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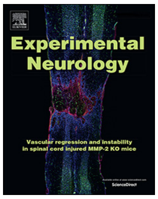

Review article

Gastrointestinal dysfunction after spinal cord injury

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ABSTRACT

The gastrointestinal tract of vertebrates is a heterogeneous organ system innervated to varying degrees by a local enteric neural network as well as extrinsic parasympathetic and sympathetic neural circuits located along the brainstem and spinal axis. This diverse organ system serves to regulate the secretory and propulsive reflexes integral to the digestion and absorption of nutrients. The quasi-segmental distribution of the neural circuits innervating the gastrointestinal (GI) tract produces varying degrees of dysfunction depending upon the level of spinal cord injury (SCI). At all levels of SCI, GI dysfunction frequently presents life-long challenges to individuals coping with injury. Growing attention to the profound changes that occur across the entire physiology of individuals with SCI reveals profound knowledge gaps in our understanding of the temporal dimensions and magnitude of organ-specific co-morbidities following SCI. It is essential to understand and identify these broad pathophysiological changes in order to develop appropriate evidence-based strategies for management by clinicians, caregivers and individuals living with SCI. This review summarizes the neurophysiology of the GI tract in the uninjured state and the pathophysiology associated with the systemic effects of SCI.

1. Introduction

It is commonly accepted that the annual United States incidence of spinal cord injury (SCI) is approximately 17,000 individuals (National Spinal Cord Injury Statistical Center, 2016) while the incidence worldwide reaches approximately 250,000 – 500,000 persons each year (Lee et al., 2014). The loss of motor function is plainly evident to casual observation while impairments to the autonomic nervous system control of bodily homeostasis are not widely recognized. In addition to cardiovascular compromise, the prevalence of gastric, colonic and anorectal dysfunction after SCI presents a significant clinical challenge for both caregivers as well as to the overall health status of the individual living with SCI. Reports of gastrointestinal (GI) complications account for approximately 11% of hospitalizations (Jaglal et al., 2009; Middleton et al., 2004) and present a serious quality of life issue in the SCI population (Anderson, 2004). For example, individuals with SCI may experience life-threatening septicemia, possibly as the result of bacterial translocation across compromised epithelial barriers of the intestinal lumen (DeVivo et al., 1993; Fynne et al., 2012; Miller et al., 1975). Neurogenic bowel is perhaps the most common GI complaint among SCI individuals and may present an incidence ranging from 20-60% (Coggrave and Norton, 2013; Lynch et al., 2001). The symptoms most commonly associated with neurogenic bowel include slow colonic transit, constipation and/or impaction. Furthermore, neurogenic bowel may be accompanied by the potential social embarrassment associated with episodes of overflow incontinence. More importantly the noxious below-injury level stimuli associated with neurogenic bowel are a frequent trigger of the paroxysmal hypertension characteristic with life-threatening autonomic dysreflexia.

Despite the wide-ranging impact to overall quality of life, GI symptoms following injury remain largely understudied and significant knowledge gaps persist regarding the mechanisms leading to post-spinal injury GI impairments. Limited evidence-based standards of care further complicate the consistency with which therapeutic interventions are applied and achieve durable success. This review presents evidence that GI dysfunction is a multifactorial consequence of systemic mediators as well as loss of central (i.e., supraspinal) control. Specifically, while post-SCI loss of descending control to lumbosacral reflex circuits is typically considered to play an important role in colonic and anorectal dysfunction, gastric dysmotility occurs as an indirect or secondary pathology affecting vagal afferent signaling following SCI. Specifically, emerging data points toward diminished sensitivity of vagal afferents to GI neuroactive peptides, neurotransmitters and, possibly, macronutrients while the loss of descending pathways to lumbosacral segmental circuits are superimposed upon pathophysiological remodeling of the intrinsic neurocircuitry of the colon.

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2. Essential components of the neural control of the GI tract

Anatomically, the alimentary canal of vertebrates forms a through-gut system from the oral cavity to the anus. Regional specialization along this canal provides distinct functional roles in the digestive process. The common anatomical organization of the alimentary canal in humans and the animal models most frequently used in SCI research is comprised of the oropharynx, esophagus, stomach, small intestine, colon and rectoanal region. The liver and the pancreas are also visceral organs that play important accessory roles in digestion and share similar sources of innervation (Berthoud and Neuhuber, 2000; Berthoud, 2004). The normal neurophysiological control of the alimentary canal is dependent upon a heterogeneous assembly of 1) local enteric circuits; 2) autonomic input through the parasympathetic and sympathetic nervous systems; and 3) higher cortical processes that in some organisms, including humans, serve to impose additional constraints in response to species-specific and/or social dictates.

