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REVIEW ARTICLE

# Intestinal barrier dysfunction following traumatic brain injury

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**Abstract**
Traumatic brain injury (TBI) can cause non-neurological injuries to other organs such as the intestine. Newer studies have shown that paracellular hyperpermeability is the basis of intestinal barrier dysfunction following TBI. Ischemia–reperfusion injury, inflammatory response, abnormal release of neurotransmitters and hormones, and malnutrition contribute to TBI-induced intestinal barrier dysfunction. Several interventions that may protect intestinal barrier function and promote the recovery of TBI have been proposed, but relevant studies are still limited. This review is to clarify the established mechanisms of intestinal barrier dysfunction following TBI and to describe the possible strategies to reduce or prevent intestinal barrier dysfunction.

**Keywords** Intestinal barrier dysfunction · Multiple organ dysfunction syndrome · Traumatic brain injury

## Introduction

Traumatic brain injury (TBI), induced by severe trauma, is a major cause of death and disability and has become a global public health problem. The number of victims of TBI exceeded 2.5 million with 56,000 succumb in the USA in 2013 [1]. Characterized by a primary penetrating or non-penetrating injury of the head, TBI is not an isolated event but a biological process associated with numerous non-neurological injuries, such as systemic inflammation and organ dysfunction involving cardiovascular, respiratory, and gastrointestinal systems [2–4]. These often occur minutes to months after initial mechanical injury to the brain and substantially contribute to morbidity and mortality [3].

The intestinal mucosa is the largest surface of interaction between the internal milieu and the external environment [5]. Intestinal epithelium curtains off the contents of the lumen, preventing the invasion of pathogenic antigens. Following brain injury, intestinal epithelial cell dysfunction or apoptosis may occur due to ischemia and/or hypoxia, oxidative stress, and inflammatory reaction [6]. Consequently, the permeability of the intestinal mucosa increases. TBI-induced intestinal permeability can cause the translocation of endotoxins and bacteria in the intestinal tract, further inducing or aggravating the systemic inflammatory response and resulting in multiple organ failure and death [7]. Maintaining the integrity of the intestinal mucosal structure and protecting intestinal barrier function can improve the prognosis of TBI. This paper reviews the progression of intestinal barrier dysfunction following TBI.

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## An overview of the intestinal barrier

The intestinal barrier comprises a mechanical, chemical, biological, and immune barrier, and is one of the most important defense barriers in the human body. It serves a dual function, permitting the absorption of nutrients, water, and electrolytes on the one hand, while limiting host contact with noxious luminal antigens on the other [8].

### Mucus layer

The entire intestinal mucosa is covered with a layer of mucus over a thickness of 100 μm, which is secreted by the goblet cells in the intestinal mucosa. Mucus is composed of water, phospholipids, negatively charged mucins, various trefoil factors, and other antibacterial substances such as secretory IgA, antimicrobial peptides, and defensins [9]. The mucous layer protects the intestinal mucosa from damage by shear forces and the adhesion and invasion of microorganisms, toxins, and antigens. It also preserves mucous membrane secretions

containing antibacterial peptides and digestive enzymes and keeps the intestinal mucosa epithelium hydrated. Mucus not only forms a nonspecific physical barrier but also restricts the immunogenicity of gut antigens by delivering tolerogenic signals [10].

### Epithelial cell layer

The intestine is lined with a monolayer of columnar epithelial cells with a thickness of about 20 μm, which separates the intestinal lumen from the internal milieu. In addition to intestinal epithelial cells, the epithelial cell layer contains secretory cells, which are mainly goblet cells, Paneth cells (which mainly secrete antimicrobial peptides), and intestinal endocrine cells [11]. The integrity of the intestinal epithelium and the tight junctions between epithelial cells are important factors in the maintenance of the intestinal barrier function.

Intestinal epithelial cells are key components of the epithelial cell layer and their most important function is to maintain the integrity of the intestinal mechanical barrier. The movement of molecules, solutes, and ions across the intestinal epithelial cell layer takes place via the transcellular or paracellular pathway, which allows the passage of larger particles (such as nutrients, proteins, and bacteria and their products) through the epithelial cells via endocytosis or exocytosis [8, 12]. The intercellular spaces between the neighboring intestinal epithelial cells are sealed by the apical junction complex, which contains tight junctions and adherens junctions, and by subjacent desmosomes [8]. Tight junctions are important connections among epithelial cells, forming an important barrier to prevent translocation of intestinal bacteria and toxins. They form a continuous network at the top of the outer membrane of the epithelial cell, which prevents small molecules transferring into the submucosa through the intercellular space [13, 14]. Tight junctions are composed of multiple protein complexes, including transmembrane proteins such as occludin, claudins, junctional adhesion molecules, and cytoplasmic proteins such as zonula occludens (ZO). Actin and myosin loops are also formed around the epithelial cells. Claudins and occludin that form charge- and size-selective paracellular channels are regulated by intracellular scaffolding proteins, as well as by myosin light chain kinase (MLCK) [15, 16]. Paracellular permeability pathways can be classified into three types: pore pathways, leak pathways, and unrestricted pathways [17]. Tight junctions are not stable structures. Altered expression, post-translational modification, localization, or the activity of tight junction proteins or their regulators can change the degree of permeability to macromolecules [3]. When epithelial cells are apoptotic, necrotic, or ulcerated, substances in the intestinal lumen can enter into the submucosa through the unrestricted pathway.

