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Interaction of Catecholamines with Microorganisms, Neurons, and Immune Cells

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Abstract—The review presents current data on cellular communication in the binary host–microbiota system. Microbial communication systems are widely spread in the bacterial realm and resemble those characteristic of eukaryotic multicellular organisms Microorganism engage in an ongoing dialogue with hpst cells and perform a plethora of functions in the composite superorganism. Literature data and the authors' own studies indicate the important role of catecholamines (biogenic amines), both in intra- and interspecific microbial communication and in the bidirectional microbiota-host dialog. The importance of this dialog for the maintenance of human health, psyche and social behavior, as well as the possibility of the creation of new drugs with targeted neurochemical effects, are discussed.

Keywords: neurotransmitters, catecholamines, serotonin, dopamine, norepinephrine, histamine, communication of microorganisms

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INTRODUCTION

Catecholamines (dopamine, norepinephrine, and epiephrine) are derivatives of the amino acid tyrosine whose hydroxylation yields dihydroxyphenylalanine (DOPA), the immediate precursor of catecholamines. In vertebrates, catecholamines are mainly produced by cells in the adrenal medulla and the axons of the sympathetic nervous system, which is responsible for the body's response to stress; they are also formed in the brain. Significant catecholamine concentrations are characteristic of the gastrointestinal tract; for example, about 50% of the dopamine in the human body is found in the intestine (Liang et al., 2018). It was established that dopamine and norepinephrine have neurotransmitter functions, but this is questionable in the case of epinephrine (Boldyrev et al., 2010).

Catecholamines are widespread and perform important functions in invertebrates, in particular, in insects (Gritsai, 2017), plants (Roshchina, 2010; Kulma and Szopa, 2007), and various unicellular organisms (Roshchina, 2010). Interestingly, in an analogy to higher animals, catecholamines are released in plants in response to stress: stressed tomatoes (under cold stress) significantly increase the production of catecholamines (Lyte, 2014). In recent years, a significant amount of data has been presented that catecholamines are also capable of affecting the physiology and viability of various prokaryotic organisms and modulating immune-responses in the human body.

CATECHOLAMINE INTERACTION WITH MICROORGANISMS

There is a significant body of data in the literature (Freestone et al., 2007) on the stimulating effect of catecholamines on the growth of various microorganisms. An increase in the norepinephrine level in the mouse body via the destruction of norepinephrine-containing endings of sympathetic nerves with the neurotoxin 6-hydroxydopamine increased the number of *E. coli* cells in the mouse cecum by about 10000 times. In vitro treatment of *Salmonella enterica* var. *typhimurium* cells with norepinephrine increased the reproduction rate of this pathogen in various tissues of experimentally infected pigs (Verbrugghe et al., 2012).

These facts account for the fact that cold stress in mice, which is accompanied by the release of catecholamines into the bloodstream, like the administration of norepinephrine (Williams et al., 2006), increases the incidence of *Salmonella* infection in them. Cases of gangrene and fulminant sepsis with a fatal outcome have been described in patients with urticaria who were prescribed adrenaline when insufficiently sterilized reusable syringes were used, which allowed the accumulation of *Clostridium perfringens* spores (Lyte, 2011, 2014).

Interestingly, norepinephrine and epinephrine also increase plant sensitivity to bacterial and fungal infections (Lyte, 2014).

Bacterial growth in the tissues of the host organism can be stimulated by catecholamines, due to a direct and an indirect action of these compounds on microorganisms. Norepinephrine and other catecholamines can suppress the synthesis and excretion of immunoglobulin A, as well as the migration of phagocytes to the site of infection. This reduces the antimicrobial efficiency of the local immune system (Lyte, 2014). Catecholamines, which stimulate the secretion of bile and accelerate ion transport through the epithelium of the intestinal mucosa, create physicochemical conditions in the digestive tract that stimulate the growth of certain representatives of the intestinal microbiota, e.g., bacteria of the genus *Bacteroides* (Verbrugghe et al., 2012).

The direct stimulating effect of catecholamines on microorganism growth was demonstrated on the example of various pathogenic, opportunistic, and saprotrophic bacteria: *Yersinia enterocolitica*, enterotoxic, enterohemorrhagic strains *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 jejuni*, *Borrelia burgdorfii*, *Mycoplasma hyopneumoniae*, *Staphylococcus epidermidis*, and symbiotic *E. coli* strains (Anuchin et al., 2008; Freestone et al., 2007), as well as the yeast *Saccharomyces cerevisiae* (Malikina et al., 2010; Oleskin et al., 2010). In *C. jejuni*, which grows under microaerophilic conditions (in the presence of oxygen in a gas mixture at concentrations lower than in atmospheric air), norepinephrine, in addition to accelerating growth, enables growth in the complete absence of oxygen (Lyte, 2014).

