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“Dialogue” between the Human Microbiome and the Brain

Natalia Beloborodova and Andrey Grechko

Abstract

In conditions of severe gut dysbiosis, there is a risk of developing diseases of the host organism in general and of the brain in particular, as evidenced by a growing number of studies. This chapter focuses on several groups of low-molecular-weight compounds that originate primarily from the gut microbiota. It discusses the results of experimental and clinical studies on the effect of microbial metabolites (such as short-chain fatty acids, phenolic metabolites of tyrosine, indolic metabolites of tryptophan, trimethylamines) on the brain. Several studies have proven that the microbial metabolite profiles in the gut and serum are interlinked and reflect a disruption of the gut microbial community. Using 16S ribosomal RNA gene sequencing, it was found that the gut microbiota of patients with positive or negative dynamics of neurological status differ taxonomically. The chapter also presents data obtained from animal germ-free (GF) models. Many researchers would like to consider the gut microbiota as a new therapeutic target, including for the treatment of brain diseases, stroke prevention, reduction of neuroinflammation, and more successful neurorehabilitation of patients.

Keywords: human microbiome, microbial metabolites, brain damage, gut microbiota dysbiosis, mental health, Alzheimer’s disease, autism, stroke, critical ill patients, neurorehabilitation

1. Introduction

The human gut microbiome is a community of trillions of microorganisms that produce and use many molecules of microbial origin. Normally, the epithelial–immune–gut barrier supports homeostasis in the host body. The importance of the function of the gut microbiota for the host organism allows us to consider it as a large but “invisible organ” [1]. In conditions of severe gut dysbiosis, there is a risk of developing diseases of the host organism in general and of the brain in particular, as evidenced by a growing number of studies [2, 3]. The relevance of studying the relationship between the human microbiome and the brain is confirmed by a 20-fold increase in the number of publications on this topic in the PubMed database over the past 10 years (**Figure 1**).

Today, modern technologies allow us to identify hundreds of types of microorganisms in the human gut. Various microbial metabolites are also available for measurement in biological material samples, including feces, blood, urine, cerebrospinal fluid (CSF), and so on [1–3]. Thus, the possibilities of determining microbiota metabolites have expanded to studying their role both in healthy people and in patients with various diseases.

Figure 1.

Graph showing a 20-fold increase from 2010 to 2019 in the number of publications on the relationship between the human microbiome and the brain, according to PubMed. Keyword search results: microbiome and brain, microbiome and behaviour.

The results of numerous studies show that the gut microbiota affects the development of diseases of the central nervous system (CNS), including motor and behavioral disorders, neurodegenerative diseases, and cardiovascular and neuroimmune-mediated disorders [4–6]. The existence of the microbiome–gut–brain axis is now generally recognized. There are several different mechanisms of gut bacteria action on the nervous system, including changes in the activity of the stress-related hypothalamic–pituitary–adrenal axis, vagus nerve stimulation, and the secretion of short-chain fatty acids (SCFAs), which can activate microglial cells and affect the permeability of the blood–brain barrier. Evolutionarily conserved signals that are involved in the communication between microbiota and the host, which include different neuroactive substances, are known as neurochemicals [7].

This chapter focuses on several groups of low-molecular-weight compounds that originate primarily from the gut microbiota; their involvement in the interaction of the microbiota and the brain has been studied in various experimental and clinical studies.

2. Some molecules involved in the “dialogue”

2.1 Short-chain fatty acids

SCFAs as byproducts of microbiota fermentations are widely studied. It is proven that microbial SCFAs (acetate, propionate, butyrate) are involved in the energy metabolism of the host [8, 9]. Attempts to cope with metabolic disorders in several diseases, including those of the brain, with the help of diets were unsuccessful. One study found different amounts of SCFAs were produced in the guts of subjects following the same diet (in terms of the amount and composition of fiber), since initially different gut microbiota can trigger different fermentation pathways of indigestible carbohydrates [6].

In their review, Dalile et al. [10] describe the effects of SCFAs on cellular systems and their interaction with gut–brain signaling pathways through immune, endocrine, neural, and humoral mechanisms. The researchers concluded that SCFAs can

penetrate the blood–brain barrier (BBB) to directly interact with brain tissues and even contribute to strengthening the integrity of the BBB. In addition, SCFAs promote serotonin biosynthesis and affect the levels of certain neurotrophic proteins, in particular, brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) [10]. SCFAs also interfere with pathological mechanisms that are important for Alzheimer’s disease. Thus, SCFAs are able to inhibit the formation of soluble beta-amyloid (A β) aggregates, which are associated with synaptic dysfunction and neurotoxicity. Another study examined the formation of neurotoxic amyloid aggregates (in vitro) and the dose-dependent effects of individual SCFAs on this process [11]. The authors call for the development of a new generation of probiotics that can metabolize individual dietary fibers to form valerian, butyric, and propionic acids and thus reduce the risk of developing neurodegenerative disorders. Unfortunately, animal and in vitro studies using pure fatty acid substances have several limitations. The source of SCFAs in vivo is the gut microbiota, and it remains unclear whether physiologically significant concentrations of SCFAs can be created in the human brain [10].

