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SYSTEMATIC REVIEW

Traumatic Brain Injury and Gut Brain Axis: The Disruption of an Alliance

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Abstract: ***Background*:** Traumatic brain injury (TBI) can be considered a "silent epidemic", causing morbidity, disability, and mortality in all age cohorts. Therefore, a greater understanding of the underlying pathophysiological intricate mechanisms and interactions with other organs and systems is necessary to intervene not only in the treatment but also in the prevention of complications. In this complex of reciprocal interactions, the complex brain-gut axis has captured a growing interest.

***Scope*:** The purpose of this manuscript is to examine and systematize existing evidence regarding the pathophysiological processes that occur following TBI and the influences exerted on these by the brain-gut axis.

***Literature Review*:** A systematic review of the literature was conducted according to the PRISMA methodology. On the 8th of October 2021, two independent databases were searched: PubMed and Scopus. Following the inclusion and exclusion criteria selected, 24 (12 from PubMed and 12 from Scopus) eligible manuscripts were included in the present review. Moreover, references from the selected articles were also updated following the criteria mentioned above, yielding 91 included manuscripts.

Discussion: Published evidence suggests that the brain and gut are mutually influenced through four main pathways: microbiota, inflammatory, nervous, and endocrine.

***Conclusion*:** These pathways are bidirectional and interact with each other. However, the studies conducted so far mainly involve animals. An autopsy methodological approach to corpses affected by traumatic brain injury or intestinal pathology could represent the keystone for future studies to clarify the complex pathophysiological processes underlying the interaction between these two main systems.

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1. INTRODUCTION

Traumatic brain injury (TBI) could be defined as "the silent epidemic" of modern times, considering that it represents one of the main causes of morbidity, disability, and mortality in all-age cohorts [1-2]: in Europe, the incidence can be estimated, according to some series, up to 849 per 100,000 population per year, of which mortality rates ranged from 3.3 to 28.10 per 100,000 population per year [3]. From an epidemiological point of view, these rates have unfortunately not undergone gross changes over the years compared to previous cases, while, from the etiological point of view, the onset would seem to be shifting in Europe from road traffic incidents to falls in more recent studies. Furthermore, this condition heavily affects different health systems or structures with an immense expense both for the in-hospital management of patients and for the related morbidity [4-5].

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Head trauma is responsible for two categories of neuronal damage: primary damage, directly during the initial insult, and secondary damage, related to tissue and cellular consequences. Primary brain injuries, in turn, can be divided into focal and diffuse brain injuries, of which approximately 70% of TBI cases are represented by diffuse axonal damage (DAI) [6-7]. On one hand, the focal lesion concerns the area drawn from the blow with the appearance of hematomas, epidural, subdural, and intracerebral hemorrhages, which can lead to neuronal and glial cell necrosis due to inadequate blood supply [8]. A secondary contusion can develop in the tissues opposite or surrounding the blow, according to backlash dynamics, due to the impact of the brain against the skull [9]. On the other hand, diffuse brain injury depends on acceleration and deceleration mechanisms that cause damage to neuronal axons, oligodendrocytes, and the vascular system, causing brain edema and ischemic brain damage [10] and extensive damage to the vascular axons in subcortical tissue and deep white matter such as the brain stem and corpus callosum, which involves impaired axonal transport. The degree of axonal damage and neuronal degeneration determines the severity of the head injury [11]. The breakdown of the blood-brain barrier (BBB) and the death of neuronal cells during TBI underlie secondary damage. First of all, the appearance of BBB allows the infiltration of circulating leukocytes into the damaged brain parenchyma, which release proinflammatory cytokines such as IL-1β, IL-6, and TNF-α, with consequent aggravation of the permeability to BBB [12]. This process leads to the formation of edema. This is followed by the excessive release of aspartate and glutamate from presynaptic nerve endings [13-14]; the latter activates receptors, including the N-methyl-d-aspartate (NMDA) receptor, causing depolarization of the neuronal membrane. This causes an increase in post-synaptic intracellular Ca2 + ion, which triggers the activation of various cell signaling cascades. Furthermore, the glutamate pathway can directly trigger the activation of phospholipase C/inositol-1,4,5-triphosphate, which in turn mobilizes the release of Ca2 + from intracellular deposits in the cytosol. The excess of Ca2 + activates proteins involved in cell death by apoptosis, such as calcineurin, calpain, and caspase. Caspases are also activated by the TNF-α-ligand Fas bond [15-18].