All catecholamines stimulated the growth (judging by the increase in the optical density of the culture and the number of colony-forming units) of the probiotic *Lactobacillus acidophila* NK-1 and its biochemical activity (a decrease in the pH of the medium as a result of the formation of organic acids). Dopamine also stimulated the growth and antibacterial activity of all tested strains (K-205, K-729, K-194, F-116) of the probiotic *Lactococcus lactis* subsp. *lactis*, while other tested amines (adrenaline and serotonin) had a stimulatory effect on only one of these strains, K-194 (Vodolazov et al., 2018).

Dopamine at low concentrations stimulated the luminescence (bioluminescence) of the strain *E. coli* TGI with integrated luciferase *lux*-genome from *Photorhabdus luminescencens* ZMI, and it inhibited the luminescence at high concentrations. Norepinephrine inhibited fluorescence at all tested concentrations. This bioluminescence is considered as an integral characteristic of the physiological state of *E. coli* cells (Oleskin et al., 2017b).

High concentrations of catecholamines are capable of exerting a cytotoxic effect, which is associated with the possibility of their induction of oxidative stress. Thus, millimolar concentrations of dopamine (as well as 6-hydroxydopamine) not only suppressed yeast growth (*S. cerevisiae*, *Pichia pastoris*, *Candida albicans,* and others)—it also killed them. The addition of antioxidants (axorbate and glutathione) to the culture medium relieved the inhibitory and toxic effects of dopamine (Macreadie et al., 2010).

Catecholamines enhance the adhesion of gastrointestinal microorganisms to the intestinal mucosa, the formation of type-I pili (which are necessary for adhesion in symbiotic strains *E. coli*), the adhesion of *Staphylococcus epidermidis* to skin cells, and the formation of biofilms by these microorganisms (Lyte, 2010, 2011). In addition to cell proliferation, catecholamines also stimulated the formation of toxins and adhesins in an enterotoxic *E. coli* strain (Freestone et al., 2007). An increase in virulence and the ability to colonize the gastrointestinal tract was noted under these conditions for other pathogenic bacteria (Shpakov, 2009; Clarke et al., 2006).

Under the influence of norepinephrine, there is an increase in the expression of virulence factors in *Salmonella typhimurium*, especially those of the type-III secretion system (a molecular needle used to inject bacterial proteins into the cytoplasm of host cells), and the flagellar motility also increases (Lyte, 2011). The adhesion of enterohaemorrhagic *E. coli* cells (strain O157:H7), in particular, to the mucous wall of the cecum in the presence of norepinephrine, is enhanced (Lyte, 2011) due to its ability to induce the expression of F5 pili, which are responsible for the attachment of bacterial cells to the epithelium of the small intestine (Verbrugghe et al., 2012). Norepinephrine also enhances the internalization of a pathogenic strain of *E. coli* into Peyer's patches (intestinal lymphoid tissue) (Lyte, 2011).

It was demonstrated in a mouse model that the partial surgical removal of the liver stimulated adhesion *Pseudomonas aeruginosa* to its mucous membrane by increasing the norepinephrine concentration in the intestinal lumen (Freestone et al., 2007).

The effects of catecholamines varied depending on the concentration and taxonomic affiliation of the tested microorganisms. Norepinephrine, epinephrine, and dopamine stimulated the growth of *Vibrio parahaemolyticus* and *V. mimicus* but not *V. vulnificus* or *V. cholerae* (Nakano et al., 2007). Norepinephrine inhibited the growth of *Mycoplasma hyopheunomiae* by suppressing the expression of genes necessary for proliferation (Oneal et al., 2008). Dopamine significantly stimulated proliferation in the yeast *Saccharomyces cerevisiae*; norepinephrine, conversely, was ineffective

(Malikina et al., 2010). When added to dense nutrient media, dopamine and norepinephrine differed in their effect on the formation of *E. coli* K-12 microcolonies: norepinephrine stimulated this process, while dopamine inhibited it (Anuchin et al., 2008). Norepinephrine and epinephrine shift the balance between *Clostridium* and *Bacteroides* in favor of *Clostridium* species (Bailey et al., 2011).

