Psychiatria Danubina, 2018; Vol. 30, No. 2, pp 136-141 https://doi.org/10.24869/psyd.2018.136 *Mini review*

THE ROLE OF MICROBIOTA IN DEPRESSION - A BRIEF REVIEW

Bojan Zalar[1], Alexander Haslberger[2] & Borut Peterlin[3]

[1]*University Psychiatric Clinic Ljubljana, Ljubljana, Slovenia*
[2]*University of Vienna, Department of Nutritional Sciences, Vienna, Austria*
[3]*Clinical Institute of Medical Genetics, University Medical Centre Ljubljana, Ljubljana, Slovenia*

received: 11.5.2018; revised: 15.5.2018; accepted: 29.5.2018

SUMMARY

The microbiota-gut-brain axis is a bidirectional homeostatic route of communication between both of the organs direct via receptors of the CNS or via epigenetic mechanisms of divers metabolites e.g. SCFA, GABA, β-hydroxybutyrate. Thus, a modulation of gut microbiota via nutrition, lifestyle etc. might be effective for emotional status and depressive disorders.

The dietary composition has an influence on gut microbiota composition, microbial metabolite profile and the according consequences on emotional status and depression within a system biologic approach. There are changes in gut microbiota composition and gut microbial profile (butyrate, GABA, β-hydroxybutyrate) effecting epigenetic regulation (histone acetylation, DNA methylation) and gene expression of receptors and mediators (SLC6A4, BDNF, GABA, GPRs) involved in depressive disorders.

Key words: *depression – microbiota - translation*

* * * * *

INTRODUCTION

Depressive disorder (DD) presents a major health burden for individuals, families and the society. Lifetime risks vary from 10 to 25% for women and 5 to 12% for men, one third population that needs help from psychiatrists are depressed, one in five persons in developed countries will be depressed and the situation in poverty population is even worse. It is the 4th leading course of disability around the world (Friedrich 2017). DD is defined by episodes of low mood and/or anhedonia with changes in physical and psychological function. It is one of the most frequent diagnosis of mental health disorders and antidepressants are most often prescribed medicines. DD is additionally associated with an increased risk of developing atherosclerosis, heart disease, hypertension, stroke, cognitive decline, and dementia, immune impairments and metabolic disorders including type 2 diabetes. Episodes of depression are highly recurrent; many adult cases of depression emerge in adolescence suggesting a stable and chronic lifelong course. DD is regarded as a complex disorder in which both genetic and environmental factors contribute to the etiology. There are different reasons for depression and actual thesis is the role of microbiota.

The "microbiota-gut-brain axis" is composed of central nervous system (CNS), the neuroendocrine and neuroimmune systems, the autonomic nervous system (sympathetic and the parasympathetic), enteric nervous system and the gut microbiota (Mayer 2011).

There is numerous evidence confirming the role of the microbiota in anxiety disorders and similar behavioural disorders. Constant stress influences changes in the structure of microbiota in mice (Bailey et al. 2011). Certain strains of *Lactobacillus* and *Bifidobacterium* secrete gama-aminobutyric acid (GABA) (Barrett et al. 2012), which is the key inhibitory transmitter in the CNS; imbalanced or modified GABA signaling pathways are linked to anxiety disorders and depression (Cryan & Kaupmann 2005).

Influence of microorganisms in our gut has also been explored by the research in which pathogen bacteria *Campylobacter jejuni* were injected into the gut of mice and induced changes in the behaviour (increased anxiety) of the affected animals (Lyte et al. 1998).

Some research shows that the microbiota-gut-brain connection influences the development of the CNS pathways, involved in stress response (Neufeld et al. 2011, Heijtz et al. 2011). In 2004, direct link was confirmed between microbiota and the hypothalamic-pituitary-adrenal (HPA) stress response. This demonstrated that ″germ free″ (aseptic, with no organisms) mice respond to mild stress induction with high adrenocorticotropic hormone (ACTH) in plasm and corticosterone when compared to the control animals. The stress response is recovered to normal levels after injection of *Bifidobacterium infantis*. The sterile mice also demonstrated lower expression values of brain-derived neutrophic factor (BDNF) (Sudo et al. 2004).

