

# Intestinal Microbiota and its Possible Effect on the Brain Pathology



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## Abstract

According to previous knowledge, human body is a complex biological system in which several microorganisms, especially bacteria, play an important role. It is reported that the number of bacterial cells is up to ten times higher than the number of somatic cells. With microorganisms, we are also tied in terms of evolution and individual development. It is assumed that humans would never have developed such cognitive skills without the presence of bacteria. Microorganisms produce a range of neurochemical active substances that are crucial to our life. In addition, microorganisms contribute to digestion, vitamin synthesis, or elimination of pathogens. The term microbiota (also microflora) refers to the community of microorganisms living in an environment. A set of all their genes is called microbiome.

**Keywords:** Gut-Microbiota; Brain; Intestinal Microbiota-CNS Pathway

**Abbreviations:** sIgA: Secretory Immunoglobulin A; GF: Germ-Free; CNS: Central Nervous System; CRH: Corticotropin Releasing Hormone; HPA: Hypothalamo-Pituitary-Adrenal Pathway; PNS: Peripheral Nervous System

## Introduction

### Intestinal Microbiota

Approximately from 10<sup>13</sup> to 10<sup>14</sup> microorganisms live in the human gastrointestinal tract. The presence of bacteria has also been demonstrated in the meconium of healthy new-borns, resulting from the transfer of microorganisms from mother to child. During the first year of life, guts are colonized by the microbiota, which is relatively stable at the end of the first year of life of the infant. The composition of the microbiota is different at everyone. According to the dominant representation of certain microorganisms we classify microbiota into so-called enterotypes [1]. In the gastrointestinal tract, the amount and variability of microorganisms increases from the stomach to the colon. The intestinal microflora is linked to the neuro-endocrine-immune pathway, thanks to which there originated an idea of a brain-intestinal microbiota pathway. Many animal studies suggest that imbalance in the microflora composition may lead to neurochemical and behavioural changes. However, it is unquestionable that the microbiota fundamentally affects the health of the organism, namely in three main ways: defending against pathogens by the production of antimicrobial agents and by the nutritional competition; enhancing intestinal epithelium and inducing production of secretory Immunoglobulin A (sIgA) antibodies; and processing indigestible food residues. Studies show

that animals bred under sterile conditions (germ-free; GF) show lower resistance to infections, reduced digestive enzyme activity and thinner epithelial layers.

The microbiota also produces substances such as choline, short-chain fatty acids or bile acids used by the host organism. Some works show the effect of microflora on the host epigenome, which is manifested not only in the gene expression and in the development of nervous system, but also in neuronal plasticity, learning and memory, and in the emergence of various diseases such as depression, addiction, schizophrenia and cognitive disorders. Based on these findings, the question arises as to whether the above-mentioned diseases are primarily caused by the microbiota (or its disorder) and whether it would be possible to influence the disease by affecting the microbiota. Epigenome is highly variable and its possible binding to the microbiota could be crucial for linking interventions to the microbiota with the therapy and prevention. Microbiota is also affected by many host's factors such as diet, infections suffered, medications, stress, but also by genetic predispositions. The most critical time to affect microbiota (and therefore brain development) is childhood and adolescence. It has been also shown that aging leads to reduction of microbial diversity. At the same time, a healthy lifestyle correlates with a varied microflora [2].

## Intestinal Microbiota-CNS Pathway

The connection between the brain and the intestinal microflora is indisputable. Bacteria communicate with the brain through several nerve-, hormonal- and immune-signalling pathways. The central nervous system (CNS) interferes with the microbiota through endocrine response and during stress. These two-way interactions include the production of bacterial metabolites, immune mediators and direct signalling through the wandering nerve. The immune system also enables this two-way communication and is even responsible for the fact that CNS is the primary target of bacterial mediators. In addition, microbiota and probiotics act on the immature immune system, which can result in changes in the levels of pro- and anti-inflammatory cytokines that affect areas such as hypothalamus. Hypothalamus produces corticotropin releasing hormone (CRH), the main regulator of the hypothalamo-pituitary-adrenal pathway (HPA). In addition, the anti-inflammatory factors induce the activity of indolamine-2,3-deoxygenase and hepatic tryptophan-2,3-dioxygenase enzymes, which catalyse the metabolism of tryptophan-derived kynurenine,

as well as the neurotransmitter serotonin.

