)
Autism spectrum disorder (ASD)	(31,32)	Cancers	(50–52)
Attention deficit hyperactivity disorder (ADHD)	(33,34)		

MICROBIOTA–GUT–BRAIN AXIS

Bidirectional interactions with top–down and bottom–up regulations between the brain and gut microbiota have received increasing attention in recent years. The impulse for studies on association of the brain and gut microbiota came from the increasing emotional and psychosocial pressure on people who suffered with such gastrointestinal symptoms as heartburn, indigestion, acid reflux, bloating, pain, constipation, and diarrhea (53). Moreover, dysbiosis and/or alterations of the gut microbiota were shown to be implicated in the pathogenesis and pathophysiology of some immunological, neurological, and psychiatric disorders (see Box 3). Communication among cellular components of the microbiota–gut–brain axis can be conducted through two independent pathways. The first can be seen in the defects of host epithelial barriers, the second occurs through neuronal connections of the brain and gut (Fig. 1). The lumen of the intestine contains a myriad of molecules, some of which are significantly biologically active. Among them are nutrition components, microbial metabolites, signaling molecules originated from the cells of gut associated lymphoid tissues, and neuropeptides or hormones produced by enteroendocrine cells. Diverse molecular components of this complex mixture have the character of signaling molecules. For example, peptidoglycans or lipopolysaccharides derived from gut microbiota membrane can cross the intestinal epithelial barrier in response to certain stress conditions, can translocate into the brain and activate specific pattern recognition receptors of the innate immune system, and thereby can affect brain behavior or produce a backward signal via activation of the hypothalamic–pituitary–adrenal axis (56,57).

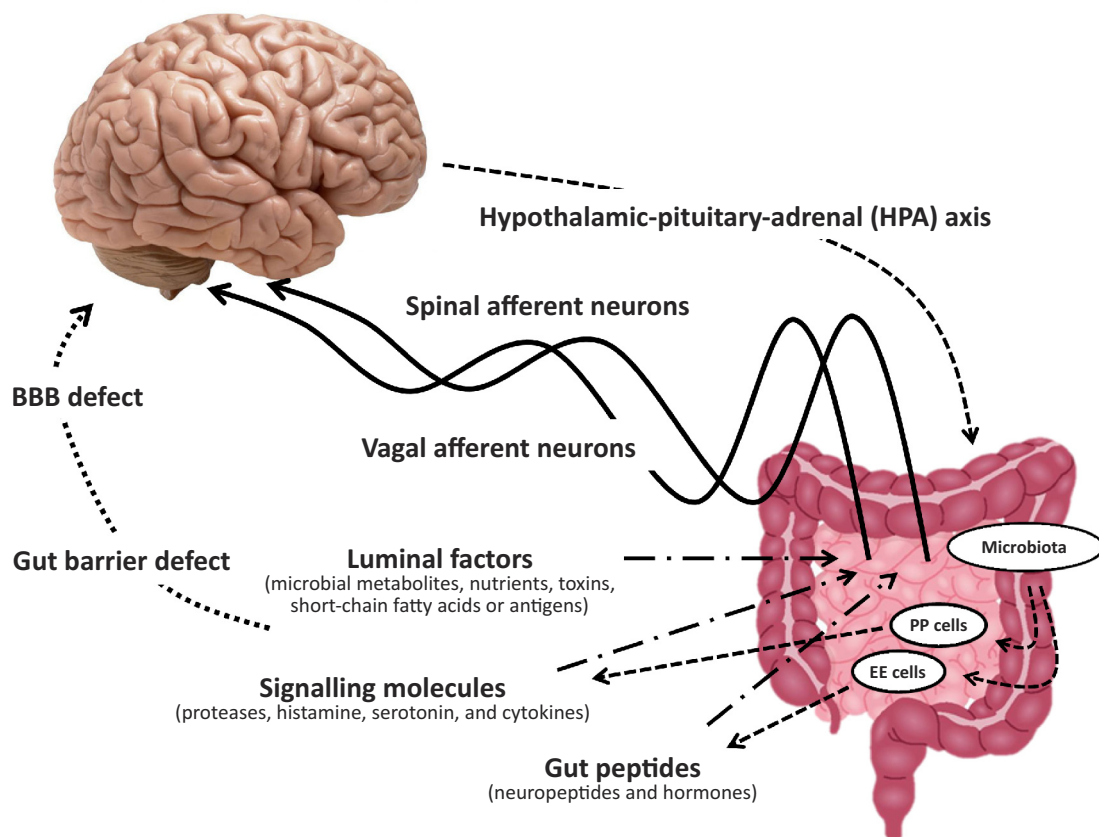


Figure 1. Schematic representation of gut–brain signaling axis. The intraluminal factors can penetrate through damaged intestinal mucosa into the bloodstream and/or lymphatics. In cases of blood–brain–barrier (BBB) defects, these can directly influence the brain cells. Luminal factors have similar effects that might be sensed by vagal and spinal afferent neurons constituting gut–brain connections (54,55). Conversely, the brain regulates gut cell functions through signals transmitted by the hypothalamic–pituitary–adrenal (HPA) axis (56). Abbreviations: EE cells - enteroendocrine cells, PP cells – Peyer’s patch cells, BBB defect – blood-brain-barrier defect