Recent research show that the microbiota plays an important role in the organization of the HPA axis in the early phases of life and influences the stress response throughout the life cycle (Foster & McVey Neufeld 2013).

Microbiota represents all microorganisms living on/in the human body of which there are 10^{14} microbe

cells in our gut (Clemente et al. 2012, Whitman et al. 1998). The gut microbiota functions are important for the functions of the host organism, such as regulation and cumulation of fat, processing of nutrients, immune response (Turroni et al. 2008). Concerning the impact of microbiota on behavioural patterns of host, most of the research was conducted on mice or rats while the relation between the microbiota and depression in humans remains undiscovered. This is partly due to the fact, that microbiota cannot be cultivated in cultures. Changes in macrobiotic communities can however be observed in the patients with depression by using different technologies.

Different methods are used in research of microbiota influence on brain are used, such as fecal microbiota transplantation (Kelly et al. 2016), diet changes (Carmody et al. 2015), use of probiotics (Messaoudi et al. 2011) and use of antibiotics (Sandler et al. 2000). The samples are further analyzed by techniques such as 16S rRNA sequencing, DNA microarrays, fluorescence *in situ* hybridization (FISH), real time PCR and metagenome analyses. Gut microbiota interacts with the host via neuroimmune, neuroendocrine and neural pathways (Kelly et al. 2016). The capability of bacteria to synthesize and recognize the same neurotransmitters as found in the host enables environment of reciprocal impact of microbiome and the host (Lyte 2013). More research that is pre-clinical suggests that microbes influence the development and function of brain as well as behavior of the host via microbiota-gut-brain axis. In depression, the gut microbiota triggers dysregulation of neuroimmune –neuroendocrine pathway (Kelly et al. 2016). Gastrointestinal tract (GIT) includes autochthonous species of bacteria, permanent residents of the gastrointestinal tract, as well as alochtone species, which are dependent on diet and other environmental factors (Turroni et al. 2008). Microbiome is thus a dynamic composition system, depending on a combination of factors such as genetics, metabolism, age, geography, medicine (antibiotics) and stress (Foster & Neufeld 2013).

The 16S rRNA analysis of healthy persons' feces samples showed that most represented in numbers were bacteria from phylum *Firmicutes* in *Bacteroidetes – representing* 70–75% of entire microbiome. The bacteria represent smaller numbers are from phylums *Proteobacteria*, *Actinobacteria, Fusobacteria* and *Verrucomicrobia* (Eckburg et al. 2005). Patients with depressive disorders show different proportions in numbers of microbiota. Most significantly higher is the number of order *Bacteroidales* and lower number of family *Lachnospiraceae,* compared to the control individuals (Naseribafrouei et al. 2014), and lower numbers of family *Prevotellaceae* and of the *Prevotella* species (Jiang et al. 2015). Similar study from 2015 detects higher level of the bacteria *Bacteroidetes, Proteobacteria* and *Acinobacteria,* and at the same time significantly lower number of *Firmicutes* in the patients with depressive disorders (Jiang et al. 2015). It has lately been discovered, there is a link between depression, weaker microbiotic diversity and lower numbers of microbiotic representation (Kelly et al. 2016). The same study shows that rats with transplanted feces sample, taken from patients suffering from depression disorder, developed behavioural and physiological (changes in the tryptophan metabolism) signs, characteristic for depression disorders; this indicates the possibility of microbiota influencing the development of signs of depression. This could consequently be the treatment target and prevention of this disorder (Kelly et al. 2016).

Several research on animals demonstrated that treatments of animals with certain probiotics, antibiotics and pathogenic bacteria, which influence the composition of microbiota, also change behavioural patterns of the treated individuals (Foster & Neufeld 2013).

