Unmasking the gut-brain axis: How the microbiota influences brain and behavior.

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Abstract

Translational Research seems to occupy the center of health research. A proof of this is that articles about metabolites depending on the metabolism of the intestinal microbiota associating with the gut-brain axis. Human gut harbors trillions of bacteria affecting immune system homeostasis, production of essential nutrients and protection against pathogenic germs. The intestinal mesenteric lymphatic system, gut-associated lymphoid tissue is an interface between blood and intestinal lymphatic fluid and provides activated immune cells to the intestinal epithelium and to the lamina propria. Environmental factors such as, diet, use of antibiotics, environmental contamination, exposure to microorganisms, among others, thus increasing the risk of bacterial imbalance. Gut dysbiosis affects central nervous system (CNS) responses activated by circumventricular organs during systemic inflammation. Besides, the vagal afferent pathway also mediates immune system (IS) signals to the CNS. One of the ways in which the CNS communicates with the IS is through the autonomic nervous system and myenteric plexus. The link between gut functions, emotional and cognitive processes is provided by bi-directional afferent and efferent neural projection pathways, neuroendocrine signals, immunological activation and gut-brain signals, altered gut permeability, and modulation of sensorimotor reflexes. Gut microbiota developed as a critical component that has potential to affect immuno-neuro-endocrine pathways. Studies have shown that the intestinal microbiota substantially affects the neuroendocrine axis.

Keywords: Microbiota, Symbiotic, Synbiotic, Probiotic, Brain, Kefir, Behavior.

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Introduction

Translational Research (TR) seems to be occupying the center of health research at the turn of the century. It was initiated in United States of America (USA), but has spread quickly throughout the world. When it was originated, the term TR was associated with research conducted at the National Cancer Institute (NCI) and only in the first decade of this century was it expanded to other fields of health research. In 2003, the National Institutes of Health (NIH) published the results of a broad national survey conducted in 2002 and addressed to the scientific community with the goal of guiding a long-term policy [1]. The research identified three major targets, one of them called "Reengineering the Clinical Research Enterprise". This objective highlighted, among other actions, the promotion of the "establishment of academic environments for clinical and translational research". The next step was taken in 2006, with the creation, at the NIH, of a line of institutional promotion specifically linked to this goal, the "Clinical and Translational Science Awards" (CTSA). Finally, in 2012, a new NIH unit was created, specifically dedicated to support the creation of TR-oriented research centers, the "National Center for Advancing Translational Sciences" (NCATS) [2]. A proof of this is that in that same year, Wilson Tang WH et al. published a NIH-funded article using TR and concluding that the metabolite TriMethylAmine-N-Oxide (TMAO) obtained from dietary phosphatidylcholine is dependent of (metabolized by) gut microbiota, and that there is a relationship between increased levels of TMAO and increased risk of adverse cardiovascular events, which is a clear evidence of interaction of the intestinal microbiota with the gut-brain axis [3].

Interactions Gut Microbiota-Host

Over the years, it was observed that the gut microbiota has been associated to initiate and develop several diseases and conditions, including intestine disorders, CNS diseases and different systemic diseases [4-7]. The gut, as the body's largest immune organ, harbors trillions of bacteria. The genome of all microorganisms in the gut microbiota contains 150 times more genes than the human genome [8]. All these genes have a fundamental impact on host health, because of how they affect IS homeostasis, production of essential nutrients for the organism and protection against pathogenic germs [9]. Thus, the gut microbiota play a key role of variable in the way, the organism interacts and how it responds to its environment. It also plays an important role in the mechanism by which the host is affected and responds to environmental stimuli. This constant symbiotic action of the gut microbiota is crucial for the maintenance of the intestinal homeostasis. The Gut Associated Lymphoid Tissue (GALT) has its immune preparation initiated and based on this interaction. GALT supplies activated immune cells to the intestinal epithelium and to the lamina propria, due

the way they interact with the gut microbiota [10]. Even when healthy, several lymphocytes and other immunity effector cells reside in the intestinal tissues, to react with and/or tolerate the gut microbiota. Therefore, gut microbiota plays a critical role by determining several immunological responses and several other signalling events in the host. It has been demonstrated the relevance of maintaining the intestinal and systemic homeostasis tightly controlled by regulatory immunity mechanisms, which are determined by interactions between trillions of beneficial microbes, gene microbial-derived products, and pattern recognition receptors (PRRs). Disruption of this balance by hostile signals has significant consequences that can result in many diseases. Therefore, fragmentation of this interaction may result in many diseases [11]. Published results from the Human Microbiome Project have shown that thousands of microbes inhabit our intestines. Although they present wide variation in composition between individuals, microbial genes involved in maintaining basic metabolic activities are functionally similar among individuals [12].

