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REVIEW ARTICLE

The Brain-gut Axis-where are we now and how can we Modulate these Connections?

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Abstract: A traumatic brain injury (TBI) initiates an inflammatory response with molecular cascades triggered by the presence of necrotic debris, including damaged myelin, hemorrhages and injured neuronal cells. Molecular cascades prominent in TBI-induced inflammation include the release of an excess of proinflammatory cytokines and angiogenic factors, the degradation of tight junctions (TJs), cytoskeletal rearrangements and leukocyte and protein extravasation promoted by increased expression of adhesion molecules. The brain-gut axis consists of a complex network involving neuroendocrine and immunological signaling pathways and bi-directional neural mechanisms. Importantly, modifying the gut microbiome alters this axis, and in turn may influence brain injury and neuroinflammatory processes. In recent years it has been demonstrated that the activity and composition of the gastrointestinal (GI) microbiome population influences the brain through all of above-mentioned pathways affecting homeostasis of the central nervous system (CNS). The GI microbiome is involved in the modulation of cellular and molecular processes which are fundamental to the progression of TBI-induced pathologies, including neuroinflammation, abnormal blood brain barrier (BBB) permeability, immune system responses, microglial activation, and mitochondrial dysfunction. It has been postulated that interaction between the brain and gut microbiome occurs mainly *via* the enteric nervous system and the vagus nerve through neuroactive compounds including serotonin or dopamine and activation by bacterial metabolites including endotoxin, neurotransmitters, neurotrophic factors, and cytokines. In recent years the multifactorial impact of selected immunomodulatory drugs on immune processes occurring in the CNS and involving the brain-gut axis has been under intensive investigation.

Keywords: Traumatic brain injury, secondary brain damage, trauma, cells interactions, microbiome, immunomodulation.

1. INTRODUCTION

A brain injury is the common cause of death among young male adults [1]. In survivors, mechanical external forces that cause the primary cause of brain injury, often involving the white matter, initiate a severe destructive and very protracted inflammation recently elucidated in the rat spinal cord injury model [2, 3]. While primary brain injury is irreversible as it occurs in an accident, the inflammatory damage, with neuronal dysfunction related to trauma-induced oxidative stress, apoptotic cell death, microglial activation and mitochondrial dysfunction, ischemia, edema and phagocytic macrophage activation and invasion, is amenable to treatment [4, 5]. Permanent neuronal loss with apoptosis of neurons and oligodendrocytes occurs along a very protracted course of severe destructive inflammation and may still be observed 1 year after brain trauma [6, 7]. Neural cell death involves impairment of function with increased calcium level in the cytosol [8]. Damage to the blood-brain barrier (BBB) in the CNS around the site of inflammation can result in an uncontrolled release of metalloproteinases, inflammatory cytokines, and proteases and the inappropriate activation and dysfunction of endothelial cells and extravasation of oedema fluid into the interstitial space [9]. The first

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peak of increased BBB permeability is noted within the initial few hours after injury and persists for 3-4 days, and a second peak may occur after 5 days as a result of inflammatory response and microglial activation [10]. Damage to the BBB may offer an opportunity for the therapeutic access of anti-inflammatory drugs administered parenterally, however, a "leaky" BBB may still be a barrier to large anti-inflammatory molecules such as Serp-1 and M-T7, immunomodulatory proteins isolated from Myxoma virus, indicating the need for pre-clinical testing of each candidate anti-inflammatory compound [11]. Although subdural infusion of Serp-1 resulted in lowering of the numbers of macrophages in the COI in the rat model of SCI, intraperitoneal infusion resulted in no effect [11]. Secondary axotomy and axonal degeneration are the result of destructive neuroinflammatory processes and involve proteolysis, excitotoxicity and mitochondrial dysfunction [12]. The site of trauma and supervening inflammation are localized by increasingly severe astrocytic reaction that not only walls off the site but also appears to actively transfer edema fluid from surrounding CNS tissue thus contributing to the formation of the COI [2]. Progressively severe astrogliosis around the COI may also participate in anti-inflammatory mechanisms that are water soluble and ultimately lead to inhibition and elimination of macrophage infiltration in the COI and result in a mature syrinx following the SCI [2, 13].