2.1. Enteric nervous system

The local regulation of many GI reflex functions is governed by enteric neurocircuitry that is capable of independent secretory (reviewed in Vanner and Macnaughton, 2004) and motor (propulsive) reflexes (see Wood, 2016) as well as regulating the homeostatic requirements of the GI tissues such as blood flow (Vanner and Macnaughton, 2004). Clinical assessment of enteric neuropathies is inconsistently sought and only profound disease states have received concerted attention (see Knowles et al., 2011). The congenital absence of enteric neuronal ganglia in Hirschprung's disease and autoimmune degeneration of enteric neurocircuitry in chronic Chagas' disease are both clearly associated with colonic dysmotility and functional obstruction in humnas. Diminished enteric innervation of the gut is often reported for the constellation of symptoms referred to as so-called "functional" GI disorders (e.g., nausea, bloating, pain), but these highly variable changes are frequently considered correlative and remain controversial. As with other visceral functions, much of our mechanistic understanding of enteric control of the GI tract is from preclinical evidence.

Enteric neurocircuitry throughout the esophagus and stomach is not sufficient to provide the quasi-autonomous control of the GI tract as is found within the myenteric and submucosal ganglia of the intestinal wall (reviewed in Furness et al., 2014). Instead, well described parasympathetic vago-vagal reflexes activate esophageal (reviewed in Hornby et al., 2002) and gastric (see Holmes, 2012) motor responses. Conversely, the neural circuits contained within the intestinal ganglia are sophisticated enough to produce appropriate propagating motor responses such that they remain even in *ex vivo* preparations such as guinea pig and murine colon (Hoffman et al., 2011; Spear et al., 2018). This "mini-brain" of the gut contains roughly as many cells as the spinal cord and is comprised of intrinsic primary afferent neurons (IPANs), interneurons and excitatory or inhibitory efferent neurons (see Furness et al., 2014). A major feature of this inherent circuitry is that activation of IPANs at any given point activates ascending interneurons that target excitatory smooth muscle motor neurons to produce a contraction at the oral aspect of the stimulus while simultaneously activating descending interneurons that target inhibitory smooth muscle motor neurons to produce a simultaneous relaxation of the smooth muscle at the anal aspect of the stimulus. One final, though still debated, component contributing to the paced, quasi-autonomous activity of the smooth muscles, are non-neuronal fibroblast-derived cells known as interstitial cells of Cajal (ICCs; Farrugia, 2008; Huizinga et al., 2009; Sanders et al., 2010). These motor neurons and ICCs form the neuromuscular compartment that is the final common pathway to reflexive smooth muscle contraction. Ultimately, the neuromuscular compartment is under important extrinsic parasympathetic and sympathetic regulation in order to meet the higher-order homeostatic needs of the organism.

2.2. Parasympathetic nervous system

While parasympathetic and sympathetic involvement has been extensively described in clinical diagnoses of functional GI disorders, vagal parasympathetic abnormalities, particularly in the context of diabetes mellitus and obesity dominate the clinical picture (Masi et al., 2018). Clinical attempts at resolving peptic ulcer through vagotomy led to cases of unintended GI dysfunction including gastric dumping (Lagoo et al., 2014; Scott, 1968; Starup-Linde et al., 2016). Frequently, vagally-mediated GI disorders overlap with a spectrum of small fiber derangements including cardiovascular dysregulation (Chan and Wilder-Smith, 2016). From preclinical studies it is widely recognized that gastric enteric neurons are heavily innervated by pre-ganglionic vagal fibers and to a greater extent than the intestinal myenteric neurons (Holst et al., 1997). The esophagus and the stomach are dominated by necessary parasympathetic vago-vagal innervation to regulate the propulsive, storage, milling and emptying reflexes associated with digestion. The fundamental organization of vago-vagal reflexes begins with mechanical and paracrine chemical signals (Page et al., 2002) that are transmitted via the afferent vagus nerve to neurons of the nucleus tractus solitarius (NTS). The NTS integrates this sensory information with signals from throughout the CNS (Blevins et al., 2004; Blevins and Baskin, 2010; Morton et al., 2005) including the spinal cord (Gamboa-Esteves et al., 2001; Menetrey and Basbaum, 1987; Menetrey and de Pommery, 1991) and circulating factors that are capable of passing the fenestrated capillaries of the NTS (Gross et al., 1990). Next, glutamatergic and GABAergic NTS neurons project to other nuclei, including the preganglionic parasympathetic neurons of the dorsal motor nucleus of the vagus (DMV; McMenamin et al., 2016). The final limb of this vago-vagal reflex loop for the stomach is comprised of DMV preganglionic neurons projecting to gastric myenteric neurons, again, through the efferent vagus nerve (for further review see Greenwood-Van Meerveld et al., 2017). The cell bodies for vagal parasympathetic sensory input from the viscera reside within the nodose ganglion (Altschuler et al., 1989) and vagal afferents outweigh motor innervation by a factor of ten. Much of the afferent information from the small intestine carries signaling from the local paracrine detection of release of GI peptides (see Dockray, 2014).

Finally, vagal parasympathetic innervation of the colon diminishes by the splenic flexure in humans though projections to the distal colon exist in rats (Herrity et al., 2014) and direct vagal modulation of the entire colon has been reported in nonhuman primates (Dapoigny et al., 1992). Instead, parasympathetic innervation to the colon arises within the sacral spinal cord (spinal S2-S4 in humans) and travels by way of the pelvic nerve (Callaghan et al., 2018).

