

Traumatic Brain Injury and the Effect on the Brain–Gut Axis

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ABSTRACT

Traumatic brain injury (TBI) is a leading cause of disability worldwide. One commonly overlooked effect of TBI is the disruption of the brain–gut axis, leading to gastrointestinal dysfunction. The brain–gut axis consists of the cortical areas of the insular cortex, cingulate, and hypothalamus that have bidirectional communication with the visceral enteric nervous system through afferent and efferent projections into the pontine vagal complex and nucleus tractus solitarius. Communication with the brain also

occurs through messenger signals from the gut's microbiota, involving gut peptides, cytokines, and lipopolysaccharides. Disruption of the brain–gut axis from TBI can lead to a chronic, inflammatory, vicious sequela, involving both the brain and the gastrointestinal system, with both neuroregulatory and neuroimmunological loops. (*Altern Ther Health Med.* 2015;21(suppl 3):28-33.)

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Traumatic brain injury (TBI) is a leading cause of disability and death worldwide, and up to 7 million individuals are treated annually for TBI in hospitals in the United States alone.¹ Individuals who suffer from TBI potentially can also suffer from chronic digestive disorders.² That medical issue appears to be the consequence of a disruption in communication between the brain and the gastrointestinal system, called the brain–gut axis.³ Input from areas of the brain, such as the hypothalamus, insular cortex, and cingulate, is involved in neuroendocrinal and neuroimmunological integration of the viscera via the vagus complex and the nucleus tractus solitarius in the pons.⁴ Projections from the vagal nuclei, which carry both afferent and efferent inputs to and from the viscera, innervate the enteric nervous system, establishing a link between the brain and gut.⁵ In addition, communication with the brain also

occurs through messenger signals from the gut's microbiota, involving gut peptides, cytokines, and lipopolysaccharides that connect the gut to the brain through noncanalized pathways (Figure 1).⁶

Disruption of the brain–gut axis through neuroregulatory and neuroimmunological loops can lead to vicious sequelae promoting chronic gastrointestinal dysfunction, systemic inflammation, and disability.⁷

Alterations from TBI in the appropriate neural integration in the vagus complex can lead to (1) gastrointestinal autonomic dysregulation (ie, dysautonomia); (2) disorders of visceral interoceptive processing; (3) intestinal permeability; (4) intestinal-mucosa compromise; (5) a breakdown of the blood–brain barrier (ie, blood–brain barrier permeability); (6) brain immune consequences (ie, systemic immune dysregulation); and (7) reduced intestinal contractility (ie, impaired intestinal motility) (Figure 2). Those mechanisms can lead to the sequela of chronic gastrointestinal disorders after injury to the brain, which the author discusses in the following sections of the current article.

GASTROINTESTINAL AUTONOMIC DYSREGULATION

Acceptance has been growing for the idea that alterations in autonomic function can play a significant role in functional disorders of the gut.⁸ Disruption of the corticopontine projections into the gut that occur specifically after brain injury can lead to various autonomic imbalances, called dysautonomia.⁹ Dysautonomia occurs commonly after brain injury and has been found in 8% to 33% of individuals with TBI.¹⁰

Figure 1.