The inflammatory response after TBI involves both the resident microglia and infiltrating inflammatory cells, primarily phagocytic, CD68+/CD163- macrophages apparently stimulated by large quantities of damaged myelin and markedly elevated inflammatory cytokines including IL1, IL-6, IFN and chemokines with degradation of tight junctions (TJs), cytoskeletal rearrangements and protein promoted by adhesion molecules [14]. The inflammatory response is histologically evident on day 3 post-injury in the rat model of the SCI when large numbers of phagocytic macrophages begin to infiltrate the necrotic areas, become sequestered in the forming COI where they remove the myelin-rich necrotic debris and haemorrhage within 2 weeks post-SCI [2]. Large numbers of phagocytic macrophages persist in the COI for over 4 weeks apparently sustained by a mechanism of a vicious cycle where damaged myelin is potently chemotactic and chemokines elevated, resulting in activation of infiltrating macrophages that coincides with additional damage to the surrounding CNS with damage to oligodendrocytes and myelin resulting in more macrophage chemotaxis [15, 16]. The extraordinarily destructive and protracted inflammation initiated by trauma involving the white matter is therefore of the primary interest to therapeutic efforts leading to neuroprotection. The inflammatory response involves the release of DAMPS (danger associated molecular patterns): HMGB1, heat-shock, S100 proteins, ATP, which are bound by PRRs (Pattern Recognition Receptors) such as TLR [17]. PRRs recognise ligands and triggers, directly or by oligomerisation to inflammasomes (NLRP1 and NLRP3), with subsequent production of proinflammatory cytokines. Inflammasomes' activation of caspase-1 catalyses the cleavage of pro-interleukins into the active forms of interleukin-18 and IL-1β [18]. Kimbler *et al*. documented that blockade of P2X7 receptor with NLRP3 activating properties, extends the lesion and increases brain oedema, directly at 12 and 24 hours post injury in an animal model [19]. NADPH oxidase 2 (NOX2) is a main contributor to oxidative stress and NOX2-dependent inflammasome activation contributes to TBI pathology. Importantly inhibition of NADPH oxidase enzymes provides neuroprotective effects and reduces superoxide production [20]. Although increased synthesis of pro-inflammatory cytokines such as IL-1β, IL-6, IL-18 and TNFα, accompanied by rising levels of anti-inflammatory cytokines including IL-8, IL-10 and production of chemokines such as MCP1 and CCL5 has been attributed to activate blood-borne and CNS-resident immune cells, notably neutrophils, microglia and T-cells [21]. Recent systematic study on the progression of inflammation initiated by the SCI indicates that the CNS response, specifically astrogliosis plays an important role in the inhibition and elimination of infiltrating macrophages, thus eliminating the inflammation [2]. With this in mind, effective anti-inflammatory therapies should result in inhibiting destructive inflammation leading to its accelerated elimination and neuroprotection also reducing edema, neurodegeneration, cognitive deficits and improving overall neurological recovery [22]. It needs to be emphasized that TBI is a pro-inflammatory condition that affects not only the brain, but also impairs functions of other organs including eyes, lung, intestines, myocardium, and vascular circulation with long lasting effects and complications which need to be considered in medical practice [23].

2. BRAIN-GUT AXIS DURING TBI

In recent years the relationship between gut microbiome and brain has been an important topic. Gut microbiome plays a fundamental role in the functionality of the immune system. Over the past few years, some data have been presented that communities of microbes play a pivotal role in controlling aspects of host physiology [24]. The nervous system is strictly connected with the gut microbiome. This axis consists of a complex network involving neuroendocrine and immunological signalling pathways and direct neural mechanisms [25, 26]. It has been demonstrated that the activity and composition of the GI microbiome population influence the brain through a variety of pathways, including homeostasis of the CNS.

In mouse models, the gut microbiome is associated with changes in permeability of the BBB [27]. Braniste *et al*., demonstrated decreased expression of occludin by brain endothelial cells in reference to sensitive changes in the intestinal gut microbiota. In this study bacterial metabolites, including short fatty acids; butyrate, acetate or propionate, have affected the permeability of the BBB [27].

It is postulated that brain-gut microbiome communication occurs mainly *via* the enteric nervous system and the vagus nerve through neuroactive compounds and activation by bacterial metabolites, neurotransmitters, neurotrophic factors, cytokines, and endotoxins [28, 29]. Sympathetic and parasympathetic nervous systems have a pivotal role in the modulation of gut functions as regional motility, intestinal permeability, immune response of the mucosa, epithelial fluid maintenance and production of gastric acid, mucus, bicarbonate, gut peptides and antimicrobial peptides [30]. Therefore the autonomic nervous system mediates communication between the CNS and viscera. The HPA (hypo-

thalamus-pituitary-adrenal) axis activity, stimulated in response to environmental factors such as stress, reacts to microbiota-related energy sources production related to gut microbiota metabolic activity, which also results in restoration of absorbable nutrients and energy [31]. Bacteria stimulate gut-microbiota axis by synthesizing neuroregulators and neurotransmitters, which connect *via* Meissner's plexus with antigen presenting cells [32]. In addition, dysbiosis predisposes to adult stress responsiveness [33]. Previous research showed association between gut microbiome with autism, major depressive disorder, and Guillain-Barre syndrome [34]. Gut microbiota composition maintains homeostasis of the immune system. Different bacteria promote or antagonize production of pro- or anti-inflammatory cytokines, and importantly regulate the differentiation of T cells. Therefore, changes in the gut microbiome may result in dysregulation in the immune system and in the nervous system. Per example, in multiple sclerosis patients *Acinetobacter calcoaceticus* and *Akkermansia muciniphila* increased production of proinflammatory Th1 phenotype of peripheral mononuclear cells [35]. The GI microbiome is involved in the modulation of cellular and molecular processes which are fundamental to the progression of TBI-induced pathologies, including neuroinflammation, BBB permeability, immune system responses, microglial activation, and mitochondrial dysfunction, as well as intestinal motility and permeability [25, 36].