Dopamine and epinephrine stimulated spore germination in actinobacteria *Saccharopolyspora erythraea* (strains RIA 1387 and RIA 120) and stabilized the composition of its population, increasing the proportion of colony-forming units of the dominant phenotype (the most effective producer of the antibiotic erythromycin). At the same time, only dopamine, notepinephrine, increased survival and promoted the transition to an active (vegetative) state of spores *S. erythraea* after storage for three months or short-term (10-min) freezing, i.e., in this system, there is a difference in the effects of different catecholamines on microorganisms (Filippova et al., 2010).

Norepinephrine and dopamine alter the gene expression profile in a number of prokaryotes: *Mycoplasma hyopneumoniae*, *Salmonella enterica* serovar *typhimurium*, and *Vibrio parahaemolyticus* (Lyte, 2014).

There are two explanations in the literature for the effects of catecholamines on microorganisms.

First, these compounds can chelate ferric iron, removing it from lactoferrin and transferrin in blood serum and other biological fluids. The iron bound by catecholamines becomes available to microorganisms, which use special carriers, siderophores (enterobactin), 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*, *Pseudomonas aeruginosa*, *Listeria monocytogenes,* and coagulase-negative staphylococci is stimulated (Verbrugghe et al., 2012). This mechanism of the effect of catecholamines accounts for the fact that the incubation of enterobacteriaceae in a nutrient-poor, iron-limited medium, which to a certain extent reproduces the conditions in the host's body, with the addition of norepinephrine leads to an increase in the number of bacteria by several orders of magnitude as compared with a control system without catecholamines (Lyte, 2011). The fewer bacterial cells are taken for inoculation, the more significant are the effects of catecholamines. It is the presence of catecholamines in the host organism that can explain why a very small number of cells of pathogenic bacteria, e.g., the enterohemorrhagic strain *E. coli* O157:H7, appears to be sufficient for foodborne infections (Lyte, 2011).

The second explanation interprets the effects of catecholamines on bacterial objects in terms of quorum-sensing communication (Clarke et al., 2006; Bansal et al., 2007). It is assumed that they function as analogs of the AI-3 autoinducer and, like it, bind to receptor histidine kinases QseC and QseE, which can therefore be considered functional analogs of eukaryotic cell receptors, although they differ in structure from eukaryotic G-protein receptors (Clarke et al., 2006; Hughes et al., 2009). In addition to representatives of the genera *Salmonella* and *Shigella* and species *Haemophilus influenzae*, genes related to the QseC histidine kinase gene were also found in a large number of bacteria not associated with the human body, e.g., *Erwinia carotovora*, *Thiobacillus denitrificans*, and *Psychrobacter* sp., as well as the mushroom *Aspergillus nidulans* (Shpakov, 2009). This indicates that such receptors may be involved in the control of the development of microbial communities.

Bacterial QseC receptors functionally resemble eukaryotic α-adrenergic receptors, since their interaction with catecholamines norepinephrine and epinephrine, as well as AI-3, is blocked by the α-adrenergic blockers phentolamine, phenoxybenzamine, and prazosin, but not by the β-adrenergic blocker propranol in the pathogenic strain *E. coli* O157:H7, *Salmonella enterica*, and *Yersinia enterocolitica* (Clarke et al., 2006; Freestone et al., 2007). In particular, it was found that norepinephrine stimulates the adhesion of *E. coli* O157:H7 to the cecal epithelium and the internalization of cells of the pathogenic *E. coli* strain in Peyer's patches is prevented via the pretreatment of intestinal tissue with phentolamine (Freestone et al., 2007; Lyte, 2011).

In light of the available data, it can be assumed that the receptor systems of microorganisms in the gastrointestinal tract, which interact with the autoinducer AI-3 and catecholamines, contribute to the communication of microbial cells with each other and the chemical dialogue between microorganisms and the host organism. Stressing agents and factors that increase the level of catecholamine synthesis can affect the amount, species diversity, and function of the microbiota inhabiting the gastrointestinal tract and, possibly, the skin and mucous membranes of other parts of the body of mammals, including humans. The AI-3 molecules synthesized by symbiotic bacteria, in turn, can modify the effector systems of the host cells and the cells of the microbial communities inhabiting it (Shpakov, 2009). In the course of the long-term, joint evolution of the host organism and its microbiota, neuroactive substances of eukaryotic and/or prokaryotic origin have probably become a necessary part of the notification system for both host cells and pathogenic and opportunistic bacteria (Trueba and Ritz, 2013).

Antagonists of adrenergic and dopamine receptors are of potential medical interest. For example, adrenergic antagonists can inhibit the AI-3, epinephrine, or norepinephrine-dependent quorum-sensing cascade in pathogenic *E. coli* strains, depriving them of the ability to express virulence genes. These antagonists

could become a new class of antimicrobial drugs (Clarke et al., 2006).