Furthermore, activation of NMDA receptors promotes the production of reactive oxygen species (ROS) and nitric oxide (NO), which determine the inhibition of ATP synthesis [19], causing the deterioration of oxidative phosphorylation processes. In addition to blocking the metabolic reactions necessary for cell survival, an increase in membrane permeability occurs through the activation of the transition pore of mitochondrial permeability [20-21]. Furthermore, cytochrome c and apoptosis-inducing factors are released into the mitochondrial cytosol, promoting cell death [22-23]. Oxidative stress is also associated with the "lipid peroxidation" of polyunsaturated fats in membrane phospholipids, further damaging cell membranes [24].

All these processes activate and promote cell death by apoptosis of neuronal cells and oligodendrocytes, which would seem, finally, to be aggravated by the inhibition of lysosomal function and, therefore, of autophagy with a consequent pathological accumulation of autophagosomes, exacerbating the death of neuronal cells and the severity of the trauma [25].

Therefore, a greater understanding of the clinical characteristics and the underlying pathophysiological complex mechanisms and interactions with other organs and systems is necessary to intervene not only in the treatment of the underlying pathology but also in the prevention of complications [26-27].

In this complex of reciprocal influences, the complex brain-gut axis has captured a growing interest. The complexity is already related only to the number of microorganisms inhabiting the adult human gut, generally, more than 1000, which is significantly greater than the number of human cells in the body and contains more than 100 times the number of genes in the genome [28-29]. This complexity raises new questions in neuroscience, as new evidence indicates that appropriate diversity in the gut microbiota is essential for the normal physiological functioning of the brain. On the other hand, since the brain depends on gut microbes for essential metabolic products, not surprisingly, dysbiosis can have serious negative consequences from both a neurological and mental health perspective.

Therefore, the purpose of this manuscript is to examine and systematize existing Evidence Regarding the pathophysiological processes that occur following a head injury and the influences exerted on these by the brain-gut axis.

2. MATERIALS AND METHODS

Information Sources and Search: The criteria for systematic reviews and meta-analysis (PRISMA) were met for conducting this systematic review as shown in Fig. (**1**), PRISMA flow diagram [30]. Two authors conducted two independent searches of the literature. The results were combined to ensure that the literature was sufficiently reviewed and

Table 1. Inclusion and exclusion criteria according to PRISMA guidelines.

Inclusion criteria	Exclusion criteria
English language	No English language
Full text available	No full text available
Pathophysiology analyzed	Only-treatment analyzed
Research and review paper	Duplicate manuscript
In vitro/cell/animal/human model utilized	No TBI model