Several studies have identified the existence of one group of commensal bacteria genera, including *Lactobacillus*, *Clostridium*, *Bifid bacterium*, *Bacteroides*, *Streptococcus* and Enterobacterium [7,13]. Moreover, the composition of the microbiota in the intestines is a dynamic process that can be affected by several factors, including maternal breastfeeding, gastrointestinal infections, genetics, age, stress and medications [14]. Type of diet profoundly affects the intestinal microbiota, and studies in humans and animals have shown modifications in the microbial composition of individuals using various diets. For example, one study compared traditional Western lifestyle with individuals who consume African diet showed differences in bacterial profiles [15].

The diet can have even more pronounced impact when probiotics are offered. The administration of live microorganisms in adequate quantities gives health benefits [16].

Probiotics are used in long-term bases consumption and, when administered in foods containing sufficient amounts to safely reach the gastrointestinal tract, offer health benefits. Currently, the number of publications about the synbiotic kefir is growing; originally consumed by communities in the Caucasus Mountains. The drink has a slightly viscous texture with acid taste, low levels of alcohol and, in some cases, slight carbonation. The most studied kefir is made with cow's milk, although it can be made from milk from other sources, animals and vegetables [17-20]. One of the characteristics that distinguish kefir from many other fermented dairy products is the requirement for the presence of kefir grains in the fermentation process, as well as the presence of a large population of yeasts [21,22]. The potential benefits of kefir has motivated enormous interest in the scientific community due to important properties, including better digestion and tolerance to lactose, anti-inflammatory effect, reducing cholesterol, glucose, hypertension, antioxidant, anticancer activity and antiallergic [23-30]. In addition to recovering vascular endothelium from SHR rats with kefir treatment for 60 days, for partially restoring ROS / NO imbalance and endothelial architecture due to recruitment of endothelial progenitor cells [31]. Obviously, changes in homeostasis with infections and diseases affect the composition of the intestinal microbiota and, consequently, could cause damage to the host. For example, imbalances of the intestinal microbiota in young rats lead to an instance, in the threshold of visceral pain, a stress-related trait, as in irritable bowel syndrome [32]. Changes in intestinal microbiota have also been associated with inflammatory bowel disease and obesity [33]. In addition, the use of assorted medications such as antibiotics, antacids and H2 blockers may profoundly affect the intestinal microbiota [34,35]. Intestinal dysbiosis can result from these situations and is usually characterized by a change in symbiosis between this bacterial population and the growth of harmful bacteria) [36]. The presence of certain metabolites in the intestinal lumen may select disobeying microbes, resulting in insulin resistance and abnormally low levels of short chain fatty acids (SCFAs), among other metabolic disorders [37,38]. Inflammatory bowel diseases (IBD), which are associated with chronic intestinal inflammation and the loss of the intestinal barrier attributed to dysbiosis [39]. In addition to the role of prebiotics in promoting the growth of certain beneficial bacteria (typically *Bifidobacterium* and *Lactobacillus*), they further promote reduction of pathological permeability (hyperpermeability) and intestinal inflammation [40,41].

Gut-brain axis

The human gastrointestinal tract houses a population of germs with more than anaerobic bacteria, yeasts, fungi and viruses [42]. Bacterial colonization in the gastrointestinal tract depends on several factors, including type of delivery and method of postnatal feeding [43,44]. Subsequently, gut microbiota is transferred from mother to child and its composition may be affected over time by various environmental factors, such as diet, use of antibiotics, environmental contamination, exposure to microorganisms, among others, thus increasing the risk of bacterial imbalance. This condition is also known as gut dysbiosis and is characterized by the substitution of healthy intestinal flora by one that is harmful to the host's health, which can negatively influence the central nervous system in several intertwined ways that, together, form the gut-brain axis.