The dialog in the microbiota–host system, which is carried out by catecholamines, has a bidirectional character, since not only the host cells but also the microorganisms themselves actively produce this group of biogenic amines. High-performance liquid chromatography (HPLC) with amperometric detection was used to quantify the catecholamine content in the cultures of many pro- and eukaryotic microorganisms (Tsavkelova et al., 2000). For example, norepinephrine at concentrations of 0.2–2 μM was present in the biomass of *B. mycoides*, *B. subtilis*, *P. vulgaris* and *S. marcescens*; dopamine was present in an amount of 0.5–2 μM in the biomass of most of the tested prokaryotes. Their concentrations significantly exceeded those in human blood, which contains 0.1–0.5 nM dopamine and 1–2 nM norepinephrine (Eldrup, 2004).

It was shown in the example of the matrix-rich bacterium *Bacillus subtilis* (strain M) that neurotransmitter amines (norepinephrine and dopamine) are not contained intracellularly but in the matrix coating the cells. This fact provides an argument in favor of the possible intercellular communicative role of these amines, since the biopolymers composing the matrix facilitate the diffusion of low molecular weight chemical signals within the colony or biofilm. In most microorganisms, metabolic products (oxidative deamination) of neurotransmitters were also found, such as 5-hydroxyindoleacetic acid (5-HIAA) and dihydrophenylacetic acid (DHFUA) (Tsavkelova et al., 2000).

Dopamine was also detected in micromolar concentrations in *M. morganii* (2.46 mg/L, ~16 μM), *K. pneumonia* (1.06 mg/L; 6.9 μM), and *H. alvei* (0.73 mg/L; 4.7 μM) isolated from fish products (Özogul, 2004). Some researchers are convinced of the universal prevalence of dopamine in the world of pro- and eukaryotic microorganisms (Vidal-Gadea and Pierce-Shimomura, 2012). Quite high concentrations of norepinephrine were found in *Saccharomyces cerevisiae* and *Penicillium chrysogenum*: 0.21 and 21.1 μM, respectively (Tsavkelova et al., 2000). Norepinephrine and dopamine were mainly present in *B. subtilis* outside the cell wall, not intracellularly. In light of the assumption of the communicative function of neurotransmitters, they may serve as information molecules of a limited range of action, not only in animals, where they transmit information from neuron to neuron, but also in prokaryotes.

It was shown in an *E. coli* model (Shishov et al., 2009) that the maximal (micromolar) catecholamine concentrations accumulate in the lag phase of culture growth, based on which it can be assumed that neurotransmitter amines are a kind of trigger that activate cell growth and division in the initial phase of microbial culture ontogenesis. This is comparable to the effects of other known autoregulatory compounds. *E. coli*, *S. cerevisiae*, *Bacillus cereus*, *Lactobacilli* were also shown to produce DOPA, the precursor of catecholamines in animal cells. Besides, products of the oxidative deamination of catecholamines, DOPACand homovanillic acid, were detected.

Analysis of relevant literature data suggests that the pathways of the metabolism of neurotransmitter amines are universal for prokaryotic and eukaryotic organisms and proceed according to the following scheme:

Tyrosine → DOPA → **Dopamine** → **Norepinephrine**

↘

DOPAC → Homovanillic acid

with the participation of enzymes for the synthesis of catecholamines (hydroxylases and decarboxylases of amino acids) and their degradation such as monoamine oxidases (MAOs). There is evidence of the presence of such MAOs in microorganisms. Thus, *Sarcina lutea* contains MAOs, which are capable of oxidizing dopamine but not histamine or diamines (Yagodina et al., 2000).

The presence of all stages of the pathway of catecholamine synthesis in microorganisms is consistent with the hypothesis that intercellular signaling in vertebrates (including the transmission of impulses through the synaptic cleft between neurons) was the result of horizontal gene transfer from the microbiota (Lyte, 2011).

Analysis of the culture fluid of *E. coli* grown on a synthetic mineral medium revealed that it contains nanomolar concentrations of extracellular serotonin, dopamine, and norepinephrine (Shishov et al., 2009) in the later phases of bacterial growth. These levels are sufficient for the binding of these neurotransmitters to the corresponding receptors of the digestive tract of animals or humans.

