THE INTESTINAL MICROBIOTA
Leader of our behavior and health

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INTRODUCTION

There is a **bidirectional communication** between the **central nervous system** (CNS) and **gastrointestinal tract** (GIT), which are communicated through the vagus nerve and the hypothalamic–pituitary–adrenal (HPA) axis. Recent years have witnessed the rise of the **gut microbiota** as a key factor in this communication, contributing to maintain the **homeostasis** and influencing the **brain function and behavior**. The **deregulation** of this axis could lead to a variety of disorders like irritable bowel syndrome (IBS), stress, obesity, pain, autism and multiple sclerosis. This emerging concept suggests **therapeutic opportunities** in which the gut microbiota represents a tractable strategy for the management of complex CNS disorders.

OBJECTIVES

This review aims to:

- Introduce the basics and relationship of brain–gut–microbiota axis.
- Describe the importance of intestinal microbiota, mechanisms of action and their influence on the CNS and health.
- Introduce therapeutic applications with the goal of treating CNS disorders.

METHODOLOGY

- Data comes from reviews searched on **PubMed Central** and **ScienceDirect** since September (2014) to February (2015).
- **Paper selection**: use of different strategies in order to search the most relevant reviews. These were selected according to their historical importance and data of publication.
  — Strategy example: *"Brain-Gut-Microbe[All Fields] AND ("communication"[MeSH Terms] OR "communication"[All Fields]) AND (("in"[All Fields] AND "health"[All Fields]) OR "in health"[All Fields]) AND ("disease"[MeSH Terms] OR "disease"[All Fields])".*

INTESTINAL MICROBIOTA [1]

The GIT is inhabited with **10^{13} – 10^{14} microorganisms**, with 1000 species and more than 7000 strains. The microbiome 70–75% is defined by two phylotypes, ***Bacteroidetes*** and ***Firmicutes***. There is a significant interpersonal variation in the enteric microbiota, but there seems to be a balance that confers health benefits and an alteration can negatively influence the wellbeing of the individual. Several factors may alter the microbiome such as infection, disease, diet, and antibiotics.

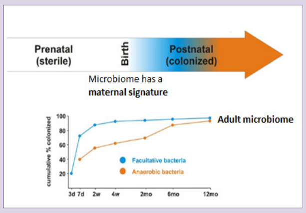

Figure 1 *(modified)*. Development of the microbiome in early life [1]

FUNCTIONAL RELEVANCE OF THE MICROBIOTA [1]

The studies with **germ-free** (GF) **animals** have offered the most revealing insights about function of the microbiota.

The **microbiota is essential** for:

- Normal GIT motility and maintenance of intestinal barrier function.
- Expression of TLR family in GIT.
- Development of the gut associated lymphoid tissue (GALT) and in IgA secretion.
- Support normal digestion and host metabolism (a significant energy source for humans is the bacterial metabolite short-chain fatty acids (SCFAs).
- Prevention of colonization by pathogens.

MICROBIOTA AND CENTRAL NERVOUS SYSTEM [1,4]

The **microbiota** use a huge variety of **mechanisms to influence CNS function**, the vagus nerve and tryptophan metabolism are the most important. The other mechanisms are:

- Altering microbial composition
- Immune activation
- Microbial metabolites
- Microbial neurometabolites
- Bacterial cell wall sugars

There are different **pathways involved in bidirectional communication** between the gut microbiota and the brain. The neuroimmune and neuroendocrine systems, the autonomic nervous system (sympathetic and parasympathetic) and the enteric nervous system are the pathways that allow the communication between the gut microbiota and the CNS.

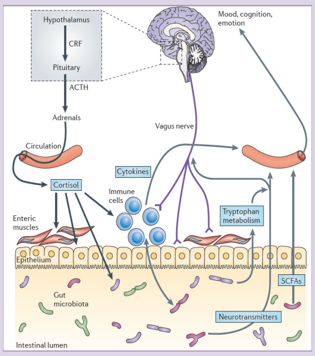

Figure 2. Pathways involved in bidirectional communication between the gut microbiota and the brain [4]

BIDIRECTIONAL INFLUENCE BETWEEN MICROBIOTA AND CNS IN STRESS [1,4]

The **HPA axis** is the endocrine core of the stress system; recent studies demonstrated that the composition of the intestinal **microbiota influences** the development of an appropriate **stress** response later in life. Moreover, there is a critical window in early life which colonization must occur to ensure normal development of the HPA axis.

