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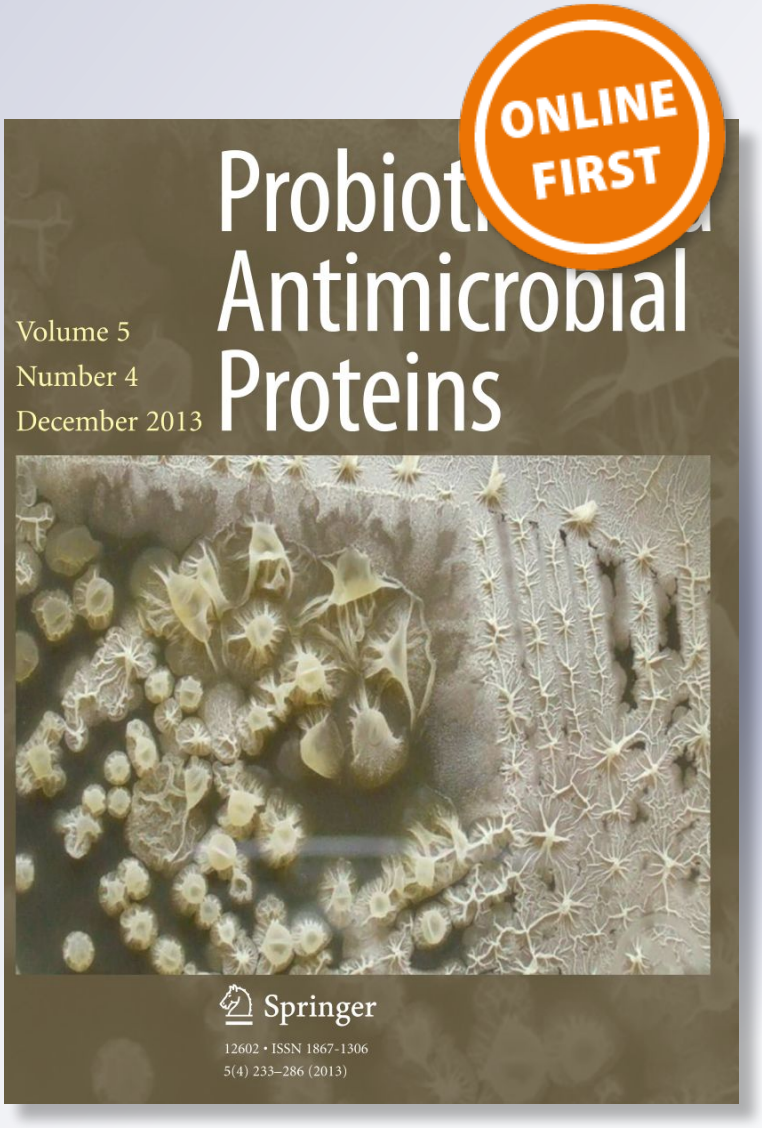

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Probiotics and Psychobiotics: the Role of Microbial Neurochemicals

Alexander V. Oleskin[1] · Boris A. Shenderov[2]

Abstract
In light of recent data, microorganisms should be construed as organisms that are capable of communication and collective behaviors. Microbial communication signals are involved both in interactions among microbial cells within microbial social systems, including the human body-inhabiting microconsortium, and the dialog between the microbiota and the host organism. The microbiota inhabits various niches of the host organism, especially the gastrointestinal (GI) tract. Microorganisms release diverse signal molecules and, in addition, specifically respond to host signals. This enables them to constantly interact with the nervous system including the brain and the immune system of the host organism. Evolutionarily conserved signals that are involved in the communication between microbiota and the host include neuroactive substances (*neurochemicals*) such as peptides, amino acids, biogenic amines, short-chain fatty acids, and gaseous substances. This ongoing dialog may either stabilize the host's physical and mental health state or, alternatively, cause serious health problems. Attempts are made to correct imbalances in the *brain-gut-microbiota* axis with *probiotics* including their subgroup called *psychobiotics* that release neuroactive substances directly influencing the human brain, psyche, and behavior. A number of recent review works address the microbiota–host system and its communication signals. Some of the publications focus on the involvement of neurochemicals in the bidirectional communication within the host–microbiota system. However, this work concentrates on the impact of bacterial cell components, metabolites, and signal molecules as promising alternatives to the currently widespread probiotics that have both advantages and disadvantages. Such biologically active agents of microbial origin are referred to as postbiotics or, alternatively, *metabiotics* (the term preferred in this work).

Keywords Biofilms · Probiotics · Psychobiotics · Metabiotics · Neurochemicals · Nervous system · Immune system · Biogenic amines · Neuroactive amino acids · Short-chain fatty acids

Introduction

This work is focused on useful microorganisms whose collective behaviors and communication are of direct relevance to human neurophysiology and medicine. In the human organism, there is an ongoing dialog between the microbiota and the host. The microbiota inhabits a wide variety of niches in the human organism; it is particularly abundant and diverse in the gastrointestinal (GI) tract. Of special interest from the neurological, endocrinological, and immunological viewpoint is the fact that the microbiota uses ancient, evolutionarily conserved, biomolecular "languages" to communicate with the host organism. These chemicals include biogenic amines, amino acids, peptides, short-chain fatty acids, gaseous agents, etc. They are synthesized and released by microorganisms and serve as molecular signals in the microbial world. Many microbial signals are "intelligible" for the host organism because they also function as human neurochemicals, hormones, or cytokines. The microbiota can exert a strong influence on the endocrine, nervous, and immune system of the human organism. In addition, the microbiota can specifically respond to the aforementioned compounds if they are produced by the host organism. Understanding this bidirectional interactivity within the *host–microbiota* system is of both theoretical and practical importance. It enables us to develop a new generation of drugs that promote harmonious interactions between the human organism and its microbial inhabitants (Fig. 1).

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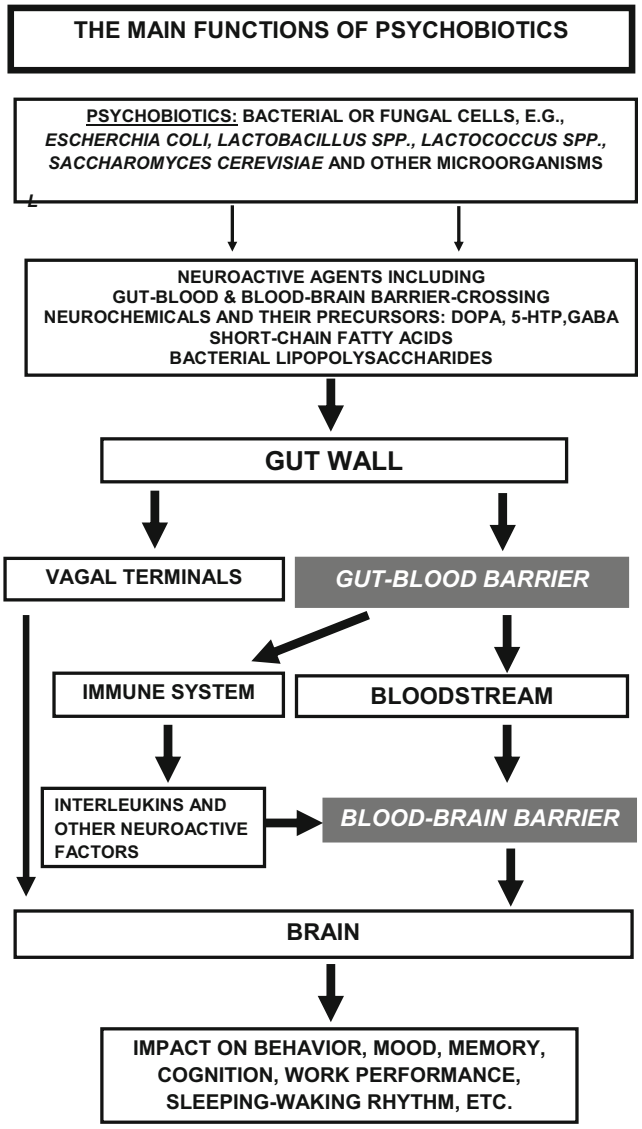