It is noteworthy that 3,4-dihydroxyphenylalanine (DOPA), a catecholamine precursor, was detected in micromolar concentrations in *E. coli* culture grown on M-9 medium, both in the cells and the culture fluid. Presumably, DOPA acts as a long-range regulator, and its conversion to dopamine, which stimulates *E. coli* growth (Anuchin et al., 2008), occurs inside a cell that has absorbed DOPA. The reduction of the lag phase

and stimulation of the proliferation of bacterial culture cells under the influence of the cell-free culture supernatant of the exponential growth phase (which has been known for more than a hundred years), along with the other already found autostimulants, can also be due to the action of extracellular DOPA.

Unlike *E. coli*, *S. cerevisiae* accumulated both neurotransmitters (dopamine, norepinephrine, and serotonin) and the products of their metabolism (homovanillic acid, DHFUA) only intracellularly. When grown on the neurotransmitter-rich Sabouraud medium, the concentrations of all these compounds decreased during yeast cultivation, which indicates their active absorption from the medium by *S. cerevisiae* cells (Malikina et al., 2010; Shishov, 2010; Oleskin et al., 2010). Apparently, neurotransmitter amines do not serve as intercellular communication factors in *S. cerevisiae* populations, but they can participate in the regulation of the development of yeast cultures in the case of their synthesis by other ecosystem components, because yeast reacts to exogenous neurotransmitters.

Catecholamines and serotonin are chemically similar to aromatic alcohols (phenylethanol and tryptopol) that function in *S. cerevisiae* as autoregulators that control cytodifferentiation from single cells to branched filaments (pseudomycelium) with a deficiency of nitrogen sources in the culture medium (Chen and Fink, 2006) and may be perceived by yeast cells as their functional analogs. The autoregulator tyrosol, which is structurally similar to the precursor of catecholamines tyrosine, was found in yeast (Chen et al., 2004). It belongs to the family of alkyloxybenzenes, which control the formation of dormant forms in many prokaryotes and yeasts (El-Registan et al., 2006).

The detection of catecholamines in fermented milk products fermented with probiotic bacteria is of great importance. Thus, norepinephrine and dopamine were detected in various yogurt samples at concentrations of 0.1–2 and 1–10 μM, respectively, while the norepinephrine content in the initial raw material (whole milk with a 2.5% fat content) did not exceed 0.09 μM, and dopamine was completely absent. DOPA was contained in yogurts in amounts of 80–250 μM, while its content in milk did not exceed 57 μM (Zhilenkova et al., 2013).

Starter lactobacillus strains (*Lactobacillus helveticus* 100ash, *L. helveticus* NK-1, *L. casei* K3III24, *L. delbrueckii* subsp. *bulgaricus*) differed in their catecholamine productivity: in 1% milk or a medium with pancreatic milk hydrolyzate, dopamine was synthesized only by *L. helveticus* NK-1 and *L. delbrueckii* subsp. *bulgaricus*; all strains except *L. casei* K3III24 enriched both media with norepinephrine. All strains formed DOPA; the maximum concentration (over 5 μM) was achieved with the NK-1 strain (Oleskin et al., 2014a, 2014b). Since DOPA crosses the intestinal and blood-brain barrier (BBB) and is used to treat Parkinson's disease (Dubynin et al., 2010), these results open up prospects for the use of fermented milk products as a source of DOPA. DOPA production was also detected in the unicellular, parasitic protozoan *Toxoplasma gondii*. In the brain tissue of the intermediate host (mouse or rat), Toxoplasma cells convert tyrosine to DOPA, which then converts to dopamine, the concentration of which in the hippocampus and amygdala of the brain increases by about 14%. As a result, the behavior of the rodent becomes more active; moreover, it begins to be attracted by the smell of cat urine. This increases the likelihood of a cat eating a mouse or rat infected with *Toxoplasma*, which allows *Toxoplasma* to enter the body of its final host, the cat (Rohrscheib and Brownlie, 2013).

When it enters the human brain, *T. gondii* causes mental disorders (delusions and hallucinations). In addition to the production of the dopamine precursor, toxoplasma changes the expression of genes associated with the synthesis of dopamine in the host's body; the parasite also affects the expression of genes necessary for the functioning of other neurochemical systems in the brain, which depend on serotonin, glutamic, and γ-aminobutyric acids. The production of antibodies to toxoplasma is increased in individuals with severe mental disorders, including schizophrenia. A hypothesis was put forward about the role *T. gondii* in the onset of schizophrenia (which is characterized by increased concentrations of dopamine in the functional areas of the brain) and, possibly, manic-depressive psychosis (Yolken and Torrey, 2015).