2.2 Metabolites of aromatic amino acids

Tyrosine and tryptophan are two of the nine essential amino acids that cannot be synthesized in the human body. Various metabolic pathways of metabolism of aromatic amino acids, such as tyrosine and tryptophan, with different endogenous and microbial enzymes, have been previously described [1]. Most often, the products of microbial protein biodegradation are associated with negative or toxic effects [2, 12]. At the same time, results of various studies suggest that the products of anaerobic bacteria from a healthy human gut (metabolites of some *Clostridium* species, *Bacteroids*, *Bifidobacterium*, etc.) can be useful [8, 11–13], including for brain function, which we discuss later in the chapter.

2.2.1 Phenolic metabolites of tyrosine

Phenylcarboxylic acids (PhCAs) are metabolites of tyrosine that circulate in the blood of a healthy human in a constantly low concentration, normally not exceeding 5 μ M [12]. Their microbial origin has been proven [12, 13], as have the causes of a significant increase in the number of certain PhCAs, such as *p*-HPhLA, PhLA, and *p*-HPhAA, in the blood serum of patients with sepsis and sepsis-associated encephalopathy [2]. Serum and fecal profiles of these aromatic microbial metabolites reflect gut microbiota disruption in critically ill patients, including those with brain pathology. It has been shown that the aromatic microbial metabolite profiles in the gut and serum are interlinked and reflect a disruption of the gut microbial community [14].

The taxonomic composition of microbiota and the profile of microbial metabolites of PhCAs were studied in critically ill patients with severe brain damage in comparison with other groups of patients, including healthy individuals. Using the 16S-ribosomal RNA (16S-*r*RNA) gene sequencing method, it was found that patients with positive dynamics were more characterized by a shift in the balance of the gut microbiota towards the predominance of *Clostridium* taxa [14]. The Glasgow Coma Scale (GCS), the National Institutes of Health Stroke Scale (NIHSS), the Rivermead Mobility Index Scale, and the Rankin scale were used to assess neurological status over time, while the monitoring of serum PhCAs levels was performed by gas chromatography–mass spectrometry (GC–MS). Results showed that the positive dynamics of neurological status in patients with brain damage was associated with serum level of phenylpropionic acid (PhPA) [15]. Based on studies that have established that PhPA is the end product of tyrosine metabolism by *Clostridia sporogenes*

[16, 17], we believe that special attention should be paid to further confirmation of the involvement of *C. sporogenes* and studying the pathophysiological role of its metabolites in the process of neurorehabilitation.

2.2.2 Indolic metabolites of tryptophan

The essential amino acid tryptophan is the only amino acid that contains the structure of an indole-bicyclic compound consisting of a six-membered benzene ring connected to a five-membered N-containing pyrrole ring, according to the Human Metabolome Database. Tryptophan is absorbed in the small intestine and metabolized to kynurenine, serotonin, and melatonin via the host's endogenous pathways. Manipulating heavily depleted tryptophan by way of diet has helped to identify patients who are prone to depression or other mood-lowering symptoms associated with dysfunctional monoaminergic systems, which can be attributed to serotonin deficiency [18]. The part of tryptophan that reaches the colon can be catabolized by the gut bacteria resulting in a variety of indole derivatives, such as indole, tryptamine, indoleethanol, indolepropionic acid (IPA), indolelactic acid (ILA), indoleacetic acid (IAA), skatole, indolealdehyde (IAld), and indoleacrylic acid [18, 19]. It is known that some products of bacterial biodegradation of tryptophan can be toxic, for example, indole, as well as indoxyl sulfate (IS), which is produced in the liver from indole and has a cytotoxic effect in high concentrations [19]. However, research shows that microbial tryptophan metabolites may also have a positive impact on host physiology. Tryptophan metabolites can modulate both the function of intestinal immune cells and astrocytes in the CNS via the aryl hydrocarbon receptor (AHR) [19, 20]. In experimental autoimmune encephalomyelitis, the effect of limiting inflammation of the CNS by affecting astrocytes in mice treated with antibiotics was shown by adding microbial metabolites of tryptophan from the gut microbiota (indole, indoxyl-3-sulfate, IPA, IAld) or the bacterial enzyme tryptophanase as AHR agonists [20].

Several studies have noted that IPA and IAA have anti-oxidative and anti-inflammatory effects. A comparison of the varying data on the blood concentrations of IPA and IAA in patients with different diseases suggests that levels of both indole metabolites (IPA and IAA) are reduced in cancer [21]. Unfortunately, no studies to date have analyzed the behavior of these metabolites in patients with brain tumors, which could be extremely interesting.

There is information about the bacteria of the gut microbiota that is associated with the production of specific metabolites of indole. Interestingly, many species of anaerobes from different families are able to carry out biotransformation of tryptophan in vitro with the formation of IAA (nine species of *Clostridium*, four of *Bacteroides*, three of *Bifidobacterium*, and one of *Peptostreptococcus*). However, the ability to produce IPA was found only in three species of *Clostridiaceae*, and one of *Peptostreptococcus* [16, 21]. At the same time, the results obtained in vivo are more modest. In an experimental study of germ-free (GF) mice, production of IPA was completely dependent on gut colonization only by *C. sporogenes* [22].

The severity of stroke outcome in patients is associated with a stroke-induced inflammatory response, which in turn is linked with an increase in tryptophan catabolism [23, 24]. In Parkinson disease (PD) patients, CSF levels of tryptophan and kynurenic acid have been found to be significantly lower compared to healthy controls [25]. Future investigations are required to decipher how tryptophan metabolites derived from microbes are linked to inflammation in brain disorders [5]. The search and modification of methods for accurate measurement of microbial tryptophan metabolites continues. The availability of methods for determining

concentrations of microbial tryptophan metabolites in serum and CSF is currently limited and better quantitative analytical methods targeting a larger variety of microbial tryptophan metabolites are needed [26].