### Immune barrier

About 70% of the immune cells in the human body are located in the gastrointestinal tract and form gut-associated lymphoid tissue (GALT). Organized GALT mainly includes Peyer's patches, mesenteric lymph nodes, isolated lymphoid follicles, lymphocytes, and antigen-presenting cells [9]. Diffuse GALT includes intraepithelial lymphocytes and lymphocytes in the lamina propria. The majority of intraepithelial lymphocytes are CD8+ T cells, which constantly monitor and respond to luminal bacteria and other antigens [9]. Intestinal immunity is mainly an innate immune response, the key components of which include pattern recognition receptors and antimicrobial peptides [9]. The gut microbiota also establishes the intestinal barrier, assists in mucus production, and promotes the regeneration of intestinal epithelial cells [18].

## Intestinal Barrier dysfunction induced by TBI

Gastrointestinal dysfunction often occurs after TBI. In the first few weeks following the injury, most patients with moderate to severe TBI have reduced intestinal contractile activity and absorption, which manifests as vomiting and abdominal distension [3]. TBI destroys the intestinal barrier and increases mucosal permeability. As a result, some of the ions, solutes, proteins, bacteria, and bacterial products move freely in and out of the intestinal cavity. Severe consequences such as malnutrition, electrolyte disorders, bacterial translocation, systemic inflammatory response, sepsis, and multiple organ failure may occur due to the injured intestinal barrier, which further increases mortality and prolongs the length of hospital stay. Many severe TBI patients die from multiple organ dysfunction syndrome rather than TBI itself [19]. A study using the TBI Drosophila model has shown that death after TBI is closely related to intestinal barrier dysfunction [20].

## Pathogenesis of TBI-induced intestinal barrier dysfunction

Pathogenesis of intestinal barrier dysfunction following TBI is not yet clear. The gut–brain axis, a bidirectional communication system between the brain and the gastrointestinal tract, incorporates both afferent and efferent signals of neural, hormonal, and immunological origins [21]. Primary and secondary brain injury can disrupt the axis resulting in disturbances of digestion and absorption, immunomodulation, neuroendocrine signaling, and intestinal barrier function [22]. The gut–brain axis and related findings may be helpful to understand and explore the pathophysiological mechanisms of intestinal barrier dysfunction following TBI.

## Paracellular hyperpermeability of intestinal epithelium

Paracellular hyperpermeability is the basis of intestinal barrier dysfunction following TBI. Determination of urinary lactulose and mannitol ratio is useful for assessing disorders characterized by changes in gut permeability [23]. The presence of lactulose in urine indicates the permeability of para-epithelial cells, while mannitol indicates the permeability of epithelial cells. Increased permeability of para-epithelial cells after TBI can be observed in animal experiments [24, 25]. In addition, the destruction of the intestinal epithelial barrier of rodents with TBI is often accompanied by the decreased expression of the tight junction proteins such as occludin and ZO-1, as well as the increased expression of intestinal MLCK [26, 27]. The observation also supports the opinion that the increase in intestinal permeability after TBI is mainly through the para-epithelial cell pathway rather than the trans-epithelial cell pathway. The gap between the tight junctions, which is greater than 0.25 μm, contributes to bacterial invasion [28].

## Ischemia–reperfusion injury

The effect of oxygen free radicals and apoptosis of intestinal epithelial cells increase intestinal permeability following TBI. The body is in a state of significant stress and often suffers from hypovolemic shock, which significantly reduces gastrointestinal blood flow and causes ischemia and hypoxia of intestinal mucosa. Ischemia and hypoxia further cause intestinal mucosal injury and barrier dysfunction [28]. After reperfusion, the protease and oxygen free radicals are released by the activated neutrophils and result in intestinal mucosal edema, cell necrosis, and apoptosis. Oxidative stress after TBI leads to hyperpermeability of intestinal epithelium, which is related to a decreased expression of ZO-1 and occludin. Mitochondria are considered the main targets of oxidative damage after TBI, and mitochondrial dysfunction may play an important role in TBI-induced intestinal dysfunction. Zhu et al. [29] found that the respiratory function of mitochondria and the activity of enzymes in enterocytes are compromised in rats after TBI. A study by Liu et al. [6] has shown that the extracellular signal-regulated kinase/nuclear factor-erythroid 2 related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) pathway, which has antioxidant properties, plays an important protective role in mitochondrial autophagy regulation in the process of TBI-induced intestinal mucosal injury and intestinal epithelial barrier dysfunction.