Fig. 1 Psychobiotics represent microbial cells, their fragments or products. They are expected to produce beneficial effects on the host's nervous system, especially the brain, and, therefore, to positively influence human behavior, mood, cognition, etc. Apart from the representatives of bacteria and fungi that are given in the figure, there is a multitude of other potentially applicable microbial species. The figure demonstrates the three main pathways used by psychobiotics: (i) via the vagus nerve, (ii) via the immune system that produces blood–brain barrier (BBB)-crossing neuroactive cytokines and other compounds (see [1]), and (iii) by crossing the two main barriers, i.e., the gut–blood barrier and the BBB. The production of the neurochemicals listed in the figure has been experimentally demonstrated in a number of recent publications, including the authors' own work (reviewed, [1–3]). Abbreviations: DOPA, dihydroxyphenylalanine (the precursor of catecholamines); 5-HTP, 5-hydroxytryptophan (the precursor of serotonin); GABA, γ-aminobutyric acid. Note: In addition to the vagus nerve mentioned in the figure, the effects of psychobiotics on the brain may be mediated by other neuronal pathways within the peripheral nervous system and its part located in the intestines (the enteric nervous system)

A large number of recent reviews address the complexity of the microbiota–host system and the contributions of both microbial and host-produced chemicals to the impact of the microbiota on the somatic and mental health state of humans (e.g., [4–18]). Some of the aforementioned publications and especially the latest works by Mark Lyte [19–21] focus on the involvement of neurochemicals in the bidirectional communication within the host–microbiota system. This issue was also addressed in the authors' previous works [1–3, 22, 23]. However, this work concentrates on the impact of microbially produced chemicals and cell fragments [22, 23] as a promising alternative to the currently widespread probiotics that have both advantages and disadvantages, which are discussed in detail in the "*Probiotics and Metabiotics*" section below.

Starting from the early 1980s, much attention has been given by the global microbiological community to intercellular interactions and signal exchange in the microbial world as well as to the structure and functioning of microbial colonies and biofilms. We suggest calling this new promising approach to microbiology the "*population organization and communication-centered paradigm*". Its development was foreshadowed by important relevant studies that were initiated over a century ago. At the turn of the twentieth century, Otto Rahn [24] in Germany studied the development of microbial populations and substances that are produced by them and accelerate or decelerate this process. Likewise, William Penfold [25] revealed that the culture liquid at the initial growth stage (the lag phase) of a bacterial culture contains substances that promote the culture's transition to the next stage (the exponential phase). Further research on the same subject was conducted with prokaryotic and eukaryotic microorganisms during the course of the past century.

Bacteria and also unicellular eukaryotes form supracellular structures such as compact colonies (on the surface of a nutrient medium or inside it), biofilms, and local cell conglomerations in a liquid medium including microcolonies, flocs, and larger formations exemplified by millimeter-sized granules that are formed by methanogenic microbial associations. Recently, special attention has been paid to studies on *biofilms* as spatially and metabolically structured microbial communities enclosed in an extracellular polymer matrix and located at an air–liquid, solid–air, solid–liquid, or liquid–liquid interphase [26, 27].

The term *sociomicrobiology* was suggested in the literature with reference to the subfield of microbiology that is focused on communication and collective behaviors in microorganisms [28]. Even though the application of the term *social behavior* to microorganisms is somewhat debatable, there is much evidence in the literature that microbial cells are characterized by phenomena that are analogous to cooperation, communication, and behavior synchronization and coordination in other life forms. Microorganisms display them in colonies or biofilms [29–33]. In particular, cooperation in microbial systems can be interpreted as "costly behavior that confers fitness benefits on same-species recipients" [32]. Classical

examples of microbial cooperation include collective hunting by *Myxococcus*, aggregation and subsequent progammed cell death in *Dictyostelium* stalks, and biofilm formation in *Pseudomonas fluorescens* and *Bacillus subtilis* [32, 33]. Cooperation enables the cells of the colonies of some microbial species exemplified by myxobacteria to move in unison over the substrate surface [34]. This fact was mentioned by James Shapiro [35] who highlighted important similarities between bacterial supracellular structures and multicellular organisms.

It should be noted that quasi-social phenomena are characteristic both of free-living unicellular organisms such as bacteria, fungi, microalgae, and protozoans and of the cells of various plants and animals grown as cell cultures.

GI Microbiota

The human being is considered a "superorganism" that includes a consortium of a vast number of prokaryotic and eukaryotic cells and viruses. The prokaryotic cells are more numerous than the eukaryotic cells [36]. Microorganisms grow on the skin, on the eye conjunctiva, and on the mucosa of the upper respiratory tract and of the urogenital system. However, it is in the gastrointestinal (GI) tract that the microbiota is particularly abundant and heterogeneous. Microorganisms exist as planktonic cells in the intestinal lumen or as biofilms on non-digested food particles, including insoluble dietary fibers, in the mucus layer lining the epithelium, in the mucus within intestinal crypts, and on the surface of mucosal epithelial cells [37]. Apart from GI microbial cells, such biofilms contain a matrix that includes microbial exopolysaccharides and other biopolymers as well as host-produced substances, especially goblet cell-synthesized mucin. Microbial biofilms cover most of the mucosa of the large intestine, including the cecum and the vermiform appendix. They directly interact with the epithelial layer (with its tight junctions) that performs the barrier function. The layer controls the entry of ions and organic molecules into the submucosal layers and, ultimately, their transfer into the bloodstream [38].

The number of types of eukaryotic cells in human tissues and organs barely exceeds 200. The total number of bacterial cells amounts to hundreds of trillions and, together with viruses, exceeds one quadrillion. The number of microbial species that are detected by modern molecular techniques may amount to 10,000. Only 1200–1500 species are culturable. Among the 160–300 microbial species that dominate the microbiota, only 18 are detected in all tested individuals, 57 in 90%, and 75 in 50% of the tested subjects. The microbiota is dominated by the *Cytophaga–Flavobacterium–Bacteroides* (phylum *Bacteroidetes*) and the *Clostridium–Eubacterium* (phylum *Firmicutes*) groups, with each group accounting for approximately 30–40% of all microorganisms detected in the large intestine. *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, and *Cyanobacteria* are comparatively less abundant. In many individuals, large numbers of methanogenic and methane-oxidizing archaea are present [4–8, 22, 23].

The number of genes in human chromosomes is about 25,000 while the microbial genome in the body of an adult contains up to 3–10 millions genes [5, 6]. About 80% of the energy in the human organism is produced by the mitochondria of the eukaryotic cells, whereas intestinal microorganisms yield 20% of the total energy. About 90% of the energy required for the functioning of the cells of the GI tract is produced by intestinal bacteria [9, 23, 39]. The microbiome is currently referred to as the "second human genome"; its potential impact on human health and well-being is comparable to that of the human DNA [10, 11, 22].

The microbiota of each region of the human body performs a large number of vitally important functions. It is involved in an individual's development (the *ontogenetic* function), promotes the maintenance of the normal physiological state of the tissues and organs, and helps the organism regulate the gas composition, the pH level, the water-salt balance, and the metabolism of proteins, carbohydrates, lipids, nucleic acids, and other substances (the *homeostatic* function) (reviewed, [22, 23]).

