The Gut–Brain Axis

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The gut–brain axis (GBA) it is a complex network in which the CNS and the enteric nervous system (ENS) interact with each other in a bilateral manner by several mechanisms, including nervous, hormonal, metabolic, and immunological ones. Recently, this relationship has been described as the ‘microbiota–gut–brain axis’ because of the known role of the gut microbiota in maintaining a physiological brain–gut relationship and its participation in the pathogenesis of several diseases. In this complex network, a plethora of interactions take place.

Keywords: nervous system ; gut–brain axis ; Parkinson’s disease ; Alzheimer’s disease ; multiple sclerosis ; Guillain–Barré syndrome ; Bickerstaff brainstem encephalitis ; Devic syndrome ; stroke ; migraine ; Helicobacter pylori ; Central Nervous System

1. Introduction

The brain—a central, coordinating element of the GBA—receives and releases information via the enteric, sympathetic, and autonomic nervous systems [1][2][3] Further, the hypothalamus–pituitary axis (HPA) as well as sympathetic and cortisol-related immune regulations are involved [4]. The GBA is bidirectional; the CNS takes part in the modulation of ENS functions in several ways—directly and indirectly (directly through changes induced in the microenvironment of the gastrointestinal tract, and indirectly through signaling molecules)—both antagonistically and synergistically [5][4][6]. Three major pathways of GBA communication can be distinguished—the vagus nerve pathway, the neuroendocrine pathway, and the immune-related pathway [7].

It has been proverbially said, that immunity derives from the intestine and this is not an unjustified statement, as the human gut contains the largest concentration of immune cells in the organism [5]. The proper functioning of the intestines appears crucial in guarding autoimmunity, especially due to the fact that the intestines are capable of recognizing and distinguishing potentially harmful bacteria from commensal ones [8]. The latter are involved in both adaptive and innate immunity. The microbiota, through microbe-associated molecular patterns (MAMPs), is involved in promoting the function of cells and cytokines affecting the CNS, which mainly include Il-6, Il-1a, IL-1b, and TNF-α [7].

A vast majority of the gastrointestinal tract functions are controlled by the autonomic nervous system and include bile secretion, motility of the gut, mucosal production, and even the immune response [9]. Normally, in the case of the human body, each action triggers a response; therefore, the information entering the CNS through the autonomic nervous system (ANS) is subsequently transmitted to the organs of the body through closed positive and negative feedback loops [5][10]. The HPA works mainly through the so-called stress hormones and is responsible for the rapid reactions of the body; therefore, disturbances in its functioning exert a significant impact on the entire organism. It seems that in both human and animal models, the HPA is overreactive when the gut microbiota is disturbed, and this overactivity may reversely result in disturbances of the gut microbiota [11][12][13]. The mucosal barrier in the gastrointestinal tract is an extremely important element, constituting the organ’s border and connecting many systems in the human body. It consists of both building and functional elements, including a layer of mucus and phospholipids. Furthermore, the submucosal blood flow has a regulatory effect on the production and release of several mediators. The maintenance of mucosal barrier homeostasis depends on a plethora of bidirectional interacting elements, with a significant role played by the gut–brain axis. As Dolores Sgambato et. al. observed, among the mechanisms included in this cooperation we can find the aforementioned hypothalamus–pituitary–adrenocortical (HPA) system, GABAergic and glutamatergic neurotransmission, thyrotropin release hormone, physiologically active lipids, CGRP, melatonin, as well as peptides such as GLP-1, YY peptide, leptin, and ghrelin. The complexity of this physiology results in a similarly complex pathophysiology: any disturbance in this system can have a negative effect on the integrity of the mucosal barrier [14].

Several microbial molecules are similar to the human ones. Intestinal cells (e.g., enterocytes and secretory cells) are capable of producing and releasing cytokines, chemokines, and, most importantly, endocrine and neurotransmitter molecules (e.g., PYY, GLP-1, 5-HT, GABA) [15][16][17][18]. Furthermore, the microbiota is able to produce metabolites with

neuromodulatory properties, with visible results in the ANS [5][19]. Those metabolites include dopamine, 5-HT, GABA, short-chain fatty acids (SCFAs) capable of crossing the brain–blood barrier (BBB), thus influencing neurotransmission within the CNS [7]. Interestingly, several different polymodal receptors are observed within the vagus nerve. The vagus nerve is responsible for gastrointestinal tract innervation and thus it is able not only to recognize physical stimuli like stretching but also to detect the previously mentioned bacteria-produced molecules [20][21]. A study of the so-called 'cholinergic anti-inflammatory pathway' proved that the efferent part of the vagus nerve has protective abilities through the inhibition of proinflammatory cytokines [22]. Interestingly, patients who undergo vagotomy because of ulcers appear to be more susceptible to neuropsychiatric diseases [23][24]. On the other hand, stimulation of the vagus nerve in mice increased neurogenesis in the hippocampus [25].

