Editorial

Neurogastroenterology: Gastrointestinal dysfunctions from the window of acute brain injury

Gastrointestinal (GI) dysfunctions remain the most common complications in patients with TBI. Some of the most frequent GI complications are bowel incontinence, stress ulcers, dysphagia, constipation, bowel incontinence, and liver dysfunction.[1]

Traumatic Brain Injury continues to be a major medical problem in the United States, costing over 4$ billion annually in health care costs and loss of productivity.[2]

GI dysfunction is a common complication of stress. It is a building epidemic throughout Asia and the Middle East, and affects every nation of the world, regardless of the economic development, racial or religious predominance or political ideology. What is becoming increasingly apparent are the systemic physiological effects following TBI, including autonomic dysfunction, systemic inflammation, and organ dysfunction,[2] including pneumonia, cardiovascular disorders, autonomic abnormalities, intestinal dysfunction, and multiorgan system failure. GI dysfunction, specifically, is frequently observed in TBI patients, including motility abnormalities and mucosal alterations that can lead to ulceration, inflammation, blunting of the intestinal villi, and increased gut permeability.[2] These complications may result in a delayed and ineffective outcome, an increased risk of aspirated or hospital-acquired pneumonia, prolonged length of ICU stay, and increased mortality rates.[3]

Therefore, it is of great importance to study and solve the GI dysfunction problems encountered in the process of TBI treatment.

This editorial presents the reasons for GI dysfunctions following severe TBI, the current theories, and other related issues.

Access this article online	
Quick Response Code:	Website: www.ijsronline.com
	DOI: 10.4103/2230-7095.113804

GASTROINTESTINAL DYSFUNCTION FOLLOWING TRAUMATIC BRAIN INJURY: REASONS AND DISCUSSION

Basically the GI dysfunctions occur due to the following reasons:[4-9]

1. Impaired gastrointestinal motility
2. Reduced gut absorption
3. Hypoalbuminemia, high metabolic expenditure, and increased nitrogen catabolism

Intestinal epithelial cells function as a physical barrier between the intestinal lumen and the underlying vasculature and lymphatics. This is largely due to the structural integrity of cellular-tight junctions, which maintain compartments of cell to cell integrity, notably in the gut and lung, by playing a critical role in preventing systemic contamination by microbes and toxins.[10]

Tight junctions are composed of a series of interacting transmembrane proteins, including claudins, occludin, and junctional adhesion molecules. The loss of tight junction barrier integrity has been correlated with increased intestinal permeability, and hypothetically, bacterial translocation.[10,11]

Tight junction structural proteins Zona occludens protein-1 (ZO-1) and occludin are significantly decreased following systemic brain injury, TBI or torso injury in mice, due to a heightened adrenergic state.[2] Many patients with severe TBI often die of Multi Organ Dysfunction (MODS), but not of the injury itself. MODS often follows the stress of severe trauma, burns, and acute necrotizing pancreatitis. The gut origin hypothesis suggests that damage of the intestinal mucosal barrier as a result of these stress factors occurs at an earlier stage, permitting bacterial overgrowth and endotoxin translocation, which triggers the systemic inflammatory response syndrome (SIRS) and MODS, as the levels of endotoxin and D-xylose increase due to increased intestinal mucosal permeability. This stressful situation is a multifaceted disorder involving the dysregulation within the brain–gut axis. Upon activation of this axis the release of brain–gut peptides profoundly affect the gastrointestinal physiology and are frequently associated with the GI motor dysfunction, that is, decrease in motility, as evidenced by significant decelerations of the intestinal propulsion ratio of a semisolid colored marker (Bioink) and significant decrease in the Gastrointestinal Mucosal Blood Flow (GIMBF), as

evidenced by the Laser Doppler Technique.[10] Intestinal mucosal barrier function damage alters the ingested behaviors and associated physiological events, such as, gastric acid secretion and GI motility. The mast cells translate the stress signal that has been transmitted through the brain–gut axis, to release a wide range of neurotransmitters and proinflammatory mediators. Some of them are brain–gut peptides such as 5-HT, substance-P, Calcitonin gene-related protein (CGRP), Cholecystokinin (CCK), nitric oxide (NO), and *vasoactive intestinal peptide (*VIP), and they change the intestinal motility, modulate the tight junction proteins, and increase intestinal permeability.[10] As the intestinal mucosa is very sensitive to the shortage of blood and oxygen, and the intestinal mucosal blood flow (IMBF) plays a vital role in the intestinal mucosal defense system, as it brings oxygen and nutrients to the mucosal cells. This maintains the normal structure and function of the intestinal mucosa and is closely associated with the pathogenesis and healing of the intestinal mucosal lesions and intestinal motility – which is a normal cleansing mechanism of the intestine.[10,12] Thus, the major changes of GI dysfunction after TBI can be summarized in four aspects [11]:-