The connection between the gastrointestinal tract and the CNS is well established and thoroughly studied, demonstrating that it is essential for intestinal modulation, immunological, health maintenance, and neurological, hormonal, immunological and metabolic signaling. Disturbances in this intense exchange of information can result in compromising one's health [45]. For example, changes in host behavior may be related to gut inflammation, which leads to changes in gut-brain interactions, a condition related to anxiety [14]. Chronic noncommunicable diseases (NCDs), such as type 2 diabetes mellitus (DM2), hypertension, dyslipidemia and Atherosclerosis, are becoming increasingly relevant in global public health due to the disabilities they cause and early mortality. Excess of body fat plays a central role in the origin and maintenance of these diseases, and the increase in obesity in Brazil and other countries is alarming [46]. The participation of intestinal bacteria in the etiopathogenetic of these and other NCDs is arousing attention due to the possibility of being a potential target for intervention) [47-51]. There are expected around 15.4 million deaths worldwide due to DNTs [52]. Data from the National Health and Nutrition Examination Survey (NHANES) indicate that the prevalence of hypertension

in adults over 20 years of age has been estimated at 34.0% from 2011 to 2014. This contrasts with the 67.2% among those with over 60 years of age [53]. Increasing evidence suggests that treatment-resistant hypertension is accompanied by a low-grade chronic inflammatory profile that facilitates damage to target organs maintaining the hypertensive state, suggesting a close connection between the sympathetic nervous system (SNS) and the immune system [54]. Environmental factors are perceived by the central nervous system (CNS) through the peripheral nervous system. The afferent is processed by the CNS that organizes the results into efferent behavioral responses, among others [55]. In this way, the autonomic nervous system (ANS) involuntarily regulates homeostasis. The two branches of SNA, SNS and the parasympathetic nervous system (SNP) cooperate to regulate organs in an antagonistic and synergistic manner) [56]. An important aspect of stress response, involves the hypothalamic-pituitary-adrenal axis (HPA) and various hormones that provide appropriate reactions to perceived threats [57]. Chronic stress in a sustained manner continuously activates the HPA axis, resulting in the continuous release of glucocorticoid hormone, cortisol (human) or corticosterone (rodent) and renin-angiotensin-aldosterone system (RAAS) [58].

The gut-brain axis involves bidirectional communication between the intestinal microbiota, the enteric nervous system and the SNC [55,59]. CNS responses can be activated by circumventricular organs (CVOs). During systemic inflammation the circumventricular organs (CVOs) can receive hematogenic information from the intestine, and activate the CNS), as it has been demonstrated in some intestine disorders [60,61]. CVOs are specialized structures that lack the blood-brain barrier (BBB), allowing direct communication between the cerebral parenchyma and peripheral fluids. As a result, these highly vascular CVOs can identify hormonal changes and cytokines in the circulation [62,63]. In addition, the vagal afferent pathway also mediates immune system signals to the CNS. One of the ways in which the CNS communicates with the immune system through the autonomic nervous system (ANS). Sympathetic nerves are present in the primary lymphatic organs (bone marrow and thymus) and secondary lymphatic organs (spleen, lymph nodes, mucosa-associated lymphoid tissue- MALT). Norepinephrine released from the sympathetic terminals of postganglionic neurons, bind to adrenergic receptors expressed in adaptive immune cells. Adaptive immune cell cells respond to NHS signals predominantly via the β2 adrenergic receptor, and the stimulation of β2 receptors in these immune cells modulates several aspects [64]. In the bone marrow, hematopoietic stem cells from the bone marrow (HSCs) receive direct afferent NHS through adrenergic receptors on the cell surface. This sympathetic physiological response to immune system benefits the mobilization of hematopoietic and progenitor stem cells (HSPC), in anticipation of possible infections and lesions [65]. In the secondary lymphatic organs, the sympathetic nerves accompany the local vascularization pathway and the connective tissue, forming neuro-effector junctions with the immune cells in the parenchyma. The intestinal lymphoid tissue (GALT) is also innervated by the sympathetic nerves that extend from the vascular beds in the intestines) [66]. Interestingly, the sympathetic nerve impulse prevents innervation of the germinal center where differentiation and maturation of B cells occurs, although it is known that B cells can be modulated by substances released from sympathetic terminals [67,68]. Interestingly, the effects of adrenergic signaling on cells of the immune system occur in pro-inflammatory and anti-inflammatory responses), depending on the level of activation of specific immune cells and the stage of disease [64]. The parasympathetic system also participates in the regulation of immune system Electrical stimulation experiments of the vagus nerve demonstrated attenuation of the inflammatory systemic activity to the endotoxin, reducing the pro-inflammatory responses to TNF, but not to the anti-inflammatory IL-10 [69]. In subsequent research, it has been shown that alpha-7 nicotinic acetylcholine (α7nAChR) receptors present on macrophages are regulators of the anti-inflammatory effects resulting from vagus nerve stimulation [70]. Therefore, temporary activation of the vagus nerve leads to the release of anti-inflammatory acetylcholine that binds α7nAChR + macrophage and suppresses the production of pro-inflammatory cytokines [71]. However, chronic inflammation, as observed in hypertension, is associated with attenuation of the afferent vagal flow and efferent response [72]. From this, it is tempting to propose that afferent vagal signals from the gut can alter the profiles of immune cells by modulating efferent cholinergic tonus, reducing the inflammatory response of the mucosa and maintaining intestinal homeostasis [61].

