Can we promote neural regeneration through microbiota-targeted strategies? Introducing the new concept of neurobiotics

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The human body is populated by a large number of microbial colonies, with an estimated 10–100 trillion microbes. The total genome size of human microbial colonies by far overwhelms the size of the host's genome. This heterogenous group of microbial colonies (primarily bacteria, but also archaea, eukaryotes and viruses) is referred to with the term microbiota, and although most of them populate the gut, microbes are also detectable in many other organs of the body, especially in the distal tracts of the genitourinary system and the skin. Over the last years, an increasing amount of evidence has been accumulated on how the microbiota exerts a significant influence on the development and physiology of the human body. The nervous system interacts extensively with the microbiota. To refer to communication between gut microbes and neurons, we have recently suggested that the traditionally established term microbiota-gut-brain axis be replaced with a more specific brain-bacteria axis, which emphasizes the direct interrelationship between these two entities (Herrera-Rincon et al., 2020; Murciano-Brea et al., 2021).

Based on this premise, a question has been asked in recent years: can we design innovative neurotherapeutics for treating brain disorders based on the existence of a strict bi-directional relationship between the gut microbiota and the nervous system? In other words, can we design microbiota-targeted interventions to cure diseases of the brain?

Based on the large emerging body of scientific evidence, the answer is certainly yes, especially when considering psychiatric disorders (Murciano-Brea et al., 2021). This observation has led to the definition of the scientific concept of "psychobiotics", which has been coined to refer to those probiotics (live organisms, mainly gut bacteria) and prebiotics (the fiber used by the psychobiotics) with potential applications in treating psychiatric and mood disorders (Dinan et al., 2013). Yet, an increasing body of evidence is emerging regarding the potential of microbiota-targeted interventions for treating other neurological disorders that involve injury and/or degeneration (Kigerl et al., 2018). Based on this evidence, in this perspective article we propose the adoption of the new scientific concept of "neurobiotics" to name any substance (mainly probiotics and prebiotics, but also specific diets, microbiota transplants or antibiotics) that exerts a gut-microbiota-mediated effect with potential applications in promoting neural repair and regeneration after neurological disorders (**Figure 1**).

Neurological disorders represent an enormous burden to society both in medical and economic terms. They are mainly due to neurodegeneration (such as Parkinson's disease, motor neuron diseases and demyelinating diseases), ischemic lesions (e.g., stroke) and trauma, which may result from mechanical injuries (e.g., road, domestic and weapon injuries), compression injuries (especially as a consequence of neoplastic masses) and iatrogenic injuries (especially following radical surgery).

Unlike other systems and organs of the human body, the nervous system has more limited repair potential. Therefore, the identification of effective strategies for improving neural repair and regeneration is one of the key goals of today's neuroscience translational research because the reduction/abolition of the long-term consequences of neurological disorders may result in relevant advantages for both improving patient well-being and reducing the economic burden to society.

Various studies have clearly shown that the microbiota-gut-brain axis is key to normal neurodevelopment, not only limited to the enteric nervous system. In addition, it has been shown that the microbiota-gut-brain axis may regulate brain health and behavior, raising the potential of targeting the gut microbiota in the development of novel therapeutic approaches to treat the disorders of nervous system (Herrera-Rincon et al., 2020). In the investigation of the microbiota-brain interaction, researchers first focused on the negative effects on the brain of various pathological conditions, especially alimentary disorders (Parekh et al., 2015). More recently, research has addressed the cross-talk between microbiota and the nervous system in non-pathological conditions, suggesting that the gut microbiota is also a key mediator of gut-brain axis signaling in normal conditions (Wiley et al., 2021). Using germ-free models in rodents, the growing evidence on the gut microbiota-brain interaction – involving nervous, endocrine and immune signaling mechanisms – has led to a re-thinking of the term gut-brain axis to a more specific bacteria-brain interkingdom communication as well as to the identification of several putative mechanisms to explain how the gut microbiota affects brain function and development (Herrera-Rincon et al., 2020). Interestingly, it has been shown that bacteria communicate with each other by means of electrical and chemical mechanisms that are similar to those adopted by neurons and might perform both individually and as super-organisms (Beagle and Lockless, 2015). Moreover, it is emerging clearly that neurological disorders alter the composition of the gut microbiota and *vice versa* (**Figure 1**). On the one hand, degeneration or injury to the nervous system upsets the intestinal wall motility and its permeability, inducing changes in the microbiota composition. This phenomenon can be detected weeks after injury and ultimately leads to gut dysbiosis (Rice et al., 2019). For example, following spinal cord injury, Bacteroidales (phylum Bacteroidetes) decreased by approximately 30%, whereas Clostridiales (phylum Firmicutes) increased by approximately 250% (Kigerl et al., 2016). On the other hand, microbiota alterations may have effects on various disorders of the nervous system through several mechanisms, such as microglia-induced synaptic pruning that is altered by the dysregulation of microbiota (Eltokhi et al., 2020).

