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Abstract

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Keywords

gastrointestinal functions, microbiome, neurotrauma, nodose ganglia, spinal cord injury, traumatic brain injury

Disciplines

Medicine and Health Sciences | Neurology | Other Medicine and Health Sciences | Trauma

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Review

Altered physiology of gastrointestinal vagal afferents following neurotrauma

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Abstract

The adaptability of the central nervous system has been revealed in several model systems. Of particular interest to central nervous system-injured individuals is the ability for neural components to be modified for regain of function. In both types of neurotrauma, traumatic brain injury and spinal cord injury, the primary parasympathetic control to the gastrointestinal tract, the vagus nerve, remains anatomically intact. However, individuals with traumatic brain injury or spinal cord injury are highly susceptible to gastrointestinal dysfunctions. Such gastrointestinal dysfunctions attribute to higher morbidity and mortality following traumatic brain injury and spinal cord injury. While the vagal efferent output remains capable of eliciting motor responses following injury, evidence suggests impairment of the vagal afferents. Since sensory input drives motor output, this review will discuss the normal and altered anatomy and physiology of the gastrointestinal vagal afferents to better understand the contributions of vagal afferent plasticity following neurotrauma.

Key Words: gastrointestinal functions; microbiome; neurotrauma; nodose ganglia; sensory neuropathy; spinal cord injury; traumatic brain injury; vagal afferents; visceral reflexes

Introduction

Central nervous system (CNS) trauma, or neurotrauma, is a result of sudden insult or mechanical force to the head or spine (Chang and Badjatia, 2014; Wang et al., 2018; Yates et al., 2019). The types of neurotrauma vary but include concussion, skull fractures, traumatic brain injury (TBI), spinal column fractures, and spinal cord injuries (SCI; Icahn, 2020). The World Health Organization (WHO) has recognized neurotrauma as a “critical public health problem” which leads to significant losses to the injured individual, the individual’s family, and the entire community as a result of lifelong disabilities or death (WHO, 2020). One comorbidity that is often overlooked following neurotrauma is dysregulation of the gastrointestinal (GI) organs associated with nutrient homeostasis. The function of the GI tract in health and disease is well-studied in the neurally-intact organism. Due to increased survivability after neurotrauma, it is imperative to understand the long-term consequences of neural injury and plasticity towards repair and regain of function of this vital organ system.

In the USA, there are approximately 1.7–2.0 million incidents of TBI annually (Huang, 2013; Wang et al., 2018), and there are about 5.3 million Americans currently living with permanent TBI-related comorbidities (Wang et al., 2018). These comorbidities include derangements in physical, emotional, and behavioral functions, neurocognitive disabilities (Langlois et al., 2006; McCrory et al., 2009; Daneshvar et al., 2011) and a vegetative state (McKee and Daneshvar, 2015). While there are both intracranial and extracranial complications post-TBI, the extracranial deficits are systemic and may involve any organ system. The most

commonly affected organ systems include the vagally-innervated respiratory, cardiovascular, and GI systems. GI dysfunctions following TBI (Pilitsis and Rengachary, 2001; Hang et al., 2003; Zygun et al., 2005; Kemp et al., 2008; Masel and DeWitt, 2010; Olsen et al., 2013; Katzenberger et al., 2015; Vance et al., 2015) affect greater than 50% (Qi et al., 2011) of TBI individuals and include impaired swallowing (Mackay et al., 1999; Morgan and Mackay, 1999), decreased pharyngeal sensation, prolonged transit, (Morgan and Mackay, 1999), GI bleeding (Kamada et al., 1977; Brown et al., 1989; Lu et al., 1997), gastric reflux (Saxe et al., 1994; Kao et al., 1998), delayed gastric emptying (Qi et al., 2011), decreased tone in the lower esophageal sphincter (Kamada et al., 1977; Brown et al., 1989; Philip, 1992; Saxe et al., 1994; Pedoto et al., 1995; Lu et al., 1997; Kao et al., 1998; Pilitsis and Rengachary, 2001), gastroparesis (Brown et al., 1989; Jackson and Davidoff, 1989; Pilitsis and Rengachary, 2001), decreased intestinal peristalsis (Philip, 1992; Pedoto et al., 1995), mucosal damage with increased gut permeability (Bansal et al., 2009; Katzenberger et al., 2015), and altered GI motility (Jackson and Davidoff, 1989). Of the post-TBI GI complications, the most common comorbidity is gastritis with a reported incidence of 74–100% (Kamada et al., 1977; Brown et al., 1989). Lastly, 68% of TBI individuals suffer from chronic malnourishment (Horneman et al., 2005) which further exacerbates system-wide deficits from lack of nutrients. GI dysfunctions contribute to post-TBI morbidity and mortality (Qi et al., 2011); yet, the exact mechanisms for GI dysfunctions following TBI remain unclear.

The devastating losses in motor, GI, bladder, and sexual function are continually rated as the top regain of function priorities for SCI individuals (Anderson, 2004; Simpson et

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al., 2012; van Middendorp et al., 2016). Bladder and GI dysfunctions have been described as the “most debilitating” of these burdens because they not only impact the health of SCI individuals, but greatly limit their relationships and social interactions, further diminishing their quality of life (Simpson et al., 2012; Braaf et al., 2017). Specifically, reports indicate that high thoracic or cervical spinal trauma most often lead to delayed gastric emptying, early satiety, dysphagia, constipation, incontinence, nausea, bloating, and abdominal pain (Wolf and Meiners, 2003; Park and Camilleri, 2006; Fynne et al., 2012).

