One more role for the gut: microbiota and blood brain barrier

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Submitted Sep 24, 2015. Accepted for publication Sep 29, 2015.
doi: 10.3978/j.issn.2305-5839.2015.10.16
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.10.16

The gut/brain axis

The gut microbiota is composed of trillions of microbes that perform several tasks which are essential to our physiology. Recent emerging evidences have suggested the important contribution of gut microbiota in several biological functions of mammals, such as the regulation of the immune system, metabolism, intestinal development or brain physiology (1-4). In fact, recent work, mainly performed in experimental model of Multiple Sclerosis (MS), have demonstrated that resident commensal microbiota can modulate central nervous system (CNS) autoimmunity (5-8). The microbiota is now known to shift the balance between protective and pathogenic immune responses, in the CNS, but also in other organs. A growing body of evidence in animal support also the concept that the gut microbiota influences emotional behavior (9,10) and that its products and metabolites may promote metabolic effects such as reduced body weight, reduced adiposity, and improved glucose control (11). As regards, CNS physiology, the gut microbiota influence synaptogenesis, regulate neurotransmitters and neurotrophic factors release and function (4).

But what are the products and metabolites produced by these microbes that influence all these biological functions? The intestinal microbiota produces innumerable biologically active ligands, such as the short chain fatty acids (SCFAs), i.e., acetate, butyrate or propionate. These chain fatty acids are the results of the fermentation of polysaccharides by intestinal microbes. They are known to exert anti-inflammatory functions not only in the gut but also in others organs (12,13). Others microbial products which may play a role in autoimmunity have been identified as PSA, lipid 654 or peptidoglycan (14). Even if numerous functions of this microbiota have been reported, its influence on blood-brain barrier (BBB) integrity and development has not been established even if suspected (15).

The BBB development

The brain and spinal cord are often reported as immune-privileged organs, a concept derived from the observation that a very limited number of peripheral derived immune cells patrol the CNS. This privileged immunological status depends on the presence of specialized vascular barriers which restrict the passage of large molecules and cells, from the blood to the brain. The prototypical barrier of the CNS is the BBB. The BBB is constituted by microvascular endothelial cells (ECs) which elaborate a continuous network of intercellular tight junctions (TJs). ECs of the BBB also lack fenestrations and present a low rate of transcytosis. The term "neurovascular unit" (NVU) refers to BBB-ECs but also to astrocytes, pericytes, neurons, microglia and extra cellular matrix component that provide functional and structural support to the BBB. Development of the BBB starts when endothelial progenitor cells invade the embryonic neuroectoderm (16). Neural progenitor cells secrete factors that guide sprouting ECs, as VEGF (Vascular Endothelial Growth Factor) and Wnt ligands. In a second step, astrocytes and pericytes make contact with microvascular ECs which promote barrier properties, by the release of Sonic hedgehog (Shh) for astrocytes and by production of Ang-1 by pericytes. These interactions lead to the development of functional (impermeable) TJs, down-regulation of leukocytes adhesion molecules on the surface of the ECs and inhibition of transcytosis.

Microbiota and BBB development

Although CNS related mechanisms underlying the development of the BBB are the topic of innumerable publications, the impact of the non-CNS environmental factors has not yet been explored. Recently, Braniste *et al*. (17) identified the gut microbiota as a probable regulator of BBB integrity, in both the fetal and adult mouse brain. They elegantly demonstrated that the lack of a normal gut flora in adult germ-free (GF) mice is associated with increased BBB permeability, both in the adult animal and in the embryos of GF mice. This dysfunction of the BBB is associated with a disorganization of the TJs, including a down-regulation of occludin and claudin 5. Interestingly, the "conventionalization" of GF adult mice by colonization with flora from pathogen-free (PF) mice was associated with enhanced integrity of the BBB, decreased extravasation of Evans blue dye inside the parenchyma, and a re-expression of occludin and claudin 5 in some regions of the brain. A similar and rapid correction of BBB dysfunction was observed using monocolonization by bacterial strain producing mainly butyrate, acetate and propionate [short chain fatty acids (SCFAs)]. The exact mechanisms by which SCFAs produced by bacteria affect BBB maturity and function remains unknown. Those will need to be addressed in future studies and might lead to significant developments in the fields of neuro-therapeutics, including in neuro-oncology. Interestingly, the influence of SCFAs has previously been identified to impact on brain development and function (18-20), including in long-term memory consolidation (19), angiogenesis and neurogenesis (21), but also in the BBB dysfunction during ischemia (15).

What is next?

Despite the important observations that SCFAs from bacteria influence BBB development and maintenance, the exact mechanisms underlying this effect of SCFAs remain unknown. Is this effect of SCFAs direct (on ECs) or indirect (on astrocytes, on pericytes or on other CNS or non-CNS cells)? The authors suggest that these carbohydrates could impact histone acetylation status and therefore mediate gene expression changes, in ECs directly. In fact, so far, researchers suggested that SCFAs could operate in two manners: by binding G-protein membrane receptors (GPR41 and GPR43) (22) or by entering inside the cells, working as Histone Deacetylase (HDAC) inhibitors and so modulate epigenetic processes. Several important publications confirm the importance of the latter in different contexts including inflammatory diseases (23-26). Additional investigations are therefore needed to understand the way SCFAs impact the development of TJs in embryos, and the maintenance of these structures but also in adult. Additional pathways could also impact BBB permeability, and inflammation is well known to increase BBB permeability [for review, (16)]. Are SCFAs able to control inflammatory signals? Some studies suggest that SCFAs impact on dendritic cells function and T cell proliferation (12,13,24). This manuscript by Braniste *et al*. (17) brings a new link between the gut microbiota and brain development/function. The challenge now will be to translate these animal data into specific therapies. Some predict that within the next few years, there will be significant investments to support the development of microbiome therapies (27), even if Probiotics have failed to demonstrate a significant impact on human diseases.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Editorial commissioned by Section Editor Ning Ding, PhD (Department of Respiratory Medicine, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China).
Conflicts of Interest: A Prat has no conflicts of interest to declare. L Michel received honoraria for consulting from Merck Serono and Novartis.

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Cite this article as: Michel L, Prat A. One more role for the gut: microbiota and blood brain barrier. Ann Transl Med 2016;4(1):15. doi: 10.3978/j.issn.2305-5839.2015.10.16