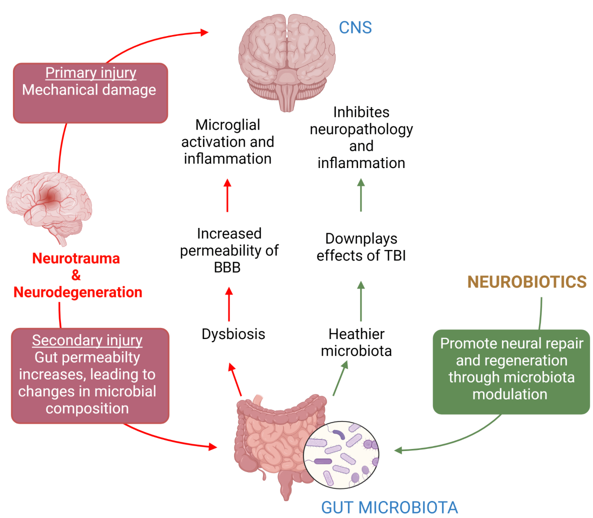

Figure 1 | Neurobiotics: targeting the gut microbiota as a strategy to promote neural repair and regeneration.
The microbiota-gut-brain axis is disrupted in the context of many neurological disorders. Acting on gut dysbiosis through eubiotic therapies can trigger neuroprotective and neuroregenerative responses. BBB: Blood-brain barrier; CNS: central nervous system; TBI: traumatic brain injury. Created with BioRender.com.

Gut dysbiosis is central to many neurotrauma and neurodegenerative disorders and it can aggravate pathology and symptoms, by disrupting the permeability of the blood-brain barrier and triggering an inflammatory response. Furthermore, the experimental dysregulation of the composition of the gut microbiota (using a broad-spectrum antibiotic prior to the nervous system injury) has been shown to decrease the survival rates in an ischemic murine model (Winek et al., 2016). Thus, targeting gut dysbiosis associated with neurological disorders might be effective to ameliorate the devastating changes in the brain. Numerous preclinical and clinical data have demonstrated the efficacy of eubiotic interventions (prebiotics, probiotics, diet, fecal transplant, etc.) to cure gut dysbiosis. It is now time to expand the research to specific treatments that by modulating microbiota composition and treating neurotrauma-induced gut dysbiosis, named here under the new concept of "neurobiotics", lead to an improvement in neural repair and regeneration. Preclinical studies using spinal cord injury mice have shown that probiotics containing lactic-acid-producing bacteria induce a protective immune response in gut-associated lymphoid tissues, enhancing neuroprotection and improving locomotor recovery (Kigerl et al., 2016). In addition, the transplantation of fecal microbiota can ameliorate stroke-induced neuroanatomical damage, leading to functional improvements in animal models of stroke (Singh et al., 2016). Besides regulating inflammation and offering neuroprotection, neurobiotics might act by inducing neurogenesis. Although neurogenesis occurs mainly during development and early postnatal life, it is now widely recognized to occur during adult life both in the central and peripheral nervous systems, as one of the main ways by which the brain may cope with tissue damage. An intriguing hypothesis that has emerged is that the gut microbiota contributes to neural repair by supporting neurogenesis (Liu et al., 2022). This view is supported by the observation that in germ-free mice, the number of neurons in the myenteric nervous system is reduced. Yet, the presence of an increased number of poorly differentiated neurons undergoing neuronal maturation is triggered by the gut microbiota. Interestingly, the greatest number of premature neurons was found in the intestinal tracts (caecum and proximal colon), where a richer microbial population is detectable. A possible mechanism to explain microbiota-driven neurogenesis in the adult nervous system involves the release of serotonin (5-HT) and subsequent activation of the 5-HT4 receptor in neurons (De Vadder et al., 2018). However, it has been shown that the gut microbiota exerts a neurogenic effect through lipopolysaccharide release and Toll-like receptor 4 activation of enteric glia. Another interesting piece of evidence for the role of microbiota on stimulating neurogenesis has emerged regarding the hippocampus – one of the major neurogenetic sites in the adult brain – with a proposed mechanism of action related to the influence of the microbiota on hippocampal brain-derived neurotrophic factor levels.

Taken together, the above-described considerations allow us to propose that the introduction of a new scientific conceptualization of "neurobiotics" can stimulate further progress of research on how the gut microbiota can be targeted in the development of novel approaches to improve neural repair and regeneration and eventually enrich our armamentarium for treating neurological disorders. Based on these premises, it can also be proposed that exogenous lifestyle factors, known to specifically modulate the gut microbiota, can influence the onset, progression and/or outcome of lesions to the nervous system. Food-related factors seem like promising approaches to promote neural repair (Yildiran et al., 2020), as the gut microbiota is modulated continuously and repeatedly by diet (David et al., 2014). Dietary interventions that balance an increased Firmicutes:Bacteroidetes ratio and/or that promote the production of bacterial metabolites such as short chain fatty acids (mainly from dietary fiber and resistant starch) might be good initial candidates.

The study of neural repair and regeneration is particularly important in light of the high clinical incidence of neurological disorders and the observation that, unfortunately, the clinical outcome after neural degeneration and/or injury is often far from satisfactory. Indeed, functional recovery is almost never complete, leading to a heavy burden on the patients and society. The possibility that microbiota-targeted therapeutic strategies might positively affect neurological disorders therefore represents an unprecedented stimulus to conduct new research on "neurobiotics".

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