https://doi.org/10.31925/farmacia.2022.3.4 **REVIEW**

SIGNALLING THROUGH THE MICROBIOTA-GUT-BRAIN TRIADE

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Abstract

Gut microbiota is well known for its role in regulation of intestinal function. However, intriguing evidence indicates that gut microbes can also modulate the development and activity of the nervous system through a bidirectional communication pathway, so called the microbiota-gut-brain axis. One of the ways through commensal microbial strains in intestinal lumen could signal to the brain, is by producing similar neurotransmitters with those found in mammalian organisms, such as GABA, serotonin, catecholamines and histamine. Given the fact that mental disorders relate to the imbalance of neuroactive compounds, and several gut microorganisms could alter neurotransmitters levels, it was assumed that gut microbiota could influence mood, stress and behaviours and be also a determinant factor for the onset or evolution of neurological and psychiatric pathologies. This review aims to assess the relationship between the intestinal microbiome and the brain, by focusing on the main neurotransmitters secreted by the gut microbes.

Rezumat

Microbiota intestinală este bine cunoscută pentru rolul ei în reglarea funcției intestinale. Totuși, există studii care au arătat faptul că microorganismele pot, de asemenea, modula dezvoltarea și activitatea sistemului nervos printr-o cale de comunicare bidirecțională, așa numita axă microbiotă-intestin-creier. Una din căile prin care tulpinile microbiene comensale din lumenul intestinal pot trimite semnale către creier este prin producerea de neurotransmițători similari cu cei întâlniți la mamifere: GABA, serotonină, catecolamine și histamină. Dat fiind faptul că bolile mintale sunt asociate cu dezechilibrul compușilor neuroactivi, și multe microorganisme intestinale pot altera nivelurile neurotransmițătorilor, s-a considerat că microbiota intestinală poate influența starea de spirit, stresul și diferitele comportamente și poate, de asemenea, reprezenta un factor determinant pentru debutul sau evoluția unor patologii neurologice sau psihiatrice. Acest *review* își propune să evalueze relația dintre microbiomul intestinal și creier, concentrându-se pe principalii neurotransmițători secretați de microorganismele intestinale.

Keywords: microbiota, neurotransmitters, microbiota-gut-brain axis

Introduction

The microbiota residing in the human gastrointestinal tract is considered a virtual organ as it encounters more than 10^{14} microorganisms, which means 10 times more bacteria than human cells number. The collective genomes of the microorganisms, referred as microbiome, are also 100 times larger than the human genomic content. Most of the microorganisms within the intestinal lumen are represented by bacteria, but viruses, fungi and protozoa are also important parts of gut microbiota [47, 48]. Microbiota composition is shaped from the early life, depending on various infant factors like gestational age at birth, mode of delivery, types of milk feeding (breast or formula), weaning period and external factors such as using of antibiotics. The microbes acquired during the first period of life will be relatively stable during lifetime and individual variations are due to differences in enterotypes, body mass index (BMI), ethnicity, lifestyle and dietary habits [36]. 90% of the gut microbiota is represented by *Firmicutes* and *Bacteroidetes phyla*. Other important phyla are *Actinobacteria, Proteobacteria, Fusobacteria* and *Verrucomicrobia*, but they are less abundant at intestinal level [35].

The bacteria from the gut are involved in host processes like nutrient and xenobiotic metabolism, maintenance of integrity of the intestinal mucosal barrier, immune modulation and antimicrobial protection [21]. In a study conducted on dogs presenting gut dysbiosis, it was revealed that the shaping of gut bacteria using probiotics led to a decrease in the inflammatory status of the host, which is a proof of the antiinflammatory effect of a healthy microbiota. [24] Due to its essential role in host health, microbiota has become a target for a large range of chronic diseases, such as metabolic syndrome, diabetes and obesity [12]. Obesity was associated with an imbalanced microbiota and there have been described therapeutic strategies including probiotics (*Lactobacillus* strains)

combined with prebiotics and antibiotics that could restore compromised intestinal microflora and facilitate weight loss [12].