Bacteria themselves can produce several neurotransmitters and neuromodulators. For example, some bacteria of the *Lactobacillus* and *Bifidobacterium* strains produce  $\gamma$ -aminobutyric acid (GABA); *Escherichia*, *Bacillus* and *Saccharomyces* spp. produce norepinephrine, *Lactobacillus* F produces acetylcholine and *Bacillus* produces dopamine. It appears that neurotransmitters produced by the microorganisms in the intestinal lumen activate epithelial cells, which then produce molecules acting on the peripheral nervous system axons (PNS) (Figure 1) [3-5]. Previously, microorganisms have never been considered important in the development and functioning of the nervous system or in the pathophysiology of chronic brain diseases such as the Parkinson's or Alzheimer's disease. However, a turnaround occurred when it was shown that the *Toxoplasma gondii* parasite can influence the host's brain in terms of, for example, a reduction in self-preservation or increased sexual activity. Another milestone was the suspicion that intestinal microbiota is responsible for the occurrence of autism spectrum disorders.

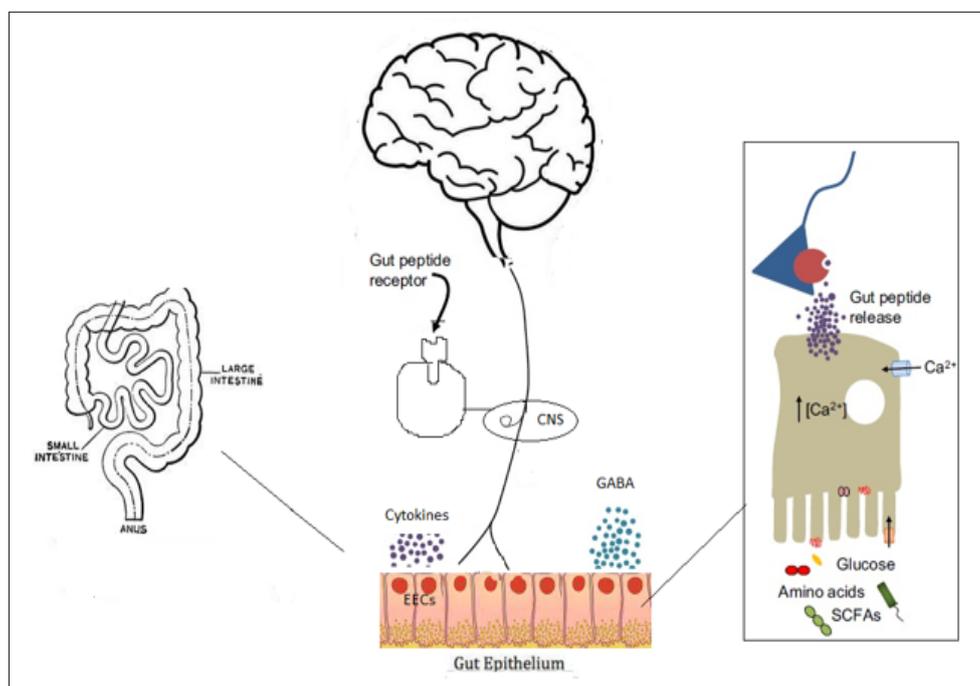


Figure 1: Intestinal microbiota-CNS pathway.

Nevertheless, after the discovery of the human microbiome, its possible association with neuropsychiatric disorders has been ignored for some time. Following the discovery of the signalling pathways, there has been a sharp rise in the interest not only of experts but also of the general public, about this fascinating concept of impact on the brain by intestinal microorganisms. Most current studies on this subject are then based on an analysis of the bacteria present in the faeces. In some articles, words such as “psychobiotic” or “melancholic” microbes occur, or thesis that the human body is just a vehicle for 100 trillion of microorganisms. In addition to the mentioned influence on CNS's neurochemistry, it appears that the

microbiota also played an important role in the evolution of the social brain [6].

## Conclusion

With increasing knowledge, the belief about the intestinal microbiota-brain pathway is growing. The microbiota controls the basic aspects of the CNS, immunity and behaviour of the organism at both the physiological and pathological conditions. Still, the role of microbiota in neuropsychiatric disorders is not yet fully explained. It remains to clarify how the immune, nervous and endocrine systems participate in this pathway during pathological conditions.

At the same time, it must be considered that we have been limited to animal models until now and that the human organism can behave completely differently. The research of microbiota importance gives the hope to patients with serious illnesses, and results of studies sound favourable. The known mechanisms participating in the communication between the intestinal microbiota and the brain have been described, and studies showing the effect of different microflora composition on the health of laboratory animals have been shown. The fecal bacteriotherapy, a method developed a long time ago, has been shown as a possible therapeutic tool, which is however hampered by methodological deficiencies and a few ethical issues.

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