We are IntechOpen, the world's leading publisher of Open Access books
Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Chapter

Beyond the Quality of Life in Bowel Dysfunction after Spinal Cord Injury: Approaches to the Consequences in Motility, Immune System, and Microbiome

Estefanía de la Cruz-Castillo and Elisa García-Vences

Abstract

Spinal cord injury (SCI) is a harmful event that involves several repercussions on sensory and motor function that affects the quality of life (QoL) of patients. After SCI, many damage mechanisms are activated that impact on both autonomous extrinsic and intrinsic innervation toward the gut, and these changes modify the gut motility causing bowel dysfunction (BD), an entity that affects 40% of patients with SCI, being the second comorbidity after loss of mobility with no recognized cure. The severity of complications is ruled by the level and severity of injury, having a worse prognosis with an injury that is the most proximal to the brain. In the last 5 years, some experiments have tried to elucidate the consequences of dysbiosis in the gut and aggregated proinflammatory processes. The goal of this chapter is to establish the importance of bacterial composition and immune system repercussions in bowel dysfunction after SCI and how could it give rise to new therapies.

Keywords: neurogenic bowel dysfunction, autonomic dysreflexia, gut microbiota, spinal cord injury

1. Introduction

Spinal cord injury (SCI) refers to the traumatic damage to the spinal cord and represents a harmful event that involves several repercussions on sensory and motor function that affects the quality of life (QoL) of patients (Furlan, Global incidence and prevalence of traumatic spinal cord injury) [1].

The most severe consequences of SCI are partial or complete loss of sensory function or motor control of arms, legs, and/or body, followed by the neurogenic bowel and bladder dysfunction, and other autonomic dysreflexia (AD) signs [1, 2].

In addition, if that was not enough, due to several comorbidities, patients have 1.29-fold increased risk of depression or anxiety [3].

1.1 Epidemiology and public health

SCI is a worldwide disease; prevalence is estimated in 1298 per million, while the global incidence varies depending on the geographical region, so it has been calculated between 8 and up to 246 cases per million per year [2, 4, 5].

In the last 30 years, these data have been increasing [6–8], and most frequent etiology is traumatic, representing 90% of cases [8]; vehicle accidents are the main cause [9], followed by injury due to falls in elderly population.

Males are most at risk, corresponding to the 80% of those affected, with a male to female ratio of 3.2:1 [4, 10] aged between 16 and 35 years [6, 11].

SCI represents a public health problem as it affects the working age population, with a mortality risk two to five times more likely to die prematurely than healthy people; several studies report a mortality rate during the first year after trauma of about 15% [12].

Also, this disease demands financial resources from patients, their families, and the government [13]. Annually, the economic waste associated to SCI in the United States amounts up to approximately 21.5 billion dollars, while in other health systems, such as Canada, an investment of up to 2.67 billion dollars is estimated, considering direct and indirect costs, which range from posttraumatic infections, medical consultations, caregiver services and rehabilitation, etc. [14].

2. Systemic complications induced by SCI

These acute and chronic changes arise and are worsened by the gradual multiple organ dysfunction that in combination with an increasingly sedentary lifestyle leads the SCI patient to metabolic syndrome (trunk fat, low HDL levels, and high triglyceride levels), which affects more than a half of SCI patients [15], implying threefold increased risk of developing cardiovascular disease and fivefold increased risk of developing diabetes [16], as well as other systemic alterations like hematological (anemia in acute phase, thrombocytosis) and biochemical [low concentrations of albumin and globulins and high concentration of aspartate aminotransferase (AST)] [17], decreased immune function (spinal cord injury-induced immune deficiency syndrome SCI-IDS) [18], bowel dysfunction, and gut dysbiosis [19], perhaps, the last three caused by autonomic dysreflexia [20].

2.1 Is autonomic dysreflexia responsible for other comorbidities in SCI?

Clinically, patients with SCI have several comorbidities associated to the level of injury; when the lesion is above the seventh thoracic vertebra, it usually produces sympathetic hyperactivity causing symptoms like systemic vasoconstriction and parasympathetic activity, below and above the site of injury, respectively; this set of alterations are called autonomic dysreflexia (AD) [21].

AD is defined as "episodic hypertension and concomitant baroreflex-mediated bradycardia initiated by unmodulated sympathetic reflexes in the decentralized cord" [22]. This ambiguous definition identifies the elevation in systolic blood pressure as the main sign; however, these diagnostic criteria are not well defined [23]; in addition, these patients can suffer other symptoms such as headache, sweating, anxiety, and arrhythmia [24].

AD incidence in patients with lesion at or above T6 segment is 92.8% and, in some cases, could be asymptomatic, up to 42.9% [25] depending on intensity, level, and time elapsed since SCI. It is important because it represents the principal

cause of mortality and must be diagnosed timely to prevent severe complications like cardiac arrest, stroke, and seizures [22].

The impaired visceral or somatic stimulation of the sympathetic preganglionic neurons (SPN), due to colon and bladder overdistension (most frequent), skin lacerations, and pressure sores, results in a massive sympathetic reflex as a result from three things: (1) the maladaptive plasticity of neural network, (2) the imbalance between excitatory and inhibitory neurotransmitters, and (3) the enhanced peripheral adrenergic sensitivity, which is predominantly established in chronic phase, 3–6 months after injury [21].

In addition, other less recognized alteration is in the immunomodulatory response, described as the SCI-IDS, characterized by decreased lymphocyte activity with poor proliferation of hematopoietic progenitor cells and spleen (secondary lymphoid organ) atrophy due to the loss of negative feedback on releasing catecholamines causing poor maturation of T and B lymphocytes [26].

Is well-known that the disruption of the parasympathetic nervous system (PNS) also affects cell proliferation [27, 28], and recent findings had confirmed that parasympathetic activity is linked to cell proliferation and cell cycle-related gene expression above the neurological level of injury rather than below it; in which case, the main neurotransmitter involved is the acetylcholine in the upregulation of some genes that participate in the chromosomal instability [29].

This suggests that SCI goes beyond the patient's locomotor impairment explaining the increased risk of cancer in these patients and the severe repercussions to the gastrointestinal tract conditioning BD (gastric ulcers, paralytic ileus, anal incontinence, anal fissures, and hemorrhoids) [22], a complex phenomenon secondary to hypoxia caused by the massive sympathetic discharge.

3. Bowel dysfunction

Bowel dysfunction (BD) is one of the most frequent complications in patients with SCI, with a frequency of 25–41% of cases [30–32].

In BD, there are changes in the extrinsic autonomous innervation that goes to the gut, resulting in impaired motility (constipation in 46% and anal/fecal incontinence in 41%), sphincter control (31% of cases), and abdominal cramps (18%) [32, 33].

On the other hand, intrinsic enteric innervation remains intact, but over time, it may lose its integrity due to changes in the extrinsic system [34].