2.3 Trimethylamines

The formation of trimethylamine (TMA) occurs in the intestine via biotransformation of dietary lecithin, choline, or L-carnitine found in certain animal products (red meat, egg yolks) and is associated with bacteria of the genera *Anaerococcus*, *Clostridium*, *Escherichia*, *Proteus*, *Providencia*, and *Edwardsiella*. It is known that TMA is absorbed into the blood and oxidized in the liver by the flavin monooxygenase enzyme to form trimethylamine N-oxide (TMAO) [27]. TMAO is found in CSF, indicating its ability to penetrate the blood–brain barrier [28].

The role of TMAO in neurodegenerative diseases, including AD, has been investigated extensively in the last five years. A study by Xu et al. [29] analyzed 20 metabolites that are significantly associated with cognitive decline in patients with AD. Potential genetic pathways underlying the strong association between TMAO and AD have been investigated. Employing an integrated computational approach, researchers identified nine main pathways and found that AD is closely related to TMAO. Thus, common genetic pathways underlying known biomarkers of AD were identified, with TMAO identified as the top-ranked microbial metabolite [29].

Researchers studied TMAO as a biomarker of AD by comparing three groups of patients: those with AD clinical syndrome, those with mild cognitive impairment (MCI), and cognitively unimpaired individuals. All patient groups had undergone lumbar puncture with CSF collection (n = 410), as well as TMAO and other biomarkers of AD quantification. Metabolites of microbiota TMAO were significantly elevated in CSF and associated with other biomarkers of AD pathology (phosphorylated tau and phosphorylated tau/A β 42) and neuronal degeneration (total tau and neurofilament light chain protein), which confirms gut microbial involvement in AD [30].

2.4 Neurotransmitters

The gut microbiota can produce and/or consume numerous neurotransmitters, including dopamine, norepinephrine, serotonin, or gamma-aminobutyric acid (GABA) [4, 31]. Microbiota-dependent effects on gut serotonin significantly impact host physiology. For example, it is known that the gut contains the bulk of the body's serotonin (more than 85 percent 5-hydroxytryptamine (5-HT)), but the mechanisms that control the metabolism of 5-HT obtained from the gut are still unclear. A mammalian experiment showed that indigenous spore-forming bacteria from mouse and human microbiota promote 5-HT biosynthesis from colonic enterochromaffin cells, which supply 5-HT to the mucosa, lumen, and circulating platelets [32].

3. Special experimental models

Disorders of the gut microbiome have been experimentally documented in some brain diseases and stroke. In animal models of AD, PD, and acute stroke, dysbiosis, intestinal motility disorders, and/or increased intestinal permeability were demonstrated. A pro-inflammatory immune response and increased microglia reactivity were recorded, compared with a non-diseased condition. Special experimental

models of non-microbial or GF animals were used to determine the influence of microbiota on the mechanisms of stroke development [33].

From these gnotobiotic animals, it is possible to decipher mechanisms of communication between specific members of the microbiota and the host organism. Animals lacking microbiota have extraordinarily different development and physiology than animals hosting commensal bacteria. GF animals have impaired immune systems, dysregulated hormone signaling, altered metabolism, and differences in neurotransmission from their conventional counterparts [34, 35].

GF mice show an underdeveloped microglia phenotype, which is manifested by an incomplete immune response to damage. In an experimental stroke model, GF mice showed an incomplete response to brain damage; there was no delineation of the damage locus, which was manifested by an increase in the volume of damage compared to normal animals. Thus it was determined that the microglia of GF animals is morphologically immature [36].

The most common form of dementia is AD, a neurodegenerative disorder associated with impaired cognitive function. This pathology is characterized by extracellular beta-amyloid (A β) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein [37].

When studying the connection of microbiota with the brain, one of the tasks is to find evidence of bacterial participation in AD pathogenesis through the formation of amyloid. The results of an experimental model of AD on transgenic mice revealed a tendency to the expression of amyloid precursor protein- β (APP). When these mice were kept in non-microbial conditions, cerebral β -amyloid plaques were less developed than in a normal environment [38]. This experiment indicates that the microbiota is involved in triggering adverse changes in the brains of transgenic animals, but undoubtedly this depends on the species composition and metabolic activity of the bacteria. For example, in AD participants, the gut microbiome has a reduced microbial diversity and taxonomically differs from the control age and sex correspondences of individuals, in particular, in AD compared to the control the number of *Firmicutes* and *Bifidobacterium* was reduced, but the number of *Bacteroidetes* was increased. The potential amyloidogenic properties of gut bacteria were evaluated and the composition of the microbiota and the aggregation of cerebral amyloid- β were also influenced by nutrients [11, 39, 40].

Several studies have reported that the microbiome of young mice differs significantly from that of older mice, in particular in the ratio of *Firmicutes* to *Bacteroidetes*. The benefits of the microbiota of young mice were demonstrated in an experiment on stroke models, in which transplantation of the gut microbiota from young to old mice contributed to an improvement in the outcome of stroke [41].

There are some limitations in experiments with GF animals because animals with a diverse microbiota have more developed intestinal epithelium than GF animals, which affects the functioning of the body as a whole. Studying the participation of microbiota in the functioning of the brain may be not always correct in case of comparison of the results obtained in GF and normal animals. The new approach avoids these difficulties by using special mice with a modified microbiota, called the altered Schaedler flora (ASF) mouse line, because they are colonized by only eight species of known bacteria [42].

