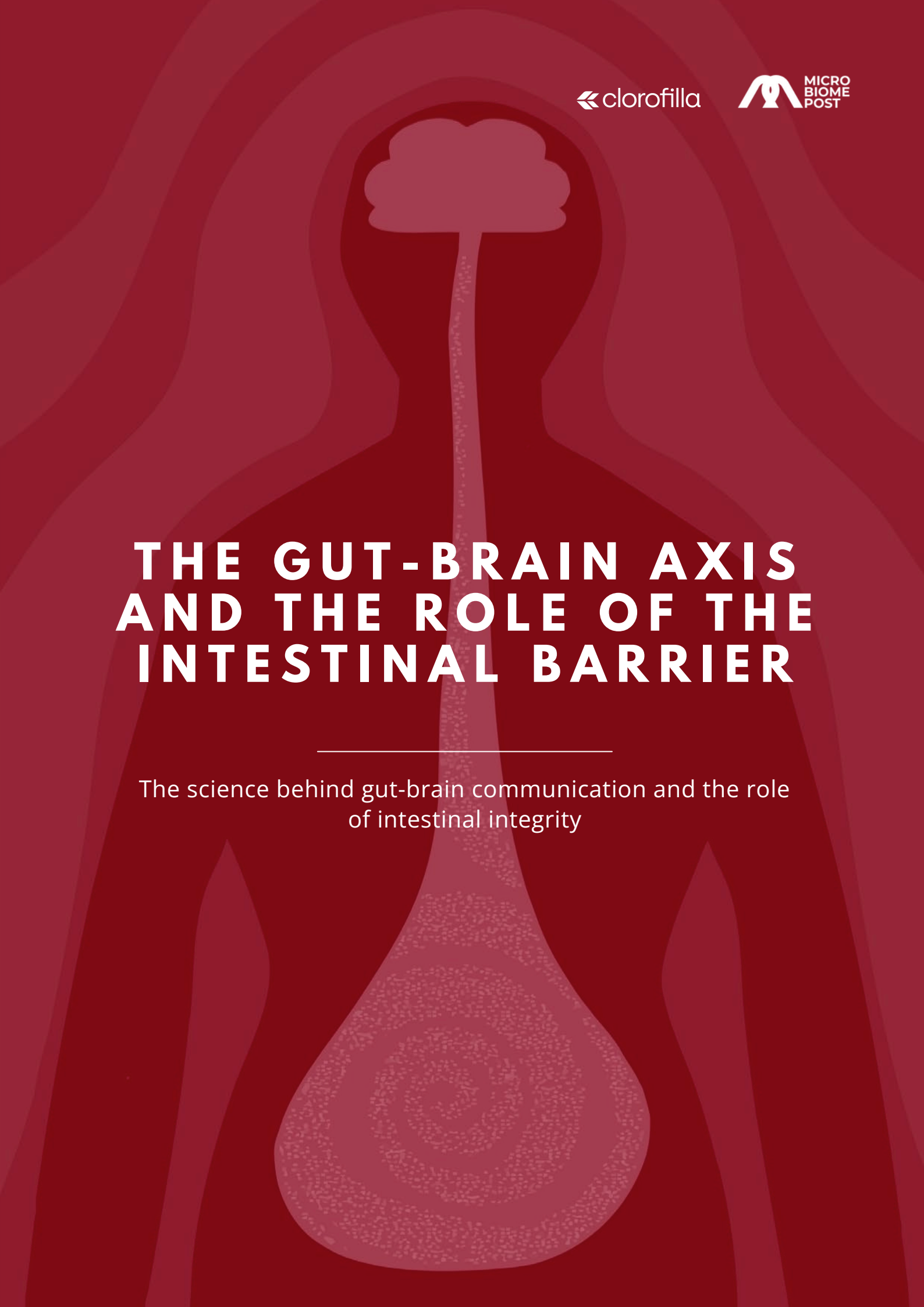
clorofilla

MICRO BIOME POST

THE GUT-BRAIN AXIS AND THE ROLE OF THE INTESTINAL BARRIER

The science behind gut-brain communication and the role of intestinal integrity

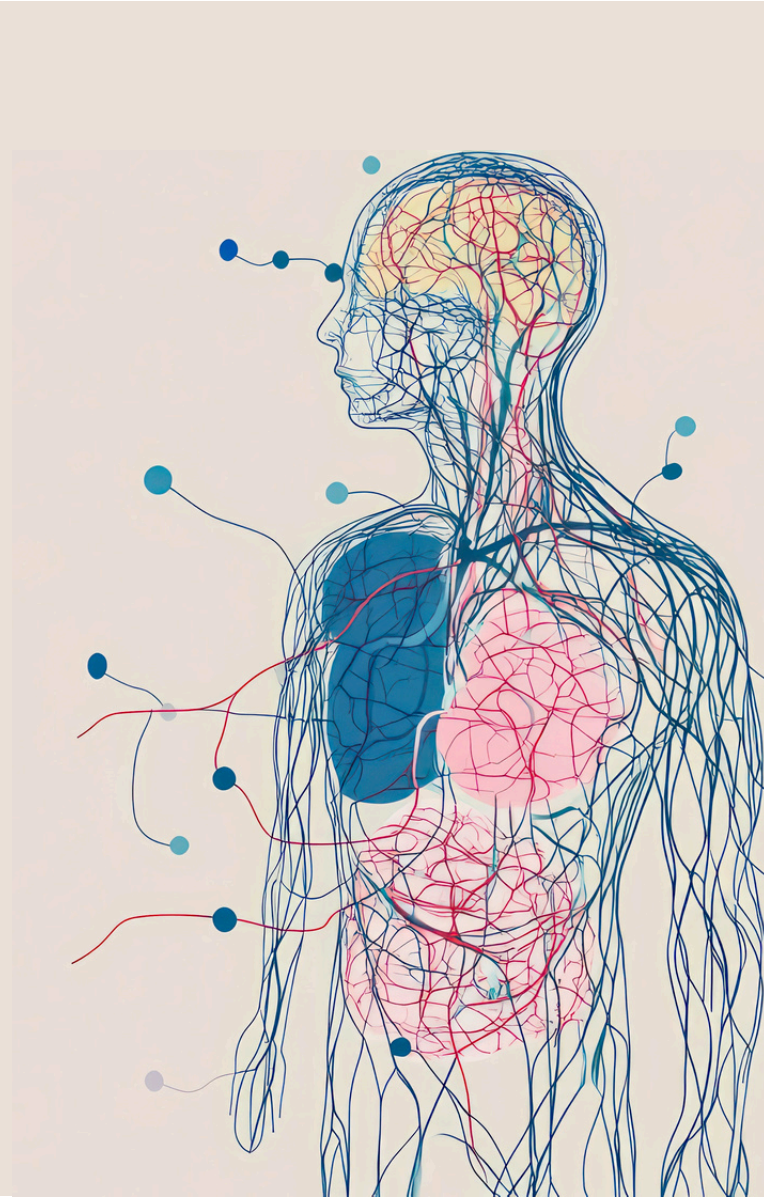


Publisher
Clorofilla srl – scientific publishing

Publishing Director
Massimo Barberi

Clorofilla srl - scientific publishing
Via Podgora 12A, 20122 Milano
Tel +39 02 39523784
www.clorofillaweb.it
info@clorofillaweb.it
ROC Registration n. 25358

The gut-brain axis is a complex, bidirectional communication network that connects the gastrointestinal tract with the central nervous system.
This system integrates neuronal, immune, endocrine, and metabolic signals, all of which play essential roles in maintaining intestinal, cerebral, and microbiome homeostasis.



Over the past decade, scientific evidence has increasingly highlighted the gastrointestinal tract and its resident **microbiota as influential players in neurological function and the pathogenesis of neurodegenerative diseases**, including Parkinson's disease, Alzheimer's disease, Huntington's chorea, motor neuron diseases, various forms of ataxia, and major depressive disorder.