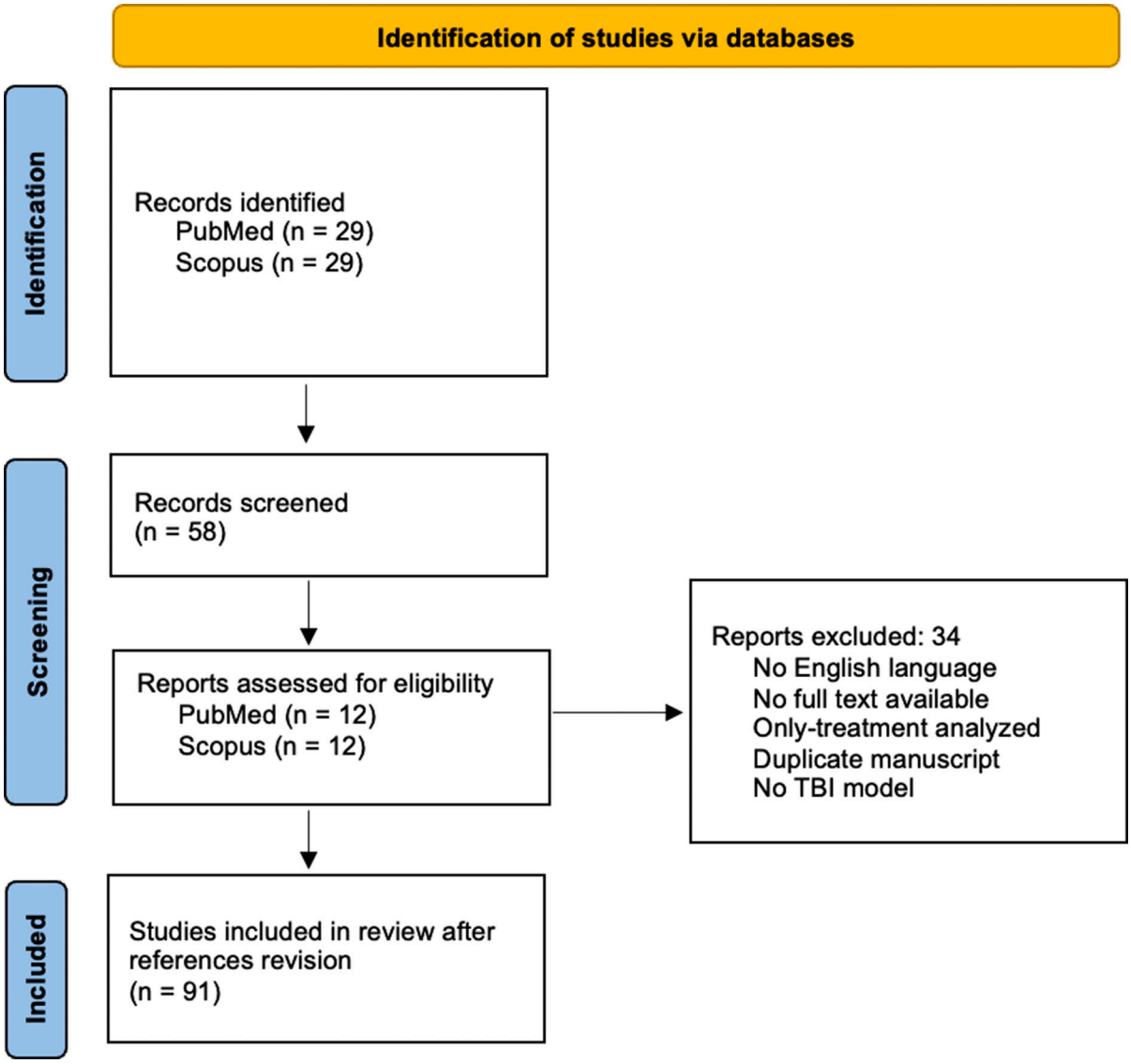

Fig. (1). PRISMA Flow diagram. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

that all appropriate articles for inclusion were found. On 8 October 2021, 2 independent databases were searched: PubMed and Scopus. To structure the search, the Boolean operators were used as follows: (1) '(traumatic brain injury) AND (gut-brain axis)'; (2) '(TBI) AND (gut-brain axis)'; (3) '(traumatic brain injury) AND (GBA)' and (4) '(TBI) AND (GBA)'.

After this search, the articles were found as follows: 29 (PubMed) and 29 (Scopus).

Study Selection: Two authors independently examined the titles and abstracts of each article generated by the literature search. The selection criteria are summarized in Table **1** [10]:

Synthesis: Following these procedures, 24 (12 from PubMed and 12 from Scopus) eligible studies were included in the present review. Moreover, references from the selected articles were also updated following the criteria mentioned above, yielding 91 included manuscripts. (Fig. **2**; Table **2**).

3. RESULTS AND DISCUSSION

This literature review highlights four pathways linking brains and gut (Fig. **2**): microbiota, inflammatory, nervous, and endocrine (Table **2**) [31].

Fig. (**2**) summarizes the four pathways of GBA. Four keywords have been associated with each pathway to explain the most important mechanisms involved. On the left, the brain is represented, from top to bottom, with autoptic samples, of which: 1) hematoxylin-eosin (HE) staining showing subarachnoid hematoma, indicated by red arrows; 2) intraparenchymal hemorrhage (HE staining), indicated by blue arrows; 3) positive Perl's histochemical staining [2]. The gut on the right is exemplified, from top to bottom, with cadaver samples, of which: 1) colon sample, with alteration of the mucosal component (HE staining); 2) inflammatory infiltrate in the context of the visceral wall (HE staining); 3) alterations of the epithelial component at higher magnification (HE staining).