The brain injury generates microbiome disruptions through neuroendocrine and immunological pathways. These perturbations contribute to bi-directional imbalance even greater in the microbiome composition and induce secondary damage [37]. In experimental models, brain injury has induced disruption of the motility and permeability of intestinal wall, and finally changed the gut microbiome composition [38].

Theories about how TBI alters intestinal permeability are still under investigation. Some authors have indicated that increased NF-kB, leading to up-regulation of ICAM-1 and production of cytokines including IL-6 predispose to declined expression of tight junction proteins [39]. Another theory focuses on reduced vagal stimulation of the enteric system after brain trauma [40]. Holulden *et al*. have documented that damage to the CNS can lead to gut dysbiosis [41]. Brain injury predisposes to changes of cecal microbiota composition with specific changes involving *Peptococcaceae* and *Prevotellaceae* and may be affected by altered autonomic activity [41]. Expanded brain lesion correlates with increased levels of *Firmicutes sp.* which is composed of more than 200 different genera such as *Lactobacillus sp., Bacillus sp., Clostridium sp., Enterococcus sp.,* and *Ruminicoccus sp*. [39, 42, 43]. It is important to note that this imbalance correlates with the extent of injury and the impact of the pathophysiology of brain injury [44-46]. Lesion volume in MRI and loss of behavioural function correlates with philogenic changes and alpha diversity [37]. In the rat model of post-ischemic stroke, intestinal dysbiosis is linked to worse neurological outcomes [47]. Kigerl *et al*. demonstrated in the post-TBI period disruption of microbiome evident as suppression in *Bacteroides sp*. and proliferation of *Firmicutes sp.* [48]. Authors observed changes even 1 month after injury [48]. This disruption of the physiological balance resulted in elevation of Th1 cells, Th17 cells and in increased expression of IFN-γ, and IL-17 in mouse model of stroke [25]. In recent years experimental animal data have demonstrated remarkable changes in gut microbiota, even 2 hours after brain injury, which correlated with TBI lesion volume and predicted the degree of locomotor impairment [37, 49, 50]. Howard *et al*. reported an imbalance in gut microbiome in injured patients within 72 h of TBI, resulting in the decrease in *Bacteroidales sp., Fusobacteriales sp., Verrucomicrobiales sp.,* and increase in *Clostridiales sp.,* and *Enterococcus sp*. [51]. Changes in the GI microbiome can affect the BBB given the part of bacterial translocation, LPS exposure or activation of gdT-cells with other parallel mechanisms such neutrophil induced release of TNF alpha and MMP 9 [52]. Moreover, dysbiosis predisposes to alterations of the integrity and permeability of the BBB initiated by the inflammatory response [27]. Imbalances in intestinal content can be associated with increased severity of neuroinflammation, increased microglial activity and intensified neuropathology processes [53-56]. Total absence of intestinal bacteria in axenic animal model, results in impaired immune response of the microglia, in amplifying of myelination, in hyperactivity of the HPA axis, in changes in brain neurochemistry and in decreased anxiety and social behaviors [53, 57-60]. Additionally mitochondrial dysfunction after TBI is probably also impacted by microbiome disruptions [61-64].

3. MODULATION OF MICROBIOME AND IMMUNITY AFTER BRAIN INJURY

Alterations to the gut microbiome affect the brain-gut axis, and in turn brain injury impacts inflammatory processes that may alter the gut microbiome (Fig. **1**) [25].

3.1. Eubiotic Therapies

Eubiotic therapies as transplants and administration of pre/probiotics are novel proposition for patients after brain trauma [65]. These eubiotic therapies probably have the potential to shift the gut microbiome composition to a balanced, beneficial state, especially in a period of TBI-induced inflammatory progression. The window of 24-72 hours following the TBI is considered ideal for administration for an eubiotic therapy [51]. Preclinical studies showed that an effective eubiotic therapy reduces lesion volume and microglial activation, inhibits neuroinflammation, improves mitochondrial activity, and stabilises the immune system processes and intestinal functions [47].

The probiotic supplementation leads to recovery of the basic synaptic transmission in diabetic rats as well as to enhanced activation of superoxide dismutase [66]. Recent data suggest that the administration of probiotics may modulate mitochondrial homeostasis *via* production of short-chain fatty acid (SCFAs) products such as butyrate, propionate, and acetate [67]. Microbial-derived SCFAs have beneficial effects on the host energy metabolism [68]. Furthermore, supplementation with *Lactobacillus sp.* probiotic before myocardial infarction reclaims myeloid cell proportions to normal, shifts SCFAs balance and has cardioprotective effects [69]. Probiotic treatment improves the intestinal and peripheral tissue environment since it upregulates fatty acid