Gastric functions and other upper GI functions are dominated by and dependent on extrinsic parasympathetic nervous system circuits for regulation (Browning and Travagli, 2014; Travagli and Anselmi, 2016). The vagus nerve (VN) contains the visceral afferent and efferent fibers essential for parasympathetic nervous system-mediated reflexes. In both TBI and SCI, the VN remains anatomically intact following injury; however, evidence suggests that the parasympathetic nervous system and the enteric nervous system (ENS) within the gut no longer cooperatively coordinate GI functions suggesting a disruption in the vago-vagal reflexes. The normal anatomy and physiology of the VN has been extensively discussed by others (Lal et al., 2001; Browning and Mendelowitz, 2003; Udem et al., 2004; Blackshaw et al., 2007; Wang and Powley, 2007; Browning and Travagli, 2011; Potenzieri et al., 2012; Holmes et al., 2013; Bonaz et al., 2016; Grabauskas and Owyang, 2017; Breit et al., 2018; Driessen, 2019; Fülling et al., 2019). For our purposes, the following brief summary of VN anatomy and physiology is provided to give a frame of reference for our discussion of vagal neuroplasticity following CNS trauma. This review highlights the role of the VN in GI sensory signaling and the neuroplasticity that occurs following TBI and SCI.

The PubMed database was used between November 2019 and January 2020, using the search terms: traumatic brain injury/TBI, spinal cord injury/SCI, stroke, nodose ganglia, vagal afferents, vagus nerve, microbiome, and various combinations of these search terms.

Normal Anatomy and Physiology of the Vagus Nerve

Gastrointestinal vago-vagal reflex

The autonomic regulation of the GI tract in the context of SCI has recently been reviewed (Holmes and Blanke, 2019). Briefly, the VN is a central link in the brain-gut axis and contributes to the neural modulation of digestive (i.e., vago-vagal) reflexes. The vagal afferents transmit glutamatergic signals to the nucleus tractus solitarius (NTS) in response to GI mechanical and chemical stimuli (**Figure 1**). Within the caudal medulla, NTS interneurons may inhibit or excite cholinergic vagal efferents of the dorsal motor nucleus of the vagus (DMV). These DMV efferent neurons complete the vago-vagal circuit (Browning and Travagli, 2010) by synapsing onto parasympathetic postganglionic cholinergic or non-adrenergic non-cholinergic neurons in the submucosal and myenteric plexuses of the ENS. The functional response of the postganglionic enteric neurons may be excitatory causing an increase in GI tone, motility, and secretion or inhibitory preventing GI digestive functions (Travagli et al., 2006; Browning and Travagli, 2011). Proper GI functioning is dependent upon vagal reflexes, and any disruption in the circuit leads to GI pathologies in the neurally intact including but not limited to gastroparesis, dyspepsia, esophageal reflux, colitis, anorexia and bulimia nervosa (Yamano et al., 1997; Hornby and Abrahams, 2000; Andrews and Sanger, 2002; Thumshirn, 2002; Saito et al., 2006; Ghia et al., 2007; Faris et al., 2008).

Our research focuses on how CNS trauma modifies the GI

vago-vagal reflex and leads to GI dysfunction. Previously, we have shown that gastric vagal efferents are intact following experimental SCI, and DMV neurons projecting to the stomach respond similarly to uninjured controls (Swartz and Holmes, 2014). Vagal afferents demonstrate a significant amount of plasticity during both normal physiology and pathophysiology such as high fat diet, diabetes, inflammation, and direct vagal injury (Browning, 2003; Browning and Mendelowitz, 2003; Li and Owyang, 2003; Raybould, 2010; Dockray and Burdyga, 2011; Kentish and Page, 2014; de Lartigue, 2016; Travagli and Anselmi, 2016; Browning et al., 2017; Grabauskas and Owyang, 2017; Cawthon and de La Serre, 2018; de Lartigue and Xu, 2018). Therefore, we propose that vagal afferent alterations may be, in part, responsible for GI dysfunction following neurotrauma.

Gastrointestinal vagal afferent physiology

The GI vagal afferent cell bodies are contained within the nodose ganglia (NG) and have both peripheral and central projections (**Figure 1**). The vagal afferent terminal nerve endings are diffusely spread throughout layers of the walls of the proximal GI tract (reaching from mouth to transverse colon in humans (Rea, 2014) and distal colon in rats (Altschuler et al., 1993; Herrity et al., 2014). They consist of mechanoreceptor morphological specializations, known as intraganglionic laminar endings, for detecting tension and stretch in the muscle wall and intramuscular arrays which transduce stretch of the organ wall (Powley and Phillips, 2002). Additionally, chemical stimuli such as gut peptides like cholecystokinin (CCK) and ghrelin are detected by chemoreceptors (Powley and Phillips, 2002) on vagal afferent peripheral endings within GI mucosa or on the vagal afferent somas within the NG. CCK and ghrelin elicit opposite responses on the vagal afferents. CCK is released from enterochromaffin I-cells when proteins and lipids are taken into the GI tract. CCK then binds to CCK 1/A receptors on the vagal afferents or NG, thus causing the vagal afferent nerve firing to increase (Moran et al., 1990; Berthoud and Patterson, 1996; Moriarty et al., 1997; Broberger et al., 2001; Patterson et al., 2002). Ghrelin on the other hand, is released from enterochromaffin X/A-cells during the fasting state. Ghrelin acts on the growth-hormone secretagogue receptor A on both the vagal afferents and NG to inhibit vagal afferent firing (Kojima et al., 1999; Date et al., 2000, 2005; Page et al., 2007). Other gut peptides act on and alter vagal afferent firing such as: leptin, bombesin, PYY, secretin, GLP-1, serotonin, and VIP. The actions of CCK, ghrelin, and these other gut peptides have been thoroughly reviewed (Grabauskas and Owyang, 2017). The expression of the receptors of these gut peptides have been shown to change based on the nutrient state of the organism (Grabauskas and Owyang, 2017); demonstrating plasticity under normal physiological conditions.