The microbiota is also implicated in processing food, optimizing host cell energetics, and recycling bile acids and sterol hormones. There is little doubt that the microbiota is involved in the epigenetic regulation of the activities of prokaryotic and eukaryotic nucleic acids and other macromolecules. Microorganisms produce and modulate various biologically and pharmacologically active compounds and are partly responsible for GI colonization resistance (the *barrier* function). The microbiota influences the oxidative/antioxidative balance and detoxifies exogenous and endogenous compounds and metabolites. Of note is the capacity of the microbiota to both stimulate and to inhibit mutagenesis, depending on the situation (the *mutagenic/antimutagenic* function [40, 41]). The microbiota has been shown to influence the host's behavioral activities in a way that helps the microbiota survive and spread within the host organism [22]. It plays a significant role in the etiology and/or progression of a large number of GI disorders and other diseases [5, 6, 12–14, 22, 23, 42].

The microbiota is as an integral part of the GI tract, which is envisaged as the largest digestive, immune, and endocrine organ of the human organism. While containing enteroendocrine cells (EECs) and the immunologically important gut-associated lymphoid tissue (GALT), the GI tract also includes the numerous cells of the enteric nervous system (ENS) that is partly independent of the brain [15].

The weight of the total microbial biomass in the GI tract may reach 1.5–2 kg, i.e., it may equal or even exceed the weight of the brain [16]. The total per diem weight of dietary and endogenous substrates that are microbially metabolized in

the GI tract may be as high as 350–500 g. These substances include indigestible food water-soluble components such as resistant starches, inulin, pectins, beta-glucans, and oligosaccharides (20–30 g); insoluble dietary fibers including cellulose, hemicellulose, lignin, and chitin (40–80 g); indigested food proteins (10–40 g), organic acids (2–5 g), nitrate and nitrite (2–5 g), lipids (2–5 g), urea (7–10 g), the mucopolysaccharides of the nasal, pharyngeal, and GI mucosa (20–25 g); saliva components (1,5 L, 20–35 g), bile (0,5–1.0,L 20-25 g); gastric (2,5 L, 20-25 g) and duodenal juice (1 L); and the juice of the small (2,5 L) and the large (0,05 L) intestine (40–60 g). There are also food-, water-, and air-borne microorganisms (2,5-3 g), dead gut symbiotic bacteria (50–150 g), and dead digestive tract epithelial cells (10 g) [5, 6, 13, 42].

The fecal metabolome of 786 tested human individuals was found to contain 1116 different metabolites. Among them, 570 metabolites were identified in at least 80% of these individuals [13].

The microbial metabolome comprises low-molecular-weight metabolites such as lactones, peptide pheromones, furanones, proteins, peptides, amino acids, nucleic acids, nucleotides, nucleosides, volatile fatty acids and other organic acids, gaseous compounds (CH_4, H_2S, NO, and CO), vitamins, amines, polyamines, hormone-similar substances, neurotransmitters (serotonin, acetylcholine, dopamine, GABA, glutamate, norepinephrine and others), polysaccharides, oligosaccharides, peptidoglycans, lipoteichoic acids, glycopeptides, lipopolysaccharides, antimicrobial compounds, lectins, biosurfactants, pigments, and others [5, 6, 13, 14, 17, 22, 23].

Metabolites and signaling molecules of microbial origin bind to cell surface, membrane, cytoplasm, and nucleic acid receptors and coordinately activate specific genes. This enables then to stabilize the host genome and the microbiome, to modulate the epigenomic regulation of gene expression and post-translation protein modification, and to facilitate information exchange in numerous bacterial and bacteria-host systems. Indigenous microbiota-produced molecules exert their local and systemic effects via neuroendocrine, immune, metabolic, and epigenetic mechanisms [2, 3, 18, 22, 23, 42]. There is much chemical and functional similarity between the metabolites, cofactors, enzymes, and signaling molecules that are synthesized by host eukaryotic cells and those produced by indigenous and probiotic microorganisms or contained in food ingredients. Hence, a large number of low-molecular-weight agents of various origins can serve as global (universal) regulators of communication among bacterial or eukaryotic cells as well as between the microbiota and the host [1–3, 22, 23, 42].

Gut bacteria can influence the enteric and the central nervous system by altering the activity of the hypothalamic-pituitary-adrenal axis, stimulating the vagus, producing vasopressin, oxytocin, opioid peptides, serotonin, catecholamines, and other hormones/neurochemicals and synthesizing short-chain fatty acids (SCFAs). SCFAs are known to affect the permeability of the BBB and modulate the activity of neurochemical systems either directly or via host biosynthesis pathways [3, 17].

Microbial Communication

Recently, microbiologists have presented much evidence that bacteria, like all other living organisms, can accumulate, process, and utilize information on their environment during the course of their lifecycle. Exchanging information and obtaining it from other living beings is referred to as communication [43, 44]. Microbial communication, similar to any other kind of communication among living organisms, includes three main stages [44]: (1) detecting a signal, which may involve its binding to a receptor; (2) interpreting the signal's meaning, for instance, cAMP molecules are interpreted by *Dictyostelium discoideum* cells as an instruction to start cell aggregation; and (3) effectuating the response to the signal. In this regard, communicating cell groups resemble neuronal networks or their artificial analogs such as perceptrons. Such networks are composed of several layers that are responsible for information perception, information processing, and response regulation, respectively.

Extensive data have been obtained regarding quorum sensing (QS) systems, i.e., systems that stimulate or inhibit processes carried out by bacterial cells and the formation of complex structures including biofilms, depending on the density of a microbial population [45–53]. An increase in population density results in increasing the autoinducer concentration formed by microbial cells. The autoinducer binds to the proteinaceous response regulator. The resulting complex binds to specific operons and stimulates or suppresses their expression. Quorum sensing systems of most gram-negative bacteria use N-acetylated homoserine lactones (N-AHLs), referred to as autoinducers-1, or AI-1, in the literature.

Importantly, bacteria possess QS systems for both intra- and interspecies communication. Accordingly, there are species-specific and interspecies QS signals [49]. Some signals, including N-AHLs, only function as QS autoinducers, while other signals are less specialized and may perform several different functions. For instance, autoinducers AI-2 (2-methyl-2,3,3,4-tetrahydroxytetrahydrofurans, or THMFs) serve as interspecies QS signals and, in addition, as sinks for some waste metabolites that accumulate in bacterial cells.

Of relevance to the following sections of this work is the fact that bacterial QS systems are also involved in communication between microorganisms and their hosts. Some LuxR-type proteins can also bind signals that are produced by plant or animal hosts, including catecholamines, which represent homologs of a QS signal, AI-3 [2, 54]. Interestingly, such

Table 1 Low-molecular-weight compounds of microbial origin that can be used as new-generation drugs for suppressing the operation of the QS systems of potential pathogens (according to [22]). Note: some of these compounds can be employed as metabiotics (see below for explanation)

Type of QS systems-inhibiting drugs	Examples
Protein synthesis inhibitors	Antibiotics that inhibit ribosome-dependent protein synthesis, antimicrobial peptides
QS receptor antagonists	Microbial trans-isomers of fatty acids, bacteriocines
Inhibitors of signal transduction in peptide-dependent QS systems	Histidine kinase inhibitors
Inhibitors of signal transduction in *N*-acyl homoserine lactone-dependent QS systems	Microbial halogenated furanones
QS signal-degrading enzymes	Microbial acylases, lactonases, and proteases

communication is bidirectional because the host can specifically respond to bacterial QS signals. Some of them behave as immunomodulators that stimulate lymphocyte activity and antibody production [55]. 3-oxo-dodecanoyl-homoserine lactone, a major QS autoinducer of *Pseudomonas aeruginosa*, inhibits TNF-α and inteleukin-12 synthesis by immunocytes and stimulates the production of pro-inflammatory γ-interferon as well as interleukin-8; this regulatory effect implicates transcription factor NF-κB and activator protein 2 [37]. The same signal affects intestinal epithelial cells, disrupts the function of tight junction proteins, and, therefore, increases the permeability of the intestinal barrier.