Acetylcholine is the ubiquitous neurotransmitter of the parasympathetic preganglionic neurons and targets postsynaptic nicotinic receptors (Schemann and Grundy, 1992). The neurochemical phenotype of the postganglionic neurons on the stomach that receive parasympathetic pre-ganglionic input are distributed across excitatory cholinergic-mediated neurotransmission that targets muscarinic receptors (Tobin et al., 2009) and inhibitory non-adrenergic, non-cholinergic phenotypes (Abrahamsson, 1973; Abrahamsson, 1986; Takahashi and Owyang, 1995; Venkova and Krier, 1994) that promote smooth muscle relaxation by non-adrenergic, non-cholinergic (NANC) activation of nitric oxide, VIP or purinergic release (Durnin et al., 2013; Groneberg et al., 2016; Rivera et al., 2011).

2.3. Sympathetic nervous system

Gastrointestinal sensory input to the thoracolumbar spinal cord is derived by way of the hypogastric nerve originating in the thoracolumbar spinal cord (spinal level T12-L1). Sympathetic inputs to the GI tract innervate the myenteric ganglia, blood vessels and sphincters. While sympathetic input is largely inhibitory of motor and secretory processes and provokes vasoconstriction (Bornstein et al., 1988), the magnitude of sympathetic control of the GI tract appears to be low as evidenced by Cannon's pioneering research demonstrating no ill effects of sympathectomy in cats (Cannon et al., 1929). While hypogastric nerve stimulation elevates internal anal sphincter (IAS) pressure (Thatikunta et al., 1993), hypogastric-mediated sympathoexcitation of the IAS has been reported to occur only in response to supramaximal levels of the rectal stimuli necessary to evoke the rectoanal inhibitory reflex (Shibamoto et al., 1994). Finally, the transmission, and the ultimate perception, of visceral nociceptive stimuli is generally considered to be relayed through the sympathetic splanchnic nerves and terminating within the spinal cord (Gebhart and Bielefeldt, 2016). However, emerging attention is focused toward a vagal route of noxious stimulus transmission (Hanani, 2015).

2.4. Somatic innervation

Voluntary control of the GI tract is limited to the oropharyngeal region which is mediated through vagal efferents originating in the nucleus ambiguus and the external anal sphincter (EAS) which receives innervation from motoneurons located within Onuf's nucleus and projecting through the pudendal nerve (Onuf, 1900). The pelvic floor in humans contains additional anatomical structures to supplement continence as a consequence of upright posture including the levator ani muscle group consisting of the puborectalis, pubococcygeus and iliococcygeous muscles; all of which must be relaxed in order to dismantle the rectosigmoid angle. Changes in anorectal motility after brainstem stroke (Weber et al., 1985) provided evidence of descending modulation of the distal GI tract predating the preclinical evidence of a colorectal homolog to the pontine micturition center within Barrington's nucleus (Callaghan et al., 2018; Pavcovich et al., 1998; Vizzard et al., 2000). It is the disrupted control of the EAS by the aforementioned ponto-medullary as well as corticospinal (Loening-Baucke et al., 1994; Vasquez et al., 2015) pathways that is most often considered following SCI as will be discussed shortly.

3. Pathophysiology of the GI tract after spinal cord injury

3.1. Esophagus

Clinically, derangements in the propulsive movement of ingesta to the stomach and the prevention of gastroesophageal reflux of gastric contents is recognized, yet sparsely investigated (Abel et al., 2004; Gore et al., 1981; Posillico et al., 2018; Radulovic et al., 2015; Shin et al., 2011; Silva et al., 2008). Self reports indicate a higher incidence of heartburn and esophageal chest pain in SCI subjects as well as endoscopic and histological evidence of esophagitis plus diminished esophageal contractility has been reported (Stinneford et al., 1993). However, the prevalence of gastroesophageal reflux disease may be underreported in the SCI population due to the lower prevalence of diagnostic endoscopies for SCI individuals (Singh and Triadafilopoulos, 2000). Diagnoses of dysphagia in a cervical SCI population provide some confirmation and are consistent with the rostral CNS organization of these reflexes (Wolf and Meiners, 2003). However, these authors also identified a potential confound between dysphagia and both artificial ventilation techniques (including tracheotomy) as well as anterior vs. posterior approaches during spinal stabilization. Finally, comparisons have been made between quadriplegic and paraplegic subjects (Silva et al., 2008). While cervical injury did significantly increase subjective reflux ratings, high-level injury did not predispose subjects to differences in endoscopic, manometric or histological indications of esophagogastric abnormalities. Thus, the prevalence and potential mechanism of esophageal dysfunction after human SCI remains largely unresolved. Qualitative observations of esophageal dysmotility in experimental animal models in response to gavage feeding and physiological assessments of gastric pressure and compliance have been made (Holmes, unpublished), however, no quantitative animal studies have been published.