The fibers which carry the detected mechanical and chemical stimuli can be classified into two primary groups: lightly myelinated A-type and unmyelinated C-type afferent fibers (Schild et al., 1994). A- and C-fibers have different biophysical properties which have been thoroughly reviewed (Browning, 2003). The types of fibers can be distinguished by their myelination, firing rate, conduction velocity, and action potential kinetics. A-fibers are lightly myelinated, tonic firing neurons with a conduction velocity of 3–30 m/s and unremarkable action potentials. While C-fibers are unmyelinated, phasic firing neurons with a conduction velocity of 0.8–1.2 m/s and distinguishing action potentials. C-fibers make up 80–90% of the vagal afferents and have a noticeable hump during the repolarization phase of their action potential. A- and C- fibers are also distinguished by their different ion channels which contribute to their action potential. Of particular importance, I_{KCa}^S , I_D , I_A , I_H , TTX-S and TTX-R I_{Na} , and T- and L- type I_{Ca} currents give vagal afferent fibers unique action potential features depending upon the

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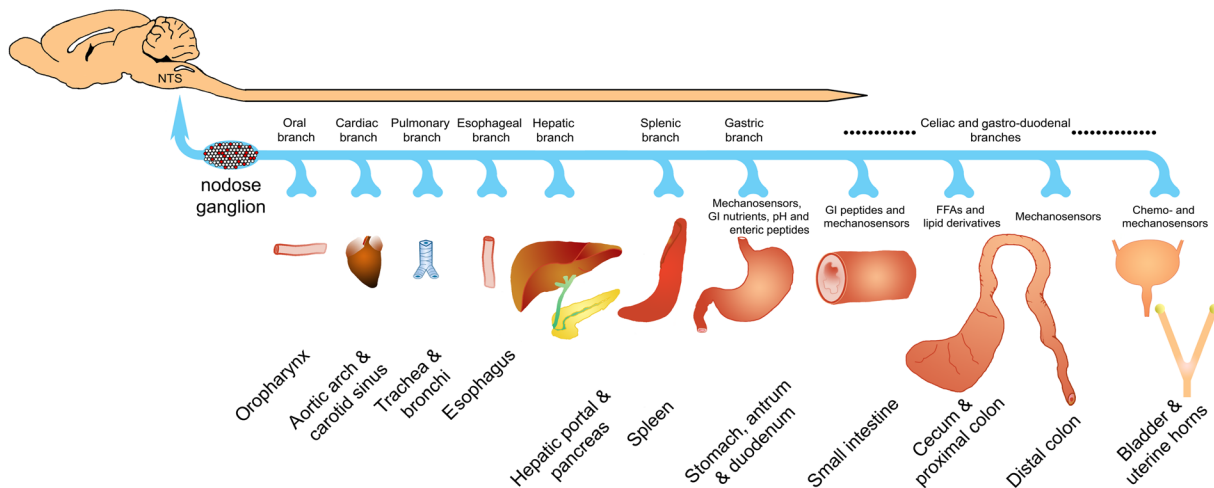


Figure 1 | Major vagal afferent innervation.

The majority of the vagus nerve is comprised of sensory fibers and the cell bodies of vagal afferents are contained within the co-joined jugular and nodose ganglia. The afferent vagus innervates from the oral cavity to the transverse colon in humans, but tracing studies in rodent models have demonstrated afferent projections as caudal as the rectum, bladder, and reproductive tract. Vagal afferents carry mechanical and/or chemical sensory

information to the caudal medulla, specifically the NTS and nucleus ambiguus. The cell bodies of the gastrointestinal viscera are distributed throughout the nodose ganglia (depicted in red) and vagally-mediated reflexes dominate esophageal and gastric reflexes. Functional alterations within all visceral organs following pathophysiological remodeling may become more pronounced in some disease and injury states. GI: Gastrointestinal; NTS: nucleus tractus solitarius.

ion channel expression (Schild et al., 1994).

Beyond A- and C-fibers, vagal afferents can also be classified by their neurochemistry. The neurochemistry of the vagal afferent neurons of the NG includes the neurotransmitters glutamate, catecholamines, serotonin, and acetylcholine, as well as a considerable number of neuropeptides including substance P, neurokinin A, vasoactive intestinal peptide, calcitonin gene-related peptide, galanin, enkephalin, somatostatin, CCK, neuropeptide Y, calcium-binding proteins, and other neuroactive molecules (i.e., nitric oxide; Zhuo et al., 1997). Additionally, beyond the mechanical and chemical stimuli, there is emerging evidence that vagal afferents transmit nociceptive information (Surdenikova et al., 2012). Transient receptor potential (TRP) channels have been shown to be expressed in GI-projecting vagal afferents (Yu et al., 2016). These fibers respond to acid, heat, cold, stretch, capsaicin, menthol, inflammatory mediators, and other stimuli which are associated with pain. Together under normal conditions, these vagal afferents contribute to the precise control and modulation of GI functions.

Altered Physiology of Gastrointestinal Vagal Afferents Following Neurotrauma

Since the mid-nineteenth century, GI comorbidities have been noted with CNS traumas (Cushing, 1932). These profound changes to the GI system after CNS trauma suggest there is VN involvement. In other pathophysiological states such as high fat diet, diabetes, inflammation, and direct vagal injury (Browning, 2003; Browning and Mendelowitz, 2003; Li and Owyang, 2003; Raybould, 2010; Dockray and Burdyga, 2011; Kentish and Page, 2014; de Lartigue, 2016; Travagli and Anselmi, 2016; Browning et al., 2017; Grabauskas and Owyang, 2017; Cawthon and de La Serre, 2018; de Lartigue and Xu, 2018), vagal afferents have been shown to be extremely plastic. The combination of GI dysfunction and vagal afferent plasticity in other pathophysiological models suggests vagal afferent plasticity after CNS trauma, as well. Therefore, this section focuses on the altered physiology of vagal afferents following neurotrauma and identifies major knowledge gaps within the field.