Using the model of microbial-free mice intragastrically inoculated with a mixture of 46 species of Clostridia groups *coccoides* and *leptum* (*Clostridium*-cocktail), it was established that the content of dopamine and norepinephrine in the lumen of the cecum exceeded that before the introduction of these bacteria. Moreover, in the intestines of control mice, 90% of the dopamine and 40–50% of the norepinephrine were in a bound form, while 90% of catecholamines were in a free, active form in clostridia-colonized mice (Asano et al., 2012). Based on these observations, the authors concluded that the gut microbiota plays an important role in the formation of biologically active forms of catecholamines in the intestinal lumen (Asano et al., 2012).

The use of probiotics is of great importance for catecholamine production. It causes changes in the neurochemical processes of the intestine and the microbiome of higher animals.

The widespread class of metalloenzymes allows gut microbes to metabolize catecholamines from the host and the diet. The bacteria *Eggerthella lenta* in the human intestine produces the enzyme Dadh, which can metabolize dopamine. It has implications for the interaction between the gut microbiome and the ner-

vous system and is inextricably linked to human health (Maini Rekdal et al., 2020).

CATECHOLAMINE INTERACTION WITH THE NERVOUS SYSTEM

The catecholamines dopamine and norepinephrine are among the most important neurotransmitters and are, at the same time, hormones (norepinephrine is an adrenal hormone, dopamine is a hypothalamic neurohormone). Epinephrine (adrenaline) is an adrenal hormone but is probably not a neurotransmitter, unlike norepinephrine, which combines the hormonal and neurotransmitter function. The blood levels of catecholamines increase under stress. The functional role of catecholamines in the body is associated with the activation of the sympathetic part of the peripheral nervous system, which prepares the body for the implementation of fight-or-flight responses. This involves accelerating the heart rate, increasing myocardial contractions, and elevating the blood pressure. Catecholamines also have more specific functions. For example, dopamine promotes the dilation of blood vessels (at low concentrations); causes an increase in cardiac output; improves blood flow; stimulates glycogen degradation and the excretion of sodium ions by the kidneys; it also suppresses insulin secretion by the pancreas and intestinal motility (Bronwen and Knights, 2011). Catecholamines are involved in the general regulation of the endocrine system. They are also implicated in cognitive processes, memorization, and emotions (Averina and Danilenko, 2017; Oleskin et al., 2017a).

The activity of dopamine is due to its binding to five subtypes of D-receptors (D1–5), which are coupled with G-proteins. Receptors D1 and D5 activate adenylate cyclase, and receptors D2–4 inhibit it, increasing and decreasing, respectively, the level of intracellular cyclic adenosine monophosphate (cAMP). The recently described additional receptor TAAR1 (trace amine-associated receptor 1) also acts on the activity of intracellular adenylate cyclase (Grandy et al., 2016). D1 receptors prevail, constituting about three quarters of all dopamine receptors in the human body (Dubynin et al., 2010).

As a neurotransmitter of the central nervous system, dopamine is produced by the nerve cells of the brain stem zones, the substantia nigra and the midbrain lining, as well as in various nuclei of the hypothalamus (Dubynin et al., 2010). The release of dopamine by neurons in the ventral part of the tectum leads to their propagation along axons into the nucleus accumbens of the hypothalamus and into the prefrontal cortex (the mesolimbic and mesocortical pathways). In these ways, the dopaminergic system of the brain promotes active wakefulness and the search for interesting activities and pleasures (hedonic behavior). Dopamine is involved not only in the motivation for receiving pleasure but also, along with opioids (through the stimulation of their release), in the very act of enjoying a delicious meal, favorite game, or video (Arias-Carrión, Pöppel, 2007). Already the anticipation of a particular reward leads to an increase in the level of dopamine in the brain, and many drugs stimulate the release of dopamine or block the reuptake of dopamine by the neuron that secreted it. Part of the dopaminergic system of the brain, substantia nigra, is of key importance for motivation and the emotional regulation of maternal behavior (Markov, 2011).

To reiterate, the precursor of dopamine is DOPA, which can cross the barrier between the intestine and the bloodstream and the BBB. This has important implications for the microbiota–gut–brain axis, since DOPA-producing microorganisms, both probiotic (lactobacilli) and potentially pathogenic, including *Bacillus cereus* (Shishov, 2010; Oleskin et al., 2010), can cause a state of euphoria in an individual in contact with them as a result of the conversion of microbial DOPA into dopamine in the brain. Such euphoria will be especially conspicuous in the case of pathogenic DOPA producers, since it will develop against the background of a bacterial infection and a deteriorated general condition. The improving mood of the patient despite the painful symptoms of the disease may seem paradoxical.