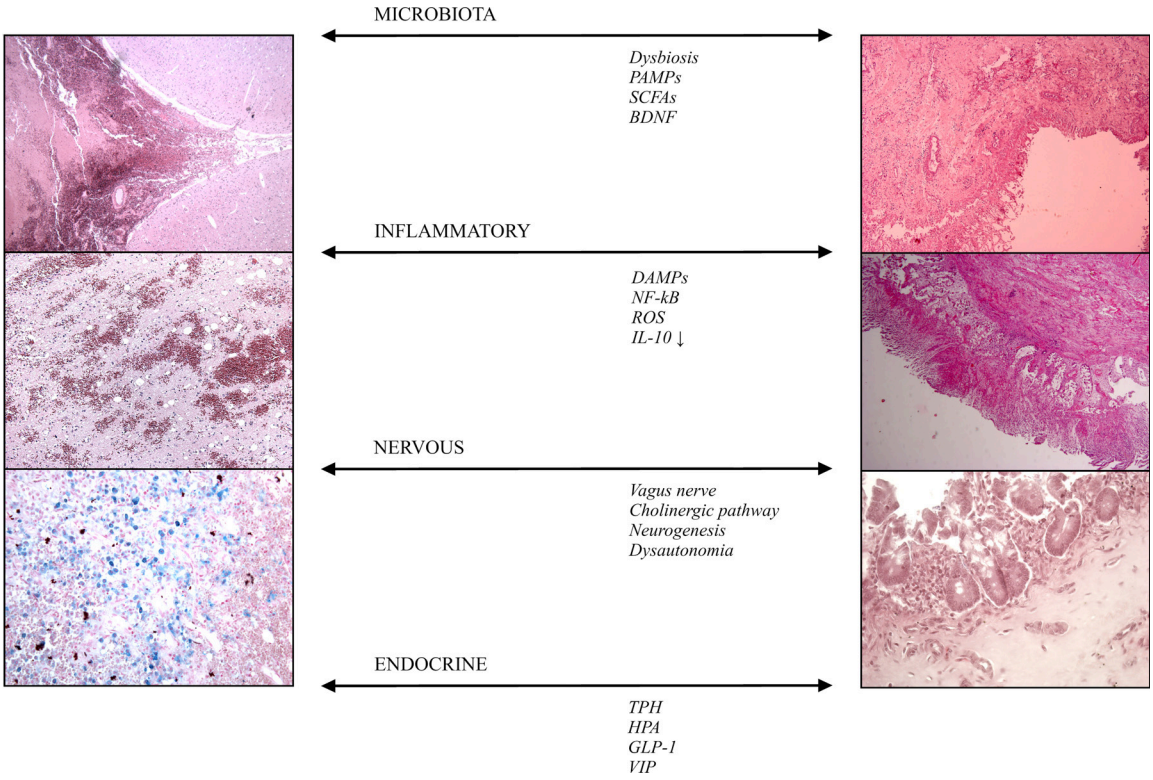

Fig. (2). The four pathways of GBA. Four keywords. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

The four pathways that connect the brain and gut are fully described in the following section.

3.1. Microbiota Pathway

These microorganisms differ from individual to individual and are influenced by various factors, including environmental conditions [32]. The central role intestinal microorganisms play in maintaining central nervous system homeostasis is now well established by numerous pieces of evidence showing that changes in the microbiota could play an anti-inflammatory role or potentiate autoimmune phenomena in the brain.

Critical illnesses and some neuropathological conditions such as depression, Alzheimer's disease, stress, spinal cord injury, and TBI can modify the gut microbiota [33-43].

According to "The Beehive Theory" proposed by Norins, the long-term neurological damage in TBI would be due to microorganisms present both in the brain and in other parts of the body. In a physiological state, various microbial species are in balance with the organism, bringing benefits to health [44]. Norins suggest that in addition to the well-known cerebral effects of intestinal dysbiosis, head trauma interferes with the balance of brain microorganisms that produce deleterious metabolites and create local damage. Commensal bacteria found elsewhere in the body can also penetrate *via* blood, altering the blood-brain barrier and contributing to brain damage [44].

Dysbiosis refers to the altered composition of the gut microbiota so that commensal bacteria are overwhelmed by pathogens [45]. A preclinical study demonstrated the link between the brain and the microbiota by showing variations of intestinal microorganisms in mouse models with experimental stroke and traumatic brain damage, and a recent study found that TBI causes significant changes in the microbiota within 24 hours of brain injury in murine models [46-47]. Matharu *et al*. point out that repeated traumatic brain injury in murine models produces appreciable jejunic dysbiosis, and a study conducted by Urban and colleagues showed significant differences in the fecal microbiota of subjects with TBI compared to subjects belonging to the control group [48-49].

A review by Pathare *et al*. aimed at investigating the impact of TBI on the microbiota found similar changes in bacterial flora in humans, although it is uncertain if these changes are attributable exclusively to TBI or also depend on the diseases affecting the population involved in the studies [50].

Multiple preclinical studies found that the gut microbiota can promote intestinal pro-inflammatory and anti-inflammatory responses through multiple mechanisms, including stimulating regulatory T cells, which are critical in preventing inflammation as they produce the anti-inflammatory cytokine IL 10 [51].