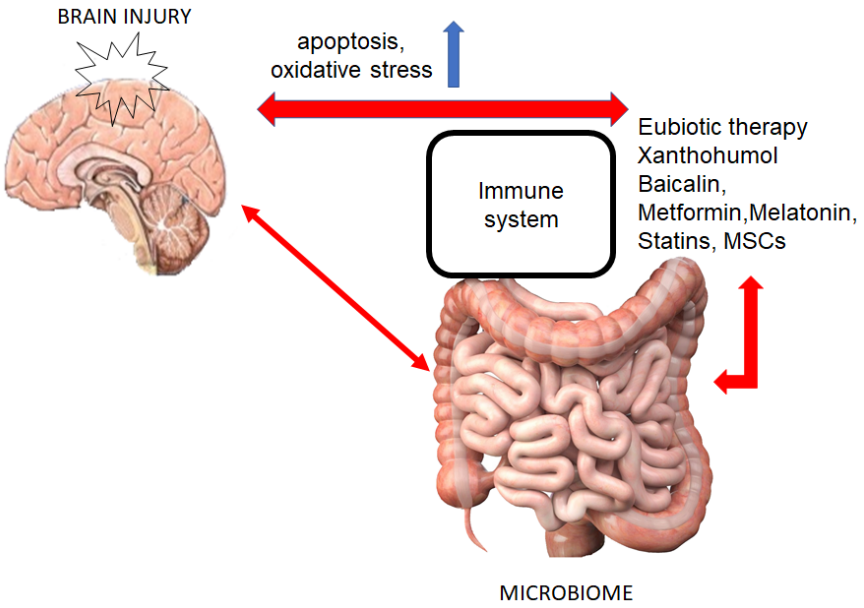

Fig. (1). Connection between gut microbiome -brain and selected therapeutic interventions. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

oxidation in the muscle and liver [68]. In addition, it improves sympathetic activity, gut brain neural circuit gluconeogenesis and thermogenesis [68]. Gut microbiome also produces alternative energy sources, including dietary ketones, important metabolites to regenerate bioenergetic status after TBI [70]. The butyrate is an important mediator of host-microbe crosstalk that promotes histone acetylation and up-regulates gene expression in host cells [71]. These effects are generated *via* the β-oxidation pathway and because butyrate is an inhibitor of histone deacetylases (HDACs) that can also ameliorate cognitive functions in neuropsychiatric disease and play a crucial role in neuroprotection [72, 73]. Li *et al*. have shown in mouse models that butyric acid produced by *Clostridum butyricum* improved neurological deficits and BBB impairment in TBI and in stroke [3, 56, 74]. These treatments significantly upregulated the expression of TJ proteins such as occluding and zonula occludens-1 but also p-Akt and Bcl-2, as well as down-regulated expression of Bax [74]. They also augmented the secretion of intestinal GLP-1 and induced expression of cerebral GLP-1R [74]. The propionic acid, a prominent microbiome metabolite, modulates mitochondrial functions in cells line [64]. Frye *et al*. have demonstrated that increased ROS levels lead to a detrimental effect of propionic acid resulting in mitochondrial dysfunction in individuals with inflammatory processes in the gut [64].

Probiotics rich in bacteria producing lactic acid decrease levels of circulating TNF-α, attenuate cerebral monocyte infiltration and reduce microglial activation [75, 76]. D'Mello *et al*. suggested that probiotics reduce microglial activation and monocyte infiltration and alter behavior [75]. In recent animal studies, probiotic supplementation after the SCI improved locomotor recovery and shifted immune response to protective mode by elevation in the Treg cell numbers (CD4+CD25+FoxP3+ T cells and CD11c+ DCs) [48]. In a randomized study by Min Tan *et al*. probiotic administation resulted in increased levels of IL-12p70 and IFN-γ in patients after brain trauma [77]. In addition, levels of IL-4 and IL-10 were reduced and these patients had decreased incidence of nosocomial infections, and lowered mortality rate within the 28-day period [77]. Daily probiotic prophylaxis can restore deviated TH1/TH2 response, reduce ventilator-associated pneumonia involving infections caused by *P.aeruginosa,* decreased GI dysfunction, and shorten the length of stay in the ICU [78-80].

A transplant of a normal fecal microbiota can prevent dysbiosis after SCI, and has a neuroprotective effect [81]. Anti-inflammatory effects of the normal microbiome are demonstrated in an animal model of ischemic stroke. Dysbiosis influences proinflammatory T cell activation in the immune compartment and in brain with lymphocyte migration to the CNS [47]. Thus, fecal transplantation can reduce the brain lesion and markedly improve stroke outcome *via* its anti-inflammatory effect.

Approximately one quarter of TBI patients develop a progressive neurodegenerative syndrome related to neurodegenerative proteinopathy or to neuroinflammation [82, 83]. Both processes initiated by brain trauma are the subject of ongoing studies [84]. The immune response to brain injury may be both a destructive contributor to outcomes and also a therapeutically tractable target mechanism. The impact of selected immunomodulatory drugs on inflammatory processes occurring in the neurotrauma with their role in affecting the brain-gut axis is a novel topic in recent years (Table **1**).