In the research with the use of functional magnetic resonance (fMRI), the brain scans demonstrated effects of the consumed probiotic cocktail on the activities in the regions of brain, responsible for processing emotions and feelings (Tillisch et al. 2013).

More research followed, confirming the hypothesis that microbiota is of key importance also in the development of social behavior in mice (Desbonnet et al. 2013) as well as in people, where the link was discovered between the brain-gut-microbiota axis and autism (Cao et al. 2013).

We searched the PubMed database using the combination of the following words: microbiota, depression, stress, serotonin, dopamin and GABA. We searched for original papers published in the last ten years.

THE "MICROBIOTA-GUT-BRAIN AXIS"

Depending on the dietary composition, gut microbiota subpopulations and fermentation end products (e.g. short chain fatty acids (SCFAs), y-Aminobutyric acid (GABA), etc.) influence the host metabolism via the "microbiota-gut-brain axis" (Dinan & Cryan 2013, De Vadder et al. 2014) a complex bidirectional communication system between the central nervous system (CNS) and the gastrointestinal tract. A healthy human gut is colonized by *Bacteroidetes* and *Firmicutes*, the two predominant bacterial phylotypes (95%), *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Verrucomicrobia* although varying in relative abundance (Karlsson et al. 2010, Remely et al. 2013). An altered intestinal composition or bacterial overgrowth affects host health. Depressive disorders, which are known to respond to dietary manipulations, are known to be affected by four major information carriers that also play a role in the "microbiota-gut-brain axis". These are (1) neural messages carried by vagal and spinal afferent neurons, (2) immune messages carried by cytokines, (3) endocrine messages carried by gut hormones and (4) microbial derived products (e.g. fermentation end products, cell wall components, neuropeptides). The latter may directly affect the brain via the blood stream but may also interact with the other 3 transmission pathways.

Table 1. Depression, Microbiota, Stress, Dopamine, Serotonine and GABA – original papers in PubMed database