At the **neuronal level**, GF animals had:

- ↓ Brain-derived neurotrophic factor (**BDNF**)
- ↓ NMDA receptor subunit 2A (**NR2A**)
- ↓ Serotonin receptor 1A (**5-HT 1A**)

↑ Anxiety

The **CNS also can alter the microbiome**. The stress induces changes in the motility, secretion and intestinal permeability, thus altering the GIT environment in which bacteria reside what in turns alters the composition of the microbiome.

INFLUENCE OF THE MICROBIOTA IN INTESTINAL DISORDERS [1]

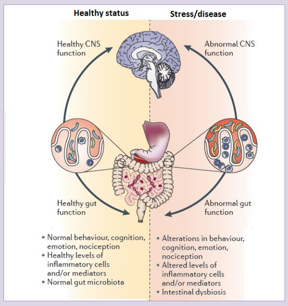

Figure 3 *(modified)*. Impact of the gut microbiota on the gut–brain axis in health and disease [4]

Inflammatory bowel disease (IBD) is a disorder with a GIT microbial signature although it isn't clear whether these changes are responsible for causing this disease. The **changes in the microbiota** are characterized by increases in *Proteobacteria* and a decline in *Firmicutes* and *Bacteroidetes*. Although the pathogenesis is still not completely understood, it is clear that the psychological stress, a factor which can perturb the microbiota, exacerbates the condition.

The best evidence to date **the involvement of the microbiota in disease** states comes from **irritable bowel syndrome** (IBS). There is a role of the microbiota in the pathophysiology of IBS which describes the development of IBS following an episode of bacteriologically confirmed gastroenteritis (post-infectious IBS).

THE MICROBIOTA IN CNS-RELATED CONDITIONS [4]

The **microbiota composition** is involved in some **behavioral disorders** such as stress, anxiety and depression. However, this composition of gut microbiota may also have a role in several other conditions that involve the CNS.

THERAPEUTIC OPPORTUNITIES OF PROBIOTICS [2,3]

Probiotics are emerging as potential therapeutics for stress-related gastrointestinal disorders such as IBS, reducing the anxiety and stress response and improving mood in IBS patients. The **mechanisms** by which probiotics works is a very complex network of events like displacement of pathogens, production of bacteriocins, enhancement of mucosal barrier function and modulation of the immune system.

PROBIOTIC	EFECTS ON THE HOST
***Bifidobacterium infantis* 35624**	Normalize immune responses and restore basal noradrenaline concentrations in rats subjected to early life stress (maternal separation).
***Lactobacillus rhamnosus* JB-1**	Decrease anxiety, reduce the stress-induced by high corticosterone levels in plasma and alter the mRNA expression of $GABA_A$ and $GABA_B$ receptors in brain.

Table 1. Examples of probiotics and brief description of its effects on the host

CONCLUSIONS

The **intestinal microbiota** plays an important role in the communication between the CNS and the TGI, it have consequences in our health and in some aspects of our behavior. **Changes in intestinal microbiota** or lack of it in germ-free animals involves a wide range of **problems** such as an increase in responses to stressors, lower likelihood of obesity, worse development of the immune system and higher probability to develop irritable bowel disease.

The communication between **the brain–gut–microbiota in health and disease**, still require a broad understanding of the intervention of the intestinal microbiota and fully be able to differentiate between normal microbiota and which is found during a disease. The discovery of the influence of the intestinal microbiota in different aspects of behavior and health leads to suggest new **therapeutic applications** as the use of probiotics to solve some disorders.

REFERENCES

1. Grenham, S., Clarke, G., Cryan, J.F., and Dinan, T.G. (2011). **Brain–Gut–Microbe Communication in Health and Disease**. *Frontiers in Physiology*, 2, 94. doi:10.3389/fphys.2011.00094.
2. Cryan, J. F. and Dinan, T. G. (2012). **Regulation of the stress response by the gut microbiota: Implications for psychoneuroendocrinology.** *Psychoneuroendocrinology*, 1369,1378, doi:10.1016/j.psyneuen.2012.03.007.
3. Bravo, J.A., Julio-Pieper, M., Forsythe, P., Kunze, W., Dinan, T.G., Bienenstock, J. and Cryan, J.F. (2012). **Communication between gastrointestinal bacteria and the nervous system**. *Current Opinion in Pharmacology*, 667,672. doi: 10.1016/j.coph.2012.03.010.
4. Cryan, J.F. and Dinan, T.G. (2012). **Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour**. *Nature Reviews Neuroscience*, 701,712. doi:10.1038/nrn3346.

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