The majority of research showing that microbiota can influence the nervous system has been performed in animals. As such, there is a strong need for well-designed human cohorts. Neuroactive compounds of microbial origin can directly modulate not only neuronal function and plasticity but also human behavior also [5].

4. Microbiome and human mental health

The metabolism of tryptophan via the kynurenine pathway leads to the formation of kynurenine and its neuroactive metabolites, such as 3-hydroxykynurenine, kynurenic acid, quinolic acid, and xanthurenic acid. The involvement of kynurenine and its metabolites in the pathogenesis of depressive disorders and schizophrenia is being studied [43]. For example, in patients with schizophrenia, an increased concentration of 3-hydroxykynurenine in the blood was measured. It is important to note that after targeted treatment, the level of this metabolite was normalized. This fact indirectly confirms the initial violation of tryptophan metabolism along the kynurenine pathway in schizophrenia [44].

According to the 2016 report, "The Five Year Forward View for Mental Health," from the independent Mental Health Taskforce to the NHS in England, mental disorders in the modern world affect every fourth person on the planet [45], which is a serious justification for the search for new mechanisms of the influence on mental status, including by studying and correcting the microbiome.

A clinical study examined how the gut microbiota and its associated metabolites were changed in sleep disorders in children with autism spectrum disorders (ASD). There was a decrease in the abundance of *Faecalibacterium* and *Agatobacterium*, a decrease in 3-hydroxybutyric acid and melatonin, and an increase in serotonin levels. These changes can worsen sleep problems and major symptoms in children with ASD [46].

Some studies have reported interesting correlations between severity of behavioral and gastrointestinal symptoms; others have demonstrated potential benefits of probiotics in correcting dysbiosis and reducing the severity of ASD symptoms. The general conclusion of these studies is that future research based on more randomized controlled studies with larger population sizes and standardized use of strains, concentration of probiotics, duration of treatments, and methods of DNA extraction is needed in this area, which may lead to more robust results [47].

According to the World Health Organization, mental disorders are quite common even in people who lead a seemingly normal lifestyle [48]. At the same time, new evidence suggests that less than 10 percent of mental and neurodegenerative diseases have a strict genetic etiology. Other predisposing and concomitant factors, such as stress, environmental exposures to potentially toxic elements, and other factors may influence neurometabolism, which may increase the risk for depression, autism, sclerosis, PD, and AD [49, 50]. Among these factors, an important place is occupied by the gut-brain microbiome relationship at the level of metabolomic connections, which allow us to conceptually rethink the causes and mechanisms of mental health disorders. Possibly in some categories of people with predisposition, the metabolic activity of the gut microbiome may affect not only the development, but also the severity of depressive disorder [51].

5. Microbiome and inflammatory events after stroke

The gut inflammatory and immune response can play a key role in the pathophysiology of severe course and development of complications after stroke. This can be judged by studying the mechanisms that occur in the brain when damaged. Proinflammatory T cells are often associated with increased inflammatory damage, but research of the gut inflammatory and immune response after stroke is still in its initial stage [52]. It would be crucial to understand which metabolites from the gut

microbiome may affect the degree of brain damage, stroke outcome, and concomitant post-stroke diseases.

An experimental stroke model of GF mice clearly demonstrated the role of microbiota. When the mice were recolonized using a dysbiotic post-stroke microbiota, an increase in the volume of brain damage and functional deficit was observed [53]. In another experimental study, after the use of a cocktail of antibiotics in animals, a significant decrease in the volume of the heart attack in the acute phase of stroke was observed. The neuroprotective effect was varied depending on the type of antibiotic and correlated with the specific microbial population, rather than with the overall bacterial density. In particular, a link was found between the large and small size of a brain infarction and the enzymatic pathway of the aromatic metabolism in certain strains of *Bacteroidetes* [54].

In clinical pilot research, which included patients with severity of neurologic deficit, the taxonomic composition of the gut microbiota using real-time polymerase chain reaction (PCR) was studied. Correlation analysis revealed some connection between microbiology and clinical and laboratory indicators, for example, strong negative correlations between Glasgow coma scale scores and the abundance of *Enterococcus* spp. ($r = -0.77$, $p < 0.05$). It is interesting that statistically significant negative correlations between cortisol levels and the abundance of *B. thetaiotaomicron* or *F. prausnitzii* ($r = -0.57$, $r = -0.62$, respectively) were detected only in patients in a vegetative state [55].

Many authors report dysbiosis in stroke patients [56–58]. Some authors associate the dominance of SCFA producers, such as *Akkermansia*, *Odoribacter*, *Ruminococcaceae*, and *Victivallis*, with positive clinical outcomes, while the genus *Enterobacter* had significantly negative correlation with the dynamics of neurological status [56]. At the same time, in another study, *Akkermansia* was reduced in patients with cerebral infarction compared with a group of healthy people ($p < 0.05$) [57].

Pluta et al. [58] presented taxonomic findings in stroke patients. The authors launched an active discussion and tried to find explanations for the metabolic features of various genera and types of microbes, which, according to various data, dominated in the gut of stroke patients. For example, *A. muciniphila* uses mucin to produce acetate, which can be used by other bacteria, such as bacteria from the *Ruminococcaceae* and *Odoribacter* families, to produce butyrate [59]. However, despite many studies in this direction, significant differences and even sometimes contradictions of taxonomic findings lead us to conclude that the available information is not enough to form a coherent hypothesis.