Moreover, age related neurodegenerative diseases have some common characteristics implying low levels of neurotransmitters, chronic inflammation and oxidative stress, noxious effects that could be prevented by maintaining a healthy gut environment. It was also emphasized that the most patients suffering from Alzheimer or Parkinson, are also affected by gastro-intestinal comorbidities and a good management of the microbiota might ease the specific manifestations of these diseases [53]. The role of gut microbes in the neurodevelopment is particularly important as the brain and microbiota development are two parallel processes. A disruption of microbiota in early life has been reported to increase the risk for depression. So is not unpredictable that impaired gut microbiome is often associated with brain related conditions such as anxiety, Parkinson, Alzheimer and schizophrenia [40].

Moreover, it was introduced the term Psychobiotics, to describe a subgroup of probiotics including *Lactobacilli* and *Bifidobacteria*, that can influence brain functions, alleviate stress, regulate the mental status of the host and beside these, support in management of various psychiatric and neurodegenerative disorders. This concept emerged as the neuro-mediators/neuro-transmitters secreted by some bacteria, including those that are components of the gut microbiota, have been found to determine psychotropic effects within the host. There is a large range of neuroactive compounds produced within the intestinal lumen by microbial inhabitants, similar with those produced by the host, including GABA, serotonin, histamine, acetylcholine and catecholamines (dopamine and noradrenaline). Other than producing human homologous neuroactive components, some bacteria have also the ability of regulating endocannabinoid receptor expression [9, 17, 27]. This fact was demonstrated the easiest way by analysing stress response into the germ free (GF) mice or mice having the microbiota affected by anti-biotics. Following this, events like depression and anxiety were observed, but also reversed once normal microbiota was transplanted to the mice. Restoring the host healthy mental status was also possible by using adequate probiotics [22].

Gastrointestinal tract (GI) could interact with the brain *via* a bidirectional communication, so called gut-brain axis. This communication includes three major systems: neural (enteric nervous system, vagal and spinal nerves), immune (cytokines) and endocrine (hypothalamic pituitary adrenal axis) [26]. However, in the last years, microbiota gained attention as one of the factors implicated in the modulation of gut-brain axis. The mechanisms behind the pathways of communication between microbiota and brain are not known, but they extend from neuronal circuits to molecular messaging systems. Besides the routes of communication between brain and gut, microbiota comes with its derived neurohormones compounds as another way to signalling to the brain. This link between brain and microbiota led to associations between gut-derived microorganisms and the aetiologies of neurologic and psychiatric disorders [13].

The vagus nerve (VN) is a component of para-sympathetic nervous system that binds the brain with the gastro-intestinal tract through a very large bundle of nerves. The communication between the gut microbiome and the central nervous system is mediated by the interceptive awareness role of the VN. Accordingly, afferent fibres of the VG are able to sense the bacteria metabolites and transfer signals to the central nervous system (CNS). After the information is integrated into the central network, brain will be generating responses through effector fibres of the VN. Then it is not surprising that the constant dialog between gut bacteria and the vagus nerve might be associated with control or swings in mood, emotions, stress and behaviours [5]. The vagal connection between the brain and the gut microbiota was analysed by an experiment done by Bravo *et al*., when administered to mice, the probiotic strain *Lactobacillus rhamnosus* proved decreased anxiety, lower corticosterone levels and an increase of central GABA receptors number. After vagotomy, all these benefice effects disappeared, which suggests that vagal innervation of the gut is mandatory for some microbes as a signalling path to the brain [6].

