Gut Microbiota Alterations in Multiple Sclerosis

Subjects: Pathology

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Multiple sclerosis (MS) is a neuroinflammatory disease characterized by immune cell infiltration in the central nervous system and destruction of myelin sheaths. Alterations of gut bacteria abundances are present in MS patients. In mouse models of neuroinflammation, depletion of microbiota results in amelioration of symptoms, and gavage with MS patient microbiota exacerbates the disease and inflammation via Th17 cells.

gut microbiota multiple sclerosis neuroinflammation

1. Introduction

Multiple sclerosis (MS) is a complex inflammatory disease of the central nervous system (CNS) that causes a wide range of clinical symptoms, including physical and cognitive deficits. Despite its origin being unknown, the pathology involves both genetic and environmental factors [1], leading to immune cell infiltration and destruction of myelin sheaths and axons. This neurodegenerative disorder is characterized by sporadic abnormalities and gradual neurodegeneration and is triggered by complex, dynamic interplay between the immune system, glial cells, and neurons. New treatments targeting immune cells are now efficient in MS patients reducing relapse, lesion load in CNS, and delaying progression of the disease [2][3][4]. However, some patients with aggressive disease forms do not respond to the treatments, and patients with progressive disease forms still undergo accumulation of CNS lesions and disabilities. Therefore, the need for new therapies in MS is crucial and depends on a better understanding of pathological mechanisms occurring in MS. Since 2015, the first descriptions of gut microbiota dysbiosis in MS patients [5][6] have opened new perspectives for therapies in MS. In parallel, exploration of immune responses linked to microbiota modifications highlighted the potential deleterious and regulatory effects of different cell types. Investigations using germ-free (GF) mice have demonstrated the impact of the gut microbiota on MS experimental models. In experimental autoimmune encephalomyelitis (EAE), an experimental model of MS, the gut microbiota influences the immune response by affecting Th1-Th17/Th2 cell balance, Treg cells, and humoral immunity [7].

2. Gut Microbiota Alterations in Multiple Sclerosis

2.1. Gut-Brain Axis

With the discovery of numerous nerve endings in the intestine, the enteric nervous system has been considered the second brain [8]. Indeed, there is a close link between the brain and the gut consisting of a bidirectional

communication system described as the gut-brain axis (summarized in **Figure 1**). Indeed, the central nervous system (CNS) has the ability to regulate intestinal motility as well as to orchestrate local immunity [9] via neuromediators involving the vagus nerve and the hypothalamic-pituitary-adrenal axis. In return, the digestive system can regulate components of the nervous system such as appetite [10] or mood [11]. These communications take place mainly through the neuroendocrine pathways, involving cytokines, neurotransmitters, and neuropeptides [12]. The immune system, interacting with the intestinal microbiota, is also a major player in these communications.

