The microbiota-immune interaction in the gut-brain axis

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***Abstract**: The growing body of evidence on the role of the gut microbiota (GM) in regulating the bidirectional gut-brain axis suggests the existence of a complex network that also involves the immune system (IS). The interaction between GM and IS is crucial for the development and modulation of immune responses, through microbial metabolites such as short-chain fatty acids (SCFAs), which influence both mucosal immunity and neuroinflammation. SCFAs regulate immune homeostasis and the function of the blood-brain barrier (BBB), affecting microglia, astrocytes, and neurons. These mechanisms are particularly relevant in neurological disorders such as Parkinson's disease, where dysbiosis and SCFA alterations contribute to neurodegeneration. Although most results derive from preclinical studies and should be interpreted with caution, the use of probiotics, prebiotics, and postbiotics represents a promising therapeutic approach. The "microbiota-immune-brain" model opens new insights for the prevention and treatment of neurological and psychiatric disorders, although larger and more specific clinical trials are needed to confirm its applicability in humans.*

***Key words:** Psychoneuroendocrinoimmunology (PNEI), Short-chain fatty acids (SCFA), Intestinal barrier, Blood-brain barrier, Probiotics, Parkinson's disease*

Introduction

The gut-brain interaction has long been a focus of scientific and clinical research, due to its therapeutic potential in gastrointestinal, metabolic, psychiatric, and neurological disorders (Dinan & Cryan, 2017). Bidirectional communication pathways between the gut and the brain are well established and include (Carabotti *et al.*, 2015):

- neural pathways: interactions between the central nervous system (CNS), enteric nervous system (ENS), and the autonomic nervous system;
- endocrine pathways: particularly via the hypothalamic-pituitary-adrenal (HPA) axis and gastrointestinal hormones that regulate food intake;
- microbial pathways: mediated by the activity of the gut microbiota (GM) through its metabolites;
- immune pathways: involving cytokines produced by the gut-associated lymphoid tissue (GALT).

The paradigm of psychoneuroendocrinoimmunology (PNEI) emphasizes that these communication pathways function as an integrated network, supported by signaling molecules recognized by cells across all organs and systems (Bottaccioli & Bottaccioli, 2017). The IS plays a significant role in the gut-brain interaction, both influencing and being influenced by other systems. A key mechanism is the effect of GM-derived metabolites on immune cells, whose production depends on the host's PNEI balance. The IS thus acts as a coordinator in the microbiota-gut-brain communication and represents a potential target for new preventive and therapeutic strategies in mental and neurological health (O'Riordan *et al.*, 2025).

Microbiota and immune system in the gastrointestinal tract

Although until recently the IS was viewed solely as a defense mechanism, within the PNEI framework it is now considered a regulatory system, together with the nervous and endocrine systems. Moreover, the IS acquires the ability to protect the host from pathogenic microbes in part through its interaction with the GM. This interaction, which occurs through various mechanisms throughout life, is essential for the proper and complete development of both the innate and adaptive immune responses (Chung *et al.*, 2012; Ratsika *et al.*, 2023).

Most of our knowledge about the interaction between the IS and the microbiota comes from studies on germ-free (GF) mice (Luczynski *et al.*, 2016), which are born and raised under sterile conditions and therefore lack microbial colonization. GF mice exhibit immature GALT, reduced numbers of intestinal lymphocytes, decreased production of immunoglobulin A (IgA), and impaired secretion of antimicrobial peptides (Round *et al.*, 2009). Many of these deficits can be reversed by re-

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa20961

colonization of the gut; however, some alterations can only be corrected if colonization occurs during early developmental stages (Hansen *et al.*, 2012).

Conversely, innate immunity contributes to the stabilization of the mutualistic symbiosis between microbiota and host by regulating mucus secretion, antimicrobial peptides, and antibodies along the intestinal epithelium (Kinnebrew & Pamer, 2012). Animal model studies have shown that defects in Toll-like receptor (TLR)-dependent signaling are associated with dysbiosis and intestinal inflammation (Araki *et al.*, 2005). Adaptive immunity also plays a regulatory role on the GM. For instance, mice lacking T and B cells exhibit dysbiosis and reduced microbial diversity (Kwon *et al.*, 2015), while the absence of B cells and antibodies results in altered microbial composition, characterized by a decrease in Clostridiaceae and an increase in the genera *Paracoccus* and *Lactococcus* (Shulzhenko *et al.*, 2011).

