ISSN 0026-2617, Microbiology, 2016, Vol. 85, No. 1, pp. 1–22. © Pleiades Publishing, Ltd., 2016.
Original Russian Text © A.V. Oleskin, G.I. El'-Registan, B.A. Shenderov, 2016, published in Mikrobiologiya, 2016, Vol. 85, No. 1, pp. 3–25.

REVIEWS

Role of Neuromediators in the Functioning of the Human Microbiota: "Business Talks" among Microorganisms and the Microbiota-Host Dialogue

A. V. Oleskin[a, 1], G. I. El'-Registan[b], and B. A. Shenderov[c]

[a] *Department of General Ecology, Faculty of Biology, Lomonosov Moscow State University, Moscow, Russia*
[b] *Winogradsky Institute of Microbiology, Research Center of Biotechnology, Russian Academy of Sciences, Moscow, Russia*
[c] *Gabrichevskii Institute of Microbiology and Immunology, Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing, Moscow, Russia*

Received May 28, 2015

Abstract—Current concepts concerning the social behavior of microorganisms inhabiting the human gastrointestinal (GI) tract and their role in the formation of integrated supracellular structures and in intercellular communication in the host–microbiota system are reviewed. The analysis of the literature data and of the results obtained by the authors indicates an important role of neuromediators (biogenic amines, amino acids, peptides, and nitric oxide) in intra- and interspecies microbial communication, as well as in the microbiota–host dialogue. The role of this dialogue for human health, its effect on the human psyche and social behavior, and the possibility of construction of probiotic preparations with a target-oriented neurochemical effect are discussed.

Keywords: neuromediators, biogenic amines, catecholamines, dopamine, norepinephrine, serotonin, histamine, neuroactive amino acids, GABA, neuropeptides, nitric oxide, symbiotic microbiota, gastrointestinal tract, probiotics

DOI: 10.1134/S0026261716010082

INTRODUCTION

In terms of a concept that has received much attention in biology in recent decades, populations of unicellular organisms are to be regarded as analogs of multicellular organisms. The capacity of microorganisms to engage in collective activities (social behavior), to exchange information (communication), and to form associations composed of many individual cells (social, or biosocial, systems) can manifest itself in such systems. Microorganisms form colonies on substrata, biofilms at phase boundaries, and suspensions and local aggregations (microcolonies, flocs, and larger formations) in a liquid medium. In the literature, the term "sociomicrobiology" was coined with respect to the subfield of microbiology that is concerned with communication and collective behavior in microorganisms (Sekowska et al., 2009). Importantly, social phenomena and their analogs occur both in free-living unicellular organisms (bacteria, fungi, microalgae, and protozoans) and in cell layers formed by tissues of various plants and animals.

Biofilms are the most ubiquitous form of microbial social structures. They are "matrix-enclosed microbial accretions that adhere to biological or non-biological surfaces" (Hall-Stoodley et al., 2004, p.95), which are formed at interphase boundaries and may consist of cells belonging to a single species or, alternatively, to different species, genera, and even kingdoms (Nikolaev and Plakunov, 2007). Microbial biofilms are characterized by structural heterogeneity, which is in many cases associated with functional differentiation among the cell types they comprise, advanced cell behavior coordination, a unitary developmental cycle (ontogeny) of the whole system, and capacity for reproduction and regeneration upon injury, i.e. by the properties that are typical of an *organism* (Sumina, 2006; Karatan and Watnick, 2009).

Coordination of cell behavior in various organizational types of microbial biosocial systems (colonies, biofilms, suspensions, etc.) was shown to depend on a number of different channels of *intercellular communication*, implicating contact, chemical, and presumably distant physical interaction (Nikolaev, 2000; Worthington et al., 2012). As regards microorganisms, *signal molecule*-based interactivity has been particularly well characterized (Aaronson, 1981; Khokhlov, 1988; Oleskin et al., 2000; El'-Registan et al., 2006; Nikolaev et al., 2006; Khmel', 2006).

[1] Corresponding author (e-mail: aoleskin@rambler.ru).

Of paramount importance is chemical communication. Special attention should be given to its subtype based upon quorum sensing (QS) systems. QS systems regulate a wide variety of bacterial population density-dependent processes. An increase in population density results in increased concentrations of bacterial autoinducers released by the cells and eliciting specific responses. In gram-negative bacteria, the autoinducer function is performed by *N*-acylated homoserine lactones (N-AHLs), also referred to as autoinducers-1 (AIs-1). They activate expression of the operons that control the development of the biofilm phenotype, persister cell formation, antibiotic synthesis, bioluminescence, and a large number of other processes, including, importantly, the synthesis of the autoinducer per se (Khmel', 2006; Zaitseva et al., 2014).

In gram-positive bacteria, oligopeptides function as QS autoinducers; they are recognized by two-component receptor complexes (Karatan and Watnick, 2009). For instance, a thiolactone ring-containing peptide (AIP) downregulates biofilm formation upon binding to the response regulator protein (AgrC) in *Stapylococcus aureus.*

In some QS systems, 2-methyl-2,3,4,5-tetrahydroxyhydrofurane (AI-2) is the autoinducer; several optical isomers of AI-2 were described (reviewed, Shpakov, 2009). This signal molecule, which influences *Pseudomonas aeruginosa* virulence and biofilm formation in patients with lung cystic fibrosis, is synthesized by the normal oro-pharyngal microbiota that stimulates infection (Duan et al., 2003). In a large number of enterobacteria, AI-2 functions as an interspecies signal agent (Zaitseva et al., 2014).

Saprophytic and pathogenic *E. coli* strains, *Klebsiella pneumonia, Enterobacter cloacaceae, Shigella* spp., and *Salmonella* spp. contain QS systems that depend on autoinducer AI-3 (Sircili et al., 2004; Walters et al., 2006). AI-3 is an aromatic compound; its receptors are histidine kinases QseC and QseE that control the activation of transcription of the genes that are responsible for flagellar motility (*flhDC*) and virulence (*LEE*) of the pathogenic strain *E. coli* O157:H7 (Clarke et al., 2006; Hughes et al., 2009; Shpakov, 2009).

Density-dependent regulators of a different chemical type belong to alkylhydroxybenzenes (alkylresorcinols and tyrosol); they are synthesized by many bacteria and yeasts. Unlike QS autoinducers, these regulators control transition of a culture to the stationary phase; they convey messages concerning not the minimal necessary cell number per medium volume (the quorum) for carrying out a specific process, but the maximal possible cell number (El'-Registan et al., 2006).

At specific concentrations, alkylhydroxybenzenes (AHBs) suppress the growth of microbial cultures and biofilms (Martyanov et al., 2015) and induce cell differentiation and the development of dormant bacterial forms (El'-Registan et al., 2006). The mechanism of action of AHBs is based upon their ability to modify the structure and activity of cell biopolymers (proteins and the DNA), to increase the microviscosity of biological membranes, and to influence ion transport and the cell's water balance (Bukharin et al., 2005; El'-Registan et al., 2006; Nikolaev et al., 2006). Importantly, AHBs affect the activity of cell innate immunity effectors (Deryabin et al., 2013a, 2013b) and the functional and operational stability of antibodies (Deryabin et al., 2010).

However, there is another group of low molecular weight regulators that includes various chemical agents. They are synthesized in symbiont–parasite-containing systems by both the host organism and the microbiota. These agents perform a common function, which is reflected in the term *neuromediators* applied to all of them. This review is mainly focused on the synthetic activity of the host and the microbiota with respect to neuromediators, as well as on their diversity and functional roles in terms of the development of microbial populations and the ongoing symbiotic microbiota–host dialogue.

SYMBIOTIC MICROBIOTA

Symbiotic microorganisms inhabit various niches of an animal organism. In humans, they are present on the skin, the eye conjunctiva, and the mucosa of the upper airway and the uro-genital tract. However, they are particularly abundant and diverse in the gastro-intestinal (GI) tract. In the large intestine, the concentration of microbial cells can be as high as 10^{12}/ cm^3, and their total number is at least 10^{14} cells, i.e., about ten times the number of the cells of an adult human individual. Up to 10000 microbial species can be detected in the GI tract of an adult human individual. Only 700–1000 species are culturable. The total weight of the microbial biomass is over 1.5 kg. 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 methanolgenic and methane-oxidizing archaea are present (Clarke et al., 2014; Shenderov, 2014a).

It was reported that human individuals can be classified into three "bacteriotypes" that are characterized by the predominance of representatives of one of the genera, *Prevotella, Bacteroides,* or *Ruminococcus,* in their large intestine (Clarke et al., 2014). The microbiota of the GI tract exists in the planktonic form (in the gut lumen) or as a biofilm on the surface of the intes-

tinal epithelium and inside the mucosa of intestinal crypts (i.e., depressions in the surface of the mucosa) (Kaper and Sperandio, 2005).

Despite the constant influence of various environmental stress factors on the symbiotic microbiota, GI microbiota of each individual is relatively stable in time, in terms of its composition (O'Mahony et al., 2014). However, massive doses or repeated administration of antibiotics, antiseptics, antihistamine preparations, antidepressants, and tranquilizers, as well as the ingestion of heavy metal salts, pesticides, and other toxic compounds, result in harmful alterations in the whole ensemble of the microbiota (i.e., in dysbiosis). Enriching food in fructans, in contrast, can promote the proliferation of useful bacteria, including those of the genus *Bacteroides* (Norris et al., 2013; Shenderov, 2014a).

In the mammalian (human) organism, the microbiota operates as a specific *microbial organ* that is directly or indirectly involved in virtually all physiological functions and in the metabolic, behavioral, and communicative responses of the macroorganism.

Using germ-free and conventional (laboratory-bred) animals as models and also conducting studies with humans provided compelling evidence that symbiotic microbiota is implicated in metabolic, defensive, and trophic activities and in the operation of the immune system (Verbrugghe et al., 2012; Shenderov, 2014a; O'Mahony et al., 2014; Guarner, 2014). The recently revealed ability of the intestinal microbiota to exchange chemical messages with the brain and, therefore, to influence its development and functioning has additionally contributed to our knowledge regarding the multifarious effects of low molecular weight compounds of microbial origin on the animal/human organism. The microbiota of the GI tract provides the host organism with vitamins and short-chain fatty acids as well as with polypeptides, biogenic amines, and amino acids; a large number of these compounds function as neuromediators or are involved in their synthesis.

It is becoming increasingly apparent that the normal operation of the brain does not only depend on the host organism, but is also influenced by the symbiotic microbiota. Since bacteria can both recognize and synthesize neuroendocrine hormones, we should agree with Wenner (2008) that "if you mess around with the gut microbes, you mess around with brain chemistry in major ways." The interaction between the GI microbiota and the mammalian brain was documented in a large number of works (Asano et al., 2012; Norris et al., 2013; Lyte, 2013; Stilling et al., 2014). The American researcher Mark Lyte (2010), one of the founders of *microbial endocrinology,* the field of science dealing with the role of hormones and neuromediators in intermicrobial interaction and the host macroorganism–microbiota dialogue, emphasized the following aspects of the interactivity between the GI microbiota and the nervous system:

(1) The host's nervous system exerts a significant influence on the "microbial organ."

(2) The microbial organ, in its turn, is involved in the maintenance of the adequate functional state of the organism and its neuropsychological and metabolic homeostasis in health and disease.

(3) The microbiota of the GI tract collectively performs its functions, influences other organs in the host organism, and responds to the substances secreted by them; therefore, the symbiotic microbiota satisfies the criteria implicit in the conceptual definition of the term "organ" (Lyte 2010, 2011, 2013; Clarke et al., 2014).

The intestinal microbiota interacts directly with the *enteric nervous system* (ENS). The ENS incorporates at least 0.5 million neurons and auxiliary cells such as astroglia, which secure the diffusion barrier between gut capillaries and ENS ganglia. Taking into account our expanding knowledge concerning the role of the GI microbiota in terms of the health and psyche of human individuals, it was suggested to change the popular term "*gut–brain axis*" to the term "*microbiota–gut–brain axis"* (Shenderov, 2008; Oleskin and Shenderov, 2013; Lyte, 2010, 2011, 2013; Stilling et al., 2014). Norris et al. (2013) attribute the host's gustatory and dietary preferences to the nutritional requirements of the GI microbiota. The symbiotic microbiota can influence emotions associated with food choice and intake by regulating the operation of the dopaminergic system and affecting feelings of satiety or hunger. These feelings involve neuropeptides whose synthesis is under the influence of short-chain fatty acids of microbial origins.

Importantly, the symbiotic microbiota of the human organism, like a sensitive tuning fork, is responsive not only to various exogenous factors and agents but also to changes in the physiological and, notably, psychological state of the host (Stilling et al., 2014). For example, emotions of anger and fear markedly increase the percentage of *Bacteroides fragilis* subsp. *theaiotaomicron* cells in the microbiome of the large intestine (Hawrelak, 2004). In the feces of children suffering from autism, a disorder that impedes their interaction with the environment and disrupts social behavior, increased numbers of cells of the species *Anaerofustis stercohominis, Anaerotruncus colihominis, Clostridium bolteae,* and *Cetobacterium someria* are contained (Valyshev and Gil'mutdinova, 2006). In Alzheimer disease, the antigens of *Treponema socranskii* and *T. pectinovorum* are present in the brain cortex, the subcortical structures (the pons and the hippocampus), and the trigeminal ganglia (Hawrelak, 2004). Experimental stress in macaque infants was accompanied by a significant decrease in the number of lactobacilli and increase in that of *Shigella* and *Campylobacter* species (Hawrelak, 2004). Accu-

mulation of opportunistic pathogens and a decrease in the number of bifidobacteria and lactobacilli were observed in cosmonauts during a long-term space flight, which was attributed to social stress developing in a closed compartment (Valyshev and Gil'mutdinova, 2006).

In its turn, the microbiota influences the host's physiological state. Consumption of fermented dairy products that contain the cells and metabolites of bifidobacteria and lactobacilli improves health and psyche because the deteriorated microbial ecological situation (intestinal dysbiosis) is ameliorated and the activity of the brain areas that respond to serotonin and are involved in human cognitive capacities is optimized (O'Mahony et al., 2014). Probiotics based on *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175A considerably attenuated psychological stress and suppressed anxious behavior in animals and humans (Lyte, 2011). Conversely, an increase in *Helicobacter pylori* content in the gastric and duodenal mucosa under stress resulted in active gastroduodenal ulcers (Murrison, 2001). Deterioration of the microbial ecology of the GI tract is attended by the onset and progression of diseases associated with the metabolic syndrome (Shenderov, 2008). This can be illustrated by obesity development in germ-free mice after transplanting the GI microbiota of obese individuals to them, as well as by weight decrease after transplanting the microbiota of mice which have lost weight because of a surgical bypass in their stomach (Clarke et al., 2014). Individuals with autistic spectrum disorders (autism per se and Asperger syndrome) are characterized by a decrease in the number of bifidobacteria in the GI microbiota and an increase in that of clostridia and other potential pathogens (de Thiji et al., 2014).