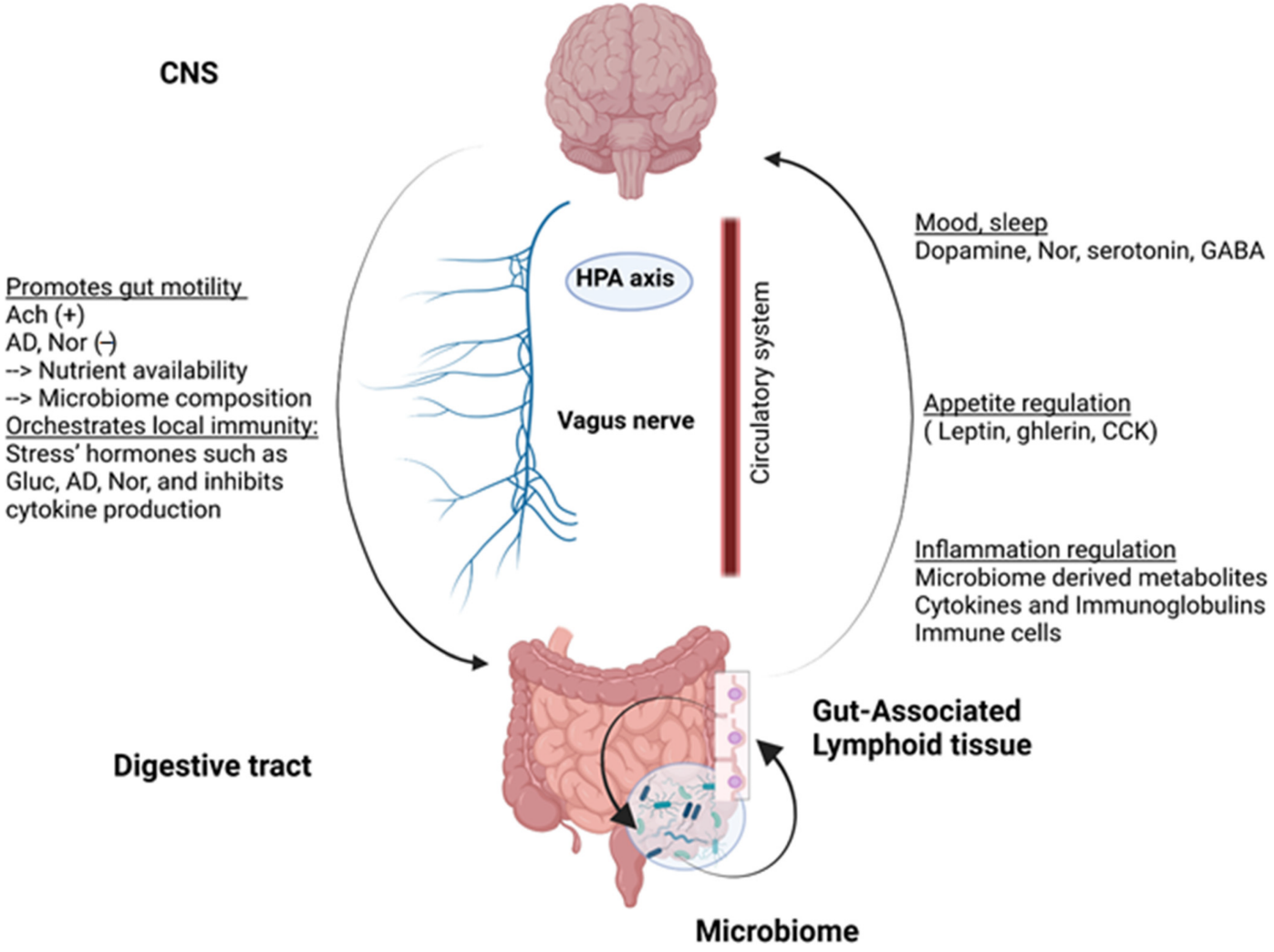

Figure 1. Gut-brain axis, a multidirectional communication system: Communications take place through the neuroendocrine pathway. While acetylcholine (Ach) promotes smooth muscle contractions, adrenergic neurons can decrease bowel movement. Moreover, stress hormones, mainly glucorticoïds (Gluc), adrenaline (AD), and noradrenaline (Nor), create a strong suppressive response on the immune system. On the other side, the digestive system can release large amounts of bioactive hormones and molecules in cooperation with the constantly interacting microbiome and immune system. HPA: hypothalamic-pituitary-adrenal axis, GABA: γ-aminobutyric acid, CCK: cholecystokinin.

2.2. The Human Gut Microbiota: A Key Role in Maintaining Host Homeostasis

The human gut microbiota is constituted by trillions of microorganisms (bacteria, viruses, fungi, and other protozoa) living at the surface of the mucosa [13][14]. These microorganisms harbor 150 times more genes than the human genome and are essential for health [15]. Nonexistent at the fetal stage, the microbiota rapidly diversifies during infancy with bacteria that metabolize lactose in the first place. When solid food is introduced, a shift to carbohydrate, protein, and fat-metabolizing bacteria occurs [16].