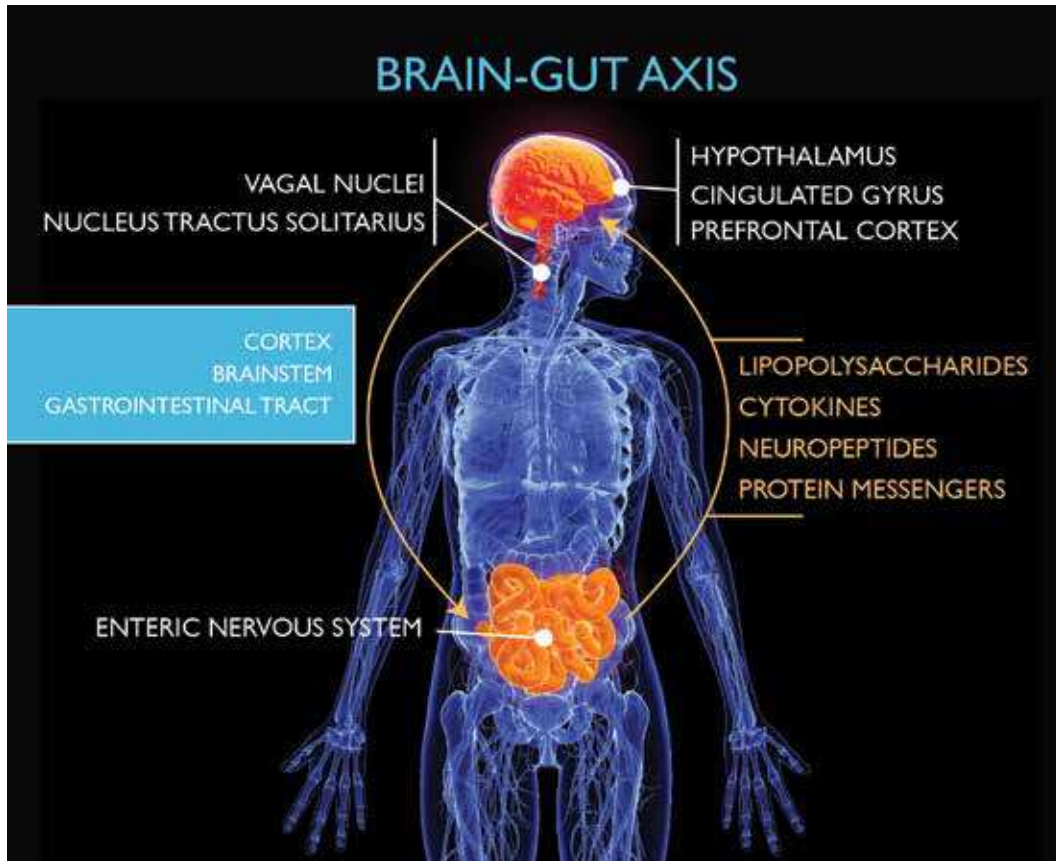
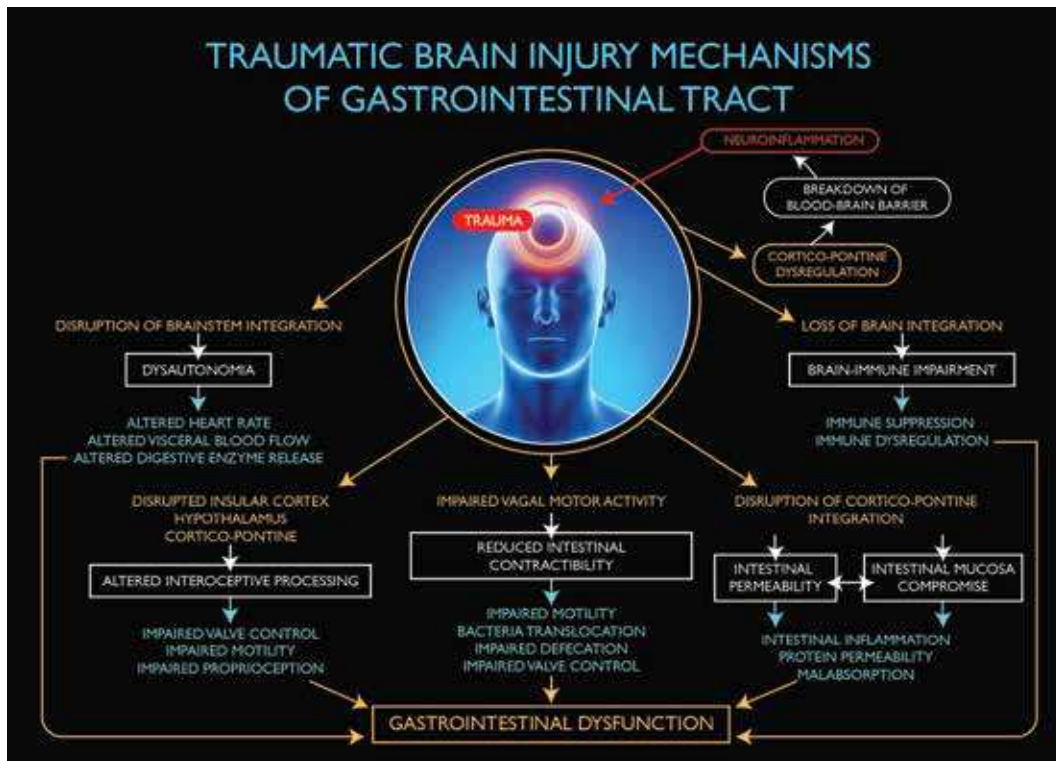