Gut epithelial cells express pattern recognition receptors (PRRs), including several receptor subtypes, such as toll-like receptors (TLRs).PRRs are part of innate immunity and can recognize pathogen-associated molecular patterns (PAMPs) produced by pathogenic microorganisms. Activation of TLRs results in activation of NFkB and mitogen-activated protein kinases, resulting in the production of inflammatory

Table 2. Selected manuscripts were classified by the main described pathways.

Microbiota	Inflammatory	Nervous	Endocrine
Sender *et al*. [32];	Bailey and Cryan [73];	Borovikova *et al*. [97];	Dimopoulou *et al*. [112];
Chernevskaya *et al*. (2021) [33];	Maysinger and Zhang [74];	Wang *et al*. [98];	Roth *et al*. [113];
Chernevskaya *et al*. (2020) [34];	Mossad and Erny [75];	Ghia *et al*. [99];	Naseem and Parvez [114];
Stower H [35];	Arya and Hu [76];	Baguley *et al*. [100];	Sinz *et al*. [115];
Shao *et al*. [36];	Loane and Kumar [77];	Lv *et al*. [101];	Biteghe-Bi-Nzeng *et al*. [116];
Li *et al*. [37];	Marsh *et al*. [78];	Kigerl *et al*. [102];	Grundy *et al*. [117];
Galley *et al*. [38];	Plesnila [79];	Patel *et al*. [103];	Vanuytsel *et al*. [118];
Bajaj *et al*. [39];	Zhang *et al*. [80];	Bansal *et al*. [104];	Rowe *et al*. [119];
Wen *et al*. [43];	Lawrence [81];	Nagahara and Tuszynski [105];	Hang *et al*. [120];
Norins (2019) [44];	Hang *et al*. [82];	Neufeld *et al*. [106];	Delgado *et al*. [121];
Ochoa-Repáraz *et al*. [45];	Feighery *et al*. [83];	Clarke *et al*. [107];	Lopez *et al*. [122];
Houlden *et al*. [46];	Patterson *et al*. [84];	Neren *et al*. [108];	Della Valle *et al*. [123];
Treangen *et al*. [47];	Amoo *et al*. [85];	Zhou *et al*. [109];	Rachmany *et al*. [124];
Matharu *et al*. [48];	Hines *et al*. [86];	Forsythe *et al*. [110];	Li *et al*. [125]
Urban *et al*. [49];	Sandiego *et al*. [87];	Tang *et al*. [111]	
Pathare *et al*. [50];	Wen *et al*. (2018) [88];		
Round *et al*. [51];	Dumitrescu *et al*. [89];		
Kawai and Akira [52];	Qin *et al*. [90];		
Chen *et al*. [53];	Kumar *et al*. [91];		
Caricilli, *et al*. [54];	Reddy *et al*. [92];		
Singh *et al*. [55];	He *et al*. [93];		
Braniste *et al*. [56];	Ates *et al*. [94];		
Chodobski *et al*. [57];	Wang *et al*. [95];		
Tyler and Grandhi [58];	Buchmann Godinho *et al*. [96]		
Sundman *et al*. [59];			
Giannoni [60]			
Erny *et al*. [61];			
Wolf *et al*. [62];			
Kim *et al*. [63];			
Parker *et al*. [64];			
Mao *et al*. [65];			
Liu *et al*. [66];			
Hou *et al*. [67];			
David *et al*. [68];			
Rice *et al*. [69];			
Molina *et al*. [70];			
Zhu *et al*. [71];			
Brenner *et al*. [72]			

cytokines, including interleukins (IL), tumor necrosis factor (TNF), and type of IFN [52-53].

Consequently, the alteration of gut microorganisms that interact with intestinal receptors leads to chronic inflammation and tissue damage [54]. Furthermore, the microbiota can influence the brain. Recolonization of germ-free mice with dysbiotic post-stroke microbiota worsens the injury and functional deficits after inducing experimental stroke, and therapeutic transplantation of fecal microbiota improves stroke outcome [55]. A study conducted in mice showed that bacterial dysbiosis affects the permeability of the blood-brain barrier, which is already altered by the effects induced by head trauma [56-57]. This evidence shows a bidirectional communication between the brain and the intestinal microbiota [58-60].