Moreover, until recently, the fields of neuroscience and microbiology were rarely studied together. (However, progress in the field of intestinal microbiota and its influence on health and disease, in addition to the relationship with obesity and inflammatory bowel diseases, sparked interest in the possibility of this commensal community affecting physiology. Increasing evidence has shown that the intestinal microbiota also plays a role in CNS function through metabolic, neuroendocrine and immune functions [73].

Interactions between the Gut-Microbiota Axis and Behavior

The link between gut functions on the one hand and emotional and cognitive processes on the other hand is provided by bi-directional afferent and efferent neural projection pathways, neuroendocrine signals, immunological activation and gut-brain signals, altered gut permeability, and modulation of sensorimotor reflexes [73,74]. Gut microbiota emerged as a critical component potentially affecting all immuno-neuro-endocrine pathways [75,76]. For example, even short-term exposure to stress may impact the microbiota community profile by altering the relative size of the major phyla, modifying the microbiota [77]. This behavior is similar to anxiety and the adjustment point for the activation of the stress neuroendocrine hypothalamic-pituitary-adrenal (HPA) axis [76,78-81].

Attention Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that begins in childhood, characterized by a pattern of persistent inattention and hyperactive-impulsive behavior. The disorder is associated with deterioration of social, academic, and occupational behavior [82]. The worldwide prevalence of ADHD is 7.2% [83]. Several environmental risk factors for ADHD are related, such as tobacco use during pregnancy, low birth weight,

prematurity, among others, such as adoption. However, studies with families, twins and adopted children find the influence of a strong genetic component, with an average of 76% [84]. Despite all the efforts to pinpoint risk factors, the genetic variants identified so far only explain a small proportion (<10%) of the estimated inheritance of the disorder [84-87]. With these data, investigating the association of epigenetic factors became mandatory. Among the possible mechanisms of gut microbiota involved in the effects on the brain highlighted in ADHD are (1) change in gut permeability: increased permeability between cells of the intestinal epithelium would allow bacterial products, cytokines and chemokines to enter the circulation and be able to cross the blood-brain barrier. This could contribute to systemic inflammation and, consequently, neuroinflammation, causing in turn, effects on behavior; (2) synthesis of neuropeptides involved in the disorder (dopamine, noradrenaline, serotonin) and their precursors (phenylalanine, tyrosine, tryptophan), which are analogous in structure to the host's nervous system. These precursors are produced by components of the microbiota and can be absorbed through the gut epithelium, enter the circulation and also cross the blood-brain barrier; (3) higher synthesis of harmful compounds (ammonia, phenols, indoles, sulfur and amines); (4) activation/deactivation of the autonomic nervous system, which connects directly to the nucleus of the solitary tract ON/OFF of the via autonomic system, nucleus of the solitary tract; (5) modulation of brain-derived neurotrophic factor (BDNF) and microRNA, which influence the genetic expression of the hippocampus [44,88-91]. Therefore, changes in the composition of the intestinal microbiota or increase in the number of pathogenic bacteria can alter the axis of the gut-brain and increase the risk of neurodevelopmental disorders [92].