Short-chain fatty acids as immunoregulatory molecules

Starting from dietary components and host-derived molecules, the GM synthesizes a vast array of metabolites, some of which act as signaling molecules capable of integrating into the PNEI network, thereby contributing to host physiological regulation. Among the microbial metabolites exerting such regulatory functions, the most prominent examples are short-chain fatty acids (SCFAs), which include, among others, acetate, propionate, and butyrate. SCFAs are produced in the colon through the fermentation of indigestible plant polysaccharides, particularly oligofructose, inulin, pectin, and arabinoxylan (Kumar *et al.*, 2012).

SCFAs generated in the intestinal lumen are absorbed and partially utilized as an energy substrate by intestinal epithelial cells. In the human gastrointestinal tract, the colon contains the highest concentrations of SCFAs, with a typical ratio of 60:20:20 for acetate, propionate, and butyrate, respectively (Cummings *et al.*, 1987). The enzymatic capacity to produce SCFAs varies considerably among microbial taxa. Bacteria belonging to the phylum *Firmicutes* – particularly the genera *Faecalibacterium*, *Clostridium*, *Roseburia*, *Eubacterium*, and *Anaerostipes* – are major butyrate producers. *Bifidobacterium* species mainly produce acetate, whereas both acetate and propionate can be derived from mucus fermentation by mucin-degrading bacteria such as *Akkermansia muciniphila* (Rivière *et al.*, 2016; Derrien *et al.*, 2004).

SCFAs reinforce the integrity of the intestinal epithelial barrier by promoting the assembly of tight junctions (TJs) and supporting the homeostasis of regulatory T (Treg) cells (Kelly *et al.*, 2015; Smith *et al.*, 2013). SCFAs can also reach peripheral organs, where they exert both metabolic and immunomodulatory effects via multiple mechanisms.

First, SCFAs may enter various cell types, including immune cells, through pas-

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa20961

sive diffusion or via monocarboxylate transporters (MCTs). B cells can absorb and metabolize SCFAs, leading to elevated acetyl-CoA levels that support fatty acid synthesis and fuel the tricarboxylic acid cycle – an essential energy source for immune cell differentiation (Kim *et al.*, 2016).

Second, SCFAs act as key epigenetic regulators. In particular, propionate and butyrate are known inhibitors of histone deacetylases (HDACs), thereby modulating gene expression (Licciardi *et al.*, 2011).

Third, SCFAs function as bona fide signaling molecules. Like hormones, neurotransmitters, and cytokines, they bind to specific membrane receptors, notably G protein-coupled receptors (GPCRs) such as Ffar2 and Ffar3 (Brown *et al.*, 2003). In the IS, Ffar3 is expressed by medullary thymic epithelial cells, B lymphocytes, splenic $CD8^+$ dendritic cells, neutrophils, ILC3 $Nkp46^+$, and circulating monocytes. Ffar2 is also found on leukocytes including eosinophils, basophils, neutrophils, monocytes, and dendritic cells (Kim *et al.*, 2014). Another SCFA receptor, Olfr78, is expressed by T lymphocytes ($CD8^+$, γδ, and NKT cells), B lymphocytes (follicular and germinal center), and ILC2 (Kim, 2021).

Through these combined mechanisms, SCFAs can exert a significant impact on the IS. For instance, they differentially regulate the activity of various innate lymphoid cell (ILC) populations, particularly enhancing ILC3 responses, thereby increasing host resistance to *Clostridium difficile* infection (Kim, 2021).

Microbiota, metabolites, immunity and brain

Alterations in the GM and in the production of microbial metabolites have been associated with a wide range of immune-related neurological disorders, including neurodevelopmental and neurodegenerative conditions (Sittipo *et al.*, 2022). Once again, GF mice have proven instrumental in revealing the importance of the GM in immune and neural functions. These animals display impaired brain function in terms of learning, recognition, and behavior, associated with altered serotonergic neurotransmission and reduced levels of brain-derived neurotrophic factor (BDNF) (Heitz *et al.*, 2011; Bercik *et al.*, 2011).