Numerous studies indicate a correlation between microglia and microbiota. In germ-free mice, microglia was unable to activate secondary to an infection. The administration of short-chain fatty acids produced by fermentation of the microbiota restored its functionality. This evidence suggests that the gut microbiota is related to the normal function of microglia and that intestinal dysbiosis could affect the neuroinflammatory mechanisms mediated by this cell population in patients with TBI [61-62]. In a mouse model, injection of sodium butyrate, a product of SCFAs by the microbiota fermentation of dietary fibers, promote neurogenesis [63]. Other gut microbiota metabolites deriving from dietary components can regulate BBB permeability and neuron functionality and contrast inflammation [64-65].

Administration of probiotics to normalize the gut microbiota could represent a possible therapeutic strategy in patients with neurological diseases, including TBI [66-67]. The gut microbiota is influenced by diet. David *et al*. found that the animal diet, compared to the vegetal one, can induce important changes in the intestinal microbiota, suggesting that a specific diet could represent an additional therapeutic option to ameliorate outcomes in TBI patients [68]. Therefore, fecal microbiota transplantation in subjects with TBI could be a therapeutic key to restoring commensal flora and preventing secondary brain damage. Nevertheless, further studies are needed to develop an effective eubiotic therapy to understand the specific variations of the microbiota relating to the type and severity of TBI, age, and gender [69].

Similarly, probiotics have proved to be useful, as they increase the production of IL-10, reduce pro-inflammatory cytokines, and reduce intestinal permeability by acting on the hypothalamus-pituitary-adrenal axis [70-72].

3.2. Inflammatory Pathway

TBI lead damaged tissue to activate a pro-inflammatory cascade that results in a two-way loop involving the brain and gut. Microglial cells are resident macrophages that play a critical role in the neuroinflammation after TBI [73].

Microglia is a component of the innate immune system supporting neuronal development and growth by secreting neurotrophic factors such as insulin-like growth factor (IGF-1) and brain-derived neurotrophic factor (BDNF). Metabolites produced by the intestinal microbiota, including short-chain fatty acids (SCFAs), modulate their activity [74].

Following brain trauma or stroke, damaged neuronal cells release damage-associated molecular patterns (DAMPs) [75]. DAMPs bind to specialized pattern recognition receptors (PRRs), which include Toll-like receptors (TLRs) found on microglial cells [76]. TLRs play a vital role in the pathogenesis of central nervous system alterations, including stroke and TBI [77]. The interaction between DAMP and TLR triggers local inflammation, characterized by releasing inflammatory molecules such as cytokines, chemokines, and complement proteins [78-80]. The nuclear factor NFkB plays a central role in the BGA inflammatory pathway [81]. In mouse models, TBI induces overexpression of NFkB in the intestine. The hyperexpression of NFkB is responsible for an increased release of pro-inflammatory cytokines such as IL-6, TNF-α, IL-1β, and upregulation of the ICAM-1 cell adhesion molecule [82-83]. Such pro-inflammatory molecules in rats alter the permeability of the intestinal barrier by reducing the expression of tight junctions and causing apoptosis of intestinal epithelial cells [84, 85].

In addition, TBI induces dysfunction of the blood-brain barrier (BBB), characterized by the loss of tight junctions with a consequent increase in the permeability of this structure [86]. The intestinal barrier impairment promotes the passage of inflammatory cytokines and bacterial lipopolysaccharide (LPS) into the circulation. Microglia state can be divided into two different phenotypes: M1, which has cytotoxic effects, or M2, which is neuroprotective. LPS binds TLR4 expressed in brain microglia [84], promoting: i) its activation, shifting from the M2 state toward the M1 pro-inflammatory phenotype, with the consequent peripheral release of inflammatory mediators ([87]; ii) increases the brain production of ROS; makes neural cells more sensitive to oxidative stress [88]; iii) and stimulates the production of TNF-αin the periphery, which through the circulation reaches the blood-brain barrier sustaining a neuroinflammatory state that can persist up to 10 months [89]. The activated microglia release microparticles containing pro-inflammatory molecules that boost the inflammatory response in the brain and at the systemic level. Therefore, neuroinflammation results from inflammation initiated directly by trauma and the peripheral inflammatory process [90].

Phenolic compounds (such as paeonol or resveratrol) help improve neuroinflammation, and their neuroprotective action has been proved in various neurodegenerative diseases [91-92]. A study by He *et al*. on mouse models with acute stroke showed that the administration of paeonol reduces circulating pro-inflammatory cytokines and reduces the extent of brain tissue damage, while Ates *et al*. found that resveratrol reduced oxidative stress and lesion volume in rats with TBI [93-94]. Minocycline, a tetracycline that in animal models has been shown to improve outcomes by reducing inflammation and protecting BBB integrity, could be a potential therapy to treat TBI-related neuroinflammation. Statins attenuate the brain inflammatory response in mouse models of TBI. Treatment with atorvastatin reduced TNF-α and improved functional outcomes [95-96]. Physical exercise may be an interesting approach to reducing secondary brain injury after TBI, given its antioxidant and neurotrophic effects.

