Link between Gastrointestinal Microbiome and Neurologic Injury

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Contributor: Brandon Lucke-Wold

Communication between the enteric nervous system (ENS) of the gastrointestinal (GI) tract and the central nervous system (CNS) is vital for maintaining systemic homeostasis. Intrinsic and extrinsic neurological inputs of the gut regulate blood flow, peristalsis, hormone release, and immunological function. The health of the gut microbiome plays a vital role in regulating the overall function and well-being of the individual. Microbes release short-chain fatty acids (SCFAs) that regulate G-protein-coupled receptors to mediate hormone release, neurotransmitter release (i.e., serotonin, dopamine, noradrenaline, γ-aminobutyric acid (GABA), acetylcholine, and histamine), and regulate inflammation and mood. Further gaseous factors (i.e., nitric oxide) are important in regulating inflammation and have a response in injury.

gut microbiome neurologic injury enteric nervous system

1. Introduction

An intricate communication between the gastrointestinal (GI) tract's enteric nervous system (ENS) and the central nervous system (CNS) creates a unique dynamic unlike any other peripheral organ system. Together, the GI tract's intrinsic and extrinsic neurologic inputs influence its movement patterns, blood flow, reflexes, and interactions with the gut immune and endocrine systems [1]. While the GI tract's intrinsic neural plexuses allow the system a degree of autonomy in executing many of these functions, the CNS plays an integral role in regulating and modulating these in response to external stimuli [1][2].

Extrinsic neuronal communication with the GI tract occurs via vagal, spinal thoracolumbar, and spinal lumbosacral innervation [1][2]. Vagal efferents arising from the dorsal motor nucleus (DMN) consist of both excitatory and inhibitory lower motor neurons (LMNs) as well as preganglionic parasympathetic fibers [3]. Vagal influence on the GI tract is most prominent in the esophagus and stomach, where responsibilities include upper esophageal sphincter (UES) contraction, striated and smooth muscle peristalsis, and regulation of hormonal release [1][3]. Without vagal efferents, the upper and lower esophagus can no longer propel its contents forward [4][5]. Vagal sensory neurons, or afferents, at the level of the esophagus, stomach, and proximal small intestine communicate with the CNS to mediate numerous vasovagal reflexes in addition to sensing satiety [6][7]. Similar to vagal innervation in the upper GI tract, thoracolumbar innervation on the middle GI tract consists of both efferents and afferents. Thoracolumbar preganglionic sympathetic efferents innervate their postganglionic counterparts in the celiac, superior mesenteric, and inferior mesenteric ganglia. In addition to their significant influence on GI tract vasculature, these fibers function in slowing transit times of tract contents directly via sphincter contraction and

indirectly via inhibition of myenteric and submucosal ganglia [1][2][8]. Thoracolumbar afferents compromise the majority of thoracolumbar innervation in the GI tract. Although primarily inactive in nonpathological states, sensitization of thoracolumbar afferents via gut inflammation plays a role in pain sensation [1][6]. Lumbosacral input on the GI tract is primarily in the form of parasympathetics which innervate their respective postganglionic cell bodies in the pelvic plexus or act indirectly via the ENS myenteric plexus [2][9]. Similar to vagal parasympathetics in the upper GI tract, lumbosacral parasympathetic efferents provide excitatory and inhibitory innervation to the distal colon to increase or decrease motility, respectively [2][10]. Lumbosacral afferents communicate stretch and pain to the CNS, namely Barrington's nucleus [2][11][12][13]. Lumbosacral sensory and motor neurons also function in important lower GI reflexes, such as defecation [1][14][15].

Despite the importance of CNS innervation in proper digestive system functioning described above, the ENS gives the GI tract the ability to maintain many of its functions independent of extrinsic support [16][17][18][19]. The ENS consists of approximately 20 neuronal subtypes dispersed in its two major ganglia, the myenteric extending from esophagus to anus and submucosal in the small and large intestines [1]. In the esophagus, nitric oxide producing enteric neurons allow for sphincter relaxation independent of vagal inhibition [1][20]. ENS innervation in the stomach is responsible for gastric acid secretion through its direct innervation of gastrin-releasing G cells [5][20][21]. In the small and large intestines, enteric neurons function in fluid movement and balance; blood flow; nutrient handling; gut-wall integrity; and communicating with local and peripheral neural, endocrine, and immune cells [1][5][22]. Through intrinsic sensory neurons, interneurons, and motor neurons, the ENS is responsible for controlling small intestine motility and propulsion [5][23][24]. Likewise, the migrating motor complex (MMC), a small intestinal phenomenon important for preventing bacterial overgrowth, is dependent entirely on ENS neurons [25][26]. Enteric nociceptive neurons are important for retropulsive reflexes such as vomiting in the small intestine and for propulsive contractions and copious fluid secretion in the colon [5][27][28]. With the support of sympathetic pathways, small intestinal secretomotor neurons regulate fluid movement and electrolyte secretion between the intestinal lumen and body fluid compartments [1][29][30][31][32][33]. In the colon, the ENS is capable of reproducing the defecation reflex with lumbosacral stimulation independent of central command [34].