## Inflammatory response

In response to injuries, the first line of defense is the innate immune system in which macrophages, neutrophils, dendritic cells, natural killer cells, and γδT cells are involved in the innate immune response to cerebral damage [30]. The activation of immune cells causes the release of inflammatory mediators such as nuclear factor κB (NF-κB), tumor necrosis factor-α (TNF-α), interleukin 1 beta (IL-1β), nitric oxide, and platelet-activating factor causing intestinal mucosal injury. TNF-α is the core factor inducing intestinal hyperpermeability through tight junctions. Pathogen-associated molecular patterns (PAMPs) and NF-κB form a positive feedback loop. PAMP activates the Toll-like receptors of submucosal macrophages and other cells, thus promoting the transcription of TNF-α. The binding of TNF-α to the TNF receptor of intestinal epithelial cells activates several pathways, such as the NF-kB pathway, and upregulates the gene encoding of IL-1β and IL-6, thus increasing the permeability of tight junctions. A positive feedback loop might be also anchored by damage-associated molecular patterns, molecules such as nucleic acids that are released from apoptotic and necrotic cells following TBI, causing intestinal mucosal damage [3]. Nrf2-deficient TBI mice have higher expression of TNF-α and higher intestinal permeability than wild-type mice [25].

## Abnormal release of neurotransmitters and hormones

A large amount of catecholamines are released from the adrenal medulla and sympathetic endings following TBI, which causes increased excitability of the sympathetic nerves in the whole body, appearance of visceral vasospasm, decrease in the intestinal mucosal blood flow, damage to the intestinal mucosal barrier, and entry of endotoxins into the blood circulation. Neuropeptide Y (NPY) is widely distributed in the central and peripheral nervous system and is usually released simultaneously with norepinephrine. NPY functions simultaneously with norepinephrine at the sympathetic nerve junction. Duan et al. [31] found that the plasma concentration of NPY and jejunal gene and protein expressions of NPY increased significantly in TBI rats, suggesting that NPY could be involved in intestinal dysfunction following TBI. Dopamine is an important neurotransmitter in the central nervous system and is widespread in the nervous system and peripheral tissues. Its signal system plays an important role in the pathogenesis of TBI. The digestive tract contains many dopaminergic cells. Dopaminergic neuronal excitement in the nervous system can lead to the release of dopamine into the synaptic cleft, which may reduce the blood supply to the gastrointestinal tract and damage the intestinal mucosal barrier [28]. In the state of stress, the hypothalamic pituitary adrenal axis (HPA) is excited and cortisol is released from the adrenal glands, influencing the activities of intestinal functional effector cell [32].

### Malnutrition

In the early stage following TBI, the body is often malnourished. Brain injury can cause neuroendocrine changes causing more catabolism than anabolism, resulting in hypoproteinemia and decreased regeneration ability of intestinal epithelial cells. Malnutrition is associated with small intestinal histological abnormalities, including villous blunting, reduction in mucus-secreting goblet cells, and inflammation [33]. In a malnourished state, the secretion of various digestive enzymes in the intestinal tract also reduces and the chemical bactericidal action of the enzymes is weakened which is conducive to the excessive reproduction of intestinal foreign bacteria. In a malnourished state, the secretion of various digestive enzymes in the intestinal tract is also reduced and its chemical sterilization effect is weakened, which is conducive to the excessive reproduction of intestinal foreign bacteria. In addition, in the early stage of severe trauma, fasting is often needed. Without the stimulation of nutrients, intestinal mucosal atrophy is likely to occur, causing damage to the intestinal barrier function.

## Strategies to preserve intestinal barrier function following TBI

There is no doubt that intestinal barrier dysfunction increases the severity of primary diseases. Matthew et al. [17] classified the intervention measures addressing intestinal barrier dysfunction into two categories: (1) restoring intestinal epithelium, which includes intestinal stem cell transplantation and treatment with epidermal growth factor and r-spondin-1 and (2) regulating tight junctions, mainly for MLCK and claudin-2. However, research into these is still underway.

In addition to the treatment of brain primary injury, corresponding interventions according to different pathophysiological mechanisms of intestinal barrier dysfunction occurs following TBI may be helpful in preventing intestinal bacterial translocation and sepsis.