Different studies have found alterations in microbial species in patients with mental disorders, such as autism and ADHD. A recent study by Aarts et al. found that the microbiota was different between patients with ADHD and healthy individuals, with increased function of the bacterial gene that encodes the enzyme cyclohexadienyl dehydratase, involved in the synthesis of phenylalanine, a precursor of dopamine [93].

Currently, there is great interest in modulating or balancing gut microbiota to treat ADHD [94]. Scientific evidence indicates that diet and dietary supplementation by administration of probiotics, prebiotics and other nutrients may be an alternative or adjunctive treatment to improve ADHD, mainly due to the microbiota responding rapidly to dietary change, suggesting possibilities for dietary interventions [94-96]. According to a meta-analysis, 30% of children with ADHD have excellent response to a diet that eliminates food allergens, with a reduction of more than 40% of symptoms [97]. Studies that have found changes in the permeability of the gut of patients with other neuropsychiatric disorders, such as autism, corroborate the correlation between this aspect and the disorder [98,99].

Microbiota and Short-chain Fatty Acids (SCFAs)

Short chain fatty acids (AGCCs) are formed from the process of anaerobic fermentation of complex carbohydrates by the intestinal microbiota and bring benefits to the host [37,100,101]. Acetic, butyric and propionic acids are the main ones, and of these, butyrate is the most studied. After their production in the intestinal lumen, they are released into the circulation and are in the brain and reach the brain [102-104]. We conclude that both the presence and the absence of SCFAs in the circulation can affect the CNS positively or negatively [105,106]. SCFAs bind primarily to G protein-coupled receptors) (GPCRs) and olfactory receptors (ORs) in mice (homology with ORs in rats) that trigger intracellular signaling [41,43,78]. These receptors are expressed extensively in organs/tissues, including sympathetic ganglia, epithelial cells, juxtaglomerular apparatus, endothelial cells and smooth muscle cells [107-109]. Among the major SCFAs, butyrate is the most widely studied. The butyrate exhibits effects on the intestine-brain axis on the SI, metabolic regulation and direct effect on the nervous system. It also participates in the recruitment of circulating leukocytes to inflamed sites, suppression of proinflammatory cytokines and modulation of production and release of chemokines in addition to the expression of adhesion molecules in neutrophils) [110,111]. Butyrate supplementation in the potable water of rodents improved expression of the Foxp3 gene and induced the production of regulatory T cells *in vivo*, suppressing inflammation) [112]. The anti-inflammatory properties of butyrate also have epigenetic implications because it strongly inhibits histone deacetylase (HDAC) and contributes to hyperacetylation and histone transcription. The direct result of this hyperacetylation is bi-directional changes in gene expression [11,113]. Since this is a reversible modification, different than genetic defects, it highlights the potential of butyrate in new therapies [114,115]. In addition, the inhibition of HDAC exhibits anti-inflammatory effects, suppressing the activation of nuclear factor κB (NFκB), important in inflammatory signaling pathways [116]. Due to this range of beneficial effects on immune system, butyrate is being studied for autoimmune diseases such as inflammatory bowel diseases (IBD) [117]. The addition of 5% butyrate in the diet showed a satisfactory improvement in insulin resistance and reduced fat), suggesting metabolic effects [39]. The beneficial metabolic effects of butyrate appear to be by direct action on its mitochondrial action. At the periphery, butyrate increased respiration and mitochondrial energy) [39]. In addition, *ex vivo* incubation of butyrate in germ-free mouse (GF) colonocytes rescued mitochondrial respiratory deficits and inhibited energy-induced autophagy deprivation [118]. In the CNS, the role of astrocytes in the communication of neuroglia is enhanced by their ability to donate mitochondrial fragments to neurons, favoring the recovery of neurons from oxidative stress induced by ischemia [119]. In addition, peripheral butyrate can be detected directly by sensitivity to afferent receptors) [120]. These afferent nerve responses are abolished in rats submitted to vagotomy, indicating the involvement of vagal afferents in the response to butyrate. Thus, the potential impact of butyrate on epigenetics in immunoregulatory mechanisms deserves attention, since these mechanisms can lead to specific and effective therapeutic strategies in the prevention and treatment of various diseases) [106,121].