Although gut dysbiosis is clearly implicated in the onset of neurological disorders, it remains unclear whether microbiome alterations are a consequence of brain dysfunction or a contributing causal factor.

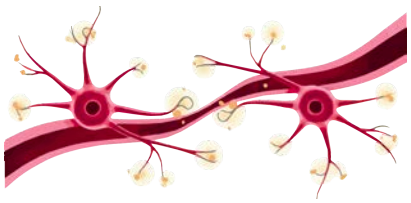
The gut microbiota is capable of producing **a wide range of neuroactive metabolites**, including neurotransmitters such as GABA, norepinephrine, dopamine, and serotonin; amino acids like tryptophan and tyramine; and microbial-derived compounds like short-chain fatty acids (SCFAs) — butyrate, acetate, and propionate — as well as 4-ethylphenyl sulfate.

These substances influence brain physiology through both **direct mechanisms** — such as crossing the blood-brain barrier, altering gut permeability, or promoting local inflammation — and **indirect mechanisms**, including modulation of immune responses or neuronal signaling.

COMMUNICATION PATHWAYS

The gut and brain are in constant dialogue through a network of signals that involve the nervous, immune, and endocrine systems, along with numerous microbiota-derived metabolites.

The enteric nervous system (ENS), often called the "**second brain**," consists of a dense network of neurons capable of functioning independently from the rest of the central nervous system. **The vagus nerve serves as the main communication channel within the gut-brain axis**. It transmits gut-derived signals to the brain and enables central regulation of intestinal functions such as motility, secretion, appetite, satiety, neuroendocrine responses, and inflammatory reflexes.



Certain gut bacteria produce neurotransmitters and bioactive molecules — including GABA, dopamine, serotonin, and acetylcholine — t**hat the ENS uses to maintain continuous communication with the brain**. These molecules can activate the vagus nerve and influence mood, anxiety, and cognitive function.

Gut-brain communication also occurs systemically, independent of direct neural innervation, through **hormones, immune signals, and gut-derived metabolites**. The intestinal endocrine system, composed of a variety of enteroendocrine cells, releases hormones into the bloodstream in response to food intake. These hormones regulate hunger, glycemic balance, and relay satiety signals to the brain — particularly to the hypothalamus and brainstem nuclei, which govern energy homeostasis.

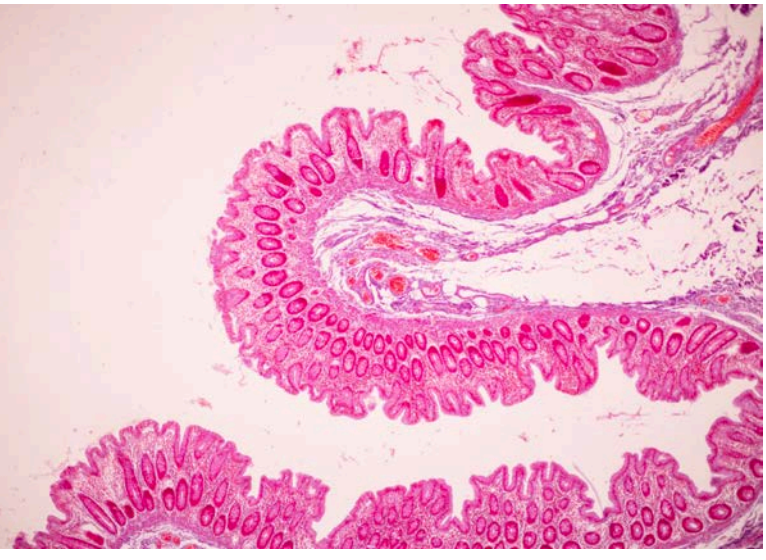
The gut-associated lymphoid tissue (GALT), the body's largest immune cell reservoir, **is another key site of host-microbiota interaction**. Cytokines and chemokines produced within this tissue can enter systemic circulation and interact with the nervous system either through vagal activation or by crossing the blood-brain barrier.
This immune-to-brain communication contributes to neuroinflammatory processes and is implicated in the pathophysiology of various neuropsychiatric disorders.