3.2. Stomach

Functionally, the stomach serves a dual purpose. Initially, the stomach is a reservoir for ingested solids and liquids. As digestion progresses, the stomach reduces particle size of solids by digestive secretions and mechanical churning achieved by propagating contractions and relaxations. As particle size is reduced, these contractions also serve to propel the gastric chyme into the duodenum in a feedback-controlled manner.

Classically described as "Cushing's ulcer" following trauma (Cushing, 1932), gastroduodenal bleeding has been reported in the acute phase following SCI, particularly with lesions above T5 (Berlly and Wilmot, 1984; Kewalramani, 1979; Kuric et al., 1989; Tanaka et al., 1979). One potential mechanism leading to gastroduodenal bleeding after SCI has been the reported neurogenic elevation in gastrin secretion (Bowen et al., 1974). Gastrin release is one component in the complex neural and humoral regulation of acid secretion (Brock et al., 2014; Schubert, 2010). In the chronic phase of SCI, gastroduodenal bleeding has a prevalence that is similar to the general population (McKinley et al., 2002; Stone et al., 1990). Preclinical investigations of pathophysiological alterations to this complex system following SCI have not been performed.

The majority of clinical reports indicate pathophysiological reductions in upper gastrointestinal emptying and motility. This is particularly true for SCI occurring above the mid-thoracic spinal segments (Berlly and Wilmot, 1984; Fealey et al., 1984; Kao et al., 1999; Kewalramani, 1979; Nino-Murcia and Friedland, 1991; Rajendran et al., 1992; Segal et al., 1995; Stinneford et al., 1993; Williams et al., 2011). If difficulties arise in feeding tolerance, aggressive nutrient supplementation is often initiated through enteral, parenteral, or invasive surgical interventions in order to maintain positive energy and nitrogen balance (Dvorak et al., 2004; Dwyer et al., 2002; Oakley et al., 2001; Rowan et al., 2004).

Preclinical studies of rodent models of upper thoracic SCI reveal gastric dysmotility patterns similar to humans. Beginning with the novel reports that gastric emptying of a liquid test meal is delayed in spinally-transected rats (Gondim et al., 1999; Gondim et al., 2001) studies of gastric motor function have demonstrated reduced baseline gastric contractions after high (spinal T3) but not lower (spinal T9) thoracic contusion injury (Tong and Holmes, 2009) in anesthetized rats. The involvement of vagally-mediated reflexes in this study was proposed in light of data demonstrating that physiological distension of the esophagus failed to elicit a reflex relaxation of the stomach and that the reduction in gastric reflex activity was not altered by sympathectomy (Tong and Holmes, 2009). These results were in agreement with earlier conclusions that post-SCI dysmotility was mediated through possible alterations in the anatomically intact vagal neurocircuitry (Gondim et al., 2001). While the anesthetic used in the gastric reflex study (Tong and Holmes, 2009) has no demonstrated suppression of autonomic function (Buelke-Sam et al., 1978; Qualls-Creekmore et al., 2010b), studies using [^{13}C]-octanoate breath testing to indirectly measure gastric emptying of a solid meal in awake animals confirmed the presentation of gastric dysmotility and extended the previous findings by demonstrating that the delay in gastric emptying persists up to 6 weeks after T3-SCI (Qualls-Creekmore et al., 2010a).

As described above, vago-vagal gastric reflexes consist of vagal afferent and efferent fibers that are necessary for medullary regulation of gastric contractions. Subsequent studies began to investigate the locus for this dysfunction by pharmacologically targeting the endogenous receptors for GI hormones with well-established effects upon vago-vagal gastric reflexes. Cholecystokinin (CCK) is released by lipid- and protein-sensing enteroendocrine cells in the duodenum and has been implicated in the regulation of motility (reviewed in Dockray, 2014). Briefly, CCK activates C-type vagal afferent fiber terminals that project to nucleus tractus solitarius cells (Rinaman et al., 1993; Sullivan et al., 2007; Zittel et al., 1999) as well as acting upon nodose ganglion cells (Burdyga et al., 2008; Johnston et al., 2018) and centrally within the dorsal vagal complex (Holmes et al., 2009). Activation at each of these levels provokes gastroinhibition.

The sensitivity of vagally-mediated gastric reflexes to the sulfated cholecystokinin octapeptide (CCK-8s) was tested in T3-SCI rats and detected a significant reduction in peripheral and/or central sensitivity (Tong et al., 2011). Specifically, systemic CCK-8s 3 days after injury induced significantly less c-Fos activation in the nucleus tractus solitarius than in uninjured control rats (Tong et al., 2011) while the adjacent area postrema displayed similar activation in both groups, thereby suggesting that gastric neurocircuitry was selectively impaired. Furthermore, central microinjection of CCK-8s into the DVC of T3-SCI rats did not provoke a gastric efferent vagal response which persisted at least 3 weeks after injury (Tong et al., 2011). These data supported the hypothesis that post-injury dysmotility is mediated through alterations in gastric vagal neurocircuits (Holmes, 2012) but did not fully resolve whether this was due to afferent or efferent dysfunction. To address the possibility that efferent outflow was responsible for gastric dysmotility, a series of studies utilized the potent neuroexcitatory properties of thyrotropin releasing hormone (TRH) as a pharmacological tool to activate central gastric circuits (McCann et al., 1989; Travagli et al., 1992). Peripheral and central administration of TRH in T3-SCI rats demonstrated that the ultimate functionality of the efferent limb of vagally-mediated gastric contractions remained unchanged (Swartz and Holmes, 2014).