The influence of the GI microbiota on the human organism and its neuropsychological status is largely mediated by the microbial impact on the *hypothalamus–pitiutary–adrenals* axis. Modification of the functioning of this axis by microbial neuroactive compounds predisposes individuals to depression, anxiety, the bipolar disorder (with alternate periods of mania and depression), emotional burnout, and chronic fatigue. Normalizing the intestinal microbiota, especially by means of bifidobacteria-based probiotics, decreases the risk of the aforementioned neuropsychological disorders. For instance, administering *Bifidobacterium infantis* to germ-free mice at an early age reduced their stress response to the normal level, approximating that of conventional animals (Clarke et al., 2014).

EFFECT OF NEUROMEDIATORS ON THE INTESTINAL SYMBIOTIC MICROBIOTA

The brain is the central regulator of human psychical activity and social behavior. Its normal functioning requires *neuromediators,* i.e., the substances that transmit messages between nervous cells (neurons) or from a neuron to a muscular of glandular cell that carries out the neuron's command. Neuromediators are subdivided into the following groups: (1) biogenic amines, including catecholamines (dopamine, norepinephrine, and epinephrine), serotonin, histamine, and others; (2) amino acids (aspartic, glutamic, and γ-aminobutyric acid, glycine, and others); (3) peptides such as endorphins, enkephalins, dynorphins, substance P, etc.; and (4) "gasotransmitters" including nitric oxide, carbon monoxide, and hydrogen sulfide. Many neuromediators are multifunctional agents: they combine the roles of neuromediators, hormones, and local tissue factors (histohormones). Some neuromediators perform communicative and regulatory functions in diverse taxa of animals (Dubynin et al., 2003), plants (Roshchina, 1991, 2010), fungi (Buznikov, 1987, 2007), and protozoans (Roshchina, 2010), which enables us to use the more general term *biomediators* (Roshchina, 2010).

In the authors' opinion, biomediators should also include *resorcinols (alkylhydroxybenzenes, AHBs)*. They represent multifunctional signal/regulatory compounds that can be found in representatives of various kingdoms in nature (El'-Registan et al., 2006). Recently, much attention has been given to the biomediators that are involved in regulating the activities not only of eukaryotes but also of a large number of prokaryotic organisms. Experimental data were presented which suggest that AHB-dependent systems represent a new mechanism of controlling the activities of cell effectors of innate immunity. A prerequisite for this mechanism is a bimodal pattern of AHB activity with respect to their structure and concentrations (Deryabina et al., 2010, 2013a, 2013b). This review is focused upon the biomediators that regulate the functioning of the bacteria which interact with the human organism in health and disease, as well as on the operation of the supracellular systems formed by them (Table 1).

Catecholamines

Catecholamines (dopamine, norepinephrine, and epinephrine) are hydroxylated derivatives of the amino acid tyrosine. Dopamine and norepinephrine combine the functions of neuromediators and hormones (norepinephrine is an adrenal hormone, while dopamine is a hypothalamic hormone which downregulates lactation in females; these two substances also function as neuromediators, whereas epinephrine is an adrenal hormone performing no major neuromediator function). Catecholamines are also released into the intestinal lumen by the neurons of the enteric nervous system (Freestone et al., 2007). The catecholamine level in the bloodstream increases under stress. Under these conditions, norepinephrine and epinephrine exert a stimulatory influence on the cardiac function. Dopamine is involved in maintaining the normal

Table 1. Effects of neuromediators on microbial populations and associations

Neuromediators	Effects	Subjects and sources
Biogenic amines		
Catecholamines (dopamine, norepinephrine, epinephrine)	Stimulation of growth and, in pathogens, of virulence, and adherence to host cells	*Escherichia coli* (commensal and pathogenic strains), *Shigella* and *Salmonella* species, *Pseudomonas aeruginosa* (Lyte and Ernst, 1993; Freestone et al., 1999, 2007; Anuchin et al., 2008); *Bordetella pertussis*, *B. broncioseptica*, (Freestone and Lyte, 2008); *Aeromonas hydrophila* (Kinney et al., 1999); *Helicobacter pylori*, *Haemophilus influenza*, *Klebsiella pneumonia* (reviewed, Shpakov, 2009); *Listeria monocytogenes* (Verbrugghe et al., 2012), *Campylobacter jejunii* (Lyte et al., 2004), *Staphylococcus epidermidis* (Cogan et al., 2003), *Saccharomyces cerevisiae* (Malikina et al ., 2010)
Additional effects of individual catecholamines:		
Dopamine	Inhibition of cell aggregation	*E. coli* K-12 (Anuchin et al., 2008)
Norepinephrine	Stimulation of cell aggregation	*E. coli* K-12 (Anuchin et al., 2008)
Serotonin	Growth stimulation	Commensal (Oleskin et al., 1998a; Anuchin et al., 2008) and, to a lesser extent, pathogenic (M. Lyte, personal communication) strains of *E. coli, Enterococcus faecalis* (Strakhovskaya et al., 1993); *Rhodospirillum rubrum* (Oleskin et al., 1998a); *Polyangium* sp. (Oleskin et al., 1998a); *Candida guillermondii* (Strakhovskaya et al., 1993); *Saccharomyces cerevisiae* (Malikina et al., 2010; Oleskin et al., 2010)
	Stimulation of cell aggregation	*E. coli* K-12 (Oleskin et al., 1998; Anuchin et al., 2008), *Polyangium* sp. (Oleskin et al., 1998a).
	Growth inhibition	Chlamydia (Rahman et al., 2005)
	Virulence attenuation	*Candida albicans* (Mayr et al., 2005)
Histamine	Growth stimulation	*E. coli* K-12 (Anuchin et al., 2008), *S. cerevisiae* (Malikina et al., 2010)
	Stimulation of cell aggregation	*E. coli* K-12 (Anuchin et al., 2008)
Neuromediator amino acids		
Aspartate	Regulation of colony macro- and microstructure	*E. coli* (Budrene and Berg, 1991, 2002; Mittal et al., 2003)
	Growth inhibition	*E. coli* M-17 (Vakhitov and Sitkin, 2014)
Glutamate	Growth stimulation	*E. coli* M-17 (Vakhitov and Sitkin, 2014)
GABA	Stimulation of virulence and germ tube formation	*C. albicans* (Reyes-García et al., 2012)
Neuropeptides		
Dynorphin	Stimulation of virulence	*P. aeruginosa* (Zaborina et al., 2007)
$[Met]^5$-Enkephalin	Growth inhibition	*P. aeruginosa, Staphylococcus aureus*, *Seratia marcescens* (Zagon and McLaughlin, 1992)

Table 1. (Contd.)

Neuromediators	Effects	Subjects and sources
α-Melanocyte-stimulating hormone	Growth inhibition	*S. aureus* (Shireen et al., 2015)
Substance P	Antimicrobial effect	Many gram-positive and gram-negative bacteria and yeast; the data are discordant (see text)
Neuropeptide Y		
Gasotransmitter		
Nitric oxide: Low (nanomolar) concentrations	Inhibition of biofilm formation and acceleration of biofilm dispersal	*P. aeruginosa* (Barraud et al., 2006), *S. marcescens*, *Vibrio cholerae, E. coli* (pathogenic strain BW20767), *Staphylococcus epidermidis*, *Bacillus licheniformis*, *C. albicans* (Barraud et al., 2009a)
High (micro- and millimolar) concentrations	Stimulation of biofilm formation, cytotoxic and stressor effects	*P. aeruginosa* (Barraud et al., 2006); *Azospirillum brasilense*, *Neisseria gonorrhoeae* (reviewed: Medinets et al., 2015); *Mycobacterium tuberculosum* (Robinson et al., 2014)

level of locomotive activity and the active wakeful state; it also promotes pleasure-seeking behavior (hedonic behavior) (Berridge and Robinson, 1998).

In the literature, there is a considerable body of evidence of the stimulatiory effect of catecholamines on the growth of various microorganisms (Lyte, 1993, 2010, 2011; Freestone et al., 2007). Pretreating *Salmonella enterica* var. *typhimurium* with norepinephrine in vitro increased the proliferation rate of this pathogen in various tissues of experimentally infected pigs (Verbrugghe et al., 2012). This finding may explain why cold stress in mice—which is accompanied by release of catecholamines into the bloodstream (Previne et al., 1970)—as well as administering norepinephrine to the animals (Williams et al., 2006) increased the frequency of *Salmonella* infection. Gangrene with a fatal outcome was reported to develop in some patients to whom epinephrine was administered (published in 1929, cited according to: Lyte, 2011).

The stimulation of bacterial growth by catecholamines in an animal organism can be due to both the *direct* and the *indirect effect* of these compounds on microorganisms. Norepinephrine and other catecholamines suppress the synthesis and excretion of immunoglobulin A, decreasing the antimicrobial activity of the local immune system (Lyte, 2010, 2011). By stimulating peristalsis and bile release, catecholamines accelerate the transit of a food bolus through the GI tract and ion transfer through the intestinal epithelium. Therefore, physicochemical conditions are created in the GI tract that stimulate the growth of some representatives of the intestinal microbiota, e.g., of bacteria belonging to the genus *Bacteroides* (Verbrugghe et al., 2012).

A direct stimulatory effect of catecholamines on microbial growth was revealed in vitro for a wide variety of pathogenic, opportunistic, and saprotrophic bacteria, including *Yersinia enterocolitica,* a number of enterotoxic and enterohemorrhagic strains of *E. coli, Shigella* spp., *Salmonella* spp., *Pseudomonas aeruginosa* (Freestone et al., 2007), *Bordetella pertussis, B. bronchiseptica,* (Freestone and Lyte, 2008), *Aeromonas hydrophila* (Kinney et al., 1999), *Helicobacter pylori, Haemophilus influenza, Klebsiella pneumonia* (Shpakov, 2009), *Listeria monocytogenes* (Verbrugghe et al., 2012), *Campylobacter jejunii* (Cogan et al., 2008), some *E. coli* symbiotic strains (Freestone et al., 2007; Anuchin et al., 2008), and the yeast *Saccharomyces cerevisiae* (Malikina et al., 2010; Oleskin et al., 2010).

When applied at high concentrations, catecholamines can produce a cytotoxic effect, which is attributed to their ability to induce oxidative stress. Apart from suppressing the growth of yeasts (*S. cerevisiae, Pichia pastoris, Candida albicans,* etc.), high concentrations of dopamine (and 6-hydroxydopamine) killed yeast cells. Addition of antioxidants (ascorbate and glutathione) to the cultivation medium relieved the inhibitory and toxic effect of dopamine (Macreadie et al., 2010).

Catecholamines promote adherence of the GI microorganisms to the intestinal mucosa and formation of adherence-enabling type I pili in symbiotic *E. coli* strains, attachment of *Staphylococcus epidermidis* to skin cells, and biofilm formation by these microorganisms (Lyte, 2010, 2011). Apart from cell proliferation, catecholamines stimulated toxin and adhesin formation in an enterotoxic *E. coli* strain (Freestone et al., 2007). Under these conditions, other pathogenic bacteria also increased their virulence and capacity for colonizing the GI tract (Lyte et al., 1996; Clarke et al., 2006; Shpakov, 2009). The adherence of the cells of the enterohemorrhagic *E. coli* strain O157:H7 in the presence of norepinephrine increases because of its capacity for induction of expression of F5 pili, which are involved in attaching bacterial cells

to the intestinal mucosal epithelium (Verbrugghe et al., 2012).

In studies with the mouse model, it was established that partial removal of the liver, which results in increasing the norepinephrine concentration in the intestinal lumen, stimulated *Pseudomonas aeruginosa* adherence to the intestinal mucosa (Freestone et al., 2007).

The effects of catecholamines varied depending on their concentrations and 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* (Nakano et al., 2007); norepinephrine inhibited the growth of *Mycoplasma hyopneumoniae* by suppressing the expression of the genes required for proliferation (Oneal et al., 2008). Dopamine drastically stimulated proliferation of the yeast *S. cerevisiae*; conversely, norepinephrine produced little effect in this system (Malikina et al., 2010). 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 (Anuchin et al., 2008).

Two different hypotheses can be invoked to account for the catecholamine effects. According to the first of them, these compounds can chelate ferric iron, removing it from the lactoferrin and transferrin of the blood serum and other biological fluids. Catecholamine-bound iron becomes available to microorganisms that use specific carriers—siderophores such as enterobactin (Lyte et al., 1996; Sandrini et al., 2010)—to transfer it into the cell. As a result, the growth of iron-dependent strains of *E. coli, Salmonella enterica* var. *enteritidis, Campylobacter jejuni, Bordetella bronchiseptica, P. aeruginosa, Listeria monocytogenes,* and coagulase-negative staphylococci is stimulated (Verbrugghe et al., 2012).

In accordance with the more popular alternative hypothesis, the catecholamine effects on bacteria should be interpreted in terms of quorum-sensing communication (Clarke et al., 2006; Bansal et al., 2007). It is assumed that catecholamines operate as autoinducer AI-3 analogs. Like AI-3, they bind to histidine kinases QseC and QseE. Therefore, they can be regarded as functional analogs of the receptors of eukaryotic cells even though they differ from eukaryotic receptors (known as G proteins) in structural terms (Clarke et al., 2006; Hughes et al., 2009). The genes related to the histidine kinase gene (*qseC*) were revealed, apart from *Haemophila influenza* and representatives of the genera *Salmonella* and *Shigella*, in a large number of bacteria that are of no relevance to the human organism, including *Erwinia carotovora, Thiobacillus denitrificans, Psychrobacter* sp., and the fungus *Aspergillus nidulans* (Shpakov, 2009). This suggests that such receptors may be involved in controlling the development of microbial communities.