2. Neurologic Control of the Gut Microbiome

The gut microbiome contains trillions of bacteria, viruses, and fungi that are critical for the health of the organism. The majority of these microbes are symbiotic; however, pathogenic bacteria can invade the gut and lead to diseases such as cancer, autoimmunity, and multiple sclerosis [35]. Thus, tight neuronal control of this system is critical in order to maintain homeostasis and prevent disease. This control is achieved through intrinsic (enteric) and extrinsic innervation of the gut.

2.1. Intrinsic (Enteric) Nervous System

Intrinsic, or enteric, neurons function to regulate the motility, secretion, and immunologic defense of the gut largely independent of CNS control [36]. There are nearly 600 million enteric neurons within the gastrointestinal (GI) smooth muscle stemming from the myenteric and submucosal plexuses [37][38]. These neurons communicate with

enteric glial cells to control the enteroendocrine cells on the epithelial lining which are responsible for secreting peptide hormones that regulate GI inflammation, secretion, and motility [38][39]. One such hormone is glucagon-like peptide 2 (GLP-2) which acts to decrease intestinal inflammation [40]. Within the ENS there are afferent neurons, interneurons, and motoneurons [41]. Afferent neurons, or intrinsic primary afferent neurons (IPANs), are responsible for relaying stimuli from the gut to the ENS [42]. IPANs relay information to the interneurons. Interneurons of the ENS are subdivided into ascending and descending interneurons [43]. Ascending interneurons are those that are projected orally and release acetylcholine (Ach), and descending interneurons are those that are projected anally and are grouped into three classes based on the signaling molecule they produce/release. Descending interneurons can release (1) acetylcholine, nitric oxide (NO), and vasoactive intestinal peptide (VIP); (2) acetylcholine and somatostatin; or (3) acetylcholine and serotonin [44][45]. Interneurons then pass the signal to motoneurons which function to innervate the musculature of the GI tract. There are excitatory motoneurons which secrete Ach and substance P (SP) and inhibitory motoneurons which secrete NO and VIP. Through muscular innervation, these neurons direct GI motility from mouth to anus.

2.2. Microbiome Effect on Enteric Nervous System

The microbes that make up the gut microbiome are capable of releasing short-chain fatty acids (SCFAs), neurotransmitters, gaseous factors, and lipopolysaccharides that have an effect on the functions of the ENS [41]. Lipopolysaccharides have been shown to act on toll-like receptors (TLRs) 2 and 9 in the ENS, leading to anti-inflammatory effects [46]. Similarly, SCFAs are natural byproducts of microbial metabolism which have been shown to bind G-protein-coupled receptors (GPCRs) located on the enteroendocrine cells, leading to hormone modulation and motility effects [47]. Additionally, there are many strains of bacteria that are known to release neurotransmitters serotonin, dopamine, noradrenaline, γ-aminobutyric acid (GABA), acetylcholine, and histamine [48]. These neurotransmitters have a wide effect including anti-inflammation through histamine, impacts on mood and behavior through serotonin and tryptamine, and increases in motility and gastric emptying through GABA.

2.3. Extrinsic Innervation of Gut

Extrinsic innervation of the gut describes communication from the brain to the gut (brain–gut axis) through autonomic neurons and from the gut to the brain (gut–brain axis) through somatosensory neurons. The extrinsic somatosensory neurons contain nerve endings in the gut that project into the central nervous system [41]. This allows a connection between the gut and CNS that gives information about the condition of the gut. The connection is achieved through vagal and spinal pathways [49]. Cholecystokinin (CCK) is another major mediator of gastrointestinal feedback to the central nervous system through the afferent component of the vagus nerve [37].

As previously mentioned, the gut microbiota is capable of consuming and releasing neurotransmitters such as γ-aminobutyric acid (GABA), serotonin, glutamate, dopamine, and norepinephrine [50]. It has been shown that the presence of GABA-producing bacteria can lead to depression, showing a relationship between the gut microbiome and the CNS [51].