3.3. Nervous Pathway

The vagus nerve represents the main nerve communication pathway between the brain and the visceral organs. Several studies suggest that the vagus nerve can communicate indirectly with the gut microbiota.

Borovikova *et al*. demonstrated that the brain can regulate the systemic inflammatory response triggered by bacterial endotoxins through the vagus nerve and called this physiological mechanism the "cholinergic anti-inflammatory pathway". The primary neurotransmitter of the vagus nerve, Acetylcholine, has an anti-inflammatory effect as it attenuates the release of tumor necrosis factor (TNF), interleukins IL-1β, IL-6, and IL-18 in LPS-stimulated human macrophage cultures [97].

Afterward, Wang and colleagues pointed out that the α7 subunit of the nicotinic acetylcholine receptor has a crucial

role in the vagal attenuation of LPS-induced inflammation [98].

Subsequent studies showed that the interaction between the vagus nerve and peripheral macrophages attenuates the release of inflammatory cytokines as a result of circulating bacterial endotoxins in acute colitis [99]. TBI can be associated with a dysregulation of the autonomic nervous system known as dysautonomia [100].

This clinical syndrome is characterized by tachycardia, tachypnea, hypertension, diaphoresis, increased muscle tone, and increased body temperature. Its incidence in patients with TBI ranges from 8 to 33% and is associated with adverse outcomes. Although there is currently no evidence linking dysautonomia and an altered intestinal bacterial composition in patients with TBI, these two clinical conditions could be related [101].

A recent study found poorer neurological outcomes in spinal cord injury (SCI) patients with induced dysbiosis. This may be due to the reduced release of intestinal bacterial metabolites after SCI, such as serotonin precursors and short-chain fatty acids [102]. Similarly, dysautonomia in TBI could worsen the secondary injury by inducing dysbiosis, although further studies are needed to connect these two conditions. TBI is associated with an increase in intestinal permeability [103]. The intestinal dysfunction in these patients is probably multifactorial, and a role could be played by the vagus nerve, as its nerve endings are close to the intestinal mucosal cells. This hypothesis is supported by a study on mouse models in which vagal stimulation before the induced head injury prevented an increase in intestinal permeability [104].

The intestinal microbiota may play a role in vagus-mediated neuronal development. Brain-derived neurotrophic factor (BDNF) is a neurotrophin with a relevant function in neurodifferentiation and neuronal repair. Altered levels of BDNF are associated with numerous neurological conditions, including Alzheimer's disease and depression [105]. Some authors demonstrated that vagotomy performed on mice is associated with a reduced expression of BDNF mRNA in the hippocampus, while studies conducted on germ-free mice showed an altered expression of BDNF at the hippocampal level [106-109].

These findings suggest that gut microbiota could influence neurogenesis *via* the vagus nerve. Vagus nerve stimulation represents a possible therapeutic option in patients with TBI. Several studies prove that continuous vagus nerve stimulation in an animal model of brain injury leads to better results as it reduces brain edema and blood-brain barrier breakdown [110].

Furthermore, vagal stimulation has anti-inflammatory effects related to the decrease in TNF-α and IL-1β levels and the overexpression of IL-10 and reduces oxidative stress and apoptosis [111].

3.4. Endocrine Pathway

Dimopoulou *et al*. have found that over 50% of patients with TBI have endocrine alterations, which can induce repercussions in the brain and may be implicated in the pathogenesis of gastrointestinal alterations [112].

TBI-induced intestinal dysbiosis alters the synthesis of serotonin, a hormone that regulates the function of several organs, including the brain. Serotonin is mainly synthesized in the gastrointestinal tract from tryptophan (TPH), metabolized *via* the serotonin pathway, the kynurenine pathway, and the indole pathway [113].

The catabolites resulting from the kynurenine pathway in brain injury are dysregulated [114].

A study conducted in a rabbit head injury model showed overexpression of the enzyme indoleamine2,3-dioxygenase (IDO), involved in the kynurenine pathway, around the injury for several weeks after the injury and a significant increase in circulating kynurenine, while TPH and quinolinic acid, a metabolite of the kynurenine pathway, increase in the cerebrospinal fluid of patients with a severe head injury [114-115].