3.1 Effect of neurogenic bowel dysfunction in quality of life following spinal cord injury

Most of the time, paraplegic patients receive special attention for the treatment of movement limitations instead of managing the patient like a whole entity setting aside another secondary health conditions and most importantly, quality of life.

In accordance to A. Donabedian, the Committee on Quality Health Care in America published "Crossing the Quality Chasm," focusing on six fundamental concepts, especially the third should be noted, as it points out to respectful patient-centered care in response to its values and necessities [35].

We must define QoL as the patient's perception of its own position in life, conditioned by its culture, value, goals, expectations, and concerns, and its importance is intimately associated with hospitalization, diminished social interaction, poor involvement in rehabilitation, and early death [36].

It is well-known that all comorbidities in SCI-reduced QoL patients injured at C5-T1 have the worst punctuation, being the most important causing pressure ulcers, respiratory complications, and BD [37]. BD is a major physical and psychological problem pointed out by several authors; constipation, gastrointestinal pain, and megacolon and fecal incontinence influence daily activities leading to social isolation [33].

There are about 13 questionnaires to determine objectively QoL in SCI like the Spinal Cord Independence Measure (SCIM III), a tool that indirectly evaluates some areas of self-care, respiration, sphincter control, and mobility. Another is the World Health Organization Quality of Life Assessment (WHOQOL-BREF), with four domains, physical and psychological health, social relationships, and environment [38], and the Short Form 36 (SF-36) that measures both physical and mental health component [39]. However, they have bad sensitivity in the identification of poor QoL dependent of BD, except the Health Utility Index Mark III (HUI-III) that additionally analyzes secondary health conditions with a good discrimination from patient with or without BD [40, 41].

Although there are a great variety of tools to evaluate QoL, it is not a usual practice in medical consultation, and in most cases, the problem is not properly addressed, only focusing on treating the symptoms until it is too late and an invasive procedure like colostomy is imminently required. The evidence has demonstrated the poor or null influence of this type of therapies in QoL [42], perhaps because they are not curative therapies.

Other authors suggest an individualized plan that includes diet and medication [43]; however, the lack of information about the pathophysiology has not allowed scientific advances in the development of strategies to restore intestinal motility and function.

3.2 How could BD in SCI patients be explained?

According to Mazzone and Farrugia, gastrointestinal motility is the property of the intestinal walls to contract and relax so that the contents of the intestine go from one place to another, allowing the proper absorption of nutrients [44].

First, we must remember that in this physiological process, three structures are involved: (a) the CNS, (b) enteric nervous system (ENS) [Meissner (submucosal) and Auerbach (myenteric) nerve plexus], and (c) autonomic nervous system (ANS) (sympathetic and parasympathetic).

The ENS connects with the CNS through afferent or sensory pathways (responsible for maintaining the reflexes and sensation of the visceral organs) and efferent or motor pathways (innervate all the smooth muscles of the body and glands) of the ANS. The ANS is organized into four ganglion groups: (a) paravertebral, (b) prevertebral, (c) paravisceral, and (d) intramural [45].

The paravertebral nodes are connected to each other and form two ganglionic or sympathetic chains, which connect to the spinal nerves through the communicating branches. The prevertebral nodes also connect with each other and form the abdominal plexus, consisting of the celiac and the superior mesenteric ganglion [46].

The paravisceral ganglion encompasses some viscera and highlights the cardiac and pelvic plexus. Meanwhile, the intramural ganglion is located in the wall of the gastrointestinal tract (GIT) and the bile duct [45].

In summary, paravertebral and prevertebral ganglia are the most important components of the sympathetic system (whose origins are in the thoracic and lumbar spinal cord segments) and the autonomic cranial ganglia of the parasympathetic system, which involves the vagus nerve and the pelvic plexus

(sacral portion of the spinal cord), which also receives sympathetic innervation. Specifically, the intramural ganglion of the intestine is not considered sympathetic or parasympathetic because both pathways are interconnected, constituting the ENS [47].

The ENS has two main components, the Meissner plexus and the Auerbach plexus. The first is located between the inner layers of the circular and submucosal muscle layer, and its function is to regulate the function of digestion and absorption at the level of the mucosa and blood vessels, especially in the small intestine and colon. Meanwhile, the Auerbach is located between the circular and longitudinal muscular layer and is responsible for coordinating the contraction/relaxation of muscle layers along the entire GIT [46, 48].

Reaffirming, the consequences after SCI directly depend on the level of trauma, as well as intensity and type of injury, having a worse prognosis with lesions that are the most proximal to the brain. Classically, lesions can be divided by severity depending on the neurological level in (a) cervical, (b) thoracic, (c) lumbar, or (d) sacral. Based on this classification, the American Spinal Cord Injury Association (ASIA) designated the neurological standards of spinal cord injury [1].

The neurological level is defined as the most distal segment of the spinal cord with normal motor and sensory function on both sides of the body, while the severity is defined as complete/incomplete sensory and incomplete motor with preserved function in more than a half of the key muscles or incomplete motor with preserved function in at least half of the key muscles [49]. For example, those patients injured in segments C6–C8 will require additional care to avoid comorbidities caused by BD or neurogenic bladder (NB) [50].

These changes fail to explain the mechanisms of intestinal dysmotility [51, 52]; however, other explanations arise: the microbiota-gut-brain axis (MGBA), which communicates with each other via various routes, including endocrine, the vagus nerve, and immune signaling, whose main function is the monitoring and integration of intestinal function [53].

Other mechanisms of gut motility are the effect exerted by the substances generated at this level on the excitability of smooth muscle, peripheral enteric nerves, and central ones [54], as well as the direct action of microbial metabolites as signaling molecules in the brain [48].

3.2.1 What happens after spinal cord injury?

The SCI pathophysiology can be divided into two phases, primary and secondary. The primary injury occurs immediately, from seconds to minutes, causing cellular and extracellular damage induced by the mechanism of injury, whether mechanical or nonmechanical. This serves as the origin to trigger the secondary injury constituted by the mechanisms of damage, which involve vascular, cellular, and biochemical events that cause damage to the resident cells that survived the initial damage, which will take place in minutes to weeks [55].

Due to its temporality, the SCI is classified into three phases: the acute phase, the secondary or subacute phase, and the chronic phase. In each phase several groups of cells and molecules of the nervous, immune, and vascular system are involved [56, 57].

The acute phase occurs due to the direct damage of the trauma, causing cellular, physical, and biochemical alterations both locally and systemically. These reactions are triggered by hemorrhage, destruction of the blood spinal cord barrier, and infiltration of inflammatory cells causing systemic hypotension, spinal shock, vasospasm, ischemia, plasma membrane involvement, ionic homeostasis disorders, and neurotransmitter accumulation [58].

Subacute phase is carried out minutes after the injury, lasting for weeks or months. Further the ionic imbalance, edema and necrosis, and other events happen, such as the formation of free radicals, glutamate-induced delayed calcium (Ca^{2+}) entry, lipoperoxidation, demyelination, and cell death by apoptosis [56, 57]. These damage mechanisms establish an interconnected network characterized by an incessant feedback that self-propagates and perpetuates once the trauma has begun, promoting other secondary self-destructive mechanisms causing more damage to the neural tissue [59].