In light of the available data, it seems likely that, by interacting with autoinducer AI-3 and catecholamines, microbial receptor systems contribute to the "talk" among microbial cells and to the chemical "dialogue" between the microbiota and the host organism. Stress agents and catecholamine synthesis-promoting factors may influence the abundance, composition, and operation of the microbiota of the GI tract and, presumably, of other mucous membranes and of the skin of mammals, including the human species. Moreover, AI-3 molecules synthesized by symbiotic bacteria can modify the effector systems of host cells and those of the microbial communities inhabiting the host organism. During the course of long-term co-evolution of the host organism and the microbiota, neuroactive substances of prokaryotic and/or eukaryotic origins became an integral part of the "alerting system" used by both the host cells and pathogenic or opportunistic bacteria (Trueba and Ritz, 2013). Antagonists of adrenergic and dopaminergic receptors are of potential medical interest. For instance, andenergic receptor antagonists can inhibit the AI-3-, epinephrine-, or norepinephrine-dependent quorum-sensing cascade in the pathogenic strain *E. coli* EHEC, preventing the expression of its virulence genes. These antagonists can become a new class of antimicrobial preparations (Clarke et al., 2006).

Serotonin

Serotonin (5-hydroxytryptamine), a derivative of the amino acid tryptophan, combines the functions of a neuromediator and a histohormone. As a neuromediator, it is involved in inhibiting neuronal excitation by limiting the intensity of stimulus perception and activating the sleep centers of the brain (Dubynin et al., 2003). Outside the central nervous system, serotonin is implicated in regulating blood pressure, immunity, thrombocyte aggregation, and the functioning of a number of other organs and systems. Lymphocytes, monocytes, macrophages, and other cells of the immune system and of the ENS contain multiple receptors to serotonin (O'Mahony et al., 2014). Serotonin also serves as the key mediator of the microbiota–gut–brain axis by regulating GI secretory activity, peristalsis, vascular tone, and pain perception.

Serotonin slightly stimulated the growth of *Aeromonas hydrophila* at very high concentrations (Kinney et al., 1999) and caused a statistically significant increase in the growth of *Enterococcus faecalis* (Strakhovskaya et al., 1993), *Escherichia coli, Rhodospirillum rubrum* (Oleskin et al., 1998), and the yeasts *Candida guillermondii* (Strakhovskaya et al., 1993) and *S. cerevisiae* (Malikina et al., 2010; Oleskin et al., 2010).

The capacity of serotonin for acceleration of plant growth (radish seed germination) (Roshchina, 1991) is attributed to its chemical similarity to auxin, or 3-indoleacetic acid, a plant hormone. In studies

with *S. cerevisiae,* a photo- and radioprotective effect of serotonin was established (Fraikin et al., 1985).

Serotonin at a concentration of ~1 μM stimulated cell aggregation and microcolony formation in *E. coli* K-12 (Oleskin et al., 1998; Anuchin et al., 2008), *R. rubrum,* and the myxobacterium *Polyangium* sp. (Oleskin et al., 1998). At concentrations of 25–100 μM and above, in contrast, serotonin caused deaggregation of *E. coli* and *Polyangium* sp. cells, suppressed formation of the intercellular matrix, and inhibited the growth of the aforementioned bacteria (Oleskin et al., 1998). Interestingly, serotonin suppressed the development of intracellular chlamydia (Rahman et al., 2005) and attenuated the virulence of *Candida albicans* (Mayr et al., 2005).

The stimulatory effect of serotonin on pro- and eukaryotic cells can be hypothetically attributed to the presence of receptors to serotonin and, presumably, to related compounds (e.g., indole) in them. The inhibitory effect of high concentrations may be nonspecific: serotonin can behave as a membrane uncoupler, similar to bacterial d_2 factors (unsaturated fatty acids) (Bukharin et al., 2005; El'-Registan et al., 2006).

Histamine

Histamine, a derivative of the amino acid histidine, combines the functions of a neuromediator and a histohormone (a local inflammatory factor). Histamine is actively produced by microorganisms; it is present in various food items (Shenderov, 1998). Histamine stimulates biomass accumulation, cell aggregation, and colony formation in *E. coli* K-12 (the maximum effect is attained with ~0.1 μM histamine), as well as cell proliferation in *S. cerevisiae* (Anuchin et al., 2008; Malikina et al., 2010; Oleskin et al., 2010).

Neuromediator Amino Acids

Neuromediator amino acids stimulate (glutamic and aspartic acid) or inhibit (γ-aminobutyric acid and glycine) the activity of the nervous system and produce diverse effects on the functioning of the animal organism. Importantly, microorganisms utilize amino acids as nutrient substrates, including those active as neuromediators.

The specific regulatory influence of neuroactive amino acids is exemplified by the data that glutamate (along with lysine, methionine, and succinate) stimulates and aspartate (along with lactate and formate) inhibits the growth of the probiotic strain *E. coli* M-17. Under the same conditions, aspartate, in contrast, produced a stimulatory effect on the strain *E. coli* BL (Vakhitov et al., 2000; Vakhitov and Sitkin, 2014). Overall, the effects of these autoregulators vary depending on their dose, the tested strain, the culture growth phase, and medium composition.

The neuromediator γ-aminobutyric acid (GABA), apart from inhibiting the spreading of impulses in the brain and regulating the operation of the ENS, decreases the production of pro-inflammatory cytokines and immune cell proliferation (Auteri et al., 2015). GABA stimulates expression of the pathogenic factors of *C. albicans,* which manifests itself in the intensification of the synthesis of phospholipase B1-encoding mRNA, germ tube formation, and subsequent hypha development; in combination, these events contribute to the development of infection (Reyes-Garcia et al., 2012).

Peptide Neuromediators

Peptide neuromediators predominantly perform the function of neuromodulators: they increase or decrease the efficiency of other neurotransmitters in transferring the impulses across synapses. Opiates (endophines, enkephalins, and dynorphins) bind to specific receptors (that also bind morphine, heroin, and a number of other drugs) and block the transfer of impulses, including those involved in pain perception. Opiates are pain relievers and "pleasure substances" (causing euphoria).

Studies with the strain *Pseudomonas aeruginosa* PAO1 (with a pyocyanin synthesis-controlling QS system) revealed that dynorphin and its analog U50,488 (i) increased pyocyanin production and the antagonistic activity of *P. aeruginosa* with respect to *Lactobacillus plantarum* and *L. rhamnosum,* which form a part of the GI microbiota, and (ii) influenced the synthesis of virulence factors and biofilm formation in *P. aeruginosa* (Zaborina et al., 2007). Elevated opiate concentrations in the GI tract in response to stress activate the QS system of *P. aeruginosa,* which results in decreased colonization resistance of the intestine and therefore in a sharp increase in *P. aeruginosa* abundance (Shpakov, 2009).

The opioid factor [Met]^5-enkephalin, which decelerates cell proliferation in vertebrate tissues, can inhibit the growth of *P. aeruginosa, Staphylococcus aureus,* and *Serratia marcescens* (Zagon and McLaughlin, 1992). *S. aureus* possesses receptors to [Met]^5-enkephalin that is present in the culture liquid at a concentration of up to 1.6 ng/mL.

It was suggested that opiates had been performing their growth-modifying function millions of years before the emergence of higher animals with their complex nervous system (Zagon and McLaughlin, 1992).

Neuropeptides that influence microbial growth include substance P and neuropeptide Y, which consist of 12 and 36 amino acids, respectively. Substance P is present in the hypothalamus, the amygdala, and the gray matter of the brain (which contain receptors for it); it is involved in pain perception, anxiety development, stress, the stimulation of

GI motility, and the inhibition of the secretory activity of GI glands. Neuropeptide Y functions as a neurotransmitter in brain cells and the peripheral nervous system and produces a vasoconstrictor effect. In contrast to substance P, it mitigates anxiety and stress and relieves pain. Apart from the neuromediator action, peptides P and Y exert antimicrobial effects with respect to various gram-negative and gram-positive bacteria, as well as fungi; these effects vary depending on the tested strain and the peptide concentration applied; the data presented in different works are partly discordant (see, e.g., Kowalska et al., 2002; Hansen et al., 2005; El Karim et al., 2008).

α- and β-defensins, α-melanocyte-stimulating hormone (α-MSH), and other peptides with neuromediator functions also exert an influence on the microbiota (de Freitas Lim et al., 2014; Shireen et al., 2015). For example, α-MSH suppresses the growth of *S. aureus* (Shireen et al., 2015). The macrophage- and polynuclear leucocyte-produced peptide LL-37 (catelicidin) stimulates the quinolone-dependent QS system that is involved in virulence factor synthesis in *P. aeruginosa* and concomitantly enhances the tolerance of *P. aeruginosa* to the antibiotics ciprofloxacin and gentamycin (Stempel et al., 2013).

Nitric Oxide

Nitric oxide (NO) is a gasotransmitter that exhibits a variety of neuromediator and regulatory activities. In the animal (human) organism, NO functions as a regulator of gene transcription and post-translation modification. It is involved in cell proliferation and differentiation as well as in apoptosis. NO dilates blood vessels, lowers blood pressure (vasodilator effect), and stimulates intestinal peristalsis, penial erection, and the development of the retina tissue. As a neuromediator, nitric oxide is implicated in memory operation and learning processes.

NO formation involves NO synthases that catalyze conversion of the amino acid arginine to citrulline with the liberation of an NO molecule. Vertebrates possess several types of NO synthases (endothelial, neuronal, and inducible NO synthases). Activation of the inducible NO synthase proceeds under the influence of microbial metabolites and inflammatory cytokines that are formed during infection and upon tissue injury (Althaus and Clauss, 2013; Tinajero-Trejo et al., 2013).

When applied at nanomolar concentrations, NO predominantly performs regulatory functions, whereas its higher (micro- and millimolar) concentrations are toxic to both mammalian cells and microbial symbionts. Blood immune cells (macrophages) release NO and exert a cytotoxic effect on tumor cells and other kinds of foreign cells. By interacting with protein FeS groups, NO binds to cytochrome hemes. Interaction with molecular oxygen and superoxide radical yields toxic compounds, such as NO_2, N_2O_3, and especially $ONOO^-$ (peroxynitrite) that inactivate the thiol groups of organic molecules and react with the tyrosyl residues of proteins and the nitrogenous bases of the DNA (Tinajero-Trejo et al., 2013; Robinson et al., 2014). Apart from immune cells, NO is synthesized by hepatocytes, vascular endothelium cells, and others. NO production enables the cells to destroy pathogenic protozoans, helminths (James, 1995), and bacteria (Chen et al., 2015).

During bacterial infection, pathogens neutralize NO by oxidizing it to nitrate with NO dioxygenase or reducing it to nitrous oxide or ammonia/ammonium with various types of NO reductases (Medinets et al., 2015). Microbial cells are also capable of eliminating NO-caused damage. A mutant strain of *Mycobacterium tuberculosis* with an impaired DNA excision repair system (with a mutant *uvrB* gene) exhibited enhanced sensitivity to NO and decreased virulence (Robinson et al., 2014). Potentially, a new generation of antibacterial preparations can be developed. They will disrupt NO detoxification and repair systems in pathogenic microorganisms and, therefore, facilitate their elimination by nitric oxide produced by the host cells in the inflammation area or intentionally delivered to the infection focus.

High NO concentrations stimulate biofilm formation in *Pseudomonas aeruginosa,* which is interpreted in the literature in terms of the stressor effect of NO, since it is assumed that biofilms are formed in response to stress (Barraud et al., 2006).

Pediococcus acidilactici (strains S2 and S3) and *Lactobacillus plantarum* (strain T119) that were isolated from fermented dairy items, pickled food, and silage synthesized cytotoxic NO concentrations (about 50 μM) (Gündoğdu et al., 2006) that can inactivate some antibiotics, e.g., acridines, by nitrosylating them (Medinets et al., 2015).

Similar to eukaryotes, prokaryotes use NO as a regulatory agent at low (nanomolar) concentrations. Unlike high concentrations of NO, low concentrations inhibited biofilm formation in *P. aeruginosa* (Barraud et al., 2006, 2009b), *S. aureus* (Schlag et al., 2007), and *Nitrosomonas europea* (Ramirez-Mata et al., 2014). Nitric oxide also stimulated the flagellar motility of *P. aeruginosa* (Barraud et al., 2006). Treating the biofilms of *P. aeruginosa* (Barraud et al., 2006), *Serratia marcescens, Vibrio cholerae, E. coli, Staphylococcus epidermidis, Legionella pneumophila, Shewanella woodyi* (Ramírez-Mata et al., 2014), *Bacillus licheniformis* (Barraud et al., 2009a), and the yeast *Candida albicans* (Barraud et al., 2009a) with NO donors (sodium nitroprusside, *S*-nitroso-*N*-acetylpenicillamine, or *S*-nitroso-L-glutathione) results in a decreased area of the biofilms. The inhibitory effect of low NO concentrations on biofilm formation is attributed to its interaction with cyclic diguanylmonophosphate (c-di-GMP), one of the main intracellular regulators of biofilm formation (Barraud et al.,

2009b). The ability of NO to cause biofilm dispersal can be regarded as a microecological strategy that promotes the spreading of planktonic cells to new ecological niches and successful colonization of the host organism.

Although low (nanomolar) NO concentrations inhibit biofilm formation in a large number of microorganisms, these NO concentrations, nonetheless, stimulate the same process in some pathogenic bacteria, e.g., in *Neisseria gonorrhoeae* (Ramírez-Mata et al., 2014), and the nitrifiers *Nitrosomonas europaea, Nitrosolobus multiformis,* and *Nitrospira briensis* (Medinets et al., 2015). Apparently, the effects of the regulatory agent NO vary depending on the taxonomic position of the microorganisms involved and the conditions to which they are adapted. Of practical interest is the capacity of low NO concentrations for enhancing the antimicrobial effect of tobramycin, hydrogen peroxide, and sodium dodecyl sulfate, which facilitates the elimination of harmful microbial biofilms (Barraud et al., 2006, 2009a).

BIOSYNTHESIS OF NEUROMEDIATORS BY SYMBIOTIC MICROORGANISMS

Pioneering studies on the formation of neuromediators by microscopic organisms were conducted in the early 20th century; the fungus *Claviceps purpurea* (ergot) was the first microorganism shown to produce histamine (quoted according to: Roshchina, 2010). Subsequently, in the late 20th century, reports on the production of indole and catecholamines by other eukaryotic microorganisms, including protozoans, were published (Buznikov, 1987). It was approximately in the same historical period that the capacity of *Enterococcus faecalis* for serotonin synthesis was revealed (Strahkovskaya et al., 1993). Production of this amine was also established in a number of bacteria that inhabit the intestines of parasitic nematodes (Hsu et al., 1986), and the maximum amounts of serotonin were detected in *Staphylococcus aureus*. The data on the synthesis of neuromediators by representatives of the symbiotic intestinal microbiota, published by the end of the 20th century, were discussed in a review by B.A. Shenderov (1998). In recent decades, employment of new preparative techniques for purifying and identifying low molecular weight compounds for practical analytical purposes has resulted in a drastic increase in the number of research works on microbial synthesis of various neuromediators.