Reference	PMID	Main findings
Li et al. 2018	29382834	Altered metabolite composition and changed lipid network in liver was distinguished in the mouse model of depression. Certain microbes (″depression microbes″) could disturb the liver and other parts of the body carrying out metabolic functions.
Yang et al. 2017	28368029	Bifidobacterium was detected in significant appearance in stress resilient mice, whereas in control and stress susceptible mice it could not be detected. Bifidobacterium supplements may prevent the onset of depression from stress in humans.
Hoban et al. 2016	27742460	Depletion of gut microbiota (by antibiotic administration) during adulthood results in an increase in depressive-like behaviours, lower visceral hypersensitivity and impaired cognition. Intact gut microbiota is crucial for normal tryptophan availability and the CNS serotonergic system. Chronic antibiotic exposure during adulthood remarkably reduced the diversity of the gut microbiota particularly it caused a decrease in both *Firmicutes* and *Bacteriodetes.*
Mika et al. 2017	27763700	Early life supplementation of prebiotics and/or glycoprotein lactoferrin promote behavioural stress resistance and uniquely modulate gene expression in corresponding circuits in rats.
Moya-Pérez et al. 2017	28512033	Evidence that Bifidobacterium pseudocatenulatum CECT 7765 beneficially modulates the consequences of chronic stress on the HPA response caused by maternal separation during infancy through modulation of the intestinal neurotransmitter and cytokine network resulting in short and long-term consequences in brain biochemistry and behavior. Administration of *Bifidobacterium pseudocatenulatum* CECT 7765 to mice subjected to chronic stress due to maternal separation weakened some of the effects of the exaggerated stress response of the HPA axis (reduction of the increased basal corticosterone concentration in juvenile mice and reduction of the overproduction of corticosterone at baseline and in response to subsequent acute stress in adulthood).
Liu et al. 2016	26522841	Administration of *Lactobacillus plantarum* PS128 increased the level of serotonin and dopamin in the striatum however it showed no significant effects in the depression-like behaviors of germ-free mice.
Liang et al. 2015	26408987	Supplementation of *Lactobacillus helveticus* NS8 improves chronic restraint stress-induced behavioral (anxiety and depression) and cognitive dysfunction. Furthermore it lowers plasma corticosterone (CORT) and adrenocorticotropic hormone (ACTH) levels, results in higher plasma interleukin-10 (IL-10) levels, restored hippocampal serotonin (5-HT) and norepinephrine (NE) levels, and causes more of the hippocampal brain-derived neurotrophic factor (BDNF) mRNA expression (compared to chronic stress rats). The therapeutic potential of L. helveticus NS8 in stress-related and other kinds of depression is suggested.
Janik et al. 2016	26577887	Due to a treatment with *Lactobacillus* strain JB-1 significant changes in the levels of GABA, N-acetyl aspartate + N-acetyl aspartyl glutamic acid and glutamate were observed.
Naseribafrouei et al. 2014	24888394	Several correlations between depression and fecal microbiota were found.The order Bacterioidales showed an overrepresentation and the family Lachnospiraceae showed an underrepresentation of Operational Taxonomic Units associated with depression.
Bravo et al. 2011	21876150	Chronic administration of *Lactobacillus rhamnosus* (JB-1) induced increased expression of GABA(B1b) mRNA in cortical regions of the brain (cingulate and prelimbic) and reduced expression in the hippocampus, amygdala, and locus coeruleus. GABA(Aα2) mRNA expression was reduced in the prefrontal cortex and amygdala, but increased in the hippocampus after *L. rhamnosus* (JB-1) treatment. *L. rhamnosus* (JB-1) reduced stress-induced corticosterone and anxiety- and depression-related behavior.
Jiang et al. 2015	25882912	Patients with acute major depressive disorder were found to have increased fecal bacterial α-diversity compared to healthy control persons. In patients with major depressive disorder levels of *Bacteroidetes, Proteobacteria*, and *Actinobacteria* were significantly increased, whereas level of *Firmicutes* was reduced. A negative correlation was observed between Faecalibacterium and the severity of depressive symptoms.
Heijtz et al. 2011	21282636	In comparison to mice containing normal gut microbiota, germ free mice (GF) show increased motor activity and reduced anxiety.
Sudo et al. 2004	15133062	GF mice display elevated plasma ACTH and corticosterone levels and reduced expression of brain-derived neutrophic factor in the cortex and hippocampus, compared to specific pathogen free mice.

Table 1. Continues

Reference	PMID	Main findings
Bailey et al. 2011	21040780	Mice exposed to a social disruption stressor had altered microbiota community structure. This was especially evident immediately after exposure to stressor. The stressor exposure treatment resulted in the decrease in relative abundance of bacteria in the genus *Bacteroides* and increase in the genus *Clostridium*. Additionally social stressor also increased circulating levels of IL-6 and MCP-1 cytokines.
Kelly et al. 2016	27491067	Microbiota from depressed patients was transplanted to microbiota-depleted rats, which resulted in the appearance of certain behavioural and physiological features common in depressive phenotype. The most noticable difference between healthy and depressed group was observed in the reduction of Prevotellaceae family (and within this the Prevotella genus). Furthermore depressed patients and rats receiving fecal microbiota transplantation from depressed patients display reduced richness and alpha diversity. At the fecal metabolomic level there were no significant differences between depressed patients and healthy individuals.

All tour pathways do not act in isolation, but are closely interconnected with each another (Holzer & Farzi 2014). Crucially, microbial metabolites are not only circulating in peripheral blood but are also present in the brain (Crawford et al. 2009). In addition, vice versa, influences of the brain on the gut microbial composition are of great interest, given limited research on this matter.