In order to test the universality of vagal afferent insensitivity to gut peptides following T3-SCI, rats were administered the pro-kinetic peptide, ghrelin. Ghrelin is secreted from oxyntic cells within the gastric mucosa (Date et al., 2000; Grönberg et al., 2008) and is known to exert stimulatory effects upon gastric motility and acid secretion (Ariga et al., 2007; Ariga et al., 2008; Kobashi et al., 2009; Masuda et al., 2000; Wang et al., 2008). Furthermore, ghrelin has been frequently proposed as an endogenous promotility agent (Greenwood-Van Meerveld et al., 2011). A central excitatory effect has been demonstrated *in vitro* within brainstem vagal neurocircuits and *in vivo* with gastric corpus contractions in fasted animals (Swartz et al., 2014). Conversely, rats with T3-SCI demonstrated insensitivity to ghrelin that was similar to, although with a different time course than, that of CCK (Besecker et al., 2018).

Taken as a whole, the preclinical data suggest that gastroparesis following T3-SCI involves a diminished sensitivity of vago-vagal neurocircuitry to enteroendocrine signaling molecules, particularly ghrelin and CCK-8s. These changes in sensitivity very likely contribute to central signaling changes in the brainstem neural circuits. The universality of this compromised vagal sensory input to mechanical stimuli remains to be determined as does the chronic plasticity of these vago-vagal circuits. The acute phase appears to consist of a generalized blunting of viscerosensory drive from vagal afferents that drive pre-injury excitatory (e.g., ghrelin) and inhibitory (e.g., CCK) circuits and mechanisms for functional recovery during the chronic phase remain obscure.

3.3. Colon

The heterogeneous functions and neurocircuitry found in the upper GI tract continue within the colon, rectum and the internal anal sphincter. This region of the GI tract serves to perform the final digestive processing, water reabsorption, storage, transport and elimination of colonic contents (reviewed in Callaghan et al., 2018; Palit et al., 2012).

While the autonomic and somatic reflexes essential for colonic transit remain similar across vertebrates, the anatomical arrangement of the pelvic floor musculature of humans is unique in order to accommodate bipedal posture (Dubrovsky and Filipini, 1990; White and Holmes, 2018). Considerable attention has been directed at the prevalence of the voiding complications present in SCI individuals frequently referred to as neurogenic bowel. Since the parasympathetic and somatic neural circuits for voiding reside within the sacral cord of humans and the sympathetic innervation of the colon exits spinal level T12-L1, neurogenic bowel is perhaps the most prevalent GI co-morbidity following SCI. Neurogenic bowel is frequently described as colonic dysfunction that presents as reduced colonic contractions and transit, constipation, disordered evacuation reflexes and potential overflow incontinence (Coggrave and Norton, 2013; Lynch et al., 2001). Unlike other physiological processes, the social stigma associated with fecal incontinence remains high and as a result, individuals with SCI often become socially isolated. Beyond this social isolation, neurogenic bowel is often a triggering mechanism for the comorbidity stemming from the pathophysiological cardiovascular remodeling that occurs following SCI (Furlan et al., 2003; Maiorov et al., 1998; Wan and Krassioukov, 2013). Known commonly as autonomic dysreflexia, the noxious visceral stimulation that accompanies severe constipation triggers a life-threatening increase in sympathetic discharge below the injury level; particularly in individuals with SCI at or above the T5-T6 spinal cord (reviewed in Al Dera and Brock, 2018) and is evoked in rodent models soon after complete SCI as well (Rummery et al., 2010).

Despite frequent calls for concerted investigations of colorectal, bladder and sexual dysfunction by the SCI population (Anderson, 2004; Lynch et al., 2001; Simpson et al., 2012; Wheeler et al., 2018), preclinical investigation of bowel dysfunction is profoundly lacking and substantial knowledge gaps persist between the neurotrauma and gastroenterological fields in understanding neurogenic bowel. The research to date frequently addresses the loss of supraspinal regulation of somatic (Callaghan et al., 2018; Holmes et al., 1998; Holmes et al., 2005) and autonomic circuitry of the spinal cord (Callaghan et al., 2018; Chung and Emmanuel, 2005; Ferens et al., 2011). Certainly, the hyperreflexic contractions of the EAS following experimental SCI that presumably hinder evacuation (Holmes et al., 1998) support the notion of interrupted supraspinal control of sacral defecation reflexes. This supraspinal control is at least partially resident in the brainstem since targeted supraspinal lesions also provoke EAS dysfunction (Holmes et al., 2002)