Dopaminergic neurons are involved in the maintenance of the level of motor activity and, in addition, allow a person (animal) to perform voluntary movements accurately, suppressing involuntary ones. As the activity of the dopaminergic systems of the brain increases, the activation threshold for the implementation of various forms of motor behavior decreases. The feeling of flexibility and lightness, the joy of relief from fatigue, arises from the activation of dopaminergic synapses and is often associated with the pleasure obtained, for example, from dance and sports exercises.

Dopamine is also needed to shift attention from one stage of cognitive activity to another.

Dopamine deficiency in functionally important areas of the brain (olfactory and visual cortex, frontal cortex, amygdala, thalamus, and hypothalamus, etc.) leads to apathy and a loss of initiative; a more serious deficiency leads to a complete inability to take active action, so that a rat deprived of dopamine drowns in water. Difficulty starting movements (akinesia), increased muscle tone (rigidity), tremors of the limbs (tremors), and obsessive repetitive movements are characteristic of Parkinson's disease, in which most of the neurons in the substantia nigra that form dopamine die. Drugs that increase the dopamine levels in the brain are stimulants of human physical and mental activity. Some of these drugs have also acquired the status of narcotics (e.g., amphetamines, which stimulate the release of dopamine into the synaptic cleft).

The neurotransmitter function of norepinephrine is associated with brain activation, increased levels of

motor activity and aggressiveness (Dubynin et al., 2010). The neurotransmitter and hormonal action of norepinephrine (and only the hormonal action of epinephrine) is due to their binding to metabotropic α- and β-receptors. The α-receptors include the α1 subtype, in which norepinephrine binding activates phospholipase C and increases intracellular concentrations of inositol triphosphate and calcium ions; the α2 subtype functions by inhibiting adenylate cyclase and lowering cAMP levels. B-type receptors (subtypes β1, β2, β3) are associated with G-proteins and, conversely, activate adenylate cyclase upon the binding of norepinephrine.

In the brain, norepinephrine is mainly produced by neurons of the locus coeruleus, the lateral reticular formation, the medulla oblongata, and the nuclei of the solitary tract (Boldyrev et al., 2010); their axons form dense synapses in different parts of the central nervous system, including the cerebellar cortex and cerebral hemispheres (Dubynin et al., 2010). Norepinephrine enhances blood supply to the brain, promotes the wakeful state of the central nervous system (inhibiting sleep centers), increases physical activity, reduces anxiety, increases aggression, and participates in the development of excitement and risk-taking behavior, as well as in the learning process. Norepinephrine is called the rage hormone, since an aggressive response always occurs as a result of the release of norepinephrine into the blood, and muscle strength is significantly increased. Norepinephrine promotes alertness, stimulates information memorization and retrieval, and increases anxiety and anxious behavior. Norepinephrine takes part in implementing fight-or-flight responses, accelerating the heart rate, increasing blood pressure, stimulating the release of stored glucose into the bloodstream, increasing the blood supply to skeletal muscles, and, at the same time, reducing blood flow through the vessels of the gastrointestinal tract, which slows down intestinal motility and suppresses the emptying of the bladder. This affects the conditions for the microbiota colonization of the gastrointestinal tract (e.g., it promotes the adhesion of microbial biofilms to epithelial cells). Norepinephrine dilates the pupils and increases eye hydration with tears.

The action of norepinephrine, as well as its methylated epinephrine derivative, on the heart is associated with its stimulating effect on the β-adrenergic receptors (β-AR) of the heart muscle, which leads to an increase in cardiac output and an acceleration of heart contractions. The hormonal effect of norepinephrine as a stress response factor is complemented by its neurotransmitter effect for brain mobilization brain during stress. The norepinephrine level in the brain, especially in the area of the locus coeruleus, is minimal during sleep (dropping to almost zero during dreaming (REM) sleep) and increases in the waking state (Berridge et al., 2012); additional amounts of norepinephrine are released upon exposure to stress factors, shock, trauma, blood loss, burns, anxiety, fear, or nervous tension; with severe stress, the analgesic (analgesic) effect of norepinephrine becomes essential (Dubynin et al., 2010).

CATECHOLAMINE INTERACTION WITH THE IMMUNE SYSTEM

Immunocytes react to biogenic amines and, at the same time, synthesize and secrete these compounds. Of the catecholamine receptors, the immune cells express β2-AR to the greatest extent. The response of macrophages and monocytes to β2-AR stimulation is mainly anti-inflammatory. The dendritic cells responsible for antigen presentation express both α-AR and β-AR. In this case, α-AR are primarily considered to be receptors associated with the stimulation of the immune response, while interaction with β-AR is accompanied by inhibition of the activity of the immune system.