MICROBIOTA AND NEUROTRANSMITTERS

The chemical signaling molecules, particularly dopamine, 5-Hydroxytryptamin (5-HT) and GABA, play key roles in the processing of affect and reward. The neurotransmitter dopamine is thought to be central to reward-seeking behaviors. It is known to be central to the way how animals and humans flexibly choose actions in pursuit of rewards on a trial-and-error basis, hence dopamine plays a fundamental role in reward learning (Pessiglione et al. 2006, Eisenegger et al. 2014). More than 50% of the dopamine is established from intestine, especially *Escherichia coli, Bacillus cereus, Bacillus mycoides, Bacillus subtilis, Proteus vulgaris, Serratia marcescens* and *Staphylococcus aureus* are named to contribute to dopamine release. Concentrations of dopamine in culture of these bacteria were shown to be 10-100 times higher than the typical concentration in human blood (Alcock et al. 2014).

5-HT is involved in anxiolysis and fear recognition. For instance, tryptophan depletion has been shown to impair recognition of facial expression of fear (Harmer et al. 2003), which points to an important role of Trp1 producing microbes in this process. More than 90% of the body's 5-HT is synthesized in the gut (Yano et al. 2015). Production and release of neuroactive factors, the gut microbiota is relevant in production and allocation of metabolites relevant in the synthesis of transmitters of the nervous system e.g. tryptophan (precursor of 5-HT) from shikimic acids (Crawford et al. 2009). Tryptophan decarboxylases also represent in the intestinal microbiota raise the possibility of microbes to confiscate tryptophan from the diet by converting into tryptamine and thereby alter the representation of tryptophan metabolites in the host, by reducing the production of serotonin in the brain (Williams et al. 2014). An absence of microbial colonization, germ-free mice, is associated with reduced 5-HT concentrations compared to conventionally raised controls (Yano et al. 2015). In addition, especially spore - forming bacteria (primarily from the Clostridium genus) are suggested to produce serotonin themselves. Lactobacillus brevis is supposed to influence the number and function of enterochromaffin cells, thereby promoting the release of 5-HT (Yano et al. 2015).

Lactobacilus rhamnosus effects on GABA neurotransmission are expected to impact on recognition of anger, as administration of the GABA-A receptor agonist diazepam causes selective impairments in the recognition of facial anger, in addition to its well-established anxiolytic effects.

J3-hydroxybutyrate, produced during starvation, caloric restriction, fasting, high-intense exercise or by gut microbiota high in *Bacteroidetes* and low in *Firmicutes* has been mentioned to suppress sympathetic nervous system activity by reducing histone deacetylases (HDAC) activity and increasing acetylation (Youm et al. 2015, Aslim et al. 1998). A systemic injection of butyrate induced histone hyperacetylation (H3, H4) and the expression of BDNF receptor in hippocampus and frontal cortex and showed antidepressant effects in mice by influencing the enteric nervous system (Bravo et al. 2011, Schroeder et al. 2007) (Table 1).

CONCLUSION

This review combines fundamental and translational research. Results of this review yield essential novel insight into how gut microbiota shape patho-epigenetics of the gut-brain enteric microbiota axis in both healthy volunteers and a clinical population. The review comprises inflammatory and neuroactive pathways involved in depression and thus has a bearing on several other psychiatric disorders characterized by inflammatory and neurodegenerative processes.

Acknowledgements:

The research J3 8215 "The Role of The Microbiome in Depression" (Bojan Zalar, project leader) has financial grant by Slovenian Research Agency (ARRS) 2017-2020.None.

Conflict of interest: None to declare.

Contribution of individual authors:

Bojan Zalar: author of first draft and editing;

Alexander Hasselberger: intellectual contribution to second draft;

Borut Peterlin: intellectual contribution to second draft and draft review.