It should be noted that the data on the taxonomic composition of the gut microbiota in most studies were obtained by examining samples from patients in the early stages (first and second day) after a stroke. The study of the composition of the gut microbiota in patients with a complicated course after stroke is even more relevant. These patients need intensive care for a long time due to the development of so-called chronic critical illness (CCI) [60]. Loss of microbial diversity and pathogen domination of the gut microbiota has been noted in such patients [61]. Significant differences were found for four genera: *Prevotella*, *Klebsiella*, *Streptococcus*, and *Clostridium* XI [62], which were previously mentioned in connection with some neuropsychiatric disorders [63, 64].

The interrelation of factors influencing the development of a CCI as a result of long-term violation of the functions of the brain and the gut microbiota has been studied [15]. The results confirm the association of taxonomic composition and profile of certain aromatic metabolites of the gut microbiota with the progression or reversibility of neurological disorders in CCI patients. A gross imbalance of microbial metabolism contributes to the formation of general metabolic dysfunction of the human body (**Figure 2**).

Figure 2.
Post-stroke complications and mechanisms of chronic critical illness are closely related to taxonomy disorders and metabolic dysfunction in the gut microbiota.

It is important to remember that microbial diversity and composition of the microbiota can be influenced by many personal and environmental factors (diet, infection, concomitant diseases, use of antibiotics and other medications, social stress, etc.), which can significantly affect the microbiota–gut–brain axis at all stages of life [65]. This fact should be considered in the future when developing methods to correct the dysfunction of the microbiota.

6. Conclusion

Due to growing interest in the human microbiome and rapid development of diagnostic technologies, the taxonomy of the gut microbiota in various diseases and disorders of the brain is quickly accumulating. Most researchers are coming to a common understanding of the importance of the communication between the human microbiome and the brain and are investigating binding small molecules as biomarkers and pathophysiological effects. Soon, the significance of particular microbial metabolites in the human metabolome will be evaluated in more detail. Figuratively speaking, this will allow us to master the “language” of the “dialogue” between the microbiome and the brain. Already, many researchers would like to consider the gut microbiota as a new therapeutic target, including for the treatment of brain diseases, stroke prevention, reduction of neuroinflammation and more successful neurorehabilitation of patients.

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References

- [1] Beloborodova N.V., Grechko A.V., Olenin A.V. Metabolomic Discovery of Microbiota Dysfunction as the Cause of Pathology, Metabolomics - New Insights into Biology and Medicine, Wael N. Hozzein, Published: July 1st 2020 IntechOpen, DOI: 10.5772/intechopen.87176.
- [2] Beloborodova N.V., Olenin A.Yu., Pautova A.K. Metabolomic findings in sepsis as a damage of host-microbial metabolism integration. // JOURNAL OF CRITICAL CARE, 2018, 43, 246-255, <https://doi.org/10.1016/j.jcrc.2017.09.014>
- [3] Benakis C, Martin-Gallausiaux C, Trezzi JP, Melton P, Liesz A, Wilmes P. The microbiome-gut-brain axis in acute and chronic brain diseases. Curr Opin Neurobiol. 2020;61:1-9. doi:10.1016/j.conb.2019.11.009
- [4] Vogt NM, Kerby RL, Dill-McFarland KA, Harding SJ, Merluzzi AP, Johnson SC, Carlsson CM, Asthana S, Zetterberg H, Blennow K, Bendlin BB, Rey FE. Gut microbiome alterations in Alzheimer's disease. Sci Rep. 2017 Oct 19;7(1):13537. doi: 10.1038/s41598-017-13601-y. PMID: 29051531; PMCID: PMC5648830
- [5] Strandwitz P. Neurotransmitter modulation by the gut microbiota. Brain Res. 2018 August 15; 1693(Pt B): 128-133. doi:10.1016/j.brainres.2018.03.015
- [6] Cani PD, Van Hul M, Lefort C, Depommier C, Rastelli M, Everard A. Microbial regulation of organismal energy homeostasis. Nat Metab. 2019;1(1):34-46. doi:10.1038/s42255-018-0017-4
- [7] Oleskin AV, Shenderov BA. Probiotics and Psychobiotics: the Role of Microbial Neurochemicals. Probiotics Antimicrob Proteins. 2019 Dec;11(4):1071-1085. doi: 10.1007/s12602-019-09583-0. PMID: 31493127 Review.
- [8] Oleskin AV, Shenderov BA. Neuromodulatory effects and targets of the SCFAs and gasotransmitters produced by the human symbiotic microbiota. Microb Ecol Health Dis. 2016;27:30971. Published 2016 Jul 5. doi:10.3402/mehd.v27.30971
- [9] Schonfeld P., Wojtczak, L. Short- and medium-chain fatty acids in energy metabolism: the cellular perspective. J. Lipid Res. , 2016, 57, 943-954.
- [10] Dalile B, Van Oudenhove L, Vervliet B, Verbeke K. The role of short-chain fatty acids in microbiota-gut-brain communication. Nat Rev Gastroenterol Hepatol. 2019;16(8):461-478. doi:10.1038/s41575-019-0157-3
- [11] Ho L, Ono K, Tsuji M., Mazzola P., Singh,R., Pasinetti G. M. Protective roles of intestinal microbiota derived short chain fatty acids in Alzheimer's disease-type beta-amyloid neuropathological mechanisms. Expert Rev. Neurother. 2018, 18, 83-90. doi: 10.1080/14737175.2018.1400909
- [12] Beloborodova NV, Khodakova AS, Bairamov IT, Olenin AY. Microbial origin of phenylcarboxylic acids in the human body. Biochemistry (Mosc). 2009 Dec;74(12):1350-1355. doi: 10.1134/s0006297909120086. PMID: 19961416.
- [13] Dodd D, Spitzer MH, Van Treuren W, et al. A gut bacterial pathway metabolizes aromatic amino acids into nine circulating metabolites. Nature. 2017;551(7682):648-652. doi:10.1038/nature24661
- [14] Chernevskaya E, Beloborodova N, Klimenko N. et al. Serum and fecal profiles of aromatic microbial metabolites reflect gut microbiota disruption in critically ill patients: a prospective observational pilot study. Crit Care 24, 312 (2020). <https://doi.org/10.1186/s13054-020-03031-0>