Short-chain fatty acids

The ability of microbes to ferment indigestible carbohydrate fibers means they can generate molecules having a variety of physiological and pathophysiological functions. Among these are acetic, butyric, and/or propionic acids, which are the most widely studied short-chain fatty acids (SCFAs). Dominant producers of SCFAs among human gut microbiota are members of the bacterial families *Bacteroidaceae*, *Prevotellaceae*, and *Rikenellaceae* from the phylum *Bacteroidetes*, members of the families *Lachnospiraceae*, *Ruminococcaceae*, *Veillonellaceae*, and *Erysipelotrichaceae* from the phylum *Firmicutes*, as well as some *Actinobacteria* and *Verrucomicrobia* are (58). SCFAs, most namely butyrate, can enhance the proportion of cholinergic enteric neurons via epigenetic mechanisms (59), can utilize a gut barrier defect, and, after leaking from the gut, can cross the blood–brain barrier and thus activate the vagus nerve and hypothalamus (60). Moreover, butyrate has been studied extensively as a histone deacetylase inhibitor and as a ligand for a subset of G protein-coupled receptors (61).

Neurotransmitters

Bacteria are among the neurotransmitter producers and/or inducers in the gut. They produce these neuroactive molecules either directly, according to their physiological state, or indirectly by interaction with enteroendocrine cells, which are internal producers of neuropeptides, hormones, and signaling molecules.

Gamma-aminobutyric acid

Commensal bacteria of the *Bacteroidaceae*, *Bifidobacteriaceae* or *Lactobacillaceae* family are known to produce *gamma-aminobutyric acid* (GABA), which is the dominant inhibitory neurotransmitter of the central nervous system. GABA's receptors are widely distributed throughout the host cells, thus giving GABA a wide range of possibilities for affecting the behavior of cellular systems. Through its alteration of GABAergic neurotransmission, GABA can influence numerous central nervous system disorders, including behavioral disorders, pain, and sleep (62). There are data showing that GABA is engaged in modulation of such physiological processes as intestinal motility, gastric emptying, nociception, and acid secretion by destabilization of enteric nerves signaling (63).

Serotonin (5-hydroxytryptamine)

Serotonin (5-HT), a biologically active substance and monoamine neurotransmitter, is distributed within the mammalian body but mainly in the gastrointestinal tract. 5-HT plays a critical role during central nervous system development, neuronal differentiation, myelination, and synapse formation (64). The link between specific species of the enteric microbiome, 5-HT, and gastrointestinal symptoms has already been demonstrated using a multi-omics study in children with autism spectrum disorder (65). The presence and frequency of several enteric mucosa-associated Clostridial species are closely correlated with levels of either tryptophan or serotonin in mucosal supernatants. Although several strains of bacteria have been reported to produce 5-HT, no such data exists for gut microbiota. Their association with 5-HT production in the gut seems to be mediated rather indirectly via their effect upon enteroendocrine cells by secretion of such other biologically active effectors as, for example, SCFAs (66).

Dopamine, epinephrine, and norepinephrine

Neurotransmitters of the catecholamine category can play an important role in regulating the gut–brain axis. The endogenous catecholamines include dopamine, epinephrine, and norepinephrine. This type of neurotransmitters provides the acute stress response, also known as fight–or–flight response, to severe harmful events (67,68). Their functional association with the microbiota–gut–brain axis seems to be a functional loop. Some enteric bacteria, such as members of the genera *Klebsiella*, *Pseudomonas*, *Enterobacter*, and *Staphylococcus*, respond to catecholamine molecules by intensified proliferation and/or increased motility, biofilm formation, and virulence (69–71). Some, as for example *Escherichia coli*, *Proteus vulgaris*, *Serratia marcescens*, and *Bacillus subtilis*, produce molecules with neuroactive potential (72). The majority of data in this area, however, has originated from various *in vitro* systems and it is questionable whether these results can be regarded as valid for *in vivo* systems. Moreover, these molecules can function as effectors for interkingdom signaling (i.e., for bidirectional communication between the host and its microbiota) between prokaryotic and eukaryotic cells. For prokaryotic cells, such molecules

as epinephrine and norepinephrine represent signals for quorum sensing and function as global regulators of virulence. Bacteria of the families *Enterobacteriaceae* and *Pasteurellaceae* sense the host stress hormones epinephrine and norepinephrine in combination with iron via the two-component QseBC sensor system (73,74). Overall, however, it should be emphasized that the effect of catecholamines on gut bacterial populations may alter the proportions of bacterial families responsible for metabolism, metabolite utilization, and gut cell–microbe signaling. Ultimately, they may affect microbiota–gut–brain axis signaling.