3.2. Xanthohumol

Xanthohumol is a natural flavonoid present in hops *(Humulus lupulus* L), which possesses antioxidant, anti-inflammatory and chemopreventive properties [47]. Importantly, this natural substance, as a possible enhanced component of nutrition may become a significant element support-

Table 1. Medications tested for the microbiome modulation.

Agents/Therapy	Immune System Effect	Microbiome Interactions	Others
Eubiotic therapie	-inhibit inflammation -improve mitochondrial -stabilize immune system functions	-shift the microbiome composition -reduce lesion volume -reduce microglial activation	-improve locomotion recovery -reduce ventilator associated pneumonia -decrease gastrointenstinal dysfunction -short leigh of stay in ICU
Xanthohumol	-inhibit oxidative stress -improve anti-inflammatory reactions	- decrease intenstinal microbiota diversity - alters bile acid metabolism	-regulate fat metabolism -modulate triglyceride and cholesterol levels -control glucose and insulin levels -inhibits Notch signaling and induces apoptosis in carcinoma (anticancer activity)
Baicalin	--inhibit oxidative stress -improve anti-inflammatory reactions	-increase of *Proteobacteria*, *Euryarchaeota*, and *Fusobacteria* -reduce of *Firmicutes*, *Actinobacteria,* and *Bacteroidetes*	-antitumor and antiviral properties -neuroprotective effects *via* Akt/Nrf2 and PI3K/AKT/FoxO1 pathway
Metformin	--inhibit oxidative stress -improve proinflammatory reactions	-adjust abundance of microbiome -decrease *Intestinibacter, Bacteroides fragilis* -increase bile acid glycoursodeoxycholic acid (GUDCA	-hypoglycemic effect -reduce cerebral edema -reduce neuronal apoptosis -improve neurological deficits
Melatonine	-reduce inflammation -modulate superoxide dismu-tase,gluthione, gluthione peroxidase -inhibit apoptotic pathways	-reduce dysbiosis in mice after spinal injury -ameliorate intenstinal integrity	-attenuate brain edema and hyperpermeability -ameliorate locomotion recovery
Ketamine	-inhibit neuronal apoptosis	-reduce *Deferrribacteres Mollicutes* -increase *Turicibacterales*	-reduce neurological deficits -inhibit neuronal apoptosis -reduce brain edema
Statins	-immunomodulatory and anti-inflammatory effects -reduce apoptosis	-increase the abundance of *Es-cherichia/Shigella,Ruminococcaceae UCG 014, Sutterella, Bacteroides, Butyricimonas*, and *Mucispirillum* -decrease short chain fatty acids production	-reduce triglyceride levels -raise HDL levels -reduce risk of blood clots, heart attack and stroke
Mesenchymal cells	-augments transcription of immuno-modulatory genes -inhibit inflammation -inhibit apoptosis -regulate IgA production	-restore gut functions -induce gut microbiome diversity	

ing the treatment of many diseases [85]. The available information on the possible effects of Xanthohumol in brain injury is limited but it was found to have neuroprotective effect in cerebral infarction studies in the rat, presumably related to its anti-inflammatory activities. The focal cerebral ischemia in the rat model was associated with increases in hypoxia-inducible factor (HIF)-1α, tumor necrosis factor (TNF)-α, inducible nitric oxide synthase (iNOS), and active caspase-3 protein expressions in ischemic regions [47]. Yen *et al*. showed that expression of these genes was inhibited by treatment with Xanthohumol [86]. The neuroinflammatory response in Parkinson's disease is mediated by the presence of activated microglial cells in the substantia nigra, with increased levels of proinflammatory cytokines in the striatum and the substantia nigra, and activation of the NF-κB proinflammatory pathway, which regulates target genes encoding proinflammatory cytokines, chemokines, growth factors and inducible enzymes [87]. In experimental models, Xanthohumol significantly reduced the production of proinflammatory cytokines IL-1β and TNF-α, and decreased the imbalance between pro- and anti-apoptotic factors observed in the brain [88]. Moreover, Xanthohumol increased the expression of the neurotrophic factor BDNF what suggests a capacity to modulate inflammatory responses in the brain [89]. Xanthohumol inhibits iNOS and activation of Ito cells, central mediators of hepatic fibrogenesis [90]. It induces apoptotic processes and prevents DNA damage secondary to carcinogens in liver and colon [91]. In addition, Zhang and al. have demonstrated that Xanthohumol administration decreases the diversity of intestinal microbiota and reduces counts of *Tenericutes sp*. [92]. Xanthohumol alters bile acid metabolism and specifically reduces inflammation in metabolic syndrome and in obesity.