After this, the glial cells, which originally provided support to the neurons, will secrete cytokines in response to mechanical damage. The activation of astrocytes and pericytes and the recruitment of peripheral fibroblasts and Schwann cells [60] will result in the chronic phase, characterized by the formation of glial scar (cellular and fibrotic or acellular) and a cystic cavity around the epicenter of spinal cord injury within 28–42 days after the injury [60].

The scar is characterized in that the astrocytes, previously activated by TGF-β (in addition to the activation of microglia and macrophages and the deposition of fibronectin and laminin) [61], pericytes, and perivascular cells infiltrate within the nucleus of the lesion where they promote the secretion of extracellular matrix components (EMC; fibronectin, laminin, and collagen) [62]; meanwhile, peripheral Schwann cells infiltrate the epicenter where they upregulate fibroblast markers contributing to the addition of EMC components.

This process is aimed at neural regeneration (neurotrophin production, cell debris removal, repair of the blood spinal cord barrier, and sequestration of reactive species [63]); however, it is hindered by proliferative astrocytes and a cumulus of EMC superimposed around the lesion, which will become rigid, keeping up intact chronically, avoiding cell migration, and becoming a regulator of axonal growth and regeneration [60].

Each stage is well characterized by a group of inflammatory events that will determine the severity of sequelae in the patient.

These systemic changes also have an important impact in the gastrointestinal tract, and it has been proven that higher levels of tissue loss at the lesion epicenter are directly proportional to gastroparesis and delayed gastric emptying with a specific proinflammatory pattern, especially during the acute-subacute phase in which a mild inflammatory cascade produced by the mesenteric hypoperfusion takes place with macroscopic alterations as gastrointestinal atrophy, necrosis, phagocyte infiltration, serosa and submucosa fibrosis, and decreased villi in the duodenum at high lesion levels with absorption commitment [64].

3.2.2 From general to specific: the inflammatory response in BD after SCI

The immune response in the SCI begins in the acute phase, making cellular and molecular responses that lead to the development of the inflammatory response, which plays an important role in the cascade events caused by the secondary lesion [65].

Physiologically, the goal of any inflammatory process is to phagocyte cell debris at the site of injury; however, the CNS is considered an immune privileged organ; that is why an uncontrolled and exacerbated response is triggered, which causes damage to healthy tissue adjacent to the site of injury, so its role seems to be harmful rather than beneficial [65, 66].

In this inflammatory process, four categories of immune cells are mainly distinguished: neutrophils, monocytes, microglia, and T lymphocytes.

Neutrophils are the first to arrive at the site of injury, and their arrival is by recruitment of the circulatory system through the expression of adhesion molecules

in their membranes, called chemokines. The neutrophils will be in charge to remove the remaining tissue; in addition, they will release cytokines, proteases, and free radicals. This activates other cells in the inflammatory cascade, triggering damage and neuronal death [67].

Shortly after the arrival of neutrophils, monocytes infiltrate the spinal cord, differentiating themselves into macrophages and acquiring a pro-inflammatory phenotype, contributing to the production of free radicals and pro-inflammatory cytokines such as interleukin (IL) 8, IL-1 beta (IL-1β), and tumor necrosis factor alpha (TNF-α) [66].

Free radicals and pro-inflammatory cytokines contribute to the expansion of the lesion, worsening the impact of the damage; this is because free radicals derived from nitrogen and oxygen can form highly neurotoxic compounds such as per-oxynitrite and unchain the phenomenon of lipoperoxidation and subsequent axonal demyelination, losing electrical conductivity below the site of injury [66–68].

On the other hand, the microglia are the innate immune cells of the CNS, being the first cells to acquire an inflammatory phenotype, along with macrophages; when it is damaged, these produce IL-6 and nitric oxide and could activate lympho-cytes in the injury site [69].

The role that lymphocytes play in SCI is controversial, because they can be acti-vated by neural antigens such as the myelin basic protein and considered self-reac-tive T lymphocytes that have self-destructive and inflammatory properties, which together with all the inflammatory mechanism eventually promote demyelination, causing the loss of the function of the neuronal connections with the peripheral nervous system (PNS) [68].

All these alterations provoke the impairment of the ANS [70], therefore result-ing in poor intestinal irrigation and BD with all its negative consequences, previ-ously described. At the upper GIT, proinflammatory chemokines *Cc13*, *Cc12*, and *Icam1* are upregulated the first 3 days after trauma triggering an inflammatory response in the intestine causing an increased intestinal permeability that allows bacterial translocation, a vicious circle that maintains BD [64].

Recently, Pde4b [cAMP-specific, *Pde4* subfamily *b* (*Pde4b*)] enzyme activated in macrophages, in gut dysbiosis, has been associated in the induction of proinflam-matory state in the CNS and the white matter loss after SCI through the production of LPS-induced TNF-α, IL-1, and nitric oxide contributing to neural damage [70].

3.3 The role of microbiome in bowel dysfunction after SCI

The GIT is the main interface of interaction and nutritional exchange between the inside of the individual and the outside of the world [71]. Around the 90% of the cells found in the human body are not human, but most have a *prokaryotic* origin, derived from at least 40,000 bacterial strains of 1800 different *genera*. During an average lifetime, about 60 tons of food passes through the human GIT, and with it are a large number of microorganisms from the environment [72].

The GIT is colonized by approximately 100 trillion of commensal microorgan-isms which is given the definition to gut microbiota that involves mostly *Archaea* and *Eukarya* bacteria, with up to 1000 species and more than 7000 strains [73].

The so-called microbiome encompasses the total microorganisms along with their genetic material, which corresponds to our genome 100 times larger.

Recent research has shown that at least 70% of the gut microbiota is integrated by two phylotypes, *Bacteroidetes* and *Firmicutes*, and in less quantity, *Proteobacteria, Actinobacteria, Fusobacteria*, and *Verrucomicrobia* [74].

Several factors, such as immune mechanisms, diet, and intestinal motility, as well as other stress mechanisms such as sepsis, burn, trauma, and infection, could

modify bacterial composition [75]. However, there have been some studies that support the therapeutic restoration of the microbiota with the use of probiotics, prebiotics, or symbiotics.

The microbiota offers many benefits for the host by maintaining a symbiotic relationship, such as strengthening the integrity of the mucous barrier, which provides nutrients like vitamins and also protection against pathogens and immunomodulation [76]. Meanwhile, dysbiosis can alter the balance and induce disease [77].

In the last 10 years, there have been many researchers investigating the effects of these microorganisms and their metabolites at different levels with beneficial findings in the irritable bowel syndrome, visceral pain, psychiatric disorders, alterations in the memory, and traumatic injuries in the CNS such as stroke [71, 78].