Moreover, both GF mice and antibiotic-treated dysbiotic mice exhibit abnormalities in the development of the microglia, the main immune cells responsible for CNS homeostasis, as well as dysregulated production of inflammatory cytokines. GF mice also show increased permeability of the blood-brain barrier (BBB), accompanied by decreased expression of TJ proteins, closely resembling the loss of intestinal barrier integrity observed under dysbiosis and inflammation (Braniste *et al.*, 2014). This increased BBB permeability facilitates the entry of harmful molecules into the brain, leading to neuroinflammation. However, microbial colonization or

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa20961

correction of dysbiosis – particularly when performed during early developmental stages – can restore BBB integrity and reverse the associated dysfunctions (Wang *et al.*, 2018; Erny *et al.*, 2015).

There is now substantial evidence that SCFAs are among the key mediators of microbiota effects on the brain, through mechanisms that often involve immunoregulatory pathways, either directly or indirectly. For instance, by binding to their receptors on enteroendocrine cells, SCFAs stimulate the release of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), which not only transmit satiety signals to the brain but also contribute to the regulation of neuroinflammation (Christiansen *et al.*, 2018).

Butyrate supplementation has been shown to prevent BBB disruption and promote neurogenesis via HDAC inhibition (Fessler *et al.*, 2013). Strengthening BBB integrity by SCFAs plays a crucial role in controlling nutrient transport from the bloodstream into the brain and in maintaining CNS homeostasis. Propionate, for example, interacts with the Ffar3 receptor on endothelial cells, providing protection against nonspecific microbial infections and oxidative stress at the BBB (Hoyles *et al.*, 2018).

Monocarboxylate transporters (MCTs), which are abundantly expressed in endothelial and brain tissues, may facilitate SCFA transport across the BBB (Pierre & Pellerin, 2005). Within the CNS, SCFAs can be recognized by microglia, astrocytes, and neurons, which then modulate neurological and behavioral processes (Silva *et al.*, 2020).

In murine models, SCFA treatment induces functional shifts in microglia toward an anti-inflammatory and neuroprotective phenotype. For example, butyrate administration suppresses microglial activation and lipopolysaccharide (LPS)-induced depressive-like behavior (Yamawaki *et al.*, 2017). In cortical astrocytes, acetate upregulates genes involved in anti-inflammatory pathways, while propionate increases IL-22 expression (Spichak *et al.*, 2021). Furthermore, SCFAs promote the proliferation of human neural progenitor cells (Yang *et al.*, 2020). Overall, SCFAs play a key role in the microbiota-gut-brain axis by both modulating BBB integrity and crossing it to directly influence CNS cell populations.

New therapeutic horizons: the example of Parkinson's disease

Recent evidence linking the GM to psychiatric and neurological disorders through the involvement of the IS has led to the development of therapeutic strategies aimed at modulating the GM to influence immune responses and brain function. Several approaches are currently under investigation, including probiotics, prebiotics, synbiotics, postbiotics, and fecal microbiota transplantation (FMT), ideally combined with dietary education and healthy lifestyle interventions that support long-term efficacy and serve a critical preventive function. Given the data discussed

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa20961

above, the direct use of microbial metabolites – particularly SCFAs – represents a highly promising strategy deserving of further investigation (O'Riordan *et al.*, 2025).

Parkinson's disease (PD) offers a compelling pathogenic framework for exploring microbiota-immune-brain interactions in both the development and treatment of the disorder. PD is a progressive, age-related neurodegenerative disease characterized by the accumulation of alpha-synuclein (α-syn), loss of dopaminergic neurons, and consequent motor dysfunction. It is also associated with immune dysregulation and neuroinflammation (Tan *et al.*, 2020). Notably, constipation often arises during the prodromal phase, years before clinical diagnosis, suggesting that intestinal inflammation and dysbiosis may play a role in the pathogenesis (Abbott *et al.*, 2001).

Most PD patients exhibit increased intestinal permeability (Forsyth *et al.*, 2011), and animal models have shown that the GM modulates pathways that promote α-syn aggregation, impairs clearance of insoluble protein aggregates, triggers α-syn-dependent microglial activation, and facilitates motor dysfunction (Sampson *et al.*, 2016). Compared to healthy individuals, PD patients present lower levels of butyrate-producing bacteria such as *Blautia, Coprococcus, Roseburia,* and *Faecalibacterium* (Keshavarzian *et al.*, 2015). Consistent with this, fecal SCFA concentrations are reduced in PD patients relative to controls (Aho *et al.*, 2021).