Quorum sensing (QS) systems, unfortunately, are widely spread in opportunistic and pathogenic microorganisms (e.g., *Pseudomonas aeruginosa* and *Vibrio cholera*), enabling them to synthesize toxins, adhesins, and other virulence factors if their population density is sufficiently high [49–53]. Such QS systems should be used as the targets of a new generation of drugs [22, 23] for preventive and therapeutic purposes, including the following chemicals:

- Antagonists of receptors for QS signals (trans-isomers of fatty acids, L-isomers of sugars, and lectins)
- Inhibitors of QS systems, exemplified by halogenated furanones that disrupt the operation of *N*-AHL-dependent QS systems
- Inhibitors of histidine kinases that are required for the functioning of peptide-dependent QS systems, which are widespread among gram-positive bacteria [49]
- Enzymes that catalyze the degradation of QS signals, including microbial acylases, lactonases, etc.

Additional information concerning prospective QS systems-targeted drugs is contained in Tables 1 and 2.

Microbiota, Neurochemicals, and Dietetics

Over the course of the last decades, new data on the microbiota and its interaction with the human microbiota lent additional weight to nutritional science. Of considerable interest is the recently initiated *nutritional psychiatry*. It proceeds from the idea that the diet can be used for preventing or treating mental disorders. It places special emphasis on dietetics because the diet is as important for psychiatry as it is for cardiology, endocrinology, and gastroenterology [5, 56].

The currently widespread westernized high-calorie diet is not sufficiently rich in valuable nutrients, including folic acid and other B group vitamins, vitamin D, S-adenosinomethionine, *N*-acetylcysteine, zinc, magnesium, and dietary fibers. Using this kind of diet results in people being both overfed and undernourished. This contributes to the current spreading of diseases (comorbidities) that affect both the organism's physiological state, including the functioning of the GI system, and the individual's mental health. Serious problems may be caused by a lack of nutritional cofactors and phytochemicals that protect the organism from oxidative stress associated with oxygen radicals [56]. The westernized diet alters the GI microbiota, decreasing the number of fiber-degrading microorganisms and increasing the concentration of animal protein and lipid decomposers [5].

The primary colonization of the gut by microorganisms during the perinatal period and the first 3–4 years of an individual's life is of paramount importance in health terms, especially with respect to the education and maturation of the immune system, as emphasized in the recent "Old Friends" hypothesis [57, 58]. Therefore, special attention should be given to the mother's and the young infant's diet.

Of note in the context of the *microbiota–gut–brain* axis are *prebiotics*, i.e., substances that stimulate the development of the GI microbiota; they are exemplified by oligosaccharides, polyunsaturated fatty acids (particularly, ω-3 fatty acids), dietary fibers, and polyphenols [22, 23]. For instance, there is evidence that ω-3 fatty acids and oligosaccharides can be successfully used for treating patients with mental problems [15]. Of much promise is the health-promoting strategy that combines an innovative probiotics-, prebiotics-, and metabiotics[1]-enriched diet with more traditional psychiatric techniques including psychotherapy.

Of direct relevance to diet therapy is the fact that food products and additives contain *biologically active substances* (*BASs*), including those of microbial origin, which impact the

[1] Metabiotics are discussed in the next section of this work

Table 2 Neuroactive compounds of microbial origin that function as hormones and/or neurochemicals in the host organism and can potentially be used as metabiotics [22]

Type of chemicals	Examples
Biogenic amines	Serotonin, dihydroxyphenylalanine (DOPA), norepinephrine, dopamine, histamine, acetylcholine, tryptamine
Amino acids	Aspartic acid, glutamic acid, glycine, taurine, tryptophan, γ-aminobutyric acid (GABA)
Short-chain fatty acids	Butyric, propionic, acetic, lactic acid
Gaseous substances	NO, CO, H_2S, H_2, CH_4, NH_3

whole "triangle" that comprises the microbiota, the nervous system, and the immune system. BASs include *nootropics* that stimulate brain activity, cognition, and creativity [59], as well as produce other positive psychological effects.

For instance, gamma-aminobutyric acid (GABA) mitigates anxiety and improves sleep quality. In addition, the oral administration of GABA or GABA-supplemented food/beverages (containing about 50–100 mg of GABA) has positive effects on human health. These effects include: (i) the reduction of psychological stress in people who perform arithmetic tasks, (ii) the reduction of stress in acrophobic subjects exposed to heights, and (iii) an increased ability to perform prioritized planned actions [60]. Apart from food, GABA is also supplied by the microorganisms that contain the necessary enzyme glutamic acid deaminase (GAD) [14, 17].

Of relevance is also ferulic acid (trans-4-hydroxy-3-methoxycinnamic acid, FA) that is contained in seed plants (rice, wheat, and oats), vegetables (tomatoes and carrots), and fruits (pineapple and orange; [8]). Plants with a high FA content were traditionally used in Chinese medicine as anti-inflammatory drugs. FA is a strong antioxidant that can be used for treating neurodegenerative diseases, obesity, and diabetes. FA stimulates the proliferation of the stem cells of the nervous system. Chronic administration of FA to mice relieved Alzheimer's-specific behavioral symptoms, reduced the number of pathological amyloid Aβ fibrils, mitigated neuroinflammation, and alleviated oxidative stress [8]. Apart from food, large FA amounts are synthesized by the GI microbiota that produces the necessary esterase enzyme. The probiotic bacterial strain *Lactobacillus fermentum* NCIMB 5221 [8] displays high FA-synthesizing activity. Therefore, its application is a reasonable alternative to administering FA in the form of drugs or using an FA-enriched diet.

A potentially useful food additive could be prepared by mixing several neuroactive amino acids, e.g., glutamic acid, an excitatory neurochemical, and GABA, an inhibitory neurochemical. When mixed at an appropriate ratio, these two neurochemicals could help adjust a patient's brain activity level during the premorbid and the initial stage of chronic mental diseases. However, BASs (and nootropics) should be used with caution. Their excessive concentrations can produce negative effects, even if these BASs are contained in food ingredients [60]. For instance, high glutamic acid concentrations may induce apoptosis in brain and heart cells. This poses a threat to one's health and may even cause a heart attack or a stroke [61, 62]. Likewise, despite the useful effects of GABA, only its moderate concentrations should be administered to patients. It should be noted that high GABA concentrations (300–720 nmol per 1 g of dry weight) are present in many plant foods including brown rice germs and sprouts, spinach, barley, and bean sprouts. Fermented foods are characterized by still higher GABA levels that are released by bacteria during fermentation [17, 60].

Probiotics and Metabiotics

In recent decades, increasing global attention has been given to *probiotics* (this term was coined by the German nutritionist Werner Kollath in the 1950s who contrasted them with risky antibiotics; see [63]). According to the official definition given by FAO/WHO [64], probiotics are live microorganisms that, "when administered in adequate amounts, confer a health benefit on the host". Commercially available probiotics are supplied in the form of drug preparations and biologically active food additives that contain microbial cultures.