Figure 2.



Dysautonomia after brain injury is characterized by episodes of increased heart rate, temperature, blood pressure, muscle tone, and posturing and of profuse sweating.¹¹ Dysautonomia leading to improper sympathetic and parasympathetic integration occurs in functional bowel disorders, leading to chronic gastrointestinal disorders.¹²

A common presentation of dysautonomia is persistent sympathetic overactivity in response to nociceptive stimuli and development of chronic pain after TBI.^{13,14} In addition to the chronic pain and gastrointestinal complaints that occur from TBI-induced dysautonomia, altered heart rate variability has been observed and has been postulated to occur from a disrupted cortical pontine disconnection.¹⁵ Those outcomes have also been found to be worse in individuals who suffer from posttraumatic hypertension, and they have been linked to a poor long-term outcome.¹⁶

TBI appears to disrupt the corticopontine connection and its projections to autonomic control via the vagal nuclei complex and vagus nerve, leading to dysautonomia. Those autonomic changes have the potential to cause diverse changes in gastrointestinal function, leading to TBI-induced gastrointestinal dysfunction.

DISORDER OF VISCERAL INTEROCEPTIVE PROCESSING

For proper digestive system function to occur, the brain must process the somatotopic orientation of the intestines and recognize visceral stimuli, such as pH, distention, ischemia, inflammation, touch, and smooth muscle contractions. The ability of the brain to interpret those afferent inputs in various brain regions is called interoceptive processing. The insula cortex, hypothalamus, and corticopontine loops are involved with the interoceptive processing of viscera.¹⁷

Disruption of the interoceptive processing circuits has been demonstrated with brain imaging studies to be a central mechanism of irritable bowel syndrome.¹⁸ Central integration of interoceptive processing is critical for the proper vagal, temporal summation and autonomic regulation that are necessary for regulating the proper intestinal afferent and efferent communication. TBI has the potential to lead to alterations of the interoceptive processing of viscera and to contribute to loss of regulation of the brain–gut axis.

Hang et al¹⁹ have demonstrated that brain injury can cause significant changes in the brain–gut peptides in both the plasma and the small intestine that are involved with interoceptive processing. Cortical interoception and integration are critical for proper bowel function, and the association of bowel disorders with a lack of cortical-level integration of visceral inputs has been demonstrated with percept-related functional magnetic resonance imaging (fMRI).²⁰

It appears that TBI can lead to an altered gastrointestinal function due to a lack of cortical processing related to the afferent and efferent circuits that involve the enteric nervous system, vagal complex, insula cortex, and corticopontine loops. Those alterations may partly explain how TBI can lead to chronic gastrointestinal impairments.

INTESTINAL PERMEABILITY

One of the major consequences of TBI is the lack of cortical activation of the pontine vagal system, leading to an alteration of postsynaptic autonomic changes. Those alterations promote decreased intestinal autonomic and increased inflammatory reactions, leading to intestinal permeability. Intestinal permeability occurs when the tight junctions of the epithelial, multiprotein complex are compromised, allowing for abnormal trafficking of large macromolecules.²¹

Evidence from one study suggests that intestinal permeability plays a role in the onset of autoimmune diseases.²² That study also has shown that such permeability precedes inflammatory bowel disease, promotes cytokine responses locally at the intestines, and encourages chronic, systemic inflammatory responses.²²