Neurotransmitters Produced *Via* Gut Microbiota

The microorganisms inside the intestinal lumen are capable to produce/secrete and recognize neuroactive compounds with similar structures as the ones released by the host. Microbiome modulatory effects on neuro-transmitters could therefore impact host behaviour and nervous functions. This bidirectional communication between bacteria and their host neurophysiological system through hormonal signals is called microbial endocrinology or interkingdom signalling and is the most probable path by which microbiota and the host influence each other [23]. The hormonal effects of microbiota on the host could be direct, when bacteria are secreting the neurohormones themselves or indirect, when bacteria modulate the adrenal cortex or inflammation and immune system. There are two classes of hormones implicated in bacterial control over the host, defined by neurohormones (catechol-amines, histamine, GABA, serotonin and acetylcholine) and stress hormones (cortisol, corticosterone, adreno-corticosterone and corticotropin). Although neuro-hormones enter the systemic circulation through the blood, they can also act as neurotransmitters [29]. The neurotransmitters released by the microbes into the gut, directly interact with afferent neurons of enteric nervous system and modulate nervous signals sent

further to the CNS, affecting both brain function and host behaviour. Starting from this perspective, such bacteria acting as a source for neuroactive molecules could be used as probiotics and perceived as delivery vehicles that could contribute to the prevention/ treatment of neurological and neurophysiological conditions [50].

GABA

GABA (gamma-aminobutyric acid) is the main inhibitory neurotransmitter that along with excitatory neurotransmitter glutamate, maintains neuronal homeostasis. GABA relieves pain, regulates heart rate and blood pressure and lessens nervous conditions like anxiety. GABA is formed primarily in the GABAergic interneurons through decarboxylation of glutamate by the enzyme *gad* (glutamate decarboxylase). This enzyme could be the key point of biosynthesis and accumulation of GABA at gut level too as its presence is described in intestinal microorganisms like lactic acid bacteria [38, 39]. Strandwitz *et al.* found multiple gut bacteria with the capacity to modulate GABA levels by raising its expression *in vitro* through a study utilizing co-culture screens and metagenomic datasets. Among those studied genera, *Bacteroides*, *Parabacteroides* and *Escherichia* were mostly shown to produce the inhibitory neurotransmitter at the human gut level. Interestingly, *Bacteroides* strains are the most likely to produce GABA within the pH range 6 - 7, specific to human large intestine. *Bifidobacterium* and *Eubacterium* were identified also as GABA producers. However, in Strandwitz survey, no association was found between the high levels of faecal *Bacteroides* and depressive disorders, generally associated with an altered GABA-mediated response [42]. Another survey on 77 *Bifidobacterium* taxa done by Duranti *et al*., revealed that *B. adolescentis*, especially 2 strains (PRL2019 and HD17T2H) generated the highest levels of GABA and *gad* genes *in vitro*, a fact that was further correlated *in vivo* with increased probability of developing psychiatric illness like anxiety and depression [18]. Pokusaeva *et al*. demonstrated that microbial GABA could modulate microbiome-gut-brain axis and alleviate abdominal pain in a rat model of hypersensitivity. In their research, GABA was specific produced by a *Bifidobacterium dentum* strain which encoded the glutamate decarboxylase gene *gadB* [31]. The difference between GABA levels in germ free mice and specific pathogen-free (SPF) mice was analysed also, taking three domains into considerations: colonic lumen content, cardiac plasma and brain. The results showed lower concentrations of GABA at intestinal and plasma level for the GF mice, but no differences at cerebral level. That way, it can be assumed that blood brain barrier (BBB) is not permeable for microbiota-derived GABA so gut bacteria could not directly modulate the cerebral GABA levels [25]. For some authors, the transport of peripheral microbial-derived GABA through the BBB does not seem impossible and is questionable if can be done by mechanisms like diffusion or active transport and even through specialized GABA transporters expressed on BBB [14].

Microbiota-derived GABA is considered synthetized from its precursor glutamate. In a screening conducted by Yunes *et al*. on human-derived *Lactobacillus* and *Bifidobacterium* spp, the highest GABA producers were *Bifidobacterium* strains. The survey also emphasized *L. plantarum*, *L. brevis*, *B. adolescentis*, *B. angulatum* and *B. dentium* as the main intestinal lactobacilli and bifidobacteria which encode *gad* genes and respectively possess the capacity to produce GABA [54]. Besides decarboxylation of glutamate, GABA is formed within the human body starting from biologic compounds like putrescine, arginine or ornithine. *Blautia* is a genus of gut microbiota, correlated with arginine metabolism and thus GABA production. Additionally, it was postulated that gut derived GABA is obviously reduced in patients suffering from Alzheimer's dementia. Therefore, Zhuang *et al*. established that elevated levels of GABA, as a *Blautia*-dependent metabolite, are associated with a lower risk of Alzheimer. This finding supports again the idea of microbiota as an important factor between gut and brain communication [55].

