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Impact of gut microbiota on neurogenesis and neurological diseases during infancy

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The first years of life constitute a crucial period for neurodevelopment and a window of opportunity to develop new strategies to prevent neurological and mental diseases. Different studies have shown the influence of gut bacteria in neurogenesis and a functional relationship between gut microbiota and the brain, known as 'gut–brain axis', in which the intestinal microbiota is proposed to play a key role in neurophysiological processes. It has been observed that certain microbiome metabolites could be related to the development of neurological disorders through mechanisms still unknown. Then, more studies are needed to broaden the knowledge regarding the relationship between the Central Nervous System and the gastrointestinal tract, which could help to develop new preventive and treatment protocols.

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Introduction

During childhood, the brain is exposed to environmental factors that can shape synaptic connections and neuronal circuits, with subsequent influence on behavior and learning processes [1,2]. Over the crucial periods of neurodevelopment, the neuronal circuits are extremely plastic and can be easily subjected to remodel in response to experience, which constitute windows of opportunity [3]. Furthermore, gut microbiota colonization occurs simultaneously with this dynamic phase of postnatal brain development, including cell differentiation, axon myelination and synaptogenesis, and the rapid emergence of infant cognitive functions [4]. Subsequently, the diversity of commensal species within less-heterogeneous communities increases with age as well as the metabolic landscape of gut microbial metabolic pathways and the repertoire of microbiota-derived molecules [5] that have been shown to modulate brain development and influence the fine maturation of the brain with long lasting effects [4]. Accordingly, recent studies support a functional communication between the central nervous system (CNS) and the gastrointestinal (GI) tract, known as gut–brain axis, in which the intestinal microbiome is proposed to play a key role in these neurophysiological processes. The complex relationship between gut microbiota and the host has given rise to the notion of the microbiota-gut–brain axis [6,7]. In spite of the specific mechanisms underlying this influence, these mechanisms remain still unknown. On one side, the neuroendocrine, neuroimmune and autonomic nervous systems, and in the other side, the microbiotic toxin production, have been proposed as potential communication routes between gut microbiota and the brain [8].

In this review, we discuss the knowledge about the contribution of gut microbiota during the development of the nervous system and the main mechanisms of communication between microbiota-gut–brain axis. Finally, we address the role of microbiota in the pathogenesis of CNS disorders.

Neurogenesis: the link with gut microbiota

Broad evidence suggests that the birth of new neurons, known as neurogenesis, has an important role in learning and memory and responses to stress and antidepressant drugs [9]. The literature indicates that the permeability of maternal-fetal interface allows bacterial peptidoglycan to traverse the placenta to activate Toll-like receptor 2 (TLR2), causing alterations in fetal neural development and having a potential impact on cognitive function later in life [10,11]. In fact, it has been suggested that probiotic (Ecologic®825) administration can change brain activation patterns in humans in response to emotional memory and emotional decision-making tasks [12••].

Recent studies have shown an important influence of gut bacteria modulating and directing the developmental progress of neurogenesis in CNS, specifically in the hippocampus [13,14]. A study conducted in germ-free (GF) mice showed that when they were injected with bromo-deoxyuridine to label proliferating cells, they exhibited an increased adult hippocampal neurogenesis, predominantly in the dorsal hippocampus. However, postweaning microbial colonization did not prevent changes in adult hippocampal neurogenesis [15]. These results indicate the existence of a crucial window in early life, during which microbial colonization influences adult hippocampal neurogenesis. Möhle *et al.* observed that the treatment of adult mice with antibiotics decreases hippocampal neurogenesis and memory retention, which is partially mediated by Ly6Chi monocytes [16•]. Findings using probiotic combination of specific bacterial strains to restore neurogenesis deficiency in adult patients, have strengthened this connection between gut microbiota and hippocampal neurogenesis [17,18]. It is to note that in contrast to theories involving neurogenesis in cognitive processes, absence/rarity of neurogenesis in the hippocampus of primates and adult humans was recently suggested and is under intense debate [19].

Another interesting finding is linked to neurotrophic factors, which are a family of biomolecules that support the growth differentiation and survival of neurons during development and maturation. In particular, brain-derived neurotrophic factor (BDNF) plays a key role in several aspects of hippocampal neuronal plasticity and function, by intervening on gut–brain signaling [20]. Oleary *et al.* found in vagotomized mice a decrease of BDNF mRNA in all areas of the hippocampus and a reduced proliferation and survival of newly born cells. Moreover, these mice had a decrease in the number of immature neurons, especially those with complex dendritic morphology [21••]. Since the vagus nerve is a route, through which gut bacterial can communicate with the brain, it is possible that the vagus nerve activity may be by itself an important modulator of hippocampal plasticity, though more studies are needed.