TBI-induced intestinal permeability may be a consequence of a lack of postsynaptic activation of the pontine vagal complex. In a mouse model of TBI, vagal stimulation prevented TBI-induced intestinal permeability and also increased enteric glial activity.²³ That study supported the notion that the vagal-nuclei disruption resulting from TBI is the central mechanism for development of intestinal permeability and that vagal activation has a modulating effect on the neuroinflammatory responses of the enteric glia. In addition, TBI has been shown to induce an increase in intestinal permeability, which may lead to bacterial translocation, sepsis, and systemic inflammation.^{24,25}

Further, TBI-induced intestinal permeability has the potential to promote a vicious inflammatory cascade involving the brain-to-gut axis and the gut-to-brain axis. Intestinal permeability has been found to increase proinflammatory cytokines at the level of intestinal mucosa and to cause translocation of lipopolysaccharides that can disrupt brain function.^{26,27} Therefore, the alteration of corticopontine integration from TBI can lead to inflammatory consequences in the gastrointestinal tract from intestinal permeability. Those consequences potentially can further suppress brain function, leading to a chronic, inflammatory, vicious cycle between the brain and the gastrointestinal system.

TBI can lead to proinflammatory immune activation in the peripheral blood stream, leading to systemic inflammatory response syndrome.²⁸ TBI, therefore, has the potential to lead to the promotion of a vicious cycle involving both brain inflammation and gut inflammation and to play a significant disruptive role in the brain–gut axis of a chronic inflammatory nature.

INTESTINAL MUCOSA COMPROMISE

At the intestinal level, many changes take place in the intestinal mucosa directly after brain injury, including mucosal ischemia, mucosal atrophy, and activation of intestinal inflammatory cascades.²⁹ Those reactions can occur as early as 3 hours following brain injury and can last for more than 7 days, with marked mucosal atrophy.³⁰

In addition, TBI can induce profound ischemic effects on gastrointestinal mucosa and can cause motility

dysfunction.³¹ The inflammatory reactions that occur in the intestinal mucosa following TBI appear to increase the expression of intestinal nuclear factor kappa B (NF- κ B) and intercellular adhesion molecule 1 (ICAM-1) in the intestine. Those results can lead to acute mucosal injury of the gut following TBI.^{32,33} A rapid and persistent upregulation of myeloid differentiation primary responses protein 88 (MYD88) occurs, in combination with activation of systemic inflammatory cytokines.³⁴

The inflammatory changes that occur after TBI are immediate and illustrate how cortical injury can lead to inflammatory consequences in the lining of the peripheral gastrointestinal mucosa. In essence, injury to the brain leads to a brain immune response that creates an inflammatory intestinal cascade. That cascade compromises the intestinal mucosa, leading to intestinal inflammation that has been induced by brain injury.

BREAKDOWN OF THE BLOOD–BRAIN BARRIER

The blood–brain barrier plays a critical role in protecting the brain from immune-activating substances. However, widespread breakdown of the blood–brain barrier occurs immediately after brain trauma, leading to a susceptibility to circulating proteins and the promotion of inflammatory sequelae.³⁵ It appears that the breakdown of the blood–brain barrier occurs within hours of TBI; cerebral vascular permeability can increase 4-fold within 6 hours of an initiating trauma.

It has also been found that vagal nerve stimulation can attenuate cerebral vascular permeability and decrease upregulation of perivascular aquaporin 4 after TBI.³⁶ Therefore, TBI-induced corticopontine dysregulation of the vagal nuclei appears to be a central mechanism for both intestinal and blood–brain permeability.

Specifically, TBI induces a profound breakdown of the blood–brain and blood cerebrospinal fluid barriers (BCSFB) as well as a release into the cerebrospinal fluid (CSF) of a major chemoattractant for monocytes, chemokine (C-C motif) ligand 2 (CCL-2), by the choroid plexus epithelium at the side of the BCSFB. That release can lead to posttraumatic invasion of monocytes, promoting the recruitment of inflammatory cells to the injured brain.³⁷ Those inflammatory changes in the neurovascular network of the blood–brain barrier have been found to lead, ultimately, to delayed neuronal function and degeneration.³⁸

In summary, TBI-associated loss of corticopontine processing disrupts vagal network integration and increases inflammatory sequelae, promoting the breakdown of the neurovascular network of the blood–brain barrier and leading to a loss of brain barrier protection and a susceptibility to further neuroinflammation.