Microglia, the brain's resident immune cells, play essential neurological roles. **Under chronic stress or dysbiosis, microglia may become dysregulated, triggering sustained neuroinflammation**. Gut microbiota modulate this immune response by producing metabolites such as SCFAs and regulating intestinal barrier integrity. When the barrier is compromised, bacterial components can translocate into circulation, triggering cytokine release and microglial activation.

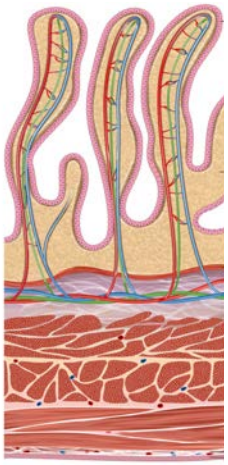
THE INTESTINAL BARRIER: A NEUROIMMUNE GATEKEEPER

The intestinal barrier is a critical regulator of gut-brain axis function. Alongside the blood-brain barrier and meninges, it forms an integrated biological defense system. When this system is compromised, glial cell activation and neurodegenerative cascades may ensue. **Preserving the integrity of these barriers is thus a key strategy for preventing neuroimmune inflammation and associated brain damage**.

Among all biological barriers, the intestinal barrier — due to its direct interaction with the microbiota — represents the most accessible target for gut-brain axis modulation. Anatomically and functionally, it comprises **three primary layers**: the mucus layer, the intestinal epithelium, and the vascular barrier. Together, these layers defend the host against physical and chemical threats while also **preventing the systemic spread of proinflammatory signals and potentially neurotoxic metabolites**.



The **intestinal epithelium** forms the first line of defense against ingested pathogens and is the primary interface between host and microbes. Intestinal epithelial cells (IECs) actively participate in immune signaling through antimicrobial peptide production and antigen presentation.



These cells are bound by tight junctions, whose integrity is regulated by microbial signals, cytokines, and SCFAs. Disruption of tight junctions increases gut permeability, enabling the translocation of pathogens and inflammatory mediators into systemic circulation.

The **mucus layer**, a dynamic and selectively permeable physical barrier, separates gut lumen contents from the intestinal wall. In addition to its protective and lubricating roles, this layer modulates immune activity and inflammation by shaping the microbiota composition and host interactions. Microbiota also directly influence mucus layer homeostasis.

The **vascular barrier** prevents uncontrolled diffusion of molecules from the portal vein to the rest of the body. However, in states of dysbiosis, inflammation, or stress, this protective layer can be weakened, contributing to peripheral immune activation and fueling systemic inflammation.

NEUROTRANSMITTERS AND NEUROACTIVE METABOLITES

The gut microbiota can produce a wide array of neurotransmitters and neuroactive metabolites that profoundly affect brain physiology via the gut-brain axis.

Among the most significant metabolites are **short-chain fatty acids** (SCFAs), produced by the fermentation of indigestible dietary fibers. SCFAs regulate numerous physiological processes, including intestinal homeostasis, immune responses, lipid and glucose metabolism, and provide protection against neuroinflammatory and neurodegenerative processes.

Bile acids, synthesized in the liver and modified by the microbiota, also have neuroactive properties, contributing to inflammation control and neuronal preservation.

Conversely, **trimethylamine-N-oxide** (TMAO), generated via microbial and hepatic processing, has proinflammatory effects and can accumulate in the brain, exacerbating neurodegeneration.

Polyunsaturated fatty acids (PUFAs), essential for brain development and function, are transformed by the microbiota in ways that enhance their biological activity, influencing neuroinflammation, synaptic plasticity, and neurogenesis.

Branched-chain amino acids (BCAAs), derived from diet and microbial metabolism, exhibit anti-inflammatory effects and modulate microglial phenotypes toward anti-inflammatory states.

The microbiota also directly participates in the synthesis and regulation of key neurotransmitters.