Microbial Catecholamines

High-performance liquid chromatography (HPLC) with amperometric detection was used to identify and quantitatively determine catecholamines in the cultures of a large number of pro- and eukaryotic microorganisms (Tsavkelova et al., 2000) (Table 2). Norepinephrine was present at concentrations of 0.2–2 μM in the biomass of *Bacillus mycoides, B. subtilis, Proteus vulgaris,* and *Serratia marcescens*; dopamine at concentrations of 0.5–2 μM was found in the biomass of the majority of the tested prokaryotes. These catecholamine concentrations considerably exceed those in human blood, which contains 0.1–0.5 nM dopamine and 1–2 nM norepinephrine (Eldrup, 2004). Micromolar concentrations of dopamine were also detected in *Morganella morganii* (2.46 mg/L, i.e., ~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 (Özogul, 2004). Most of the tested microorganisms also contained dihydroxyphenylacetic acid (DHPAA), the product of oxidative deamination of dopamine (Tsavkelova et al., 2000). 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" (Vidal-Gadea and Pierce-Shimomura, 2012, p. 440). *S. cerevisiae* and *Penicillium chrysogenum* contain sufficiently high concentrations of norepinephrine (0.21 and 21.1 μM, respectively) (Tsavkelova et al., 2000). In *B. subtilis,* norepinephrine and dopamine are mainly present outside the cell wall and not intracellularly. In light of the aforementioned suggestion that neurotransmitters perform communicative functions, catecholamines presumably serve as informational molecules with a limited action range, not only in animals (where they transfer information from neuron to neuron), but also in prokaryotes.

Using the *E. coli* model, it was established (Shishov et al., 2009) that maximum (micromolar) catecolamine concentrations accumulate during the lag phase of culture growth. In light of these data, it should be suggested that neuromediator amines behave as triggers that activate growth processes and cell division during the initial phase of the ontogeny of the microbial culture. This is comparable with the effects of other known autoregulatory compounds. The biomass of *E. coli, S. cerevisiae, Bacillus cereus,* and lactobacilli also contained (i) L-3,4-dihydroxyphenylalanine (DOPA), the catecholamine precursor in animal cells and (ii) the products of oxidative deamination of catecholamines (DHPAA and homovanillic acid). Analysis of the data available in the literature gives grounds for the suggestion that the metabolic pathways of neuromediator amines are universal for prokaryotic and eukaryotic organisms and follow the pattern shown below:

Tyrosine → DOPA → **Dopamine** → **Norepinephrine** (products of norepinephrine oxidation not shown) → DHPAA → Homovanillic acid.

Table 2. Production of neuromediators by microorganisms

Neuromediators	Subjects	Sources
Biogenic amines and their precursor		
Dopamine	*Bacillus cereus, B. mycoides, B. subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Proteus vulgaris*, *Saccharomyces cerevisiae*	Tsavkelova et al., 2000; Shishov et al., 2009; Malikina et al., 2010; Oleskin et al., 2010
	Morganella morganii, Klebsiella pneumonia, *Hafnia alvei*	Özogul, 2004
	Lactobacillus helveticus NK-1, *L. delbrueckii* subsp. *bulgaricus*	Oleskin et al., 2014a, 2014b
Norepinephrine	*B. mycoides*, *B. cereus*, *B. subtilis*, *P. vulgaris*, *S. marcescens*, *E. coli*, *S. cerevisiae*, *Pennicilum chrysogenum*	Tsavkelova et al., 2000; Shishov et al., 2009; Malikina et al., 2010; Oleskin et al., 2010
	L. helveticus 100ash, *L. helveticus* NK-1, *L. casei* K3III24, *L. delbrueckii* subsp. *bulgaricus*	Oleskin et al., 2014a, 2014b
DOPA	*E. coli* K-12, *S. cerevisiae, B. cereus*	Shishov et al., 2009; Malikina et al., 2010; Oleskin et al., 2010
	L. helveticus 100ash, *L. helveticus* NK-1, *L. casei* K3III24, *L. delbrueckii* subsp. *bulgaricus*	Oleskin et al., 2014a, 2014b
	Toxoplasma gondii	Review: Rohrscheib and Brownlie, 2013
Serotonin	*S. aureus*	Hsu et al., 1986
	Enterococcus faecalis	Strakhovskaya et al., 1993
	Rhodospirillum rubrum, *B. subtilis*, *S. aureus*, *E. coli* K-12, *S. cerevisiae*	Oleskin et al., 1998a; Tsavkelova et al., 2000; Shishov et al., 2009; Malikina et al., 2010
	Morganella morganii, Klebsiella pneumonia, *Hafnia alvei*	Özogul, 2004
	Lactococcus lactis subspecies *cremoris* MG 1363, *L. lactis* subspecies *lactis* IL 1403, *Lactobacillus plantarum* NCFB2392	Özogul et al., 2012
	L. helveticus 100ash	Oleskin et al., 2014a, 2014b
Histamine	*Morganella mogranii*, *Proteus vulgaris*, *P. mirabilis*, *Klebsiella* sp., *Enterobacter aerogenes*, *E. cloacaceae*, *Citrobacter freundii*, *Raoultella orhithinolytica*, *Pantoea agglomerans*, *Enterobacter amnigenus, Vibrio alginolyticus*, *Acinetobacter lowfli*, *Pseudomonas fluorescens*, *P. putida, Aeromonas* spp., *Clostridium* spp., *Photobacterium* spp.	Reviews: Roshchina, 2010; Nei et al., 2013; Lin et al., 2014
	E. coli K-12	Oleskin, unpublished
	Lactobacillus buchneri	Halász et al., 1994
	Streptococcus thermophilus PRI60	Gardini et al., 2012
Indole	*E. coli*, *Bacteroides ovatus*, *Clostridium bifermentes*, *P. aeruginosa*, *P. fluorescens*	Smith et al., 1996; Lee et al., 2007b; Vega et al., 2002

Table 2. (Contd.)

Neuromediators	Subjects	Sources
Neuroactive amino acids		
Glutamate	*E. coli*	Vakhitov and Sitkin, 2014
	Lactobacillus helveticus 100ash, *L. helveticus* NK-1, *L. casei* K3III24, *L. delbrueckii* subsp. *bulgaricus*	Oleskin et al., 2014, 2014b
Aspartate	*E. coli*	Vakhitov and Sitkin, 2014
GABA	*Lactobacillus brevis*, *L. rhamnosus*, and *Lactococcus lactis* strains	Lee et al., 2010; Liao et al., 2013; Diana et al., 2014
	L. helveticus 100ash, *L. helveticus* NK-1, *L. casei* K3III24, *L. delbrueckii* subsp. *bulgaricus*	Oleskin et al., 2014a, 2014b
Glycine		
Taurine		
Neuropeptides		
β-Endorphin	*Tetrahymena pyriformis*, *Amoeba proteus*	Lenard, 1992
[Met]^5-Enkephalin	*S. aureus*	Zagon and McLaughlin, 1992
Corticotropin	*Tetrahymena pyriformis*	Lenard, 1992
Somatostatin	*B. subtilis*, *Plasmodium falciparum*	
α-Factor, a homologue of gonadotropin-liberating factor	*S. cerevisiae*	
Insulin	*E. coli*, *Neurospora crassa*	
Gasotransmitter		
Nitric oxide	Many microorganisms; representatives of the phyla *Firmicutes*, *Actinobacteria*, *Proteobacterium,* and of archaea (e.g., *Euryarchaeota*) possess an NO synthase	Zunft, 1995; Barraud et al., 2006; Ramírez-Mata et al., 2014; Medinets et al., 2015

These pathways involve the enzymes that catalyze catecholamine synthesis (hydroxylases and decarboxylases of aromatic amino acids) and degradation (monoamino oxidases, MAOs).

The culture liquid of *E. coli* grown in the M-9 medium, a synthetic mineral medium with glucose, contained nanomolar concentrations of extracellular serotonin, dopamine, and norepinephrine at the later stages of bacterial growth (Shishov et al., 2009). These concentrations are sufficiently high to enable the neuromediators to bind to the specific receptors of the gastrointestinal tract of animals and humans.

Of special interest is the fact that an *E. coli* culture grown in the M-9 medium contained the catecholamine precursor DOPA that was present at micromolar concentrations both intracellularly and in the culture liquid. Presumably, DOPA functions as a long action range regulator; its conversion into dopamine that stimulates *E. coli* growth (Anuchin et al., 2008) occurs within the cell upon taking up a DOPA molecule. It has been known for over one hundred years that the lag phase is shortened and cell proliferation in a bacterial culture is stimulated under the influence of the cell-free supernatant of an exponential-phase culture (Rahn, 1904; Penfold, 1914). This phenomenon may be accounted for by the effects of extracellular DOPA, along with those of other autostimulators.

Unlike *E. coli, S. cerevisiae* accumulates neuromediators (dopamine, norepinephrine, and serotonin), the products of their metabolism (homovanillic acid and dihydroxyphenylacetic acid), and the precursor DOPA only intracellularly. They were present at micromolar concentrations if the yeast was grown in a synthetic medium that was bound to contain no neuromediators. If the neuromediator-containing Sabouraud's medium was used, the concentrations of all tested compounds decreased during the cultivation of the yeast, which was indicative of their active uptake from the medium by *S. cerevisiae* cells (Malikina et al., 2010; Shishov, 2010; Oleskin et al., 2010). Apparently, neuromediator amines do not function as intercellular communicative factors in *S. cerevisiae* populations. Nevertheless, since yeasts respond to exogenous neuromediators (see the preceding section), the amines

may be involved in regulating the development of yeast cultures if their synthesis is carried out by other ecosystem components.

Catecholamines and serotonin are chemically similar to the aromatic alcohols phenylethanol and tryptophol that function as autoregulators in *S. cerevisiae*. These alcohols control cell differentiation during the transition from solitary cells to branched filaments (pseudomycelium) in a nitrogen-limited medium (Chen and Fink, 2006). Presumably, yeast cells respond to the neuromediators because they represent functional analogs of the yeast autoregulators. Several yeast species contain the autoregulator tyrosol that is structurally related to tyrosine, the DOPA precursor (Batrakov et al., 1993; Chen et al., 2004). Tyrosol belongs to alkylhydroxybenzenes that control the formation of dormant forms in a large number of prokaryotes and yeasts (El'-Registan et al., 2006).

Of paramount importance is the presence of catecholamines in dairy products that are fermented by probiotic bacteria. For instance, norepinephrine and dopamine were present at concentrations of 0.1–2 μM and 1–10 μM, respectively, in various yogurt samples, whereas the growth substrate per se (unskimmed milk) maximally contained 0.09 μM norepinephrine and lacked dopamine. DOPA was present in the yogurts at concentrations of 80–250 μM, while its content in milk did not exceed 57 μM (Zhilenkova et al., 2013).

Starter strains of lactobacilli (*Lactobacillus helveticus* 100ash, *L. helveticus* NK-1, *L. casei* K3III24 and *L. delbrueckii* subsp. *bulgaricus*) differed in catecholamine production activity. On media with milk (1%) or pancreatic hydrolysate of milk, dopamine was only synthesized by *L. helveticus* NK-1 and *L. delbrueckii* subsp. *bulgaricus*; all of the strains, except *L. casei* K3III24, enriched both kinds of media in norepinephrine. All tested strains formed DOPA, and its maximum concentration (over 5 μM) was attained with strain *L. helveticus* NK-1 (Oleskin et al., 2014a, 2014b). Since DOPA passes the gut–blood and the blood–brain barriers and, therefore, is used to treat Parkinson disease (Dubynin et al., 2003), these results hold much promise with respect to the employment of DOPA-containing drugs in the form of dairy products fermented by overproducers of this catecholamine precursor.

DOPA production was also documented in the parasitic protozoan *Toxoplasma gondii*. In the brain tissue of its intermediate hosts (mice or rats), toxoplasma cells convert tyrosine to DOPA that is thereupon transformed into dopamine. Therefore, the dopamine concentration in the hippocampus and the amygdala increases by approximately 14%. As a result, the behavior of the rodent becomes more active; moreover, it finds the odor of cat urine attractive. This increases the probability of the ingestion of a toxoplasma-infected mouse/rat by a cat, which enables the toxoplasma to enter the organism of the definitive host (Rohrscheib and Brownlie, 2013).

In the model of germ-free mice intragastrically treated with the *Clostridium* cocktail, i.e., a mixture of 46 *Clostridium* species (belonging to the *coccoides* and *leptum* groups), it was established that the content of dopamine and norepinephrine in the coecal lumen was increased by this treatment. In the intestine of the control mice, 90% of the dopamine and 40–50% of the norepinephrine pool was in the bound form, whereas 90% of the catecholamine pool of the *Clostridium*-treated mice was in the unbound form. From these results, the conclusion was drawn (Asano et al., 2012) that the intestinal microbiota is essential for conversion of catecholamines into biologically active forms in the gut lumen.

Serotonin

Serotonin production is a sufficiently widespread phenomenon in the microbial realm, including representatives of the symbiotic and parasitic microbiota of animals and humans (Shenderov, 1998; Rook et al., 2012). A low concentration of a serotonin-like substance was detected in *Rhodospirillum rubrum* cells (Oleskin et al., 1998). Serotonin was present in *Bacillus subtilis* and *Staphylococcus aureus* cells at concentrations of ~1 μM (Tsavkelova et al., 2000), which are comparable to its concentrations in blood, which normally contains 0.5–1.5 μM serotonin (*Henry's*, 2011). The product of enzymatic oxidation of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), was present at micromolar or submicromolar concentrations in the aforementioned microorganisms, as well as in other tested species, even though they lacked serotonin per se. The maximum concentrations of 5-HIAA (10.8 μM) were detected in the biomass of the eukaryote *Penicillium chrysogenum* (Tsavkelova et al., 2000). High serotonin concentrations were detected in the cultures of the bacteria *Morganella morganii* (4.96 mg/L, i.e., ~28 μM serotonin), *Klebsiella pneumonia* (3.23 mg/L, ~18 μM), and *Hafnia alvei* (2.69 mg/L, ~15 μM) (Özogul, 2004).