Gut's bacteria, specifically those found at the ileocecal valve and colon, produce some carbohydrate-active enzymes, which gives them the ability to produce complex carbohydrates through anaerobic fermentation generating metabolites such as short-chain fatty acids (SCFA). Three SCFA are mainly recognized, propionate, butyrate, and acetate, typically found in the ratio 1:1:3. The SCFA are rapidly absorbed by colonocytes in order to participate in the cellular regulation processes such as gene expression, chemotaxis, differentiation, proliferation, and apoptosis [79].

Smaller monocarboxylic acids, with less than six carbon atoms, are participants in pleiotropic signaling [75].

Those involved in the microbiota-gut-brain axis (MGBA) develop in parallel, mostly being important in the first 3 years of life because the blood-brain barrier (BBB) is more permeable and could allow the intake of toxins into the brain when the patient is under stress, as in the case of inadequate bowel colonization, altering proliferation, myelination, and neuronal plasticity. This may worsen as an exacerbated response to stress carried out by the hypothalamic-pituitary-adrenal axis (HPA), which could also condition the development of the vagus nerve. Therefore, MGBA development must be considered especially important [80].

This axis is formed by the CNS, the neuroendocrine and neuroimmune system, branches of the sympathetic and parasympathetic ANS, the enteric nervous system, and the gut microbiota [81, 82].

In summary, signals are sent by the brain and could affect the motor, sensory, and secretory function of the bowel, while bidirectionally, visceral signals influence brain function [81].

Several routes of communication between the brain and gut have been described, such as the activation of afferent sensory fibers of the vagus nerve, neuroimmune pathways, neuroendocrine pathways, microbial metabolites such as SCFA, and microbiota-derived neurotransmitters, such as gamma-aminobutyric acid (GABA), serotonin, catecholamines, and acetylcholine [81, 83].

Both SCFA and gastrointestinal hormones and cytokines, whether pro-/anti-inflammatory, travel through the portal circulation and the meningeal lymphatic system to the CNS [81]. Its action mechanisms are carried out directly and indirectly; this means that it is not necessary for SCFA to get in the CNS; however, its transport through cell membranes is done with pH-dependent transporters, H^+-coupled, called monocarboxylate transporters (MCTs) and sodium-coupled (SMCTs) transporters [81]. These families transport pyruvate, lactate, and butyrate, as well as other ketone bodies [84].

MCTs and SMCTs are found at the apical surface of colonocytes, and their expression is regulated by lumen butyrate concentrations, through NF-κB signaling [85].

However, they are not only expressed in the intestine, they are also present in liver, kidney, intestinal dendritic cells [85, 86]. In the CNS, neurons have SMCT1, while astrocytes have a greater amount of MCT1 [84], although microglia [87] and oligodendrocytes also express them [88].

Meanwhile, in the blood-brain barrier (BBB), MCT1 is also expressed; its importance has been proven in experimental models with decreased butyrate levels where it is associated with loss of integrity and increased permeability. The ability of butyrate to cross the blood-brain barrier has been demonstrated in different studies where it has been administered orally and there is a dose-dependent increase in acetylation of histone H3 in neurons and glia [89].

The effects of SCFA can also be carried out by activating surface butyrate-related receptors [90]; there are four G protein-coupled receptors (GPCRs): free fatty acid receptor-2 (FFAR2), free fatty acid receptor-3 (FFAR3), hydroxycarboxylic acid receptor-2 (HCAR2), and olfactory receptor-51E1 (OR51E1) [91].

FFAR2, FFAR3, and OR51E1 are found in enteroendocrine cells; this is where the interaction between probiotics and prebiotics takes place, promoting the production of SCFA and catalyzing the release of hormones such as cholecystokinin (CCK), the tyrosine-tyrosine peptide (PYY), and the glucagon-like peptide type-1 (GLP-1). In the last one, prebiotics have greater effects than those of probiotics [92, 93].

Symbiotics promote the production of dopamine (DA), serotonin (5-HT), norepinephrine (NA), and GABA [94], which modulate the proximal synapse in the ENS, which in turn, will allow gut-brain communication when synapsing with the vagus nerve [95].

The regulation of the MGBA also has effects at the HPA axis level, by modifying the levels of the adrenocorticotropic hormone (ACTH) and/or corticosteroids (CORT) [96]. In addition, it can directly influence the biochemistry of the CNS by altering the levels of the brain-derived neurotrophic factor (BDNF) who plays an important role in the development and plasticity of the nervous system, memory, and learning. It has been reported that higher butyric acid levels, for example, by *Bifidobacterium breve* and *Clostridium butyricum*, in turn increases the levels of BDNF who inversely decreases the production of pro-inflammatory cytokines such as interleukin-1 beta (IL-1β) [97], c-Fos, and GABA [98].

As previously mentioned, the immune system is also influenced by regulating the production of limited pro-inflammatory cytokines which will consequently influence the CNS.

3.3.1 How does the microbiota influence the immune system?

Immune system is influenced by MGBA through the inhibition of histone deacetylase HDACs, a protein family capable to catalyze the removal of acetyl groups from lysine residues [57].

This type of intracellular signaling can modify the activation of transcriptional or posttranslational processes in more than 1700 proteins; more frequently, they are carried out in nucleosome where their acetylation provokes the activation of transcription [58].

The HDAC family is divided into five subclasses, and its function is triggered by endogenous products such as butyrate which inhibits HDAC I and IIa (more beneficial subtypes for the host). Through this activation/inactivation mechanism, butyrate has effects on the immune system by regulating the activity of T-regulatory cells (Tregs), T CD4+ and T CD8+, lymphocytes, and microglia. In addition, monitoring the gut microbiota is done when changes in butyrate levels are detected [55].

Inhibition of HDAC and activation of FFAR2 induce the differentiation of Tregs expressing FoxP3, producing anti-inflammatory cytokines such as transforming growth factor-beta (TGF-β) and IL-10, suppressing the production of IL-2 and interferon-gamma (IFN-γ), inhibiting the production of inducible nitric oxide synthase (iNOS), and inducing apoptosis of active or resting TCD4+ and TCD8 through HDAC inhibition [55].

Propionate is also capable of upregulating the Foxp3 and IL-10 production showing that SCFA work selectively [61].

Butyrate modulates the activity of microglia in non-inflammatory situations by interfering with their maturation, morphology, and functioning or inflammatory, by reducing NF-*κB* signaling and inducing neuroprotective effects [68].

3.4 Microbiota and SCI: a close relationship?

It is suspected that there are SCFA in the CNS due to the expression of trans-membrane receptors and transporters in neurons; however, there is no evidence of physiological concentrations of butyrate in brain or cerebrospinal fluid; perhaps butyrate peaks that have not been measured in previous studies must be quantified. In in vitro studies, butyrate concentrations ranging from 0.4 to 0.7 mmol/L have been determined [83].