3.3. Baicalin

Baicalin is a 7-D-Glucuronic acid-5,6-dihydroxyflavone, an active flavonoid isolated from the radix of *Scutellaria baicalensis*, with antitumor, antiviral, antimicrobial anti-

inflammatory antioxidative and neuroprotective effects [93]. In recent studies, Baicalin administration reduced brain edema, apoptotic cell death and activated antioxidative enzymes [94]. Baicalin demonstrates neuroprotective effect *via* activating the Akt/Nrf2 pathway and through the inhibition of TLR4 expression *via* the PI3K/AKT/FoxO1 pathway [93, 94]. Application of baicalin significantly decreased levels of IL-1, IL-6 and TNF-α in the hippocampus.

Baicalin-aluminium complexes altered the composition of the gut microbiome in piglets [95]. In animals treated with Baicalin-aluminium complexes, the counts of *Viruses noname, Proteobacteria sp.*, *Euryarchaeota sp.*, and *Fusobacteria sp.,* were increased, while the counts of *Firmicutes sp.*, *Actinobacteria sp.,* and *Bacteroidetes sp.,* were reduced [95]. In addition, Kang *et al*. demonstrated that intestinal microbiota may play a crucial role in the pharmacokinetics of Baicalin administered orally [96].

3.4. Metformin

Metformin is an oral hypoglycaemic drug with anti-inflammatory, antioxidative, and anti-ischemic activity [97]. In an animal model of TBI, metformin reduced cerebral oedema and neuronal apoptosis, and significantly improved neurological deficits presumably related to a neuroprotective effect. Metformin reduced levels of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6, inhibited microglial activation and the translocation into the cellular nucleus of NF-κB p65 and the phosphorylation of ERK1/2 and p38 MAPK [98]. Tao *et al*. have shown neuroprotective effect of metformin in TBI associated with its anti-inflammatory effect involving specific intracellular pathways indicated above [98]. In a randomized study, metformin had a strong effect on the gut microbiome by reducing abundance in microbiome, of γ Proteobacteria including *Escherichia coli* and *Firmicutes sp* [99]. These authors also observed decreased counts of *Intestinibacter sp. and* increased counts of *Bifidobacterium sp*. In addition, recent data demonstrated connection between the administration of metformin and the abundance of *Akkermansia muciniphila* and potentially related metabolic effects [100-103]. *A. muciniphila* contributed to metformin antidiabetic effect *via* increased mucin degradation and enrichment of SCFA secretion [104]. Sun *et al*. have shown that individuals treated with metformin had decreased *Bacteroides fragilis* counts in the gut and increased levels of glycoursodeoxycholic acid (GUDCA) in the bile related to inhibition of intestinal farnesoid X receptor (FXR) signaling [105].

3.5. Melatonin

Melatonin is another agent with a neuroprotective activity whose administration attenuates early brain damage and behavioral deficits after TBI [106]. In addition, exogenous melatonin reduces inflammation; attenuates levels of IL-1β, TNF-α, IL-10, IL-4, superoxide dismutase, glutathione, glutathione peroxidase, and inhibits mitochondrial apoptotic pathways [106, 107]. In recent studies, melatonin attenuated brain edema and increased permeability of the BBB [108, 109]. Furthermore, Jing *et al*. have shown that administration of melatonin reduced gut dysbiosis in mice after SCI [110]. Gut microbiome in animals treated with melatonin had decreased relative counts of *Clostridia sp*. [110]. In addition, reduction of monocyte chemotactic protein 1 expression and of gut barrier permeability were correlated with increase in counts of *Lactobacillales sp.* and *Lactobacillus sp.* [110]. Animal studies have shown that administration of melatonin improved locomotor recovery and intestinal integrity [111]. https://www.nature.com/articles/s41598-020-59314-7 In addition, melatonin significantly elevated goblet cells, Reg3β, and *Firmicutes sp.* to *Bacteriodetes sp.* ratio by inhibiting Gram-negative bacteria through TLR4 signaling [112]. Herein, it is showed that melatonin administration suppresses proinflammatory mediators in colitis and has a regulatory effect on microbiota in the intestine [113].

3.6. Ketamine

Ketamine has anti-inflammatory activity and inhibits neuronal apoptosis [114, 115]. In addition, ketamine interacted with gut microbiota as it reduced counts of *Deferrribacteres sp.* and *Mollicutes sp*. and increased the abundance of *Turicibacterales sp.* [116]. Furthermore, low *Sarcia sp.* levels were associated with inflammatory actions due to changes in degradation of polysaccharides complex to short chain fatty acids including butyrate, and ketamine significantly increased counts of these bacteria [117].

3.7. Statins

Recent studies demonstrated immunomodulatory and anti-inflammatory effects of statins. In animal models of TBI statins reduced apoptosis of microglia and downregulated expression of TNF-α [118, 119]. Atorvastatin reduced neuroinflammation by increasing the proportion of regulatory T cells (Tregs), IL-10 and transforming growth factor (TGF)-β1 [120]. *In vitro* research showed gut microbiota composition changes during statins treatment. Administration of fluvastatin increased the abundance of *Escherichia/Shigella sp., Ruminococcaceae UCG 014,* and *Sutterella sp.* [121] with concurrent reduction in production of short chain fatty acids. However, gut composition after rosuvastatin, simvastatin and atorvastatin treatment were almost unchanged. Kummen *et al*. have shown that patients treated with resuvastatin demonstrated a decreased genetic potential to transport and metabolize TMAO (pro-atherogenic metabolite trimethylamine-N-oxide) [122]. Furthermore, authors observed elevated metabolites of betaine and γ-butyrobetaine in plasma. Atorvastatin and rosuvastatin markedly elevated the counts of *Bacteroides sp., Butyricimonas sp.*, and *Mucispirillum sp*. in the gut [122]. Changes in the content of gut microbiota in the ileum corresponded to the levels of IL-1β and TGFβ1 [123].