Studies on the dynamics of serotonin synthesis during the growth of *E. coli* and *S. cerevisiae* (Shishov et al., 2009; Shishov, 2010; Malikina et al., 2010; Oleskin et al., 2010) demonstrated that serotonin concentrations, similar to catecholamine concentrations, tend to decrease with the aging of the culture. Low serotonin concentrations (10 nM) were detected in the culture liquid of *E. coli* only at the late stages of culture growth. The yeast released neither serotonin nor catecholamines, as mentioned above, even though it accumulated these substances inside its cells. The biomass of *E. coli* and *S. cerevisiae* contained 5-hydroxytryptophan, the serotonin precursor in the animal organism-specific metabolic pathway starting from tryptophan, and 5-HIAA, the product of oxidative deamination of serotonin. In *E. coli,* 5-HIAA was also present in the

culture liquid. Taken together, these facts suggest that serotonin synthesis and degradation pathways are likely to include the following animal organism-specific enzyme reactions:

Tryptophan → 5-Hydroxytryptophan
→ **Serotonin** → 5-HIAA.

This pathway presumably involves enzymes that are homologous or functionally analogous to the animal enzymes tryptophan hydroxylase (catalyzing the tryptophan → 5-hydroxytryptophan conversion), decarboxylase of aromatic amino acids (catalyzing the 5-hydroxytryptophan → serotonin conversion), and monoamino oxidases (responsible for oxidative deamination).

There is evidence that serotonin is synthesized by some lactobacilli, including *Lactococcus lactis* subsp. *cremoris* MG 1363, *L. lactis* subsp. *lactis* IL 1403, and *Lactobacillus plantarum* NCFB2392 (Özogul et al., 2012). It was also established that serotonin is present in fermented food items including Chinese rice wine (particularly its semi-sweet variety) that also contains other neuromediator amines (histamine and tyramine) (Ye et al., 2012). Serotonin was also detected in the culture liquid of *Lactobacillus helveticus* 100ash at a concentration of 0.4 μM, but not in that of *L. helveticus* NK-1, *L. casei* K3III24, and *L. delbrueckii* subsp. *bulgaricus*. The serotonin metabolite 5-HIAA was synthesized by *L. helveticus* NK-1 and *L. delbrueckii* subsp. *bulgaricus* (Oleskin et al., 2014a, 2014b).

A large number of bacterial species, including those inhabiting the animal/human intestines (*E. coli, Bacteroides ovatus,* and *Clostridium bifermentus*) (Smith and Macfarlane, 1996), synthesize high concentrations of indole (up to 600 μM and above), the bicyclic backbone of serotonin (Domka et al., 2006). Indole inhibits biofilm formation in *E. coli* (Bansal et al., 2007; Lee et al., 2007a) and, conversely, stimulates biofilm formation in *Pseudomonas aeruginosa* and *P. fluorescens* (Lee et al., 2007b). Indole accelerates the growth of *Salmonella enterica* var. *enteridis* (Vakhitov and Sitkin, 2014) and stimulates the formation of antibiotic-tolerant persister cells (Vega et al., 2012). In intestinal epithelial cells, indole was reported to induce the expression of the genes that are responsible for the barrier function, mucin formation, and the synthesis of anti-inflammatory cytokine IL-10, while concomitantly suppressing the synthesis of cytokine IL-8 (Bansal et al., 2010). Some derivatives of indole, such as 7-hydroxyindole and 5-hydroxyindole, inhibited biofilm formation in saprotrophic *E. coli* strains, whereas another derivative, isatin (indole-2,3-dion), stimulated biofilm formation in enterohemorrhagic *E. coli* strain EHEC (O157:H7) (Lee et al., 2007a). The effect of indole on microbial biofilms seems to be due to its capacity to function as an analog of autoinducers AI-1 (N-AHLs) in bacterial QS systems (Ryan and Dow, 2008; Karatan and Watnick, 2009).

Histamine

Histamine is synthesized by both pro- and eukaryotes. Histamine produced by microbial decarboxylation of histidine is present in food items that are stored for a long time, e.g., in fish (particularly in bonito, scad, saury, mackerel, tuna, herring, sprat, and salmon), cheese, meat, wine, beer, sauerkraut, and pickled food (Halász et al., 1994; Ladero et al., 2008; Hwang et al., 2010; Roshchina, 2010; Lin et al., 2014). The capacity for histamine synthesis and its release into the cultivation medium was established for a wide variety of bacteria, including *Morganella mogranii, Proteus vulgaris, P. mirabilis, Klebsiella* sp., *Enterobacter aerogenes, E. cloacaceae, Citrobacter freundii, Raoultella orhithinolytica, Pantoea agglomerans, Enterobacter amnigenus* (Devalia et al., 1989; Shenderov, 1998; Roshchina, 2010; Nei et al., 2013; Lin et al., 2014), *Streptococcus thermophilus* (Gardini et al., 2012), *Vibrio alginolyticus, Acinetobacter lwofii, P. aeruginosa, P. putida, Aeromonas* spp., *Clostridium* spp., *Photobacterium* spp. (Lin et al., 2014), and *Lactobacillus buchneri* (Halász et al., 1994; Gardini et al., 2012).

Apart from functioning as a neurotransmitter, histamine is involved in inflammatory and allergic responses in the human organism. This largely accounts for the symptoms of the poisoning caused by its toxic doses (75 mg/kg of food product and above) (Ladero et al., 2008; Roshchina, 2010). Toxic concentrations (up to 180 mg/kg) of microbial histamine may be present in a large number of food items; they cause poisoning, inflammation, and allergic responses that manifest themselves in skin itching, nausea, diarrhea, rash, headache (histamine migraine), fever sensation, and hypotension (Ladero et al., 2008; Roshchina, 2010; Gardini et al., 2012). Histamine produced by gram-negative pathogens such as *Branhamella catarrhalis, Haemophilus parainfluenzae,* and *Pseudomonas aeruginosa* (Devalia et al., 1989) can exacerbate the relapses of chronic bronchitis or pneumonia, particularly in patients suffering from heritable cystic fibrosis (Roshchina, 2010). Histamine enhances the virulence of the aforementioned gram-negative pathogens but not that of the gram-positive species *S. aureus* and *Streptococcus pneumonia* (Devalia et al., 1989).

Amino Acids

Amino acids that function as neuromediators (aspartic, glutamic, and γ-aminobutyric acid, glycine, etc.) are synthesized by diverse microorganisms, including symbiotic species in which they are used as autoregulators (Shenderov, 1998; Budrene and Berg, 2002; Mittal et al., 2003; Vakhitov and Sitkin, 2014). In the human organism, γ-aminobutyric acid (GABA) is a prerequisite for normal pain sensitivity of the intestine and for the operation of the immune system. GABA mitigates inflammation processes and

allergic responses by suppressing the activity of T lymphocytes (Auteri et al., 2015). An imbalance in the GI microbiota frequently results in decreased microbial production of GABA, which increases the risk of irritated bowel syndrome and other inflammatory intestinal diseases (Babin et al., 1994). Among microbial producers of amino acid neuromediators (biomediators, according to Roshchina, 2010), an important role is played by lacto- and bifidobacteria that (i) represent valuable probiotics and are widely spread within the microbiota of the gastrointestinal and urogenital tracts of mammals, including the human species and (ii) occur in fermented dairy items and fermented products prepared from vegetables, meat, and fish.

In human blood plasma and spinal fluid, GABA is present at concentrations of ~0.6 and ~0.3 μM, respectively (Abbot et al., 1982), which are close to those produced by lactobacilli. The strain of *L. delbrueckii* subsp. *bulgaricus* synthesized 0.32 ± 0.02 μM GABA on a milk-containing medium (Oleskin et al., 2014a, 2014b). GABA partially penetrates the gut-blood and the blood-brain barrier. Presumably, the effects produced by this amino acid—which improves sleep, concentration, and attention, exerts a relaxing and pacifying influence on the human brain, stimulates metabolic processes in the brain, promotes creative thinking, helps restore speech and locomotive activity after injuries, and functions as an antioxidant—are due to the combined action of the GABA contained in food and that produced by the macroorganism and its microbiota.

Highly efficient GABA-producing bacteria that accumulate millimoles of GABA in the medium include *Lactobacillus brevis* and *Lactococcus lactis* isolated from Italian cheese (Siragusa et al., 2007), *L. lactis* subsp. *lactis* and *Lactobacillus rhamnosus* GG isolated from Chinese adzuki beans (Liao et al., 2013), and *L. brevis* from fermented cod intestines (Lee et al., 2010). Apart from GABA, *L. brevis* BJ20 cultivated in a medium with seaweed enriched the medium in other neuroactive amino acids, such as taurine, glycine, and β-alanine (Lee et al., 2010), which also positively influence the human brain and psyche.

Neuropeptides

The data concerning microbially produced neuropeptides are still rather fragmentary (Fetissov et al., 2008). It was established that *Staphylococcus aureus* synthesizes the autoregulator [Met]^5-enkephalin, a microbial opiate that functions as a neuromediator (Zagon and McLaughlin, 1992). Another opiate, β-endorphin, is synthesized by some unicellular eukaryotes, such as the infusorian *Tetrahymena pyriformis* and the amoeba *Amoeba proteus* (Lenard, 1992).

To an extent, the boundary between the classes of hormones and neuromediators is arbitrary and changeable. To reiterate, it seems reasonable that a number of researchers have suggested the concept of *microbial endocrinology,* a field that is concerned with the operation and the functional roles of both classes of compounds in microbial systems (Lyte, 1993, 2010, 2011). As a hormone, insulin increases the permeability of plasma membranes for glucose, stimulates the formation of glycogen from glucose in the liver, and suppresses the activities of glycogen- and lipid-degrading enzymes. As a neuromediator, insulin is involved in transmitting information concerning feelings of hunger and satiety into the brain. In this capacity, insulin functions in combination with other neuropeptides (ghrelin, leptin, and peptide YY). It was established that insulin is produced by *E. coli* and the fungus *Neurospora crassa,* which contains a gene that is homologous to the insulin gene of mammals. In *N. crassa,* insulin is implicated in the regulation of carbohydrate metabolism (Lenard, 1992). Microorganisms are capable of producing corticotropin (*Tetrahymena pyriformis*), somatostatin (*Bacillus subtilis* and *Plasmodium falciparum*), progesterone (*Trychophyton mentagrophytes*), and α-factor (*S. cerevisiae*), a homologue of the gonadotropin-liberating hormone of higher animals (Lenard, 1992) that, apart from its hormone function, regulates brain activity (Dubynin et al., 2003).

Microorganisms also synthesize homologues of animal/human regulatory peptides that are widespread among symbiotic and pathogenic bacteria and fungi. Symbiotic *E. coli* strains synthesize homologues of the following neuroactive peptides: leptin, insulin, ghrelin, peptide YY, neuropeptide Y, agouti-related peptide, orexin, α-melanocyte-stimulating hormone (α-MSH), adrenocorticotropic hormone (ACTH), oxytocin, and vasopressin (Fetissov et al., 2008). A leptin homologue was detected in *L. lactis*. Microbial homologues of neuroactive compounds induce the synthesis of antibodies that cross-react with the neuropeptides of the host organism. Microbial peptides can modify animal and human behavior. Thus, the homologues of leptin, insulin, α-MSH, and ACTH that are synthesized by *Helicobacter pylori* can decrease appetite. A relationship between streptococcal infection and anorexia nervosa (chronic suppression of appetite) was revealed, and the likely reason is that pathogenic streptococci produce leptin and gonadotropin-liberating hormone (Fetissov et al., 2008).

In addition to the presence of similar or identical mediators in neuronal networks and microbial cultures, microorganisms contain proteins that are functionally analogous and/or structurally homologous to neuromediator receptors. They are exemplified by (i) the QseC/QseE type catecholamine receptors of a number of microorganisms (Clarke et al., 2006; Hughes et al., 2009) mentioned earlier in this review, (ii) the opiate receptor of the ζ type of *S. aureus* (Zagon and Maughlin, 1992), and (iii) a homologue of the GABA receptor detected in the purple phototro-

phic bacterium *Rhodobacter sphaeroides* (Baker and Fanestil, 1991).

Nitric Oxide

A large number of microorganisms produce nitric oxide. It is generated via either nitrate reduction (Zumft, 1993; Barraud et al., 2006) or ammonium oxidation (Medinets et al., 2015). Many representatives of the phyla *Firmicutes, Actinobacteria,* and *Proteobacterium,* as well as some archaeans, contain an NO synthase that is functionally analogous to the enzyme of eukaryotic cells which catalyzes the synthesis of NO from arginine (Medinets et al., 2015). The data on the microbial synthesis of NO in conjunction with its regulatory effect enable us to regard this compound as an autoregulator of morphogenetic processes in microbial populations.

Microbial NO produces diverse effects on eukaryotic organisms. In the case of the worm *Caenorhabditis elegans,* it was demonstrated that *B. subtilis*- and *E. coli*-synthesized NO behaves as a transcription activator. It induces the processes in the worm's enterocytes that enhance its heat resistance and prolong its lifespan (Gusarov and Nudler, 2005). A similar mechanism may operate in higher animals; it represents an important aspect of the beneficial influence of the intestinal microbiota that may increase the host's longevity. Gram-positive bacteria of the genera *Lactobacillus, Streptococcus,* and *Lactococcus* possess NO synthases (Yarullina et al., 2011). The NO they release into the GI tract can perform cyto-, vaso-, and neuroprotective functions, along with endogenous NO (Medinets et al., 2015). Apart from direct synthesis of NO, lactobacilli and bifidobacteria (Ryu et al., 2009), as well as the probiotic strain *E. coli* Nissle 1917 (Zidek et al., 2010), are capable of stimulating NO production by host cells.

CONCLUSION: THE IMPACT OF THE NEUROCHEMICAL MICROBIOTA–HOST DIALOGUE ON HUMAN HEALTH, PSYCHE, AND SOCIAL BEHAVIOR

Communication between the symbiotic microbiota and the host organism has increasingly been considered in recent years from the perspective of microbial endocrinology (Lenard, 1992; Lyte, 1993, 2010, 2011, 2013; Oleskin et al., 1998). In terms of this area of research, the neuropsychological status and the social behavior of higher animals including the humans is subject to regulation by signal agents (hormones and neuromediators) that are produced, apart from the host organism, by symbiotic and pathogenic microorganisms. The operation of the *microbiota–gut–brain* axis provided for co-evolution of the microbiota and the physiological systems of mammals and significantly contributed to the development of their social behavior. Therefore, changes in the composition and abundance of the symbiotic microbiota can be associated with disruptions in the development of the brain and in its functions that are responsible for behavioral phenomena. At the same time, alterations in social behavior and neuropsychological activities can result in permanent or reversible changes in the structure of the intestinal microbiota and may therefore disrupt the production of relevant hormones and mediators that regulate the activities of various brain areas (Stilling et al., 2014).