Under pathological circumstances, negative effects on microbiome have been described; particularly, SCI has negative effects on the gut microbiota as described by some authors (**Table 1**).

One more research that has not concluded is the multicenter, double-blind randomized placebo-controlled study that is ambitiously looking for better bowel

Experimental model	Outcome	Microbial composition identified	Reference
Fecal microbiota transplantation in one tetraplegic patient with severe recurrent *Clostridium difficile* infection	Patient recovered after transplantation and did not relapse from *C. difficile* infection until 12 weeks later	—	[99]
SCI-T9 mice	Bacterial translocation in the gut Increased gut epithelial permeability Increased activation of immune cells in the gut-associated lymphoid tissue (GALT) Gut dysbiosis results in a worse prognosis for locomotor recovery	Decreased relative abundance of *Bacteroidetes* and increased in *Firmicutes* (*Clostridium*)	[100]
Adult SCI patients [upper motor neuron (UMN); lower motor neuron(LMN)] vs. healthy adult patients	Decreased relative abundance of c members with differences between the different levels of injury (higher levels of injury provoke worse gut dysbiosis)	Decreased relative abundance of *Roseburia* and *Pseudobutyrivibrio* Genus associated with the increased production of butyrate is depleted	[13]
Thoracic SCI rat with antibiotic treatment	Significant differences in the gut microbiota beta diversity between SCI and healthy rats 35 OTUs were enriched Increased levels of proinflammatory cytokines (IL-12, MIP-2, and TNF-α) in the intestinal tissue	Increased relative abundance of *Lactobacillus intestinalis*, *Clostridium disporicum* and *Bifidobacterium choerinum* Depleted levels of *Clostridium saccharogumia*	[101]

Experimental model	Outcome	Microbial composition identified	Reference
Men with traumatic complete SCI (quadriplegics and paraplegics) vs. healthy patients	Significant differences in microbial composition Negative correlation with high-density lipoprotein cholesterol (cHDL) levels in the blood Increased gut epithelial permeability	Increased relative abundance of *Bacteroides* and *Bifidobacterium*	[102]
Adult male patients with traumatic cervical spinal cord injury vs. healthy male patients	Moderate bowel dysfunction in patients with SCI Decreased beta diversity of gut microbiota in SCI vs. healthy patients Decreased *Faecalibacterium* correlates with increased levels of triglycerides and cLDL Significantly decreased abundance of fatty acid metabolism in level 3 of the KEGG metabolic pathway hierarchy	Increased relative abundance of *Bacteroides* and *Blautia* Decreased levels of *Megamonas* and *Prevotella* correlate with lipid metabolism markers *Lactobacillus* positively correlates with serum glucose levels	[103]
Anxiety-like model in incomplete unilateral cervical SCI rats	Treatment with fecal transplant shows the reduction of anxiety-like behavior	112 OTUs (not specified) were found statistically different at day 3 post injury between SCI and healthy rats	[104]

Table 1.
Most important findings in the research field of SCI microbiota.

management and an increase in quality of life in SCI patients after their treatment with a multispecies probiotic [105].

In animal models, these results have been consistent, although in clinical studies it should be considered that there are confusing variables that cannot be controlled such as the intake of the same diet or the same level and intensity of injury, age of patients, diet intake, and administration of drugs that could modify the intestinal microbiota such as antibiotics.

4. Conclusion: what is next?

Spinal cord injury is a complex disease that involves several negative repercussions in the individual and society.

Its medical approach exclusively had been the treatment of movement impairment; however, in the last 14 years, the investigation is focusing on the treatment of other important comorbidities as the bowel dysfunction, which is responsible in decreasing the quality of life in patients with SCI that could worsen their health condition.

The answer apparently has been elucidated in the interaction between the individual and the gut microbiota.

Although, the study of the microbiota-gut-brain axis reveals with greater certainty the symbiotic dynamics that allow us to sustain homeostasis with our external environment; in this moment, the knowledge is still insufficient, with more reason in the SCI field.

Perhaps if the correct characterization of gut microbiota in this type of patients, considering their personalized features as the age, level, and severity of injury, is

achieved, it could be possible to propose a targeted nutraceutical treatment aiming to restore the eubiosis and, with this, modulate the exacerbated inflammatory response in SCI at the spinal cord and the bowel hoping for neuroprotection and less damage.

Acknowledgements

Author details

Estefanía de la Cruz-Castillo and Elisa García-Vences*
Centro de Investigación en Ciencias de la Salud (CICSA), Universidad Anáhuac México Campus Norte, Mexico

*Address all correspondence to: edna.garcia@anahuac.mx

IntechOpen

References

[1] Kirshblum SC, Waring W, Biering-Sorensen F, Burns SP, Johansen M, Schmidt-Read M, et al. Reference for the 2011 revision of the international standards for neurological classification of spinal cord injury. The Journal of Spinal Cord Medicine. 2011;**34**(6):547-554

[2] Furlan JC, Sakakibara BM, Miller WC, Krassioukov AV. Global incidence and prevalence of traumatic spinal cord injury. The Canadian Journal of Neurological Sciences. 2013;**40**(4):456-464

[3] Lim S, Shiue Y, Ho C, Yu S, Kao P, Wang J, et al. Anxiety and depression in patients with traumatic spinal cord injury : A nationwide population-based cohort study. PLOS One. 2017;**12**(1):e0169623

[4] Cripps RA, Lee BB, Wing P, Weerts E, Mackay J, Brown D. A global map for traumatic spinal cord injury epidemiology: Towards a living data repository for injury prevention. Spinal Cord. 2011;**49**(4):493-501

[5] Ma VY, Chan L, Carruthers KJ. Incidence, prevalence, costs, and impact on disability of common conditions requiring rehabilitation in the United States: Stroke, spinal cord injury, traumatic brain injury, multiple sclerosis, osteoarthritis, rheumatoid arthritis, limb loss, and back pa. Archives of Physical Medicine and Rehabilitation. 2014;**95**(5):986.e1-995.e1

[6] Singh A, Tetreault L, Kalsi-Ryan S, Nouri A, Fehlings MG. Global prevalence and incidence of traumatic spinal cord injury. Clinical Epidemiology. 2014;**6**:309-331

[7] Wyndaele M, Wyndaele JJ. Incidence, prevalence and epidemiology of spinal cord injury: What learns a worldwide literature survey? Spinal Cord. 2006;**44**(9):523-529

[8] Lee BB, Cripps RA, Fitzharris M, Wing PC. The global map for traumatic spinal cord injury epidemiology: Update 2011, global incidence rate. Spinal Cord. 2014;**52**(2):110-116

[9] WHO. Spinal Cord Injury [Internet]. 2013. Available from: https://www. who.int/en/news-room/fact-sheets/ detail/spinal-cord-injury [Accessed: 20 November 2019]

[10] Pérez R, Del Campo M, Renan S, Durán-Ortíz S. Aspectos epidemiológicos de la lesión medular de la población del Centro Nacional de Rehabilitación. Revista Mexicana de Medicina Física y Rehabilitación. 2008;**20**(3-4):74-82