Traumatic brain injury

Vagal afferent plasticity following TBI is significantly understudied, yet, it is known that brain-gut axis (or

neuroenteric axis; Bansal et al., 2010) disturbances are a major cause of GI dysfunction post-TBI (Browning and Travagli, 2011; Kharrazian, 2015). Vago-vagal circuit disturbances contribute to several GI dysfunctions (Browning and Travagli, 2011). Yet, the exact mechanisms of GI dysfunction following TBI remain unclear. Several functional bowel disorders, which lead to chronic GI disorders, are associated with long-term dysregulation of the autonomic nervous system (Tougas, 2000). TBI commonly presents with neural deficits and autonomic dysfunctions and is capable of causing chronic GI disorders. However, the neural and autonomic dysregulation is variable across studies but often results in decreased GI motility among other GI complaints (Tougas, 2000). Autonomic imbalances, or dysautonomia, are hypothesized to occur when the sympathetic and parasympathetic divisions of the ANS fail to properly integrate signals between the brain and viscera (Baguley et al., 2008). Dysautonomia has been reported in 8–33% of TBI individuals and is characterized by chronic sympathetic over-activity (Kirk et al., 2012) which may suggest parasympathetic dysfunction. ANS dysfunction is evident following TBI (Esterov and Greenwald, 2017) and persistent disruption of brain-visceral axes may be one culprit of multi-organ dysfunction following TBI. However, we are interested in the vagal afferent signaling following the axis disturbances.

The vago-vagal synaptic transmission is modulated by a variety of signals including afferent inputs and neurohormones (such as CCK; Browning and Travagli, 2011). Vagal afferent sensitivity can decrease depending on specific receptor activation. Particularly, CCK-A receptors have been found on vagal afferents (Li, 2007) and electrophysiological activation of these receptors alters the sensitivity of the fibers which then modulates efferent output to the GI tract. Decreased sensitivity, from activation of CCK-A receptors on vagal afferents, can directly affect second messenger systems in NTS neurons and activate GI-inhibitory efferent pathways in the circuit. This modulation and subsequent GI-inhibition has been shown experimentally with CCK (Browning and Travagli, 2011). In an animal model of TBI, several GI pathologies were discovered including gastric distension, intestinal dilation, and intestinal effusion suggesting delayed gastric emptying and paralytic ileus. Additionally, plasma and jejunum CCK levels were elevated in the post-TBI rats potentially altering the GI vagal afferent responses (Forster et al., 1990; Higham et al., 1997; Shoji et al., 1997; Hang et al., 2004). Increased CCK levels following TBI may be one source

of GI dysfunction through activation of the vago-vagal NTS-inhibitory pathway from altered vagal afferent input.

Vagal afferent inputs to NTS neurons are further influenced by tumor necrosis factor alpha (TNF- α ; Travagli et al., 2006). In a preclinical model, TNF- α has been shown to favor the GI-inhibitory state by acting on the vago-vagal circuit (Emch et al., 2000). Specifically, it has been shown to cause gastric stasis (Hermann et al., 2005) through modulation of NTS-DMV synaptic transmission. Experimental models have revealed increased circulating TNF- α following TBI (Taupin et al., 1993; Tchelingierian et al., 1993; Shohami et al., 1994; Fan et al., 1996; Gourin and Shackford, 1997; Knoblach et al., 1999; Schmidt et al., 2005), alters synaptic transmission by selectively activating inhibitory or inhibiting excitatory NTS neurons which then synapse with DMV neurons for efferent outflow. The modulation occurs through changes in the glial environment, specifically through astrocyte gene expression changes which may cause long-term changes in the sensitivity of the vago-vagal circuit. The glial-neuronal communication may be responsible for leading to the activation of the GI-inhibitory efferent output and potentially be a therapeutic target. However, while TNF is elevated post-TBI, TNF has displayed both neuroprotective and neurotoxic effects in various models of CNS injury (Longhi et al., 2013).

Additional preclinical studies investigating the glial-neuronal communication between astrocytes and NTS neurons (Hermann et al., 2009; Vance et al., 2015) have also been found to disrupt vago-vagal circuitry. In a rat model, Hermann et al. (2009) showed a significant reduction in gastric transit by using a protease-activated receptor agonist to mimic the autonomic disruption first described by Cushing (1932) which occurs following a bleeding head injury. In this study, the interaction of thrombin with protease-activated receptors in the dorsal vagal complex activated astrocytes which in turn excited inhibitory-NTS neurons evoking inhibition of gastric motility. It is important to note that the autonomic astrocytes may play a role similar to that of neurons in the vago-vagal circuitry. The glial-neuronal interactions are multi-directional and visceral afferent inputs regulate astrocyte activity (McDougal et al., 2011; Accorsi-Mendonça et al., 2013). Therefore, alterations in vagal afferent input following TBI, may affect more than the neuronal synapses in the vago-vagal circuit. Modification of the vago-vagal reflex circuit following TBI, remains a contributing factor of brain-gut axis disruption (Kharrazian, 2015). These vago-vagal alterations are largely involved in GI dysfunction and elicit greater research on the vagal afferent changes post-TBI.