Serotonin, largely produced in the gut by enterochromaffin cells in response to luminal stimuli, is regulated by microbiota-driven availability of its precursor, tryptophan. Microbial metabolism of tryptophan generates indole derivatives with immunomodulatory properties implicated in several neurodegenerative diseases.
GABA, the main inhibitory neurotransmitter in the brain, is synthesized by microbial strains such as Bacteroides, Bifidobacterium, and Lactobacillus. It is crucial for excitatory-inhibitory balance, synaptic plasticity, and motor control.
Dopamine, central to motivation, reward, and motor regulation, is influenced by gut microbial composition.
Acetylcholine, essential for learning, memory, and attention, may be diminished under dysbiosis due to increased acetylcholinesterase activity.
Glutamate, the primary excitatory neurotransmitter, is also microbiota-regulated; its dysregulation can contribute to excitotoxicity and neurodegeneration.

Additionally, gut microbes can influence the production and action of neuroactive peptide hormones.

Ghrelin, involved in appetite and neurogenesis, is affected by microbiota composition.
Leptin, secreted by adipose tissue, plays roles in energy metabolism and brain inflammation and varies with microbiota changes — with potential relevance for cognitive decline.
GLP-1, an incretin hormone with neuroprotective effects, is produced in response to food intake and regulated by microbial metabolites such as SCFAs, bile acids, indoles, and PUFAs.

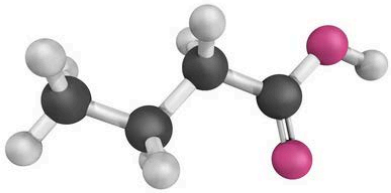
THE CENTRAL ROLE OF BUTYRATE

Among all microbiota-derived metabolites, butyrate stands out for its **broad benefits on the gut, immune system, and brain.**

It is a key regulator of the gut-brain axis and, along with other SCFAs, helps reinforce intestinal epithelial barrier integrity. Butyrate enhances expression of tight junction proteins like claudin-1, and promotes the cellular localization of occludin and zonula occludens-1.
It also stimulates mucin-2 expression, a glycoprotein critical for mucus layer formation and mucosal protection.

Because all non-vagal microbiota-to-brain signaling must traverse both the intestinal epithelium and the blood-brain barrier, **a well-maintained intestinal barrier is essential for balanced communication**.

In the enteric nervous system, butyrate **promotes serotonin and gut hormone release, activating vagal pathways and endocrine responses** with significant effects on the brain.



Immunologically, butyrate shapes both peripheral and neuroimmune environments. It **supports anti-inflammatory responses** by promoting regulatory T-cell differentiation, enhancing anti-inflammatory cytokines like IL-10 and TGF-β, and inhibiting dendritic cell maturation.

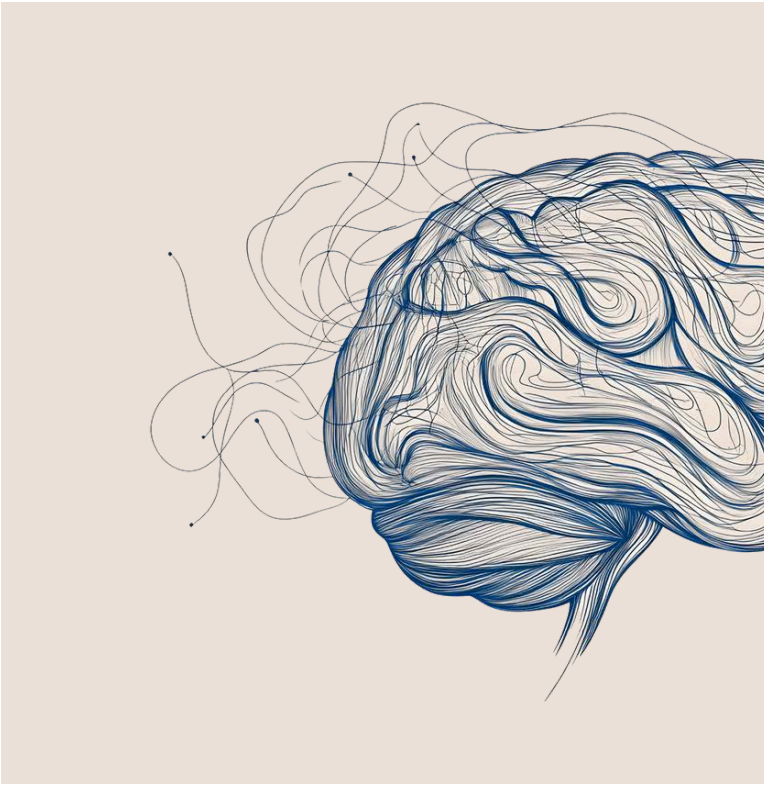
It also **suppresses proinflammatory cytokines** (e.g., IFN-γ, TNF-α, IL-6) via NF-κB inhibition in macrophages and endothelial cells, protects microglia from overactivation, and promotes apoptosis of hyperactive immune cells — all contributing to reduced neuroinflammatory damage.