3. Mechanisms of Microbiome Disruption in Neurologic Disease

The brain–gut axis [52] is a well-characterized, multidirectional interaction between the gastrointestinal, immune, and nervous systems. Injury, disease, or other perturbation of these systems affects the function of the others [53][54]. For example, activation of certain neuronal circuits can increase immune response to bacterial infection, and microbiota-depleted mice display altered behavioral patterns and CNS structure [55][56][57]. The precise mechanisms by which these systems interact in health and disease are still under investigation. The leading hypotheses suggest immune cell education and development in the gut and CNS alter trafficking patterns and proinflammatory pathway activation after injury. Immune cells, which are constantly surveilling both the gut and CNS, respond to neurotransmitters, providing a straightforward mechanism for neuronal activity to alter immune cell function [58][59][60].

Another possible mechanism is the function of gut microbiota-derived metabolites. Microbiota depletion disrupts microglia development and function; however, treatment with microbiota-derived short-chain fatty acids (SCFAs) can restore these phenotypes. Further, knockout of an SCFA receptor causes microglia phenotypes similar to those seen in microbiota-depleted mice [61]. Other gut flora-associated metabolites, particularly those of tryptophan, are associated with CNS regulation, possibly acting through aryl hydrocarbon receptors [62][63][64].

3.1. Ischemic Stroke

The contribution of the gut microbiota to ischemic stroke is unique in that it affects both risk and outcome. Cross-sectional clinical studies indicate that patients with the most known risk factors for ischemic stroke have significantly altered microbiota composition [65]. Further, high-risk patients have decreased butyrate-producing bacteria and lower fecal butyrate concentrations. Other human studies evaluating outcome after ischemic stroke also find decreased SCFA concentrations in stroke patients compared to healthy controls [66]. Fecal SCFA concentration is also inversely associated with functional outcome at 90 days poststroke. However, it is important to note that these changes could be an epiphenomenon of the disease rather than causative.

3.2. Spinal Cord Injury

The precise mechanisms of how gut microbiota can affect spinal cord injury (SCI) pathology remain unclear, but there is clearly a functional role for the microbiota in disease progression. Mice, like humans, develop gut dysbiosis after SCI, which can be reduced with fecal transplant [67]. Fecal transplant and probiotic treatment also improve some parameters of behavioral and functional outcome after SCI in mice, suggesting that gut dysbiosis does exacerbate the pathophysiological process [67][68]. On the other hand, a broad-spectrum depletion of microorganisms worsens recovery [68]. A more targeted approach to microbiota manipulation could further elucidate the mechanisms by which the microbiota regulates SCI pathology.

3.3. Traumatic Brain Injury

As in ischemic stroke, the brain–gut axis is functionally bidirectional after traumatic brain injury (TBI); in recent mouse studies, neurological injury appears to induce gut dysbiosis which in turn aggravates neuroinflammation and worsens outcome [54][69]. Gut-dysbiosis-induced neuroinflammation seems to be at least partially mediated by microglia and astrocytes, which have also been shown to be regulated by enteric metabolites [54][61][64]. Restoration of healthy microbiota can interrupt this process and improve neurological deficits after TBI [70]. Consistent with the general model of the gut–brain axis, SCFA metabolism seems to be a critical element of TBI-induced gut dysbiosis. The abundance of SCFA-producing bacteria is diminished after TBI, and SCFA supplementation is sufficient to improve neurological function [71].

The role of the gut microbiota after TBI is distinguished from that of the other previously discussed neurological injuries in several ways. First, broad-spectrum antibiotic treatment seems to be neuroprotective after TBI [72]. Similar antibiotic regimens used in models of ischemic stroke and SCI worsen histologic and/or behavioral pathology [73][68]. Another unique element of TBI pathology is that its relationship with the gut microbiota is dependent on the mechanism of injury. While most studies use a model of single, severe cortical impact, others use mild, repetitive TBI as a model of sports- or military-related injury. When mice are subjected to this model of TBI, their microbiota is minimally altered [74].

3.4. Hemorrhagic Cerebrovascular Lesions

Intracerebral hemorrhage (ICH), which can be caused by many lesions, including CCMs [75], is also associated with gut dysbiosis [76]. Fecal transplant is capable of improving neurological outcome after ICH [76], though the exact bacterial populations responsible for this effect remain uncertain.

Another type of hemorrhagic stroke, spontaneous subarachnoid hemorrhage (SAH), is primarily caused by intracranial aneurysms [77][78]. There is some evidence that the gut microbiota influences aneurysm formation; depletion of gut bacteria through orally administered broad-spectrum antibiotics reduces aneurysm formation in mice [79].

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