Apart from live probiotic cultures, special importance should be attached to dead microbial cells, their fragments, and microbial metabolites including signal molecules. Such biologically active agents of microbial origin were referred to as postbiotics in a number of recent publications [65, 66]. However, the authors prefer using the alternative term *metabiotics*, originally coined by Shenderov (see [22]). This term contains the Greek prefix *meta-* (change, transformation), referring to the metabiotics' ability to initiate a large number of hormonal and neurochemical processes. In contrast, the prefix *post-* (after, posterior to) in the word "postbiotics" merely emphasizes the "post mortem" nature of these compounds that either work after a microbial cell has been killed and broken down into fragments or represent substances that have been separated from it.

Metabiotics tend to have a longer shelf life than probiotics, and they are more target-specific and safe in terms of their interaction with the human organism. It is relatively easy to adjust their dosage in a clinical setting. They are comparatively quickly removed from the organism. The following health-

promoting functions can be performed both by probiotics and metabiotics, the effects of metabiotics often being more reliable and predictable [22]:

1. *They help the human organism stabilize the GI microbiota and optimize its qualitative and quantitative composition.* They also suppress harmful microorganisms because they contain antimicrobial factors (short-chain fatty acids, bacteriocins and their analogs, hydrogen peroxide, nitric oxide, etc.); live probiotics prevent the spreading of potentially pathogenic microorganisms by successfully competing with them for ecological niches in the human organism [22]. Both probiotics and metabiotics can potentiate the immune response to pathogens. An eukaryotic probiotic, the yeast *Saccharomyces cerevisiae* strain 905, was established to protect the mouse gut from the pathogenic enterobacteria *Salmonella typhimurium* and *Clostridium difficile* [67]. These two pathogens are also suppressed by the probiotic strains *Lactobacillus*, *Bifidobacterium*, *Lactococcus*, *Streptococcus*, and *Bacillus*; this is due to the production of short-chain fatty acids, including formic, acetic, and lactic acid, by the probiotics [68]. The inhibition of pathogens by probiotics and metabiotics also depends on their capacity to increase membrane permeability and to oxidize the sulfhydryl groups of membrane lipids [58].
2. *The low-molecular-weight compounds contained in probiotics/metabiotics neutralize toxins and other metabolites that are harmful for the host organism.* These small-size molecules disrupt pathogen-specific communication mechanisms, including quorum sensing systems. Importantly, while suppressing potentially pathogenic microorganisms, probiotics and metabiotics do not inhibit the functioning of the GI symbiotic microbiota, in contrast to antibiotics [58].
3. *Probiotics and metabiotics supply the host organism with nutrients*, *antioxidants*, *growth factors*, *enzymes*, *organic acids*, *polyphenols*, *vitamins*, *bile acids*, *gaseous substances*, *and other BASs* that beneficially influence the salt water, lipid, amino acid, and energy metabolism; the redox balance at the local (intestinal) and systemic (general) levels; and the development and operation of the peripheral, especially enteric, and central nervous system. The BASs also exercise epigenomic control over the expression of host genes and modulate the systemic responses of the innate and adaptive immune system [5, 22, 23].
4. *Probiotics and metabiotics exhibit anticarcinogenic activity* [65], as exemplified by the strong anticancer effects of the *Lactobacillus acidophilus* 36YL strain on four tested cancer cell lines (AGS, HeLa, MCF-7, and HT-29), in which the strain induces cell death (apoptosis) [69].
5. *Probiotics and metabiotics produce antiallergic*, *antidiabetic*, *and anti-inflammatory effects.* The probiotic strain *Lactobacillus plantarum* 06CC2 relieved allergic symptoms in mice treated with the allergen ovalbumin. It decreased the amount of ovalbumin-specific immunoglobulin IgE and the total IgE level. Concomitantly, the concentrations of the antiallergic factors interleukin-4 and γ-interferon increased [58]. The administration of probiotic bifido- and lactobacteria causes an increase in morning melatonin content in the saliva, which is associated with attenuation of the irritated bowel syndrome (IBS) [60]. Probiotic strains of lactobacilli promote the production of anti-inflammatory interleukin-10 and influence the development of the dendritic cells of the immune system [70].
6. *Probiotics and metabiotics beneficially influence metabolism*, *and they can be used for treating obesity* (*metabolic syndrome*). Probiotics and metabiotics also help patients with anorexia and malnutrition. It was revealed that probiotics improve the health state of rodents after a period of starvation [7].
7. Beneficial microbial agents can potentially be used *to improve the symptoms of aging*; this point was already made by Elia Metchnikov over a century ago in his famous work *Etudes sur la nature humaine: essai de philosophie optimiste* [71].
8. *These agents promote the growth of blood vessels* (*angiogenesis*) in the intestinal tissue by producing factor VEGF (vascular endothelial growth factor) [58].
9. *Some probiotics produce a pain-relieving effect*, particularly with respect to abdominal pain. This effect may result in complete analgesia (a lack of pain sensitivity), which is attributable to the capacity of lactobacilli including *Lact. acidophilus* to induce the expression of μ-opioid and cannabinoid receptors in the intestinal epithelium [14].
10. *Probiotics and metabiotics can relieve stress*. This is characteristic of preparations that are based on bifidobacteria and lactobacilli which are contained in fermented dairy products. Consumption of dairy products that contain such metabiotics as the metabolites of bifidobacteria and lactobacilli promotes physical and mental health by ameliorating the patient's microecological system and optimizing the activity level of the brain areas that are responsible for cognitive capacities. An important mechanism is based on the optimization of tryptophan metabolism because the essential brain neurochemical serotonin is produced from tryptophan [72].
11. *Probiotics and metabiotics regulate the activity of the intestinal part of the immune system that is referred to as the gut-associated lymphoid tissue* (*GALT*). They modulate immune responses, normalize the balance of

pro- and anti-inflammatory cytokines, lower the antigen load of GALT, decrease gut wall permeability, increase immunoglobulin IgA secretion, induce the activity of anti-inflammatory T_{reg} cells, and promote the production of anti-inflammatory interleukin-10 [15, 73].

12. *These agents systemically strengthen the whole immune system and the organism's natural barriers*, including the gut–blood barrier and the blood–brain barrier (BBB) by increasing the expression of proteins involved in forming tight junctions between cells. In this fashion, they help prevent brain problems and, accordingly, cognitive and behavioral disorders [15]. Under stress, they improve the gut wall's protective function, decrease the concentrations of circulating corticosteroids and pro-inflammatory cytokines, while increasing those of anti-inflammatory cytokines. The latter contribute to the strengthening of the BBB and the gut–blood barrier and attenuate systemic inflammation [22].

It should be emphasized that the useful effects of probiotics and metabiotics are produced not by individual microbial substances, but by a sophisticated complex of low-molecular-weight compounds [22, 23] that are present either in their functional form or as precursors. These microbially produced complexes influence the host organism and its microbiota in combination with other BASs that are either ingested or produced by the resident microbiota.

Psychobiotics: Their Useful Effects

Probiotics include a subgroup that is denoted as *psychobiotics*, i.e., living microorganisms that, when administered in adequate amounts, confer a health benefit on patients with psychiatric problems [17, 74]. Apart from microbial cells per se, psychobiotics also include their neurologically and psychologically active fragments and products. It should be noted that classifying certain probiotics as *psychobiotics* is predominantly based on psychological/psychiatric criteria. Although many probiotics release neuroactive compounds under certain conditions (see next section), the term "psychobiotics," in the author's opinion, should only be used for microorganisms (and their specific strains) that predictably produce sufficiently strong positive effects on the brain and, therefore, on an individual's mental health and behavior. There is a growing body of evidence that probiotics can significantly influence the brain and, therefore, affect behavior, mood, and cognition both in experimental and clinical settings [9].