### Ghrelin

Ghrelin is a type of brain–gut peptide containing 28 amino acids and is mainly secreted by the stomach. Ghrelin is an endogenous ligand for growth hormone secretagogue receptor (GHS-R), so it has various biological functions. Ghrelin can bind to GHS-Rs on immune cells and inhibit the release of TNF-α induced by PAMP [34]. Exogenous supplementation of ghrelin can prevent intestinal barrier dysfunction following TBI. A study has shown that the use of ghrelin in a TBI mouse model inhibited the overexpression of intestinal TNF-α and MLCK and prevented intestinal permeability [27]. Cheng et al. [35] found in an intracranial hemorrhage (ICH) mouse model that ghrelin reduced intestinal mucosa damage, restored the expression of ZO-1 and claudin-5, inhibited intestinal endotoxin translocation, and improved survival rate, indicating that ghrelin is a potential therapeutic agent in ICH-induced intestinal barrier dysfunction.

### Vagus nerve stimulation

Vagus nerve stimulation (VNS) was observed to enhance motor and cognitive recovery, attenuate cerebral edema and inflammation, reduce blood–brain barrier breakdown, and confer neuroprotective effects [36]. VNS can promote the release of acetylcholine from the efferent vagus nerve, thus inhibiting the production of TNF-α in immune cells expressing acetylcholine receptor. In a mouse model of TBI, VNS prevented TBI-induced intestinal permeability, prevented intestinal injury, and significantly reduced intestinal TNF-α [37]. One study of a TBI mouse model showed that VNS decreased the level of serum TNF-α and increased the level of ghrelin significantly and that the inhibition of the ghrelin receptor weakened the anti-inflammatory effect of VNS [38]. More studies are needed to confirm the value of VNS in post-TBI intestinal barrier dysfunction.

### Lower sympathetic tone

Adrenergic blockers can block the activation of HPA caused by the locus coeruleus, norepinephrine, and the sympathetic nervous system, thus reducing the stress response and expanding the intestinal mucosal vessels. Labetalol is a high-selective αl receptor blocker. Lang et al. [39] showed that intraperitoneal injection of labetalol in TBI rats reduced plasma adrenaline level, prevented the increase of intestinal mucosal permeability, and decreased the expression of TNF-α in the gut. Other drugs that reduce sympathetic activity may also be considered, such as urapidil, which blocks α1 receptor and depresses the central sympathetic nervous system.

### *tert*-Butylhydroquinone

*tert*-Butylhydroquinone (tBHQ) is an inducer of Nrf2, which has a strong antioxidant activity and a certain bacteriostatic effect. A TBI mouse model studied by Jin et al. [40], oral treatment with 1% tBHQ for 1 week prior to TBI, markedly decreased NF-κB activation and inflammatory cytokine production and significantly attenuated TBI-induced intestinal mucosal apoptosis. The results suggest that tBHQ may be an effective therapeutic drug for the treatment of TBI-induced gut injury, with the upregulation of the Nrf2 signaling pathway as the potential mechanism [40].

### Rational enteral nutrition

Timely, appropriate, and adequate nutrition has a direct impact on the prognosis of TBI. Routine enteral nutrition cannot improve the functional status of the intestine after TBI [41]. Early enteral nutrition and the addition of special nutrients contribute to the recovery of intestinal mucosal barrier function after TBI. Moderate TBI may result in alteration of the gastrointestinal microbiome [42]. Probiotic supplementation helps maintain the normal flora of the gut and prevents the invasion of new and harmful bacteria. Zhang et al. [28] reported that intestinal supplementation with probiotics, or a combination of glutamine and probiotics, lowered the increased intestinal mucosal permeability, bacterial translocation and dopamine receptor D1 (DRD1) and DRD2 mRNA, and protein expression in rat intestinal mucosa after TBI. A TBI mouse model studied by Li and colleagues [43] revealed that *Clostridium butyricum* treatment significantly reduced neurological dysfunction and brain edema and also significantly increased the expression of tight junction proteins (occludin and ZO-1). Another study also demonstrated that the treatment of TBI mice with *Lactobacillus acidophilus* efficiently improved the terminal ileum villus morphology, restored the impaired interstitial cells of Cajal (ICC), and the disrupted ICC networks after TBI [44]. A recent systematic review of three clinical studies involving TBI patients showed that treatment with probiotics improved the health of patients compared with control groups [45].

## Conclusion

To sum up, many mechanisms are involved in the intestinal barrier dysfunction following TBI. Interventions targeting different mechanisms may protect intestinal barrier function and further contribute to recovery from TBI. However, the incidence of intestinal barrier dysfunction following TBI is not clear, the exact pathogenesis needs to be further elucidated and relevant targeted intervention studies remain limited. More attention to intestinal barrier dysfunction following TBI is, therefore, required. The bidirectional gut–brain axis (or microbiome–gut–brain axis), as a significant shift in neuroscience, provides a promising way for studying TBI.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.



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