References

1. *Alcock J, Maley CC, Aktipis CA: Is eating behavior manipulated by the gastrointestinal microbiota? Evolutionary pressures and potential mechanisms. Bioessays 2014; 36:940–9*
2. *Aslim B, Calişkan F, Beyatli Y, Gündüz U: Poly-beta-hydroxybutyrate production by lactic acid bacteria. FEMS Microbiol Lett 1998; 159:293–7*
3. *Bailey MT, Dowd SE, Galley JD, Hufnagle AR, Allen RG, Lyte M: Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor induced immunomodulation. Brain Behav Immun 2011; 25:397–407*
4. *Barrett E, Ross RP, O'Toole PW, Fitzgerald GF, Stanton C: Gamma-aminobutyric acid production by culturable bacteria from the human intestine. J Appl Microbiol 2011; 113:411–7*
5. *Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, et al.: Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci USA 2011; 108:16050-5*
6. *Cao X, Lin P, Jiang P, Li C: Characteristics of the gastrointestinal microbiome in children with autism spectrum disorder: a systematic review. Shanghai Arch Psychiatry 2013; 25:342-53*
7. *Carmody RN, Gerber GK, Luevano JM Jr, Gatti DM, Somes L, Svenson KL, et al.: Diet dominates host genotype in shaping the murine gut microbiota. Cell Host Microbe 2015; 17:72-84*
8. *Clemente JC, Ursell LK, Parfrey LW, Knight R: The impact of the gut microbiota on human health: an integrative view. Cell 2012; 148:1258-70*
9. *Cryan JF & Kaupmann K: Don't worry 'B' happy!: a role for GABA(B) receptors in anxiety and depression. Trends Pharmacol Sci 2005; 26:36–43*
10. *Desbonnet L, Clarke G, Shanahan F, Dinan TG, Cryan JF: Microbiota is essential for social development in the mouse. Mol Psychiatry 2014; 19:146-8*
11. *De Vadder F, Kovatcheva-Datchary P, Goncalves D, Vinera J, Zitoun C, Duchampt A, et al.: Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell 2014; 156:84-96*
12. *Dinan TG & Cryan JF: Melancholic microbes: a link between gut microbiota and depression? Neurogastroenterol Motil 2013; 25:713–9*
13. *Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, et al.: Diversity of the human intestinal microbial flora. Science 2005; 308:1635–8*
14. *Eisenegger C, Naef M, Linssen A, Clark L, Gandamaneni PK, Müller U, et al.: Role of dopamine D2 receptors in human reinforcement learning. Neuropsychopharmacology 2014; 39:2366–75*
15. *Foster JA & McVey Neufeld KA: Gut–brain axis: how the microbiome influences anxiety and depression. Trends Neurosci 2013; 36:305-12*
16. *Friedrich M: Depression Is the Leading Cause of Disability Around the World. JAMA 2017; 317:1517*
17. *Harmer CJ, Rogers RD, Tunbridge E, Cowen PJ, Goodwin GM: Tryptophan depletion decreases the recognition of fear in female volunteers. Psychopharmacology 2003; 167:411–7*
18. *Heijtz RD, Wang S, Anuar F, Qian Y, Björkholm B, Samuelsson A, et al.: Normal gut microbiota modulates brain development and behavior. Proc Natl Acad Sci USA 2011; 108:3047–52*
19. *Holzer P & Farzi A: Neuropeptides and the microbiota-gut-brain axis. Adv Exp Med Biol 2014; 817:195–219*
20. *Jiang H, Ling Z, Zhang Y, Mao H, Ma Z, Yin Y, et al.: Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav Immun 2015; 48:186-94*
21. *Karlsson FH, Ussery DW, Nielsen J, Nookaew I: A closer look at bacteroides: phylogenetic relationship and genomic implications of a life in the human gut. Microb Ecol 2010; 61:473–85*
22. *Kelly CR, Khoruts A, Staley C, Sadowsky MJ, Abd M, Alani M, et al.: Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent Clostridium difficile Infection: A Randomized Trial. Ann Intern Med 2016; 165:609-16*
23. *Kelly JR, Borre Y, O' Brien C, Patterson E, El Aidy S, Deane J, et al.: Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat. J Psychiatr Res 2016; 82:109-18*
24. *Lyte M: Microbial endocrinology in the microbiome-gut-brain axis: how bacterial production and utilization of neurochemicals influence behavior. PLoS Pathog 2013; 9:e1003726*
25. *Lyte M, Varcoe JJ, Bailey MT: Anxiogenic effect of subclinical bacterial infection in mice in the absence of overt immune activation. Physiol Behav 1998; 65:63–68*
26. *Mayer EA: Gut feelings: the emerging biology of gut-brain communication. Nat Rev Neurosci 2011; 12:453-66*
27. *Messaoudi M, Lalonde R, Violle N, Javelot H, Desor D, Nejdi A, et al.: Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. Br J Nutr 2011; 105:755–64*
28. *Naseribafrouei A, Hestad K, Avershina E, Sekelja M, Linlokken A, Wilson R, et al.: Correlation between the human fecal microbiota and depression. Neurogastroenterol Motil 2014; 26:1155-62*
29. *Neufeld KAM, Kang N, Bienenstock J, Foster JA: Effects of intestinal microbiota on anxiety-like behavior. Commun Integr Biol 2011; 4:492–4*