In addition to its role as a barrier against pathogens, the intestinal microbiota participates in the production of essential nutrients such as vitamin K and vitamin B [17]. Indeed, germ-free rats and thus deprived of intestinal microbiota were shown to need greater intakes of these vitamins compared to mice raised in a normal environment [18][19]. Moreover, bacteria belonging to the *Firmicutes* phylum are able to produce short-chain fatty acids (SCFA) acetate (C_2), propionate (C_3), and butyrate (C_4) as the main products of anaerobic fermentation, which represent the main source of energy for the colonic epithelial cells [20]. Bacteria living in the mucus layer also play a role in its maturation and recycling [21].

Another major role of the microbiota is in the modulation of the immune system and enteric nervous system, which are constantly stimulated and shaped by the microbial antigens [22][23]. Indeed, germ-free mice fed with sterile food exhibit altered enteric nervous systems compared to normal mice as well as altered immune responses (systemic T and B response deficiencies) [24][25], suggesting that exposure to microbial antigens is essential to educate a healthy immune system modulating both the innate and the adaptive immunity. Among these microbial compounds: SCFA secreted by some anaerobic bacteria were shown to harbor important modulatory properties toward the immune system. They appear to be major modulators of cytokine production (TNF-α, IL-2, IL-6, and IL-10) and migratory properties of leukocytes [26]. Pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), are important sensors of the microbiota present at the surface of epithelial cells and innate immune cells. For instance, Lipopolysaccharide (LPS), a key component of Gram-negative bacteria cell walls, creates a strong inflammatory response by macrophage and monocyte with production of IL-1β, TNFα, IL-6, and monocyte chemoattractant protein 1 (MCP-1) [27]. On the other hand, polysaccharide (PSA) arising from *Bacteroides fragilis* colonization activates anti-inflammatory genes in TLR1-TLR2-dependent way and drives naive CD4 T cell and B cells toward regulatory phenotypes (IL-10 and IL-12-producing cells) [28][29], attenuating inflammation. Moreover, certain strains of commensal Clostridia are known to be strong regulatory T cell inducers [30].

On the other hand, colonization by proinflammatory segmented filamentous bacteria promotes Th17 T cell differentiation and elicits the production of proinflammatory cytokines IL-17, IL-21, and IL-22 [31]. Finally, other compounds arising from bacterial activity, such as aryl hydrocarbon receptor (AhR) ligands or specific sphingolipids, are known to have regulatory effects on the immune system [32][33].

Under normal circumstances, these interconnections are finely regulated, and a balance between inflammation and regulation, response, and tolerance is maintained. Many environmental factors have been described as being able to modulate the microbiota composition. Among them, age, diet, or the use of certain medications are the main ones [34][35]. Long-term alterations in the microbiota/mucosal interface can result in systemic translocation of commensal microorganisms, susceptibility to pathogenic invasion, and chronic inflammatory immune responses.

Disturbances of the microbiota leading to a pathological state constitute the dysbiotic state. Intestinal dysbiosis has been described in many inflammatory pathologies targeting a wide range of systems ranging from the gut with inflammatory bowel disease (IBD) [36][37] but was also observed in systemic diseases such as type 2 diabetes [38], lupus [39], or rheumatoid arthritis [40]. Recent studies highlighted that diseases affecting the CNS such as Parkinson's and Alzheimer's diseases [41][42], autism [43], or multiple sclerosis are also linked to gut dysbiosis to some extent. Indeed, the CNS is connected to the gut via sympathetic and parasympathetic nerves with close proximity to the microbiota, making it a potential target of interest both in exploring CNS disease mechanisms and as potential therapeutic leverage. The gut could be a relevant place to apply interventional therapeutics as molecules arising in the gut can have action on the CNS, either by retrograde axonal transport or by the circulatory system.