Several studies have demonstrated the protective effects of butyrate in murine models of PD, where treatment led to neurobehavioral improvements, prevention of dopaminergic neurodegeneration, improved BBB function, and increased production of intestinal peptides such as GLP-1 (Liu *et al.*, 2017). It is hypothesized that therapies involving probiotics and butyrate may help counteract the detrimental effects of α-syn on Treg differentiation – typically inhibited by α-syn, which promotes Th17 polarization – through histone acetylation regulation and upregulation of anti-inflammatory cytokines such as IL-4 and IL-10 (Troy & Kasper, 2010; Li *et al.*, 2023).

Overall, probiotics, prebiotics, synbiotics, and FMT may alleviate both intestinal and motor symptoms in PD through multiple mechanisms. Neuroprotective effects are thought to involve the reduction of BBB damage, glial cell activation, neuroinflammation, and α-syn aggregation. At the same time, microbial therapies can help restore eubiosis, dampen inflammation, and repair the intestinal barrier, thereby improving mucosal immune responses (Zhang *et al.*, 2023).

However, the role of SCFAs in PD remains complex and controversial. For instance, SCFA administration in GF mice overexpressing α-syn has been shown to induce neuroinflammation by promoting α-syn aggregation, microglial activation, and motor deficits (Sampson *et al.*, 2016). In another murine model, butyrate exacerbated dopaminergic neuronal loss, enhanced neuroinflammation, increased microglial and astrocyte activation, and promoted colonic inflammation (Qiao *et al.*, 2020).

PNEI review – ISSNe 2532-2826 – DOI: 10.3280/pnei2025oa20961

Conclusions

The communication pathways initially known as the "gut-brain axis", and later refined as the "microbiota-gut-brain axis," have revealed an increasingly complex level of organization, in which the IS plays a central and integrative role. This has led to the formulation of a network model of microbiota-immune-brain interactions (Figure 1). It is important to reiterate, however, that most of the current knowledge on these interactions derives from animal models, which inherently fail to replicate the full complexity of human physiology. As such, results must be interpreted with caution. Future research should prioritize clinical, observational, and longitudinal studies that incorporate genetic, environmental, social, and cognitive factors unique to the human species to better understand the actual impact of microbiota-immune-brain interactions on human health.

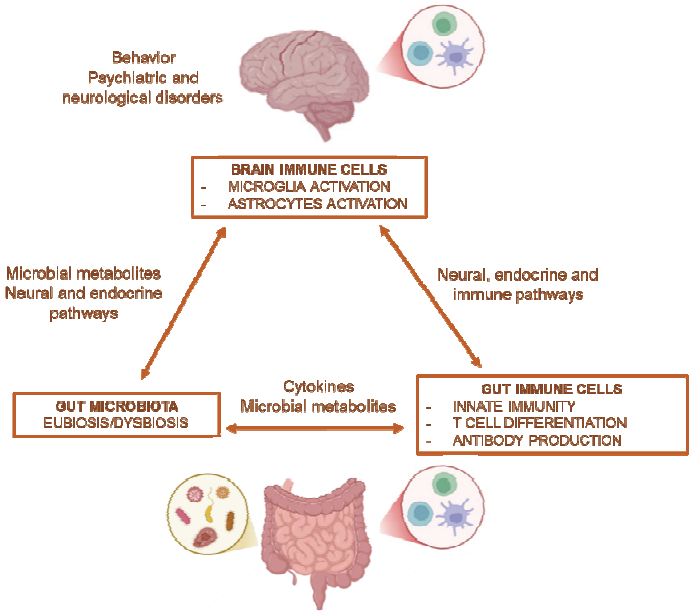

Figure 1. Microbiota-immunity-brain interactions. The GM, primarily through the production of metabolites, shapes the development and function of the IS both at the intestinal and brain levels. In turn, the IS contributes to the establishment and maintenance of a healthy GM (eubiosis) under physiological conditions. Dysbiosis, accompanied by altered microbial metabolite production, is associated with immune dysfunction that, in the brain, involves microglia and astrocytes. In a network-based model, microbiota-immune-brain interactions regulate cerebral homeostasis, whose disruption may lead to behavioral alterations and the onset of psychiatric and neurological disorders. Created with https://BioRender.com

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