Catecholamines

The three main catecholamines circulating within the body are norepinephrine (noradrenaline, NE), epinephrine (adrenaline) and dopamine (DA). The first two are peripheral catecholamines known for their role in the "fight or flight" response to stress, while dopamine is acting as a central neurotransmitter involved in reward pathway, among other neuronal responses [28]. Evidence shows that NE and DA are released into the gut by enteric nervous system, through sympathetic and respectively non-sympathetic fibres. Adrenaline is not produced into the intestine. In addition to the levels of catecholamines already produced within the body, evidence shows that gut microbiota could also contribute with secreting analogue neurohormones [37]. Asano *et al*. performed a study which evaluated luminal dopamine and norepinephrine levels within the intestines of specific pathogen-free (SPF), germ-free (GF) and gnotobiotic mice. The major finding was the presence of high levels of free catecholamines in the gut lumen of SPF mice, compared to abundant presence of conjugated, biologically inactive catecholamines in GF animals. Moreover, the association of GF mice with β-glucuronidase-expressing bacterial strains, determined a drastic raise of free DA and NE. However, the research found no eloquent difference in the overall dopamine levels (free and conjugated form), from the caecal lumen among the GF, SPF

and gnotobiotic mice. In contrast, the total norepinephrine amounts were still lower in GF mice than in SPF or gnotobiotic mice. That indicates that gut microbiota plays a role at least in producing of NE, and microbiota rich in β-glucuronidase activity is a source of free catecholamines [2]. *Enterococcus* genus is a commensal and an opportunistic pathogen of normal intestinal microbiome and has been presumed to impact dopaminergic pathways and participate to dopamine synthesis. This process is facilitated by bacterial tyrosine hydroxylase (TH) activity, the rate-limiting enzyme that enables the conversion of tyrosine into L-dopa. Despite that, the issue interferes with the preferential conversion of tyrosine to tyramine *via Enterococcus* decarboxylase enzyme, leading to a depletion of dopamine precursors. Fortunately, this preferential transformation path could be abolished by α-flouromethyltyrosine, therefore precursors will be metabolized to dopamine [19]. Some micro-organisms, including *E. coli*, present a functional transporter for catecholamines, similar to Leu T which is a member of bacterial neurotransmitter sodium symporter family. For this reason, is hard to establish if the NE and DA within the bacteria originate from bacterial production *via* the action of tyrosine hydroxylase-like enzyme or from the gut itself *via* Leu T-like transporter [44]. Wang and colleagues performed a study where they demonstrated the favourable action of oral berberine on accelerating the production of L-Dopa by two gut inhabitants, *Enterococcus faecalis* or *Enterococcus faecium*. Berberine is a promotor of tetrahydrobiopterin (BH_4), the coenzyme that enhances the TH activity. The higher amounts of L-Dopa obtained this way are transported through the circulation to the brain and converted to DA at this level. Following this experiment in a mice model of Parkinson's disease (PD), it was observed a significant increase in brain dopamine that came along with ameliorated PD manifestations. Brain imaging also showed elevated striatal dopamine levels [52]. Another study displayed that the presence of bacterial tyrosine decarboxylase enzyme, originated from some *Enterococcus* and *Lactobacillus* gut strains, led to the transformation of L-Dopa to DA into the intestines. Unlike the human enzyme, it was also observed that the activity of this bacterial enzyme is not inhibited by DOPA decarboxylase inhibitors. As peripheral dopamine is unable to cross the BBB, lowering the intestinal L-Dopa bioavailability will negatively affect Parkinson's disease patients under L-dopa treatment [49].