Furthermore, butyrate **enhances brain-derived neurotrophic factor (BDNF) expression**, crucial for neuronal development, synaptic plasticity, and memory.

Dysbiosis is associated with decreased BDNF levels and impaired cognitive function.

Observational studies in older adults have linked higher dietary butyrate intake to better cognitive performance, especially in executive functions, memory, and processing speed — effects that appear dose-dependent and biologically plausible due to butyrate's anti-inflammatory, neuroprotective, and epigenetic actions.

While further research is needed to fully elucidate its direct effects on the central nervous system, current evidence supports butyrate as a key molecule in gut-brain communication, capable of sustaining immune balance, regulating inflammation, and promoting mental well-being.



REFERENCE

1. Silva YP, Bernardi A, Frozza RL. The Role of Short-Chain Fatty Acids From Gut Microbiota in Gut-Brain Communication. Front Endocrinol (Lausanne). 2020 Jan 31;11:25. doi: 10.3389/fendo.2020.00025. PMID: 32082260; PMCID: PMC7005631.

2. Loh JS, Mak WQ, Tan LKS, Ng CX, Chan HH, Yeow SH, Foo JB, Ong YS, How CW, Khaw KY. Microbiota-gut-brain axis and its therapeutic applications in neurodegenerative diseases. Signal Transduct Target Ther. 2024 Feb 16;9(1):37. doi: 10.1038/s41392-024-01743-1. PMID: 38360862; PMCID: PMC10869798.

3. Munir MU, Ali SA, Chung KHK, Kakinen A, Javed I, Davis TP. Reverse engineering the Gut-Brain Axis and microbiome-metabolomics for symbiotic/pathogenic balance in neurodegenerative diseases. Gut Microbes. 2024 Jan-Dec;16(1):2422468. doi: 10.1080/19490976.2024.2422468. Epub 2024 Nov 10. PMID: 39523450; PMCID: PMC11556280.

4.Stilling RM, van de Wouw M, Clarke G, Stanton C, Dinan TG, Cryan JF. The neuropharmacology of butyrate: The bread and butter of the microbiota-gut-brain axis? Neurochem Int. 2016 Oct;99:110-132. doi: 10.1016/j.neuint.2016.06.011. Epub 2016 Jun 23. PMID: 27346602.

5. Elford JD, Becht N, Garssen J, Kraneveld AD, Perez-Pardo P. Buty and the beast: the complex role of butyrate in Parkinson's disease. Front Pharmacol. 2024 Apr 17;15:1388401. doi: 10.3389/fphar.2024.1388401. PMID: 38694925; PMCID: PMC11061429.

6. Suda K, Matsuda K. How Microbes Affect Depression: Underlying Mechanisms via the Gut-Brain Axis and the Modulating Role of Probiotics. Int J Mol Sci. 2022 Jan 21;23(3):1172. doi: 10.3390/ijms23031172. PMID: 35163104; PMCID: PMC8835211.

7. Tu J, Zhang J, Chen G. Higher dietary butyrate intake is associated with better cognitive function in older adults: evidence from a cross-sectional study. Front Aging Neurosci. 2025 Mar 28;17:1522498. doi: 10.3389/fnagi.2025.1522498. PMID: 40224959; PMCID: PMC11985818.