Beyond the supraspinal regulation of bowel reflexes, recently emerging evidence suggests that colonic dysregulation is accompanied by remodeling of the enteric neuromuscular compartment. An analysis of human archival colonic tissue revealed increased collagen deposition within the longitudinal muscle layer as well as a general reduction in myenteric neuronal density in individuals with chronic SCI (den Braber-Ymker et al., 2017). Unfortunately, the semi-quantitative measures and inconsistent patient histories of this retrospective study somewhat limit the strength of the conclusions. In an experimental model of acute (3 day) and chronic (3 week) severe contusion injury, both the proximal and distal regions of the rat colon demonstrated reduced spontaneous contractions in vivo (White and Holmes, 2018). In addition, collagen deposition was elevated within the smooth muscle and the density of neurons within the myenteric plexus was reduced (White and Holmes, 2018). Functional and pharmacological support for this observation was recently presented demonstrating an impairment of cholinergic-mediated contraction of colonic smooth muscle four weeks following complete spinal transection (Frias et al., 2019). Conversely, other pharmacological targets have shown promising results. In addition to the gastric motor reflexes discussed previously, ghrelin has received attention for colonic prokinetic effects (Fraser et al., 2009; Hirayama et al., 2010; Pustovit et al., 2014; Venkova et al., 2007). In experimental SCI, a centrally-acting ghrelin mimetic elevated contractions of the experimentally fluid-filled colon (Ferens et al., 2011). Limited evidence of the central colokinetic responses have also been reported in response to noradrenergic stimulation (Abysique et al., 1998; Naitou et al., 2018; Naitou et al., 2015) though this mechanism might be restricted to contractions in response to noxious stimuli (Naitou et al., 2018).

Finally, there is emerging evidence for the role of neurokinin receptor modulation of colonic contractions in experimental SCI (Kullmann et al., 2017; Marson et al., 2018). Clearly, a greater understanding of the long-term remodeling of the enteric and spinal neurons that serve as the final common pathway for smooth muscle contractions is necessary in order to identify pitfalls for the restoration of voiding reflexes following injury (see White and Holmes, 2019). For example, evidence for remodeling of enteric neurocircuitry in response to a single inflammatory event has been presented (Mawe, 2015) and vagal afferent neuroplasticity has also been recognized as part of the daily fluctuations in feeding and energy homeostasis that occurs rapidly in response to altered levels of GI neuropeptides (Broberger et al., 2001; Burdyga et al., 2010). Serotonin is recognized as a signaling molecule between the gut lumen and the vagal afferent nerves and is trophic for enteric neurons (Liu et al., 2009) and dystrophic changes to vagal afferents have been reported in response to aging (Phillips and Powley, 2007) though mechanistic insights to these age-related changes remain unresolved. The alterations in local serotonergic circuitry within the post-SCI gut have not been addressed. Lastly, the resilience of vagal efferent input demonstrated for the post-SCI stomach (Swartz and Holmes, 2014) needs to be expanded to the remainder of the GI tract as do the sacral parasympathetic efferent inputs to the colon.

4. Management of GI pathophysiology after spinal cord injury

Interventions offered to the SCI individual are limited and often invasive or non-existent (Multidisciplinary Association of Spinal Cord Injured Professionals, 2012; Wheeler et al., 2018). Utilization of these strategies is frequently tailored to patient needs by trial and error. Behavioral and pharmacological treatment of upper GI dyspepsia is limited to that offered the able-bodied. For example, acid-suppression may be achieved with proton-pump inhibitors while dysmotility along the entire GI tract may be targeted with prokinetics (Carone et al., 1993; Ellis et al., 2014; Krogh et al., 2002; Rosman et al., 2008) although prokinetics such as the 5-HT4 agonist cisapride have been removed from the market. Pharmacological targeting of bladder overactivity with anticholinergics has become commonplace, with the potential for unintended side effects of diminished GI motility. In addition to prokinetics, neurogenic bowel is resolved by increasingly invasive procedures. If diet and fluid management combined with manual evacuation are unsuccessful, individuals may resort to chemical stimulants containing glycerine or bisacodyl. Fluid management is problematic as individuals balance the need to bladder catheterize with demands of a bowel program. Extreme cases of colonic dysmotility may lead individuals to consider surgical procedures such as antegrade continence enema (Herndon et al., 2004; Malone et al., 1990), colostomy (Bolling Hansen et al., 2016), or sacral nerve stimulation (Rasmussen et al., 2015). Greater understanding of GI pathophysiology coupled with resulting improvements in effectiveness and refinement of each of these strategies remain a high priority for SCI individuals (Wheeler et al., 2018).