The exposure of dendritic cells in the presence of norepinephrine after stimulation by agonists of Toll-like receptors results in a decrease in the secretion of IL-12, IL-6, TNF-α, and IL-23, an increase in the secretion of IL-10 and, as a consequence, in potential immunosuppression and impaired Th1 priming. Norepinephrine may contribute to the stress-induced progression of Th2-associated diseases (e.g., various allergic pathologies). The use of β2-AR agonists, conversely, may be successful in the treatment of predominantly Th1-mediated diseases (e.g., multiple sclerosis, type-1 diabetes) (Cosentino and Marino, 2012). Catecholamines (including norepinephrine, epinephrine, and dopamine) can also be synthesized by various immune cells. The synthesis and metabolism of these compounds in the immune system is similar to those in the cells of the neurohumoral system. Both cells express tyrosine hydroxylase, as well as enzymes for the degradation of catecholamines, MAO and catechol-*O*-methyltransferase (Jiang et al., 2006; Cosentino et al., 2013).

It is assumed that the secretion of norepinephrine in immunocytes, similar to chromaffine adrenal cells, is acetylcholine- and calcium-dependent (Jiang et al., 2006). Dopamine receptors are expressed on the surface of all cells of the immune system (including T and B lymphocytes, dendritic cells, macrophages, neutrophils, natural killer (NK) cells, and T regulatory cells) (Cosentino et al., 2013). Autoimmune T cells and leukemic and lymphoma T cells also express dopamine receptors. Dopamine plays an important autocrine and paracrine role at fairly low concentrations (~10^{-8} M) (Levite, 2016). The anti-inflammatory effect of dopamine is manifested in the suppression of macrophage functions. Thus, in a model of murine peritoneal macrophages, it was found that dopamine inhibits the synthesis of the inflammation activator IL-12p40 in response to the bacterial LPS antigen and enhances the production of the inflammation inhibitor IL-10

(Orlova et al., 2012). Dopamine is also involved in the suppression of activated T cells (Cosentino et al., 2013).

There is a significant amount of published data indicating the immunostimulatory effects of dopamine. Thus, dopamine is able to activate resting/naive T cells. In naive T-lymphocytes, dopamine stimulated adhesion to fibronectin through D2/D3 receptors. In addition, by interacting with the D2/D3 and D1/D5 receptors of these lymphocytes, dopamine could stimulate the secretion of TNF-α and IL-10 (Cosentino et al., 2013). The activation of resting T-cells by dopamine is effectuated both by direct action on them and by inhibition of the activity of T-regulatory cells (T_{reg}). T_{reg} β cells play an important role in immunosuppression. They have dopamine receptors, and it is through them that this catecholamine is involved in the autocrine and paracrine regulation of T_{reg}.

The dopamine-induced stimulation of D1 receptors in human T regulatory cells ($CD4^+CD25^{+\ high}$) suppresses their immunosuppressive activity, and the production of IL-10 and TGF-β decreases (Orlova et al., 2012). As a suppressor of immunosuppression, dopamine is able to exert an activating effect on the immune response. This is also confirmed by the fact that dopamine inhibits the functions of the second most important cellular component of immunosuppression, myeloid derived suppressor cells (MDSCs). Studies have shown that dopamine, acting on the D1 receptors of MDSCs, largely neutralizes their suppressive activity in relation to the proliferation and secretion of T cells, enhancing, in particular, antitumor immunity. This effect of dopamine has also been linked to its anti-inflammatory properties (Levite, 2016). It is known that dopamine is a happiness mediator. The immunomodulatory properties of dopamine may partly account for its beneficial effect on a human individual's emotional state.

CONCLUSIONS

Gut bacteria contain enzymes that metabolize neurotransmitters. This is essential for the interaction between the gut microbiome and the human nervous and immune systems. Neurotransmitters are capable of acting as food substrates, effectors, and cofactors, which is most important in the context of their effect on the microbial consortium and on the host organism. They are a major type of metabiotics that represents the structural components of microorganisms, their metabolites, and signaling molecules with a specific chemical structure that can affect the host's organism and its microecological, nervous, and immune systems. This has important implications for present-day medicine, psychology, and biotechnology.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests. The authors declare that they have no conflicts of interest.

Statement on the welfare of humans or animals. This article does not contain any studies involving animals performed by any of the authors.

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