A large number of low-molecular-weight compounds of microbial origin can modify the psychological and behavioral features of humans and animals. They include, e.g., the lipopolysaccharides of *Bifidobacterium breve* 2003, which induce gut epithelial cells to synthesize substances that modulate signal transmission by afferent axons of nervous cells within the gut–brain axis [16].

By modulating the GABA-dependent brain system, the psychobiotic strain *Lact. rhamnosus* JB-1 inhibited the anxiety-like behavior of mice in a complex maze and an open field test and prevented depression-like symptoms in the forced swimming test [19, 70]. After administering *Lact. rhamnosus* JB-1 to the mice, the transcription of the genes encoding the receptors for GABA was increased in the hippocampus and decreased in the prefrontal cortex of the brain [14, 17, 20, 75–80]. Vagotomy (severing the vagus nerve connecting the enteric nervous system to the brain) abolished the psychobiotic effects. In similar fashion, the anxiolytic (anxiety-relieving) effect of the psychobiotic *Bifidobacterium longum* NC3001 was also removed by vagotomy [75].

A *B. longum* 1714 + *B. breve* 1205 combination ameliorated anxiety-like behavior in mice, and its efficiency was comparable to that of the anxiolytic drug escitalopram [79]. Administration of *Lact. rhamnosus* and *B. longum* improved the behavior of mice that were infected by the parasite *Trichuris muris* and suffered from colitis caused by dextran sodium sulfate, respectively [81, 82]. The practically important conclusion was drawn that such microorganisms as well as the butyrate-producing *Faecalibacterium* and *Coprococcus* bacteria can be used for treating stress-related psychiatric problems, including anxiety and depression [83].

Studies with aseptically raised (germ-free, GF) mice demonstrated that colonizing their GI tract with *Lact. plantarum* PS128 increased their motor activity, decreased anxiety in an extended maze test, and increased the concentrations of dopamine and serotonin in the striatum of their brain [83].

Of relevance are also the data obtained with rats. Their anxiety-like behavior caused by an electric shock is relieved by the psychobiotic strains *Lact. helveticus* R0052 and *B. longum* R0175. Restraint stress in rats (keeping a rat in a fixed position for a period of time) results in depressive behavior which is accompanied by GI dysbiosis. In this model system, the probiotic strain *Lact. helveticus* NS8 relieves depression and, moreover, restores the normal microbiota [15]. Young rats separated from their mothers display depressive behavior in the forced swimming test, which is relieved by administering the psychobiotic *B. infantis* strain 35624 [84]. This psychobiotic increased the blood level of tryptophan, the serotonin precursor, in the rats [14, 16], which might account for its antidepressant effect. It is known that depression is often correlated with a lowered activity of serotonergic brain areas. Introducing *B. infantis* into the GI tract of maternal separation-stressed rats also increases the brain norepinephrine level, which is lowered by stress [17, 84]. Psychobiotic strains positively influence memory and learning [9, 14, 79].

Ameliorating the GI microbiota by administering psychobiotics in studies with animal models reduces

inflammation-induced alterations in the gut and improves behavioral symptoms, e.g., in mice with an autism-like disorder. Normalizing the microbiota with psychobiotics was shown to decrease the risk of neurological and psychiatric problems. For instance, administration of *B. infantis* to GF mice at an early age reduces their stress response to the normal level, so that the GF mice become similar to conventional mice in this respect [4].

The strain *Lact. paracasei* NCC2461 restored the normal composition of the intestinal microbiota and decreased the pain sensitivity of the colon of NIH Swiss mice with disrupted microbiota and antibiotic-enhanced visceral pain sensitivity (antibiotic-induced hyperalgesia). The same psychobiotic mitigated visceral pain in maternal separation-stressed rats whose colon was distended. *Lact. acidophilus* NCFM induced the expression of pain sensitivity-reducing opioid and cannabinoid receptors in the intestinal epithelium, causing analgesia (a lack of pain sensitivity) in rats [75].

Female mice on a lipid-enriched diet give birth to pups with disrupted social behavior, GI dysbiosis, and a decreased number of oxytocin-producing neurons in the hypothalamus; all these symptoms are improved by treating them with the psychobiotic *Lact. reuteri* MM4-1A (ATCC-PTA-6475) [85]. These effects of psychobiotics are apparently due to their positive influence on the hypothalamus–pituitary–adrenals (HPA) axis that is essential for a stress response; the HPA function may be impaired under stress, as well as in GF animals.

In humans, anxiety and depression can be efficiently treated with a combination of several probiotics [82]. Administration of probiotic/psychobiotic strains, e.g., of the species *Lactobacillus casei*, to patients with chronic fatigue syndrome (CFS) and irritable bowel syndrome (IBS) made them less anxious and stressed. The GI microbiota of individuals with CFS was enriched in lactobacilli and bifidobacteria under the influence of the strain *Lact. casei* Shirota [86]. A psychobiotic strain (strain 35624) of the species *B. infantis* relieved pain in IBS patients and normalized the serum concentrations of pro-inflammatory cytokines [75, 76]. A psychobiotic combination of *Lact. helveticus* and *B. longum* strains improved depressive symptoms after myocardial infarction [9].

Apart from relieving depression and anxiety, psychobiotics and dairy products containing them improve mood and cognitive capacities. For instance, the aforementioned depression-relieving psychobiotic strain *Lact. rhamnosus* JB-1 promoted information memorization and learning [19]. The *Lact. acidophilus*, *Lact. fermentum*, and *B. animalis* subsp. *lactis* cocktail ameliorated the cognitive capacities and electroencephalographic data of subjects suffering from diabetes [9]. In healthy volunteers, oral administration of the *Lact. helveticus* B0052 and *B. longum* R0175 combination attenuated stress caused by psychological factors [58].

Gut-inhabiting bacteria belonging to the genera *Dialister* and *Coprococcus* are regarded as potential psychobiotics. Metagenomic studies revealed that their amounts in the GI tract are decreased in patients diagnosed with depression [78]. In studies with human subjects, it was also established that a dairy product that contains *B. animalis* subsp. *lactis* (strain number I-2494 in French National Collection of Cultures of Microorganisms (CNCM, Paris, France), also referred as DN-173010), *Streptococcus thermophilus* (CNCM strain number I-1630), *Lact. delbrueckii* subsp. *bulgaricus* (CNCM strain numbers I-1632 and I-1519), and *Lactococcus lactis* subsp. *lactis* (CNCM strain number I-1631) lowers the intensity of the brain response to emotional stimuli. According to fMRI data, the brain structures involved in emotion perception become less activated during a test in which subjects recognize the emotions of the faces that are demonstrated to them. Probiotics also relieved sadness and reduced aggressiveness, according to the questionnaire filled in by the subjects [87]. Similar results were obtained after 4 weeks of administering of a combination of probiotic strains (*B. bifidum* W23, *B. lactis* W52, *Lact. acidophilus* W37, *Lact. brevis* W63, *Lact. casei* W56, *Lact. salivarius* W24, and *L. lactis* W19 and W58). After this treatment, the subjects exhibited less aggressiveness, rumination, and other negative behavioral responses to disagreeable stimuli, compared to the control (placebo-receiving) group of subjects [88]. Using a dairy product with the probiotic *Lact. casei* Shirota improved the mood of patients that had displayed depression symptoms prior to the treatment [89].

In contrast, opportunistic and pathogenic bacteria exert a detrimental influence on the human brain and, therefore, psyche. The lipopolysaccharides of staphylococci bring about anxiety and depression and worsen cognitive capacities [9]. Anxious behavior also occurs during the infection that is caused by the pathogens *Campylobacter jejuni* and *Citrobacter amalonaticus.* This behavioral effect depends on the vagus nerve and is abolished by severing it in animals [15, 17].