5. Emerging frontiers in GI pathophysiology after spinal cord injury

5.1. Gastroparesis and multiorgan pathophysiology after SCI

Gastrointestinal dysfunction is not a stand-alone consequence of SCI. Multiorgan dysfunction following SCI is due, in part, to the dysregulation of the supraspinal control of the autonomic nervous system below the lesion. Visceral and somatic tissues are affected beginning minutes to weeks after SCI and include the cardiovascular, pulmonary, renal, skeletomuscular and hepatic systems (Anthony and Couch, 2014; Sun et al., 2016). As previously described, the upper GI tract is under dominant control by the parasympathetic nervous system (vagus) which remains anatomically intact following SCI. Emerging evidence has shown that neuroendocrine changes along the hypothalamic-pituitary-adrenal axis elevate circulating macrophage migration inhibitory factor (Lerch et al., 2014). Even lower-thoracic SCI has been shown to provoke hepatic dysfunction, thereby suggesting that disruption of segmental circuits are not the sole mechanism of multiorgan dysfunction (Sauerbeck et al., 2015). Other investigators have extended hepatic involvement to hypothesize that the systemic inflammatory response is initiated in the spinal cord injury site and, likely, spills over to the circulation. This so-called spill over is magnified through acute-phase hepatic pro-inflammatory release whereby the eventual elevation of leukocytes mediates damage to multiple organs (Anthony and Couch, 2014); essentially creating a pathophysiological feed-forward circuit.

5.2. Epidural stimulation

Utilized initially as an intervention for chronic pain (Shealy et al., 1970) epidural stimulation has been applied in an effort to facilitate motor modulation (Rejc et al., 2016). In support of anecdotal reports of improved voiding function during locomotor training, epidural stimulation is rapidly emerging as a co-component to locomotor training for potentially reactivating or regenerating visceral functions (Aslan et al., 2018; Darrow et al., 2019; Herrity et al., 2018; Walter et al., 2018). Unlike the early informal reports, focused attention is being directed at greater quantification of recovered function (Hubscher et al., 2018). While the mechanisms leading to these global improvements in function remain obscure, the activation of sensory, motor and autonomic neural circuits at the segmental level appear likely and are avenues for exploration in emerging preclinical research.

5.3. Gastrointestinal microbiome

In recent years, the microbiome-gut-brain axis has become a rapidly expanding interest regarding human health and disease (Lynch and Pedersen, 2016). While identification of all the genera populating the gut reveals broad diversity, the gut microbiome can be reduced to Gram-negative and Gram-positive phyla (Bacteroidetes and Firmicutes, respectively; Zhernakova et al., 2016).The ratios inherent to this overall biodiversity are quite labile depending upon gut conditions and these ratios are frequently the association reported in disease shifts. However, the interpretation of microbiome data is fraught with challenges (Falony et al., 2019). Casual survey of the literature reveals positive associations between the microbiome variability and virtually every physiological process. Restricting discussion to CNS injury, it is known that the microbiome is greatly altered after stroke (Sadler et al., 2017; Yin et al., 2015) and traumatic brain injury (Ma et al., 2017; Treangen et al., 2018). Interactions between SCI and the microbiome are also beginning to emerge. More thorough reviews of the current SCI microbiome research can be found (David et al., 2019). Thus far, only a few studies have investigated the SCI microbiome in both the patient population and rodent models.

The clinical studies of SCI and the microbiome in 30 SCI patients found decreased Bacteroidetes, specifically the genera Megamonas and Dialister, in addition to decreased Firmicutes (the genera Rosebura, Pseudobutyribibrio and Marvnbryantia; Gungor et al., 2016). Another study conducted on male patients found the abundance of Firimucutes specifically, Veillonellaceae, increased, while Bacteroidetes specifically, Bacteroidaceae and Bacteroide, decreased, with the exception of Prevotellacea which decreased (Zhang et al., 2018).

Therapeutic options investigated in other disease states such as obesity have often employed probiotic therapies containing bacteria of the phylum Firmicutes, though there have been mixed effects (Cerdo et al., 2019). Other treatments, such as fecal transplants, have also been proposed, but studies investigating the feasibility of this in preclinical models are lacking. One clinical case report demonstrated a fecal transplant in a tetraplegic male in which a systemic inflammatory response was triggered. Following a seven-day antimicrobial treatment after the fecal transplant, the patient did not relapse with C. difficile infection Brechmann et al., 2015. This case report demonstrated there is some feasibility with fecal transplants in SCI individual; however, more extreme precautious should be taken because more extreme adverse events may occur. More research must be conducted before this practice can become a feasible treatment option for SCI individuals.

Preclinical rodent models have found differing results. In one study, the population of Bacteroidetes decreased while Firimucutes increased within the GI tract of SCI (Kigerl et al., 2016). Conversely, a recent murine study found the opposite where the Bacteroidetes are expanded and Firmicutes are reduced (Myers et al., 2019). Additionally, this latter study notes the expansion in Proteobacteria, and the total bacterial load is increased. A rat model showed a high prevalence of Firmicutes (O'Connor et al., 2018). Additionally they noted an increase in Bifidobacteriaceae as well. Despite the inconsistencies between these studies, it can be said there is an alteration to the ratio of the Bacteroidetes and Firimucutes which negatively affects GI health through distinct, though interconnected, mechanisms.