1. GI mucosal ischemia
2. Gut motility dysfunction
3. Disruption of the gut barrier
4. Alteration of the intestinal mucosa and its absorptive function

Apoptosis is an important factor in GI physiological cell renewal, triggered by noxious stimuli such as trauma and ischemia, leading to gut barrier damage and increased permeability of the intestinal epithelium, leading to possible translocation of the intraluminal microbes and bacterial toxins by factors such as, nuclear factor kappa β, TNF-α, IL-1β, IL-6, and ICAM-1.[11] The intestinal cell damage after trauma causes increased levels of the circulating intestinal fatty acid binding protein – a specific biomarker for damage of differentiated enterocytes, and their levels correlate with the subsequent development of an inflammatory response.[12]

Traumatic brain injury can induce significant damage of the gut structure and impairment of the barrier function, which occurs rapidly, as early as three hours following brain injury and lasts for more than seven days, with marked mucosal atrophy. Histopathological alterations of the gut mucosa that occur include, shedding of the epithelial cells, fracture of the villi, focal ulcer, fusion of the adjacent villi, dilation of the central chyle duct, mucosal atrophy, vascular dilation, congestion and edema in the villous interstitium, and lamina propria.[13]

Bowel dysfunction is also a common complaint in patients with brain damage due to stroke and TBI like anal incontinence, constipation, a delayed but significant decrease in intestinal contractility in the ileum, leading to delayed transition in the colon as well, maybe due to the damage of the pontine and suprapontine regions, leading to a dysfunction in the modulation of the defecation reflex arch.[14,15]

Traumatic injury to the central nervous system is regarded as the initial step in a series of biochemical and pathophysiological events that may have, as a consequence, irreversible tissue damage. Several factors are involved in this secondary injury process, including ion changes, excitatory amino acids release, formation of reactive oxygen species, and metabolic energy perturbations. Data obtained with animal models of TBI show that high levels of excitatory amino acids, through the activation of N-methyl-d-aspartate receptor / ion channels, increase the intracellular Ca^{2+} concentration. Maintenance of Ca^{2+} homeostasis is critical after injury, to avoid triggering of potentially harmful biochemical and metabolic cascades. After brain injury, the reactive oxygen and nitrogen species may be generated through several different cellular pathways, including Ca^{2+}-activated phospholipases, nitric oxide synthase, xanthine oxidase, and the Fenton and Haber-Weiss reactions, by inflammatory cells. Recent research suggests that the traumatic deformation of axons is responsible for triggering abnormal ionic influxes through several channels. There is evidence to support that some of the channels activated after trauma are mechano-sensitive. Mechano-sensitive ion channels are ion channels whose gating can be altered by mechanical forces. Mechanical stress is subsequently transformed into an electrical or chemical response. Gadopentetate dimeglumine (GAD) with gentamicin and amiloride act as relatively selective blocker of mechano-sensitive membrane ion channels. A previous study has reported that GAD administration up to 30 minutes after trauma could prevent many of the changes observed after TBI (e.g., increased brain edema, lipid peroxidation, and catalase activity).[16]

A study done to prevent intestinal dysfunction after TBI, by stimulating the cervical vagus nerve in selected mice, found decreased levels of TNF-α as compared to the TBI cases without vagal stimulation, who had high levels of the same. The levels of the glial fibrillary acidic protein (GFAP) – a marker of glial activity – were found to be significantly higher in the vagal stimulated group.[17]

In cases of severe traumatic brain injury, patients are often transferred to rehabilitation units with artificial nutrition devices, like a central nervous catheter or a nasogastric tube, with a trend toward a better outcome in terms of survival and disability, by preventing intestinal mucosal atrophy and preservation of the normal gut flora, but in recent times Percutaneous Endoscopic Gastrostomy (PEG) has become a usual procedure for patients with prolonged disorders of consciousness after brain injuries, permitting adequate nutrition with a morbidity rate of 94% according to a recent large meta-analysis.[15]