Lastly, in a mouse model of TBI, Bansal et al. (2009) showed that following TBI, intestinal permeability increased while protein expression of cell junction proteins decreased. Furthermore, there was an increase in intestinal TNF- α and other investigators have also reported increased expression of inflammatory cytokines post-TBI (Hang et al., 2005a, b; Katzenberger et al., 2015). While it is not clear whether the inflammation leads to the increased intestinal permeability, a preclinical study used a knockout mouse model equipped against inflammation to support the hypothesis that specific pro-inflammatory cytokines correlate with higher intestinal permeability following TBI (Jin et al., 2008). Yet, the source of intestinal inflammation post-TBI remains unclear. Alternatively, the source of increased intestinal permeability has been proposed as a heightened adrenergic state post-TBI, further highlighting the significance of a healthy brain-gut axis in proper gut functioning (Bansal et al., 2009).

The significance of diminished barrier integrity and heightened inflammatory state is revealed in an animal study by Ammori et al. (2008) that reported cellular degeneration in DMV vagal efferent neurons following experimental colitis. The potential for inflammatory cytokines to traverse the gut-brain axis (or

enteric-neuro axis) and negatively affect neuronal survival provides another source of vago-vagal alteration (Bansal et al., 2010). Furthermore, preclinical studies reveal significant ENS changes caused by intestinal inflammation such as neuronal loss (Sanovic et al., 1999), hyperexcitability (Linden et al., 2003), and altered neurotransmitter release (Linden et al., 2005) causing changes in sensory interoceptive input and DMV structure (Ammori et al., 2008). Consistent with the negative impact of intestinal inflammation on neuronal populations of DMV and ENS neurons, DMV apoptosis is reversed by the anti-inflammatory role of ghrelin in an animal model (Qi et al., 2011). In addition to the cell loss, the time course of neuronal damage and plasticity caused by intestinal inflammation post-TBI is unknown.

Spinal cord injury

There is limited research investigating GI vagal function and plasticity in human SCI individuals. Of the few clinical studies examining SCI vagal function in general, one study utilized functional magnetic resonance imaging to measure brain activation from bladder fullness in complete SCI individuals (Krhut et al., 2017). Krhut et al. (2017) found a subset of subjects that had activation in nuclei (NTS and parabrachial nucleus) associated with vagal afferent activity. Under normal conditions these nuclei are not activated by bladder fullness, and suggest following SCI, there is vagal afferent plasticity or collateral sprouting occurring to re-innervate the bladder. Studies investigating female genital sensation after complete SCI also demonstrated new NTS activation, similarly suggesting new vagal afferent plasticity after SCI (Whipple and Komisaruk, 2002; Komisaruk et al., 2004). These studies demonstrate vagal plasticity after SCI, and GI vagal afferent dysfunction could be a promising avenue for further clinical research.

Preclinical rodent models of SCI also exhibit GI dysfunction. Our lab along with Gondim et al. have shown delayed gastric emptying and decreased GI transit time in SCI rats (Gondim et al., 1998; Tong and Holmes, 2009; Qualls-Creekmore et al., 2010) indicating a disruption in the vago-vagal reflexes. Gondim and colleagues' studies were the first to observe an upper thoracic (T1 or T5) spinal cord transection in rats leads to delayed gastric emptying and delayed GI transit of liquid (Gondim et al., 1998, 2001; Rodrigues et al., 2001). We expanded these findings by demonstrating that upper thoracic T3-SCI animals show a diminished food intake (Primeaux et al., 2007), a significant reduction in gastric motility (Tong and Holmes, 2009) that lasts as long as 6 weeks after injury, and a delay in gastric emptying of a ¹³C-tagged solid meal (Qualls-Creekmore et al., 2010). It has been hypothesized that GI dysfunction is due to a vagally-mediated mechanism (Gondim et al., 2001; Tong and Holmes, 2009; Holmes, 2012).

Our lab has further found that vagal efferents remain anatomically and functionally intact after T3-SCI (Swartz and Holmes, 2014) but are silent due to lack of presynaptic stimuli (Tong et al., 2011). For example, NTS neurons are not activated after central or peripheral administration of CCK-8s in a T3-SCI model but respond to other depolarizing drugs, such as 4-aminopyridine, suggesting that afferents within the NTS are capable of releasing neurotransmitters but are not stimulated by GI peptides (Tong et al., 2011). However, the NTS receives afferent input from many brain regions, vagal afferents, and spinal afferents; therefore, this study could not conclude that the vagal afferents were altered specifically.

Our most recent study demonstrates directly that vagal afferents are hyposensitive to stimuli, both chemical and mechanical, after SCI (Besecker et al., 2020). We confirmed hyposensitivity of vagal chemoreceptors to CCK-8s and demonstrated novel mechanical hyposensitivity to von Frey Hair stimuli, and interestingly, TRPV1 receptor agonist,

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capsaicin, showed hypersensitivity in vagal afferents after SCI. These data suggest SCI provokes exceptional functional vagal plasticity and impairs vagal afferent signaling necessary for proper GI reflexes. Furthermore, another recent study of ours has reported this hyposensitivity is not specific to CCK and mechanical stimuli, but includes ghrelin (Besecker et al., 2018) and may involve other GI peptides not yet tested (Besecker et al., 2017).

A recent investigation in a chronic SCI rodent model, studied vagal afferents as a whole (i.e., not organ specific; Herrity et al., 2015). They demonstrated that SCI impacts the neurochemical characteristics of vagal afferents, by increasing P2X3 receptor expression and decreasing isolectin 4 binding in whole NG (Herrity et al., 2014). This study demonstrated SCI has the ability to change the phenotype of vagal afferents, but specific changes within GI vagal afferents remain to be determined.