The microbiome has been shown to influence host metabolism, primarily through the production of short-chain fatty acids (SCFAs) through the process of fermentation (den Besten et al., 2013). The most common SCFAs are in the form of acetate, propionate and butyrate and are rapidly absorbed by colonocytes (Cook and Sellin, 1998). Subsequently, Firmicutes-derived butyrate regulates GI energy and ultimately tissue integrity (Donohoe et al., 2011). An additional interconnected factor in the gut microbiome balance is the population of Gram negative Bacteroidetes that serve as a source of circulating pro-inflammatory lipopolysaccharide (LPS; Mullen et al., 2015). In addition to the incidence of barrier permeability for luminal contents to enter the systemic circulation following SCI (Medeiros et al., 2008), vagal afferents also serve a likely role in local sensing of both microbial metabolism as well as efferent activation of anti-inflammatory mechanisms (Bonaz et al., 2018).

From the small number of preclinical studies investigating the SCI microbiome, two treatment options have been employed and have shown evidence of improving recovery after SCI. Both probiotics and melatonin have shown to restore some of the microbiota disturbances triggered by SCI (Jing et al., 2019; Kigerl et al., 2016). The unrestricted availability of these supplements warrant further investigation, especially in controlled clinical settings. Importantly, future research should focus on the temporal changes of the SCI-induced dysbiosis and focus on acute therapeutic interventions. Microbial shifts can potentiate inflammation which is known to occur following SCI and add to the chronic inflammatory state of SCI individuals (Noller et al., 2017). Specifically, lipopolysaccharides (LPS) from Gram-negative bacteria can trigger inflammation (Carvalho and Saad, 2013) due to the bacterial translocation that occurs with SCI (Kigerl et al., 2016; Liu et al., 2004). Furthermore, LPS can have a direct neural effect upon GI neural circuits (Barajon et al., 2009; Hermann et al., 2002) thereby initiating a cascade of neuroimmune responses (Keita and Söderholm, 2010). Both preventing this inflammation and reversing the inflammation in chronic SCI individuals are viable treatment avenues that call for longitudinal studies of the microbiome both in preclinical and clinical models.

5.4. *Gastrointestinal hypoperfusion*

Derangements in sympathetic tone are particularly problematic for injuries rostral to T5 in that the interruption of medullary presympathetic vasomotor neurons provokes cardiovascular instability, arterial hypotension, and pooling of blood in the extremities all of which has been documented clinically (West et al., 2013) and experimentally (Laird et al., 2006). The proper functioning of the GI tract requires adequate blood flow during the digestion and absorption of nutrients in order to maintain tissue integrity and maintain proper fluid balance. The importance of GI blood supply is reflected in the fact that resting GI blood flow can reach approximately 20-25% of the total cardiac output (Chou, 1983). Extended hypoperfusion of the mesentery deprives GI tissues of the oxygen needed to maintain luminal barrier integrity (Chou and Coatney, 1994). The resulting ischemia and reperfusion cycle provokes a multifactorial tissue injury response including intercellular adhesion molecule-1 (*Icam1*) mediated increase in adherent leukocytes as well as upregulated chemokines, and pro-inflammatory cytokines (Granger et al., 2015; Wehner et al., 2007).

Mesenteric outflow obstruction is clinically reported (Desai et al., 2014) and may be exacerbated by abdominal wall weakness leading to duodenal or superior mesenteric artery (SMA) compression due to the postural consequences of wheelchair use, and constipation associated with prolonged colon transit time. Insufficiency of SMA blood flow with accompanying intestinal inflammation has been reported following experimental SCI (Besecker et al., 2017). Despite a high degree of vascularization, intestinal epithelial cells border the anaerobic and nonsterile lumen of the gut and are exposed to a steep physiologic oxygen gradient. Thus, the intestine is highly sensitive to hypoxic insult and GI hypoxia rapidly induces the production of inflammatory mediators and dysmotility. Studies have found that the colon is the most susceptible GI tissue to oxidative damage due to it having comparatively lower levels of antioxidant defenses than other regions (Blau et al., 1999; Lih-Brody et al., 1996).

The numerous mechanisms underlying the etiology of remote tissue dysfunction following SCI have not been thoroughly illuminated, but it is apparent that multiple organ dysfunction after SCI is a complex multi-factorial response that is unlike any other disease process. To date, the SCI microbiome and the interrelationship with diminished mesenteric perfusion and circulating inflammatory mediators remains a large knowledge gap that deserves greater investigation. While recent studies have begun to advance this field in the both the preclinical and clinical settings, the interplay of these two emerging fields require a clearer determination of the associations between post-SCI changes in the ratio of Bacterodiete and Firimucutes microbes and the likely confounders in the SCI populations: such as, antibiotic overuse, stress, and GI dysfunction. This begs the question if SCI GI dysfunction causes the microbiome dysbiosis or does the microbiome dysbiosis cause the GI dysfunction or somehow is it both?

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