Hormones

The production of biologically active molecules by gut microbiota might also be a critical event in regulating microbiota–gut–brain, host metabolic pathways, and functional systems. A dominant role might be played by neuroendocrine hormones produced by enteroendocrine cells in response to interaction with members of the microbiota or their products (Fig. 2). In a context of so-called microbial endocrinology, the vast array of enteroendocrine cell receptors recognizing pathogen-associated molecular patterns (PAMPs) or acyl homoserine lactones, which are bacterial quorum-sensing molecules, as well as signals originating from molecules of gut lumen content, produce a number of hormones that influence interrelated physiological processes of the host (75,76).

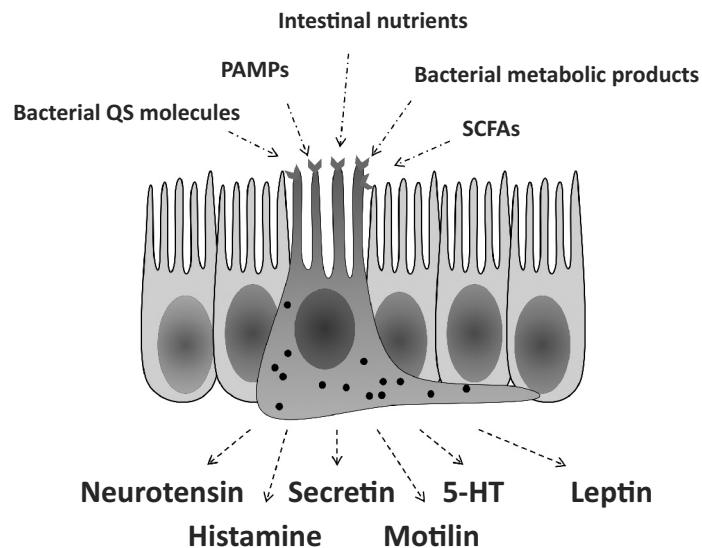


Figure 2. Schematic representation of the possible role of gut microbiota in regulating physiological processes of the host. Bacteria, bacterial components, as well as bacterial communication system molecules activate the enteroendocrine cell subtypes to produce basic regulatory hormones of different physiological processes.

For example, cholecystokinin, its sulfated octapeptide isoform, or derived peptides have been demonstrated to have anxiogenic (77), panicogenic (78), and hallucinogenic (79) effects. Ghrelin produced by A (X-like) cells regulates glucose hemostasis by inhibiting insulin secretion and regulating gluconeogenesis and glycogenolysis in the liver (80) and plays crucial roles in general energy homeostasis, cardioprotection, muscle atrophy, and bone metabolism (81). Other hormones from enteroendocrine cells production have functions in gastrointestinal motility (somatostatin, gastrin) or body fluid homeostasis (secretin) and/or they play roles in mucosal immunity (somatostatin, cholecystokinin, neurotensin, histamine, and leptin) (82).

Hormones produced by different types of enteroendocrine cell subtypes create bridges between functional systems of the body. Due to direct or indirect interaction with enteroendocrine cells, the gut microbiota and their dynamic consortia contribute to and modulate the responses of these body functional systems to internal signals originating from nutrition as well as to external signals originating from the environment. These signals might be psychological, physical, or arising from interactions with other (micro)organisms.

CONCLUSIONS AND PERSPECTIVES

A harmonious gut ecosystem clearly plays important roles during ontogeny and from birth to senescence. It is important for development, maintaining organism integrity, and ensuring proper functioning of metabolic pathways and of organ cell systems. We must emphasize the word “harmonious” here, because only a balanced consortium of microbiota can ensure proper functioning of the host’s interconnected functional systems. The various genera of different phyla produce diverse neuroactive molecules. An example can be seen in the importance for balanced representation of the phyla *Bacteroidetes* and *Firmicutes*. Their ratio is often changed in connection with certain diseases or after host exposure to stress. Within the gut, on the one hand, acetate and propionate are mainly produced by bacteria of the *Bacteroidetes* phylum. Butyrate, on the other hand, is generated by bacteria of the phylum *Firmicutes* (83). Data is accumulating to demonstrate that the gut microbiota influences the perception of pain (84); that it can influence the pathogenesis of Alzheimer’s disease (85-87), Parkinson’s disease (88), and some psychiatric disorders (89), such as attention deficit hyperactivity disorder (90) and autism spectrum disorder (91); and that it can be associated with problems of cognitive impairment (92). The relationship between various health problems and activation of the microbiota–gut–brain axis is schematically presented in Fig. 3.