In another study, the hormone Ghrelin, which has several anti-inflammatory properties in addition to its function of hunger and satiety, prevents intestinal injury following TBI by its action on the dorsal motor nucleus of the vagus. It was evidenced by the fact that intestinal permeability decreased in the Ghrelin–TBI group, when measured after six hours of TBI, by serum levels of FITC-Dextran and TNF-α. Expression of the tight junction proteins MLCK, ZO-1, and Occludin increased, thereby, decreasing intestinal permeability. Ghrelin also preserved the intestinal architecture.[18] Also, oxidative stress from the reacting oxygen species (ROS) is believed to be involved in the progression of GI dysfunction secondary to TBI. The antioxidant transcription factor, nuclear factor erythroid 2-related factor (Nrf2), and inducer *tert-butylhydroquinone* (*tBHQ)* have been shown to markedly decrease the levels of NF-κβ activation, IL-1β, IL-6, and ICAM-1, and to significantly attenuate TBI-induced intestinal mucosal apoptosis, when administered orally.[11]

Also, it has been found that post TBI-progesterone injections inhibit intestinal NF-κβ p65 activation and its binding activity, protein expression, and proinflammatory cytokine IL-1β, TNF-α expression, thereby, reducing cerebral edema, preventing neuronal loss, and improving functional outcomes.[19] NF-κβ functions as the homo- or heterodimer of the Rel family of Proteins, which includes p50, p65, c-Rel, p52, and relb. The most common combination of subunits is the heterodimers of the p50 and p65 proteins. NF-κβ normally exists in the cytoplasm of cells bound by a member of the inhibitor kappa B (I-κβ) protein family. NF-κβ activation occurs by inducers, such as, IL-1β and TNF-α, which leads to phosphorylation and degradation of the I-κβ protein, allowing NF-κβ translocation to the nucleus where it can then bind to the specific sites within the promoter sequence of the target genes, whose products like the proinflammatory cytokines, inducible nitric oxide synthase, cyclooxygenase-2 (COX-2), and acute phase proteins, are critical to inflammatory processes. This kind of positive feedback in the interaction of NF-κβ with proinflammatory cytokines may occur through extracellular mechanisms. This has been confirmed by several studies. NF-κβ activation enhances the transcription of the TNF-α and IL-1β bands and these cytokines are known to in turn activate NF- κβ. The positive feedback is believed to serve in amplifying inflammatory signals.[20]

It is now clear that biological sex alters the incidence of, and outcome from ischemic and traumatic brain injury, for example, stroke is more common in the male sex. The female sex has more resistance to stress and GI lesions occur in fewer instances in the female than in the male sex. The use of estrogen or progesterone alone or a combination of these two hormones reduces brain edema following TBI, which determines the anti-inflammatory role of female sex steroids, because it maintains the level of the calcitonin gene-related peptide (CGRP), which has a protective role in mucosal injuries, exaggeration of mucosal secretion, increment of bicarbonate secretions, change of the hypothalamus pituitary axis (HPA) response to stress, inhibition of oxidative stress, modulation of NO secretion production, adjustment of ANS activity, interaction with melatonin at the gastric mucosal level, upgrading of angiogenesis, reduction of TNF-α, inhibition of apoptosis due to ischemia, decreased pepsin secretion due to modulation of gastrin and CCK production, modulation of NO production, and modulation of the release of IL-1 and TNF-α.[21]

CONCLUSIONS

The gut–brain axis is one of the most important and least recognized factors in human health. The complex mechanisms and reasons for GI dysfunction in patients with severe TBI pose the challenge of how to prevent and solve the problem. In summary, damage of the intestinal mucosal barrier function following TBI is caused by multiple factors, the close correlation between the decrease of intestinal mucosal blood flow (IMBF) and motility and increase of intestinal permeability, support the hypothesis that both of them might play a role in the regulation of intestinal epithelial barrier dysfunction during and after TBI, and that the restoration of intestinal blood flow and motility might be a useful method to maintain the barrier function.

Therefore, maintaining the intestinal barrier function is a systematic engineering project. Further research that more precisely characterizes the role of intestinal mucosal blood flow and intestinal motility in diseases could put new insights into new therapies for stress-induced injury of the intestinal mucosal barrier function. Also, a concept of the neuro-enteric axis is emerging as an interesting physiological mechanism in the pathogenesis of GI diseases.

ACKNOWLEDGMENTS

The author would like to thank Dr. Saranjeet Singh Bedi, Dr. Mohammad Akheel, and Dr. Shikha Singh for their great editing effort and the anonymous referees for their insightful and constructive comments and suggestions that have led to an improved version of this article.

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Cite this article as: Singh SP. Neurogastroenterology: Gastrointestinal dysfunctions from the window of acute brain injury. Int J Stud Res 2013;3:1-4.

Source of Support: No, **Conflict of Interest:** No.