BRAIN IMMUNE CONSEQUENCES

Immune system dysregulation can occur after TBI, specifically immunodeficiency and vulnerability to infections.^{39,40} It appears that brain injury can lead to systemic

immune responses in which chemokine signals from the central nervous system (CNS) activate the production of hepatic immune responses and changes in systemic immunity.⁴¹

TBI can alter immune homeostasis, contributing to immunosuppression from the decreased phagocytic functions of neutrophils and macrophages as well as monocyte deactivation. Those changes result in a decreased capacity for antigen presentation to lymphocytes.⁴² Those immune suppressive reactions may have long-term expressions.

It has been found that brain injury can lead to immunodepression for months and to chronic CNS and systemic immune activation for years after the initial injury.⁴³ Studies of the pre- and postinjury immunological states of animals have demonstrated that immunological changes occur after brain injury.^{44,45} Those 2 studies of lesions induced in the cerebellums of animals, using localized kainic acid microinjections, resulted in a reduction in the lymphocyte percentage in peripheral white blood cells and an inhibition of the number and functions of T cells, B cells, and natural killer cells. That finding suggests that the cerebellum may play a role in neuroimmunomodulation.

Another study showed changes indicating a compromised immune system secondary to brain lesions.⁴⁶ That study created a kainate lesion of the vestibulocerebellum. The chemical lesion induced a depressed secretion of hematopoietic cytokines in tissue cultures of the bone marrow and thymus.

It appears that the brain and immune system are intimately connected and that neuroimmunomodulation may be impaired after TBI, leading to immunological compromise and susceptibility to infection. It is possible for those immunological consequences to affect not only overall immunity but also gut immunity.

REDUCED INTESTINAL CONTRACTIBILITY

TBI causes a delay and a significant decrease in intestinal smooth-muscle contractile activity, leading to delayed transit time.⁴⁷ A reduction in transit time can lead to clinical symptoms of chronic constipation and dyssynergic defecation.⁴⁸ In addition, a delayed transit time increases the potential to develop small-intestine bacterial overgrowth (SIBO).⁴⁹

An abnormal brain–gut interaction is associated with impaired motility, autonomic dysfunction, and immune dysregulation, which are the hallmarks of the pathophysiology of SIBO and irritable bowel syndrome (IBS).⁵⁰ Injury to the brain leading to impairment of vagal motor activity to the intestinal tract can lead to alterations in the smooth-muscle contractions that are necessary not only for intestinal motility but also for intestinal valve control. Impaired motility and valve control can increase the susceptibility to abnormal translocation of bacteria from the large intestine into the small intestine, leading to a cascade of SIBO pathophysiology that includes chronic abdominal distention, malabsorption syndrome, and chronic intestinal inflammation.

CONCLUSIONS

TBI can lead to chronic gastrointestinal dysfunction through impaired neurological integration, involving areas of the insular cortex, cingulate, and hypothalamus, which have bidirectional communication with the visceral enteric nervous system through afferent and efferent projections into the pontine vagal complex and nucleus tractus solitarius. Disruption of those cortical and brainstem regions has the potential to induce dysregulation of the brain-gut axis, resulting in complex and diverse physiological outcomes.

Alterations in the appropriate neural integration of the brain-gut axis from TBI can lead to (1) gastrointestinal autonomic dysregulation (ie, dysautonomia); (2) disorders of visceral interoceptive processing; (3) intestinal permeability; (4) intestinal mucosa compromise; (5) a breakdown of the blood-brain barrier (ie, blood-brain barrier permeability); (6) brain immune consequences (ie, systemic immune dysregulation); and (7) reduced intestinal contractility (ie, impaired intestinal motility). Those physiological consequences can lead to a vicious cycle of chronic brain and intestinal inflammation leading to overlooked disability and chronic gastrointestinal dysfunction.

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