Microbial consortia that colonize the intestinal mucosa and other niches of the human organism constantly interact with one another, as well as with the neural network of the GI tract and the whole nervous and humoral system of the host organism. The symbiotic microbiota behaves like a "tuning fork": it is responsive to changes in the somatic state, stress level, and mood of a human individual that manifest themselves in neurochemical alterations.

Apart from responding to human neurochemicals, the microbiota exerts a strong influence on human health, psyche, and social behavior. The aforementioned data on the synthesis of extracellular DOPA by symbionts, including lactobacilli, provide an important example. Microbial DOPA penetrates into the brain tissue and is converted into dopamine and, thereupon, norepinephrine, which influence the locomotive activity, sociability (communicability), and emotionality of a human individual. Normalizing and optimizing the catecholamine concentrations by means of probiotic microorganisms would help people to overcome depression, adynamia, and other consequences of stress. This is the reason behind the efforts of researchers that aim to design *a new generation of probiotics* that could produce target-oriented neuropsychological effects exemplified by antidepressant activity. Apart from DOPA and the catecholamines produced from it in the organism, especially in its central nervous system, probiotics (psychobiotics) can also synthesize other neuroactive substances (taurine, glycine, and GABA) that beneficially influence the brain and the whole human organism. It seems feasible to enhance the therapeutic and preventive neurochemical effects of fermented dairy products. Starter cultures that produce, for instance, sufficient amounts of GABA should be used for this purpose (Lyte, 2011).

In the authors' opinion, it is also feasible to develop probiotic *overproducers* of neuromediators. Such overproducer strains can be obtained using traditional selection methods as well as genetic engineering and the cell fusion technique.

Apart from the substances produced by lactobacilli, humankind has been using, since time immemorial, yeast fermentation products (e.g., beer and wine). To reiterate, yeast synthesizes neuroactive substances that accumulate intracellularly, without releasing them into the culture liquid. Therefore, the consumption of unfiltered drinks that contain yeast cells should enable

us to make use of yeast-produced neurochemicals. Target-oriented production of unfiltered yeast-containing drinks would supplement the spectrum of the probiotic effects of yeast that have been described in the literature (Martins et al., 2005) with direct neurochemical influence on the human organism.

Special emphasis should be placed on the potential use of fermented dairy products for the purpose of improving physical and mental health as well as social behavior. There are about 400 different commercial fermented dairy products (Shenderov, 2013); various kinds of lactic acid bacteria, fungi, and their complexes are used in their production. A number of starter cultures used in the dairy industry, as well as the microorganisms contaminating dairy products, synthesize significant amounts of neuroactive compounds (dopamine, norepinephrine, serotonin, GABA, etc.) (Zhilenkova et al., 2013; Oleskin et al., 2014a, 2014b).

Microbial hormones and neurotropic compounds interact with the receptors of nervous cells; these compounds optimize their functions both directly and in an epigenomic processes-mediated fashion. Therefore, they are expected to influence the functioning of the nervous system and psyche not only of individual consumers but, presumably, that of whole ethnicities (Stilling et al., 2014; Shenderov and Mitvedt, 2014). Supposedly, long-term consumption of fermented dairy products (for decades, centuries, and millennia) has exerted a significant influence on human brain, psyche, and social behavior. Enlarging the spectrum of tested dairy products and detailed analysis of their starter cultures and technology can enable us to set up a bank of microbial neurochemical producers and, moreover, to find out how microorganisms used for preparing food items are involved in the evolution of the brain and the enteric nervous system, as well as in the development and implementation of human behavioral patterns. Using animals with intentionally modified microbiota, including those inoculated with human intestinal microorganisms (Asano et al., 2012; Shenderov, 2014a, 2014b), and applying modern OMIC technology (Shenderov, 2012) will help us to optimize the impact of fermented dairy products on human health and psyche and provide for the target-oriented production of functional probiotic preparation with nootropic effects (Oleskin and Shenderov, 2013; Lyte, 2013).

REFERENCES

Aaronson, S., *Chemical Communication at the Microbial Level,* Boca Raton: CRC Press. Inc., 1981, vol. 1, p. 189, vol. 2, p. 203.

Abbott, R.J., Pye, I.F., and Nahorski, S.R., CSF and plasma GABA levels in Parkinson's disease, *J. Neurol. Neurosurg. Psychiatry,* 1982, vol. 45, pp. 253–256.

Althaus, M. and Clauss, W.G., Gasotransmitters: novel regulators of ion channels and transporters, *Front. Physiol.,* 2013, vol. 4 (27). doi: 10.3389/fphys.2013.00027

Anuchin, A.M., Chuvelev, D.I., Kirovskaya, T.A., and Oleskin, A.V., Effects of monoamine neuromediators on the growth-related variables of *Escherichia coli* K-12, *Microbiology* (Moscow), 2008, vol. 77, no. 6, pp. 674–680.

Asano, Y., Hiramoto, T., Nishino, R., Aiba, Y., Kimura, T., Yoshihara, K., Kimura, T., Yoshihara, K., Koga, Y., and Sudo, N., Critical role of gut microbiota in the production of biologically active, free catecholamines in the gut lumen of mice, *Amer. J. Physiol. Gastrointest. Liver Physiol.,* 2012, vol. 303, pp. 1288–1295.

Auteri, M., Zizzo, M. G., and Serio, R., GABA and GABA receptors in the gastrointestinal tract: from motility to inflammation, *Pharmacol. Res.,* 2015, vol. 93., pp. 11–21.

Babin, V.N., Domaradskii, I.V., Dubinin, A.V., and Kondrakova, O.A., Biochemical and molecular aspects of human–human microflora symbiosis, *Ross. Khim. Zh.,* 1994, vol. 38, pp. 66–78.

Baker, M.E. and Fanestil, D.D., Mammalian peripheral-type benzodiazepine receptor is homologous to CrtK protein of *Rhodobacter capsulatus*, a photosynthetic bacterium, *Cell,* 1991, vol. 65, pp. 721–722.

Bansal, T., Englert, D., Lee, J., Hegde, M., Wood, T.K., and Jayaraman, A., Differential effects of epinephrine, norepinephrine, and indole on *Escherichia coli* O157:H7 chemotaxis, colonization, and gene expression, *Infect. Immun.*, 2007, vol. 75, pp. 4597–4607.

Bansal, T., Alaniz, R.C., Wood, T.K., and Jaraman, A., The bacterial signal indole increases epithelial-cell tight-junction resistance and attenuates indicators of inflammation, *Proc. Natl. Acad. Sci. U. S. A.,* 2010, vol. 107, pp. 228–233.

Barraud, N., Hassett, D.J., Hwang, S.-H., Rice, S.A., Kjelleberg, S., and Webb, J.S., Involvement of nitric oxide in biofilm dispersal of *Pseudomonas aeruginosa, J. Bacteriol.,* 2006, vol. 188, pp. 7344–7353.

Barraud, N., Schleheck, D., Klebensberger, J., Webb, J.S., Hassett, D.J., Rice, S.A., and Kjelleberg, S., Nitric oxide signaling in *Pseudomonas aeruginosa* biofilms mediates phosphodiesterase activity, decreased cyclic di-GMP levels, and enhanced dispersal, *J. Bacteriol.*, 2009a, vol. 191, pp. 7333–7342.

Barraud, N., Storey, M.V., Moore, Z.P., Webb, J.S., Rice, S.A., and Kjelleberg, S., Nitric oxide-mediated dispersal in single- and multi-species biofilms of clinically and industrially relevant microorganisms, *Mol. Microbiol.,* 2009b, vol. 2, pp. 370–378.

Batrakov, S.G., El'-Registan, G.I., Pridachina, N.N., Nanashev, V.A., Kozlova, A.N., Gryaznova, M.N., and Zolotareva, I.N., Tyrosol as autoregulatory factor d_1 in the yeast *Saccharomyces cerevisiae, Microbiology* (Moscow), 1993, vol. 62, no. 4, pp. 387–391.

Bearson, B.L., Bearson, S.M., Lee, I.S., and Brunelle, B.W., The *Salmonella enterica* serovar *typhimurium* QseB response regulator negatively regulates bacterial motility and swine colonization in the absence of the QseC sensor kinase, *Microb. Pathog.*, 2010, vol. 48, pp. 214–219.

Berridge, K.C. and Robinson, T.E., What is the role of dopamine in reward: hedonic impact, reward learning or

incentive salience?, *Brain Res.: Brain Res. Rev.*, 1998, vol. 28, no. 3, pp. 309–369.

Budrene, E.O. and Berg, H.C., Dynamics of formation of symmetrical patterns by chemotactic bacteria, *Nature,* 2002, vol. 376, pp. 49–53.

Bukharin, O.V., Gintsburg, A.L., Romanova, Yu.N., and El'-Registan, G.I., *Mekhanizmy vyzhivaniya bakterii* (Mechanisms of Bacterial Survival), Moscow: Meditsina, 2005.

Buznikov, G.A., *Nierotransmirrery v embriogeneze* (Neurotransmitters in Embryogenesis), Moscow: Nauka, 1987.

Buznikov, G.A., Preneural transmitters as regulators of embryogenesis, Modern state of the problem, *Ontogenez,* 2007, vol. 38, no. 4, pp. 262–270.

Chen, H., Fujita, M., Feng, Q., Clardy, J., and Fink, G.R., Tyrosol is a quorum-sensing molecule in *Candida albicans, Proc. Natl. Acad. Sci. U. S. A.,* 2004, vol. 101, pp. 5048–5052.

Chen, H. and Fink, G.R., Feedback control of morphogenesis in fungi by aromatic alcohols, *Genes Dev.,* 2006, vol. 20, pp. 1150–1161.

Chen, T., Nai-Kei Wong, N.-K., Jiang, X., Luo, X., Zhang, L., Yang, D., Ren, C., and Hu, C., Nitric oxide as an antimicrobial molecule against *Vibrio harveyi* infection in the hepatopancreas of Pacific white shrimp, *Litopenaeus vannamei, Fish Shellfish Immunol.*, 2015, vol. 42, pp. 114–120.

Clarke, M.B., Hughes, D.T., Zhu, C., Boedeker, E.C., and Sperandi, V., The QseC sensor kinase: A bacterial adrenergic receptor, *Proc. Natl. Acad. Sci. U. S. A.,* 2006, vol. 103, pp. 10420–10425.

Clarke, G., Stilling, R.M., Kennedy, P.J., Stanton, C., Cryan, J.F., and Dinan, T.G., Gut microbiota: the neglected endocrine organ, *Mol. Endocrinol.*, 2014. doi: 10.1210/me.2014-1108

Cogan, T.A., Thoma, A.O., Rees, L.E., Taylor, A.H., Jepson, M.A., Williams, P.H., Ketley, J., and Humphrey, T.J., Norepinephrine increases the pathogenic potential of *Campylobacter jejuni, Gut,* 2007, vol. 56, pp. 1060–1065.

de Freitas Lima, S.M., de Pádua, G.M., da Costa Sousa, M.G., de Souza Freire, M., Franco, O.L., and Rezende, T.M.B., Antimicrobial peptide-based treatment for endodontic infections—biotechnological innovation in endodontics, *Biotechnol. Adv.,* 2014. http://dx.doi.org/ doi 10.1016/j.biotechadv.2014.10.013

Deryabin, D.G., Romanenko, N.A., and El'-Registan, G.I., The effect of alkylhydroxybenzenes on functional and operational stability of antibodies, *Microbiology* (Moscow), 2010, vol. 79, no. 3, pp. 300–306.

Deryabin, D.G., Romanenko, N.A., and El'-Registan, G.I., Antibody specificity in the presence of alkylhydroxybenzenes, chemical analogs of bacterial autoregulatory molecules, *Immunologiya,* 2013a, no. 1, pp. 27–30.

Deryabin, D.G., Sviridova, T.G., El'-Registan, G.I., and Chereshnev, V.A., Impact of bacterial autoregulatory molecules (homoserine lactones and alkylhydroxybenzenes) on the oxidative metabolism of the cell effectors of natural immunity, *Microbiology* (Moscow), 2013b, vol. 82, no. 2, pp. 126–132.

de Theije, C.G.M., Wopereis, H., Ramadan, M., van Eijndthoven, T., Lambert, J., Knol, J., Garssen, J., Kraneveld, A. D., and Oozeer, R., Altered gut microbiota and activity in a murine model of autism spectrum disorders, *Brain Behav. Immun.*, 2014, vol. 37, pp. 197–206.

Devalia, J.L., Grady, D., Harmanyeri, Y., Tabaqchali, S., and Davies, R.J., Histamine synthesis by respiratory tract micro-organisms: possible role in pathogenicity, *J. Clin. Pathol.*, 1989, vol. 42, pp. 516–522.

Domka, J., Lee, J., and Wood, T.K., YliH (BssR) and YceP (BssS) regulate *Escherichia coli* K-12 biofilm formation by influencing cell signaling, *Appl. Environ Microbiol.*, 2006, vol. 72, pp. 2449–2459.

Duan, K.M., Dammel, C., Stein, J., Rabin, H., and Surette, M.G., Modulation of *Pseudomonas aeruginosa* gene expression by host microflora through interspecies communication, *Mol. Microbiol.,* 2003, vol. 50, pp. 1477–1491.

Dubynin, V.A., Kamenskii, A.A., Sapin, M.R., and Sivoglazov, V.N., *Regulyatornye sistemy organizma cheloveka* (Regulatory Systems of the Human Organism), Moscow: Drofa, 2003.

El Karim, I.A., Linden, G.J., Orr, D.F., and Lundy, F.T., Antimicrobial activity of neuropeptides against a range of micro-organisms from skin, oral, respiratory and gastrointestinal tract sites, *J. Neuroimmunol.*, 2008, vol. 200, pp. 11–16.

Eldrup, E., Significance and origin of DOPA, DOPAC and dopamine-sulfate in plasma, tissue and cerebrospinal fluid, *Dan. Med. Bull.*, 2004, vol. 31, pp. 34–62.

El'-Registan, G.I., Mulyukin, A.L., Nikolaev, Yu.A., Suzina, N.E., Gal'chenko, V.F., and Duda, V.I., Adaptogenic functions of extracellular autoregulators of microorganisms, *Microbiology* (Moscow), 2006, vol. 75, no. 4, pp. 380–389.