Myoenteric plexus

The enteric nervous system (ENS) is a complex and extensive neuron network that extends from the esophagus to the anal sphincter, composed of ganglia, interconnected fibers and neuron fibers that affect tissue effectors including smooth

muscle, epithelial lining, endocrine cells, gastroenteropancreatic and blood vessels) [122]. All aspects of the gastrointestinal tract are controlled by the ENS, including: motility patterns, gastric secretion, nutrient management, fluid transport through the epithelium, blood flow , participation in endocrine modulation of the intestine and interaction with the immune system [123,124]. A unique property of the ENS in relation to any other section of the peripheral nervous system is that the enteric ganglia can maintain their correct functioning even in the absence of entry into the central nervous system. For example, the intestine may increase peristaltic reflex or generate migratory myo-electric complex, regardless of extrinsic innervation [123]. The ENS, however, is not autonomous regarding neuron control of the gastrointestinal tract, because it depends on a system of interactions between local reflexes, reflexes that go through sympathetic ganglia and reflexes that go to the gut and back to the CNS via vagal, splanchnic and pelvic nerves [122,125]. The ENS is composed of a high number of neurons (200 to 600 million in humans), the same number of neuron Found in the human spinal cord, which originate the three main nervous plexuses: the subserosal, the myoenteric (Auerbach's, located between the two smooth muscle layers) and submucosal (Meissner is in the submucosal layer). The latter is absent from the esophagus to the stomach [122,126]. We have studied approximately 20 different types of neurons, classified according to their morphology, physiology, neurochemical coding, target functions and projections. From a functional point of view, three main classes of neurons were identified: intrinsic primary afferent neurons, interneurons, and inhibitory motor neurons [126].

Several studies in recent years have demonstrated that enteric glial cells, in analogy with astrocyte function, do not only contribute to create a protective local microenvironment, but also play a functional role in the transfer of enteric information, responding to the variety of neuron connections [127,128]. A distinctive feature of the ENS is that the enteric neurons communicate with different cell types, which constitute the enteric microenvironment [129]. Enteral neurons can exchange information with enteric glial cells, interstitial cells of Cajal, which are considered intestinal pacemaker cells, smooth muscle cells, immune system cells contributing in neuroimune modulation [129].

Gut-Microbiota Axis and the Vagus Nerve

Approximately 90% of the fibers of the vagus nerve are afferent, participating taking sensory information from the periphery to the CNS [130]. The main site of the spinal cord that receives the afferent information of visceral organs, including the intestine is the nucleus of the solitary tract (NTS). The vagal effusion in the medulla is made mainly by the dorsal nucleus of the vagus nerve.

Vagal afferent

The vagal afferent fibers are present inside the lamina propria and in the crypts of the gastrointestinal tract, and from there they transmit sensory information afferent to the CNS. In this way, the chemical and mechanical receptors, present in the vagal afferents, perceive changes in intestinal homeostasis [131,132]. This information is retransmitted and informs the CNS about mechanical distention of the gut, chemical/pH changes and inflammatory state of the tissue. In view of the latter, it has been demonstrated that administration of lipopolysaccharide (LPS) or IL-1β may lead to activation of the intestinal vagal afferents [133,134]. This mechanism is dominant when inflammatory bowel cytokines are undetectable in circulation by CVOs during low-grade inflammation. In addition, the presence of the Toll-like receptor 4 (TLR4) in the nodal ganglia also plays a role in vagal afferent detection of systemic immune molecules, in addition to localized intestinal inflammation [135]. (NTS plays an essential role in the reception of afferent vagal information Glutamate is the main neurotransmitter that carries information from the vagal afferents into the NTS. The glutamatergic and GABAergic (gamma-aminobutyric acid releasing) neurons, secondary to the NTS level, detect the afferent glutamatergic entry, forming a narrow network that processes these incoming signals and subsequently projects them to other brain regions, as well as to cholinergic efferents. This signal relay eventually results in excitatory or inhibitory effects in the gut, i.e. neurons are modulating peripheral responses), (as well as in the cardiovascular system and immune system [135,136].