In contrast, it is well known that NF-κB involves several signaling pathways in microbiota-neuron axis [22]. Thus, Lim *et al.* isolated anti-inflammatory Lactobacillus johnsonii CJLJ103 (LJ) from human fecal microbiota and they provided it orally to mice, observing a suppression of LPS-induced NF-κB activation in the hippocampus and an increase of LPS-suppressed brain-derived neurotrophic factor expression [23•]. Moreover, other study showed that gut microbiota alteration by extrinsic stress increases NF-κB activation and TNF-α expression, inducing memory impairment in animal models, alleviating neuroinflammation symptoms in the hippocampus when they restored gut microbiota composition [24].

The above mentioned conditions demonstrate that further studies are required to define-specific pathways and microbial species that mediate neurogenesis and CNS health.

From gut microbiota to brain: communication mechanisms

In the past decade, several studies have shown mechanisms that relate CNS and gut microbiota community, which involve microbiota metabolites, the vagus nerve, the hypothalamic-pituitary-adrenal (HPA) axis modulation and the immune system. Communication from the gut microbiota to the CNS primarily occurs through microbial-derived intermediates, such as short-chain fatty acids (SCFAs) [25], tryptophan metabolites [26] and secondary bile acids (2BAs) [27]. Some of these intermediates interact directly with enterochromaffin cells, enteroendocrine cells and the mucosal immune system to propagate bottom-up signaling [28]. Furthermore, SCFAs may activate vagal chemoreceptors and generate inappropriate responses in the CNS [29]. Many studies suggest that vagus nerve activation may reduce peripheral inflammation, improve intestinal barrier integrity and inhibit the release of pro-inflammatory cytokines [30,31]. In addition, a study has shown that gut toxins can induce the formation of α-syn aggregates in the ENS, which may be transmitted in aprion-like manner to the CNS through the vagus nerve [32].

In contrast, the HPA axis modulates the immune system and also the gastrointestinal function by producing glucocorticoids (cortisol and corticosterone), mineralocorticoids (aldosterone) and catecholamines (dopamine, epinephrine and noradrenaline) [33]. Hantsoo *et al.* have shown in pregnant women that changes in gut microbiota composition during pregnancy contribute to an altered inflammatory and glucocorticoid response to stress, giving rise to multiple childhood adversities [34]. Furthermore, other study has shown that cortisol response to acute stress during pregnancy was associated with differential abundance of several gut taxa via HPA axis [35].

The most abundant innate immune cells of the CNS are macrophages of the brain, known as microglia, which comprise between a 10% and a 15% of all glial cells. Those cells are involved in the antigen presentation, phagocytosis, and the modulation of inflammation throughout life [36]. Bacterial-derived SCFAs have been shown to have a key role in microglial maturation and its efficient functioning. Moreover, it has been demonstrated that GF mice show decreases in both microglial maturity and number, while mice treated with antibiotic show decreased microglial maturity only [37•].

Another well-characterized interaction between microbiota and CNS involves other diverse group of glial cells named astrocytes. Astrocytes have significant roles in the ion homeostasis, neurotransmitter clearance, maintenance

of the blood brain barrier (BBB), support of neuronal signaling, and protection against neuroinflammation [38]. It is noteworthy that bacteria and immune-active substances released from peripheral sites under the influence of the microbiome can cross the BBB, altering its integrity, and changing its transport rates, or inducing the release of neuroimmune substances from the barrier cells, leading to mental disturbances [39]. Indeed, studies have shown that bacterial metabolites can activate the aryl hydrocarbon receptor (AhR), decreasing the inflammation through regulation of type I interferon signaling in the astrocytes [40]. Furthermore, Vermali Rodriguez *et al.* observed in spontaneously hypertensive (SHR) rats, higher levels of specific inflammatory cytokines in astrocytes in comparison to normotensive (S-D) rats. When they treated them with butyrate, they found an increased expression of tumor necrosis factor in astrocytes from SHR, but not from S-D rats [41]. In contrast, type 2 diabetes mellitus (T2DM) has been associated with increased levels of glial cell-derived neurotrophic factor (GDNF), which is an indicator of astrocytes activity, glial fibrillary acidic protein (GFAP), and inflammatory markers (IL-17, IL-6, and TLR-2) in colon and brain. Recently, Hosseinifard *et al.* have observed in rats with T2DM treated with Lactobacillus (L.) a decrease in levels of inflammatory cytokines and a significant decrease in TLR-2, GDNF and GFAP in the amygdala. However, when they treated rats with L. plantarum and inulin, they observed changes in colon, amygdala, and prefrontal cortex [42]. This study promotes a better understanding of the role of microbial metabolites in the regulation of astrocyte function.