Fetissov, S.O., Sinno, M.H., Coëffier, M., Bole-Feysot, C., Ducrotté, P., Hökfelt, T., and Déchelott, P., Autoantibodies against appetite-regulating peptide hormones and neuropeptides: putative modulaton by gut microflora, *Nutrition,* 2008, vol. 24, pp. 348–359.

Fraikin, G.Ya., Strakhovskaya, M.G., and Ivanova, E.V., Effect of serotonin on the yield of UV-induced thymine dimers in DNA, *Biofizika,* 1985, vol. 30, no. 4, pp. 564–567.

Freestone, P.P.E., Haigh, R.D., and Lyte, M., Blockade of catecholamine-induced growth by adrenergic and dopaminergic receptor antagonists in *Escherichia coli* O157:H7, *Salmonella enterica* and *Yersinia enterocolitica, BMC Microbiol.*, 2007, vol. 7, p. 8.

Freestone, P.P. and Lyte, M., Microbial endocrinology: experimental design issues in the study of interkingdom signaling in infectious disease, *Adv. Appl. Microbiol.*, 2008, vol. 64, pp. 75–108.

Gardini, F., Rossi, F., Rizotti, L., Torriani, S., Grazia, L., Chiavari, C., Coloretti, F., and Tabanelli, G., Role of *Streptococcus thermophilus* PRI60 in histamine accumulation in cheese, *Int. Dairy J.*, 2012, vol. 27, pp. 71–76.

Gootenberg, D.B. and Turnbaugh, P.J., Companion Animal Symposium: Humanized animal models of the microbiome, *J. Anim. Sci.*, 2011, vol. 89, pp. 1531–1537.

Guarner, F., Functions of the gut microbiota. World Digestive Health Day, *WGO Handbook on Gut Microbes,* 2014, pp. 8–10.

Gündoğdu, A.K., Karahan, A.G., and Cakmakçi, M.L., Production of nitric oxide (NO) by lactic acid bacteria isolated from fermented products, *Eur. Food Res. Technol.*, 2006, vol. 223, pp. 35–38.

Gusarov, I. and Nudler, E., NO-mediated cytoprotection: instant adaptation to oxidative stress in bacteria, *Proc. Natl. Acad. Sci. U. S. A.*, 2005, vol. 102, pp. 13855–13860.

Halász, A., Baráth, Á., Simon-Sarkadi, L., and Holzapfel, W., Biogenic amines and their production by microorganisms in food, *Trends Food Sci. Technol.*, 1994, vol. 5, pp. 42–49.

Hall-Stoodley, L., Costerton, J. W., and Stoodle, P., Bacterial biofilms: from the natural environment to infectious diseases, *Nat. Rev. Microbiol.,* 2004, vol. 2, pp. 95–108.

Hansen, C.J., Burnell, K.K., and Brogden, K.A., Antimicrobial activity of Substance P and Neuropeptide Y against laboratory strains of bacteria and oral microorganisms, *J. Neuroimmunol.*, 2006, vol. 177, pp. 215–218.

Hawrelak, J.A., The causes of intestinal dysbiosis: a review, *Alt. Med. Rev.*, 2004, vol. 9 (2), pp. 180–197.

Henry's Clinical Diagnosis and Management by Laboratory Methods, McPherson, R.A. and Pincus, M.R., Eds., Philadelphia: Elsevier Saunders, 2011.

Hsu, S.C., Johansson, K.R., and Donahne, M.J., The bacterial flora of the intestine of *Ascaris suum* and 5-hydroxytryptamine production, *J. Parasitol.*, 1986, vol. 72, pp. 545–549.

Hughes, D.T., Clarke, M.B., Yamamoto, K., Rasko, D.A., and Sperandi, V., The QseC adrenergic signaling cascade in enterohemorrhagic *E. coli* (EHEC), *PLoS Pathog.*, 2009, vol. 5, p. e1000553.

Hwang, C.-C., Lee, Y.-C., Huang, Y.-R., Lin, C.-M., Shian, C.-Y., Hwang, D.-F., and Tsai, Y.-H., Biogenic amines content, histamine-forming bacteria and adulteration of bonito in tuna candy products, *Food Control,* 2010, vol. 21, pp. 845–850.

Iyer, L.M., Aravind, L., Coon, S.L, Klein, D.C., and Koonin, E., Evolution of cell-cell signaling in animals: did late horizontal gene transfer from bacteria have a role?, *Trends Genet.*, 2004, vol. 20, no. 7, pp. 292–299.

James, S.L., Role of nitric oxide in parasitic infections, *Microbiol. Rev.*, 1995, vol. 59, pp. 533–547.

Kaper, J. and Sperandi, V., Bacterial cell-to-cell signaling in the gastrointestinal tract, *Infect. Immun.*, 2005, vol. 73. pp. 3197–3209.

Karatan, E. and Watnic, P., Signals, regulatory networks, and materials that build and break bacterial biofilms, *Microbiol. Mol. Biol. Rev.*, 2009, vol. 73, pp. 310–347.

Khmel, I.A., Quorum-sensing regulation of gene expression: fundamental and applied aspects and the role in bacterial communication, *Microbiology* (Moscow), 2006, vol. 75, no. 4, pp. 390–397.

Khokhlov, A.S., *Nizkomolekulyarnye mikrobnye autoregulatory* (Low-Molecular-Weight Microbial Autoregulators), Moscow: Nauka, 1988.

Kinney, K.S., Austin, C.E., Morton, D.S., and Sonnenfeld, G., Catecholamine enhancement of *Aeromonas hydrophila* growth, *Microb. Pathog.*, 1999, vol. 25, pp. 85–91.

Kowalska, K., Carr, D.B., and Lipkowski, A.W., Direct antimicrobial properties of substance P, *Life Sci.*, 2002, vol. 71, pp. 747–750.

Ladero, V., Linares, D.M., Fernandez, M., and Alvarez, M.A., Real time detection of histamine-producing lactic acid bacteria in cheese: relation with histamine content, *Food Res. Intern.*, 2008, vol. 41, pp. 1015–1019.

Lee, B.-J., Kim, J.-S., Kang, Y.M., Lim, J.-H., Kim, Y.-M., Lee, M.-S., Jeong, M.-H, Ahn, C.-B., and Je, J.-Y., Antioxidant activity and γ-aminobutyric acid (GABA) content in sea tangle fermented by *Lactobacillus brevis* BJ20 isolated from traditional fermented foods, *Food Chem.*, 2010, vol. 122, pp. 271–276.

Lee, J., Jayaraman, A., and Wood, T.K., Indole is an interspecies biofilm signal mediated by SdiA, *BMC Microbiol.*, 2007a, vol. 7, p. 42.

Lee, J., Bansal, T., Jayaraman, A., Bentley, W.E., and Wood, T.K., Enterohemorrhagic *Escherichia coli* biofilms are inhibited by 7-hydroxyindole and stimulated by isatin, *Appl. Environ. Microbiol.*, 2007b, vol. 73, pp. 4100–4109.

Lenard, J., Mammalian hormones in microbial cells, *Trends Biochem. Sci.*, 1992, vol. 17, pp. 147–150.

Liao, W.-C., Wang, C.-Y., Shyu, Y.-T., Yu, R.-C., and Ho, K.-C., Influence of preprocessing methods and fermentation of adzuki beans on γ-aminobutyric acid (GABA) accumulation by lactic acid bacteria, *J. Functional Foods,* 2013, vol. 5, pp. 1108–1115.

Lin, C.-S., Tsai, H.-C., Lin, C.-M., Huang, C.-Y., Kung, H.-F., and Tsai, Y.-H., Histamine content and histamine-forming bacteria in mahi-mahi (*Coryphaea hippurus*) fillets and dried products, *Food Control,* 2014, vol. 42, pp. 165–171.

Lyte, M., The role of microbial endocrinology in infectious disease, *J. Endocrinol.*, 1993, vol. 137, pp. 343–345.

Lyte, M., The microbial organ in the gut as a driver of homeostasis and disease, *Medical Hypotheses,* 2010, vol. 74, pp. 634–638.

Lyte, M., Probiotics function mechanistically as delivery vehicles for neuroactive compounds: microbial endocrinology in the design and use of probiotics, *Bioessays*, 2011, vol. 33, pp. 574–581.

Lyte, M., Microbial endocrinology and nutrition: a perspective on new mechanisms by which diet can influence gut-to brain-communication, *Pharma Nutrition,* 2013, vol. 1, pp. 35–39.

Lyte, M., Frank, C.D., and Green, B.T., Production of an autoinducer of growth by norepinephrine-cultured *Escherichia coli* O157:H7, *FEMS Microbiol. Lett.*, 1996, vol. 139, nos. 2–3, pp. 155–159.

Macreadie, I.G., Bartone, N., and Sparrow, L., Inhibition of respiratory growth and survival in yeast by dopamine and counteraction with ascorbate or glutathione, *J. Biomol. Screen.,* 2010, vol. 15, pp. 297–301.

Malikina, K.D., Shishov, V.A., Chuvelev, D.I., Kudrin, V.S., and Oleskin, A.V., Regulatory role of neurotransmitters in *Saccharomyces cerevisiae* cels, *Appl. Biochem. Microbiol.,* 2010, vol. 46, no. 6, pp. 620–625.

Mart'yanov, S.V., Zhurina, M.V., El'-Registan, G.I., and Plakunov, V.K., Activation of formation of bacterial biofilms by azithromycin and prevention of this effect, *Microbiology* (Moscow), 2014, vol. 83, no. 6, pp. 723–732.

Martin, G., Asensi, V., Montes, A.H., Collazos, J., Alvarez, V., Pérez-Is, L., Carton, J.A., Taboada, F., and Valle-Garay, E., Endothelial (*NOS3 E298D*) and inducible (*NOS2 exon 22*) nitric oxide synthase polymorphisms, as well as plasma NOx, influence sepsis development, *Nitric Oxide,* 2014, vol. 42, pp. 79–86.

Martins, F.S., Nardi, R.M.D., Arantes, R.M.E., Rosa, C.A., Neves, M.J., and Nicoli, J.R., Scanning of yeasts as probiotics based on capacities to colonize the gastrointestinal tract and to protect against enteropathogenic challenge in mice, *J. Gen. Appl. Microbiol.*, 2005, vol. 51, pp. 83–92.

Mayr, A., Hinterberger, G., Dierich, M.P., and Lass-Flörl, C., Interaction of serotonin with *Candida albicans* selectively attenuates fungal virulence in vitro*, Int. J. Antimicrob. Agents,* 2005, vol. 26, pp. 335–337.

Medinets, S., Skiba, U., Rennenberg, H., and Butterbach-Bahl, K., A review of soil NO transformation: associated processes and possible physiological significance on organisms, *Soil Biol. Biochem*. 2015, vol. 80, pp. 92–117.

Mittal, N., Budrene, E.O., Brenner, M.P., and Van Oudenaarden, A., Motility of *Escherichia coli* cells in clusters formed by chemotactic aggregation, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, vol. 100, pp. 13259–13263.

Murrison, R., Is there a role for psychology in ulcer disease?, *Integrative Psychol. Behav. Sci.*, 2001, vol. 36, pp. 75–83.

Nakano, M., Takahashi, A., Sakai, Y., Kawano, M., Harada, N., Mawatari, K., and Nakaya, Y., Catecholamine-induced stimulation of growth in *Vibrio* species, *Lett. Appl. Microbiol.*, 2007, vol. 44, pp. 649–653.

Nei, D., Kawasaki, S., Inatsu, Y., Yamamoto, K., and Satoni, M., Effectiveness of gamma-irradiation in the inactivation of histamine-producing bacteria, *Food Control,* 2013, vol. 28*,* pp. 143–146.

Nikolaev, Yu.A., Distant interactions in bacteria, *Microbiology* (Moscow), 2000, vol. 69, no. 5, pp. 497–503.

Nikolaev, Yu.A., Mulyukin, A.L., Stepanenko, I.Yu., and El'-Registan, G.I., Autoregulation of stress response in microorganisms, *Microbiology* (Moscow), 2006, vol. 75, no. 4, pp. 415–419.

Nikolaev, Yu.A. and Plakunov, V.K., Biofilm—"City of microbes" or an analogue of multicellular organisms?, *Microbiology* (Moscow), 2007, vol. 76, no. 2, pp. 125–138.

Norris, V., Molina, F., and Gewirtz, A.T., Hypothesis: bacteria control host appetites, *J. Bacteriol.,* 2013, vol. 195, pp. 411–416.

Oleskin, A.V., Kirovskaya, T.A., Botvinko, I.V., and Lysak, L.V., Effects of serotonin (5-hydroxytryptamine) on the growth and differentiation of microorganisms, *Microbiology* (Moscow), 1998, vol. 67, no. 3, pp. 251–257.

Oleskin, A.V., Botvinko, I.V., and Tsavkelova, E.A. Colonial organization and intercellular communication in microorganisms, *Microbiology* (Moscow), 2000, vol. 69, no. 3, pp. 249–265.

Oleskin, A.V., Shishov, V.I., and Malikina, K.D., *Symbiotic Biofilms and Brain Neurochemistry,* Hauppauge (New York): Nova Science, 2010.

Oleskin, A.V. and Shenderov, B.A., Biopolitical approach to rehabilitology: potential role of microbial neurochemistry, *Vestn. Vosst. Med.,* 2013, no. 1, pp. 60–67.

Oleskin, A.V., Zhilenkova, O.G., Shenderov, B.A., Amerkhanova, A.M., Kudrin, V.S., and Klodt, P.M., Starter cultures of lactobacilli producing neuromediators: biogenic amines and amino acids, *Mol. Prom.,* 2014a, no. 9, pp. 42–43.

Oleskin, A.V., Zhilenkova, O.G., Shenderov, B.A., Amerhanova, A.M., Kudrin, V.S., and Klodt, P.M., Lactic-acid bacteria supplement fermented dairy products with human behavior-modifying neuroactive compounds, *J. Pharm. Nutrit. Sci.*, 2014b, vol. 4, pp. 199–206.

O'Mahony, S.M., Clarke, G., Borre, Y.E., Dinan, T.G., and Cryan, J.F., Serotonin, tryptophan metabolism, and the brain-gut-microbiome axis, *Behav. Brain Res.*, 2014. http://dx.doi.org/ doi 10.1016/j.bbr.2014.07.027

Oneal, M.J., Schafer, E.R., Madsen, M.L., and Minion, F.C., Global transcriptional analysis of *Mycoplasma hyopneumoniae* following exposure to norepinephrine, *Microbiology* (UK), 2008, vol. 154, pp. 2581–2588.