Serotonin

Serotonin (5-HT/5-hydroxytryptamine) is having multiple roles within the body, acting as a neuro-transmitter, blood factor and hormone. Beyond its physiologic functions, 5-HT is also involved in neurological/psychiatric disorders (depression, anxiety, addiction, Parkinson's and Alzheimer's disease) and peripheral organs disfunctions (gastrointestinal and cardiac disease) [15]. Serotonin primary known biologic functions include the modulation of gut motility and secretions, platelet activation and aggregation, bone development and cardiac functions, but it also supports immune function and inflammation processes [34].

From the total amount of body's serotonin, approx. 90% is surprisingly produced outside the brain, within the intestinal lumen, by the enterochromaffin (EC) endocrine cells. The presence of gut microbiota was associated to the production of mucosal 5-HT, but not connected to the neuronal 5-HT. For the production of serotonin at gut level, the EC cells are using tryptophan hydroxylase 1 (TPH1), which is the rate limiting enzyme having the ability to transform local tryptophan into serotonin. The following activation of serotonin receptors 5-HT4 within the enteric nervous system was demonstrated to result in neurogenerative and neuroprotective effects [16]. The mechanism by which microbiota plays an indirect role in serotonin production and regulation, is the stimulatory effect of its metabolites, short-chain fatty acids (butyrate and acetate). These metabolites are impacting EC cells by promoting the transcription of TPH1 and consecutively, the secretion of mucosal serotonin [33]. Besides the EC cells as the primary source of intestinal serotonin, there have been discovered some gut resident bacteria that have also the ability to produce this neurotransmitter. It's worth mentioning *Escherichia coli K12* and *Lactobacillus plantarum* as examples of microorganisms that could secrete serotonin, at least *in vitro* [11]. Another indirect role of gut microbes in the production of serotonin is demonstrated by Sudo, in a study that compared concentrations of serotonin in GF mice and conventionally colonized mice. Given that fact that half of non-microbial derived serotonin in GF mice is present in conjugated form, and in the SPF mice the neurotransmitter is almost completely un-conjugated, it was assumed that microbiota produces free 5-HT *via* bacterial deconjugation of conjugated 5-HT [45].

Although microbiota could influence CNS homeostasis, through gut-brain axis, there is a lack of data related to its modulatory effects on serotoninergic neuro-transmission. It was observed that GF animals have higher hippocampal concentrations of serotonin and its metabolite, 5-hydroxyindoleacetic acid, when compared to control animals. These cerebral abnormalities are impossible to reverse when colonization of the gut is done after the weaning period. The precursor of serotonin is tryptophan. Given the fact that tryptophan levels were also discovered elevated in GF mice plasma, this might be considered a humoral path through which the bacteria can influence CNS serotonergic system. Despite the forever affected brain serotonin levels, colonization of GF mice any time in life, was found to regulate peripheral tryptophan and interestingly,

to reduce anxiety. Therefore, restoration of gut microbiota later in life could regulate behaviour, but not the aberrant neurotransmission in the brain [10]. Alzheimer is a condition characterized by a drop in overall brain serotonin content. The serotonin produced into the intestinal lumen could be involved in the onset or evolution of Alzheimer's disease and this indirect effect might implicate the microbiota-gut-brain axis. A direct mechanism of action for the gut neuromediator is excluded because serotonin is not capable to cross blood-brain barrier [1]. However, the major role of microbial-derived serotonin is considered to be the regulation of membranes permeability, including probably the BBB permeability. Given the fact that there are diverse drugs and environmental factors which can perturb gut microbiota composition and thus the process of serotonin synthesis, their negative action could be reflected also in impaired vascular permeability within the whole body [46].