[11] Pérez MD, Martínez CR, Zhurbenko R. Aspectos fundamentales sobre el género enterococcus como patógeno de elevada importancia en la actualidad. Revista Cubana de Higiene y Epidemiologia. 2010;**48**(2):147-161

[12] Azarhomayun A, Aghasi M, Mousavi N, Shokraneh F, Vaccaro AR, Haj Mirzaian A, et al. Mortality rate and predicting factors of traumatic thoracolumbar spinal cord injury; a systematic review and meta-analysis. Bulletin of Emergency and Trauma. 2018;**6**(3):181-194

[13] Gungor B, Adiguzel E, Gursel I, Yilmaz B, Gursel M. Intestinal microbiota in patients with spinal cord injury. PLOS One. 2016;**11**:e0145878

[14] Krueger H, Noonan VK, Trenaman LM, Joshi P, Rivers CS. The economic burden of traumatic spinal cord injury in Canada. Chronic Diseases and Injuries in Canada. 2013;**33**(3):113-122

[15] Nelson MD, Widman LM, Abresch RT, Stanhope K, Havel PJ, Styne DM, et al. Metabolic syndrome

in adolescents with spinal cord dysfunction. The Journal of Spinal Cord Medicine. 2007;**30**(Suppl 1):127-139

[16] Isomaa B, Almgren P, Tuom T. Cardiovascular morbidity and mortality. Diabetes Care. 2001;**24**(4):683-689

[17] Ibarra A, Ríos-Hoyo A, Suarez-Meade P, Malagon E, Colin-Rodríguez A. Influence of the level, severity and phase of spinal cord injury on hematological and biochemical parameters. Journal of Trauma & Treatment. 2014;**3**(4):2167-1222

[18] Brommer B, Engel O, Kopp MA, Watzlawick R, Müller S, Prüss H, et al. Spinal cord injury-induced immune deficiency syndrome enhances infection susceptibility dependent on lesion level. Brain. 2016;**139**:692-707

[19] Myers SA, Gobejishwili L, Saraswat Ohri S, Wilson CG, Andres KR, Riegler AS, et al. Following spinal cord injury, PDE4B drives an acute, local inflammatory response and a chronic, systemic response exacerbated by gut dysbiosis and endotoxemia. Neurobiology of Disease. 2019;**124**:353-363

[20] Wallin BG, Stjernberg L. Sympathetic activity in man after spinal cord injury: Outflow to skin below the lesion. Brain. 1984;**107**(1):183-198

[21] Eldahan KC, Rabchevsky AG. Autonomic dysreflexia after spinal cord injury. Autonomic Neuroscience. 2018;**209**:59-70

[22] Karlsson AK. Autonomic dysfunction in spinal cord injury: Clinical presentation of symptoms and signs. Progress in Brain Research. 2006;**152**:1-8

[23] Sharif H, Hou S. Autonomic dysreflexia: A cardiovascular disorder following spinal cord injury. Neural Regeneration Research. 2017;**12**(9):1390-1400

[24] Karlsson AK. Scientic review autonomic dysreflexia. Spinal Cord. 1999;**37**:383-391

[25] Lee ES, Joo MC. Prevalence of autonomic dysreflexia in patients with spinal cord injury above T6. BioMed Research International. 2017;**2017**:1-6

[26] Lucin KM, Sanders VM, Jones TB, Malarkey WB, Popovich PG. Impaired antibody synthesis after spinal cord injury is level-dependent and is due to sympathetic nervous system dysregulation. Experimental Neurology. 2007;**207**(1):75-84

[27] Pieper MP, Chaudhary NI, Park JE. Acetylcholine-induced proliferation of fibroblasts and myofibroblasts in vitro is inhibited by tiotropium bromide. Life Sciences. 2007;**80**:2270-2273

[28] Kurzen H, Henrich C, Booken D, Poenitz N, Gratchev A, Klemke CD, et al. Functional characterization of the epidermal cholinergic system in vitro. The Journal of Investigative Dermatology. 2006;**126**:2458-2472

[29] Baek A, Shin JC, Lee MY, Kim SH, Kim J, Cho SR. Parasympathetic effect induces cell cycle activation in upper limbs of paraplegic patients with spinal cord injury. International Journal of Molecular Sciences. 2019;**20**:5982

[30] Braddom R. Physical Medicine and Rehabilitation. 2nd ed. Philadelphia: WB Saunders Company; 2000. p. 1532

[31] Stone JM, Nino-Murcia M, Wolfe VA, Perkash I. Chronic gastrointestinal problems in spinal cord injury patients: A prospective analysis. The American Journal of Gastroenterology. 1990;**85**(9):1114-1119

[32] Glickman S, Kamm MA. Bowel dysfunction in spinal-cord-injury patients. Lancet. 1996;**347**(9016):1651-1653

[33] Lynch AC, Antony A, Dobbs BR, Frizelle FA. Bowel dysfunction

following spinal cord injury. Spinal Cord. 2001;**39**(4):193-203

[34] Levi R, Hultling C, Nash MS, Seiger A. The Stockholm spinal cord injury study: 1. Medical problems in a regional SCI population. Paraplegia. 1995;**33**(6):308-315

[35] Insua JT. Principialismo, bioética personalista y principios de acción en medicina y en servicios de salud. Persona y Bioética. 2018;**22**(2):223-246

[36] Whoqol Group. Development of the WHOQOL: Rationale and current status. International Journal of Mental Health. 1994;**23**(3):24-56

[37] Mashola MK, Mothabeng DJ. Associations between health behaviour, secondary health conditions and quality of life in people with spinal cord injury. African Journal of Disability. 2019;**8**:a463

[38] Catz A, Itzkovich M. Spinal cord Independence measure: Comprehensive ability rating scale for the spinal cord lesion patient. Journal of Rehabilitation Research and Development. 2007;**44**(1):65-68

[39] Ware JEJ, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical Care. 1992;**30**(6):473-483

[40] Craven C, Hitzig SL, Mittmann N. Impact of impairment and secondary health conditions on health preference among Canadians with chronic spinal cord injury. The Journal of Spinal Cord Medicine. 2012;**35**(5):361-370

[41] Choukou MA, Best KL, Craven BC, Hitzig SL. Identifying and classifying quality of life tools for assessing neurogenic bowel dysfunction after spinal cord injury. Topics in Spinal Cord Injury Rehabilitation. 2019;**25**(1):1-22

[42] Bølling Hansen R, Staun M, Kalhauge A, Langholz E, Biering-Sørensen F. Bowel function and quality of life after colostomy in individuals with spinal cord injury. The Journal of Spinal Cord Medicine. 2016;**39**(3):281-289

[43] Stone J, Wolfe V, Nino-Murcia M, Perkash I. Colostomy as treatment for complications of spinal cord injury. Archives of Physical Medicine and Rehabilitation. 1990;**71**(7):514-518