3.8. Mesenchymal Stem/Stromal Cells

The ribosome, glycolysis, amino acid biosynthesis, carbon metabolism, and oxidative phosphorylation are involved in regulation of mesenchymal stem/stromal cell (MSC) proliferation and differentiation. The HIF-1 and several infection/inflammation signaling pathways are connected with chemokine and cytokine up-regulation by MSC [124]. These immunomodulatory effects have been assessed after TBI. Normal microbiota is involved in immunomodulatory properties of bone marrow stromal cells (MSCs). Microbiome induced immune-regulatory mediator secretions, cytokine

gene transcription and surface protein expressions in MSCs [125]. These MSC-microbiome interactions markedly augmented transcription of immunomodulatory genes including COX2, IL-6, and IL-8 and upregulated secretion of prostaglandin E2 (PGE2), IL-6, and IL-8 [126]. Gut microbiome markedly activated T-cell apoptosis and cytokine secretion [125]. Experimental data indicate that MSCs influenced by microbiota had enhanced expression of chemokines and IL-10 [125, 127]. This MSC-gut microbiome axis may lead to novel discoveries in therapeutics helping regulate pathologic inflammatory processes. In animal models of bowel inflammatory disease, administration through systemic infusion or local inoculation of MSC restored the physiologic composition of gut microbiome and enhanced suppression of pathogenic bacteria [128]. Furthermore, subepithelial MSC induced diversity of gut microbiome and regulated IgA production [127]. MSC interacts directly with the gut epithelium to control expression of CCL20 and microfold (M) cell differentiation [127]. These combined influences of microbiome and MSC therapy inhibited inflammation and restored gut function [128]. The cytosolic bacterial peptidoglycan Nod2 triggered MSC protective effect against oxidative stress-mediated apoptosis [129]. In addition pluripotent stem cells therapy increased numbers of Lgr5+ intestinal stem cells, increased proliferation of intestinal epithelial cells, promoted angiogenesis and restored changes of gut microbiome composition in a mouse model [130]. Thus interactions between MSC and gut microbiome could be used in addressing therapies for inflammatory diseases including the TBI. Recent data demonstrated that MSC administrated by systematically infusion or intracerebral injection migrates preferentially to the ischemic area [131, 132]. MSC therapy and migration in TBI depends on specific signals crosstalk with the brain tissue involving the stromal-derived factor-1 (SDF1), a chemokine expressed in astrocytes, neurons and endothelial cells and CXCR4 (receptor of SDF-1) expressed in MSCs [133]. MSC can reduce apoptosis of astrocytes in the ischemic boundary zone of the TBI and augment astrocyte proliferation post-ischemia. Gao *et al*. demonstrated that these processes may specifically involve activation of mitogen-activated protein kinase/extracellular signal-regulated kinase and phosphoinositide 3-kinase/threonine protein kinase pathways [134]. Transplantation of MSC elicited upregulation of brain-derived neurotrophic factor (BDNF), epidermal growth factor (EGF), fibroblast growth factor 2 (FGF2), insulin-like growth factor 1 (IGF1) and vascular endothelial growth factor (VEGF). The increase in the production of growth factors stimulated regeneration of resident brain cells [135]. Promising data have shown that MSCs can reduce inflammation and edema [131]. MSC with purified immune cells including NK, dendritic cells, naive and effector T cells, upsurge the production of interleukins IL-4 and IL-10 and inhibit TNF-α and IFN-γ expression [136]. In rat model of hemorrhagic stroke intraventricular infusion BM-MSCs suppressed pro-inflammatory cytokine expression including IL-6, IL-1α, and IFN-γ [137]. It is important to note that increased IL-4 levels opposite to decreased INF-γ reverse the helper T cell subsets, from cytotoxic Th1 cells to Th2 cells [131]. Furthermore, MSC therapy inhibits T cells proliferation and finally, these may correlate with alterations of cell damage [136]. In recent years BM-MNCs therapy is a subject of clinical trials for TBI. Cox *et al*. have shown in twenty-five patients that intravenous delivery of BM-MNCs is safe and had no severe adverse effects [138].