Based upon these studies, we propose that SCI-induced pathophysiological plasticity occurs within vagal afferents and NG though the degree remains unknown. Multiple mechanisms can be proposed to account for the loss-of-function in vagal afferents, such as altered trafficking of receptors, receptor plasticity and/or adaptation, disruption of intracellular signaling pathways, ionic imbalances, degeneration of nerve endings, or loss of function of gated ion channels. In the case of SCI, it is unknown what electrophysiological phenotype is exhibited in vagal afferents after injury. However, following SCI in rodent models, other sensory afferents, such as the dorsal root ganglia, have shown to have both decreased (Yoshimura and de Groat, 1997; Black et al., 2003) and increased (Black et al., 2003; Yang et al., 2014) expression and function of TTX-R Na_v channels: thus, resulting in hyperexcitability or hypoexcitability of sensory afferents depending on the target organ they innervate similar to what is seen in vagal afferents in our SCI model (Besecker et al., 2020). Other voltage-gated channels, such as $K_v3.4$ (Ritter et al., 2015), in dorsal root ganglia have been shown to be altered by SCI, as well. The SCI-induced changes in electrophysiological properties of sensory afferents have not been expanded to the vagal afferents, thus opening more promising avenues for further research.

Gastrointestinal Microbiome

The GI microbiome plays a critical role in health and disease (Kigerl et al., 2016; Sherwin et al., 2016; O'Connor et al., 2018). The bidirectional pathway or the microbiota-gut-brain axis (Rhee et al., 2009; Bercik, 2011; Cryan and O'Mahony, 2011; Cryan and Dinan, 2012; Burokas et al., 2015; Mayer et al., 2015) is emerging as a critical communication line between the GI microbiome and brain (Sherwin et al., 2018) via the VN, immune mediators, microbial metabolites, and modulation of circulating tryptophan (O'Mahony et al., 2015; Scott et al., 2015; Foster et al., 2016; Sarkar et al., 2016; Sherwin et al., 2016). GI microbes indirectly influence neural communication, such as the vagal afferents, via the production of metabolites (e.g., short-chain fatty acids), synthesis of neurotransmitters (e.g., gamma-aminobutyric acid, noradrenaline, and dopamine), and immune system modulation (Sherwin et al., 2016). Disruptions in the microbiota-gut-brain axis of the VN contribute to both GI (Mulak and Bonaz, 2004; Bonaz and Bernstein, 2013; Oświęcimska et al., 2017) and neurodegenerative disorders (Cenit et al., 2017; Kobayashi et al., 2017; Quigley, 2017). Vagal afferents use gut endocrine cell interactions (Raybould, 2010), direct and receptor activation (Goehler et al., 1999; Lal et al., 2001), and CCK-mediated mechanisms (Lal et al., 2001) to detect GI microbial compounds or metabolites and carry the information to the brain. The NG contributes to the brain-relay by responding to bacterial products such as lipopolysaccharide (Hosoi et al.,

2005). Information along the vagal pathway reaches the brain to elicit adaptations or inappropriate responses, the latter contributes to GI and neurodegenerative pathophysiology (Eisenstein, 2016; Tse, 2017).

While several preclinical studies have shown vagal nerve activity in response to GI microbes (Gaykema et al., 2004; Tanida et al., 2005; Raybould, 2010; Bravo et al., 2011; Perez-Burgos et al., 2013), clinical vagal afferent activation via GI microbiota remains hypothetical (Bonaz et al., 2018). For further review of GI microbiota and the microbiome-gut-brain axis, please see (Burnet and Cowen, 2013; Wang and Kasper, 2014; Kelly et al., 2015; Moos et al., 2016). Additionally, a preclinical model has shown evidence of gut microbiota modulating satiety signals, specifically increasing GLP-1 and PYY plasma levels, favoring anorexigenic signaling to the brain (Breton et al., 2016); such GI microbiota influence on feeding behaviors may be responsible for the GI dysfunction following neurotrauma. Gaining a better understanding of the influence altered gut microbes have on the brain following trauma, may lead to interventions for reduced comorbidities and improved functional outcomes. However, there are limited clinical studies on the microbiome-gut-brain axis following TBI and SCI (O'Connor et al., 2018).

Dysbiosis following traumatic brain injury

Dysbiosis is a result of pathogenic bacteria outnumbering beneficial nonpathogenic gut bacteria resulting in undesired health outcomes. GI dysbiosis occurs within 2 to 24 hours after TBI (Treangen et al., 2018; Nicholson et al., 2019) and remains altered in chronic TBI (Ma et al., 2017) in rodent models. In the study by Treangen et al. (2018) the microbiota changes post-TBI include decreased *Ruminococcus flavieciens*, increased *Eubacterium ventriosum*, and increased *Marvinbryantia formatexigens*. Thus, this study demonstrated a change in Firmicutes/Bacteroidetes ratio and succinate-producing microbes. Sherwin et al. (2018) noted that the surge in SNS activation may be responsible for altering post-TBI microbiota as observed in a study in mice (Houlden et al., 2016). This work demonstrated a decrease in the intestinal microbiota family *Prevotellaceae* post-TBI, while levels of norepinephrine release and noradrenergic innervation in the cecum increased in mice (Houlden et al., 2016). Additionally, norepinephrine levels have been shown to increase, in both animal and human studies, following trauma (Millen et al., 1985; Woolf et al., 1992; Lyte and Bailey, 1997) exuding a sympathetic dominance which may contribute to the GI dysfunction. However, norepinephrine has recently been shown to reduce the relative abundance of certain species of the genus *Prevotella* (from the family *Prevotellaceae*) *in vitro* (Jentsch et al., 2013). Less is understood about the family *Peptococcaceae*, but increases (as demonstrated in mice (Houlden et al., 2016)) have been correlated with increased expression of the proinflammatory cytokine (CCL5) which has been linked to colitis development (Elinav et al., 2011) in mice.