- [15] Chernevskaya E, Klimenko N, Pautova, A, Buyakova I, Tyakht A, Beloborodova N. Host-Microbiome Interactions Mediated by Phenolic Metabolites in Chronically Critically Ill Patients. *Metabolites* 2021, 11, 122. <https://doi.org/10.3390/metabo11020122>
- [16] Elsdén S R, Hilton M G, Waller J M. The end products of the metabolism of aromatic amino acids by clostridia. *Arch. Microbiol.*,1976, 107, 283-288
- [17] Beloborodova NV, Bairamov IT, Olenin AY, Khabib ON, Fedotcheva NI. Anaerobic Microorganisms from Human Microbiota Produce Species-Specific Exometabolites Important in Health and Disease. 2014. *Global Journal of Pathology and Microbiology*. Vol. 2. № 1. 43-53
- [18] Palego L, Betti L, Rossi A, Giannaccini G. Tryptophan biochemistry: structural, nutritional, metabolic, and medical aspects in humans. *J Amino Acids*. 2016;2016:8952520. doi: 10.1155/2016/8952520.
- [19] Roager HM, Licht TR: Microbial tryptophan catabolites in health and disease. *Nat Commun* 2018, 9:1-10 [http://refhub.elsevier.com/S0959-4388\(19\)30108-4/sbref0275](http://refhub.elsevier.com/S0959-4388(19)30108-4/sbref0275)
- [20] Rothhammer V, Mascanfroni ID, Bunse L, Takenaka MC, Kenison JE, Mayo L, Chao CC, Patel B, Yan R, Blain M, Alvarez JI, Kébir H, Anandasabapathy N, Izquierdo G, Jung S, Obholzer N, Pochet N, Clish CB, Prinz M, Prat A, Antel J, Quintana FJ. Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor. *Nat Med*. 2016 Jun;22(6):586-597. doi: 10.1038/nm.4106.
- [21] Beloborodova NV, Chernevskaya EA, Getsina ML. Indolic Structure Metabolites as Potential Biomarkers of Non-infectious Diseases. *Curr Pharm Des*. 2021;27(2):238-249. doi: 10.2174/1381612826666201022121653.
- [22] Wikoff WR, Anfora AT, Liu J, Schultz PG, Lesley SA, Peters EC et al. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. *PNAS* 2009 March 10;106(10): 3698-3703 DOI:10.1073/pnas.0812874106
- [23] Brouns R, Verkerk R, Aerts T, De Surgeloose D, Wauters A, Scharpe' S, De Deyn PP: The role of tryptophan catabolism along the kynurenine pathway in acute ischemic stroke. *Neurochem Res* 2010, 35:1315-1322. [http://refhub.elsevier.com/S0959-4388\(19\)30108-4/sbref0280](http://refhub.elsevier.com/S0959-4388(19)30108-4/sbref0280)
- [24] Ormstad H, Verkerk R, Aass HCD, Amthor K-F, Sandvik L: Inflammation-induced catabolism of tryptophan and tyrosine in acute ischemic stroke. *J Mol Neurosci* 2013, 51:893-902. [http://refhub.elsevier.com/S0959-4388\(19\)30108-4/sbref0285](http://refhub.elsevier.com/S0959-4388(19)30108-4/sbref0285)
- [25] Szabo N, Kincses ZT, Toldi J, Vécsei L: Altered tryptophan metabolism in Parkinson's disease: a possible novel therapeutic approach. *J Neurol Sci* 2011, 310:256-260. [http://refhub.elsevier.com/S0959-4388\(19\)30108-4/sbref0290](http://refhub.elsevier.com/S0959-4388(19)30108-4/sbref0290)
- [26] Pautova A, Khesina Z, Getsina M, Sobolev P, Revelsky A, Beloborodova N. Determination of tryptophan metabolites in serum and cerebrospinal fluid samples using microextraction by packed sorbent, silylation and GC-MS detection // *Molecules*, 2020, 25 (14), #3258 <https://doi.org/10.3390/molecules25143258>
- [27] Romano KA, Vivas EI, Amador-Noguez D, Rey FE. Intestinal microbiota composition modulates choline bioavailability from diet and accumulation of the proatherogenic metabolite trimethylamine-N-oxide. *MBio*. 2015;6:e02481. doi:10.1128/mBio.02481-14.