3.9. The Stable Gastric Pentadecapeptide (BPC 157)

The stable gastric pentadecapeptide is a small anti-ulcer and anti-inflammatory peptide founding in the human gastric juice [139]. It is freely soluble in water at pH 7.0 and in saline [140]. BPC 157 presents multiorgan activity. It was successfully used for the treatment of esophagus, stomach, duodenum, intestine, liver and pancreas lesions [141, 142]. Interestingly, BPC 157 also presents neuroprotective properties [143, 144]. Experimental study has confirmed the BPC 157 counteracts the immediate consequences of severe head injury and reduces post-traumatic brain oedema, number and size of haemorrhagic post-traumatic lacerations, intensity of subarachnoidal bleeding and intraventricular haemorrhage [144]. Additionally, BPC 157 significantly reduces the cuprizone-induced demyelination and then risk of severe encephalopathy [141, 145]. A single dose of pentadecapeptide BPC 157 improved motor function and decreased limb spasticity induced by experimental spinal cord injury [146]. The administration of BPC 157 30 sec after 20 minutes experimental-induced cerebral ischemia significantly reduced neuronal damage and attenuated or even completely prevented ischemia/reperfusion-induced behavioural deficits and motor dysfunction [147]. The neuroprotective effect of BPC 157 may result from its interaction with dopaminergic and serotonergic system, however BPC 157 also affects GABAergic system, upregulates the GABAergic-dependent neurotransmission and interacts with opioid system [148-150]. Ultimately, neuro-beneficial activity of peripheral administration of the stable gastric pentadecapeptide BPC 157 can document the link between intestinal and brain, however, this relationship should be confirmed in further clinical studies.

4. QUERCETIN AND ANTI-QUORUM SENSING ACTIVITY

Quorum sensing (QS) plays a crucial role in the activity of important microbial physiology processes, including production of biofilm [151]. Populations of bacteria synchronize their gene expression by range of intra and intercellular signals, and production of different compounds including autoinducer-1, autoinducer-2, autoinducer-3, *Pseudomonas quinolone* signal (PQS) and diffusible signal factors (DSFs). Because these processes are connected with virulence, there is a theory that anti-quorum activity of some agents reduces pathogenicity and may present smaller effect on the host of commensal microbes and modulation of gut microbiome [152]. Recent studies share an interest in the use of new anti quaorum therapies to limit collateral damage to microbiota by antibiotics [153, 154]. Experimental study has confirmed the anti-quorum sensing activity of the quercetin and reduction the formation of *Pseudomonas aeruginosa* PAO1 biofilm [155]. Quercetin is natural aglycone flavonoid occurring in fruits and vegetables, with anti-inflammatory, anti-proliferative and antioxidative effects [156]. In addition these commands alleviate cerebral edema, decrease neuronal degeneration, reduce oxidative stress in the mitochondria. Additionaly quercetin attenuate neuronal apoptosis *via* inhibition of extracellular signal-regulated kinase 1/2 phosphory-

lation and activated Akt serine/threonine protein kinase phosphorylation [157, 158]. The administration of quercetin resulted in the modulation of the Nrf2 pathway and presented antioxidant enzyme activity on mitochondrial biogenesis after TBI [159]. In mice model of atherosclerosis quercetin significantly effects on gut microbiom and Firmicutes phyla were the most sensitive commensals [160]. However, the relationship between quercetin and host of commensals needs more further studies.

CONCLUSION

Influences of microbiome on the CNS constitute a potential target for therapeutic interventions in neurotrauma. Further detailed investigations are needed to better understand complex brain-gut interactions in respect to regulation of destructive inflammation initiated by neurotrauma.

LIST OF ABBREVIATIONS

ATP	=	Adenosin-triphosphate
Bax/Bcl	=	Pro-apoptotic /anti-apoptotic proteins
BBB	=	Blood-brain barrier
BDNF	=	Brain-derived neurotrophic factor
BPC 157	=	Stable gastric pentadecapeptide
CNS	=	Central nervous system
COI	=	Cavities of injury
DAMPS	=	Danger associated molecular patterns
EGF	=	Epidermal growth factor
FGF2	=	Fibroblast growth factor 2
GLP-1	=	Glucagon-like peptide-1
GUDCA	=	Glycoursodeoxycholic acid
HDACs	=	Inhibitor of histone deacetylases
HIF	=	Hypoxia-inducible factor
HMGB 1	=	High mobility group box 1 protein
HPA axis	=	Hypothalamus-pituitary-adrenal axis
ICU	=	Intensive Care Unit
IGF1	=	Insulin-like growth factor 1
MSC	=	Bone marrow stromal cells
NADPH	=	Nicotinamide adenine dinucleotide phosphate
NOS	=	Nitric oxide synthase
NOX	=	NOXs, NADPH oxidase
PGE2	=	Prostaglandin E2
PRRs	=	Pattern Recognition Receptors
ROS	=	Reactive products of oxygen
SCFA	=	Short-chain fatty acids
SCI	=	Spinal cord injury
TBI	=	Trauma brain injury
TJs	=	Tight junctions
TLR	=	Toll like receptors
TMAO	=	Trimethylamine-N-oxide
TNFα	=	Tumor necrosis factor
Treg	=	Regulatory T cells
VEGF	=	Vascular endothelial growth factor

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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

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