Antibiotics disrupt the functioning of the GI microbial consortium and worsen cognitive capacities. Specifically, they suppress the operation of working and spatial memory systems. Subsequent administration of psychobiotics improves memory [15].

The psychobiotic *B. fragilis* ATCC 9343 normalizes the gut wall permeability and ameliorates autism-like symptoms in mice, including stereotypic behavior, impaired communication, and anxiety-like symptoms [79, 80]. In children with autistic spectrum disorders (ASDs), the administration of the psychobiotic strain *Lact. plantarum* WCFS1 improves their performance at school [58].

The *c-fos* transcription regulator genes are activated in the hypothalamus under the influence of psychobiotics, e.g., *Bifidobacterium infantis* and non-pathogenic *Escherichia coli* strains [9].

Despite the promising data, serious questions should be raised with regard to probiotics and, more specifically, psychobiotics and their potential use in therapeutic and nootropic terms. One of the issues is whether the microbial agents called psychobiotics in this work really improve cognitive capacities. No compelling evidence has been presented in studies with humans. There are only data obtained with animal models in which psychobiotics promote memorization and learning. Even a negative influence of probiotics on the brain and psyche of their consumers cannot be ruled out. Obviously, further extensive research on probiotics, including psybiotics, should address these issues.

Microbial Production of Neuroactive Substances

The functioning of the GI microbiota involves the production of a large number of microbial low-molecular-weight compounds that behave as effectors, cofactors, and/or signals and regulate the rate and direction of a wide variety of physiological and metabolic processes [22, 23]. The microbial production of such compounds significantly influences the concentrations of various metabolites in the blood of mammals [16, 18, 83]. For a long time, it was generally assumed that food is the only source of low-molecular-weight bioactive molecules. However, recent research has provided compelling evidence that the symbiotic intestinal microbiota is also actively involved in (i) metabolizing a large number of plant poly- and oligosaccharides, animal and endogenous (human cells- and microbiota-produced) proteins, and a wide variety of other compounds and (ii) synthesizing and recycling many macro- and micronutrients, signal molecules, and agents that regulate interaction among prokaryotic and eukaryotic cells as well as between these two kinds of cells [5, 17, 22, 23].

More specifically, both intra- and intercellular communication and the host–microbiota dialog are based on a large spectrum of chemical agents, including amino acids, biogenic amines, short-chain fatty acids, serpins, sirtuins, lectins, and many others. The symbiotic microbiota is the source of a multitude of endogenous mono- and multifunctional signal molecules that maintain the state of health of humans and, nonetheless, pose the threat of diseases from infancy to old age [5, 22].

Depending on their site of action, signal molecules are subdivided into autocrine signals that act on the cells producing them, paracrine signals that target adjacent cells, and endocrine signals (hormones) that are released by endocrine glands into the bloodstream and are involved in regulating many important metabolic process at the systemic level. Microbially produced low-molecular-weight compounds are metaphorically denoted as "the words" of the language that is used in microbiota–host communication [1–3, 22, 23]. Some of the important "words" will be discussed below in some detail. Unfortunately, the molecular mechanisms that are employed by microorganisms have not been completely understood yet; further research is required.

Microorganisms produce diverse hormone-like and neuroactive substances; they also modify host-synthesized hormones. For instance, microorganisms regulate the level of estrogens, female hormones, in the host organism, because they possess β-glucuronidase that converts estrogens from the inactive conjugated to the active free form [17, 90]. The microbiota also regulates the release of thyroid hormones.

The peptide ghrelin causes hunger and anxiety and, in addition, promotes information memorization. The serum concentration of ghrelin varies depending on the composition of the GI microbiota. This concentration decreases with an increase in the number of lactobacilli and bifidobacteria that, therefore, relieve hunger. On the contrary, the ghrelin concentration increases as *Bacteroides* and *Prevotella* representatives accumulate. The microbiota also influences the concentration of peptide YY that, among other effects, improves memory, stimulates anxiety, and increases the excitability of nervous cells [9].

Since communication in the microbiota–host system is bidirectional, host-produced chemical factors exert a significant and, in many cases, specific influence on the growth-related, physiological, biochemical, genetic, and behavioral features of microorganisms [5, 17]. Some silent genes of symbiotic bacteria become activated if they are transferred into the GI tract. In *Lact. plantarum* WSFS 1, the expression of 72 genes is induced in the host gut. Bidirectional interaction within the microbiota–host system is illustrated by the activation of 400 host genes by the bacterium *Lact.* GG [22].

Such bidirectional interaction also involves neuroactive compounds (*neurochemicals*), such as biogenic amines (catecholamines, serotonin, histamine, etc.), amino acids (GABA, glutamic acid, aspartic acid, etc.), neuropeptides, gaseous neurotransmitters (NO, H_2S, and CO), and short-chain fatty acids. All these substances are produced by the microbiota and the host organism and used by both partners as communication signals [3, 17, 78].

This is exemplified by the role of catecholamines (dopamine, norepinephrine, and epinephrine). They were detected in the cultures of a large number of prokaryotic and eukaryotic microorganisms using high-performance liquid chromatography (HPLC) with amperometric detection [91–93]. For instance, norepinephrine at concentrations of 0.2–2 μM was present in the biomass of *Bacillus mycoides*, *B. subtilis*, *Proteus vulgaris*, and *Serratia marcescens*, dopamine at concentrations of 0.5–2 μM in the biomass of most tested prokaryotes. The catecholamine concentrations significantly exceeded those of the human blood that contains 0.1–0.5 nM dopamine and 1–2 nM norepinephrine [94].

In the example of *B. subtilis*, it was demonstrated that catecholamines are mostly located in the extracellular matrix and not inside bacterial cells [91]. This fact is consistent with the suggestion that the neurochemicals perform communicative functions in prokaryotes and in the microbiota–host system. Many microorganisms, e.g., *Staphylococcus aureus*, *E. coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Coprococcus comes*, and *C. catus*, also contain dihydroxyphenylacetic acid (DHPAA) and/or dihydroxyphenylacetaldehyde (DOPAC), the products of oxidative deamination of dopamine [17, 78, 91].

Micromolar concentrations of dopamine were also detected in *Morganella morganii* (2.46 mg/L, ~16 μM), *Klebsiella pneumonia* (1.06 mg/L; 6.9 μM), and *Hafnia alvei* (0.73 mg/L; 4.7 μM) that were isolated from fish products [95]. Some researchers are convinced that dopamine is ubiquitous in the world of pro- and eukaryotic microorganisms: "in bacteria, fungi, protozoans… dopamine seems present wherever it is sought" [96]. The eukaryotes *S. cerevisiae* and *Penicillium chrysogenum* contain high concentrations of norepinephrine (0.21 and 21.1 μM, respectively) [2, 91].

Apart from producing neurochemicals, many microorganisms (including some probiotics) specifically respond to them. A direct stimulatory effect of catecholamines on microbial growth was revealed in vitro in a wide variety of pathogenic, opportunistic, and saprotrophic bacteria (reviewed, [1, 2, 17]).

Nevertheless, the effects of catecholamines varied depending on the taxonomic position of the tested microorganisms. Norepinephrine, epinephrine, and dopamine stimulated the growth of *Vibrio parahaemolyticus* and *V. mimicus*, but not *V. vulnificus* and *V. cholera* [97]. Norepinephrine inhibited the growth of *Mycoplasma hyopneumoniae* by suppressing the expression of the genes required for proliferation [98]. Dopamine drastically stimulated proliferation of the yeast *S. cerevisiae*; conversely, norepinephrine produced little effect in this system [93]. When added to a solid medium, dopamine and norepinephrine differed in terms of their effect on microcolony formation in *E. coli* K-12: norepinephrine stimulated and dopamine inhibited this process [2, 99].