2.3. Alterations in Gut Microbiota of Multiple Sclerosis Patients

In terms of diversity, two components are widely used in the field of ecology. First, the α diversity index, mainly corresponding to the specific richness and Shannon indices, representing the number of species identified in a sample and the richness mitigated by the evenness, respectively. Consequently, it is likely that there is no difference in the alpha diversity indices between MS and HV in their gut microbiota. Another considered index is β diversity. This index accounts for global differences between two groups of samples. In this case, 11 studies were able to show differences in β diversity index between MS and HV, suggesting an altered gut microbiome in MS with a global dysbiosis state. When looking at the taxonomic level, modification in the relative abundances of several bacteria occurs. Indeed, several genera were identified as impacted in several independent studies. Although results are highly variable, consensus seems to be emerging in some genera.

Among them, the decreased abundance in Firmicutes such as *Faecalibacterium prausnitzii* has been identified in 10 of the considered studies (one of them reported an increase). Moreover, decreased *Prevotella and Roseburia* genera were also reported (in 10 and 5 studies, respectively). On the other hand, increases in *Akkermansia*, *Streptococcus*, and *Blautia* were reported (in seven, six, and five studies, respectively).

While it is widely known that commensal bacteria can promote both inflammatory responses (Th1 and Th17) and regulatory (Th2) immune pathways, it seems that the balance between those two antagonist systems is broken in MS. Indeed, several of the major SCFA producers harboring regulatory properties, such as *F.prausnitzii*, *Prevotella*, and *Butyricimonas*, have been shown as decreased in the gut of MS. Moreover, the decrease in *Prevotella* has been associated with a Th17 expansion [44]. Other decreases in regulatory bacteria such as *Parabacteroides* or *Adlercreutzia* seem to occur. *Parabacteroides* can produce a compound called lipid 654, a TLR2 ligand significantly reduced in serum samples from MS patients compared with healthy subjects. This compound could be involved in the activation and regulation of immune responses, maintaining a certain level of TLR-2 and IFN-β signaling [45]. In addition, *Adlercreutzia* can process dietary phytoestrogens into monomeric compounds, decreasing oxidative stress and inflammatory cytokines, such as chemo-attracting proteins-1 (major monocyte recruiters) and IL-6, presenting high levels in MS [46]. Finally, the decrease in Bacteroides could decrease the induction of Treg.

On the other hand, increased genera such as *Methanobrevibacter* or *Akkermansia* and several Proteobacteria appear to be inflammation promoters. While *Methanobrevibacter* activates dendritic cells [47] and is associated with shorter time to relapse in a pediatric study [48]; *Akkermansia* is involved in the degradation process of the mucus layer, resulting in increased exposure of the resident immune cells to microbial antigens [49]. The increase in *Akkermansia municiphila* and *Acinetobacter calcoaceticus* found in a group of MS patients provoked proinflammatory responses in human peripheral blood mononuclear cells. Particularly, the in vitro results suggested that the MS-associated *Akkermansia municiphila* enhances the growth of Th1 cells from human T lymphocytes [50]. Finally, the increase in segmented filamentous bacteria and Enterobacteriaceae can orient to a Th17 immune response.

Altogether, it confirms a dysbiotic state in the gut of MS patients with a decrease in regulatory bacteria favoring proinflammatory pathobionts. This state is involved in a low-grade inflammation process that is constantly present during the course of this inflammatory disease. Finally, although the scientific community grew more and more results regarding gut microbiome alteration in MS, the last tend to be inconsistent. These differences are likely due to the naturally high interindividual variability, as well as to the fact that there is no real consensus in the analysis techniques (16s rRNA hypervariable regions, references, databases). In addition, microbiome analysis suffers from many confounding factors. Indeed, the content of the microbiome naturally evolves with many variables such as age, dietary habits, and medications. In order to take into consideration, all these sources of variability, very stringent study designs embedding larger sample sizes should be implemented. To reduce confounding factors, two studies emphasized the interest of using household paired design studies. Indeed, the International Multiple Sclerosis Microbiome Study consortium (iMSMS) highlighted that household is the first source of variability in the microbiome composition [51], while another study [52] included twins discordant for the disease, enabling them to account for both the environmental and genetic factors.

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