Özogul, F., Production of biogenic amines by *Morganella morganii, Klebsiella pneumonia* and *Hafnia alvii* using a rapid HPLC method, *Eur. Food Res. Technol.*, 2004, vol. 219, pp. 465–469.

Özogul, F., Kuley, E., Özogul, Y., and Özogul, I., The function of lactic acid bacteria on bio-genic amines production by food-borne pathogens in arginine decarboxylase broth, *Food Sci. Technol. Res.*, 2012, vol. 18, pp. 795–804.

Pearson, S.J., Czudek, C., Mercer, K., and Reynolds, G.P., Electrochemical detection of human brain transmitter amino acids by high-performance liquid chromatography of stable *o*-phtalaldehyde-sulphite derivatives, *J. Neural Transm.: Gen. Sect*. 1991, vol. 86, pp. 151–157.

Penfold, W.J., On the nature of the bacterial lag, *J. Hygiene,* 1914, vol. 14, pp. 215–241.

Previte, J.J., Alden, J.C., Gagliardi, M., William, M., and Shampine, J., Invasiveness of *Salmonella* administered orally to cold-exposed mice, *Infect. Immun.*, 1970, vol. 2, pp. 274–278.

Rahman, M.A., Azuma, Y., Fukunaga, H., Murakami, T., Sugi, K., Fukushi, H., Miura, K., Suzuki, H., and Shirai, M., Serotonin and melatonin, neurohormones for homeostasis, as novel inhibitors of infection by the intracellular parasite *Chlamydia, J. Antimicrob. Chemother.*, 2005, vol. 56, pp. 861–868.

Rahn, O., Über den Einfluß der Stoffwechselprodukte auf das Wachstum der Bakterien, *Zbl. Bakteriol. Parasitenk.*, 1906, vol. 16, pp. 417–429.

Ramírez-Mata, A., Fernández-Domínguez, I.J., Nuñez-Reza, K.J., Xiqui-Vázquez, M.L., and Baca, B.E., Redes de señalización en la producción de biopelículas en bacterias: quorum sensing, di-GMPc y óxido nitric, *Rev. Argent Microbiol.*, 2014, vol. 46, pp. 242–255.

Reyes-García, M.G., Hernández-Hernández, F., and García-Tamayo, F., Gamma-aminobutyric acid (GABA) increases in vitro germ-tube formation and phospholipase B1 mRNA expression in *Candida albicans, Mycoscience,* 2012, vol. 53, pp. 36–39.

Robinson, J.L., Adolfsen, K.J., and Brynildsen, M.P., Deciphering nitric oxide stress in bacteria with quantitative modeling, *Curr. Opin. Microbiol.*, 2014, vol. 19, pp. 16–24.

Rohrscheib, C.E. and Brownlie, J.C., Microorganisms that manipulate complex animal behaviours by affecting the

host's nervous system, *Springer Sci. Rev.*, 2013, vol. 1, pp. 133–140.

Rook, G.A.W., Raison, C.L., and Lowry, C.A., Can we vaccinate against depression?, *Drug Discovery Today,* 2013, vol. 17 (9/10), pp. 451–458.

Roshchina, V.V., *Biomediatory v rasteniyakh. Atsetilkholin i biogennye aminy* (Biomediators in Plants. Acetylcholine and Biogenic Amines), Pushchino: NTs, 1991.

Roshchina, V.V., Evolutionary considerations of neurotransmitters in microbial, plant, and animal cells, in *Microbial Endocrinology: Interkingdom Signaling in Infectious Disease and Health,* Lyte, M. and Freestone, P.P.E., Eds., New York: Springer, 2010, pp. 17–52.

Ryan, R.P. and Dow, J.M., Diffusible signals and interspecies communication in bacteria, *Microbiology* (UK), 2008, vol. 154, pp. 1845–1858.

Ryu, Y.H., Baik, J.E., Yang, J.S., Kang, S.S., Im, J., Yun, C.H., Kim, D.W., Lee, K., Chung, D.K., Ju, H.R., and Han, S.H., Differential immunostimulatory effects of Gram-positive bacteria due to their lipoteichoic acids, *Internat. Immunopharmacol.*, 2009, vol. 9, pp. 127–133.

Sandrini, S.M., Shergill, R., Woodward, J., Muralikuttan, R., Haigh, R.D., Lyte, M., and Freestone, P.P.E., Elucidation of the mechanism by which catecholamine stress hormones liberate iron from the innate immune defense proteins transferrin and lactoferrin, *J. Bacteriol.*, 2010, vol. 192, pp. 587–594.

Schlag, S., Ners, C., Birkenstock, T.A., Altenberend, F., and Gotz, F., Inhibition of staphylococcal biofilm formation by nitrite, *J. Bacteriol.*, 2007, vol. 189, pp. 7911–7919.

Sekowska, A., Masson, J.B., Celani, A., and Vergassola, M., Repulsion and metabolic switches in the collective behavior of bacterial colonies, *Biophys. J.*, 2009, vol. 97, pp. 688–697.

Shenderov, B.A., Socio-ecological consequences of imbalance in microbial ecology of humans and animals, in *Meditsinskaya mikrobnaya ekologiya i funktsional'noe pitanie* (Medical Microbial Ecology and Functional Nutrition), vol. 2., Moscow: Grant, 1998.

Shenderov, B.A., *Funktsional'noe pitanie i ego rol' v profilaktike metabolicheskogo sindroma* (Functional Nutrition and Its Role in Prevention of the Metabolic Syndrome), Moscow: DeLi Print, 2008.

Shenderov, B.A., OMIC technologies and their role in modern preventive and recovery medicine, *Vestn. Vosst. Med.,* 2012, no. 3 (49), pp. 70–78.

Shenderov, B.A., Innovative products and ingredients, drivers of the dairy market, *Mol. Prom.,* 2013, no. 6, pp. 62–66.

Shenderov, B.A., Microbial ecology and its role in health preservation, *Metamorfozy*, 2014a, no. 5, pp. 72–80.

Shenderov, B.A., Directions of development in gnotobiology: theoretical and applied aspects, *Lechen. Profilakt.,* 2014b, no. 1 (9), pp. 80–84.

Shenderov, B.A. and Midtvedt, T., Epigenomic programing: a future way to health?, *Microb. Ecol. Health Dis.*, 2014, vol. 25:24145. doi: 10.3402/mehd.v25.24145

Shireen, T., Basu, A., Sarkar, M., and Mukhopadhyay, K., Lipid composition is an important determinant of antimicrobial activity of alpha-melanocyte stimulating hormone, *Biophys. Chem.*, 2015, vol. 196, pp. 33–39.

Shishov, V.A., Biogenic amines in microbial growth dynamics, *Extended Abstract Cand. Sci. (Biol.) Dissertation,* Biological Faculty, Moscow State University, 2010.

Shishov, V.A., Kirovskaya, T.A., Kudrin, V.S., and Oleskin, A.V., Amine neuromediators, their precursors, and oxidation products in the culture of *Escherichia coli* K-12, *Appl. Biochem. Microbiol.*, 2009, vol. 45, no. 5, pp. 494–497.

Shpakov, A.O., QS-type bacterial signal molecules of non-peptide origin, *Microbiology* (Moscow), 2009, vol. 78, no. 2, pp. 133–143.

Siragusa, S., De Angelis, M., Di Cagno, R., Rizzello, C.G., Coda, R., and Gobbetti, M., Synthesis of γ-aminobutyric acid by lactic acid bacteria isolated from a variety of Italian cheeses, *Appl. Environ. Microbiol.*, 2007, vol. 73, pp. 7283–7290.

Sircili, M.P., Walters, M., Trabulsi, L.R., and Sperandi, V., Modulation of enteropathogenic *Escherichia coli* virulence by quorum sensing, *Infect. Immun.*, 2004, vol. 72, pp. 2329–2337.

Smith, E.A. and Macfarlane, G.T., Enumeration of human colonic bacteria producing phenolic and indolic compounds: effects of pH, carbohydrate availability and retention time on dissimilatory aromatic amino acid metabolism, *J. Appl. Bacteriol.*, 1996, vol. 81, pp. 288–302.

Stilling, R.M., Bordenstein, S.R., Dinan, T.G., and Cryan, J.F., Friends with social benefits: host-microbe interactions as a driver of brain evolution and development?, *Front. Cell. Infect. Microbiol.,* 2014, vol. 4. doi: 10.3389/fcimb.2014.00147

Strakhovskaya, M.G., Ivanova, E.V., and Fraikin, G.Ya., Stimulatory effect of serotonin on growth of the yeasts *Candida guillermondii* and bacteria *Streptococcus faecalis, Mikrobiologiya,* 1993, vol. 62, pp. 46–49.

Strempel, N., Neidig, A., Nusser, M., Geffers, R., Vieillard, J., Lesouhaitier, O., Brenner-Weiss, G., and Overhage, J., Human host defense peptide LL-37 stimulates virulence factor production and adaptive resistance in *Pseudomonas aeruginosa*, *PLoS One*, 2013, vol. 8, no. 12, p. e82240.

Sumina, E.L., Behavior of filamentous cyanobacteria in laboratory culture, *Microbiology* (Moscow), 2006, vol. 75, no. 4, pp. 459–464.

Tinajero-Trejo, M., Jesse, H.E., and Poole, R.K., Gasotransmitters, poisons, and antimicrobials: it's a gas, gas, gas!, *F1000Prime Report* 2013.5:28, doi: 10.12703/P5-28

Trueba, A.F. and Ritz, T., Stress, asthma, and respiratory infections: pathways involving airway immunology and microbial endocrinology, *Brain, Behav. Immun.*, 2013, vol. 29, pp. 11–27.

Tsavkelova, E.A., Botvinko, I.V., Kudrin, V.S., and Oleskin, A.V., Detection of neurotransmitter amines in microorganisms with the use of high-performance liquid chromatography, *Doklady Biochem.,* 2000, vol. 372, pp. 115–117.

Ueno, Y., Hayakawa, K., Takahashi, S., and Oda, K., Purification and characterization of glutamate decarboxylase from *Lactobacillus brevis* IFO 12005*, Biosci. Biotechnol. Biochem.,* 1997, vol. 61, pp. 1168–1171.

Vakhitov, T.Ya., Yashina, O.Yu., Petrov, L.N., and Korolyuk, A.M., Study of the effect of a growth autostimulator of *Escherichia coli* M-17 (preparation Aktoflor) on the

growth of pure and mixed bacterial cultures, *Zh. Mikrobiol.,* 2000, no. 3, pp. 20–24.

Vakhitov, T.Ya. and Sitkin, S.I., The concept of superorganism in biolgy and medicine, *Exp. Klin. Gastroenterol.*, 2014, vol. 107, no. 7, pp. 72–85.

Valyshev, A.V. and Gil'mutdinova, F.G., Microbial ecology of the human digestive tract, in *Ekologiya mikroorganismov cheloveka* (Ecology of Human-Associated Microorganisms), Bukharin, O.V., Ed., Ekaterinburg: Inst. Klet. Vnutriklet. Simb., 2006, pp. 169–290.

Vega, N.M., Allison, K.R., Khalil, A.S., and Collins, J.J., Signaling-mediated bacterial persister formation, *Nat. Chem. Biol.*, 2012, vol. 8, pp. 431–433.

Verbrugge, E., Boyen, F., Gaastra, W., Bekhuis, L., Leyman, B., Van Pari, A., Haesebrouck, F., and Pasmans, F.Ta., The complex interplay between stress and bacterial infections in animals, *Veter. Microbiol.*, 2012, vol. 155, pp. 115–127.

Vidal-Gadea, A.G. and Pierce-Shimomura, J.T., Conserved role of dopamine in the modulation of behavior, *Commun. Integr. Biol.*, 2012, vol. 5, pp. 440–447.

Walters, M., Sircili, M.P., and Sperandi, V. AI-3 synthesis is not dependent on *luxS* in *Escherichia coli, J. Bacteriol.*, 2006, vol. 188, pp. 5668–5681.

Wenner, M., Going with his gut bacteria, *Sci. Amer.*, 2008, July, pp. 90–92.

Williams, P.H., Rabsc, W., Methner, U., Voigt, W., Tschäpe, H., and Reissbrodt, R., Catecholate receptor proteins in *Salmonella enterica*: role in virulence and implications for vaccine development, *Vaccine,* 2006, vol. 24, pp. 3840–3844.

Worthington, R.J., Richards, J.J., and Melander, C., Small molecule control of bacterial biofilms, *Org. Biomol. Chem.*, 2012, vol. 10, pp. 7457–7474.

Yarullina, D.R., Smolentseva, O.A., and Ilinskaya, O.N., Modulation of nitric oxide (NO) biosynthesis in lactobacilli, *Mos.Univ. Biol. Sci. Bull.*, 2011, pp. 79–80.

Ye, J.Z.X., Fang, Z., Xie, G., Liao, N., Shu, J., and Liu, D., Determination of biogenic amines in semi-dry and semi-sweet Chinese rice wine from the Shaoxing region, *Food Control,* 2012, vol. 28, pp. 151–156.

Zaborina, O., Lepine, F., Xiao, G., Valuckaite, V., Chen, Y., Li, T., Ciancio, M., Zaborin, A., Petroff, E., Turner, J.R., Rahme, L.G., Chang, E., and Alverdy, J.C., Dynorphin activates quorum sensing quinolone signaling in *Pseudomonas aeruginosa, PLoS Pathogens,* 2007, vol. 3, p. e35.

Zagon, I.S. and McLaughlin, P.J., An opioid growth factor regulates the replication of microorganisms, *Life Sci.,* 1992, vol. 50, pp. 1179–1187.

Zaitseva, Yu.V., Popova, A.A., and Khmel', I.A., Quorum-sensing regulation in bacteria of the family *Enterobacteriaceae, Russ. J. Genet.,* 2014, vol. 50, pp. 323–340.

Zhilenkova, O.G., Shenderov, B.A., Klodt, P.M., Kudrin, V.S., and Oleskin, A.V., Dairy products as a potential source of compounds affecting consumer behavior, *Mol. Promysh.,* 2013, no. 10, pp. 16–19.

Zídek, Z., Kmoníčková, E., Kostecká, P., and Tlaskalová-Hogenová, H., Decisive role of lipopolysaccharide in activating nitric oxide and cytokine production by the probiotic *Escherichia coli* strain Nissle 1917, *Folia Microbiol.*, 2010, vol. 55, pp. 181–189.

Zumft, W.G., The biological role of nitric oxide in bacteria, *Arch. Microbiol.,* 1993, vol. 160, pp. 253–264.

Translated by A. Oleskin