The work by Durham et al. (2016) as well as several other studies (Rogers et al., 2016; Duvallet et al., 2017; Sun and Shen, 2018; Winter et al., 2018) indicate the involvement of the brain-gut axis in TBI-related neuropathologies which has recently expanded to include TBI-GI pathologies suggesting microbiome-gut-brain-axis (Mayer et al., 2015; Martin and Mayer, 2017; Sundman et al., 2017) disruption. The paradox remains in that GI microbial shifts alter VN activity (microbiota-gut-brain axis) and GI dysfunction alters GI microbial populations (brain-gut-microbiota axis). However, evidence is beginning to indicate that probiotic treatments may be capable of healing the injured brain by repairing post-TBI gut dysbiosis (Treangen et al., 2018).

Dysbiosis following spinal cord injury

Reviews of the current SCI microbiome literature can be

found in (Holmes and Blanke, 2019; Wallace et al., 2019) but briefly, investigators have shown that gut dysbiosis occurs following SCI. Similar to the TBI-microbiome preclinical study, Kigerl et al. (2016) showed that the Firmicutes/Bacteroidetes ratio also increased following SCI in mice. Additionally, in another SCI rodent model, the following GI microbiota changes were detected: increased *Lactobacillus intestinalis*, *Clostridium disporicum*, and *Bifidobacterium choerinum* while relative abundance of *Clostridium saccharogumia* decreased (O'Connor et al., 2018). High prevalence of Lactobacillaceae family has been correlated with carbohydrate fermentation to lactic acid, and Kigerl et al. (2016) revealed post-SCI functional recovery correlations to lactic acid supplementation. *Clostridium* spp. have been found to be both helpful and harmful but the functional implications of *C. disporicum* remain to be further understood. In humans, the family of Bifidobacteriaceae is probiotic and found in healthy guts conferring positive health benefits (O'Callaghan et al., 2015). Lastly, while literature reveals deleterious effects on the host when *C. saccharogumia* is depleted, the significance of this is low with the increased relative abundance of the other commensal microbes (O'Connor et al., 2018).

These microbiota changes were inversely correlated with intestinal inflammatory changes. The intestinal proinflammatory cytokines likely suppressed microbial taxa responsible for butyrate production in the GI tract. Butyrate plays a critical role in gut health through its anti-inflammatory properties by supporting intestinal cell cycles, its pathogen-protection activities, modulation of the immune system, and reduction of cancer progression (Gungor et al., 2016; O'Connor et al., 2018). Previous preclinical studies analyzed the effects of *Faecalibacterium prausnitzii*, a known butyrate-producing microbe, and found it to have protective effects on the gut (Miquel et al., 2013). O'Connor et al. (2018) noted *F. prausnitzii* to be depleted in SCI mice with significantly increased levels of proinflammatory cytokines (Miquel et al., 2013; Kigerl et al., 2016). Similarly, a decrease in the abundance of butyrate-producing bacteria correlates with gut dysbiosis in clinical SCI (Ferrante et al., 2003; Sun et al., 2015; Butchbach et al., 2016; Gungor et al., 2016; Li et al., 2016). As observed with the TBI-microbiota changes, the microbial shift post-SCI is towards a recovery profile to the host; yet many health-related microbes are depleted due to the chronic inflammatory state of the GI tract post-neurotrauma.

While much remains to be understood with microbiota effects on system physiology, characterizing GI microbiota is critical following neurotrauma. The characterization, identification of physiological roles, and determination of critical time-points of the changing microbiota will help in designing therapeutic interventions for TBI- and SCI-related GI comorbidities.

Conclusion

Neurotrauma causes profound changes to ANS control of the GI system. GI dysfunction contributes to increased morbidity and mortality. However, neural plasticity offers the ability to target specific mechanisms and treat GI dysfunctions following CNS injury, but the exact mechanisms of disruption remain largely under-researched. Following TBI, the GI vagal afferents exhibit modified receptor-, peptide-, and glial-interactions which favor the inhibitory-NTS vagal efferent pathway. Vagal efferent and ENS neuronal populations decrease following intestinal inflammatory insult, and may be an on-going cycle across synapses in the vago-vagal reflex circuit. These vagal afferent and efferent interactions and reactions may serve as suitable therapeutic targets in repairing GI dysfunction post-TBI, but the exact mechanisms which contribute to these changes and the system-wide interactions from such plasticity need to be better understood.

The effects of SCI on GI dysfunction still remains a significant

knowledge gap. From the above studies, we know human vagal afferents show significant re-wiring post-SCI to activate once-quiet NTS neurons. This modified afferent input following SCI remains unclear but shows potential for re-activation of vago-vagal reflexes. In animal models of SCI, it has been shown that GI vago-vagal reflexes are disrupted. While the vagal efferents remain intact, they fail to respond spontaneously due to lack of presynaptic stimuli. This further suggests vagal afferent alterations. Furthermore, we have reported that GI vagal afferents are hyposensitive to chemical and mechanical stimuli but selectively hypersensitive to noxious chemical stimuli. Lastly, SCI changes phenotypic profiles of NG by increasing P2X3 receptor expression and decreasing isolectin 4 binding. While little is known about the plasticity of GI-vagal afferents following SCI, the research suggests that vago-vagal reflexes are affected and responsive to changing conditions. Upon further understanding of the mechanisms of plasticity in the vago-vagal circuit, we will strengthen the efforts of finding treatments for GI pathologies following neurotrauma.