Gut microbiota and CNS disorders

Since gut microbiota influences CNS through various pathways, it is necessary to take into account its contribution in the development of neurological disorders.

In patients with autism spectrum disorder (ASD), have been identified mutations and deletion of proteins of the SH3 and multiple ankyrin repeat domains (SHANK) gene-family, which have a role in the CNS synaptogenesis [43]. Recently, Sauer *et al.* observed in Shank3 knockout (KO) mice the expression of that protein in the gastrointestinal (GI) epithelium, higher *E. coli* lipopolysaccharide levels in the liver, and an increase in Interleukin-6 and activated astrocytes, which might contribute to the ASD phenotype by extracerebral mechanisms [44]. In contrast, cumulative causal evidence reveals that the gut microbiota and SCFAs play an important role in gastrointestinal disorders and ASD [45]. Liu *et al.* observed in autistic children a decrease in abundance of key butyrate-producing taxa (*Ruminococcaceae*, *Eubacterium*, *Lachnospiraceae* and *Erysipelotrichaceae*), together with low levels of SCFAs detected in fecal samples of those patients [46••]. Thus, the study of butyrate-producing bacteria could be a promising strategy for the treatment of ASD.

In the past seven years, many new cases of multiple sclerosis (MS) have been diagnosed in children. MS is an inflammatory disease characterized by the immune-mediated demyelination of axon [47]. A novel study assessed in MS first-degree family members the intestinal microbiome profiles. They observed that asymptomatic individuals at higher risk of developing MS had intestinal microbiome profiles associated with decreased SCFA production [48••]. This coincides with other previous studies, which have shown potential beneficial effects of SCFAs in the development and course of MS [49].

Even though several mechanisms have been proposed for the pathogenesis of schizophrenia, such as immune disturbance, abnormal neurodevelopment or dysregulation of neutransmitters, its etiology remains unknown [50]. According to a recent study, Syeda *et al.* showed in obese rats (Tripletransgenic 3xTg-AD) that bioactive food restored their gut microbiota composition, which was characterized by pro-inflammatory bacteria, improving cognition through a decrease in malondialdehyde levels, astrocyte and microglial activation, PSD-95, synaptophysin, GluR1 and ARC protein levels [51]. Therefore, neuropeptides derived from bioactive food, probably mediated for gut microbiota, may alter brain function. In addition, a recent clinical study compared gut microbiota composition of patients with schizophrenia versus demographically matched non-psychiatric subjects. The authors found an increase of phylum *Proteobacteria*, a correlation between *Ruminococcaceae* with lower severity of the symptoms and an association of *Bacteroides* with worse depressive symptoms in such patients [52••]. Despite the fact that studies in humans are limited, the above-mentioned findings provide evidence of an altered gut microbial composition in persons with chronic schizophrenia, opening a new avenue for future treatments of this disease.

Finally, during the last few years, a number of association studies have related changes in the gut microbiota with temperament and stress alterations in infants [53]. Specifically, in a recent study, young children presented increased surgency/extraversion, sociability and high-intensity pleasure, which were associated with increased alpha diversity in both sexes [54•]. Regarding stress, infants of mothers with high cumulative stress during pregnancy presented significantly higher relative abundance of Proteobacterial groups and lower relative abundance of lactic acid bacteria [55].

Altogether, these findings provide a basis for future studies regarding the microorganisms and pathways involved in the progression of CNS disorders.

Future perspectives and conclusions

It is necessary to develop new effective strategies for the treatment of CNS diseases, as consequence of their

complicated etiologies and absence of biomarkers in humans.

Recent findings have shown that microbial metabolites, directly or indirectly, may give rise to changes in immunological activities in the brain, leading to neurological alterations and making a link between microbiota, immune signaling and the CNS.

New therapeutic modulators have been found in several mood disorders, delivering promising results. However, the mechanisms by which gut microbiota community influences the development of certain pathologies are still unclear. On this basis, future studies are needed to clarify the specific pathways and the details of gut–brain axis.

The ongoing research may establish the basis for advanced therapeutic treatments and the identification of novel biomarkers, which will allow an early diagnosis and intervention of CNS disorders.

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Conflict of interest statement

Nothing declared.

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