Vagal efferent

Because this cross-talk exists between SNE, primarily via vagal and CNS afferent, the latter monitors the homeostatic state of the GI tract and regulates its contractile properties such as acid secretion through the vagus-vagal reflex. In contrast, intestinal contraction/distension, local blood flow, and nutrient absorption are regulated locally within the intestine. The removal of the vagovagal reflex, therefore, has minor impacts on general gut function [122].

Gut-Microbiota-Brain Axis and Neuroendocrine System

Angiotensin II (Ang II) is a vasoactive peptide RAS that can raise blood pressure direct vasoconstriction, activation of SNS, activation of immune system and induction of aldosterone biosynthesis. Although the SRA presents two distinct parts (peripheral and central), they are interconnected and may contribute to the elevation of BP, via the circumventricular organs that connect the peripheral and central effects of angiotensin II. The presence of dysbiosis and intestinal inflammation were found in Ang II induced hypertension, characterized by dysfunctional ANS and central inflammation, but it is unclear whether these changes are cause or consequence of hypertension, and whether there is a prominent role of Ang II in modulation of the microbiota. Recently, it has been shown that Ang II hypertension and vascular dysfunction are decreased in GF mice [7,137,138] suggesting that the intestinal microbiota contributes to an increase in Ang II-induced BP [51].

5-hydroxytryptamine, 5-HT (Serotonin)

It is a monoaminated neurotransmitter derived from tryptophan, found mainly in the gastrointestinal tract, blood platelets and CNS [139]. (More than 90% of 5-HT is synthesized in the gut, diffuses into the circulation and is transported by platelets, or binds to its receptors that are widely distributed in neurons, enterocytes, and immune cells) [139].

Although it is generally accepted that serotonin cannot translocate from the peripheral circulation to the brain because it does not cross the blood-cerebrospinal barrier, it has been suggested that changes in the intestinal microbiota affect 5-HT levels in the hippocampus and that endothelial cells in the brain actively express Ht transporters) [140,141]. In addition, the presence of 5-HT receptors in the surrounding organs (CVOs) may also mediate the connection between the intestine and the brain [142,143]. Notably, has been associated with hypertension due to the discovery that anorectic agents, indirect serotonin receptor agonists, can cause pulmonary arterial hypertension) [144]. Potential mechanisms contributing to pulmonary arterial hypertension include increased expression of 5-HT receptors, reduction in serotonin transporters (SERT) and generation of reactive oxygen species (ROS) in the lung [145]. (The role of serotonin in blood pressure control has been reviewed in other studies [140]. the unbalanced production of serotonin in addition to being related to anxiety and depression are also with increased BP) [146]. Psychosocial stressors are associated with anxiety disorders that induce the activation of ANS and the HPA axis, which consequently predisposes individuals to the development of hypertension [147].

Glutamate, Dopamine and GABA

GABA is a pan-inhibitory neurotransmitter in the CNS of mammals. GABAergic neurons are present and involved in regulating the excitation of various cardiorregulatory brain regions and modulating vagal signals in NTS. High GABA signaling in NTS has been associated with hypertension and diabetes [148,149]. GABA has cardioregulatory action in the paraventricular nucleus of the hypothalamus (PVN), where it supposedly contributes to sympathetic control. For example, microinjection of a GABA antagonist into PVN produced a significant, dose-dependent increase in renal sympathetic nerve activity, suggesting inhibitory modulation in the presympathetic neurons of the PVN [150]. Identification of glutamate as a neurotransmitter in the CNS dates to the mid-1980s. Since then, several evidence demonstrating that a complex "glutamatergic neurotransmitter mechanism" is responsible for regulating the amino acid synthesis, release and reuptake into neurons and glial cells [151]. Glutamate is an important excitatory neurotransmitter in the CNS, it does not exceed the hematoliquic barrier and is produced by neurons through the transamination of α acetoglutarate, originated from the glycolysis, and the deamination of the glutamine amino acid (obtained from the diet) by the phosphate activated glutaminase [152,153]. Glutamate, via activation of vagal, splanchnic or pelvic afferents, whose cellular bodies are contained within the vagus nodose ganglion (VNG) and dorsal root ganglion (DRG), participate in the transport of sensory information to areas of the brain involved in the regulation of different gut functions. Activation of glutamate receptors can regulate both excitation and inhibition of the gastrointestinal tract via the efferent pathways of the dorsal vagus nucleus (DNV) [122,154,155]. Glutamate is an important excitatory neurotransmitter in the CNS. Activation of vagal afferents results in the release of glutamate in the NTS and alters the membrane potentials of the second order NTS neurons by binding with amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) or N-Methyl -D-aspartate (NMDA), which may contribute to maintaining the membrane potential at rest or regulate the convergence of excitatory stimuli, respectively [156]. Injection of glutamate into NTS causes dose-dependent hypotension [157]. On the other hand, microinjection of glutamate into PVN produced dose-dependent increase in BP; effects that can be blocked by the NMDA receptor antagonist) [150].