- [28] Del Rio D, Zimetti F, Caffarra P, Tassotti M, Bernini F, Brighenti F, et al. The gut microbial metabolite trimethylamine-N-oxide is present in human cerebrospinal fluid. *Nutrients*. 2017;9:1-7. <https://doi.org/10.3390/nu9101053>.
- [29] Xu R, Wang Q. Towards understanding brain-gut-microbiome connections in Alzheimer's disease. *BMC Syst Biol*. 2016;10(Suppl 3):63. doi: 10.1186/s12918-016-0307-y
- [30] Vogt NM, Romano KA, Darst BF et al. The gut microbiota-derived metabolite trimethylamine N-oxide is elevated in Alzheimer's disease. *Alz Res Therapy* 10, 124 (2018). <https://doi.org/10.1186/s13195-018-0451-2>
- [31] Jameson KG, Hsiao EY. Linking the Gut Microbiota to a Brain Neuro-transmitter. *Trends Neurosci*. 2018 Jul;41(7):413-414. doi: 10.1016/j.tins.2018.04.001.
- [32] Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, Nagler CR, Ismagilov RF, Mazmanian SK, Hsiao EY. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell*. 2015 Apr 9;161(2):264-276. doi: 10.1016/j.cell.2015.02.047. Erratum in: *Cell*. 2015 Sep 24;163:258.
- [33] Luczynski P, McVey Neufeld KA, Oriach CS, Clarke G, Dinan TG, Cryan JF. Growing up in a Bubble: Using Germ-Free Animals to Assess the Influence of the Gut Microbiota on Brain and Behavior. *Int J Neuropsychopharmacol* 19: pyw020, 2016. doi:10.1093/ijnp/pyw020.
- [34] Kawase T, Nagasawa M, Ikeda H, Yasuo S, Koga Y, Furuse M. Gut microbiota of mice putatively modifies amino acid metabolism in the host brain. *Br J Nutr* 2017, 117: 775-783,. doi:10.1017/S0007114517000678
- [35] Neufeld KM, Kang N, Bienenstock J, Foster JA. Reduced anxiety-like behavior and central neurochemical change in germ-free mice. *Neurogastroenterol Motil* 23: 255-264.e119, 2011. doi:10.1111/j.1365-2982.2010.01620.x.
- [36] Erny D, Hrab_e de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, Keren-Shaul H, Mahlakoiv T, Jakobshagen K, Buch T et al.: Host microbiota constantly control maturation and function of microglia in the CNS. *Nat Neurosci* 2015, 18:965-977
- [37] Scheltens P, Blennow K, Breteler MMB, De Strooper B, Frisoni GB, Salloway S, et al. Alzheimer's disease. *Lancet*. 2016;388:505-517.
- [38] Harach T, Marungruang N, Dutilleul N, Cheatham V, Mc Coy K, Neher J, Jucker M, Fåk F, Bolmont T. Reduction of Alzheimer's disease beta-amyloid pathology in the absence of gut microbiota. *arXiv:1509.02273v2*. 2015.]
- [39] Jiang C, Li G, Huang P, Liu Z, Zhao B. The Gut Microbiota and Alzheimer's Disease. *J Alzheimers Dis*. 2017;58(1):1-15. doi: 10.3233/JAD-161141. PMID: 28372330
- [40] Pistollato F, Sumalla Cano S, Elio I, Masias Vergara M, Giampieri F, Battino M. Role of gut microbiota and nutrients in amyloid formation and pathogenesis of Alzheimer disease. *Nutr Rev*. 2016 Oct;74(10):624-634. doi: 10.1093/nutrit/nuw023
- [41] Spychala MS, Venna VR, Jandzinski M, Doran SJ, Durgan DJ, Ganesh BP, Ajami NJ, Putluri N, Graf J, Bryan RM et al.: Age-related changes in the gut microbiota influence systemic inflammation and stroke outcome. *Ann Neurol* 2018, 84:23-36.
- [42] Lyte JM, Proctor A, Phillips GJ, Lyte M, Wannemuehler M. Altered Schaedler flora mice: a defined microbiota animal model to study the microbiota-gut-brain axis. *Behav Brain Res* 356: 221-226, 2019. doi:10.1016/j.bbr.2018.08.022.