2. Pathophysiology of Helicobacter pylori Infection

The human body has a two-way axis—the brain–gut–microbiota axis—which enables communication between the cognitive and emotional regions of the brain and the functioning of the digestive system [26]. Apart from endocrine and immune pathways, this axis includes the neural one. The HPA axis and the vagus nerve with parasympathetic fibers-produced corticotropin-releasing factor (CRF) play a key role in the communication in this specific network. The fact that, in animal models, bacteria, as a stress factor, can activate the above pathways and induce an anti-inflammatory response through α7-nicotinic acetylcholine receptors (nAChRs) seems to be confirmed [27].

Three possible routes by which *H. pylori* can enter the brain have been identified. The first is the oro–naso–olfactory pathway which enables the penetration of bacteria into the brain through the epithelium in the mouth or the nasopharynx. Another hypothesis assumes that infected monocytes, due to an autophagy defect, can migrate through the BBB, damaged by chronic infection and the production of pro-inflammatory cytokines such as TNF-α. This hypothesis is known as the "Trojan horse theory" and explains the participation of bacteria in *H. pylori*-dependent neuroinflammation, consequently leading to neurodegeneration [28]. Another possible route involves GIT-associated retrograde axonal transport pathways, through which pathogens can also affect the brain [29][30][31][32].

It should be emphasized that *H. pylori* induces pro-inflammatory mechanisms during colonization. The most important factor of virulence is the so-called multifunctional compound VacA, which also plays an important role in the pathogenesis of gastric cancer. Its action on gastric mucosa cells is based on the formation of anion-selective channels, vacuolization, and induction of cellular apoptosis. This, in turn, may affect the functioning of the BBB, as VacA affects bone marrow-derived mast cells (BMD-MCs), resulting in the production of a significant amount of pro-inflammatory cytokines including the interleukins IL-1, IL-6, IL-8, IL-1β, IL-10, IL-12, interferon (IFN) γ, and TNF-α, involved in microgliitis and direct neurotoxicity. TNF-α disrupts the integrity of the BBB by activating matrix metalloproteinases [28]. The protein that induces migration and activation of neutrophils is *H. pylori*-NAP (HP-NAP), which is a pro-inflammatory protein commonly found in individuals with *H. pylori*-related gastritis. Due to a prolonged exposure, the BBB is damaged, and its permeability increases, which induces demyelinating, inflammatory, and edema processes in the CNS. The released inflammatory mediators affect the functions of the hypothalamus and the brainstem by disrupting the neuroendocrine–immune system and activating the HPA axis, which is associated with increased secretion of cortisol and adrenaline [33][34]. It has been proven that *H. pylori* infection can lead to the release of several other neurotransmitters, such as acetylcholine, noradrenaline, dopamine, adrenaline, and serotonin [35].

It should not be forgotten that, in the case of chronic *H. pylori* infection, mucosa atrophy occurs and, consequently, the absorption of vitamin B12 is reduced. It is known that this vitamin exerts a significant influence on the functioning of the nervous system as it produces a neurotrophic and immune-modulating effect in the nervous system. Besides, vitamin B12 is a co-factor in the formation of myelin. B12 hypovitaminosis causes pathological changes in the white and gray matter of the brain, such as sensorimotor polyneuropathy, subacute complex degeneration of the spinal cord, cognitive impairment, and optic neuropathy [36][37]. It is also worth noting that in patients diagnosed with multiple sclerosis, decreased levels of vitamin B12 were detected [38]. This is also a risk factor for cognitive disorders as well as Alzheimer's disease. A dangerous consequence of B12 avitaminosis may be an indirect increase in the risk of ischemic stroke due to increased levels of homocysteine, whose metabolism involves B12 [39]. The increased level of homocysteine causes an increased number of free radicals and the occurrence of oxidative stress, which is responsible for damage to blood vessels and lipid peroxidation [40].

Beside various gastrointestinal impairments such as peptic ulcer disease, MALT lymphoma, and adenocarcinoma, *H. pylori* infection has been reported to be associated with other extragastric diseases. Frequent *H. pylori* infection leads to significant alterations in the composition of the gastrointestinal microbiome, the production of free radicals, changes in neuropeptide expression, as well as both axonal and neuronal damage that might lead to the induction of neurological

impairments or alter the outcome of already existing ones e.g., due to the exacerbation of symptoms. The gut–brain axis plays a crucial role in infection and further clinical outcomes. It should be taken into consideration that any alterations in the gut microbiota (e.g., due to *H. pylori* infection) could have a significant impact on other systems of the organism. So far, on the basis of a thorough review of the currently available literature, we assume that *H. pylori* infection might be linked to such neurological disorders/impairments as PD, AD, MS, GB, BBE, Devic syndrome, or even stroke. Even though there are several studies published regarding a possible link between the *H. pylori* infection and neurological disorders, the literature is still scarce, and this matter requires further investigation and proper evaluation. It is also worthwhile mentioning that *H. pylori* is one of the most widely described species, while the other species of *Helicobacter* have hardly been studied.

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