[44] Mazzone A, Farrugia G. Evolving concepts in the cellular control of gastrointestinal motility: Neurogastroenterology and enteric sciences. Gastroenterology Clinics of North America. 2007;**36**(3):499-513

[45] Gabella G. Autonomic nervous system. In: Paxinos G, editor. The Rat Nervous System. 3 ed. United States of America: Elsevier; 2004:77-109

[46] Navarro X. Fisiología del sistema nervioso autónomo. Revista de Neurologia. 2002;**35**:553-562

[47] Newgreen D, Young HM. Enteric nervous system: Development and developmental disturbances—Part 2. Pediatric and Developmental Pathology. 2002;**5**(4):329-349

[48] Romero-Trujillo JO, Frank-Márquez N, Cervantes-Bustamante R, Cadena-León JF, Montijo-Barrios E, Zárate-Mondragón F, et al. Sistema nervioso entérico y motilidad gastrointestinal. Acta Pediátrica de México. 2012;**33**(4):207-214

[49] Valles M, Mearin F. Alteraciones intestinales en pacientes con lesión medular. Gastroenterología y Hepatología. 2012;**35**(5):330-336

[50] Sekhon LH, Fehlings MG. Epidemiology, demographics, and pathophysiology of acute spinal cord injury. Spine (Phila Pa 1976). 2001;**26**(24 Suppl):S2-S12

[51] Longo WE, Ballantyne GH, Modlin IM. The colon, anorectum, and spinal cord patient. A review of the functional alterations of the denervated hindgut. Diseases of the Colon and Rectum. 1989;**32**(3):261-267

[52] Emmanuel A. Neurogenic bowel dysfunction. F1000Research. 2019;**8**(F1000 Faculty Rev):1800

[53] Emmanuel AV, Chung EA, Kamm MA, Middleton F. Relationship between gut-specific autonomic testing and bowel dysfunction in spinal cord injury patients. Spinal Cord. 2009;**47**(8):623-627

[54] Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. Annals of Gastroenterology. 2015;**28**(2):203-209

[55] Martin AR, Aleksanderek I, Fehlings MG. Diagnosis and acute management of spinal cord injury: Current best practices and emerging therapies. Current Trauma Reports. 2015;**1**(3):169-181

[56] Mataliotakis GI, Tsirikos AI. Spinal cord trauma: Pathophysiology, classification of spinal cord injury syndromes, treatment principles and controversies. Orthopaedics and Traumatology. 2016;**30**(5):440-449

[57] Oyinbo CA. Secondary injury mechanisms in traumatic spinal cord injury: A nugget of this multiply cascade. Acta Neurobiologiae Experimentalis. 2011;**71**(2):281-299

[58] Witiw CD, Fehlings MG. Acute spinal cord injury. Journal of Spinal Disorders & Techniques. 2015;**28**(6):202-210

[59] Tator CH, Fehlings MG. Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. Journal of Neurosurgery. 1991;**75**(1):15-26

[60] Orr MB, Gensel JC. Spinal cord injury scarring and inflammation: Therapies targeting glial and inflammatory responses. Neurotherapeutics. 2018;**15**(3):541-553

[61] Franze K, Janmey PA, Guck J. Mechanics in neuronal development and repair. Annual Review of Biomedical Engineering. 2013;**15**:227-251

[62] Wanner IB, Anderson MA, Song B, Levine J, Fernandez A, Gray-Thompson Z, et al. Glial scar borders are formed by newly proliferated, elongated astrocytes that interact to corral inflammatory and fibrotic cells via STAT3-dependent mechanisms after spinal cord injury. The Journal of Neuroscience. 2013;**33**(31):12870-12886

[63] Faulkner JR, Herrmann JE, Woo MJ, Tansey KE, Doan NB, Sofroniew MV. Reactive astrocytes protect tissue and preserve function after spinal cord injury. The Journal of Neuroscience. 2004;**24**(9):2143-2155

[64] Besecker EM, Deiter GM, Pironi N, Cooper TK, Holmes GM. Mesenteric vascular dysregulation and intestinal inflammation accompanies experimental spinal cord injury. American Physiological Society. 2017;**312**(1):R146-R156

[65] Tashiro S, Nakamura M, Okano H. The prospects of regenerative medicine combined with rehabilitative approaches for chronic spinal cord injury animal models. Neural Regeneration Research. 2017;**12**(1):43-46

[66] Gadani SP, Walsh JT, Lukens JR, Kipnis J. Dealing with danger in the CNS: The response of the immune system to injury. Neuron. 2015;**87**(1):47-62

[67] Carlson SL, Parrish ME, Springer JE, Doty K, Dossett L. Acute inflammatory response in spinal cord following impact injury. Experimental Neurology. 1998;**151**(1):77-88

[68] Donnelly DJ, Popovich PG. Inflammation and its role in neuroprotection, axonal regeneration and functional recovery after spinal cord injury. Experimental Neurology. 2008;**209**(2):378-388

[69] Gartner L. In: Gartner L, Hiatt JL, editors. Texto Atlas de Histología. 2nd ed. China: McGraw-Hill; 2007. p. 539

[70] Kigerl KA, Mostacada K, Popovich PG. Gut microbiota are disease-modifying factors after traumatic spinal cord injury. Neurotherapeutics. 2018;**15**:60-67

[71] Stilling RM, Dinan TG, Cryan JF. Microbial genes, brain & behaviour—Epigenetic regulation of the gut-brain axis. Genes, Brain, and Behavior. 2014;**13**(1):69-86

[72] Vernocchi P, Del Chierico F, Putignani L. Gut microbiota profiling: Metabolomics based approach to unravel compounds affecting human health. Frontiers in Microbiology. 2016;**7**:1144

[73] Estrada-Mondaca S, Carreón-Rodríguez A, Parra-Cid MC, León CI, Velasquillo-Martínez C, Vacanti CA, et al. Spinal cord injury and regenerative medicine. Salud Pública de México. 2007;**49**(6):437-444

[74] Stilling RM, van de Wouw M, Clarke G, Stanton C, Dinan TG, Cryan JF. The neuropharmacology of butyrate: The bread and butter of the microbiota-gut-brain axis? Neurochemistry International. 2016;**99**:110-132

[75] Robles Alonso V, Guarner F. Linking the gut microbiota to human health.