- [43] Shilov YE, Bezrukov MV. Kynurenines in pathogenesis of endogenous psychiatric disorders. *Annals of the Russian Academy of Medical Sciences*. 2013;68(1):35-41. (In Russ).] doi: 10.15690/vramn.v68i1.535].
- [44] Myint AM, Schwarz M, Verkerk R. Imbalance of kynurenine metabolites in drug naive schizophrenia. *Brain Behav. Immun*. 2011; 25 (8): 1576-1581.
- [45] Mental Health Taskforce for NHS England The Five Year Forward View for Mental Health: A Report from the Independent Mental Health Taskforce to the NHS in England. London; February 2016
- [46] Hua X, Zhu J, Yang T, Guo M, Li Q, Chen J, Li T. The Gut Microbiota and Associated Metabolites Are Altered in Sleep Disorder of Children With Autism Spectrum Disorders. *Front. Psychiatry*, 02 September 2020 <https://doi.org/10.3389/fpsyt.2020.00855>
- [47] Abdellatif B, McVeigh C, Bendriss G, Chaari A. The Promising Role of Probiotics in Managing the Altered Gut in Autism Spectrum Disorders. *Int J Mol Sci*. 2020;21(11):4159. Published 2020 Jun 10. doi:10.3390/ijms21114159
- [48] World Health Organization, Available from: <https://www.who.int/news-room/fact-sheets/detail/depression> Accessed 01.03.2021.
- [49] Cabral Pinto MMS, Marinho-Reis AP, Almeida A, Ordens CM, Silva MMVG, Freitas S, Simões MR, Moreira PI, Dinis PA, Diniz ML, Ferreira da Silva EA, Condesso de Melo MT. Human predisposition to cognitive impairment and its relation with environmental exposure to potentially toxic elements. *Environ Geochem Health*. 2018 Oct;40(5):1767-1784. doi: 10.1007/s10653-017-9928-3.
- [50] Levey DF, Polimanti R, Cheng Z. et al. Genetic associations with suicide attempt severity and genetic overlap with major depression. *Transl Psychiatry* 9, 22 (2019). <https://doi.org/10.1038/s41398-018-0340-2>
- [51] Chen JJ, Zhou CJ, Zheng P, et al. Differential urinary metabolites related with the severity of major depressive disorder. *Behav Brain Res*. 2017;332:280-287. doi: 10.1016/j.bbr.2017.06.012
- [52] Arya AK, Hu B. Brain-gut axis after stroke. *Brain Circ*. 2018;4(4):165-173. doi:10.4103/bc.bc_32_18
- [53] Singh V, Roth S, Llovera G, et al. Microbiota Dysbiosis Controls the Neuroinflammatory Response after Stroke. *J Neurosci*. 2016;36(28):7428-7440. doi:10.1523/JNEUROSCI.1114-16.2016
- [54] Benakis C, Poon C, Lane D, Brea D, Sita G, Moore J, Murphy M, Racchumi G, Iadecola C, Anrather J. Distinct Commensal Bacterial Signature in the Gut Is Associated With Acute and Long-Term Protection From Ischemic Stroke. *Stroke*. 2020 Jun;51(6):1844-1854. doi: 10.1161/STROKEAHA.120.029262. Epub 2020 May 14. PMID: 32404038
- [55] Chernevskaya EA, Meglei AYü, Buyakova IV, Kovaleva NYü, Gorshkov KM, Zakharchenko VE, Beloborodova N.V. Taxonomic dysbiosis of gut microbiota and serum biomarkers reflect severity of central nervous system injury. *Bulletin of RSMU*. 2020; (5): –. DOI: 10.24075/brsmu.2020.053
- [56] Li N, Wang X, Sun C, Wu X, Lu M, Si Y, Ye X, Wang T, Yu X, Zhao X. et al. Change of intestinal microbiota in cerebral ischemic stroke patients. *BMC Microbiol*. 2019, 19, 191.
- [57] Ji W, Zhu Y, Kan P, Cai Y, Wang Z, Wu Z, Yang P. Analysis of intestinal microbial communities of cerebral infarction and ischemia patients based on high throughput sequencing technology and glucose and lipid

metabolism. *Mol Med Rep.* 2017 Oct;16(4):5413-5417. doi: 10.3892/mmr.2017.7227.

[58] Zeng, X.; Gao, X.; Peng, Y.; Wu, Q.; Zhu, J.; Tan, C.; Xia, G.; You, C.; Xu, R.; Pan, S.; et al. Higher risk of stroke is correlated with increased opportunistic pathogen load and reduced levels of butyrate-producing bacteria in the gut. *Front. Cell. Infect. Microbiol.* 2019, 9, 4.

[59] Pluta, R.; Januszewski, S.; Czuczwar, S.J. The Role of Gut Microbiota in an Ischemic Stroke. *Int. J. Mol. Sci.* 2021, 22, 915. <https://doi.org/10.3390/ijms22020915>

[60] Nelson, J.E.; Cox, C.E.; Hope, A.A.; Carson, S.S. Chronic critical illness. *Am. J. Respir. Crit. Care Med.* 2010, 182, 446-454.

[61] Ravi, A.; Halstead, F.D.; Bamford, A.; Casey, A.; Thomson, N.M.; Schaik, W.; Snelson, C.; Goulden, R.; Foster-Nyarko, E.; Savva, G.M.; et al. Loss of microbial diversity and pathogen domination of the gut microbiota in critically ill patients. *Microb. Genom.* 2019, 5, e000293.

[62] Zaborin A, Smith D, Garfield K, Quensen J, Shakhsher B, Kade M, Tirrell M, Tiedje J, Gilbert J.A, Zaborina O. Membership and behavior of ultra-low-diversity pathogen communities present in the gut of humans during prolonged critical illness. *mBio* 2014, 5, e01361–e01314.

[63] Leslie DL, Kozma L, Martin A, Landeros A, Katsoyich L, King RA, Leckman JF. Neuropsychiatric disorders associated with streptococcal infection: A case-control study among privately insured children. *J. Am. Acad. Child. Adolesc. Psychiatry* 2008, 47, 1166-1172.

[64] Lin P, Ding B, Feng C, Yin S, Zhang T, Qi X, Lv H, Guo X, Dong K, Zhu Y, Li Q. *Prevotella* and *Klebsiella* proportions in fecal microbial communities are potential characteristic

parameters for patients with major depressive disorder. *J. Affect. Disord.* 2017, 207, 300-304.

[65] Cryan JF, O’Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, Codagnone MG, Cusotto S, Furling C, Golubeva AV et al.: The microbiota-gut-brain axis. *Physiol Rev* 2019, 99:1877-2013