30. Nicodemus KK, Elvevag B, Foltz PW, Rosenstein M, Diaz-Asper C, Weinberger DR: Category fluency, latent semantic analysis and schizophrenia: a candidate gene approach. Cortex J Devoted Study Nerv Syst Behav 2014; 55:182-91
31. O'sullivan E, Barrett E, Grenham S, Fitzgerald P, Stanton C, Ross RP, et al.: BDNF expression in the hippocampus of maternally separated rats: does Bifidobacterium breve 6330 alter BDNF levels? Benef Microbes 2011; 2:199-207
32. Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD: Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature 2006; 442:1042–5
33. Remely M, Aumueller E, Merold C, Dworzak S, Hippe B, Zanner J, et al.: Effects of short chain fatty acid producing bacteria on epigenetic regulation of FFAR3 in type 2 diabetes and obesity. Gene 2013; 537:85–92
34. Sandler RH, Finegold SM, Bolte ER, Buchanan CP, Maxwell AP, Vaisanen ML, et al.: Short-term benefit from oral vancomycin treatment of regressive-onset autism. J Child Neurol 2000; 15:429–35
35. Schroeder FA, Lin CL, Crusio WE, Akbarian S: Antidepressant-like effects of the histone deacetylase inhibitor, sodium butyrate, in the mouse. Biol Psychiatry 2007; 62:55–64
36. Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu XN, et al.: Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. J Physiol 2004; 558:263-75
37. Tillisch K, Labus J, Kilpatrick L, Jiang Z, Stains J, Ebrat B, et al.: Consumption of fermented milk product with probiotic modulates brain activity. Gastroenterology 2013; 144:1394-1401
38. Turroni F, Ribbera A, Foroni E, van Sinderen D, Ventura M: Human gut microbiota and bifidobacteria: from composition to functionality. Antonie Van Leeuwenhoek 2008; 94:35-50
39. Whitman WB, Coleman DC, Wiebe WJ: Prokaryotes: the unseen majority. Proc Natl Acad Sci USA 1998; 95:6578-83
40. Williams BB, Van Benschoten AH, Cimermancic P, Donia MS, Zimmermann M, Taketani M, et al.: Discovery and characterization of gut microbiota decarboxylases that can produce the neurotransmitter tryptamine. Cell Host Microbe 2014; 16:495–503
41. Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, et al.: Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell 2015; 161:264–76
42. Youm YH, Nguyen KY, Grant RW, Goldberg EL, Bodogai M, Kim D, et al.: The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. Nat Med 2015; 21:263–69

Correspondence:

Prof. Borut Peterlin, MD, PhD
Clinical Institute of Medical Genetics, University Medical Centre Ljubljana
Šlajmerjeva 4, 1000 Ljubljana, Slovenia
E-mail: borut.peterlin@guest.arnes.si