The British Journal of Nutrition. 2013;**109**(Suppl):S21-S26

[76] Thursby E, Juge N. Introduction to the human gut microbiota. The Biochemical Journal. 2017;**474**(11):1823-1836

[77] Wang H, Lee IS, Braun C, Enck P. Effect of probiotics on central nervous system functions in animals and humans: A systematic review. Journal of Neurogastroenterology & Motility. 2016;**22**(4):589-605

[78] Clark J, Coopersmith C. Intestinal crosstalk: A new paradigm for understanding the gut as the "motor" incomplete spinal cord injury: Comparison with patients with motor complete spinal cord injury. Diseases of the Colon and Rectum. 2009;**52**:1589-1597

[79] Corrêa-Oliveira R, Fachi JL, Vieira A, Sato FT, Vinolo MA. Regulation of immune cell function by short-chain fatty acids. Clinical & Translational Immunology. 2016;**5**(4):e73

[80] Wiley NC, Dinan TG, Ross RP, Stanton C, Clarke G, Cryan JF. The microbiota-gut-brain axis as a key regulator of neural function and the stress response: Implications for human and animal health. Journal of Animal Science. 2017;**95**(7):3225-3246

[81] Dinan TG, Cryan JF. Melancholic microbes: A link between gut microbiota and depression? Neurogastroenterology and Motility. 2013;**25**(9):713-719

[82] Sherwin E, Sandhu KV, Dinan TG, Cryan JF. May the force be with you: The light and dark sides of the microbiota-gut-brain axis in neuropsychiatry. CNS Drugs. 2016;**30**(11):1019-1041

[83] Cryan JF, O'Mahony SM. The microbiome-gut-brain axis: From bowel to behavior. Neurogastroenterology and Motility. 2011;**23**(3):187-192

[84] Vijay N, Morris M. Role of monocarboxylate transporters in drug delivery to the brain. Current Pharmaceutical Design. 2014;**20**(10):1487-1498

[85] Ganapathy V, Thangaraju M, Gopal E, Martin PM, Itagaki S, Miyauchi S, et al. Sodium-coupled monocarboxylate transporters in normal tissues and in cancer. The AAPS Journal. 2008;**10**(1):193

[86] Ho JS, Anzai N, Enomoto A, He X, Do KK, Endou H, et al. Novel liver-specific organic anion transporter OAT7 that operates the exchange of sulfate conjugates for short chain fatty acid butyrate. Hepatology. 2007;**45**(4):1046-1055

[87] Moreira TJTP, Pierre K, Maekawa F, Repond C, Cebere A, Liljequist S, et al. Enhanced cerebral expression of MCT1 and MCT2 in a rat ischemia model occurs in activated microglial cells. Journal of Cerebral Blood Flow and Metabolism. 2009;**29**(7):1273-1283

[88] Lee Y, Morrison BM, Li Y, Lengacher S, Farah MH, Hoffman PN, et al. Oligodendroglia metabolically support axons and contribute to neurodegeneration. Nature. 2012;**487**(7408):443-448

[89] Minamiyama M, Katsuno M, Adachi H, Waza M, Sang C, Kobayashi Y, et al. Sodium butyrate ameliorates phenotypic expression in a transgenic mouse model of spinal and bulbar muscular atrophy. Human Molecular Genetics. 2004;**13**(11):1183-1192

[90] Bolognini D, Tobin AB, Milligan G, Moss CE. The pharmacology and function of receptors for short-chain fatty acids. Molecular Pharmacology. 2016;**89**(3):388-398

[91] Singh N, Gurav A, Sivaprakasam S, Brady E, Padia R, Shi H, et al.

Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. Immunity. 2014;**40**(1):128-139

[92] Nøhr MK, Pedersen MH, Gille A, Egerod KL, Engelstoft MS, Husted AS, et al. GPR41/FFAR3 and GPR43/FFAR2 as cosensors for short-chain fatty acids in enteroendocrine cells vs FFAR3 in enteric neurons and FFAR2 in enteric leukocytes. Endocrinology. 2013;**154**(10):3552-3564

[93] Sarkar A, Lehto SM, Harty S, Dinan TG, Cryan JF, Burnet PWJ. Psychobiotics and the manipulation of bacteria–gut–brain signals. Trends in Neurosciences. 2016;**39**(11):763-781

[94] Liu YW, Liu WH, Wu CC, Juan YC, Wu YC, Tsai HP, et al. Psychotropic effects of *Lactobacillus plantarum* PS128 in early life-stressed and naïve adult mice. Brain Research. 1631;**2016**:1-12

[95] Bercik P, Park AJ, Sinclair D, Khoshdel A, Lu J, Huang X, et al. The anxiolytic effect of *Bifidobacterium longum* NCC3001 involves vagal pathways for gut-brain communication. Neurogastroenterology and Motility. 2011;**23**(12):1132-1139

[96] Liang S, Wang T, Hu X, Luo J, Li W, Wu X, et al. Administration of *Lactobacillus helveticus* NS8 improves behavioral, cognitive, and biochemical aberrations caused by chronic restraint stress. Neuroscience. 2015;**310**:561-577

[97] O'Sullivan E, Barrett E, Grenham S, Fitzgerald P, Stanton C, Ross RP, et al. BDNF expression in the hippocampus of maternally separated rats: Does *Bifidobacterium breve* 6330 alter BDNF levels? Beneficial Microbes. 2011;**2**(3):199-207

[98] Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG,

et al. Ingestion of lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proceedings of the National Academy of Sciences of the United States of America. 2011;**108**(8):16050-16055

[99] Brechmann T, Swol J, Knop-Hammad V, Willert J, Aach M, Cruciger O, et al. Complicated fecal microbiota transplantation in a tetraplegic patient with severe *Clostridium difficile* infection. World Journal of Gastroenterology. 2015;**21**(12):3736-3740

[100] Kigerl KA, Hall JCE, Wang L, Mo X, Yu Z, Popovich PG. Gut dysbiosis impairs recovery after spinal cord injury. The Journal of Experimental Medicine. 2016;**213**(12):2603-2620

[101] O'Connor G, Jeffrey E, Madorma D, Marcillo A, Abreu MT, Deo SK, et al. Investigation of microbiota alterations and intestinal inflammation post-spinal cord injury in rat model. Journal of Neurotrauma. 2018;**35**(18):2159-2166

[102] Zhang C, Zhang W, Zhang J, Jing Y, Yang M, Du L, et al. Gut microbiota dysbiosis in male patients with chronic traumatic complete spinal cord injury. Journal of Translational Medicine. 2018;**16**:353

[103] Zhang C, Jing Y, Zhang W, Zhang J, Yang M, Du L, et al. Dysbiosis of gut microbiota is associated with serum lipid profiles in male patients with chronic traumatic cervical spinal cord injury. American Journal of Translational Research. 2019;**11**(8):4817-4834

[104] Schmidt EKA, Torres-Espin A, Raposo PJF, Madsen KL, Kigerl KA, Popovich PG, et al. Fecal transplant prevents gut dysbiosis and anxiety-like behaviour after spinal cord injury in rats. PLOS One. 2020;**15**(1):e0226128

[105] Faber WXM, Nachtegaal J, Stolwijk-Swuste JM, Achterberg-Warmer WJ, Koning CJM, Besseling-van der Vaart I, et al. Study protocol of a double-blind randomised placebo-controlled trial on the effect of a multispecies probiotic on the incidence of antibiotic-associated diarrhoea in persons with spinal cord injury. Spinal Cord. 2020;**58**:149-156