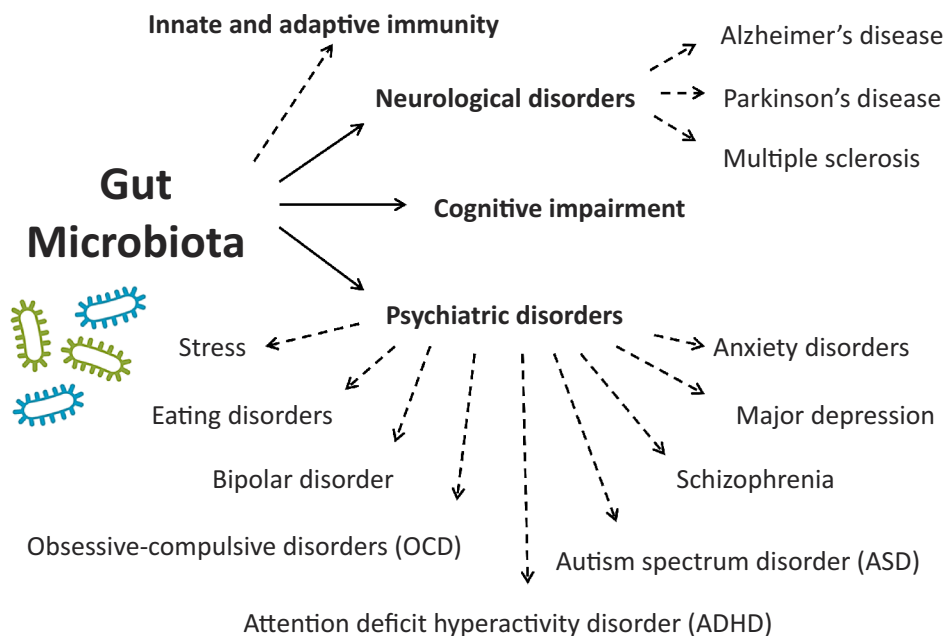


Figure 3. Mutually intertwined relationships among microbiota and various developmental and health problems associated with activation of the microbiota–gut–brain axis.

Nevertheless, there still exist the questions of what is the primary signal leading to gut dysbiosis and what is the sequence of events leading up to manifestation of a disease. The interrelationships among the microbiota and physiological regulatory and functional systems resembles a magical pentagram. The pentagram is a very old symbol of elements (in traditional Chinese medicine dating back before the third century BC and representing fire, earth, metal, water, and wood), which, to put it simply, controlled or regulated the health profile of human beings and in a larger sense their very existence. Within the concept of our classical western medicine, these elements can be regulatory systems (microbiota, enteroendocrine regulation, neurohormonal regulation, natural immune regulation, and finally, at the top of the pentagram, the overall genomic regulation controlling the developmental and integrity status of the organism). Inclusion of microbiota among the systems regulating and controlling the physiological status of the host further justifies creation of the holobiont concept introduced into the scientific literature by Linn Margulis, which was at that time elaborated into a system for defining itself and the concept of hologenome as one of the tools of evolution (93-97).

The analyses performed to date demonstrate the importance of maintaining a dynamic equilibrium of bacterial species in the intestinal microbiome. From this point of view, it seems very worthwhile to seek such nutritional supplements as will help to reverse dysbiosis caused by disease or disbalance of the gut–brain axis to restore original microbial composition. Supplementing just one of the bacterial species without knowing the immediate composition of the microbiome can in certain situations be counterproductive. Moreover, issues regarding the use of probiotics, such as horizontal gene transfer, possible presence of bacteriophage genes in probiotic bacteria, and metabolic changes influencing the gut–brain axis, are not yet fully resolved (98,99). Despite all the shortcomings in our knowledge of the gut–brain axis, it is necessary to gradually accept the concept that certain immunological, neurological, and psychiatric problems related to current lifestyles will be treated by targeting the microbiota–gut–brain axis using natural nutritional supplements to restore the host's original gut microbiota composition.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest regarding the publication of this article.

AUTHOR CONTRIBUTION

Both authors contributed equally to the work.

ADHERENCE TO ETHICAL STANDARDS

This article does not contain any studies involving animals performed by any of the authors. This article does not contain any studies involving human participants performed by any of the authors.

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