By screening the database of the Human Microbiome Project, Kovtun et al. [100] revealed that the intestinal microbiota contains enzymes that are involved in the production of diverse neuroactive compounds.

Microorganisms as Neurochemical-Producing Biofactories?

The potentially promising biotechnological idea of converting neurochemical-synthesizing microorganisms into "biofactories" that produce neuromediators, their precursors, and metabolites presents serious difficulties. The concentrations of such microbial neurochemicals typically are too low to be used for biotechnological industrial production. Nevertheless, it is to be hoped that modern efficient selection techniques including genetic engineering will enable us to create microbial *overproducers* of valuable neurochemicals and related BASs.

Successful attempts to develop such overproducers can be illustrated in the example of neuroactive amino acid-producing microorganisms. *Lactobacillus* and *Lactococcus* strains were obtained from Italian cheese, Chinese adzuki beans, and fermented cod bowels that produce over 1 mmol/L of GABA (reviewed, [2]). The cultures of lactobacilli and bifidobacteria that were isolated from the people living in the Central Region of Russia exhibited a comparable efficiency in producing GABA. For instance, the strain *Bifidobacterium adolescentis* 150 produced up to 5.6 g/L, i.e., ~50 mM GABA [101]. The microbial producers of GABA are of special interest because GABA is sufficiently widely used for medical purposes. It is known that GABA, a neuron excitation-inhibiting neuromediator, produces many beneficial effects (see "*Microbiota, Neurochemicals, and Dietetics*").

Bacteria also produce sufficiently high concentrations of other neuroactive amino acids that can be used in functional food items and drug preparations for therapeutic and preventive purposes. The probiotic strain *Lact. casei* K_3III_{24} releases micromolar concentrations of glutamic acid and taurine into the medium [102]. Importantly, taurine improves vision, in addition to other beneficial effects. The culture of *Lact. brevis* BJ20 that was grown on a seaweed-containing medium considerably enriched the medium with neuroactive amino acids, such as taurine, glycine, β-alanine, and GABA [103].

The bacteria *E. coli*, *Bacillus cereus*, and *Lact.* spp. form catecholamines and, still more important, their precursor 2,3-dihydrophenylalanine (DOPA) [53, 92, 102]. DOPA crosses the BBB; in the brain, it is converted to dopamine and thereupon to norepinephrine. It should be emphasized that dopamine and norepinephrine regulate important brain processes. DOPA is used as a remedy for diseases that are characterized by lowered dopamine levels in functionally important brain areas. Importantly, a decrease in dopamine content in the *substantia nigra* of the brain is typical of Parkinson's disease. Screening human symbiotic microorganisms for efficient DOPA producers could be an important biotechnological project that has relevance to the aforementioned idea of using psychobiotics for amelioration of the operation of the human brain.

In contrast to the tested bacteria, the yeast *Saccharomyces cerevisiae* accumulates neurochemicals such as catecholamines, DOPA, and serotonin inside its cells without releasing them into the culture liquid [53, 93]. This fact has some practical implications because humankind has been using yeast culture liquid as wine and beer since time immemorial. If preparing a beverage involves separating (by filtering or centrifugation) the culture liquid from the yeast cells, then the

beverage is expected to contain no neurochemicals. However, if yeast cells (without prior heating) directly form a part of the beverage and are taken in, the human organism is exposed to the effects of the neurochemicals that are liberated from yeast cells during the digestion process.

These data indicate that microorganisms can be considered important producers of neuroactive compounds that impact human physical and mental health. This provides the foundations for target-oriented biotechnological developments and the production of customized functional food with predictable physiological and psychological effects. Current research is providing us with new options for subtly manipulating human behavior by modifying the diet, which includes introducing neurochemically active substance-producing microorganisms or their components and metabolites into the human GI tract.

Apart from obtaining neurochemical overproducers, genetic engineering enables us to develop other projects that are aimed at ameliorating microbiota–host interactions. Suffice to mention the idea of obtaining genetically modified probiotic strains that produce immunomodulatory substances. The genes that enable such probiotics to synthesize lipoteichoic acids, anti-inflammatory interleukin-10, and other immunomodulators should be inserted into their DNA [58].

Conclusion

The present work deals with a new paradigm that can be referred to as the *population organization and communication-centered paradigm.* This paradigm is gradually developing in modern microbiology. It is primarily concerned with the intrinsic *complexity* of microorganisms. They are no longer considered as mere "conglomerations of enzymes," i.e., from a strictly biochemical viewpoint. Instead, emphasis is placed on the fact that microorganisms, like humans, animals, plants, etc., are living organisms. Like animals, they are currently known to engage in communication and certain primitive forms of social behavior. Of particular importance are quorum sensing (QS) signals that are almost ubiquitous among microorganisms.

In light of recent data, microorganisms should be regarded as living organisms that form sufficiently sophisticated structures. Special attention should be paid to biopolymer matrix-cemented microbial biofilms. In social structures including biofilms, microbial cells are morphologically differentiated and, in many structures, functionally specialized.

This work emphasizes the importance of understanding microbial communication in terms of neurophysiology and medicine. In the human organism, there is an ongoing dialog between the microbiota (including both beneficial and harmful microorganisms) and the host. The microbiota inhabits a wide variety of niches in the human organism; it is particularly abundant and diverse in the GI tract.

Of special interest from the neurological, endocrinological, and immunological viewpoint is the fact that the microbiota uses evolutionarily conserved biomolecular "languages" to communicate with host organism. They include biogenic amines, peptides, amino acids, peptides, short-chain fatty acids, gaseous agents, etc. that function as neurochemicals in humans and animals. They are synthesized and released by microorganisms because they serve as molecular signals in the microbial world [17]. There are important analogies between neurochemical-based communication and regulatory systems in microorganisms and in plants. Suffice it to mention that serotonin stimulates seedling elongation and is involved in pollen germination [104].

At the same time, many microbial signals are also "intelligible" for the host organism because they also function as human neurochemicals, hormones, or cytokines. Alternatively, microbes produce close homologs/analogs of human-specific informational molecules. The microbiota can exert a strong influence on the endocrine, nervous, and immune system of the human organism. In addition, the microbiota can specifically respond to the aforementioned compounds if they are produced by the host organism. Therefore, the microbiota is in fact responsive to alterations in the host's physiological and even psychological state, including those caused by stress factors. Understanding this bidirectional interactivity within the *host–microbiota* system is of both theoretical and practical importance. It enables us to develop a new generation of drugs that are aimed at treating or preventing dysbiosis, i.e. abnormal changes in the qualitative and quantitative composition of the human microbiota that prevent harmonious interactions between the human organism and its microbial inhabitants and may result in various somatic disorders and mental diseases [17].

Recent data on microbial communication hold much potential value in terms of biotechnology and medicine. It is imperative that new strategies of treating and preventing diseases should take account of the *brain–gut–microbiota* system. Good use is currently made of *probiotics* including *psychobiotics*. The beneficial effects of these microorganisms on the brain and the whole human organism are largely based on their signal molecules that function as useful *metabiotics*, i.e., small molecules that represent microbial structural components or metabolites with a chemical structure that enables them to directly impact the host organism with its nervous and immune system [1–3, 22, 23].

Hence, this work places emphasis on the biomedical importance of the aforementioned population organization and communication-centered paradigm discussed in the "Introduction." Its practical applications are still in their infancy. However, it has already become possible to produce specialized microbial cultures that colonize the GI tract and other niches in the human organism and exert an influence on human physical and mental health.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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