Since tryptophan catabolites derived from the kynurenine pathway are involved in regulating neuronal activity, the altered metabolism of this amino acid can be implicated in secondary brain damage.

TBI induces alterations in the hypothalamic-pituitary-adrenal (HPA) axis. Twenty-four hours after TBI, there is an increase in cortisol, ACTH, and gastrin, in proportion to the severity of the lesion. An experimental model of TBI showed an increase in the levels of corticotropin-releasing hormone [116-117], which can enhance the permeability of the intestinal barrier [118].

Animal studies pointed out that TBI causes chronic corticosterone dysfunction. High corticosterone levels are associated with an inhibition of neuronal plasticity, suggesting the bidirectional communication between the brain and gut [119]. Following TBI, cholecystokinin and vasoactive intestinal peptide (VIP) levels markedly increase in plasma and jejunum. While cholecystokinin promotes delayed gastric emptying, VIP can cause paralytic dilation of the small intestine [120].

However, VIP also has a neuroprotective role, as it can inhibit the production of TNF-α, IL-6, IL-1β, and nitric oxide in activated microglia [121]. Exogenous administration of ghrelin in a severe TBI mice model prevented volume loss of TBI and neuronal degeneration [122].GLP-1 is a chemical mediator that links the gut-brain [123]. Gut microbial changes have been associated with variation in glucagon-like peptide-1 (GLP-1) levels released by intestinal L cells of the ileum and colon. In particular, the release of GLP-1 is considered regulated by SCFAs produced by the gut microbiota. Studies in mice inducing severe head injury have shown that the analogue of injectable GLP-1, liraglutide, has neuroprotective effects [124]. A promising treatment for TBI could be the long-acting GLP-1 receptor agonist exendin-4 mitigates cognitive disturbances in mouse models of TBI. Furthermore, Iwai *et al*. showed that GLP-1 can act at the glial level by inhibiting the production of IL-1β, inhibiting the pro-inflammatory response of astrocytes [125]. Treatment with *Clostridium Butirricum*, a probiotic used to treat diarrhea, increases the intestinal secretion of GLP-1 in mice with TBI, resulting in neuroprotective effects.

CONCLUSION

Published evidence suggests that the brain and gut mutually influence each other through four main pathways: microbiota, inflammatory, nervous, and endocrine. These processes appear to be integrated rather than interdependent, which may allow them to have a negative feedback loop effect on the harm caused by a TBI (TBI induces dysfunction of the GUT, causing an aggravation of the TBI, which in turn aggravates the dysfunction of the gut). An explanation could be, for example, the following cause-consequence relationship: TBI - local inflammation - passage of cytokines and chemokines into the circulation - permeability of the intestinal barrier - passage of LPS into the circulation - worsening of neuroinflammation. Similarly, dietary supplementation with probiotics and polyphenols could reduce the secondary damage of TBI, also providing ideas for possible therapeutic approaches to support the treatments already envisaged by current guidelines.

However, the studies conducted so far mainly involve animals. Postmortem studies in Alzheimer's disease patients have shown the presence of bacterial nucleic acids in the brain, suggesting that bacteria can enter brain tissue [126]. Future research to understand the intricate pathophysiological mechanisms underlying the interplay between these two major systems may be based on an autopsy methodological approach to corpses with intestinal pathology or traumatic brain injury.

LIST OF ABBRIVIATIONS

HE	=	Hematoxylin-eosin
NMDA	=	N-methyl-d-aspartate
NO	=	Nitric oxide
PAMPs	=	Pathogen-associated molecular patterns
PRRs	=	Pattern recognition receptors
ROS	=	Reactive oxygen species

AUTHORS' CONTRIBUTIONS

Conceptualization, G.B. (Giuseppe Bertozzi); methodology, M.F. (Michela Ferrara) and R.L.R. (Raffaele La Russa); validation: C.Z. (Christian Zanza) and Y.L. (Yaroslava Longhitano); literature search: G.V. (Gianpietro Volonnino) and C.E.L. (Cristiano Ernesto Lauritano); literature review, F.P. (Fabio Piccolella) and A.M. (Aniello Maiese); writing-original draft preparation, G.B, M.F. and A.C.M. (Alice Chiara Manetti); writing-review and editing, A.M., C.Z., and Y.L.; supervision, R.L.R. All authors have read and agreed to the published version of the manuscript.

CONSENT FOR PUBLICATION

Not applicable.

STANDARD OF REPORTING

PRISMA checklist were followed in the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

SUPPLEMENTARY MATERIAL

PRISMA checklists is available as supplementary material on the publisher's website along with the published article.

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