There is an emerging discussion that neurotrauma is a systemic pathology (**Figure 2**). The vago-vagal reflex circuit is anatomically intact after TBI and SCI, suggesting the derangements to the GI vago-vagal reflexes must be due to a secondary cascade of events. The components of the vago-vagal reflex are optimally poised to sense secondary events such as systemic inflammation. Immediately following trauma to the CNS, regardless of location, a systemic inflammatory response (SIR) ensues (Anthony and Couch, 2014; Schwab et al., 2014; Sun et al., 2016). SIR following SCI has been thoroughly reviewed (Sun et al., 2016; Bloom et al., 2020). For SCI, the SIR is characterized by increased levels of circulating inflammatory mediators and cells, activation of resident glial and immune cells, and infiltration of neutrophils, macrophages and lymphocytes, all of which culminate in multiple organ failure (Sun et al., 2016; Bloom et al., 2020). The SCI-induced SIR is triggered within hours and persists for weeks following injury, and currently there is no clinical evidence to support the use of any neuroprotective drugs to improve functional outcomes after SCI (Popovich et al., 2001; Campbell et al., 2005; Gris et al., 2008; Wing, 2008; Sauerbeck et al., 2015; Bloom et al., 2020). Studies of other inflammatory disease models have examined the effects of systemic inflammation on vagal afferents and have been reviewed (Browning et al., 2017). Briefly, inflammation has shown to decrease vagal afferent response to leptin and CCK, while increasing mechanosensitivity, TRP and P2X receptors and NaV channel expression (Browning et al., 2017). Our preclinical SCI reports of decreased GI vagal afferent response to CCK (Tong et al., 2011; Besecker et al., 2020), increased TRPV1 expression and hypersensitivity (Besecker et al., 2019), along with the preclinical report by Herrity et al. (2015) of increased P2X3 receptor expression in NG after SCI, insinuate a similar mechanism. This suggests systemic inflammation may cause pathophysiological plasticity within vagal afferents after SCI (**Figure 2**). Lastly, inflammation has been shown to alter the GI microbiota preclinically (O'Connor et al., 2018). The inflammatory profile causes dysbiosis causing disruption to the microbiota-gut-brain axis. This disruption may be the culprit of the chronic GI and neurological disorders seen in neurotrauma individuals. By understanding the GI microbiome, and developing a healthy gut profile, we may be equipped with probiotics necessary to reverse the long-term GI and neural deficits in TBI- and SCI individuals.

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Review

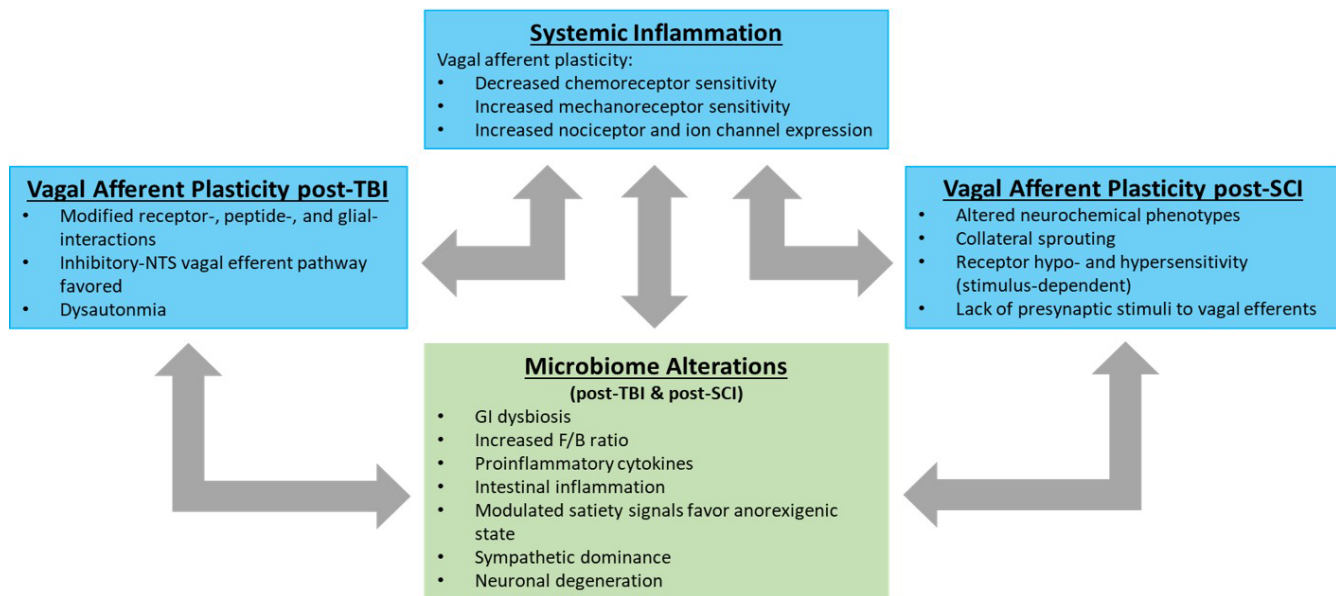


Figure 2 | Vagal afferent plasticity following neurotrauma.

Neurotrauma is emerging as systemic phenomenon whereby multiple organ systems demonstrate post-injury pathophysiology. Vagal afferents remain anatomically intact after TBI and SCI, yet they demonstrate significant remodeling following injury. Systemic inflammation contributes to multi-organ compromise, including the gastrointestinal tract. Whether this systemic

inflammation causes vagal afferent plasticity or the plasticity of the vagal afferents contributes to the systemic inflammation has yet to be determined. This dysregulation may exist in concert with, or independent of, alterations in the gut microbiome. F/B: Firmicutes/Bacteroidetes ratio; GI: gastrointestinal. NTS: Nucleus tractus solitarius; SCI: spinal cord injury; TBI: traumatic brain injury.

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