Histamine

The fact that gut microbiota could influence the brain levels of histamine was one of the first published evidence wherein intestinal microbes might have a contribution to the regulation of brain chemistry. It was established back then, that the germ-free animals had lower levels of histamine in the hypothalamus than the conventionally raised animals [20]. Histamine is a biogenic amine that mediates host allergic reactions, being also an important neurotransmitter for the brain and a modulator of the vestibular system [7]. The main source of histamine in the human body is represented by mast cells and basophils. Histidine decarboxylase (HDC) is the enzyme required for biosynthesis of histamine. Evidence suggests that gut microbiota has the ability to produce this neurotransmitter by decarboxylation of amino acids, which made promising the assumption of a possible impact on histamine availability in the brain. The production of histamine within the intestines is important with regards histamine poisoning, concerning for those suffering with a deficit of amine detoxification (patients on MAOIs or genetic susceptible) [45]. In human brain, histaminergic neurons have a wide distribution. Brain-derived histamine is a critical factor in the modulation of physiological functions such as thermoregulation, circadian rhythms, neuroendocrine secretion and behaviours like food and drink intake, wakefulness, cognitive function, emotional reaction and aggressivity [32]. In Alzheimer's disease, numerous areas of the brain are deficient in histamine, including hippocampus, temporal cortex and hypothalamus, suggesting a degeneration of histaminergic neurons that plays subsequently a role in memory loss. It's not surprising then that histamine regulation through the gut microbiota became an interest as a possible route for the therapy of neurodegeneration. The probiotic *Lactobacillus reuteri* was also reported to suppress the production of the inflammatory marker TNF and mediate the signalling in the enteric nervous system, effects linked to bacterium's ability to produce histamine [50]. For numerous strains of fermentative bacteria such as *Enterobacter*, *Lactobacillus*, *Lactococcus* and *Streptococcus* have been demonstrated their capacity to secrete histamine [43]. The histamine-secreting bacteria were highly documented as a marker of food spoilage, especially when it comes to scombroid poisoning, which is caused by consumption of fish contaminated with high levels of histamine. Histamine is present in fish following improper storage and handling, when the bacteria is starting to metabolize histidine. The presence of microbiota capable to secrete histamine within the intestines is still not investigated by detail [4]. It was demonstrated by Barcik *et al*. that microbial-derived HDC was present in every faecal sample, but large quantities were found especially in asthma patients. Interestingly, the samples of obese patients with asthma have shown lower bacterial HDC when compared to normoponderal asthmatic patients, which highlights the existence of other factors than histamine, implicated in the development of asthma. It can be speculated that intestinal histamine derived from microbiota adds up to the systemic levels that can drive allergic reactions and histamine related pathologies. Moreover, it was revealed that *E. coli*, *M. morganii* and *L. vaginalis* were the most potent histamine-producing bacteria isolated from faecal samples of asthma patients [3]. While the microbiota has been shown to influence gut histamine levels, more work is required to establish whether it can influence the central histaminergic transmission.

Acetylcholine

Acetylcholine is the key cholinergic neurotransmitter acting in the central and peripheral nervous systems. The acetylcholine imbalance is strongly correlated with the development of neurologic conditions such as Alzheimer's disease. Some bacteria that could colonize the intestinal lumen have been discovered as acetylcholine-producers: *Lactobacillus plantarum*, *Bacillus subtilis*, *Escherichia coli* and *Staphylococcus aureus.* [8, 41]. Besides accumulation of amyloid plaques and neurofibrillary tangles, AD pathogenesis is associated with cholinergic neurons degeneration and acetylcholine deficit. In a survey carried out by Nimgampalle and Kuna, *L. plantarum* displayed anti-Alzheimer properties by antagonizing AD manifestations induced by D-Galactose. After 60 days of treatment, acetylcholine levels and histopathological features were brought back to normal and cognitive deficits were ameliorated. The mechanisms behind the positive effects are supposed to be the potential antioxidant nature of the bacterial strain and the bi-directional

communication between gut-brain axis [30]. Moreover, administration of *L. plantarum* concomitant with memantine, common Alzheimer medication, was found to act synergistically in improving AD manifestations [51].

Conclusions

Although the complex communication mechanisms between bacteria within the human gut and the brain are not yet fully understood, it is clear the fact that gut microbiota is a source of neurotransmitters that can directly influence the brain chemistry.
More work is still needed in order to determine the implications and therapeutic opportunities of gut derived neurotransmitters in the onset and development of psychiatric and neurodegenerative disorders.

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Conflict of interest

The authors declare no conflict of interest.

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