Both GABA and glutamate have been shown to be abundant in the gut [158,159], and the gastrointestinal tract hosts a large amount of gram-positive anaerobic bacteria facultative bacteria *Lactobacillus* and *Bifidobacterium*, capable of metabolizing glutamate and producing GABA [160]. Several studies support two basic pathways by which GABA derived from the gut can be detected and used by the CNS: (1) GI derived from GI may be able to diffuse into the circulation and cross the BBB [161,162]; and (2) GABA derived from GI can be detected by GABA receptors within the enteric nervous system, which communicate directly with the vagal afferents [163,163].

However, direct evidence is still lacking to reach a robust conclusion. Dopamine (D) has a neuronal and non-neuronal production and almost half of the dopamine produced in the body comes from the gastrointestinal tract [165]. Locally produced dopamine (i.e., proximal renal tubule, jejunum, *Bacillus cereaus*, *B. mycoides*, *B. subtillis*) is independent of innervation and has shown significant effects on the regulation of BP via renal receptors similar to D1 that modulate NaCl excretion [166,167]. Long-term treatment of the D1 receptor antagonist increased BP, and involvement of the receptor similar to renal D1 was associated with hypertension [168].

Microbiota Immune System

The brain has the means to generate a local immune response, and this defense mechanism mainly involves glial cells. It has been shown that the excessive or sustained activation of central immunity by systemic stimuli results in an imbalance, and even damage, in neurons that can lead to neuroinflammation and neurodegeneration [169]. Microglia and astroglia, constitute two large populations of glial cells, where microglia corresponds to 5-20% and astróglia 20-40% of the total population of the glial CNS. Microglia reacts to environmental antigens, limits apoptotic cell debris and maintains systemic homeostasis immune, while astroglia beyond the structural and supporting role, also provide nutrients to the neurons) [170]. Astroglia, with thousands of dendrites and synapses, dynamically communicates with neighboring neurons and other glial cells, where the minor changes perceived in the environment may result in the release of cytokines / hormones in glia. Severe chronic threatening of the brain environment causes microglia and astroglia to perpetuate increased CNS inflammation that has a profound impact on neuronal activity [170,171]. The association between intestinal flora composition and cognitive processes, such as learning and memory, besides contributing to the initial development of normal social and cognitive behaviors, aid the metabolism by breaking down complex polysaccharides in the diet, modulates gut motility, homeostasis of the GI barrier, fat distribution, controls of colonization of pathogens in the gut, modulate host energy by changes in mitochondrial metabolism and function [172-177]. T-lymphocytes differentiation and interleukin-6 (IL-

6) levels increase in patients with advanced clinical status and may contribute to disease impairment through a compromised adaptive immune response due to accelerated aging of the immune system [178].

Conclusions

With all the scientific evidence known till day, from a continuous and intense cross talk between the intestinal microbiota and the CNS, this virtual organ that we housed in our intestine, with genetic material of 150 times that of ours, aroused great scientific questions, easily avid by the intense scientific production on this subject worldwide. Intestinal dysbiosis was related as one of the causative factors of non-transmissible chronic inflammatory diseases and among them neuro-degenerative diseases. Much evidence has shown that the administration of probiotics could mitigate many manifestations of these non-logical conditions. However, the great difficulty still faced by researchers is to optimize the applicability of these supplements and so further research such as large clinical trials in specific neurological and psychiatric disorders are necessary for the implementation of these supplements to be made safely and effectively in clinical practice.

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